frontiers | Research Topics

Clinical nutrition and oncologic outcomes, volume II

Edited by
Paula Ravasco, Antti Mäkitie, Faith Ottery,
Kalliopi-Anna Poulia and Lucio Lara Santos

Published in
Frontiers in Nutrition

ISSN 1664-8714
ISBN 978-2-8325-3853-1
DOI 10.3389/978-2-8325-3853-1

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Clinical nutrition and oncologic outcomes, volume II

Topic editors

Paula Ravasco — Catholic University of Portugal, Portugal
Antti Mäkitie — University of Helsinki, Finland
Faith Ottery — Ottery & Associates, LLC, United States
Kalliopi-Anna Poulia — Agricultural University of Athens, Greece
Lucio Lara Santos — Portuguese Institute of Oncology Francisco Gentil, Portugal

Citation

Ravasco, P., Mäkitie, A., Ottery, F., Poulia, K.-A., Santos, L. L., eds. (2023). *Clinical nutrition and oncologic outcomes, volume II*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-3853-1

Table of contents

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 25 August 2022
DOI 10.3389/fnut.2022.967902

OPEN ACCESS

EDITED BY
Paula Ravasco,
Catholic University of Portugal, Portugal

REVIEWED BY
Yan Mardian,
Indonesia Research Partnership on Infectious Disease (INA-RESPOND), Indonesia
Erin Stella Sullivan,
University College Cork, Ireland

*CORRESPONDENCE
Ming Liu
mingliu35@hrbmu.edu.cn

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 13 June 2022
ACCEPTED 01 August 2022
PUBLISHED 25 August 2022

CITATION
Wang Y, Wang Y, Li G, Zhang H, Yu H, Xiang J, Wang Z, Jiang X, Yan G, Liu Y, Wang C, Xiong H, Wang G, Shi H and Liu M (2022) Associations of intermuscular adipose tissue and total muscle wasting score in PG-SGA with low muscle radiodensity and mass in nonmetastatic colorectal cancer: A two-center cohort study. *Front. Nutr.* 9:967902. doi: 10.3389/fnut.2022.967902

Associations of intermuscular adipose tissue and total muscle wasting score in PG-SGA with low muscle radiodensity and mass in nonmetastatic colorectal cancer: A two-center cohort study

Yang Wang[1], Yuliuming Wang[1], Guodong Li[2], Hao Zhang[1], Hang Yu[1], Jun Xiang[1], Zitong Wang[1], Xia Jiang[1], Guoqing Yan[1], Yunxiao Liu[1], Chunlin Wang[1], Huan Xiong[1], Guiyu Wang[1], Hanping Shi[3] and Ming Liu[1]*

[1]Cancer Center, The Second Affiliated Hospital of Harbin Medical University, Harbin, China, [2]Department of General Surgery, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, China, [3]Departments of Gastrointestinal Surgery and Department of Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University, Beijing, China

Backgrounds: The patient-generated subjective global assessment (PG-SGA) is one of the screening criteria for malnutrition, the skeletal muscle radiodensity (SMD) and skeletal muscle mass index (SMI) are associated with survival in colorectal cancer patients. Body composition parameters can be easily assessed; however, few studies have examined the association between total muscle wasting scores in PG-SGA and body composition parameters and two muscle abnormalities.

Methods: This cohort study included 1,637 stage I-III CRC patients from 2 clinical centers in China, who were enrolled in the training cohort (n = 1,005) and validation cohort (n = 632). Baseline data were collected prospectively from patients including age, BMI, staging, gait speed, hand grip strength (HGS), peak expiratory flow (PEF), neutrophil-lymphocyte ratio (NLR), intermuscular adipose tissue (IMAT), visceral fat area (VFA) and total muscle wasting score in PG-SGA. Relevant risk factors were subjected to logistic regression analysis and Cox regression analysis to identify characteristics associated with muscle abnormalities and survival. Based on the logistic model results, normograms were established to predict muscle abnormalities, and its discrimination and calibration were assessed using the receiver operating characteristic (ROC) curve and calibration curve. The Kaplan-Meier curves were used to assess the survival of colorectal cancer patients with malnutrition or sarcopenia in an inflammatory state (assessed by NLR).

Results: The mean age of all participants was 57.7 ± 10.6 years (56.9% males) and the prevalence of low SMD and low SMI was 32.2 and 39.5%, respectively. Low SMD rate was significantly associated with age, TNM stage, BMI, IMAT,

walking speed, total muscle wasting score and NRS2002 score by logistic regression analysis ($p < 0.05$). Low SMI rate was significantly correlated with age, NLR, BMI, PEF, handgrip strength, calf circumference, walking speed, total muscle wasting score and NRS2002 score ($p < 0.05$). The AUCs of the diagnostic nomograms were 0.859 (95% CI, 0.831–0.886) for low SMD and 0.843 (95% CI, 0.813–0.871) for low SMI in the validation cohort. We also found that patients with colorectal cancer with malnutrition or sarcopenia had a worse prognosis when NLR ≥3.5.

Conclusion: Muscle abnormalities and malnutrition are strongly associated with mortality in patients with non-metastatic colorectal cancer. Early identification and intervention of the associated risk factors may offer new ways to improve patient prognosis.

KEYWORDS

low muscle radiodensity, low muscle mass, total muscle wasting score, PG-SGA, intermuscular adipose tissue, nonmetastatic colorectal cancer

Introduction

Skeletal muscle is the organism's effector organ for various simple and complex movements, accounting for about 40% of body weight, and it also plays an important role in the metabolism of carbohydrate, fat and protein (1, 2). Studies have shown that most tumor patients can experience varying degrees of muscle hypofunction and muscle atrophy at different stages of disease development (3), resulting in tumor-associated sarcopenia, which affects the normal metabolism of body components, resulting in higher rates of clinical complications, longer hospital stays, and lower prognosis for survival (4–6).

Globally, colorectal cancer (CRC) accounts for approximately one tenth of diagnosed and fatal cases of malignancy (7). In China, the National Cancer Center has recently reported that colorectal cancer is the second most common malignancy and the fourth most common mortality, and has shown an increasing trend in incidence and mortality since 2000–2016 (8). Cohort studies have shown that the prevalence of sarcopenia in colorectal cancer ranges from ∼12–71% (9, 10). The two key components of skeletal muscle loss are quality and quantity, expressed by skeletal muscle radiodensity (SMD) and skeletal muscle mass index (SMI), respectively (11). Computed tomography (CT), long used in cancer diagnosis, is emerging as a cutting-edge strategy for quantifying low SMD and low SMI, while extracting highly accurate body composition data. For example, intermuscular adipose tissue (IMAT) can be obtained by CT (12), but to our knowledge, few studies have explored the association between intermuscular infiltration of excess fat and low SMD and low SMI.

According to the expert consensus of the 2018 Annual Meeting, European Society of Parenteral and Enteral Nutrition (ESPEN) released the Global Leadership Initiative on Malnutrition (GLIM), guidelines stating that reduced muscle mass and low BMI are indicative of malnutrition (13). The PG-SGA also acts as a diagnostic tool for malnutrition and cancer cachexia (14), was developed according to ISPOR principles and is available for download (www.pt-global.org). In this work, we use the term total muscle wasting score to refer to the scored subjective rating of muscle mass in worksheet 4 of the PG-SGA (proposed by FD Ottery et al.), and the study demonstrated that it allows clinicians to make a more visual, graded and dynamic determination of patients' muscle status (15, 16). However, the PG-SGA total muscle wasting score is often overlooked in clinical practice and may be one of the most valid ways to determine low SMD and SMI.

Secondary prevention (i.e., prevention of complications after diagnosis) is one of the key strategies to reduce the heavy burden of colorectal cancer. Low SMD and low SMI are an emerging prognostic factor in colorectal and other cancers (9, 17, 18).

Abbreviations: PG-SGA, patient-generated subjective global assessment; CRC, colorectal cancer; CT, computed tomography; ESPEN, European Society of Parenteral and Enteral Nutrition; GLIM, Global Leadership Initiative on Malnutrition; EWGSOP-2, European Working Group on Sarcopenia in Older People 2; NCCN, National Comprehensive Cancer Network; NLR, neutrophil-lymphocyte ratio; CRP, C-reactive Protein; BMI, body mass index; TNM, tumor-node-metastasis; MUAC, mid-upper arm circumference; TSF, triceps skinfold thickness; MAMC, mid-arm muscle circumference; CC, Calf circumference; PEF, Peak expiratory flow; FEV1, Forced Expiratory Volume In 1s; VC, Vital Capacity; IMAT, intermuscular adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; L3, third lumbar vertebra; DCA, decision curve analysis; AUC, area under the curve; ROC, receiver-operating characteristic; HU, Hounsfield unit; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; LSMI, low skeletal muscle mass index; LSMD, low skeletal muscle radiodensity; NRS, nutritional risk screening; QLQ-C30, Quality of Life Questionnare-Core 30.

Little is known about the risk factors for low SMD and low SMI in CRC. Recognizing and modifying these risk factors may help predict and improve the overall prognosis of colorectal cancer patients. The aim of this study was to investigate the associations of IMAT and total muscle wasting scores in PG-SGA with low SMD and low SMI, and we also comprehensively collected patients' demographic characteristics, hematological parameters, anthropometric measurements, lung function, body composition parameters and nutritional status scores to explore other risk factors associated with low SMD, low SMI, and survival.

Subsequently, we constructed corresponding nomograms and assessed the survival of patients with non-metastatic colorectal cancer under different risk factors.

Materials and methods

Study population and setting

For our training dataset, we selected patients aged 18–85 years with stage I-III colorectal cancer who underwent radical surgery at the Fourth Hospital of Harbin Medical University from January 2014 to March 2017 for the prospective study. All pre-op patients undergone a standard nutritional status assessment (anthropometric measurements, hematology and nutritional status score, etc.), pulmonary function and abdominal CT scan. Inclusion criteria also included (1) patients with a histological diagnosis of colorectal adenocarcinoma; (2) patients who were conscious, without communication problems, and who agreed to participate in the study. Exclusion criteria include (1) local recurrence or $\geq$2 primary tumors; (2) no eligible preoperative CT scan available; (3) patients with acute medical conditions or a history of other tumors. For our validation dataset, we selected patients aged 18–85 years with stage I-III colorectal cancer undergoing radical surgery at the Second Hospital of Harbin Medical University from March 2020 to March 2022 with the same admission and exclusion criteria. The primary study outcome was the presence of low SMD and low SMI. The flowchart representing nonmetastatic colorectal cancer patient selection is shown in Figure 1. This study was approved by the ethics committee of the Second Hospital of Harbin Medical University and the Fourth Hospital of Harbin Medical University.

Data collection

Prospectively collect the following data from patients with non-metastatic colorectal cancer: (1) Demographic characteristics and tumor characteristics: sex, age, diabetes, smoking history (patient who had smoked more than 100 cigarette cumulatively in his or her lifetime) (19), alcohol consumption (patients who have previously drunk alcohol more than once per week), herbal teas with a putative biological effect consumption (patients who have previously drunk tea more than once per week), and weight loss (involuntary weight loss within 1 month), cancer stage; (2) Hematological Biomarkers: creatinine, hemoglobin, prealbumin, serum albumin, neutrophil to lymphocyte ratio (NLR), CRP: C-reactive Protein; (3) Anthropometric measures: body mass index (BMI), handgrip strength (HGS), mid-upper arm circumference (MUAC), triceps skinfold thickness (TSF), mid-arm muscle circumference (MAMC), calf circumference (CC), walking speed; (4) Pulmonary Function: peak expiratory flow (PEF), forced expiratory volume in 1s (FEV1) and vital capacity (VC); (5) Body composition: Intermuscular adipose tissue (IMAT), visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT); (6) Nutritional status scores: total muscle wasting score in PG-SGA (20), NRS-2002 score (21) and QLQ-C30 score (22). All of these variables (anthropometry and pulmonary function, etc.) were measured by clinicians who were uniformly trained to ensure reproducibility. Relevant data is recorded and stored in an electronic database within 1 week of admission.

Special parameters are measured as follows: (1) Handgrip strength (kg): the patient stands upright with the feet naturally apart and the non-dominant hand grip strength is measured using an electronic grip strength device (EH101; CAMRY). A total of 3 sets are tested, with a 1 min rest after each set, and values are taken to an accuracy of 0.1 kg; (2) MUAC (cm): the physician measures the distance between the surface of the scapula on the dorsal side of the non-dominant arm and the eminence of the elbow, marks the midpoint, asks the patient to drape the upper limb relaxed to the side of the body, wraps the tape measure around the midpoint of the upper arm and ties it tightly, and takes the value to 0.1 cm; (3) TSF (mm): the skin and subcutaneous tissue are pinched up with the thumb and index finger of the left hand at a point 1 cm above the midpoint of the dorsal aspect of the upper arm (from the crest of the shoulder to the midpoint of the ulnar eminence), with the skin fold parallel to the longitudinal axis of the upper arm; the thickness of the skin fold at the midpoint is determined within 3 seconds by the measuring physician with a skin-fold thickness gauge in the right hand, to an accuracy of 0.1 mm; (4) MAMC (cm) = MUAC (cm) -0.314 * TSF (mm); (5) CC (cm): the patient is seated with the calf at a 90 degree angle to the seat and the left leg is selected for measurement. After exposing the calf, the physician places a tape measure around the thickest part of the calf to measure the circumference and takes the value to 0.1 cm; (6) Walking speed (m/s): the patient walks at the start line at normal speed and the time recorded is from the first foot moving to the first foot over the 6 m finish line. All the above parameters are measured three times, the maximum value is recorded for the step speed and the average value for the other parameters. At the same time, Supplementary Table 1 shows how the total

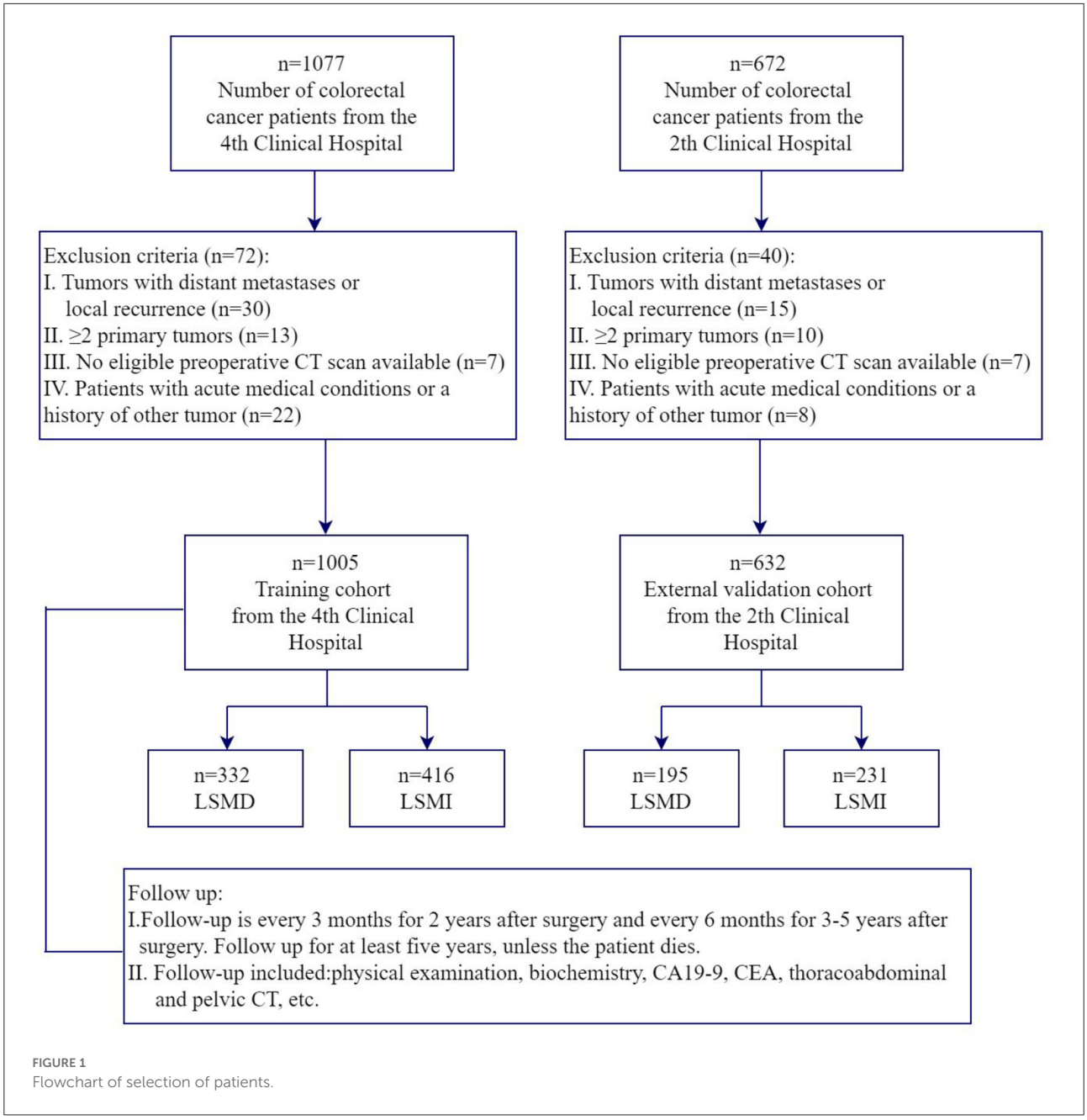


FIGURE 1
Flowchart of selection of patients.

muscle wasting score in PG-SGA is assessed: the score with the highest number of occurrences of the "Muscle Loss Assessment" is counted as the total score for this item. For example, four of the seven muscle scores are 2 and three are 3, giving an overall score of "2." In our study, the total muscle wasting score in PG-SGA included an assessment of muscle consumption in seven areas: temporalis in the temporal region, deltoid in the clavicular region, deltoid in the shoulder region, interosseous in the hand region, latissimus dorsi, rhomboid and deltoid in the scapular region, quadriceps in the thigh region and gastrocnemius in the calf region.

SMD, SMI and other body composition parameters

Body composition was measured by diagnostic non-enhanced CT scanning (Somtom Definition Flash, Siemens AG, Erlangen, Germany) prior to radical surgery. Body composition was measured by clinicians who were uniformly trained. Cross-sectional CT images of the third lumbar vertebra (L3) are closely correlated with whole-body adipose and muscle tissue in both cancer patients and healthy populations (23), and it is the de facto gold standard for measuring body composition

TABLE 1 Baseline characteristics of colorectal patients in the two centers[a].

Characteristics	Training cohort, $n = 1,005$				External validation cohort, $n = 632$			
	Overall	Female ($n = 435$)	Male ($n = 570$)	*P* value	Overall	Female ($n = 270$)	Male ($n = 362$)	*P* value
Demographics								
Age	59.7 ± 10.3	57.7 ± 10.2	61.3 ± 10.1	<0.001	54.4 ± 10.1	53.9 ± 10.2	54.8 ± 10.1	0.226
Diabetes, *n* (%)	177(17.6)	80(18.3)	97(17.0)	0.571	78(12.3)	35(12.9)	43(11.8)	0.682
Alcohol, *n* (%)	165(16.4)	52(11.9)	113(19.8)	0.001	86(13.6)	8(2.9)	78(21.5)	<0.001
Smoking history, *n* (%)	222(22.0)	46(10.5)	176(30.8)	<0.001	121(19.1)	18(6.6)	103(28.4)	<0.001
Tea drinking, *n* (%)	98(9.7)	41(9.4)	57(10.0)	0.761	72(11.3)	30(11.1)	42(11.6)	0.848
Weight loss, *n* (%)				0.106				0.192
Stable	530(52.7)	240(55.2)	290(50.9)		492(77.8)	204(32.3)	288(79.6)	
0–4.9%	354(35.2)	153(35.2)	201(35.3)		124(19.6)	61(9.7)	63(17.4)	
≥5%	121(12.1)	42(9.6)	79(13.9)		16(2.6)	5(0.8)	11(3.0)	
Cancer stage, *n* (%)				<0.001				0.965
I	154(15.3)	68(15.6)	86(15.1)		248(39.2)	106(16.8)	142(39.2)	
II	292(29.1)	158(36.3)	134(23.5)		188(29.7)	79(12.5)	109(17.2)	
III	559(55.6)	209(48.1)	350(61.4)		196(31.1)	85(13.4)	111(30.6)	
Hematological biomarkers								
Creatinine, mg/dl	65.1 ± 17.7	61.1 ± 15.8	68.1 ± 18.5	<0.001	76.2 ± 37.8	71.1 ± 49.4	79.9 ± 25.4	0.004
Hemoglobin, g/L	130.3 ± 19.2	128.9 ± 18.7	131.4 ± 19.5	0.041	130.7 ± 23.4	124.9 ± 20.6	135.1 ± 24.4	<0.001
Prealbumin, mg/L	258.2 ± 55.2	260.2 ± 54.8	256.7 ± 55.4	0.318	264.9 ± 51.5	263.4 ± 48.3	266.0 ± 53.7	0.536
Albumin, g/L	44.6 ± 6.3	45.0 ± 6.2	44.3 ± 6.3	0.157	43.3 ± 5.2	43.5 ± 5.3	43.1 ± 5.1	0.330
NLR	3.1 ± 2.1	3.0 ± 1.9	3.2 ± 2.2	0.234	2.5 ± 1.6	2.3 ± 1.2	2.6 ± 1.8	0.031
CRP				0.885				0.492
≤10	836(83.2)	475(83.3)	361(83.0)		519(82.1)	294(81.2)	225(83.3)	
>10	169(16.8)	95(16.7)	74(17.0)		113(17.9)	68(18.8)	45(16.7)	
Human body measurement								
BMI, kg/m^2	21.8 ± 4.0	21.2 ± 4.0	21.9 ± 4.1	0.708	23.7 ± 3.6	23.5 ± 3.4	23.7 ± 3.7	0.959
Handgrip strength, kg	22.2 ± 7.1	20.5 ± 5.9	24.4 ± 7.8	<0.001	22.2 ± 9.0	20.4 ± 9.0	23.5 ± 8.8	<0.001
MUAC, cm	23.2 ± 3.6	23.0 ± 3.4	23.4 ± 3.8	0.097	25.4 ± 3.6	24.5 ± 3.5	26.1 ± 3.5	<0.001
TSF, mm	20.6 ± 6.9	21.1 ± 6.8	18.9 ± 6.8	0.042	20.9 ± 7.6	22.2 ± 7.4	19.9 ± 7.6	<0.001
MAMC, cm	16.7 ± 3.9	18.7 ± 3.6	17.0 ± 4.1	0.007	18.8 ± 4.2	17.5 ± 4.0	19.8 ± 4.11	<0.001
CC, cm	30.9 ± 4.7	30.2 ± 4.4	32.0 ± 4.8	<0.001	32.5 ± 4.4	31.9 ± 4.4	32.9 ± 4.3	0.013
Walking speed m/s	1.0 ± 0.6	1.2 ± 0.6	1.1 ± 0.6	0.137	1.1 ± 0.7	1.0 ± 0.6	1.1 ± 0.7	0.570
Pulmonary function								
PEF, L/s	4.5 ± 1.3	4.2 ± 1.4	4.7 ± 1.2	<0.001	4.3 ± 1.3	4.2 ± 1.3	4.4 ± 1.3	0.044
FEV1, L	2.0 ± 0.5	1.8 ± 0.4	2.2 ± 0.5	<0.001	1.9 ± 0.4	1.8 ± 0.4	2.0 ± 0.4	<0.001
VC, L	2.7 ± 0.7	2.6 ± 0.7	2.8 ± 0.6	0.232	2.6 ± 0.6	2.4 ± 0.6	2.7 ± 0.5	<0.001
Body composition								
IMAT, cm^2	15.9 ± 6.8	16.1 ± 6.8	15.7 ± 6.7	0.671	14.7 ± 6.4	15.2 ± 6.2	14.2 ± 6.5	0.077
VAT, cm^2	131.9 ± 54.4	108.5 ± 50.2	149.8 ± 50.5	<0.001	135.3 ± 50.9	115.4 ± 46.1	150.0 ± 49.3	<0.001
SAT, cm^2	148.7 ± 48.3	171.0 ± 43.5	131.7 ± 44.9	<0.001	147.3 ± 46.2	165.2 ± 42.9	133.8 ± 43.9	<0.001
SMD, HU	36.0 ± 6.1	35.1 ± 5.8	36.6 ± 6.2	<0.001	36.0 ± 6.3	35.6 ± 6.4	36.3 ± 6.3	0.137
SMI, cm^2/m^2	44.4 ± 11.8	41.8 ± 12.2	46.5 ± 11.1	<0.001	44.3 ± 11.4	40.5 ± 10.9	47.2 ± 11.0	<0.001
LSMD, *n* (%)	332(33.0)	136(31.2)	196(34.3)	0.297	195(30.8)	81(30.0)	114(31.5)	0.688
LSMI, *n* (%)	416(41.3)	175(40.2)	241(42.2)	0.513	231(36.5)	99(36.6)	132(36.4)	0.958

(Continued)

TABLE 1 (Continued)

Characteristics	Training cohort, $n = 1,005$				External validation cohort, $n = 632$			
	Overall	Female ($n = 435$)	Male ($n = 570$)	*P*-value	Overall	Female ($n = 270$)	Male ($n = 362$)	*P*-value
Scores								
Total muscle wasting score, *n* (%)				0.091				0.824
0	337(33.5)	133(30.6)	204(35.8)		345(54.6)	150(55.6)	195(53.8)	
1	207(20.6)	100(23.0)	107(18.8)		98(15.5)	38(14.1)	60(16.5)	
2	251(25.0)	102(23.4)	149(26.1)		100(15.8)	42(15.5)	58(16.0)	
3	210(20.9)	100(23.0)	110(19.3)		89(14.1)	40(14.8)	49(7.7)	
NRS-2002 score, *n* (%)				0.892				0.475
<3	613(61.0)	264(60.7)	349(61.2)		538(85.1)	233(86.3)	305(84.3)	
≥3	392(39.0)	171(39.3)	221(38.8)		94(14.9)	37(13.7)	57(15.7)	
QLQ-C30 score	49.1 ± 14.1	50.4 ± 15.2	48.0 ± 13.1	0.192	50.6 ± 11.3	50.7 ± 11.0	50.5 ± 11.5	0.779

[a]Values are *n* (%) or means ± SDs. NLR, neutrophil to lymphocyte ratio; CRP, C-reactive Protein; BMI, body mass index; MUAC, mid-upper arm circumference; TSF, triceps skin fold; MAMC, mid-arm muscle circumference; CC, Calf circumference; PEF, Peak expiratory flow; FEV1, Forced Expiratory Volume In 1s; VC, Vital Capacity; IMAT, Intramuscular adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; HU, Hounsfield unit; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; LSMI, low skeletal muscle mass index; LSMD, low skeletal muscle radiodensity; NRS, nutritional risk screening; QLQ-C30, Quality of Life Questionnare-Core 30. A chi-square test was used for categorical variables to assess differences between groups and Student's *t*-test or Mann-Whitney U-test was used for continuous variables.

(muscle and adipose compartments) in oncology (24). The muscles at the L3 level, including the rectus abdominis, internal oblique, external oblique, transverse abdominis, psoas major, psoas square and erector spinae muscles. We selected a single image of the third lumbar vertebra (L3) for body composition quantification, including all skeletal muscle mass, visceral adipose tissue (VAT), intermuscular adipose tissue (IMAT) and subcutaneous adipose tissue (SAT). For adipose tissue, standard CT values range from −190 to −30 Hounsfield Units for IMAT and SAT, and from −150 to −50 Hounsfield Units for VAT; for muscle tissue, the standard CT values range from −29 to 150 Hounsfield Units (HU) (23, 25). We used SliceOmatic Software version 5.0 (TomoVision) to measure tissue area, total abdominal muscle area (TAMA) measured at L3 divided by the square of height as SMI (cm^2/m^2), and the mean radiation attenuation value of the muscle group measured at L3 as SMD (HU).

Definitions of malnutrition and sarcopenia

Malnutrition is defined according to the GLIM criteria, which consists of two modules: phenotypic criteria and etiological criteria. There are 2 possible etiological criteria: (1) reduced food intake or digestive and absorptive function; (2) inflammation or disease burden; And 3 possible phenotypic criteria: (1) weight loss; (2) low BMI; and (3) reduced muscle mass. The NRS2002 was used as the initial screening step as part of GLIM and included into the all patients' routine preoperative assessment. Patients at risk of malnutrition (NRS2002 ≥ 3) were diagnosed as malnourished if they met at least one etiological criterion and one phenotypic criterion at the same time. With regard to the etiological criteria of inflammation, recruitment and activation of inflammatory cells can promote tumor progression, and tumor cells in turn can secrete chemokines, pro-inflammatory cytokines and inflammatory enzymes (26). Therefore, all colorectal cancer patients were considered to have met the etiological criteria by virtue of their diagnosis In our study, we defined low BMI (kg/m^2) using Asian criteria, with BMI <20 for patients aged over 70 years and <18.5 for those aged <70 years (13). Also, we used the validated value of LSMI to define muscle mass loss.

The diagnosis of sarcopenia is made up of two components: low muscle mass or low muscle quality and low grip strength according to the EWGSOP-2 Asian consensus (11). A diagnosis of sarcopenia is made when 2 criterias are met simultaneously. The cutpoints for low SMD is 32.5 HU in women and 35.5 HU in men (27). Low SMI cutpoints were ≤36.2 and ≤29.6 cm^2/m^2 for men and women, respectively (28, 29). In addition, low grip strength is defined as <18 kg for women and <26 kg for men (30).

Follow-up assessments

We followed up patients at the Fourth Hospital of Harbin Medical University by telephone or in hospital according to National Comprehensive Cancer Network (NCCN) follow-up principles (31). The follow-up visits included physical examination, biochemistry, CA19-9, CEA, abdominal and pelvic ultrasound, thoracoabdominal and pelvic CT or MRI and

colonoscopy. Follow-up is every 3 months for 2 years after surgery and every 6 months for 3–5 years after surgery. The last follow-up was in March 2022. Overall survival is calculated from the first day after surgery to the time of death due to any cause.

Statistical analysis

Statistical analyses of all data were performed using SPSS statistics version 25.0 (IBM, Armonk, NY), R version 4.1.2 (R Project for Statistical Computing, Vienna, Austria), X-tile plots (Yale University School of Medicine, New Haven, Connecticut, USA) and MedCalc software version 20.106 (MedCalc, Mariakerke, Belgium). Continuous data were expressed as means ± SDs and compared using Student's *t*-test. Categorical variables were expressed as frequencies (%) and compared using Pearson's chi-square test or Fisher's exact test. In the training cohort, logistic regression analysis was used to predict low SMD and low SMI, respectively. Significant preoperative factors from the univariate logistic regression analysis ($p < 0.05$) were included in the multivariate logistic regression analysis. Risk factors that proved to be significant in the training cohort were used to create nomograms and the validity of the associated predictive factors was evaluated in the validation cohort. The utility of the developed model was also assessed by calibration curves, decision curve analysis (DCA) and area under the curve (AUC). The calibration and discrimination of the nomogram were assessed using AUC and calibration curves. Also, the net clinical benefit of the nomogram at different threshold probabilities was quantified using DCA (32). In survival analysis, overall survival (OS) was analyzed using standard Cox regression analysis based on the proportional risk assumption. Univariate and multivariate Cox proportional regression was used to analyze preoperative continuous and categorical data, and Kaplan-Meier curves were used to represent survival in patients with low SMD, low SMI, malnutrition, or sarcopenia.

Results

Patient characteristics

A total of 1,637 patients were enrolled in the two centers, with 1,005 patients included in the training cohort (the 4th Clinical Hospital) and 632 patients in the validation cohort (the 2nd Clinical Hospital). The baseline characteristics of the patients in terms of demographic, hematological indicators, anthropometric measurements, lung function, body composition parameters and nutritional status scores are shown in Table 1. Males had higher Grip strength, calf circumference, SMD and SMI than females. In the training cohort, the prevalence of low SMD and low SMI was 31.2 and 40.2% in females and 34.3 and 42.2% in males, respectively. In the validation cohort, the prevalence of low SMD and low SMI was 30.0 and 36.6% in females and 31.5 and 36.4% in males, respectively.

Predictors associated with low SMD and low SMI

A total of 31 hypothesized risk factors were included in this study. In the training cohort, multivariable logistic regression analysis showed that age, tumor-node-metastasis (TNM) stage, BMI, IMAT, walking speed, total muscle wasting score in PG-SGA and NRS2002 score were significantly associated with low SMD ($P < 0.05$; Table 2); age, NLR, BMI, PEF, handgrip strength, Calf circumference, walking speed, total muscle wasting score in PG-SGA and NRS2002 score were significantly correlated with low SMI ($P < 0.05$; Table 3). We further found that patients with lower age, TNM stage, IMAT, total muscle wasting score in PG-SGA and NRS2002 score had a lower risk of LSMD, while patients with low BMI and low walking speed had a higher risk of LSMD. In addition, patients with lower BMI, PEF, handgrip strength, calf circumference, walking speed had a higher risk of LSMI. Notably, BMI was a strong predictor of low SMD and low SMI, with AUC values of 0.793 and 0.766 in the training cohort, respectively. The best cutpoint for BMI in stratifying LSMI was 18.5 kg/m^2, similar to the phenotypic criteria for low BMI in the GLIM criteria. As the total muscle wasting score in PG-SGA progressively increases from 0 to 3, the risk of low SMD and low SMI also progressively increases. In terms of body composition parameters, patients with an IMAT >18.6 cm^2 have a higher risk of low SMD.

Nomograms construction, validation and clinical performance

Based on the low SMD rate in the training cohort, we constructed a nomogram using seven independent predictors including age, TNM stage, BMI, IMAT, walking speed, total muscle wasting score in PG-SGA and NRS2002 score (Figure 2) after multivariate logistic regression analysis. Similarly, the predictive nomogram containing all the independent risk factors for low SMI in the training cohort is shown in Figure 3. In the validation cohort, we included the above risk factors associated with low SMD and low SMI to demonstrate the validity of the identified risk factors and nomogram. The calibration curve was close to 45 degrees, which indicated that the low SMD and low SMI probabilities predicted by the nomogram in both the training and validation cohorts were in good agreement with the actual probabilities (Figure 4). The DCA curves showed good clinical performance of the two models in diagnosing low SMD and low SMI in both clinical centers (Supplementary Figure 1).

TABLE 2 Univariate and multivariate logistic regression analyses of the risk factors associated with low SMD in the training cohort[a].

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographics				
Sex	0.87(0.67,1.13)	0.297		
Age	1.06(1.04,1.07)	<0.001	1.03(1.02,1.05)	<0.001
Diabetes, *n* (%)	0.87(0.61,1.23)	0.431		
Alcohol, *n* (%)	1.05(0.74,1.49)	0.787		
Smoking history, *n* (%)	1.04(0.76,1.43)	0.788		
Tea drinking, *n* (%)	1.52(1.00,2.33)	0.052		
Weight loss, *n* (%)		<0.001		0.363
Stable	Reference		Reference	
0–4.9%	1.36(1.01,1.82)		1.31(0.87,1.97)	
≥5%	3.29(2.20,4.95)		0.94(0.53,1.69)	
Cancer stage, *n* (%)		<0.001		<0.001
I	Reference		Reference	
II	2.68(1.56,4.62)		2.84(1.41,5.72)	
III	5.08(3.05,8.45)		4.36(2.28,8.33)	
Hematological biomarkers				
Creatinine, mg/dl	1.01(1.00,1.01)	0.099		
Hemoglobin, g/L	1.01(1.00,1.01)	0.082		
Prealbumin, mg/L	1.00(0.99,1.00)	0.541		
Albumin, g/L	0.99(0.97,1.01)	0.516		
NLR	1.27(1.17,1.37)	<0.001	1.07(0.97,1.18)	0.176
CRP	1.05(0.90,1.22)	0.080		
Anthropometric measurements				
BMI, kg/m^2	0.74(0.71,0.78)	<0.001	0.92(0.87,0.97)	0.002
Handgrip strength, kg	0.99(0.97,1.01)	0.223		
MUAC, cm	1.00(0.96,1.04)	0.994		
TSF, mm	1.00(0.98,1.02)	0.800		
MAMC, cm	1.00(0.96,1.03)	0.893		
CC, cm	1.01(0.98,1.04)	0.428		
Walking speed, m/s	0.30(0.24,0.39)	<0.001	0.40(0.29,0.54)	<0.001
Pulmonary function				
PEF, L/s	1.04(0.94,1.15)	0.459		
FEV1, L	0.89(0.67,1.18)	0.432		
VC, L	0.83(0.68,1.02)	0.071		
Body composition				
IMAT, cm^2	1.06(1.04,1.09)	<0.001	1.10(1.07,1.14)	<0.001
VAT, cm^2	1.00(0.99,1.01)	0.676		
SAT, cm^2	0.99(0.99,1.00)	0.268		
VAT/SAT	1.11(0.91,1.35)	0.299		
Scores				
Total muscle wasting score, *n* (%)		<0.001		<0.001
0	Reference		Reference	
1	4.50(2.76,7.35)		3.77(2.10,6.76)	
2	10.76(6.81,17.06)		4.37(2.52,7.58)	
3	14.71(9.16,23.63)		7.18(4.03,12.81)	
NRS-2002 score, *n* (%)		<0.001		<0.001
<3	Reference		Reference	
≥3	10.85(7.97,14.77)		5.43(3.43,8.60)	
QLQ-C30 score	1.02(1.01,1.03)	0.002	1.01(0.99,1.02)	0.313

[a]Data are analyzed by univariate and multivariate logistic regression analysis. Risk factors with significance in univariate analysis were included in the multivariate analysis ($p < 0.05$). NLR, neutrophil-lymphocyte ratio; CRP, C-reactive Protein; BMI, body mass index; MUAC, mid-upper arm circumference; TSF, triceps skinfold thickness; MAMC, mid-arm muscle circumference; CC, Calf circumference; PEF, Peak expiratory flow; FEV1, Forced Expiratory Volume In 1s; VC, Vital Capacity; IMAT, intermuscular adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; HU, Hounsfield unit; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; LSMI, low skeletal muscle mass index; LSMD, low skeletal muscle radiodensity; NRS, nutritional risk screening; QLQ-C30, Quality of Life Questionnare-Core 30.

To compare the predictive performance of the nomogram with other risk factors, we calculated area under the curve (AUC) (Supplementary Table 2) and plotted the ROC curves for the associated risk factors and nomograms (Figure 5). The AUC values for low SMD and low SMI were 0.890 (95% CI, 0.875 to 0.908) and 0.916 (95% CI, 0.897 to 0.933) in the training cohort and 0.859 (95% CI, 0.831 to 0.886) and 0.843 (95% CI, 0.813 to 0.871) in the validation cohort, respectively.

Survival analyses

The Kaplan-Meier analysis showed that the 3- and 5-year overall survival rates were 83.2 and 62.8% in the training cohort. A total of 31 preoperative factors were included in the univariate and the multivariate Cox regression analyses. Multivariate Cox proportional risk analysis showed that TNM stage, low SMD and low SMI were significantly associated with OS ($P < 0.05$; Supplementary Table 3). Low SMD [hazard ratio (HR) 2.11, $p < 0.0001$] indicates that patients with LSMD have a 1.11-fold increased risk of death compared to those without LSMD. Low SMI [hazard ratio (HR) 2.31, $p < 0.0001$] indicates that patients with LSMI have a 1.31-fold increased risk of death compared to those without LSMI. Relevant patients were screened according to the criteria of malnutrition and sarcopenia. We found that the prevalence of malnutrition was 33.8% ($n = 340$) and sarcopenia was 34.0% ($n = 342$).

As observed in the Kaplan-Meier curve, patients with low SMD (Figure 6A), low SMI (Figure 6B), malnutrition (Figure 6C), or sarcopenia (Figure 6D) had worse survival rates

TABLE 3 Univariate and multivariate logistic regression analyses of the risk factors associated with low SMI in the training cohort[a].

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Demographics				
Sex	0.92(0.71,1.18)	0.513		
Age	1.09(1.08,1.11)	<0.001	1.07(1.05,1.10)	<0.001
Diabetes, *n* (%)	0.82(0.58,1.14)	0.222		
Alcohol, *n* (%)	0.93(0.66,1.31)	0.691		
Smoking history, *n* (%)	1.05(0.78,1.42)	0.745		
Tea drinking, *n* (%)	1.23(0.81,1.87)	0.339		
Weight loss, *n* (%)		<0.001		0.369
Stable	Reference		Reference	
0–4.9%	1.35(1.03,1.78)		1.12(0.79,1.82)	
≥5%	2.61(1.74,3.91)		0.76(0.39,1.45)	
Cancer stage, *n* (%)		<0.001		0.125
I	Reference		Reference	
II	0.94(0.62,1.41)		0.66(0.35,1.22)	
III	1.83(1.26,2.66)		1.06(0.60,1.85)	
Hematological biomarkers				
Creatinine, mg/dl	1.00(0.99,1.01)	0.998		
Hemoglobin, g/L	1.00(1.00,1.01)	0.400		
Prealbumin, mg/L	0.99(0.99,1.01)	0.679		
Albumin, g/L	1.02(1.00,1.04)	0.071		
NLR	1.55(1.41,1.70)	<0.001	1.24(1.12,1.37)	<0.001
CRP	0.99(0.99,1.00)	0.550		
Anthropometric measurements				
BMI, kg/m^2	0.78(0.75,0.82)	<0.001	0.92(0.87,0.97)	0.003
Handgrip strength, kg	0.91(0.89,0.93)	<0.001	0.93(0.90,0.96)	<0.001
MUAC, cm	0.99(0.95,1.02)	0.473		
TSF, mm	0.99(0.98,1.01)	0.461		
MAMC, cm	1.00(0.96,1.03)	0.797		
CC, cm	0.89(0.87,0.92)	<0.001	0.91(0.87,0.95)	<0.001
Walking speed m/s	0.34(0.27,0.42)	<0.001	0.43(0.32,0.58)	<0.001
Pulmonary function				
PEF, L/s	0.64(0.57,0.71)	<0.001	0.61(0.53,0.71)	<0.001
FEV1, L	1.15(0.87,1.50)	0.327		
VC, L	0.96(0.79,1.16)	0.679		
Body composition				
IMAT, cm^2	0.99(0.97,1.01)	0.297		
VAT, cm^2	1.00(1.00,1.01)	0.099		
SAT, cm^2	0.99(0.99,1.00)	0.596		
VAT/SAT	1.04(0.86,1.26)	0.707		
Scores				
Total muscle wasting score, *n* (%)		<0.001		<0.001
0	Reference		Reference	
1	3.3(2.17,5.15)		2.38(1.37,4.13)	
2	11.23(7.46,16.91)		4.91(2.88,8.36)	
3	16.70(10.79,25.86)		8.47(4.81,14.91)	
NRS-2002 score, *n* (%)		<0.001		<0.001
<3	Reference		Reference	
≥3	6.38(4.82,8.45)		2.56(1.56,4.22)	
QLQ-C30 score	1.01(1.00,1.02)	0.003	1.01(0.99,1.02)	0.336

[a]Data are analyzed by univariate and multivariate logistic regression analysis. Risk factors with significance in univariate analysis were included in the multivariate analysis ($p < 0.05$). NLR, neutrophil-lymphocyte ratio; CRP, C-reactive Protein; BMI, body mass index; MUAC, mid-upper arm circumference; TSF, triceps skinfold thickness; MAMC, mid-arm muscle circumference; CC, Calf circumference; PEF, Peak expiratory flow; FEV1, Forced Expiratory Volume In 1s; VC, Vital Capacity; IMAT, intermuscular adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; HU, Hounsfield unit; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; LSMI, low skeletal muscle mass index; LSMD, low skeletal muscle radiodensity; NRS, nutritional risk screening; QLQ-C30, Quality of Life Questionnare-Core 30.

compared to normal patients. We used X-tile to determine that the cut-off value of NLR is 3.5. When only NLR was considered, the KM curve and log-rank test results indicated a significant difference in the distribution of overall survival (OS) between nonmetastatic CRC patients with high NLR (≥3.5) and low NLR (<3.5). Neutrophil-lymphocyte ratio (NLR) is a measure of systemic inflammation, and NLR ≥ 3.5 meets the criteria of moderate to high inflammation. Our study found that patients with NLR ≥ 3.5 and malnutrition had a nearly 1-fold increased risk of death compared to patients with NLR < 3.5 and malnutrition (log-rank $P < 0.001$) (Figure 6E). In addition, a similar presentation was found in patients with sarcopenia (log-rank $P < 0.001$) (Figure 6F). The study suggests that moderate-to-severe inflammatory status may influence survival in nonmetastatic CRC patients with malnutrition or sarcopenia.

Discussion

To our knowledge, this is the first study to assess the predictive ability of total muscle wasting score in PG-SGA and intermuscular adipose tissue (IMAT) for CT-derived muscle radiodensity and muscle mass, and the largest study to explore demographic and medical characteristics associated with low SMD and low SMI in colorectal cancer patients based on a Chinese population. We found that as the total muscle wasting risk score in PG-SGA increased from 0 to 3, the risk of low SMD and low SMI also increased, which may be the most direct indicator for clinical assessment of muscle abnormalities. Intermuscular adipose tissue (IMAT), a body composition

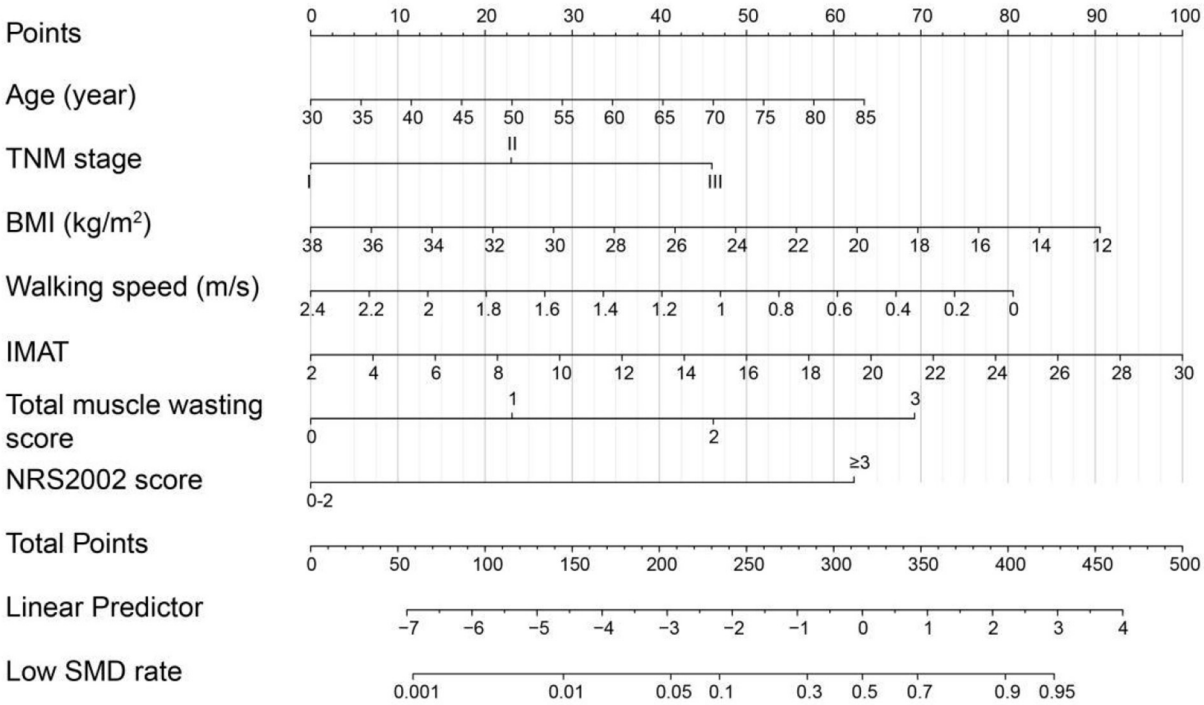


FIGURE 2
The nomogram for predicting low SMD based on the training cohort ($n = 1,005$).

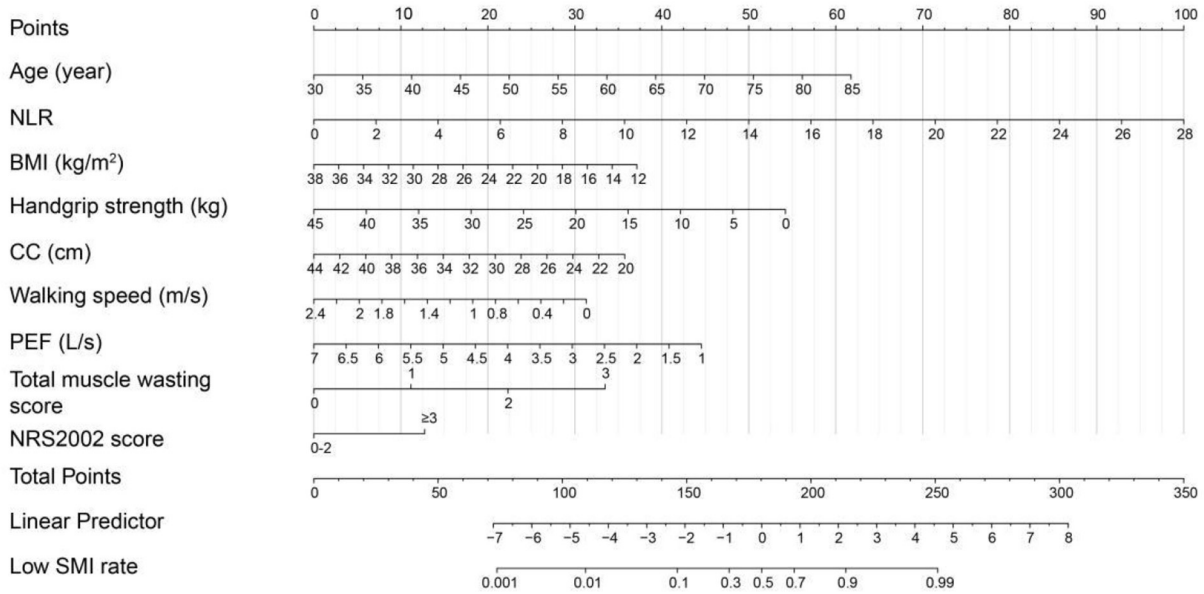


FIGURE 3
The nomogram for predicting low SMI based on the training cohort ($n = 1,005$).

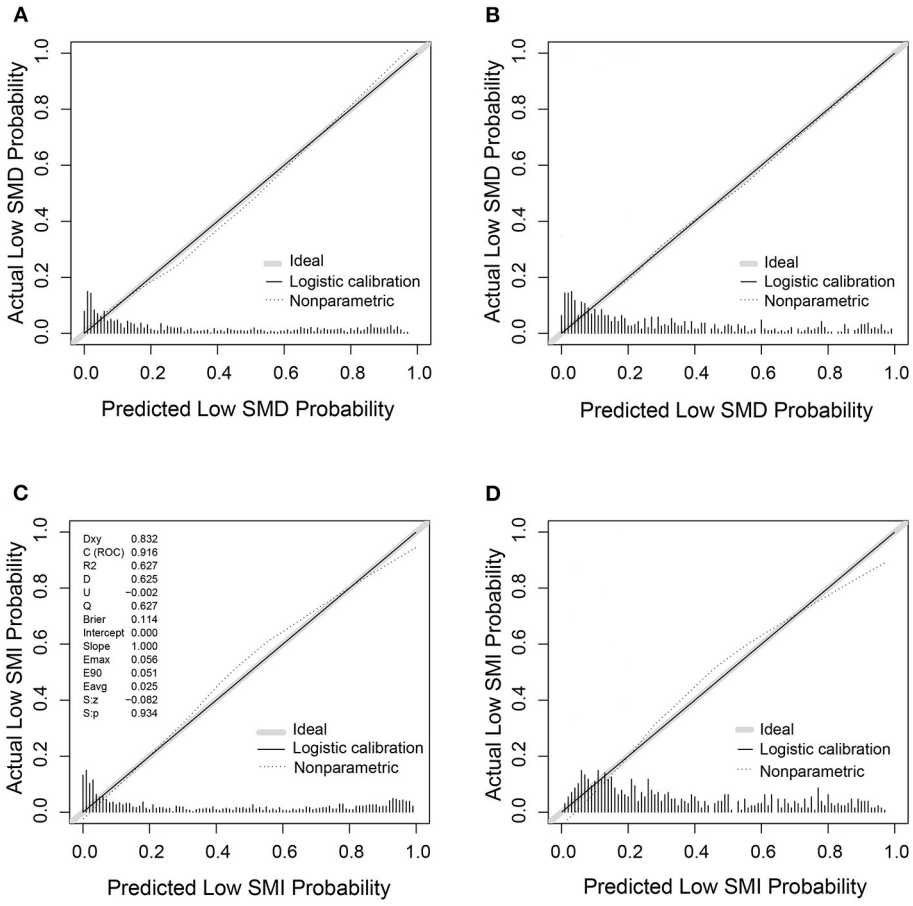


FIGURE 4
The calibration curves of nomogram for predicting low SMD and low SMI based on the training (n = 1,005) and validation (n = 632) cohorts. **(A)** The calibration curve for low SMD predictions in the training cohort. **(B)** The calibration curve for low SMD predictions in the validation cohort. **(C)** The calibration curve for low SMI predictions in the training cohort. **(D)** The calibration curve for low SMI predictions in the validation cohort.

parameter, better predicted low SMD, but did not correlate clearly with low SMI. When IMAT >18.6 cm^2, the patient's low SMD rate increased considerably.

To ensure a more comprehensive determination of risk factors for low SMD and low SMI, we collected a total of 31 preoperative risk factors based on six aspects: demographic characteristics, hematological parameters, anthropometry, lung function, body composition parameters and nutritional status score. Our study showed that age, TNM stage, BMI, IMAT, walking speed, total muscle wasting score in PG-SGA and NRS 2002 score were independent factors for low SMD; age, NLR, BMI, PEF, handgrip strength, calf circumference, walking speed, total muscle wasting score in PG-SGA and NRS 2002 score were independent factors for low SMI. The diagnostic nomogram consisting of these preoperative factors successfully predicted low SMD and low SMI in the training cohort and validation cohort with good discrimination and accuracy. It has the potential to help us to identify patients with muscle abnormalities early and to intervene in the early treatment of these patients.

In survival analyses, we found that patients with low SMD, low SMI, malnutrition or sarcopenia had a poorer prognosis. Furthermore, the co-occurrence of malnutrition or sarcopenia and inflammation were associated with a high risk of death, which is consistent with previous results on exploring the coexistence of NLR and sarcopenia in small cell lung cancer (33). One possible explanation is that high NLR is due to a relatively increased neutrophil count, suggesting that the inflammatory state alters the tumor micro-environment, impairing the patient's immune response to malignancy and thereby promoting tumor progression and metastasis (34); it could also be due to a relatively depleted lymphocyte count, which can act as tumor-promoting leucocytes by producing IL-10 and TGF-β, thereby inducing matrix metalloproteinases and regulatory T-cell pathways in the tumor micro-environment (35). NLR, as a marker of systemic inflammation, is not only

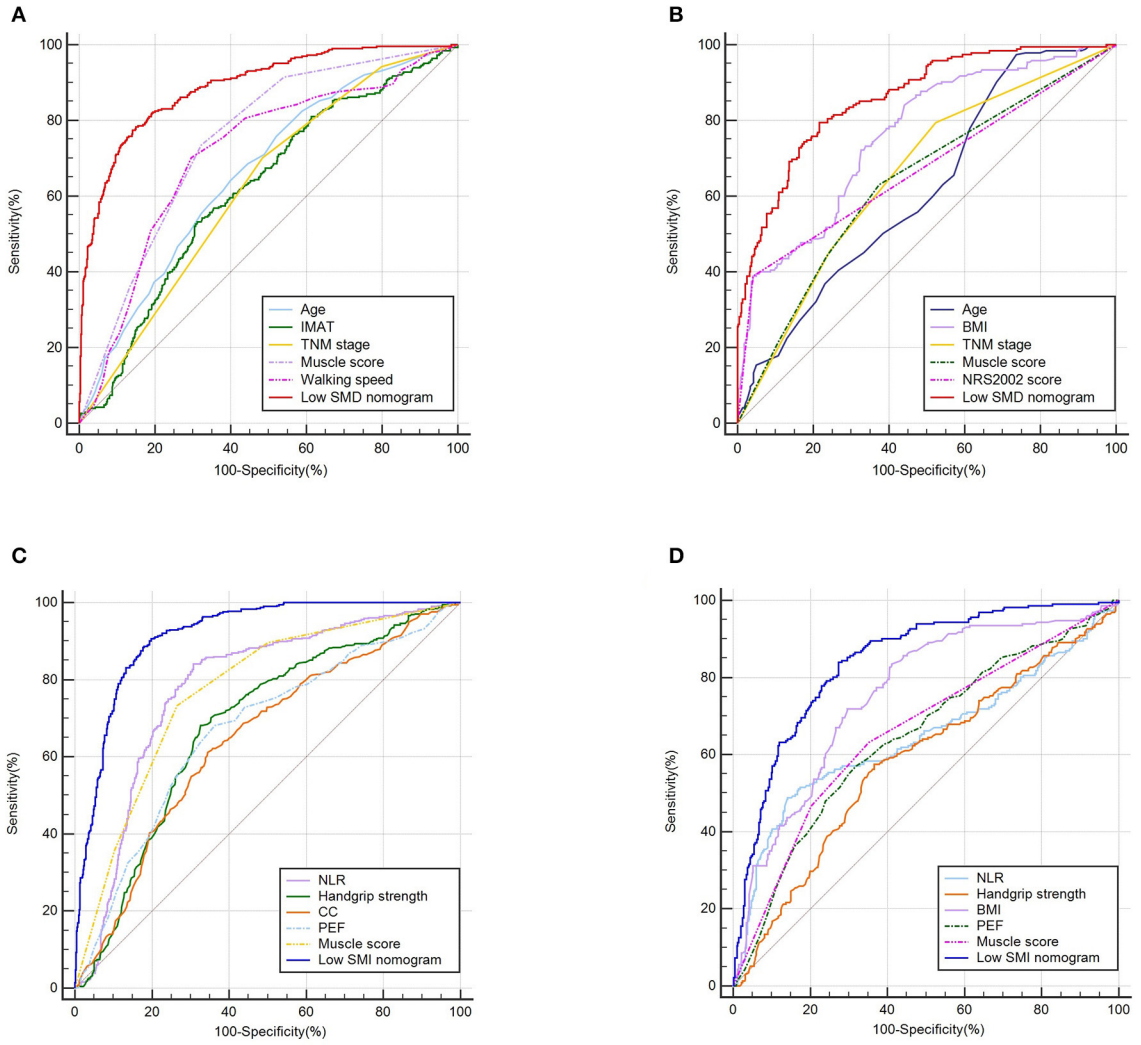


FIGURE 5
The ROC curves of predictive factors and nomograms for predicting low SMD and low SMI based on the training (n = 1,005) and validation (n = 632) cohorts. The ROC curves of predictive factors and nomograms for predicting low SMD based on the training **(A)** and validation **(B)** cohorts. The ROC curves of predictive factors and nomograms for predicting low SMI based on the training **(C)** and validation **(D)** cohorts.

associated with elevated concentrations of various cytokines in the colorectal cancer circulation (36), but also an enhancer of muscle destruction. For example, a state of systemic inflammation can increase tumor necrosis factor production by tumor or surrounding cells, thereby inhibiting skeletal muscle cell differentiation and promoting muscle atrophy (37, 38).

IMAT is one of the reported measures of myosteatosis (39). Myosteatosis can be understood as a pathological accumulation of fat in muscle, associated with reduced mitochondrial lipid oxidation, insulin resistance and reduced muscle activity (23). Our study showed a direct correlation between IMAT and low SMD, which can be interpreted as an indication that excessive intermuscular infiltration of fat leads to reduced skeletal muscle function as well as reduced CT values of skeletal muscle over a cross-sectional area. We hypothesize that SMD is more influenced by metabolic factors and that high circulating free fatty acid concentrations are thought to impair intermuscular fat metabolism and mitochondrial oxidation, thus leading to fat accumulation into muscle (40). Future studies will be necessary to investigate the exact association between decreased SMD and metabolic disturbances in patients with colorectal cancer.

Muscle atrophy and senescence are important signs of body aging. Increasing age is often accompanied by accelerated muscle loss (41) and redistribution of adipose tissue between or within skeletal muscles (42). The association between old age and muscle abnormalities has also been observed in

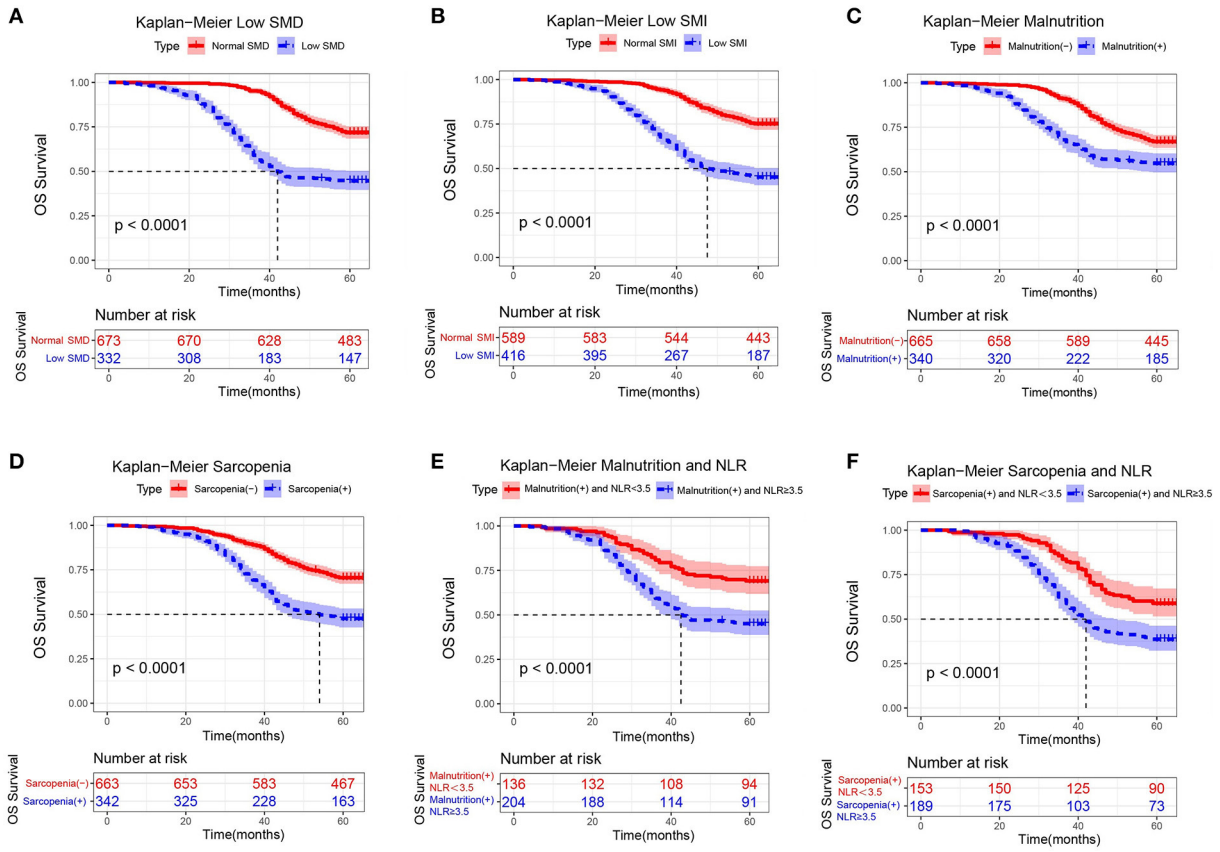


FIGURE 6
Kaplan-Meier curves for overall survival, stratified by **(A)** low SMD, **(B)** low SMI, **(C)** malnutrition, **(D)** sarcopenia, **(E)** malnutrition and NLR, and **(F)** sarcopenia and NLR in the training cohorts (n = 1,005).

nonmalignant diseases (43) and other cancers (44). In our training cohort of patients aged ≥60, 62.6% had low SMI and 44.1% had low SMD. Studies have shown that decreases in age-related hormones (e.g., insulin, growth hormone, insulin-like growth factor, testosterone) are strongly associated with the development of sarcopenia (45). As the rapid increase in the world's aging population and elderly cancer patients, the mechanisms of interaction between aging and intramuscular (distributed within muscle tissue) and intermuscular (localized between muscle groups) fat penetration must be explored, and the prevention and treatment of muscle abnormalities has profound implications for improving the quality of life of older people and reducing the burden of diseases such as sarcopenia on society.

Anthropometric (AM) measures such as BMI, walking speed, grip strength (HGS) and calf circumference (CC), MUAC, mid-upper arm circumference (MUAC), triceps fold thickness (TSF), mid-arm muscle circumference (MAMC) may be inexpensive, non-invasive, reproducible, extensive, rapid and simple alternatives to assess sarcopenia, malnutrition, low SMD or low SMI in cancer patients (46). Our findings regarding the association of grip strength (47), calf circumference (48), BMI (49), and walking speed (50) with low muscle mass are consistent with previous studies. After middle age, HGS declines with age at a rate of approximately 1% per year (51). The European guidelines for sarcopenia (11) suggest that grip strength, a supportive measure of sarcopenia, has a significant impact on clinical prognosis in cancer patients. Interestingly, we found that HGS was associated with low SMI but not low SMD, and it is possible that there is no linear association between muscle radiodensity and muscle strength. TSF, one of the components of malnutrition screening, is often used to assess free fat mass. However, we did not find a direct association between TSF and low SMD or low SMI. The study highlights the importance of considering anthropometric parameters simultaneously to provide additional information when assessing risk or planning intervention strategies for these patients.

Sarcopenia not only affects the extremities, but also causes a loss of strength and mass in a wider range of skeletal muscles, including respiratory muscles (e.g., the diaphragm) (52). The

decline in respiratory strength associated with aging can also be termed "respiratory sarcopenia" (53). In clinical work, patients often routinely undergo preoperative pulmonary function tests as an important tool to determine the risk of anesthesia. However, few have explored the correlation between pulmonary function indicators and muscle radiodensity and muscle mass. Our study included pulmonary function parameters such as PEF and FEV1, and the results showed a clear association between PEF and low SMI in patients with non-metastatic colorectal cancer compared to FEV1. The reason for this may be that FEV1 is largely confounded by airway obstruction. In contrast, PEF, determined by the strength of the respiratory muscles, is obtained during early expiration prior to airway obstruction (54). Thus, PEF is unaffected by airway obstruction.

Overall, the nomogram allows us to assess the probability of patients developing LSMI and LSMD based on the scores of each relevant factor, so that we can carry out nutritional interventions for such risk groups, which is of great importance for clinical work. However, the current study has some limitations worth noting. First, the mean BMI in our study was low and may be more representative of the Chinese population than other populations. Further studies are needed to validate our findings in overweight or class I-III obese populations. Secondly, selection bias may affect the generalisability of the results as this study only included patients with curable colorectal cancer. Therefore, the lack of data on patients with metastatic colorectal cancer may limit the scope of its application. Third, even with relatively large cohorts, more data is needed to determine cut-off values for these predictors so that clinicians could be given definitive guidance in determining low SMD and low SMI. Finally, because it is a cross-sectional study and it could not determine the causality between low SMI/SMD and enrolled factors, which should be deemed as one of the limitations in the present research.

Conclusion

In conclusion, our study is the first to demonstrate the predictive value of total muscle wasting score in PG-SGA and intermuscular adipose tissue (IMAT) for muscle abnormalities. The study also shows that demographic characteristics combined with nutrition-related medical parameters can provide a more comprehensive risk assessment of low SMD and low SMI in patients with non-metastatic colorectal cancer. These two distinct muscle abnormalities suggest different biological mechanisms of fat penetration and muscle failure, which may explain why low SMD and low SMI uniquely affect patient prognosis. Furthermore, we found that patients with malnutrition or sarcopenia in a systemic inflammatory state were at higher risk of death. Future exploration of the mechanisms of muscle abnormalities and inflammatory states may provide new directions for clinical intervention.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

This study was reviewed and approved by the Research Ethics Committee of the Second Affiliated Hospital of Harbin Medical University and the Fourth Affiliated Hospital of Harbin Medical University, China. Patients/participants provided written informed consent to participate in this study.

Author contributions

YaW designed the study, contributed to project conception, performed the statistical analysis, and wrote the paper. YuW and GL contributed to project conception, data analysis, interpretation, editing, and critical review. HZ and HY contributed to study design, interpretation, and editing. JX and ZW conducted the literature search and collected the data. XJ and GY collected the data and contributed to analysis and editing. YL, CW, and HX contributed to interpretation and editing. HS and GW contributed to editing and critical review. ML contributed to project conception, interpreted the results, development of the overall research plan, data analysis, interpretation, editing, and critical review. All authors read and approved the final version submitted.

Funding

This project was supported by the Natural Science Foundation of Heilongjiang Province, China-Joint Guidance Project (Grant No. LH2020H066).

Acknowledgments

The authors would thank all the patients for their commitment and patience during the study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.967902/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Decision curve analysis (DCA) of the nomogram for predicting low SMD and Low SMI based on the training ($n = 1,005$) and validation ($n = 632$) cohorts. **(A)** The DCA for low SMD predictions in the training cohort. **(B)** The DCA for low SMD predictions in the validation cohort. **(C)** The DCA for low SMI predictions in the training cohort. **(D)** The DCA for low SMI predictions in the validation cohort.

SUPPLEMENTARY TABLE 1
Assessment of muscle wasting.

SUPPLEMENTARY TABLE 2
Area under the curve (AUC) for preoperative predictive factors in the training and validation cohort.

SUPPLEMENTARY TABLE 3
Univariate and multivariate cox regression analyses for overall survival (OS) in the training cohort.

References

1. Frontera WR, Ochala J. Skeletal muscle: a brief review of structure and function. *Calcif Tissue Int.* (2015) 96:183–95. doi: 10.1007/s00223-014-9915-y

2. Larsson L, Degens H, Li M, Salviati L, Lee YI, Thompson W, et al. Sarcopenia: aging-related loss of muscle mass and function. *Physiol Rev.* (2019) 99:427–511. doi: 10.1152/physrev.00061.2017

3. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. *Semin Cell Dev Biol.* (2016) 54:2–10. doi: 10.1016/j.semcdb.2015.09.001

4. Barret M, Antoun S, Dalban C, Malka D, Mansourbakht T, Zaanan A, et al. Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. *Nutr Cancer.* (2014) 66:583–9. doi: 10.1080/01635581.2014.894103

5. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res.* (2009) 15:2920–6. doi: 10.1158/1078-0432.CCR-08-2242

6. Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. *Proc Nutr Soc.* (2016) 75:188–98. doi: 10.1017/S0029665115004279

7. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660

8. Zheng R, Zhang S, Zeng H, Wang S, Sun K, Chen R, et al. Cancer incidence and mortality in China, 2016. *J Natl Cancer Inst.* (2022) 5:38. doi: 10.1016/j.jncc.2022.02.002

9. Malietzis G, Currie AC, Athanasiou T, Johns N, Anyamene N, Glynne-Jones R, et al. Influence of body composition profile on outcomes following colorectal cancer surgery. *Br J Surg.* (2016) 103:572–80. doi: 10.1002/bjs.10075

10. Pedziwiatr M, Pisarska M, Major P, Grochowska A, Matlok M, Przeczek K, et al. Laparoscopic colorectal cancer surgery combined with enhanced recovery after surgery protocol (ERAS) reduces the negative impact of sarcopenia on short-term outcomes. *Eur J Surg Oncol.* (2016) 42:779–87. doi: 10.1016/j.ejso.2016.03.037

11. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* (2019) 48:601. doi: 10.1093/ageing/afz046

12. Muresan BT, Sanchez Juan C, Artero A, Hernandez Machancoses A, Almendros-Blanco P, Montoro A, et al. Measurement of body composition in cancer patients using CT planning scan at the third lumbar vertebra. *Nutr Hosp.* (2019) 36:1307–14. doi: 10.20960/nh.2435

13. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr.* (2019) 38:1–9. doi: 10.1016/j.clnu.2018.08.002

14. De Groot LM, Lee G, Ackerie A, van der Meij BS. Malnutrition Screening and Assessment in the Cancer Care Ambulatory Setting: Mortality Predictability and Validity of the Patient-Generated Subjective Global Assessment Short form (PG-SGA SF) and the GLIM Criteria. *Nutrients.* (2020) 12:2287. doi: 10.3390/nu12082287

15. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the Patient-Generated Subjective Global Assessment. *Curr Opin Clin Nutr Metab Care.* (2017) 20:322–9. doi: 10.1097/MCO.0000000000000389

16. Erickson N, Storck LJ, Kolm A, Norman K, Fey T, Schiffler V, et al. Tri-country translation, cultural adaptation, and validity confirmation of the Scored Patient-generated subjective global assessment. *Support Care Cancer.* (2019) 27:3499–507. doi: 10.1007/s00520-019-4637-3

17. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol.* (2013) 31:1539–47. doi: 10.1200/JCO.2012.45.2722

18. Cespedes Feliciano EM, Avrutin E, Caan BJ, Boroian A, Mourtzakis M. Screening for low muscularity in colorectal cancer patients: a valid, clinic-friendly approach that predicts mortality. *J Cachexia Sarcopenia Muscle.* (2018) 9:898–908. doi: 10.1002/jcsm.12317

19. Foxon F, Selya AS. Electronic cigarettes, nicotine use trends and use initiation ages among US adolescents from 1999 to 2018. *Addiction.* (2020) 115:2369–78. doi: 10.1111/add.15099

20. Bauer J, Capra S, Ferguson M. Use of the scored patient-generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr.* (2002) 56:779–85. doi: 10.1038/sj.ejcn.1601412

21. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M, Educational and Clinical Practice Committee, et al. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* (2003) 22:415–21. doi: 10.1016/S0261-5614(03)00098-0

22. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* (1993) 85:365–76. doi: 10.1093/jnci/85.5.365

23. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE, et al. practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab.* (2008) 33:997–1006. doi: 10.1139/H08-075

24. van Vugt JL, Levolger S, Gharbharan A, Koek M, Niessen WJ, Burger JW, et al. A comparative study of software programmes for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients. *J Cachexia Sarcopenia Muscle.* (2017) 8:285–97. doi: 10.1002/jcsm.12158

25. Yip C, Dinkel C, Mahajan A, Siddique M, Cook GJ, Goh V. Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic

obesity may impact on clinical outcome. *Insights Imaging.* (2015) 6:489–97. doi: 10.1007/s13244-015-0414-0

26. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. *Ann Afr Med.* (2019) 18:121–6. doi: 10.4103/aam.aam_56_18

27. Kroenke CH, Prado CM, Meyerhardt JA, Weltzien EK, Xiao J, Cespedes Feliciano EM, et al. Muscle radiodensity and mortality in patients with colorectal cancer. *Cancer.* (2018) 124:3008–15. doi: 10.1002/cncr.31405

28. Fujiwara N, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol.* (2015) 63:131–40. doi: 10.1016/j.jhep.2015.02.031

29. Mardian Y, Yano Y, Ratnasari N, Choridah L, Wasityastuti W, Setyawan NH, et al. "Sarcopenia and intramuscular fat deposition are associated with poor survival in Indonesian patients with hepatocellular carcinoma: a retrospective study". *BMC Gastroenterol.* (2019) 19:229. doi: 10.1186/s12876-019-1152-4

30. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc.* (2014) 15:95–101. doi: 10.1016/j.jamda.2013.11.025

31. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, et al. NCCN Guidelines Insights: Colon Cancer, Version 2.2018. *J Natl Compr Canc Netw.* (2018) 16:359–69. doi: 10.6004/jnccn.2018.0021

32. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol.* (2008) 26:1364–70. doi: 10.1200/JCO.2007.12.9791

33. Go SI, Park MJ, Song HN, Kang MH, Park HJ, Jeon KN, et al. Sarcopenia and inflammation are independent predictors of survival in male patients newly diagnosed with small cell lung cancer. *Support Care Cancer.* (2016) 24:2075–84. doi: 10.1007/s00520-015-2997-x

34. Shu Y, Qin M, Song Y, Tang Q, Huang Y, Shen P, et al. M2 polarization of tumor-associated macrophages is dependent on integrin beta3 via peroxisome proliferator-activated receptor-gamma up-regulation in breast cancer. *Immunology.* (2020) 160:345–56. doi: 10.1111/imm.13196

35. Grenader T, Nash S, Plotkin Y, Furuse J, Mizuno N, Okusaka T, et al. Derived neutrophil lymphocyte ratio may predict benefit from cisplatin in the advanced biliary cancer: the ABC-02 and BT-22 studies. *Ann Oncol.* (2015) 26:1910–6. doi: 10.1093/annonc/mdv253

36. Kantola T, Klintrup K, Vayrynen JP, Vornanen J, Bloigu R, Karhu T, et al. Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. *Br J Cancer.* (2012) 107:1729–36. doi: 10.1038/bjc.2012.456

37. Guttridge DC, Mayo MW, Madrid LV, Wang CY, Baldwin AS Jr. NF-kappaB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia. *Science.* (2000) 289:2363–6. doi: 10.1126/science.289.5488.2363

38. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. *Cell Metab.* (2012) 16:153–66. doi: 10.1016/j.cmet.2012.06.011

39. Goodpaster BH, Bergman BC, Clark RV, Goodpaster BH, Bergman BC, Clark RV, et al. Myosteatosis in the context of skeletal muscle function deficit: an interdisciplinary workshop at the national institute on aging. *Front Physiol.* (2020) 11:963. doi: 10.3389/fphys.2020.00963

40. Miljkovic I, Zmuda JM. Epidemiology of myosteatosis. *Curr Opin Clin Nutr Metab Care.* (2010) 13:260–4. doi: 10.1097/MCO.0b013e328337d826

41. Delmonico MJ, Harris TB, Lee JS, Visser M, Nevitt M, Kritchevsky SB, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. *J Am Geriatr Soc.* (2007) 55:769–74. doi: 10.1111/j.1532-5415.2007.01140.x

42. Stout MB, Justice JN, Nicklas BJ, Kirkland JL. Physiological aging: links among adipose tissue dysfunction, diabetes, and frailty. *Physiology.* (2017) 32:9–19. doi: 10.1152/physiol.00012.2016

43. Stangl MK, Bocker W, Chubanov V, Ferrari U, Fischereder M, Gudermann T, et al. Sarcopenia-endocrinological and neurological aspects. *Exp Clin Endocrinol Diabetes.* (2019) 127:8–22. doi: 10.1055/a-0672-1007

44. Weinberg MS, Shachar SS, Muss HB, Deal AM, Popuri K, Yu H, et al. Beyond sarcopenia: characterization and integration of skeletal muscle quantity and radiodensity in a curable breast cancer population. *Breast J.* (2018) 24:278–84. doi: 10.1111/tbj.12952

45. Janssen I, Baumgartner RN, Ross R, Rosenberg IH, Roubenoff R. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. *Am J Epidemiol.* (2004) 159:413–21. doi: 10.1093/aje/kwh058

46. Cao J, Xu H, Li W, Guo Z, Lin Y, Shi Y, et al. Nutritional assessment and risk factors associated to malnutrition in patients with esophageal cancer. *Curr Probl Cancer.* (2021) 45:100638. doi: 10.1016/j.currproblcancer.2020.100638

47. Moreau J, Ordan MA, Barbe C, Mazza C, Perrier M, Botsen D, et al. Correlation between muscle mass and handgrip strength in digestive cancer patients undergoing chemotherapy. *Cancer Med.* (2019) 8:3677–84. doi: 10.1002/cam4.2238

48. Souza NC, Gonzalez MC, Martucci RB, Rodrigues VD, de Pinho NB, Qureshi AR, et al. Comparative analysis between computed tomography and surrogate methods to detect low muscle mass among colorectal cancer patients. *JPEN J Parenter Enteral Nutr.* (2020) 44:1328–37. doi: 10.1002/jpen.1741

49. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. *J Gerontol A Biol Sci Med Sci.* (2002) 57:M772–7. doi: 10.1093/gerona/57.12.M772

50. Beavers KM, Beavers DP, Houston DK, Harris TB, Hue TF, Koster A, et al. Associations between body composition and gait-speed decline: results from the health, aging, and body composition study. *Am J Clin Nutr.* (2013) 97:552–60. doi: 10.3945/ajcn.112.047860

51. Rantanen T, Masaki K, Foley D, Izmirlian G, White L, Guralnik JM. Grip strength changes over 27 yr in Japanese-American men. *J Appl Physiol.* (1985) 85:2047–53. doi: 10.1152/jappl.1998.85.6.2047

52. Ro HJ, Kim DK, Lee SY, Seo KM, Kang SH, Suh HC. Relationship between respiratory muscle strength and conventional sarcopenic indices in young adults: a preliminary study. *Ann Rehabil Med.* (2015) 39:880–7. doi: 10.5535/arm.2015.39.6.880

53. Kera T, Kawai H, Hirano H, Kojima M, Watanabe Y, Motokawa K, et al. Definition of respiratory sarcopenia with peak expiratory flow rate. *J Am Med Dir Assoc.* (2019) 20:1021–5. doi: 10.1016/j.jamda.2018.12.013

54. Kera T, Kawai H, Hirano H, Kojima M, Fujiwara Y, Ihara K, et al. Relationships among peak expiratory flow rate, body composition, physical function, and sarcopenia in community-dwelling older adults. *Aging Clin Exp Res.* (2018) 30:331–40. doi: 10.1007/s40520-017-0777-9

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 07 September 2022
DOI 10.3389/fnut.2022.974903

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Xiang Zhang,
Shandong University, China
Xiaohui Du,
People's Liberation Army General Hospital, China

*CORRESPONDENCE
Yun Lu
luyun@qdu.edu.cn
Shang-Long Liu
liushanglong@qdu.edu.cn

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 21 June 2022
ACCEPTED 17 August 2022
PUBLISHED 07 September 2022

CITATION
Xiang S, Yang Y-K, Wang T-Y, Yang Z-T, Lu Y and Liu S-L (2022) Development and validation of a nomogram to predict anastomotic leakage in colorectal cancer based on CT body composition. *Front. Nutr.* 9:974903. doi: 10.3389/fnut.2022.974903

Development and validation of a nomogram to predict anastomotic leakage in colorectal cancer based on CT body composition

Shuai Xiang[1], Yong-Kang Yang[1], Tong-Yu Wang[2], Zhi-Tao Yang[2], Yun Lu[1]* and Shang-Long Liu[1]*

[1]Department of Gastroenterology, Affiliated Hospital of Qingdao University, Qingdao, China, [2]Department of Radiology, Affiliated Hospital of Qingdao University, Qingdao, China

Background: Anastomotic leakage (AL) is one of the most serious postoperative complications. This study aimed to investigate the predictive value of preoperative body composition for AL in patients with colorectal cancer (CRC).

Methods: We first reviewed data from 3,681 patients who underwent radical CRC resection 2013–2021 in our hospital, and 60 patients were diagnosed with AL after surgery. We designed a nested case-control study and two controls were randomly selected for each case according to the time and position of surgery. Body composition was measured at the level of the third lumbar vertebra based on computed tomography (CT) images. The risk factors of AL were analyzed by univariate and multivariate analysis. Nomogram was built using binary regression analysis and assessed for clinical usefulness, calibration, and discrimination.

Results: In the multivariate analysis, gender, blood glucose, nutrition risk screening (NRS), skeletal muscle area (SMA) and visceral fat area (VFA) were independent risk factors for developing anastomotic leakage after surgery. The prognostic model had an area under the receiver operating characteristic curve of 0.848 (95% CI, 0.781–0.914). The calibration curve showed good consistency between the predicted and observed outcomes. Decision curve analysis indicated that patients with colorectal cancer can benefit from the prediction model.

Conclusions: The nomogram that combined with gender, blood glucose, NRS, SMA, and VFA had good predictive accuracy and reliability to AL. It may be conveniently for clinicians to predict AL preoperatively and be useful for guiding treatment decisions.

KEYWORDS

body composition, anastomotic leakage, colorectal cancer, prediction, nomogram

Introduction

Colorectal cancer (CRC) is one of the most common cancers of the digestive system. According to statistics, CRC is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths in the world (1). Currently, there are different types of treatment for patients with CRC, such as chemoradiotherapy, targeted therapy and surgery. However, according to SEER estimates for 2019, the 5-year survival rate for CRC in the United States was only 64.6% (2). High quality surgery is still the mainstay of CRC curative treatment.

Although the surgical techniques for CRC have improved significantly during the past decades, postoperative complications still plague surgeons. Among these complications, anastomotic leakage (AL) remains one of the most potentially life-threatening sequelae in CRC surgery due to its devastating impact on patients' mortality, short- and long-term morbidity, quality of life and survival, with the incidence ranging from 1% to 30% (3–6). Moreover, AL leads to the growth of health care costs and an extended hospital stay. It is well known that the etiology of AL is multifactorial. Previous studies have indicated that male sex, preoperative usage of steroids and elevated blood glucose were risk factors of AL (7, 8); however, all these factors lack specificity. Therefore, it is of great scientific and clinical significance to find and study more specific biomolecular markers for AL.

Computed tomography (CT) is a radiographic method commonly used in medical imaging. In terms of its usefulness in body composition measurement, it produces thin cross-sectional high-resolution images that can be processed to differentiate and measure volumes of fat and lean tissue. CT-based multiple body composition parameters have been used in various groups of patients to predict prognosis (9–12). Previous studies have showed that single-slice measurements at L2/L3 were strongly associated with total compartment volumes. Compared with body mass index (BMI), these parameters can fully reflect the detailed information of body composition and quantitatively reflect the density of skeletal muscle and adipose tissue.

Although almost all patients with CRC underwent abdominal CT examination prior to surgery, assessment of CT examination was limited to assessing tumor stage and the presence of distant metastases. The value of CT images reflecting body composition and patient fitness has not been used in clinical practice. Therefore, our purpose was to develop a helpful nomogram calculating each patient's individual probability based on predictive parameters of epidemiological, surgery-related data and laboratory parameters on the development of AL and examined the predictive value of body composition parameters.

Materials and methods

Study participants

A total of 3,681 patients received radical resection of CRC at our center between September 2013 and September 2021. There were 60 patients who were diagnosed with AL. We firstly performed a nested case-control study to identify the risk factors for AL, and two controls were randomly selected for each case according to the time (±1 month) and position (rectum or colon) of surgery. Patients who met the following criteria were included: (1) age ≥18 years; (2) primary colorectal adenocarcinoma confirmed by histopathology; (3) available abdominal CT examination within 2 wk before surgery; (4) no neoadjuvant chemoradiotherapy was performed before surgery. The exclusion criteria were as follows: (1) patients who had definite metastasis before surgery; (2) insufficient clinical information; (3) palliative resections. Finally, 180 patients with pathologically confirmed colorectal adenocarcinoma were included. All surgeries were performed with experienced gastrointestinal surgeons as the principal operator and in strict accordance with the standard surgical procedures. Smoking status was defined as smoking more than 1 cigarette a day for more than a year, regardless of their age at quitting and length of time since they quit. Alcohol status was defined as drinking more than twice a week for more than half of the year.

This retrospective non-intervention study was approved by the Ethics Committee of our hospital, and the requirement for informed consent was waived.

Diagnosis of AL

AL was diagnosed based on clinical and radiologic manifestations: (1) suppurative or intestinal secretions through the drainage tube; or (2) the presence of air or abscess near the anastomotic site detected on CT; or (3) leakage found by X-ray contrast examination.

Imaging analysis

Preoperative CT images of all enrolled patients at the middle level of L3 were extracted from the institutional PACS (Picture Archiving and Communication System). All relevant images were anonymized, transferred to a personal computer, and analyzed using Tomovision's SliceOmatic (v5.0, Magog, Quebec, Canada). The CT HU thresholds were −29 to +150 for skeletal muscle area (13), −150 to −50 for visceral adipose and −190 to −30 for subcutaneous adipose tissue and intermuscular adipose (14, 15). Two experienced radiologists (T.Y.W and Z.T.Y) identified skeletal muscle and adipose tissue area independently. During the identification process, the radiologists were not

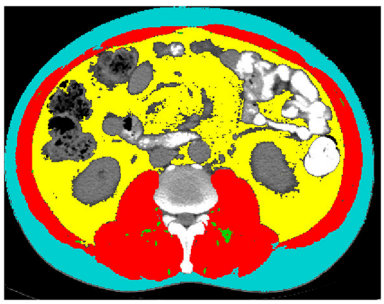


FIGURE 1
Example segmentations of subcutaneous fat area (SFA, turquoise), visceral fat area (VFA, yellow), intermuscular fat area (IMFA, green) and skeletal muscle area (SMA, red) at the third lumbar vertebra.

aware of the occurrence of AL, which minimizes the bias. Intraclass correlation coefficient (ICC) was used to evaluate the interobserver measurement consistency for these parameters. These different body compositions are shown in Figure 1.

Handling of missing data

Some data were missing for variables, including white blood cell (WBC), platelet, albumin (Alb), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). We filled in missing data using the technique of multiple imputation by chained equations, which samples imputed values from the posterior predictive distributions of missing data. We assumed data were missing at random. The imputation model was specified on all predictors, outcomes, and dummy variables for study. Five imputations were carried out as this has a relatively high efficiency (16). We generated 5 datasets for analysis that were identical with respect to non-missing data but could vary on imputed values. In all, we imputed 38 of the 4,860 values (0.78%). All analyses were performed with the R software (version 4.1.2) using the rms and MICE packages.

Statistical analysis

All statistical analyses were done by SPSS 25.0 software and R-software version 4.1.2. Pearson's chi-square test was used to analyze categorical variables. Student *t*-test or Mann-Whitney U test was used to analyze continuous variables according to normal distribution. Shapiro-Wilk test was used to check the normality. Univariate and multivariate analyses logistic regression analysis were used to determine independent risk factors. We carried out an internal verification process with 1,000 bootstrap resamples. The discrimination of the model was calculated using the area under the receiver operating characteristic curve (AUC), and the calibration power was analyzed using the calibration curve. Decision curve analysis (DCA) and clinical impact curves were used to calculate the net benefit. All tests were two-sided, and a value of $p < 0.05$ was considered to have statistical significance.

Results

Characteristics of included patients

A total of 180 patients [109 men and 71 women; age range, 31–89y; mean 62.80±11.419y (SD)] were included in the present study. All patients underwent radical resection of CRC through laparotomy or laparoscopy and 60 patients were diagnosed with AL among them. There were statistically significant differences in gender, WBC, Alb, blood glucose and NRS. The detailed characteristics of these patients are presented in Table 1.

Median and Q1∼Q3 of SMA, VFA, SFA, IMFA at the L3 spinal level, resulting from area-based quantification, were provided in Table 2. Among them, SMA and VFA showed statistical difference between AL and non-AL.

Tests of the application presuppositions of the logistic model

According to the results of the univariate analysis in Tables 1, 2, seven factors with $p < 0.05$ were significantly related to AL, namely gender, WBC, Alb, blood glucose, NRS, SMA and VFA. Before incorporating multivariate regression analysis, we examined these factors for linearity test, multi-collinearity and influential point.

Linearity test

Box-Tidwell transformation was used for this test. A total of 12 factors were included in the analysis in this study, including 5 continuous variables and their respective natural logarithm (ln), and 2 categorical variables. Therefore, $p = 0.0042$ was used as the significance level. Our results showed that all the transformed continuous independent variables in the model (ln_WBC, ln_Alb, ln_Blood glucose, ln_SMA and ln_VFA) have a *p*-value > 0.0042, indicating that each of them had a linear relationship with the outcome variable (Supplementary Table S1).

Multi-collinearity test

The Variance Inflation Indicator (VIF) and tolerance factor are used to show whether a predictor has a strong linear relationship with the other predictor(s). If the tolerance is <0.1 or the VIF is >10, then there is multi-collinearity. In this case, the variance inflation factor (VIF) for all the independent variables was between 1.024 and 1.109, while tolerance was

TABLE 1 Clinical and histopathologic features of the patients.

Patient characteristics	Non-AL	AL	*Z*	*p*
Surgical approach, *n* (%)				0.268
Laparotomy	63 (52.5)	37 (61.7)		
Laparoscopy	57 (47.5)	23 (38.3)		
Surgical site, *n* (%)				1.000
Rectum	86 (71.7)	43 (71.7)		
Colon	34 (28.3)	17 (28.3)		
Age, mean (SD), y	62.94 (11.498)	62.17 (11.560)		0.671
Gender, *n* (%)				0.000*
Male	61 (50.8)	48 (80)		
Female	59 (49.2)	12 (20)		
BMI, M (Q1∼Q3), kg/m2	24 (21.58∼26.17)	25.1 (22.45∼27.73)	−1.789	0.074
T stage, *n* (%)				0.398
T1	4 (3.3)	1 (1.7)		
T2	23 (19.2)	9 (15)		
T3	83 (69.2)	40 (66.7)		
T4	10 (8.3)	10 (16.7)		
N stage, *n* (%)				0.496
N0	74 (61.7)	32 (53.3)		
N1	31 (25.8)	17 (28.3)		
N2	15 (12.5)	11 (18.3)		
Differentiation degree, *n* (%)				0.248
Well	2 (1.7)	3 (5.0)		
Moderately	107 (89.1)	47 (78.3)		
Poor	11 (9.2)	10 (16.7)		
Laboratory indicators	3.33 (2.68∼4.44)	3.92 (2.91∼5.07)	−1.788	0.074
Neutrophil, M (Q1∼Q3), 10^9/L				
Lymphocyte, mean (SD), 10^9/L	1.68 (0.662)	1.65 (0.684)		0.794
NLR, M (Q1∼Q3)	1.94 (1.42∼3.13)	2.36 (1.64∼3.49)	−1.849	0.065
WBC, M (Q1∼Q3), 10^9/L	5.87 (4.7∼7.0)	6.61 (5.13∼7.73)	−2.053	0.040*
Platelet, M (Q1∼Q3), 10^9/L	231 (203∼281)	227.5 (194∼293.75)	−0.005	0.996
APTT, M (Q1∼Q3), sec	31 (28.2∼34)	31.5 (28.95∼34.47)	−0.857	0.391
Alb, M (Q1∼Q3), g/L	40.6 (36.7∼43.3)	38.49 (35.8∼41.44)	−2.28	0.023*
ALT, M (Q1∼Q3), U/L	12.5 (9.1∼17)	14 (10.52∼18.75)	−1.589	0.112
AST, M (Q1∼Q3), U/L	14.1 (11.8∼18.3)	15.65 (12.07∼18.75)	−1.403	0.161
AT-III, M (Q1∼Q3), %	95 (85∼107)	90 (81.25∼101.75)	−1.776	0.076
Blood glucose, M (Q1∼Q3), mmol/L	4.9 (4.58∼5.23)	6.71 (5.17∼7.73)	−2.067	0.000*
Hypertension, *n* (%)				0.910
Yes	21 (17.5)	11 (18.3)		
No	99 (82.5)	49 (81.7)		
CHD, *n* (%)				0.837
Yes	7 (5.8)	4 (6.7)		
No	113 (94.2)	56 (93.3)		
Smoking, *n* (%)				0.320
Yes	38 (31.9)	24 (40)		
No	82 (68.1)	36 (60)		
Drinking, *n* (%)				0.381
Yes	31 (25.8)	20 (33.3)		
No	89 (74.2)	40 (66.7)		
NRS, *n* (%)				0.027*
<3	35 (29.2)	13 (21.7)		
≥3 and <5	78 (65.0)	36 (60.0)		
≥5	7 (5.8)	11 (18.3)		

AL, anastomotic leak; M (Q1∼Q3), median (Q1∼Q3); BMI, body mass index; NLR, neutrophil-lymphocyte ratio; WBC, white blood cell; PT, prothrombin time; APTT, activeated partial thromboplasting time; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB, fibrinogen; AT-III, antithrombin III; CHD, coronary heart disease; NRS, nutrition risk screening.
*$p < 0.05$.

TABLE 2 Preoperative CT body composition of the patients.

	Non-AL	AL	*Z*	*p*
SMA, M (Q1∼Q3), cm^2	128 (111.6∼153.7)	115.5 (99.04∼129.42)	−3.230	0.001*
VFA, M (Q1∼Q3), cm^2	128.5 (84.28∼174.8)	156.15 (117∼202.77)	−2.845	0.004*
SFA, M (Q1∼Q3), cm^2	123.9 (83.83∼175.5)	109.7 (87.41∼139.15)	−1.014	0.310
IMFA, M (Q1∼Q3), cm^2	2.65 (1.49∼4.37)	2.07 (1.07∼3.63)	−1.630	0.103

SMA, skeletal muscle area; VFA, visceral fat area; SFA, subcutaneous fat area; IMFA, intermuscle fat area.
*$p < 0.05$.

between 0.902 and 0.977, so there is no multi-collinearity (Supplementary Table S2).

Influential data points test

Cook's distance is used in regression analysis to identify influential data points that may negatively affect your regression model. Any point with a Cook's distance over 4/n (where n is the total number of data points) is considered to be an outlier. Our results showed that the Cook's distance for each observation is less than the threshold, indicating that there are no influential data points in the dataset (Supplementary Figure S1).

Variables with $p < 0.05$ were further included in the multivariable model. The results showed that gender, blood glucose, NRS, SMA and VFA were independent risk factors for the occurrence of AL (Table 3). Regarding gender, men had a higher risk of developing AL than women (OR 3.746, 95% CI, 1.503–9.335, $p = 0.005$). Further, blood glucose proved to be a significant independent predictor, AL was more likely to occur in patients with higher blood glucose (OR 2.011, 95% CI, 1.444–2.802, $p = 0.000$). Additionally, lower SMA and higher VFA were more likely to develop AL (OR 0.974, 95% CI, 0.958–0.990, $p = 0.001$; OR 1.006, 95% CI, 1.001–1.012, $p = 0.027$). Concerning NRS, the risk of AL was the highest in NRS ≥5 (OR 4.735, 95% CI, 1.068–20.988, $p = 0.041$). On this basis, we established a nomogram (Figure 2). In the AL nomogram, blood glucose accounted for the largest proportion, followed by SMA, VFA, NRS and gender.

TABLE 3 Multivariate analysis of prognostic factors for AL.

	Std. Err	Exp (B)	95% CI,	*p*
Gender	0.466	3.746	(1.503∼9.335)	0.005*
WBC, 10^9/L	0.086	1.140	(0.963∼1.350)	0.128
Alb, g/L	0.038	0.963	(0.894∼1.036)	0.311
Blood glucose, mmol/L	0.169	2.011	(1.444∼2.802)	0.000*
NRS				
<3	/	/	/	0.117
≥3 and <5	0.481	1.378	(0.537∼3.534)	0.505
≥5	0.760	4.735	(1.068∼20.988)	0.041*
SMA, cm^2	0.008	0.974	(0.958∼0.990)	0.001*
VFA, cm^2	0.003	1.006	(1.001∼1.012)	0.027*

WBC, white blood cell; Alb, albumin; NRS, nutrition risk screening; SMA, skeletal muscle area; VFA, visceral fat area.
*$p < 0.05$.

Predictive model performance

The bootstrap procedure was employed for internal validation and tested the performance of predictive model with 1,000 repetitions. Based on the receiver operating characteristic (ROC) analysis, the area under the curve (AUC) of the nomogram was 0.848 (95% CI, 0.781–0.914), indicating that the nomogram can predict AL effectively (Figure 3A). Furthermore, the calibration plot of the nomogram demonstrated that the observed and predicted probabilities of AL correlated well in our model (Figure 3B). The Hosmer-Lemeshow goodness-of-fit test of the nomogram harvested a non-significant statistic in the cohort with P-values as 0.343. Then we performed decision curve analysis (DCA) to evaluate the net benefit for patients in clinical practice. The results suggested that the nomogram has good clinical application value (Figure 3C). The clinical impact curve showed good consistency between the prediction of the nomogram and the actual observed outcomes (Figure 3D).

Correlation analysis of BMI to CT body composition

The results of the correlation analysis of the BMI with CT body composition were shown in Supplementary Figures S2–S5. BMI was significantly positively correlated with VFA ($R = 0.57$, $P < 0.001$), SMA ($R = 0.29$, $P < 0.001$), SAT ($R = 0.54$, $P < 0.001$), but not with IMF ($R = 0.13$, $P = 0.082$).

Discussion

AL is one of the most serious complications after CRC surgery, resulting in severe morbidity, prolonged hospital stays, intensive use of medical resources, and increased risk of death.

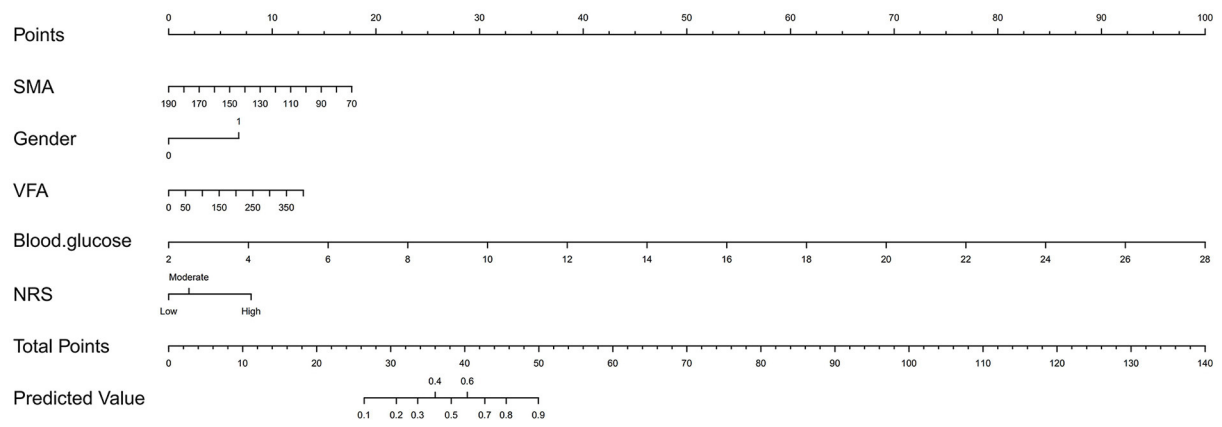


FIGURE 2
Nomogram for predicting postoperative anastomotic leakage in patients with colorectal cancer.

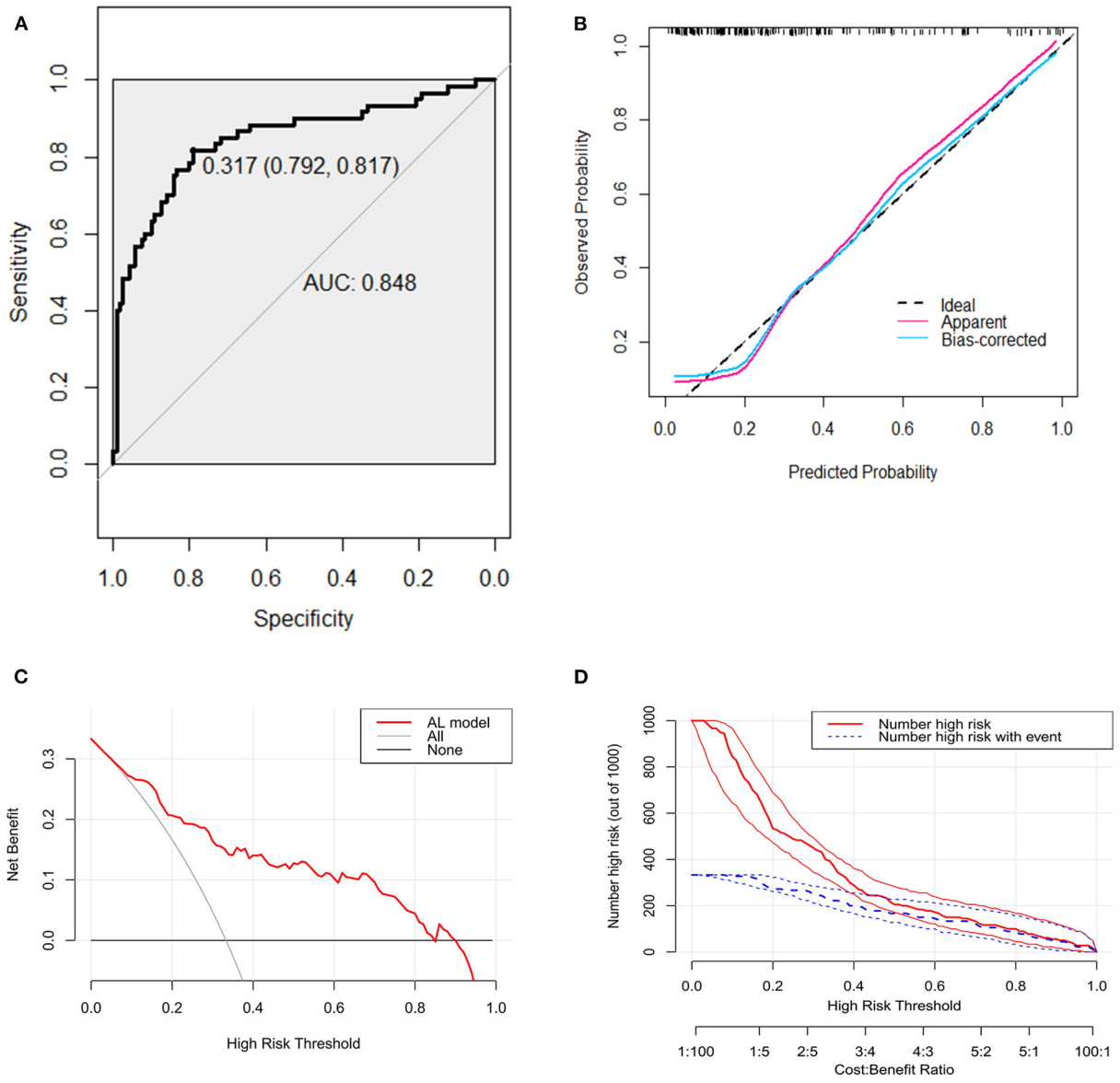


FIGURE 3
Receiver operating characteristic curve, calibration curve, decision curve analysis (DCA), and clinical impact curve for predicting anastomotic leakage (AL) in patients with colorectal cancer (CRC). **(A)** Area under the curve for predicting the AL of patients with CRC. **(B)** Calibration plot of the prediction model (bootstrap method, 1,000 repetitions). **(C)** Decision curve analysis of the model for predicting the risk of AL for patients with CRC. The x-axis means the threshold probability and the y-axis means the net benefit. The black line assumes that no patient has AL. The gray line assumes that all patient has AL. **(D)** Clinical impact curve. The red curve (Number high risk) represents the number of people classified as positive (high risk) by the model at each threshold probability; the blue curve (Number high risk with event) is the number of true positives under each threshold probability.

Previous studies have shown that obesity, gender, history of diabetes, etc. are risk factors for the occurrence of AL (17). However, there are few studies on the clinical value of body composition determined by preoperative CT images in predicting postoperative AL.

In our study, gender, blood glucose, NRS, SMA and VFA were independent factors for AL occurrence in CRC. Blood glucose is the most significant influencing factor, and the risk of AL was significantly higher in patients with higher preoperative blood glucose levels. Similar to our findings, the study by Kotagal et al. showed that diabetic (DM) patients had significantly higher rates of postoperative adverse events than non-diabetic (NDM) patients. Even among NDM patients, hyperglycemic patients had an increased risk of

adverse events compared with normoglycemic patients. A dose-response relationship exists between blood glucose levels and composite adverse events in NDM patients (18). The underlying mechanism may be related to the inflammatory response. Hyperglycemia exacerbates inflammatory, oxidative stress responses and cytokine, potentially creating a vicious circle (19–21). Resolution of hyperglycemia was associated with normalization of the inflammatory response (20). Our study revealed that SMA and VFA are two other important risk factors. Patients with lower SMA or higher VFA are more likely to develop AL. A retrospective study of 2011 patients showed that VFA was an independent risk factor for AL in the elective colon resection group. A study by Wang et al. including 859 patients also reported similar results that preoperative high VFA was an independent risk factor for postoperative complications. Nowadays, adipose tissue is considered an endocrine and paracrine organ whose function affects many physiological processes, including inflammation, fat and glucose metabolism, energy balance. The levels of VEGF and IL-6, along with the proportion of CD8+ T cells and NKT cells, were significantly increased in visceral adipose tissue (22). Inflammatory cells, including macrophages and T cells, are abundant in visceral adipose tissue, and excess visceral adipose tissue induces a chronic systemic inflammatory state with associated insulin resistance and metabolic dysfunction (23). These may be potential causes of postoperative AL. Due to the influence of gastrointestinal tumors, patients may experience gastrointestinal symptoms such as loss of appetite and reduced dietary intake before surgery. In addition, general malaise and mental anxiety also reduce nutritional intake and physical activity, resulting in reduced skeletal muscle mass. Some studies show that nutritional support can increase calorie and protein intake in patients (24, 25). Decreased skeletal muscle wasting favors maintenance of the amount of myokines secreted by skeletal muscle and is expected to improve tolerance to surgery. A study by Shiro Fujihata et al. showed that lower skeletal muscle mass index, especially in the erector spinae muscle, was significantly associated with higher AL (26). Therefore, adequate nutritional support before surgery is necessary to prevent the occurrence of AL. In addition, male is also an independent risk factor for postoperative AL, which is similar to previous studies (27–29). The content of androgens in intestinal microcirculation may be related to anastomotic healing (30). An animal experiment found that in the early stage of wound healing, the collagen metabolism in the colonic anastomosis of male rats was worse than that of female rats (31). The NRS is a nutritional risk screening tool that reflects the patient's current nutritional status. Several studies have reported that NRS nutritional assessment results are associated with outcomes of in-hospital patients (32–34). Patients with nutritional risks who require colorectal cancer surgery should be carefully managed.

The results of correlation analysis between BMI and body composition showed that BMI was significantly positively correlated with VFA, SMA and SAT, but not with IMF. In multivariate analysis, VFA and SMA were independent risk factors for postoperative AL, suggesting that VFA and SMA may be more sensitive predictors of AL than BMI (35, 36).

Nomogram is a graphical representation of a complex mathematical formula (37), and one of its main advantages is the ability to estimate individualized risk based on patient and disease characteristics. The nomogram can incorporate disease-related continuous and categorical variables into the model, with a friendly interface, which is helpful for clinical decision-making and promotes the development of personalized medicine.

Commonly used nutritional status assessment tools, such as BMI and NRS scores, can only observe the overall status, but cannot obtain individual components of the body, such as regional fat distribution and muscle composition. More and more studies have confirmed that nutritional assessment based on body composition can better reflect the patient's metabolic status and physiological reserve, and may be a decisive factor affecting postoperative outcomes (38). Almost all patients with CRC underwent whole abdominal CT before surgery, so CT images of L3 level are very easy to obtain. At the same time, with the help of nomogram, clinicians can predict the occurrence of AL in patients with more basis before surgery. For those patients with high predicted probability and preoperative nutritional risk, active nutritional support should be provided, which will help maintain proper nutritional status and reduce the number and severity of postoperative complications (39). In addition, the predicted probability can also provide a certain reference when clinicians are hesitant to perform preventive ostomy.

There are some limitations to our study. First, this is a single-center retrospective study with a small sample size, the established nomogram lacks external validation, and its performance in an external cohort remains to be studied. Second, although we selected controls as representative as possible, selection bias may still exist. Third, we only assessed preoperative body composition and lacked information on postoperative body composition changes and prognostic data. Further, some indicators were meaningful in univariate analysis but not in multivariate analysis, which may be due to the small sample size. Therefore, larger prospective multicenter studies are necessary in order to approve these preliminary results.

Conclusion

In conclusion, based on the clinical data and imaging information we collected, we developed a nomogram that can predict AL in patients with CRC. The performance of nomogram was verified by various methods, and the results showed that the nomogram had high accuracy and

reliability in predicting AL. Preoperative prediction of AL can help surgeons make appropriate therapeutic decisions in clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

S-LL and YL: conceptualization and supervision. SX, S-LL, T-YW, and Z-TY: data curation, methodology, and software. SX and Y-KY: writing original draft. S-LL: writing—review and editing. All authors contributed to the article and approved the submitted version.

Funding

The study was supported by the National Natural Science Foundation of China (Grant No. 81802888), the Key Technology Research and Development Program of Shandong (No. 2018GSF118088), and the General Financial Grant from the China Postdoctoral Science Foundation (No. 2016M592143).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.974903/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660

2. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin.* (2019) 69:363–85. doi: 10.3322/caac.21565

3. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg.* (2015) 102:462–79. doi: 10.1002/bjs.9697

4. Moghadamyeghaneh Z, Hanna MH, Alizadeh RF, Carmichael JC, Mills S, Pigazzi A, et al. Contemporary management of anastomotic leak after colon surgery: assessing the need for reoperation. *Am J Surg.* (2016) 211:1005–13. doi: 10.1016/j.amjsurg.2015.07.025

5. Phitayakorn R, Delaney CP, Reynolds HL, Champagne BJ, Heriot AG, Neary P, et al. Standardized algorithms for management of anastomotic leaks and related abdominal and pelvic abscesses after colorectal surgery. *World J Surg.* (2008) 32:1147–56. doi: 10.1007/s00268-008-9468-1

6. Thomas MS, Margolin DA. Management of colorectal anastomotic leak. *Clin Colon Rectal Surg.* (2016) 29:138–44. doi: 10.1055/s-0036-1580630

7. Kassis ES, Kosinski AS, Ross P Jr, Koppes KE, Donahue JM, et al. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. *Ann Thorac Surg.* (2013) 96:1919–26. doi: 10.1016/j.athoracsur.2013.07.119

8. Messager M, Warlaumont M, Renaud F, Marin H, Branche J, Piessen G, et al. Recent improvements in the management of esophageal anastomotic leak after surgery for cancer. *Eur J Surg Oncol.* (2017) 43:258–69. doi: 10.1016/j.ejso.2016.06.394

9. Kwon MR, Ko ES, Park MS, Jeong WK, Hwang NY, Kim JH, et al. Impact of skeletal muscle loss and visceral obesity measured using serial CT on the prognosis of operable breast cancers in Asian patients. *Korean J Radiol.* (2022) 23:159–71. doi: 10.3348/kjr.2020.1475

10. Liu Z, Lu S, Wang Y, Lin X, Ran P, Zhou X, et al. Impact of body composition during neoadjuvant chemoradiotherapy on complications, survival and tumor response in patients with locally advanced rectal cancer. *Front Nutr.* (2022) 9:796601. doi: 10.3389/fnut.2022.796601

11. Zhou Z, Xiong Z, Xie Q, Xiao P, Zhang Q, Gu J, et al. Computed tomography-based multiple body composition parameters predict outcomes in Crohn's disease. *Insights Imaging.* (2021) 12:135. doi: 10.1186/s13244-021-01083-6

12. Zouhry Y, Taibi A, Durand-Fontanier S, Darbas T, Forestier G, Monteil J, et al. Degradation of skeletal mass in locally advanced oesophageal cancer between initial diagnosis and recurrence. *BMC Cancer.* (2021) 21:1313. doi: 10.1186/s12885-021-09037-3

13. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol.* (1998) 85:115–22. doi: 10.1152/jappl.1998.85.1.115

14. Kvist H, Sjöström L, Tylén U. Adipose tissue volume determinations in women by computed tomography: technical considerations. *Int J Obes.* (1986) 10:53–67.

15. Vehmas T, Kairemo KJ, Taavitsainen MJ. Measuring visceral adipose tissue content from contrast enhanced computed tomography. *Int J Obes Relat Metab Disord.* (1996) 20:570–3.

16. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res.* (1999) 8:3–15. doi: 10.1191/096228099671525676

17. Parthasarathy M, Greensmith M, Bowers D, Groot-Wassink T. Risk factors for anastomotic leakage after colorectal resection: a retrospective analysis of 17 518 patients. *Colorectal Dis.* (2017) 19:288–98. doi: 10.1111/codi.13476

18. Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET, et al. Perioperative hyperglycemia and risk of adverse events

among patients with and without diabetes. *Ann Surg.* (2015) 261:97–103. doi: 10.1097/SLA.0000000000000688

19. Ling PR, Smith RJ, Bistrian BR. Hyperglycemia enhances the cytokine production and oxidative responses to a low but not high dose of endotoxin in rats. *Crit Care Med.* (2005) 33:1084–9. doi: 10.1097/01.CCM.0000163225.88827.63

20. Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. *Diabetes.* (2004) 53:2079–86. doi: 10.2337/diabetes.53.8.2079

21. Yu WK Li WQ, Li N, Li JS. Influence of acute hyperglycemia in human sepsis on inflammatory cytokine and counterregulatory hormone concentrations. *World J Gastroenterol.* (2003) 9:1824–7. doi: 10.3748/wjg.v9.i8.1824

22. Lysaght J, van der Stok EP, Allott EH, Casey R, Donohoe CL, Howard JM, et al. Pro-inflammatory and tumour proliferative properties of excess visceral adipose tissue *Cancer Lett.* (2011) 312:62–72. doi: 10.1016/j.canlet.2011.07.034

23. Doyle SL, Donohoe CL, Lysaght J, Reynolds JV. Visceral obesity, metabolic syndrome, insulin resistance and cancer. *Proc Nutr Soc.* (2012) 71:181–9. doi: 10.1017/S002966511100320X

24. Gonçalves Dias MC, de Fátima Nunes Marucci M, Nadalin W, Waitzberg DL. Nutritional intervention improves the caloric and proteic ingestion of head and neck cancer patients under radiotherapy. *Nutr Hosp.* (2005) 20:320–5.

25. Read JA, Beale PJ, Volker DH, Smith N, Childs A, Clarke SJ. Nutrition intervention using an eicosapentaenoic acid (EPA)-containing supplement in patients with advanced colorectal cancer. Effects on nutritional and inflammatory status: a phase II trial. *Support Care Cancer.* (2007) 15:301–7. doi: 10.1007/s00520-006-0153-3

26. Huh JY. The role of exercise-induced myokines in regulating metabolism. *Arch Pharm Res.* (2018) 41:14–29. doi: 10.1007/s12272-017-0994-y

27. Park JS, Choi GS, Kim SH, Kim HR, Kim NK, Lee KY, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. *Ann Surg.* (2013) 257:665–71. doi: 10.1097/SLA.0b013e31827b8ed9

28. Trencheva K, Morrissey KP, Wells M, Mancuso CA, Lee SW, Sonoda T, et al. Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients. *Ann Surg.* (2013) 257:108–13. doi: 10.1097/SLA.0b013e318262a6cd

29. Zarnescu EC, Zarnescu NO, Costea R. Updates of risk factors for anastomotic leakage after colorectal surgery. *Diagnostics.* (2021) 11:2382. doi: 10.3390/diagnostics11122382

30. Ba ZF, Yokoyama Y, Toth B, Rue LW 3rd, Bland KI, Chaudry IH. Gender differences in small intestinal endothelial function: inhibitory role of androgens. *Am J Physiol Gastrointest Liver Physiol.* (2004) 286:G452–7. doi: 10.1152/ajpgi.00357.2003

31. Kjaer M, Kristjánsdóttir H, Andersen L, Heegaard AM, Ågren MS, Jorgensen LN. The effect of gender on early colonic anastomotic wound healing. *Int J Colorectal Dis.* (2018) 33:1269–76. doi: 10.1007/s00384-018-3089-4

32. Guo W, Ou G, Li X, Huang J, Liu J, Wei H. Screening of the nutritional risk of patients with gastric carcinoma before operation by NRS 2002 and its relationship with postoperative results. *J Gastroenterol Hepatol.* (2010) 25:800–3. doi: 10.1111/j.1440-1746.2009.06198.x

33. Kwag SJ, Kim JG, Kang WK, Lee JK, Oh ST. The nutritional risk is a independent factor for postoperative morbidity in surgery for colorectal cancer. *Ann Surg Treat Res.* (2014) 86:206–11. doi: 10.4174/astr.2014.86.4.206

34. Sun Z, Kong XJ, Jing X, Deng RJ, Tian ZB. Nutritional risk screening 2002 as a predictor of postoperative outcomes in patients undergoing abdominal surgery: a systematic review and meta-analysis of prospective cohort studies. *PLoS ONE.* (2015) 10:e0132857. doi: 10.1371/journal.pone.0132857

35. Cakir H, Heus C, Verduin WM, Lak A, Doodeman HJ, Bemelman WA, et al. Visceral obesity, body mass index and risk of complications after colon cancer resection: a retrospective cohort study. *Surgery.* (2015) 157:909–15. doi: 10.1016/j.surg.2014.12.012

36. Watanabe J, Tatsumi K, Ota M, Suwa Y, Suzuki S, Watanabe A, et al. The impact of visceral obesity on surgical outcomes of laparoscopic surgery for colon cancer. *Int J Colorectal Dis.* (2014) 29:343–51. doi: 10.1007/s00384-013-1803-9

37. Grimes DA. The nomogram epidemic: resurgence of a medical relic. *Ann Intern Med.* (2008) 149:273–5. doi: 10.7326/0003-4819-149-4-200808190-00010

38. Ahima RS, Lazar MA. Physiology. The health risk of obesity–better metrics imperative. *Science.* (2013) 341:856–8. doi: 10.1126/science.1241244

39. Kabata P, Jastrzebski T, Kakol M, Król K, Bobowicz M, Kosowska A, et al. Preoperative nutritional support in cancer patients with no clinical signs of malnutrition–prospective randomized controlled trial. *Support Care Cancer.* (2015) 23:365–70. doi: 10.1007/s00520-014-2363-4

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 09 September 2022
DOI 10.3389/fnut.2022.972525

OPEN ACCESS

EDITED BY
Nicole Kiss,
Deakin University, Australia

REVIEWED BY
Erin Stella Sullivan,
University College Cork, Ireland
Nathalia Pizato,
University of Brasilia, Brazil

*CORRESPONDENCE
Carolina Trabulo
carolinafptrabulo@gmail.com

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 18 June 2022
ACCEPTED 19 August 2022
PUBLISHED 09 September 2022

CITATION
Trabulo C, Lopes J, da Silva Dias D, Gramaça J, Fernandes I, Gameiro R, Pina I, Mäkitie A, Ottery F and Ravasco P (2022) Assessment of nutritional status of oncology patients at hospital admission: A Portuguese real-world study.
Front. Nutr. 9:972525.
doi: 10.3389/fnut.2022.972525

Assessment of nutritional status of oncology patients at hospital admission: A Portuguese real-world study

Carolina Trabulo[1,2]*, Joana Lopes[1], David da Silva Dias[2,3], João Gramaça[1], Isabel Fernandes[1], Rita Gameiro[1], Idília Pina[1], Antti Mäkitie[2,4,5,6], Faith Ottery[6] and Paula Ravasco[2,7,8]

[1]Centro Hospitalar do Barreiro Montijo, Barreiro, Portugal, [2]Centre for Interdisciplinary Research in Health (CIIS), Universidade Católica Portuguesa, Lisbon, Portugal, [3]Hospital Universitário Algarve, Faro, Portugal, [4]Research Program in Systems Oncology, Faculty of Medicine, University of Helsinki, Helsinki, Finland, [5]Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden, [6]Department of Otorhinolaryngology-Head and Neck Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland, [7]Católica Medical School, Universidade Católica Portuguesa, Lisbon, Portugal, [8]Clinical Research Unit, Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Egas Moniz, Cooperativa de Ensino Superior, CRL, Almada, Portugal

Background: Nutritional status in patients with cancer has a determining role in the evolution of the disease and tolerance to treatments. Severity of undernutrition impacts morbidity and mortality in cancer patients and can limit patient response to the optimal therapies if nutritional issues are not appropriately addressed and managed. Despite the importance of malnutrition for the clinical evolution of oncology patients, there is not yet a universally accepted standard method for evaluating malnutrition in such patients. The aim of this study was to stratify the nutritional status of inpatients at an Oncology Department.

Methods: This is an observational study with 561 cancer patients, assessed at admission to a Medical Oncology Department from November 2016 to February 2020. All patients were considered eligible. Non-compliant and/or comatose patients were excluded. Nutritional status was assessed using the PG-SGA, BMI classified with the WHO criteria, and calculation of the percentage of weight loss in the previous 3–6 months.

Results: A total of 561 patients (303 F: 258 M; mean age 65 ± 13 years) were included. One-third of the patients, n=191/561 (34%), lost 6% of their weight in the month prior to admission and 297/561 (53%) patients lost 10.2% of weight in the previous 6 months. Mean BMI was 24.1 ± 5.8 kg/m^2; $N = 280/561$ (50%) patients had regular BMI according to the WHO criteria. $N = 331/561$ (59%) patients reported eating less in the month prior to admission. $N = 303/561$ (54%) had moderate/severe deficits of muscle and adipose compartments. The PG-SGA identified 499/561 (89%) patients as moderately/severely malnourished, of which 466/561 (83%) patients scored ≥9 points, meeting criteria for a critical need for nutritional support. Fifteen percent of patients scored >4 points, indicating a need for directed therapy for symptom control and only 1% scored <2 points (maintenance nutritional counseling).

Conclusion: In this oncological setting, a higher proportion of patients were nutritionally-at-risk or with moderate/severe malnutrition. The large majority of patients in this study presented with a critical need for nutritional intervention. These findings highlight the need for an integrated assessment of nutritional status at patient referral. This will allow early and timely nutrition care, which is recommended to prevent or reverse further deterioration of the condition and to optimize treatment administration.

KEYWORDS

scored patient-generated subjective global assessment, nutritional assessment, malnutrition, oncology, subjective global assessment (SGA), cancer, patient admission

Introduction

The incidence of malnutrition amongst patients with cancer ranges between 40 and 80% (1). These patients are particularly susceptible to nutritional depletion due to the physical and metabolic effects of cancer, as well as anticancer therapies. Severity of undernutrition is a major source of morbidity and mortality in cancer patients and its presence can limit patient response to even the best therapies if nutritional issues are not appropriately addressed and managed (1–3).

Unintentional weight loss is experienced in the majority of patients with gastroesophageal, pancreatic, head and neck and lung cancer. There is also a high prevalence of weight loss in patients with advanced disease such as advanced colorectal cancer (4–6).

Compromised nutritional status can adversely impact both the quantity and quality of survival and survivorship. Reports have shown that weight loss is an important predictor of decreased survival (7, 8). Chemotherapy patients have a reduced quality of life (9, 10), a higher frequency of hospital readmission, and a longer hospital stay if they are malnourished at baseline or during oncological therapy (11). It is estimated that 4–23% of cancer patients with incurable disease may eventually die because of progressive malnutrition (12). This knowledge highlights the association of malnutrition and body compositional deficit with dose-limiting toxicity (DLT), which prevents the ability to achieve optimal treatment on time and at a full dose.

Malnutrition among patients with cancer is driven by inadequate food intake, decreased physical activity and catabolic derangement in metabolism (13). Nutritional treatment of undernourished patients has been linked with better outcomes (13, 14). Evidence shows that it is paramount to have early and proactive identification of cancer patients at high nutritional risk, to allow for comprehensive nutritional assessment, establish the level of deficit and implement a clinically appropriate intervention (15). This comprehensive approach to nutrition care may lead to improvements in nutritional status, quantity and quality of life, patient satisfaction and treatment outcomes (16).

The use of standardized and validated tools, is recommended globally (17–19) for all patients admitted to hospital, and often times required for hospital accredidatation (20). However, in many countries, this practice is not routinely performed (19). Low awareness of malnutrition and its importance for outcomes and quality of care is a current area of concern in the oncology and nutrition communities (21–23).

An early and integrated nutritional assessment of all patients is mandatory. This may be achieved using the Patient-Generated Subjective Global Assessment (PG-SGA), which is identified in clinical practice and academic research as a reference method for the nutritional assessment of patients with chronic diseases, including cancer (24). It is recognized by the Academy of Nutrition and Dietetics as the reference method in cancer patients, allowing the identification of malnourished patients and the indication of the most appropriate type of nutritional intervention in hospital or outpatient settings. PG-SGA adequately addresses all dimensions of malnutrition as defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN), e.g., weight loss, food intake, symptoms, and physical function (25–28).

Our primary aim was therefore to characterize the nutritional status of patients admitted as in patients at an Oncology Department.

Materials and methods

Study design and setting

A prospective observational cohort study of 561 cancer patients admitted at the Medical Oncology Department of the Centro Hospitalar Barreiro-Montijo (Portugal) between November 2016 and February 2020. All patients

underwent nutritional assessment by an experienced registered nutritionist in the first 48 h of admission, using the PG-SGA assessment tool. Data were obtained after informed medical consent.

The Study design and procedures were conducted in accordance with good clinical practices and were approved by the Institution Ethics, which is abided by Portuguese legislation and the Declaration of Helsinki from the World Medical Association.

Patients

This study includes patients admitted as inpatients at the Medical Oncology department that undergo nutritional assessment by an experienced registered nutritionist, using PG-SGA assessment tool. Patients under 18 years of age, non-compliant and/or comatose, pregnant, and receiving medication that could alter basal metabolic rate were excluded. Forty patients were excluded due to significant missing data. The present study included a total sample size of 561 patients with cancer.

Nutritional assessment

Nutritional status was assessed using the PG-SGA. The PG-SGA® is a subjective nutritional assessment tool validated for use in cancer patients and hospital environments. This tool includes patient-reported information on clinical history, food intake and physical examination incorporating involuntary weight loss, changes in food intake, symptoms that could affect nutritional status and functional capacity changes. A health professional completes the questionnaire regarding the diagnosis and the relationship with nutritional needs, as well as the physical examination. For each component of the scored PG-SGA, points (0–4) are awarded depending on the impact of the symptom on nutritional status. Each item is given a score and the sum results in a nutritional status score are classified as: A—well-nourished, B—moderate malnutrition and C—severe malnutrition.

After this assessment, patients with special nutritional needs are identified and classified according to the attention needed: from 0 to 1 point, there is no need for nutritional intervention; from 2 to 3 points, the patient and his/her family require nutritional education; between 4 and 8 points, the patient requires nutritional intervention; and ≥9 points, the patient requires critical intervention and symptom control (9). The higher the score the greater the risk is for malnutrition.

Nutrition triage recommendations include patient and family education, symptom management and nutrition intervention such as additional food, oral nutrition supplements, enteral or parenteral nutrition.

This study used the translated and validated Portuguese version of the PG-SGA and its use was allowed by the PG-SGA/Pt-Global Platform (www.pt-global.org). All boxes were filled by the researchers, due to the characteristics of the study population.

Body mass index (BMI) was also calculated through the quotient between weight and height squared. Based on criteria outlined by the World Health Organization (WHO), BMI was classified into the following groups: underweight (<18.5 kg m^2), normal (18.5–24.9 kg m^2), overweight (25.0–29.9 kg m^2) and obese (‡30.0 kg m^2).

Statistical analysis

Continuous variables were described using measures of central tendency and dispersion such as mean, and standard deviation. Categorical variables were reported as frequencies. Missing data was addressed using listwise deletion method. All data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 25.

Results

A total of 561 patients (303 women; 258 men) with a mean age of 65 ± 13 years (range, 26–91) were admitted during the four consecutive years and underwent nutritional status evaluation. Diagnosis in this study are depicted in Figure 1. The predominant diagnoses were: colorectal cancer (n = 147/561, 26%), breast cancer (n = 116/561, 18%), and gastroesophageal (n = 72/561, 10%) (Figure 1).

One-third of the patients (191/561, 34%), had lost weight during the month prior to the assessment, with an average weight variation of 6% (range, 0–85). We also found that 297/561 (53%) of the patients had lost weight during the previous 6 months, with an average weight loss of 10.2% (range, 0–40). In a subgroup analysis, analyzing the three most frequent types of cancers, the mean weight change over the last 6 months was more prevalent in gastrointestinal tract tumors (gastro-esophageal with a weight loss observed on average of 4% and colorectal 2%) and, on the other hand, breast cancer kept a constant weight, with a mean weight change over the last 6 months of +0.12%.

Mean BMI was 24.1 ± 5.8 kg/m^2 and 280/561 (50%) of the patients had a normal weight according to the WHO criteria (Figure 2).

Regarding the physical examination of body components, we found that 54% of the patients presented moderate to severe deficits (grades 2 and 3) at their physical examination. More

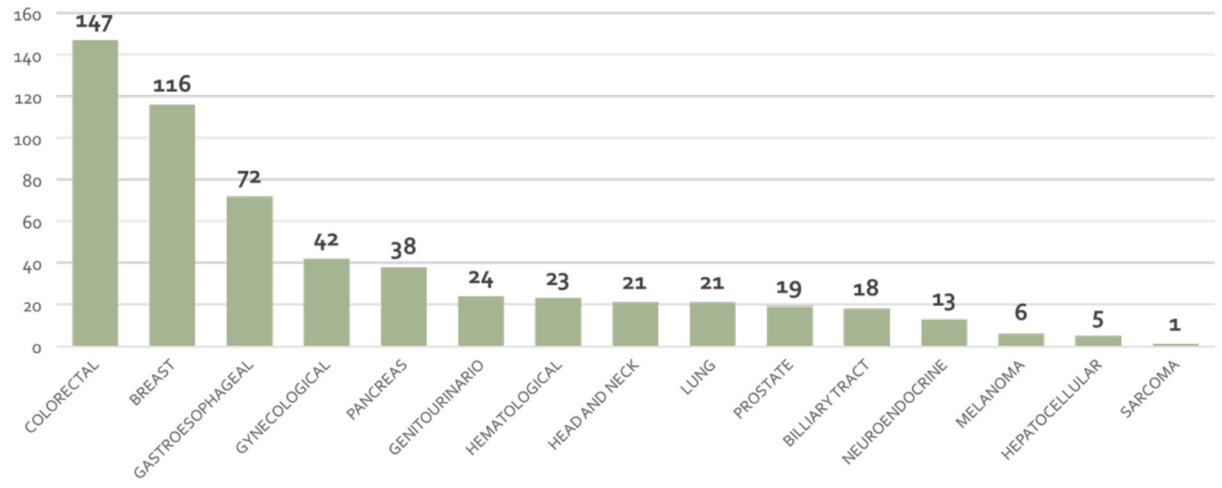


FIGURE 1
Distribution of cancer diagnoses of the series of 561 patients.

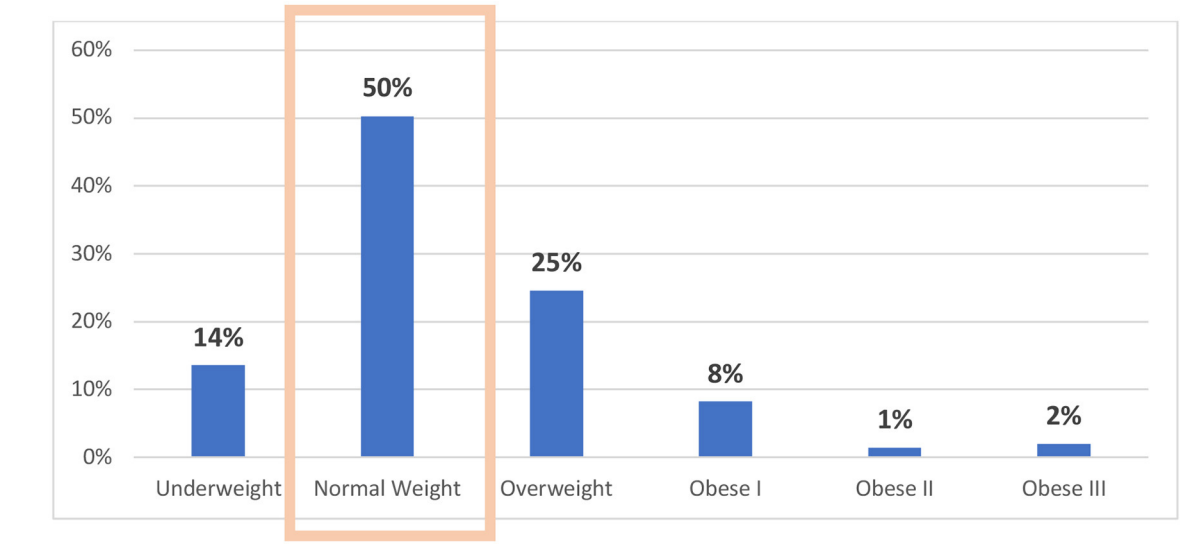


FIGURE 2
Distribution of Body Mass Index categories.

precisely, 9% presented with no deficit; 34% slight deficit; 39% moderate, and 15% presented a severe deficit.

Considering food intake during the last month, 331/561 (59%) of the patients reported eating less food as compared to their usual intake. The classification ranges from 0 to 5 where: "*I would classify my food as,* **0**—normal **1**—*normal food but less quantity* **2**—*few solid foods* **3**—*only solid foods or just nutritional supplements* **4**—*very little amount of any food* and **5**—*only tube or vein feeding*". The frequency of each category of food Intake in the previous month vs. usual intake was **0**—5%, 1–2%, 2–59%, 3–25%, 4–6%, and 5–3%.

The reported alterations in food intake were associated with various patient-reported symptoms during the past two weeks: 98% of patients reported having had at least 1 symptom that prevented them from eating adequately and thus having a nutritional impact.

Thirty seven percent (208/561) of the patients classified their functional activity as impaired ("*I don't feel able to perform most of my activities and stay in bed or sitting less than half the day*").

At hospital admission, 499/561 (89%) of the patients were classified as moderately or severely malnourished, and the remaining were classified as well nourished.

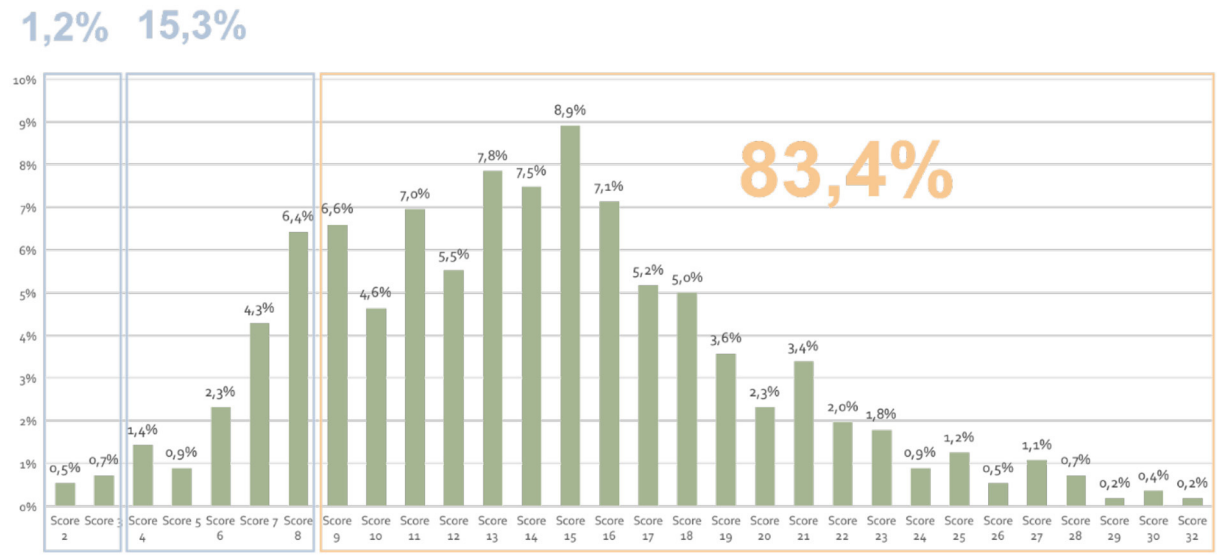


FIGURE 3
The total numerical score of the PG-SGA.

Eighty three percent (466/561) of the patients scored ≥9 points revealing a critical need for nutritional support. We found that 15% of the patients scored >4 points, indicating the need for directed therapy for symptom control, while only 1% had <2 points (nutritional counseling with pharmacological intervention) (Figure 3).

When focusing only on the three most frequent types of cancers, according to the PG-SGA Global Assessment categories (A, B or C), the prevalence of higher stages (B and C) was observed in patients with colorectal cancer—21% of patients had moderate malnutrition and 2% had severe. Breast cancer had the second highest rate—16% with moderate malnutrition and 2% with severe malnutrition; 8% of gastroesophageal cancer patients had moderate malnutrition and 5% had severe.

Among the patients with a score >9, which addresses the patients in terms of the necessity of urgent nutritional intervention, in these three groups was in concordance with the malnutrition prevalence as previously described: 23% had colorectal cancer, 17% breast cancer and 11% gastroesophageal cancer.

Only 10% of the patients in this cohort had signs of metabolic stress and 7% of them had a high-level of metabolic stress. This corresponds to the metabolic demand described in PG-SGA Worksheet 3. The score for metabolic stress is determined by multiple variables known to increase protein and caloric needs. Note: Score fever intensity or duration, whichever is greater. The score is additive so that a patient who has a fever of 38.8°C (3 points) for <72 h (1 point) and who is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Almost 54% of the patients had a clinical condition score >2, such as oncologic disease, cardiac or pulmonary cachexia, renal insufficiency, age >65 years and Acquired Immune Deficiency Syndrome (AIDS).

Discussion

The aim of this study was to characterize the nutritional status of inpatients with cancer at hospital admission, using the scored PG-SGA, in a large series of oncology patients. Typically, patients requiring hospitalization are those with more advanced stages (III/IV), most of them in need of symptomatic control or management of worsening performance status due to greater dependence (29–32).

The scored PG-SGA has shown to be accurate in distinguishing well-nourished patients from malnourished ones. The prevalence of malnutrition in this study was high, with 89% of patients being moderately or severely malnourished. These findings are expected, as patients with cancer have the highest incidence of malnutrition amongst admitted patients (1, 16).

However, at a national level, most centers do not apply nutritional assessment as a routine practice, and the question of malnutrition is oftentimes neglected.

We speculate that there could be barriers to the implementation of the scale, but some data suggest that the patients consider the PG-SGA to be an easy tool to comprehend and the professional component of the PG-SGA received adequate ratings for its content validity, comprehensibility and difficulty (33). Still, the physical exam of the professional

component of the PG-SGA usually is the most difficult to understand and use by professionals (33). Studies have shown that significant improvement in PG-SGA-naïve dietitians' perception of comprehensibility and difficulty of the PG-SGA can be achieved quickly by providing 1 day of training in the use of the PG-SGA (34).

This study's results are consistent with findings from similar translations and cultural adaptations of the PG-SGA for Norwegian, Dutch, German and Japanese languages (33–38).

Based on this study's results, and given the large sample size, the patient component of the PG-SGA is ready to be implemented in clinical practice and results confirm that no additional training is needed for patients and professionals to complete their component.

One of the benefits of the PG-SGA is having a part that scores symptoms which may adversely affect nutritional status. In this study, 98% of the patients reported at least one nutrition impact symptom (NIS) that prevented them from eating adequately. Indeed, the prevalence of NIS in this study, was consistent with other studies in patients with cancer (1, 39, 40): the large majority (83%) presented with a score $\geq$9, indicating the need for urgent nutritional intervention and symptom control. On the other hand, the recommendations for scores <9 include patient and family education, symptom management, and provision of additional food and/or oral nutrition supplements. By offering early nutritional care, we speculate it may be possible to prevent or delay deterioration in the patient's nutritional status. Thus, timely identification of NIS, e.g., decreased appetite, pain, nausea, vomiting, constipation or diarrhea is essential for early symptom management, contributing to improved diet intake.

Of critical importance is the fact that PG-SGA score correlated with percentage weight loss in the previous six months. This result goes in line with other studies where weight loss has been demonstrated to be a major prognostic indicator of poor survival in cancer patients (11). This fact is not unexpected, since weight loss in the last 1 or 6 months is a part of the PG-SGA. Although, exporting this concept to current practice, until 10% of patients with a recent diagnosis of the oncological disease can present this symptom as first sight and up to 30% to 80% during treatment and disease progression, depending on location and etiology (41). This translates to the evident need for an appropriate assessment, even at an early stage.

Contrasting with these results, using WHO criteria (42), only 13% of patients were classified as being underweight, reflecting the limitations of using only BMI to establish the cut-off points for the risk of undernutrition. This further stresses that normal and overweight cancer patients can be at risk for nutritition.

One of the other findings of this study was that the highest prevalence of nutritional risk in our inpatient population was identified in patients with colorectal cancer (25%), followed by breast cancer (21%) and other gastro-intestinal cancers (14%). However, analyzing the percentage variation over the last six months we can conclude that from these three groups the gastrointestinal followed the colorectal cancer are the ones with more prevalence of malnutrition vs. breast cancer.

The high prevalence of malnutrition in breast cancer patients could be a consequence of a bias in this study population. One of the limitations is the statute of a regional hospital and its limited variability of tumor types treated at the Medical Oncology Department. Furthermore, patients with head and neck and lung cancer are managed by a center of reference at another hospital in Lisbon and the Department of Pneumology, respectively, so our numbers do not correspond to the correct prevalence of the disease in our population.

Also, it is noteworthy that patients admitted to the hospital, as previously mentioned, may have more advanced diseases, and thus may not fully represent the spectrum of oncology patients and their nutritional problems. Because the prevalence of undernutrition in cancer patients is associated with the tumor type, location, stage, and treatment, patient differences in these parameters could have affected the proportion of patients at nutritional risk. Although the time elapsed since cancer diagnosis was not considered in the present analysis it could thus bias the ascertained nutritional risk.

These results agree with previous studies that identified these patient groups as of higher risk for nutritional impairment. Evidence shows that patients with upper gastrointestinal, head and neck cancer and advanced colorectal cancer have a worse prognosis when undernourished (4–6).

In future studies, it will be interesting to evaluate the prevalence of nutritional risk in a larger number of oncology inpatients and outpatients, stratified according to the type of tumor, stage, performance status and other comorbidities to determine the incidence of complications, mortality and response to treatments, and to characterize the costs associated with hospital malnutrition in detail.

Notwithstanding its limitations, this study provides valuable information regarding the prevalence and burden of malnutrition in a set of oncology patients representative of routine clinical practice in Portugal.

The notable strength of the present study is that nutritional assessment was performed within 48 h of hospital admission, which allows for early interventions. In this perspective, early screening and referral at hospital admission have the important purpose of reversing/improving clinical nutritional prognosis through individualized intervention (7, 8), with the possibility of reducing the length of hospital stay, the risk for readmission, morbidity, and mortality (11), as well as improving tolerance to treatment and quality of life (9, 10).

In terms of implication to the current practice, services should be designed to guarantee malnutrition risk screening ensues at the first point of contact and at systematic recesses throughout treatment and care to ensure early intervention is provided to those at risk of malnutrition. Health

services should recognize opportunities to insert malnutrition identification and prevention strategies into models of care and support key enablers including the education of all health care professionals.

Conclusion

Malnutrition incidence in cancer inpatients is high. Early screening is of paramount importance to rapidly identify patients in need of critical intervention, in an attempt to provide the best care to cancer patients and delay clinical deterioration. Understanding the magnitude of the problem and in which groups the greatest need exists is a vital step toward the recognition and management of cancer malnutrition.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Comissão de ética para a Saúde Centro Hospitalar Barreiro-Montijo. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CT, JL, PR, and DS contributed to conception and design of the study. CT, JL, RG, and IF organized the database. CT and JG performed the statistical analysis. CT wrote the first draft of the manuscript. FO and AM wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr.* (2017) 36:11–48. doi: 10.1016/j.clnu.2016.07.015

2. Ollenschlager G, Viell B, Thomas W, Konkol K, Burger B. Tumour anorexia: causes, assessment, treatment. *Rec Results Cancer Res.* (1991) 121:249–259. doi: 10.1007/978-3-642-84138-5_28

3. Kern KA, Norton JA. Cancer cachexia. *J Parenter Enteral Nutr.* (1988) 12:286–298. doi: 10.1177/0148607188012003286

4. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative oncology group. *Am J Med.* (1980) 69:491–7. doi: 10.1016/S0149-2918(05)80001-3

5. Argilés JM. Cancer-associated malnutrition. *Eur Oncol Nurs.* (2005) 9:S39–50. doi: 10.1016/j.ejon.2005.09.006

6. Laviano A, Meguid MM. Nutritional issues in cancer management. *Nutrition.* (1996) 12:358–71. doi: 10.1016/S0899-9007(96)80061-X

7. Boseeus I, Daneryd P, Lundholm K. Dietary intake, resting energy expenditure, weight loss and survival in cancer patients. *J Nutr.* (2002) 132:345S—3466S. doi: 10.1093/jn/132.11.3465S

8. Mitry E, Douillard JY, Van Cutsem E, Cunningham D, Magherini E, Mery-Mignard D, et al. Predictive factors of survival in patients with advanced colorectal cancer: an individual data analysis of 602 patients included in irinotecan phase III trials. *Ann Oncol.* (2004) 15:1013–7. doi: 10.1093/annonc/mdh267

9. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignances? *Eur J Cancer.* (1998) 34:2132–3. doi: 10.1016/S0959-8049(97)10090-9

10. Ross PJ, Ashley S, Norton A, Priest K, Waters JS, Eisen T, et al. Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? *Br J Cancer.* (2004) 90:1905–11. doi: 10.1038/sj.bjc.6601781

11. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs was evaluated through a multivariate model analysis. *Clin Nutr.* (2003) 22:235–9. doi: 10.1016/S0261-5614(02)00215-7

12. Sobotka L, Alisson S, Forbes A, Ljungqvist O, Meier RF, Pertkiewicz M, et al. *Basics in Clinical Nutrition*. 4th ed. Czech Republic (2011).

13. Huhmann MB, Cunningham RS. Importance of nutritional screening in treatment of cancer-related weight loss. *Lancet Oncol.* (2005) 6:334–43. doi: 10.1016/S1470-2045(05)70170-4

14. Unsal D, Mentes B, Akmansu M, Uner A, Oguz M, Pak Y. Evaluation of nutritional status in cancer patients receiving radiotherapy: a prospective study. *Am J Clin Oncol.* (2006) 29:183–8. doi: 10.1097/01.coc.0000198745.94757.ee

15. Von Meyenfeldt M. Cancer-associated malnutrition: an introduction. *Eur J Oncol Nurs.* (2005) 9:S35–S38. doi: 10.1016/j.ejon.2005.09.001

16. Ottery FD. Rethinking nutritional support of the cancer patient: the new field of nutritional oncology. *Sem Oncol.* (1994) 21:770–778.

17. ASPEN Board Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* (2002) 26:1SA—138SA. doi: 10.1177/014860710202600101l

18. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* (2003) 22:415–421. doi: 10.1016/S0261-5614(03)00098-0

19. Elia M, Zellipour L, Stratton RJ. To screen or not to screen for adult malnutrition? *Clin Nutr.* (2005) 24:867–84. doi: 10.1016/j.clnu.2005.03.004

20. Health Quality Service. Instituto de Qualidade em Saúde. *Norma 30.5.3 e Norma 30.8*, 1st edn. London: Health Quality Services – King's Fund (1997).

21. Monteagudo C, Dijkstra SC, Visser M. Self-perception of body weight status in older Dutch adults. *J Nutr Health Aging.* (2015) 19:612–8. doi: 10.1007/s12603-015-0486-z

22. Ziylan C, Haveman-Nies A, van Dongen EJ, Kremer S, de Groot LC. Dutch nutrition and care professionals' experiences with undernutrition awareness, monitoring, and treatment among community-dwelling older adults: a qualitative study. *BMC Nutr.* (2015) 1:38. doi: 10.1186/s40795-015-0034-6

23. Craven DL, Pelly FE, Isenring E, Lovell GP. Barriers and enablers to malnutrition screening of community-living older adults: a content analysis of survey data by Australian dietitians. *Aust J Primary Health Care.* (2016) 23:196–201. doi: 10.1071/PY16054

24. Sealy MJ, Nijholt W, Stuiver MM, van der Berg MM, Roodenburg JL, van der Schans CP, et al. Content validity across methods of malnutrition assessment in patients with cancer is limited. *J Clin Epidemiol.* (2016) 76:125–36. doi: 10.1016/j.jclinepi.2016.02.020

25. Ottery FD. Patient-Generated Subjective Global Assessment. In: McCallum PD, Polisena CG, editors. *The Clinical Guide to Oncology Nutrition.* Chicago: The American Dietetic Association (2000). p. 11–23.

26. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Eur J Clin Nutr*. (2017) 36:49–64. doi: 10.1016/j.clnu.2016.09.004

27. White JV, Guenter P, Jensen G, Malone A, Schofield M, Group AM, et al. Consensus statement: academy of nutrition and dietetics and American society for parenteral and enteral nutrition. characteristics recommended for the identification and documentation of adult malnutrition (Undernutrition). *J Parenteral Enteral Nutr*. (2012) 36:730–38. doi: 10.1016/j.jand.2012.03.012

28. Bauer J, Capra S, Ferguson M. Use of the scored patient-generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr.* (2002) 56:779–85. doi: 10.1038/sj.ejcn.1601412

29. Marshall KM, Loeliger J, Nolte L, Kelaart A, Kiss NK. Prevalence of malnutrition and impact on clinical outcomes in cancer services: a comparison of two time points. *Clin Nutr.* (2019) 38:644–51. doi: 10.1016/j.clnu.2018.04.007

30. Correia MI, Campos AC. Prevalence of hospital malnutrition in Latin America: the multicenter ELAN study. *Nutrition.* (2003) 19:823–25. doi: 10.1016/S0899-9007(03)00168-0

31. Planas M, Álvarez-Hernández J, León-Sanz M, Celaya-Pérez S, Araujo K, García de Lorenzo A. Prevalence of hospital malnutrition in cancer patients: a sub-analysis of the PREDyCES® study. *Supportive Care Cancer.* (2016) 24:429–35. doi: 10.1007/s00520-015-2813-7

32. Correia MI, Hegazi RA, Higashiguchi T, Michel JP, Reddy BR, Tappenden KA, et al. Evidence-based recommendations for addressing malnutrition in health care: an updated strategy from the feedM.E. Global Study Group. *J Am Med Dir Assoc*. (2014) 15:544–50. doi: 10.1016/j.jamda.2014.05.011

33. Tobberup R, Jager-Wittenaar H, Sørensen J, Luise HPK, Svarstad P, Sætre P, et al. Translation and cultural adaptation of the scored patient-generated subjective global assessment (PG-SGA©). *Clin Nutr ESPEN.* (2022) 47:215–20. doi: 10.1016/j.clnesp.2021.12.012

34. Sealy MJ, Ottery FD, van der Schans CP, Roodenburg JLN, Jager-Wittenaar H. Evaluation of change in dietitians' perceived comprehensibility and difficulty of the patient-generated subjective global assessment (PG-SGA) after a single training in the use of the instrument. *J Hum Nutr Dietetics.* (2017) 31:58–66. doi: 10.1111/jhn.12491

35. Sealy MJ, Haß U, Ottery FD, van der Schans CP, Roodenburg JL, Jager-Wittenaar H. Translation and cultural adaptation of the scored patient-generated subjective global assessment: an interdisciplinary nutritional instrument appropriate for Dutch cancer patients. *Cancer Nurs.* (2018) 41:450–462. doi: 10.1097/NCC.0000000000000505

36. Erickson N, Storck LJ, Kolm A, Norman K, Fey T, Schiffler V, et al. Tri-country translation, cultural adaptation, and validity confirmation of the scored patient-generated subjective global assessment. *Support Care Cancer*. (2019) 27:3499–507. doi: 10.1007/s00520-019-4637-3

37. Henriksen L, Thoresen B, Fjøseide SS, Lorentzen TR, Balstad F, Ottery D, et al. Linguistic and content validation of the translated and culturally adapted PG-SGA, as perceived by Norwegian cancer patients and healthcare professionals. *Clin Nutr ESPEN.* (2020) 38:178–84. doi: 10.1016/j.clnesp.2020.05.006

38. Miura T, Elgersma R, Okizaki A, Inoue MK, Amano K, Mori M, et al. A Japanese translation, cultural adaptation, and linguistic and content validity confirmation of the scored patient-generated subjective global assessment. *Support Care Cancer*. (2021) 29:7329–38. doi: 10.1007/s00520-021-06310-w

39. Grosvenor M, Bulcavage L, Chlebowski RT. Symptoms potentially influencing weight loss in cancer population. *Cancer.* (1989) 63:330–334. doi: 10.1002/1097-0142(19890115)63:2<330::aid-cncr2820630221>3.0.co;2-u

40. Langer CJ, Hoffman JP, Ottery FD. Clinical significance of weight loss in cancer patients: rationale for the use of anabolic agents in the treatment of cancer-related cachexia. *Nutrition.* (2001) 17:1. doi: 10.1016/S0899-9007(01)80001-0

41. Hébuterne X, Lemarié E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *JPEN J.* (2014) 38:196–204. doi: 10.1177/0148607113502674

42. WHO. Physical status: The use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser.* (1995) 854:1–452.

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 21 September 2022
DOI 10.3389/fnut.2022.964591

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Shuji Isaji,
Mie University Hospital, Japan
Marwa El-Zeftawy,
New Valley University, Egypt

*CORRESPONDENCE
Hong Wu
wuhong@scu.edu.cn
Tian Lan
blue_sky_land@163.com

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 08 June 2022
ACCEPTED 29 August 2022
PUBLISHED 21 September 2022

CITATION
Cai Y, Xue S, Li J, Xiao H, Lan T and Wu H (2022) A novel nutritional score based on serum triglyceride and protein levels predicts outcomes of intrahepatic cholangiocarcinoma after curative hepatectomy: A multi-center study of 631 patients. *Front. Nutr.* 9:964591. doi: 10.3389/fnut.2022.964591

A novel nutritional score based on serum triglyceride and protein levels predicts outcomes of intrahepatic cholangiocarcinoma after curative hepatectomy: A multi-center study of 631 patients

Yunshi Cai[1], Shuai Xue[1], Jiaxin Li[1], Heng Xiao[2], Tian Lan[1]* and Hong Wu[1]*

[1]State Key Laboratory of Biotherapy and Cancer Center, Department of Liver Surgery and Liver Transplantation, West China Hospital, Sichuan University and Collaborative Innovation Center of Biotherapy, Chengdu, China, [2]Department of Hepatobiliary Surgery and Liver Transplantation, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Background: High serum triglyceride (STG) level is a well-established pathogenic factor for cardiovascular diseases and is associated with the risk of various malignancies. Nevertheless, the role of STG level in intrahepatic cholangiocarcinoma (ICC) remains uncertain.

Methods: A total of 631 ICC patients treated with curative hepatectomy in two centers (517 in the discovery set and 114 in the validation set) were retrospectively analyzed. Kaplan–Meier survival analysis was used to assess the outcomes of the patients with different STG levels. Time-dependent receiver operating characteristic (ROC) analysis was conducted to compare the prognostic value of STG with other established indexes. The Triglyceride-Albumin-Globulin (TAG) grade was introduced and evaluated using the time-dependent area under curves (AUC) analysis and decision curve analysis (DCA).

Results: Patients with increased STG levels and decreased albumin-globulin score (AGS) were correlated with improved overall survival (OS) and recurrence-free survival (RFS). STG level $\geq$ 1 mmol/L was an independent protective factor for surgically treated ICC patients. The predictive value of the TAG grade was superior to the STG or the AGS alone. In decision curve analysis, the net benefits of the TAG grade in the discovery and validation set were higher than STG and AGS.

Conclusion: The current study presented strong evidence that ICC patients with higher preoperative STG levels had preferred long-term surgical outcomes. The novel nutritional score based on serum triglyceride, albumin and globulin levels was inextricably linked to the prognosis of the surgically treated ICC patients. Evaluation of the TAG grade before curative hepatectomy may be beneficial for risk stratification and clinical decision support.

KEYWORDS

serum triglyceride, intrahepatic cholangiocarcinoma, albumin, globulin, nutritional score

Introduction

Liver cancer remains the fifth leading cause of all-cause mortality and the second most common cause of cancer-related death in China (1, 2), which leads to 37 per 10000 people of newly diagnosed cases annually (2). ICC represents a major subtype of biliary tract cancer located within the liver parenchyma (3), accounting for nearly 20% of primary liver cancers (4), of which the incidence and mortality are increasing rapidly in recent years (5). ICC is often diagnosed at an advanced stage with limited treatment options available; surgical resection remains one of the major treatment modalities (6). Recurrence is frequent after liver resection, resulting in a poor prognosis with less than 40% of surgically treated ICC patients on survive more than 5 years (7). Therefore, prognostic indicators are required to evaluate the outcomes of the surgical candidates and carry out early interventions, thus improving postoperative survival.

The population with ALD and NAFLD in China increased sharply (8, 9), as a result, the incidence and mortality of liver cancer started to soar since 2015 after a short duration of decline in the first decade of the 21st century (10). Previous studies had demonstrated that the metabolic syndrome (obesity, dyslipidemia, hypertension, and impaired fasting glucose/diabetes mellitus) was associated with increased risk of ICC (odds ratio = 1.56, $P < 0.0001$), whereas treatment with metformin was significantly related to a reduction of ICC risk (11, 12). High STG level, as an essential component of metabolic syndrome, was positively associated with the risk of multiple malignancies (lung, rectal, thyroid, renal, and gynecological cancers) and was inversely associated with the risk of non-Hodgkin's lymphoma and prostate cancer (13); however, the correlation between STG concentration and the prognosis of ICC patients have been inconclusive (14, 15).

As crucial components of human serum proteins, albumin (ALB) and globulin (GLB) levels were widely used in nutritional assessment. Previous studies have presented that elevated levels of serum ALB increased the risks of esophageal and cervical cancers (16, 17). GLBs, a group of proteins that binds estrogen, dihydrotestosterone and testosterone, play an essential role in the inflammatory immune response (18). Moreover, the high pretreatment ALB/GLB ratio has been proved to be associated with increased 5-year mortality and recurrence in different human cancers, including breast and gastric cancers (19). Similarly, another model based on serum ALB and GLB level, the AGS, has been applied in predicting the prognosis of non-small-cell lung cancer (20). As well, our recent study showed a positive correlation between the AGS and the long-term outcomes of ICC patients (21).

In the current study, we aimed to determine the correlation between STG and the long-term survival of surgically treated ICC patients. In addition, a novel nutritional score based on the STG concentration and the AGS (Triglyceride-Albumin-Globulin, TAG) was generated; we hoped to evaluate the clinical efficacy of the TAG grade in the prognosis of ICC patients after curative surgery.

Abbreviations: ACC, acetyl CoA carboxylase; AFP, alpha-fetoprotein; AGS, albumin-globulin score; AJCC, American Joint Committee on Cancer; ALB, albumin; ALBI, albumin-bilirubin index; ALD, alcoholic liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AST, aspartate aminotransferase; AUC, area under curve; BMI, body mass index; CAS, combination of albumin-globulin score and skeletal muscle index; CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; CHD, coronary heart disease; CHOL, cholesterol; CT, computed tomography; DCA, decision curve analysis; DNA, deoxyribonucleic acid; ECC, extrahepatic cholangiocarcinoma; FA, fatty acid; FASN, fatty acid synthase; FIB-4, fibrosis-4 index; GLB, globulin; GPS, glasgow prognostic score; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICC, intrahepatic cholangiocarcinoma; IL-6, interleukin-6; INR, international normalized ratio; LCR, lymphocyte-C-reactive protein ratio; LDL-C, low-density lipoprotein; MVI, microvascular invasion; NAFLD, non-alcoholic fatty liver disease; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PIVKA-II, prothrombin induced by vitamin K absence-II; PNI, prognostic nutritional index; RFA, radiofrequency ablation; RFS, recurrence-free survival; ROC, receiver operating characteristic; SCD-1, stearoyl-CoA desaturase-1; SMI, skeletal muscle index; STG, serum triglyceride; TACE, transarterial chemoembolization; TAG grade, triglyceride-albumin-globulin grade; TNF-α, tumor necrosis factor-α; TNM, tumor-node-metastasis.

Materials and methods

Study population

A total of 631 patients ICC patients received curative resection at two medical centers, West China Hospital

of Sichuan University and the First Affiliated Hospital of Chongqing Medical University, were sequentially enrolled. 517 patients underwent surgery at the West China Hospital during December 2008 and December 2017 were included as discovery set, 114 patients underwent surgery at the First Affiliated Hospital of Chongqing Medical University between May 2010 and December 2015 were included as the validation set to verify the efficiency of the novel scoring system. The inclusion criteria were as follow: (1) histologically diagnosed ICC; (2) underwent liver resection with curative intent initially; (3) no lipid-lowering treatment within 2 weeks prior to the operation; (4) serum TG measured in fasting status; exclusion criteria: (1) patients underwent preoperative RFA, TACE, radiation treatment, targeted therapy, or other anti-cancer treatment; (2) extrahepatic metastasis before the operation; (3) positive resection margin; (4) ruptured tumor; (5) patients with incomplete clinical and histological data or lost to follow-up. Written informed consents were obtained from all participants or their entrusted agents. This study was approved by the ethics committee of West China Hospital of Sichuan University (Approval number: 20211506) and the First Affiliated Hospital of Chongqing Medical University (Approval number: 2021-288), following the guidelines of the 1975 Declaration of Helsinki.

TABLE 1 Baseline characteristics of patients.

Variables	Discovery set (n = 517)	Validation set (n = 114)	P-value
Age, year, mean ± *SD*	57.2 ± 10.7	58.3 ± 11.2	0.327
Gender, *n* (%)			0.281
Male	251 (48.5%)	49 (43.0%)	
Female	266 (51.5%)	65 (57.0%)	
BMI kg/m^2, mean ± *SD*	24.8 ± 6.2	25.3 ± 5.8	0.436
Fasting glucose (mmol/L), mean ± *SD*	5.9 ± 2.1	5.6 ± 2.3	0.249
Cirrhosis, *n* (%)	145 (28.0%)	16 (14.0%)	0.007
Ascites, *n* (%)	48 (9.3%)	55 (48.2%)	<0.0001
Child score, n (%)			0.014
5	439 (84.9%)	86 (75.4%)	
6	78 (15.1%)	28 (24.6%)	
Multiple tumors, *n* (%)	156 (30.2%)	32 (28.1%)	0.709
Tumor size, *n* (%)			0.64
≥5 cm	225 (43.5%)	46 (40.4%)	
<5 cm	292 (56.5%)	68 (59.6%)	
Tumor differentiation, poor, *n* (%)	325 (66.7%)	84 (73.7%)	0.194
Hepatolithiasis, *n* (%)	87 (16.8%)	21 (18.4%)	0.709
Microvascular invasion, *n* (%)	52 (10.1%)	70 (61.4%)	<0.0001
Vascular invasion, *n* (%)	120 (23.2%)	71 (62.3%)	<0.0001
Node positivity, *n* (%)	127 (24.6%)	31 (27.2%)	0.611
Biliary invasion, *n* (%)	52 (10.1%)	58 (50.9%)	<0.0001
Perineural invasion, *n* (%)	75 (14.5%)	25 (21.9%)	0.071
Liver capsule invasion, *n* (%)	319 (61.7%)	62 (54.4%)	0.363
CA19-9, ≥22 U/mL, *n* (%)	113 (21.9%)	85 (74.6%)	<0.0001
HBsAg (positive), *n* (%)	150 (29.1%)	21 (18.4%)	0.049
HCV, *n* (%)	4 (0.8%)	1 (0.9%)	0.91
TNM stage, III, *n* (%)	361 (69.8%)	71 (62.3%)	0.378
TG, mmol/L, mean ± *SD*	1.3 ± 0.6	1.3 ± 0.8	0.426
ALB, g/L, mean ± *SD*	42.5 ± 4.7	38.6 ± 6.9	<0.0001
GLB, g/L, mean ± *SD*	29.1 ± 5.4	26.9 ± 5.2	0.005
SMI, male, mean ± *SD*	41.4 ± 6.8	42.6 ± 7.4	0.356
SMI, female, mean ± *SD*	36.5 ± 7.1	35.7 ± 7.8	0.562
Overall survival, month, median (interquartile range)	17.8 (9.8–33.6)	25.1 (9.6–58.8)	0.006

CA19-9, cancer antigen 19-9; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; TG, triglyceride; ALB, albumin; GLB, globulin; SMI, skeletal muscle index.

Data collection and follow-up

All the clinical and histopathological data were accessed from the electronic medical record system. Preoperative information was collected as follows: platelet counts; bilirubin, albumin (ALB), and globulin (GLB) levels; triglyceride (TG), cholesterol (CHOL), and low-density lipoprotein (LDL-C), ALT, and AST levels; HBV and HCV viral loads; carbohydrate antigen 19-9 (CA19-9) level; furthermore, the height and weight of the patients were obtained to calculate the body mass index (BMI) as weight divided by height squared (kg/m^2). The normal range of the TG was 0.29–1.83 mmol/L according to the determination kit's instruction. The optimal cut-off values of the TG, CHOL and LDL-C were determined as 1, 3.8, and 2.6 mmol/L, respectively (**Supplementary Figure 1**). As we previously reported, the cut-off values of the ALB and GLB were 41.7 and 28.6 g/L, respectively (21); the AGS was characterized as following criteria: patients with both normal values of the ALB (>41.7 g/L) and GLB (≤28.6 g/L) were defined as AGS 0, patients with both decreased ALB level (≤41.7 g/L) and increased GLB level (>28.6 g/L) were defined as AGS 2, those with single abnormal value were defined as AGS 1. Fibrosis-4 index (FIB-4) was calculated by $\left(ALT(U/L) \times age(year)\right) / \left(platelet(10^9/\mathrm{L}) \times \sqrt{AST(U/L)}\right)$ (22); albumin-bilirubin index (ALBI) was calculated from the following formula: $\left(log_{10}bilirubin(mol/L) \times 0.66\right) - \left(albumin(g/L) \times 0.085\right)$ (23). SMI was calculated as described in our previous study (21). The cut-off values were identified by using the X-tile software (24). Clinical and histological characteristics, including the presence of liver cirrhosis, ascites and hepatolithiasis, numbers and diameters of the tumor nodules, differentiation, lymph node positivity, microvascular invasion (MVI), vascular and perineural invasion, were also

attained. MVI was defined as the presence of tumor cells in vessels or in vascular space lined by the epithelial cells under the microscope. Vascular invasion was defined as large vessels invasion identified by imaging modalities or gross examinations. Positivity of No. 16 lymph node was regarded as extrahepatic metastasis and radical resection was not considered. The tumor-node-metastasis (TNM) stages were classified conforming to the 8th American Joint Committee on Cancer (AJCC) Staging Manual (25). Patients who received curative resections were followed-up every month within 1 year, then every 3 months within the first 2 years, and then every half year thenceforth, serum tumor markers and imaging methods (contrast-enhanced ultrasound or CT scan) were used in the surveillance of tumor recurrence. The overall survival (OS) was calculated from the date of curative hepatectomy to the date of death or the last follow-up (for those alive). The recurrence-free survival (RFS) was calculated from the date of curative hepatectomy to the detection of recurrence or the date of the last follow-up (for those without tumor relapse).

Statistical analysis

The software of EmpowerStats[1] and R[2] (v4.0.5) was used for statistical analysis; data were presented as mean ± standard

1 http://www.empowerstats.com

2 https://www.r-project.org

TABLE 2 Comparison of characteristics with the different serum triglyceride levels and AGS grades of 517 ICC patients treated with surgical resection in the discovery set.

Characteristics	STG (mmol/L)			AGS		
	<1 (*n* = 205)	≥1 (*n* = 312)	*P*-value	Low (0) (*n* = 174)	High (1, 2) (*n* = 343)	*P*-value
Age, mean ± *SD*	55.6 ± 10.9	58.3 ± 10.3	0.09	56.5 ± 11.0	57.6 ± 10.5	0.339
Gender, male, *n* (%)	103 (50.2%)	148 (47.4%)	0.532	88 (50.6%)	163 (47.5%)	0.512
BMI kg/m^2, mean ± *SD*	24.6 ± 3.4	26.4 ± 4.9	0.663	26.53 ± 4.2	25.74 ± 5.6	0.781
Cirrhosis, *n* (%)	65 (31.7%)	80 (25.6%)	0.133	50 (28.7%)	95 (27.7%)	0.804
Ascites, *n* (%)	21 (10.2%)	27 (8.7%)	0.542	12 (6.9%)	36 (10.5%)	0.183
Multiple tumors, *n* (%)	60 (29.3%)	96 (30.8%)	0.716	47 (27.0%)	109 (31.8%)	0.265
Tumor size (<5 cm), *n* (%)	115 (56.1%)	177 (56.7%)	0.887	77 (44.3%)	148 (43.1%)	0.811
Hepatolithiasis, *n* (%)	38 (18.5%)	49 (15.7%)	0.4	27 (15.5%)	60 (17.5%)	0.57
Microvascular invasion, *n* (%)	26 (12.7%)	26 (8.3%)	0.108	17 (9.8%)	35 (10.2%)	0.877
Vascular invasion, *n* (%)	49 (23.9%)	71 (22.8%)	0.763	37 (21.3%)	83 (24.2%)	0.455
Node positivity, *n* (%)	61 (29.8%)	66 (21.2%)	0.046	34 (19.5%)	93 (27.1%)	0.059
Biliary invasion, *n* (%)	18 (8.8%)	34 (10.9%	0.434	9 (5.2%)	43 (12.5%)	0.009
Perineural invasion, *n* (%)	31 (15.1%)	44 (14.1%)	0.747	20 (11.5%)	55 (16.0%)	0.166
Liver capsule invasion, *n* (%)	134 (65.4%)	185 (59.3%)	0.165	123 (70.7%)	196 (57.1%)	0.003
Tumor differentiation, poor, *n* (%)	38 (19.5%)	42 (14.4%)	0.325	20 (11.8%)	60 (18.9%)	0.098
CA19-9, ≥22 U/mL, *n* (%)	50 (25.0%)	63 (20.6%)	0.244	142 (83.5%)	251 (74.7%)	0.054
HBsAg (positive), *n* (%)	77 (37.7%)	73 (23.5%)	<0.001	48(27.6%)	102 (29.9%)	0.583
HCV, *n* (%)	2 (1.0%)	2 (0.6%)	0.738	1 (0.6%)	2 (0.6%)	0.774
Child score, *n* (%)			0.306			0.001
5	170 (82.9%)	269 (86.2%)		160 (92.0%)	279 (81.3%)	
6	35 (17.1%)	43 (13.8%)		14 (8.0%)	64 (18.7%)	
TNM stage, III, *n* (%)	149 (72.6%)	212 (78%)	0.103	131 (75.3%)	230 (67.1%)	<0.001
Overall survival, month, median (interquartile range)	15.7 (7.9–26.7)	18.8 (11.9–37.7)	<0.001	19.2 (12.8–35.3)	16.7 (9.1–32.8)	0.046

STG, serum triglyceride; AGS, albumin-globulin score; CA19-9, cancer antigen 19-9; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

deviation (SD), median (interquartile range) or proportion. Comparison of categorical and continuous variables between groups was performed with Student's *t*-test, Pearson's x^2 test and Analysis of variance (ANOVA). Non-parametric Mann–Whitney *U* test and Kruskal–Wallis test were used to analyze the data with the abnormal distribution. The ideal cut-off values of TG, CHOL, LDL-C, ALB, GLB, FIB-4, and ALBI were identified by using the software of X-tile[3]. The discriminatory ability of the indexes was assessed by the time-dependent area under receiver operating characteristic (AUROC) analysis via the "survivalROC" package in R. Comparison between ROC curves were performed by using DeLong's test via the "pROC" package in R. Kaplan–Meier curves were depicted according to the optimal cut-off values, and their differences between groups were determined by comparing the cumulative survival of the included ICC patients using the log-rank test. Cox proportional hazards regression model was used to identify potential prognostic factors for OS and RFS; clinical and histological parameters with $P < 0.2$

3 http://medicine.yale.edu/lab/rimm/research/software

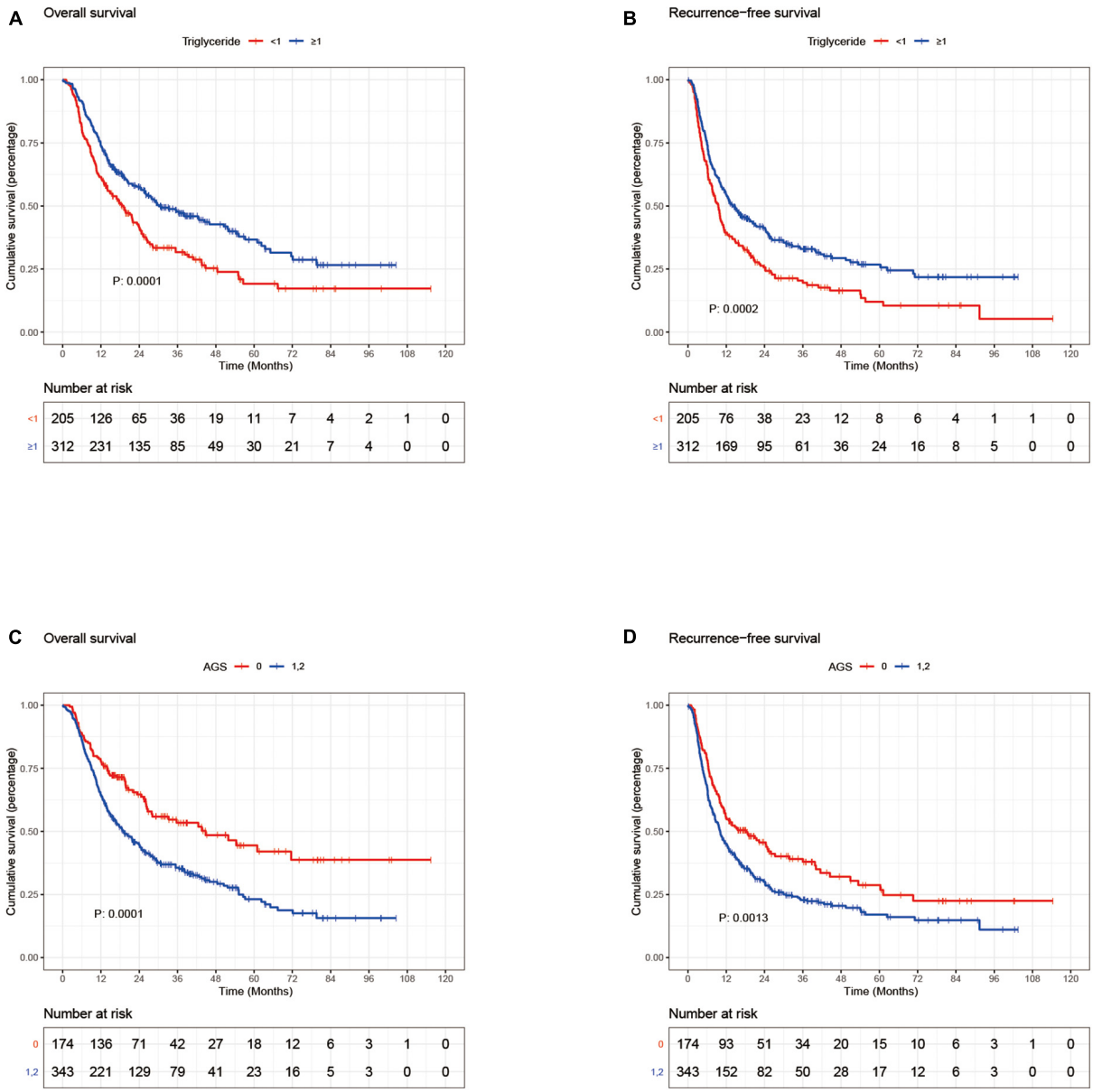


FIGURE 1
Kaplan–Meier curves for overall survival and recurrence-free survival stratified by triglyceride **(A,B)** and AGS **(C,D)** in the discovery set; AGS, albumin-globulin score.

in the univariate model were integrated into the multivariate model. Comparisons between the complex and straightforward models were conducted through decision curve analysis (DCA) via the "rmda" package in R. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the patients

Five hundred seventeen patients [251 (48.5%) male, mean (*SD*) age, 57.2 (10.7) years] in West China Hospital and 114 patients [49 (43.0%) male, mean (*SD*) age, 58.3 (11.2) years] in the First Affiliated Hospital of Chongqing Medical University were finally included into the discovery set and validation set, respectively. The BMI of the patients was lower in the discovery set (24.8 ± 6.2 kg/m^2) than those in the validation set (25.3 ± 5.8 kg/m^2). Liver cirrhosis was observed in 145 (28.0%) patients in the discovery set and 16 (14.0%) patients in the validation set. All patients were classified into Child-Pugh grade A, among which 439 (84.9%) patients in the discovery set and 86 (75.4%) patients in the validation set were Child-Pugh score 5. Multiple tumor nodules were detected in nearly 30% of the patients in both sets (156 (30.2%) in the discovery set and 32 (28.1%) in the validation set). Less than half of the patients in both sets were with tumor nodules greater than 5 cm (225 (43.5%) in the discovery set and 46 (40.4%) in the

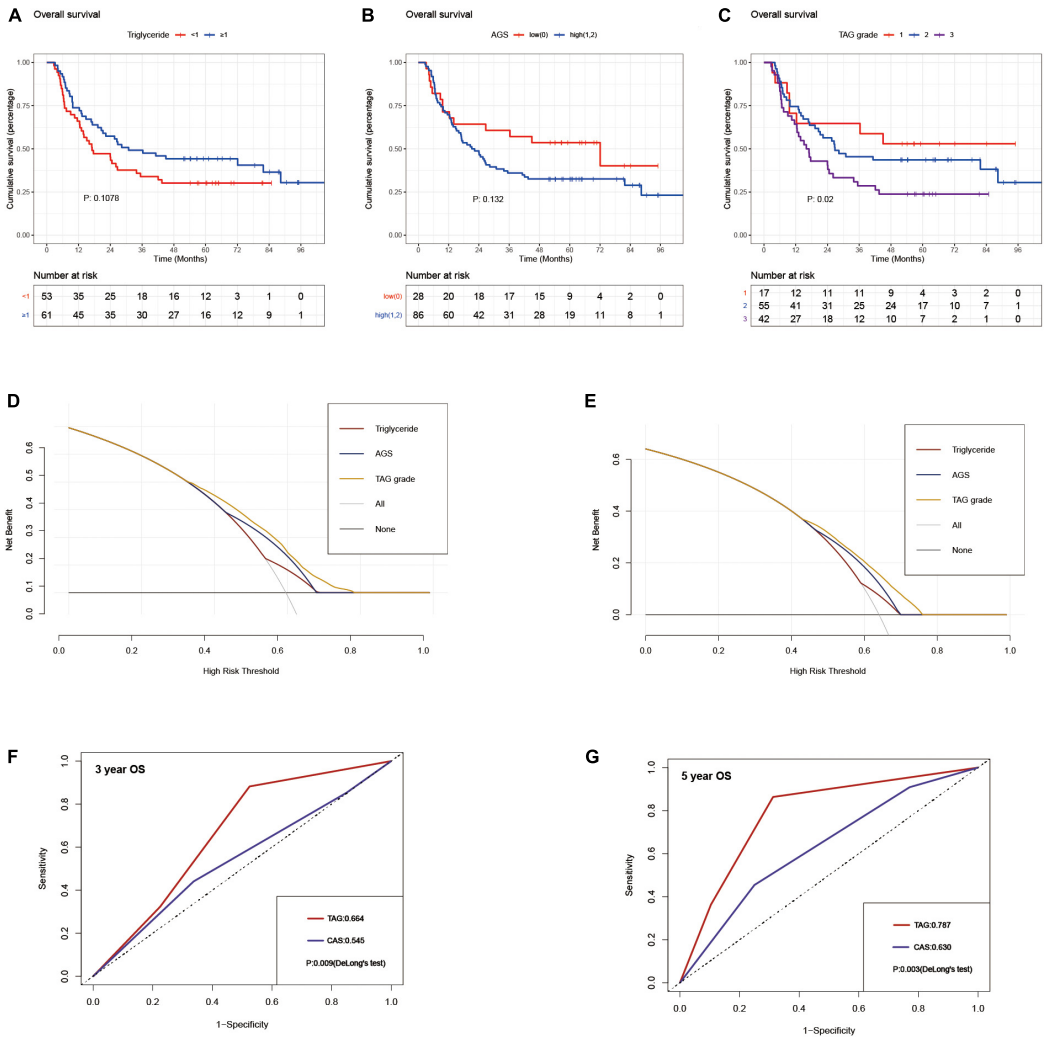


FIGURE 2
Kaplan–Meier curves for overall survival stratified by triglyceride **(A)**, AGS **(B)**, and TAG grade **(C)** in the validation set; decision curve analyses for overall survival of triglyceride, AGS and TAG grade in the discovery set **(D)** and validation set **(E)**; comparison of area under receiver operator characteristic curves for TAG and CAS grade in predicting 3-year **(F)** and 5-year **(G)** overall survival in the validation set using DeLong's test; AGS, albumin-globulin score; TAG grade, triglyceride-albumin-globulin grade; CAS grade, combination of albumin-globulin score and skeletal muscle index.

validation set). 87 (16.8%) of the patients in the discovery set and 21 (18.4%) of the patients in the validation set were with intrahepatic calculus. Positive lymph nodes were revealed in 127 (24.6%) patients in the discovery set and 31 (27.2%) patients in the validation set, respectively. The average TG levels were 1.3 ± 0.6 mmol/L in the discovery set and 1.3 ± 0.8 mmol/L in the validation set. The average ALB and GLB levels were slightly higher in the discovery set (ALB: 42.5 ± 4.7 g/L, GLB: 29.1 ± 5.4 g/L) than those in the validation set (ALB: 38.6 ± 6.9 g/L, GLB: 26.9 ± 5.2 g/L). Additionally, more than half of the patients [361 (69.8%) in the discovery set and 71 (62.3%) in the validation set] were stratified into TNM stage III. Patients' characteristics at baseline were summarized in Table 1.

Serum triglyceride level was an independent protective factor for intrahepatic cholangiocarcinoma

Several preoperative indexes related to serum lipid levels (TG, CHOL, and LDL-C) were compared, among the three indexes, only the serum TG level presented the discriminative ability for surgically treated ICC patients (Supplementary Figure 1); likewise, the upper limit of normal (ULN, 1.83 mmol/L) of TG was evaluated, no significant difference in the OS and RFS between the patients with and without hyperlipidemia (Supplementary Figure 2).

Therefore, 1 mmol/L was determined as the optimal cut-off value for serum TG level; 312 patients were with higher TG levels (≥1 mmol/L) and 205 patients were with lower levels (<1 mmol/L) in the discovery set, the correlations of characteristics with the serum triglyceride levels in the discovery and validation sets were demonstrated in Table 2 and Supplementary Table 1, respectively. Kaplan–Meier analysis suggested that the patients with higher TG levels had better OS and RFS than those with lower TG levels (median OS: 27.1 months vs. 21.5 months) (Figures 1A,B), a similar difference was further found in the validation set (Figure 2A). Models represented the preoperative hepatic function including the FIB-4 and ALBI score were also calculated; the discriminative capability of these two models and TG level to 1-, 3-, and 5-year OS and RFS were compared by using ROC; the AUC of TG were superior to that of FIB-4 and ALBI (Supplementary Figure 3). Consistently, multivariate analyses using the Cox proportional hazard model revealed that increased serum TG level was an independent protective factor for both the OS and RFS (OS: Hazard ratio, 0.66, P = 0.0014; RFS: Hazard ratio, 0.69, P = 0.0012) (Table 3).

TABLE 3 Multivariate analyses to determine independent predictors of overall survival and recurrence-free survival in the discovery set.

Variables	Overall survival			Recurrence-free survival		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Gender, female/male	0.89	0.70–1.15	0.4026	1.01	0.81–1.26	0.9562
Age, ≥60/<60 (years)	1.10	0.86–1.4	0.4402	1.03	0.84–1.29	0.7327
Impaired fasting glucose, ≥7/<7 (mmol/L)	1.42	0.89–1.97	0.0452	1.23	0.97–1.61	0.0997
Hepatolithiasis	1.11	0.82–1.53	0.4890	0.87	0.64–1.17	0.3567
Tumor number, Multiple/single	1.61	1.24–2.09	0.0003	1.62	1.28–2.05	<0.0001
Tumor size, ≥5/<5 (cm)	1.11	0.84–1.44	0.4652	1.22	0.96–1.56	0.1063
Tumor differentiation						
Well	Reference			Reference		
Moderate	1.30	0.73–2.34	0.3733	1.74	1.01–2.98	0.0463
Poor	2.26	1.21–4.26	0.0110	2.15	1.19–3.87	0.0110
Microvascular invasion	1.18	0.82–1.70	0.3746	1.42	1.02–1.99	0.0389
Node positivity	1.70	1.28–2.25	0.0002	1.38	1.06–1.79	0.0151
Liver capsule invasion	0.93	0.71–1.21	0.5752	0.96	0.76–1.23	0.7842
Perineural invasion	1.42	0.99–2.02	0.0501	1.24	0.89–1.72	0.1981
STG, ≥1/<1 (mmol/L)	0.66	0.52–0.85	0.0014	0.69	0.55–0.87	0.0014
CAS						
Grade 1	Reference			Reference		
Grade 2	1.54	1.14–2.06	0.0044	1.40	1.08–1.81	0.0100
Grade 3	2.84	1.90–4.24	<0.0001	2.29	1.58–3.33	<0.0001
CA199 grade, ≥22/<22 (U/ml)	1.92	1.44–2.57	<0.0001	1.49	1.14–1.95	0.0035

STG, serum triglyceride; CA19-9, cancer antigen 19-9; CAS, combination of albumin-globulin score and skeletal muscle index.

Albumin-globulin score was associated with prognosis of intrahepatic cholangiocarcinoma patients after curative resection

Intrahepatic cholangiocarcinoma Patients were stratified into two groups according to the AGS; higher AGS stratification (1, 2) was associated with poor OS and RFS than the lower AGS stratification (0) in the discovery set (**Figures 1C,D**). In the validation set, marginal significance was likewise obtained on the difference between the two groups ($P = 0.132$) (**Figure 2B**). The correlations of clinicopathological characteristics with the AGS in the discovery and validation sets were exhibited in **Table 2** and **Supplementary Table 1**.

The proposal and validation of triglyceride-albumin-globulin grade

The triglyceride-albumin-globulin (TAG) grade was proposed as follows: patients with high TG level (≥1 mmol/L) and low AGS (0) were classified into TAG grade 1, those with low TG level (<1 mmol/L) and high AGS (1, 2) were classified into TAG grade 3, the rest of the patients were classified into TAG grade 2. In the discovery set, the patients in TAG grade 2 had superior 1-, 3-, and 5-year cumulative OS and RFS than those in TAG grade 3 (OS: 69.4, 24.1, and 8.6% vs. 57, 17.7, and 3.7%; RFS: 48.9, 16.2, and 6.8% vs. 34.1, 10.4, and 2.2%), but worse than those in TAG grade 1 (OS: 69.4, 24.1, and 8.6% vs. 83.7, 28.8, and 11.5%; RFS: 48.9, 16.2, and 6.8% vs. 60.6, 24, and 9.6%) (**Figures 3A,B**). A similar result was also generated in the patients of the validation set (**Figure 2C**). Moreover, the TAG grade possessed stronger predictive ability than the single use of TG or AGS through the result of time-dependent AUC analysis (**Figures 3C,D**). Subgroup analyses were conducted to further validate the efficacy of TAG grade in multiple clinical conditions, including different gender, age, number and diameter of tumor nodules, tumor differentiation, CA19-9 level and Child score; with or without liver cirrhosis, vascular invasion, positive lymph node, perineural and liver capsule invasion. The results of subgroup analyses shown in **Figures 4A,B** suggested that the ICC patients in higher TAG grades were related to decreased OS and RFS in various clinical conditions. Survival analyses based on Cox proportional hazard models in the discovery and validation sets presented that the TAG grade remained the independent risk factor for postoperative outcomes of surgically treated ICC patients (**Table 4** and **Supplementary Table 3**). As shown in **Figures 2D,E**, the TAG grade demonstrated preferable net

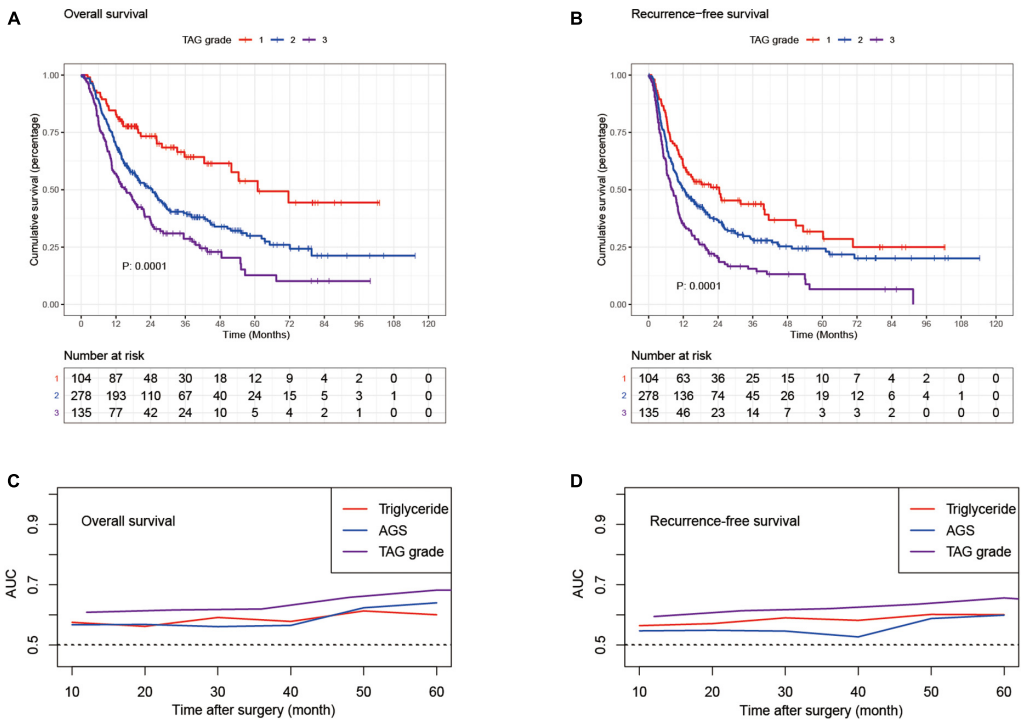


FIGURE 3
Kaplan–Meier curves for overall survival and recurrence-free survival stratified by TAG grade **(A,B)** in the discovery set; time-dependent AUROC curves of triglyceride, AGS and TAG grade for overall survival **(C)** and recurrence-free survival **(D)** in the discovery set; AUROC, area under receiver operating characteristic; AGS, albumin-globulin score; TAG grade, triglyceride-albumin-globulin grade.

benefits within a wider range of threshold probability than the single use of either TG or AGS in predicting OS for the patients in both the discovery and validation sets. Moreover, in the validation set, the predicting abilities of the TAG grade were superior to the CAS grade in our previous study (21) (**Figures 2F,G**). The correlations between clinical characteristics and the TAG grade in the discovery and validation set were presented in **Table 5** and **Supplementary Table 2**.

Discussion

The present study revealed that elevated preoperative serum TG was an independent protective factor for ICC patients after curative liver resection. TG showed the greatest predictive effectiveness among several parameters related to hepatic function and serum lipid level. Likewise. AGS demonstrated discriminative capability in predicting long-term surgical

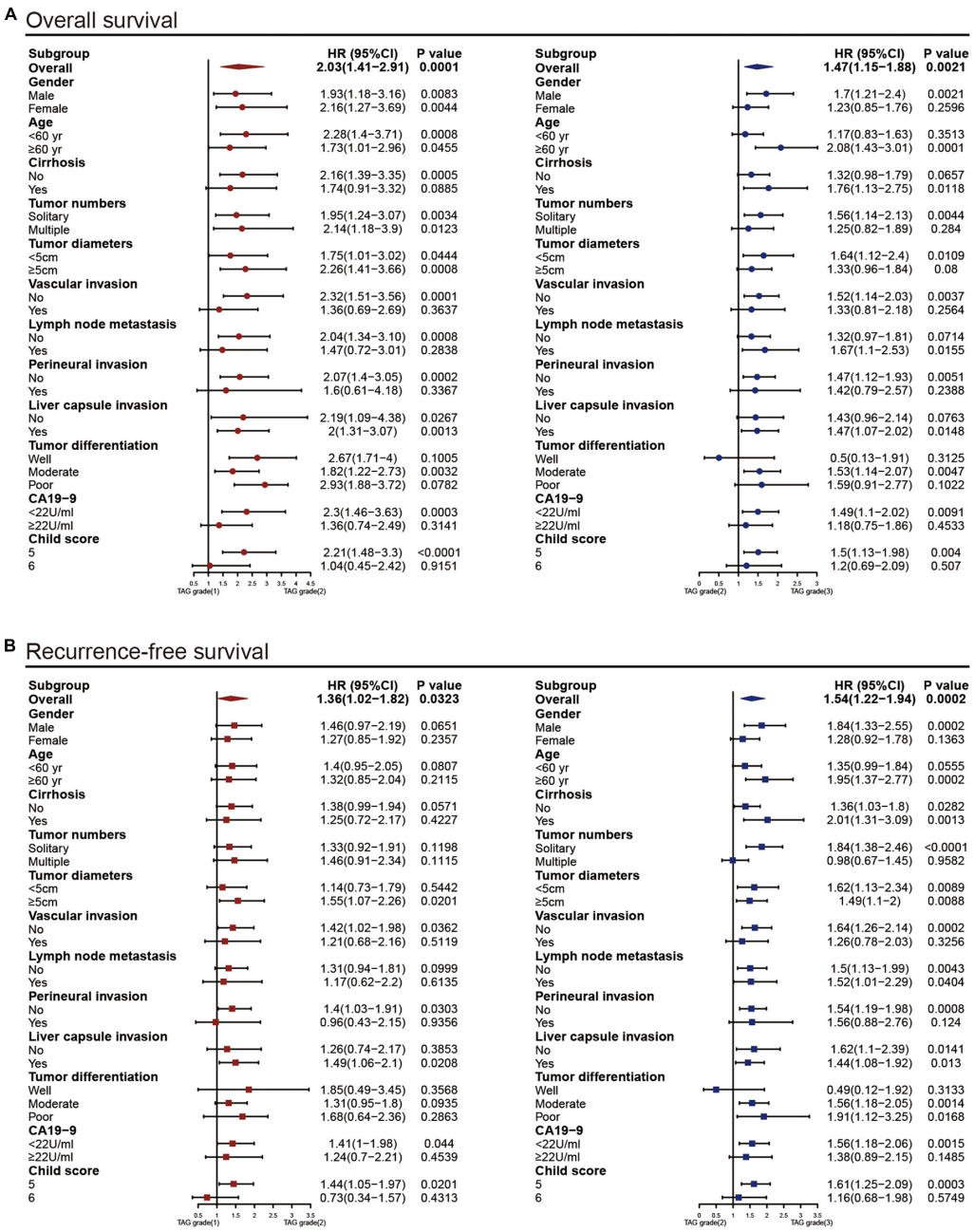


FIGURE 4
Subgroup analyses to assess the discrimination ability of the TAG grade for overall survival **(A)** and recurrence-free survival **(B)** in patients with different clinical characteristics; HR, hazard ratio; CI, confidence interval; TAG grade, triglyceride-albumin-globulin grade.

outcomes of the ICC patients. The serum TG level and AGS were further combined into a novel nutrition grade called TAG grade, the ICC patients in different TAG grades displayed markedly different postoperative survival rates; these differences were maintained in various subgroups as well. Additionally, with superior predictive ability than the TG and AGS, the TAG grade was a desirable model in the prognosis prediction of ICC patients who underwent curative hepatectomy.

There is evolving evidence that preoperative serum markers play essential roles in the prognosis prediction of patients with primary liver cancers. Conventional markers including AFP, PIVKA-II, and carbohydrate antigen 19-9 (CA19-9) have been extensively studied and applied in HCC and ICC patients (26, 27). By combining inflammation-related indexes (counts of lymphocyte, monocyte, neutrophil and platelet; concentration of C-reactive protein) and liver function parameters [levels of bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT)], several prognostic scores including the Glasgow Prognostic Score (GPS), Prognostic Nutritional Index (PNI), and lymphocyte-C-reactive protein ratio (LCR) were introduced and validated in predicting outcomes of ICC patients following surgical treatments (28, 29). Nutritional status has been broadly reported to be implicated in cancer progression and prognosis (30); an effective nutritional assessment before surgery is crucial for achieving optimal short- and long-term survival of ICC patients. In our previous study (21), the SMI generated from the CT was used to evaluate the nutritional status of ICC patients prior to the operation, which exhibited a good clinical efficacy. However, interpretation of the radiographic based SMI required the assistances of the experienced radiologists, which limited its application, especially in primary health-care facilities. therefore, an easy-to-use serological index was needed. Notwithstanding, serological indicators for preoperative evaluation of nutritional status are limited.

TG is the most common type of fat derived from dietary intake or extra calories. The correlation between circulating TG concentration and a range of metabolic diseases including diabetes and CHD has been extensively studied recently (31, 32). In 1991, elevated serum TG level was reported to be associated with a higher incidence of developing breast cancer (33). In the male population, fasting TG and glucose levels were significantly correlated with the risk of non-small-cell lung cancer (34). In a large cohort study involving 1,56,153 participants in Austria, serum TG concentration was found to be positively or reversely associated with multiple malignancies (13). Liu et al. (14) demonstrated that the serum TG level less than 0.81 mmol/L

TABLE 4 Univariate and multivariate analyses to determine independent predictors of overall survival in the discovery set.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Gender, female/male	0.8073	0.64–1	0.0606	0.828	0.64–1.06	0.1348
Age, ≥60/<60 (years)	0.9603	0.76–1.2	0.7239			
Cirrhosis	1.2573	0.98–1.6	0.066	1.6133	1.23–2.12	0.0006
Hepatolithiasis	1.3263	1.1–1.75	0.0484	1.1299	0.83–1.55	0.4465
Tumor number, multiple/single	1.6661	1.32–2.1	<0.0001	1.6544	1.27–2.15	0.0002
Tumor size, ≥5/<5 (cm)	1.2161	0.96–1.52	0.0916	1.1344	0.87–1.48	0.3523
Tumor differentiation						
Well	Reference			Reference		
Moderate	1.79	1.02–3.13	0.0415	1.188	0.67–2.12	0.5602
Poor	2.6893	1.46–4.92	0.0014	1.8792	1–3.53	0.0497
Microvascular invasion	1.7008	1.22–2.37	0.0018	1.1927	0.83–1.71	0.3411
Vascular invasion	1.1532	0.89–1.49	0.2816	0.9944	0.74–1.33	0.9699
Node positivity	2.3488	1.85–2.98	<0.0001	1.8416	1.39–2.43	<0.0001
Liver capsule invasion	1.0749	0.85–1.35	0.5392			
Perineural invasion	1.5583	1.15–2.11	0.004	1.3597	0.95–1.94	0.0892
TAG grade						
1	Reference			Reference		
2	2.0244	1.41–2.9	0.0001	1.9632	1.35–2.86	0.0004
3	2.9832	2.04–4.37	<0.0001	2.443	1.64–3.65	<0.0001
CA199 grade ≥22/<22 (U/ml)	2.5093	1.96–3.21	<0.0001	2.0296	1.52–2.72	<0.0001
HBV	1.1162	0.87–1.43	0.3783			

TAG grade, triglyceride-albumin-globulin grade; CA19-9, cancer antigen 19-9; HBV, hepatitis B virus.

was a predictor for a worse prognosis of HCC patients in the absence of liver cirrhosis. Andreotti et al. (15) reported a positive correlation between STG and biliary malignancies (gall bladder, extrahepatic bile duct and the ampulla of Vater). Interestingly, a robust negative correlation between TG level and poor prognosis of ICC patients following liver resection was discovered in the present study. Apart from conventional risk factors such as primary sclerosing cholangitis, biliary tract cysts and hepatolithiasis for both ECC and ICC; chronic hepatitis, obesity, alcoholic, and non-alcoholic liver diseases are emerging as major concerns in the etiology of ICC (35). These diversities may explain why the increased STG levels were associated with higher prevalence of ECC but better prognosis of ICC.

The mechanism underlying the relationship between TG and liver cancer has not been fully elucidated. Lipid metabolism is emerging as an essential factor in tumor initiation and progression; several targets evolved in lipid metabolism have been reported as potential therapeutic targets in the treatment of primary liver cancer. During the *De- novo* FA synthesis of liver cancer, glucose is taken up in the HCC cell and converted into FA for storage in the form of TG, which plays crucial roles in cancer cell survival by inducing autophagy, influencing intracellular signaling and gene expression, meanwhile increasing energy production (36). Related targets include SCD1 (37), FASN (38) and ACC (39) and their inhibitors have been intensely investigated in the proliferation and metastasis of liver cancer. Moreover, some of the canonical cancer signal transduction pathways such as AMP-activated protein kinase (AMPK) (40), Wnt and Ras pathways were considered to have an impact on TG composition, thus affecting hepatic tumorigenesis (41).

The ALB is one of the most frequently used markers for evaluating the nutritional statuses of cancer patients (42). Serum ALB may act as a tumor suppressor through the following mechanisms: on the one hand, the activated pro-inflammatory cytokines including IL-6 and TNF-α inhibit the secretion of ALB by hepatic cells, these cytokines are critical molecules driving liver cancer progression (43); on the other hand, ALB serves as a stabilizer of cell growth and DNA replication by scavenging the free radicals, thereby maintains the endocrine homeostasis (44).

Given the prognostic values of TG and AGS in surgically treated ICC patients, a novel nutritional model (TAG grade) was proposed by combining these two markers. The TAG grade exhibited optimal discriminatory capability and reliable clinical efficacy, superior to the CT-based CMI grade in our previous study (21).

TABLE 5 Comparison of characteristics with the different TAG grades of 517 ICC patients treated with surgical resection in the discovery set.

Characteristics	TAG grade			
	1 (n = 104)	2 (n = 278)	3 (n = 135)	P-value
Age, mean ± *SD*	57.7 ± 10.3	57.6 ± 10.9	56.1 ± 10.4	0.332
Gender, male, *n* (%)	54 (51.9%)	128 (46.0%)	69 (51.1%)	0.466
BMI kg/m^2, mean ± *SD*	24.9 ± 4.8	26.1 ± 4.3	28.6 ± 5.9	0.635
Cirrhosis, *n* (%)	31 (29.8%)	68 (24.5%)	46 (34.1%)	0.113
Ascites, *n* (%)	10 (9.6%)	19 (6.8%)	19 (14.1%)	0.059
Multiple tumors, *n* (%)	30 (28.8%)	83 (29.9%)	43 (31.9%)	0.869
Tumor size (<5 cm), *n* (%)	45 (43.3%)	122 (43.9%)	58 (43.0%)	0.983
Hepatolithiasis, *n* (%)	16 (15.4%)	44 (15.8%)	27 (20.0%)	0.516
Microvascular invasion, *n* (%)	10 (9.6%)	23 (8.3%)	19 (14.1%)	0.182
Vascular invasion, *n* (%)	24 (23.1%)	60 (21.6%)	36 (26.7%)	0.517
Node positivity, *n* (%)	15 (14.4%)	70 (25.2%)	42 (31.1%)	0.011
Biliary invasion, *n* (%)	6 (5.8%)	31 (11.2%)	15 (11.1%)	0.266
Perineural invasion, *n* (%)	12 (11.5%)	40 (14.4%)	23 (17.0%)	0.487
Liver capsule invasion, *n* (%)	74 (71.2%)	160 (57.6%)	85 (63.0%)	0.049
Tumor differentiation, poor, *n* (%)	10 (9.9%)	42 (16.2%)	28 (22.0%)	0.176
CA19-9, ≥22 U/mL, *n* (%)	83 (81.4%)	219 (80.5%)	91 (68.9%)	0.019
HBsAg (positive), *n* (%)	22 (21.2%)	77 (27.8%)	51 (38.1%)	0.013
HCV, *n* (%)	0 (0.0%)	2 (0.7%)	1 (0.7%)	0.803
Child score, *n* (%)				0.008
5	94 (90.4%)	241 (86.7%)	104 (77.0%)	
6	10 (9.6%)	37 (13.3%)	31 (23.0%)	
TNM stage, III, *n* (%)	79 (76.0%)	185 (66.5%)	97 (71.8%)	0.056
Overall survival, month, median (interquartile range)	20.1 (14.0–38.1)	17.9 (10.7–33.5)	14.0 (7.2–27.4)	<0.001

TAG grade, triglyceride-albumin-globulin grade; CA19-9, cancer antigen 19-9; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

This study is noticeable in the following aspects. Firstly, this was the first study to elucidate the correlation between serum TG and prognosis of ICC in a large cohort of 631 patients including multiple medical centers. Secondly, as far as we are aware, this was the first study that combined serum TG, ALB, and GLB levels to assess the long-term survival of ICC patients after curative resection. The results may be profitable for nutritional assessment and patient selection prior to surgical treatment.

Despite the positive outcomes, there were significant restrictions: (1) the two involved centers were situated in the southwest part of mainland China, because of the high frequency of hepatolithiasis in this area, the accuracy of the TAG grade may be restricted by the etiological agents and retrospective design, further prospective worldwide studies were required to confirm our initial findings. (2) A small part of patients underwent retreatment at different medical facilities following tumor recurrence; as a result, this study was unable to examine the impact of postoperative treatment for recurrent ICC, which may affect the outcomes of this part of patients. (3) The glucose level was not assessed as a covariate; given the potential impact that the hyperglycemia had on the TG level, the results might be confounded.

Conclusion

Elevated serum TG concentration was independently associated with better long-term outcomes of ICC patients following curative hepatectomies. It is beneficial to consider the proposed TAG grade as a surrogate nutritional score in risk classification for surgically treated ICC patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

Ethics statement

Written informed consents were obtained from all participants or their entrusted agents. This study was approved by the Ethics Committee of West China Hospital of Sichuan University and the First Affiliated Hospital of Chongqing Medical University, following the guidelines of the 1975 Declaration of Helsinki.

Author contributions

YC, TL, and HW: conceptualization. YC, JL, HX, and SX: data curation. YC and TL: formal analysis and writing—original draft. HW and TL: supervision. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants from the Natural Science Foundation of China (82173124 and 81972747).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.964591/full#supplementary-material

References

1. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* (2019) 394:1145–58.

2. Cao M, Li H, Sun D, Chen W. Cancer burden of major cancers in China: a need for sustainable actions. *Cancer Commun.* (2020) 40:205–10. doi: 10.1002/cac2.12025

3. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology.* (2013) 145:1215–29.

4. Khan AS, Dageforde LA. Cholangiocarcinoma. *Surg Clin North Am.* (2019) 99:315–35.

5. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on

the rise. *Oncologist.* (2016) 21:594–9. doi: 10.1634/theoncologist.2015-0446

6. Javle M, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, et al. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. *J Clin Oncol.* (2018) 36:276–82.

7. Job S, Rapoud D, Dos Santos A, Gonzalez P, Desterke C, Pascal G, et al. Identification of four immune subtypes characterized by distinct composition and functions of tumor microenvironment in intrahepatic cholangiocarcinoma. *Hepatology.* (2020) 72:965–81. doi: 10.1002/hep.31092

8. Wang FS, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. *Hepatology.* (2014) 60:2099–108.

9. Zhou J, Zhou F, Wang W, Zhang XJ, Ji YX, Zhang P, et al. Epidemiological features of NAFLD From 1999 to 2018 in China. *Hepatology.* (2020) 71:1851–64. doi: 10.1002/hep.31150

10. Zhou F, Zhou J, Wang W, Zhang XJ, Ji YX, Zhang P, et al. Unexpected rapid increase in the burden of NAFLD in China from 2008 to 2018: a systematic review and meta-analysis. *Hepatology.* (2019) 70:1119–33. doi: 10.1002/hep.30702

11. Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology.* (2011) 54:463–71. doi: 10.1002/hep.24397

12. Chaiteerakij R, Yang JD, Harmsen WS, Slettedahl SW, Mettler TA, Fredericksen ZS, et al. Risk factors for intrahepatic cholangiocarcinoma: association between metformin use and reduced cancer risk. *Hepatology.* (2013) 57:648–55. doi: 10.1002/hep.26092

13. Ulmer H, Borena W, Rapp K, Klenk J, Strasak A, Diem G, et al. Serum triglyceride concentrations and cancer risk in a large cohort study in Austria. *Br J Cancer.* (2009) 101:1202–6. doi: 10.1038/sj.bjc.6605264

14. Liu X, Li M, Wang X, Dang Z, Jiang Y, Wang X, et al. Effect of serum triglyceride level on the prognosis of patients with hepatocellular carcinoma in the absence of cirrhosis. *Lipids Health Dis.* (2018) 17:248. doi: 10.1186/s12944-018-0898-y

15. Andreotti G, Chen J, Gao Y-T, Rashid A, Chang S-C, Shen M-C, et al. Serum lipid levels and the risk of biliary tract cancers and biliary stones: a population-based study in China. *Int J Cancer.* (2008) 122:2322–9.

16. Huang L, Mo Z, Zhang L, Qin S, Qin S, Li S. Diagnostic value of albumin to fibrinogen ratio in cervical cancer. *Int J Biol Markers.* (2020) 35:66–73.

17. Matsuda S, Takeuchi H, Kawakubo H, Fukuda K, Nakamura R, Takahashi T, et al. Cumulative prognostic scores based on plasma fibrinogen and serum albumin levels in esophageal cancer patients treated with transthoracic esophagectomy: comparison with the Glasgow prognostic score. *Ann Surg Oncol.* (2015) 22:302–10. doi: 10.1245/s10434-014-3857-5

18. Meyer EJ, Nenke MA, Rankin W, Lewis JG, Torpy DJ. Corticosteroid-binding globulin: a review of basic and clinical advances. *Horm Metab Res.* (2016) 48:359–71. doi: 10.1055/s-0042-108071

19. Lv GY, An L, Sun XD, Hu YL, Sun DW. Pretreatment albumin to globulin ratio can serve as a prognostic marker in human cancers: a meta-analysis. *Clin Chim Acta.* (2018) 476:81–91.

20. Li X, Qin S, Sun X, Liu D, Zhang B, Xiao G, et al. Prognostic significance of albumin-globulin score in patients with operable non-small-cell lung cancer. *Ann Surg Oncol.* (2018) 25:3647–59. doi: 10.1245/s10434-018-6715-z

21. Li H, Dai J, Lan T, Liu H, Wang J, Cai B, et al. Combination of albumin-globulin score and skeletal muscle index predicts long-term outcomes of intrahepatic cholangiocarcinoma patients after curative resection. *Clin Nutr.* (2021) 40:3891–900. doi: 10.1016/j.clnu.2021.04.038

22. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology.* (2007) 46:32–6. doi: 10.1002/hep.21669

23. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol.* (2015) 33:550–8. doi: 10.1200/JCO.2014.57.9151

24. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res.* (2004) 10:7252–9. doi: 10.1158/1078-0432.CCR-04-0713

25. Chun YS, Pawlik TM, Vauthey JN. 8th edition of the AJCC cancer staging manual: pancreas and hepatobiliary cancers. *Ann Surg Oncol.* (2018) 25:845–7. doi: 10.1245/s10434-017-6025-x

26. Park H, Kim SU, Park JY, Kim DY, Ahn SH, Chon CY, et al. Clinical usefulness of double biomarkers AFP and PIVKA-II for subdividing prognostic groups in locally advanced hepatocellular carcinoma. *Liver Int.* (2014) 34:313–21. doi: 10.1111/liv.12274

27. Feng F, Gao Q, Wu Y, Liu C, Yu Y, Li B, et al. Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy vs. cytoreductive surgery alone for intrahepatic cholangiocarcinoma with peritoneal metastases: a retrospective cohort study. *Eur J Surg Oncol.* (2021) 47:2363–8. doi: 10.1016/j.ejso.2021.05.014

28. Lin J, Fang T, Zhu M, Xu X, Zhang J, Zheng S, et al. Comparative performance of inflammation-based prognostic scores in patients operated for intrahepatic cholangiocarcinoma. *Cancer Manag Res.* (2019) 11:9107–19.

29. Lu LH, Zhong C, Wei W, Li SH, Mei J, Zou JW, et al. Lymphocyte-C-reactive protein ratio as a novel prognostic index in intrahepatic cholangiocarcinoma: a multicentre cohort study. *Liver Int.* (2021) 41:378–87. doi: 10.1111/liv.14567

30. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr.* (2017) 36:1187–96. doi: 10.1016/j.clnu.2017.06.017

31. Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet.* (2010) 375:1634–9. doi: 10.1016/S0140-6736(10)60545-4

32. Pirillo A, Casula M, Olmastroni E, Norata GD, Catapano AL. Global epidemiology of dyslipidaemias. *Nat Rev Cardiol.* (2021) 18:689–700.

33. Potischman N, McCulloch CE, Byers T, Houghton L, Nemoto T, Graham S, et al. Associations between breast cancer, plasma triglycerides, and cholesterol. *Nutr Cancer.* (1991) 15:205–15.

34. Yan X, Gao Y, Tong J, Tian M, Dai J, Zhuang Y. Association between triglyceride glucose index and non-small cell lung cancer risk in Chinese population. *Front Oncol.* (2021) 11:585388. doi: 10.3389/fonc.2021.585388

35. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. *Lancet.* (2005) 366:1303–14.

36. Pope ED III, Kimbrough EO, Vemireddy LP, Surapaneni PK, Copland JA III, Mody K. Aberrant lipid metabolism as a therapeutic target in liver cancer. *Expert Opin Ther Targets.* (2019) 23:473–83.

37. Igal RA. Stearoyl-CoA desaturase-1: a novel key player in the mechanisms of cell proliferation, programmed cell death and transformation to cancer. *Carcinogenesis.* (2010) 31:1509–15. doi: 10.1093/carcin/bgq131

38. Buckley D, Duke G, Heuer TS, O'Farrell M, Wagman AS, McCulloch W, et al. Fatty acid synthase - Modern tumor cell biology insights into a classical oncology target. *Pharmacol Ther.* (2017) 177:23–31. doi: 10.1016/j.pharmthera.2017.02.021

39. Abramson HN. The lipogenesis pathway as a cancer target. *J Med Chem.* (2011) 54:5615–38.

40. Muoio DM, Seefeld K, Witters LA, Coleman RA. AMP-activated kinase reciprocally regulates triacylglycerol synthesis and fatty acid oxidation in liver and muscle: evidence that sn-glycerol-3-phosphate acyltransferase is a novel target. *Biochem J.* (1999) 338(Pt. 3):783–91.

41. Yao Y, Sun S, Wang J, Fei F, Dong Z, Ke AW, et al. Canonical Wnt signaling remodels lipid metabolism in zebrafish hepatocytes following ras oncogenic insult. *Cancer Res.* (2018) 78:5548–60. doi: 10.1158/0008-5472.CAN-17-3964

42. McMillan DC, Watson WS, O'Gorman P, Preston T, Scott HR, McArdle CS. Albumin concentrations are primarily determined by the body cell mass and the systemic inflammatory response in cancer patients with weight loss. *Nutr Cancer.* (2001) 39:210–3. doi: 10.1207/S15327914nc392_8

43. Chojkier M. Inhibition of albumin synthesis in chronic diseases: molecular mechanisms. *J Clin Gastroenterol.* (2005) 39(4 Suppl. 2):S143–6.

44. Yildirim M, Yildiz M, Duman E, Goktas S, Kaya V. Prognostic importance of the nutritional status and systemic inflammatory response in non-small cell lung cancer. *J BUON.* (2013) 18:728–32.

frontiers | Frontiers in Nutrition

TYPE Systematic Review
PUBLISHED 23 September 2022
DOI 10.3389/fnut.2022.972034

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Hajime Suzuki,
Kagoshima University, Japan
Semra Paydaş,
Çukurova University, Turkey

*CORRESPONDENCE
Yunxiang Li
liyunxiang369@126.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 17 June 2022
ACCEPTED 26 August 2022
PUBLISHED 23 September 2022

CITATION
Meng C, Gan L, Li K, Yi F, Peng L, Li J and Li Y (2022) Prognostic nutritional index before surgical treatment may serve as a prognostic biomarker for patients with upper tract urothelial carcinoma: A systematic review and meta-analysis.
Front. Nutr. 9:972034.
doi: 10.3389/fnut.2022.972034

Prognostic nutritional index before surgical treatment may serve as a prognostic biomarker for patients with upper tract urothelial carcinoma: A systematic review and meta-analysis

Chunyang Meng[1†], Lijian Gan[1†], Kangsen Li[1], Fulin Yi[2], Lei Peng[1], Jinze Li[3] and Yunxiang Li[1*]

[1]Department of Urology, The Affiliated Nanchong Central Hospital of North Sichuan Medical College (University), Nanchong, China, [2]Department of Anesthesiology, North Sichuan Medical College (University), Nanchong, China, [3]Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China

Objective: This meta-analysis aims to assess whether the prognostic nutritional index (PNI) score before treatment can be an independent biomarker of the prognosis of patients with upper tract urothelial carcinoma (UTUC).

Materials and methods: We systematically search PubMed, Embase, Scopus database, and Cochrane Library,and the search time is up to April 2021. Use STATA 16.0 software for data processing and statistical analysis.

Results: Six studies, including seven cohorts, were eventually included in our meta-analysis. The meta-analysis results showed that low PNI scores are associated with worse OS (HR: 1.92; 95% CI 1.60 to 2.30; $P < 0.01$), DFS/RFS/PFS (HR: 1.57; 95% CI 1.33 to 1.85; $P < 0.01$), and CSS/DSS (HR: 1.79; 95% CI 1.49 to 2.16; $P < 0.01$), which supported the PNI score as an independent prognostic biomarker for survival outcomes. The subgroup analysis and Begg's test showed that the results were stable.

Conclusion: Based on current evidence, this meta-analysis proves that the PNI score of UTUC patients before treatment is an independent prognostic biomarker. It performs well on OS, DFS/RFS/PFS, and CSS/DSS. This conclusion needs to be verified by a prospective cohort study with larger sample size and a more rigorous design.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022338503], identifier [CRD42022338503].

KEYWORDS

prognostic nutritional index, upper tract urothelial carcinoma, prognostic biomarker, meta-analysis, PNI

Introduction

Upper tract urothelial carcinoma (UTUC) is a malignant tumor, that locates from the calyx system to the distal ureter. UTUC is relatively rare, accounting for only 5–10% of urothelial carcinoma (1, 2). Currently, the standard treatment of non-metastatic UTUC remains radical nephroureterectomy (RNU) with bladder cuff excision. However, approximately 60% of patients with UTUC are invasive at diagnosis, and the prognosis is poor (3). Previous studies show that the 5-year specific survival is < 50% for UTUC patients with pT2 or pT3 and < 10% for pT4 (2). Some preoperative and postoperative factors, such as tumor stage, tumor grade, tumor size, and lymph node involvement, were suggested to predict prognosis in UTUC (4). Nonetheless, not every UTUC patient can receive surgical treatment or undergo radical surgery (5). Thus, the potential pretreatment prognostic marker is particularly important in UTUC.

The prognostic nutritional index (PNI) was originally described by Onodera et al. (6), which were calculated by serum albumin levels and peripheral lymphocyte count (7). PNI is a simple and easily accessible index used to evaluate the perioperative immune and nutritional status and risk of post-operative complications (8). Research has shown that PNI has been validated as an independent prognostic factor for various types of cancer (8–10).

Although some studies have been published, the role of PNI as a predictor of prognosis is still controversial in UTUC (7, 11). This study aims to evaluate whether the PNI may serve as an independent prognostic biomarker for patients with upper tract urothelial carcinoma, to assist clinicians in improving the prognosis of UTUC patients.

Materials and methods

Literature search and eligibility criteria

Based on the guidelines of Preferred Reporting Items for Systematic Reviews (12), we performed a systematic search to identify studies in PubMed, Embase, Scopus database, and Cochrane Library. The latest search time was April 2022. Search terms included: "upper tract urothelial cancer," "UTUC," "malignant tumor," "radical nephroureterectomy," "treatment," "surgical*," "prognostic nutritional index," "PNI," "predict*," "prognostic*," "factor," "indicators." Combine the above search fields with logical operators to get as many search results as possible. Besides, some research references were searched manually.

The inclusion and exclusion of the study were as follows: (1) Upper tract urothelial cancer was pathologically diagnosed, and there were no other types of malignant or metastatic cancer. (2) Before treatment, the prognostic nutritional index was calculated. (3) All the patients received surgical intervention: NU or RNU and did not receive other surgical treatment during the same period. (4) The researchers followed up with the patients for a certain period and were able to obtain at least one of the over survival (OS), cancer-specific survival (CSS), disease-specific survival (DSS), recurrence-free survival (RFS), progression-free survival (PFS), or disease-free survival (DFS). (5) The effects between the low PNI group and the high PNI group on the prognosis of surgical patients were evaluated, and the hazard ratio (HR) was presented in the study. (6) The design type of included study was retrospective or prospective. Letters, case reports, reviews, repeated studies, studies unrelated to the topic, animal experiments, and research without available data were excluded.

The process of identifying studies was completed independently by two authors (CM and LG). At the same time, data extraction and quality assessment were performed for the included studies. Negotiating between the two authors resolved the differences, and a consensus result was reached.

Quality evaluation

Based on the results of the identifying process, we used the NOS scale to assess the quality of included studies (13). The scale includes three question areas for selection, comparability, and exposure. The scale ranged from zero to nine stars, and studies with a score of six stars or more were considered high quality.

Data extraction

The researchers used the standard table to extract the following information from included studies: first author's name, publication year, region, study design, sample size, intervention, mean age, cutoff value, follow-up time, survival statistics, hazard ratio (HR) and 95% confidence intervals (95% CI).

Data analysis

Data analysis was done by using Stata version 16.0 (StataCorp LP, University City, Texas, United States). Using the HR and its 95% CI of the multivariate analysis in each study to assess the importance of the PNI score for the prognosis of UTUC patients. In the meta-analysis, when the effect index is HR, the risk ratio is usually taken as the logarithm as the effect value (14). Therefore, we enter commands in the Stata 16 software to find the logarithmic values of HR, the upper limit of HR's 95% CI, and the lower limit of HR's 95% CI, and then perform the meta-analysis. The others can be extracted directly from the original study without conversion. We performed

the Q test and χ^2 test to value the heterogeneity between the included literatures. If $I^2 > 50\%$, the differences between the studies are considered significant, and random effect models are used (15). In addition, a sensitivity analysis is also carried out on this basis (16). We did subgroup analyses for each survival statistic based on the cutoff value. Begg's test was used to test for publication bias between studies, and $P < 0.05$ was considered biased (17).

Results

Description of studies

By the search process, 214 studies were screened from the established database, and two studies were searched manually. Six studies, including seven cohorts, were eventually included in our meta-analysis (7, 11, 18–21). The detailed systematic search process is shown in **Figure 1**. The baseline data of the included studies are given in **Table 1**, including age, region, type of study design, sample size, surgical type, cutoff value, follow-up time, grouping, and survival outcomes. Six studies, including 2,324 patients, were published between 2015 and 2022. The included studies were all retrospective studies.

Quality assessment

According to the scoring rules of the NOS scale, we assessed the quality of the studies. The quality scores of the included studies are recorded in **Table 2**. The quality scores of all included studies are ≥ 6 stars and are considered high quality.

Survival outcomes

The relationship between over survival and prognostic nutritional index score

Five studies, including six cohorts, revealed the correlation between preoperative PNI score and OS (7, 11, 18, 20, 21). According to the results of the heterogeneity test, there was

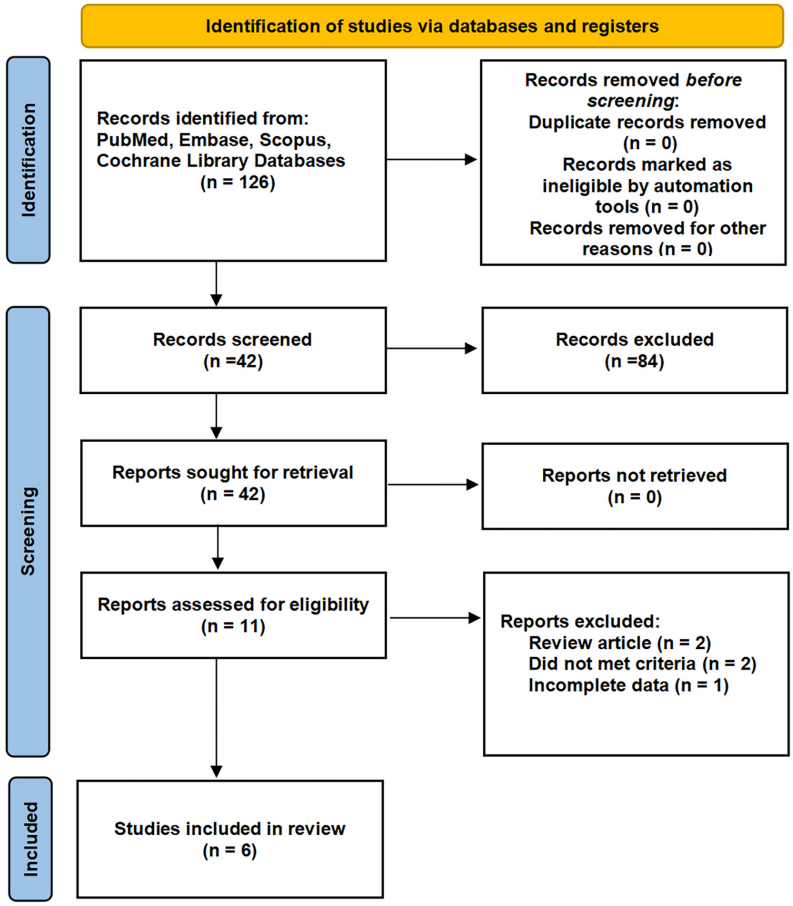


FIGURE 1
Flow diagram of the studies selection process.

TABLE 1 Baseline data for studies included in the meta-analysis.

Author, year	Region	Study design	Sample size	Intervention	Age[a]	Cutoff[b]	Follow-up time[c]	Group by cutoff	Survival outcomes
Kim et al. (19)	Korea	Retrospective	277	NU[d]	63.7 (29.5–90)	45	57.2 mon (6.8–158.3)	PNI <45 (n = 44) PNI ≥ 45 (n = 233)	DSS[f], DFS[g]
Huang et al. (20)	China	Retrospective	425	RNU[e]	65.9 ± 11.1	46.78	50 mon	PNI<46.78(n = 102) PNI ≥ 46.78(n = 323)	OS[h], CSS[i]
Xue et al. (21)	China	Retrospective	717	RNU	67	46.91	38.5 mon (23–62)	PNI<46.91(n = 298) PNI ≥ 46.91(n = 419)	OS, CSS, RFS[j]
Itami et al. (18)	Japan	Retrospective	125	RNU	72 (38–90)	50	51 mon (6–227)	PNI ≤ 50 (n = 60) PNI>50 (n = 65)	OS, DSS
Zheng et al. (11)	China	Retrospective	253	RNU	67.59 ± 10.49	47.83	33.8 mon (16.7–64.4)	PNI<47.83(n = 100) PNI ≥ 47.83(n = 153)	OS, CSS, RFS
Zheng et al. (11)	China	Retrospective	272	RNU	65.87 ± 10.35	47.83	44.6 mon (26.8–65.3)	PNI<47.83(n = 146) PNI ≥ 47.83(n = 126)	OS, CSS, RFS
Liu et al.(7)	China	Retrospective	255	RNU	69 ± 10.37	50.5	43.93 mon (19.30–82.77)	PNI<50.5 (n = 174) PNI ≥ 50.5 (n = 81)	OS, CSS, PFS[k]

[a]Age, Mean ± SD/Mean(Range)/Mean. [b]Cutoff, cutoff value of PNI score. [c]Follow-up time, Mean/Mean(Range)/Mean[Interquartile range]. [d]Nephroureterectomy. [e]Radical nephroureterectomy. [f]DSS, Disease-specific survival. [g]DFS, Disease-free survival. [h]OS, Over Survival. [i]CSS, Cancer-specific survival. [j]RFS, recurrence-free survival. [k]PFS, progression-free survival.

no heterogeneity among the studies (I^2 = 0%), and a fixed effects model was used to combine the effect size of each study. The outcomes of the meta-analysis demonstrated that lower preoperative PNI scores were associated with poorer OS (HR: 1.92; 95% CI 1.60 to 2.30; $P < 0.01$ Figure 2A).

The relationship between disease-free survival/recurrence-free survival/progression-free survival, and prognostic nutritional index score

A total of five eligible studies revealed the prognostic role of pre-treatment PNI score on DFS/RFS/PFS in patients with UTUC (7, 11, 19, 21). Since there was no heterogeneity among studies (I^2 = 0%), we used a fixed effects model to perform the meta-analysis. The ultimate result showed that the lower the preoperative PNI score of UTUC patients, the decreased their DFS/RFS/PFS (HR: 1.57; 95% CI 1.33 to 1.85; $P < 0.01$ Figure 2B).

The relationship between cancer-specific survival/disease-specific survival, and prognostic nutritional index score

Six studies, including seven cohorts, showed the correlation between preoperative PNI score and CSS/DSS (7, 11, 18–21). Given the heterogeneity test outcome (I^2 = 0%), we used the fixed effects model. Our results suggested that a lower level of preoperative PNI was associated with decreased CSS/DSS (HR: 1.79; 95% CI 1.49 to 2.16; $P < 0.01$ Figure 2C).

Subgroup analysis

Owing to the lack of sufficient data, subgroup analysis was only performed in terms of cutoff value. Stratified analysis by the size of cutoff value also showed that a low pre-treatment PNI score was associated with the worse OS, DFS/RFS/PFS, and CSS/DSS (Table 3).

Sensitivity analysis

Sensitivity analysis was performed by excluding one single study once a time and recalculating the effect size of the remaining part. It reflected the impact of the individual on the whole. The result of our sensitivity analysis showed that no single study significantly influenced the pooled HR and 95% CI. This meant that our results were stable (Figure 3).

Publication bias

In terms of OS or DFS/RFS/PFS or CSS/DSS, Publication bias was evaluated by Begg's test. The P values of them were all

TABLE 2 Quality evaluation of the eligible studies with Newcastle–Ottawa scale.

Study	Selection				Comparability		Exposure			Total points
	REC	SNEC	AE	DO	SC	AF	AO	FU	AFU	
Kim et al. (19)	-	*	*	-	*	*	*	*	*	7
Huang et al. (20)	*	*	*	*	*	-	*	-	-	6
Xue et al. (21)	*	*	*	*	*	-	*	-	*	7
Itami et al. (18)	*	*	*	*	*	-	*	-	-	6
Zheng et al. (11)	*	*	*	*	*	-	*	-	*	7
Zheng et al. (11)	*	*	*	*	*	-	*	-	*	7
Liu et al. (7)	*	*	*	*	*	-	*	-	*	7

REC representativeness of the cohort, SNEC selection of the none posed cohort, AE ascertainment of exposure, DO demonstration that outcome of interest was not present at start of study, SC study controls most important factors, AF study controls for other important factors, AO assessment of outcome, FU follow-up long enough for outcomes to occur, AFU adequacy of follow-up of cohort (≥ 80%). *Indicates criterion met, -indicates significant of criterion not met.

above 0.05, showing no significant publication bias was found (Figure 4). That is to say, the results of our meta-analysis were reliable based on the available articles.

Discussion

Although RNU was the standard treatment for UTUC, approximately one-third of UTUC patients who undergo surgery will experience early recurrence, and 80% of them will eventually die from UTUC (22). The current pre-operative prognostic indicters, such as c-reactive protein (23), fibrinogen (24), pre-treatment lymphocyte-monocyte ratio (25), and pre-treatment neutrophil-to-lymphocyte ratio (26), are helpful to the prediction of survival outcomes of UTUC patients, but it only focuses on inflammatory conditions. As is well-known, the nutritional status of tumor patients is closely related to their prognosis (27). Based on body mass index, serum albumin, and preoperative weight loss, Gregg et al. developed a simple model to predict 90-day mortality and 3-year OS in patients with bladder cancer (28). Moreover, a study conducted by Huang et al. (29) showed that decreased preoperative pre-albumin levels as an independent prognostic factor for CSS and OS in patients with UTUC.

Prognostic nutritional index (PNI) was a simple and accessible preoperative indicator that could provide a comprehensive and objective assessment of the inpatient's condition. Due to the particularity of the PNI score composition, it could reflect the body's protein metabolism and immune function, which were usually associated with the body's nutritional status and immune response. Several retrospective studies have reported that PNI may be one of the potential predictors of postoperative survival outcomes in UTUC patients (7, 18). Consequently, we performed a meta-analysis to evaluate the impact of PNI on the prognosis outcomes in UTUC patients after surgical treatment.

This meta-analysis provided an evidence-based medicine analysis of six published studies exploring the prognostic and survival indicators of PNI in patients with UTUC. Our results showed that low PNI scores are associated with worse OS, DFS/RFS/PFS, and CSS/DSS, which supported the PNI score as an independent prognostic biomarker for survival outcomes.

Increasing evidence shows that the presence of nutritional deficiencies and systematic inflammatory response might play an important position in the development and progress of human cancers (30). Albumin is the main component of serum proteins, reflecting the nutritional status of the human body to a certain extent. It could regulate inflammatory reaction and exert antioxidant effects against carcinogens (31). In addition, low albumin levels reflect nutritional deficiencies, which could lead to reduced immune function and poor anticancer response (32). Recently, studies have shown that preoperative low albumin is an independent predictor of poor prognosis in patients with malignant tumors (33, 34). A study involving 214 glioblastoma patients have shown that serum albumin levels correlated with OS (HR = 0.966; 95% CI 0.938 to 0.995, P = 0.023) (35). Another study indicated that compared with those with hypoalbuminemia, vulvar cancer patients with normal albumin levels had a longer 5-year OS (58.6 vs. 17.1%, P = 0.004) (36). Furthermore, albumin levels are related to the systemic inflammatory response (37). Previous studies have found that albumin synthesis was reduced with the release of tumor necrosis factor. Under inflammatory conditions, the increased permeability of the vascular endothelium leads to albumin escape (38). Ishizuka et al. found that the relationship between hypoalbuminemia and poor postoperative outcome in patients with colorectal cancer was associated with increased inflammation (39). These studies proved the vital role of serum albumin as a nutritional indicator in cancer and inflammation, which supported the conclusions of this meta-analysis.

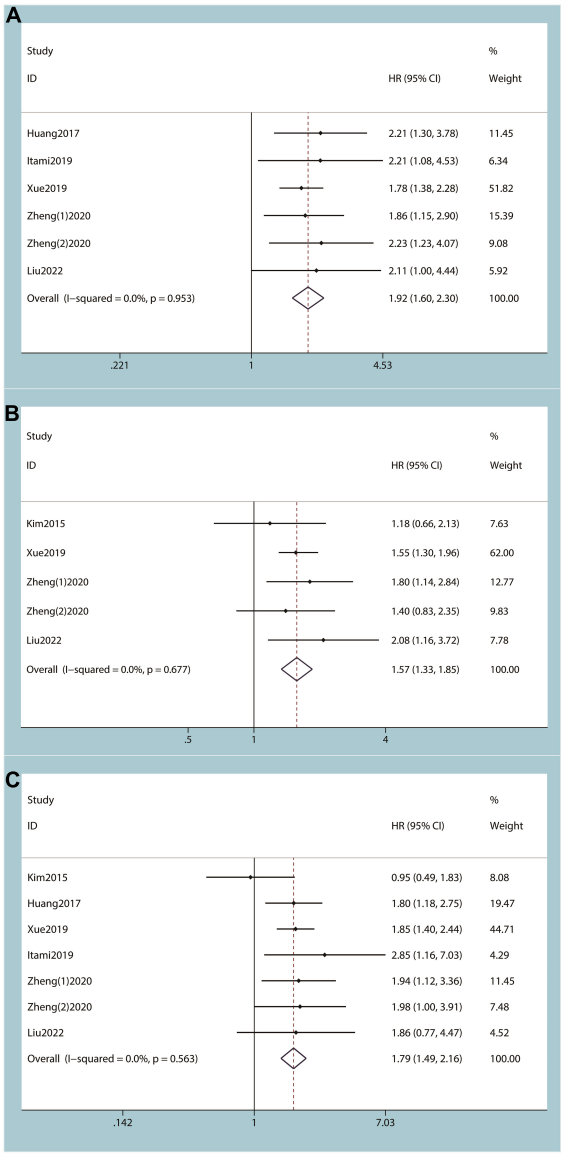


FIGURE 2
Forest plot and meta-analysis. **(A)** Forest plot and meta-analysis of the relationship between over survival (OS) and prognostic nutritional index (PNI) score. **(B)** Forest plot and meta-analysis of the relationship between disease-free survival/recurrence-free survival/progression-free survival, and prognostic nutritional index score. **(C)** Forest plot and meta-analysis of the relationship between cancer-specific survival/disease-specific survival, and prognostic nutritional index score.

TABLE 3 Subgroup analysis of survival outcomes.

Subgroup	Cutoff value	Included cohort	Effect model	HR (95%CI)	*P*	Heterogeneity	
						I^2(%)	P
OS							
Cut-off value	<47	2	fixed	1.85 (1.47, 2.32)	<0.01	0	0.464
	≥ 47	4	fixed	2.05 (1.52, 2.76)	<0.01	0	0.960
CSS/DSS							
Cut-off value	<47	3	fixed	1.70 (1.37, 2.12)	<0.01	0	0.176
	≥ 47	4	fixed	2.05 (1.44, 2.93)	<0.01	0	0.893
RFS/DFS/PFS							
Cut-off value	<47	2	fixed	1.51 (1.24, 1.83)	<0.01	0	0.392
	≥ 47	3	fixed	1.72 (1.28, 2.31)	<0.01	0	0.589

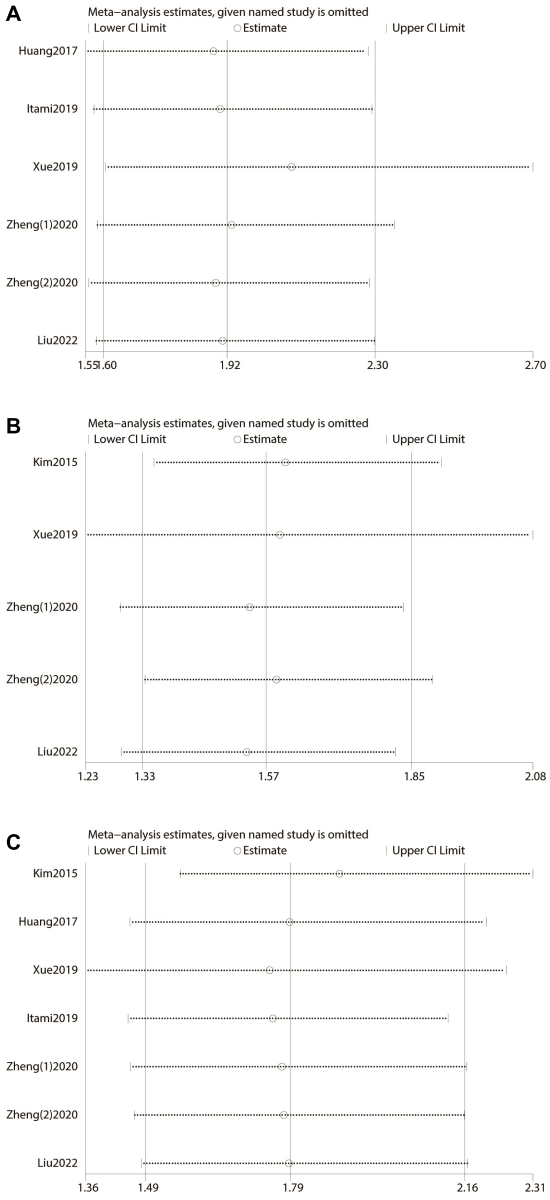


FIGURE 3
Forest plot and sensitivity analysis. **(A)** Forest plot and sensitivity analysis of the relationship between over survival (OS) and prognostic nutritional index (PNI) score. **(B)** Forest plot and sensitivity analysis of the relationship between disease-free survival/recurrence-free survival/progression-free survival, and prognostic nutritional index score. **(C)** Forest plot and sensitivity analysis of the relationship between cancer-specific survival/disease-specific survival, and prognostic nutritional index score.

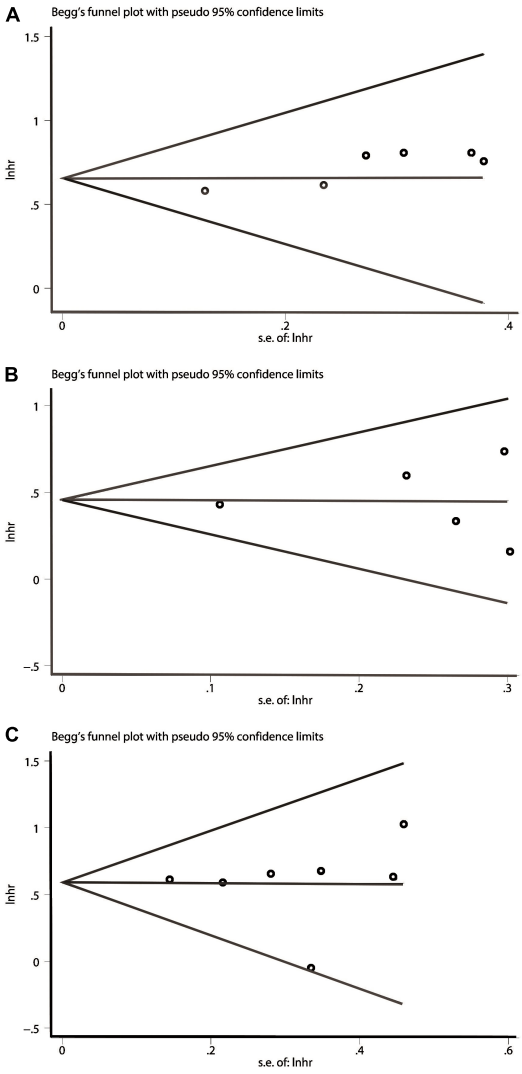


FIGURE 4
Begg's test for publication bias. **(A)** Over survival (OS). **(B)** Disease-free survival/recurrence-free survival/progression-free survival (DFS/RFS/PFS). **(C)** cancer-specific survival/disease-specific survival (CSS/DSS).

The relationship between inflammation and cancer was first described in the mid-19th century (40). In recent years, there has been increasing evidence of an association between inflammation, which is thought to be a pivotal event in the early development of cancer, and poor oncological prognosis (41, 42). Lymphocytes are common inflammatory cells in the tumor microenvironment and play an important anti-tumor effect in the immune system (42). In the advanced stage, tumor cells could destroy lymphocytes by editing proapoptotic ligands, and eventually achieve immune escape. In addition, the anti-tumor immune response mediated by $CD8^+$ T lymphocytes also has an important role in the treatment of tumors. However, it doesn't work endlessly. Some cancer-associated cells, such as fibroblasts, macrophages, and regulatory T cells, might produce an immune barrier to counteract the immune function of T cells, leading to a decrease in the number of T lymphocytes, tumor cell proliferation, and metastasis (43).

To our knowledge, this is the first meta-analysis to focus on the prognostic value of PNI in UTUC patients, and we followed PRISM guidelines strictly to perform this meta-analysis. However, some limitations cannot be avoided. First, the included studies are all retrospective studies, and the level of evidence is low. Second, the included studies are limited to East Asia, making the research results less universal. Third, due to the small number of studies available, not enough information is available to perform subgroup analysis to identify high-risk populations.

Conclusion

In conclusion, this meta-analysis revealed that the preoperative PNI is a potential independent biomarker of the postoperative prognosis of UTUC patients. A low PNI score predicts worse OS, DFS/RFS/PFS, and CSS/DSS in patients. Therefore, the clinician can individualize disease management for patients based on the PNI score for better treatment outcomes. This conclusion requires a larger sample size and a more rigorously designed prospective study to prove it.

Data availability statement

The original contributions presented in this study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YL conceived and designed the experiments. CM, LP, and KL analyzed the data. LG, KL, and JL contributed reagents, materials, and analysis. CM, LG, and FY wrote the manuscript. All authors have read and approved the final manuscript.

Funding

This study was supported by Sichuan Science and Technology Program under Grant number: 2020YFS0320.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Roupret M, Babjuk M, Burger M, Capoun O, Cohen D, Comperat EM, et al. European association of urology guidelines on upper urinary tract urothelial carcinoma: 2020 update. *Eur Urol.* (2021) 79:62–79. doi: 10.1016/j.eururo.2020.05.042

2. Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupret M, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. *Eur Urol.* (2012) 62:100–14. doi: 10.1016/j.eururo.2012.02.030

3. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration. *Cancer.* (2009) 115:1224–33. doi: 10.1002/cncr.24135

4. Soria F, Shariat SF, Lerner SP, Fritsche HM, Rink M, Kassouf W, et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). *World J Urol.* (2017) 35:379–87. doi: 10.1007/s00345-016-1928-x

5. Krabbe LM, Bagrodia A, Westerman ME, Gayed BA, Haddad AQ, Sagalowsky AI, et al. Molecular profile of urothelial carcinoma of the upper urinary tract: are pelvicalyceal and ureteral tumors different? *World J Urol.* (2016) 34:105–12. doi: 10.1007/s00345-015-1584-6

6. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. *Nihon Geka Gakkai Zasshi.* (1984) 85:1001–5.

7. Liu J, Wu P, Lai S, Song X, Wang M, Wang X, et al. Clinicopathological and prognostic significance of preoperative prognostic nutritional index in patients with upper urinary tract urothelial carcinoma. *Nutr Cancer.* (2022) 74:2964–74. doi: 10.1080/01635581.2022.2049829

8. Hu X, Wang YH, Lia T, Yang ZQ, Shao YX, Yang WX, et al. Prognostic value of preoperative prognostic nutritional index in patients with renal cell carcinoma after nephrectomy. *Clin Chim Acta.* (2020) 509:210–6. doi: 10.1016/j.cca.2020.06.025

9. Wang D, Hu X, Xiao L, Long G, Yao L, Wang Z, et al. Prognostic nutritional index and systemic immune-inflammation index predict the prognosis of patients with HCC. *J Gastrointest Surg.* (2021) 25:421–7. doi: 10.1007/s11605-019-04492-7

10. Hayasaka K, Shiono S, Suzuki K, Endoh M, Okada Y. Postoperative prognostic nutritional index as a prognostic factor after non-small cell lung cancer surgery. *Gen Thorac Cardiovasc Surg.* (2020) 68:1163–71. doi: 10.1007/s11748-020-01366-7

11. Zheng Y, Yu D, Yu Z, Zhao D, Chen Y, Chen W, et al. Association of preoperative systemic immune-inflammation index and prognostic nutritional index with survival in patients with upper tract urothelial carcinoma. *J Cancer.* (2020) 11:5665–77. doi: 10.7150/jca.44915

12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71

13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z

14. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med.* (1998) 17:2815–34. doi: 10.1002/(sici)1097-0258(19981230)17:243.0.co;2-8

15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

16. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *Int J Epidemiol.* (2008) 37:1148–57. doi: 10.1093/ije/dyn065

17. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics.* (2018) 74:785–94. doi: 10.1111/biom.12817

18. Itami Y, Miyake M, Tatsumi Y, Gotoh D, Hori S, Morizawa Y, et al. Preoperative predictive factors focused on inflammation-, nutrition-, and muscle-status in patients with upper urinary tract urothelial carcinoma undergoing nephroureterectomy. *Int J Clin Oncol.* (2019) 24:533–45. doi: 10.1007/s10147-018-01381-y

19. Kim M, Moon KC, Choi WS, Jeong CW, Kwak C, Kim HH, et al. Prognostic value of systemic inflammatory responses in patients with upper urinary tract urothelial carcinoma. *World J Urol.* (2015) 33:1439–57. doi: 10.1007/s00345-015-1484-9

20. Huang J, Yuan Y, Wang Y, Chen Y, Kong W, Xue W, et al. Preoperative prognostic nutritional index is a significant predictor of survival in patients with localized upper tract urothelial carcinoma after radical nephroureterectomy. *Urol Oncol.* (2017) 35:.e1–671. doi: 10.1016/j.urolonc.2017.07.028

21. Xue W, Tan P, Xu H, Yang L, Wei Q. Impact of the preoperative prognostic nutritional index on survival outcomes in upper tract urothelial carcinomas. *Cancer Med.* (2019) 8:2971–8. doi: 10.1002/cam4.2161

22. Cha EK, Shariat SF, Kormaksson M, Novara G, Chromecki TF, Scherr DS, et al. Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. *Eur Urol.* (2012) 61:818–25. doi: 10.1016/j.eururo.2012.01.021

23. Luo Y, Fu SJ, She DL, Xiong HU, Yang LI. Preoperative C-reactive protein as a prognostic predictor for upper tract urothelial carcinoma: a systematic review and meta-analysis. *Mol Clin Oncol.* (2015) 3:924–8. doi: 10.3892/mco.2015.553

24. Pichler M, Dalpiaz O, Ehrlich GC, Stojakovic T, Martin Hernandez JM, Mannweiler S, et al. Validation of the preoperative plasma fibrinogen level as a prognostic factor in a European cohort of patients with localized upper tract urothelial carcinoma. *J Urol.* (2014) 191:920–5. doi: 10.1016/j.juro.2013.10.073

25. Luo Z, Jiao B, Huang T, Zhao H, Zhang G. What is the role of the preoperative blood-based inflammation biomarkers in the prognosis of upper tract urothelial carcinoma with radical nephroureterectomy? A single-centre retrospective study. *Technol Cancer Res Treat.* (2022) 21:15330338221095667. doi: 10.1177/15330338221095667

26. Vartolomei MD, Mathieu R, Margulis V, Karam JA, Roupret M, Lucca I, et al. Promising role of preoperative neutrophil-to-lymphocyte ratio in patients treated with radical nephroureterectomy. *World J Urol.* (2017) 35:121–30. doi: 10.1007/s00345-016-1848-9

27. Mbeutcha A, Roupret M, Kamat AM, Karakiewicz PI, Lawrentschuk N, Novara G, et al. Prognostic factors and predictive tools for upper tract urothelial carcinoma: a systematic review. *World J Urol.* (2017) 35:337–53. doi: 10.1007/s00345-016-1826-2

28. Gregg JR, Cookson MS, Phillips S, Salem S, Chang SS, Clark PE, et al. Effect of preoperative nutritional deficiency on mortality after radical cystectomy for bladder cancer. *J Urol.* (2011) 185:90–6. doi: 10.1016/j.juro.2010.09.021

29. Huang J, Wang Y, Yuan Y, Chen Y, Kong W, Chen H, et al. Preoperative serum pre-albumin as an independent prognostic indicator in patients with localized upper tract urothelial carcinoma after radical nephroureterectomy. *Oncotarget.* (2017) 8:36772–9. doi: 10.18632/oncotarget.13694

30. Tong T, Guan Y, Xiong H, Wang L, Pang J. A meta-analysis of glasgow prognostic score and modified glasgow prognostic score as biomarkers for predicting survival outcome in renal cell carcinoma. *Front Oncol.* (2020) 10:1541. doi: 10.3389/fonc.2020.01541

31. Arroyo V, Garcia-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol.* (2014) 61:396–407. doi: 10.1016/j.jhep.2014.04.012

32. Ahluwalia N. Aging, nutrition and immune function. *J Nutr Health Aging.* (2004) 8:2–6.

33. Liu M, Wang L. Prognostic significance of preoperative serum albumin, albumin-to-globulin ratio, and prognostic nutritional index for patients with glioma: a meta-analysis. *Medicine (Baltimore).* (2020) 99:e20927. doi: 10.1097/MD.0000000000020927

34. Omura S, Taguchi S, Miyagawa S, Matsumoto R, Samejima M, Ninomiya N, et al. Prognostic significance of the albumin-to-globulin ratio for upper tract urothelial carcinoma. *BMC Urol.* (2020) 20:133. doi: 10.1186/s12894-020-00700-8

35. Han S, Huang Y, Li Z, Hou H, Wu A. The prognostic role of preoperative serum albumin levels in glioblastoma patients. *BMC Cancer.* (2015) 15:108. doi: 10.1186/s12885-015-1125-0

36. Bekos C, Polterauer S, Seebacher V, Bartl T, Joura E, Reinthaller A, et al. Pre-operative hypoalbuminemia is associated with complication rate and overall survival in patients with vulvar cancer undergoing surgery. *Arch Gynecol Obstet.* (2019) 300:1015–22. doi: 10.1007/s00404-019-05278-7

37. Almasaudi AS, Dolan RD, Edwards CA, McMillan DC. Hypoalbuminemia reflects nutritional risk, body composition and systemic inflammation and is independently associated with survival in patients with colorectal cancer. *Cancers (Basel).* (2020) 12:1986. doi: 10.3390/cancers12071986

38. Kim S, McClave SA, Martindale RG, Miller KR, Hurt RT. Hypoalbuminemia and clinical outcomes: what is the mechanism behind the relationship? *Am Surg.* (2017) 83:1220–7. doi: 10.1177/000313481708301123

39. Ishizuka M, Nagata H, Takagi K, Horie T, Kubota K. Inflammation-based prognostic score is a novel predictor of postoperative outcome in patients with colorectal cancer. *Ann Surg.* (2007) 246:1047–51. doi: 10.1097/SLA.0b013e3181454171

40. Balkwill F, Mantovani A. Inflammation and cancer: back to virchow? *Lancet.* (2001) 357:539–45. doi: 10.1016/S0140-6736(00)04046-0

41. Kim J, Bae JS. Tumor-associated macrophages and neutrophils in tumor microenvironment. *Mediators Inflamm.* (2016) 2016:6058147. doi: 10.1155/2016/6058147

42. Sung HH, Jeon HG, Jeong BC, Seo SI, Jeon SS, Choi HY, et al. Clinical significance of prognosis using the neutrophil-lymphocyte ratio and erythrocyte sedimentation rate in patients undergoing radical nephroureterectomy for upper urinary tract urothelial carcinoma. *BJU Int.* (2015) 115:587–94. doi: 10.1111/bju.12846

43. Farhood B, Najafi M, Mortezaee K. CD8(+) cytotoxic T lymphocytes in cancer immunotherapy: a review. *J Cell Physiol.* (2019) 234:8509–21. doi: 10.1002/jcp.27782

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 30 September 2022
DOI 10.3389/fnut.2022.995295

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Médéa Locquet,
Institut de Radioprotection et de Sûreté Nucléaire, France
Chengyu Liu,
Beijing Hospital, Peking University, China

*CORRESPONDENCE
Weiteng Zhang
jyzwt545@126.com
Xian Shen
shenxian5166@gmail.com
Xiaodong Chen
15167797063@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 15 July 2022
ACCEPTED 14 September 2022
PUBLISHED 30 September 2022

CITATION
Cai W, Yang H, Zheng J, Huang J, Ji W, Lu Y, Yang X, Zhang W, Shen X and Chen X (2022) Global leaders malnutrition initiative-defined malnutrition affects long-term survival of different subgroups of patients with gastric cancer: A propensity score-matched analysis. *Front. Nutr.* 9:995295. doi: 10.3389/fnut.2022.995295

Global leaders malnutrition initiative-defined malnutrition affects long-term survival of different subgroups of patients with gastric cancer: A propensity score-matched analysis

Wentao Cai[1,2†], Hui Yang[2†], Jingwei Zheng[2†], Jianqiang Huang[2], Weiping Ji[2], Yangbin Lu[2], Xinxin Yang[1], Weiteng Zhang[1*], Xian Shen[1,2*] and Xiaodong Chen[1*]

[1]Department of Gastrointestinal Surgery, The First Affiliated Hospital, Wenzhou Medical University, Wenzhou, China, [2]Department of Gastrointestinal Surgery, The Second Affiliated Hospital, Wenzhou Medical University, Wenzhou, China

As defined by the Global Leaders Malnutrition Initiative (GLIM), malnutrition is strongly associated with a lower quality of life and poor prognosis in gastric cancer patients. However, few studies have precisely explored the predictors of malnutrition, as defined by the GLIM, for overall survival (OS) after gastric cancer surgery in subgroups of patients stratified according to population characteristics. Our research aimed to analyze whether the predictors of malnutrition defined by the GLIM for postoperative OS in gastric cancer patients differ across subgroups. Patients who underwent radical gastric cancer surgery at our center between July 2014 and February 2019 were included in the study. Propensity score matching (PSM) was used to minimize bias. The study population was divided into malnourished and normal groups based on whether they were malnourished as defined by the GLIM. Univariate and multivariate analyses were performed to identify the risk factors affecting OS. The Kaplan–Meier curve and log-rank test were performed to determine the survival rate difference between subgroups. Overall, 1,007 patients were enrolled in the research. Multivariate analysis showed that malnutrition among the patients was 33.47%. Additionally, GLIM-defined malnutrition was an independent risk factor [hazard ratio (HR): 1.429, $P = 0.001$] for a shorter OS in gastric cancer patients. Furthermore, subgroup analysis showed that the GLIM was more appropriate for predicting OS in older aged patients (≥65 years), females, those with comorbidities (Charlson comorbidity index ≥ 2), and those with advanced gastric cancer (TNM stage = 3). GLIM-defined malnutrition

affects the long-term survival of gastric cancer patients, especially older patients, females, patients with comorbidities, and patients with advanced gastric cancer.

KEYWORDS

GLIM, gastric cancer, overall survival, subgroups, malnutrition

Introduction

Gastric cancer has the fifth highest incidence among cancers and is the third most common cause of cancer-related death. Every year, at least 1 million new cases are diagnosed worldwide, most of which are in Asia, Eastern Europe, and South America (1). Currently, surgical resection remains the most effective treatment (2). Although gastric cancer incidence and mortality rates have decreased, the mortality rate still reaches 75% (3), which places a significant burden on the economy, society, and the patient's family. Hence, it is critical to anticipate and improve factors that reduce the survival rates of gastric cancer patients after surgery to improve outcomes. Malnutrition has been a major issue in international health care and is not only associated with a poor prognosis but also results in higher rates of infection and complications (4), prolonged hospital stays, and increased mortality (5, 6). Malnutrition is more prevalent in cancer patients, especially older age in some community hospitals (7); hence, its adverse effects result in more severe outcomes. Therefore, it is necessary to focus on the nutritional status of cancer patients (8). Previously, malnutrition awareness was low, resulting in improper management of malnutrition. Additionally, there was no general understanding of malnutrition's definition, prevalence, and identification (9). The Global Leadership Initiative in Malnutrition (GLIM) was successfully held in 2016 to define a consensus on malnutrition. It proposes a diagnostic criterion for malnutrition that can be adapted to different clinical settings, is simple to implement and has global expert consensus. The result of the meeting is a two-step model for screening and assessment of malnutrition. Using these criteria, patients with malnutrition, especially the older aged, were found to have an increased risk of death during the community follow-up (10), affecting both the postoperative overall and disease-free survival in gastric cancer patients (11). However, no other research has reported GLIM-defined malnutrition's predictive capability in subgroups of populations with different characteristics. Hence, we aimed to investigate whether the predictive value of GLIM-defined malnutrition differs in subgroups of populations and whether this definition may more accurately predict the individual overall survival (OS) of gastric cancer patients.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; GLIM, Global Leaders Malnutrition Initiative; OS, overall survival; PSM, Propensity score matching; SMI, skeletal muscle index.

Materials and methods

Patients

The basic information of all patients who underwent radical gastrectomy in the First Affiliated Hospital of Wenzhou Medical University from July 2014 to February 2019 was collected retrospectively. The inclusion criteria were: (1) diagnosis of gastric adenocarcinoma confirmed by preoperative or postoperative pathology; (2) American Association of Anesthesiologists grade $\leq$ III; and (3) no distant metastasis. The exclusion criteria were: (1) patients who underwent palliative resection or emergency surgery; (2) patients who received chemotherapy before surgery; and (3) patients without basic clinical information or computed tomography (CT) data 1 month before surgery. All surgeries were performed by a single surgical team, thus avoiding possible bias caused by the effectiveness of surgical treatment. The research was performed in compliance with the Declaration of Helsinki. Ethical approval was obtained from the First Affiliated Hospital, Wenzhou Medical University. All participants provided written informed consent.

Skeletal muscle index assessment

We used the image processing system (GE ADW 4.5) to process the patient's CT images within the first month before surgery. We adjusted the Hounsfield unit threshold to -29 to +150 to differentiate skeletal muscle from other tissues. Then a trained investigator manually outlined the area of skeletal muscle at the third lumbar spine (L3) level, which includes the psoas major, erector spinae, quadratus lumborum, oblique abdominis, external and internal oblique muscles, and rectus abdominis. The outlined area of skeletal muscle at the L3 level normalized by height (m^2) was used to obtain the skeletal muscle mass index (SMI).

Global leaders malnutrition initiative assessment

As a two-step model for screening and diagnosing malnutrition, the first step of GLIM is to identify individuals who may be at potential risk of malnutrition through some internationally recognized malnutrition risk screening scales; here, we chose the Nutrition Risk Screening 2002 (12). The second step is to evaluate identified individuals and classify them according to their diagnosis and severity of malnutrition. The GLIM comprises phenotypic and etiological criteria. Malnutrition based on the GLIM must meet at least one phenotype combined with one etiological criterion. Phenotypic criteria include muscle mass loss, low BMI, and non-volitional weight loss. Etiological criteria include the reduction of food intake or assimilation, disease burden, or inflammation. Our target population comprised patients with gastric cancer. As cancer already meets the etiological standard of disease burden, malnutrition can be diagnosed as long as they meet a phenotypic criterion. Non-volitional weight loss is weight loss >5% within half a year or >10% beyond half a year. Low BMI is a BMI <20 and <18.5 kg/m^2 for patients ≥70 and <70 years old, respectively (12). We chose the SMI of the L3 level as an index to assess muscle mass. According to our previous research, the critical value of SMI is 34.9 cm^2/m^2; for males, the value is 40.8 cm^2/m^2 (13). Therefore, a diagnosis of malnutrition can be made if our patients meet any of the above phenotypic criteria.

TABLE 1 Patient baseline characteristics.

Factors	Malnutrition (n = 337)	Normal (n = 670)	P
Sex			0.008*
Female	107 (31.80%)	160 (23.90%)	
Male	230 (68.20%)	510 (76.10%)	
Age, years			0.001*
<65	131 (38.90%)	332 (49.60%)	
≥65	206 (61.10%)	338 (50.40%)	
Hypoalbuminemia			<0.001*
No	221 (65.60%)	537 (80.10%)	
Yes	116 (34.40%)	133 (19.90%)	
Charlson comorbidity index			0.447
≤1	286 (84.90%)	556 (83.00%)	
≥2	51 (15.10%)	114 (17.00%)	
Operation method			<0.001*
Open	243 (72.10%)	408 (60.90%)	
Laparoscopy	94 (27.90%)	262 (39.10%)	
Type of resection			0.102
Subtotal gastrectomy	199 (59.10%)	431 (64.30%)	
Total gastrectomy	138 (40.90%)	239 (35.70%)	
Differentiation			<0.001*
High/Middle	79 (23.40%)	236 (35.20%)	
Low	258 (76.60%)	434 (64.80%)	
TNM stage			<0.001*
	62 (18.40%)	286 (42.70%)	
	82 (24.30%)	135 (20.10%)	
	193 (57.30%)	249 (37.20%)	
Length of hospitalization	14.00 (8)	13.00 (6)	0.004*
Hospitalization costs	63166.13 (23444.79)	57010.58 (20629.87)	<0.001*

*Statistically significant (P < 0.05, two-tailed).

Data collection

We retrospectively collected the clinical information of all patients who met the inclusion criteria in this study. The clinical data were divided into three categories: (1) basic clinical information before the operation, including age, sex, BMI, recent weight loss, preoperative CT images, serum albumin concentration (<35 g/L is considered hypoalbuminemia), American Society of Anesthesiologists grade, and Charlson comorbidity index (CCI); (2) surgery and tumor-related data, including operation method, type of resection, tumor differentiation, and TNM stage; and (3) postoperative clinical outcomes, including length of hospitalization, hospitalization costs, postoperative survival condition, and postoperative survival time. Experienced physicians obtained postoperative survival outcomes over the phone or on an outpatient basis. Telephone follow-ups were conducted every 3 months. Five years of follow-up or the patient's death were considered the end of follow-up.

Statistical analysis

Propensity score matching (PSM) was performed to reduce differences in clinical information between the GLIM-defined malnutrition group and the normal group. The matched factors differed between the two groups and affected the OS of patients (statistically significant factors in univariate regression analysis). We selected age, sex, hypoalbuminemia, operation method, differentiation, and TNM stage as matching factors to construct the PSM model based on the preliminary statistical results. We used a 1:2 ratio for matching with a matching precision of 0.05. All normally distributed continuous variables are expressed as a mean and standard deviation. Otherwise, they are expressed as median and interquartile ranges. The independent sample t-test and chi-square test (or Fisher's exact test) were used to analyze the differences between continuous variables and classify variables between the two groups. The Kaplan–Meier curve and log-rank test were used to determine the survival difference between the groups. The proportional

hazards model was used to determine the risk factors affecting survival. Factors that were statistically significant in the univariate analysis were included in the multivariate analysis to identify independent risk factors affecting the OS of patients. A double-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA).

Results

Patients

From July 2014 to February 2019, 1,007 eligible patients were enrolled. As shown in Table 1, there were 337 patients in the GLIM-defined malnutrition group and 670 patients in the normal group, with a malnutrition rate of 33.5%. For the

TABLE 2 Univariate and multivariate Cox regression analysis of factors associated with overall.

	Univariate analysis		Multivariate analysis	
Factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, years				
<65	Ref		Ref	
≥65	1.831 (1478–2.268)	<0.001*	1.726 (1.385–2.151)	<0.001*
SEX				
Female	Ref			
Male	1.274 (0.999–1.625)	0.051		
BMI				
Normal	Ref			
Low	1.859 (1.475–2.342)	<0.001*		
Weight loss				
No	Ref			
yes	2.064 (1.657–2.572)	<0.001*		
SMI				
Normal	Ref			
Low	1.718 (1.352–2.184)	<0.001*		
Malnutrition				
Normal	Ref		Ref	
Defined by GLIM	2.085 (1.699–2.559)	<0.001*	1.429 (1.159–1.762)	0.001*
Charlson comordity index				
≤1	Ref			
≥2	1.090 (0.831–1.429)	0.534		
Hypoalbuminemia				
No	Ref		Ref	
Yes	1.868(1.508–2.314)	<0.001*	1.148 (0.920–1.433)	0.222
Operation method				
Open	Ref		Ref	
Laparoscopy	0.552 (0.435–0.700)	<0.001*	0.846 (0.664–1.079)	0.178
Type of resection				
Subtotal gastrectomy	Ref		Ref	
Total gastrectomy	2.034 (1.658–2.495)	<0.001*	1.450 (1.178–1.784)	< 0.001*
Differentiation				
High/middle	Ref		Ref	
Low	2.165 (1.678–2.794)	<0.001*	1.504 (1.160–1.951)	0.002*
TNM stage				
I	Ref		Ref	
II	2.934 (1.962–4.389)	<0.001*	2.162 (1.432–3.263)	<0.001*
III	8.071 (5.742–11.344)	<0.001*	5.738 (4.009–8.215)	<0.001*

*Statistically significant ($P < 0.05$, two-tailed).

TABLE 3 Patient baseline characteristics after PSM.

Factors	Malnutrition (n = 301)	Normal (n = 463)	P
Gender			0.065
Female	100 (33.20%)	125 (27.00%)	
Male	201 (66.80%)	338 (73.00%)	
Age, years			0.297
<65	125 (41.50%)	210 (45.40%)	
≥65	176 (58.50%)	253 (54.60%)	
Hypoalbuminemia			0.418
No	219 (72.80%)	349 (75.40%)	
Yes	82 (27.20%)	114 (24.60%)	
Charlson comorbidity index			0.505
≤1	257 (85.40%)	387 (83.60%)	
≥2	44 (14.60%)	76 (16.40%)	
Operation method			0.308
Open	214 (71.10%)	313 (67.60%)	
Laparoscopy	87 (28.90%)	150 (32.40%)	
Type of resection			0.763
Subtotal gastrectomy	182 (60.50%)	285 (61.60%)	
Total gastrectomy	119 (39.50%)	178 (38.40%)	
Differentiation			0.605
High/Middle	73 (24.30%)	120 (25.90%)	
Low	228 (75.70%)	343 (74.10%)	
TNM stage			0.294
I	62 (20.60%)	117 (25.30%)	
II	77 (25.60%)	118 (25.50%)	
III	162 (53.80%)	228 (49.20%)	
Length of hospitalization	14.00 (8)	13.00 (7)	0.178
Hospitalization costs	62890.34 (23048.06)	57249.26 (21104.70)	0.004*

*Statistically significant ($P < 0.05$, two sides).

population characteristics, the malnourished group had a higher proportion of women ($P = 0.008$), were older ($P < 0.001$), and had lower albumin levels ($P < 0.001$). For surgical selection and tumor information, the malnourished group preferred open surgery ($P < 0.001$), had less tumor differentiation ($P < 0.001$) and had a higher TNM stage ($P < 0.001$).

Univariate and multivariate analyses related to survival outcomes

Table 2 shows that in the univariate analysis, age, GLIM-defined malnutrition, hypoalbuminemia, laparoscopic surgery, total gastrectomy, tumor differentiation, and TNM stage all affected OS after surgery. As the three phenotypic criteria of GLIM, low BMI, weight loss and low SMI were also

TABLE 4 Univariate analysis of GLIM-defined malnutrition on overall survival in subgroups.

Sub-group	Univariate analysis	
	HR (95% CI)	P
Age, years		
<65	1.359 (0.944–1.957)	0.098
≥65	1.406 (1.071–1.845)	0.014*
Sex		
Female	3.055 (1.914–4.874)	<0.001*
Male	1.112 (0.861–1.435)	0.417
Charlson comorbidity index		
≤1	1.266 (0.996–1.610)	0.054
≥2	2.427 (1.436–4.105)	0.001*
TNM stage		
	1.410 (0.678–2.935)	0.358
	1.427 (0.862–2.361)	0.167
	1.336 (1.034–1.726)	0.026*

*Statistically significant ($P < 0.05$, two sides).

significantly associated with the survival of gastric patients. In the multivariate analysis, considering the large correlation between these three phenotypic criteria and GLIM, if they and GLIM were included in the multivariate analysis at the same time, it would cause unavoidable bias to the results, so we did not include them in the multivariate analysis, after adjusting for TNM stage, age, hypoalbuminemia, laparoscopic surgery, total gastrectomy, and tumor differentiation, GLIM-defined malnutrition was revealed to be an independent risk factor for postoperative OS [hazard ratio (HR): 1.429, $P = 0.001$]. Similarly, age (HR: 1.726, $P < 0.001$), total gastrectomy (HR: 1.450, $P < 0.001$), tumor differentiation (HR: 1.504, $P = 0.002$), and TNM stage (II/I HR: 2.162, $P < 0.001$; III/I HR: 5.738, $P < 0.001$) were independent risk factors for postoperative OS in gastric cancer patients.

Propensity score matching and subgroup analysis based on population characteristics

Matching factors were included as described previously. We selected age, sex, hypoalbuminemia, lumpectomy, tumor differentiation, and TNM stage as matching conditions, after matching, the total number of patients was reduced from 1007 to 764, including 301 in the malnutrition group and 463 in the normal group. There was no statistical discrepancy in the basic clinical information between the two groups, as shown in Table 3. After PSM, subgroup analyses showed that malnutrition defined by the GLIM had a better predictive capability for OS in gastric cancer patients in the following subgroups: aged ≥ 65 years (HR: 1.406, $P = 0.014$); females (HR: 3.055,

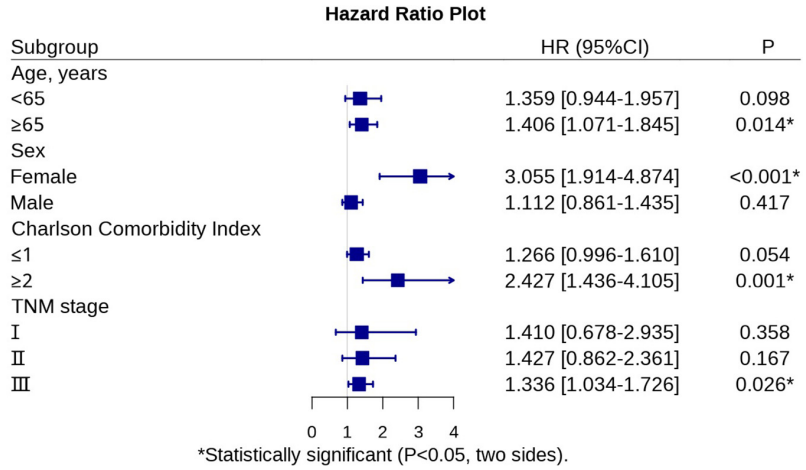


FIGURE 1
Hazrad ratio plot of subgroups analysis.

$P < 0.001$); CCI $\geq$ 2 (HR: 2.427, $P = 0.001$); and TNM stage 3 (HR: 1.336, $P = 0.026$) (Table 4). We have created Figure 1 to represent the subgroup analysis results clearly. Figure 2 show the differences in survival curves between the malnourished and normal groups in the different subgroups. Survival was lower in the malnourished group among those aged ≥65 years, whereas in those aged <65 years, there was no statistical discrepancy in survival between the two groups. Correspondingly, in females and those with a CCI ≥ 2 and TNM stage 3, survival was lower in the malnourished group than in the normal group, as shown in Table 4.

Discussion

Depending on the diagnostic criteria, the prevalence of GLIM-defined malnutrition ranged from 19 to 48.4% in different populations (14–16). In our study, 1,007 patients were enrolled, of which 337 (33.47%) were malnourished, as defined by the GLIM. Multivariate analysis in this study showed that malnutrition, defined by the GLIM, was an independent risk factor for OS in gastric cancer patients who underwent surgical treatment. Several studies have pointed out that malnutrition has a considerable negative effect on the OS of cancer patients. Zhang et al. showed that malnutrition, identified by comprehensive geriatric assessment, increased all-cause mortality in older patients diagnosed with solid tumors (6). Li et al. showed that, based on the midarm circumference or hand grip strength, severe malnutrition defined by the GLIM increases the risk of death in gastric cancer patients (17). Huang et al. pointed out that malnutrition, defined by GLIM based on the SMI obtained from abdominal CT images, affects the survival time of gastric cancer patients (18). All these results are consistent with ours. Therefore, identifying malnutrition and early nutritional intervention is critical to prolonging the survival of gastric cancer patients.

This study mainly aimed to explore the characteristics of populations suitable for GLIM assessment of malnutrition to predict OS more accurately. The differences in characteristics between the malnourished and normal groups converged after PSM, leading to more robust results after univariate analysis. In the subgroup analysis, malnutrition defined by the GLIM had a better predictive capability for OS in patients aged ≥65 years, females, patients with CCI ≥ 2, and patients with progressive gastric cancer (TNM stage = 3).

Age is an independent risk factor for the prognosis of patients with cancer, and this has been confirmed in many studies, a study by Xu et al. (19) found that age ≥70 years was an independent risk factor in postoperative gastric cancer patients. Of the patients included in this study, 61.10 and 50.40% of patients in the malnourished and normal groups were older (aged ≥65 years), indicating that this subgroup may be at greater risk for malnutrition. Rodríguez-Mañas et al. (20) also showed that malnourished people are often older and in worse physical condition. Therefore, older patients are at greater risk of malnutrition and have a poorer physiological profile. Hence, malnourishment before surgery is less likely to be corrected after surgery, resulting in shorter survival. In contrast, younger patients' overall nutritional and physiological status is better. Thus, even if malnutrition is diagnosed preoperatively, it can be corrected postoperatively with appropriate interventions. Therefore, preoperative malnutrition may not accurately predict postoperative OS in the younger population.

Keaver et al. noted that women with cancer are at a higher risk of malnutrition and are more likely to reach the clinical significance thresholds for quality-of-life subscales, such as physical functioning, fatigue, and pain, compared to men (21). Park et al. showed that female is an independent risk factor for

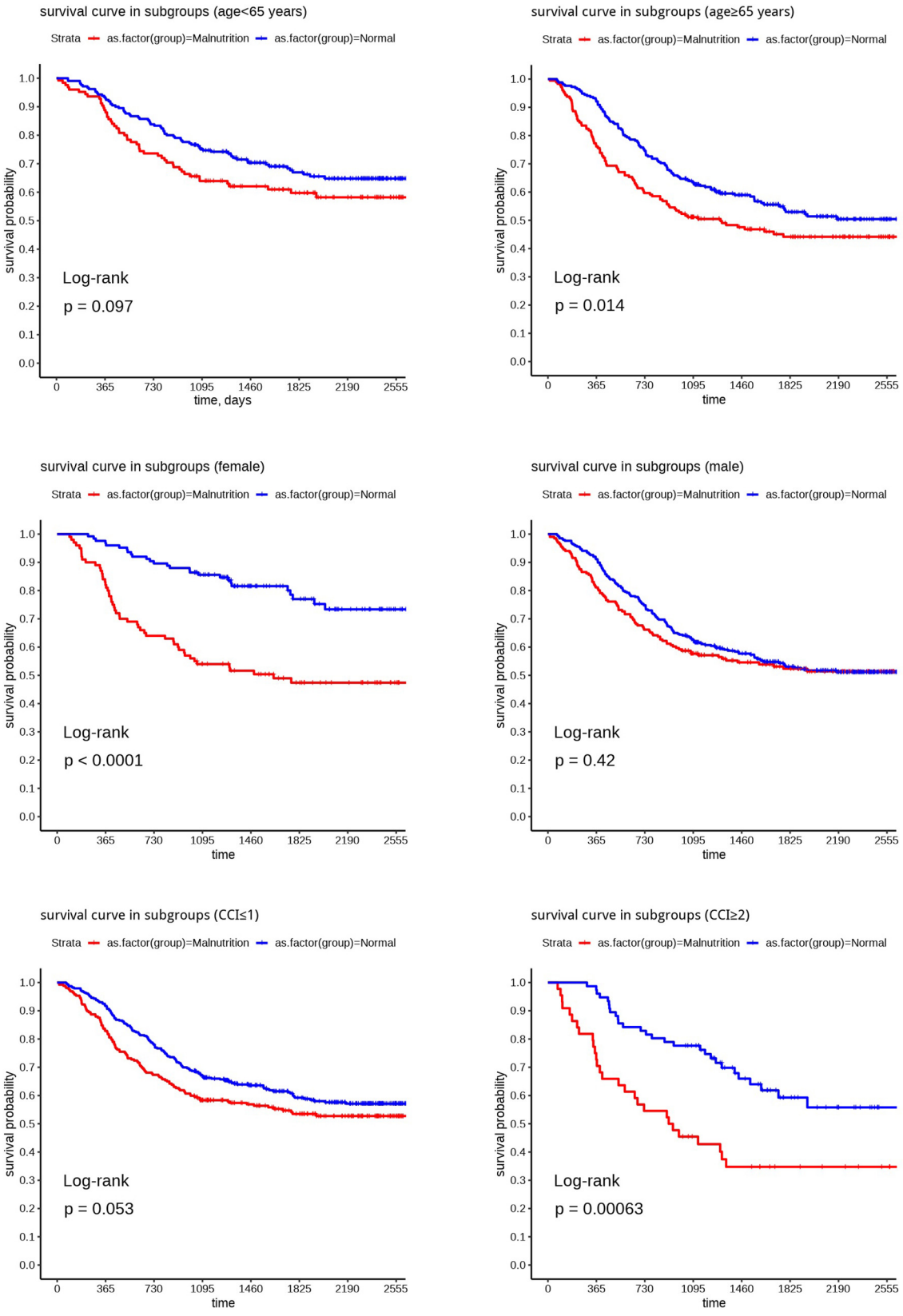


FIGURE 2
(Continued)

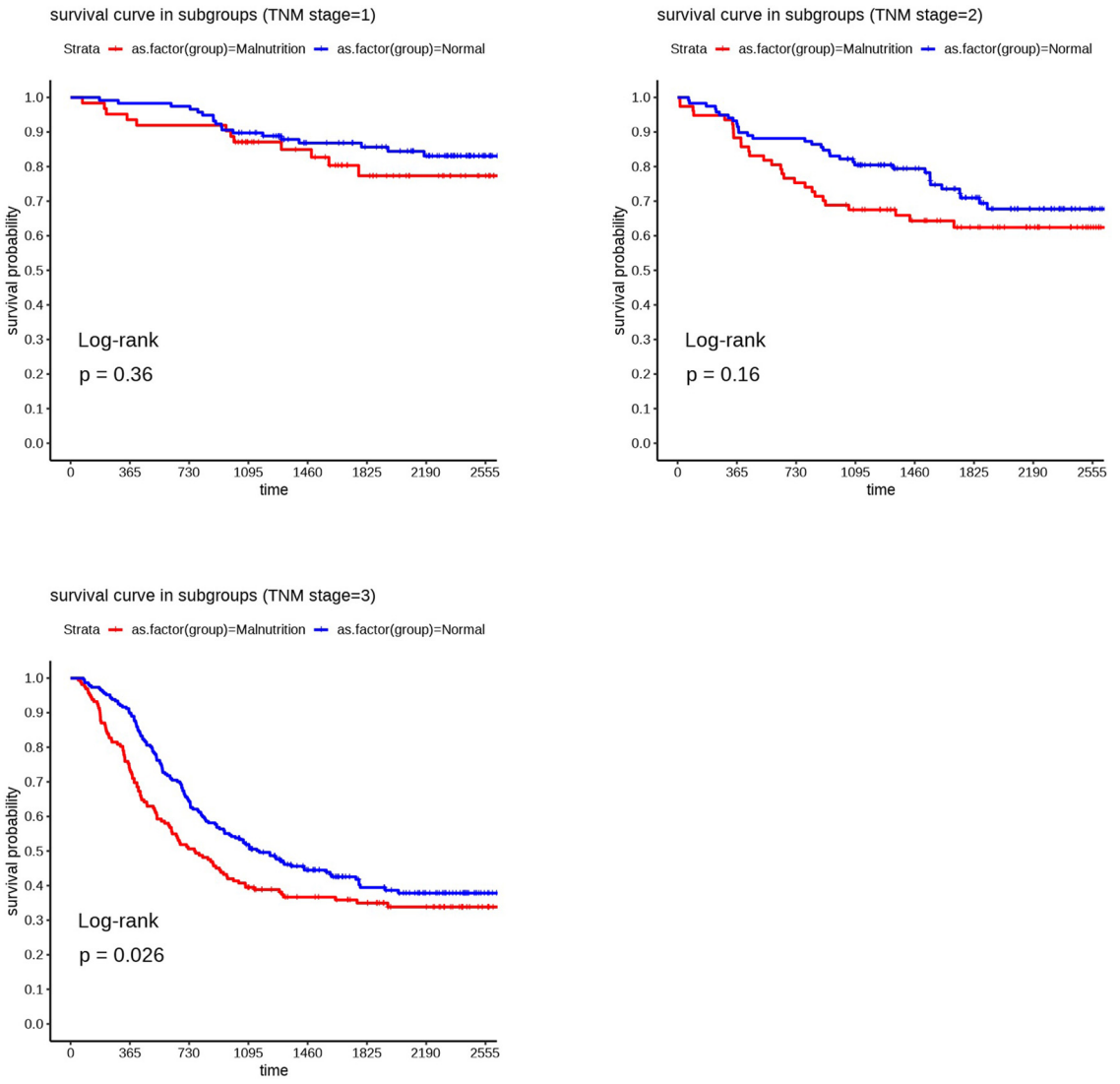


FIGURE 2
The Kaplan–Meier curve of subgroups.

malnutrition within 6 months after gastrectomy (22). Therefore, the susceptibility to malnutrition among female patients may make it difficult for clinicians to correct malnutrition after gastric cancer surgery, leading to the shorter survival of malnourished female patients.

The CCI is an objective quantification of comorbidity, and it has been shown that a CCI $\geq$ 2 shortened OS by 3 years in patients with esophageal cancer (23). In our research, we used an age-adjusted CCI, where patients with a CCI $\geq$ 2 and a higher risk of malnutrition (as defined by GLIM) exhibited low OS. However, the difference in survival between the malnourished and normal groups having a CCI $\leq$ 1 was not observed. The CCI consists of scores for circulatory disorders, digestive disorders, and other malignancies. We hypothesize that when malnutrition is combined with these disorders, it can cause severe damage to the patient's physiological metabolism and body functions, leading to an increased risk of death.

It is well known that the TNM stage significantly impacts the prognosis of patients; the higher the stage, the worse the survival (24). Our results showed that GLIM-defined malnutrition shortened the postoperative OS of gastric cancer patients beginning at TNM stage 3. Therefore, we hypothesize that the physical status, mental health, and overall quality of life of patients with advanced gastric cancer are reduced. Furthermore, the interaction between malnutrition and disease may lead to more pronounced physiological decline and accelerate tumor progression, further contributing to shorter OS in malnourished patients.

For the present, this study is the first to assess the difference in predictive value of malnutrition defined by GLIM for patient

OS across different subgroups of the population. However, the study has some limitations. Firstly, this is a retrospective study, and further prospective trials are needed to validate it in the future further. Secondly, all patients in this study were from the same center, which may result in selection bias. Finally, the cut-off values for muscle mass reduction defined in this study were derived from our previous large sample study. Whether this applies to other regional populations needs to be validated in further studies.

This study summarizes the differences in the effects of GLIM-defined malnutrition in different subgroups of the population. This can guide clinicians in treating gastric cancer patients, especially older women and those with comorbidities and advanced tumors. These patients may need to focus on preoperative and postoperative nutritional interventions to improve their malnutrition status as much as possible, thus effectively improving their long-term survival rate.

In conclusion, GLIM-defined malnutrition is an independent risk factor for OS in patients with gastric cancer. However, its predictive value is more advantageous in older patients, females, patients with comorbidities, and patients with advanced tumor stage.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

WZ, XS, and XC were main manuscript authors and had contributed substantially to the study's conception and design and gave final approval and revised the manuscript. HY, JH, YL, and JZ were involved in the data collection. XY and WJ were responsible for the data analysis and revision of the manuscript. WC wrote this manuscript. All authors have read and approved the final manuscript.

Funding

This work was supported by the Major scientific and technological project of medical and health in Zhejiang Province (NO. WKJ-ZJ-1806).

Acknowledgments

We sincerely thank all the medical staff of the Department of Gastrointestinal Surgery of the First Affiliated Hospital of Wenzhou Medical University for supporting this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660

2. Johnston FM, Beckman M. Updates on management of gastric cancer. *Curr Oncol Rep.* (2019) 21:67. doi: 10.1007/s11912-019-0820-4

3. Fock KM. Review article: the epidemiology and prevention of gastric cancer. *Aliment Pharmacol Ther.* (2014) 40:250–60. doi: 10.1111/apt.12814

4. Lou N, Chi CH, Chen XD, Zhou CJ, Wang SL, Zhuang CL, et al. Sarcopenia in overweight and obese patients is a predictive factor for postoperative complication in gastric cancer: a prospective study. *Eur J Surg Oncol.* (2017) 43:188–95. doi: 10.1016/j.ejso.2016.09.006

5. Neumayer LA, Smout RJ, Horn HG, Horn SD. Early and sufficient feeding reduces length of stay and charges in surgical patients. *J Surg Res.* (2001) 95:73–7. doi: 10.1006/jsre.2000.6047

6. Zhang X, Pang L, Sharma S, Li R, Nyitray A, Edwards B. Malnutrition and overall survival in older patients with cancer. *Clin Nutr.* (2021) 40:966–77. doi: 10.1016/j.clnu.2020.06.026

7. Kirkland L, Shaughnessy E. Recognition and prevention of nosocomial malnutrition: a review and a call to action! *Am J Med.* (2017) 130:1345–50. doi: 10.1016/j.amjmed.2017.07.034

8. Pressoir M, Desne S, Berchery D, Rossignol G, Poiree B, Meslier M, et al. Prevalence, risk factors and clinical implications of malnutrition in french comprehensive cancer centres. *Br J Cancer.* (2010) 102:966–71. doi: 10.1038/sj.bjc.6605578

9. Elia M. Defining, recognizing, and reporting malnutrition. *Int J Low Extrem Wounds.* (2017) 16:230–7. doi: 10.1177/1534734617733902

10. Yeung SSY, Chan JHY, Chan RSM, Sham A, Ho SC, Woo J. Predictive value of the GLIM criteria in chinese community-dwelling and institutionalized older adults aged 70 years and over. *J Nutr Health Aging.* (2021) 25:645–52. doi: 10.1007/s12603-021-1610-x

11. Huang D, Yu D, Wang W, Song H, Luo X, Wu G, et al. Global leadership initiative in malnutrition (GLIM) criteria using hand-grip strength adequately predicts postoperative complications and long-term survival in patients underwent radical gastrectomy for gastric cancer. *Eur J Clin Nutr.* (2022) 76:1323–31. doi: 10.1038/s41430-022-01109-2

12. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr.* (2019) 38:1–9. doi: 10.1016/j.clnu.2018.08.002

13. Zhuang C, Huang D, Pang W, Zhou C, Wang S, Lou N, et al. Sarcopenia is an independent predictor of severe postoperative complications and long-term survival after radical gastrectomy for gastric cancer: analysis from a large-scale cohort. *Medicine.* (2016) 95:e3164. doi: 10.1097/MD.0000000000003164

14. Allard JP, Keller H, Gramlich L, Jeejeebhoy KN, Laporte M, Duerksen DR. GLIM criteria has fair sensitivity and specificity for diagnosing malnutrition when using SGA as comparator. *Clin Nutr.* (2020) 39:2771–7. doi: 10.1016/j.clnu.2019.12.004

15. Zhang X, Tang M, Zhang Q, Zhang KP, Guo ZQ, Xu HX, et al. The GLIM criteria as an effective tool for nutrition assessment and survival prediction in older adult cancer patients. *Clin Nutr.* (2021) 40:1224–32. doi: 10.1016/j.clnu.2020.08.004

16. Kiss N, Steer B, de van der Schueren M, Loeliger J, Alizadehsani R, Edbrooke L, et al. Comparison of the prevalence of 21 GLIM phenotypic and etiologic criteria combinations and association with 30-day outcomes in people with cancer: a retrospective observational study. *Clin Nutr.* (2022) 41:1102–11. doi: 10.1016/j.clnu.2022.03.024

17. Li Q, Zhang X, Tang M, Song M, Zhang Q, Zhang K, et al. Different muscle mass indices of the global leadership initiative on malnutrition in diagnosing malnutrition and predicting survival of patients with gastric cancer. *Nutrition.* (2021) 89:111286. doi: 10.1016/j.nut.2021.111286

18. Huang DD, Yu DY, Song HN, Wang WB, Luo X, Wu GF, et al. The relationship between the GLIM-defined malnutrition, body composition and functional parameters, and clinical outcomes in elderly patients undergoing radical gastrectomy for gastric cancer. *Eur J Surg Oncol.* (2021) 47:2323–31. doi: 10.1016/j.ejso.2021.02.032

19. Xu L, Shi M, Huang Z, Zhang W, Zhang H, Shen X, et al. Impact of malnutrition diagnosed using global leadership initiative on malnutrition criteria on clinical outcomes of patients with gastric cancer. *JPEN J Parenter Enteral Nutr.* (2022) 46:385–94. doi: 10.1002/jpen.2127

20. Rodríguez-Mañas L, Rodríguez-Sánchez B, Carnicero J, Rueda R, García-Garcia F, Pereira S, et al. Impact of nutritional status according to GLIM criteria on the risk of incident frailty and mortality in community-dwelling older adults. *Clin Nutr.* (2021) 40:1192–8. doi: 10.1016/j.clnu.2020.07.032

21. Keaver L, O'Callaghan N, O'Sullivan A, Quinn L, Loftus A, McHugh C. Female cancer survivors are more likely to be at high risk of malnutrition and meet the threshold for clinical importance for a number of quality of life subscales. *J Hum Nutr Diet.* (2021) 34:868–80. doi: 10.1111/jhn.12877

22. Park J, Kim E, Seol E, Kong S, Park D, Yang H, et al. Prediction model for screening patients at risk of malnutrition after gastric cancer surgery. *Ann Surg Oncol.* (2021) 28:4471–81. doi: 10.1245/s10434-020-09559-3

23. Kubo Y, Tanaka K, Yamasaki M, Yamashita K, Makino T, Saito T, et al. Influences of the charlson comorbidity index and nutrition status on prognosis after esophageal cancer surgery. *Ann Surg Oncol.* (2021) 28:7173–82. doi: 10.1245/s10434-021-09779-1

24. Son T, Sun J, Choi S, Cho M, Kwon IG, Kim HI, et al. Multi-institutional validation of the 8th AJCC TNM staging system for gastric cancer: analysis of survival data from high-volume Eastern centers and the SEER database. *J Surg Oncol.* (2019) 120:676–84. doi: 10.1002/jso.25639

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 20 October 2022
DOI 10.3389/fnut.2022.983038

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Masaichi Ohira,
Osaka City University, Japan
Marcio F. Chedid,
Clinical Hospital of Porto Alegre, Brazil

*CORRESPONDENCE
Yong Yuan
yongyuan@scu.edu.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 30 June 2022
ACCEPTED 04 October 2022
PUBLISHED 20 October 2022

CITATION
Fang P, Yang Q, Zhou J, Yang Y, Luan S, Xiao X, Li X, Gu Y, Shang Q, Zhang H, Chen L, Zeng X and Yuan Y (2022) The impact of geriatric nutritional risk index on esophageal squamous cell carcinoma patients with neoadjuvant therapy followed by esophagectomy.
Front. Nutr. 9:983038.
doi: 10.3389/fnut.2022.983038

The impact of geriatric nutritional risk index on esophageal squamous cell carcinoma patients with neoadjuvant therapy followed by esophagectomy

Pinhao Fang[1†], Qian Yang[2†], Jianfeng Zhou[1†], Yushang Yang[1], Siyuan Luan[1], Xin Xiao[1], Xiaokun Li[1], Yimin Gu[1], Qixin Shang[1], Hanlu Zhang[1], Longqi Chen[1], Xiaoxi Zeng[3] and Yong Yuan[1*]

[1]Department of Thoracic Surgery, Med+X Center for Informatics, West China Hospital, Sichuan University, Chengdu, China, [2]Anesthesia Operation Center of West China Hospital, West China School of Nursing, Sichuan University, Chengdu, China, [3]Biomedical Big Data Center of West China Hospital, Med+X Center for Informatics, Sichuan University, Chengdu, China

Background: The Geriatric Nutritional Index (GNRI) has been indicated as a nutritional index which is highly associated with complications and mortality in older hospitalized patients. Moreover, early studies had suggested that GNRI is a potential prognostic indicator for some malignances. However, the prognostic value of GNRI in esophageal squamous cell carcinoma (ESCC) patients underwent neoadjuvant therapy followed by esophagectomy remains elusive.

Materials and methods: This retrospective study incorporated 373 patients with ESCC who had underwent neoadjuvant therapy followed by radical esophagectomy at West China Hospital of Sichuan University between April 2011 and September 2021. The GNRI formula was: 1.489 × albumin (g/dl) + 41.7 × current weight/ideal weight. Patients were classified as GNRI-low (GNRI < 98.7) or GNRI high (GNRI ≥ 98.7). The association between GNRI and clinical survival status were assessed utilizing Kaplan-Meier methods and Cox regression analysis.

Results: Three hundred and seventy three patients were retrospectively included in this study. 80 (21.5%) and 293 (78.5%) patients had been divided into the GNRI-low and GNRI-high groups respectively. Pathological T stage and the rate of nodal metastasis were significantly higher in the GNRI low group than in the GNRI high group ($P = 0.003$ and $P = 0.001$, respectively) among the examined demographic parameters. Furthermore, GNRI was significantly correlated with postoperative complications, patients with lower GNRI had a higher postoperative complication rate as compared with GNRI high group [Odds ratio: 2.023; 95% confidence interval (CI): 1.208–3.389; $P = 0.007$]. Univariate analysis of 5-year overall survival

(OS) and disease-free survival (DFS) found that the rate of survival was considerably lower in the GNRI-low group than in the GNRI-high group ($P < 0.001$). However, multivariate analysis demonstrated that GNRI was not an independent risk factor.

Conclusion: In patients with ESCC, low GNRI exhibited a poor nutritional indicator and related to postoperative complications after neoadjuvant therapy. Intensive follow-up after surgery should be performed for ESCC patients with low GNRI.

KEYWORDS

esophageal cancer, neoadjuvant therapy, geriatric nutritional risk index, postoperative complications, prognosis

Introduction

Esophageal carcinoma (EC) is one of the most aggressive malignant tumors and is also the world's sixth-leading cause of cancer-related death (1). Squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) are two main pathological types of EC, and ESCC is the most common pathological type. Surgical therapy plays a predominate role in EC treatment and the surgery types are mainly represented by the following: Ivor-Lewis, Mckeown, Sweet and transhiatal esophagectomy (2–4). Though the therapy of EC had advanced rapidly in recent decades (5), the overall 5-year survival rate of EC patients remained unsatisfactory. In patients with advanced localized EC, neoadjuvant therapies such as chemoradiotherapy could downstage the primary tumor and prolong the prognosis of EC patients after surgery (6). Nutritional evaluation and support are important parts during the whole management of cancer. Malnutrition is typically manifested as a low BMI which has been reported to associate with higher postoperative complications rate and a poor prognosis in individuals with benign or malignant diseases (7). Due to the invasive, malignant characteristics and of malignant digestive strictures of EC, patients with EC may experience dysphagia and progress into malnutrition (8).

As a novel nutritional evaluating index, geriatric nutritional index (GNRI) was first reported by Bouillanne et al. (9) in 2005. The exact value of GNRI could be easily calculated from serum albumin level and the ratio of normal body weight to ideal body weight, and GNRI was more closely connected with nutrition-related complications and deaths in older hospitalized patients than BMI and serum albumin level alone (8). Early studies had indicated that GNRI was a potential prognosis indicator in EC patients, and low GNRI could usually lead to reduce the quality of life (10). However, the effect of GNRI on postoperative outcomes in ESCC patients treated with neoadjuvant therapy followed by esophagectomy has not been well-studied. We hypothesized that GNRI was a better predictor of postoperative complications and a more independent prognostic factor in individuals receiving esophagectomy than a low BMI alone. As a result, this study was to investigate the impact of GNRI status on the prognosis for patients with ESCC.

Materials and methods

Study patients

All the ESCC patients included in had been treated with neoadjuvant therapy and followed by esophagectomy. The criteria for inclusion and exclusion were as follows: (1) patients were pathological diagnosed as ESCC; (2) patients had underwent esophagectomy resection; (3) patients had been treated with neoadjuvant therapy before esophagectomy; (4) patients had been followed-up enough time. Exclusion criteria were: (1) patients with distant tumor metastases; (2) patients treated with chemoradiotherapy after surgery; (3) patients underwent immunotherapy. Overall survival (OS) and disease-free survival (DFS) was selected as the duration from primary operation to death or tumor recurrence. Three hundred and seventy three patients pathologically diagnosed as ESCC underwent esophagectomy were included in this retrospective analysis at West China Hospital, Sichuan University.

Patient's therapy

Patients with locally advanced ESCC (T2-T4 or N1-3 M0) had received the neoadjuvant therapy before surgery according to the guideline (11). Neoadjuvant therapy was administered to patients in accordance with national recommendations. In general, the neoadjuvant chemotherapy regimen involved two cycles, with a 3 week break between each cycle. All

patients received paclitaxel (175 mg/m^2 body-surface area, D1) and cisplatin (75 mg/m^2 body-surface area, D1) intravenously over through the period of two cycles. As the aspect of neoadjuvant chemoradiotherapy regimen, all patients received a total radiation dosage of 40–50.4 Gy in 23–28 fractions (1.8–2.0 Gy/fraction), two cycles of the simultaneous chemotherapy drugs paclitaxel (175 mg/m^2 body-surface area, D1, q3w) and cisplatin (75 mg/m^2 body-surface area, D1, q3w). Intensity-modulated radiotherapy was used to provide radiation to all the patients. Surgery for surgical resection was carried out using the typical McKeown, Ivor-Lewis and Sweet methods 6–8 weeks following the end of neoadjuvant treatment. All patients had standard two-field (abdominal and thoracic) lymph node excision. Three-field lymph node dissection was not commonly used in the research, and cervical lymph node dissection was selected for patients with suspicious cervical lymph node metastases as determined by preoperative CT and ultrasound. Detailed surgical techniques have already been documented (9, 12). All patients in the research cohort were followed until death or September 2021, whichever occurred first. For the first 5 years after surgery, all patients had neck, abdomen, and thoracic computed tomography scans and biochemical blood tests every 4 months, as well as an endoscopy every year. Overall survival (OS) was calculated from the day of operation to September 2021 or until death was confirmed. Disease-free survival (DFS) was assessed from the day of surgery to the day of cancer recurrence, death, or September 2021.

Index calculation

The assessment of GNRI in all patients was performed during the period after neoadjuvant therapy and before esophagectomy. Based on the results from the X-tile program, the optimal cutoff points for overall survival were determined to be 98.7 (**Supplementary Figure 1**). The GNRI was calculated as follows: GNRI = 1.489 × albumin (g/dl) + 41.7 × usual weight/ideal weight. The Lorentz formula calculated ideal weight: ideal weight = 22 × height (m) × height (m). The total GNRI score was classified as no risk (GNRI ≥ 98.7) or risk (GNRI < 98.7) of malnutrition.

The Union for International Cancer Control TNM Classification of Malignant Tumors (8th edition) was used for pathological diagnosis and disease classification (13). The Clavien Dindo classification was used to assess the severity of postoperative complications (14). The postoperative complication was defined in this study as the presence of grade II complications according to the Clavien Dindo grading system (14). All the patient characteristics were collected from their medical and nursing records. The ethics committee of West China Hospital, Sichuan University, authorized this study. All patients gave their informed permission.

Statistics analysis

The Mann-Whitney's U test was used to compare continuous variables, whereas, the Fisher's exact test was used to compare categorical variables. The risk variables for postoperative complications were evaluated using logistic multivariate analysis. The Kaplan-Meier method was used to calculate OS and DFS within subgroups, and the log-rank test was applied to compare prognoses between groups. For univariate and multivariate analysis, the Cox proportional hazards model was utilized to identify independent prognostic indicators for OS and DFS. $P < 0.05$ represented statistical significance. For all statistical analyses, the SPSS software (version 26.0; SPSS) was utilized.

Results

Clinicopathological characteristics according to geriatric nutritional index

Three hundred and five males and 68 females met the inclusion criteria and were finally incorporated into analysis. The tumor was found in the middle thoracic esophagus in 61.7% (230/373) of the cases, while nodal metastasis was found in 35.4% (132/373) of the patients. Overall, all patients had neoadjuvant chemotherapy or chemoradiotherapy. The 5-year OS and DFS rates for the entire cohort were 66.6% and 58.5%, respectively.

The characteristics of patients stratified by GNRI risk are shown in **Table 1**. In summary, 80 (21.5%) and 293 (78.5%) patients were in the GNRI-low and GNRI-high group respectively. No statistically significant differences were found in age or gender between the two groups. BMI was significantly lower in the GNRI-low group than in the GNRI-high group ($P < 0.001$). The pathological T stage and rate of nodal metastasis in the GNRI-low group were markedly higher than in the GNRI-high group ($P = 0.003$ and $P = 0.001$, respectively).

Geriatric nutritional index and short- and long-term outcomes of curative surgery following neoadjuvant therapy

Figure 1 demonstrated both groups' Kaplan Meier curves for OS and DFS based on GNRI group. In summary, the 5-year OS and DFS rates in the GNRI-low group

TABLE 1 Patient characteristics and geriatric nutritional index (GNRI).

	Cases	GNRI		*P-value*
	(*n* = 373)	Low [*N* = 80] (21.5%)	High [*N* = 293] (78.5%)	
Sex				
Male	305	67 (83.3%)	238 (81.2%)	0.605
Female	68	13 (16.3%)	55 (18.8%)	
Age				
<60	149	25 (31.3%)	124 (42.3%)	0.073
≥60	224	55 (68.8%)	169 (57.7%)	
BMI				
<18.5	42	37 (46.3%)	5 (1.7%)	**<0.001**
≥18.5	331	43 (53.8%)	288 (98.3%)	
Localization				
Upper	45	11 (13.8%)	34 (11.6%)	0.313
Middle	230	44 (55.0%)	186 (63.5%)	
Lower	96	24 (30.0%)	72 (24.6%)	
Gastroesophageal junction	2	1 (1.3%)	1 (0.3%)	
Pathological T stage				
pT0, 1, 2	248	42 (52.5%)	206 (70.3%)	**0.003**
pT3, 4	125	38 (47.5%)	87 (29.7%)	
Pathological N stage				
N negative	241	39 (48.8%)	202 (68.9%)	**0.001**
N positive	132	41 (51.2%)	91 (31.1%)	
Differentiation grade				
Well	170	27 (33.8%)	143 (48.8%)	0.056
Moderated	94	24 (30.0%)	70 (23.9%)	
Poor	109	29 (36.2%)	80 (27.3%)	
Tumor length, cm				
<3	238	38 (47.5%)	200 (68.3%)	**0.001**
≥3	135	42 (52.5%)	93 (31.7%)	
Surgery type				
Sweet	16	5 (6.3%)	11 (3.8%)	0.527
Ivor-Lewis	228	49 (61.3%)	179 (61.1%)	
Mckeown	129	26 (32.5%)	103 (35.2%)	
Preoperative treatment				
Neoadjuvant chemoradiotherapy	296	62 (77.5%)	234 (79.9%)	0.643
Neoadjuvant chemotherapy	77	18 (22.5%)	59 (20.1%)	
TRS				
TRS = 0, 1	197	33 (41.3%)	164 (56.0%)	**0.019**
TRS = 2, 3	176	47 (58.8%)	129 (44.0%)	

BMI, body mass index; GNRI, geriatric nutritional index; TRS, tumor regression scoring. The bold values indicated the *P*-value lower than 0.05 with statistical differences.

were 52.3% and 46.7%, respectively, substantially lower than the GNRI-high group (70.5% and 61.7%, $P < 0.001$ and $P < 0.001$, respectively). Patients in the GNRI-low group had a higher 90-day mortality rate (8.8%) after surgery compared with those in GNRI-high group (2.0%, $P = 0.009$). Table 2 demonstrated the association between GNRI, another conventional nutritional index BMI and the correlated postoperative complication rate. The postoperative complications rate was significantly higher in the GNRI-low group than in the GNRI-high group. Except anastomotic leakage [14.3% (6/42) vs. 5.1% (17/331), $P = 0.020$], no significant differences were found in BMI between the two groups. Table 3 showed the results of logistic regression analysis used to investigate risk variables for postoperative complications. The univariate analyses results showed that GNRI was a risk factor of postoperative complications [Odds ratio (OR),

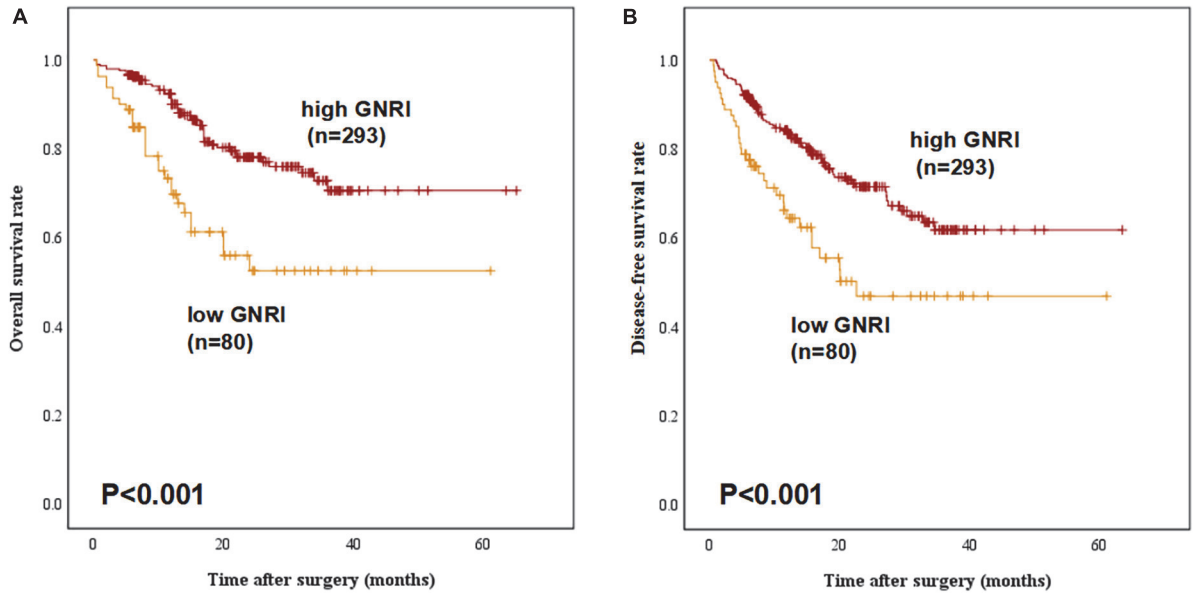


FIGURE 1
Overall survival and disease-free survival curves stratified by geriatric nutritional index (GNRI) status: **(A)** overall survival and **(B)** disease-free survival of all study patients ($n = 373$).

TABLE 2 Postoperative complications stratified by geriatric nutritional index (GNRI), the level of serum albumin, and body mass index (BMI) value.

	Cases ($n = 373$)	GNRI-low ($N = 80$)	GNRI-high ($N = 293$)	*P-value*
Lung complication	111	34 (42.5%)	77 (26.3%)	**0.005**
Anastomotic leakage	23	10 (12.5%)	13 (4.4%)	**0.008**
Pleural effusion	56	21 (26.3%)	35 (11.9%)	**0.002**
	Cases ($n = 373$)	**BMI-low ($N = 42$)**	**BMI-high ($N = 331$)**	***P-value***
Lung complication	111	17 (40.5%)	94 (28.4%)	0.107
Anastomotic leakage	23	6 (14.3%)	17 (5.1%)	**0.020**
Pleural effusion	56	9 (21.4%)	47 (14.2%)	0.217

BMI, body mass index; GNRI, geriatric nutritional index.

TABLE 3 Logistic regression analysis for clinical factors associated with complications after surgery.

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
Sex (male/female)	1.826 (0.968–3.446)	0.063	1.806 (0.952–3.426)	0.070
Age (≥60/<60)	1.441 (0.908–2.287)	0.121		
Smoke (yes/no)	0.901 (0.578–1.403)	0.643		
Coronary artery disease (present/absent)	1.076 (0.330–3.505)	0.904		
Hypertension (present/absent)	1.217 (0.654–2.263)	0.536		
Preoperative treatment (nCRT/nCT)	0.973 (0.573–1.713)	0.973		
BMI (low/high)	1.689 (0.873–3.270)	0.120		
GNRI (low/high)	2.037 (1.219–3.404)	**0.007**	2.023 (1.208–3.389)	**0.007**

BMI, body mass index; GNRI, geriatric nutritional index; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy. The bold values indicated the *P*-value lower than 0.05 with statistical differences.

2.037; 95% confidence interval (CI), 1.219–3.404; $P = 0.007$]. Additionally, the results of multivariate analysis demonstrated that GNRI was an independent predictor of postoperative complications (OR, 2.023; 95% confidence interval CI, 1.208–3.389; $P = 0.007$). However, BMI was proved not associated with the postoperative complications (OR, 1.689; 95% CI, 0.873–3.270; $P = 0.120$).

According to the univariate analysis, sex [Hazard ratio (HR), 2.686; 95% CI, 1.235–5.841; $P = 0.013$], tumor length (HR, 1.906; 95% CI, 1.219–2.981; $P = 0.005$), pT (HR, 2.830; 95% CI, 1.809–4.429; $P < 0.001$), pN (HR, 4.056; 95% CI, 2.549–6.455; $P < 0.001$), tumor differentiation grade (HR, 1.616; 95% CI, 1.243–2.100; $P < 0.001$), tumor regression scoring (TRS) (HR, 2.576; 95% CI, 1.601–4.147; $P < 0.001$), BMI (HR, 2.650; 95% CI, 1.547–4.540; $P < 0.001$) and GNRI (HR, 2.601; 95% CI, 1.635–4.137; $P < 0.001$) significantly affected the OS of ESCC patients (Table 4A). However, the multivariate analysis results showed that GNRI (HR, 1.678; 95% CI, 0.916–3.075; $P = 0.094$) or BMI (HR, 1.193; 95% CI, 0.575–2.474; $P = 0.636$) were not independent prognostic factor of OS (Table 4B).

Additionally, the univariate analysis also demonstrated that sex (HR, 2.025; 95% CI, 1.109–3.695; $P = 0.020$), tumor length (HR, 1.702; 95% CI, 1.160–2.497; $P = 0.007$), pT (HR, 2.737; 95% CI, 1.864–4.019; $P < 0.001$), pN (HR, 3.175; 95% CI, 2.151–4.687; $P < 0.001$), tumor differentiation grade (HR, 1.565; 95% CI, 1.250–1.961; $P < 0.001$), TRS (HR, 2.303; 95% CI, 1.543–3.438; $P < 0.001$), BMI (HR, 2.292; 95% CI, 1.407–3.733; $P = 0.001$) and GNRI (HR, 2.101; 95% CI, 1.390–3.175; $P < 0.001$) were significantly correlated with DFS of ESCC patients (Table 5A). Nevertheless, GNRI was indicated not to be an independent prognostic factor through multivariate analysis (HR, 1.438; 95% CI, 0.848–2.440; $P = 0.178$), and the results of multivariate analysis also demonstrated that lower BMI was not associated with poorer DFS (HR, 1.290; 95% CI, 0.681–2.446; $P = 0.435$), whereas pT (HR, 1.810; 95% CI, 1.008–3.252; $P = 0.047$) and pN (HR, 2.322; 95% CI, 1.524–3.538; $P < 0.001$) stage were proved to be independent prognosis factors (Table 5B).

TABLE 4A Univariate analysis of prognostic factors associated with overall survival.

Factors	Univariate analysis	
	HR (95% CI)	*P-value*
Sex (male/female)	2.686 (1.235–5.841)	**0.013**
Age (≥60/<60)	0.989 (0.630–1.554)	0.963
Tumor length (≥3/<3 cm)	1.906 (1.219–2.981)	**0.005**
Localization	0.849 (0.588–1.227)	0.384
pT stage	2.830 (1.809–4.429)	<**0.001**
pNstage	4.056 (2.549–6.455)	<**0.001**
Differentiation grade	1.616 (1.243–2.100)	<**0.001**
Preoperative treatment (nCRT/nCT)	1.184 (0.691–2.029)	0.539
TRS (2, 3/0, 1)	2.576 (1.601–4.147)	<**0.001**
BMI (<18.5/≥18.5)	2.650 (1.547–4.540)	<**0.001**
GNRI (low/high)	2.601 (1.635–4.137)	<**0.001**

TRS, tumor regression scoring; BMI, body mass index; GNRI, geriatric nutritional index; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy. The bold values indicated the *P*-value lower than 0.05 with statistical differences.

TABLE 4B Multivariate analysis of prognostic factors associated with overall survival.

Factors	Multivariate analysis	
	HR (95% CI)	*P-value*
Sex (male/female)	1.887 (0.854–4.167)	0.116
Tumor length (≥3/<3 cm)	1.384 (0.863–2.220)	0.177
pT stage	1.549 (0.784–3.057)	0.208
pN stage	2.791 (1.679–4.639)	<**0.001**
Differentiation grade	1.088 (0.745–1.589)	0.663
TRS (2,3/0,1)	0.973 (0.443–2.136)	0.945
BMI (<18.5/≥18.5)	1.193 (0.575–2.474)	0.636
GNRI (low/high)	1.678 (0.916–3.075)	0.094

TRS, tumor regression scoring; BMI, body mass index; GNRI, geriatric nutritional index. The bold values indicated the *P*-value lower than 0.05 with statistical differences.

Geriatric nutritional index is a prognostic indicator for esophageal squamous cell carcinoma patients with normal body mass index

A comparison of 5-year OS and DFS rates between the GNRI-high and GNRI-low groups that were stratified according to BMI revealed that only among patients with BMI ≥ 18.5, 5-year OS was significantly worse in the GNRI-low group than in the GNRI-high group (61.1% vs. 70.6%, $P = 0.027$). In contrast, no significant differences were noted between the two groups among patients with BMI < 18.5 (42.0% vs. 66.7%, $P = 0.207$) and no significant differences were found in DFS (Figure 2).

Geriatric nutritional index is a prognostic indicator for patients underwent various types of esophagectomy

In the group of different esophagectomy types, low-GNRI was proven to be a worse predictor for the OS ($P < 0.001$) and DFS ($P = 0.001$) in patients underwent Ivor-Lewis esophagectomy. In ESCC patients underwent

Mckeown esophagectomy, low-GNRI was demonstrated not associated with poorer OS ($P = 0.248$) nor DFS ($P = 0.387$) (Figure 3).

Geriatric nutritional index is a prognostic indicator of overall survival for patients underwent different preoperative treatments

In the subgroup of preoperative treatments, low-GNRI was proven to be a poorer predictor for the OS ($P < 0.001$) and DFS ($P = 0.001$) in ESCC patients underwent neoadjuvant chemoradiotherapy before esophagectomy. But in patients with neoadjuvant chemotherapy preoperatively, low-GNRI was proved not associated with worse OS ($P = 0.201$) nor DFS ($P = 0.238$) (Figure 4).

Discussion

Bouillanne et al. had first proposed using GNRI as a risk index to evaluate nutritional status in elderly patients. They had shown that GNRI is an objective and simple parameter which could be calculated through routine clinical measurement (9). In our study, we discovered that GNRI was an independent predictor of the postoperative complications in patients with ESCC treated with neoadjuvant therapy followed by esophagectomy. In EC patients, convention nutritional index such as BMI had been evaluated and was proved to associated with EC prognosis before. As a novel index to measure the nutritional level, GNRI is a simple objective nutritional evaluation score calculated through serum albumin levels and body weight. GNRI has been proven to have clinical relevance as a nutritional morbidity and mortality evaluation tool for older hospitalized patients, as well as those with cardiovascular disease (15), hemodialysis (16), and chronic renal failure (17). However, few investigations have explored the use of GNRI in cancer patients. According to Shoji et al. preoperative GNRI was a predictive factor in older patients with non-small cell lung cancer (18). Some studies have explored the correlation between GNRI and surgical outcomes in EC: Bo et al. found that GNRI was an independent predictive factor for OS in elderly EC patients who underwent radiotherapy (19). Furthermore, Kubo et al. proposed that GNRI was not an independent risk factor for developing pulmonary complications in patients with stage III ESCC but was strongly connected with long-term survival following curative surgery (20). These studies illustrated that preoperative nutritional level associated with the prognosis of patients after surgery and indicated that intervention might ameliorate malnutrition to improve the surgical outcomes of individuals with low GNRI. Few studies had been conducted to determine whether GNRI impacts complications and long-term prognosis in ESCC patients after neoadjuvant treatment. To our knowledge, among all studies investigating the prognostic value of GNRI in ESCC, the sample size in our study is the largest and we had also detected the impact of GNRI on the DFS to gain a more comprehensive understanding of GNRI on survival outcomes of ESCC patients. In addition, all the ESCC patients incorporated into analysis of our study had underwent neoadjuvant therapy and followed by surgery, which made the research patients in our study more specific and more targeted. Furthermore, we had also conducted subgroup analysis to investigate the prognostic value of GNRI in depth basing on the conventional nutritional index BMI, different surgery types and preoperative therapies.

By univariate analysis, there was a significant connection between low GNRI and poor survival in the current research.

TABLE 5A Univariate analysis of prognostic factors associated with disease-free survival.

Factors	Univariate analysis	
	HR (95% CI)	*P-value*
Sex (male/female)	2.025 (1.109–3.695)	**0.020**
Age (≥60/<60)	0.992 (0.672–1.464)	0.969
Tumor length (≥3/<3 cm)	1.702 (1.160–2.497)	**0.007**
Localization	0.867 (0.634–1.187)	0.374
pT stage	2.737 (1.864–4.019)	<**0.001**
pNstage	3.175 (2.151–4.687)	<**0.001**
Differentiation grade	1.565 (1.250–1.961)	<**0.001**
Preoperative treatment (nCRT/nCT)	1.067 (0.667–1.708)	0.786
TRS (2,3/0,1)	2.303 (1.543–3.438)	<**0.001**
BMI (<18.5/≥18.5)	2.292 (1.407–3.733)	**0.001**
GNRI (low/high)	2.101 (1.390–3.175)	<**0.001**

TRS, tumor regression scoring; BMI, body mass index; GNRI, geriatric nutritional index; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy. The bold values indicated the *P*-value lower than 0.05 with statistical differences.

TABLE 5B Multivariate analysis of prognostic factors associated with disease-free survival.

Factors	Multivariate analysis	
	HR (95% CI)	*P-value*
Sex (male/female)	1.500 (0.812–2.771)	0.195
Tumor length (≥3/<3 cm)	1.310 (0.875–1.960)	0.189
pT stage	1.810 (1.008–3.252)	**0.047**
pN stage	2.322 (1.524–3.538)	<**0.001**
Differentiation grade	1.109 (0.807–1.524)	0.525
TRS (2,3/0,1)	0.888 (0.457–1.724)	0.725
BMI (<18.5/≥18.5)	1.290 (0.681–2.446)	0.435
GNRI (low/high)	1.438 (0.848–2.440)	0.178

TRS, tumor regression scoring; BMI, body mass index; GNRI, geriatric nutritional index. The bold values indicated the *P*-value lower than 0.05 with statistical differences.

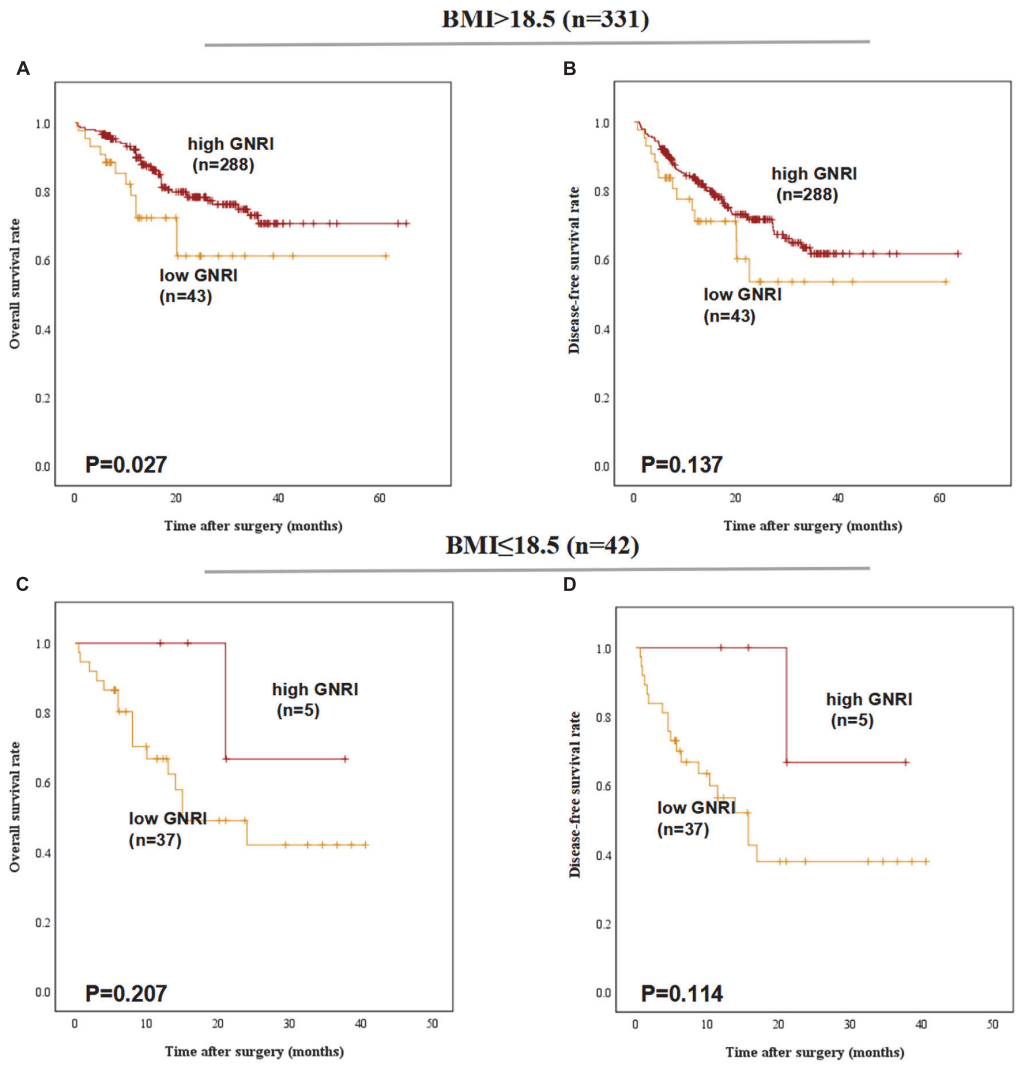


FIGURE 2
Postoperative outcomes of patients with high or low geriatric nutritional index (GNRI) according to BMI: **(A)** overall survival, **(B)** disease-free survival of BMI > 18.5 patients ($n = 331$), **(C)** overall survival, and **(D)** disease-free survival of BMI ≤ 18.5 patients ($n = 42$).

Especially in group of BMI higher than 18.5, patients with GNRI below 98.7 were related to a considerably higher likelihood of poorer OS than those patients with higher GNRI, which indicated that in EC patients with normal BMI, GNRI is a sensitive parameter to predict EC patients with or without better prognosis when treated with neoadjuvant therapy followed by esophagectomy. In multivariate analysis, however, GNRI was not an independent prognostic factor. Furthermore, the subgroup analysis basing on the surgery types showed that in patients underwent Ivor-Lewis esophagectomy, low-GNRI was a poor indicator for both OS and DFS. However, in the group of Mckeown esophagectomy, such significances were not detected. Jezerskyte et al. (21) had conducted a clinical research, the study results showed that EC patients underwent McKeown esophagectomy were more likely to have eating problems such as: vomit, appetite loss and dysphagia compared with those underwent Ivor-Lewis esophagectomy, which might partly account for such discrepancy among survival outcomes. For the 16 patients treated with Sweet esophagectomy, the sample size was too small to get a convincing conclusion, thus the subgroup analysis results need to be further verified by expanding the sample size, and more large-cohort and multi-center studies are needed better to assess the correlation between GNRI and postoperative survival. On the other hand, low-GNRI was shown to be a robust predictor of survival outcomes in patients treated by neoadjuvant chemoradiotherapy.

We evaluated the reliabilities of GNRI as a risk factor for postoperative complications compared with conventional nutritional index BMI. In short term, GNRI was an independent predictor of postoperative complication rate after neoadjuvant

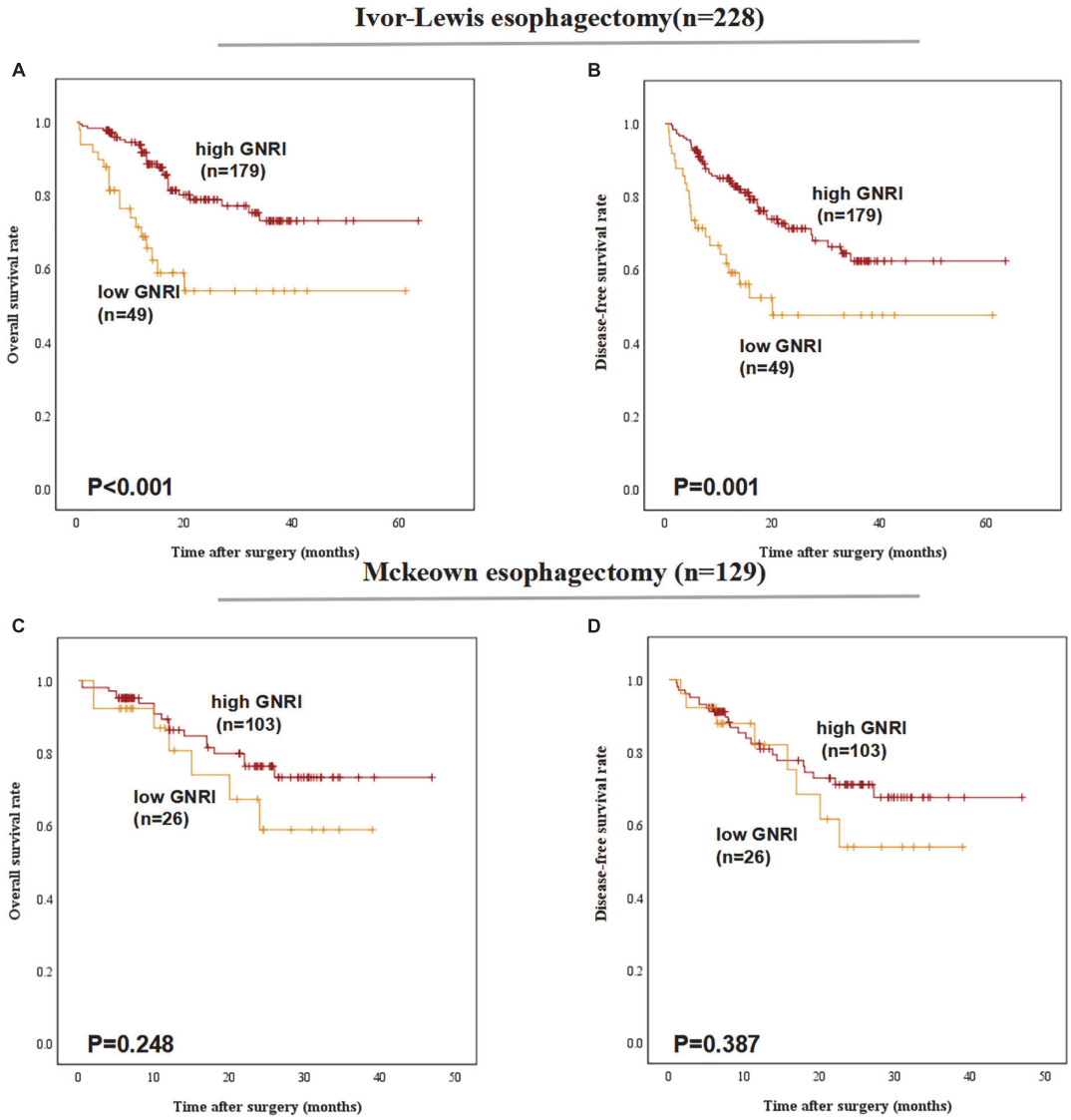


FIGURE 3
Postoperative outcomes of patients with high or low geriatric nutritional index (GNRI) basing on different surgery types: **(A)** overall survival, **(B)** disease-free survival of esophageal squamous cell carcinoma (ESCC) patients underwent Ivor-Lewis esophagectomy ($n = 228$), **(C)** overall survival, and **(D)** disease-free survival of ESCC patients underwent Mckeown esophagectomy ($n = 129$).

treatment, whereas BMI was proved had no significant association on complications rates after surgery according to the results of multivariate analysis. Since the GNRI was based on the serum level of albumin, and GNRI was considered as a marker which can reflect nutritional status. The level of serum albumin was a sensitive and valuable indicator which can indicate malnutrition in EC patients. Low albumin level had been proved to associated with worse survival in patients with various cancer (22). GNRI, that consisted by combination of both serum albumin and body weight might be one valuable nutritional parameter. An effective nutritional assessment tool should be low-cost, simple, calculated through available data and convenient to use. GNRI can be easily calculated by routine clinical test, and the prognostic prediction value of GNRI had been proved by previous studies which was superior to serum albumin and BMI alone (23). According to the results of our study, GNRI might be a superior index compared with BMI which was similar to findings in early studies, and the univariate analysis indicated that low-GNRI was associated with poorer survival outcomes of ESCC patients. However, either low-BMI or low-GNRI was shown to have no significant association with OS or DFS according to the results of multivariate analysis, which suggested that other nutritional status evaluating indexes are in need to predict long-time survival outcomes.

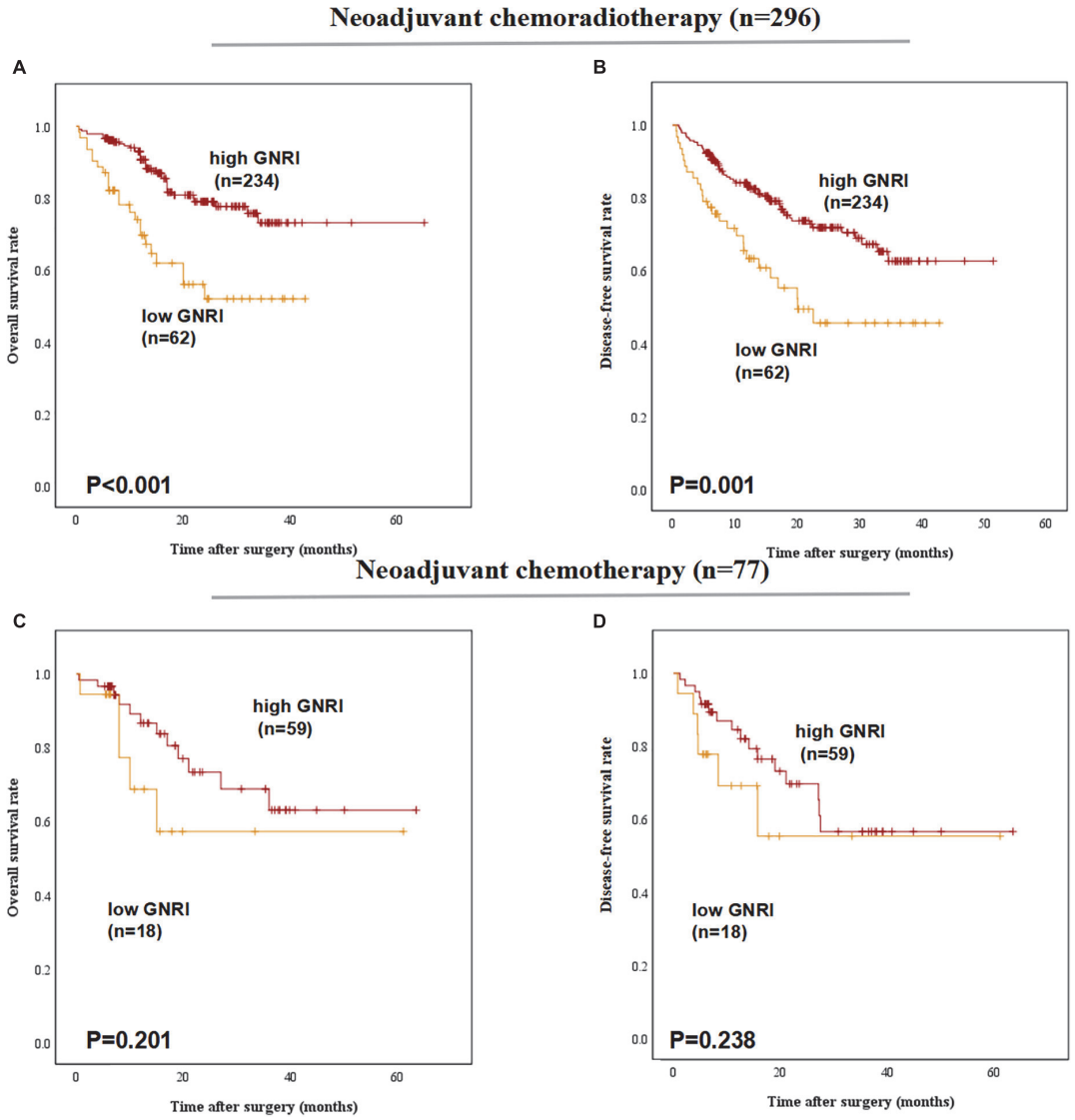


FIGURE 4
Postoperative outcomes of patients with high or low geriatric nutritional index (GNRI) basing on different preoperative treatment: **(A)** overall survival, **(B)** disease-free survival of ESCC patients underwent neoadjuvant chemoradiotherapy ($n = 296$), **(C)** overall survival, and **(D)** disease-free survival of ESCC patients underwent neoadjuvant chemotherapy ($n = 77$).

The results of our study suggested that GNRI could be utilized in clinical setting in the future for confirming ESCC patients with decreasing nutrition level and for patients who requiring nutritional support before esophagectomy. Przekop et al. (24) had proved that GNRI could provide useful prognostic information in patients with head and neck cancer patients qualified for home enteral nutrition (HEN), and they had also suggested nutritional management should be also initiated earlier during the management of cancer patients. Liu et al. (25) demonstrated that HEN and preoperative nutritional support was safe, and beneficial to the recovery of EC patients who had underwent esophagectomy. Therefore, combining the results of GNRI and nutritional support in EC patients during the whole treatment progression seems feasible. It was suggested that in EC patients with low GNRI, providing them with required energy and protein through oral or jejunostomy feeding preoperatively might reduce the postoperative complications rates. Additionally, nutritional support after esophagectomy such as HEN for EC patients may also ameliorate their survival outcomes.

In our study, ESCC patients with lower GNRI were proved to associated subsequent complications, some potential reasons could partly explain the reason. The wound healing after esophagectomy needed adequate energy and nutritional support during the progression of proliferation. Sufficient nutrition supply is of great necessity during the whole

progression of EC patients' management. After neoadjuvant therapy, the swallowing and oral feeding function of EC patients were decreased to some degree because of the side-effects of chemoradiation. Thus, some EC patients were likely to get insufficient nutritional support and progressed into malnutrition. However, malnutrition was a chronic state involving various physiological activities and was difficult to be capture reliably (26). Unlike traditional nutrition evaluating index, the GNRI considered not only the weight of patients, but also the ideal weight and albumin level in peripheral blood and it made GNRI become a screening tool for evaluating nutritional status (27). Previous studies had also found a correlation between malnutrition and immune suppression in cancer patients, leading to postoperative complications and cancer recurrence after surgery (28). Up to now, the main mechanism involving in the relationship between low GNRI and postoperative complications in EC patients following neoadjuvant treatment remains unknown. More molecular biology studies are needed to determine the specific molecular mechanism between malnutrition and postoperative complications in EC patients.

This is a retrospective study assessing the ability of GNRI to predict surgical outcomes in a single, high-volume institute. Notwithstanding, the current study was retrospective in design with all the inherent limitations of such studies. Patients were treated with different dose of radiation or chemotherapy before esophagectomy. Such discrepancy might lead the results of our study deviate from the truth to some extent. Finally, the exact GNRI cutoff value had not reached on consensus which might make it hard to determine the optimal GNRI value in evaluating clinical nutritional status of EC patients. Therefore, more extensive prospective studies involving multiple institutions are warranted in the future.

In conclusion, GNRI was found to be an independent predictive factor of postoperative complications for ESCC patients underwent neoadjuvant therapy followed by surgery. Intensive follow-up nutritional support before surgery should be performed for ESCC patients with low GNRI.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YYu conceptualized the study and revised and proofed the manuscript. PF, QY, and JZ conceptualized the study drafted and proofed the manuscript. YYa, SL, XX, XL, YG, QS, HZ, LC, and XZ collected the literature. All authors contributed to the manuscript revision and revised it critically for intellectual content.

Funding

This work was supported by the National Nature Science Foundation of China (81970481 and 82000514), Sichuan Science and Technology Program (2022YFS0048 and 2021YFS0222), 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (2020HXFH047, ZYJC18010, 20HXJS005, and 2018HXFH020), and China Postdoctoral Science Foundation (2020M673241).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.983038/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Kaplan–Meier survival curve stratified by optimal cutoff points in patients with decreased geriatric nutritional index (GNRI) by X-tile software.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660

2. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet.* (2013) 381:400–12. doi: 10.1016/s0140-6736(12)60643-6

3. Orringer MB. Transhiatal esophagectomy: How I Teach It. *Ann Thorac Surg.* (2016) 102:1432–7. doi: 10.1016/j.athoracsur.2016.09.044

4. Vieira FM, Chedid MF, Gurski RR, Schirmer CC, Cavazzola LT, Schramm RV, et al. Transhiatal esophagectomy in squamous cell carcinoma of the esophagus: What are the best indications? *Arq Bras Cir Dig.* (2021) 33:e1567. doi: 10.1590/0102-672020200004e1567

5. Li, X, Chen L, Luan S, Zhou J, Xiao X, Yang Y, et al. The development and progress of nanomedicine for esophageal cancer diagnosis and treatment. *Semin Cancer Biol.* (2022):doi: 10.1016/j.semcancer.2022.01.007 [Epub ahead of print].

6. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A Randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (Jcog9907). *Ann Surg Oncol.* (2012) 19:68–74. doi: 10.1245/s10434-011-2049-9

7. Schwegler I, von Holzen A, Gutzwiller JP, Schlumpf R, Mühlebach S, Stanga Z. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. *Br J Surg.* (2010) 97:92–7. doi: 10.1002/bjs.6805

8. Mullen JT, Davenport DL, Hutter MM, Hosokawa PW, Henderson WG, Khuri SF, et al. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. *Ann Surg Oncol.* (2008) 15:2164–72. doi: 10.1245/s10434-008-9990-2

9. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric nutritional risk index: A new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr.* (2005) 82:777–83. doi: 10.1093/ajcn/82.4.777

10. Zhou J, Fang P, Li X, Luan S, Xiao X, Gu Y, et al. Prognostic value of geriatric nutritional risk index in esophageal carcinoma: A systematic review and meta-analysis. *Front Nutr.* (2022) 9:831283. doi: 10.3389/fnut.2022.831283

11. Obermannová, R, Alsina M, Cervantes A, Leong T, Lordick F, Nilsson M, et al. Oesophageal cancer: Esmo clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol.* (2022):doi: 10.1016/j.annonc.2022.07.003 [Epub ahead of print].

12. Kubo N, Ohira M, Yamashita Y, Sakurai K, Lee T, Toyokawa T, et al. Thoracoscopic esophagectomy in the prone position versus in the lateral position for patients with esophageal cancer: A comparison of short-term surgical results. *Surg Laparosc Endosc Percutan Techn.* (2014) 24:158–63. doi: 10.1097/SLE.0b013e31828fa6d7

13. Chang X, Deng W, Ni W, Li C, Han W, Gao LR, et al. Comparison of two major staging systems in predicting survival and recommendation of postoperative radiotherapy based on the 11th japanese classification for esophageal carcinoma after curative resection: A propensity score-matched analysis. *Ann Surg Oncol.* (2021) 28:7076–86. doi: 10.1245/s10434-021-10046-6

14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* (2004) 240:205–13. doi: 10.1097/01.sla.0000133083.54934.ae

15. Narumi T, Arimoto T, Funayama A, Kadowaki S, Otaki Y, Nishiyama S, et al. Prognostic importance of objective nutritional indexes in patients with chronic heart failure. *J Cardiol.* (2013) 62:307–13. doi: 10.1016/j.jjcc.2013.05.007

16. Panichi V, Cupisti A, Rosati A, Di Giorgio A, Scatena A, Menconi O, et al. Geriatric nutritional risk index is a strong predictor of mortality in hemodialysis patients: data from the riscavid cohort. *J Nephrol.* (2014) 27:193–201. doi: 10.1007/s40620-013-0033-0

17. Beberashvili I, Azar A, Sinuani I, Shapiro G, Feldman L, Sandbank J, et al. Geriatric nutritional risk index, muscle function, quality of life and clinical outcome in hemodialysis patients. *Clin Nutr (Edinburgh, Scotland).* (2016) 35:1522–9. doi: 10.1016/j.clnu.2016.04.010

18. Shoji F, Matsubara T, Kozuma Y, Haratake N, Akamine T, Takamori S, et al. Preoperative geriatric nutritional risk index: A predictive and prognostic factor in patients with pathological stage i non-small cell lung cancer. *Surg Oncol.* (2017) 26:483–8. doi: 10.1016/j.suronc.2017.09.006

19. Bo Y, Wang K, Liu Y, You J, Cui H, Zhu Y, et al. The geriatric nutritional risk index predicts survival in elderly esophageal squamous cell carcinoma patients with radiotherapy. *PLoS One.* (2016) 11:e0155903. doi: 10.1371/journal.pone.0155903

20. Kubo N, Sakurai K, Tamura T, Toyokawa T, Tanaka H, Muguruma K, et al. The impact of geriatric nutritional risk index on surgical outcomes after esophagectomy in patients with esophageal cancer. *Esophagus.* (2019) 16:147–54. doi: 10.1007/s10388-018-0644-6

21. Jezerskyte E, Saadeh LM, Hagens ERC, Sprangers MAG, Noteboom L, van Laarhoven HWM, et al. Long-Term health-related quality of life after mckeown and ivor lewis esophagectomy for esophageal carcinoma. *Dis Esophagus.* (2020) 33:doaa022. doi: 10.1093/dote/doaa022

22. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: A population-based study. *Lancet Oncol.* (2008) 9:629–35. doi: 10.1016/s1470-2045(08)70153-0

23. Fuggle N, Shaw S, Dennison E, Cooper C. Sarcopenia. *Best Pract Res Clin Rheumatol.* (2017) 31:218–42. doi: 10.1016/j.berh.2017.11.007

24. Przekop Z, Szostak-Wêgierek D, Milewska M, Panczyk M, Zaczek Z, Sobocki J. Efficacy of the nutritional risk index, geriatric nutritional risk index, bmi, and glim-defined malnutrition in predicting survival of patients with head and neck cancer patients qualified for home enteral nutrition. *Nutrients.* (2022) 14:1268. doi: 10.3390/nu14061268

25. Liu K, Ji S, Xu Y, Diao Q, Shao C, Luo J, et al. Safety, feasibility, and effect of an enhanced nutritional support pathway including extended preoperative and home enteral nutrition in patients undergoing enhanced recovery after esophagectomy: A pilot randomized clinical trial. *Dis Esophagus.* (2020) 33:doz030. doi: 10.1093/dote/doz030

26. Saroul N, Pastourel R, Mulliez A, Farigon N, Dupuch V, Mom T, et al. Which assessment method of malnutrition in head and neck cancer? *Otolaryngol Head Neck Surg.* (2018) 158:1065–71. doi: 10.1177/0194599818755995

27. Cereda E, Pedrolli C. The geriatric nutritional risk index. *Curr Opin Clin Nutr Metab Care.* (2009) 12:1–7. doi: 10.1097/MCO.0b013e3283186f59

28. Alwarawrah Y, Kiernan K, MacIver NJ. Changes in Nutritional Status Impact Immune Cell Metabolism and Function. *Front Immunol.* (2018) 9:1055. doi: 10.3389/fimmu.2018.01055

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 15 November 2022
DOI 10.3389/fnut.2022.976216

OPEN ACCESS

EDITED BY
Clelia Madeddu,
University of Cagliari, Italy

REVIEWED BY
Dong Wu,
Third Affiliated Hospital of Second Military Medical University, China
Yang Deng,
Shandong First Medical University, China

*CORRESPONDENCE
Shuangyi Tang
tshy369@sina.com
Jialiang Gan
gjl5172@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 23 June 2022
ACCEPTED 31 October 2022
PUBLISHED 15 November 2022

CITATION
Xie H, Wei L, Liu M, Liang Y, Yuan G, Gao S, Wang Q, Lin X, Tang S and Gan J (2022) Neutrophil-albumin ratio as a biomarker for postoperative complications and long-term prognosis in patients with colorectal cancer undergoing surgical treatment.
Front. Nutr. 9:976216.
doi: 10.3389/fnut.2022.976216

Neutrophil-albumin ratio as a biomarker for postoperative complications and long-term prognosis in patients with colorectal cancer undergoing surgical treatment

Hailun Xie[1,2†], Lishuang Wei[3†], Mingxiang Liu[1,2], Yanren Liang[1,2], Guanghui Yuan[1,2], Shunhui Gao[1,2], Qiwen Wang[1,2], Xin Lin[2,4], Shuangyi Tang[5*] and Jialiang Gan[1,2*]

[1]Department of Colorectal and Anal Surgery, The First Affiliated Hospital, Guangxi Medical University, Nanning, China, [2]Guangxi Key Laboratory of Enhanced Recovery After Surgery for Gastrointestinal Cancer, Nanning, China, [3]Department of Geriatric Respiratory Disease Ward, The First Affiliated Hospital, Guangxi Medical University, Nanning, China, [4]Grade 2018, Department of Clinical Medicine, Guangxi Medical University, Nanning, China, [5]Department of Pharmacy, The First Affiliated Hospital, Guangxi Medical University, Nanning, China

Background: To explore the prognostic value of the preoperative neutrophil-albumin ratio (NAR) in patients with colorectal cancer (CRC) undergoing surgical treatment.

Materials and methods: The standardized log-rank statistic was used to determine the optimal cut-off value for NAR. A logistic regression model was used to evaluate the value of NAR in predicting postoperative complications. Cox proportional hazards models were used to assess the independent association of NAR with progression-free survival (PFS) and overall survival (OS) in CRC patients. Restricted cubic splines were used to assess the relationship between continuous NAR and survival in CRC patients. The Kaplan–Meier method and log-rank test were used to compare survival differences between low and high NAR groups. NAR-based prognostic nomograms were constructed to predict the 1–5-year PFS and OS of CRC patients. The concordance index (C-index) and calibration curve were used to evaluate the prognostic accuracy of the nomograms.

Results: A total of 1,441 CRC patients were enrolled from January 2012 to December 2016. There were 904 men (62.7%) and 537 women (37.3%), with an average age of 58.12 ± 13.15 years. High NAR was closely associated with low BMI, advanced pathological stage, colon cancer, large tumors, vascular invasion, poor differentiation, high CEA levels, long hospital stay, and recurrence and metastasis. A high NAR was an independent risk factor for postoperative complications in CRC patients (OR: 2.298, 95% CI: 1.642–3.216,

$p < 0.001$). Patients with a high NAR had worse PFS (40.7 vs. 59.5%, $p < 0.001$) and OS (42.6 vs. 62.4%, $p < 0.001$). After adjusting for confounders, high NAR was independently associated with PFS (HR: 1.280, 95% CI: 1.031–1.589, $p = 0.025$) and OS (HR: 1.280; 95% CI: 1.026–1.596, $p = 0.029$) in CRC patients. The C-index and calibration curves showed that the NAR-based prognostic nomograms had good predictive accuracy.

Conclusion: High NAR was an independent risk factor for postoperative complications and long-term prognosis of CRC patients. NAR-based research could provide references for prognostic judgment and clinical decision-making of CRC patients.

KEYWORDS

neutrophil-albumin ratio, systemic inflammation, nutrition, colorectal cancer, complication, prognosis

Introduction

Colorectal cancer (CRC) is a common malignancy of the gastrointestinal tract. CRC had the third highest incidence and second highest mortality among all cancers worldwide, according to the latest data (1). In China, the incidence of CRC ranks fourth and mortality ranks fifth among all malignancies (2). CRC causes a serious social burden, and the prevention and treatment of CRC has become an important public health problem. Therefore, there is an urgent need to identify effective prognostic biomarkers to improve the survival of patients with CRC.

Serological biomarkers have attracted increasing attention because of their simplicity and ease of availability. Serum markers can be used to predict patient prognosis and treatment effects and to formulate individualized treatment interventions that play an important role in the treatment and prognosis evaluation of CRC (3–6). As is known to all, systemic inflammation, as a leading factor in the tumorigenesis process, plays a crucial role and actively participates in the occurrence and development of malignancies (7, 8). In clinical practice, peripheral blood parameters are used as direct indicators of the host environment. Systemic inflammation can be reflected by peripheral blood parameters such as neutrophils, lymphocytes, monocytes, and albumin.

Recently, the newly developed neutrophil-albumin ratio (NAR) has been used to assess prognosis in a variety of diseases, including cerebrovascular disease, pancreatic cancer, and non-small cell lung cancer (9–11). NAR is a novel marker of systemic inflammation and disease severity, which can be calculated using peripheral serum markers (neutrophils and albumin) and has the advantages of being simple, inexpensive, and non-invasive. Neutrophils play an important role in tumorigenesis and tumor progression. A high neutrophil count is thought to be closely associated with poor prognosis of malignancy. Neutrophils can secrete cytokines and chemokines to create a tumor microenvironment suitable for tumor cell proliferation, invasion, and microvascular formation, thereby promoting tumor development and progression (12, 13). Albumin is the most abundant protein in the extracellular matrix synthesized in liver tissue. Decreased albumin level is associated with malnutrition and cancer progression (14–16). Recently, serum albumin was reported to play an important role in systemic inflammation. The decrease in serum albumin may be the result of a combination of protein synthesis recombination in the liver and albumin redistribution in and out of the blood vessels under high systemic inflammation conditions (17). NAR, which combines the advantages of neutrophils and albumin, is a promising biomarker for predicting cancer prognosis.

Currently, there are few studies on the relationship between preoperative NAR and prognosis of patients with CRC. NAR is an emerging indicator of CRC. Therefore, this single-center retrospective study aimed to explore the prognostic value of preoperative NAR in patients with CRC undergoing surgical treatment.

Patients and methods

Study population

This cross-sectional retrospective study recruited patients with CRC who underwent surgical treatment at the Colorectal and Anal Surgery Department of The First Affiliated Hospital of Guangxi Medical University from January 2012 to December 2016. Patient information was anonymized during the study period. All enrolled patients met the following inclusion criteria: diagnosis of CRC based on histological or cytological evidence, curative surgery for treatment purposes, and complete preoperative serological data. Patients with multiple primary

malignancies, preoperative neoadjuvant chemoradiotherapy, or clinical evidence of infection or other inflammatory diseases were excluded. This study was approved by the ethics review committee of the center. Written informed consent was obtained from all the patients or their close relatives. This study was conducted in strict accordance with the principles of the Declaration of Helsinki.

Data collection

The following clinicopathological data were collected: sex, age, height, weight, hypertension, diabetes, neutrophil count, albumin level, serum CEA level, T stage, N stage, metastasis, tumor-node-metastasis (TNM) stage, perineural invasion, vascular invasion, pathological type, differentiation, tumor location, tumor size, and surgical approach (laparoscopic or open). Blood characteristics were collected from blood tests performed within 1 week before surgery. All pathological characteristics were obtained from the evaluation of the excised tissue samples by professional pathologists. TNM stage was classified according to the eighth edition of the Union for International Cancer Control (UICC) Pathology classification. The NAR was defined as neutrophil (10^9)/albumin (g/dL). Body mass index (BMI) was defined as weight (kg)/square height (m^2) (low, $<$18.5; normal, 18.5–24; high, $\geq$24).

Follow-up and outcomes

In this study, the survival status of all the patients was determined through an outpatient clinic visit or telephone call. Follow-up was performed every 3–6 months in the first year after surgery and every 6–12 months in the second year, until the patient died. The main contents of the follow-up were basic living conditions, serological tests, tumor marker tests, imaging tests, and colonoscopy after surgery. The last follow-up was on July 31, 2021. In this study, the primary outcome was overall survival (OS), and secondary outcomes were progression-free survival (PFS) and postoperative complications. OS was defined as the time interval from the date of diagnosis to death from any cause or the date of the last follow-up. PFS was defined as the time interval from tumor resection to the first recurrence, death, or last follow-up.

Statistical analysis

Categorical variables were expressed as counts (percentages) and analyzed using Pearson's chi-squared test or Fisher's exact test. Continuous variables are expressed as mean (standard deviation) or median (interquartile range) and were analyzed using a *t*-test or non-parametric test. The standardized log-rank statistic was used to determine the optimal cut-off value for NAR by "survminer" R package. Restricted cubic splines (RCS) were used to assess the relationship between NAR and survival of patients with CRC. The Kaplan–Meier method was used to describe survival curves, and the log-rank test was used to compare differences in survival. Univariate and multivariate analyses were performed using the Cox proportional hazards model to evaluate the important factors affecting patient prognosis. Survival risks are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). The R package "survival" was used to construct prognostic nomograms to predict 1–5-year PFS and OS in patients with CRC. The concordance index (C-index) and calibration curve were used to evaluate the prognostic accuracy of the nomograms. Time-dependent receiver operating characteristic (ROC) curves were used to compare the ability to predict prognosis. A logistic regression model was used to identify the risk factors for complications. Predicted risks are expressed as odds ratios (ORs) and 95% CI. Finally, we randomly divided the total population into two internal validation datasets at a 7:3 ratio to evaluate the generalizability of the results. All p-values were two-sided, and *p*-values below 0.05 were considered statistically significant. R (version 4.0.2) was used for all analyses.

Results

Clinicopathologic characteristics

In total, 1,441 patients with CRC were included in this study. There were 904 men (62.7%) and 537 women (37.3%), with an average age of 58.12 $\pm$ 13.15 years. A total of 284 patients (19.7%) had stage I, 480 (33.3%) had stage II, 540 (37.5%) had stage III, and 137 (9.5%) had stage IV disease. At the last follow-up, 400 (27.8%) patients had recurrence and metastasis and 582 (40.4%) patients had died. The median follow-up time was 65.23 months (1–106 months). The optimal cut-off value for NAR in patients with CRC was 1.65 (**Supplementary Figure 1**). Based on this cut-off value, 1,237 patients were identified as having low NAR and 204 patients as having high NAR. We found that high NAR was closely associated with low BMI, metastasis, advanced pathological stage, colon cancer, large tumors, vascular invasion, poor differentiation, and high CEA levels. In addition, patients with CRC with high NAR had a hospital stay that was nearly 3 days longer, a higher risk of recurrence and metastasis, and a higher risk of death (**Table 1**).

The relationship between neutrophil-albumin ratio and complications

A total of 299 patients (26.2%) developed varying degrees of postoperative complications. According to the modified Clavien

TABLE 1 The relationships between the neutrophil-albumin ratio (NAR) and clinicopathological factors of colorectal cancer (CRC) patients.

Features	Overall (n = 1,441)	NAR		*P-value*
		Low (n = 1,237)	High (n = 204)	
Gender (male)	904 (62.7)	767 (62.0)	137 (67.2)	0.183
Age (≥60)	724 (50.2)	616 (49.8)	108 (52.9)	0.449
Age [mean (SD)]	58.12 (13.15)	58.15 (13.07)	57.93 (13.67)	0.819
BMI (median [IQR])	22.04 (19.95, 24.31)	22.14 (20.00, 24.46)	21.5(19.32, 23.74)	0.005
BMI				0.003
	182 (12.6)	142 (11.5)	40 (19.6)	
	854 (59.3)	736 (59.5)	118 (57.8)	
	405 (28.1)	359 (29.0)	46 (22.5)	
Hypertension (Yes)	241 (16.7)	202 (16.3)	39 (19.1)	0.375
Diabetes (Yes)	90 (6.2)	72 (5.8)	18 (8.8)	0.137
Liver disease (Yes)	56 (3.9)	49 (4.0)	7 (3.4)	0.717
T stage				0.232
	50 (3.5)	46 (3.7)	4 (2.0)	
	318 (22.1)	279 (22.6)	39 (19.1)	
	770 (53.4)	660 (53.4)	110 (53.9)	
	303 (21.0)	252 (20.4)	51 (25.0)	
N stage				0.158
	808 (56.1)	705 (57.0)	103 (50.5)	
	398 (27.6)	338 (27.3)	60 (29.4)	
	235 (16.3)	194 (15.7)	41 (20.1)	
Clinical distant metastasis (Yes)	137 (9.5)	97 (7.8)	40 (19.6)	<0.001
TNM stage				<0.001
	284 (19.7)	254 (20.5)	30 (14.7)	
	480 (33.3)	420 (34.0)	60 (29.4)	
	540 (37.5)	466 (37.7)	74 (36.3)	
	137 (9.5)	97 (7.8)	40 (19.6)	
Perineural invasion (Yes)	149 (10.3)	128 (10.3)	21 (10.3)	0.999
Vascular invasion (Yes)	247 (17.1)	201 (16.2)	46 (22.5)	0.035
Macroscopic type				0.001
Protrude type	406 (28.2)	335 (27.1)	71 (34.8)	
Infiltrating type	113 (7.8)	88 (7.1)	25 (12.3)	
Ulcerative type	922 (64.0)	814 (65.8)	108 (52.9)	
Differentiation (Poor)	190 (13.2)	147 (11.9)	43 (21.1)	<0.001
Tumor location (Rectal)	736 (51.1)	670 (54.2)	66 (32.4)	<0.001
Tumor size (median [IQR])	4.50 (3.50, 6.00)	4.20 (3.50, 5.50)	6.00 (4.00, 8.00)	<0.001
CEA (High)	594 (41.2)	483 (39.0)	111 (54.4)	<0.001
Surgical method (Endoscopic)	837 (58.1)	774 (62.6)	63 (30.9)	<0.001
Operation time (median [IQR])	188.00 (150.00, 245.00)	183.00 (146.00, 240.00)	216.50(172.75, 278.25)	<0.001
Intraoperatve blood loss (median [IQR])	100.00 (50.00, 200.00)	100.00 (50.00, 200.00)	200.00 (100.00, 300.00)	<0.001
Length of stay (median [IQR])	17.00 (11.00, 21.00)	16.00 (11.00, 20.00)	19.00 (14.00, 24.00)	<0.001
Radiotherapy (Yes)	134 (9.3)	125 (10.1)	9 (4.4)	0.014
Chemotherapy (Yes)	657 (45.6)	571 (46.2)	86 (42.2)	0.323
Recurrence and metastasis (Yes)	400 (27.8)	330 (26.7)	70 (34.3)	0.024
Death (Yes)	582 (40.4)	465 (37.6)	117 (57.4)	<0.001

CRC, colorectal cancer; BMI, body mass index; NAR, neutrophil-albumin ratio.

complication classification system, there were 147 (10.2%) grade I complications, 108 (7.5%) grade II complications, 17 (1.2%) grade IIIa complications, 13 (0.9%) grade IIIb complications, seven (0.5%) grade IVa complications, six (0.4%) grade IVb complications, and one (0.1%) grade V complication. Compared with the low-NAR group, CRC patients in the high-NAR group had a significantly higher incidence of total postoperative complications, especially grade I–III complications (**Supplementary Table 1**). Logistic regression analysis showed that high NAR was an independent risk factor for postoperative complications in patients with CRC. Compared with patients with low NAR, patients with

high NAR had a 1.298-fold higher risk of postoperative complications (OR: 2.298, 95% CI: 1.642–3.216, $p < 0.001$) (Supplementary Table 2).

Comparison of the survival differences between the low and high neutrophil-albumin ratio groups

Compared with patients with low NAR, those with high NAR had worse PFS (40.7 vs. 59.5%, $p < 0.001$) (Figure 1A). Patients with a high NAR had significantly worse OS than those with a low NAR (42.6 vs. 62.4%, $p < 0.001$) (Figure 1B). In addition, we also performed subgroup analysis of different CEA levels, and found that regardless of whether CEA levels were normal or high, the PFS and OS of patients in the high NAR group were significantly lower than those of patients in the low NAR group (Supplementary Figure 2). Notably, NAR can effectively stratify the prognosis of patients with CRC at different pathological stages. For early stages (TNM stage I–II), the PFS and OS of the high NAR group were significantly poorer than those of the low NAR group (Figures 2A,B). For advanced stages (TNM stage III–IV), NAR still provides effective prognostic differentiation and has stronger discriminative power in patients with CRC (Figures 2C,D).

Relationship between neutrophil-albumin ratio and survival

There was a clear dose-response relationship between NAR and survival in patients with CRC under different adjustment models, and NAR was inversely associated with prognosis (Figures 3A,B). After adjusting for confounders, high NAR was independently associated with PFS (HR: 1.280, 95% CI: 1.031–1.589, $p = 0.025$) and OS (HR: 1.280, 95% CI: 1.026–1.596, $p = 0.029$) in patients with CRC (Tables 2, 3). We also conducted a trend test for the relationship between NAR and PFS/OS. The results showed that NAR was independently associated with PFS/OS and OS in patients with CRC, either as a continuous variable or as a categorical variable (Supplementary Table 3). In addition, high NAR was a risk factor affecting the vast majority of patient subgroups (Supplementary Figure 3).

Construction of prognostic nomograms

Based on the results of the Cox proportional hazards model of PFS, we developed a PFS nomogram to predict postoperative 1–5-year PFS in patients with CRC (Figure 4A), which included age, NAR, T stage, N stage, metastasis, and CEA. Age and NAR were used as continuous variables to improve the predictive accuracy of the nomograms. The nomogram showed that with increasing age/NAR, progression of T stage/N stage, metastasis, and increasing CEA levels, the predicted score increased, indicating that the risk of poor prognosis also increased. In the survival analysis of OS, six factors including age, NAR, T stage, N stage, metastasis, vascular invasion, differentiation, and CEA were confirmed to be independently associated with the prognosis of CRC patients. Therefore, we included these prognostic factors to construct an OS nomogram for predicting postoperative 1–5-year OS in CRC patients (Figure 4B). The nomogram showed that with increasing age/NAR, progression of T stage/N stage, metastasis, poor differentiation, emergence of vascular invasion, and increased CEA, the predicted score increased, indicating that the risk of poor prognosis also increased.

Utility evaluation of survival nomograms

The C-indices of the PFS and OS nomograms were 0.720 (95% CI: 0.699–0.741) and 0.728 (95% CI: 0.706–0.750), respectively. The calibration curves for both the 3- and 5-year PFS (Supplementary Figures 4A,B) and OS (Supplementary Figures 4C,D) demonstrated the best agreement between the predicted survival probabilities and actual observations. These results demonstrated that the nomograms had good predictive accuracy in predicting the prognosis of patients with CRC. Furthermore, we compared these nomograms with the traditional TNM staging system by using time-dependent ROC curves. The results showed that our nomograms had better resolution and accuracy in predicting 3- and 5-year PFS (Supplementary Figures 5A,B) and OS (Supplementary Figures 5C,D) than TNM stage did.

Internal validation

We performed randomized internal validation by dividing the total population into validation a (1,009) and validation b (432) cohorts at a 7:3 ratio. Supplementary Table 4 compares the clinicopathological factors of the two cohorts, and the results show that the two internal cohorts were independent. NAR still provided a valid prognostic assessment in patients in the validation a (Figures 5A,B) and validation b cohorts (Figures 5C,D). Compared with patients with low NAR, those with high NAR have a higher risk of poor prognosis. Next, we internally validated the PFS and OS nomograms. In validation a, the C-indices of the PFS and OS nomograms were 0.712 (0.688, 0.737) and 0.726 (0.701, 0.751), respectively. In validation b, the C-indices of the PFS and OS nomograms were 0.742 (0.706, 0.778) and 0.738 (0.701, 0.775), respectively. The calibration curves for 3- and 5-year PFS and OS both demonstrated the best

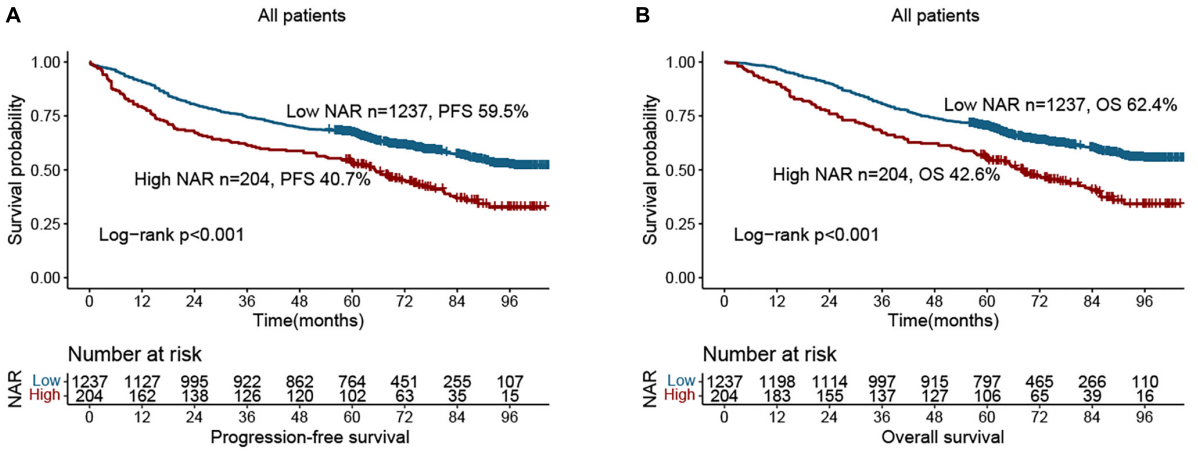


FIGURE 1
Kaplan-Meier curve of neutrophil-albumin ratio (NAR) in colorectal cancer (CRC) patients. **(A)** Progression-free survival; **(B)** overall survival.

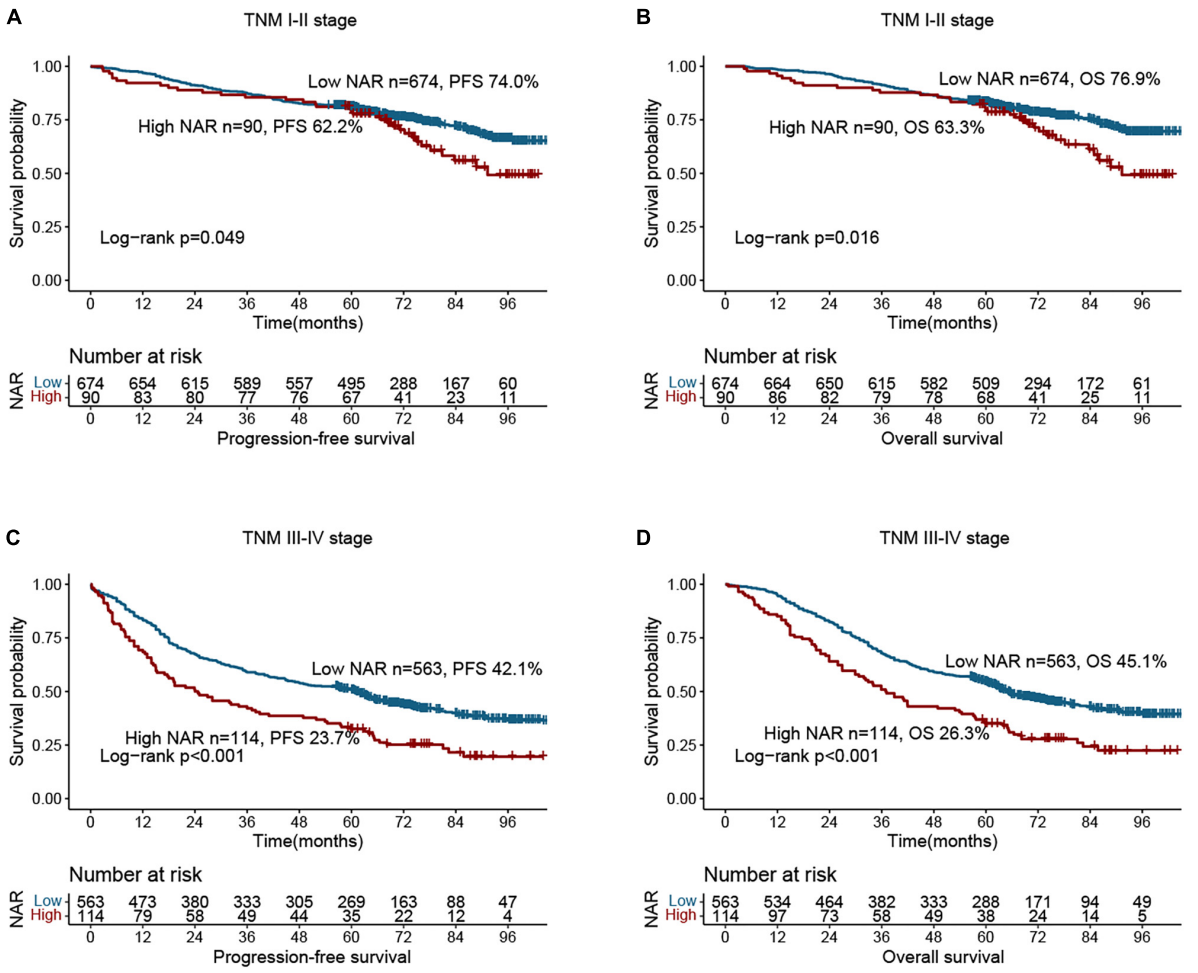


FIGURE 2
Stratified survival analysis of neutrophil-albumin ratio (NAR) based on tumor-node-metastasis (TNM) stage. **(A)** Progression-free survival of TNM I-II stage; **(B)** overall survival of TNM I-II stage; **(C)** overall survival of TNM III-IV stage; **(D)** overall survival of TNM III-IV stage.

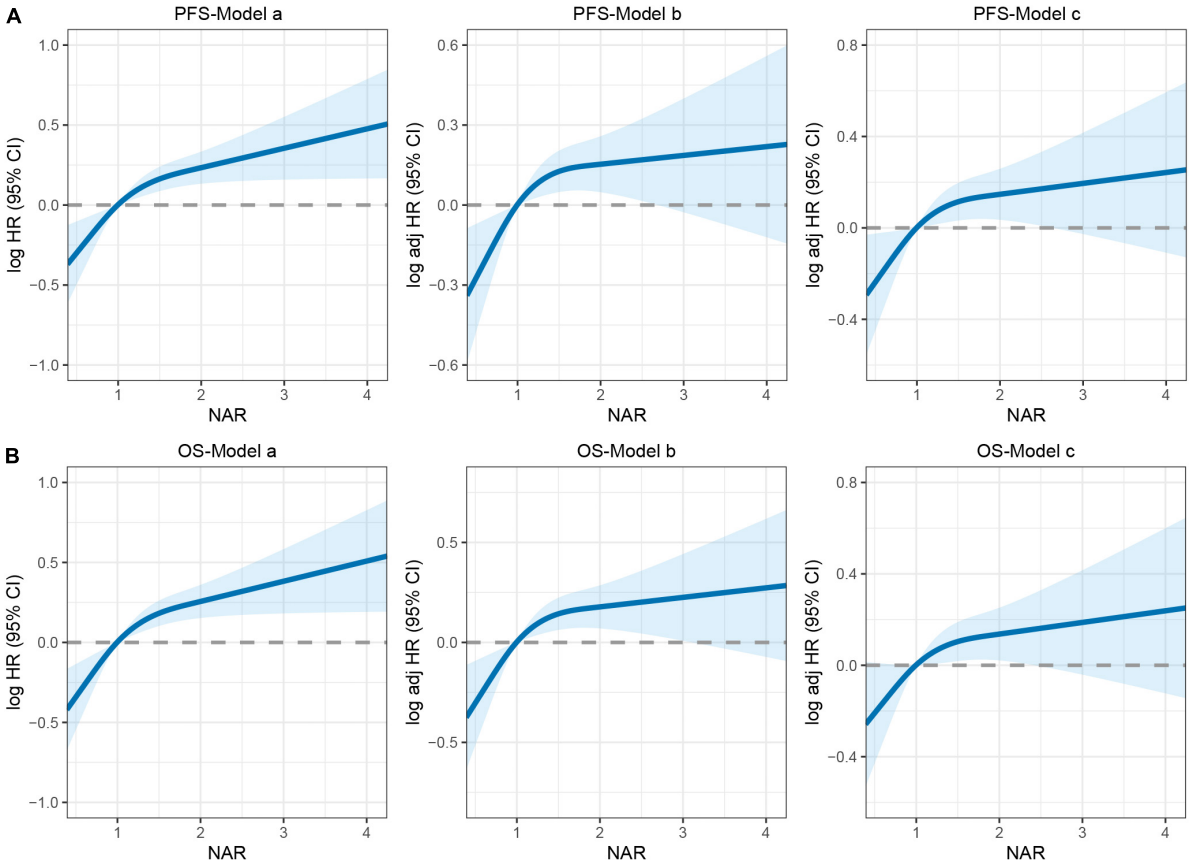


FIGURE 3
The association between neutrophil-albumin ratio (NAR) and survival in patients with colorectal cancer (CRC). **(A)** Progression-free survival; **(B)** overall survival. Model a: no adjusted. Model b: adjusted for gender, age, and BMI. Model c: adjusted for gender, age, BMI, hypertension, diabetes, T stage, N stage, metastasis, tumor location, tumor size, perineural invasion, vascular invasion, macroscopic type, differentiation, surgical approach, operating time, blood loss.

agreement between predicted survival probabilities and actual observation in validation a (**Supplementary Figure 6A**) and validation b (**Supplementary Figure 6B**).

Discussion

Systemic inflammation is considered to be the seventh hallmark of cancer and is involved in tumor development, proliferation, metastasis, aging, and apoptosis. Ostan et al. suggested that inflammation triggers genetic mutations or changes in epigenetic mechanisms that promote cancer initiation, metastasis, and progression (18, 19). Changes in inflammatory cells and inflammatory proteins in the peripheral venous blood can reflect tumor progression. Therefore, as markers of systemic inflammation, peripheral venous blood counts and albumin levels may provide additional information about the outcomes of patients with malignancies.

In this study, we found that an elevated preoperative NAR may reflect more aggressive tumor features. Patients with a high preoperative NAR had longer hospital stays and a higher risk of poor prognosis, suggesting that NAR can be used to assess disease burden. In addition, high preoperative NAR was closely associated with postoperative complications, especially grade I–III complications. In our study, approximately 20.7% of patients with CRC had varying degrees of postoperative complications, and the proportion of patients with postoperative complications in the high NAR group was 37.7%, while it was only 17.9% in the low NAR group. Multivariate logistic regression analysis showed that a high preoperative NAR was an independent risk factor for postoperative complications in patients with CRC.

Multivariate RCS showed that with increasing NAR, the prognosis of patients became progressively worse. We found that patients with high NAR had a significantly worse prognosis than those with low NAR. Multivariate survival analysis showed that a high NAR was an independent risk factor for shorter PFS and OS in patients with CRC. The TNM staging system is currently recognized as the most reliable tool for evaluating the prognosis of CRC patients. However, it has been reported that patients with the same TNM stage may still have different

TABLE 2 Univariate and multivariate Cox regression analysis of clinicopathological characteristics associated with progression-free survival (PFS) in colorectal cancer (CRC) patients.

Characteristic	Progression-free survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P-value*	HR (95% CI)	*P-value*
Gender (Female)	1.014 (0.862–1.193)	0.866		
Age (≥60 years)	1.28 (1.093–1.499)	0.002	1.32 (1.122–1.554)	0.001
BMI		0.108		0.783
Low	Ref.		Ref.	
Normal	0.871 (0.694–1.095)	0.237	0.938 (0.741–1.187)	0.595
High	0.762 (0.589–0.986)	0.038	0.91 (0.697–1.188)	0.486
Hypertension (Yes)	1.198 (0.979–1.466)	0.079		
Diabetes (Yes)	1.152 (0.845–1.57)	0.371		
NAR (High)	1.703 (1.396–2.077)	<0.001	1.280 (1.031–1.589)	0.025
T stage (T3–4)	2.364 (1.896–2.947)	<0.001	1.426 (1.123–1.811)	0.004
N stage		<0.001		<0.001
N0	Ref.		Ref.	
N1	1.872 (1.553–2.257)	<0.001	1.531 (1.261–1.859)	<0.001
N2	4.055 (3.338–4.927)	<0.001	2.798 (2.254–3.472)	<0.001
Distant metastasis (Yes)	5.384 (4.411–6.572)	<0.001	3.048 (2.442–3.805)	<0.001
Tumor location (Colon)	0.918 (0.784–1.075)	0.287		
Tumor size (≥5 cm)	1.192 (1.019–1.395)	0.028	0.96 (0.814–1.132)	0.627
Perineural invasion (Positive)	1.755 (1.403–2.195)	<0.001	1.127 (0.877–1.447)	0.352
Vascular invasion (Positive)	1.997 (1.663–2.397)	<0.001	1.21 (0.978–1.496)	0.080
Macroscopic type		0.003		0.313
Protrude type	Ref.			
Infiltrating type	1.466 (1.075–1.998)	0.016	1.214 (0.887–1.662)	0.225
Ulcerative type	1.366 (1.129–1.653)	0.001	1.151 (0.944–1.403)	0.165
Differentiation (High/Medium)	0.7 (0.563–0.869)	0.001	0.869 (0.693–1.091)	0.228
Surgical approach (Laparoscope)	0.673 (0.575–0.788)	<0.001	0.882 (0.741–1.051)	0.161
Operating time (median) (≥192 min)	1.205 (1.029–1.412)	0.021	1.048 (0.887–1.239)	0.581
Blood loss (median) (≥100 ml)	1.246 (1.052–1.477)	0.011	1.078 (0.901–1.291)	0.412
CEA (≥5 ng/ml)	1.988 (1.698–2.328)	<0.001	1.474 (1.245–1.746)	<0.001
Radiotherapy (Yes)	1.151 (0.885–1.496)	0.293		
Chemotherapy (Yes)	1.141 (0.974–1.336)	0.101		

CRC, colorectal cancer; BMI, body mass index; NAR, neutrophil-albumin ratio.

clinical outcomes, suggesting that other prognostic indices need to be assessed to achieve a more accurate prognostic evaluation in the setting of the same TNM stage (20). We found that NAR was also effective in the prognostic stratification of different pathological stages, suggesting that it could be an effective complement for evaluating the prognosis of CRC patients with the same pathological stage.

For convenience and intuitive use in clinical studies, we constructed novel and effective prognostic nomograms. These nomograms consist of specific clinical features, each feature corresponding to a specific point, and a score for that feature can be calculated by drawing a straight line on the point axis, and then positioning the sum of these feature scores on the total point axis. The risk probability can then be calculated by plotting down to the prediction axis. These nomograms have the advantage of integrating individual profiles, tumor characteristics, serum tumor markers, and nutritional inflammation-related markers and can be used for personalized assessment of 1–5-year PFS and OS in patients with CRC. The results of the C-index and calibration plots of the overall cohort and internal validation cohorts confirmed the good predictive accuracy of our constructed prognostic nomogram. For patients with higher scores, indicating greater tumor aggressiveness and higher tumor-associated inflammation, closer follow-up monitoring and even

TABLE 3 Univariate and multivariate Cox regression analysis of clinicopathological characteristics associated with overall survival (OS) in colorectal cancer (CRC) patients.

Characteristic	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P-value*	HR (95% CI)	*P-value*
Gender (Female)	1.013 (0.857–1.198)	0.881		
Age (≥60 years)	1.344 (1.141–1.583)	<0.001	1.356 (1.145–1.606)	<0.001
BMI		0.060		0.579
Low	Ref.		Ref.	
Normal	0.858 (0.678–1.085)	0.200	0.919 (0.721–1.171)	0.492
High	0.73 (0.56–0.952)	0.020	0.864 (0.656–1.138)	0.299
Hypertension (Yes)	1.202 (0.976–1.48)	0.084		
Diabetes (Yes)	1.188 (0.865–1.632)	0.287		
NAR (High)	1.769 (1.444–2.167)	<0.001	1.280 (1.026–1.596)	0.029
pT stage (T3–4)	2.495 (1.975–3.151)	<0.001	1.464 (1.138–1.885)	0.003
pN stage		<0.001		<0.001
N0	Ref.		Ref.	
N1	1.875 (1.544–2.277)	<0.001	1.519 (1.242–1.859)	<0.001
N2	4.079 (3.339–4.983)	<0.001	2.658 (2.127–3.32)	<0.001
Distant metastasis (Yes)	5.609 (4.581–6.866)	<0.001	3.186 (2.546–3.987)	<0.001
Tumor location (Colon)	0.976 (0.83–1.149)	0.772		
Tumor size (≥5 cm)	1.308 (1.112–1.539)	0.001	1.069 (0.901–1.267)	0.444
Perineural invasion (Positive)	1.713 (1.359–2.159)	<0.001	1.075 (0.829–1.393)	0.587
Vascular invasion (Positive)	2.039 (1.691–2.459)	<0.001	1.256 (1.01–1.562)	0.041
Macroscopic type		0.006		0.399
Protrude type	Ref.			
Infiltrating type	1.448 (1.05–1.997)	0.024	1.175 (0.848–1.627)	0.333
Ulcerative type	1.366 (1.12–1.665)	0.002	1.147 (0.934–1.409)	0.192
Differentiation (High/Medium)	0.648 (0.521–0.807)	0.001	0.789 (0.627–0.993)	0.044
Surgical approach (Laparoscope)	0.648 (0.551–0.763)	<0.001	0.89 (0.743–1.066)	0.207
Operating time (median) (≥192 min)	1.21 (1.028–1.426)	0.022	1.075 (0.904–1.278)	0.413
Blood loss (median) (≥100 ml)	1.263 (1.059–1.506)	0.009	1.104 (0.916–1.331)	0.298
CEA (≥5 ng/ml)	2.036 (1.73–2.397)	<0.001	1.472 (1.236–1.754)	<0.001
Radiotherapy (Yes)	0.939 (0.705–1.252)	0.67		
Chemotherapy (Yes)	1.047 (0.889–1.233)	0.581		

CRC, colorectal cancer; BMI, body mass index; NAR, neutrophil-albumin ratio.

more aggressive anticancer therapy could be considered to improve prognosis.

It is well-known that neutrophils are an important defense line of the body's immunity, and albumin is a commonly used indicator to reflect the nutritional status of patients in clinical practice (21, 22). NAR, combined the parameters of immune and nutrition, comprehensively reflects the perioperative nutritional reserve and anti-attack ability of CRC patients, which may be the reason why low NAR is closely related to postoperative complications of CRC patients. Neutrophils release chemokines and cytokines that play important roles in stimulating angiogenesis, cytogenesis, antiviral defense, and modulating immune responses (12). Serum albumin is associated with activated systemic inflammation during tumor proliferation and invasion (17). Therefore, NAR is not only an index reflecting the nutritional status, but also a novel marker indicating systemic inflammation and disease severity. Systemic inflammation is the basis of cancer development and progression, so NAR has a good predictive effect on the prognosis of CRC patients.

Uludag et al. found that NAR may be a useful predictive marker for advanced colon cancer, providing more detailed prognostic information for patients with colon cancer and physicians (23). Tawfik et al. found that NAR can be a predictor of pathological complete response after neoadjuvant chemoradiotherapy in patients with rectal cancer (24). However,

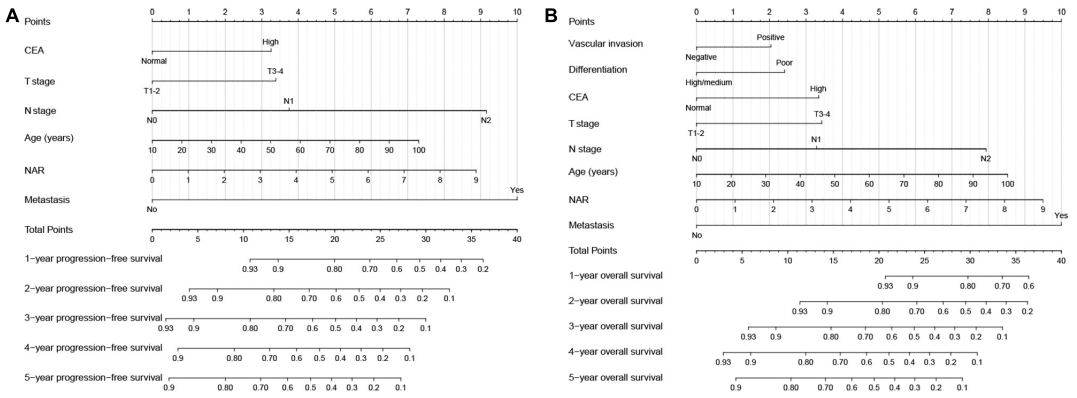


FIGURE 4
Construction the neutrophil-albumin ratio (NAR)-based prognostic nomograms in colorectal cancer (CRC) patients. **(A)** The progression-free survival nomogram; **(B)** the overall survival nomogram.

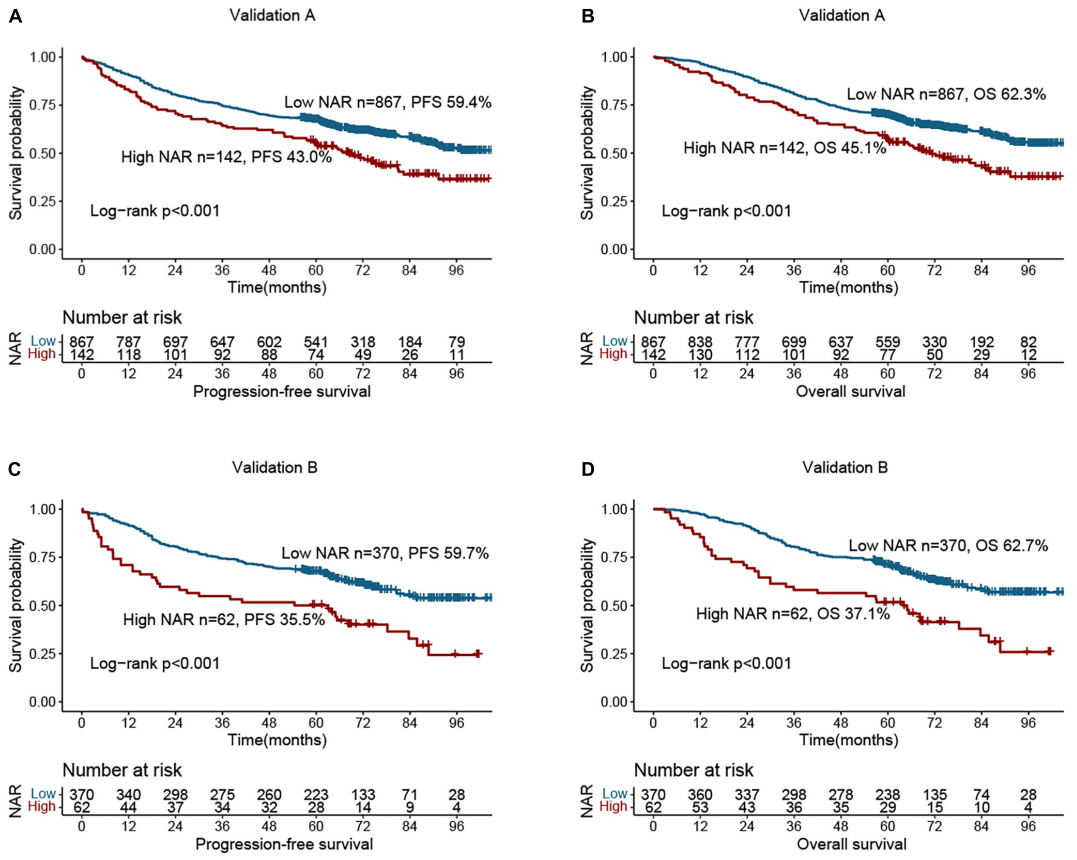


FIGURE 5
Survival analysis of neutrophil-albumin ratio (NAR) in colorectal cancer (CRC) patients at internal validation cohorts. **(A)** Progression-free survival of NAR at validation A; **(B)** overall survival of NAR at validation A; **(C)** progression-free survival of NAR at validation B; **(D)** overall survival of NAR at validation B.

their small sample size and short follow-up period led to certain limitations. In addition, no studies have reported the relationship between preoperative NAR, postoperative complications, and long-term outcomes in patients with CRC. Therefore, this study is the first to report that a high preoperative NAR is an independent risk factor for postoperative complications and prognosis in patients with CRC. Furthermore, we constructed the NAR-based prognostic

nomograms that can directly help clinicians quantify the prognostic risk of CRC patients, thereby making it more convenient and personalized to formulate appropriate treatment strategies for CRC patients. However, our study has some limitations. As this was a single-center retrospective study, there may be a potential selection bias, such as selection bias, follow-up bias, etc. Although we performed an internal validation of the nomograms, further validation in external cohorts is required before the nomogram can be used clinically.

Conclusion

High NAR was an independent risk factor affecting postoperative complications and long-term prognosis of patients with CRC. NAR-based nomograms have good predictive accuracy and can provide a personalized reference for prognostic judgment and clinical decision-making of patients with CRC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University, with the approval number: 2021 (KY-E-043). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JG had full access to all the data in the study, took responsibility for the integrity of the data and the accuracy of the data analysis, and performed conception and design. JG and ST provided management support. HX, GY, and ML did data collection. HX did data analysis and professional drafting. HX and LW wrote the manuscript. All authors agreed to publish, contributed to the manuscript, and approved the submitted version.

Funding

This study was supported by the Guangxi College Students' Innovation and Entrepreneurship Training Program (No. 202110598306), the Guangxi Natural Science Foundation (No. 2019GXNSFAA245064), and the Guangxi Medical and Health Appropriate Technology Development and Application Project (No. S2021095).

Acknowledgments

We would like to thank all authors for their substantial work on data collecting and follow-up.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.976216/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49.

2. Zhang S, Sun K, Zheng R, Zeng H, Wang S, Chen R, et al. Cancer incidence and mortality in China, 2015. *J Natl Cancer Center.* (2021) 1:2–11.

3. Xie H, Wei L, Yuan G, Liu M, Tang S, Gan J. Prognostic value of prognostic nutritional index in patients with colorectal cancer undergoing surgical treatment. *Front Nutr.* (2022) 9:794489. doi: 10.3389/fnut.2022.794489

4. Yamamoto T, Kawada K, Obama K. Inflammation-related biomarkers for the prediction of prognosis in colorectal cancer patients. *Int J Mol Sci.* (2021) 22:8002.

5. Jia W, Yuan L, Ni H, Xu B, Zhao P. Prognostic value of platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and lymphocyte-to-white blood cell ratio in colorectal cancer patients who received neoadjuvant chemotherapy. *Technol Cancer Res Treat.* (2021) 20:15330338211034291. doi: 10.1177/15330338211034291

6. Naszai M, Kurjan A, Maughan TS. The prognostic utility of pre-treatment neutrophil-to-lymphocyte-ratio (NLR) in colorectal cancer: a systematic review and meta-analysis. *Cancer Med.* (2021) 10:5983–97. doi: 10.1002/cam4.4143

7. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity.* (2019) 51:27–41.

8. Taniguchi K, Karin M. NF-κB, inflammation, immunity and cancer: coming of age. *Nat Rev Immunol.* (2018) 18:309–24.

9. Varim C, Celik FD, Sunu C, Öztop KE, Aydın A, Yaylaci S, et al. The role of neutrophil albumin ratio in predicting the stage of non-small cell lung cancer. *Eur Rev Med Pharmacol Sci.* (2022) 26:2900–5.

10. Tingle SJ, Severs GR, Goodfellow M, Moir JA, White SA. NARCA: a novel prognostic scoring system using neutrophil-albumin ratio and Ca19-9 to predict overall survival in palliative pancreatic cancer. *J Surg Oncol.* (2018) 118:680–6. doi: 10.1002/jso.25209

11. Chen Z, Xie D, Li Y, Dai Z, Xiang S, Chen Z, et al. Neutrophil albumin ratio is associated with all-cause mortality in stroke patients: a retrospective database study. *Int J Gen Med.* (2022) 15:1–9. doi: 10.2147/IJGM.S323114

12. Tecchio C, Micheletti A, Cassatella MA. Neutrophil-derived cytokines: facts beyond expression. *Front Immunol.* (2014) 5:508. doi: 10.3389/fimmu.2014.00508

13. Galdiero MR, Varricchi G, Loffredo S, Mantovani A, Marone G. Roles of neutrophils in cancer growth and progression. *J Leukoc Biol.* (2018) 103:457–64.

14. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J.* (2010) 9:69. doi: 10.1186/1475-2891-9-69

15. Joliat GR, Schoor A, Schäfer M, Demartines N, Hübner M, Labgaa I. Postoperative decrease of albumin (ΔAlb) as early predictor of complications after gastrointestinal surgery: a systematic review. *Perioper Med.* (2022) 11:7. doi: 10.1186/s13741-022-00238-3

16. Xie HL, Zhang Q, Ruan GT, Ge YZ, Hu CL, Song MM, et al. Evaluation and validation of the prognostic value of serum albumin to globulin ratio in patients with cancer cachexia: results from a large multicenter collaboration. *Front Oncol.* (2021) 11:707705. doi: 10.3389/fonc.2021.707705

17. Evans DC, Corkins MR, Malone A, Miller S, Mogensen KM, Guenter P, et al. The use of visceral proteins as nutrition markers: an ASPEN position paper. *Nutr Clin Pract.* (2021) 36:22–8.

18. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* (2011) 144:646–74.

19. Ostan R, Lanzarini C, Pini E, Scurti M, Vianello D, Bertarelli C, et al. Inflammaging and cancer: a challenge for the Mediterranean diet. *Nutrients.* (2015) 7:2589–621. doi: 10.3390/nu7042589

20. Lea D, Håland S, Hagland HR, Søreide K. Accuracy of TNM staging in colorectal cancer: a review of current culprits, the modern role of morphology and stepping-stones for improvements in the molecular era. *Scand J Gastroenterol.* (2014) 49:1153–63. doi: 10.3109/00365521.2014.950692

21. Liew PX, Kubes P. The Neutrophil's role during health and disease. *Physiol Rev.* (2019) 99:1223–48.

22. Oñate-Ocaña LF, Aiello-Crocifoglio V, Gallardo-Rincón D, Herrera-Goepfert R, Brom-Valladares R, Carrillo JF, et al. Serum albumin as a significant prognostic factor for patients with gastric carcinoma. *Ann Surg Oncol.* (2007) 14:381–9.

23. Uludag SS, Sanli AN, Zengin AK, Ozcelik MF. Systemic inflammatory biomarkers as surrogate markers for stage in colon cancer. *Am Surg.* (2022) 88:1256–62.

24. Tawfik B, Mokdad AA, Patel PM, Li HC, Huerta S. The neutrophil to albumin ratio as a predictor of pathological complete response in rectal cancer patients following neoadjuvant chemoradiation. *Anticancer Drugs.* (2016) 27:879–83. doi: 10.1097/CAD.0000000000000411

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 17 November 2022
DOI 10.3389/fnut.2022.1069113

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Thanutchaporn Kumrungsee,
Hiroshima University, Japan
Iman Zarei,
University of Eastern Finland, Finland

*CORRESPONDENCE
Hanping Shi
shihp@ccmu.edu.cn
Binyan Wang
binyanwang163@163.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 13 October 2022
ACCEPTED 02 November 2022
PUBLISHED 17 November 2022

CITATION
Liu T, Wang X, Jia P, Liu C, Wei Y, Song Y, Li S, Liu L, Wang B and Shi H (2022) Association between serum arginine levels and cancer risk: A community-based nested case-control study. *Front. Nutr.* 9:1069113. doi: 10.3389/fnut.2022.1069113

Association between serum arginine levels and cancer risk: A community-based nested case-control study

Tong Liu[1,2,3†], Xiaomeng Wang[4†], Pingping Jia[1,2,3†], Chenan Liu[1,2,3], Yaping Wei[5], Yun Song[6], Shuqun Li[6], Lishun Liu[6], Binyan Wang[6*] and Hanping Shi[1,2,3*]

[1]Department of Gastrointestinal Surgery/Clinical Nutrition, Capital Medical University Affiliated Beijing Shijitan Hospital, Beijing, China, [2]Beijing International Science and Technology Cooperation Base for Cancer Metabolism and Nutrition, Beijing, China, [3]Key Laboratory of Cancer FSMP for State Market Regulation, Beijing, China, [4]Department of Education, Capital Medical University Affiliated Beijing Shijitan Hospital, Beijing, China, [5]Key Laboratory of Precision Nutrition and Food Quality, Ministry of Education, Department of Nutrition and Health, College of Food Sciences and Nutritional Engineering, China Agricultural University, Beijing, China, [6]Shenzhen Evergreen Medical Institute, Shenzhen, China

Objective: The effect of arginine on tumors appears to be bidirectional. The association of serum arginine with the risk of incident cancer remains uncovered at present. We aimed to investigate the prospective relationship of baseline serum arginine concentrations with the risk of incident cancer in hypertensive participants.

Materials and methods: A nested, case-control study with 1,389 incident cancer cases and 1,389 matched controls was conducted using data from the China H-Type Hypertension Registry Study (CHHRS). Conditional logistic regression analyses were performed to evaluate the association between serum arginine and the risk of the overall, digestive system, non-digestive system, and site-specific cancer.

Results: Compared with matched controls, cancer patients had higher levels of arginine (21.41 μg/mL vs. 20.88 μg/mL, $p < 0.05$). When serum arginine concentrations were assessed as quartiles, compared with participants in the lowest arginine quartile, participants in the highest arginine quartile had a 32% (OR = 1.32, 95% CI: 1.03 to 1.71), and 68% (OR = 1.68, 95% CI: 1.09 to 2.59) increased risk of overall and digestive system cancer, respectively, in the adjusted models. In the site-specific analysis, each standard deviation (SD) increment of serum arginine was independently and positively associated with the risk of colorectal cancer (OR = 1.35, 95% CI: 1.01 to 1.82) in the adjusted analysis.

Conclusion: We found that hypertensive individuals with higher serum arginine levels exhibited a higher risk of overall, digestive system, and colorectal cancer.

KEYWORDS

arginine, cancer, serum, hypertension, Chinese

Introduction

As the world's most populous country, China has made significant progress in health promotion in recent decades. However, due to increases in the severity of cancer risk factors, especially an aging population, poor diet, and higher rates of obesity, diabetes, and environmental pollution, China continues to experience a growing cancer burden with almost 22 and 27% of the global cancer cases and deaths, respectively, occurring in China in 2015 (1). The established risk factors for cancer include use of tobacco products (2), infectious agents (3), alcohol consumption (4), obesity (5), environmental pollution (6), and poor diet (7). Researchers estimate that almost 60% of cancer could be prevented by reducing these risk factors, many of which are modifiable (8). It is important to investigate numerous carcinogenic factors to determine potential screening and prevention methods.

Arginine, a semi-essential amino acid, plays a crucial role in the urea cycle and the synthesis of protein, polyamines, creatine, and nitric oxide (NO) (9). L-arginine supplementation has been demonstrated to be beneficial for endothelium-derived NO production and endothelial function in numerous studies, reducing systemic blood pressure in some forms of experimental hypertension (10). Animal studies have shown that arginine reduces white fat mass while increasing brown fat and skeletal muscle mass, increases several lipolytic enzymes, and reduces the levels of insulin resistance (IR) (11–14). Moreover, L-arginine concentrations in the intracellular environment have a direct impact on the metabolic fitness and survival capacities of T cells which are crucial for anti-tumor immunity (15). Arginine may reduce the risk of cancer due to its beneficial effect on the regulation of nutrient metabolism and T cells. In recent years, however, arginine's role in carcinogenesis has received increasing attention because it promotes cell growth in cancerous tissues (16). Cancer microenvironments are profoundly affected by arginine availability and the activation of arginine-related pathways (16). Notably, polyamines and NO, synthesized solely from arginine, may affect tumor initiation, progression, tumor-cell adhesion, differentiation, angiogenesis, and immunosuppression (17–19). In addition, clinical trials have shown positive results with arginine deprivation in cancer therapy (20).

In short, the effect of arginine on tumors appears to be bidirectional. However, as an important amino acid, the precise role of serum arginine concentrations on the occurrence of cancer is poorly understood. This study aimed to explore the association of serum arginine levels with incident cancer risk by drawing data from a case-control study, nested within a community-based, prospective cohort among hypertensive participants, thereby providing possible implications for early diagnosis and treatment of cancer.

Materials and methods

Study population

The population in the current study was obtained from the China H-Type Hypertension Registry Study (CHHRS; URL[1]; unique identifier: ChiCTR1800017274), which is an ongoing, community-based, observational, and real-world registry study. The CHHRS aimed to establish a national registry of H-type hypertensive patients, to assess the prevalence, treatment, and prognosis of H-type hypertension in China. Individuals aged 18 years and over with essential hypertension, defined as seated, systolic blood pressure (SBP) $\geq$ 140 mmHg and/or seated, diastolic blood pressure (DBP) $\geq$ 90 mmHg at the screening visit were eligible for participation. Participants were excluded if they had a psychological or nervous system impairment that prevented them from giving informed consent or from being followed up according to the study protocol. There were two stages in this study: (1) recruitment and (2) observation follow-up which was scheduled every 3 months during the 3-year trial period. At each visit, SBP, DBP, heart rate, medication usage, adverse events, and study outcomes were recorded. The primary outcome was the first composite of cardiovascular events and consisted of non-fatal strokes, myocardial infarcts, and vascular deaths. Other outcomes included cancer, kidney disease, and all-cause mortality.

1 http://www.chictr.org.cn/showprojen.aspx?proj=28262

Outcome assessment

Ascertainment of cancer was carried out by the Centers for Disease Control and Prevention (CDC) of Rongcheng, or through electronic linkage to hospitalizations where patients had received treatment for malignant tumors, or from active follow-up. In the absence of pathological results, potential cancer cases were further evaluated by two oncologists. Cancer cases could only be identified when the diagnoses were confirmed by both oncologists and were coded using the International Classification of Diseases, Tenth Revision (ICD-10).

Nested case-control study

We conducted a case-control study nested within the CHHRS. The controls were selected from the study population who were cancer-free at the end of the follow-up period and were matched with cases by age (± 1 year), sex, and region in a 1:1 ratio. The initial sample consisted of 1,419 incident cases and 1,419 matched controls. After excluding 31 participants with missing serum arginine measurements and 29 unpaired individuals, a total of 2,778 participants (1,389 cancer cases vs. 1,389 matched controls) were included in the final analysis (**Figure 1**). Participants were further divided into four groups based on arginine quartiles, with cut-off values of 17.62, 21.16, and 25.64 μg/mL, respectively.

Exposure and covariates

A morning serum sample was collected from all participants following an overnight fast at the baseline screening. Serum arginine was measured using liquid chromatography with tandem quadrupole mass spectrometry (LC-MS/MS) in a commercial lab (Beijing DIAN Medical Laboratory, China[2]). The descriptions of LC-MS/MS setting parameters, the modes and type of the instrument are described in **Supplementary material**. Biochemical indexes including alanine aminotransferase (ALT), albumin (ALB), triglycerides (TG), total cholesterol (TC), uric acid (UA), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), creatinine, homocysteine (HCY), and folate were analyzed using automatic clinical analyzers (Beckman Coulter) at the central laboratory of the National Clinical Research Center for Kidney Disease, (Nanfang Hospital, Guangzhou, China). Information on age, sex, marital status, education level, smoking status, alcohol consumption, sleep quality, history of chronic disease, antihypertensive drug usage, and family history of cancer was collected using a standard questionnaire. Participant height and weight were measured by trained medical staff, and body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m^2).

Statistical analysis

Participant baseline characteristics were presented as means ± SDs, medians (IQR), and proportions for normally distributed, skewed distributed, and categorical variables; differences between the cases and controls were compared using paired *t*-tests, non-parametric Kruskal-Wallis tests, and chi-square tests (Fisher's exact test), respectively. The dose-response relationship between arginine (per SD) and cancer risk was calculated by restricted cubic spline regression (RCS). Odds ratios (ORs) and 95% confidence intervals (CIs) for the association of serum arginine levels (per SD, and quartiles) with overall, digestive system, and non-digestive system cancer risk were estimated using conditional logistic regression with models unadjusted and adjusted for the variables including BMI, smoking status, alcohol drinking status, SBP, TG, TC, UA, glucose, HDL-C, creatinine, ALB, ALT, HCY, sleep quality, anti-hypertensive drug usage, and family history of cancer. In addition, we further explored the effect of serum arginine levels on the occurrence of site-specific cancers. A subgroup analysis on the association was also conducted on the variables age (median, < 69 vs. ≥ 69 years), sex, smoking status (never vs. past or current), drinking status (never vs. past or current), folate levels (median, < 6.13 vs. ≥ 6.13 ng/mL), and BMI (< 24 vs. 24–27.9 vs. ≥ 28 kg/m^2). The association of serum arginine with cancer risk was reanalyzed after further dividing participants by their median follow-up interval according to the time of cancer occurrence (< median vs. ≥ median follow-up period) to avoid any possible influence of preclinical disease on the results. A two-tailed $P < 0.05$ was considered statistically significant in all analyses. R software (version 3.4.1[3]) and SAS (version 9.4) were used for all statistical analyses.

Results

Baseline characteristics of the participants

The current study included 1,389 cancer cases, with 543 digestive system cancer cases and 846 non-digestive system cancer cases. The most common cancer types were lung (n = 361), followed by colorectal (n = 180), gastric (n = 160), liver (n = 107), breast (n = 85), head and neck (n = 82), prostatic

2 http://www.dazd.cn

3 http://www.R-project.org

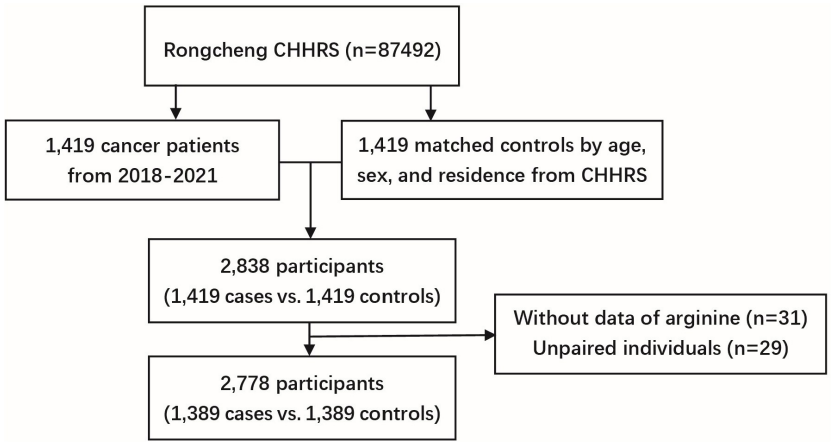


FIGURE 1
Flow chart of study participants in the nested case-control study within the HHPCP.

TABLE 1 Baseline characteristics of the cancer cases and matched controls.

Variables	Controls (n = 1,389)	Cases (n = 1,389)	p-value
Age, y	69.32 ± 7.76	69.32 ± 7.76	0.999
Males, n (%)	779 (56.08)	779 (56.08)	1.000
BMI, kg/m^2	25.73 ± 3.60	25.72 ± 3.83	0.953
Baseline SBP, mmHg	148.48 ± 21.26	147.52 ± 21.30	0.237
Baseline DBP, mmHg	83.73 ± 11.33	83.07 ± 11.76	0.134
ALT, U/L	8.05 (7.0, 13.0)	10.0 (7.0, 14.0)	0.148
ALB, g/L	45.43 ± 2.45	44.75 ± 2.97	< 0.001
TG, mmol/L	1.21 (0.86, 1.77)	1.19 (0.84, 1.80)	0.630
TC, mmol/L	6.51 ± 1.23	6.44 ± 1.30	0.202
UA, μmol/L	320.0 (269.0, 371.0)	314.0 (264.0, 374.0)	0.393
HDL-C, mmol/L	1.23 ± 0.24	1.22 ± 0.27	0.795
FBG, mmol/L	6.25 ± 1.71	6.29 ± 1.83	0.626
Creatinine, μmol/L	45.84 (27.03, 51.00)	52.0 (10.0, 64.0)	0.748
Folate, ng/mL	6.14 (4.03,9.66)	6.11 (4.22, 10.12)	0.466
HCY, μmol/L	12.01 (10.31, 14.66)	12.25 (10.06, 15.03)	0.886
Arginine, μg/mL	20.88 (17.34, 25.11)	21.41 (17.94, 26.25)	0.001
Marital status, [married, n (%)]	1144 (82.36)	1178 (84.81)	0.354
High school education or above, n (%)	108 (7.78)	103 (7.42)	0.720
Current smoker, n (%)	334 (24.05)	401 (28.87)	0.011
Current drinker, n (%)	388 (27.93)	370 (26.64)	0.359
History of CKD, n (%)	14 (1.01)	25 (1.80)	0.076
History of CHD, n (%)	0 (0)	165 (11.88)	< 0.001*
History of stroke, n (%)	0 (0)	64 (4.61)	< 0.001*
Family history of cancer, n (%)	47 (3.38)	50 (3.60)	0.918
Poor sleep quality, n (%)	191 (13.75)	259 (18.65)	0.002
Antihypertensive drug usage, n (%)	494 (35.57)	557 (40.10)	0.014

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; ALB, albumin; TG, triglycerides; TC, total cholesterol; UA, uric acid; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; HCY, homocysteine; CKD, chronic kidney disease; CHD, coronary heart disease. *Compared by Fisher's exact test.

(n = 58), lymphoma and leukemia (n = 57), pancreatic (n = 48), uterine and cervical (n = 47), and bladder cancer (n = 41). Table 1 shows the characteristics of cancer patients and matched controls. Compared with matched controls, cancer patients had higher levels of arginine (21.41 μg/mL vs. 20.88 μg/mL, $p < 0.05$). Significant differences were found in concentrations

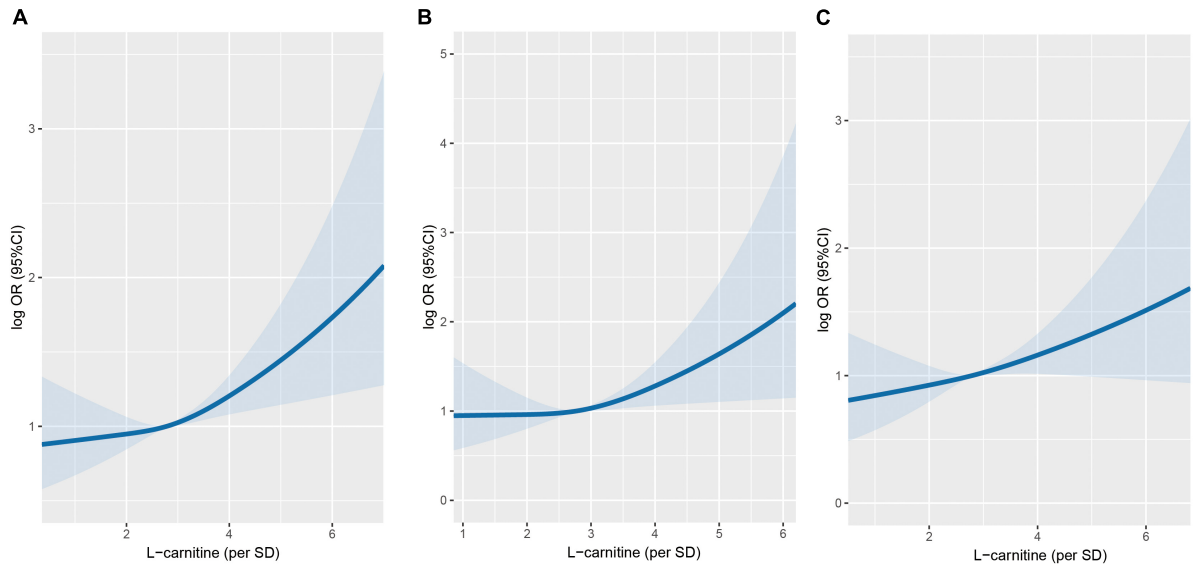


FIGURE 2
Association between serum arginine concentrations and cancer risk using restricted cubic spline (RCS). **(A)** Overall cancer. **(B)** Digestive system cancer. **(C)** Non-digestive system cancer. Models were adjusted for BMI, smoking status, alcohol drinking, systolic blood pressure, triglycerides, cholesterol, uric acid, glucose, HDL-C, creatinine, ALB, ALT, HCY, sleep quality, antihypertensive drug usage, and family history of cancer.

of ALB, and percentage rates of the current smoker, history of stroke, history of CHD, poor sleep quality, and antihypertensive drug usage between cases and matched controls. In addition, there were no differences between cancer patients and controls in terms of age, sex, BMI, blood pressure, ALT, TG, TC, UA, HDL-C, FBG, creatinine, folate, HCY, marital status, current drinker, history of CKD, and family history of cancer (all p-values for differences > 0.05).

Association of arginine with the risk of cancer

Figure 2 shows the dose-response relationship between arginine concentrations (per SD) and incident cancer risk. Arginine was found to be positively, and non-linearly correlated with the risk of overall and digestive system cancer, but not with the risk of non-digestive system cancer. Tables 2, 3 show the ORs (95% CI) of arginine associated with the risk of overall, digestive system cancer, and non-digestive system cancer. Each standard deviation (SD) increment of serum arginine concentration significantly elevated the risk of overall cancer (OR = 1.13, 95% CI: 1.03 to 1.24) and digestive system cancer (OR = 1.21, 95% CI: 1.04 to 1.42) in the multivariate analysis. Compared with participants in the lowest arginine quartile (Q1), patients in the highest arginine quartile (Q4) had a 32% (OR = 1.32, 95% CI: 1.03 to 1.71), and 68% (OR = 1.68, 95% CI: 1.09 to 2.59) increased risk of overall and digestive system cancer in the adjusted models, respectively. Table 4 shows the effect of arginine on the occurrence of site-specific cancers. Each standard deviation (SD) increment of serum arginine was independently and positively associated with the risk of colorectal cancer in the adjusted analysis (OR = 1.35, 95% CI: 1.01 to 1.82).

Subgroup analyses

Figure 3 illustrates the results of the subgroup analysis of the association between serum arginine concentrations and overall cancer risk. None of the factors, including age, sex, smoking status, drinking status, folate levels, body mass index, and follow-up period, had an effect on the association between arginine concentrations and overall cancer risk (all p for interaction < 0.05). Significant, positive associations of arginine levels with overall cancer risk were found among all age subgroups, males, past/current smokers, and those with lower folic acid levels, normal BMI and whose cancer occurred prior to the median of the follow-up period.

Discussion

In this case-control study nested within a population-based, prospective cohort study, we found that hypertensive individuals with higher serum arginine levels exhibited a higher risk of overall cancer. Significant associations were similarly observed for digestive system cancer, especially colorectal

TABLE 2 The association of serum arginine with overall cancer risk.

Arginine (μg/mL)	Cases/Controls (Ratio 1:1)	Crude model		Adjusted model	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Per SD	1389/1389	**1.16 (1.07, 1.26)**	**< 0.001**	**1.13 (1.03, 1.24)**	**0.007**
Quartiles					
Q1 (< 17.62)	327/368	Ref.		Ref.	
Q2 (17.62– < 21.16)	343/352	1.12 (0.90, 1.38)	0.309	1.05 (0.83, 1.32)	0.681
Q3 (21.16– < 25.64)	339/354	1.11 (0.89, 1.38)	0.348	1.13 (0.89, 1.45)	0.321
Q4 (≥ 25.64)	380/315	**1.43 (1.14, 1.79)**	**0.002**	**1.32 (1.03, 1.71)**	**0.031**

Models were adjusted for ALT, ALB, BMI, smoking status, alcohol drinking, SBP, TC, TG, UA, HDL-C, glucose, creatinine, folate, HCY, sleep quality, antihypertensive medication, and family history of cancer. Statistically significant values are shown in bold with all *p* values < 0.05.

TABLE 3 The association of arginine with the digestive system and non-digestive system cancer risk.

Arginine (μg/mL)	Digestive system			Non-digestive system		
	Cases/Controls	OR (95% CI)	*p*-value	Cases/Controls	OR (95% CI)	*p*-value
Per SD	543/543	**1.21 (1.04, 1.42)**	**0.017**	846/846	1.09 (0.97, 1.22)	0.135
Quartiles						
Q1 (< 17.62)	133/153	Ref.		194/215	Ref.	
Q2 (17.62– < 21.16)	129/134	1.08 (0.73, 1.59)	0.694	214/218	1.01 (075, 1.36)	0.953
Q3 (21.16– < 25.64)	139/139	1.30 (0.86, 1.96)	0.207	200/215	1.06 (0.78, 1.46)	0.704
Q4 (≥ 25.64)	142/117	**1.68 (1.09, 2.59)**	**0.018**	238/198	1.15 (0.83, 1.60)	0.397

Models were adjusted for ALT, ALB, BMI, smoking status, alcohol drinking, SBP, TC, TG, UA, HDL-C, glucose, creatinine, folate, HCY, sleep quality, antihypertensive medication usage, and family history of cancer. Statistically significant values are shown in bold with all *p* values < 0.05.

TABLE 4 The association of serum arginine (per SD) with site-specific cancer risk.

Arginine (μg/mL)	Cases/Control (Ratio 1:1)	Crude model		Adjusted model	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Lung cancer	361/361	**1.22 (1.04, 1.43)**	**0.015**	1.15 (0.96, 1.37)	0.131
Colorectal cancer	180/180	**1.40 (1.10, 1.76)**	**0.006**	**1.35 (1.01, 1.82)**	**0.048**
Gastric cancer	160/160	1.23 (0.95, 1.59)	0.118	1.34 (0.97, 1.86)	0.077
Liver cancer	107/107	0.87 (0.63, 1.19)	0.379	0.89 (0.58, 1.36)	0.589
Breast cancer	85/85	1.13 (0.82, 1.51)	0.487	1.05 (0.70, 1.59)	0.813
Head and neck cancer	82/82	**1.67 (1.14, 2.44)**	**0.008**	1.48 (0.93, 2.35)	0.096
Lymphoma and leukemia	57/57	1.19 (0.80, 1.78)	0.167	2.23 (0.72, 6.93)	0.167
Prostatic cancer	58/58	0.97 (0.68, 1.38)	0.878	0.90 (0.53, 1.53)	0.695
Pancreatic cancer	48/48	1.06 (0.68, 1.68)	0.788	0.57 (0.16.2.12)	0.405
Bladder cancer	41/41	1.07 (0.71, 1.59)	0.759	0.46 (0.14, 1.55)	0.210
Uterine and cervical cancer	47/47	0.90 (0.55, 1.47)	0.664	0.66 (0.31, 1.40)	0.282

Models were adjusted for ALT, ALB, BMI, smoking status, alcohol drinking, SBP, TC, TG, UA, HDL-C, glucose, creatinine, HCY, sleep quality, antihypertensive medication, and family history of cancer. Statistically significant values are shown in bold with all *p* values < 0.05.

cancer. We also observed significant associations of arginine levels with overall cancer risk among all age subgroups, males, past/current smokers, and individuals with lower folic acid levels, normal BMI and with cancer occurring before the median follow-up period.

This study is the first to find that serum arginine levels are positively associated with overall and colorectal cancer risk in hypertensive cancer-free participants. However, results from several previous studies partly support our findings as follows: A study including *in vivo* results in mice and epidemiologic results in human cancer cases found that an arginine diet resulted in higher tumor grades in mice, and meat consumption (a major source of dietary arginine) resulted in adverse outcomes for patients suffering from familial CRC (21); Yerushalmi HF et al.

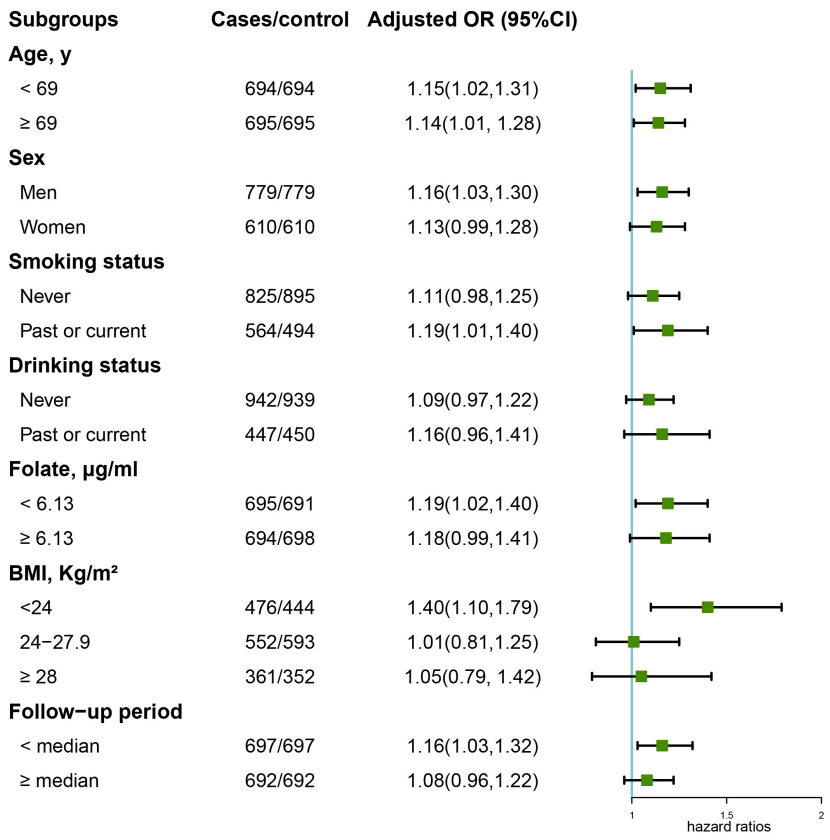


FIGURE 3
Stratified analyses of the association of serum arginine (per SD) with the risk of overall cancer. Models were adjusted for BMI, smoking status, alcohol drinking, systolic blood pressure, triglycerides, cholesterol, uric acid, glucose, HDL-C, creatinine, ALB, ALT, HCY, sleep quality, antihypertensive drug usage, and family history of cancer except for the stratified factors.

evaluated the roles of dietary arginine and inducible nitric oxide synthase (NOS2) in Apc-dependent intestinal tumorigenesis in Min mice with or without a functional NOS2 gene, and found that dietary arginine increased colon tumorigenesis in ApcMin/ + mice (22); Some tumors (auxotrophic tumors) require arginine for growth, and disturbances in arginine metabolism is a distinct feature of the presence of a malignant tumor. Several previous studies also found a significant decrease in arginine levels among cancer patients (23–25).

Nitric Oxide (NO) is a ubiquitous signal transduction molecule generated by arginine metabolism, and NO has been linked to a large number of cancer-related events (16). Despite its simplistic biochemistry, NO plays an extremely complex role in tumor biology. One study found that ulcerative colitis patients might be more likely to develop cancer because chronic colonic inflammation increases NO production (17). Furthermore, NO has also been implicated in the development of cholangiocarcinoma (18) and hepatocellular carcinoma (26) in experimental studies. Moreover, several lines of investigation have suggested that arginine-derived NO could influence the initiation, progression, apoptosis, angiogenesis, and metastasis of numerous neoplasms (27–29).

Many cancer cells show deficiencies in arginine metabolic pathways and thus rely on the uptake of arginine for rapid metabolism and proliferation. The auxotrophy of cancer cells to arginine renders these cancer cells vulnerable to the deprivation of this specific amino acid. Thus, arginine deprivation has become an accessible choice for cancer treatment. Arginine deprivation drugs are necessary since dietary restriction only reduces circulating arginine by 30% (30). Thus far, two types of protein drugs, arginine deiminase (ADI) and human arginase (hArg), have been developed to deplete arginine for cancer treatment (31, 32).

It is evident that arginine, and its availability, affect lymphocyte performance. Infiltrating macrophages (TIM) possess high arginase levels, which may modulate arginine availability in the tumor's microenvironment. This inhibiting effect of arginine supplementation on immunogenic tumors may be due to its beneficial effects on the immune system, particularly macrophages, natural killer cells, and T cell cytotoxicity (33). Early studies have found that arginine

supplementation increases T-cell proliferation and reverses post-traumatic T-cell suppression (34, 35). Arginine is also shown to enhance T-cell responses in nude mice (36), although those effects have not been observed in other immune-activated states (37). A nested, case-control study within the European Prospective Investigation into Cancer cohort (EPIC) including 1,124 breast cancer cases and 1,124 matched controls, found that concentrations of arginine were inversely associated with breast cancer risk (OR [per SD] = 0.79, 95% CI = 0.70–0.90) (38).

Recently, other amino acids rather than arginine are demonstrated to be closely associated with cancer development. First, asparagine (Asn) suppresses apoptosis by negatively modulating endoplasmic reticulum stress and translation-dependent apoptosis (39). Cancer cells that express a low level or are deficient in Asn synthetase (ASNS) may be induced by Asn starvation (40). Second, a high level of glutamine (Gln) is essential for maintaining TCA cycle anaplerosis and supporting the survival of cancer cells (41). Third, cancer cells exhibit elevated levels of ROS intracellularly due to alterations in the microenvironment and metabolism (42). As a counterbalance to excessive ROS levels, tumor cells maintain reduced forms of glutathione (GSH) in part to produce more reducing equivalents (43). As cysteine (Cys) is one of the building blocks of GSH, elevated production of Cys may exhaust endogenous sources of the substance (44).

The main strength of the current study is its novelty, for it uncovers the association of serum arginine levels with the risk of incident cancer among a hypertensive Chinese population. Furthermore, it has the advantage of being a nested, case-control study that was derived from a large, prospective cohort study, thus avoiding recall bias. The serum arginine levels of participants were determined before any cancer diagnosis, eliminating the possibility of a causal association.

Several limitations should also be noted in the current study. First, serum arginine levels were only measured at baseline, regular measurements would have provided a better understanding of the dynamic relationship between cancer risk and changes in arginine levels. Second, the small number of cancer cases and the short follow-up period prevented further analysis on subtypes of cancer, a larger population is needed to validate the findings. Third, this case-control study was nested within CHHRS, which was designed to assess the prevalence, treatment, and prognosis of H-type hypertension in China. Therefore, the population in this study was hypertensive adults. It is unclear if the findings can be generalized to non-hypertensive populations. However, blood pressure was also adjusted for in the multivariate analysis, which minimized the impact of blood pressure in the current study. Fourth, although we found a positive association between arginine and cancer risk, whether the higher levels of blood arginine are the possible cause or as the major precursor for synthesis of cancer-associated compounds such as NO, and NO synthetase need to be better elucidated in the future studies. Last, our results were based on a nested, case-control study; further explorations of this association in large-scale cohort studies and randomized trials are needed.

Conclusion

In this nested, case-control study among a hypertensive adult population, we found an independent effect of serum arginine concentrations on the risk of incident cancer. In light of the heavy burden and the fatality of cancer in China and throughout the world, our study's findings could provide a safe and straightforward mechanism for cancer prevention.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the CHHRS and the present study were approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TL: methodology, software, and writing—original draft preparation. XW: writing—reviewing and editing. PJ: methodology and software. CL: visualization. YW, LL, and BW: supervision and validation. YS: investigation. SL: supervision. HS: conceptualization, funding acquisition, resources, and supervision. All authors contributed to the article and approved the submitted version.

Funding

This study was HS reports financial support by grants from the National Key Research and Development Program (2022YFC2009600) and the Beijing Municipal Science and Technology Commission (SCW2018-06). BW

reports funding from the Science, Technology, and Innovation Committee of Shenzhen (JSGG20180703155802047).

Acknowledgments

We thank all the staff and participants of the HHPCP for their important contributions.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1069113/full#supplementary-material

References

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* (2016) 66:115–32.

2. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* (2018) 392:1923–94.

3. Liu T, Song C, Zhang Y, Siyin ST, Zhang Q, Somg M, et al. Hepatitis B virus infection and the risk of gastrointestinal cancers among Chinese population: a prospective cohort study. *Int J Cancer.* (2022) 150:1018–28.

4. Pflaum T, Hausler T, Baumung C, Ackermann S, Kuballa T, Rehm J, et al. Carcinogenic compounds in alcoholic beverages: an update. *Arch Toxicol.* (2016) 90:2349–67.

5. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body fatness and cancer–viewpoint of the IARC working group. *N Engl J Med.* (2016) 375:794–8. doi: 10.1056/NEJMsr1606602

6. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev.* (2005) 14:1847–50. doi: 10.1158/1055-9965.EPI-05-0456

7. Eliassen AH, Liao X, Rosner B, Tamimi RM, Tworoger SS, Hankinson SE. Plasma carotenoids and risk of breast cancer over 20 y of follow-up. *Am J Clin Nutr.* (2015) 101:1197–205. doi: 10.3945/ajcn.114.105080

8. Wang JB, Jiang Y, Liang H, Li P, Xiao HJ, Ji J, et al. Attributable causes of cancer in China. *Ann Oncol.* (2012) 23:2983–9.

9. Mangoni AA, Rodionov RN, McEvoy M, Zinellu A, Carru C, Sotgia S. New horizons in arginine metabolism, ageing and chronic disease states. *Age Ageing.* (2019) 48:776–82. doi: 10.1093/ageing/afz083

10. Gokce N. L-arginine and hypertension. *J Nutr.* (2004) 134(10 Suppl):2807S–11S.

11. McKnight JR, Satterfield MC, Jobgen WS, Smith SB, Spencer TE, Meininger CJ, et al. Beneficial effects of L-arginine on reducing obesity: potential mechanisms and important implications for human health. *Amino Acids.* (2010) 39:349–57. doi: 10.1007/s00726-010-0598-z

12. Ball RO, Urschel KL, Pencharz PB. Nutritional consequences of interspecies differences in arginine and lysine metabolism. *J Nutr.* (2007) 137(6 Suppl 2):1626s–41s. doi: 10.1093/jn/137.6.1626S

13. Morris SM Jr. Arginine metabolism: boundaries of our knowledge. *J Nutr.* (2007) 137(6 Suppl 2):1602s–9s. doi: 10.1093/jn/137.6.1602S

14. McNeal CJ, Meininger CJ, Reddy D, Wilborn CD, Wu G. Safety and effectiveness of arginine in adults. *J Nutr.* (2016) 146:2587s–93s.

15. Geiger R, Rieckmann JC, Wolf T, Basso C, Feng Y, Fuhrer T, et al. L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity. *Cell.* (2016) 167:829–42.e13. doi: 10.1016/j.cell.2016.09.031

16. Lind DS. Arginine and cancer. *J Nutr.* (2004) 134(10 Suppl):2837S–41S.

17. Lagares-Garcia JA, Moore RA, Collier B, Heggere M, Diaz F, Qian F. Nitric oxide synthase as a marker in colorectal carcinoma. *Am Surg.* (2001) 67:709–13.

18. Jaiswal M, LaRusso NF, Shapiro RA, Billiar TR, Gores GJ. Nitric oxide-mediated inhibition of DNA repair potentiates oxidative DNA damage in cholangiocytes. *Gastroenterology.* (2001) 120:190–9. doi: 10.1053/gast.2001.20875

19. Morbidelli L, Donnini S, Ziche M. Role of nitric oxide in tumor angiogenesis. *Cancer Treat Res.* (2004) 117:155–67.

20. Zhang Y, Chung SF, Tam SY, Leung YC, Guan X. Arginine deprivation as a strategy for cancer therapy: an insight into drug design and drug combination. *Cancer Lett.* (2021) 502:58–70. doi: 10.1016/j.canlet.2020.12.041

21. Zell JA, Ignatenko NA, Yerushalmi HF, Ziogas A, Besselsen DG, Gerner EW, et al. Risk and risk reduction involving arginine intake and meat consumption in colorectal tumorigenesis and survival. *Int J Cancer.* (2007) 120:459–68. doi: 10.1002/ijc.22311

22. Yerushalmi HF, Besselsen DG, Ignatenko NA, Blohm-Mangone KA, Padilla-Torres JL, Stringer DE, et al. The role of NO synthases in arginine-dependent small intestinal and colonic carcinogenesis. *Mol Carcinog.* (2006) 45:93–105. doi: 10.1002/mc.20168

23. Vissers YL, Dejong CH, Luiking YC, Fearon KC, von Meyenfeldt MF, Deutz NE. Plasma arginine concentrations are reduced in cancer patients: evidence for arginine deficiency? *Am J Clin Nutr.* (2005) 81:1142–6. doi: 10.1093/ajcn/81.5.1142

24. Bi X, Henry CJ. Plasma-free amino acid profiles are predictors of cancer and diabetes development. *Nutr Diabetes.* (2017) 7:e249. doi: 10.1038/nutd.2016.55

25. Fukutake N, Ueno M, Hiraoka N, Shimada K, Shiraishi K, Saruki N, et al. A novel multivariate index for pancreatic cancer detection based on the plasma free amino acid profile. *PLoS One.* (2015) 10:e0132223. doi: 10.1371/journal.pone.0132223

26. Majano PL, Garcia-Monzon C. Does nitric oxide play a pathogenic role in hepatitis C virus infection? *Cell Death Differ.* (2003) 10(Suppl 1):S13–5.

27. Roy B, Guittet O, Beuneu C, Lemaire G, Lepoivre M. Depletion of deoxyribonucleoside triphosphate pools in tumor cells by nitric oxide. *Free Radic Biol Med.* (2004) 36:507–16. doi: 10.1016/j.freeradbiomed.2003.11.028

28. Reveneau S, Arnould L, Jolimoy G, Hilpert S, Lejeune P, Saint-Giorgio V, et al. Nitric oxide synthase in human breast cancer is associated with tumor grade, proliferation rate, and expression of progesterone receptors. *Lab Invest.* (1999) 79:1215–25.

29. Xie K, Huang S. Contribution of nitric oxide-mediated apoptosis to cancer metastasis inefficiency. *Free Radic Biol Med.* (2003) 34:969–86. doi: 10.1016/s0891-5849(02)01364-3

30. Dillon BJ, Holtsberg FW, Ensor CM, Bomalaski JS, Clark MA. Biochemical characterization of the arginine degrading enzymes arginase and arginine deiminase and their effect on nitric oxide production. *Med Sci Monit.* (2002) 8:Br248–53.

31. Tomlinson BK, Thomson JA, Bomalaski JS, Diaz M, Akande T, Mahaffey N, et al. Phase I trial of arginine deprivation therapy with ADI-PEG 20 plus docetaxel in patients with advanced malignant solid tumors. *Clin Cancer Res.* (2015) 21:2480–6. doi: 10.1158/1078-0432.CCR-14-2610

32. Patil MD, Bhaumik J, Babykutty S, Banerjee UC, Fukumura D. Arginine dependence of tumor cells: targeting a chink in cancer's armor. *Oncogene.* (2016) 35:4957–72. doi: 10.1038/onc.2016.37

33. Thomsen LL, Miles DW. Role of nitric oxide in tumour progression: lessons from human tumours. *Cancer Metastasis Rev.* (1998) 17:107–18.

34. Daly JM, Reynolds J, Thom A, Kinsley L, Dietrick-Gallagher M, Shou J, et al. Immune and metabolic effects of arginine in the surgical patient. *Ann Surg.* (1988) 208:512–23.

35. Albaugh VL, Pinzon-Guzman C, Barbul A. Arginine-Dual roles as an onconutrient and immunonutrient. *J Surg Oncol.* (2017) 115:273–80. doi: 10.1002/jso.24490

36. Kirk SJ, Regan MC, Wasserkrug HL, Sodeyama M, Barbul A. Arginine enhances T-cell responses in athymic nude mice. *JPEN J Parenter Enteral Nutr.* (1992) 16:429–32. doi: 10.1177/0148607192016005429

37. Torre PM, Ronnenberg AG, Hartman WJ, Prior RL. Oral arginine supplementation does not affect lymphocyte proliferation during endotoxin-induced inflammation in rats. *J Nutr.* (1993) 123:481–8.

38. His M, Viallon V, Dossus L, Gicquiau A, Achaintre D, Scalbert A, et al. Prospective analysis of circulating metabolites and breast cancer in EPIC. *BMC Med.* (2019) 17:178. doi: 10.1186/s12916-019-1408-4

39. Zhang J, Fan J, Venneti S, Cross JR, Takagi T, Bhinder B, et al. Asparagine plays a critical role in regulating cellular adaptation to glutamine depletion. *Mol Cell.* (2014) 56:205–18. doi: 10.1016/j.molcel.2014.08.018

40. Story MD, Voehringer DW, Stephens LC, Meyn RE. L-asparaginase kills lymphoma cells by apoptosis. *Cancer Chemother Pharmacol.* (1993) 32:129–33.

41. DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S, et al. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *Proc Natl Acad Sci USA.* (2007) 104:19345–50. doi: 10.1073/pnas.0709747104

42. Trachootham D, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? *Nat Rev Drug Discov.* (2009) 8:579–91. doi: 10.1038/nrd2803

43. Harris IS, Treloar AE, Inoue S, Sasaki M, Gorrini C, Lee KC, et al. Glutathione and thioredoxin antioxidant pathways synergize to drive cancer initiation and progression. *Cancer Cell.* (2015) 27:211–22. doi: 10.1016/j.ccell.2014.11.019

44. Zhang W, Trachootham D, Liu J, Chen G, Pelicano H, Garcia-Prieto C, et al. Stromal control of cystine metabolism promotes cancer cell survival in chronic lymphocytic leukaemia. *Nat Cell Biol.* (2012) 14:276–86. doi: 10.1038/ncb2432

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 17 November 2022
DOI 10.3389/fnut.2022.994499

OPEN ACCESS

EDITED BY
Lidia Santarpia,
University of Naples Federico II, Italy

REVIEWED BY
Antonietta Gigante,
Sapienza University of Rome, Italy
Clare Shaw,
Royal Marsden NHS Foundation Trust, United Kingdom

*CORRESPONDENCE
Massimo Pellegrini
massimo.pellegrini@unimore.it

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 14 July 2022
ACCEPTED 27 October 2022
PUBLISHED 17 November 2022

CITATION
Bardoscia L, Besutti G, Pellegrini M, Pagano M, Bonelli C, Bonelli E, Braglia L, Cozzi S, Roncali M, Iotti C, Pinto C, Pattacini P and Ciammella P (2022) Impact of low skeletal muscle mass and quality on clinical outcomes in patients with head and neck cancer undergoing (chemo)radiation. *Front. Nutr.* 9:994499. doi: 10.3389/fnut.2022.994499

Impact of low skeletal muscle mass and quality on clinical outcomes in patients with head and neck cancer undergoing (chemo)radiation

Lilia Bardoscia[1†], Giulia Besutti[2,3†], Massimo Pellegrini[4*], Maria Pagano[5], Candida Bonelli[5], Efrem Bonelli[2], Luca Braglia[6], Salvatore Cozzi[1], Massimo Roncali[7], Cinzia Iotti[1], Carmine Pinto[5], Pierpaolo Pattacini[2] and Patrizia Ciammella[1]

[1]Radiation Oncology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [2]Radiology Unit, Department of Imaging and Laboratory Medicine, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [3]Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy, [4]Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy, [5]Oncology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [6]Research and Statistics Infrastructure, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [7]Nuclear Medicine Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy

The study aimed to explore the impact of low skeletal muscle mass and quality on survival outcomes and treatment tolerance in patients undergoing radical chemo-radiation therapy for head and neck cancer (HNC). This is significant given the growing interest in sarcopenia as a possible negative predictive/prognostic factor of disease progression and survival. From 2010 to 2017, 225 patients were included in the study. Pre-treatment computed tomography (CT) scans of HNC patients undergoing (chemo)radiation therapy were retrospectively reviewed. The skeletal muscle area, normalized for height to obtain the skeletal muscle index (SMI), the skeletal muscle density (SMD) and the intramuscular adipose tissue area (IMAT) were measured at the level of the L3 vertebra. Low SMD and low SMI were defined according to previously reported thresholds, while high IMAT was defined using population-specific cut-point analysis. SMI, SMD, and IMAT were also measured at the proximal thigh (PT) level and tested as continuous variables. Clinical morpho-functional parameters, baseline nutritional markers with a known or suspected impact on HNC treatment, clinical outcomes and sarcopenia were also collected. In multivariate analyses, adjusted by age, sex, stage, diabetes, body mass index (BMI), and weight loss, L3-SMI was not significantly associated with survival, while poor muscle quality was negatively associated with overall survival (OS) (HR = 1.88, 95% CI = 1.09–3.23, p = 0.022 and HR = 2.04, 95% CI = 1.27–3.27, p = 0.003, for low L3-SMD and high L3-IMAT, respectively), progression-free survival (PFS) (HR = 2.26, 95% CI = 1.39–3.66, p = 0.001 and HR = 1.97, 95% CI = 1.30–2.97, p = 0.001, for low L3-SMD and high L3-IMAT, respectively) and

cancer-specific survival (CSS) (HR = 2.40, 95% CI = 1.28–4.51, p = 0.006 and HR = 1.81, 95% CI = 1.04–3.13, p = 0.034, for low L3-SMD and high L3-IMAT, respectively). Indices at the PT level, tested as continuous variables, showed that increasing PT-SMI and PT-SMD were significant protective factors for all survival outcomes (for OS: HR for one cm^2/m^2 increase in PT-SMI 0.96; 95% CI = 0.94–0.98; p = 0.001 and HR for one HU increase in PT-SMD 0.90; 95% CI = 0.85–0.94; $p < 0.001$, respectively). PT-IMAT was a significant risk factor only in the case of CSS (HR for one cm^2 increase 1.02; 95% CI = 1.00–1.03; p = 0.046). In conclusion, pre-treatment low muscle quality is a strong prognostic indicator of death risk in patients affected by HNC and undergoing (chemo)radiotherapy with curative intent.

KEYWORDS

head and neck cancer, sarcopenia, myosteatosis, muscle quality, muscle quantity, radiotherapy, clinical outcomes, overall survival

Introduction

Head and neck cancers (HNCs) include malignant tumors of the lip, oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, and salivary glands and are responsible for more than 450,000 deaths annually (1). Besides classical risk factors like older age, tumor stage, dietary factors, alcohol and tobacco consumption, as well as HPV status, the assessment of multiple body composition parameters has been recently regarded as an important predictor of clinical outcome (2, 3).

Sarcopenia has been defined as a generalized skeletal muscle disorder associated with an increased likelihood of adverse outcomes (4) and its importance for survival analysis and radio-chemotherapy toxicity in cancer patients has been recognized for different tumors including HNC (3, 5, 6). The diagnosis of sarcopenia is confirmed by the occurrence of a low muscle mass or a low muscle quality, associated with reduced muscle strength and performance (4). The assessment of the CT cross-sectional skeletal muscle area (SMA) or SMA normalized for height to obtain the SMI, at the level of the third lumbar vertebra (L3), is the current gold standard for inferring total skeletal muscle mass (7, 8).

Following CT segmentation at L3, SMD and intermuscular adipose tissue (IMAT) infiltration can be measured, giving an indication of skeletal muscle mass quality. SMD is measured in Hounsfield units (HU), and a lower density highlights that more intramuscular lipid infiltration or myosteatosis is present (8). Increasing IMAT, instead, indicates a higher fat infiltration within the muscle fibers and underneath the fascia, providing another index of poor muscle quality (9).

Besides L3, CT muscle indices in different muscle groups have been used in the assessment of sarcopenia (8, 10–12). We have recently found a good correlation between muscle indices at the PT with OS and PFS in patients with hematologic malignancies (13). Others have studied the predictive power of CT-cross-sectional measurements at the level of the third cervical vertebra in HNC patients (2, 14).

Radiotherapy (RT) plays a key role in the curative treatments of HNC (15). Ganju et al. showed that low muscle mass reduces chemo-radiation therapy (CRT) compliance and increases chemotherapy (CHT) toxicity in patients with locally advanced HNC (16). Grossberg et al. showed that pre- and post-treatment low muscle mass is associated with poorer OS in a cohort of 190 HNC patients, treated with CRT (17): a significant reduction in OS, from 75 to 62%, was observed in sarcopenic patients, by comparison with non-sarcopenic patients. Post-treatment reduction in muscle mass was also associated with a reduction in OS, relative to non-sarcopenic patients (17, 18). Importantly, generalized weight loss was not associated with any significant changes in patient outcomes (6, 17, 18), thus emphasizing the importance of measuring body composition, rather than simply total body weight.

Head and neck cancer (HNC) patients undergo CT evaluations at the baseline and at multiple timepoints during their treatment, thus body composition data may represent a powerful and easily available additional prognostic factor. Should the prognostic value of CT parameters be confirmed, they may also be used to guide interventions based on nutritional support and exercise (19). However, the available experiences of the impact of low muscle quality on cancer patients, in particular HNC patients treated with RT, with or without additional systemic treatment, are still deficient in the literature.

In this retrospective study of the body composition of HNC patients undergoing definitive CRT, we aimed to explore the impact of pre-treatment low muscle mass and quality on survival outcomes and treatment tolerance.

TABLE 1 Study cohort description, including patients' clinical characteristics, main cancer features, radiation treatment type, and main outcomes.

		Patients (n = 225)
Sex	Female, n (%)	55 (24.4)
	Male, n (%)	170 (75.6)
Age (years) median (IQR)		64.5 (56.3–72.35)
	≥ 60 years old, n (%)	146 (65)
	< 60 years old, n (%)	79 (35)
BMI, median (IQR)		24.6 (22.15–27.4)
Weight loss in the previous 6 months (kg) median (IQR)		0 (0–1)
Comorbidities, n (%)	Hypertension	85 (37.8)
	DM	28 (12.4)
	COPD	18 (8)
	Alcohol abuse	14 (6.2)
PS ECOG, n (%)	0	98 (43.75)
	1	97 (43.3)
	2	26 (11.6)
	3	3 (1.34)
Smoke, n (%)		156 (69.3)
Tumor site, n (%)	Oral cavity	12 (5.3)
	Hypopharynx	35 (15.6)
	Larynx	38 (16.9)
	Oropharynx	101 (44.9)
	Occult primary	10 (4.4)
	Nasopharynx	28 (12.4)
	Paranasal Sinuses	1 (0.4)
TNM stage, n (%)	I	11 (4.9)
	II	23 (10.2)
	III	52 (23.2)
	IV	1 (0.4)
	IVa	127 (56.49)
	IVb	11 (4.9)
HPV status, n (%)	Positive	49 (22.0)
	Negative	48 (21.5)
	Unknown	126 (56.5)
EBV status, n (%)	Positive	8 (3.6)
	Negative	3 (1.4)
	Unknown	212 (95)
	Chemoradiation (CRT)	124 (55.1)
Treatment type, n (%)	CRT after induction CHT	42 (18.7)
	Radiotherapy alone	57 (25.3)
Concomitant CHT regimen	Platinum-based (CDDP)	136 (80.9)
	Cetuximab	30 (17.9)
	1	19 (8.4)
Acute toxicity	2	151 (67.1)
CTCAE v4.0 grade, n (%)	3	54 (24)
	4	1 (0.4)
RT suspension > 10 days, n (%)		134 (79.8)
	Complete Response	176 (78.2)
	Partial Response	10 (4.4)
Response to therapy, n (%)	Stable Disease	23 (10.2)
	Progressive Disease	9 (4)
	Not evaluable	7 (3.1)
Local recurrence, n (%)		62 (27.6)
Death, n (%)		96 (42.7)
	HNC	71 (74)
Cause of death, n (% on	Toxicity	2 (2)
total deaths)	Other	23 (24)

Continuous variables are presented as median and interquartile range while categorical data are reported as frequency and percentage. BMI, body mass index; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CHT, chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; RT, radiotherapy; HNC, head and neck cancer.

Materials and methods

Study design

We conducted a monocentric retrospective study with the primary aim of evaluating the association between baseline skeletal muscle quality and quantity, and OS. Secondary endpoints were: acute toxicity (within 6 months after the end of the treatment) ≥ G3 according to CT-CAE v4.0 Classification (20); treatment compliance with temporary or definitive treatment suspension; local control of the disease, defined as the absence of any clinical or radiological evidence of local recurrence after complete response to primary treatment until the last follow up visit; PFS and CSS.

The present study was given final approval by the Area Vasta Emilia Nord Ethical Committee (AUSLRE protocol number 2019/0066663 on 05/06/2019 and AUSLRE protocol number 2021/0070072 on 28/05/2021) and was performed in accordance with the principles of Good Clinical Practice (GCP) in respect of the ICH GCP guidelines and the ethical principles contained in the Helsinki Declaration and its subsequent updates (21). Given the retrospective nature of the data collection, the Ethics Committee authorized the use of a patient's data without his/her informed consent if all reasonable efforts have been made to contact that patient to obtain it.

Patient selection and treatment

All consecutive patients with histologically confirmed HNC, undergoing definitive RT with or without concurrent CHT or induction CHT and subsequent chemo-radiation, who were

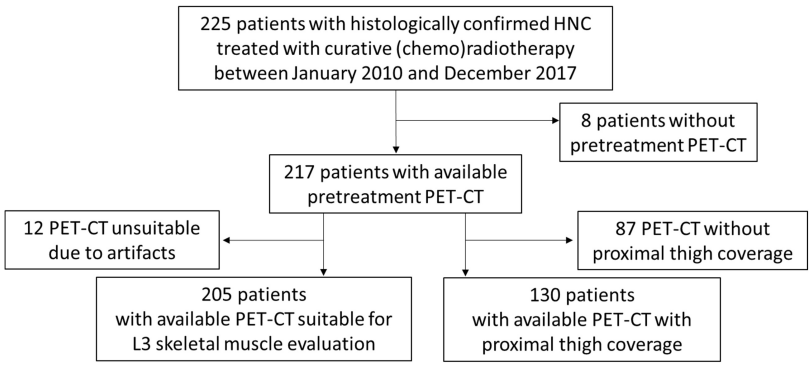


FIGURE 1
Patient inclusion flow-chart. Flow-chart representing patient inclusion and subgroups of patients with available L3-and proximal thigh (PT)-computed tomography (CT) parameters of muscle quantity and quality.

treated with curative intent at our institution between January 2010 and December 2017, were eligible. The diagnostic work up for all the recruited patients included total body 20-deoxy-20-[18F] fluoro-*D*-glucose (FDG) positron emission tomography, in combination with a CT scan (PET-CT), a contrast-enhanced CT (CE-CT) of the head, neck and chest, with or without magnetic resonance (MRI).

Data regarding patient age, gender, cancer type, tumor stage, tumor site, Eastern Cooperative Oncology Group (ECOG) score, smoking status, alcohol use, total protein level, albumin level, glycemia, lactate dehydrogenase (LDH), human papillomavirus (HPV) p16 status, tumour-node-metastasis (TNM) stage (22), Charlson Comorbidity Index (CCI) (23), therapeutic details and any complications experienced during and after treatment were obtained from the patients' medical records.

Following CRT, patients started a regular follow up (FU) at our institution: every 2 months for the first year, then every 3 to 4 months during the second year; every 4 to 6 months 3 years after the treatment and every 6 months to the 1-year FU (for early-stage disease only) until the fifth year after the treatment. Each FU visit included an interview for the assessment of CTCAE v4.02 ear-nose-throat (ENT)-related symptoms (20), ENT clinical examination and flexible endoscopy. A restaging of the disease with 18F-FDG PET-CT was required 3 months after the end of (chemo)radiation, then a neck and chest CT scan was carried out annually and, in some cases, a head and neck MRI was performed every four to 6 months until the end of the FU period.

Computed tomography muscle assessment

Skeletal muscle quality and quantity were evaluated on staging, pre-treatment CT scan imaging, using images acquired without contrast media administration during the PET-CT scan. Manual segmentation of the skeletal muscle at the level of the L3 was performed by a single trained operator under the supervision of a senior radiologist, using the commercially available software package, Osirix, after having applied a radiodensity range between -29 and +150 HUs, which is specific for muscle tissue. The lean muscle cross-sectional area was normalized for the squared height to obtain the SMI. SMD was collected for the same region of interest selected for lean muscle cross-sectional area measurement. The IMAT area (the fat area between muscle fibers and within the fascia) was measured by applying a density range between −180 and −30 HU, thresholds specific for fat tissue. Low SMD and low SMI were defined according to previously reported threshold values (SMD < 41 HU for BMI < 25, < 33 HU for BMI ≥ 25; SMI < 41 cm^2/m^2 in women and < 43 cm^2/m^2 or < 53 cm^2/m^2

TABLE 2 Distribution of computed tomography (CT) parameters of skeletal muscle quality and quantity, and prevalence of sarcopenia according to different parameters and different cut-off values.

CT body composition parameters and prevalence of sarcopenia		
L3-SMD (HU), median (IQR) (n = 203)		39.5 (34.0–44.0)
L3-SMI (cm^2/m^2), median (IQR) (n = 205)		52.11 (46.0–59.1)
L3-IMAT (cm^2), median (IQR) (n = 203)		10.5 (7.0–17.8)
PT-SMD (HU), median (IQR) (n = 130)		50.0 (47.0–53.0)
PT-SMI (cm^2/m^2), median (IQR) (n = 130)		83.8 (72.3–92.9)
PT-IMAT (cm^2), median (IQR) (n = 130)		18.0 (10.0–28.0)
Prevalence of sarcopenia, n (%), (95% CI)	L3-SMD Martin's cut-offs[a]	84 (40.0%), (33.32–47.0%)
	L3-SMI Martin's cut-offs[a]	49 (23.3%), (17.8–29.7%)
	L3-IMAT cut-point analysis cut-offs[b]	97 (47.1%), (40.1–54.2%)

L3, third lumbar vertebrae; SMD, skeletal muscle density; SMI, skeletal muscle index; IMAT, intermuscular adipose tissue; PT, proximal thigh; IQR, interquartile range; CI, confidence interval.
[a]Cut-offs according to Martin et al. (11).
[b]Cut-offs according to cut-point analysis on our population.

in men, with a BMI < 25 or ≥ 25 respectively), while high IMAT was defined using population-specific, cut-point analysis (**Supplementary Table 1**) (11). SMI, SMD and IMAT were also measured at the PT level, as previously reported, when included in the PET-CT scan (13).

Statistical analysis

In the absence of *a priori* hypothesis and given the exploratory nature of the study, no formal sample size calculation was performed. Clinical and demographic data were expressed in terms of frequency and percentage for categorical variables, median and interquartile range (IQR) for quantitative variables. The project's main aim was to test the prognostic value of Martin et al.'s cut-offs for SMI and SMD on treatment interruption/response and survival outcomes; furthermore, we researched cut-offs for IMAT in an exploratory way in our sample. OS time was measured from the time that RT ended until death or the last FU. We also estimated cancer specific survival (CSS), which differs from OS in terms of non-cancer-death censoring. Finally, PFS was calculated from RT ending to relapse or death, whichever came first, or to the last FU. Optimal cut-point analysis for IMAT, targeted to OS and split by BMI and age, followed the methodology by Contal and O'Quigley (24). The association between markers and CHT/RT interruption, severe AE (CTCAE ≥ 3) and local control was estimated with logistic regressions. Survival functions were estimated using the Kaplan-Meier method. The association between markers and survival outcome was estimated with univariate and multivariate Cox regressions. Proportional hazard assumption was assessed by testing scaled Schoenfeld residuals' correlation with time; no violation of the assumption was found. Unless otherwise specified, confidence intervals (CIs) were two-tailed and calculated considering a 0.95 confidence level. Performed tests were considered statistically significant if the *p*-values were < 0:05. Statistical analysis was performed using R 3.5.2 R Core Team (2021).

Results

Clinical characteristics of the patients

A total of 225 consecutive patients diagnosed with histologically confirmed HNC undergoing treatment between January 2010 and December 2017 were included in the present study. Patients, tumor and treatment characteristics are summarized in **Table 1**. Among the 225 included patients, 170 (75.6%) were male; the median age was 64.5 years (IQR 56.3–72.4 years); the median baseline BMI was 24.8, with substantial weight stability in the 6 months before CRT (weight loss: median 0, third quartile 1 kg). According to some of the parameters that define malnutrition (25), we found that 42 (18.67%) patients lost > 5% body weight in the 6 months before diagnosis and 31 (13.78%) patients had a low BMI in relation to age (BMI < 20 in patients < 70 years old and BMI < 22 in patients ≥ 70 years old), for a total of 60 (26.7%) patients with at least one of the two parameters. Nearly 70% of patients were smokers. Of the 225 patients, 98 (43.8%) showed good performance status with the ECOG 0 or 1, while 97 (43.3%) showed intermediate performance status (ECOG > 1). Blood test results are reported in **Supplementary Table 2**.

The tumor site was most frequently oropharynx (44.9%), followed by larynx (16.9%), hypopharynx (15.5%), and nasopharynx (12.4%), and the most represented stage was III/IV (84.9% of cases) according to TNM. Histologically, 193 tumors (85.8%) were squamous cell carcinoma (SCC), while five (2.2%) patients exhibited a histology other than SCC (i.e., lymphoepithelioma-like carcinoma of the nasopharynx, non-keratinizing carcinoma, adenocarcinoma). Positive HPV staining was found in 49 (22%) of the patients.

Regarding treatment options, RT was mainly administered using intensity-modulated techniques, such as volumetric multiple arc therapy (VMAT) in 35 (15.5%) patients and helical tomotherapy was used in 176 (78.2%) patients with an average number of 31 sessions; of these 176 patients, 124 (55.1%) received this treatment concurrently with CHT. Altered fractionation 2.12 Gy up to 2.35 Gy/fraction was preferred (EQD2Gy 66 to 70 Gy). Platinum-based regimens were more frequently used as concomitant CHT and the anti-EGFR drug,

TABLE 3 Univariate logistic regressions between low muscle quantity and low muscle quality with short-term outcomes.

Short-term outcomes

		OR	95% CI	*P*-value
RT suspension	Low L3-SMD (Martin)[a]	1.28	0.52–3.13	0.58
	Low L3-SMI (Martin)[a]	0.96	0.30–2.59	0.94
	High L3-IMAT (cut-point)[b]	1.78	0.70–4.74	0.23
CHT suspension	Low L3-SMD (Martin)[a]	1.17	0.52–2.61	0.70
	Low L3-SMI (Martin)[a]	0.83	0.29–2.10	0.70
	High L3-IMAT (cut-point)[b]	1.96	0.87–4.49	0.11
CTCAE ≥ 3	Low L3-SMD (Martin)[a]	1.40	0.74–2.64	0.30
	Low L3-SMI (Martin)[a]	0.98	0.45–2.02	0.96
	High L3-IMAT (cut-point)[b]	1.30	0.69–2.47	0.42
Local disease control	Low L3-SMD (Martin)[a]	0.56	0.29–1.09	0.09
	Low L3-SMI (Martin)[a]	1.28	0.59–3.03	0.55
	High L3-IMAT (cut-point)[b]	0.81	0.42–1.58	0.54

Univariate logistic regressions between low muscle quantity (low L3-SMI) and low muscle quantity (low L3-SMD or high L3-IMAT) and short-term outcomes including RT and CHT suspension, toxicity (CTCAE ≥ 3 events), and complete response to therapy. OR, odds ratio; CI, confidence interval; L3, third lumbar vertebrae; SMD, skeletal muscle density; SMI, skeletal muscle index; IMAT, intermuscular adipose tissue.

[a]Cut-offs according to Martin et al. (11).

[b]Cut-offs according to cut-point analysis on our population.

cetuximab, was offered as an alternative option in a minority of patients (17.9%). Forty-four (19.6%) patients underwent induction CHT and a combination of fluoropyrimidine and cisplatin with and without taxanes was administered to six (13.6%) and 38 (86.4%) patients, respectively. RT was suspended for more than 10 days in 13 (5.8%) patients, due to the worsening of their general health, while concurrent CHT was suspended due to complications in 34 (20.2%) patients.

Grade 3 and 4 acute toxicity was reported in 55 (24.4%) patients. After a median FU time of 5.6 years (95% CI 5.0–6.4), 96 (42.7%) patients had died, 71 (74%) of them due to HNC-related causes. After therapy, 176 (78.22%) patients were in complete remission and 62 patients exhibited a recurrence of the disease during their FU.

Association between muscle quality and quantity and patient outcomes

Among the 225 patients included in the study, the baseline PET-CT scan was not available in the case of eight patients and was not suitable for muscle quality and quantity assessment at the L3 level in 12 patients due to artifacts, while the CT images at the PT level were only available for 130 patients (**Figure 1**). The distribution of muscle quality and quantity parameters, assessed by the CT scans, is reported in **Table 2**, as well as the prevalence estimates of sarcopenia applying cutoffs provided by Martin et al. (11) and by our cut-point analysis on IMAT (see **Supplementary Table 1**).

Short-term outcomes

Univariate logistic models for short-term outcomes including RT and CHT suspension, CTCAE $\geq$ 3 events and local control, showed no statistically significant association between low muscle quality and quantity and outcomes (**Table 3**). However, from a clinical standpoint, low muscle quality, defined as lower-than-threshold SMD or higher-than-threshold IMAT was positively associated with treatment suspension and CTCAE $\geq$ 3 events. For example, the ORs of high IMAT (compared to low IMAT) were 1.78 (95% CI = 0.7–4.7, $p = 0.23$) for RT suspension, and 1.96 (95% CI 0.87–4.49, $p = 0.11$) for CHT suspension, while the OR of low SMD (compared to high SMD) for CTCAE $\geq$ 3 events was 1.40 (95% CI = 0.74–2.64, $p = 0.30$). Lower-than-threshold L3-SMD also showed a not statistically significant association with diminished local disease control (OR = 0.56; 95% CI = 0.29–1.09; $p = 0.09$).

Survival

During FU (median 5.6 years), 62 recurrences and 96 deaths (71/96 caused by HNC) were recorded. The median OS was 7.6 years (95% CI 4.7-NA) while median PFS was 4.7 years (95% CI 2.8–7.6). Five-year and 10-year OS were 55.9% (49.1–63.6%) and 44.8% (36.7–54.7%), respectively; five-year and 10-year PFS were 48.3% (41.8–55.9) and 37.3% (29.8–46.7%), respectively and 5-year and 10-year CSS were 65.6% (58.9–73%) and 59.5% (51.3–69%), respectively (**Figure 2**).

Univariate analyses showed a significant association of low muscle quality (in terms of both lower-than-thresholds L3-SMD and higher-than-thresholds L3-IMAT) with lower survival rates, while lower-than-thresholds L3-SMI (low muscle quantity) was not significantly associated with survival (**Figure 3** and **Table 4**). These results were confirmed in multivariate analyses adjusted for other prognostic factors, including age, sex, stage, diabetes, BMI, and weight loss in the previous 6 months. In particular, no significant association was found for low muscle quantity, while both low L3-SMD and high L3-IMAT were associated with OS (HR = 1.88, 95% CI = 1.09–3.23, $p = 0.022$ and HR = 2.04, 95% CI = 1.27–3.27, $p = 0.003$, for low L3-SMD and high L3-IMAT, respectively), PFS (HR = 2.26, 95% CI = 1.39–3.66, $p = 0.001$, and HR = 1.97, 95% CI = 1.30–2.97, $p = 0.001$, for low L3-SMD and high L3-IMAT, respectively) and CSS (HR = 2.40, 95% CI = 1.28–4.51, $p = 0.006$ and HR = 1.81, 95% CI = 1.04–3.13, $p = 0.034$, for low L3-SMD and high L3-IMAT, respectively). As for other prognostic factors (results not shown), covariate HRs suggested a detrimental prognostic effect for higher age, stage III-IV, male sex, having diabetes, lower BMI and higher

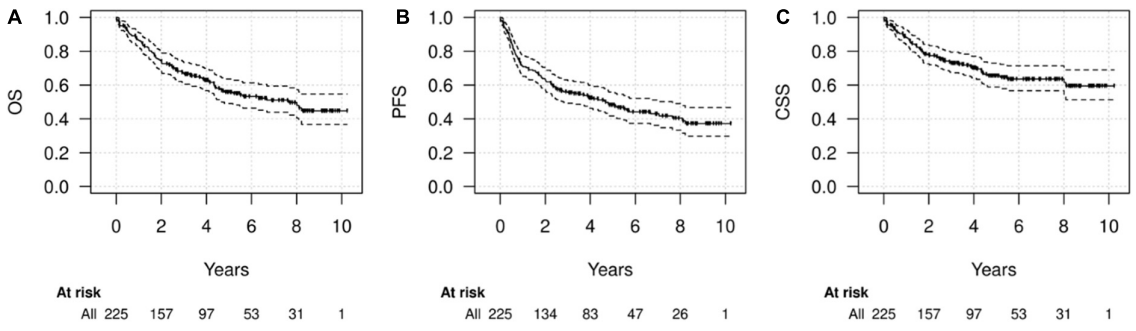


FIGURE 2
Survival of the whole cohort. Kaplan-Meier diagrams for overall survival (OS) **(A)**, progression-free survival (PFS) **(B)**, and cancer-specific survival (CSS) **(C)** in the whole cohort.

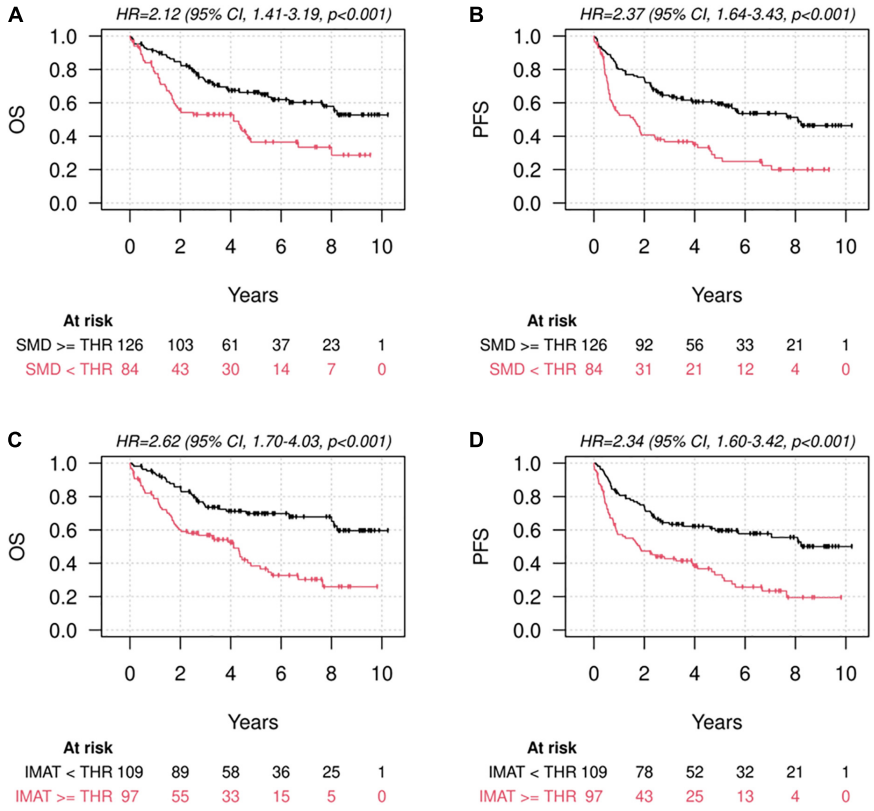


FIGURE 3
Survival according to muscle quantity and quality. Kaplan-Meier diagrams for Overall Survival (OS) **(A,C)** and Progression-Free Survival (PFS) **(B,D)**, subdivided by higher-and lower-than-thresholds skeletal muscle density at the level of L3 (L3-SMD) according to the cut-offs defined by Martin et al. (11) **(A,B)** and higher-and lower-than-thresholds intermuscular adipose tissue area at the level of L3 (L3-IMAT), according to the cut-offs defined by means of cut-point analysis on our population **(C,D)**.

weight loss in the previous 6 months; regarding these factors, the associations were not statistically significant for all the estimates but had a common direction.

Since indices assessed at the PT level were not used to define muscle quality and quantity according to specified cut-offs, due to the high proportion of missing values, they were tested as continuous variables in multivariable Cox models for survival, adjusted by age, sex, BMI, and stage (Table 5). At the PT level, increasing muscle quantity defined by PT-SMI was a significant protective factor (HR for one cm^2/m^2 increase 0.96; 95% CI = 0.94–0.98; $p = 0.001$ for OS). Increasing muscle quality, described by increasing PT-SMD was also protective (HR for one HU increase 0.90; 95% CI = 0.85–0.94; $p < 0.001$ for OS), while increasing PT-IMAT was a significant risk factor (and at a borderline level) only in the case of CSS (HR for one cm^2 increase 1.02; 95% CI = 1.00–1.03; $p = 0.046$).

Similar models on the same subgroup of patients and with parameters of muscle quality/quantity used as continuous variables, were also evaluated for L3-SMD, L3-SMI, and L3-IMAT (Supplementary Table 3). In this subgroup analysis, increasing L3-SMI did not exhibit any protective effect, as opposed to PT-SMI.

Discussion

The key finding in our study is that pre-treatment low muscle quality is a convincing prognostic indicator of a death risk in patients affected by HNC, undergoing RT or chemo-RT with curative intent. In fact, this retrospective study on 225 patients showed that a high intramuscular fat depot and high IMAT accumulation represent important risk factors for OS and CSS, as well as for disease progression in HNC patients. Indeed, low SMD and high IMAT at L3 were significantly associated with OS, PFS and CSS, and these data were confirmed in multivariate analyses adjusted for other prognostic factors including age, sex, stage, diabetes and BMI. In our study, skeletal muscle mass did not represent a prognostic factor and pre−treatment L3-SMI was not associated with clinical outcome. In this regard the predictive role of skeletal muscle quantity in HNC patients is still being debated. In a metanalysis

TABLE 4 Univariate and multivariate associations between low muscle quantity (low L3-SMI) and low muscle quality (low L3-SMD or high L3-IMAT) and OS, PFS, or CSS.

	Univariate analyses			Multivariate analyses (Adjusted by age, sex, stage, diabetes, BMI, and previous weight loss)		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Overall survival						
Low L3-SMD (Martin)[a]	2.12	1.41–3.19	< 0.001	1.88	1.09–3.23	0.022
Low L3-SMI (Martin)[a]	1.19	0.74–1.93	0.47	0.86	0.50–1.47	0.574
High L3-IMAT (cut-point)[b]	2.62	1.71–4.03	< 0.001	2.04	1.27–3.27	0.003
Progression free survival						
Low L3-SMD (Martin)[a]	2.37	1.64–3.43	< 0.001	2.26	1.39–3.66	0.001
Low L3-SMI (Martin)[a]	1.18	0.78–1.81	0.45	0.84	0.51–1.36	0.469
High L3-IMAT (cut-point)[b]	2.34	1.60–3.42	< 0.001	1.97	1.30–2.97	0.001
Cancer-specific survival						
Low L3-SMD (Martin)[a]	2.46	1.53–3.96	< 0.001	2.40	1.28–4.51	0.006
Low L3-SMI (Martin)[a]	1.25	0.72–2.16	0.43	0.94	0.51–1.74	0.854
High L3-IMAT (cut-point)[b]	2.56	1.56–4.23	< 0.001	1.81	1.04–3.13	0.034

Multivariate associations were adjusted by age, sex, HNC stage (III and IV vs. I and II), diabetes, BMI, and previous weight loss. HR, Hazard Ratio; CI, confidence interval; L3, third lumbar vertebrae; SMD, skeletal muscle density; SMI, skeletal muscle index; IMAT, intermuscular adipose tissue; PT, proximal thigh.
[a]Cut-offs according to Martin et al. (11).
[b]Cut-offs according to cut-point analysis on our population.

of seven studies, Takenaka et al. found that sarcopenia, defined as low SMI at L3, predicted OS but the timing of sarcopenia assessment was not reported (2). Other metanalyses showed that radiologically defined sarcopenia was a negative predictor of OS (26–28). Findlay and colleagues in a study of 79 HNC patients found that post-treatment but not pre-treatment low SMI predicted reduced OS on multivariate analysis, with no difference in terms of RT or CHT treatment completion (6). The same author in a subsequent study on 277 HNC patients found that the association between low muscle quantity with OS was not significant on adjusted analysis (29). The discrepancies of the results among different studies may be attributed to the heterogeneity amongst the analyses with a lack of consensus regarding sarcopenia assessment, the different SMI threshold values that were applied or the dissimilar ethnicities of the patients.

Skeletal muscle radiation attenuation or density is another index of muscle status and represents a measure of intramuscular lipid depot or myosteatosis. Myosteatosis is an established, poor prognostic factor in many cancers (30), however, there is a scarcity of studies in patients with HNC. Findlay and colleagues (6) found that pre-treatment myosteatosis predicted reduced OS, and Yoshimura et al. similarly described an association between higher intramuscular adipose tissue content and reduced survival (31), however, in another study on 277 patients the same author did not find a significant association between myosteatosis and OS (29).

The present study on 225 HNC patients confirms that a low SMD is significantly associated with reduced survival even after adjusting for other prognostic factors and introduces important elements of novelty.

The first new fact is the CT assessment of IMAT. The clinical significance of IMAT in oncological patients has been reported (13, 32) but to the best of our knowledge, this is the first study that considers IMAT as a radiological marker of muscle quality and a predictor of clinical outcome in HNC patients. Muscle function and strength are essential elements in the clinical diagnosis of sarcopenia. In this regard, a low muscle quality (low IMAT and/or high SMD) might be a better surrogate marker of muscle function than muscle mass itself (9, 33). In our group of patients, a high IMAT was a predictor of lower OS, PFS, and CSS, similar to a low SMD.

TABLE 5 Multivariate associations of indices of low muscle quality and quantity at the PT level (used as continuous variables) with OS, PFS, and CSS.

	HR	**95% CI**	***P*-value**
Overall survival			
PT-SMD (for one HU increase)	0.90	0.85–0.94	< 0.001
PT-SMI (for one cm^2/m^2 increase)	0.96	0.94–0.98	0.001
PT-IMAT (for one cm^2 increase)	1.01	1.00–1.03	0.132
Progression-free survival			
PT-SMD (for one HU increase)	0.92	0.87–0.96	< 0.001
PT-SMI (for one cm^2/m^2 increase)	0.97	0.95–0.99	0.006
PT-IMAT (for one cm^2 increase)	1.00	0.99–1.02	0.80
Cancer-specific survival			
PT-SMD (for one HU increase)	0.89	0.84–0.94	< 0.001
PT-SMI (for one cm^2/m^2 increase)	0.96	0.93–0.99	0.007
PT-IMAT (for one cm^2 increase)	1.02	1.00–1.03	0.046

Adjusting factors were: age, sex, BMI, and stage. HR, Hazard Ratio; CI, confidence interval; PT, proximal thigh; SMD, skeletal muscle density; SMI, skeletal muscle index; IMAT, intermuscular adipose tissue area.

Another novel element is the anatomical site of CT body composition assessment. Besides L3, we have found that muscle status at the PT level represents a valuable prognostic indicator in HNC patients. Indeed, CT-muscle indices of a higher muscle quality or quantity at the PT, tested as continuous variables in multivariable analysis for the absence of specific cut-offs in literature, represented a significant protective factor. Accordingly, in a recent paper we have shown a significant association between PT muscle indices and survival in patients affected by hematological malignancies (13). Muscle status at the PT level could better denote the physical performance status of the patient and thus represent a better marker of the severity of the sarcopenic status (34–36). In particular, it is remarkable that the increase in muscle quantity, as defined by PT-SMI, denoted a significant protective factor differently from L3-SMI.

As for shorter term outcomes, lower-than-threshold L3-SMD showed a weak inverse association with local disease control, while treatment suspension and CTCAE $\geq$ 3 events were only weakly associated with SMD, confirming the data reported by others (6).

Besides these strengths, the limitations of this study include the retrospective design which needs future confirmation in prospective studies and the high proportion of patients with missing CT scans with PT coverage. The parameters of muscle quality/quantity at PT level were used as continuous variables for the absence of established cut-offs values. To overcome possible interpretation biases, similar models with continuous variables were applied on the same subgroup of patients, also including skeletal muscle parameters at L3 level, confirming the results obtained with the cut-offs. In fact, even in this case, L3-SMI did not show any protective effect, as opposed to PT-SMI.

In conclusion, our study emphasizes that CT−muscle status evaluation, which can be obtained using examinations routinely performed in clinical practice, has a meaningful prognostic value for HNC patients from a clinical perspective. We found that low muscle quality rather than muscle mass was associated with decreased survival and disease progression. Future prospective studies will be necessary to confirm the potential clinical utility of CT muscle assessment for the identification of patients in need of nutritional or pharmacological intervention to fight sarcopenia and to improve muscle quality.

Data availability statement

The data underlying this study are available on request for researchers intending to conduct research and respect confidentiality (even if anonymous data are provided, they should be published in aggregated form) in studies with objectives consistent with those of the original study. In order to obtain the data, approval must be obtained from the Area Vasta Emilia Nord (AVEN) Ethics Committee which will check the consistency of the objective and planned analyses and will then authorize the authors to provide aggregated or anonymized data.

Ethics statement

The studies involving human participants were reviewed and approved by Area Vasta Emilia Nord Ethical Committee. The patients/participants provided their written informed consent to participate in this study. Given the retrospective nature of the data collection, the Ethics Committee authorized the use of a patient's data without his/her informed consent if all reasonable efforts have been made to contact that patient to obtain it.

Author contributions

LBa, GB, MPe, CI, CP, PP, and PC contributed to the study concept and design. MPa, CB, SC, EB, and MR collected the data. LBr conducted the data analysis. LBa, GB, MPe, EB, and PC interpreted the results. All authors critically reviewed and approved the final version of the manuscript to be submitted.

Funding

This study was partially supported by Italian Ministry of Health; Annual Program Ricerca Corrente.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.994499/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660

2. Takenaka Y, Takemoto N, Oya R, Inohara H. Prognostic impact of sarcopenia in patients with head and neck cancer treated with surgery or radiation: a meta-analysis. *PLoS One.* (2021) 16:e0259288. doi: 10.1371/journal.pone.0259288

3. Findlay M, White K, Stapleton N, Bauer J. Is sarcopenia a predictor of prognosis for patients with head and neck cancer undergoing radiotherapy of curative intent? a systematic review and meta-analysis. *Clin Nutr ESPEN.* (2020) 40:422–3. doi: 10.1016/j.clnesp.2020.09.058

4. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* (2018) 48:16–31. doi: 10.1093/ageing/afy169

5. Au PC-M, Li H-L, Lee GK-Y, Li GH-Y, Chan M, Cheung BM-Y, et al. Sarcopenia and mortality in cancer: a meta-analysis. *Osteoporos Sarcopenia.* (2021) 7:S28–33. doi: 10.1016/j.afos.2021.03.002

6. Findlay M, Brown C, De Abreu Lourenço R, White K, Bauer J. Sarcopenia and myosteatosis in patients undergoing curative radiotherapy for head and neck cancer: impact on survival, treatment completion, hospital admission and cost. *J Hum Nutr Dietetics.* (2020) 33:811–21. doi: 10.1111/jhn.12788

7. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M-P, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol.* (2004) 97:2333–8. doi: 10.1152/japplphysiol.00744.2004

8. Anjanappa M, Corden M, Green A, Roberts D, Hoskin P, McWilliam A, et al. Sarcopenia in cancer: risking more than muscle loss. *Tech Innovat Patient Supp Radiat Oncol.* (2020) 16:50–7. doi: 10.1016/j.tipsro.2020.10.001

9. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: the health ABC study. *J Appl Physiol.* (2001) 90:2157–65.

10. Addison O, Marcus RL, Lastayo PC, Ryan AS. Intermuscular fat: a review of the consequences and causes. *Int J Endocrinol.* (2014) 2014:309570. doi: 10.1155/2014/309570

11. Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer Cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol.* (2013) 31:1539–47. doi: 10.1200/JCO.2012.45.2722

12. Almada-Correia I, Neves PM, Mäkitie A, Ravasco P. Body composition evaluation in head and neck cancer patients: a review. *Front Oncol.* (2019) 9:1112. doi: 10.3389/fonc.2019.01112

13. Besutti G, Massaro F, Bonelli E, Braglia L, Casali M, Versari A, et al. Prognostic impact of muscle quantity and quality and fat distribution in diffuse large B-Cell lymphoma patients. *Front Nutr.* (2021) 8:620696. doi: 10.3389/fnut.2021.620696

14. Wendrich AW, Swartz JE, Bril SI, Wegner I, de Graeff A, Smid EJ, et al. Low skeletal muscle mass is a predictive factor for chemotherapy dose-limiting toxicity in patients with locally advanced head and neck cancer. *Oral Oncol.* (2017) 71:26–33. doi: 10.1016/j.oraloncology.2017.05.012

15. Caudell JJ, Gillison ML, Maghami E, Spencer S, Pfister DG, Adkins D, et al. NCCN Guidelines§insights: head and neck cancers, version 1.2022. *J Natl Compr Canc Netw.* (2022) 20:224–34. doi: 10.6004/jnccn.2022.0016

16. Ganju RG, Morse R, Hoover A, TenNapel M, Lominska CE. The impact of sarcopenia on tolerance of radiation and outcome in patients with head and neck cancer receiving chemoradiation. *Radiother Oncol.* (2019) 137:117–24. doi: 10.1016/j.radonc.2019.04.023

17. Grossberg AJ, Chamchod S, Fuller CD, Mohamed ASR, Heukelom J, Eichelberger H, et al. Association of body composition with survival and locoregional control of radiotherapy-treated head and neck squamous cell carcinoma. *JAMA Oncol.* (2016) 2:782–9. doi: 10.1001/jamaoncol.2015.6339

18. Ahern E, Brown TE, Campbell L, Hughes BGM, Banks MD, Lin CY, et al. Impact of sarcopenia and myosteatosis on survival outcomes for patients with head and neck cancer undergoing curative-intent treatment. *Br J Nutr.* (2022):1–25. [Online ahead of print]. doi: 10.1017/S0007114522000435

19. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: clinical nutrition in cancer. *Clin Nutr.* (2021) 40:2898–913. doi: 10.1016/j.clnu.2021.02.005

20. Cancer Therapy Evaluation Program [CTEP]. *Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP.* (2022). Available online at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed March 1, 2022).

21. World Medical Association [WMA]. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* (2013) 310:2191–4. doi: 10.1001/jama.2013.281053

22. Sobin LH, Gospodarowicz MK, Wittekind C (eds). International union against cancer. *TNM Classification of Malignant Tumours.* 7th ed. Chichester: Wiley-Blackwell (2010).

23. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol.* (2004) 57:1288–94. doi: 10.1016/j.jclinepi.2004.03.012

24. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. *Computat Stat Data Anal.* (1999) 30:253–70.

25. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr.* (2019) 38:1–9. doi: 10.1016/j.clnu.2018.08.002

26. Wong A, Zhu D, Kraus D, Tham T. Radiologically defined sarcopenia affects survival in head and neck cancer: a meta-analysis. *Laryngoscope.* (2021) 131:333–41. doi: 10.1002/lary.28616

27. Hua X, Liu S, Liao J-F, Wen W, Long Z-Q, Lu Z-J, et al. When the loss costs too much: a systematic review and meta-analysis of sarcopenia in head and neck cancer. *Front Oncol.* (2019) 9:1561. doi: 10.3389/fonc.2019.01561

28. Findlay M, White K, Stapleton N, Bauer J. Is sarcopenia a predictor of prognosis for patients undergoing radiotherapy for head and neck cancer? A meta-analysis. *Clin Nutr.* (2021) 40:1711–8. doi: 10.1016/j.clnu.2020.09.017

29. Findlay M, White K, Brown C, Bauer JD. Nutritional status and skeletal muscle status in patients with head and neck cancer: impact on outcomes. *J Cachexia Sarcopenia Muscle.* (2021) 12:2187–98. doi: 10.1002/jcsm.12829

30. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: systematic review and meta-analysis. *Crit Rev Oncol Hematol.* (2020) 145:102839. doi: 10.1016/j.critrevonc.2019.102839

31. Yoshimura T, Suzuki H, Takayama H, Higashi S, Hirano Y, Tezuka M, et al. Prognostic role of preoperative sarcopenia evaluation of cervical muscles with long-term outcomes of patients with oral squamous cell carcinoma. *Cancers (Basel).* (2021) 13:4725. doi: 10.3390/cancers13184725

32. Deluche E, Leobon S, Desport JC, Venat-Bouvet L, Usseglio J, Tubiana-Mathieu N. Impact of body composition on outcome in patients with early breast cancer. *Support Care Cancer.* (2018) 26:861–8. doi: 10.1007/s00520-017-3902-6

33. Hilton TN, Tuttle LJ, Bohnert KL, Mueller MJ, Sinacore DR. Excessive adipose tissue infiltration in skeletal muscle in individuals with obesity, diabetes mellitus, and peripheral neuropathy: association with performance and function. *Phys Ther.* (2008) 88:1336–44. doi: 10.2522/ptj.20080079

34. Beavers KM, Beavers DP, Houston DK, Harris TB, Hue TF, Koster A, et al. Associations between body composition and gait-speed decline: results from the health, aging, and body composition study. *Am J Clin Nutr.* (2013) 97:552–60. doi: 10.3945/ajcn.112.047860

35. Addison O, Young P, Inacio M, Bair W-N, Prettyman MG, Beamer BA, et al. Hip but not thigh intramuscular adipose tissue is associated with poor balance and increased temporal gait variability in older adults. *Curr Aging Sci.* (2014) 7:137–43.

36. Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. *J Am Geriatr Soc.* (2002) 50:897–904. doi: 10.1046/j.1532-5415.2002.50217.x

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 18 November 2022
DOI 10.3389/fnut.2022.1013643

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Anthony Bernard Miller,
University of Toronto, Canada
Leticia Goñi,
University of Navarra, Spain

*CORRESPONDENCE
Yaxu Wang
300897@hospital.cqmu.edu.cn
Xiaodong Zhao
zhaoxd530@aliyun.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 07 August 2022
ACCEPTED 26 October 2022
PUBLISHED 18 November 2022

CITATION
Peng L, Xiang L, Xu Z, Gu H, Zhu Z, Tang Y, Jiang Y, He H, Wang Y and Zhao X (2022) Association between low-fat diet and liver cancer risk in 98,455 participants: Results from a prospective study. *Front. Nutr.* 9:1013643. doi: 10.3389/fnut.2022.1013643

Association between low-fat diet and liver cancer risk in 98,455 participants: Results from a prospective study

Linglong Peng[1†], Ling Xiang[2†], Zhiquan Xu[1†], Haitao Gu[1], Zhiyong Zhu[1], Yunhao Tang[1], Yahui Jiang[1], Hongmei He[1], Yaxu Wang[1*] and Xiaodong Zhao[3*]

[1]Department of Gastrointestinal Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2]Department of Clinical Nutrition, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, [3]The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China

Background: Low-fat diet reduces the risk of chronic metabolic diseases such as obesity and diabetes, which exhibit overlapping mechanisms with liver cancer. However, the association between low-fat diet and liver cancer risk remains unclear.

Aim: To investigate whether adherence to low-fat diet is associated with a reduced risk of liver cancer in a prospective study.

Materials and methods: Data of participants in this study were collected from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. A low-fat diet score was calculated to reflect adherence to low-fat dietary pattern, with higher scores indicating greater adherence. Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for liver cancer incidence with adjustment for potential covariates. Restricted cubic spline model was used to characterize liver cancer risk across the full range of the low-fat diet score. Prespecified subgroup analyses were used to identify potential impact modifiers. Sensitivity analyses were performed to test the robustness of this association.

Results: A total of 98,455 participants were included in the present analysis. The mean (standard deviation) age, low-fat diet score, and follow-up time were 65.52 (5.73) years, 14.99 (6.27) points, and 8.86 (1.90) years, respectively. During 872639.5 person-years of follow-up, 91 liver cancers occurred, with an overall incidence rate of 0.01 cases per 100 person-years. In the fully adjusted Cox model, the highest versus the lowest quartile of low-fat diet score was found to be associated with a reduced risk of liver cancer ($HR_{Q4vs.Q1}$: 0.458; 95% CI: 0.218, 0.964; P = 0.035 for trend), which remained associated through a series of sensitivity analyses. The restricted cubic spline model showed a linear dose–response association between low-fat diet score and liver cancer incidence (p = 0.482 for non-linear). Subgroup analyses did not

show significant interaction between low-fat diet score and potential impact modifiers in the incidence of liver cancer.

Conclusion: In this study, low-fat diet score is associated with reduced liver cancer risk in the US population, indicating that adherence to low-fat diet may be helpful for liver cancer prevention. Future studies should validate our findings in other populations.

KEYWORDS

low-fat diet, liver cancer, prevention, prostate, lung, colorectal, ovarian cancer screening trial, cox regression analysis

Introduction

Primary liver cancer is one of the seven most common cancers and the second leading cause of cancer deaths worldwide. In 2020, approximately 905,677 cases were newly diagnosed with liver cancer, and an estimated 830,180 individuals died from liver cancer (1). It is well-established that hepatitis B/C virus infection and alcohol consumption are the main risk factors for liver cancer (2). However, a proportion of cases cannot be explained by traditional risk factors. Emerging evidence concerning diet, including single nutrients and dietary patterns has confirmed a close association between liver cancer risk and diet, and certain dietary patterns are advised for liver cancer prevention (3). For example, in a US population study with average follow-up time of 32 years, the incidence of liver cancer was reduced by a maximum of 39% in participants with a high healthy eating index (4). In a study integrating two Chinese cohorts, a total of 132,837 participants were divided into quartiles based on a vegetable-based dietary pattern, and the risk of liver cancer for participants in the highest quartile was reduced by 42% compared with the lowest quartile (5). Although both dietary patterns were not specifically developed to prevent cancer, they were related to each other and share low-fat dietary components. Low-fat diet is a dietary pattern designed to reduce total fat and calorie intake, which has been shown to be beneficial in reducing the risk of chronic metabolic diseases such as obesity and diabetes (6–8). Additionally, human and animal studies also suggest that low-fat diet has the potential to reduce the secretion of inflammatory cytokines and mediators, including interleukins, tumor necrosis factor-α, Toll-like receptors and complements, and the activity of the transcription factor NF-kB, which was demonstrated to be closely related to increased cancer risk including liver cancer (9–11). However, there are currently large knowledge gaps regarding the association between low-fat diet and liver cancer risk. Thus, the aim of this study was to investigate the association of low-fat diet with the risk of liver cancer in a large population.

Materials and methods

Study design and population

All data included in this study were from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial administered by the National Cancer Institute (NCI). The PLCO trial is a large randomized controlled study involving 154,887 participants in ten United States centers from 1993 to 2001, and its main purpose is to determine whether mortality from prostate, lung, colorectal, and ovarian cancers can be reduced using related screening methods in people between the ages of 55 and 74 years (12). According to the design of the PLCO trial, participants were randomly assigned to control or intervention groups in equal proportions after providing informed consent; usual care was received in the control group and screening exams were performed in the intervention group. Several questionnaires, including Baseline Questionnaire (BQ), Diet History Questionnaire (DHQ), and Supplemental Questionnaire (SQX), were completed by the participants in a self-reported manner. The BQ was used to collect the baseline risk factors, such as demographics and medical history, at the time of participant randomization. The DHQ was used to collect the dietary information of participants based on the 137-item Food Frequency Questionnaire (FFQ), and multiple studies have confirmed that the FFQ is a good nutrient assessment pattern (13, 14). The SQX was used to supplement some data not collected by the BQ. Detailed information on the PLCO trial is provided in the literature (12). Our present study was approved by the NCI (Project ID: PLCO-987).

Participants for this study were excluded using the following exclusion criteria: (I) participants who did not return the BQ (n = 4,918); (II) participants with an invalid DHQ, identified as participants who lacked 8 + frequency responses on the DHQ, whose calorie intake was extreme (the first and last percentile) for each gender as assessed by the DHQ, and the DHQ completion date was available and prior to the date of death (n = 38,462); (n = 38,462); (III) participants with a

personal history of any cancer prior to DHQ analysis (n = 9,684); (IV) participants with an outcome event between randomization and DHQ completion, which for the present study were defined as those participants who developed liver cancer, died, or were lost to follow-up (n = 72); and (V) participants with potentially unreliable dietary intake, defined as very low or high caloric intake (< 600 or > 3,500 kcal/day for female and < 800 or > 4,200 kcal/day for male) (15) (n = 3,296). Finally, a total of 98,455 participants were eligible for inclusion (**Figure 1**).

Assessment of low-fat diet score

The low-fat diet score was calculated according to the criteria reported by Shan et al. (15). Specifically, individuals were classified into 11 strata based on each of percentage of energy from carbohydrate, protein, and fat (**Supplementary Table 1**). For carbohydrate and protein, individuals in the lowest stratum received 0 points and those in the highest stratum received 10 points. For fat, the order of the strata was reversed. Then, the points for the three macronutrients were summed to calculate each participant's low-fat diet score, which ranged from 0 to 30. Thus, the higher the score, the more closely the participant's diet followed the pattern of a low-fat diet. In the present study, nutrient variables used for computing the low-fat diet score were extracted from the above-mentioned DHQ. DHQ nutrient variables are calculated from the questionnaire responses by the DietCalc software, which takes into account serving size, food frequency, and other responses, and uses these in conjunction with CSFII nutrient databases to calculate the daily intake of all nutrients (16). Of note, although the dietary information collected through the DHQ was a one-time inquiry of participants' dietary status over the past 12 months and was not cumulatively updated during follow-up, the reproducibility and validity of the DHQ have been demonstrated elsewhere (17).

Assessment of covariates

In this study, demographic, lifestyle, and medical information, including sex, race, educational level, arm (intervention or control group), body mass index (BMI), smoking status, pack-years of smoking, history of diabetes, history of liver comorbidities (hepatitis or cirrhosis), and aspirin use, were assessed with the BQ. BMI was calculated as weight (kg) divided by height squared (m^2). Age at DHQ completion, drinking status, alcohol consumption, and macronutrients intake were assessed with the DHQ. Physical activity level was collected with the SQX and defined as the summarized minutes of self-reported moderate to vigorous activity per week.

Determination of liver cancer

Individuals diagnosed with primary liver cancer were collected through annual reporting methods including but not limited to self-reports, family reports, and death certificates. Cancer reports were tracked and ascertained by extracting any

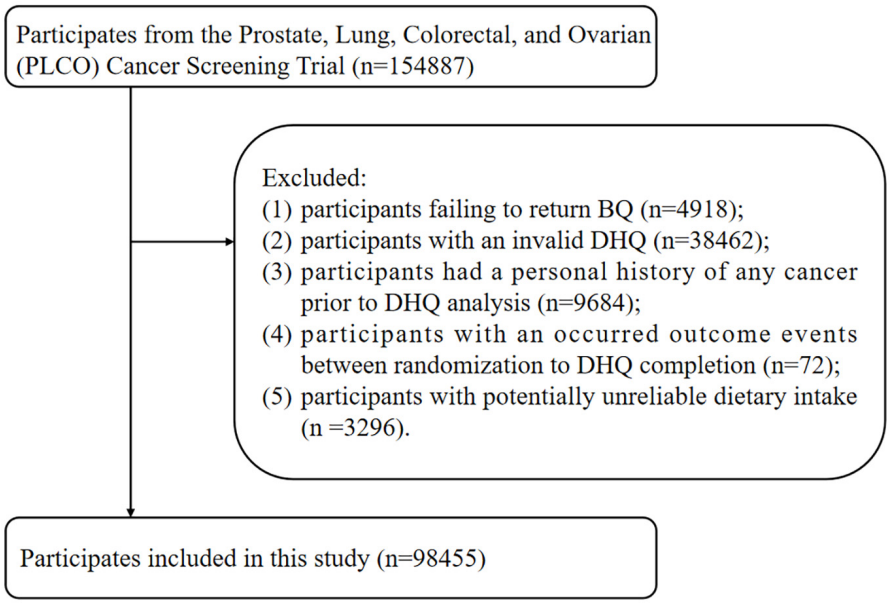


FIGURE 1
The study flow chart of identifying eligible participants. PLCO, Prostate, Lung, Colorectal, and Ovarian; BQ, baseline questionnaire; DHQ, diet history questionnaire.

available medical records. In this study, the end point was the incidence of primary liver cancer which included hepatocellular carcinoma (ICD-O-2, C220) and intrahepatic bile duct cancer (ICD-O-2, C221).

Statistical analysis

For categorical and continuous covariates with < 5% missing values, modal and median values were used to impute missing data, respectively. The covariate "physical activity level" was imputed by the multiple imputation method as up to 25.3% of the values were missing (18). More detail information of imputation data was shown in **Supplementary Table 2**, and statistical analyses were performed using the imputed datasets.

A Cox proportional hazards regression model was used to assess the association between low-fat diet and liver cancer risk, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with follow-up time as the time metric. It is worth noting that the follow-up time in this study refers to the date from DHQ completion to the occurrence of liver cancer, death, loss to follow-up, or the end of follow-up (i.e., December 31, 2009), whichever came first (**Figure 2**). In this model, the low-fat diet scores were divided into quartiles, and the person-years of each quartile were calculated based on the length of the follow-up period. A trend test across quartiles of low-fat diet score for the liver cancer risk estimation was also performed in the Cox regression model by treating the quartiles as a continuous variable with the lowest quartile as the reference group. In multivariate analyses, Model 1 was adjusted for age, sex, and race. Model 2 was further adjusted for education level, arm, BMI, smoking status, smoking pack-years, drinking status, alcohol consumption, aspirin use, history of liver comorbidity, history of diabetes, physical activity level and energy intake from diet. To further characterize liver cancer risk across the full range of the low-fat diet score, a restricted cubic spline model was employed in this study. In addition, we further analyzed the effect of poly-unsaturated fatty acids (PUFA), mono-unsaturated fatty acids (MUFA), and saturated fatty acids (SFA) on the risk of liver cancer using the above-mentioned methods. Specially, PUFA, MUFA, and SFA intakes were derived from DHQ and divided into quartiles, with the lowest quartile as the referent.

A series of subgroup analyses were conducted after stratifying for age (> 65 versus ≤ 65 years), sex (male versus female), BMI (≤ 25 versus > 25 kg/m^2), smoking status (never versus current/former), drinking status (no versus yes), alcohol consumption (≤ medium versus > medium), history of liver comorbidity (no versus yes), history of diabetes (no versus yes), physical activity (≤ medium versus > medium), and energy intake from diet (≤ medium versus > medium). A $P_{interaction}$ was computed by comparing models with and without multiplicative interaction terms before performing the above subgroup analyses to avert spurious subgroup effects.

We conducted several sensitivity analyses to test the robustness of our findings. (I) we repeated the primary

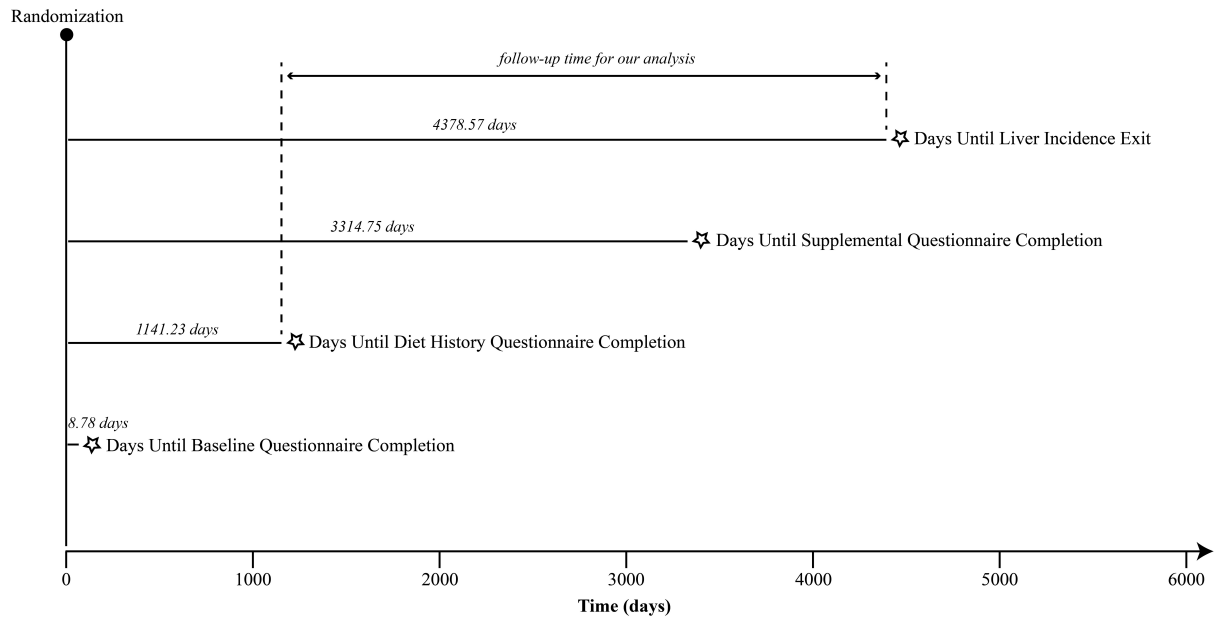


FIGURE 2
The timeline and follow-up scheme of our study.

analysis in participants with non-missing data; (II) we excluded participants with a history of diabetes, as these participants may be prone to a high-fat diet; (III) we excluded participants with a history of liver comorbidity, as these participants may be more likely to develop liver cancer; and (IV) we excluded cases observed within the first 2 and 4 years of follow-up to address the concern of reverse causality.

The statistical analyses were conducted using R 4.1.1 software. A two-tailed *P* value less than 0.05 was considered significant.

TABLE 1 Baseline characteristics of study population according to overall low-fat diet score.

Characteristics	Overall	Quartiles of overall low-fat diet score				*P*-value
		Quartile 1 (≤ 10)	Quartile 2 (11–15)	Quartile 3 (16–20)	Quartile 4 (≥ 21)	
Number of participants	98,455	26,718	26,149	24,762	20,826	
Low-fat diet score	14.99 ± 6.27	7.33 ± 2.40	12.98 ± 1.42	18.03 ± 1.43	23.75 ± 2.36	0.000
Age	65.52 ± 5.73	65.08 ± 5.63	65.24 ± 5.67	65.73 ± 5.77	66.19 ± 5.79	<0.001
Sex						0.000
Male	47216 (47.96%)	14774 (55.30%)	13806 (52.80%)	11265 (45.49%)	7371 (35.39%)	
Female	51239 (52.04%)	11944 (44.70%)	12343 (47.20%)	13497 (54.51%)	13455 (64.61%)	
Race						<0.001
White	91218 (92.65%)	25096 (93.93%)	24417 (93.38%)	22401 (90.47%)	19304 (92.69%)	
Non-white	7237 (7.35%)	1622 (6.07%)	1732 (6.62%)	2361 (9.53%)	1522 (7.31%)	
Education level						<0.001
College below	62597 (63.58%)	17942 (67.15%)	16899 (64.63%)	15568 (62.87%)	12188 (58.52%)	
College graduate	17352 (17.62%)	4486 (16.79%)	584 (17.53%)	4334 (17.50%)	3948 (18.96%)	
Postgraduate	18506 (18.80%)	4290 (16.06%)	4666 (17.84%)	4860 (19.63%)	4690 (22.52%)	
Arm						<0.001
Intervention	50150 (50.94%)	13918 (52.09%)	13441 (51.40%)	12532 (50.61%)	10259 (49.26%)	
Control	48305 (49.06%)	12800 (47.91%)	12708 (48.60%)	12230 (49.39%)	10567 (50.74%)	
Body mass index (kg/m^2)	27.20 ± 4.79	27.58 ± 4.86	27.47 ± 4.75	27.04 ± 4.72	26.57 ± 4.74	<0.001
Smoking status						0.000
Never	47232 (47.97%)	10722 (40.13%)	11889 (45.47%)	12775 (51.59%)	11846 (56.88%)	
Current	8992 (9.13%)	3752 (14.04%)	2557 (9.78%)	1799 (7.27%)	884 (4.24%)	
Former	42231 (42.89%)	12244 (45.83%)	11703 (44.76%)	10188 (41.14%)	8096 (38.87%)	
Smoking pack-years	17.49 ± 26.40	22.72 ± 29.80	18.69 ± 26.92	15.08 ± 24.24	12.14 ± 21.78	0.000
Drinking status						<0.001
No	26679 (27.10%)	6023 (22.54%)	6389 (24.43%)	7258 (29.31%)	7009 (33.66%)	
Yes	71776 (72.90%)	20695 (77.46%)	19760 (75.57%)	17504 (70.69%)	13817 (66.34%)	
Alcohol consumption (g/day)	8.78 ± 19.23	14.40 ± 28.94	9.90 ± 18.18	6.05 ± 10.80	3.43 ± 6.36	0.000
Aspirin use						0.052
No	52239 (53.06%)	14308 (53.55%)	13781 (52.70%)	13219 (53.38%)	10931 (52.49%)	
Yes	46216 (46.94%)	12410 (46.45%)	12368 (47.30%)	11543 (46.62%)	9895 (47.51%)	
History of liver comorbidity						0.978
No	94937 (96.43%)	25759 (96.41%)	25209 (96.41%)	23877 (96.43%)	20092 (96.48%)	
Yes	3518 (3.57%)	959 (3.59%)	940 (3.59%)	885 (3.57%)	734 (3.52%)	
History of diabetes						0.116
No	91988 (93.43%)	25032 (93.69%)	24362 (93.17%)	23139 (93.45%)	19455 (93.42%)	
Yes	6467 (6.57%)	1686 (6.31%)	1787 (6.83%)	1623 (6.55%)	1371 (6.58%)	
Physical activity level (min/week)	123.28 ± 108.77	109.20 ± 102.98	119.45 ± 106.92	128.16 ± 109.97	140.34 ± 114.02	<0.001
Energy intake from diet (kcal/day)	1728.69 ± 658.01	1936.74 ± 722.78	1785.82 ± 657.27	1634.16 ± 603.07	1502.44 ± 529.56	0.000
Total Carbohydrate (% energy)	51.99 ± 9.36	43.36 ± 6.86	49.37 ± 6.04	56.42 ± 7.29	61.10 ± 5.89	0.000
Total fat (% energy)	31.78 ± 7.52	39.44 ± 6.15	33.61 ± 4.13	28.47 ± 4.27	23.59 ± 3.97	0.000
Total protein (% energy)	15.44 ± 2.93	14.34 ± 2.72	15.48 ± 2.89	15.28 ± 3.02	16.98 ± 2.39	0.000

Descriptive statistics are presented as (mean ± standard deviation) and number (percentage) for continuous and categorical.

Results

Baseline characteristics

In the 98,455 included participants, the mean (standard deviation) for low-fat diet score was 14.99 (6.27). Based on the score, we divided participants into quartiles [Quartile 1 (LFD score $\leq$ 10), n = 26,718; Quartile 2 (LFD score 11–15), n = 26,149; Quartile 3 (LFD score 16–20), n = 24,762; Quartile 4 (LFD score $\geq$ 21), n = 20,826]. The higher the quartile, the more likely the participants were to follow a low-fat dietary pattern. Compared with participants in the lowest quartile group (Quartile 1), participants in the highest quartile group (Quartile 4) were more likely to be older and female and to have a higher educational level, and total carbohydrate and protein intake; but were less likely to have a higher BMI, physical activity level, diet energy and total fat intake. There were more non-smokers and non-drinkers in the highest quartile than in the lowest quartile, and fewer pack-years of current or former smokers and less alcohol consumption by drinkers were observed in the highest quartile. The detailed baseline characteristics of the study population according to quartiles of low-fat diet scores are shown in **Table 1**.

Association between low-fat diet score and the incidence of liver cancer

During 872639.5 person-years of follow-up, we documented a total of 91 liver cancer cases, with an overall incidence rate of 0.01 cases per 100 person-years. The mean (standard deviation) follow-up length was 8.862 (1.897) years. In the unadjusted model, participants in the highest quartile had a significantly lower risk of liver cancer than those in the lowest quartile ($HR_{Q4vs.Q1}$: 0.369; 95% CI: 0.182, 0.749; P = 0.003 for trend) (**Table 2**). After full adjustment for potential confounders, the inverse association of the low-fat diet score with the risk of liver cancer was also observed ($HR_{Q4vs.Q1}$: 0.458; 95% CI: 0.218, 0.964; P = 0.035 for trend) (**Table 2**). Notably, this inverse relationship was not altered when repeated analysis was performed using non-missing data ($HR_{Q4vs.Q1}$: 0.277; 95% CI: 0.076, 1.010; P = 0.032 for trend) (**Table 3**). For fat components, liver cancer risk was not significantly associated with PUFA (**Supplementary Table 3**), MUFA (**Supplementary Table 4**), and SFA (**Supplementary Table 5**) in the full adjusted model.

Additional analyses

We employed a restricted cubic spline model to describe the liver cancer risk across the range of low-fat diet scores, and the results showed that the low-fat diet score was inversely associated with the risk of liver cancer in a linear dose–response manner (P = 0.482 for non-linear) (**Figure 3**). In subgroup analyses, we did not observe a significant interaction between low-fat diet score and age, sex, BMI, smoking status, drinking status, alcohol consumption, history of liver comorbidity, history of diabetes, physical activity level or energy intake from diet in the incidence of liver cancer (all $P > 0.05$ for interaction) (**Table 4**). In sensitivity analyses, the associations remained similar when we further excluded participants with a history of liver comorbidity or diabetes and excluded cases observed within the first 2 years or 4 years of follow-up, indicating a good robustness of the inverse association of low-fat diet score with liver cancer risk (**Table 3**).

Discussion

In this study, we explored whether adherence to low-fat diet is associated with a reduced risk of liver cancer in a large prospective multicenter study. Our results showed a

TABLE 2 Hazard ratios of the association of low-fat diet score with the risk of liver cancer.

Quartiles of low-fat diet score	Number of cases	Person-years	Incidence rate per 100 person-years (95% CI)	HR (95% CI)		
				Unadjusted	Model 1[a]	Model 2[b]
Quartile 1 ($\leq$ 10)	33	232789.8	0.014 (0.010, 0.020)	1.000 (reference)	1.000 (reference)	1.000 (reference)
Quartile 2 (10–15)	28	230061.6	0.012 (0.008, 0.018)	0.856 (0.517, 1.416)	0.869 (0.525, 1.437)	0.898 (0.536, 1.505)
Quartile 3 (16–20)	20	221039.3	0.009 (0.006, 0.014)	0.633 (0.363, 1.103)	0.672 (0.385, 1.174)	0.725 (0.406, 1.295)
Quartile 4 ($\geq$ 21)	10	188748.8	0.005 (0.003, 0.010)	0.369 (0.182, 0.749)	0.428 (0.210, 0.874)	0.458 (0.218, 0.964)
P_{trend}				0.003	0.013	0.035

HR, hazard ratio; CI, confidence interval. [a]Adjusted for age (years), sex (male, female), and race (white, non-white). [b]Adjusted for model 1 plus educational level (college below, college graduate, postgraduate), arm (intervention, control), body mass index (kg/m^2), smoking status (never, current, former), smoking pack-years (continuous), drinking status (no, yes), alcohol consumption (g/day), aspirin use (no, yes), history of liver comorbidity (no, yes), history of diabetes (no, yes), physical activity level (min/week), and energy intake from diet (kcal/day).

TABLE 3 Sensitivity analyses on the association of low-fat diet scores with the risk of liver cancer.

Categories	HR Quartile 4 vs. Quartile 1 (95% CI)[a]	P_{trend}
Repeated analysis in participants with non-missing data	0.277 (0.076, 1.010)	0.032
Excluded participants with a history of liver comorbidity[b]	0.383 (0.161, 0.910)	0.025
Excluded participants with a history of diabetes[c]	0.454 (0.194, 1.058)	0.052
Excluded cases observed within the first 2 years of follow-up	0.474 (0.215, 1.042)	0.054
Excluded cases observed within the first 4 years of follow-up	0.425 (0.176, 1.029)	0.051

HR, hazard ratio; CI, confidence interval. [a]HRs were adjusted for age (years), sex (male, female), race (white, non-white), educational level (college below, college graduate, postgraduate), arm (intervention, control), body mass index (kg/m^2), smoking status (never, current, former), smoking pack-years (continuous), drinking status (no, yes), alcohol consumption (g/day), aspirin use (no, yes), history of liver comorbidity (no, yes), history of diabetes (no, yes), physical activity level (min/week), and energy intake from diet (kcal/day). [b]HR was not adjusted for history of liver comorbidity. [c]HR was not adjusted for history of diabetes.

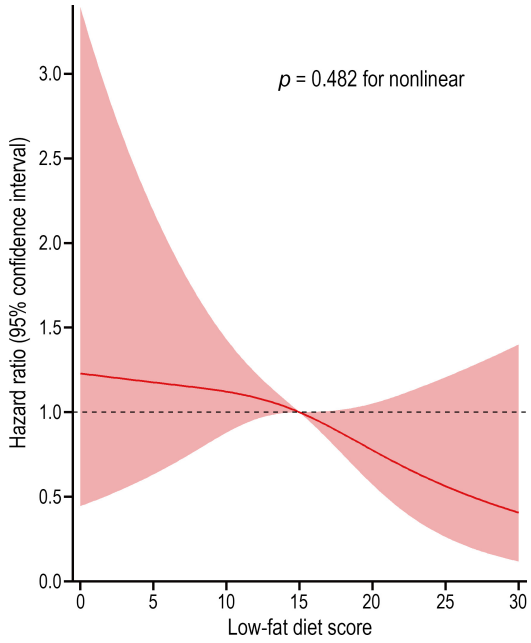


FIGURE 3
Dose-response association between low-fat diet score and the risk of liver cancer. Hazard ratio was adjusted for age, sex, race, educational level, arm, body mass index, smoking status, smoking pack-years, drinking status, alcohol consumption, aspirin use, history of liver comorbidity, history of diabetes, physical activity level, and energy intake from diet (p = 0.482 for non-linear).

significant inverse association between low-fat diet score and the occurrence of liver cancer, regardless of adjustment for suspected and established confounders. The restricted cubic spline model revealed that this correlation is a non-linear dose-dependent relationship, which means that people who followed a low-fat dietary pattern had a lower risk of liver cancer. In addition, this inverse association remained unchanged even after we excluded several confounding factors through multiple sensitivity analyses.

For decades, the focus on low-fat diet mainly stemmed from the established evidence that low-fat diet can prevent the risk of obesity and diabetes (6, 7). Although dietary recommendations suggest that low-fat diet may be beneficial for cancer prevention, relevant studies are incomplete and controversial due to the wide variety of cancers and conflicting results (19). For example, in a study with a median follow-up time of 8.1 years, the low-fat diet group had a 36% reduced risk in ER-positive and PR-negative breast cancers (20). However, in another cohort study with a mean follow-up of 10 years, the risk of invasive breast cancer was not affected by intervention with low-fat diet in a high-risk population (21). Moreover, the risk for relapse and death was not reduced by the low-fat diet in a population with a very low-risk of breast cancer during a 7.3-year follow-up period (22). In addition to breast cancer, published studies have also linked low-fat diet to pancreatic cancer and skin cancer. In these studies, a reduced risk of pancreatic cancer was observed in women with overweight (BMI $\geq$ 25 kg/m^2) among 46,200 participants followed up to 14.7 years (23), but low-fat diet did not decrease the risk of non-melanoma skin cancer (24). One possible reason for these contradictory results is that the definition of low-fat diet was inconsistent among these studies.

To our knowledge, no published data have investigated the association of low-fat diet with liver cancer risk in large populations. The low-fat diet score used in our study has been proven to be very reliable for assessing a low-fat dietary pattern that comprehensively consider the effects of fats, carbohydrates, proteins and energy (15), not just the percentage of fat in total energy (usually < 30% energy) (25). In our study of 98,455 participants with a mean follow-up length of 8.9 years, the incidence of liver cancer was reduced by 55% in participants in the highest quartile of low-fat diet scores compared with the lowest quartile. The risk of liver cancer decreased linearly with increasing low-fat diet score, as an inverse linear association was observed in the restricted cubic spline model (p for non-linear = 0.482). For fat components, we did not find a significantly association between liver cancer risk and the intakes of PUFA, MUFA, and SFA in our analyses. However, multiple studies involving fat intake-related dietary patterns, rather than low-fat diet, have obtained contradictory results in relation to liver cancer risk. Polesel et al. reported that the risk of hepatocellular carcinoma can be decreased by 40% in participants with a higher intake of PUFA (26). A significant inverse association between hepatocellular carcinoma risk and total fat intake (HR = 0.80) and MUFA (HR = 0.71) was also observed in a prospective study from Europe (27).

The observed association between low-fat diet and liver cancer risk may be explained by the following mechanisms. Physically, the liver connects to the gut through the bile duct,

TABLE 4 Subgroup analyses on the association of low-fat diet score with the risk of liver cancer.

Subgroup variable	Number of participates	Number of cases	HR $_{\text{Quartile 4 vs. Quartile 1}}$ (95% CI)	$P_{\text{interaction}}$
Age (years)				0.634
≤ 65	24634	22	0.539 (0.184, 1.581)	
> 65	22910	21	0.496 (0.165, 1.496)	
Sex				0.344
Male	22145	31	0.638 (0.254, 1.603)	
Female	25399	12	0.325 (0.082, 1.298)	
Body mass index (kg/m^2)				0.796
≤ 25	16695	10	0.394 (0.090, 1.723)	
> 25	30849	33	0.489 (0.198, 1.208)	
Smoking status				0.275
Never	22568	11	0.674 (0.188, 2.416)	
Current/Former	24976	32	0.365 (0.132, 1.003)	
Drinker				0.887
No	13032	9	0.356 (0.082, 1.547)	
Yes	34512	34	0.553 (0.224, 1.367)	
Alcohol consumption (g/day)				0.732
≤ medium	23807	21	0.336 (0.133, 1.004)	
> medium	23737	22	0.633 (0.195, 2.050)	
History of liver comorbidity				0.384
No	45851	34	0.398 (0.163, 0.974)	
Yes	1693	9	1.286 (0.317, 5.221)	
History of diabetes				0.372
No	44487	30	0.465 (0.194, 1.120)	
Yes	3057	13	0.746 (0.142, 3.928)	
Physical activity (min/week)				0.819
≤ medium	24178	14	0.323 (0.072, 1.444)	
> medium	23366	29	0.485 (0.198, 1.188)	
Energy intake from diet (kcal/day)				0.339
≤ medium	23772	19	0.631 (0.235, 1.697)	
> medium	23772	24	0.337 (0.075, 1.506)	

HR, hazard ratio; CI, confidence interval.

and the portal vein transports the products of the gut microbiota to the liver (28). Therefore, the crosstalk of gut microbiota between the liver and gut (gut-liver axis) can integrate signals into an interconnected system (29). Dietary patterns alter the gut microbiome balance and subsequently change the immune and inflammatory metabolism landscapes, eventually leading to tumor occurrence and progression (30, 31). For example, it was previously shown that gut microbiota dysbiosis induced by fiber-enriched foods (as inulin-enriched high-fat diet) prone to dysbiosis leads to inflammation, cholestasis, and hepatocellular carcinoma in mice (32). Excessive intake of high-fat diet stimulates the liver to synthesize bile acids, thereby producing large amounts of secondary bile acids in the gut (33), which have been shown to be messengers for microbiota–gut–liver interactions contributing to cancer risk (30, 34), although the underlying mechanisms are unclear. Furthermore, animal and human studies have reported that prolonged consumption of high-fat diet may produce adverse metabolic effects and up-regulate inflammatory mediators, putting the body in a state of chronic inflammation and high postprandial blood glucose and insulin response (11, 35), which is not only involved in the pathogenesis of type 2 diabetes and obesity but also closely related to hepatocarcinogenesis, as liver cancer risk consistently increases with obesity and diabetes (36–38). Conversely, low-fat diet can reduce the secretion of inflammatory mediators and inhibit the activation of tumor-related signaling pathways, ultimately preventing tumor development (39).

This study has significant strengths. This prospective analysis showed for the first time that low-fat diet reduces the incidence of liver cancer in a large population. In addition, good robustness for this inverse association was obtained by multiple sensitivity analyses. For instance, the influence of reverse causation was decreased when excluding cases that occurred in the first 2 years and 4 years of follow-up. In this study, the follow-up time was calculated based on the

date of DHQ completion rather than BQ completion, thus ensuring the reliability of low-fat diet score acquisition, and a follow-up time of up to 8 years was sufficient to ensure the occurrence of end-point events. Moreover, the results of this study were extensively adjusted for potential confounders including demographic, lifestyle, medical and dietary factors, thereby minimizing the influence of residual confounders on observed events.

However, several limitations existed in this study. First, we did not find a significant interaction on the incidence of liver cancer between low-fat diet score and potential impact modifiers in a series of subgroup analyses, although the reason may be due to the limited liver cancer cases in each subgroup, resulting in insufficient statistical power for the interaction test. Thus, we cannot provide dietary guidance for specific subgroups based on the results of this study. Second, the low-fat diet score was assessed using a one-time questionnaire without considering that the dietary habits of the participants may change during the follow-up period, which may result in non-differential bias. However, studies have reported that using cumulative averages to assess dietary patterns generally leads to a similar statistical association for disease risk analysis (40), and it is always assumed that the dietary habits of adults generally do not change in nutritional epidemiological studies (41). Third, as the population of our study was American adults aged 55–74 years, we cannot guarantee that the inverse association of low-fat diet with liver cancer risk is applicable for other age groups and non-American populations.

Conclusion

In conclusion, low-fat diet is associated with a reduced risk of liver cancer in the US population. These findings suggest that adherence to a low-fat diet is helpful for the prevention of liver cancer. Future studies should validate our findings in other populations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the National Cancer Institute and each screening center. Written informed consent was obtained from all individuals. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XZ, YW, and LP designed the study. LP, LX, and ZX collected and organized the original data. LP, ZX, and LX analyzed the data. YW, HG, and YT assisted with statistical analysis. LP, ZX, LX, HG, YT, ZZ, YJ, and HH assisted in the interpretation of the results. LP, LX, and XZ drafted the manuscript. All authors contributed to the article and approved the submitted manuscript.

Funding

This work was supported by the General Project of Chongqing Natural Science Foundation, Chongqing Science and Technology Commission, China [grant numbers: cstc2021jcyj-msxmX0153 (LP) and cstc2021jcyj-msxmX0112 (YW)].

Acknowledgments

We thank the NIH PLCO study group and the National Cancer Institute (NCI) for access to NCI's data collected by the PLCO Cancer Screening Trial. This study has been approved by the NCI (approval number: PLCO-987).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1013643/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2021) 71:209–49. doi: 10.3322/caac.21660

2. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. *J Clin Gastroenterol*. (2013) 47(Suppl):S2–6. doi: 10.1097/MCG.0b013e3182872f29

3. Yang WS, Zeng XF, Liu ZN, Zhao QH, Tan YT, Gao J, et al. Diet and liver cancer risk: a narrative review of epidemiological evidence. *Br J Nutr*. (2020) 124:330–40. doi: 10.1017/s0007114520001208

4. Ma Y, Yang W, Simon TG, Smith-Warner SA, Fung TT, Sui J, et al. Dietary patterns and risk of hepatocellular carcinoma among U.S. Men and women. *Hepatology*. (2019) 70:577–86. doi: 10.1002/hep.30362

5. Zhang W, Xiang YB, Li HL, Yang G, Cai H, Ji BT, et al. Vegetable-based dietary pattern and liver cancer risk: results from the Shanghai women's and men's health studies. *Cancer Sci*. (2013) 104:1353–61. doi: 10.1111/cas.12231

6. Astrup A, Grunwald GK, Melanson EL, Saris WH, Hill JO. The role of low-fat diets in body weight control: a meta-analysis of ad libitum dietary intervention studies. *Int J Obes Relat Metab Disord*. (2000) 24:1545–52. doi: 10.1038/sj.ijo.0801453

7. Lindström J, Peltonen M, Eriksson JG, Louheranta A, Fogelholm M, Uusitupa M, et al. High-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk: the Finnish Diabetes Prevention Study. *Diabetologia*. (2006) 49:912–20. doi: 10.1007/s00125-006-0198-3

8. Prentice RL, Aragaki AK, Howard BV, Chlebowski RT, Thomson CA, Van Horn L, et al. Low-fat dietary pattern among postmenopausal women influences long-term cancer, cardiovascular disease, and diabetes outcomes. *J Nutr*. (2019) 149:1565–74. doi: 10.1093/jn/nxz107

9. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, et al. Inflammation and tumor progression: signaling pathways and targeted intervention. *Signal Transduct Target Ther*. (2021) 6:263. doi: 10.1038/s41392-021-00658-5

10. Snodgrass RG, Huang S, Choi IW, Rutledge JC, Hwang DH. Inflammasome-mediated secretion of IL-1β in human monocytes through TLR2 activation; modulation by dietary fatty acids. *J Immunol*. (2013) 191:4337–47. doi: 10.4049/jimmunol.1300298

11. Doerner SK, Reis ES, Leung ES, Ko JS, Heaney JD, Berger NA, et al. High-fat diet-induced complement activation mediates intestinal inflammation and neoplasia, independent of obesity. *Mol Cancer Res*. (2016) 14:953–65. doi: 10.1158/1541-7786.Mcr-16-0153

12. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. *Control Clin Trials*. (2000) 21:273s–309s. doi: 10.1016/s0197-2456(00)00098-2

13. Thompson FE, Kipnis V, Midthune D, Freedman LS, Carroll RJ, Subar AF, et al. Performance of a food-frequency questionnaire in the US NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study. *Public Health Nutr*. (2008) 11:183–95. doi: 10.1017/s1368980007000419

14. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires : the Eating at America's Table Study. *Am J Epidemiol*. (2001) 154:1089–99. doi: 10.1093/aje/154.12.1089

15. Shan Z, Guo Y, Hu FB, Liu L, Qi Q. Association of low-carbohydrate and low-fat diets with mortality among US adults. *JAMA Intern Med*. (2020) 180:513–23. doi: 10.1001/jamainternmed.2019.6980

16. Dwyer J, Picciano MF, Raiten DJ. Future directions for the integrated CSFII-NHANES: what we eat in America-NHANES. *J Nutr*. (2003) 133:576s–81s. doi: 10.1093/jn/133.2.576S

17. Csizmadi I, Boucher BA, Lo Siou G, Massarelli I, Rondeau I, Garriguet D, et al. Using national dietary intake data to evaluate and adapt the US Diet History Questionnaire: the stepwise tailoring of an FFQ for Canadian use. *Public Health Nutr*. (2016) 19:3247–55. doi: 10.1017/s1368980016001506

18. Brancato G, Pezzotti P, Rapiti E, Perucci CA, Abeni D, Babbalacchio A, et al. Multiple imputation method for estimating incidence of HIV infection. The Multicenter Prospective HIV Study. *Int J Epidemiol*. (1997) 26:1107–14. doi: 10.1093/ije/26.5.1107

19. Ludwig DS, Willett WC, Volek JS, Neuhouser ML. Dietary fat: from foe to friend? *Science*. (2018) 362:764–70. doi: 10.1126/science.aau2096

20. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *Jama*. (2006) 295:629–42. doi: 10.1001/jama.295.6.629

21. Martin LJ, Li Q, Melnichouk O, Greenberg C, Minkin S, Hislop G, et al. A randomized trial of dietary intervention for breast cancer prevention. *Cancer Res*. (2011) 71:123–33. doi: 10.1158/0008-5472.Can-10-1436

22. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *Jama*. (2007) 298:289–98. doi: 10.1001/jama.298.3.289

23. Jiao L, Chen L, White DL, Tinker L, Chlebowski RT, Van Horn LV, et al. Low-fat dietary pattern and pancreatic cancer risk in the women's health initiative dietary modification randomized controlled trial. *J Natl Cancer Inst*. (2018) 110:49–56. doi: 10.1093/jnci/djx117

24. Black HS, Thornby JI, Wolf JE Jr., Goldberg LH, Herd JA, Rosen T, et al. Evidence that a low-fat diet reduces the occurrence of non-melanoma skin cancer. *Int J Cancer*. (1995) 62:165–9. doi: 10.1002/ijc.2910620210

25. Austin GL, Ogden LG, Hill JO. Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971-2006. *Am J Clin Nutr*. (2011) 93:836–43. doi: 10.3945/ajcn.110.000141

26. Polesel J, Talamini R, Montella M, Maso LD, Crovatto M, Parpinel M, et al. Nutrients intake and the risk of hepatocellular carcinoma in Italy. *Eur J Cancer*. (2007) 43:2381–7. doi: 10.1016/j.ejca.2007.07.012

27. Duarte-Salles T, Fedirko V, Stepien M, Aleksandrova K, Bamia C, Lagiou P, et al. Dietary fat, fat subtypes and hepatocellular carcinoma in a large European cohort. *Int J Cancer*. (2015) 137:2715–28. doi: 10.1002/ijc.29643

28. Tripathi A, Debelius J, Brenner DA, Karin M, Loomba R, Schnabl B, et al. The gut-liver axis and the intersection with the microbiome. *Nat Rev Gastroenterol Hepatol*. (2018) 15:397–411. doi: 10.1038/s41575-018-0011-z

29. Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: pathophysiological basis for therapy. *J Hepatol*. (2020) 72:558–77. doi: 10.1016/j.jhep.2019.10.003

30. Silveira MAD, Bilodeau S, Greten TF, Wang XW, Trinchieri G. The gut-liver axis: host microbiota interactions shape hepatocarcinogenesis. *Trends Cancer*. (2022) 8:583–97. doi: 10.1016/j.trecan.2022.02.009

31. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. (2014) 505:559–63. doi: 10.1038/nature12820

32. Singh V, Yeoh BS, Chassaing B, Xiao X, Saha P, Aguilera Olvera R, et al. Dysregulated microbial fermentation of soluble fiber induces cholestatic liver cancer. *Cell*. (2018) 175:679–94.e22. doi: 10.1016/j.cell.2018.09.004

33. Trefflich I, Marschall HU, Giuseppe RD, Ståhlman M, Michalsen A, Lampen A, et al. Associations between dietary patterns and bile acids-results from a cross-sectional study in vegans and omnivores. *Nutrients*. (2019) 12:47. doi: 10.3390/nu12010047

34. Ocvirk S, O'Keefe SJ. Influence of bile acids on colorectal cancer risk: potential mechanisms mediated by diet - gut microbiota interactions. *Curr Nutr Rep*. (2017) 6:315–22. doi: 10.1007/s13668-017-0219-5

35. Abdulmalek SA, Fessal M, El-Sayed M. Effective amelioration of hepatic inflammation and insulin response in high fat diet-fed rats via regulating AKT/mTOR signaling: role of *Lepidium sativum* seed extracts. *J Ethnopharmacol*. (2021) 266:113439. doi: 10.1016/j.jep.2020.113439

36. Campbell PT, Newton CC, Freedman ND, Koshiol J, Alavanja MC, Beane Freeman LE, et al. Body mass index, waist circumference, diabetes, and risk of liver cancer for U.S. Adults. *Cancer Res*. (2016) 76:6076–83. doi: 10.1158/0008-5472.Can-16-0787

37. Petrick JL, Freedman ND, Demuth J, Yang B, Van Den Eeden SK, Engel LS, et al. Obesity, diabetes, serum glucose, and risk of primary

liver cancer by birth cohort, race/ethnicity, and sex: multiphasic health checkup study. *Cancer Epidemiol*. (2016) 42:140–6. doi: 10.1016/j.canep.2016.04.009

38. Chen Y, Wu F, Saito E, Lin Y, Song M, Luu HN, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. *Diabetologia*. (2017) 60:1022–32. doi: 10.1007/s00125-017-4229-z

39. Heymach JV, Shackleford TJ, Tran HT, Yoo SY, Do KA, Wergin M, et al. Effect of low-fat diets on plasma levels of NF-κB-regulated inflammatory cytokines and angiogenic factors in men with prostate cancer. *Cancer Prev Res*. (2011) 4:1590–8. doi: 10.1158/1940-6207.Capr-10-0136

40. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol*. (1999) 149:531–40. doi: 10.1093/oxfordjournals.aje.a009849

41. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Méjean C, Andrianasolo RM, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). *Bmj*. (2019) 365:l1451. doi: 10.1136/bmj.l1451

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 22 November 2022
DOI 10.3389/fnut.2022.1030619

OPEN ACCESS

EDITED BY
Harriët Jager-Wittenaar,
Hanze University of Applied Sciences, Netherlands

REVIEWED BY
Wendy J. Dahl,
University of Florida, United States
Manon Van Den Berg,
Radboud University Medical Centre, Netherlands

*CORRESPONDENCE
Antti Mäkitie
antti.makitie@hus.fi

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 29 August 2022
ACCEPTED 02 November 2022
PUBLISHED 22 November 2022

CITATION
Orell HK, Pohju AK, Osterlund P, Schwab US, Ravasco P and Mäkitie A (2022) GLIM in diagnosing malnutrition and predicting outcome in ambulatory patients with head and neck cancer. *Front. Nutr.* 9:1030619. doi: 10.3389/fnut.2022.1030619

GLIM in diagnosing malnutrition and predicting outcome in ambulatory patients with head and neck cancer

Helena Kristiina Orell[1,2], Anne Katariina Pohju[1], Pia Osterlund[3,4,5,6], Ursula Sonja Schwab[2,7], Paula Ravasco[8,9] and Antti Mäkitie[10,11,12]*

[1]Clinical Nutrition Unit, Internal Medicine and Rehabilitation, Helsinki University Hospital, University of Helsinki, Helsinki, Finland, [2]Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland, [3]Department of Oncology, Tampere University Hospital, Tampere, Finland, [4]Department of Oncology/GI-cancer, Karolinska University Hospital, Stockholm, Sweden, [5]Department of Oncology/Pathology, Karolinska Institutet, Stockholm, Sweden, [6]Department of Oncology, Helsinki University Hospital, Helsinki, Finland, [7]Department of Medicine, Endocrinology and Clinical Nutrition, Kuopio University Hospital, Kuopio, Sweden, [8]Universidade Católica Portuguesa, Católica Medical School and Centre for Interdisciplinary Research in Health (CIIS), Lisbon, Portugal, [9]Clinical Research Unit, Egas Moniz Interdisciplinary Research Center, Almada, Portugal, [10]Research Program in Systems Oncology, Faculty of Medicine, University of Helsinki, Helsinki, Finland, [11]Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska University Hospital, Stockholm, Sweden, [12]Department of Otorhinolaryngology-Head and Neck Surgery, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

Aim: This study aimed to determine the prevalence of malnutrition in a head and neck cancer (HNC) population according to the Global Leadership Initiative on Malnutrition (GLIM) criteria and to assess its relation to survival. The secondary aim was to compare GLIM criteria to Patient–Generated Subjective Global Assessment (PG–SGA) and Nutritional Risk Screening 2002 (NRS 2002) methods.

Methods: The assessment was performed in a series of 65 curative patients with newly diagnosed HNC in a nutrition intervention study. Malnutrition was defined as PG-SGA classes BC and nutritional risk as NRS 2002 score $\geq$3 and was retrospectively diagnosed with GLIM criteria in prospectively collected data at diagnosis. Sensitivity, specificity, and kappa (κ) were analyzed. Predictive accuracy was assessed by calculating the area under curve (AUC) b y receiver operating characteristic (ROC) analysis. Kaplan–Meier and Cox regression analyses were used to evaluate association between malnutrition and overall survival (OS), and disease-free survival (DFS).

Results: GLIM-defined malnutrition was present in 37% (24/65) of patients. The GLIM showed 77% sensitivity and 84% specificity with agreement of $\kappa = 0.60$ and accuracy of AUC = 0.80 ($p < 0.001$) with PG-SGA and slightly higher sensitivity (83%) with NRS 2002 ($\kappa = 0.58$). Patients with GLIM-defined malnutrition had shorter OS (56 vs. 72 months, HR 2.26, 95% CI 1.07–4.77, $p = 0.034$) and DFS (37 vs. 66 months, HR 2.01, 95% CI 0.99–4.09, $p = 0.054$), than well-nourished patients. The adjusted HR was 2.53 (95% CI 1.14–5.47, $p = 0.023$) for OS and 2.10 (95% CI 0.98–4.48, $p = 0.056$) for DFS in patients with GLIM-defined malnutrition.

Conclusion: A substantial proportion of HNC patients were diagnosed with malnutrition according to the GLIM criteria and this showed a moderate agreement with NRS 2002- and PG–SGA-defined malnutrition. Even though the GLIM criteria had strong association with OS, its diagnostic value was poor. Therefore, the GLIM criteria seem potential for malnutrition diagnostics and outcome prediction in the HNC patient population. Furthermore, NRS 2002 score ≥3 indicates high nutritional risk in this patient group.

KEYWORDS

nutrition status, nutrition status assessment, nutritional risk, survival, malnutrition, nutritional risk screening 2002, Patient-Generated Subjective Global Assessment, head and neck cancer

Introduction

Malnutrition is defined as an acute or chronic state of impaired nutritional status, in which a combination of varying degrees of nutrition intake and inflammatory activity have led to harmful changes in body composition and function (1). Prevention, early identification of patients at risk, accurate diagnosis, personalized nutrition interventions, and follow–up are cornerstones of the management of malnutrition and the prevention of its unfavorable effects on treatment complications, patients' quality of life, and survival (2–6). However, variation in nutritional status criterion makes the comparison of the effectiveness of nutrition interventions across different studies challenging. Consequently, the Global Leadership Initiative on Malnutrition (GLIM) working group published in 2018 a global consensus recommendation on the criteria to be used for the identification of protein–energy malnutrition in adults (7). Since then several studies have validated these criteria in various patient cohorts, including head and neck cancer (HNC) (8–11). The GLIM criteria have often been compared either with Subjective Global Assessment or Patient-Generated Subjective Global Assessment (SGA or PG–SGA), which are judged to be the most validated standardized assessment tools of malnutrition (12). So far the GLIM criteria have shown to be an accurate, sensitive, and specific malnutrition diagnostic tool in ambulatory cancer care and in-patient settings. Furthermore, the GLIM criteria have shown high inter–rater reliability in patients with HNC (8). However, the GLIM criteria have shown only a fair agreement with the SGA (10, 11).

In 2020, almost 880,000 new cases of HNC (e.g., lip and oral cavity, larynx, nasopharynx, oropharynx, and hypopharynx) and 445,000 associated deaths were observed worldwide with an overall 5-year survival rate of around 50% (13). Throughout the HNC journey, around 11–85% of patients present with malnutrition when assessed either with PG–SGA or with the GLIM criteria (8–10, 14, 15). Nutrition care plays a crucial role for patients with HNC since tumor itself and cancer treatments cause substantial eating and swallowing difficulties resulting in decreased food intake and deteriorated nutritional status which can be effectively managed by nutritional interventions (15, 16). This warrants further attention as malnutrition reduces treatment efficacy? (2, 4), quality of life (2), and survival (3, 4), as well as increases complications (4). Moreover, a GLIM-defined malnutrition diagnosis associates with lower BMI (8) and impaired quality of life (17) and PG-SGA-defined malnutrition with shorter overall survival (OS) and disease–free survival (DFS), as we have previously shown in patients with HNC (15).

The GLIM criteria have eight possible combinations to classify patients as malnourished, and controversies in sensitivity and specificity between these combinations exist (8, 9, 12). As the GLIM criteria are based on consensus, further evidence is required for validation and reliability of testing in a variety of healthcare sectors and populations with diverse persons using these criteria (18). So far only two studies have used the GLIM criteria to diagnose malnutrition in HNC, and they have shown a prevalence of malnutrition in 11–32% of patients (8, 9). The prevalence of GLIM-defined malnutrition has been 24–70% in patients with other cancers (19–23). Furthermore, the GLIM criteria have shown their predictive value with respect to survival in various clinical conditions (10, 19–22, 24).

Nutritional risk screening 2002 (NRS 2002) is a method to obtain patients who have a risk to develop protein-energy malnutrition (25). Usually, the score ≥3 indicates nutritional risk and a need for further assessment of nutritional status either with PG-SGA or GLIM. However, in a nutritionally more vulnerable patient group such as HNC, NRS 2002 score ≥3 may already indicate malnutrition as we showed in our previous study (14).

This study aimed to determine (1) the prevalence of malnutrition according to the GLIM criteria at diagnosis of HNC; (2) the reliability of using the GLIM criteria to identify malnutrition compared to the current reference standard, namely, the PG–SGA and to the NRS 2002; and (3) the

associations between the GLIM criteria and survival, and the predictive validity of the GLIM criteria with respect to survival.

Materials and methods

This is a retrospective analysis of baseline measurements collected during a previously published randomized controlled study of adult HNC patients (14) at the Department of Otorhinolaryngology, Head and Neck Surgery, Helsinki University Hospital (HUS), Finland. Ambulatory, 18–80-year-old patients with a primary locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, nasopharynx, or larynx were eligible for inclusion. A total of 65 patients with HNC were included. All patients were under nutritional surveillance and were offered nutritional treatment when indicated (15).

Clinical prospectively collected data included age, gender, tumor histopathology, site and stage classification, and cancer treatment (definitive chemoradiotherapy, definitive radiotherapy, surgery, surgery with radiotherapy, or surgery with chemoradiotherapy). All nutritional measurements and subjective assessments, except GLIM, were performed prospectively at the time of diagnosis before surgery or adjuvant cancer treatment.

Body mass index (BMI) was calculated from the patient-reported height and measured body weight and was further categorized according to age as underweight (<18.5 kg/m^2 if <65 years or <22 kg/m^2 if ≥ 65 years); healthy weight (18.5–24.9 kg/m^2 if <65 years or 22–27 kg/m^2 if ≥ 65 years) or overweight (≥ 25 kg/m^2 if <65 years or >27 kg/m^2 if ≥ 65 years). Body composition was analyzed with bioimpedance (BIA) using a single frequency (50 kHz) two–terminal bio–impedance meter (Bodystat Ltd®, Isle of Man, UK) performed according to a standard procedure.

Nutritional status was assessed using the PG–SGA (26, 27) with classes B and C indicating malnutrition. Nutritional risk was current study the NRS 2002 score ≥ 3 was set to indicate nutritional risk (25). Patient-Generated SGA was considered as the reference method to identify protein-energy malnutrition, as this is what GLIM was designed to identify (12). Permission for the full form of scored PG-SGA© was received from Pt-Global (http://pt-global.org/). The English PG-SGA version 2001 was translated into Finnish through backward translation by a medical doctor (PÖ) and dietitian (HO) in our research group. PÖ translated it to Finish and then HO translated it back to English whereupon they both translated it to Finnish. No methodical discrepancies were observed. Research supervisors (PÖ and AM) accepted the final translation. PÖ supervised the subjective assessment of body composition, and the execution of PG-SGA. The research dietitian (HO) performed both the patient and the professional components of PG-SGA for all patients.

A GLIM diagnosis of malnutrition was assigned retrospectively when one phenotypic and one etiologic criterion were present and categorized as "malnourished" or "not malnourished" with minimum of one criteria of each existing (7). As a phenotypic criterion for malnutrition, we used body weight loss (>5% within the past 6 months), BMI (<20 kg/m^2 if age <70 years or <22 kg/m^2 if ≥ 70 years), and fat–free mass index (FFMI) by BIA (<17 kg/m^2 for men and <15 kg/m^2 for women) was used as an operationalization of the criterium "reduced muscle mass". The etiologic criterion was either reduced food intake defined as $\leq 50\%$ of estimated need or CRP >5 mg/L as a proxy for inflammation (8, 9). Food intake was compared to patients' usual eating and intake was categorized subjectively as $\leq 50\%$ of estimated need if the patient had tumor-induced eating problems and therefore ate 50% less than normally or was unable to eat *per os*. Since all patients had a chronic active disease as per GLIM etiologic criterion, CRP was used as a more specific measure to define inflammation in line with previous studies (8, 9, 11). Cancer diagnosis itself is not recommended to be used for this etiologic criterion as it does not indicate the severity of the disease burden (12).

Patient outcome measures were collected at a median of 76 (IQR 71–81) months after the initial study date assessed by Kaplan-Meier and data were obtained from the electronic medical records. Data cut-off date was assigned as March 18th, 2015. Follow-up time and overall survival (OS) was calculated from the date of randomization (i.e., at diagnosis) to the date of the last visit or death by any cause. Disease–free survival (DFS) was calculated from the completion of treatment to the detection of cancer recurrence or death of any cause. There were no cancer events during cancer treatment. One patient with a second primary of esophagus cancer was excluded from the DFS analyses.

The research clinical dietitian (HO) performed nutritional status assessments, BIA measurements, and GLIM diagnostics for all patients. Permission for the full form of scored PG–SGA© was received from Pt–Global (https://pt-global.org/). The Finnish translation of NRS 2002 has shown substantial agreement ($k = 0.8$) with PG–SGA (14). The study design was approved by the Research Ethics Board at our institution and has a research permission (HUS/186/2021) granted by our institution. All patients gave a written informed consent.

Statistical analyses

Descriptive statistics for all continuous variables were reported as median with inter–quartile range (IQR). Categorical variables were reported as frequencies and percentages. Construct (discriminant) validity was assessed using Chi–square test for categorical variables and Mann–Whitney's *U*-test for continuous variables.

Sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) for the GLIM criteria against PG–SGA, NRS 2002, and survival were calculated from a contingency table. Rating of validity test statistics followed recommended cut points for sensitivity and specificity: the professional standard 80% for sensitivity and 60% for specificity were determined.

Assessment of agreement between the GLIM criteria, the PG–SGA and survival used the Kappa statistics (κ). Values 0.81–0.99 represented "excellent" agreement, 0.61–0.80 "substantial", 0.41–0.60 "moderate" and <0.41 "poor to fair" agreement. The professional standard for kappa was set to >0.60.

Predictive accuracy between the GLIM criteria, PG-SGA and survival was assessed by calculating the area under curve (AUC) by receiver operating characteristic (ROC) analysis. Accuracy was considered very good if the ROC AUC was >0.9, good if 0.8–0.9, fair if 0.7–0.8, poor if 0.6–0.7 and not better than chance if <0.6.

Overall survival and DFS were calculated using the Kaplan–Meier method and the log-rank test. Cox proportional univariable hazards analyses (hazard ratio, HR) were performed to determine the association between GLIM-defined malnutrition diagnosis and mortality. Multivariable analyses were adjusted for age (≤65 vs. >65 years), gender, stage (I–III vs. IV), GLIM-defined malnutrition (not malnourished vs. malnourished), and smoking (<10 vs. ≥10 pack years) based on available literature (28).

All statistical analyses were performed with SPSS, Version 27.0 (IBM corp., Armonk, NY, US). We set the statistical significance level to 5%.

Results

The median age was 61 years (range 33–77) with 25% being 65 or older, and the male–to–female ratio was 3.3:1 (55 males, 15 females). Most patients had stage IV disease ($n = 44$, 68%) and were planned to receive either definitive chemoradiotherapy (65%), or either surgery alone or as a combination treatment (26%). Only 7.3% of patients had definitive radiotherapy. The median (IQR) follow-up time was 76 (71–81) months assessed by Kaplan-Meier. The descriptive data according to GLIM-defined malnutrition diagnosis are shown in Table 1.

Of the 65 patients, 37% were malnourished according to the GLIM criteria and 34% according to PG–SGA, while nutritional risk according to NRS 2002 was seen in 28% of patients at the time of cancer diagnosis and before any cancer treatment. All nutritional parameters were statistically significantly lower in patients with GLIM-defined malnutrition than in those not malnourished. Table 2 shows the numbers of patients with each phenotypic and etiologic criterion of GLIM-defined malnutrition. The criterion of unintentional weight loss was met by 40%, low BMI by 18%, low FFMI by 52%, low food intake by 25%, and inflammation by 51% of patients. We found no statistically significant differences between phenotypic or etiologic criteria between deceased patients and survivors (data not shown).

Diagnostic value of the GLIM criteria

The agreement between GLIM and PG-SGA is shown in Table 3. When considering the PG-SGA as the reference method, the sensitivity of GLIM did not reach acceptable level (>0.80) while the specificity did (>0.60). The agreement between the PG-SGA and GLIM criteria was moderate according to the Kappa statistics (0.60) and the predictive value was fair according to AUC (Figure 1). The negative predictive value (NPV) was acceptable, but the positive predictive value was less than the acceptable level (>0.80).

Association of the GLIM criteria and NRS 2002

The agreement between GLIM and NRS 2002 is shown in Table 3. When considering the NRS 2002 score ≥3 as the reference method, the sensitivity and specificity of GLIM did reach acceptable level. The agreement between the NRS 2002 and GLIM criteria was moderate according to the Kappa statistics (0.60). The negative predictive value (NPV) was acceptable, but the positive predictive value did not reach the acceptable level.

Overall and disease-free survival

The 5-year OS rate was 57% (37/65) and DFS 52% (34/65) for all patients. Altogether 28 (43%) patients died during follow-up, of which 17 (26%) patients due to HNC, six due to other cancer, and five due to other causes. Malnourished patients had significantly lower OS ($p = 0.029$) and DFS ($p = 0.047$), than not malnourished patients (Table 1), as analyzed by Kaplan-Meier analysis (Figures 2, 3). Hazard ratios for OS and DFS according to Cox regression analysis are shown in Tables 4, 5. The association of malnutrition with OS and DFS was maintained when age, gender, stage, and smoking were added as covariates in adjusted multivariate models (Tables 4, 5). The accuracy of the GLIM criteria to predict OS and DFS was poor according to *k*-value and not better than chance according to AUC (Table 3).

Discussion

Our findings showed that the GLIM criteria form an accurate, sensitive, and specific malnutrition diagnostic method

TABLE 1 Descriptive data of 65 HNC patients stratified according to GLIM-defined malnutrition diagnosis.

	GLIM-defined malnutrition diagnosis ($n = 65$)		
	Not malnourished, 41 (63.1%)	**Malnourished, 24 (36.9%)**	***p*-value**
Age, years, median (IQR)	61 (55–64)	59.5 (57–64)	0.749
Men, *n* (%)	33 (80.5)	17 (70.8)	NS
Nutritional parameters, median (IQR)			
Weight, kg	79.7 (67.0–90.1)	64.9 (56.2–77.4)	0.004
BMI, kg/m^2	25.7 (23.0–28.0)	21.6 (20.1–23.8)	<0.001
FFMI, kg/m^2	17.8 (16.1–19.3)	15.5 (14.2–16.2)	<0.001
Weight loss, kg	0.2 (1.2–0.9)	6.0 (4.4–8.4)	<0.001
Weight loss, %	0.2 (1.3–1.2)	9.3 (6.2–11.3)	<0.001
C–reactive protein, g/L	3.0 (3.0–9.0)	20.5 (9.0–53.5)	<0.001
Albumin, g/L	40.3 (38.0–42.2)	35.4 (31.6–40.0)	<0.001
Prealbumin, mg/L	275 (225–304)	180 (127–229)	<0.001
Hemoglobin, mg/L	142 (131–150)	134 (124–140)	0.015
Weight status, *n* (%)[#]			
Underweight	4 (9.8)	6 (25.0)	NS
Healthy weight	17 (41.5)	15 (62.5)	NS
Overweight	20 (48.8)	3 (12.5)	0.003
SG–PGA, *n* (%)			
Well–nourished (class A)	36 (87.8)	7 (29.2)	<0.001
Malnourished (class B or C)	5 (12.2)	17 (70.8)	<0.001
NRS 2002, *n* (%)			
Not nutritionally at risk (score <3)	38 (92.7)	9 (37.5)	<0.001
Nutritionally at risk (score ≥3)	3 (7.3)	15 (62.5)	<0.001
Smoking, pack years			
<10	25 (61.0)	17 (70.8)	NS
≥10	16 (39.0)	7 (29.2)	NS
Survival, months, median (95% CI)			
OS	67 (58–77)	54 (15–93)	0.029*
DFS	60 (50–71)	21 (0–70)	0.047*
OS status, *n* (%)			
Diseased	14 (34.1)	14 (58.3)	NS
Survivor	27 (65.9)	10 (41.7)	NS
DFS status, *n* (%)			
Event	16 (39.0)	15 (62.5)	NS
Survivor	25 (61.0)	9 (37.5)	NS
Tumor location, *n* (%)			
Oral cavity	6 (14.6)	6 (25.0)	NS
Oropharynx	16 (39.0)	7 (29.2)	NS
Hypopharynx	5 (12.2)	6 (25.0)	NS
Larynx	9 (22.0)	2 (8.3)	NS
Nasopharynx	5 (12.2)	2 (8.3)	NS
Unknown primary	0 (0)	1 (4.2)	NS
Stage, *n* (%)			
I	5 (12.2)	0 (0)	NS
II	4 (9.8)	2 (8.3)	NS
III	10 (24.4)	2 (8.3)	NS
IV	22 (53.7)	20 (83.3)	0.016
Planned mode of cancer treatment, *n* (%)			
Surgery alone or in combination	14 (34.1)	3 (12.5)	NS
Definitive radiotherapy	3 (7.3)	3 (12.5)	NS
Definitive chemoradiotherapy	24 (58.5)	18 (75.0)	NS

BMI, body mass index; DFS, disease–free survival; FFMI, fat–free mass index; GLIM, the Global Leadership Initiative on Malnutrition; IQR, interquartile range; NRS, nutritional risk screening; OS, overall survival; PG–SGA, Patient–generated Subjective Global Assessment, A = well-nourished, B= moderately and C = severely malnourished.

[#]Underweight, BMI <18.5 kg/m^2 if <65 years or <22 kg/m^2 if ≥65 years; healthy weight, BMI 18.5–24.9 kg/m^2 if <65 years or 22–27 kg/m^2 if ≥65 years; overweight, BMI ≥25 kg/m^2 if <65 years or >27 kg/m^2 if ≥65 years.

*Analyzed by Kaplan-Meier.

TABLE 2 The prevalence of the phenotypic and etiologic GLIM criteria according to malnutrition diagnosis.

GLIM criteria	GLIM-defined malnutrition diagnosis ($n = 65$), n (%)		p-value
	Not malnourished, 41 (63%)	Malnourished, 24 (37%)	
Phenotypic criteria			
Weight loss >5%	5 (12)	21 (88)	<0.001
Low BMI*	5 (12)	7 (29)	<0.001
Low FFMI#	13 (32)	21 (88)	<0.001
Etiologic criteria			
Low food intake	1 (2)	15 (62)	<0.001
Presence of inflammation	10 (24)	23 (96)	<0.001

BMI body mass index; FFMI, fat–free mass index; GLIM, Global Leadership Initiative on Malnutrition.
*BMI <20 kg/m^2 if age <70 years or <22 kg/m^2 if ≥70 years.
#FFMI <17 kg/m^2 for men and <15 kg/m^2 for women was used as an operationalization of the criterium "reduced muscle mass".
p-value by Fisher's Exact Test.

TABLE 3 Diagnostic value of GLIM criteria in predicting malnutrition and survival.

Reference method	GLIM criteria						
	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	k	AUC (95% CI)	p-value
PG–SGA BC	77.3 (57.1–90.8)	83.7 (70.7–92.4)	70.8	87.8	0.597	0.80 (0.68–0.93)	<0.001
NRS 2002 ≥3	83.3 (61.9–95.1)	80.9 (68.0–90.1)	62.5	92.7	0.582		
5-year OS	50.0 (32.2–67.8)	73.0 (57.3–85.2)	58.3	65.9	0.233	0.59 (0.44–0.74)	0.229
5-year DFS	48.4 (31.6–65.6)	73.5 (57.2–86.0)	62.5	61.0	0.221	0.62 (0.48–0.76)	0.116

AUC, area under curve; DFS, disease-free survival; GLIM, the Global Leadership Initiative on Malnutrition; k, Kappa correlation coefficient; NPV, negative predictive value; NRS, nutritional risk screening, ≥ 3 = nutritional risk; OS, overall survival; PG–SGA BC, Patient–generated Subjective Global Assessment; BC, moderately or severely malnourished; PPV, positive predictive value. p-value is for AUC.

for the HNC population. However, the GLIM criteria showed poor diagnostic value in predicting 5-yr survival in this patient population. NRS 2002 score ≥3 showed to be an accurate tool to identify malnourished patients compared against the GLIM criteria, a finding supporting our previous study (14).

Prevalence of malnutrition according to the GLIM criteria

Two previous studies have validated the GLIM criteria in patients with HNC. Prior to any cancer treatment, the prevalence of GLIM-defined malnutrition has been reported to vary from 11 to 23% and to increase up to 32% at the seventh week of HNC treatment (8, 9). Several factors might explain why our study showed a higher prevalence of GLIM-defined malnutrition than these two recent cross-sectional cohorts (8, 9). First, we used CRP as an objective measure for inflammation instead of the presence of metastatic disease, the latter of which may have resulted in some under–reporting of malnutrition in the Steer study (8). Second, Steer and colleagues assessed muscle–mass subjectively as opposed to our objective and more precise BIA analysis. Third, in the Einarsson et al. (9) study, patients were somewhat older, and Stage IV was seen in fewer patients (55%) compared with our study (65%). This high prevalence of stage IV disease indicates a more severe disease and consequently, a higher likelihood of dysphagia, cachexia, and thus higher prevalence of malnutrition already prior diagnosis (6, 29). Indeed, we have shown previously that a substantially high proportion of our patients had cachexia prior to diagnosis (3).

Diagnostic value of the GLIM criteria

Since the publishing of the GLIM criteria, several validation studies have been conducted among medical, surgical, intensive care unit (ICU), and cancer patients (8–11, 30–35). Four studies report criterion validity from fair to good when GLIM criteria were compared with SGA. The agreement with kappa statistics has varied from 0.32 to 0.55 (10, 31, 35) in patients with cancer. A higher agreement ($k = 0.85$) has been seen among ICU patients (34). Sensitivity has varied from 61 to 92% and specificity from 73 to 93% in various patient cohorts (10, 11, 30, 32–34). Our results show moderate agreement, sensitivity and specificity, which are well in line with those studies conducted

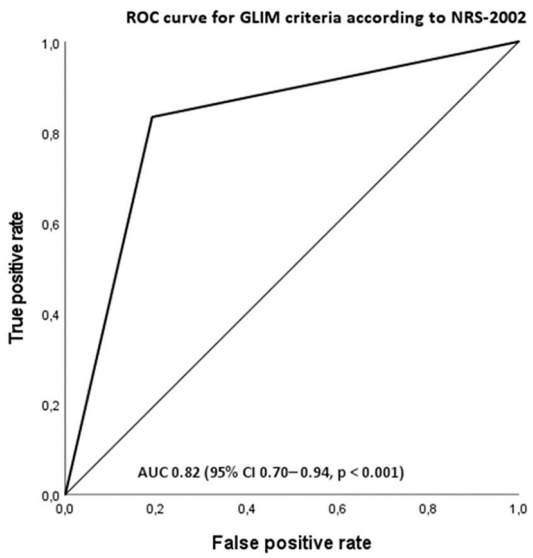


FIGURE 1
Receiver operating characteristic curve (ROC) for GLIM-diagnosed malnutrition as a measure of malnutrition according to patient-subjective global assessment (PG-SGA) group BC. The area under the curve (AUC) is 0.805 (95% CI 0.68–0.93, $p < 0.001$).

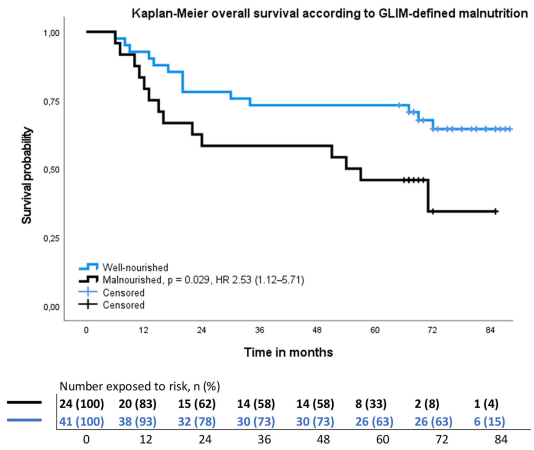


FIGURE 2
Results of the Kaplan–Meier overall survival analysis and hazard ratio for head and neck cancer patients stratified by GLIM–defined nutrition status. Hazard ratio adjusted to age, gender, stage, and smoking.

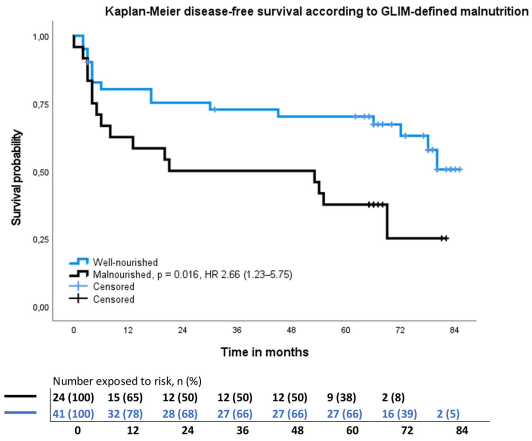


FIGURE 3
Results of the Kaplan–Meier disease-free survival analysis and hazard ratio for head and neck cancer patients stratified by GLIM–defined malnutrition. Hazard ratio adjusted to age, gender, stage, and smoking.

in cancer patients (10, 31, 35). Nevertheless, further prospective validation studies are needed to add knowledge on how to assess muscle mass and disease burden (i.e., inflammation) because the predictive validity of the GLIM criteria varies greatly (sensitivity 61–100%, specificity 55–98%) depending on the used criteria as shown in patients with surgery for gastrointestinal diseases (30).

The more precise criteria used to diagnose malnutrition in the current study may explain the better validity seen in our study compared with studies by Steer et al. (8), De Groot et al. (10), and Allard et al. (11). In addition, in the current study a clinical dietitian conducted nutrition assessment and GLIM diagnostics instead of trained coordinators or other staff (10, 11). The GLIM criteria have shown an excellent level of inter-rater agreement between two dietitians, a result suggesting that qualified medical personnel should perform GLIM diagnostics (8). Furthermore, different combinations of GLIM criteria have been compared and the best combinations seem to be either weight loss and high CRP or weight loss and low food intake, both of which we used in the present study (9, 11). A lack of consensus regarding how to accurately and practically measure and define reduced muscle mass and inflammatory burden caused by different diseases still exists, warranting further studies.

Association of the GLIM criteria and NRS 2002

To the best of our knowledge, a comparison between NRS 2002 and the GLIM criteria has not been conducted in this specific patient population. Among hospitalized patients sensitivity (84%) and specificity (94%) were good between the GLIM criteria and NRS 2002 and the concordance in diagnosing malnutrition was substantial ($\kappa = 0.784$) (24). Even better results were obtained in 637 hospitalized cancer patients evaluated at

TABLE 4 Univariable and multivariable regression analysis of overall survival in 65 HNC patients.

	Univariable analysis			Multivariable analysis		
Variables	**Hazard ratio**	**95% CI**	***p*-value**	**Hazard ratio**	**95% CI**	***p*-value**
Age, years						
≤65	Reference					
>65	0.99	0.95–1.2	0.491	0.34	0.11–1.03	0.056
Gender						
Female	Reference					
Male	2.15	0.74–6.2	0.157	2.36	0.77–7.20	0.133
Stage						
I–III	Reference					
IV	0.88	0.41–1.91	0.747	0.51	0.22–1.18	0.115
GLIM						
Not malnourished	Reference					
Malnourished	2.26	1.07–4.77	0.034	2.53	1.12–5.71	0.025
Smoking, pack year						
<10	Reference					
≥10	4.26	1.48–12.32	0.007	3.32	1.11–9.91	0.031

CI, confidence interval; GLIM, Global Leadership Initiative on Malnutrition.

admission; sensitivity 82%, specificity 98%, $\kappa = 0.823$ (36). In the current study GLIM showed high sensitivity and specificity with the NRS-2002 indicating that patients with NRS 2002 score ≥3 are at high nutritional risk and even malnourished as proposed in our previous study (14).

Survival

The association of the GLIM criteria with survival has not been previously studied in this patient population but it has been shown that GLIM-defined malnutrition is an independent prognostic factor of survival in cancer patients in general (10, 37), and in patients with gastrointestinal cancer (20), hematologic malignancies (21), and lung cancer (22) as well as in hospitalized patients (21, 24). The mortality risk associated with GLIM-defined malnutrition has varied from 2.07 in lung cancer (22) to 3.55 in hematologic malignancies (21), risk in line with our results. Lower mortality risk values have been seen among breast, gynecological and colorectal (10), lung (22), and gastric cancer (35) patients, and the mortality risk varies from 1.17 to 1.52 in moderate and from 1.47 to 2.89 in severe malnutrition. Smoking status at the time of HNC diagnosis strongly influences mortality which was seen also in the current study along with malnutrition.

We were not able to show the GLIM criteria to be accurate in predicting survival contrary to two previous studies in patients with variety of cancers (19, 20) and to one study with hospitalized patients (24). Of note, in the Zhang et al. (20) study patients were older than our study population, and in another Zhang et al. (19) study majority of patients (70%) were malnourished, which may partly explain the better accuracy in predicting survival in these studies. Indeed, it has been shown that high age (38) and malnutrition are independent risk factors for mortality (15). Noteworthy, in the study of older cancer patients (20) ROC accuracy was moderate but in another study including a majority of malnourished patients not better than chance (19). In this latter study one probable explanation for the low accuracy is the use of cancer diagnosis as a marker of inflammation instead of CRP, as recommended previously (8, 9, 11). The most likely reason for the low accuracy in our study is the small number of enrolled patients, giving rise to a need for larger multicenter studies. Another explanation might be that malnutrition alone is not strong enough of a predictor for 5-yr survival since other factors like smoking and alcohol abuse are frequently seen among this patient group. Indeed, in the current study heavy smokers had higher mortality risk than malnourished patients. Moreover, GLIM being an objective method compared to subjective PS-SGA method, GLIM may predict better short-term than long-term survival.

We are aware that our research has limitations. First, the GLIM-defined malnutrition diagnostics was performed retrospectively, not at the same time with other nutritional assessments, leading to possible misclassification of nutritional status. Second, given that our findings are based on a limited number of patients, the results from such analyses should be treated with considerable caution. Third, at the time of the original study the PG-SGA

TABLE 5 Univariable and multivariable regression analysis of disease-free survival in 64[#] HNC patients.

	Univariable analysis			Multivariable analysis		
Variables	**Hazard ratio**	**95% CI**	***p*-value**	**Hazard ratio**	**95% CI**	***p*-value**
Age, years						
≤65	Reference					
> 65	0.52	0.2–1.36	0.185	0.49	0.18–1.36	0.170
Gender						
Female	Reference					
Male	1.76	0.68–4.59	0.246	1.73	0.63–4.75	0.288
Stage						
I–III	Reference					
IV	0.83	0.40–1.70	0.605	0.57	0.25–1.28	0.171
GLIM						
Not malnourished	Reference					
Malnourished	2.01	0.99–4.09	0.054	2.10	0.98–4.48	0.056
Smoking, pack years						
<10	Reference					
≥10	5.18	1.80–14.87	0.002	4.21	1.43–12.37	0.009

CI, confidence interval; GLIM Global Leadership Initiative on Malnutrition.
[#]One patient with second primary was excluded from the DFS analyses.

translation to Finnish was not performed completely according to the ISPOR Principles which is recommended to perform in future (39). To overcome possible cap in translation process dietitian performed the whole PG-SGA. Strength of the study is that the same research dietitian conducted NRS 2002, PG-SGA, and GLIM-based nutrition diagnostics. In addition, we used objective measures of muscle mass and inflammation to diagnose GLIM-defined malnutrition.

In patients with HNC, the prevalence of malnutrition evaluated by the GLIM criteria is high. These criteria seem to be a potential method for malnutrition diagnostics and outcome prediction in the HNC patient population. NRS 2002 score ≥3 indicates high nutritional risk in this patient group.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Board at Helsinki University Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HO was the main investigator, analyzed and interpreted data, and drafted the manuscript. HO, AM, and US designed the study. AM and US supervised the project and assisted with writing the manuscript. PO, AP, and PR assisted in interpretation of the results and writing the manuscript. All authors read and approved the final manuscript.

Funding

The study was financially supported by HYKS Institute and the Helsinki University Hospital Research Funds.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Cederholm T, Barazzoni RO, Austin P, Ballmer P, Biolo GI, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr.* (2017) 36:49–64. doi: 10.1016/j.clnu.2016.09.004

2. Capuano G, Grosso A, Gentile PC, Battista M, Bianciardi F, Di Palma A, et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. *Head Neck.* (2008) 30:503–8. doi: 10.1002/hed.20737

3. Orell-Kotikangas H, Österlund P, Mäkitie O, Saarilahti K, Ravasco P, Schwab U, et al. Cachexia at diagnosis is associated with poor survival in head and neck cancer patients. *Acta Otolaryngol.* (2017) 137:778–85. doi: 10.1080/00016489.2016.1277263

4. Salas S, Deville JL, Giorgi R, Pignon T, Bagarry D, Barrau K, et al. Nutritional factors as predictors of response to radio-chemotherapy and survival in unresectable squamous head and neck carcinoma. *Radiotherapy Oncol.* (2008) 87:195–200. doi: 10.1016/j.radonc.2008.02.011

5. Liposits G, Orrevall Y, Kaasa S, Österlund P, Cederholm T. Nutrition in cancer care: a brief, practical guide with a focus on clinical practice. *JCO Oncol Pract.* (2021) 7:1–7. doi: 10.1200/OP.20.00704

6. Álvaro Sanz E, Garrido Siles M, Rey Fernández L, Villatoro Roldán R, Rueda Domínguez A, Abilés J. Nutritional risk and malnutrition rates at diagnosis of cancer in patients treated in outpatient settings: early intervention protocol. *Nutrition.* (2019) 57:148–53. doi: 10.1016/j.nut.2018.05.021

7. Cederholm T, Jensen GL, Correia MI, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – A consensus report from the global clinical nutrition community. *J Cachexia Sarcopenia Muscle.* (2019) 10:207–17. doi: 10.1002/jcsm.12383

8. Steer B, Loeliger J, Edbrooke L, Deftereos I, Laing E, Kiss N. Malnutrition prevalence according to the glim criteria in head and neck cancer patients undergoing cancer treatment. *Nutrients.* (2020) 12:1–13. doi: 10.3390/nu12113493

9. Einarsson S, Laurell G, Tiblom Ehrsson Y. Mapping the frequency of malnutrition in patients with head and neck cancer using the GLIM criteria for the diagnosis of malnutrition. *Clin Nutr ESPEN.* (2020) 37:100–6. doi: 10.1016/j.clnesp.2020.03.011

10. De Groot LM, Lee G, Ackerie A, van der Meij BS. Malnutrition screening and assessment in the cancer care ambulatory setting: mortality predictability and validity of the patient-generated subjective global assessment short form (PG-SGA SF) and the GLIM criteria. *Nutrients.* (2020) 12:1–13. doi: 10.3390/nu12082287

11. Allard JP, Keller H, Gramlich L, Jeejeebhoy KN, Laporte M, Duerksen DR, et al. Criteria has fair sensitivity and specificity for diagnosing malnutrition when using SGA as comparator. *Clin Nutr.* (2020) 39:2771–7. doi: 10.1016/j.clnu.2019.12.004

12. Keller H, de van der Schueren MA, GLIM Consortium, Jensen GL, Barazzoni R, Compher C, et al. Global Leadership Initiative on Malnutrition (GLIM): guidance on validation of the operational criteria for the diagnosis of protein-energy malnutrition in adults. *J Parent Enteral Nutr.* (2020) 44:992–1003. doi: 10.1002/jpen.1806

13. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660

14. Orell-Kotikangas H, Österlund P, Saarilahti K, Ravasco P, Schwab U, Mäkitie AA, et al. 2002 for pre-treatment nutritional risk screening and nutritional status assessment in head and neck cancer patients. *Support Care Cancer.* (2015) 23:1495–502. doi: 10.1007/s00520-014-2500-0

15. Orell H, Schwab U, Saarilahti K, Österlund P, Ravasco P, Mäkitie A. Nutritional counseling for head and neck cancer patients undergoing (chemo) radiotherapy—a prospective randomized trial. *Front Nutr.* (2019) 6:1–12. doi: 10.3389/fnut.2019.00022

16. Ferreira IB, Lima EDNS, Canto PP, Gontijo CA, Maia YC de P, Pena GDG. Oral nutritional supplementation affects the dietary intake and body weight of head and neck cancer patients during (Chemo) radiotherapy. *Nutrients.* (2020) 12:1–20. doi: 10.3390/nu12092516

17. Ehrsson YT, Fransson P, Einarsson S. Mapping health-related quality of life, anxiety, and depression in patients with head and neck cancer diagnosed with malnutrition defined by glim. *Nutrients.* (2021) 13:1–14. doi: 10.3390/nu13041167

18. De Van Der Schueren M, Keller H, Cederholm T, Barazzoni R, Compher C, Correia MI, et al. Global Leadership Initiative on Malnutrition (GLIM): guidance on validation of the operational criteria for the diagnosis of protein-energy malnutrition in adults. *Clin Nutr.* (2020) 39:2872–80. doi: 10.1016/j.clnu.2019.12.022

19. Zhang Q, Zhang KP, Zhang X, Tang M, Song CH, Cong MH, et al. Scored-GLIM as an effective tool to assess nutrition status and predict survival in patients with cancer. *Clin Nutr.* (2021) 40:4225–33. doi: 10.1016/j.clnu.2021.01.033

20. Zhang X, Tang M, Zhang Q, Zhang KP, Guo ZQ, Xu HX, et al. The GLIM criteria as an effective tool for nutrition assessment and survival prediction in older adult cancer patients. *Clin Nutr.* (2021) 40:1224–32. doi: 10.1016/j.clnu.2020.08.004

21. Yilmaz M, Atilla FD, Sahin F, Saydam G. The effect of malnutrition on mortality in hospitalized patients with hematologic malignancy. *Support Care in Cancer.* (2020) 28:1441–8. doi: 10.1007/s00520-019-04952-5

22. Yin L, Lin X, Li N, Zhang M, He X, Liu J, et al. evaluation of the global leadership initiative on malnutrition criteria using different muscle mass indices for diagnosing malnutrition and predicting survival in lung cancer patients. *J Parent Enteral Nutr.* (2021) 45:607–17. doi: 10.1002/jpen.1873

23. Kazmierczak-Siedlecka K, Skonieczna-zydecka K, Folwarski M, Ruszkowski J, Swierblewski M, Makarewicz W. Influence of malnutrition stage according to glim 2019 criteria and sga on the quality of life of patients with advanced cancer. *Nutr Hosp.* (2020) 37:1179–85. doi: 10.20960/nh.03185

24. Balci C, Bolayir B, Eşme M, Arik G, Kuyumcu ME, Yeşil Y, et al. Comparison of the efficacy of the global leadership initiative on malnutrition criteria, subjective global assessment, and nutrition risk screening 2002 in diagnosing malnutrition and predicting 5-year mortality in patients hospitalized for acute illnesse. *J Parent Enteral Nutr.* (2020) 45:1172–80. doi: 10.1002/jpen.2016

25. Kondrup J, Rasmussen HH, Hamberg OL, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr.* (2003) 22:321–36. doi: 10.1016/S0261-5614(02)00214-5

26. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition.* (1996) 12:15. doi: 10.1016/0899-9007(95)00067-4

27. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the patient-generated subjective global assessment. *Curr Opin Clin Nutr Metab Care.* (2017) 20:322–9. doi: 10.1097/MCO.0000000000000389

28. Beynon RA, Lang S, Schimansky S, Penfold CM, Waylen A, Thomas SJ, et al. Tobacco smoking and alcohol drinking at diagnosis of head and neck cancer and all-cause mortality: results from head and neck 5000, a prospective observational cohort of people with head and neck cancer. *Int J Cancer.* (2018) 143:1114–27. doi: 10.1002/ijc.31416

29. Citak E, Tulek Z, Uzel O. Nutritional status in patients with head and neck cancer undergoing radiotherapy: a longitudinal study. *Support Care Cancer.* (2019) 27:239–47. doi: 10.1007/s00520-018-4319-6

30. Henrique JR, Pereira RG, Ferreira RS, Keller H, de Van der Schueren M, Gonzalez MC, et al. Pilot study GLIM criteria for categorization of a malnutrition diagnosis of patients undergoing elective gastrointestinal operations: A pilot study of applicability and validation. *Nutrition.* (2020) 110961:79–80. doi: 10.1016/j.nut.2020.110961

31. Qin L, Tian Q, Zhu W, Wu B. The validity of the GLIM criteria for malnutrition in hospitalized patients with gastric cancer. *Nutr Cancer.* (2021) 73:2732–9. doi: 10.1080/01635581.2020.1856894

32. Theilla M, Rattanachaiwong S, Kagan I, Rigler M, Bendavid I, Singer P. Validation of GLIM malnutrition criteria for diagnosis of malnutrition in ICU patients: an observational study. *Clin Nutr.* 40:3578–84. doi: 10.1016/j.clnu.2020.12.021

33. Brito JE, Burgel CF, Lima J, Chites VS, Saragiotto CB, Rabito EI, et al. GLIM criteria for malnutrition diagnosis of hospitalized patients presents satisfactory criterion validity: a prospective cohort study. *Clin Nutr.* (2021) 40:4366–72. doi: 10.1016/j.clnu.2021.01.009

34. Shahbazi S, Hajimohammadebrahim-Ketabforoush M, Vahdat Shariatpanahi M, Shahbazi E, Vahdat Shariatpanahi Z. The validity of the global leadership

initiative on malnutrition criteria for diagnosing malnutrition in critically ill patients with COVID-19: a prospective cohort study. *Clin Nutr ESPEN*. (2021). doi: 10.1016/j.clnesp.2021.03.020

35. Xu LB, Shi MM, Huang ZX, Zhang WT, Zhang HH, Shen X, et al. Impact of malnutrition diagnosed using global leadership initiative on malnutrition criteria on clinical outcomes of patients with gastric cancer. *J Parent Enteral Nutr*. (2021) 46:385–94. doi: 10.1002/jpen.2127

36. Zhang Z, Wan Z, Zhu Y, Zhang L, Zhang L, Wan H. Prevalence of malnutrition comparing NRS2002, MUST, and PG-SGA with the GLIM criteria in adults with cancer: a multi-center study. *Nutrition*. (2021) 83:111072. doi: 10.1016/j.nut.2020.111072

37. Yin L, Cheng N, Chen P, Zhang M, Li N, Lin X, et al. Association of malnutrition, as defined by the PG-SGA, ESPEN 2015, and GLIM criteria, with complications in esophageal cancer patients after esophagectomy. *Front Nutr*. (2021) 8:632546. doi: 10.3389/fnut.2021.632546

38. Stratton RJ, Green CJ, Elia M. *Disease-Related Malnutrition: An Evidence-Based Approach to Treatment*. Edinburgh: CABI Publishing.

39. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine*. (2000) 25:3186–91. doi: 10.1097/00007632-200012150-00014

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 08 December 2022
DOI 10.3389/fnut.2022.1080714

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Majid Hajifaraji,
National Nutrition and Food Technology Research Institute, Iran
Marija Takic,
University of Belgrade, Serbia

*CORRESPONDENCE
Zheng Huangfu
jshuangfou@sina.com
Minghao Pan
2238130416@qq.com

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 26 October 2022
ACCEPTED 25 November 2022
PUBLISHED 08 December 2022

CITATION
He D, Huangfu Z and Pan M (2022) Association between nut consumption and mortality among Chinese older people: A national cohort study based on CLHLS from 2008 to 2018. *Front. Nutr.* 9:1080714. doi: 10.3389/fnut.2022.1080714

Association between nut consumption and mortality among Chinese older people: A national cohort study based on CLHLS from 2008 to 2018

Dengxin He[1], Zheng Huangfu[2]* and Minghao Pan[3]*

[1]School of Nursing, Hubei University of Chinese Medicine, Wuhan, China, [2]School of Journalism and Communication, Nanjing Xiaozhuang University, Nanjing, China, [3]School of Public Health, Wuhan University, Wuhan, China

Background: Few quantitative studies have explored the associations between nut consumption and better health outcomes among a national cohort of community-dwelling older Chinese people. Given the need for more evidence to support the health benefits of nuts among Chinese people, we investigated whether nut consumption was associated with subsequent 10-year mortality.

Methods: We analyzed data from the Chinese Longitudinal Healthy Longevity Survey. The data on nut consumption at baseline were collected using a questionnaire through face-to-face interviews. The vital status and date of death were ascertained by a close family member or village doctor of the deceased participant during the follow-up survey. Cox analyses were performed to explore the association between nut consumption and mortality. Subgroup analyses by age group (<80 or ≥ 80 years), sex (male/female), activities of daily living (impaired or normal), and physical exercise (yes or no) were performed to assess whether the association between nut consumption and mortality differed across different populations.

Results: The median survival time was 1,302 days for the 11,915 participants with complete information of survival time and nut consumption. The association between nut consumption and mortality was significant after the adjusting for significant factors in the univariate Cox analyses. The hazard ratios were lower in male participants, those who were < 80 years old, and those who did not engage in physical exercise at baseline. The association between nut consumption and mortality was not significant among participants with normal activities of daily living.

Conclusion: The association between nut consumption and mortality was not significant among participants who had normal activities of daily living but was significant among participants who had impaired activities of daily living. Including nuts in the diets cloud help to extend the lifespan in older Chinese people, especially those with impaired activities of daily living.

KEYWORDS

nuts, dietary intake, cohort study, mortality, Chinese, COX analysis

Introduction

Nuts are a nutrient dense food and have been an important part of mankind's diets since pre-agricultural times (1). Nuts are a natural plant food rich in fat, and the fatty acid content of nuts is advantageous because they are low in saturated fatty acids and rich in unsaturated fats (2). Nuts also have a rich content of other bioactive macronutrients which cloud be excellent sources of protein and often contain high amounts of L-arginine (3). As L-arginine is the precursor of the endogenous vasodilator, nitric oxide (4), nut consumption might help improve individual vascular function. Nuts also are good sources of dietary fiber which can provide 5–10% of daily fiber needs (5). Further, nuts contain large amounts of essential micronutrients, such as folate, antioxidant vitamins, and phenolic compounds, that cloud contribute to improved health status (2, 6, 7). The macronutrient, micronutrient and non-nutrient components of nuts have all been proved to be beneficial to individual better health outcomes. Further, the beneficial dietary role of nuts may be also based on their prebiotic properties (8).Thus, according to the composition of nuts, nuts may have a health effect on individuals and have become an indispensable component of healthy diets in western countries (9).

Quantitative studies in Western settings have shown that nut consumption is associated with better health outcomes. A recent study by Kim et al. (10) established that nut consumption of ≥5 g/day is associated with a lower risk of metabolic syndrome among U.S. adolescents, based on data from the National Health and Nutrition Examination Survey. Additionally, existing researches has recognized the role of nut consumption or factors associated with this nutritional behavior in reducing the risk of cardiovascular diseases (11, 12). Furthermore, a meta-analysis including a large number of studies in Western settings has shown that nut consumption is associated with reduced mortality (13).

Nuts have been suggested to improve brain function in ancient China and were also an important component of Chinese diet. However, few quantitative studies have explored the associations between nut consumption and better health outcomes among a national cohort of community-dwelling Chinese older people (13, 14). Considering the need for more evidence to support the health benefits of nuts among Chinese, we investigated whether nut consumption at baseline was associated with subsequent 10-year mortality and determined whether associations showed significant differences comparing groups by demographic characteristics, health status, or health behaviors using data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS).

Methods

Participants

The CLHLS is a nationwide cohort study. A targeted random sample design was adopted, and half of the counties and cities in 23 of 31 provinces in China were randomly selected through a multistage cluster sampling approach to ensure representativeness. The CLHLS was established in 1998, and recruitment of new participants and subsequent follow-up were conducted in 2000, 2002, 2005, 2008, 2011, 2014, and 2018. The CLHLS conformed to the principles outlined in the Declaration of Helsinki and was approved by the Ethical Review Committee of Peking University (IRB00001052–13074). All participants voluntarily agreed to participate in the study and signed an informed consent form at the time of participation. Information was collected through face-to-face interviews by the CLHLS research staff.

The current study analyzed data from the 2008 wave of the CLHLS. Follow-up surveys were conducted in 2011, 2014, and 2018. Figure 1 shows how participants in the current study were selected. The 2008 wave included 16,954 older Chinese individuals, and 2,893 participants in 2011, 591 participants in 2011, and 1,259 participants in 2018 were lost to follow-up. Until 2018, 12,211 participants were successfully followed up. For the analysis of the association between nut consumption and mortality, participants who were lost to follow-up or had missing or erroneous information for survival time or nut consumption were excluded, and 11,915 participants were finally included in the survival analysis.

Measurements

Mortality

The outcome was all-cause mortality. The vital status and date of death (for participants who died by the end of the study) were ascertained by a close family member or village doctor of the deceased participant during the follow-up survey conducted in 2011, 2014, and 2018. Participants who survived the last interview were considered censored on the date of their last interviews in 2018. The time interval from the interview date in 2008 until the date of death was considered the duration of follow-up.

Nut consumption

The important independent variables was nut consumption which was assessed during the 2008 wave. The trained research staff collected participants' self-reported information on food consumption through face-to-face interviews in the CLHLS

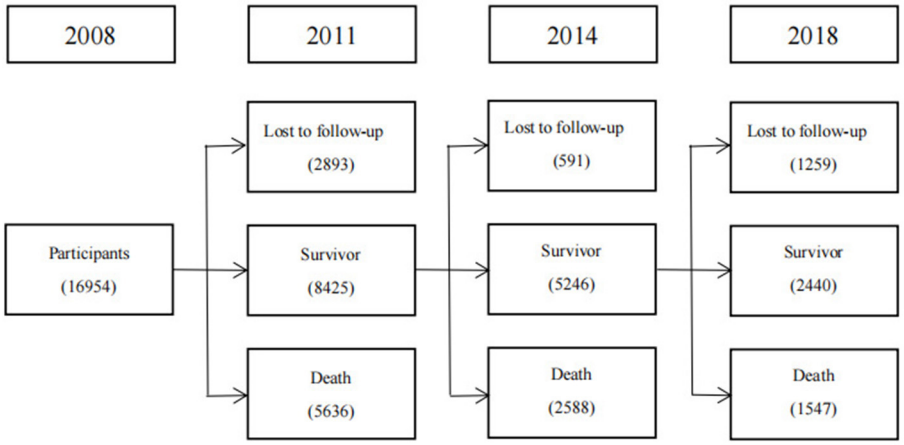


FIGURE 1
Flowchart.

(15). Participants were asked to report their frequency of nut consumption, including peanuts, walnuts, chestnuts, or melon seeds. The frequency of nut consumption was recorded as "almost every day", "at last once per week", "at least once per month", "not every month, but occasionally", or "rarely or never". The current study coded nut consumption as dichotomous variable by labeling participants answering "almost every day", "at last once per week", "at least once per month", or "not every month, but occasionally" as "1 = yes" and "rarely or never" as "0 = no".

Covariates

Covariates, including demographic characteristics, health status, and health behaviors, were assessed during the 2008 wave. Demographic characteristics included age, sex, education, place of residence (city, town or rural), living arrangement (in an institution, alone, or with household members), and economic condition (whether financial support was sufficient to pay for daily expenses).

Health status included participants' activities of daily living (ADL), chronic conditions of hypertension and diabetes. The Katz Index scale was used to measure ADL (16). The Katz Index scale includes six items assessing participants' dressing, bathing, toileting, eating, indoor activities, and continence. The Chinese version of Katz Index scale has been report to be reliable and valid (17). Each item has three response options: "independent," "needs help," or "dependent." Impaired ADL was defined as a participant's response of "dependent" or "needs help" to at least one or more activities associated with one of the six items (18). Chronic conditions, including hypertension and diabetes, were assessed based on self-reported physician's diagnosis.

Health behaviors included physical exercise, smoking, and drinking. Physical exercise (yes vs. no) was measured by asking "do you take exercise regularly in the present?". Smoking (yes vs. no) was assessed by asking "do you smoke at present?" and drinking (yes vs. no) was assessed by asking "do you drink at present?".

Data analysis

Firstly, an independent two-sample *t*-test or analysis of variance for continuous variables and Chi-squared test for categorical variables were conducted to compare characteristics by baseline follow-up status. Then, raw mortality was calculated on several factors (sex, education, residence, living arrangement, financial support, ADL, physical exercise, smoking, drinking, hypertension, and diabetes) and baseline nut consumption status was calculated. For the 11,915 participants with complete information of survival time and nut consumption, survival analysis was conducted. We used Kaplan–Meier method to graph survival curves by nut consumption. Moreover, Cox proportional hazards model was used to assess the association between nut consumption and mortality. To decide whether to control for the above covariates, the "significance-test-of-the-covariance" strategy, in which a variable is adjusted if its coefficient is significant, was conducted by adding the covariates in the model one-by-one (19).

Subgroup analyses, by age groups (<80 or ≥ 80 years), sex (male/female), ADL (impaired or normal), and physical exercise (yes or no)were performed to assess whether the association between nut consumption and mortality differs across different populations.

TABLE 1 Sample characteristic.

	Study population	Status of follow-up		
		Surviving ($N = 2,440$)	Dead ($N = 9,771$)	t/χ^2
Age		75.04 (8.272)	91.14 (9.603)	76.066***
Sex				23.542***
Male	5,170	1,139 (22.03)	4,031 (77.97)	
Female	7,041	1,301 (18.48)	5,740 (81.52)	
Education				428.750***
0 years	7,966	1,168 (14.66)	6,798 (85.34)	
1–6 years	3,223	923 (28.64)	2,300 (71.36)	
More than 6 years	986	344 (34.89)	642 (65.11)	
Residence				4.102
Rural	8,063	1,643 (20.38)	6,420 (79.62)	
City	1,691	308 (18.21)	1,383 (81.79)	
Town	2,457	489 (19.90)	1,968 (80.10)	
Living arrangement				16.137***
Alone	1,796	372 (20.71)	1424 (79.29)	
With household members	10,213	2,050 (20.07)	8,163 (79.93)	
In an institution	202	18 (8.91)	184 (91.09)	
Insufficient financial support				4.091*
Yes	9,344	1,905 (20.39)	7,439 (79.61)	
No	2,867	535 (18.66)	2,332 (81.34)	
ADL				738.414***
Impaired	2,787	53 (1.90)	2,734 (98.10)	
Normal	9,423	2,387 (25.33)	7,036 (74.67)	
Hypertension				27.059***
Yes	2,245	537 (23.92)	1,708 (76.08)	
No	9,699	1,856 (19.14)	7,843 (80.86)	
Don't know	267	47 (17.60)	220 (82.40)	
Diabetes				4.343
Yes	244	60 (24.59)	184 (75.41)	
No	11,735	2,340 (19.94)	9,395 (80.06)	
Don't know	232	40 (17.24)	192 (82.76)	
Physical exercise				169.345***
Yes	3,022	852 (28.19)	2,170 (71.81)	
No	9,189	1,588 (17.28)	7,601 (82.72)	
Smoking				53.561***
Yes	2,133	549 (25.74)	1,584 (74.26)	
No	10,078	1,891 (18.76)	8,187 (81.24)	
Drinking				40.734***
Yes	2,159	539 (24.97)	1,620 (75.03)	
No	10,052	1,901 (18.91)	8,151 (81.09)	
Nut consumption				465.164***
Yes	4,267	1,306 (30.61)	2,961 (69.39)	
No	7,935	1,130 (14.24)	6,805 (85.76)	

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

SPSS software for Windows version 20.0 (IBM Corp, Armonk, New York) was used for data analysis. A *P*-value of 0.05 or less was considered as significant.

Results

Descriptive characteristics

Among the 12,211 participants who were successfully followed up, 9,771 participants died during the three follow-up surveys. We compared the baseline characteristics of surviving and dead participants and found that females had higher raw mortality than males. Participants who had an education of 0 year, had impaired ADL, did not engage in physical exercise, and did not eat nut had a higher raw mortality (Table 1).

Kaplan–Meier curves and Cox analysis results

For the 11,915 participants with complete information on survival time and nut consumption, Kaplan–Meier survival curves and Cox analysis were conducted. Kaplan–Meier survival curves represented in Figure 2 illustrate the relationship between nut consumption and a higher probability of survival. The median survival time was 1,302 days for the 11,915 participants with complete information of survival time and nut consumption, 1,060 and 1,863 days for participants who eat nut products and did not eat nut products respectively.

The Cox analysis results are presented in Table 2. The univariate Cox analyses revealed a significant association between nut consumption and mortality (HR = 0.606, 95%CI 0.580–0.633). The results of multivariable Cox analyses showed that the association between nut consumption and mortality was still significant (HR = 0.912, 95%CI 0.872–0.955) after the adjusting for factors that were significant in the univariate Cox analyses (age, sex, education, residence, living arrangement, insufficient financial support, ADL, physical exercise, smoking, drinking, and diabetes).

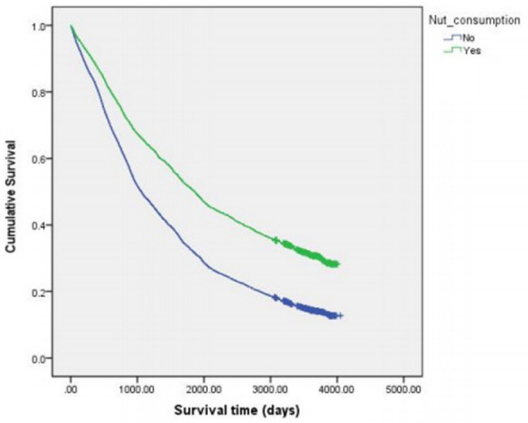


FIGURE 2
Kaplan-Meier survival curves by nut consumption.

Subgroup analyses

Table 3 shows the HRs by nut consumption for different subgroups. To assess whether mortality risks by nut consumption differed by age (<80 years old or ≥80 years old), sex (male or female), ADL (impaired or normal), and physical exercise (yes or no), we performed separate multivariable Cox models for each subgroup with full adjustment. The HRs were lower in participants who were <80 years old (HR = 0.744, 95%CI 0.662–0.835), male participants (HR = 0.858, 95%CI 0.802–0.919), and those who did not engage in physical exercise at baseline (HR = 0.865, 95%CI 0.821–0.912) than in participants who were ≥80 years old (HR = 0.866, 95%CI 0.825–0.909), female participants (HR = 0.900, 95%CI 0.847–0.957), and those who engaged in physical exercise at baseline (HR = 0.882, 95%CI 0.804–0.967), respectively. The association between nut consumption and mortality was not significant among participants with normal ADL (HR = 0.923, 95%CI 0.841–1.013), but significant among participants with impaired ADL (HR = 0.884, 95%CI 0.839–0.931).

Discussion

In this nationwide cohort study of community-dwelling Chinese older people, nut consumption was associated with an 8.8% lower risk of mortality compared with non-consumption of nuts at baseline. This result is consistent with the finding in most previous researches on this topic in Western countries (14, 20, 21). Wang et al. (20) analyzed data from 6,072 individuals who participated in the National Health and Nutrition Examination Survey and reported that higher nut consumption was significantly associated with lower all-cause mortality in the population without chronic kidney disease and nut consumption of 1–6 times per week was significantly related to lower all-cause mortality in the population with chronic kidney disease. Fernandez-Montero et al. (21) analyzed data from a Spanish cohort and found that participants who consumed nuts twice or more per week had a 56% lower risk for all-cause mortality than those who never or almost never consumed nuts. Despite the differences in the classification of nut consumption and the participants in these studies, nut consumption showed a significant effect on individuals' reduced all-cause mortality. Further, although some researchers reported inconsistent findings

TABLE 2 The Cox analysis of all variables.

	Univariate Cox analysis		Multivariable Cox analysis	
	HR	(95% CI)	HR	(95% CI)
Age	1.074***	1.072–1.077	1.045***	1.042–1.047
Sex				
Male (Ref.)				
Female	1.145***	1.009–1.193	1.305***	1.245–1.368
Education	0.958***	0.952–0.965	0.997	0.993–1.001
Residence				
Rural (Ref.)				
City	1.077*	1.015–1.143	1.037	0.974–1.105
Town	0.976	0.928–1.028	1.028	0.976–1.082
Living arrangement				
With household members (Ref.)				
Alone	0.926**	0.874–0.980	1.027	0.969–1.089
In an institution	1.395***	1.201–1.621	1.234**	1.061–1.435
Insufficient financial support				
Yes (Ref.)				
No	0.945*	0.903–0.993	1.008	0.252-4.035
ADL (normal)				
Normal (Ref.)				
Impaired	3.099***	2.958-3.247	1.258***	1.195–1.325
Hypertension				
Yes (Ref.)				
No	0.373	0.093–1.488		
Diabetes				
Yes (Ref.)				
No	0.090*	0.013–0.645	0.224	0.031–1.604
Physical exercise				
No (Ref.)				
Yes	0.671***	0.671–0.705	0.892***	0.848–0.939
Smoking				
Yes (Ref.)				
No	0.778***	0.737–0.821	0.976	0.919–1.037
Drinking				
Yes (Ref.)				
No	0.815***	0.772–0.860	0.959	0.906–1.017
Nut consumption				
No (Ref.)				
Yes	0.606***	0.580–0.633	0.912***	0.872–0.955

*P < 0.05; **P < 0.01; ***P < 0.001.

that the association between nut consumption and mortality was not quite statistically significant in their study, most of them found lower mortality in participants with high nut consumption compared with participants with low or no nut consumption (22, 23). Our findings add evidence to support the association between nut consumption and decreased mortality among older Chinese people and suggest that these older Chinese people could also benefit from nut consumption.

To the best of our knowledge, the current study is the first to show the differences in the association between nut consumption and mortality in the Chinese elderly population. We found the association between nut consumption and mortality in the subgroup analysis was consistently significant

TABLE 3 Subgroup analyses of association between nut consumption and mortality.

Subgroup	HR	95%CI
Age		
<80 years old	0.744***	0.662–0.835
≥80 years old	0.866***	0.825–0.909
Sex		
Male	0.858***	0.802–0.919
Female	0.900**	0.847–0.957
ADL		
Impaired	0.884***	0.839–0.931
Normal	0.923	0.841–1.013
Physical exercise		
Yes	0.882**	0.804–0.967
No	0.865***	0.821–0.912

**P < 0.01; ***P < 0.001.

comparing groups by age, sex, and physical exercise. These results suggest that the association between nut consumption and mortality is relatively robust in different groups divided by age, sex, and physical exercise. Interestingly, we found that the association between nut consumption and mortality was not significant among participants with normal ADL. However, we should interpret this result with caution because the finding regarding the association between nut consumption and mortality among participants with normal ADL were trending in the expected direction. And it is suggested that further research to explore the difference in the association between nut consumption and mortality in participants with different ADL needed to be conducted.

The association of nut consumption with decreased mortality could be explained by the health effects of nut consumption on the physical and mental status (24, 25). Firstly, nut consumption has been reported to be associated with improved inflammatory status, including C-reactive protein, interleukin-6, and fibrinogen, and thus reduce risk of cardiovascular disease and type 2 diabetes (26). Secondly, nuts, especially nuts rich in monounsaturated fatty acids, may have health effect on individuals oxidative status (2), and thus reduce risk of many health problems, such as cardiovascular and inflammatory diseases, and cancer (27). Thirdly, diet enriched with nuts may improve insulin sensitivity and fasting glucose levels (28, 29), therefore, nut consumption could contribute to better metabolic status (30, 31), decreased body weight as well as lower body weight gain over time and thus reduce the risk of obesity (32). Fourthly, diet with nuts, such as pistachios, could have favorable effects on vascular reactivity and reduce risk of cardiovascular disease (33–35). Finally, dietary patterns also play an important role in mental health. Higher nut consumption cloud be related to better mood state, fewer depressive symptoms, and a lower risk for depression (25). These mechanisms may contribute to the prevention of cardiovascular, other chronic, and mental diseases, leading to a reduction of all-cause mortality. Both the biological plausibility of nutrients in nuts and the findings of previous researches support the present findings of the health effects of nut consumption on mortality in an older Chinese population with impaired ADL. Thus, though the reason nut consumption was significantly associated with decreased mortality among participants with impaired ADL but not among participants with normal ADL, needs further exploration, including nuts in the diet cloud help extend lifespan in older Chinese, especially those with impaired ADL.

The current study has several strengths. It is among the few studies to explore the association between nut consumption and decreased mortality in older Chinese population. Moreover, the data we used was from the CLHLS, which is a large nationally representative survey. Thus, the results of this study have strong generalizability. Additionally, the findings of this study could add evidence to support the differences in the association between nut consumption and decreased risk of mortality among elder Chinese with different group of age, sex, physical exercise, and ADL. Additionally, the CLHLS contains detailed covariates, including age, sex, education, residence, living arrangement, financial support, ADL, smoking, drinking, and chronic diseases, which allow us to control for a large number of covariates in the multiple Cox model.

This study has several limitations. Firstly, the CLHLS did not include information on causes of death, limiting our ability to perform cause specific analysis. Secondly, we have limited information on nut consumption variables, such as the amount of nuts consumed and the specific type of nuts, limiting our ability to perform more detailed analysis.

Conclusion

In conclusion, our study explored the association between nut consumption and decreased mortality in a national of community-dwelling older Chinese individuals and specific subpopulations. The association between nut consumption and mortality was significant in overall population and specific subpopulations divided according to age, sex, physical exercise. Furthermore, the association between nut consumption and mortality was not significant among participants who had normal ADL at baseline but significant among participants who had impaired ADL at baseline. Including nuts in the diets cloud help to extend the lifespan in older Chinese people, especially those with impaired ADL.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://opendata.pku.edu.cn/dataverse/CHADS.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Committee of Peking University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DH undertook the analyses and wrote the first drafts manuscript. MP and ZH critically reviewed the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Humanities and Social Sciences Project of Henan Provincial Department of Education (2023-ZZJH-057).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med.* (1985) 312:283–9. doi: 10.1056/NEJM198501313120505

2. Ros E. Health benefits of nut consumption. *Nutrients.* (2010) 2:652–82. doi: 10.3390/nu2070652

3. Brufau G, Boatella J, Rafecas M. Nuts: source of energy and macronutrients. *Br J Nutr.* (2006) 96:S24–8. doi: 10.1017/BJN20061860

4. Huynh NN, Chin-Dusting J. Amino acids, arginase and nitric oxide in vascular health. *Clin Exp Pharmacol Physiol.* (2006) 33:1–8. doi: 10.1111/j.1440-1681.2006.04316.x

5. Salas-Salvado J, Bullo M, Perez-Heras A, Ros E. Dietary fibre, nuts and cardiovascular diseases. *Br J Nutr.* (2006) 96:S46–51. doi: 10.1017/BJN20061863

6. Segura R, Javierre C, Lizarraga MA, Ros E. Other relevant components of nuts: Phytosterols, folate and minerals. *Br J Nutr.* (2006) 96:S36–44. doi: 10.1017/BJN20061862

7. Blomhoff R, Carlsen MH, Andersen LF, Jacobs DJ. Health benefits of nuts: Potential role of antioxidants. *Br J Nutr.* (2006) 96:S52–60. doi: 10.1017/BJN20061864

8. Lamuel-Raventos RM, Onge MS. Prebiotic nut compounds and human microbiota. *Crit Rev Food Sci Nutr.* (2017) 57:3154–63. doi: 10.1080/10408398.2015.1096763

9. King JC, Blumberg J, Ingwersen L, Jenab M, Tucker KL. Tree nuts and peanuts as components of a healthy diet. *J Nutr.* (2008) 138:1736S–40S. doi: 10.1093/jn/138.9.1736S

10. Kim RJ, Wang L, Worley S, Leonard D. Nut consumption and metabolic syndrome in US adolescents. *Public Health Nutr.* (2018) 21:3245–52. doi: 10.1017/S1368980018002070

11. Becerra-Tomas N, Paz-Graniel I, W CKC, Kahleova H, Rahelic D, Sievenpiper JL, et al. Nut consumption and incidence of cardiovascular diseases and cardiovascular disease mortality: a meta-analysis of prospective cohort studies. *Nutr Rev.* (2019) 77:691–709. doi: 10.1093/nutrit/nuz042

12. Larsson SC, Drca N, Bjorck M, Back M, Wolk A. Nut consumption and incidence of seven cardiovascular diseases. *Heart.* (2018) 104:1615–20. doi: 10.1136/heartjnl-2017-312819

13. Chen GC, Zhang R, Martinez-Gonzalez MA, Zhang ZL, Bonaccio M, van Dam RM, et al. Nut consumption in relation to all-cause and cause-specific mortality: a meta-analysis 18 prospective studies. *Food Funct.* (2017) 8:3893–905. doi: 10.1039/C7FO00915A

14. Martini D, Godos J, Marventano S, Tieri M, Ghelfi F, Titta L, et al. Nut and legume consumption and human health: An umbrella review of observational studies. *Int J Food Sci Nutr.* (2021) 72:871–8. doi: 10.1080/09637486.2021.1880554

15. Zeng Y. *Introduction to the Chinese Longitudinal Healthy Longevity Survey (CLHLS).* Berlin, Germany: Springer (2008).

16. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of adl: a standardized measure of biological and psychosocial function. *JAMA.* (1963) 185:914–9. doi: 10.1001/jama.1963.03060120024016

17. Gu D, Dupre ME, Warner DF, Zeng Y. Changing health status and health expectancies among older adults in China: Gender differences from 1992 to 2002. *Soc Sci Med.* (2009) 68:2170–9. doi: 10.1016/j.socscimed.2009.03.031

18. Angleman SB, Santoni G, Von Strauss E, Fratiglioni L. Temporal trends of functional dependence and survival among older adults from 1991 to 2010 in Sweden: toward a healthier aging. *J Gerontol A Biol Sci Med Sci.* (2015) 70:746–52. doi: 10.1093/gerona/glu206

19. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol.* (1993) 138:923–36. doi: 10.1093/oxfordjournals.aje.a116813

20. Wang K, Qian D, Hu Y, Cheng Y, Ge S, Yao Y. Nut consumption and effects on chronic kidney disease and mortality in the united states. *Am J Nephrol.* (2022) 53:503–12. doi: 10.1159/000524382

21. Fernandez-Montero A, Bes-Rastrollo M, Barrio-Lopez MT, Fuente-Arrillaga CL, Salas-Salvado J, Moreno-Galarraga L, et al. Nut consumption and 5-y all-cause mortality in a Mediterranean cohort: The SUN project. *Nutrition.* (2014) 30:1022–7. doi: 10.1016/j.nut.2014.02.018

22. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart.* (1997) 78:450–5. doi: 10.1136/hrt.78.5.450

23. Gopinath B, Flood VM, Burlutksy G, Mitchell P. Consumption of nuts and risk of total and cause-specific mortality over 15 years. *Nutr Metab Cardiovasc Dis.* (2015) 25:1125–31. doi: 10.1016/j.numecd.2015.09.006

24. Gervasi T, Barreca D, Lagana G, Mandalari G. Health benefits related to tree nut consumption and their bioactive compounds. *Int J Mol Sci*. (2021) 22:5960. doi: 10.3390/ijms22115960

25. Fernandez-Rodriguez R, Jimenez-Lopez E, Garrido-Miguel M, Martinez-Ortega IA, Martinez-Vizcaino V, Mesas AE. Does the evidence support a relationship between higher levels of nut consumption, lower risk of depression, and better mood state in the general population? A systematic review. *Nutr Rev*. (2022) 80:2076–88. doi: 10.1093/nutrit/nuac022

26. Jiang R, Jacobs DJ, Mayer-Davis E, Szklo M, Herrington D, Jenny NS, et al. Nut and seed consumption and inflammatory markers in the multi-ethnic study of atherosclerosis. *Am J Epidemiol*. (2006) 163:222–31. doi: 10.1093/aje/kwj033

27. Brunelli E, La Russa D, Pellegrino D. Impaired oxidative status is strongly associated with cardiovascular risk factors. *Oxid Med Cell Longev*. (2017) 2017:6480145. doi: 10.1155/2017/6480145

28. Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med*. (2006) 145:1–11. doi: 10.7326/0003-4819-145-1-200607040-00004

29. Park SK, Oh CM, Jung JY. The association between insulin resistance and the consumption of nut including peanut, pine nut and almonds in working-aged Korean population. *Public Health Nutr*. (2021) 6:1–8. doi: 10.1017/S1368980021003803

30. Micek A, Godos J, Cernigliaro A, Cincione RI, Buscemi S, Libra M, et al. Total nut, tree nut, and peanut consumption and metabolic status in southern italian adults. *Int J Environ Res Public Health*. (2021) 18:1847. doi: 10.3390/ijerph18041847

31. Hosseinpour-Niazi S, Bakhshi B, Mirmiran P, Azizi F. Socioeconomic and lifestyle factors modifies the association between nut consumption and metabolic syndrome incidence. *Clin Nutr*. (2021) 40:4055–64. doi: 10.1016/j.clnu.2021.02.013

32. Grosso G, Estruch R. Nut consumption and age-related disease. *Maturitas*. (2016) 84:11–6. doi: 10.1016/j.maturitas.2015.10.014

33. Sari I, Baltaci Y, Bagci C, Davutoglu V, Erel O, Celik H, et al. Effect of pistachio diet on lipid parameters, endothelial function, inflammation, and oxidative status: a prospective study. *Nutrition*. (2010) 26:399–404. doi: 10.1016/j.nut.2009.05.023

34. Morgillo S, Hill AM, Coates AM. The effects of nut consumption on vascular function. *Nutrients*. (2019) 11:116. doi: 10.3390/nu11010116

35. Smeets E, Mensink RP, Joris PJ. Effects of tree nut and groundnut consumption compared with those of l-arginine supplementation on fasting and postprandial flow-mediated vasodilation: Meta-analysis of human randomized controlled trials. *Clin Nutr*. (2021) 40:1699–710. doi: 10.1016/j.clnu.2020.09.015

frontiers | Frontiers in Nutrition

TYPE Systematic Review
PUBLISHED 14 December 2022
DOI 10.3389/fnut.2022.978110

OPEN ACCESS

EDITED BY
Paula Ravasco,
Catholic University of Portugal, Portugal

REVIEWED BY
Erin Stella Sullivan,
University College Cork, Ireland
Robert Damm,
University Hospital Magdeburg, Germany
Lindsay Plank,
The University of Auckland, New Zealand

*CORRESPONDENCE
Yang Deng
dengyang3417@126.com
Le Zhang
sdzhangle@163.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 25 June 2022
ACCEPTED 02 December 2022
PUBLISHED 14 December 2022

CITATION
Jiang C, Wang Y, Fu W, Zhang G, Feng X, Wang X, Wang F, Zhang L and Deng Y (2022) Association between sarcopenia and prognosis of hepatocellular carcinoma: A systematic review and meta-analysis. *Front. Nutr.* 9:978110. doi: 10.3389/fnut.2022.978110

Association between sarcopenia and prognosis of hepatocellular carcinoma: A systematic review and meta-analysis

Chuan Jiang[1†], Yanyan Wang[2†], Wei Fu[2†], Guozhuan Zhang[3†], Xiaoshan Feng[4], Xing Wang[5], Fang Wang[6], Le Zhang[6*] and Yang Deng[6*]

[1]Department of Anoenterology, The Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Shandong Provincial Hospital of Traditional Chinese Medicine, Jinan, China, [2]Health Management Center, Qilu Hospital of Shandong University, Jinan, China, [3]Department of Pain Management, Qilu Hospital of Shandong University, Jinan, China, [4]Department of Endocrinology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China, [5]College of Clinical and Basic Medical Sciences, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, [6]School of Public Health, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China

Background: Sarcopenia, characterized by the loss of muscle mass, strength, and physical ability, occurs with aging and certain chronic illnesses such as chronic liver diseases and cancer. Sarcopenia is common in liver cirrhosis and hepatocellular carcinoma (HCC). Previous reports of association between sarcopenia and prognosis of HCC have been inconsistent. Therefore, the present systematic review and meta-analysis aimed to investigate the impact of sarcopenia on the survival of patients with HCC.

Methods: A systematic literature search was conducted using PubMed, EMBASE, and Web of Science electronic databases from inception to May 1, 2022. We included retrospective or prospective studies investigating the association between sarcopenia and overall survival (OS) and/or progression free survival (PFS) of HCC. We applied the Quality in Prognosis Studies (QUIPS) instrument to evaluate the risk of bias and quality of included studies. The primary and secondary outcomes were the associations of sarcopenia with OS and PFS, respectively, expressed by a pooled hazard ratio (HR) and corresponding 95% confidence interval (CI). Subgroup analysis and sensitivity analysis were performed. We further evaluated the publication bias by the funnel plot and Begg's test.

Results: A total of 42 studies comprising 8,445 patients were included. The majority of included studies were at an overall low risk of bias. The pooled prevalence of sarcopenia was 39% (95% CI: 33–45%) (n = 8,203). Sarcopenia was associated with an increased risk of shorter OS, with a pooled adjusted HR of 1.84 (95% CI: 1.62–2.09). An independent association between sarcopenia and reduced PFS was observed (HR = 1.33, 95% CI: 1.12–1.56).

Conclusion: The prevalence of sarcopenia was approximately 39% among patients with HCC. Sarcopenia was independently associated with reduced OS and PFS in HCC irrespective of treatment modalities. It is imperative that interventions aimed at alleviating sarcopenia and restoring muscle mass be implemented in order to improve the survival of patients with HCC.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022337797], identifier [CRD42022337797].

KEYWORDS

sarcopenia, skeletal muscle index, prognosis, hepatocellular carcinoma, meta-analysis

Introduction

Liver cancer poses a major threat to the global cancer burden, and the number of deaths is estimated to be more than one million annually by 2030 (1, 2). Hepatocellular carcinoma (HCC) is the most common histologic type of liver cancer, accounting for approximately 90% of total cases (3). Curative therapies including hepatectomy, radiofrequency or microwave ablation, and liver transplantation are recommended as the first-line treatments when possible. Locoregional therapies such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and radiation are associated with improved survival and quality of life for patients with unresectable HCC (4). However, curative therapies or locoregional therapies are not applicable to approximately 50% of HCC cases who are diagnosed at an advanced stage and have progression with transarterial therapies (5). For these patients with advanced HCC, sorafenib, lenvatinib, and atezolizumab combined with bevacizumab have been approved as the first-line systemic therapy, and regorafenib, cabozantinib and ramucirumab are second-line treatment options (6). The long-term prognosis of HCC patients is related to various factors, mainly represented by liver functional reserve, tumor size, treatment modalities, and Barcelona-Clínic Liver Cancer (BCLC) stage. Furthermore, maintenance of nutritional balance and physical ability is also an important factor in improving the prognosis of patients with advanced HCC (7).

Sarcopenia, characterized by low muscle mass in addition to impaired muscle strength and physical ability, is usually encountered in aging and patients with chronic illnesses such as chronic obstructive pulmonary disease, chronic renal failure, and cancer (8, 9). In recent years, the clinical significance of sarcopenia in cancer has attracted increasing attention. The associations between sarcopenia and the prognosis in patients with gastric cancer (10), colorectal cancer (11), lung cancer (12), ovarian cancer (13), and HCC (14, 15) have been investigated. For example, a cohort study revealed that sarcopenic patients with HCC undergoing TACE had a significantly poorer overall survival (OS) than those without sarcopenia (491 vs. 1,291 days, $P = 0.017$) (15). However, Ha et al. found that sarcopenia was not associated with OS in patients with newly diagnosed HCC (16). Thus, results of studies regarding the prognostic value of sarcopenia in patients with HCC remain inconsistent and even controversial. In this systematic review and meta-analysis, we aimed to determine the associations between sarcopenia and survival of patients with HCC following various treatment modalities, which may help identify sarcopenia as a prognostic factor for clinical decision making in patients with HCC.

Materials and methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD 42022337797.

Search strategy

We systematically searched the PubMed, EMBASE, and Web of Science electronic databases for articles published from inception through May 1, 2022. The main search terms were described as follows: ("hepatocellular carcinoma" OR "HCC" OR "hepatoma") AND ("sarcopenia" OR "sarcopenic" OR "skeletal muscle depletion"). Search results were restricted to articles published in English. The detailed search strategy is presented in **Supplementary Table 1**. Literature searching and screening were performed independently by two researchers (CJ and LZ), and disagreements between these two authors were resolved by a third researchers (YD).

Selection criteria

We employed the populations, interventions, comparators, outcomes, and study designs (PICOS) outline to determine the

eligibility of included publications as follows: (1) populations were patients diagnosed as HCC; (2) exposure was defined as sarcopenia; (3) compared to HCC patients without sarcopenia; (4) the outcomes were evaluated by prognostic indicators such as OS and/or progression free survival (PFS); (5) observational studies including retrospective and prospective studies were included. In addition, studies that met the following criteria were included for the qualitative and quantitative analysis: (1) patients diagnosed as HCC, (2) the measurement of sarcopenia or skeletal muscle mass was provided, (3) the association of sarcopenia with prognostic outcomes including OS and/or PFS were involved (4) hazard ratio (HR) with 95% confidence interval (CI) were provided or raw data were sufficient to calculate the HR and 95% CI, (5) retrospective or prospective study. The exclusion criteria included: (1) diagnostic criteria for sarcopenia were not provided, (2) sarcopenia was not regarded as a prognostic factor for OS and/or PFS in patients with HCC, (3) HR and corresponding 95% CI cannot be calculated from the data provided.

Data extraction

Two researchers (CJ and YW) independently screened the titles and abstracts of articles which met the selection criteria. Full-text of the article was reviewed when its title or abstract was judged as eligible. Discrepancies between researchers were resolved by discussion with a third researcher (GZ). A predesigned electronic form was used to extract the following data from the included studies: last name of first author, publication year, study design, country of the study population, period of patient recruitment, baseline data of patients [i.e., number, sex, age, etiology, BCLC stage, TNM stage, and treatment], sarcopenia assessment and definitions (i.e., measurement methods, cut-point, and prevalence), and HR with corresponding 95% CI and adjustment factors in multivariate analysis of factors related to OS and/or PFS.

Quality assessment

Two researchers (CJ and XF) independently employed the Quality in Prognosis Studies (QUIPS) Risk of Bias Assessment Instrument to assess the risk of bias for eligible studies (18, 19). The QUIPS instrument was used to evaluate the quality of prognosis studies, encompassing six domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) adjustment for other prognostic factors, (6) statistical analysis and reporting. Each domain was rated as high, moderate, or low risk of bias. The judgment criterion of overall risk of bias was as follows: studies with $\leq$2 moderate-risk domains and $\geq$4 low-risk domains were considered as "overall low risk of bias," those with $>$2 moderate-risk domains and $<$4 low-risk domains were classified as "overall moderate risk of bias," while studies with $\geq$1 high-risk domain were defined as "overall high risk of bias" (20).

Statistical analysis

The primary and secondary outcomes of this meta-analysis were the associations of sarcopenia with OS and PFS, respectively, expressed by a pooled HR and corresponding 95% CI. Cochran's Q test and I^2 statistics were performed to assess the heterogeneity across the included studies. A random effects model was chosen to estimate the pooled prevalence of sarcopenia and pooled HRs of associations between sarcopenia and OS or PFS. Sensitivity analysis by omitting one study at a time and then pooling the remaining studies was conducted to determine whether one study was a potentially important source of heterogeneity. We further evaluated the publication bias by the funnel plot and Begg's test. If publication bias was observed, the trim-and-fill method was applied to estimate the potential influence of imputed unpublished studies with negative results on the outcome, and fail-safe number was calculated using the Rosenthal's approach (21). All statistical analyses were performed using R software version 4.1.1 with "meta" and "metaphor" packages. A two-sided P value < 0.05 was regarded statistically significant.

Results

Literature search and study selection

Figure 1 presents the flowchart of literature search and study selection according to the PRISMA guidelines. A total of 2,036 potentially relevant publications were identified in the literature search, of which 1,556 were excluded due to duplication. After screening the titles and abstracts of remaining 480 articles, 406 articles were removed for the following reasons: no clear definition of sarcopenia (n = 60), not human studies (n = 10), reviews/case reports/editorials (n = 336). After a full-text review of the 74 articles, another 32 articles were excluded for the following reasons: no available HR and 95% CI (n = 15), same database used for several studies (n = 7), do not report the association between sarcopenia and OS/PFS (n = 10). Finally, 42 articles were included in the qualitative and quantitative synthesis.

Characteristics of included studies

Supplementary Table 2 outlines the main characteristics of the included studies. Overall, 42 studies comprising 8,445 patients (6,376 men and 2,069 women) were included. All

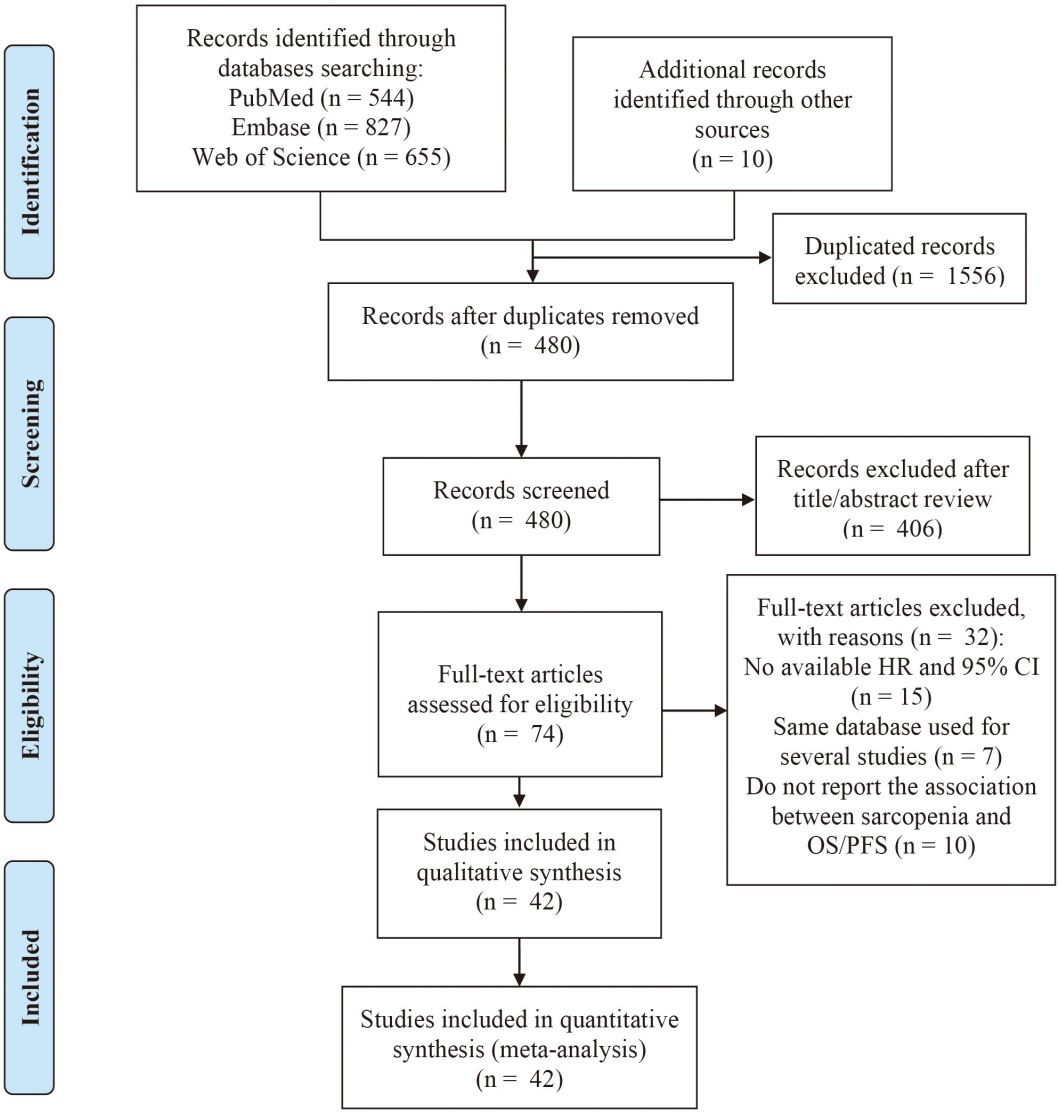


FIGURE 1
Flowchart of selecting and screening articles.

included studies were published from 2013 onward. Regarding the research design, 38 studies were designed as retrospective studies, and four studies were conducted prospectively. Twenty-two studies were included from Japan (14, 22–42), six from Korea (16, 43–47), four from China (48–51), two from Egypt (52, 53), two from Germany (15, 54), two from Italy (55, 56), one each from Netherlands, Canada, United States of America (USA), and France (57–60). HCC patients were treated by hepatectomy, sorafenib, lenvatinib, TACE, yttrium-90 radioembolization, RFA, or the combination of these. Six methods for sarcopenia assessment were reported, including computed tomography (CT)-based skeletal muscle index (SMI), psoas muscle index (PMI) and total psoas volume (TPV) at the third lumbar vertebra (L3) level, CT based transverse psoas muscle thickness per body height (TPMT/BH) and intramuscular adipose tissue content (IMAC) at the level of umbilicus, and magnetic resonance imaging (MRI) derived fat-free muscle area (FFMA) at the level of the origin of the superior mesenteric artery. SMI is the most widely used index and sarcopenia is defined as SMI < 42 cm^2/m^2 for men and <38 cm^2/m^2 for women based on the guideline proposed by Japan Society of Hepatology (JSH) (61). Among twenty-seven studies using SMI, eight studies used the cut-points proposed by JSH (14, 22, 32, 35, 42, 45, 49, 52), six studies employed the Martin cut-points (41, 53, 55, 57, 58, 60), four studies applied the Vledder cut-points (27, 28, 34, 38), and their own cut-points were measured in other studies. HR was estimated by univariate and multivariate Cox proportional hazards regression

to investigate the influence of sarcopenia on OS and/or PFS of HCC patients in the included studies.

Quality assessment

Supplementary Table 3 presents the risk of bias of included studies using the QUIPS tool. Because most of the included studies were designed as retrospective studies, the risk of bias among these studies were regard as moderate in the study participation domain. Moreover, the moderate risk of bias was determined to be due to study attrition in eight studies, adjustment for other prognostic factors in eight studies, statistical analysis and reporting in five studies. In general, of the 42 included studies, 34 studies were at an overall low risk of bias (14–16, 22–25, 28–32, 34, 35, 37, 39–44, 46, 47, 49–59), while eight were at an overall moderate risk of bias (26, 27, 33, 36, 38, 45, 48, 60).

Prevalence of sarcopenia

Prevalence of sarcopenia were reported in 40 of the 42 eligible studies, with a sample size of 8,203 patients (14, 16, 22–60). The pooled prevalence of sarcopenia was 39% (95% CI: 33–45%) in the total patients (**Figure 2**). There was a highly significant heterogeneity in the prevalence of sarcopenia among these studies (Q = 1,389.98, I^2 = 97.2%, $P < 0.01$). Subgroup analysis revealed that there were significant differences in the pooled prevalence among different methods for sarcopenia assessment (χ^2 = 9.00, P = 0.01). The pooled prevalence of sarcopenia was 40% (95% CI: 33–47%) when assessed by SMI at L3 level, 31% (95% CI: 23–41%) by PMI at L3 level, and 52% (95% CI: 42–62%) by other methods, respectively (**Supplementary Figure 1**). When grouped by the location of individual studies, the pooled prevalence was 36% (95% CI: 30–42%) among studies conducted in Asia, 60% (95% CI: 45–74%) among studies conducted in Europe, 39% (95% CI: 22–58%) among studies conducted in North America, respectively (**Supplementary Figure 2**).

Association between sarcopenia and OS

A total of 39 included studies reported the association between sarcopenia and OS of HCC patients following various treatment modalities, with a sample size of 7,547 patients (14–16, 22–32, 34–46, 48–60). The result demonstrated that sarcopenia was associated with an increased risk of shorter OS, with a pooled adjusted HR of 1.84 (95% CI: 1.62–2.09) (**Figure 3**). A significant difference was observed in the test for heterogeneity, and a random effects model was conducted (Q = 166.81, I^2 = 77%, $P < 0.01$). Subgroup analysis was performed according to the methods for sarcopenia assessment, and the pooled HRs of studies assessed by SMI at L3 level, by PMI at L3 level, and by other methods were 1.80 (95% CI: 1.53–2.11), 1.80 (95% CI: 1.48–2.18), and 2.39 (95% CI: 1.53–3.73), respectively (**Supplementary Figure 3**). In addition, we performed a subgroup analysis according to location of study. The result revealed that sarcopenia was an independent predictor of shorter OS among studies conducted in Asia (HR = 1.77, 95% CI: 1.54–2.03), in Europe (HR = 2.40, 95% CI: 1.72–3.34), and in North America (HR = 1.91, 95% CI: 1.03–3.54) (**Supplementary Figure 4**).

Association between sarcopenia and PFS

A total of 2,295 patients from 11 studies were included in the analyzing the impact of sarcopenia on the PFS (26–28, 33, 34, 37, 38, 44, 45, 48, 49, 60). An independent association between sarcopenia and reduced PFS was observed (HR = 1.33, 95% CI: 1.12–1.56), and a substantial statistical heterogeneity was exhibited (Q = 37.24, I^2 = 70%, $P < 0.01$) (**Figure 4**). Among these 11 studies, 10 studies were assessed by SMI at L3 level, and only one study was assessed by TPMT/BH at umbilical level, therefore, subgroup analysis was not performed according to the methods for sarcopenia assessment. Additionally, 10 studies were conducted in Asia, and only one study was conducted in Europe. Thus, subgroup analysis of association between sarcopenia and PFS among different study locations was not available.

Sensitivity analysis and publication bias

As shown in **Supplementary Figures 5**, **6**, the results of sensitivity analysis demonstrated that no individual study had a significant influence on the pooled HRs of the associations of sarcopenia with OS and PFS, indicating that the pooled results were robust.

The funnel plot for assessing publication bias between sarcopenia with OS was asymmetrical on visual evaluation, indicating a potential risk of publication bias, which was consistent with the result of Begg's test (P = 0.044; **Figure 5A**). The trim-and-fill method was used to generate symmetrical funnel plot through incorporating 17 imputed unpublished studies with negative findings (**Supplementary Figure 7**). After trim-and-fill method, the pooled HR was 2.10 (95% CI: 1.90–2.30), which was similar to our result (HR = 1.84, 95% CI: 1.62–2.09). Furthermore, fail-safe number calculated using the Rosenthal's approach was 3,476, suggesting that it was difficult to refute our results about the association between sarcopenia with OS. The funnel plot of association between sarcopenia and

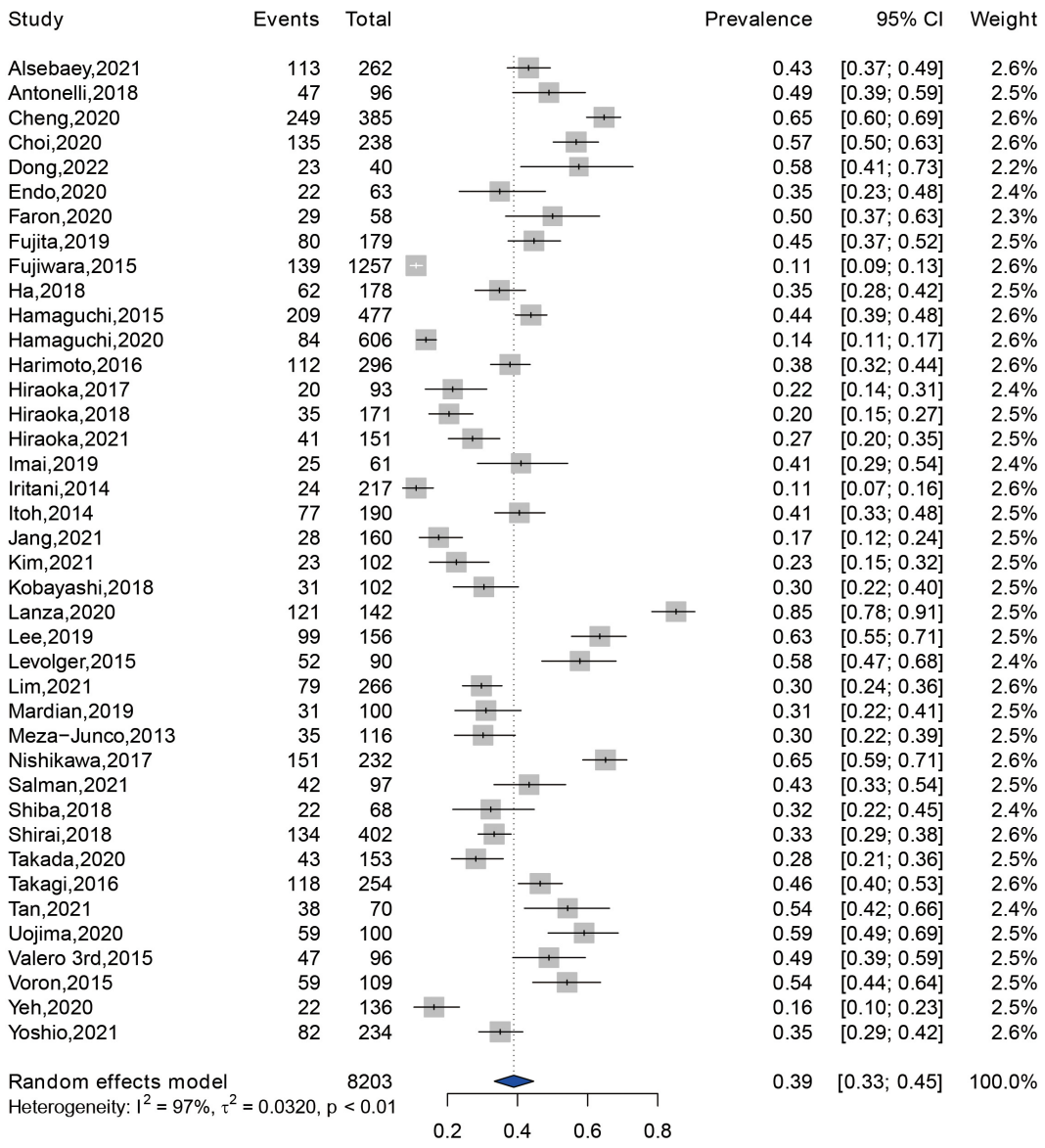


FIGURE 2
Forest plot showing the pooled prevalence of sarcopenia among patients with hepatocellular carcinoma.

PFS was visually symmetrical (**Figure 5B**), and this result was confirmed by the Begg's test ($P = 0.091$).

Discussion

Sarcopenia was first proposed by Rosenberg to describe the loss of muscle mass with aging in 1988, and it was judged by an index calculated as appendicular skeletal muscle mass/the square of height (62). The definition of sarcopenia has evolved in the past decades, and three most common diagnostic indicators include lean muscle mass, impaired muscle strength, and low physical performance (63). Sarcopenia is common in the natural aging, functional, metabolic, and immune disorders, muscle hypercatabolism during cancer, and toxicity due to anti-cancer therapy (9, 64). Previous studies have shown that sarcopenia may co-occur with cachexia, and these two syndromes overlap considerably, especially in aging patients (65, 66). Most cachectic patients are also sarcopenic, but most individuals with sarcopenia are not considered as being cachectic. It is indicated that sarcopenia can be considered as a component of cachexia (67). Traditionally, sarcopenia is regarded as an inevitable consequence of aging. Two common types of sarcopenia are primary sarcopenia associated with aging and secondary sarcopenia caused by acute and chronic disorders which are related to muscle wasting, including chronic

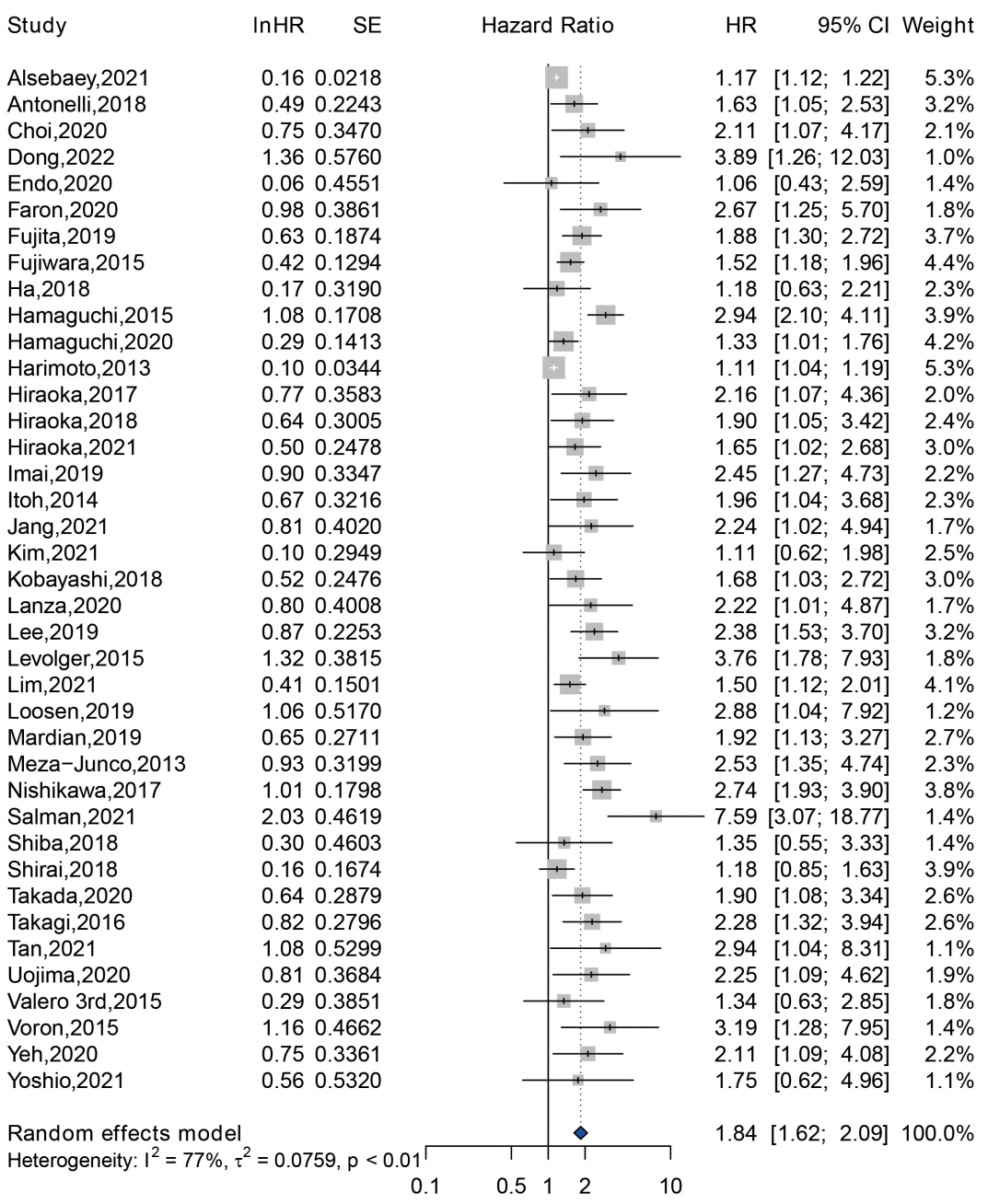


FIGURE 3
Forest plot of the pooled hazard ratio for association between sarcopenia and overall survival in patients with hepatocellular carcinoma.

liver diseases (68). Chronic liver diseases are characterized by a progression from hepatitis, cirrhosis to hepatic decompensation or HCC (69). The prevalence of sarcopenia among patients with cirrhosis and those with alcohol-related liver disease or Child-Pugh class C cirrhosis were 37.5 and 50%, respectively (70). Patients with HCC are predisposed to the sarcopenia with prevalence reported between 11 and 85% in the studies included in this systematic review and meta-analysis. The pooled prevalence of sarcopenia among patients with HCC was 39% (95% CI: 33–45%) in this study. In addition, the varying prevalence was possibly attributed to the different assessment methods for sarcopenia and heterogeneous populations.

This assessment methods for sarcopenia were diverse and not yet standardized. The most common assessment method used in the included studies was cross-sectional CT-based SMI at the L3 level, and cut-points ranged from 36 to 55 cm^2/m^2 in men and 29 to 39 cm^2/m^2 in women (41, 42, 60). Cross-sectional imaging with CT or MRI is the conventional technique for

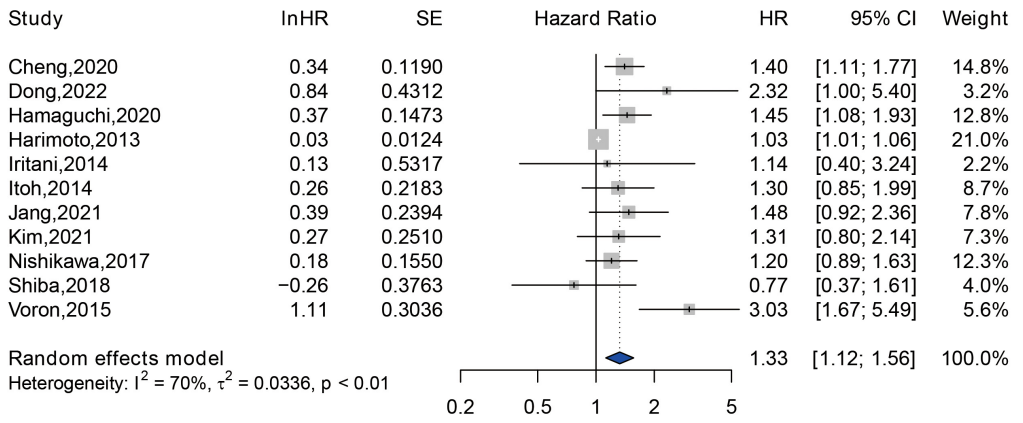


FIGURE 4
Forest plot of the pooled hazard ratio for association between sarcopenia and progression free survival in patients with hepatocellular carcinoma.

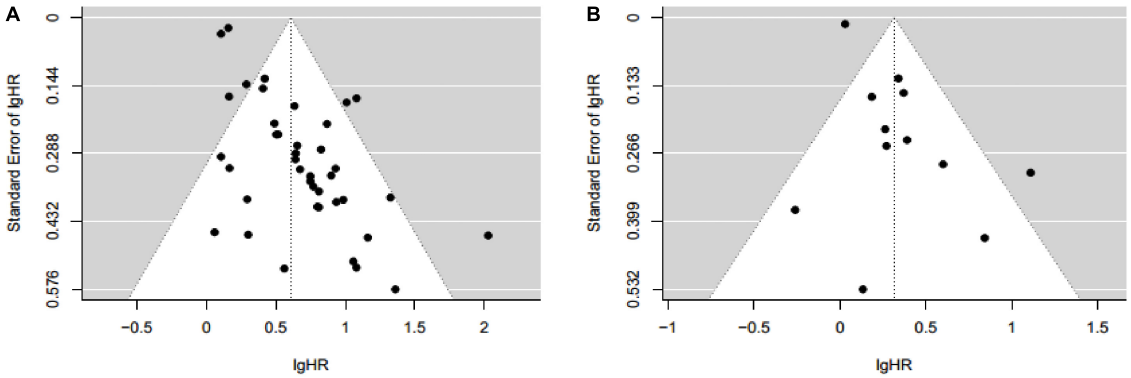


FIGURE 5
Funnel plot for assessing publication bias between sarcopenia with overall survival **(A)** and progression free survival **(B)** in patients with hepatocellular carcinoma.

diagnosis, staging, surveillance, and treatment response of HCC (71). Hence, it is available and reasonable to simultaneously evaluate muscle condition and prognosis in patients with HCC. The methods to define sarcopenia in several studies enrolled in this meta-analysis did not measure muscle strength or physical function. This is because sarcopenia was commonly used in cancer to denote low muscle mass without a measure of strength, and most of the included studies employed a retrospective design and did not include measurements of muscle strength or physical function at the data collection stage (7). Furthermore, there are several variations in the diagnosis of sarcopenia due to the different diagnostic criteria used, differences in the measurement methods used to assess muscle mass, differences in the cut-points applied, and heterogeneous study populations in the included studies. These could all contribute to the heterogeneity identified among studies (72–74). Further studies regarding the optimal method and cut-point for diagnosing sarcopenia are needed.

Accumulating evidence suggests that sarcopenia has an unfavorable impact on the prognosis of patients with HCC (56–58). Regarding the prognosis of patients with cancer, the criteria for the effectiveness of cancer drug trials proposed by U.S. Food and Drug Administration include the prolonged survival and improved clinical symptoms after therapy (75). OS and PFS are good criteria for evaluating clinical outcomes of patients with cancer. Currently, a growing number of meta-analyses have concentrated on the association between sarcopenia and prognosis of patients with cancer. In ovarian cancer, sarcopenia defined by a low SMI was associated with reduced OS (HR = 1.11, 95% CI: 1.03–1.20) (76). Yang Deng et al. observed that sarcopenia predicted a shorter OS in patients with non-small cell lung cancer (NSCLC) (HR = 2.57, 95% CI: 1.79–3.68) and small cell lung cancer (HR = 1.59, 95% CI: 1.17–2.14), but sarcopenia was not associated with PFS in NSCLC patients (HR = 1.28, 95% CI: 0.44–3.69) (20). A meta-analysis of 6 studies comprising 5,497 patients with female breast

cancer confirmed that sarcopenia was an independent predictor of higher risk of mortality (HR = 1.71, 95% CI: 1.25–2.33) (77). Among patients with colorectal cancer (CRC), sarcopenia was associated with postoperative complications, postoperative mortality, and prolonged length of stay. Moreover, CRC patients with sarcopenia had worse OS, disease-free survival, and cancer-specific survival, compared to those without sarcopenia (78). Here, we conducted this meta-analysis to confirm that sarcopenia predicted poor OS (HR = 1.84, 95% CI: 1.62–2.09) and poor PFS (HR = 1.33, 95% CI: 1.12–1.56) in HCC patients receiving diverse treatments.

The mechanisms through which sarcopenia is associated with poor survival of patients with HCC are not fully understood, but several potential mechanisms can be proposed. Firstly, skeletal muscle homeostasis is maintained by muscle hypertrophy, atrophy, and regeneration. The disequilibrium of homeostasis especially between hypertrophy and regeneration can result in sarcopenia. The main characteristics of sarcopenia are a loss in muscle mass, muscle strength, and functional ability (71). The skeletal muscle is responsible for glucose disposal, and a loss of muscle mass causes insulin resistance, which increases the production and biological activity of insulin-like growth factor 1 (IGF-1). IGF-1 regulates proliferation of hepatocytes via protein kinase B/mammalian target of rapamycin (AKT/mTOR) signaling pathway, which is associated with advanced pathological stage, high risk of recurrence, and poor prognosis of HCC (79). Secondly, cancer patients with sarcopenia characterized by impaired muscle strength and/or physical performance exhibit a poor response to cancer treatments, and are associated with an increased risk of disease progression (27, 80). Thirdly, myokines including myostatin, interleukin 6 (IL-6), follistatin are synthesized and secreted by muscle fibers, exert immunological and anti-inflammatory effects, and facilitate proinflammatory states of liver fibrosis, cirrhosis, and hepatocarcinogenesis (43). High levels of IL-6 and follistatin are regarded as poor prognostic factors for OS in patients with HCC (81).

The present study has both strengths and limitations. One strength was that we performed appropriate and comprehensive statistical analysis including sensitivity analysis and subgroup analysis to confirm the reliability and applicability of the results. In addition, the volume of data assessed within this meta-analysis is sufficient, with 8,445 participants involved in the 42 studies included. However, several limitations should be acknowledged. Firstly, studies included in this meta-analysis used different methods and cut-points to assess sarcopenia, resulting in significant heterogeneity in the pooled prevalence of sarcopenia and the association of sarcopenia with OS and PFS. Thus, we chose a random effects model for these analyses, and performed a subgroup analysis. Secondly, the majority of the included studies were retrospective (90.5%), and this meta-analysis might be susceptible to information bias and confounding bias. Thirdly, asymmetric funnel plot for OS indicates a potential risk of publication bias. To take this into account, we used the trim-and-fill method and calculated the fail-safe number to evaluate the impact of publication bias on the results about the association between sarcopenia with OS. Finally, this meta-analysis was restricted to articles published in English, and qualified articles in other languages were not included in the analysis, which might introduce bias.

Conclusion

In summary, the prevalence of sarcopenia was approximately 39% among patients with HCC. Sarcopenia was considered as an unfavorable prognostic factor and was independently associated with reduced OS and PFS in HCC irrespective of treatment modalities. It is suggested that assessment and early detection of sarcopenia, and interventions including suitable physical exercise and supplemental nutrition should be implemented to improve the prognosis of patients with HCC. A consensus on the optimal method and cut-point to assess sarcopenia needs to be reached.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

CJ, LZ, and YD designed the study protocol and conducted the literature search. CJ, YW, WF, and GZ retrieved and selected the article. CJ, XF, XW, FW, and LZ conducted data extraction. CJ, YW, WF, GZ, and YD performed the statistical analysis of the data. CJ and YW wrote the manuscript draft. LZ and YD supervised the study. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the National Natural Science Foundation of China (Grant No. 82204111), Tai'an Science and Technology Innovation Development Project (Grant Nos. 2021NS335 and 2021ZC524), and Key Topics of Health Policy Research of Shandong Province 2022 (Grant Nos. WZY202291 and WZY202292). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.978110/full#supplementary-material

References

1. Villanueva A. Hepatocellular carcinoma. *N Engl J Med.* (2019) 380:1450–62. doi: 10.1056/NEJMra1713263

2. McGlynn K, Petrick J, El-Serag H. Epidemiology of hepatocellular carcinoma. *Hepatology.* (2021) 73:4–13. doi: 10.1002/hep.31288

3. Llovet J, Kelley R, Villanueva A, Singal A, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers.* (2021) 7:6. doi: 10.1038/s41572-020-00240-3

4. Couri T, Pillai A. Goals and targets for personalized therapy for HCC. *Hepatol Int.* (2019) 13:125–37. doi: 10.1007/s12072-018-9919-1

5. Park J, Chen M, Colombo M, Roberts L, Schwartz M, Chen P, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE study. *Liver Int.* (2015) 35:2155–66. doi: 10.1111/liv.12818

6. Fan Y, Xue H, Zheng H. Systemic therapy for hepatocellular carcinoma: current updates and outlook. *J Hepatocell Carcinoma.* (2022) 9:233–63. doi: 10.2147/JHC.S358082

7. Chang K, Chen J, Wu W, Huang K, Hsu C, Han D. Association between loss of skeletal muscle mass and mortality and tumor recurrence in hepatocellular carcinoma: a systematic review and meta-analysis. *Liver Cancer.* (2018) 7:90–103. doi: 10.1159/000484950

8. Topan M, Sporea I, Dănilă M, Popescu A, Ghiuchici A, Lupușoru R, et al. Impact of sarcopenia on survival and clinical outcomes in patients with liver cirrhosis. *Front Nutr.* (2021) 8:766451. doi: 10.3389/fnut.2021.766451

9. Ruan G, Ge Y, Xie H, Hu C, Guozhuan Zhang Q, Zhang X, et al. Association between systemic inflammation and malnutrition with survival in patients with cancer sarcopenia-a prospective multicenter study. *Front Nutr.* (2022) 8:811288. doi: 10.3389/fnut.2021.811288

10. Kawamura T, Makuuchi R, Tokunaga M, Tanizawa Y, Bando E, Yasui H, et al. Long-term outcomes of gastric cancer patients with preoperative sarcopenia. *Ann Surg Oncol.* (2018) 25:1625–32. doi: 10.1245/s10434-018-6452-3

11. Lee C, Park I, Kim K, Shin Y, Lim S, Kim C, et al. Influence of postoperative changes in sarcopenia on long-term survival in non-metastatic colorectal cancer patients. *Cancers.* (2021) 13:2410. doi: 10.3390/cancers13102410

12. Nakamura R, Inage Y, Tobita R, Yoneyama S, Numata T, Ota K, et al. Sarcopenia in resected NSCLC: effect on postoperative outcomes. *J Thorac Oncol.* (2018) 13:895–903. doi: 10.1016/j.jtho.2018.04.035

13. Ataseven B, Luengo T, du Bois A, Waltering K, Traut A, Heitz F, et al. Skeletal muscle attenuation (sarcopenia) predicts reduced overall survival in patients with advanced epithelial ovarian cancer undergoing primary debulking surgery. *Ann Surg Oncol.* (2018) 25:3372–9. doi: 10.1245/s10434-018-6683-3

14. Uojima H, Chuma M, Tanaka Y, Hidaka H, Nakazawa T, Iwabuchi S, et al. Skeletal muscle mass influences tolerability and prognosis in hepatocellular carcinoma patients treated with lenvatinib. *Liver Cancer.* (2020) 9:193–206. doi: 10.1159/000504604

15. Loosen S, Schulze-Hagen M, Bruners P, Tacke F, Trautwein C, Kuhl C, et al. Sarcopenia is a negative prognostic factor in patients undergoing transarterial chemoembolization (TACE) for hepatic malignancies. *Cancers.* (2019) 11:1503. doi: 10.3390/cancers11101503

16. Ha Y, Kim D, Han S, Chon Y, Lee Y, Kim M, et al. Sarcopenia predicts prognosis in patients with newly diagnosed hepatocellular carcinoma, independent of tumor stage and liver function. *Cancer Res Treat.* (2018) 50:843–51. doi: 10.4143/crt.2017.232

17. Moher D, Liberati A, Tetzlaff J, Altman D, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097

18. Hayden J, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Int Med.* (2006) 144:427–37. doi: 10.7326/0003-4819-144-6-200603210-00010

19. Hayden J, van der Windt D, Cartwright J, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Int Med.* (2013) 158:280–6. doi: 10.7326/0003-4819-158-4-201302190-00009

20. Yang M, Shen Y, Tan L, Li W. Prognostic value of sarcopenia in lung cancer: a systematic review and meta-analysis. *Chest.* (2019) 156:101–11. doi: 10.1016/j.chest.2019.04.115

21. Rosenthal R. The file drawer problem and tolerance for null results. *Psychol Bull.* (1979) 86:638–41. doi: 10.1037/0033-2909.86.3.638

22. Endo K, Kuroda H, Kanazawa J, Sato T, Fujiwara Y, Abe T, et al. Impact of grip strength in patients with unresectable hepatocellular carcinoma treated with lenvatinib. *Cancers.* (2020) 12:2146. doi: 10.3390/cancers12082146

23. Fujita M, Takahashi A, Hayashi M, Okai K, Abe K, Ohira H. Skeletal muscle volume loss during transarterial chemoembolization predicts poor prognosis in patients with hepatocellular carcinoma. *Hepatol Res.* (2019) 49:778–86. doi: 10.1111/hepr.13331

24. Fujiwara N, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol.* (2015) 63:131–40. doi: 10.1016/j.jhep.2015.02.031

25. Hamaguchi Y, Kaido T, Okumura S, Ito T, Fujimoto Y, Ogawa K, et al. Preoperative intramuscular adipose tissue content is a novel prognostic predictor after hepatectomy for hepatocellular carcinoma. *J Hepatobiliary Pancreat Sci.* (2015) 22:475–85. doi: 10.1002/jhbp.236

26. Hamaguchi Y, Kaido T, Okumura S, Kobayashi A, Shirai H, Yao S, et al. Preoperative visceral adiposity and muscularity predict poor outcomes after hepatectomy for hepatocellular carcinoma. *Liver Cancer.* (2019) 8:92–109. doi: 10.1159/000488779

27. Harimoto N, Shirabe K, Yamashita Y, Ikegami T, Yoshizumi T, Soejima Y, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg.* (2013) 100:1523–30. doi: 10.1002/bjs.9258

28. Harimoto N, Yoshizumi T, Shimokawa M, Sakata K, Kimura K, Itoh S, et al. Sarcopenia is a poor prognostic factor following hepatic resection in patients aged 70 years and older with hepatocellular carcinoma. *Hepatol Res.* (2016) 46:1247–55. doi: 10.1111/hepr.12674

29. Hiraoka A, Hirooka M, Koizumi Y, Izumoto H, Ueki H, Kaneto M, et al. Muscle volume loss as a prognostic marker in hepatocellular carcinoma patients treated with sorafenib. *Hepatol Res.* (2017) 47:558–65. doi: 10.1111/hepr.12780

30. Hiraoka A, Otsuka Y, Kawasaki H, Izumoto H, Ueki H, Kitahata S, et al. Impact of muscle volume and muscle function decline in patients undergoing surgical resection for hepatocellular carcinoma. *J Gastroenterol Hepatol.* (2018) 33:1271–6. doi: 10.1111/jgh.14058

31. Hiraoka A, Kumada T, Kariyama K, Tada T, Tani J, Fukunishi S, et al. Clinical importance of muscle volume in lenvatinib treatment for hepatocellular carcinoma: analysis adjusted with inverse probability weighting. *J Gastroenterol Hepatol.* (2021) 36:1812–9. doi: 10.1111/jgh.15336

32. Imai K, Takai K, Miwa T, Taguchi D, Hanai T, Suetsugu A, et al. Rapid depletions of subcutaneous fat mass and skeletal muscle mass predict worse survival in patients with hepatocellular carcinoma treated with sorafenib. *Cancers.* (2019) 11:1206. doi: 10.3390/cancers11081206

33. Iritani S, Imai K, Takai K, Hanai T, Ideta T, Miyazaki T, et al. Skeletal muscle depletion is an independent prognostic factor for hepatocellular carcinoma. *J Gastroenterol.* (2015) 50:323–32. doi: 10.1007/s00535-014-0964-9

34. Itoh S, Shirabe K, Matsumoto Y, Yoshiya S, Muto J, Harimoto N, et al. Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma. *Ann Surg Oncol.* (2014) 21:3063–8. doi: 10.1245/s10434-014-3686-6

35. Kobayashi T, Kawai H, Nakano O, Abe S, Kamimura H, Sakamaki A, et al. Rapidly declining skeletal muscle mass predicts poor prognosis of hepatocellular carcinoma treated with transcatheter intra-arterial therapies. *BMC Cancer.* (2018) 18:756. doi: 10.1186/s12885-018-4673-2

36. Mardian Y, Yano Y, Ratnasari N, Choridah L, Wasityastuti W, Setyawan N, et al. Sarcopenia and intramuscular fat deposition are associated with poor survival in Indonesian patients with hepatocellular carcinoma: a retrospective study. *BMC Gastroenterol.* (2019) 19:229. doi: 10.1186/s12876-019-1152-4

37. Nishikawa H, Nishijima N, Enomoto H, Sakamoto A, Nasu A, Komekado H, et al. Prognostic significance of sarcopenia in patients with hepatocellular carcinoma undergoing sorafenib therapy. *Oncol Lett.* (2017) 14:1637–47. doi: 10.3892/ol.2017.6287

38. Shiba S, Shibuya K, Katoh H, Koyama Y, Okamoto M, Abe T, et al. No deterioration in clinical outcomes of carbon ion radiotherapy for sarcopenia patients with hepatocellular carcinoma. *Anticancer Res.* (2018) 38:3579–86. doi: 10.21873/anticanres.12631

39. Shirai H, Kaido T, Hamaguchi Y, Kobayashi A, Okumura S, Yao S, et al. Preoperative low muscle mass and low muscle quality negatively impact on pulmonary function in patients undergoing hepatectomy for hepatocellular carcinoma. *Liver Cancer.* (2018) 7:76–89. doi: 10.1159/000484487

40. Takada H, Amemiya F, Yasumura T, Yoda H, Okuwaki T, Imagawa N, et al. Relationship between presarcopenia and event occurrence in patients with primary hepatocellular carcinoma. *Sci Rep.* (2020) 10:10186. doi: 10.1038/s41598-020-67147-7

41. Takagi K, Yagi T, Yoshida R, Shinoura S, Umeda Y, Nobuoka D, et al. Sarcopenia and american society of anesthesiologists physical status in the assessment of outcomes of hepatocellular carcinoma patients undergoing hepatectomy. *Acta Med Okayama.* (2016) 70:363–70. doi: 10.18926/AMO/54594

42. Yoshio S, Shimagaki T, Hashida R, Kawaguchi T, Tsutsui Y, Sakamoto Y, et al. Myostatin as a fibroblast-activating factor impacts on postoperative outcome in patients with hepatocellular carcinoma. *Hepatol Res.* (2021) 51:803–12. doi: 10.1111/hepr.13667

43. Choi K, Jang H, Ahn J, Hwang S, Chung J, Choi Y, et al. The association of the serum levels of myostatin, follistatin, and interleukin-6 with sarcopenia, and their impacts on survival in patients with hepatocellular carcinoma. *Clin Mol Hepatol.* (2020) 26:492–505. doi: 10.3350/cmh.2020.0005

44. Jang H, Choi G, Hwang S, Jang E, Kim J, Ahn J, et al. Sarcopenia and visceral adiposity predict poor overall survival in hepatocellular carcinoma patients after curative hepatic resection. *Trans Cancer Res.* (2021) 10:854–66. doi: 10.21037/tcr-20-2974

45. Kim N, Yu J, Park H, Yoo G, Choi C, Hong J, et al. Incorporating sarcopenia and inflammation with radiation therapy in patients with hepatocellular carcinoma treated with nivolumab. *Cancer Immunol Immunother.* (2021) 70:1593–603. doi: 10.1007/s00262-020-02794-3

46. Lee J, Cho Y, Park S, Kim J, Lee I. Skeletal muscle depletion predicts the prognosis of patients with hepatocellular carcinoma treated with radiotherapy. *Front Oncol.* (2019) 9:1075. doi: 10.3389/fonc.2019.01075

47. Lim J, Kim K, Ko Y, Jang I, Lee Y, Chung Y, et al. The role of muscle depletion and visceral adiposity in HCC patients aged 65 and over undergoing TACE. *BMC Cancer.* (2021) 21:1164. doi: 10.1186/s12885-021-08905-2

48. Cheng T, Lee P, Chen Y, Chao Y, Hou M, Huang Y. Pre-sarcopenia determines post-progression outcomes in advanced hepatocellular carcinoma after sorafenib failure. *Sci Rep.* (2020) 10:18375. doi: 10.1038/s41598-020-75198-z

49. Dong D, Shi J, Shang X, Liu B, Xu W, Cui G, et al. Prognostic significance of sarcopenia in patients with hepatocellular carcinoma treated with lenvatinib: a retrospective analysis. *Medicine.* (2022) 101:e28680. doi: 10.1097/MD.0000000000028680

50. Tan Y, Duan T, Li B, Zhang B, Zhu Y, Yan K, et al. Sarcopenia defined by psoas muscle index independently predicts long-term survival after living donor liver transplantation in male recipients. *Quant Imaging Med Surg.* (2022) 12:215–28. doi: 10.21037/qims-21-314

51. Yeh W, Chiang P, Kee K, Chang C, Lu S, Chen C, et al. Pre-sarcopenia is the prognostic factor of overall survival in early-stage hepatoma patients undergoing radiofrequency ablation. *Medicine.* (2020) 99:e20455. doi: 10.1097/MD.0000000000020455

52. Alsebaey A, Sabry A, Rashed H, Elsabaawy M, Ragab A, Aly R, et al. MELD-sarcopenia is better than ALBI and MELD score in patients with hepatocellular carcinoma awaiting liver transplantation. *Asian Pac J Cancer Prev.* (2021) 22:2005–9. doi: 10.31557/APJCP.2021.22.7.2005

53. Salman A, Salman M, Moustafa A, Shaaban H, El-Mikkawy A, Labib S, et al. Impact of sarcopenia on two-year mortality in patients with HCV-associated hepatocellular carcinoma after radiofrequency ablation. *J Hepatocell Carcinoma.* (2021) 8:313–20. doi: 10.2147/JHC.S300680

54. Faron A, Sprinkart A, Pieper C, Kuetting D, Fimmers R, Block W, et al. Yttrium-90 radioembolization for hepatocellular carcinoma: outcome prediction with MRI derived fat-free muscle area. *Eur J Radiol.* (2020) 125:108889. doi: 10.1016/j.ejrad.2020.108889

55. Antonelli G, Gigante E, Iavarone M, Begini P, Sangiovanni A, Iannicelli E, et al. Sarcopenia is associated with reduced survival in patients with advanced hepatocellular carcinoma undergoing sorafenib treatment. *United Eur Gastroenterol J.* (2018) 6:1039–48. doi: 10.1177/2050640618781188

56. Lanza E, Masetti C, Messana G, Muglia R, Pugliese N, Ceriani R, et al. Sarcopenia as a predictor of survival in patients undergoing bland transarterial embolization for unresectable hepatocellular carcinoma. *PLoS One.* (2020) 15:e0232371. doi: 10.1371/journal.pone.0232371

57. Levolger S, van Vledder M, Muslem R, Koek M, Niessen W, de Man R, et al. Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma. *J Surg Oncol.* (2015) 112:208–13. doi: 10.1002/jso.23976

58. Meza-Junco J, Montano-Loza A, Baracos V, Prado C, Bain V, Beaumont C, et al. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. *J Clin Gastroenterol.* (2013) 47:861–70. doi: 10.1097/MCG.0b013e318293a825

59. Valero V III, Amini N, Spolverato G, Weiss M, Hirose K, Dagher N, et al. Sarcopenia adversely impacts postoperative complications following resection or transplantation in patients with primary liver tumors. *J Gastrointest Surg.* (2015) 19:272–81. doi: 10.1007/s11605-014-2680-4

60. Voron T, Tselikas L, Pietrasz D, Pigneur F, Laurent A, Compagnon P, et al. Sarcopenia impacts on short- and long-term results of hepatectomy for hepatocellular carcinoma. *Ann Surg.* (2015) 261:1173–83. doi: 10.1097/SLA.0000000000000743

61. Nishikawa H, Shiraki M, Hiramatsu A, Moriya K, Hino K, Nishiguchi S. Japan society of hepatology guidelines for sarcopenia in liver disease (1st edition): recommendation from the working group for creation of sarcopenia assessment criteria. *Hepatol Res.* (2016) 46:951–63. doi: 10.1111/hepr.12774

62. Rosenberg I. Sarcopenia: origins and clinical relevance. *J Nutr.* (1997) 127:990S–1S. doi: 10.1093/jn/127.5.990S

63. Chen L, Woo J, Assantachai P, Auyeung T, Chou M, Iijima K, et al. Asian Working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc.* (2020) 21:300–7.e2. doi: 10.1016/j.jamda.2019.12.012

64. Baracos V, Martin L, Korc M, Guttridge D, Fearon K. Cancer-associated cachexia. *Nat Rev Dis Primers.* (2018) 4:17105. doi: 10.1038/nrdp.2017.105

65. Fearon K, Strasser F, Anker S, Bosaeus I, Bruera E, Fainsinger R, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* (2011) 12:489–95. doi: 10.1016/S1470-204570218-7

66. Peixoto da Silva S, Santos J, Costa Silva M, Gil da Costa R, Medeiros R. Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. *J Cachexia Sarcopenia Muscle.* (2020) 11:619–35. doi: 10.1002/jcsm.12528

67. Muscaritoli M, Anker S, Argilés J, Aversa Z, Bauer J, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by special interest groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr.* (2010) 29:154–9. doi: 10.1016/j.clnu.2009.12.004

68. Bauer J, Morley J, Schols A, Ferrucci L, Cruz-Jentoft A, Dent E, et al. Sarcopenia: a time for action. An SCWD position paper. *J Cachexia Sarcopenia Muscle.* (2019) 10:956–61. doi: 10.1002/jcsm.12483

69. Craig A, von Felden J, Garcia-Lezana T, Sarcognato S, Villanueva A. Tumour evolution in hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol.* (2020) 17:139–52. doi: 10.1038/s41575-019-0229-4

70. Tantai X, Liu Y, Yeo Y, Praktiknjo M, Mauro E, Hamaguchi Y, et al. Effect of sarcopenia on survival in patients with cirrhosis: a meta-analysis. *J Hepatol.* (2022) 76:588–99. doi: 10.1016/j.jhep.2021.11.006

71. Perisetti A, Goyal H, Yendala R, Chandan S, Tharian B, Thandassery R. Sarcopenia in hepatocellular carcinoma: current knowledge and future directions. *World J Gastroenterol.* (2022) 28:432–48. doi: 10.3748/wjg.v28.i4.432

72. Barazzoni R, Jensen G, Correia M, Gonzalez M, Higashiguchi T, Shi H, et al. Guidance for assessment of the muscle mass phenotypic criterion for the global leadership initiative on malnutrition (GLIM) diagnosis of malnutrition. *Clin Nutr.* (2022) 41:1425–33. doi: 10.1016/j.clnu.2022.02.001

73. Takimoto M, Yasui-Yamada S, Nasu N, Kagiya N, Aotani N, Kurokawa Y, et al. Development and validation of cutoff value for reduced muscle mass for GLIM criteria in patients with gastrointestinal and hepatobiliary-pancreatic cancers. *Nutrients.* (2022) 14:943. doi: 10.3390/nu14050943

74. Donini L, Busetto L, Bischoff S, Cederholm T, Ballesteros-Pomar M, Batsis J, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. *Clin Nutr.* (2022) 41:990–1000. doi: 10.1016/j.clnu.2021.11.014

75. Ford R, Schwartz L, Dancey J, Dodd L, Eisenhauer E, Gwyther S, et al. Lessons learned from independent central review. *Eur J Cancer.* (2009) 45:268–74. doi: 10.1016/j.ejca.2008.10.031

76. Ubachs J, Ziemons J, Minis-Rutten I, Kruitwagen R, Kleijnen J, Lambrechts S, et al. Sarcopenia and ovarian cancer survival: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle.* (2019) 10:1165–74. doi: 10.1002/jcsm.12468

77. Zhang X, Dou Q, Zeng Y, Yang Y, Cheng A, Zhang W. Sarcopenia as a predictor of mortality in women with breast cancer: a meta-analysis and systematic review. *BMC Cancer.* (2020) 20:172. doi: 10.1186/s12885-020-6645-6

78. Trejo-Avila M, Bozada-Gutiérrez K, Valenzuela-Salazar C, Herrera-Esquivel J, Moreno-Portillo M. Sarcopenia predicts worse postoperative outcomes and decreased survival rates in patients with colorectal cancer: a systematic review and meta-analysis. *Int J Colorectal Dis.* (2021) 36:1077–96. doi: 10.1007/s00384-021-03839-4

79. Su R, Nan H, Guo H, Ruan Z, Jiang L, Song Y, et al. Associations of components of PTEN/AKT/mTOR pathway with cancer stem cell markers and prognostic value of these biomarkers in hepatocellular carcinoma. *Hepatol Res.* (2016) 46:1380–91. doi: 10.1111/hepr.12687

80. Prado C, Lieffers J, McCargar L, Reiman T, Sawyer M, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol.* (2008) 9:629–35. doi: 10.1016/S1470-204570153-0

81. Schmidt-Arras D, Rose-John S. IL-6 pathway in the liver: from physiopathology to therapy. *J Hepatol.* (2016) 64:1403–15. doi: 10.1016/j.jhep.2016.02.004

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 22 December 2022
DOI 10.3389/fnut.2022.1061996

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Zengning Li,
The First Hospital of Hebei Medical University, China
Salvatore Vaccaro,
IRCCS Local Health Authority of Reggio Emilia, Italy

*CORRESPONDENCE
Xin Wang
✉ winsun2011@163.com
Hanping Shi
✉ shihp@ccmu.edu.cn

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 05 October 2022
ACCEPTED 05 December 2022
PUBLISHED 22 December 2022

CITATION
Shi J, Xie H, Ruan G, Ge Y, Lin S, Zhang H, Zheng X, Liu C, Song M, Liu T, Zhang X, Yang M, Liu X, Zhang Q, Deng L, Wang X and Shi H (2022) Sex differences in the association of phase angle and lung cancer mortality. *Front. Nutr.* 9:1061996. doi: 10.3389/fnut.2022.1061996

Sex differences in the association of phase angle and lung cancer mortality

Jinyu Shi[1,2,3,4†], Hailun Xie[1,2,3,4†], Guotian Ruan[1,2,3,4†], Yizhong Ge[1,2,3,4], Shiqi Lin[1,2,3,4], Heyang Zhang[1,2,3,4], Xin Zheng[1,2,3,4], Chen'an Liu[1,2,3,4], Mengmeng Song[1,2,3,4], Tong Liu[1,2,3,4], Xiaowei Zhang[1,2,3,4], Ming Yang[1,2,3,4], Xiaoyue Liu[1,2,3,4], Qi Zhang[5], Li Deng[1,2,3,4], Xin Wang[1,2,3,4*] and Hanping Shi[1,2,3,4*]

[1]Department of Gastrointestinal Surgery, Beijing Shijitan Hospital, Capital Medical University, Beijing, China, [2]Department of Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University, Beijing, China, [3]Beijing International Science and Technology Cooperation Base for Cancer Metabolism and Nutrition, Beijing, China, [4]Key Laboratory of Cancer FSMP for State Market Regulation, Beijing, China, [5]Department of Colorectal Surgery, Cancer Hospital of the University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China

Background: Lung cancer is a lethal malignant tumor that is common worldwide and is associated with a high incidence of malnutrition. Phase angle (PA) is a simple, objective, and non-invasive indicator of body composition that has increasingly attracted attention as an indicator of the nutritional status and prognosis of patients with malignant tumors. This study aimed to investigate the association between the PA and overall survival in patients with lung cancer.

Methods: This study prospectively analyzed 804 lung cancer patients in the Investigation on Nutrition Status and its Clinical Outcome of Common Cancers (INSCOC) project from 40 hospitals in China. We used a restricted cubic spline to analyze the sex-specific association between PA and mortality in men and women with lung cancer. Cox regression analysis was used to evaluate the independent association between PA and mortality in men and women. Sensitivity analysis was performed. The Kaplan–Meier method was used to evaluate the survival of patients with high and low PA values.

Results: There was an L-shaped association between PA and survival in both men and women with lung cancer (p = 0.019 and p = 0.121, respectively). Kaplan–Meier survival analysis suggested that patients with a high PA showed a better survival than patients with a low PA (p = 0.007 for men and $p < 0.001$ for women). Multivariate-adjusted Cox regression analysis showed that PA was an independent risk factor for mortality in men (HR = 0.79, 95% CI = 0.65–0.95, p = 0.015), but not in women (HR = 0.83, 95% CI = 0.67–1.04, p = 0.105).

Conclusion: Phase angle is an independent risk factor for the mortality of male lung cancer patients. However, its role in predicting the mortality of female lung cancer patients seems to be limited.

KEYWORDS

phase angle, prognostic, sex differences, lung cancer, mortality

1 Introduction

Lung cancer is a lethal malignancy that is common worldwide. According to Global Cancer Statistics 2020, lung cancer ranks first in both incidence and mortality among male tumors, and third in incidence and second in mortality among female tumors (1). According to the latest data from the National Cancer Center of China, lung cancer was the most common malignancy and the leading cause of cancer-related mortality in 2016 (2). It has been estimated that 8,28,100 new lung cancer patients and 6,57,000 lung cancer-related deaths occurred China in 2016, indicating that it poses a marked threat to the lives and health of people (2).

Previous studies have shown that the incidence of malnutrition in patients with lung cancer is as high as 45–69% (3). Malnutrition not only prolongs the length of hospitalization and increases the cost of hospitalization, but also has a marked impact on the treatment efficacy and prognosis of patients. Therefore, exploring simple and effective nutrition-related indicators to predict the prognosis of patients with lung cancer, guide clinical decision-making, and reduce lung cancer-related mortality has become an urgent problem.

Previously, nutritional screening and assessment tools, such as body mass index (BMI), dual-energy X-ray absorptiometry (DXA), computed tomography (CT), have been used to evaluate the nutritional status and predict the prognosis of patients with malignant tumors, and was successful to a certain extent (4, 5). However, there are still some deficiencies in these indicators, such as the high technical requirements and radiation damage associated with DXA, the cost and unsuitability for short-term repeated applications of CT, and the inability of BMI to distinguish between muscle and fat.

As a technology for measuring body composition using electrical methods, bioelectrical impedance analysis (BIA) utilizes the differences in electrical conductivity characteristics of various components of the human body to detect intracellular fluid resistance, extracellular fluid resistance, and cell membrane capacitance, by providing constant current signals and different electrical frequencies. BIA can be used to measure patients' body composition and to assess their nutritional status in clinical practice (6, 7). However, BIA data are complex, and it is difficult to perform clinical analysis directly.

Phase angle (PA) is a nutritional status evaluation index derived from BIA, which can evaluate the integrity of cell membranes and the distribution of intracellular and extracellular water. PA is simple, convenient, non-invasive, time-saving, relatively objective, and is strongly sensitive to the nutritional status of patients (8–11). Previous studies have shown that the PA value can be used for the early assessment of malnutrition and that this value is associated with prognosis in patients with non-small cell lung cancer, breast cancer, pancreatic cancer, ovarian cancer, colorectal cancer, and other diseases (12–15). Due to physiological differences, there are obvious differences in body composition between men and women (16). It is unclear whether sex differences affect the role of PA in the prognostic evaluation of lung cancer patients. Therefore, it is unreasonable to use PA to assess the prognosis of patients uniformly.

Thus, the aim of this study was to explore sex differences in the association between PA and lung cancer mortality, to provide a reference for early clinical screening to identify malnourished patients and to assist clinicians in clinical decision-making and in improving patient outcomes.

2 Materials and methods

2.1 Study population

This was a prospective, multicenter study. The enrolled population was obtained from the Investigation on Nutrition Status and its Clinical Outcome of Common Cancers (INSCOC) project, which contains the clinical data of cancer patients from more than 40 hospitals in China, from June 2012 to June 2021. Patients were enrolled in the study if they were diagnosed with lung cancer, were older than 18 years, and underwent BIA examination. In this study, 1,003 lung cancer patients who underwent BIA examination in the INSCOC project were

Abbreviations: PA, phase angle; RCS, restricted cubic spline; DXA, dual-energy X-ray absorptiometry; CT, computed tomography; BMI, body mass index; BIA, bioelectrical impedance analysis; INSCOC, Investigation on Nutrition Status and its Clinical Outcome of Common Cancers; KPS, Karnofsky performance status; NRS-2002, Nutritional Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment.

screened, of which 199 patients were excluded because of incomplete clinical data or survival data, and the remaining 804 patients were included in the final data analysis (**Supplementary Figure 1**).

This study was approved by the institutional review boards of all participating institutions. Written informed consent for the clinical data to be used in the clinical study was obtained from the enrolled patients.

2.2 Clinicopathological variables

After admission, the general clinical characteristics, laboratory biochemical indices, anthropometric measurements, pathological types, and stages were recorded in detail and accurately. General clinical characteristics included age, sex, underlying diseases, smoking, and drinking. Laboratory biochemical indicators included white blood cells, neutrophils, lymphocytes, platelets, hemoglobin, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, total bilirubin, direct bilirubin, triglycerides, and cholesterol. Anthropometric indices mainly included height, weight, and triceps skinfold thickness The pathological types and stages of the tumors were recorded based on the pathological diagnosis and radiography data.

2.3 Measurement of BIA

Bioelectrical impedance analysis was performed on an empty stomach or 2 h after food intake using the body composition analyzer InBody S10 (Biospace, Seoul, Korea). Patients were placed in the supine position, arms and legs were naturally abducted on both sides of the body, with the back of the hand facing upward, and the fingers were naturally stretched. Two electrodes were placed in contact with the patients' hands and feet. By detecting the impedance values of the human body under different frequency currents, the instrument automatically analyzed and calculated the relevant indicators of human body composition, including PA, extracellular water, intracellular water, body fat mass, muscle mass, and lean body mass. PA was calculated by using the following equation: PA (°) = arctan (Xc/R) × (108/π).

2.4 Follow-up and outcomes

All patients were followed-up continuously, and survival data were recorded. Follow-up was continued until patients died or were lost to follow-up. The primary outcome was overall survival (OS), defined as the interval between the time of pathological diagnosis and death or the day of the last follow-up. The secondary outcomes included the Karnofsky performance status (KPS) score, Nutritional Risk Screening 2002 (NRS-2002) score, Patient-Generated Subjective Global Assessment (PG-SGA) score, cachexia, and admission 30 days post-admission survival outcome. The KPS score was used to reflect general well-being and abilities of daily life, and the NRS-2002 and PG-SGA scores were used to reflect patients' nutritional status. The diagnosis of cachexia was based on the 2011 International Consensus Framework (17).

2.5 Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range). Continuous variables with a normal distribution were subjected to Student's *t*-test, and continuous variables without a normal distribution were subjected to the Mann–Whitney *U* test. Categorical variables are expressed as frequencies or percentages, and the χ^2 test or Fisher's exact test was used. The sex-specific optimal cut-off values of PA were calculated with the "maxstat" package by an application "Evaluate Cutpoints" in R software. Patients were divided into high- and low-PA groups based on sex-specific optimal cut-off values. Three models were established: model a was not adjusted, model b was adjusted for age, TNM stage, and BMI, and model c was adjusted for age, TNM stage, BMI, smoking, alcohol consumption, diabetes mellitus, hypertension, coronary heart disease, chemotherapy, radiotherapy, and surgery. Multivariate Cox regression analysis was used to identify the independent significance of PA in mortality of patients with lung cancer. A restricted cubic spline (RCS) was used to assess sex-specific differences between PA and patients with lung cancer. The Kaplan–Meier method was applied to analyze the OS of men and women in the high- and low-PA groups, and the log-rank test was used for comparison between groups. Logistic regression models were used to assess the association between PA and the KPS score, NRS-2002 score, PG-SGA score, cachexia, and admission 30 days survival outcomes. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R software (version 4.2.1).

3 Results

3.1 Patient population

A total of 804 patients with lung cancer who underwent BIA were included in the analysis. There were 494 men (61.44%) and 310 women (38.56%), with a mean age of 60.60 ± 8.98 years. Of these, 435 patients (54.10%) were diagnosed with adenocarcinoma, 179 (22.26%) with squamous carcinoma, 160 (19.90%) with small cell lung cancer (SCLC), and 30 (3.73%) with other pathological types of lung cancer. There were 47 patients (5.85%) with stage I, 121 (15.05%) with stage II, 223 (27.74%) with stage III, and 413

(51.37%) with stage IV disease. The baseline demographic and clinicopathological characteristics stratified by sex are shown in **Supplementary Table 1**.

Supplementary Figure 2 shows that men, patients younger than 65 years, patients with a lower BMI, and patients with a lower tumor stage were more likely to have higher PA values, although the differences were not statistically significant. The results of Spearman's rank correlation test between PA and age, tumor stage, PG-SGA score, KPS score, NRS-2002 score, and global quality of life (QoL) score are shown in **Supplementary Figure 3**. PA was significantly correlated with age (men, $R = -0.46$, $p < 0.001$; women, $R = -0.24$, $p < 0.001$) and NRS-2002 score (men, $R = -0.25$, $p < 0.001$; women, $R = -0.15$, $p < 0.001$). There was no correlation between PA and tumor stage (men, $R = -0.06$, $p = 0.20$; women, $R = -0.04$, $p = 0.46$), PG-SGA score (men, $R = 0.00$, $p = 0.99$; women, $R = -0.01$, $p = 0.86$), KPS score (men, $R = 0.05$, $p = 0.26$, women, $R = 0.12$, $p = 0.04$), and global quality of life score (men, $R = -0.09$, $p = 0.06$; women, $R = -0.11$, $p = 0.05$).

3.2 Sex differences in the association of continuous PA with OS

Restricted cubic spline were generated to assess the sex-specific relationship between PA and mortality of patients with lung cancer. After adjusting for age, TNM stage, BMI, smoking, alcohol consumption, diabetes mellitus, hypertension, coronary heart disease, chemotherapy, radiotherapy, and surgery, we observed an L-shaped association between PA and survival in both men and women (**Figure 1**). PA had no statistically significant association with mortality in female lung cancer patients (p for mortality = 0.121), but was significantly associated with mortality in male patients (p for mortality = 0.019). In addition, RCS models were constructed for lung cancer patients with stage I–II, III, and IV (**Figure 2**). The RCS showed that there was still a tendency for sex-specific differences in all stages.

3.3 Sex-specific optimal cut-off values and Kaplan–Meier curves

The sex-specific optimal cut-off values for PA in terms of OS were 5.1° for men and 4.1° for women (**Supplementary Figure 4**). According to the above cut-off values, 190 men and 51 women were diagnosed with low-PA, and 304 men and 259 women were diagnosed with high-PA. Then, we established Kaplan–Meier survival curves for men and women with high- and low-PA values, respectively. As shown in **Supplementary Figure 2** (right panels), the survival of patients with high-PA values were better than that of patients with low-PA values in both men and women ($p = 0.007$ and $p < 0.0001$, respectively).

In addition, we further established Kaplan–Meier survival curves for lung patients with high- and low-PA values in stages I–II, III, and IV (**Supplementary Figure 5**). The results showed that the OS of patients with high PA tended to be longer than that of patients with low PA, regardless of stage. Among men with stage III tumors and women with stage IV tumors, the OS was significantly longer in patients with high-PA than in those with low-PA values ($p = 0.007$, $p < 0.001$, respectively).

3.4 Sex-specific association between PA and OS

Univariate Cox regression analysis showed that continuous PA was significantly associated with mortality in men with lung cancer ($p = 0.015$) (**Table 1**). After adjusting for age, TNM stage, BMI, smoking, alcohol consumption, diabetes mellitus, hypertension, coronary heart disease, chemotherapy, radiotherapy, and surgery, PA was identified as an independent risk factor for mortality in men ($p = 0.015$). Similarly, when PA was used as a binary or quartile variable, the results of the multivariate Cox regression analyses continued to identify low PA as an independent risk factor for OS in men.

In women, the univariate Cox regression analysis showed that continuous PA was significantly associated with survival ($p = 0.029$) (**Table 1**). However, after adjusting for age, TNM stage, BMI, smoking, alcohol consumption, diabetes mellitus, hypertension, coronary heart disease, chemotherapy, radiotherapy, and surgery, PA was not an independent prognostic factor for mortality in women ($p = 0.105$). Interestingly, when PA was used as a binary or quartile variable, multivariate analyses identify low PA as an independent risk factor for mortality in women.

3.5 Sensitivity analysis of the relationship between PA and mortality

After excluding patients with severe underlying diseases (including chronic obstructive pulmonary disease and cachexia), both univariate and multivariate Cox regression analyses showed that continuous PA was an independent risk factor for mortality in men with lung cancer ($p = 0.023$ and $p = 0.010$, respectively) (**Supplementary Table 2**), but not in women. In addition, we obtained similar results when we excluded patients with short term deaths (within 30 days).

3.6 Association between PA and secondary outcomes

In this study, 748 patients (460 men and 288 women) had a KPS score $\geq$ 80 points. Of the 202 patients with cachexia, 125

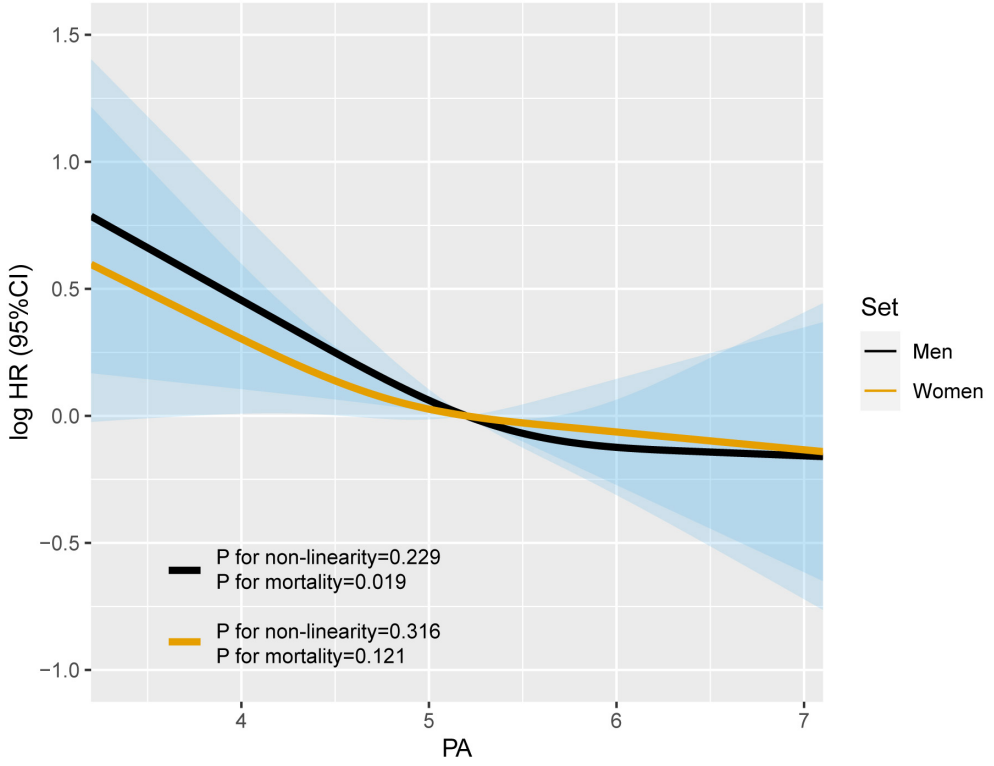


FIGURE 1
The sex differences in the association of phase angle (PA) and all-cause mortality in patients with lung cancer. Model c: Adjusted for age, TNM stage, BMI, smoking, alcohol drinking, diabetes mellitus, hypertension, coronary heart disease, chemotherapy, radiotherapy, and surgery.

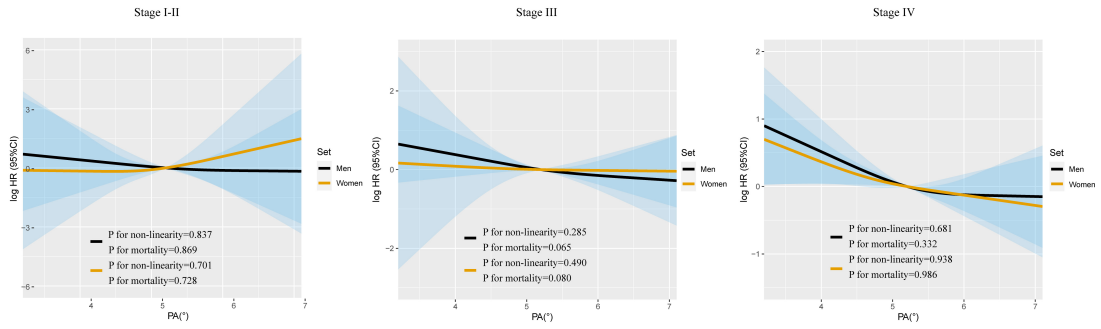


FIGURE 2
The sex-specific association between PA and all-cause mortality in patients with lung cancer based on TNM stage. Model c: Adjusted for age, TNM stage, BMI, smoking, alcohol drinking, diabetes mellitus, hypertension, coronary heart disease, chemotherapy, radiotherapy, and surgery.

were men and 77 were women. Seven patients, including 5 men and 2 women, died within 30 days. The NRS-2002 score was ≥3 points in 174 patients (108 men and 66 women). PG-SGA scores were ≥4 points in 461 patients (288 men and 173 women).

Logistic regression analysis showed that PA was significantly correlated with KPS score ≥ 80 points (men, $p < 0.001$; women, $p < 0.001$), cachexia (men, $p < 0.001$; women, $p < 0.001$), admission 30 days survival outcome (men, $p = 0.012$; women, $p = 0.027$), NRS-2002 score (men, $p < 0.001$; women, $p < 0.001$), and PG-SGA score (men, $p < 0.001$; women, $p < 0.001$) in both men and women (Table 2).

4 Discussion

The results of this study showed that PA is an independent risk factor for mortality in men with lung cancer. Although low PA is associated with a poor prognosis in women with

10.3389/fnut.2022.1061996

TABLE 1 Cox regression analyses for the associations between phase angle (PA) and all-cause mortality in patients with lung cancer.

Men						
PA	Model a	*P*-value	Model b	*P*-value	Model c	*P*-value
Continuous	0.81 (0.68–0.96)	0.015	0.79 (0.66–0.95)	0.015	0.79 (0.65–0.95)	0.015
Cutoff value		0.007		0.025		0.027
C1 (≤5.1°)	Ref		Ref		Ref	
C2 (>5.1°)	0.68 (0.51–0.90)		0.70 (0.52–0.96)		0.70 (0.51–0.96)	
Quartiles						
Q1 (<4.8°)	Ref		Ref		Ref	
Q2 (4.8°–5.4°)	0.77 (0.52–1.13)	0.185	0.77 (0.52–1.13)	0.183	0.75 (0.50–1.12)	0.160
Q3 (5.4°–6.0°)	0.65 (0.44–0.97)	0.036	0.72 (0.47–1.10)	0.125	0.70 (0.46–1.08)	0.105
Q4 (≥6.0°)	0.61 (0.41–0.91)	0.015	0.58 (0.38–0.90)	0.014	0.59 (0.38–0.91)	0.019
p for trend		0.010		0.017		0.021
Women						
Continuous	0.78 (0.62–0.98)	0.029	0.80 (0.64–1.00)	0.049	0.83 (0.67–1.04)	0.105
Cutoff value		<0.001		<0.001		0.004
C1 (≤4.1°)	Ref		Ref		Ref	
C2 (>4.1°)	0.44 (0.29–0.67)		0.47 (0.30–0.73)		0.50 (0.31–0.80)	
Quartiles						
Q1 (<4.3°)	Ref		Ref		Ref	
Q2 (4.3°–4.8°)	0.83 (0.52–1.34)	0.454	0.83 (0.51–1.34)	0.442	0.90 (0.54–1.49)	0.676
Q3 (4.8°–5.4°)	0.41 (0.23–0.71)	0.001	0.42 (0.24–0.73)	0.002	0.44 (0.24–0.79)	0.006
Q4 (≥5.4°)	0.62 (0.38–1.01)	0.056	0.61 (0.36–1.04)	0.068	0.66 (0.38–1.12)	0.131
p for trend		0.010		0.014		0.039

Model a: no adjusted.
Model b: adjusted for age, TNM stage, and BMI.
Model c: adjusted for age, TNM stage, BMI, smoking, alcohol drinking, diabetes mellitus, hypertension, coronary heart disease, chemotherapy, radiotherapy, and surgery.

lung cancer, PA was not identified as an independent risk factor for female mortality. Thus, PA is a more significant predictor of prognosis in men than in women with lung cancer. Even after excluding patients with severe underlying diseases or short-term deaths, sex differences in PA persisted in predicting prognosis in patients with lung cancer. In addition, we clarified that the optimal cut-off values of PA for men and women with lung cancer were 5.1° and 4.1°, respectively. Interestingly, there were no sex differences in the association of PA with patients' KPS score, NRS-2002 score, PG-SGA score, short-term outcomes, or cachexia, and PA was significantly associated with all of these secondary outcomes. Therefore, PA can be used to assess the ability to perform activities of daily life and general well-being, nutrition, cachexia, and short-term outcomes in both men and women.

Previous studies have shown that PA is closely associated with patients' survival. Toso et al. used an average PA of 4.5° as the cut-off value for patients with advanced lung cancer and found that the survival of patients in the low-PA group was shorter than that in the high-PA group (18). Gupta et al. found that patients with stage IV colorectal cancer with a PA > 5.57° had better survival (14). Moreover, lung cancer patients with PA < 5.3° had shorter survival times than those with high PA (19). In the present study, the optimal cut-off values of PA were 5.1° and 4.1° in men and women with lung cancer, respectively. Consistent with the results of previous studies, it was found that the survival of men and women with PA > 5.1° and >4.1° was significantly better than that of patients with low PA. Moreover, survival analysis of male and female patients was performed based on tumor stage, and the results showed that the OS of patients with a high PA tended to be longer than that of patients with a low PA. Some randomized controlled trials have demonstrated that resistance training can improve PA levels in patients, therefore, early detection of PA levels in patients and appropriate exercise are necessary (20–22).

Malnutrition is a common manifestation in patients with lung cancer (3, 23). Malnutrition works in conjunction with inflammation and the immune status to affect the health level of the body, leading to a poor prognosis (24, 25). It is one of the main factors associated with mortality. Malnutrition

TABLE 2 Logistic regression analysis between PA and secondary outcomes.

Life function (KPS ≥ 80)						
PA	Model a	*P*-value	Model b	*P*-value	Model c	*P*-value
Men	0.953 (0.933, 0.974)	0.019	0.956 (0.936, 0.977)	<0.001	0.947 (0.926, 0.969)	<0.001
Women	0.947 (0.926, 0.969)	<0.001	0.950 (0.929, 0.972)	<0.001	0.945 (0.923, 0.968)	<0.001
Cachexia (yes)						
Men	0.961 (0.948, 0.973)	<0.001	0.960 (0.948, 0.973)	<0.001	0.958 (0.946, 0.971)	<0.001
Women	0.974 (0.96, 0.988)	<0.001	0.973 (0.958, 0.987)	<0.001	0.970 (0.955, 0.985)	<0.001
Short-term outcome (admission 30 days survival outcome)						
Men	0.98 (0.97–0.99)	0.003	0.98 (0.96–1.24)	0.011	0.98 (0.97–1.00)	0.012
Women	0.99 (0.98–1.00)	0.063	0.99 (0.98–1.00)	0.032	0.99 (0.98–1.00)	0.027
Malnutrition (NRS-2002 score ≥ 3)						
Men	0.964 (0.952, 0.977)	<0.001	0.966 (0.954, 0.979)	<0.001	0.964 (0.951, 0.977)	<0.001
Women	0.965 (0.951, 0.98)	<0.001	0.966 (0.951, 0.981)	<0.001	0.962 (0.947, 0.977)	<0.001
Malnutrition (PG-SGA ≥ 4)						
Men	0.976 (0.965, 0.987)	<0.001	0.977 (0.966, 0.988)	<0.001	0.973 (0.961, 0.985)	<0.001
Women	0.973 (0.959, 0.987)	<0.001	0.974 (0.960, 0.988)	<0.001	0.968 (0.953, 0.983)	<0.001

Model a: no adjusted.
Model b: adjusted for age and TNM stage.
Model c: adjusted for age, TNM stage, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, and family history.

is characterized by altered cell membrane integrity and fluid balance. Therefore, measurement of body composition is an important part of the overall nutritional assessment of patients with cancer. As a convenient, non-invasive, and reproducible technique, PA has increasingly been used for the assessment of body composition, nutritional status, and prognosis prediction (26, 27). However, due to physiological differences between men and women, the effect of PA on the prognosis of patients of different sexes may be different. This study investigated the relationship between PA and mortality in both men and women with lung cancer. There was a sex difference in the association between PA and lung cancer mortality, and it may thus be more applicable to the prognosis assessment of men with lung cancer.

Cells consist of conductive intracellular fluid surrounded by a cell membrane that selectively allows permeation by certain ions. The electrical properties of the extracellular and intracellular fluids are close to the resistance, and the cell membrane can be equivalent to the capacitance. Thus, PA is an indicator of the relationship between resistance and capacitance (28). Previous studies have shown that PA is correlated with muscle mass and strength in cancer patients (29). Compared with women, men have a higher proportion of muscle and a higher proportion of water (including intracellular and extracellular water), so PA can more sensitively reflect changes in male body composition. Women generally have a higher percentage of body fat than men. Therefore, when evaluating the prognosis of women with lung cancer, more attention should be paid to nutritional indicators related to body fat, such as other indicators such as triceps skinfold thickness, rather than PA (5).

Phase angle detection is non-invasive, simple, objective, and easy to implement. During the diagnosis and treatment of patients with lung cancer, PA can be assessed repeatedly and dynamically in order to predict prognosis. It can be used to identify individuals with a high risk of malnutrition and poor prognosis in the early stages of the disease. During the treatment period, more clinical attention and earlier clinical intervention should be given to patients at high risk of malnutrition to avoid ineffective anti-tumor therapy and limited survival benefits and to maximize cost-effectiveness.

This study had several limitations that must be considered. First, the population included in this study was Chinese. Considering the ethnic differences in PA, this may not be applicable to populations in other countries. Second, this study may have been affected by differences in analytical instrumentation.

In summary, this study evaluated the ability of PA to predict prognosis in men and women with lung cancer. The results showed that PA does not carry equivalent prognostic value for men and for women with lung cancer, and PA was better at predicting the prognosis of male lung cancer patients than female lung cancer patients. For men, PA should be considered when performing prognostic evaluation, but for women, other nutritional indicators should be used. As an objective, convenient, non-invasive, and reproducible indicator, PA has the potential to be used widely in clinical practice to assist clinicians in the early identification and intervention in the nutritional status of lung cancer patients, to improve the prognosis of these patients.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of each hospital (Registration number: ChiCTR1800020329). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HS: conceptualization, methodology, software, and writing—reviewing and editing. JS: data curation, writing—original draft preparation, and writing—reviewing and editing. HX: writing—reviewing. GR: visualization, investigation, and writing—reviewing. YG, XinZ, CL, MS, and TL: software and validation. SL, HZ, XiaZ, and XW: supervision. MY, XL, and LD: resources. QZ: software. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Key Research and Development Program (grant numbers: 2017YFC1309200 and 2022YFC2009600) and the Beijing Municipal Science and Technology Commission (grant number: SCW2018-06).

Acknowledgments

We thank editage (www.editage.cn) for English language editing. We are grateful to all participants of the project and to the members of the study teams at different study centers who helped make this research possible.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1061996/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660

2. Zheng R, Zhang S, Zeng H, Wang S, Sun K, Chen R, et al. Cancer incidence and mortality in China, 2016. *J Nat Cancer Center.* (2022) 2:1–9. doi: 10.1016/j.jncc.2022.02.002

3. Kiss NK, Krishnasamy M, Isenring EA. The effect of nutrition intervention in lung cancer patients undergoing chemotherapy and/or radiotherapy: a systematic review. *Nutr Cancer.* (2014) 66:47–56. doi: 10.1080/01635581.2014.847966

4. Zhang X, Zhao W, Du Y, Zhang J, Zhang Y, Li W, et al. A simple assessment model based on phase angle for malnutrition and prognosis in hospitalized cancer patients. *Clin Nutr.* (2022) 41:1320–7. doi: 10.1016/j.clnu.2022.04.018

5. Xie H, Ruan G, Zhang H, Ge Y, Zhang Q, Lin S, et al. Sex differences in the association of triceps skinfold thickness and colorectal cancer mortality. *Nutrition.* (2022) 103–104:111811. doi: 10.1016/j.nut.2022.111811

6. Marini E, Campa F, Buffa R, Stagi S, Matias CN, Toselli S, et al. Phase angle and bioelectrical impedance vector analysis in the evaluation of body composition in athletes. *Clin Nutr.* (2020) 39:447–54. doi: 10.1016/j.clnu.2019.02.016

7. Norman K, Stobäus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis–clinical relevance and applicability of impedance parameters. *Clin Nutr.* (2012) 31:854–61. doi: 10.1016/j.clnu.2012.05.008

8. Kyle UG, Genton L, Pichard C. Low phase angle determined by bioelectrical impedance analysis is associated with malnutrition and nutritional risk at hospital admission. *Clin Nutr.* (2013) 32:294–9. doi: 10.1016/j.clnu.2012.08.001

9. Kyle UG, Soundar EP, Genton L, Pichard C. Can phase angle determined by bioelectrical impedance analysis assess nutritional risk? A comparison between healthy and hospitalized subjects. *Clin Nutr.* (2012) 31:875–81. doi: 10.1016/j.clnu.2012.04.002

10. Player EL, Morris P, Thomas T, Chan WY, Vyas R, Dutton J, et al. Bioelectrical impedance analysis (BIA)-derived phase angle (PA) is a practical aid to nutritional assessment in hospital in-patients. *Clin Nutr.* (2019) 38:1700–6. doi: 10.1016/j.clnu.2018.08.003

11. Mundstock E, Amaral MA, Baptista RR, Sarria EE, Dos Santos R, Filho AD, et al. Association between phase angle from bioelectrical impedance analysis and level of physical activity: systematic review and meta-analysis. *Clin Nutr.* (2019) 38:1504–10. doi: 10.1016/j.clnu.2018.08.031

12. Morlino D, Cioffi I, Marra M, Di Vincenzo O, Scalfi L, Pasanisi F. Bioelectrical phase angle in patients with breast cancer: a systematic review. *Cancers.* (2022) 14:2002. doi: 10.3390/cancers14082002

13. Schwenk A, Beisenherz A, Römer K, Kremer G, Salzberger B, Elia M. Phase angle from bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients in the era of highly active antiretroviral treatment. *Am J Clin Nutr.* (2000) 72:496–501. doi: 10.1093/ajcn/72.2.496

14. Gupta D, Lammersfeld CA, Burrows JL, Dahlk SL, Vashi PG, Grutsch JF, et al. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer. *Am J Clin Nutr.* (2004) 80:1634–8. doi: 10.1093/ajcn/80.6.1634

15. Norman K, Stobäus N, Zocher D, Bosy-Westphal A, Szramek A, Scheufele R, et al. Cutoff percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients with cancer. *Am J Clin Nutr.* (2010) 92:612–9.

16. Barbosa-Silva MC, Barros AJ, Wang J, Heymsfield SB, Pierson RN Jr. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. *Am J Clin Nutr.* (2005) 82:49–52. doi: 10.1093/ajcn.82.1.49

17. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* (2011) 12:489–95. doi: 10.1016/S1470-2045(10)70218-7

18. Toso S, Piccoli A, Gusella M, Menon D, Bononi A, Crepaldi G, et al. Altered tissue electric properties in lung cancer patients as detected by bioelectric impedance vector analysis. *Nutrition.* (2000) 16:120–4. doi: 10.1016/s0899-9007(99)00230-0

19. Gupta D, Lammersfeld CA, Vashi PG, King J, Dahlk SL, Grutsch JF, et al. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in stage IIIB and IV non-small cell lung cancer. *BMC Cancer.* (2009) 9:37. doi: 10.1186/1471-2407-9-37

20. Campa F, Schoenfeld BJ, Marini E, Stagi S, Mauro M, Toselli S. Effects of a 12-week suspension versus traditional resistance training program on body composition, bioimpedance vector patterns, and handgrip strength in older men: a randomized controlled trial. *Nutrients.* (2021) 13:2267. doi: 10.3390/nu13072267

21. Campa F, Silva AM, Toselli S. Changes in phase angle and handgrip strength induced by suspension training in older women. *Int J Sports Med.* (2018) 39:442–9. doi: 10.1055/a-0574-3166

22. Dos Santos L, Cyrino ES, Antunes M, Santos DA, Sardinha LB. Changes in phase angle and body composition induced by resistance training in older women. *Eur J Clin Nutr.* (2016) 70:1408–13. doi: 10.1038/ejcn.2016.124

23. Song M, Zhang Q, Song C, Liu T, Zhang X, Ruan G, et al. The advanced lung cancer inflammation index is the optimal inflammatory biomarker of overall survival in patients with lung cancer. *J Cachexia Sarcopenia Muscle.* (2022) 13:2504–14. doi: 10.1002/jcsm.13032

24. Xie H, Ruan G, Ge Y, Zhang Q, Zhang H, Lin S, et al. Inflammatory burden as a prognostic biomarker for cancer. *Clin Nutr.* (2022) 41:1236–43. doi: 10.1016/j.clnu.2022.04.019

25. Wang X, Yang M, Ge Y, Tang M, Rao B, Chen Y, et al. Association of systemic inflammation and malnutrition with survival in nasopharyngeal carcinoma undergoing chemoradiotherapy: results from a multicenter cohort study. *Front Oncol.* (2021) 11:766398. doi: 10.3389/fonc.2021.766398

26. Di Vincenzo O, Marra M, Di Gregorio A, Pasanisi F, Scalfi L. Bioelectrical impedance analysis (BIA) -derived phase angle in sarcopenia: a systematic review. *Clin Nutr.* (2021) 40:3052–61. doi: 10.1016/j.clnu.2020.10.048

27. Hui D, Bansal S, Morgado M, Dev R, Chisholm G, Bruera E. Phase angle for prognostication of survival in patients with advanced cancer: preliminary findings. *Cancer.* (2014) 120:2207–14. doi: 10.1002/cncr.28624

28. Matthews L, Bates A, Wootton SA, Levett D. The use of bioelectrical impedance analysis to predict post-operative complications in adult patients having surgery for cancer: a systematic review. *Clin Nutr.* (2021) 40:2914–22. doi: 10.1016/j.clnu.2021.03.008

29. Souza NC, Avesani CM, Prado CM, Martucci RB, Rodrigues VD, de Pinho NB, et al. Phase angle as a marker for muscle abnormalities and function in patients with colorectal cancer. *Clin Nutr.* (2021) 40:4799–806. doi: 10.1016/J.CLNU.2021.06.013

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 05 January 2023
DOI 10.3389/fnut.2022.997813

OPEN ACCESS

EDITED BY
Paula Ravasco,
Catholic University of Portugal, Portugal

REVIEWED BY
Antonio Macciò,
Ospedale Oncologico Armando Businco, Italy
Brittany Counts,
Indiana University Bloomington, United States

*CORRESPONDENCE
Maurizio Muscaritoli
✉ maurizio.muscaritoli@uniroma1.it

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 19 July 2022
ACCEPTED 14 December 2022
PUBLISHED 05 January 2023

CITATION
Molfino A, Emerenziani S, Tonini G, Santini D, Gigante A, Guarino MPL, Nuglio C, Imbimbo G, La Cesa A, Cicala M and Muscaritoli M (2023) Early impairment of food intake in patients newly diagnosed with cancer.
Front. Nutr. 9:997813.
doi: 10.3389/fnut.2022.997813

Early impairment of food intake in patients newly diagnosed with cancer

Alessio Molfino[1†], Sara Emerenziani[2†], Giuseppe Tonini[3], Daniele Santini[3], Antonietta Gigante[1], Michele Pier Luca Guarino[2], Chiara Nuglio[2], Giovanni Imbimbo[1], Annalisa La Cesa[3], Michele Cicala[2] and Maurizio Muscaritoli[1*]

[1]Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy, [2]Gastroenterology Unit, Campus Bio-Medico University, Rome, Italy, [3]Oncology Unit, Campus Bio-Medico University, Rome, Italy

Background: Patients with gastrointestinal or lung cancer often suffer from a loss of appetite (anorexia), resulting in reduced food intake (hypophagia) and body weight loss. This study evaluated the prevalence of anorexia, hypophagia, pre-cachexia and cachexia in patients with cancer at time of diagnosis.

Patients and methods: Patients with newly diagnosed gastrointestinal or lung cancers were included. Body mass index (BMI) and weight loss over the prior 6 months were recorded. Patients were assessed for (pre-)cachexia and for anorexia using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) and a specific anorexia questionnaire (AQ). Energy and protein intake were calculated through food diaries. Patients were considered hypophagic if intake was ≤70% of guideline-recommended levels.

Results: Overall, 102 patients [53 male; median age: 67 (range, 21–88) years] were enrolled. Mean BMI (± standard deviation) was 23.1 ± 3.4 kg/m^2; average percentage of weight loss was 10.1 ± 7.8%. At diagnosis, 68% (69/102) of patients had cachexia, and 11% (11/102) pre-cachexia. Prevalence of anorexia was 57% (58/102) and 75% (76/102) according to FAACT and AQ, respectively. Forty-eight percent (49/102) of patients had hypophagia. Patients with anorexia had lower daily energy (p = 0.002) and protein intake (p = 0.0257), and greater percentage of weight loss (p = 0.0005). In patients with hypophagia, negative correlations were observed between percentage of weight loss and total daily calorie (r = −0.40; p = 0.01) and protein intake (r = −0.340; p = 0.018).

Conclusion: Anorexia, inadequate nutritional intake and cachexia are highly prevalent in patients with gastrointestinal or lung cancer at diagnosis. Negative protein and energy balance may play an important role in the pathogenesis of cachexia. Early multimodal strategies to improve food intake are urgently needed.

KEYWORDS

cancer, food intake, early assessment, weight loss, cachexia, anorexia, hypophagia

Introduction

Cachexia is a main cause of morbidity and mortality in chronic conditions such as autoimmune disorders and cancer, particularly in late-stage disease (1). Cancer-associated cachexia is a multifactorial disorder characterized by body weight loss, including skeletal muscle and fat mass, anorexia, and metabolic and endocrine alterations, which cannot be fully reversed by nutritional support alone (2–4). Reduced food intake, a negative energy balance, and chronic inflammation are thought to play crucial roles in the pathogenesis of weight loss and cancer cachexia (3, 5).

The etiology of reduced food intake (i.e., hypophagia) associated with cancer is diverse. Tumor burden or chemotherapy may result in nausea, vomiting, or nutrient malabsorption (1, 6). Decreased upper gastrointestinal motility can also cause nausea and provide a sense of early satiety (7). Other potential causes include dysphagia, stomatitis, bowel obstructions, dyspnea, poor dietary habits, and hormonal changes (4, 6, 7), as well as pain, anxiety, and depression (6). Patients with cancer often also complain of loss of desire to eat, with anorexia further contributing to malnutrition and the onset of cachexia (8).

Cachexia has distinct tumor-driven components. Tumors undergo high rates of glycolysis and lactate production leading to high energy demands, and more-aggressive and advanced stages of cancer are associated with increased energy expenditure (9). Additional metabolic changes may be caused by the activation of the immune system, with chronic inflammation being linked to hypermetabolism (9). Tumor cells secrete pro-inflammatory cytokines that activate the immune system to induce a systemic inflammatory response. Catabolic pro-inflammatory factors acting in skeletal muscle, adipose tissue, and in the central nervous system (CNS) lead to an increase in energy expenditure (3, 8, 9). Of particular importance is the effect of chronic inflammation in the CNS, which can lead to anorexia, weight loss, skeletal muscle atrophy, and lipolysis (3). Based on this view, the action of pro-inflammatory molecules, particularly interleukin (IL)-6, in the hypothalamus may lead to an imbalance between appetite stimulants and suppressants, in turn resulting in anorexia and reduced food intake. In addition, IL-1β and tumor necrosis factor activity in the hypothalamus can trigger production of glucocorticoids by the adrenal gland, leading to skeletal muscle catabolism and rapid induction of atrophy (3).

The combination of reduced energy intake and increased expenditure leads to caloric deficits, which can be as extreme as 1,200 kcal/day (5, 6). Patients with cancer who present with weight loss also have reduced synthesis of muscle proteins; this highlights the importance of reduced dietary intake in the pathogenesis of cancer-associated sarcopenia and cachexia, and stresses the crucial role of generating an anabolic response by supplementation of nutrients able to reactivate protein synthesis (5, 6, 10, 11). Several clinical practice guidelines provide recommendations for the clinical management of cancer cachexia (12–14). Both the European Society for Clinical Nutrition and Metabolism (ESPEN) and European Society for Medical Oncology (ESMO) guidelines provide recommendations on energy and protein requirements, and estimate that total energy expenditure in patients with cancer falls in the range of 25–30 kcal/kg/day (12, 13). Protein intake recommendations set the minimum protein supply at 1 g/kg/day, with a target supply of 1.2–2 g/kg/day (12, 13, 15).

As cancer progresses, energy and protein intake are expected to deteriorate. However, the lack of awareness by many physicians regarding the nutritional status of patients frequently results in progressive and underestimated weight loss until it becomes severe and scarcely treatable (2, 16). In patients with certain types of cancer, such as gastroesophageal cancer, nutritional depletion has been detected already at early disease stages (17), underscoring the need for an early multimodal approach aimed at prevention, early recognition, and treatment of the metabolic and nutritional derangements (18). A reduction in food intake needs to be recognized early and promptly managed, and oral energy intake should be assessed at least qualitatively and, if possible, quantitatively (19).

The aims of the current study were (1) to evaluate the prevalence of anorexia and hypophagia in patients with gastrointestinal or lung cancers at the time of diagnosis, (2) to compare energy and protein intake of patients with guideline recommendations, (3) to assess the prevalence of pre-cachexia and cachexia, and (4) to determine whether nutritional

impairments were already present in these patients prior to any therapeutic intervention. In addition, potential correlations between dietary intake and weight loss were explored.

Patients and methods

Patients

Eligible patients (>18 years) were newly diagnosed with gastrointestinal tract or lung tumors and naive to any oncologic treatment (e.g., chemo- or radiotherapy and surgery). Exclusion criteria included oral feeding incapacity, dysphagia, intestinal obstruction or occlusion, severe liver failure (total bilirubin >1.5 mg/dl, and aspartate aminotransferase/alanine aminotransferase >2 × upper limit of normal or in the case of metastatic liver >5 × upper limit of normal), severe kidney failure (creatinine >2.0 mg/dl and creatinine clearance <50 ml/min), acute decompensated heart failure, active infection, primary or metastatic brain tumor, severe psychiatric disorders, and Mini-Mental State Examination <25/30 in patients >70 years of age.

Study design

This prospective, non-interventional study complied with the principles of the Declaration of Helsinki amended in 2013 and received ethics committee approval at all participating institutions. The study was approved by the local ethics committee at the Campus Bio-Medico University, Rome, Italy. Informed consent was obtained from all patients. During the predefined consecutive period of time from January 2016 to November 2017, all patients in a single center at their first oncology visit who met the eligibility criteria were enrolled.

Assessments

Nutritional status

All patients were evaluated for height and weight, and body mass index (BMI) was calculated. Weight loss over the previous 6 months was recorded (as reported by the patients). The risk of malnutrition was evaluated in all patients using the Malnutrition Universal Screening Tool (MUST), and patients were classified as being at low (MUST score = 0), medium (MUST score = 1), or high (MUST score = 2) nutritional risk (20). Malnutrition was diagnosed on the basis of the Global Leadership Initiative on Malnutrition (GLIM) criteria (21), which requires at least one phenotypic and one etiologic criterion to be present. The phenotypic criteria include unintentional weight loss, low BMI, and low fat-free mass index; etiologic criteria include reduced food intake or assimilation, disease burden, and inflammatory condition. Herein, unintentional weight loss/low BMI were used as phenotypic criteria, and the presence of inflammation [C-reactive protein (CRP)]/reduced food intake or malabsorption as etiologic criteria to diagnose malnutrition.

Anorexia, pre-cachexia, cachexia, and dietary intake assessments

Anorexia was identified by a score of ≤30 on a modified version of the Anorexia/Cachexia Subscale of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire (22, 23). Additionally, anorexia was assessed by a dedicated anorexia questionnaire (AQ) investigating the presence of early satiety, taste/smell alterations, meat aversion, and nausea/vomiting. Patients showing at least one symptom were considered positive for the presence of anorexia (24, 25).

Following standardized criteria, pre-cachexia was defined as ≤5% weight loss over the past 6 months, with anorexia (FAACT score ≤ 30) and inflammation (CRP > 10 mg/L) (26). Cachexia was defined according to Fearon et al. (7) as >5% weight loss over the past 6 months, or BMI <20 kg/m^2 and >2% weight loss.

Trained dietitians collected dietary intake data using a 3 days food record conducted on two non-consecutive weekdays and a weekend day. Energy and protein requirements were estimated following ESPEN and ESMO guidelines: 25–30 kcal/kg of body weight per day for energy intake and 1.2 g/kg of body weight per day for protein intake (12, 13). Hypophagia was defined as an energy intake of ≤70% with respect to the 30 kcal/kg recommendation.

Statistical analysis

A descriptive analysis was performed. Qualitative variables were presented as absolute frequencies and percentages. The normality of the distribution of the continuous quantitative variables was evaluated through the Shapiro-Wilk test; the variables with Gaussian distribution were reported as mean and standard deviation (SD), and those with non-Gaussian distribution as median and interquartile range.

The Mann-Whitney non-parametric test was used to compare daily energy and protein intake of patients with those recommended in ESPEN and ESMO guidelines (12, 13). Correlation analysis was performed using the Pearson correlation coefficient.

A p-value < 0.05 was considered statistically significant and all tests were two-sided. All statistical analyses were performed with the software open-source R version 3.5.1.

Results

In total, 102 patients with cancer (53 male; median age 67 years, range 21–88) were enrolled. Demographic and clinical

characteristics of patients at time of diagnosis are shown in Table 1. Most patients (>80%) had a gastrointestinal tumor, namely gastroesophageal, pancreatic/biliary tract, or colorectal. Overall, 66% (67/102) of patients presented with advanced cancer (stage III–IV), which was more prevalent among patients with gastroesophageal (76%; 19/25) and colorectal tumors (72%; 13/18).

Nutritional status

The mean BMI ± SD in the overall population was 23.1 ± 3.4 kg/m^2 and, on average, patients had experienced weight loss ± SD of 7.6 ± 6.0 kg in the previous 6 months. According to MUST scores, 26.5% (27/102) of patients were at low risk for malnutrition, 23.5% (24/102) were at medium risk, and 50% (51/102) were at high risk. Patients' risk of malnutrition by cancer type is summarized in Table 1. Malnutrition was diagnosed in 59.8% (61/102) of patients, per GLIM criteria. The prevalence of malnutrition was highest among patients with pancreatic/biliary tract cancer (71.4%; 30/42), and lowest in patients with lung cancer (41.2%; 7/17) (Table 1).

Prevalence of pre-cachexia/cachexia, anorexia, hypophagia, and weight loss

At the time of diagnosis, 10.8% (11/102) of patients were pre-cachectic, 67.6% (69/102) were cachectic, and 21.6% (22/102) were not classifiable as pre-cachectic or cachectic (their weight was stable) (Figure 1A). Patients with pancreatic/biliary tract (73.8%; 31/42) or gastroesophageal cancers (72%; 18/25)

TABLE 1 Demographic and clinical characteristics at diagnosis.

Characteristic	Overall population *N* = 102	Gastroesophageal cancer *n* = 25	Pancreatic/Biliary tract cancer *n* = 42	Colorectal cancer *n* = 18	Lung cancer *n* = 17
Proportion of total population, %	100	24.5	41.1	17.6	16.7
Gender, *n* (%)					
Male	53 (51.9)	12 (48.0)	18 (42.9)	10 (55.6)	13 (76.5)
Female	49 (48.0)	13 (52.0)	24 (57.1)	8 (44.4)	4 (23.5)
Age, median (range)	67 (21–88)	67 (36–88)	72 (40–83)	65.5 (31–82)	63.5 (21–83)
Cancer stage, *n* (%)					
I	10 (9.8)	0	3 (7.1)	2 (11.1)	5 (29.4)
II	25 (24.5)	6 (24.0)	15 (35.7)	3 (16.7)	1 (5.9)
III	18 (17.6)	6 (24.0)	5 (11.9)	4 (22.2)	3 (17.6)
IV	49 (48.0)	13 (52.0)	19 (45.2)	9 (50.0)	8 (47.1)
BMI, kg/m^2, mean (SD)	23.1 (3.4)	22.5 (3.4)	23.0 (3.4)	23.9 (2.7)	23.4 (3.6)
BMI < 20 kg/m^2, *n* (%)	16 (15.7)	5 (20.0)	8 (19.0)	0	3 (17.6)
WL, kg, mean (SD)	7.6 (6.0)	8.0 (5.6)	8.2 (5.8)	6.2 (5.3)	6.6 (7.0)
WL, %, mean (SD)	10.1 (7.8)	11.1 (7.3)	11.0 (7.5)	8.1 (7.1)	8.8 (9.0)
6 months WL > 5%, *n* (%)	70 (68.6)	17 (68.0)	30 (71.4)	11 (61.1)	12 (70.6)
CRP[a,b], mg/L, mean (SD)	16.6 (18.4)	19.0 (22.2)	18.5 (17.5)	11.6 (10.9)	14.7 (19.6)
Malnutrition risk (MUST), *n* (%)					
Low	27 (26.5)	6 (24.0)	10 (23.8)	5 (27.7)	6 (35.3)
Medium	24 (23.5)	4 (16.0)	7 (16.6)	9 (50.0)	4 (23.5)
High	51 (50.0)	15 (60.0)	25 (59.5)	4 (22.2)	7 (41.2)
Patients with, *n* (%)					
Malnutrition (GLIM)	61 (59.8)	15 (60.0)	30 (71.4)	9 (50.0)	7 (41.2)
Pre-cachexia	11 (10.7)	2 (8.0)	2 (4.8)	3 (16.7)	4 (23.5)
Cachexia	69 (67.6)	18 (72.0)	31 (73.8)	10 (55.6)	10 (58.8)

[a]A CRP of 10 mg/L was considered the upper limit of normality.
[b]CRP levels were not determined for four patients (*n* = 2 for gastroesophageal cancer; *n* = 1 pancreatic/biliary tract cancer; *n* = 1 lung cancer). BMI, body mass index; CRP, C-reactive protein; GLIM, Global Leadership Initiative on Malnutrition; MUST, Malnutrition Universal Screening Tool; SD, standard deviation; WL, weight loss.

10.3389/fnut.2022.997813

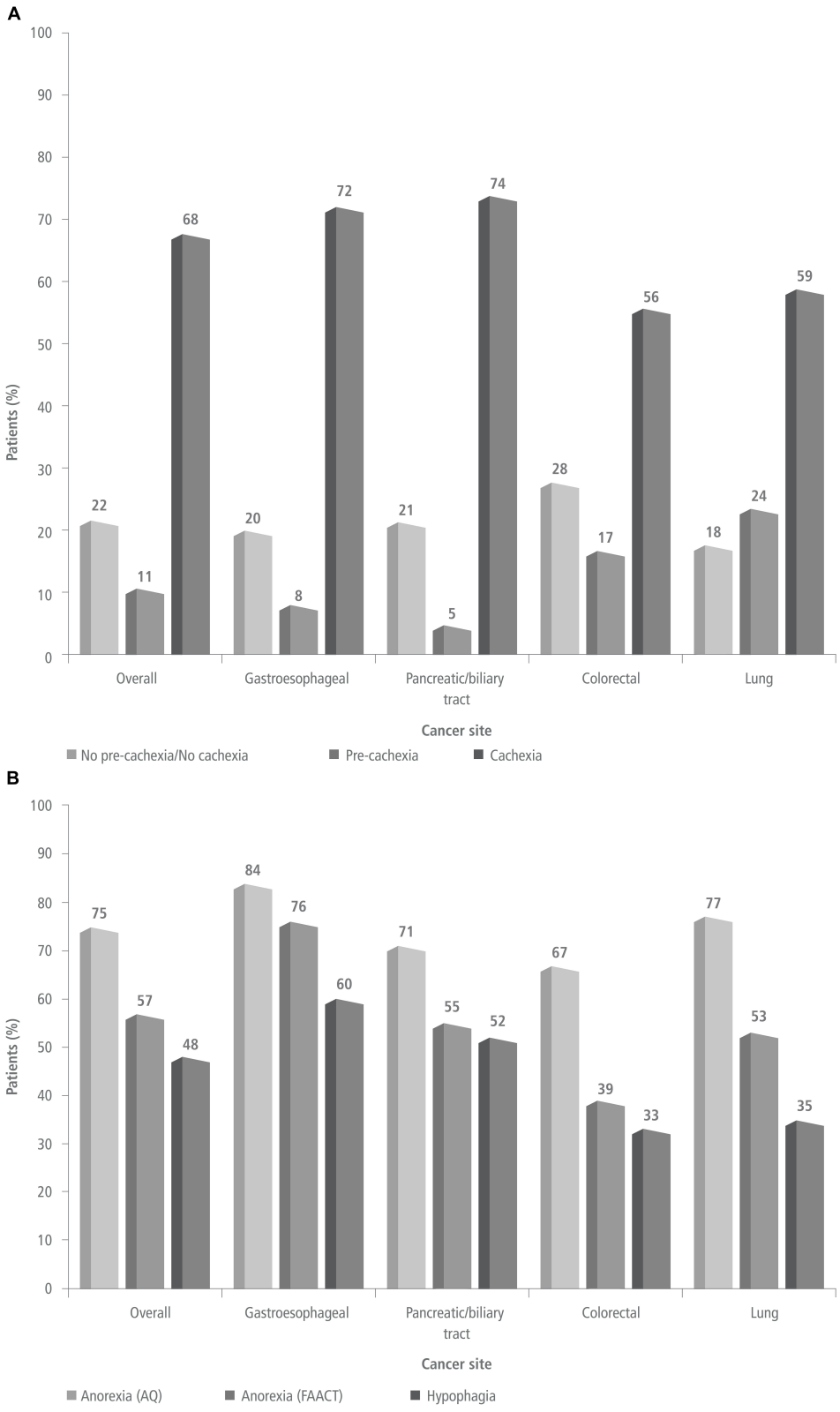


FIGURE 1
Prevalence of pre-cachexia/cachexia [panel **(A)**] and prevalence of anorexia and hypophagia [panel **(B)**] at the time of diagnosis in the overall study population and by cancer site. AQ, anorexia questionnaire; FAACT, functional assessment of anorexia/cachexia therapy.

had a higher prevalence of cachexia than patients with lung (58.8%; 10/17) or colorectal cancers (55.6%; 10/18) (Table 1). Anorexia was present in 56.8% (58/102) of patients per FAACT scores, and in 74.5% (76/102) per AQ results. Anorexia was most prevalent in patients with gastroesophageal cancer, and least prevalent in those with colorectal cancer (Figure 1B). Additionally, 48% (49/102) of patients had hypophagia, and involuntary weight loss in the prior 6 months was documented in 87 of 102 patients (85.2%). Among the patients with pre-cachexia, 7 (64%) were also hypophagic.

Energy and protein intake

In the overall population, patients had significantly lower energy intake compared with the recommended range (25–30 kcal/kg/day) ($p < 0.00001$) (Table 2 and Figure 2). Patients with gastroesophageal cancer had the lowest median energy intake [18.4 kcal/kg/day (13.4–25.6)], whereas patients with colorectal cancer had the highest [23.7 kcal/kg (19.6–26.3)]. Energy intake was significantly below the recommended 30 kcal/kg/day in all patients, except for patients with lung cancer, whose energy intake was below the daily 30 kcal/kg recommendation but the difference did not reach statistical significance. Among patients with gastroesophageal and pancreatic/biliary tract tumors, energy intake was also significantly below the recommended 25 kcal/kg/day limit. Protein intake was significantly below the 1.2 g/kg target in all patient populations, with median protein intake levels being lowest in patients with gastroesophageal cancer (Table 3).

Daily dietary intake and weight loss in patients with and without anorexia

Patients with anorexia had a significantly lower median daily energy intake [1327.5 kcal/day, interquartile range (IQR): 965.5–1263.3] compared with patients without anorexia (1480.2 kcal/day, IQR: 1263.3–1911.0) ($p = 0.002$). Median daily protein intake was also significantly lower among patients with anorexia (55.0 g/day, IQR: 43–72 vs. 62.9 g/day, IQR: 51.3–78.7; $p = 0.0257$). However, no significant differences were observed between patients with and without anorexia in terms of median daily calorie intake/body weight (20.4 kcal/kg, IQR: 13–25.8 vs. 21.5 kcal/kg, IQR: 18.2–27.8, respectively; $p = 0.064$), and median daily protein intake/body weight (0.85 g/kg, IQR: 0.64–1.10 vs. 0.90 g/kg, IQR: 0.77–1.16, respectively; $p = 0.242$). The median percentage of weight loss over the previous 6 months in patients with anorexia was significantly greater (12.4%, IQR: 7.3–17.2) than in patients without anorexia (5.1%, IQR: 0.0–9.8; $p = 0.0005$).

Daily dietary intake and weight loss correlations in patients with and without hypophagia

Among patients with hypophagia ($n = 49$), there was a significant negative correlation between total daily calorie ($r = -0.40$, $p = 0.01$) or protein ($r = -0.340$, $p = 0.018$) intake and percentage of weight loss. In patients without hypophagia ($n = 53$), no correlation was observed between total daily calorie ($r = -0.067$, $p = 0.647$) or protein ($r = -0.047$, $p = 0.751$) intake and percentage of weight loss.

Discussion

The present study demonstrates a high prevalence of anorexia and hypophagia in patients newly diagnosed with cancer and naive to treatment. These patients also present malnutrition and an increased risk for it. Our results align with those in the PreMiO observational study enrolling nearly

TABLE 2 Actual daily energy intake and European Society for Clinical Nutrition and Metabolism (ESPEN)/European Society for Medical Oncology (ESMO)-recommended energy intake.

Population	Median energy intake, kcal/kg (IQR)	Percentage of recommended 25 kcal/kg (IQR)	*P*-value (vs. 25 kcal/kg)	Percentage of recommended 30 kcal/kg (IQR)	*P*-value (vs. 30 kcal/kg)
Overall ($n = 102$)	21.1 (17.3–26.9)	84.4 (69.2–107.6)	0.001	70.3 (57.7–89.7)	< 0.001
Gastroesophageal cancer ($n = 25$)	18.4 (13.4–25.6)	73.6 (53.6–102.4)	0.014	61.3 (44.7–85.3)	< 0.001
Pancreatic/biliary tract cancer ($n = 42$)	20.7 (17.3–24.9)	82.8 (69.2–99.6)	0.004	69.0 (57.7–83.0)	< 0.001
Colorectal cancer ($n = 18$)	23.7 (19.6–26.3)	94.8 (78.4–105.2)	0.538	79.0 (65.3–87.7)	0.013
Lung cancer ($n = 17$)	21.8 (18.2–30.9)	99.0 (72.8–140.4)	1.0	72.7 (60.7–103.0)	0.066

ESMO, European Society for Medical Oncology; ESPEN, European Society for Clinical Nutrition and Metabolism; IQR, interquartile range.

10.3389/fnut.2022.997813

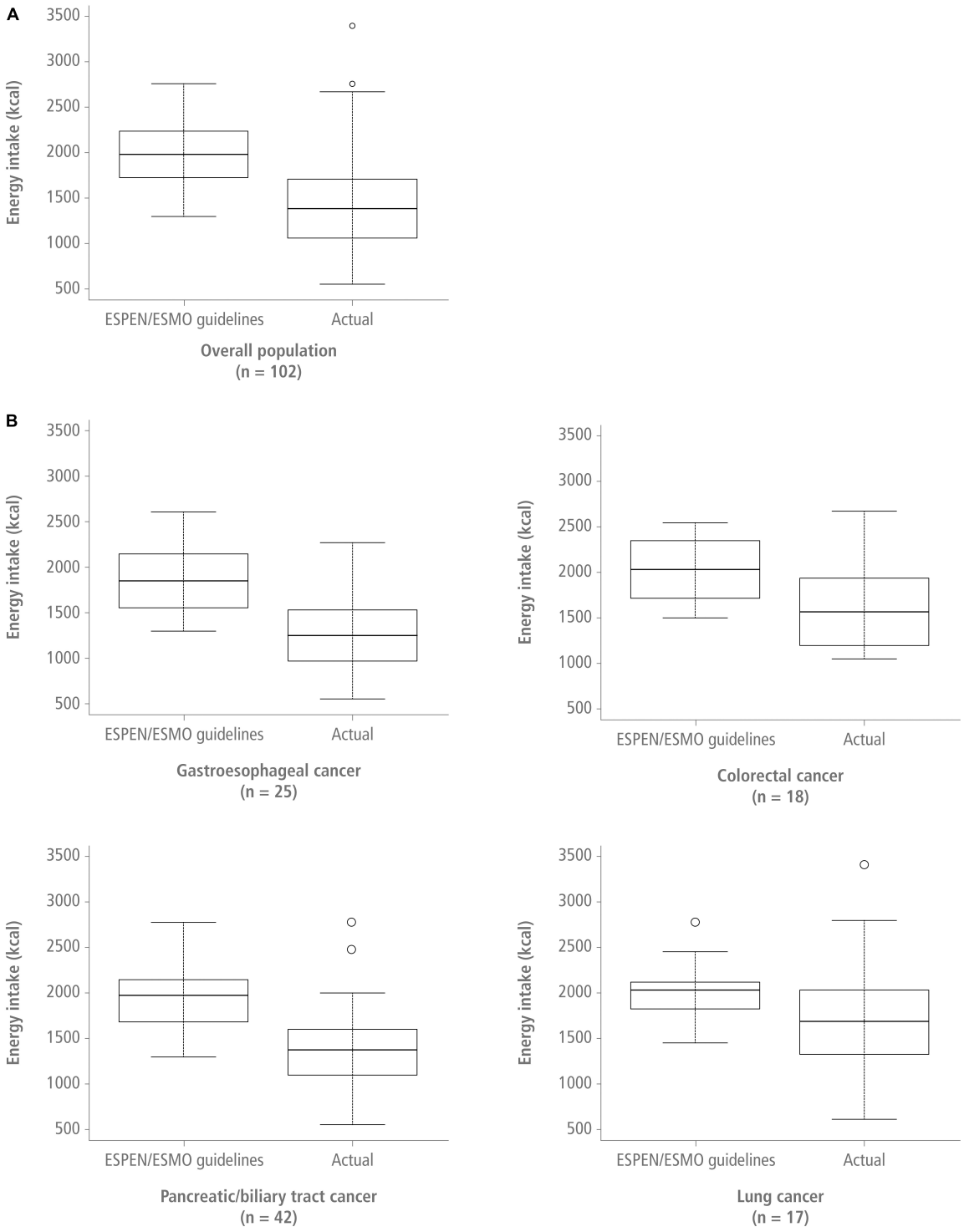


FIGURE 2
Recommended energy intake (upper limit) vs. actual energy intake in the overall population [panel **(A)**] and for the different cancer sites [panel **(B)**] presented as kcal/day. ESMO, European Society for Medical Oncology; ESPEN, European Society for Clinical Nutrition and Metabolism.

2,000 patients with cancer, which reported a 51.1% prevalence of malnutrition (27). Furthermore, we show a high prevalence of cachexia, which was present in almost 70% of patients. Additionally, we show good consistency between high risk for malnutrition, presence of malnutrition, and presence of cachexia, even before anticancer treatment start.

TABLE 3 Actual daily protein intake and European Society for Clinical Nutrition and Metabolism (ESPEN)/European Society for Medical Oncology (ESMO)-recommended protein intake.

Population	Actual protein intake g/kg (IQR)	Percentage of recommended 1.2 g/kg (IQR)	*P*-value (vs. 1.2 g/kg)
Overall (n = 102)	0.9 (0.7–1.1)	75.0 (58.3–91.7)	< 0.001
Gastroesophageal cancer (n = 25)	0.8 (0.6–1.1)	66.7 (50.0–91.7)	0.002
Pancreatic/biliary tract cancer (n = 42)	0.9 (0.7–1.2)	75.0 (58.3–100)	< 0.001
Colorectal cancer (n = 18)	1.0 (0.8–1.2)	83.3 (66.7–100)	0.017
Lung cancer (n = 17)	0.9 (0.8–1.0)	75.0 (66.7–83.3)	0.016

ESMO, European Society for Medical Oncology; ESPEN, European Society for Clinical Nutrition and Metabolism; IQR, interquartile range.

Our study shows that, already at the time of cancer diagnosis, patients' consumption of calories and protein is significantly lower than ESPEN/ESMO recommended values (12, 13), which may have contributed to increased weight loss and malnutrition. Previous studies have demonstrated that malnourishment can negatively impact clinical outcomes in patients with cancer (3, 4). Poor preoperative nutritional status negatively affected postoperative outcomes and was associated with longer hospital stay, while malnutrition correlated with lower tolerance to chemotherapeutic treatment and reduced survival (17, 28, 29). Reduced dietary intake and anorexia have been associated with advanced cancer stage (27, 29), and are main drivers for weight loss (30, 31). Early identification and treatment of reduced food intake and anorexia is recommended in clinical guidelines to potentially prevent weight loss and improve clinical outcomes (12–14). Nevertheless, further research on weight loss and anorexia is still needed (32). Our results highlight the clinical relevance of anorexia and hypophagia in weight loss in patients with cancer. These data are in line with an international study (N = 438) showing a prevalence of anorexia as high as 65.4% detected by AQ, and an association between anorexia and low food intake and weight loss over time (33). Our study revealed a negative correlation between percentage of weight loss and daily calorie or protein intake in patients with hypophagia, supporting the ESPEN/ESMO recommendations to increase dietary intake (12, 13).

Inflammation plays a key role in cancer cachexia (3). Pro-inflammatory cytokines secreted by tumor cells can activate the immune system to induce a systemic inflammatory response, which, if sustained can lead to chronic inflammation. A current study suggests that failure of the immune response to control tumor growth leads to cachexia as a tolerance defense mechanism. At the tolerance stage, cachexia is characterized by the presence of anorexia, anemia, and loss of skeletal muscle and adipose tissue aimed at limiting the tissue damage induced by the tumor and chronic inflammation (34). In our study, the mean values of the acute response protein CRP, indicative of an inflammatory response, were well above the upper limit of normality (10 mg/L) in the overall population (17 mg/L), and particularly among patients with gastroesophageal and pancreatic or biliary tract (19 mg/L for both) cancers.

The main limitation of the present study is that energy intake was calculated using 3-day food diaries in which patients recorded their food and fluid intake. This is a short time frame to capture food intake relative to the weight loss period and it does not identify day-to-day variations in diet. Nevertheless, longer food diaries were not feasible, given the goal to determine dietary intake unaffected by treatment. The use of appetite as a surrogate of food intake is not favored, as these two parameters are only moderately correlated, likely because appetite and food intake represent different aspects of food intake behavior. In fact, appetite is a dimension of ingestive behavior that also includes hunger and satiety, which together influence the food intake outcome (35).

Currently, there is no consensus on how to measure or define reduced food intake, and it has been classified as patient-reported reductions in food intake, or as energy intake below a measured energy expenditure or below the guideline-recommended energy and protein intakes (19, 36). Recently, web-based dietary tools have been developed with validity comparable to traditional methods and may reduce the burden for patients (37). However, despite the limitations of short-time food diaries, this study adds to a growing body of evidence that underscores the importance of identifying patients at risk for malnutrition early in the disease course and implementing appropriate intervention. Further research is warranted in larger patient populations and in a wider range of tumor types. The majority of patients in the current study had gastrointestinal cancers (n = 85), and only a limited number of patients with lung cancer (n = 17) were included. As such, the results for patients with lung cancer need to be interpreted with caution.

In conclusion, anorexia and inadequate nutritional intake are common in patients with gastrointestinal and lung cancer at time of diagnosis, suggesting that nutritional abnormalities may already be present at the onset of cancer. To prevent

the detrimental effects of cachexia, healthcare providers should assess all patients for nutritional status at the earliest opportunity and on an ongoing basis, implementing nutritional interventions as part of routine care. Moreover, since a negative nutritional balance is progressively being recognized as a relevant pathogenic factor in cancer-related malnutrition and cachexia (3, 30, 38), multimodal strategies aimed at improving anorexia and food intake are urgently needed. The present study underscores the need for these interventions to be implemented in the early phases of cancer development.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Local Ethics Committee at the Campus Bio-Medico University, Rome, Italy. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AM, SE, and MM contributed to the conception and design of the study. SE organized the database. DS, MG, and AL enrolled the patients. CN elaborated the food diaries. MC reviewed the manuscript. AM, AG, and GI performed the statistical analysis. AM and MM wrote the first draft of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Funding

Editorial and medical writing assistance was generously funded by Helsinn Healthcare SA. Helsinn played no role in the study design, data collection, or interpretation and writing of the manuscript. The authors are fully responsible for all the content and editorial decisions for this manuscript.

Acknowledgments

Editorial and medical writing assistance was provided by Judith Land, Ph.D., and Sandra Mendes, Ph.D., CMPP (both from Aptitude Health, The Hague, Netherlands).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sadeghi M, Keshavarz-Fathi M, Baracos V, Arends J, Mahmoudi M, Rezaei N. Cancer cachexia: diagnosis, assessment, and treatment. *Crit Rev Oncol Hematol.* (2018) 127:91–104. doi: 10.1016/j.critrevonc.2018.05.006

2. Muscaritoli M, Molfino A, Lucia S, Rossi Fanelli F. Cachexia: a preventable comorbidity of cancer. A T.A.R.G.E.T. approach. *Crit Rev Oncol Hematol.* (2015) 94:251–9. doi: 10.1016/j.critrevonc.2014.10.014

3. Baracos V, Martin L, Korc M, Guttridge D, Fearon K. Cancer-associated cachexia. *Nat Rev Dis Primers.* (2018) 4:17105. doi: 10.1038/nrdp.2017.105

4. Molfino A, Amabile M, Muscaritoli M. Nutrition support for treating cancer-associated weight loss: an update. *Curr Opin Support Palliat Care.* (2018) 12:434–8. doi: 10.1097/SPC.0000000000000383

5. Martin L, Kubrak C. How much does reduced food intake contribute to cancer-associated weight loss? *Curr Opin Support Palliat Care.* (2018) 12:410–9. doi: 10.1097/SPC.0000000000000379

6. Baracos V. Cancer-associated malnutrition. *Eur J Clin Nutr.* (2018) 72:1255–9. doi: 10.1038/s41430-018-0245-4

7. Fearon K, Strasser F, Anker S, Bosaeus I, Bruera E, Fainsinger R, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* (2011) 12:489–95. doi: 10.1016/S1470-2045(10)70218-7

8. Molfino A, Iannace A, Colaiacomo M, Farcomeni A, Emiliani A, Gualdi G, et al. Cancer anorexia: hypothalamic activity and its association with inflammation and appetite-regulating peptides in lung cancer. *J Cachexia Sarcopenia Muscle.* (2017) 8:40–7. doi: 10.1002/jcsm.12156

9. Purcell S, Elliott S, Baracos V, Chu Q, Prado C. Key determinants of energy expenditure in cancer and implications for clinical practice. *Eur J Clin Nutr.* (2016) 70:1230–8. doi: 10.1038/ejcn.2016.96

10. Engelen M, Safar A, Bartter T, Koeman F, Deutz N. High anabolic potential of essential amino acid mixtures in advanced nonsmall cell lung cancer. *Ann Oncol.* (2015) 26:1960–6. doi: 10.1093/annonc/mdv271

11. Engelen M, Klimberg V, Allasia A, Deutz N. Presence of early stage cancer does not impair the early protein metabolic response to major surgery. *J Cachexia Sarcopenia Muscle.* (2017) 8:447–56. doi: 10.1002/jcsm.12173

12. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr.* (2017) 36:11–48. doi: 10.1016/j.clnu.2016.07.015

13. Arends J, Strasser F, Gonella S, Solheim T, Madeddu C, Ravasco P, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines. *ESMO Open.* (2021) 6:100092. doi: 10.1016/j.esmoop.2021.100092

14. Roeland E, Bohlke K, Baracos V, Bruera E, Del Fabbro E, Dixon S, et al. Management of cancer cachexia: ASCO Guideline. *J Clin Oncol.* (2020) 38:2438–53. doi: 10.1200/JCO.20.00611

15. Nitenberg G, Raynard B. Nutritional support of the cancer patient: issues and dilemmas. *Crit Rev Oncol Hematol.* (2000) 34:137–68. doi: 10.1016/s1040-8428(00)00048-2

16. Muscaritoli M, Rossi Fanelli F, Molfino A. Perspectives of healthcare professionals on cancer cachexia: results from three global surveys. *Ann Oncol.* (2016) 27:2230–6. doi: 10.1093/annonc/mdw420

17. Ravasco P, Monteiro-Grillo I, Vidal P, Camilo M. Nutritional deterioration in cancer: the role of disease and diet. *Clin Oncol (R Coll Radiol).* (2003) 15:443–50. doi: 10.1016/s0936-6555(03)00155-9

18. Muscaritoli M, Molfino A, Gioia G, Laviano A, Rossi Fanelli F. The "parallel pathway": a novel nutritional and metabolic approach to cancer patients. *Intern Emerg Med.* (2011) 6:105–12. doi: 10.1007/s11739-010-0426-1

19. Willett W. Dietary assessment methods. *Br J Nutr.* (1995) 74:141–3. doi: 10.1079/bjn19950113

20. Stratton R, Hackston A, Longmore D, Dixon R, Price S, Stroud M, et al. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. *Br J Nutr.* (2004) 92:799–808. doi: 10.1079/bjn20041258

21. Cederholm T, Jensen G, Correia M, Gonzalez M, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - a consensus report from the global clinical nutrition community. *Clin Nutr.* (2019) 38:1–9. doi: 10.1016/j.clnu.2018.08.002

22. Blauwhoff-Buskermolen S, Ruijgrok C, Ostelo R, de Vet H, Verheul H, de van der Schueren M, et al. The assessment of anorexia in patients with cancer: cut-off values for the FAACT-A/CS and the VAS for appetite. *Support Care Cancer.* (2016) 24:661–6. doi: 10.1007/s00520-015-2826-2

23. Ribaudo J, Cella D, Hahn E, Lloyd S, Tchekmedyian N, Von Roenn J, et al. Re-validation and shortening of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. *Qual Life Res.* (2000) 9:1137–46. doi: 10.1023/a:1016670403148

24. Muscaritoli M, Molfino A, Chiappini M, Laviano A, Ammann T, Spinsanti P, et al. Anorexia in hemodialysis patients: the possible role of des-acyl ghrelin. *Am J Nephrol.* (2007) 27:360–5. doi: 10.1159/000103798

25. Arezzo di Trifiletti A, Misino P, Giannantoni P, Giannantoni B, Cascino A, Fazi L, et al. Comparison of the performance of four different tools in diagnosing disease-associated anorexia and their relationship with nutritional, functional and clinical outcome measures in hospitalized patients. *Clin Nutr.* (2013) 32:527–32. doi: 10.1016/j.clnu.2012.11.011

26. Muscaritoli M, Anker S, Argilés J, Aversa Z, Bauer J, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics.". *Clin Nutr.* (2010) 29:154–9. doi: 10.1016/j.clnu.2009.12.004

27. Muscaritoli M, Lucia S, Farcomeni A, Lorusso V, Saracino V, Barone C, et al. Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study. *Oncotarget.* (2017) 8:79884–96. doi: 10.18632/oncotarget.20168

28. Barret M, Malka D, Aparicio T, Dalban C, Locher C, Sabate J, et al. Nutritional status affects treatment tolerability and survival in metastatic colorectal cancer patients: results of an AGEO prospective multicenter study. *Oncology.* (2011) 81:395–402. doi: 10.1159/000335478

29. Ravasco P. Nutrition in cancer patients. *J Clin Med.* (2019) 8:1211. doi: 10.3390/jcm808121129

30. Martin L, Muscaritoli M, Bourdel-Marchasson I, Kubrak C, Laird B, Gagnon B, et al. Diagnostic criteria for cancer cachexia: reduced food intake and inflammation predict weight loss and survival in an international, multi-cohort analysis. *J Cachexia Sarcopenia Muscle.* (2021) 12:1189–202. doi: 10.1002/jcsm.12756

31. Nasrah R, Kanbalian M, Van Der Borch C, Swinton N, Wing S, Jagoe R. Defining the role of dietary intake in determining weight change in patients with cancer cachexia. *Clin Nutr.* (2018) 37:235–41. doi: 10.1016/j.clnu.2016.12.012

32. Cooper C, Burden S, Cheng H, Molassiotis A. Understanding and managing cancer-related weight loss and anorexia: insights from a systematic review of qualitative research. *J Cachexia Sarcopenia Muscle.* (2015) 6:99–111. doi: 10.1002/jcsm.12010

33. Molfino A, de van der Schueren M, Sánchez-Lara K, Milke P, Amabile M, Imbimbo G, et al. Cancer-associated anorexia: Validity and performance overtime of different appetite tools among patients at their first cancer diagnosis. *Clin Nutr.* (2021) 40:4037–42. doi: 10.1016/j.clnu.2021.02.016

34. Maccio A, Sanna E, Neri M, Oppi S, Madeddu C. Cachexia as evidence of the mechanisms of resistance and tolerance during the evolution of cancer disease. *Int J Mol Sci.* (2021) 22:2890. doi: 10.3390/ijms22062890

35. Solheim T, Blum D, Fayers P, Hjermstad M, Stene G, Strasser F, et al. Weight loss, appetite loss and food intake in cancer patients with cancer cachexia: three peas in a pod? - analysis from a multicenter cross sectional study. *Acta Oncol.* (2014) 53:539–46. doi: 10.3109/0284186X.2013.823239

36. Bingham S, Gill C, Welch A, Day K, Cassidy A, Khaw K, et al. Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. *Br J Nutr.* (1994) 72:619–43. doi: 10.1079/bjn19940064

37. Conrad J, Koch S, Nöthlings U. New approaches in assessing food intake in epidemiology. *Curr Opin Clin Nutr Metab Care.* (2018) 21:343–51. doi: 10.1097/MCO.0000000000000497

38. Marín Caro M, Laviano A, Pichard C. Nutritional intervention and quality of life in adult oncology patients. *Clin Nutr.* (2007) 26:289–301. doi: 10.1016/j.clnu.2007.01.005

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 09 January 2023
DOI 10.3389/fnut.2022.974389

OPEN ACCESS

EDITED BY
Paula Ravasco,
Catholic University of Portugal, Portugal

REVIEWED BY
Nicholas John Geraghty,
University of Wollongong, Australia
Shigeo Fuji,
Osaka International Cancer Institute, Japan

*CORRESPONDENCE
Yongjun Fang
✉ fyj322@189.cn
Weibing Tang
✉ twbcn@163.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 21 June 2022
ACCEPTED 20 December 2022
PUBLISHED 09 January 2023

CITATION
Yan M, Pan J, Huang J, Liu C, Xia X, Zhu T, Wan Y, Fang Y and Tang W (2023) Weight loss in children undergoing allogeneic hematopoietic stem cell transplantation within the first 100 days: Its influencing factors and impact on clinical outcomes.
Front. Nutr. 9:974389.
doi: 10.3389/fnut.2022.974389

Weight loss in children undergoing allogeneic hematopoietic stem cell transplantation within the first 100 days: Its influencing factors and impact on clinical outcomes

Mei Yan[1†], Jian Pan[1†], Jie Huang[2†], Changwei Liu[1], Xiaona Xia[1], Ting Zhu[1], Yuanyuan Wan[1], Yongjun Fang[2*] and Weibing Tang[1*]

[1]Department of Clinical Nutrition, Children's Hospital of Nanjing Medical University, Nanjing, China, [2]Department of Hematology and Oncology, Children's Hospital of Nanjing Medical University, Nanjing, China

Purpose/Objective: This study aimed to evaluate the nutritional status of children subjected to allogeneic hematopoietic stem cell transplantation (alloHSCT) in the first 100 days. Objectives were to clarify the effect of weight loss on clinical outcomes, and to analyze factors influencing weight loss.

Methods: Eighty pediatric patients receiving alloHSCT were enrolled in the study. Body mass index (BMI) z-scores and weight for age (WFA) z-scores were collected. A multivariate regression model was set up to investigate factors affecting weight loss. Post-transplant clinical outcomes relative to weight loss on 100 days after transplantation were analyzed.

Results: At admission, eight patients (10%) were underweight, the number had increased to 23 (30.67%) by 100 days post-HSCT. On day + 100, only nutrition screening tool for childhood cancer (SCAN) scores $\geq$ 3 (OR: 4.474, 95% CI: 1.215, 16.472; $P = 0.024$) and acute graft versus host disease (aGVHD) (OR: 9.915, 95% CI: 3.302, 29.771; $P < 0.001$) were regarded as significant influencing factors of weight loss. The Weight loss $\geq$ 5% group was associated with longer hospital stays ($P = 0.001$), greater cost of inpatient treatment ($P = 0.001$), and a higher incidence of 100-day re-admission and intensive care unit (ICU) transfer ($P = 0.03$ and $P = 0.033$, respectively). Cumulative number of fever days ($P = 0.023$) and antibiotic use ($P = 0.007$) also increased significantly. The Weight loss $\geq$ 5% group had a significantly lower one-year overall survival rate compared with the Weight loss $<$ 5% group ($P = 0.015$).

Conclusion: Pediatric patients' nutritional status declined significantly after HSCT. Weight loss within the first 100 days influenced short-term clinical outcomes and one-year overall survival.

KEYWORDS

pediatric, weight (mass), allo and autologous transplantation, screening tools, graft versus host disease

Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a complex and effective therapy for hematologic malignant and non-malignant diseases in adult and pediatric patients (1). However, myeloablative (MAC) or reduced intensity conditioning (RIC) regimens and complications of alloHSCT often cause patients undergoing HSCT to experience loss of appetite, mucositis, vomiting, and diarrhea (2). Acute graft versus host disease (aGVHD) is a major complication of alloHSCT. It is an immune disorder characterized by disrupting particular organs, consisting of the skin, gastrointestinal tract and liver, which can lead to insufficient caloric intake (3). Energy and protein requirements increase in HSCT because of the intense catabolism and the demands of physical growth in children (4). Thus, malnutrition and weight loss are common in pediatric patients.

Malnutrition is usually assessed by body mass index (BMI) and body weight for age (WFA) z-scores. BMI and weight typically decline consistently following HSCT (5). Weight loss were reported in patients at different periods of alloHSCT. A previous study showed almost 70% of adult patients had weight loss greater than 5% within 30 days (6). Urbain et al. reported that 23.8% adult patients at admission had significant weight loss (>5%) in the previous 6 months (7). Fuji found 63.5% (92/145) patients lost weight $\geq$ 5% during HSCT (8). Nutritional status is constantly changing. However, in clinical practice, many physicians are not aware of the subtle changes that contribute to weight loss over time.

Some studies have shown that weight loss in pediatric patients undergoing HSCT is associated with poor outcomes (9), and these works mainly focused on weight loss before HSCT. Weight loss following transplantation has been studied less in children. And questions remain about whether weight loss post-transplantation is associated with clinical outcomes, especially in children. Thus, the present study had two aims. First, we set out to document the nutritional status of pediatric patients with alloHSCT. Second, we aimed to evaluate the impact of weight loss on the clinical outcomes after alloHSCT, and to analyze factors affecting weight loss after HSCT. Ultimately, we sought to contribute information on appropriate timing and nutritional support to improve clinical outcomes for pediatric patients undergoing alloHSCT.

Materials and methods

Participants

Children were involved in this study if they were younger than 18 years, and had undergone alloHSCT at Children's Hospital of Nanjing Medical University between April 2018 and April 2022.

To prevent the occurrence of aGVHD, all pediatric patients received intravenous cyclosporine (CsA) at a dose of 1∼3 mg/kg/day combined with methotrexate (MTX), 15 mg/m^2 given on day 1 and 10 mg/m^2 on day 3 and 6. When grade II to IV aGVHD presents, methylprednisolone (2 mg/kg/day) along with CsA was added. If glucocorticoid resistance occurred, tacrolimus, antithymocyte globulin, mycophenolate mofetil and other second-line drugs should be added.

Dieticians regularly evaluated the dietary intake of children undergoing allo-HSCT. Children received EN and/or PN if their dietary intakes were insufficient.

Patients were grouped into a Weight loss < 5% group and a Weight loss $\geq$ 5% group. Weight loss after alloHSCT was operationally defined as the relative difference (%) between weight at engraftment and minimum weight over day 100 post-HSCT, or one week before death if patients died within the 100-day period.

The study was approved by the Ethics Committee of the Children's Hospital of Nanjing Medical University.

Assessment of nutritional status

Body weight and height were collected at admission and on the day of transplantation, and then on days 7 (day + 7), 14 (day + 14), 21 (day + 21), 30 (day + 30), and 100 (day + 100) days post-HSCT. BMI and WFA z-scores of patients under 5-years of age were calculated using WHO Anthro, and WHO

AnthroPLUS for children older than 5.[1] Nutritional status was categorized into three groups as follows: underweight (BMI z-scores ≤ -2), average-weight ($-2 <$ BMI z-scores < 2), overweight or obese (BMI z-scores ≥ 2).

Nutrition screening tool for childhood cancer (SCAN)

Screening tool for childhood cancer is a nutritional screening tool focusing on children with cancer (10). It is based on six questions: high risk cancer, intensive treatment, gastrointestinal symptoms, poor oral intake, weight loss, and signs of under nutrition. Score of 1 or 2 is for each question, with a maximum score of 10 points. Scores ≥ 3 indicate children are at risk of malnutrition and need dieticians for further evaluation.

Definitions of transplantation parameters

Acute graft versus host disease (aGVHD) was graded according to symptoms of skin, liver, and the gut, as documented in previous work (11). Clinical outcomes included the duration of hospital stay, and the costs of inpatient treatment during hospitalization. The duration of antibiotic and corticosteroid use, cumulative number of days with fever were calculated from transplantation to hospital discharge. Other outcomes were transfer to the intensive care unit (ICU) during hospitalization and hospital re-admissions within 100 days post-transplantation. Overall survival (OS) was defined as time from engraftment to death from any reason within one year after alloHSCT. Treatment-related mortality (TRM) was defined as death without relapse or disease progression within one year after alloHSCT. Cumulative incidence of relapse (CIR) was defined as time to recurrence of disease within one year after alloHSCT.

Statistical analysis

SPSS 17.0 software and Stata 16 were used for data analysis. We used the median (P25, P75) [M (P25, P75)] to describe data that was not normally distributed, and mean ± standard deviation to describe normally-distributed data. Repeated measurements analysis of Variance (RM-ANOVA) was used for multigroup comparison. The Mann–Whitney U test was used to compare two groups with non-normal data distribution. The Chi square test was used to compare categorical data. To identify the influence of potential factors on weight loss, we used binary logistic regression models with weight loss (yes or no) as the dependent variable. First, univariate models were used to assess single variable. Then, a multivariate model was built containing three variables (donor status, aGVHD, SCAN). The probability and curve of OS and TRM were computed using Kaplan–Meier survival analysis. A Cox proportional hazards regression model was applied to analyze OS. Univariate model was used to assess single variable. Multivariate model was built by choosing covariates with $P < 0.1$ in the univariate model. Directed acyclic graph is used for the chosen of confonders in multivariable analysis. We used the method of Fine and Gray for univariate and multivariate analysis of TRM and CIR. In the competing risk models for TRM, CIR was defined as a competing risk. Patients who could not be followed up were tracked in terms of their final follow-up data and were analysed as censored data. $P < 0.05$ was considered as statistically significant.

Results

Patient characteristics

Characteristics of the children undergoing alloHSCT are exhibited in **Table 1**. Eighty children undergoing alloHSCT were included in the study. The sample comprised 61.25% male and 38.75% female patients, and the median age was 5.75 years. The most common donor type was matched unrelated donors (56.25%). Fifty-seven patients (71.25%) received the MAC regimen while 23 (28.75%) followed the RIC regimen. At admission, 69 patients (86.25%) had a BMI within the normal range, while 10% were underweight, and 3.75% were overweight or obese. At engraftment, 66 patients (82.5%) were of an average weight while 13.75% were underweight, and 3.75% were overweight or obese. The number of underweight patients rose to 23 (30.67%) at day + 100 post-HSCT. The mean weight loss was 0.55 ± 2.51 kg, and 15 patients (18.75%) lost 5–10% body weight with 20 (25%) losing over 10% weight. The primary diagnoses were aplastic anemia (25%) and acute myeloid leukemia (23.75%). Other diagnoses included acute lymphoid leukemia, myelodysplastic syndrome, juvenile granular monocytic leukemia, acute biphenotypic leukemia, congenital thrombocytopenia, immunodeficiency disease, thalassemia, dyskeratosis congenita, and so on. 62.5% (50/80) of the patients were diagnosed with aGVHD following HSCT, Grade II-IV aGVHD occurred in 33 patients (41.25%). Cumulative incidences of aGVHD in each organ: skin 17 (21.25%), gut 31 (38.75%), liver 2 (2.5%). At admission, 20 patients (25%) were with SCAN scores ≥ 3.

1 http://www.who.int/childgrowth/software/en/

TABLE 1 Characteristics of child participants in the study.

Characteristic		
Median age, years (P25–P75)		5.75 (2.77–9.61)
Sex, *n* (%)		
	Female	31 (38.75)
	Male	49 (61.25)
Diagnosis, *n* (%)	**Malignant diseases**	
	Acute myeloid leukemia	19 (23.75)
	Acute lymphoid leukemia	4 (5.00)
	Juvenile granular monocytic leukemia	2 (2.50)
	Myelodysplastic syndrome	2 (2.50)
	Acute biphenotypic leukemia	2 (2.50)
	Chronic granulocytic leukemia	3 (3.75)
	Hemophagocytic syndrome	4 (5.00)
	EBV associated T-cell leukemia	1 (1.25)
	Neuroblastoma	1 (1.25)
	Non-malignant diseases	
	Aplastic anemia	20 (25.00)
	Immunodeficiency disease	8 (10.00)
	Thalassemia	3 (3.75)
	Dyskeratosis congenita	1 (1.25)
	Mucopolysaccharidosis	4 (5.00)
	Chronic granulomatous disease	1 (1.25)
	Adrenoleukodystrophy	1 (1.25)
	Congenital thrombocytopenia	2 (2.50)
	Congenital neutropenia	1 (1.25)
	Fucosidosis	1 (1.25)
Type of transplant, *n* (%)		
	Matched Related	35 (43.75)
	Matched Unrelated	45 (56.25)
Conditioning regimens, *n* (%)		
	MAC	57 (71.25)
	RIC	23 (28.75)
BMI at admission, *n* (%)		
	Underweight	8 (10.00)
	Average weight	69 (86.25)
	Overweight or obese	3 (3.75)
BMI at engraftment, *n* (%)		
	Underweight	11 (13.75)
	Average weight	66 (82.5)
	Overweight or obese	3 (3.75)
BMI at day + 100 post-HSCT, *n* (%)		
	Underweight	23 (30.67)
	Average weight	50 (66.67)
	Overweight or obese	2 (2.66)
SCAN at admission, *n* (%)		
	Score ≥ 3 points	20 (25.00)
	Score < 3 points	60 (75.00)
Weight loss after 100 days post-HSCT, *n* (%)		
	Mean ± SD (kg)	0.55 ± 2.51
	<5% weight loss	45 (56.25)
	5–10% weight loss	15 (18.75)
	>10% weight loss	20 (25.0)
aGVHD, *n* (%)		
	Grade 0-I aGVHD	47 (58.75)
	Grade II-IV aGVHD	33 (41.25)
acute gastrointestinal GVHD		31 (38.75)
acute Hepatic GVHD		17 (21.25)
acute cutaneous GVHD		2 (2.5)

MAC, myeloablative regimens; RIC, reduced intensity conditioning regimens; BMI, body mass index; HSCT, hematopoietic stem cell transplantation; SCAN, nutrition screening tool for childhood cancer; Grade II-IV aGVHD, moderate and severe acute graft versus host disease; and Grade 0-I aGVHD, none and mild acute graft versus host disease.

Nutritional assessment of children before and after alloHSCT

Patients' BMI and WFA z-scores are shown in Figure 1. The longitudinal data reveals that both BMI z-scores ($F = 16.467$, $P < 0.001$) and WFA z-scores ($F = 21.07$, $P < 0.001$). BMI z-scores declined from -0.14 ± 1.41 at admission to -0.47 ± 1.47 at engraftment, and the minimum level observed was -1.05 ± 1.67 at day + 100. Simultaneously, WFA z-scores declined from -0.22 ± 1.17 at admission to -0.42 ± 1.19 at engraftment, and the minimum level observed was -1.08 ± 1.37 on day + 100.

Impact of factors influencing weight loss

Univariate analysis indicated that donor status ($P = 0.018$), aGVHD ($P < 0.001$), oral mucositis ($P = 0.014$), duration of corticosteroid ($P = 0.001$) and Nutrition screening tool for childhood cancer (SCAN) scores ≥ 3 ($P = 0.002$) were strongly associated with weight loss ≥ 5%. A multivariate regression model was developed with variables (donor status, aGVHD, SCAN) displaying a connection ($P < 0.1$) with weight loss. However, only SCAN scores ≥ 3 (OR: 4.474, 95% CI: 1.215, 16.472; $P = 0.024$) and presence of ≥grade II acute GVHD (OR:

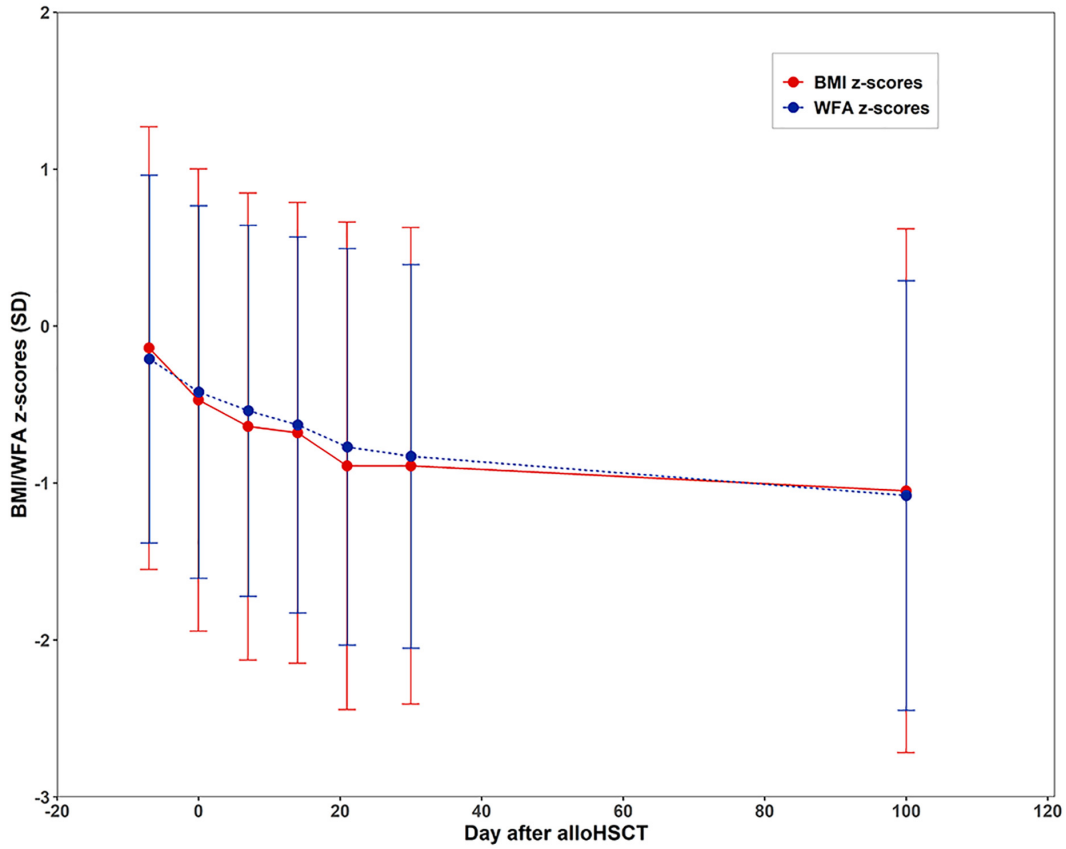


FIGURE 1
Changes of mean body mass index (BMI) z-scores and weight for age (WFA) z-scores during treatment of alloHSCT (at initial admission and the day of transplantation, day + 7, day + 14, day + 21, day + 30, and day + 100 after HSCT).

TABLE 2 Results of univariate and multivariate analyses of factors affecting weight loss ≥ 5%.

Univariate analysis			
Variables		OR (95% CI)	*P*-value
Age at admission	<5 years old vs. ≥5 years old	1.125 (0.459–2.758)	0.797
Sex	Female vs. Male	1.684 (0.679–4.180)	0.261
Diagnosis	Non-malignant diseases vs. Malignant diseases	0.615 (0.253–1.499)	0.285
Donor status	Unrelated vs. Related	3.125 (1.221–8.00)	0.018
Conditioning chemotherapy	Reduced intensity vs. Myeloablative	0.766 (0.286–2.055)	0.597
BMI at admission	Underweight vs. Average weight or Overweight	0.394 (0.074–2.085)	0.273
Oral mucositis	Positive vs. Negative	3.273 (1.266–8.458)	0.014
SCAN at admission	Scores ≥ 3 vs. Scores < 3	6.000 (1.908–18.867)	0.002
aGVHD	II-IV vs. 0-I	11.562 (4.009–33.345)	<0.001
Duration of corticosteroid		1.032 (1.012–1.052)	0.001
Multivariate analysis			
SCAN at admission	Scores ≥ 3 vs. Scores < 3	4.474 (1.215–16.472)	0.024
aGVHD	II-IV vs. 0-I	9.915 (3.302–29.771)	<0.001

Duration of corticosteroid is linear categories. SCAN, nutrition screening tool for childhood cancer; Grade II-IV aGVHD, moderate and severe acute graft versus host disease; and Grade 0-I aGVHD, none and mild acute graft versus host disease.

9.915, 95% CI: 3.302, 29.771; $P < 0.001$) were recognized as independent effect factors of weight loss in the 100 day period following HSCT (Table 2).

Post-transplant clinical outcomes relative to weight loss 100 days after transplantation

The length of hospital stay was longer in the Weight loss ≥ 5% group than the Weight loss < 5% group ($P = 0.001$) (Median: 83.0 vs. 65.0 days; Quartile: 67–110 vs. 55.5–79.5). Patients in the Weight loss ≥ 5% group had higher costs of inpatient treatment (Median: 239254.72 vs. 198188.38 CNY; Quartile: 201517.55–345488.63 vs. 160378.865–234428.355) than the Weight loss < 5% group. A longer duration of cumulative febrile episodes ($P = 0.023$), and antibiotic use ($P = 0.007$) were observed in the Weight loss ≥ 5% group. A higher incidence of 100-day re-admission ($P = 0.03$) and ICU transfer ($P = 0.033$) was also noted (Table 3).

There are 10 patients died in one year after alloHSCT. Two patients died of refractory disease progression or relapses. 8 of 10 patients died of transplant-associated complications, the causes of death were pulmonary infection ($n = 4$), heart failure ($n = 1$), aGVHD-related ($n = 3$). Kaplan Meier curves of one-year overall survival for the Weight loss < 5% group and the Weight loss ≥ 5% group indicated survival of 95.6 versus 77.1%, and means of 355.93 versus 306.72 days, respectively (Log rank, $P = 0.015$) (Figure 2). The Cox multivariate analysis revealed that Weight loss ≥ 5% (HR: 5.585, 95% CI: 1.183, 26.357; $P = 0.03$) and relapse (HR: 6.315, 95% CI: 1.285, 31.039; $P = 0.023$) had significant impacts on OS (Supplementary Table 1). One year OS for Weight loss < 5% group and Weight loss ≥ 5% groups was 97.4 versus 84.6%, respectively ($P = 0.045$) after excluding patients who died or suffered from relapse/progression within 100 days (Supplementary Figure 1).

The cumulative incidence of TRM at one year was 17.1% in the Weight loss ≥ 5% group, 4.4% in the Weight loss < 5% group (Log rank, $P = 0.058$) (Figure 3). Weight loss ≥ 5% was not associated with increased TRM (HR: 4.07, 95% CI: 0.83, 20.03; $P = 0.084$). After adjustment for age, diagnosis, gender, donor type, conditioning regimen, and aGVHD, weight loss ≥ 5% was not associated with an increased risk of TRM (HR: 3.65, 95% CI: 0.60–22.12; $P = 0.159$) (Supplementary Figure 2).

Discussion

In this study, 10% of patients were underweight in the pre-HSCT stage. These findings align with previous literature where most children are well-nourished, and the prevalence of underweight children ranges from 4 to 16.3% (12, 13). In previous studies, the percentage of overweight children ranges from 12 to 15% (12, 14). However, our study showed only three children (3.75%) were overweight or obese. This indicates that children undergoing HSCT in China might have a lower rate of over nutrition than their peers in developed countries. Inaba et al. (15) concluded that BMI z-scores in children with hematologic malignancies after alloHSCT declined significantly over time. Similarly, Campos et al. (5) identified a significant BMI decrease in pediatric patients in the 6-month period post-HSCT. We found that nutritional status of children deteriorated gradually in the 100 days after HSCT, with the lowest BMI z-scores on day 100. Weight loss (≥5%) was observed in 35 patients (43.75%) in our sample.

Nutritional status was traditionally assessed by anthropometric and laboratory measurements. In recent years, body composition measurement has become an important indicator reflecting nutritional status of pediatric patients (16). However, in developing countries, its application is restricted as the measuring instrument includes bioelectrical impedance analysis (BIA) and Dual-energy X-ray absorptiometry (DXA)–tools which are expensive and often impractical in such settings. Albumin levels can also be affected by several non-nutritional factors (15). Anthropometry mainly includes BMI and weight. Children are split into four groups: normal, wasted, severely wasted, overweight or obesity on the basis of BMI/WFA z-scores. BMI levels at different stages of HSCT have different effects on survival. However, it only represents weight in relation to height, BMI z-scores remain unchanged in the course of treatment, possibly because weight and height z-scores both decrease. Therefore, BMI/WFA z-scores alone are not very reliable to evaluate nutritional status. It should combine with weight and height change to monitor nutritional status. In comparison, periodic measurements of body weight are an easy and convenient way to assess nutritional status and can effectively contribute to nutritional improvement.

We analyzed factors that might influence weight loss in the 100-day period in children undergoing alloHSCT. Oral mucositis and ≥grade II aGVHD were found to have a significant effect on weight loss over day 100. Oral mucositis is a common complication of alloHSCT, resulting from the conditioning regimen and radiotherapy. It leads to destruction of the oral mucosal barrier and impairs oral intake because of chewing and swallowing difficulties (16). Fat-free mass index, and muscle mass demonstrate a significant decline in adult patients with severe mucositis (17). Feng et al. (18) found that glucocorticoid treatment and mucositis occurrence affected BMI z-scores and arm muscle area index in children undergoing allogeneic HSCT. Eduardo et al. (19) showed that oral mucositis was not an independent factor for weight loss in adult patients undergoing alloHSCT but was an independent factor for weight gain in HSCT. In our study, oral mucositis was strongly correlated with weight loss ≥ 5% in the univariate analysis, but was not pinpointed as an independent factor in the multivariate regression. This finding may have been restricted by the limited

TABLE 3 Post-transplant clinical outcomes relative to weight loss after transplantation.

Variable (n = 80)	Weight loss ≥ 5% (n = 35)	Weight loss < 5% (n = 45)	Parameter estimate	P-value
Median duration of hospital stay (IQR), Days	83 (67, 110)	65 (55.5, 79.5)	Z = −3.245	0.001
Median costs of inpatient treatment (IQR), CNY	239254.72 (201517.55,345488.63)	198188.38 (160378.865,234428.355)	Z = −3.302	0.001
Median length of cumulative febrile episodes (IQR), Days	10 (5, 19)	7 (2, 13)	Z = −2.279	0.023
Median duration of Antibiotic Use (IQR), Days	42 (30.0, 72.0)	33 (20.0, 48.5)	Z = −2.712	0.007
100-day re-admission, n (%)	21 (60)	16 (35.6)	χ^2 = 4.732	0.030
ICU transfer, n (%)	8 (22.86)	2 (4.44)	χ^2 = 4.535	0.033

ICU, intensive care unit; CNY, Chinese Yuan; and IQR, interquartile range.

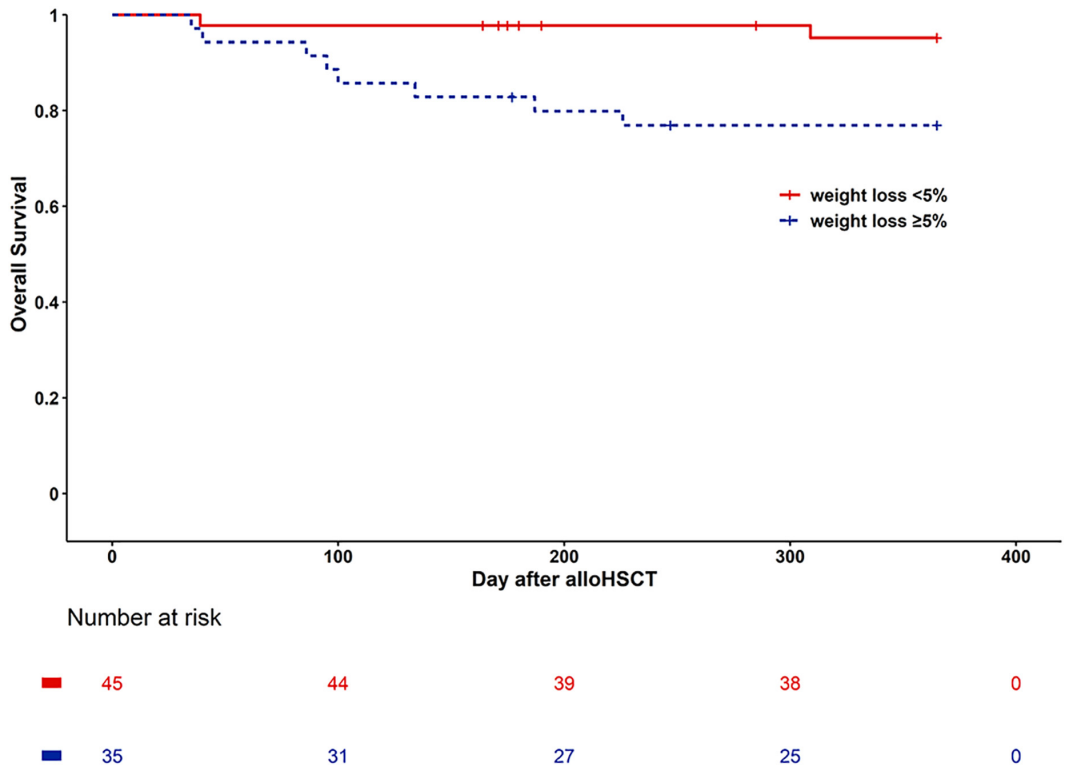


FIGURE 2
Kaplan Meier curves of survival for weight loss < 5% group (continuous line) and weight loss ≥ 5% (dashed line).

number of patients in our sample. Aggressive treatment of mucositis in patients starting to develop the condition may help improve their nutritional intake and prevent deterioration in nutritional status.

Urbain et al. (7) found that presence of ≥grade II aGVHD was an independent factor influencing weight loss in adults. Similarly, El-Ghammaz et al. (20) showed that nutritional status of adult patients experiencing ≥grade II aGVHD worsened during hospitalization and after discharge. Our study also supports these findings–presence of ≥grade II aGVHD had a significant influence on weight loss by day 100, according to the multivariate analysis. Corticosteroid and immunosuppressive drugs used for treatment of aGVHD have negative effects on muscle metabolism after HSCT (21). Some studies indicated that fat-free tissues in children with aGVHD after alloHSCT were more likely to be affected (18). Most children with aGVHD are not physically active, compounding the muscle degradation from steroids. Previous research demonstrated a significant correlation between physical function and quality of life in patients receiving HSCT (22). Therefore, prevention and treatment of aGVHD must be prioritized because of its high morbidity. Nutritional and exercise interventions are an important component of treatment for children with aGVHD.

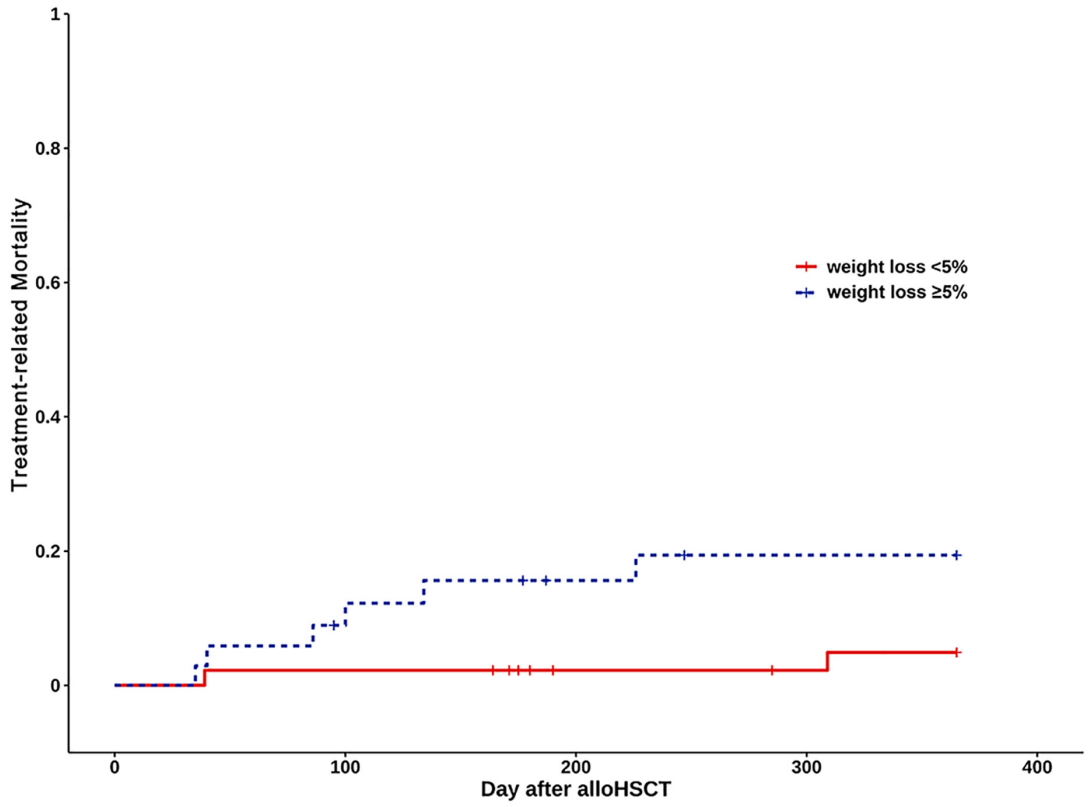


FIGURE 3
Kaplan Meier curves of treatment-related mortality (TRM) for weight loss < 5% group (continuous line) and weight loss ≥ 5% (dashed line).

According to ASPEN, all patients undergoing HSCT are at nutrition risk and should screening nutritional risk (23). There are some nutrition screening tools focus on children, but none are able to reach all the requirements of a cancer special tool. SCAN according to Murphy et al. (10) offers a simple way to identify pediatric patients with cancer who are already malnourished or at risk of malnutrition. It considers cancer type and treatment, not only nutrition related symptoms. To date, there are few studies of the application of SCAN. In our study, SCAN was shown to have prognostic associations with weight loss ≥ 5% after transplantation. SCAN is, thus, recommended as a key part of the comprehensive assessment of nutritional status in children undergoing HSCT. Children with SCAN scores ≥ 3 are at risk of malnutrition and need periodical assessment of nutrition.

Weight loss is included in some nutritional screening tools. For example, STRONG kids (24) includes weight loss as a main aspect, although the degree of weight loss has not been quantified. Fuji et al. (8) found that weight loss in adult patients undergoing HSCT has a significant effect on clinical outcomes, after assessing BMI and weight loss as part of nutritional screening. Ando et al. (9) noted that weight loss in the period from diagnosis to transplant was associated with worse OS and graft-versus-host disease-free survival for adults with acute myeloid leukemia following HSCT. Weight loss > 7% during alloHSCT (from admission to the first outpatient visit) was associated with increased time in hospital (25). These reports focus on weight loss in adult populations, but comparable data for children post-transplantation are scarce. The present study revealed that weight loss in children undergoing HSCT was associated with longer hospital stays, longer duration of antibiotic use. Children in the Weight loss ≥ 5% group also experienced greater duration of cumulative febrile episodes than the Weight loss < 5% group. Weight loss after alloHSCT was connected with lower OS. It also has higher TRM, although there is of no statistical significance. Thus, it is rational to use weight loss ≥ 5% in the 100 days following HSCT to identify pediatric patients at risk of poor clinical outcomes. Moreover, weight loss remain easy and effective ways to recognized patients at nutritional risk.

If inadequate oral intake or weight loss is detected, children should accept nutritional support so as to maintain their nutritional status. The Harris-Benedict formula is usually used to determine the target caloric intake (26). Enteral nutrition

(EN) is always favored as the first option compared to parenteral nutrition (PN). PN was administered mainly in cases of gastrointestinal failure. However, in clinical practice, PN is often preferred over EN owing to practical reasons such as the intolerance of nasogastric tubes. In our study, 43 cases received PN, and 39 cases received EN. Moreover, the utilization of EN is usually short-term and discontinuous. Nutritional counsel and education of patients and their parents are important. Children undergoing alloHSCT suffer from weight loss which was associated with poor clinical outcomes. Thus, nutritional intervention is essential. Aggressive therapy of aGVHD may help prevent weight loss and malnutrition. In addition, exercise interventions are an important component of preventing weight loss.

The limitations of our study were a small sample size, which leading to the wide confidence intervals of the variables in binary logistic regression model, and lack of detailed nutritional intervention. Future work should include a larger sample together with effective nutritional support. The body composition measurements and laboratory indexes (namely albumin/pre-albumin) were also lacking, and should therefore be covered in regression models in future research.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

MY, JP, JH, YF, and WT took part in the research design. MY, CL, XX, TZ, and YW were participated in the collection and maintenance of datas. MY, JP, and WT analyzed the data and interpreted results. MY, JH, and JP wrote the manuscript. YF and WT revised the manuscript. All authors agreed the article to be published.

Acknowledgments

We thank the patients who took part in this study and China Health Promotion Foundation for the support of the "Public welfare project of scientific research development of the Pediatric Nutrition Support Team (NST)".

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.974389/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Kaplan Meier curves of survival for weight loss < 5% group (continuous line) and weight loss ≥ 5% (dashed line) after excluding patients who died or suffered from relapse/progression within 100 days.

SUPPLEMENTARY FIGURE 2
Cumulative incidence of TRM and relapse in weight loss ≥ 5% group and weight loss < 5% group.

References

1. Ljungman P, Urbano-Ispizua A, Cavazzana-Calvo M, Demirer T, Dini G, Einsele H, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe. *Bone Marrow Transplant.* (2010) 45:219–34. doi: 10.1038/bmt.2009.141

2. Zatarain L, Savani B. The role of nutrition and effects on the cytokine milieu in allogeneic hematopoietic stem cell transplantation. *Cell Immunol.* (2012) 276:6–9. doi: 10.1016/j.cellimm.2012.05.003

3. Ramadan A, Paczesny S. Various forms of tissue damage and danger signals following hematopoietic stem-cell transplantation. *Front Immunol.* (2015) 6:14. doi: 10.3389/fimmu.2015.00014

4. Martin-Salces M, de Paz R, Canales M, Mesejo A, Hernandez-Navarro F. Nutritional recommendations in hematopoietic stem cell transplantation. *Nutrition.* (2008) 24:769–75. doi: 10.1007/s00520-009-0730-3

5. Campos D, Boguszewski C, Funke V, Bonfim C, Kulak C, Pasquini R, et al. Bone mineral density, vitamin D, and nutritional status of children submitted to hematopoietic stem cell transplantation. *Nutrition.* (2014) 30:654–9. doi: 10.1016/j.nut.2013.10.014

6. Thomaz A, Silvério C, Campos D, Kieuteka E, Rabito E, Funke V, et al. Pre-transplant arm muscle area: a simple measure to identify patients at risk. *Support Care Cancer.* (2015) 23:3385–91. doi: 10.1007/s00520-015-2850-2

7. Urbain P, Birlinger J, Lambert C, Finke J, Bertz H, Biesalski H. Longitudinal follow-up of nutritional status and its influencing factors in adults undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant.* (2013) 48:446–51. doi: 10.1038/bmt.2012.158

8. Fuji S, Mori T, Khattry N, Cheng J, Do Y, Yakushijin K, et al. Severe weight loss in 3 months after allogeneic hematopoietic SCT was associated with an increased

risk of subsequent non-relapse mortality. *Bone Marrow Transplant.* (2015) 50:100–5. doi: 10.1038/bmt.2014.228

9. Ando T, Fujisawa S, Teshigawara H, Ogusa E, Ishii Y, Miyashita K, et al. Impact of treatment related weight changes from diagnosis to hematopoietic stem cell transplantation on clinical outcome of acute myeloid leukemia. *Int J Hematol.* (2019) 109:673–83. doi: 10.1007/s12185-019-02647-5

10. Murphy A, White M, Viani K, Terezie T. Evaluation of the nutrition screening tool for childhood cancer (SCAN). *Clin Nutr.* (2016) 35:1–6. doi: 10.1016/j.clnu.2015.02.009

11. Martin P, McDonald G, Sanders J, Claudio A, Appelbaum F, Deeg H, et al. Increasingly frequent diagnosis of acute gastrointestinal graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* (2004) 10:320–7. doi: 10.1016/j.bbmt.2003.12.304

12. Heinen G, Schmit D, Campos D, Bonfim C, Rabito E, Vilela R. Short-term follow-up of the nutritional status of children with Fanconi anemia undergoing hematopoietic stem cell transplant. *Support Care Cancer.* (2018) 26:895–903. doi: 10.1007/s00520-017-3906-2

13. Aplenc R, Zhang M, Sung L, Zhu X, Ho V, Cooke K, et al. Effect of body mass in children with hematologic malignancies undergoing allogeneic bone marrow transplantation. *Blood.* (2014) 123:3504–11. doi: 10.1182/blood-2013-03-490334

14. Hoffmeister P, Storer B, Macris P, Carpenter P, Scott Baker K. Relationship of body mass index and arm anthropometry to outcomes after pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies. *Biol Blood Marrow Transplant.* (2013) 19:1081–6. doi: 10.1016/j.bbmt.2013.04.017

15. Inaba H, Yang J, Kaste S, Hartford C, Motosue M, Chemaitilly W, et al. Longitudinal changes in body mass and composition in survivors of childhood hematologic malignancies after allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol.* (2012) 30:3991–7. doi: 10.1200/JCO.2011.40.0457

16. Farias C, Campos D, Bonfin C, Vilela R. Phase angle from BIA as a prognostic and nutritional status tool for children and adolescents undergoing hematopoietic stem cell transplantation. *Clin Nutr.* (2013) 32:420–5. doi: 10.1016/j.clnu.2012.09.003

17. Hopanci Bicakli D, Ozkaya Akagunduz O, Meseri Dalak R, Esassolak M, Uslu R, Uyar M. The effects of compliance with nutritional counseling on body composition parameters in head and neck cancer patients under radiotherapy. *J Nutr Metab.* (2017) 2017:8631945. doi: 10.1155/2017/8631945

18. Feng Y, Pan L, Shen L, Chang P, Zhang B, Hong L. Changes in body composition in children with acute graft-versus host disease within the first 100 days after hematopoietic stem cell transplantation. *Eur J Clin Nutr.* (2018) 72:1167–75. doi: 10.1038/s41430-017-0057-y

19. Eduardo F, Bezinelli L, Gobbi M, Pereira A, Vogel C, Hamerschlak N, et al. Impact of oral and gastrointestinal mucositis on body weight alterations during hematopoietic stem cell transplantation. *Nutr Cancer.* (2018) 70:1–8. doi: 10.1080/01635581.2018.1412476

20. El-Ghammaz A, Ben Matoug R, Elzimaity M, Mostafa N. Nutritional status of allogeneic hematopoietic stem cell transplantation recipients: influencing risk factors and impact on survival. *Support Care Cancer.* (2017) 25:3085–93. doi: 10.1007/s00520-017-3716-6

21. Foster B, Shults J, Zemel B, Leonard M. Interactions between growth and body composition in children treated with high-dose chronic glucocorticoids. *Am J Clin Nutr.* (2004) 80:1334–41. doi: 10.1093/ajcn/80.5.1334

22. Morishita S, Kaida K, Ikegame K, Yoshihara S, Taniguchi K, Okada M, et al. Impaired physiological function and health-related QOL in patients before hematopoietic stem-cell transplantation. *Support Care Cancer.* (2012) 20:821–9. doi: 10.1007/s00520-011-1156-2

23. August D, Huhmann M, American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *J Parent Enteral Nutr.* (2009) 33:472–500. doi: 10.1177/0148607109341804

24. Hulst J, Zwart H, Hop W, Joosten K. Dutch national survey to test the STRONGkids nutritional risk screening tool in hospitalized children. *Clin Nutr.* (2010) 29:106–11. doi: 10.1016/j.clnu.2009.07.006

25. Lazarow H, Nicolo M, Compher C, Kucharczuk C, Stadtmauer E, Landsburg D. Nutrition-related outcomes for autologous stem cell transplantation patients. *Clin Lymphoma Myeloma Leukemia.* (2019) 19:e393–8. doi: 10.1016/j.clml.2019.04.002

26. Fuji S, Cheng J, Yakushijin K, Wanitpongpun C. Nutritional support in allogeneic hematopoietic stem cell transplantation Asian perspective. *Blood Cell Ther.* (2022) 5:54–60.

frontiers | Frontiers in Nutrition

TYPE Systematic Review
PUBLISHED 20 January 2023
DOI 10.3389/fnut.2022.1057057

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Gianluca Rizzo,
Independent Researcher, Messina, Italy
Mostafa Dianatinasab,
Maastricht University, Netherlands

*CORRESPONDENCE
Yongbing Liu
bingbing19950806@163.com

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 29 September 2022
ACCEPTED 09 December 2022
PUBLISHED 20 January 2023

CITATION
Bu Y, Qu J, Ji S, Zhou J, Xue M, Qu J, Sun H and Liu Y (2023) Dietary patterns and breast cancer risk, prognosis, and quality of life: A systematic review.
Front. Nutr. 9:1057057.
doi: 10.3389/fnut.2022.1057057

Dietary patterns and breast cancer risk, prognosis, and quality of life: A systematic review

Yuan Bu [1], Junchao Qu[1], Siqi Ji[1], Jingxin Zhou[1], Mengxin Xue[1], Jiling Qu[2], Huiping Sun[1] and Yongbing Liu[1]*

[1]School of Nursing and Public Health, Yangzhou University, Yangzhou, Jiangsu, China, [2]Jiangsu Vocational College of Medicine, Yancheng, Jiangsu, China

Background: Statistics indicate that the morbidity of breast cancer is increasing globally, and its (overall figures) incidence has now surpassed that of lung cancer for the first time. The relation between a whole dietary pattern, rather than of a single food or nutrient, and breast cancer (BC) should be examined for findings to capture the complexities of diet and the potential for synergism between dietary components. Hence, the effects of dietary patterns on breast cancer have recently attracted increasing attention.

Objective: To systematically review the effects of dietary patterns on breast cancer risk, prognosis, and quality of life in survivors.

Methods: This systematic review was conducted following PRISMA guidelines and was registered in PROSPERO. Data from Ovid, China Biomedical Literature Database, Wanfang Data Knowledge Service Platform, CNKI, PubMed, Weipu, The Cochrane Library, Duxiu Data, ProQuest, Embase, Web of Science, and Scopus Database were retrieved and evaluated.

Results: A total of 47 studies that investigated the association between eating patterns and breast cancer were identified. Ten studies evaluated the effect of the model on treatment outcome and prognosis of breast cancer and two cross-sectional studies examined the influence of dietary patterns on quality of life. The resulting favorable dietary patterns were shown to regulate metabolic biomarkers, antioxidants, anti-inflammatory agents, and protective genes, and inhibit cell proliferation and invasion.

Conclusion: Numerous studies have examined the effects of healthy eating, plant-based, anti-inflammation, low-fat, and other favorable dietary patterns in relation to breast cancer. However, few studies reported significant associations and the studies had limitations, suggesting that the current findings should be interpreted with caution.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, CRD42022350171.

KEYWORDS

dietary patterns, breast cancer, breast cancer risk, prognosis, quality of life

Introduction

The most recent estimates of the International Agency for Research on Cancer (IARC) indicated that breast cancer (BC) was the most prevalent cancer in women worldwide with 2.3 million diagnoses in 2020, thus surpassing lung cancer for the first time. BC is responsible for approximately 685,000 deaths per year, and it is the fifth leading cause of cancer-related deaths in women (1).

A previous study of the link between the gut and mammary glands found that diet could alter the gut microbiome and breast tumor microenvironment, thereby influencing tumorigenesis (2). Current research suggests that nutritional status affects cell invasion and lipid metabolism in BC (especially triple-negative breast cancer) (3), and can thus impact BC risk, treatment outcomes, and quality of life in survivors. Dietary research has shifted from studying single nutrients or foods to holistic dietary patterns (4), given that analysis of single nutrients and foods cannot address the effects of interactions between or changes in multiple nutrients and food components ingested together. In nutritional epidemiology, nutrients present in food are expressed based on their biological significance, and a new concept of food synergy has been established. The most reliable evidence for a link between diet and health outcomes is thus obtained by determining the overall effects of different eating patterns, considering the mutual effects of their nutrients (5, 6).

Breast cancer (BC) is the focus of extensive research, especially in countries with a high rate of the disease. Levels of consumption of animal products and all types of drinks are nearly twice as high and the consumption of plant- and grain-based foods is lower in countries with a high rate of BC. For example, in Mediterranean countries, where animal products are consumed at twice the rate of plant-based foods, the morbidity rate of BC is 51/100,000 (7). These findings highlight the need to explore the impact of dietary patterns on BC. However, most patients do not have sufficient understanding of the effects of dietary patterns and clinical factors on BC risk, disease outcomes, and quality of life in survivors, and a lack of understanding of relevant dietary patterns may lead to patients being diagnosed with advanced disease of BC (8).

A Mediterranean-style diet has been shown to reduce the risk of BC (9), while a low-fat diet reduced mortality in post-menopausal patients (10), and healthy eating patterns improved the quality of life of patients with BC (11). However, the role of dietary patterns in populations with specific BCs is inconclusive. We therefore systematically analyzed the effects of the components of different dietary patterns on BC, and determined which characteristics of the population were most affected by specific dietary patterns.

Materials and methods

Search process

The International System Review Registry Platform (PROSPERO) registration number for this project is CRD42022350171. The study is presented according to PRISMA guidelines for systematic reviews. Ovid, China Biomedical Literature Database, Wanfang Data Knowledge Service Platform, CNKI, PubMed, Weipu, The Cochrane Library, Duxiu Data, ProQuest, Embase, Web of Science, and the Scopus database were searched for relevant literature on BC and dietary patterns, using subject words and free words. The reference lists of the identified studies were also searched for additional studies. Dandamudi et al. published a systematic review of studies published up to January 2017 (12). The current search time was limited to studies published between 01 January 2017 and 30 July 2022, with no language restrictions.

The search identified articles with the following terms in the title or abstract: "Breast Neoplasms" OR "Breast Neoplasm" OR "Neoplasm, Breast" OR "Breast Tumors" OR "Breast Tumor" OR "Tumor, Breast" OR "Tumors, Breast" OR "Neoplasms, Breast" OR "Breast Cancer" OR "Cancer, Breast" OR "Mammary Cancer" OR "Cancer, Mammary" OR "Cancers, Mammary" OR "Mammary Cancers" OR "Malignant Neoplasm of Breast" OR "Breast Malignant Neoplasm" OR "Breast Malignant Neoplasms" OR "Malignant Tumor of Breast" OR "Breast Malignant Tumor" OR "Breast Malignant Tumors" OR "Cancer of Breast" OR "Cancer of the Breast" OR "Mammary Carcinoma, Human" OR "Carcinoma, Human Mammary" OR "Carcinomas, Human Mammary" OR "Human Mammary Carcinomas" OR "Mammary Carcinomas, Human" OR "Human Mammary Carcinoma" OR "Mammary Neoplasms, Human" OR "Human Mammary Neoplasm" OR "Human Mammary Neoplasms" OR "Neoplasm, Human Mammary" OR "Neoplasms, Human Mammary" OR "Mammary Neoplasm, Human" OR "Breast Carcinoma" OR "Breast Carcinomas" OR "Carcinoma, Breast" OR "Carcinomas, Breast" AND "Dietary pattern."

Eligibility criteria and study selection

The inclusion criteria were: (1) cohort study, randomized controlled trial (RCT), cross-sectional research, or case-control study; (2) full text provided; and (3) study evaluated the effects of eating patterns or dietary interventions on BC risk, all-cause/specific mortality, recurrence, and quality of life. The exclusion criteria were: (1) dietary studies combined with physical activity; (2) studies without full text, results, and key data; (3) studies of any population not explicitly defined as cancer survivors; (4) cell and animal experiments, conference abstracts without full text, reviews, and meta-analyses; and (5) duplicate studies or several publications from the same study.

Data fetch and quality evaluation

Articles were identified and the following data were retrieved by two researchers: general patient information, sample size, assessment of eating patterns, indicators of disease change, outcomes (relationship between dietary patterns and BC, 95% confidence intervals, odds ratios, correlation coefficients, hazard ratio, and p-values), and identification of confounding variables associated with BC (e.g., sex, smoking, tumor classification, estrogen, TNM staging, education, menarche, age, and menopausal age). The quality of case-control and cohort studies was assessed by the Newcastle-Ottawa scale (NOS), which includes selection of study population, comparability between groups, and outcome/exposure. The total score ranges from 0 to 9, with a score $\geq$ 6 indicating high-quality. Details of the NOS scale are provided in document S1. RCTs were assessed using Cochrane risk bias maps, with each aspect receiving a low, high, or unclear rating. The quality of the cross-sectional studies was based on the Joanna Briggs Institute (JBI) quality evaluation. This was a descriptive systematic review.

Results

The PRISMA flowchart is shown in Figure 1. The preliminary search identified 1592 articles, of which 759 articles remained after excluding duplicate studies, and 107 articles remained after excluding systematic reviews, meta-analyses, animal experiments, and content discrepancies. The full texts of these articles were read, and the selected research findings, specific data, and comparator patterns are shown in Table 1. Forty-seven studies assessed the positive and negative effects of dietary patterns on cancer risk, 10 assessed the impact of eating patterns on treatment outcomes and prognosis, and two assessed the effects of eating patterns on quality of life in patients after a cancer diagnosis. This review included 35 case-control studies, 19 cohort studies, two cross-sectional studies, and three RCTs. The results of quality evaluations of the studies are presented in Tables 2–4 and Supplementary Figure 2. All previously conducted studies, except for three RCTs with a high risk of bias, were of high quality. In the three RCTs, random sequences were generated by using a permuted block algorithm and simple randomization, respectively. For allocation hiding, only Chlebowski et al. (13) described implementation points with hidden methods, while other two did not. It is difficult to blind the participants and researchers in dietary studies, and the three RCTs were therefore not blinded. However, the outcome evaluators were blinded in two of the studies (13, 14), but not in the third study (15). The mean and standard deviation were used to estimate the missing data in all three papers, and the reasonable effect size of the missing data did not affect the final observation results. There was no risk of selective reporting bias or other bias in any of the studies.

Dietary patterns and the risk of BC

The relationship between dietary patterns and the risk of BC has been studied by researchers in 16 different countries, particularly in relation to healthy, Mediterranean, inflammatory, plant-based, and Western dietary patterns (Supplementary material).

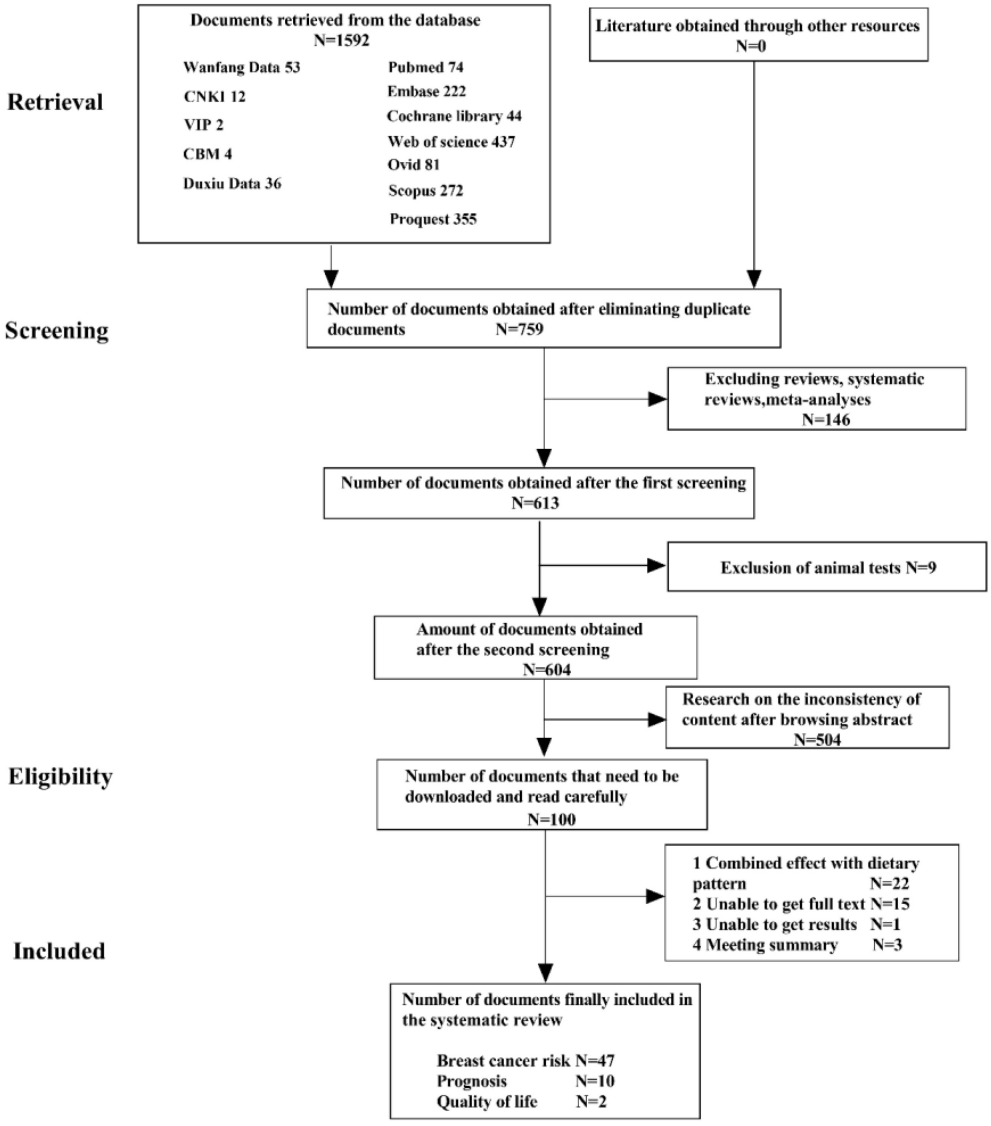


FIGURE 1
Document screening flow chart.

Healthy eating patterns were investigated in populations from various geographical locations, including, Iran (n = 5), the United States (n = 3), Pakistan (n = 1), Poland (n = 2), and Mexico (n = 1). This pattern reduced the risk of BC, whereas unhealthy eating patterns increased the risk (16–24). An unhealthy diet was positively related to the occurrence of postmenopausal BC through its proinflammatory potential. In contrast, regular consumption of low-processed vegetable products and fish was negatively related to the occurrence of cancer (25). Another study in Iran found a significant positive correlation between dietary glycemic index and the incidence rate of BC (26), while high dietary fiber intake, such as beans and grains, was shown to reduce the risk of estrogen receptor negative (ER–) and progesterone receptor negative (PR–) BC in the United States (27). Meat and processed meat diets were associated with a higher risk of BC in a Chinese study (28), while the consumption of vegetables, fruit, and soybeans reduced the risk of postmenopausal BC, especially ER– and ER–/PR– subtypes (9). The consumption of fresh fruit and nuts was negatively correlated with the risk of menopausal BC, and foods with a high sodium content were positively correlated with the risk of menopausal BC in a South African study (29), and a multigrain diet reduced the risk of BC in a South Korean study (30). These findings were consistent with the results of the study on healthy eating patterns (16, 18). However, a study conducted by American researchers showed that the Alternative Healthy Eating Index–2010 (AHEI-2010) had a weak (but insignificant) correlation with the risk of BC, but after excluding alcohol, it was negatively correlated with the risk of ER–/PR– and ER–/PR–/human epidermal growth factor receptor 2 (HER2–) BC (31), and there was no relationship between this index and BC risk in another study conducted in Pakistan (18, 19, 32, 33).

Studies on the effects of a Mediterranean diet, characterized by high intakes of fish, vegetables, beans, boiled potatoes, fruit, olives and vegetable oils, and a low intake of fruit juice, were carried out in the United States (n = 3), China (n = 2), Spain (n = 1), and Italy and Switzerland (n = 1), while studies of 'prudent' dietary patterns similar to a Mediterranean-style diet (34) have been carried out in China (n = 1), Spain (n = 1), and Poland (n = 2). A higher score for a Mediterranean diet was negatively related to BC in some studies (21–23, 28, 35, 36), especially after the menopause (37–39), while the Spanish study and two studies in the United States showed only a weak or no correlation (31, 33, 39). Prudent dietary patterns were associated with a lower risk of BC in one study (34), but had no observable effect on BC in the Spanish study (37–39).

The effects of an inflammatory diet were investigated in Iran (n = 2), the United States (n = 2), Spain (n = 1), Poland (n = 1), Jordan (n = 1), France (n = 1), and Argentina (n = 1). Inflammatory dietary patterns, including high intakes of sugary soft drinks, refined grains, red and processed meat, margarine and other hydrogenated fats, and low intakes of green leafy vegetables, cruciferous vegetables, coffee, increased the risk of BC in premenopausal and overweight postmenopausal women (40–44). In addition, a low dietary inflammation index reduced the risk of BC in obese women (45, 46). However, there was no significant relationship between the dietary inflammation index and the incidence rate of BC in a Spanish study (47), while a French study found that an inflammatory diet only increased the risks of ER+, PR+, or HER2+ breast tumor subtypes, but found no relationship with triple-negative (ER–, PR–, and HER2–) BC (48).

Plant-based diets have been investigated in Iran (n = 3), China (n = 1), Spain (n = 1), and North India (n = 1). The plant diet index (PDI) and a healthy PDI were negatively correlated with the incidence rate of BC (28, 49–51), while an unhealthy PDI was associated with an increased risk (50). Lacto-ovo vegetarians (whose diet includes plants, dairy products, and eggs) had a lower risk of BC compared with meat eaters and lacto vegetarians (vegetarian diet and dairy products) according to a multicenter case-control study of women in northern India (52). However, there was no significant correlation between PDI and the incidence of BC in the Iranian study and another study in Japan (53, 54).

The effects of a Western dietary pattern were investigated in Iran (n = 1), Spain (n = 2), and Mexico (n = 1). This pattern (high intakes of fat, sugar products, and red and processed meat) increased women's risk of BC in some studies (24, 29, 37–39). However, some studies found a positive correlation between a Western diet and the risk of invasive ductal carcinoma of the breast, but no significant correlation with the risk of invasive lobular carcinoma (55, 56).

Four beneficial dietary patterns are summarized: a healthy diet, Mediterranean diet, anti-inflammatory diet, and plant-based diet. Other dietary patterns negatively related to the risk of BC include dietary approaches to stop hypertension (DASH) (31, 57–59), Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) (60), a diet with a high intake of vitamins, trace elements, carbohydrates, fiber, and protein (61), and traditional diets (15, 56, 62). Dietary patterns positively related to the risk of BC include an estrogen-related dietary pattern (63) and a modern diet (15).

Dietary patterns and prognosis of BC

The relationship between dietary patterns and BC prognosis has been studied in four countries, particularly focusing on healthy, Mediterranean, and DASH diets. Two studies on healthy eating patterns conducted in the United States found that this pattern had the potential to reduce patient mortality (64, 65), while two studies in China found no such relationship (66, 67).

Two studies in the United States and one in Italy investigated the effects of a Mediterranean diet. The third national health and nutrition examination survey in the United States conducted in 2019 found no correlation (64), while the survey in 2021 showed that this diet was negatively related to BC mortality (65). In the Italian study, the 15-year overall survival rate among patients with high compliance to a Mediterranean diet was better than that among patients with low compliance, but there was no significant correlation with either increased or decreased mortality rates (68).

One study of the DASH diet in the United States showed that this diet reduced mortality in BC patients (65); however, a Chinese study found that adherence to the DASH diet was associated with higher mortality compared with adherence to the Chinese food pagoda CHFP-2007/2016 (66).

Dietary patterns shown to reduce mortality and improve overall survival among patients with BC include a low-fat diet (13, 69–72), diabetes risk-reduction diet (14), plant-based diet (73), and anti-inflammatory diet (74). However, different studies have shown different results in terms of all-cause mortality, specific mortality, total mortality, cancer recurrence, and non-BC-related deaths among BC patients, indicating the need for more research.

TABLE 1 Dietary patterns: Disease risk, prognosis, and survival quality.

Authors, country	Study	Sample size	Dietary assessment	Dietary pattern	Findings	Covariates included in the model
Castelló et al. (Spain) (37)	A case-control study	1063 BCs and 1469 healthy controls (20–85y), patients with recently diagnosed (< 6 month)	FFQ (154 items); 1 y prior	Western, Prudent, and Mediterranean dietary patterns	Western pattern increases the venture of BC (OR:1.53, 95%CI1.15–2.02) Mediterranean diet high adherence reduces BC risk (OR:0.72, 95%CI:0.53–0.98)	Pausimenia status, time of life, BMI, family history of BC, PA, smoking, caloric intake, alcohol intake, province, education, time at the first delivery
Sadeghi et al. (Iran) (16)	A case-control study	145 BCs and 149 controls	SQFFQ (168 items) 1 y prior	Unhealthy and healthy dietary patterns	Participants who had higher scores for unhealthy dietary patterns and healthy dietary patterns were more (OR: 4.12, 95%CI: 2.31–7.3) and less (OR: 0.17, 95%CI: 0.30–0.95) prone to develop breast cancer, respectively. A healthy dietary pattern reduced the risk of HER-2 positive breast cancer (OR: 0.11, 95% CI: 0.04–0.25).	Age, marriage, education, smoking, menarche, contraceptives, number of deliveries, menopausal status, ethnic history of breast, supplements, HRT
Lu et al. (China) (62)	A case-control study	818 BCs and 935 Controls BCs with recently diagnosed (< 12 month)	FFQ (23 items); 1 y prior	salty, vegetarian, sweet and traditional Chinese	The traditional Chinese pattern was associated with a lower risk of BC among both pre- and post-menopausal women (4th vs. 1st quartile: OR for pre-and post-menopausal women was 0.47 and 0.68, respectively). Women with high factor scores of the sweet pattern also showed a decreased risk of BC (4th vs. 1st quartile: OR for pre- and post-menopausal women was 0.47 and 0.68, respectively).	Residence, BMI, age, education, household income (5 y prior), menopausal status. age at menarche, abortion, WHR, age at first live birth
Guinter et al. (US) (63)	A nested case-control study	393 controls and 260 BCs	DQX (137items); 1 y prior	estrogen-related dietary pattern (ERDP)	A 1-unit increase in the ERDP score was associated with total (HR:1.09, 95%CI:1.01–1.18), invasive (HR:1.13; 95%CI:1.04–1.24) and ER positive (HR:1.13, 95%CI:1.02–1.24) BC risk.	PHT use at baseline, BMI, alcohol, parity, vigorous, PA, Family history of BC
Krusinska et al. (Poland) (22)	A nested case-control study	82 controls and 47 cases (40–79y)	FFQ-6(62 items); 1 y prior	Non-Healthy, Prudent, Margarine, Sweetened Dairy	The risk of BC risk was three-times higher (OR: 2.90; 95% Cl: 1.62–5.21; $p < 0.001$) in the upper tertile of the "Non-Healthy" pattern (reference: bottom tertile)	Family history, number of children, age, BMI, socioeconomic, abuse of alcohol, PA, menarche, menopausal, contraceptive, HRT, smoking, vitamin/mineral supplement, molecular of BC subtypes
Krusinska et al. (Poland) (23)	A nested case-control study	140 controls and 140 BCs (40–75 y)	FFQ-6 (62 items);	Dressings, Non-healthy, Sweet low-fat dairy, Prudent	The risk of BC was lower in the average (3–5 points) and high (6–8 points) levels of the "Polish-aMED" score compared to the low (0–2 points) level by 51% (OR: 0.49; 95%Cl: 0.30–0.80; $p < 0.01$; adjusted) and 63% (OR: 0.37; 95% Cl: 0.21–0.64; $p < 0.001$; adjusted), respectively. In the middle and upper tertiles compared to the bottom tertile of the "Prudent" DP, the risk of cancer was lower by 38–43% (crude) but was not significant after adjustment for confounders. In the upper compared to the bottom tertile of the "Non-healthy" DP, the risk of cancer was higher by 65% (OR: 1.65; 95% Cl: 1.05–2.59; $p < 0.05$; adjusted).	Age, sex, type of cancer, BMI, SES, PA, smoking, alcohol abuse.
Jalali et al. (Iran) (40)	A case-control study	134 BCs and 267 hospitalized controls	FFQ (168 items); 1 y prior	Dietary Inflammatory Index	DII pattern enhanced the risk (OR quartile 4 vs. 11/4 2.64, 95% CI: 1.12–6.25; Ptrend1/4 0.01), particularly premenopausal population (OR quartile 4 vs. 11/4 5.51, 95%CI: 1.45–20.93; Ptrend1/4 0.005);	Waist, WHR, Age, Weight, Height, BMI, Hip, Menarche age, Marriage age, First pregnancy age, Childbirth number, Child number, Breastfeeding time, OCP use time, PA, Daily energy intake, Miscarriage history, HRT, Benign breast diseases history, BC family history, Cancer family history, Night bra use, Day bra use, Inflammatory disease history, NSAIDs, Menopausal status, Marital status, Educational level, Smoking, Vitamin D

(Continued)

10.3389/fnut.2022.1057057

TABLE 1 (Continued)

Authors, country	Study	Sample size	Dietary assessment	Dietary pattern	Findings	Covariates included in the model
Heidari et al. (Iran)(18)	A case-control study	134 BCs and 267 controls	FFQ (168 items);	healthy and unhealthy	Unhealthy eating patterns enhance the risk (OR: 2.21; 95%CI: 1.04-4.69; Ptrend = 0.009).	first live birth, Age, Weight, Height, BMI, WHR, Total energy intake, PA, Menarche age, Marriage age, Breastfeeding duration, Menopausal status, Pre-Postmenopause, Smoking, Education Family history of cancer, Day bra use, Night bra use, Vitamin D supplements, OCP use
Shridhar et al. (Indian) (52)	A case-control study	400 BCs and 354 controls (30–69 y) BCs with recently diagnosed(< 6mo)	FFQ (184 items); 1 y prior	lacto-vegetarians (Only dairy products are eaten in animal products), lacto-ovo-vegetarians (included eggs), non-vegetarians	Breast cancer risk was lower in lacto-ovo-vegetarians compared to both non-vegetarians and lacto-vegetarians with OR (95% CI) of 0.6 (0.3–0.9) and 0.4 (0.3–0.7), respectively.	Breastfeeding, Age, Education, Age at menarche in years, Religion, Diabetes, Hypertension, Family history of cancer, BMI, Waist circumference, Age during first pregnancy (in years), months/child, Menopause, Age at menopause in years, Years of estrogen exposure. Oral contraceptive pills, PA, Moderate-vigorous,
Sedaghat et al. (Iran) (20)	A case-control study	267 hospitalized controls and 134 newly diagnosed BCs	FFQ (168 items); 1 y prior	Healthy Eating Index 2010 (HEI-2010)	higher HEI-2010 scores were associated with lower risk of BC only among premenopausal women (multivariate adjusted OR1/4 0.27, 95%CI: 0.10–0.69; P for trend 1/40.02).	Height, BMI, Waist, Hip, WHR, Age, Menarche age, Marriage age, First pregnancy age, Child number, Breastfeeding time, OCP use time, PA, Daily energy intake, Abortion history, HRT, BC family history, Cancer family history, Inflammatory disease history, Anti-inflammatory drugs, Menopausal status, pre-menopause, post-menopause, Marital status, University education, smoking Vitamin D supplement
Turati et al. (Italy, Switzerland) (36)	A case-control study	3034 BCs and 3392 controls	FFQ (78 items); weekly intake	Mediterranean Diet	Compared to a MDS of 0–3, the ORs for BC were 0.86 (95% CI, 0.76–0.98) for a MDS of 4–5 and 0.82 (95% CI, 0.71–0.95) for a MDS of 6–9 (p for trend = 0.008).	Oral contraceptive, Age, education, BMI, PA, smoking, parity, menopausal status/age, HRT history of diabetes, family history (first-degree relatives), non-alcohol energy intake, alcohol
Marzbani et al. (Iran) (19)	A case-control study	212 BCs and 408 controls	The middle-aged integrated health care form (11items);	Unhealthy dietary patterns	The OR of BC associated with consumption of less vegetables was 2.8 (OR: 2.8; 95%CI:1.7–4.5). The OR of BC in women who consumed more soft drinks (OR: 2.8; 95%CI:1.9–4.3), industrially produced juices (OR:2.7; 95%CI: 1.1–6.5) and solid oils (OR:1.9; 95% CI:1.3–3.0). The OR of BC in more fried foods was 4.5 (95%CI: 2.1–9.4). The OR of BC in excessive sweets was 2.6 (95%CI:1.7–3.9).	Age, Education, Location, Marital status, Job, Insurance coverage, BMI
Heidari et al. (Iran) (58)	A case-control study	136 BCs and 272 hospital-based controls (d ≥ 25 y)	FFQ (168 items); 1 y prior	DASH: Günther's, Dixon's, Fung's, and Mellen's	Women in the highest categories of the Mellen's and Günther's scores had lower odds of BC than those in the lowest quintiles (Mellen's OR:0.50; 95%CI:0.62–0.97; Ptrend:0.02; Günther's OR:0.48; 95%CI:0.25–0.93; P-trend:0.05). BC risk was reduced in postmenopausal women with higher scores on Mellen's index (OR:0.24; 95%CI:0.08–0.68; Ptrend:0.04).	Supplement, age, BMI, first live birth, PA, smoking, total energy, vitamin D, family history

(Continued)

10.3389/fnut.2022.1057057

TABLE 1 (Continued)

Authors, country	Study	Sample size	Dietary assessment	Dietary pattern	Findings	Covariates included in the model
Stasiewicz et al. (Poland) (25)	A case-control study	230 controls, 190 primaries (21 d prior before recruitment) BCs (40.0–79.9y)	FFQ-6 (62 items); 1 y prior	Pro and Neutral-inflammatory	The lower OR of BC was associated with the higher adherence to the "Pro-healthy/Neutral-inflammatory" profile (OR:0.38; 95%Cl:0.18–0.80; $p < 0.01$ for the higher level vs. lower level, crude model; OR for one-point score increment:0.61; 95%Cl: 0.42–0.87; $p < 0.01$, adjusted model). The higher OR of BC was associated with the higher adherence to the "Unhealthy/Pro inflammatory" profile (OR:3.07; 95%Cl: 1.27–7.44; $p < 0.05$ for the higher level vs. lower level, adjusted model; OR for one-point score increment:1.18; 95%Cl: 1.02–1.36; $p < 0.05$, adjusted model).	Age, BMI, socioeconomic, PA, smoking, alcohol, age at menarche, times of full-term pregnancies, contraceptive, HRT, family history (first- or second-degree relative), vitamin/mineral, molecular subtypes of BC
Hajji-Louati et al. (France) (48)	A case-control study	872 BCs and 966 controls (25-75y)	FFQ (153 items); 1 y prior	Dietary Inflammatory Index (DII)	The OR contrasting quartile 4 to quartile 1 was 1.31 (95%CI: 1.00–1.73; p-trend = 0.02).	Menopausal, BBD, Age, menarche, department, first full-term pregnancy, family history (first-degree relatives), parity, breastfeeding, menopausal hormone therapy, BMI, socioeconomic, oral contraceptive, education
Sasanfar et al. (Iran) (49)	A case-control study	412 BCs($\leq$ 1 year) and 456 healthy controls.	FFQ (168 items); 1 y prior	Unhealthful plant-based diet index (uPDI); healthful plant-based diet index (hPDI); Plant-based diet index (PDI)	a greater score of hPDI was inversely associated to the risk of breast cancer (OR: 0.63; 95%CI:0.43–0.93, $P = 0.01$), pre- and postmenopausal women in the highest quartile of hPDI score had lower risk of BC than those in the lowest quartile.	Age, energy, PA, family history, educational level, parity, marital status, BMI
Aghamohammadi et al. (Iran) (60)	A case-control study	350 BCs and 700 controls. ($\geq$ 30y)	DS-FFQ (106 items); daily intake	MIND	women in the top tertile of the MIND diet score had 60% lower odds of BC than women in the bottom tertile (OR:0.40, 95%CI: 0.29–0.55).	Smoking, Age, breastfeeding, energy intake, BMI, menopausal status, education, SES, residency, family history, PA, marital status, alcohol, supplement use,
Soltani et al. (Iran) (57)	A case-control study	350 BCs and 700 controls($\geq$ 30y) ($<$ 6 mo)	DS-FFQ (106 items); daily intake	DASH	individuals in the highest quartile of the DASH diet score had 85% lower odds of BC than women in the bottom quartile (OR: 0.15; 95% CIs: 0.09–0.24).	Marital status, Age, alcohol, BMI, supplement, PA, energy intake, menopausal status, education, residency, family history of BC, smoking, breastfeeding
Cao et al. (China) (34)	A case-control study	818 BCs and 935 healthy controls	FFQ (149 items);	Prudent, Chinese traditional, Western, Picky	Prudent-factor was associated with a lower risk of breast cancer [4th vs. 1st quartile: OR:0.70, 95%CI:0.52–0.95], Picky-factor/class was associated with a higher risk (4th vs. 1st quartile: OR:1.35, 95% CI:1.00–1.81).	First full-term delivery, Age, BMI, history of benign disease, area, education, smoking, moderate PA, OCP, HRT, menarche, parity, family history, breastfeeding, height, energy intake, menopausal status
Cao et al. (China)(80)	A case-control study	695 BCs, 804 controls	FFQ (149 items);	Prudent, Chinese traditional, Western, Picky	Compared with Prudent class, Picky class was associated with a higher risk (OR:1.42, 95%CI = 1.06–1.90)	Age (diagnosis/enrollment/menopausal/first full term delivery/menarche), BMI, area, education, smoking, tea, alcohol, PA, oral contraceptives, HRT, history of benign disease, parity, breastfeeding, height, energy intake, family history
Cao et al. (China) (35)	A case-control study	818 BCs, 935 controls	FFQ (149 items);	Mediterranean dietary pattern (MDP)	High adherence (highest quartile) to the MDP decreased the risk of breast cancer among post- but not premenopausal women, respectively (OR:0.54, 95% CI:0.38–0.78 and 0.90, 0.53–1.53).	Education, Age (diagnosis, enrollment, menarche, first full term delivery), area, smoking, family history, PA, oral contraceptives, HRT, history of benign disease, parity, breastfeeding, BMI,

(Continued)

10.3389/fnut.2022.1057057

TABLE 1 (Continued)

Authors, country	Study	Sample size	Dietary assessment	Dietary pattern	Findings	Covariates included in the model
Hammad et al. (Jordan) (45)	A case-control study	200 BCs and 200 controls (≤ 3 mo) (≥ 20 y)	FFQ (109items); 1 y prior	Dietary inflammatory index (DII)	Stratified analyses by obesity status showed that overweight/obese participants in the highest DII tertile had a >75% increased BC risk (OR: 1.77 95%CI: 1.01–3.12) compared with participants in the lowest tertile.	Education, BMI, number of pregnancies, Contraceptive use, Age, energy, lactation, cigarette, family history
Jacobs et al. (South African) (56)	A case-control study	396 BCs and 396 controls	QFFQ 1 m prior	Pattern1: Manufactured food; Pattern2: Traditional; Pattern3: Cereal-dairy breakfast	Pattern (2,3) bring down the risk (highest tertile versus lowest tertile, OR:0.72, 95%CI: 0.57–0.89, p-trend = 0.004 and OR:0.73, 95%CI: 0.59–0.90, p-trend = 0.004, respectively)	Breast-feeding, Age, ethnicity, exogenous hormones, individual income, level of education, smoking, height, waist circumference, habitual PA, age (first pregnancy, menarche, menopause), full-term pregnancy, time since menopause, parity, duration of exclusive breastfeeding, HRT, alcohol, HIV positivity, miss-reporting of energy, total energy intake, family history
Flores-Garcia et al. (Mexico) (24)	A case-control study	509 BCs and 509 controls	FFQ (119items); 1 y prior	Pattern 1: cereals, meat, high fat, and sugary), Pattern 2: corn, legumes, vegetables)	The first pattern was positively associated with BC (OR 1/4 12.62; 95%CI: 7.42-21.45); the Second pattern was inversely associated with BC (OR 1/4 0.50; 95%CI: 0.40-0.62).	Energy, Alcohol, BMI, estrogen, education, smoking, family history
Sheikhhossein et al. (Iran) (81)	A case-control study	150 BCs and 150 controls	FFQ (147items); Daily intake	MIND	we found no significant association between the MIND diet score and odds of BC, either before (ORs for comparing T3 vs. T1: 0.818; 95%CI:0.469-1.42, P-trend = 0.48) or after controlling for potential confounders (ORs for T3 vs. T1:1.32; 95%CI: 0.31-5.64, P-trend = 0.633).	Age, energy intake, age at first pregnancy, PA, education, marital status, menopause status, socioeconomic, alcohol, smoking, vitamin, medical history, OCP, age at first menarche, menopause, weight (18y), number of children, length of breastfeeding, family history, iron, folate, BMI
Rigi et al. (Iran) (50)	A case-control study	350 BCs and 700 controls	FFQ (106items); 1 y prior	Plant-based dietary patterns: PDI, hPDI, uPDI	Individuals in the highest quartile of PDI had 67% lower odds of BC than those in the lowest quartile (OR: 0.33; 95%CI: 0.22–0.50). Individuals with the greatest adherence to hPDI were 36% less likely to have BC than those with the lowest adherence, in the fully adjusted model (OR:0.64; 95%CI 0.43–0.94). In terms of uPDI, women in the top quartile had a 2.23 times greater chance of BC than those in the bottom quartile (OR:2.23; 95%CI:1.48–3.36).	Marital status, place of residence, Education, Energy intake, breastfeeding, PA, social-economic, supplement, disease history, smoking, menopausal status, BMI, age, family history, alcohol
Niclis et al. (Argentina) (46)	A case-control study	317 BCs and 526 controls	FFQ (127items); 5 y prior	Dietary Inflammatory Index (DII)	Growing DII score enhanced the BC risk (OR:1.34; 95%CI:1.05-1.70)	Age, age at menarche, number of children, smoking, SES, family history, urbanization level, BMI,
Payandeh et al. (Iran) (53)	A case-control study	150 BCs and 150 controls, BCs with recently diagnosed (< 3 month)	FFQ (147items); 1 y prior, Daily intake	PDI, hPDI, uPDI	No association between none of the PDIs and the chance of BC in Iranian women.	BMI, PA, energy intake, education, marital status, breastfeeding, oral contraceptive, climacteric, alcohol, menarche, cigarette, supplements, comorbidities, HRT, menopause, weight (18 y), first pregnancy and family history, drug,
Foroozani et al. (Iran) (55)	A case-control study	1009 BCs and 1009 controls	FFQ (168items); Daily intake	Western dietary pattern (WD)	A positive and significant association was observed between higher adherence to a WD and risk of IDC (OR comparing highest with the lowest tertile: 2.45, 95%CI 1.88-3.17; p-trend < 0.001), whereas no significant association was observed between adherence to the WD and the risk of ILC (OR comparing highest with the lowest tertile: 1.63, 95%CI 0.63-3.25) (p for heterogeneity = 0.03).	Energy intake, menarche, garden stuff, breastfeeding, family history, smoking, chest X-ray, BBD, PA, first delivery, history of miscarriage, climacteric, OCP, BMI
Toorang et al. (Iran) (59)	A case-control study	477 BCs and 507 Controls(19-80 y)	FFQ (168items); 1 y prior	DASH Diet	DASH bring down the risk (OR for comparing extreme tertiles: 0.62; 95%CI 0.44-0.78; P_{trend} = 0.004).	Parity, Age, fertility treatment, energy intake, education, alcohol, smoking, PA, family history, marital status, OCP, BMI

(Continued)

10.3389/fnut.2022.1057057

TABLE 1 (Continued)

Authors, country	Study	Sample size	Dietary assessment	Dietary pattern	Findings	Covariates included in the model
Cao et al. (China) (9)	A case-control study	818 BCs and 935 controls	FFQ (149items);	Soy-Fruit-Vegetable Pattern	The pattern brings down the postmenopausal BC risk (4th vs. 1st quartile, OR: 0.57, 95%CI:0.41-0.80; $P_{trend} < 0.001$)	Age (diagnosis/enrollment/first full-term delivery), smoking, PA, oral contraceptives use, HRT, family history, history of BBD, menarche, number of full-term births, breastfeeding, height, energy intake, menopausal, education, BMI
Sasanfar et al. (Iran) (41)	A case-control study	412 BCs and 456 controls (19–80y) patients with recently diagnosed (< 1 year)	FFQ (168items); 1 y prior	Dietary inflammatory index (DII)	Individuals in the highest quartile of DII scores had 1.5 times higher odds of breast cancer than those with the lowest (OR:1.56, 95%CI:1.04–2.35, $P_{trend} = 0.02$).	Energy, educational level, parity, age, BMI, oral contraceptive use, tobacco use, alcohol use, marital status, PA, family history
Hosseini et al. (Iran) (17)	A case-control study	150 BCs and 150 controls, BCs with recently diagnosed (< 3 mo)	FFQ (147items);	Food Quality Score	A significant association between adherence to the FQS and odds of breast cancer in the fully adjusted model (OR: 0.58; P = 0.04) and in premenopausal women in the fully adjusted model (OR: 0.45; P = 0.02);	Menopause, Age, total energy, PA, education, marital status, SES, alcohol, smoking, vitamin medication, comorbidities, HRT, OCP, BP, menarche, weight (18y), number of children, breastfeeding ages, family history of BC, BMI, zinc, potassium, magnesium, calcium
Shamsi et al. (Pakistan) (32)	A case-control study	374 BCs and 750 controls. (18-75y)	FFQ	The Modified Alternate Healthy Eating Index-2010 (MAHEI-2010)	There was no association of BC with Alternate Healthy Eating Index 2010 score (OR: 1.85; 95%CI: 0.61–1.17; $p = 0.291$).	BMI, menopausal status, SES
Rigi et al. (Iran) (26)	A case-control study	350 BCs and 700 controls. (> 30y) BCs with recently diagnosed (< 6 month)	DS-FFQ (106 items); 1 y prior	Dietary glycemic index and glycemic load (GL)	Individuals in the highest tertile of dietary GI had 47% higher odds of BC than women in the lowest tertile (OR:1.47; 95%CI: 1.02–2.12). We found no significant association between dietary GL and odds of BC either before [OR: 1.35; 95%CI: 0.99–1.84)] or after adjustment for potential confounders (OR: 1.24; 95%CI: 0.86–1.79).	Alcohol, Marital, Age, energy intake, education, SES, place of residency, supplement use, family history of BC, PA, smoking, breastfeeding, menopausal, BMI
Harris et al. (US) (44)	Cohort study	45204 registered nurses and 1,477 BCs (27–44y) women)	HS-FFQ (124 items) and FFQ	An adolescent and early adulthood diet	Women in the fifth quintile of the inflammatory pattern score had multivariable adjusted HRs for premenopausal BC of 1.35 for adolescent diet (95%CI:1.06–1.73; P_{trend} 1/4 0.002) and 1.41 for early adulthood diet (95%CI: 1.11–1.78; P_{trend} 1/4 0.006) compared with women in the first quintile.	Age at first birth, height/weight/BMI (18y), age, total adolescence calories, menarche, adolescent PA, family history, parity, OCP, adult PA, alcohol, BBD, menopausal, hormone use
Kojima et al. (Japan) (54)	Cohort study	23,172 women and 119 BCs	FFQ (39 items);	Animal food pattern; Vegetable pattern; Dairy product pattern	The animal food pattern was significantly associated with a decreased risk of breast cancer morbidity among premenopausal women by HR 0.47 for the 2nd tertile (95%CI 0.22–1.00) and HR 0.42 for the 3rd tertile (95% CI:0.18–0.93), compared with the bottom tertile (p for trend = 0.04).	first birth, age, menarche, education, exogenous female hormones, duration, area, parity, family history, daily walking habits, alcohol, smoking, total daily energy intake, BMI,
Guinter et al. (US)(82)	Cohort study	261,959 woman and 1,968 BCs (35-74y)	FFQ (110items); 1 y prior	An Estrogen-Related Pattern	There is no relationship between ERDP and total, invasive, ER + /ER- of BC.	Family members with a history of BC (number), alcohol, total energy intake, BMI (baseline/30y), PHT, race, parity, menarche, hysterectomy, menopause, Age,
Haridass et al. (US) (21)	Cohort study	96,959 (California Teachers)	Semiquantitative FFQ (103items); 1 y prior	Paleolithic index: PALEO AHEI-2010 DASH aMED	In the analysis of women at risk of postmenopausal BC at baseline, higher AHEI-2010, aMED, and DASH scores were inversely associated with incident BC. Respectively, HRs (95%CIs) comparing quintile 5 to quintile 1 for AHEI-2010, aMED, and DASH indexes were 0.87 (0.78-0.97; P-trend = 0.004), 0.91 (0.82-1.02; P-trend = 0.03), and 0.89 (0.80-1.00; P-trend = 0.03).	Smoking, Age, HRT, family history, menarche, parity, OCP, SES, PA, total energy intake, alcohol, BMI, race,

(Continued)

10.3389/fnut.2022.1057057

TABLE 1 (Continued)

Authors, country	Study	Sample size	Dietary assessment	Dietary pattern	Findings	Covariates included in the model
Haraldsdottir et al. (Iceland) (83)	Cohort study	3,326 women and 97 BCs	FFQ and AGES-FFQ (107items);	Pattern1: Rye bread, cured meat/fish, viscera sausage, oat, Milk Pattern 2: Fish meal, Fish as a side, Fruit, Vegetables Pattern 3: Fish meal/oil, viscera sausage, oat, Milk, Pattern 4: Meat, Fish meal, Potatoes	Borderline inverse association was observed for the highest adherence to a pattern high in consumption of fish, blood/liver sausage, oatmeal, fish oil, and milk in adolescence (HR:0.6, 95%CI:0.4–1.0) (P_{trend} = 0.049)	Age at (entry/menarche, first child), BMI, education,
Petimar et al. (US) (31)	Cohort study	50,884 US women and 1,700 invasive BCs (mean follow-up, 7.6 y)	FFQ (110items); 1 y prior	DASH, AHEI-2010, AMED	Individuals in the highest quartile of DASH scores had a lower risk of invasive breast cancer compared with those in the lowest quartile (HR: 0.78; 95%CI: 0.67-0.90; P_{-trend} = 0.001), after excluding alcohol, AHEI-2010 was inversely associated with risk of ER–/PR– (HR:0.64; 95%CI: 0.42-0.98; P_{-trend} = 0.04) and ER–/PR–/HER2– subtypes.	Race, alcohol, education, recent mammogram, income, breastfeeding, BMI, HRT, height, OCP, PA, menopause, smoking, menarche, total energy intake, age at first live birth, family history, parity
Gardeazabal et al. (Spain) (47)	Cohort study	10,713 graduates and 100 confirmed and 168 probable incident BCs	FFQ (136items);	Dietary inflammatory index	The multivariable-adjusted HR for participants in the 4th quartile to the 1st quartile was 1.44 (95%CI:0.76-2.72; p_{-trend} = 0.339) when confirmed cases were analyzed, and 1.20 (95%CI 0.72-1.99; p_{-trend} = 0.757) for the probable cases. We neither observed statistically significant differences in regard to menopausal status.	The years from recruitment to the beginning of risk, Age, total energy intake, height, diabetes, university (years), HRT, relatives with a history of BC (number), months of breastfeeding, smoking, pregnancy (less than 30 years), PA, number of pregnancies of more than six months, alcohol, menopause, BMI, menarche,
Dela Cruz et al. (US) (33)	Cohort study	101,291 women in the MEC sample and 7,749 BCs	FFQ (180items); Daily intake	aMED; AHEI-2010; DASH; HEI-2015	The respective HRs for Q5 vs. Q1 were: 1.06 (95%CI: 0.98–1.14) for HEI-2015, 0.96 (95%CI:0.90–1.04) for AHEI-2010, 1.01 (95%CI: 0.94–1.09) for aMED, and 0.95 (95%CI: 0.88–1.02) for DASH ($p_{trend} > 0.05$ for all). No findings on the relationship between diet quality and BC risk.	Alcohol, Age, estrogen and progestin use, total energy intake, family history, BMI, menopause, smoking, parity, PA, age at first live birth, education, menarche,
Romanos-Nanclares et al. (Spain) (51)	Cohort study	10 812 women and 101 incident BCs	FFQ (136items); 1 y prior	Provegetarian dietary patterns (PVGs): a healthful PVG (hPVG); unhealthful PVG (uPVG)	A significant inverse association with BC (comparing tertile 2 vs. tertile 1, HR:0.55; 95%CI: 0.32-0.95) was identified for a modest overall PVG, but not for hPVG and uPVG separately.	HRT, height, menopause, family history, time since recruitment, smoking, total energy intake, PA, university(years), alcohol, months of breastfeeding, BMI, pregnancy (less than 30y), menarche, number of pregnancies of > 6 months,
Gardeazabal et al. (Spain) (39)	Cohort study	10713 young and middle-aged women and 100 definite cases and 168 probable BCs	FFQ (136items); Daily intake	Western pattern (WDP); Mediterranean pattern (MDP)	A higher adherence to a WDP was associated with an increased risk of overall BC (HR for confirmed BC Q4 v. Q1:1.70; 95%CI: 0.93- 3.12; P for trend = 0.045). Contrarily, adherence to a MDP was inversely associated with premenopausal BC (HR Q4 v. Q1;0.33; 95%CI: 0.12-0.91).	Menopause, Age, the time since recruitment, height, total energy intake, university (years), diabetes, relatives with a history of BC, smoking, HRT, PA, breastfeeding, alcohol, pregnancy (less than 30y), BMI, menarche, number of pregnancies of more than six months,

(Continued)

10.3389/fnut.2022.1057057

TABLE 1 (Continued)

Authors, country	Study	Sample size	Dietary assessment	Dietary pattern	Findings	Covariates included in the model
Park et al. (US) (43)	Cohort study	43563 participants and 2619 BCs	FFQ (110items); 1 y prior	D-OBS; E-DII	Whereas there was a suggestive inverse association for the highest vs lowest quartile of D-OBS (HR:0.92, 95%CI: 0.81-1.03). The highest quartile of E-DII was associated with risk of triple-negative BC (HR:1.53 95%CI: 0.99-2.35). When the two indices were combined, a proinflammatory/prooxidant diet (highest tertile of E-DII and lowest tertile of D-OBS) was associated with increased risk for all BC (HR: 1.13, 95%CI:1.00-1.27) and for triple-negative BC (1.72, 95%CI: 1.10-2.70), compared to an anti- inflammatory/antioxidant diet (lowest tertile of E-DII and highest tertile of D-OBS).	Alcohol, Race, degree of family history of BC, education, use of non-aspirin NSAIDs, BMI, hormone therapy, use of aspirin, menopausal, ever use of hormonal, the relationship between BMI and menopausal, recent mammogram screening, smoking, family history, years, PA,
Hidaka et al. (US) (15)	RCT	220 BCs; 440 controls	Diet History Questionnaire-I (DHQ-I) servings per day	Modern pattern; Traditional diet; Average pattern	Women with a Modern diet were more likely than women with a Traditional diet to develop ER- breast cancer: OR:3.33 (95%CI: 1.31-8.98); OR:3.12 (95% CI: 1.15-9.00). compared to an Average or Traditional diet, those with a Modern diet were more likely to develop an ER- tumor: OR: 2.56 (95%CI: 1.18-5.62); OR: 2.07 (95%CI: 0.89- 4.85).	Weight, Abnormal breast biopsy, menarche, Age at first birth, nulliparous, number of biopsies, race, Height, Age, family history
Jang et al. (Korea) (74)	Cohort study	511 BCs, recurrence includes a local (n = 12) or regional reappear (n = 16), heterolateral BC (n = 10), forane recurrence (n = 50) and 44 demises	A structured 24-h recall questionnaire daily intakes	Dietary Inflammatory Index	It was positively associated with the risk for cancer recurrence (HR:2.347, 95%CI: 1.17–4.71) and overall mortality (HR: 3.049, 95%CI: 1.08–8.83) after adjusting for confounding factors.	energy intake, time of life, AJCC grading, BMI, lymphatic metastasis, pausimenia, histological differentiation, Cancer size, treatment, subtype
Karavasiloglou et al. (US) (64)	Cohort study	110 were BC survivors	A 24-h dietary recall interview the past 24 h	The Healthy Eating Index (HEI) and the Mediterranean Diet Score (MDS)	Breast cancer survivors (HRHEI good vs. poor BC = 0.49, 95% CI: 0.25–0.97).	Alcohol, ethnicity, history of menopausal hormone therapy use, the time between diagnosis and completion of a questionnaire, daily energy intake, SES, self-reported prevalent chronic diseases at baseline, marital, smoking, BMI, PA
Wang et al. (China) (66)	Cohort study	3,450 BCs and 153 total deaths	FFQ (93items); 1 y prior	HEI-2015; Chinese Food Pagoda (CHFP)-2007, CHFP-2016; DASH	Participants in the highest quartiles of CHFP-2007, CHFP-2016 and DASH had 25-34% lower risk of total mortality (HR:0.66, 95%CI: 0.48-0.89 for CHFP-2007; HR:0.75, 95%CI: 0.55-1.01 for CHFP-2016; HR:0.66, 95%CI:0.49-0.91 for DASH), and 36-40% lower risk of breast cancer specific events (HR:0.64, 95%CI: 0.44-0.93 for CHFP-2007; HR:0.67, 95%CI: 0.45-0.99 for CHFP-2016; HR:0.60, 95%CI:0.40-0.90 for DASH) comparing to the lowest quartiles.	Immunotherapy (Age/BMI/PA), dietary survey, radiation, the interval between diagnosis and dietary survey, chemotherapy, total energy intake, comorbidity, education, TNM stage, income, HER2 status, marriage, menopausal status at diagnosis, PR status, ER status
Di Maso et al. (Italy) (68)	Cohort study	1453 women with BC	FFQ (78items); 2 years before diagnosis	Mediterranean Diet	Overall survival for 15 years improved (High:63.1%; low:53.6% p = 0.013).	Total energy intake, residence, ER/PR status, diagnosis (time/age), TNM stage, menopausal, education
Wang et al. (US) (14)	Cohort study	8,482 women with BC	FFQ at least 12 months after diagnosis date	Diabetes risk reduction diet (DRRD)	Women with higher post-diagnostic DRRD score had a 20% lower risk of breast cancer-specific mortality (top vs. bottom quintile HR:0.80; 95%CI:0.65-0.97; p-trend = 0.02) and 34% lower risk of all-cause mortality (HR:0.66; 95%CI:0.58-0.76; p-trend $<$ 0.0001). Compared with women who consistently had lower score ($\leq$ median) before and after diagnosis, those whose score improved from low to high had a lower risk of breast cancer-specific mortality (HR:0.77; 95%CI:0.62-0.95) and overall mortality (HR:0.85; 95%CI:0.74-0.97).	Change in BMI from pre- to post-diagnosis, post-diagnosis smoking status, (age/time) at diagnosis, (radiation, chemotherapy, and hormonal) therapy, (aspirin/alcohol/calories/SES/PA)post-diagnosis.ER status, menarche, disease stage, menopausal, pre-diagnosis BMI, parity, family history, menopausal hormone therapy use, BBD, OCP
Ergas et al. (US) (65)	Cohort study	3660 women diagnosed with invasive BC, 461 BC relapsers, and 655 demises	The Block 2005 Food Frequency Questionnaire (139items); daily intake	ACS; aMED; DASH; HEI-2015	Adjusted comparisons between extreme quintiles showed all 4 dietary quality indices to be inversely associated with all-cause mortality, suggesting a 21%-27% lower risk (ACS HR 1/4 0.73, 95%CI 1/4 0.56-0.95; aMED HR 1/4 0.79, 95%CI 1/4 0.61-1.03; DASH HR 1/4 0.76, 95%CI 1/4 0.58-1.00; HEI HR 1/4 0.77, 95%CI 1/4 0.60-1.01).	Hormonal therapies, race; radiation, education; chemotherapy, menopausal; type of surgery, PA; HER2, smoking; PR, cancer stage at diagnosis; ER, BMI

(Continued)

10.3389/fnut.2022.1057057

TABLE 1 (Continued)

Authors, country	Study	Sample size	Dietary assessment	Dietary pattern	Findings	Covariates included in the model
Lei et al. (China) (67)	Cohort study	1226 invasive early-stage BCs	FFQ (109items); 1 y prior	Western pattern; healthy pattern	Western eating pattern did not enhance the danger of BC relapse (Ptrend = 0.89), total death rate (Ptrend = 0.48) and BC-specific death (Ptrend = 0.75). There is no relationship between a healthy dietary pattern and prognosis	Total energy intake, Age, PA, comorbidities (number), BMI, diagnosis, menopausal, ER status, adjuvant hormonal therapy usage, PR status, radiotherapy, HER2 status, chemotherapy, histology,
Anyene et al. (US) (73)	Cohort study	3646 women diagnosed with BC	The Block 2005 FFQ (139items); the past 6 months	PDI; hPDI; uPDI	Increased concordance with hPDI was associated with a reduced hazard of all-cause (HR:0.93, 95%CI: 0.83–1.05) and non-breast-cancer mortality (HR:0.83, 95%CI: 0.71–0.98), whereas increased concordance with uPDI was associated with increased hazards (HR:1.07, 95%CI: 0.96–1.2 and HR:1.20, 95%CI:1.02–1.41, respectively).	total energy intake, PA, education, race, smoking, menopausal, HER2 status, diagnosis (age)
Chlebowski et al. (US) (69)	RCT	48,835 postmenopausal women	FFQ daily intake	Low-Fat Dietary Pattern	deaths after breast cancer (n = 134) were significantly reduced (40 deaths 0.025% per year v 94 deaths 0.038% per year; HR:0.65; 95%CI: 0.45-0.94; P = 0.02) by the dietary intervention. During the 16.1-year follow-up, with 3,030 incident breast cancers, deaths after breast cancer also were significantly reduced (234 deaths 0.085% per year v 443 deaths 0.11% per year; HR:0.82; 95%CI:0.70-0.96; *P* = 0.01) in the dietary group.	NO
Chlebowski et al. (US) (72)	RCT	48,835 postmenopausal women	FFQ daily intake	Low-Fat Dietary Pattern	Breast cancer overall survival was significantly greater for women in the dietary intervention group than in the usual-diet comparison group (10-year survival of 82% and 78%, respectively; HR: 0.78; 95%CI:0.65-0.94; *P* = 0.01). In the dietary group there were fewer deaths from breast cancer (68 vs. 120; HR:0.86; 95%CI,0.64-1.17), other cancers (36 vs 65; HR:0.76; 95%CI:0.50-1.17), and cardiovascular disease (27 vs. 64; HR:0.62; 95%CI, 0.39-0.99).	NO
Kim et al. (Korea) (11)	A cross-sectional study	232 BC survivors (stage I-III) (21-79 y)	Non-consecutive 3-day dietary record	Healthy pattern; Western pattern	higher Healthy dietary pattern scores tended to have lower dyspnea scores but higher insomnia scores. For dyspnea, the least squares mean was 8.86, 95%CI: 5.05–15.52 in the bottom quartile and 2.87, 1.62–5.08 in the top quartile (p for trend = 0.005).	PA (Age/BMI/disease stage/menopausal) at diagnosis, marital, education, time since surgery, energy intake
Lei et al. (China) (75)	A cross-sectional and longitudinal study	1462 BCs, (diagnosed within 1 year)	FFQ (109items); 1 y prior	Pattern1: vegetables and fruits pattern; Pattern2: grain and animal food pattern	Pattern2 reduced scores for role functioning (B,95%CI) (−0.744, −0.147 to −0.017), dyspnea (−0.092, −0.092 to −0.092) constipation (−1.355; −2.174 to −0.536). pattern1 were positively associated with scores for global health (B,95%CI) (1.282, 0.545-2.019), physical functioning (0.545, 0.037–1.053), emotional functioning (1.426; 0.653–2.200) cognitive functioning (0.822; 0.007–1.637), while inversely associated with scores for nausea and vomiting (−0.382, −0.694 to −0.071), dyspnea (−0.570, −0.570 to −0.570), insomnia (−1.412; −2.647 to −0.177), loss of appetite (0.722, −1.311 to −0.132), constipation (−2.028, −2.775 to −1.281) diarrhea (0.929; −1.481 to −0.377)	Factor scores of the other DP (Age/menopausal/BMI/PA/total energy intake/time-points) at follow-up, hormonal therapy, education, current usage of adjuvant, income, PR status, comorbidities, ER status, AJCC stage

FFQ is an abbreviation for food frequency questionnaire; y is an abbreviation for year; OR is an abbreviation for odd ratio; CI is an abbreviation for Confidence Interval; SQFFQ is an abbreviation for Semi-Quantitative Food Frequency Questionnaire; HER2 is an abbreviation for human epidermal growth factor receptor 2; HRT is an abbreviation for hormone replacement therapy; ER is an abbreviation for estrogen receptor; PR stands for progesterone receptor; CM is an abbreviation for Chinese medicine; DQX is an abbreviation for food frequency questionnaire; SES is the abbreviation of socioeconomic state; PA is the abbreviation of physical activity; BBD stands for Benign breast disease; OCP stands for oral contraceptive; QOL stands for the quality of life Score; AJCC is short for American Joint Committee on Cancer; DP stands for Dietary pattern; BMI stands for Body Mass Index; PHT is an abbreviation for postmenopausal hormone therapy; aMED is an abbreviation for alternate Mediterranean Diet; NSAIDs is an abbreviation for Non-steroidal Antiinflammatory Drugs; WHR is an abbreviation for Waist-to-Hip Ratio; HT is an abbreviation for hormone therapy; FFP is an abbreviation for parity and age at first full-term pregnancy; DASH is an abbreviation for Dietary Approaches to Stop Hypertension; PDI is an abbreviation for Plant diet index; hPDI is an abbreviation for healthy plant diet index; uPDI is an abbreviation for Unhealthy vegetal diet index; MIND is an abbreviation for Mediterranean-DASH Intervention for Neurodegenerative Delay; D-OBS is an abbreviation for dietary oxidative balance score; E-DII is an abbreviation for Energy adjusted-Dietary Inflammatory Index; ACS is an abbreviation for American Cancer Society; HEI-2015 is an abbreviation for Healthy eating index; IDC is an abbreviation for invasive ductal carcinoma; ILC is an abbreviation for invasive lobular carcinoma.

10.3389/fnut.2022.1057057

TABLE 2 Newcastle-Ottawa Scale of 41 studies in the systematic review.

Study	Selection				Comparability	Exposure			Total star
	Definition of cases	Representativeness of cases	Selection of controls	Definition of controls		Assessment of outcome	Method of ascertainment	Non-response rate	
Castelló et al. (37)	1	1	1	1	2	1	1	0	8
Sadeghi et al. (16)	1	1	1	1	2	1	1	0	8
Lu et al. (62)	1	1	1	0	2	1	1	1	8
Guinter et al. (63)	0	1	1	1	2	1	1	1	8
Krusinska et al. (22)	1	1	0	1	2	1	1	1	8
Krusinska et al. (23)	1	1	0	1	2	1	1	1	8
Jalali et al. (40)	1	1	1	1	2	1	1	1	9
Heidari et al. (18)	1	1	1	1	2	1	1	1	9
Shridhar et al. (52)	0	1	1	1	2	1	1	0	7
Sedaghat et al. (20)	1	1	1	1	2	1	1	1	9
Turati et al. (36)	1	1	1	1	2	1	1	1	9
Marzbani et al. (19)	1	1	1	1	2	1	1	1	9
Heidari et al. (58)	1	1	0	1	2	1	1	0	7
Stasiewicz et al. (25)	1	0	1	1	2	1	1	1	8
Hajji-Louati et al. (48)	0	1	1	1	2	1	1	1	8
Sasanfar et al. (49)	1	1	0	1	2	1	1	1	8
Aghamohammadi et al. (60)	1	1	0	1	2	1	1	1	8
Soltani et al. (57)	1	1	0	1	2	1	1	1	8
Cao et al. (34)	1	1	1	1	2	1	1	1	9
Cao et al. (80)	0	1	1	1	2	1	1	0	7
Cao et al. (35)	0	1	1	1	2	1	1	1	8
Hammad et al. (45)	0	1	0	1	2	1	1	0	6
Jacobs et al. (56)	0	0	1	1	2	1	1	1	7
Flores-García et al. (24)	1	1	1	1	2	1	1	1	9
Sheikhhossein et al. (81)	1	1	0	1	2	1	1	1	8
Rigi et al. (50)	1	1	0	1	2	1	1	1	8
Niclis et al. (46)	1	1	1	1	2	1	1	1	9
Payandeh et al. (53)	0	0	0	1	2	1	1	1	6

(Continued)

10.3389/fnut.2022.1057057

10.3389/fnut.2022.1057057

TABLE 2 (Continued)

Study	Selection				Comparability	Exposure			Total star
	Definition of cases	Representativeness of cases	Selection of controls	Definition of controls		Assessment of outcome	Method of ascertainment	Non-response rate	
Foroozani et al. (55)	1	0	1	1	2	1	1	1	8
Toorang et al. (59)	1	1	0	1	2	1	1	0	7
Cao et al. (9)	0	1	1	1	2	1	1	1	8
Rigi et al. (26)	1	1	0	1	2	1	1	0	7
Sasanfar et al. (41)	0	1	0	1	2	1	1	1	7
Hosseini et al. (17)	1	1	0	1	2	1	1	1	8
Shamsi et al. (32)	1	1	0	0	2	1	1	0	6

Dietary patterns and quality of life in BC

Two studies investigated the effects of dietary patterns on quality of life in patients with BC. A Korean study showed that healthy eating habits improved dyspnea but increased insomnia in specific populations (11). A Chinese study investigated the relationship between eating more grain and animal products and poorer functions, including respiratory function and constipation, and the effects of a high-fruit and vegetable diet in improving quality of life, including physical, emotional, and cognitive functions, as well as reducing common gastrointestinal reactions, breathing problems, and insomnia (75).

Discussion

A search was conducted to find and analyze recent studies examining the influence of dietary patterns on BC, to identify dietary patterns likely to prevent BC and improve its prognosis, and enhance the quality of life for BC survivors. The available data suggested that healthy dietary patterns had the most scientific evidence to support their beneficial effects compared with other dietary patterns. The different dietary patterns are discussed below in order of scientific evidence.

Adhering to a healthy diet pattern reduced the risk of BC, BC recurrence, all-cause mortality, and overall mortality, and improved the quality of life (especially in postmenopausal women and hormone receptor-negative women). This dietary pattern was characterized by low intakes of carbohydrates, red and processed meats, and sweet foods, and increased intakes of protein, folic acid, calcium, vitamin D, and fiber. Thus, even though physical activity decreased, the dietary fat energy percentage also decreased and body weight remained unchanged. This was consistent with a study of low-fat diet patterns (10). The results of the study on a prudent diet pattern (23), characterized by more frequent consumption of dairy products, fruit, vegetables, wholewheat bread, fish, and fruit juice, were similar, especially in premenopausal women, with significance for hormone receptor-positive and -negative tumors. This dietary pattern may reduce the risk of BC by regulating plasma lipid biomarkers, and improve the prognosis by reducing the overexpression of RhoA and Rho-associated protein kinase-related (8, 34).

Current evidence shows that high adherence to a Mediterranean diet significantly reduces the incidence rate of BC, especially invasive ductal and lobular BC, it is more significant for ER- or ER+, has the best anti-tumor-metastasis effect, and reduces disease recurrence, overall mortality, and other complications such as cardiovascular disease, and has a greater beneficial impact than a prudent dietary pattern (37, 68). The mechanism involves reducing glucose, weight, and waist circumference, improving biochemical parameters, reducing the biological activities of insulin-like growth factor 1 (IGF-1), testosterone, and estradiol, increasing antioxidation, and repairing DNA (36, 65). A summary analysis of the individual components of the Mediterranean diet showed that the protective effect was mainly attributable to fruit, vegetables, and whole grains (21, 35). The protective effect of the Mediterranean diet, which contains fish, beans, nuts, seeds, whole grains, and vegetables, may be due to specific chemical components, such as lignans and polyphenols, or to its wider nutrient components, such as fatty acids, resveratrol, organic sulfur compounds, quercetin, kaempferol, and

TABLE 3 Newcastle-Ottawa Scale of 20 studies in the systematic review.

Cohort study	Selection				Comparability	Outcome			Total star
	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Harris et al. (44)	0	1	1	1	2	1	1	1	8
Kojima et al. (54)	1	1	1	1	2	1	1	0	8
Guinter et al. (82)	1	1	1	1	2	1	1	1	9
Haridass et al. (21)	0	1	1	1	2	1	1	0	7
Haraldsdottir et al. (83)	1	1	1	1	2	1	1	0	8
Petimar et al. (31)	1	1	1	1	2	1	1	0	8
Gardeazabal et al. (47)	0	1	1	1	2	1	1	1	8
Dela Cruz et al. (33)	1	1	1	1	2	1	1	1	9
Romanos-Nanclares et al. (51)	0	1	1	1	2	1	1	1	8
Gardeazabal et al. (39)	0	1	1	1	2	1	1	1	8
Park et al. (43)	1	1	1	1	2	1	1	0	8
Jang et al. (74)	1	1	1	1	2	1	1	1	9
Karavasiloglou et al. (64)	1	1	1	0	2	1	1	1	8
Wang et al. (66)	1	1	1	0	2	1	1	1	8
Di Maso et al. (68)	1	1	1	0	2	1	1	1	8
Wang et al. (14)	0	1	1	0	2	1	1	1	7
Ergas et al. (65)	1	1	1	0	2	1	0	1	7
Lei et al. (67)	1	1	1	0	2	1	1	1	8
Anyene et al. (73)	1	1	1	0	2	1	1	1	8

10.3389/fnut.2022.1057057

TABLE 4 JBI Scale of 2 studies in the systematic review.

Author	A	B	C	D	E	F	G	H	I	J	Total score
Kim et al. (11)	2	1	2	2	1	2	2	2	2	2	18
Lei et al. (75)	2	1	2	2	2	2	2	2	2	2	19

A: Whether the research objectives of the study are clear, Whether the basis for the establishment of the topic is sufficient; B: How the population was selected (whether the study subjects were randomly selected, whether stratified sampling was taken to improve sample representativeness); C: Whether the inclusion and exclusion criteria of the sample are clearly described; D: whether clearly describes the sample characteristics; E: Whether the tools for data collection are reliable and valid (e.g., investigator surveys, how reproducible are the findings); F: What are the measures to verify the authenticity of the information; G: Whether ethical issues are taken into account; H: Whether the statistical method is correct; I: Whether the statement of the findings of the study is appropriate and accurate (whether the results and inferences are distinguished, and whether the results are faithful to the data rather than inferences); J: does it make a clear elaborate of the value of the study. 0 points: does not meet the requirements; 1 point: mentioned but not described in detail; 2 points: detailed, comprehensive, correct description.

apigenin, as well as the common micronutrients zinc and selenium, and phytochemicals, such as flavonoids, carotenoids, vitamins C and E, vitamin A, natural retinoids, and omega-3 polyunsaturated fatty acids. An increase in circulating tumor cells in the body was shown to be delayed by low-fat components (76). These compounds have demonstrated anticancer properties including affecting the growth and progression of BC, cancer cell cycle growth arrest, apoptosis, inflammation, angiogenesis, and DNA methylation of the gene, which can prevent the progress of obesity-related BC, and has a positive impact on all-cause mortality (77, 78).

Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), a Mediterranean diet, and DASH diet are all plant-based diets, emphasizing the consumption of fruits and green leafy vegetables, beans, whole grains, nuts, fish, and poultry, and low intakes of saturated fats and red meat. These diets are sources of carotenoids, flavonoids, folic acid, and vitamin E. The mechanisms of this type of diet reduce the risk and mortality of BC similar to the effects of a Mediterranean diet (21, 66).

Compliance with a plant-based diet reduces the risk of BC, especially those types of BC that are more likely to become invasive, and improves the overall survival rate, especially in patients with ER–, HER2 basal-like, and luminal A BC. This diet includes more fruit and vegetables, especially cruciferous and yellow/orange vegetables, beans, nuts, seeds, and whole grains (12). The mechanism involves the reduction of IGF-1, blood glucose, and total cholesterol, while phytochemicals (allicin, hesperidin, and astragalus polysaccharide) included in this diet significantly inhibit the growth of primary tumors and metastatic lesions by reducing the expression of genes (50). Although there is a negative correlation trend between soluble fiber and estradiol levels, serum estradiol and estrone levels are not related to dietary fiber. A plant-based diet can thus improve the prognosis of BC by affecting the intestinal microbiota and hormone levels (21, 66); however, further studies are needed to clarify this.

In addition, a low-glucose diet, characterized by the intake of glucose equal to or lower than the average fasting level, improved insulin resistance (HOMA-IR) and other cancer-related serum biomarkers in some studies, thereby favorably regulating postmenopausal obesity as a postmenopausal BC prevention strategy (79). Other dietary patterns that improve the prognosis and quality of life of BC patients, such as an anti-inflammatory diet, have been shown to improve the prognosis of BC patients by reducing cardiovascular mortality (25).

It is also important to understand the mechanisms of dietary patterns that are negatively associated with disease, such as a Western diet, which is characterized by higher intakes of red and processed meat, dairy products, and saturated fats. A Western diet can lead to BC via the production of several carcinogenic compounds associated with cooking and processing meat, including nitrates, nitrites, heterocyclic amines, and polycyclic aromatic hydrocarbons (55). In an inflammatory diet, inflammatory markers increase BC risk by stimulating angiogenesis, cell proliferation, and migration, and preventing apoptosis, while other inflammatory biomarkers may reduce quality of life. In addition, the key mediators of the inflammatory response promote tumor growth, angiogenesis, and invasion through the influence of insulin resistance and increased cytokines (25). However, results on this topic are currently lacking, and more correlation studies are needed.

This study showed that a balanced dietary pattern [large amounts of protein (mainly white meat), fruits, and vegetables (rich in vitamins and minerals), nuts, beans, low omega-3 fatty acid diet of fish and seafood, whole grains, vegetable oil, and low intake of spices] may prevent BC and improve BC prognosis. However, except for alcohol intake, no studies have yet demonstrated a consistent and significant correlation for any specific foods, and the study of dietary patterns is affected by regional and cultural backgrounds. The beneficial dietary patterns summarized in this review should thus be interpreted carefully in view of the exploratory nature of the analysis. The findings are inconsistent, indicating the need for further studies to explore this topic.

Niclis et al.'s case-control study of inflammatory dietary patterns showed an association with disease risk, whereas Gardeazabal et al.'s cohort study showed no such association, which may reflect recall bias rather than a true difference (46, 47). Some studies showed that inflammatory diets increased the risk of BC (ER+, PR+, HER2+), but few studies have examined hormone-negative or triple-negative BC, and the effect of diet on heterogeneous breast risk or prognosis remains unclear (25). Foroozani et al.'s study did not assess the role of dietary patterns based on the histological subtype of breast cancer (55). Finally, although most of the included studies adjusted for a large number of confounding factors (body mass index, family history, smoking, etc.) that may confuse the association between dietary patterns and BC, not all studies adjusted for all potential confounding factors, such as physical activity and smoking. Future research should thus pay attention to this aspect. In addition, more evidence is required regarding prior and posterior eating patterns, study area, menopausal status, and hormonal status, to produce more conclusive results.

Limitations

This study had some limitations. We only retrieved published literature, which may have led to publication bias due to incomplete literature collection. In addition, the reproducibility of dietary patterns was poor, due to differences in dietary research methods, evaluation methods (factor analysis, reduced rank regression),

research populations, and regions. Because of the high heterogeneity among the included studies, the results were not analyzed by objective quantitative methods, and we were therefore unable to perform subgroup analyses due to the limited number of included studies.

Notably, despite the large number of studies, nutritional studies often produced inaccurate and/or contradictory results. In addition, BC is a multifactorial disease, and diet is only one of numerous risk factors associated with its pathology.

In addition, nutrition research has some problems. First, food surveys do not conform to reality, and different patients have different reactions to the same food as a result of interactions among genes, nutrients, and the intestinal microbiota. In addition, food nutritional profiles are affected by food practices and storage (e.g., fresh vegetables are chemically different from processed vegetables). Although clinical trials can be used to investigate simple and short-term problems, they are unsuitable for studying long-term diseases: it is difficult to randomly assign different diets to different populations and track them for many years to determine if a certain food is related to specific diseases. Furthermore the confounding factors in observational studies were not controlled, potentially leading to inaccurate results.

Conclusion

Despite these limitations, the results of different types of studies (with different environments, methods, and patients) suggested similar conclusions, indicating a link between dietary patterns and clear health outcomes. Based on these findings, it is better to propose a "healthy" diet model, rather than claim any impact of specific foods or food ingredients. BC patients should be encouraged to improve their dietary habits before, during, and after treatment, in order to improve their long-term survival and quality of life.

This study systematically reviewed the impact of dietary patterns on BC risk, treatment outcomes, prognosis, and quality of life. On one hand, most studied dietary patterns tended to prevent the occurrence of BC, while fewer studies examined their effects on the prognosis and quality of life of survivors. On the other hand, more RCTs are needed to demonstrate the effects of these dietary patterns on cancer-specific outcomes (event-free survival, recurrence), and more research is required to clarify the mechanisms underlying the correlation of dietary patterns with BC based on biological processes.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

YB and JZ: conceptualization, methodology, formal analysis, and writing—original draft. HS and MX: investigation. JCQ and SJ: resources. YL and JLQ: writing—review and editing. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by Su Jiao Ji Han (2019) No. 2, Jiangsu Province Elderly Education Learning Resource Library Sub library Project and Postgraduate Research and Practice Innovation Program of Jiangsu Province, China (Grant number: SJCX22_1829).

Acknowledgments

We thank YL for suggestions on the design and revision of the manuscript and JZ and HS for consulting the literature. We are grateful for the network equipment support policy of the School of Nursing, Yangzhou University, China. We also thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1057057/full#supplementary-material

References

1. WHO, *World Cancer Day 2021: Spotlight on IARC Research Related to Breast Cancer*. (2021). Available online at: https://www.iarc.who.int/featured-news/world-cancer-day-2021/ (accessed May 02, 2021).

2. Soto-Pantoja D, Gaber M, Arnone A, Bronson S, Cruz-Diaz N, Wilson A, et al. Diet alters entero-mammary signaling to regulate the breast microbiome and tumorigenesis. *Cancer Res.* (2021) 81:3890–904. doi: 10.1158/0008-5472.CAN-20-2983

3. Corsetto P, Montorfano G, Zava S, Colombo I, Rizzo A. Nutrient deprivation induces lipid alterations and reduction of invasivity in triple negative breast cancer cells. *Mol Living Syst.* (2019) 9(Suppl. 1):362–3.

4. Kerr J, Anderson C, Lippman S. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. *Lancet Oncol.* (2017) 18:e457–71. doi: 10.1016/s1470-204530411-4

5. Gleason P, Boushey C, Harris J, Zoellner J. Publishing nutrition research: a review of multivariate techniques–part 3: data reduction methods. *J Acad Nutr Diet.* (2015) 115:1072–82. doi: 10.1016/j.jand.2015.03.011

6. Castelló A, Buijsse B, Martín M, Ruiz A, Casas A, Baena-Cañada J, et al. Evaluating the applicability of data-driven dietary patterns to independent samples with a focus on measurement tools for pattern similarity. *J Acad Nutr Diet.* (2016) 116:1914–24.e6. doi: 10.1016/j.jand.2016.05.008

7. Radkevich L, Radkevich D. The dietary patterns are a modifying risk factor for breast cancer: an ecological study. *Doklady Biol Sci.* (2017) 472:21–7. doi: 10.1134/S0012496617010070

8. Shuvo S, Ahmad T, Paul D, Zahid M. Dietary patterns and knowledge perception of breast cancer risk patients: a case-control study in Bangladesh. *Nutr Food Sci.* (2017) 47:270–87. doi: 10.1108/NFS-05-2016-0060

9. Cao S, Liu L, Zhu Q, Zhu Z, Zhou J, Wei P, et al. Adherence to the vegetable-fruit-soy dietary pattern, a reference from Mediterranean diet, protects against postmenopausal breast cancer among Chinese women. *Front Nutr.* (2022) 9:800996. doi: 10.3389/fnut.2022.800996

10. Prentice R, Aragaki A, Howard B, Chlebowski R, Thomson C, Van Horn L, et al. Low-fat dietary pattern among postmenopausal women influences long-term cancer, cardiovascular disease, and diabetes outcomes. *J Nutr.* (2019) 149:1565–74. doi: 10.1093/jn/nxz107

11. Kim N, Song S, Jung S, Lee E, Kim Z, Moon H, et al. Dietary pattern and health-related quality of life among breast cancer survivors. *BMC Womens Health.* (2018) 18:65. doi: 10.1186/s12905-018-0555-7

12. Dandamudi A, Tommie J, Nommsen-Rivers L, Couch S. Dietary patterns and breast cancer risk: a systematic review. *Anticancer Res.* (2018) 38:3209–22. doi: 10.21873/anticanres.12586

13. Chlebowski R, Anderson G, Manson J, Prentice R, Aragaki A, Snetselaar L, et al. Low-fat dietary pattern and cancer mortality in the women's health initiative (WHI) randomized controlled trial. *JNCI Cancer Spectr.* (2018) 2:ky065. doi: 10.1093/JNCICS/PKY065

14. Wang T, Farvid M, Kang J, Holmes M, Rosner B, Tamimi R, et al. Diabetes risk reduction diet and survival after breast cancer diagnosis. *Cancer Res.* (2021) 81:4155–62. doi: 10.1158/0008-5472.CAN-21-0256

15. Hidaka B, Kimler B, Fabian C, Carlson S. An empirically derived dietary pattern associated with breast cancer risk is validated in a nested case-control cohort from a randomized primary prevention trial [comparative study; journal article; randomized controlled trial; validation study]. *Clin Nutr.* (2017) 17:8–17. doi: 10.1016/j.clnesp.2016.10.008

16. Sadeghi M, Akbari M, Rashidkhani B, Ajami M, Jamshidi-Naeini Y, Davoodi S. Association between dietary patterns with breast cancer and pathobiological factor HER-2. *J Mazandaran Univ Med Sci.* (2017) 26:76–87.

17. Hosseini F, Shab-Bidar S, Ghanbari M, Majdi M, Sheikhhossein F, Imani H. Food quality score and risk of breast cancer among Iranian women: findings from a case control study. *Nutr Cancer Int J.* (2022) 74:1660–9. doi: 10.1080/01635581.2021.1957136

18. Heidari Z, Jalali S, Sedaghat F, Ehteshami M, Rashidkhani B. Dietary patterns and breast cancer risk among Iranian women: a case-control study. *Eur J Obstetr Gynecol Reprod Biol.* (2018) 230:73–8. doi: 10.1016/j.ejogrb.2018.09.018

19. Marzbani B, Nazari J, Najafi F, Marzbani B, Shahabadi S, Amini M, et al. Dietary patterns, nutrition, and risk of breast cancer: a case-control study in the west of Iran. *Epidemiol Health.* (2019) 41:e2019003. doi: 10.4178/epih.e2019003

20. Sedaghat F, Heidari Z, Jalali S, Doustmohammadian A, Ehteshami M, Rashidkhani B. Healthy eating index 2010 and breast cancer risk. *Nutr Cancer Int J.* (2018) 70:860–6. doi: 10.1080/01635581.2018.1490781

21. Haridass V, Ziogas A, Neuhausen S, Anton-Culver H, Odegaard A. Diet quality scores inversely associated with postmenopausal breast cancer risk are not associated with premenopausal breast cancer risk in the California teachers study. *J Nutr.* (2018) 148:1830–7. doi: 10.1093/jn/nxy187

22. Krusinska B, Wadolowska L, Slowinska M, Biernacki M. Associations of dietary patterns and metabolic-hormone profiles with breast cancer risk: a case-control study. *Nutrients.* (2018) 10:2013. doi: 10.3390/nu10122013

23. Krusinska B, Hawrysz I, Wadolowska L, Slowinska M, Biernacki M, Czerwinska A, et al. Associations of Mediterranean diet and a posteriori derived dietary patterns with breast and lung cancer risk: a case-control study. *Nutrients.* (2018) 10:470. doi: 10.3390/nu10040470

24. Flores-García M, Mérida-Ortega Á, Denova-Gutiérrez E, López-Carrillo L. Dietary patterns and breast cancer risk in women from Northern Mexico. *Nutr Cancer.* (2021) 73:2763–73. doi: 10.1080/01635581.2020.1860241

25. Stasiewicz B, Wadolowska L, Biernacki M, Slowinska M, Drozdowski M. Hybrid dietary-blood inflammatory profiles and postmenopausal breast cancer: a case-control study. *Nutrients.* (2020) 12:3503. doi: 10.3390/nu12113503

26. Rigi S, Salari-Moghaddam A, Benisi-Kohansal S, Azadbakht L, Esmaillzadeh A. Dietary glycaemic index and glycaemic load in relation to risk of breast cancer. *Public Health Nutr.* (2022) 25:1658–66. doi: 10.1017/S1368980021004018

27. Sangaramoorthy M, Koo J, John E. Intake of bean fiber, beans, and grains and reduced risk of hormone receptor-negative breast cancer: the San Francisco bay area breast cancer study. *Cancer Med.* (2018) 7:2131–44. doi: 10.1002/cam4.1423

28. Chang Y, Hou Y, Chen L, Wu J, Wu C, Chang Y, et al. Is vegetarian diet associated with a lower risk of breast cancer in Taiwanese women? *BMC Public Health.* (2017) 17:800. doi: 10.1186/s12889-017-4819-1

29. Jacobs I, Taljaard-Krugell C, Ricci C, Vorster H, Rinaldi S, Cubasch H, et al. Dietary intake and breast cancer risk in black South African women: the South African breast cancer study. *Br J Nutr.* (2019) 121:591–600. doi: 10.1017/S0007114518003744

30. Shin W, Lee H, Shin A, Lee J, Lee S, Lee J, et al. Multi-grain rice diet decreases risk of breast cancer in Korean women: results from the health examinees study. *Nutrients.* (2020) 12:2273. doi: 10.3390/nu12082273

31. Petimar J, Park Y, Smith-Warner S, Fung T, Sandler D. Dietary index scores and invasive breast cancer risk among women with a family history of breast cancer. *Am J Clin Nutr.* (2019) 109:1393–401. doi: 10.1093/ajcn/nqy392

32. Shamsi U, Gill T, Khan S, Azam I, Callen D, Iqbal R. The modified alternate healthy eating index-2010 and breast cancer risk among women from Karachi, Pakistan. *J Pak Med Assoc.* (2022) 72:1289–93. doi: 10.47391/JPMA.01276

33. Dela Cruz R, Park S, Shvetsov Y, Boushey C, Monroe K, Le Marchand L, et al. Diet quality and breast cancer incidence in the multiethnic cohort. *Eur J Clin Nutr.* (2020) 74:1743–7. doi: 10.1038/s41430-020-0627-2

34. Cao S, Liu L, Zhu Q, Zhu Z, Zhou J, Wei P, et al. Association between dietary patterns and plasma lipid biomarker and female breast cancer risk: comparison of latent class analysis (LCA) and factor analysis (FA). *Front Nutr.* (2021) 8:645398. doi: 10.3389/fnut.2021.645398

35. Cao S, Zhu Z, Zhou J, Li W, Dong Y, Qian Y, et al. Associations of one-carbon metabolism-related gene polymorphisms with breast cancer risk are modulated by diet, being higher when adherence to the Mediterranean dietary pattern is low. *Breast Cancer Res Treat.* (2021) 187:793–804. doi: 10.1007/s10549-021-06108-8

36. Turati F, Carioli G, Bravi F, Ferraroni M, Serraino D, Montella M, et al. Mediterranean diet and breast cancer risk. *Nutrients.* (2018) 10:326. doi: 10.3390/nu10030326

37. Castelló A, Boldo E, Pérez-Gómez B, Lope V, Altzibar J, Martín V, et al. Adherence to the Western, Prudent and Mediterranean dietary patterns and breast cancer risk: MCC-Spain study. *Maturitas.* (2017) 103:8–15. doi: 10.1016/j.maturitas.2017.06.020

38. Li Y, Hu B, Wu X, Qi X, Jiang J, Cui X, et al. Adherence to Mediterranean diet and the risk of breast cancer: a meta-analysis. *Transl Cancer Res.* (2018) 7:1290–7. doi: 10.21037/tcr.2018.10.13

39. Gardeazabal I, Romanos-Nanclares A, Martínez-González M, Castelló A, Sánchez-Bayona R, Pérez-Gómez B, et al. Mediterranean dietary pattern is associated with lower incidence of premenopausal breast cancer in the Seguimiento Universidad de Navarra (SUN) project. *Public Health Nutr.* (2020) 23:3148–59. doi: 10.1017/s1368980019003835

40. Jalali S, Shivappa N, Hebert J, Heidari Z, Hekmatdoost A, Rashidkhani B. Dietary inflammatory index and odds of breast cancer in a case-control study from Iran. *Nutr Cancer Int J.* (2018) 70:1034–42. doi: 10.1080/01635581.2018.1494843

41. Sasanfar B, Toorang F, Mozafari Nia M, Salehi-Abargouei A, Zendehdel K. Dietary inflammatory index and breast cancer: report from a large-scale case-control study. *Nutr Cancer Int J.* (2022) 74:1692–700. doi: 10.1080/01635581.2021.1957489

42. Ghanbari M, Shahinfar H, Imani H, Safabakhsh M, Shab-Bidar S. Association of empirically derived food-based inflammatory potential of the diet and breast cancer: a hospital-based case-control study. *Clin Breast Cancer.* (2022) 22:E567–75. doi: 10.1016/j.clbc.2021.12.010

43. Park Y, Shivappa N, Petimar J, Hodgson M, Nichols H, Steck S, et al. Dietary inflammatory potential, oxidative balance score, and risk of breast cancer: findings from the sister study. *Int J Cancer.* (2021) 149:615–26. doi: 10.1002/ijc.33581

44. Harris H, Willett W, Vaidya R, Michels K. An adolescent and early adulthood dietary pattern associated with inflammation and the incidence of breast cancer. *Cancer Res.* (2017) 77:1179–87. doi: 10.1158/0008-5472.CAN-16-2273

45. Hammad S, Mahmoud R, Shivappa N, Hebert J, Marie L, Tayyem R. Dietary inflammatory index and odds of breast cancer: a case-control study. *Food Sci Nutr.* (2021) 9:5211–9. doi: 10.1002/fsn3.2493

46. Niclis C, Shivappa N, Hebert J, Tumas N, del Pilar Diaz M. The inflammatory potential of diet is associated with breast cancer risk in urban Argentina: a multilevel analysis. *Nutr Cancer Int J.* (2021) 73:1898–907. doi: 10.1080/01635581.2020.1817953

47. Gardeazabal I, Ruiz-Canela M, Sanchez-Bayona R, Romanos-Nanclares A, Aramendia-Beitia J, Shivappa N, et al. Dietary inflammatory index and incidence of breast cancer in the SUN project. *Clin Nutr.* (2019) 38:2259–68. doi: 10.1016/j.clnu.2018.09.030

48. Hajji-Louati M, Cordina-Duverger E, Laouali N, Mancini F, Guenel P. A case-control study in France showing that a pro-inflammatory diet is associated with a higher risk of breast cancer. *Sci Rep.* (2021) 11:17019. doi: 10.1038/s41598-021-95955-y

49. Sasanfar B, Toorang F, Booyani Z, Vassalami F, Mohebbi E, Azadbakht L, et al. Adherence to plant-based dietary pattern and risk of breast cancer among Iranian women. *Eur J Clin Nutr.* (2021) 75:1578–87. doi: 10.1038/s41430-021-00869-7

50. Rigi S, Mousavi S, Benisi-Kohansal S, Azadbakht L, Esmaillzadeh A. The association between plant-based dietary patterns and risk of breast cancer: a case–control study. *Sci Rep.* (2021) 11:3391. doi: 10.1038/s41598-021-82659-6

51. Romanos-Nanclares A, Toledo E, Sánchez-Bayona R, Sánchez-Quesada C, Martínez-González M, Gea A. Healthful and unhealthful provegetarian food patterns and the incidence of breast cancer: results from a Mediterranean cohort. *Nutrition.* (2020) 79–80:110884. doi: 10.1016/j.nut.2020.110884

52. Shridhar K, Singh G, Dey S, Singh Dhatt S, Paul Singh Gill J, Goodman M, et al. Dietary patterns and breast cancer risk: a multi-centre case control study among north Indian women. *Int J Environ Res Public Health.* (2018) 15:1946. doi: 10.3390/ijerph15091946

53. Payandeh N, Shahinfar H, Amini M, Jafari A, Safabakhsh M, Imani H, et al. The lack of association between plant-based dietary pattern and breast cancer: a hospital-based case-control study. *Clin Nutr Res.* (2021) 10:115–26. doi: 10.7762/cnr.2021.10.2.115

54. Kojima R, Okada E, Ukawa S, Mori M, Wakai K, Date C, et al. Dietary patterns and breast cancer risk in a prospective Japanese study. *Breast Cancer.* (2017) 24:152–60. doi: 10.1007/s12282-016-0689-0

55. Foroozani E, Akbari A, Amanat S, Rashidi N, Bastam D, Ataee S, et al. Adherence to a Western dietary pattern and risk of invasive ductal and lobular breast carcinomas: a case-control study. *Sci Rep.* (2022) 12:5859. doi: 10.1038/s41598-022-09725-5

56. Jacobs I, Taljaard-Krugell C, Wicks M, Cubasch H, Joffe M, Laubscher R, et al. Dietary patterns and breast cancer risk in Black Urban South African women: the SABC study. *Nutrients.* (2021) 13:4106. doi: 10.3390/nu13114106

57. Soltani S, Benisi-Kohansal S, Azadbakht L, Esmaillzadeh A. Association between adherence to "dietary approaches to stop hypertension" eating plan and breast cancer. *Nutr Cancer.* (2021) 73:433–41. doi: 10.1080/01635581.2020.1756354

58. Heidari Z, Mohammadi E, Aghamohammadi V, Jalali S, Rezazadeh A, Sedaghat F, et al. Dietary approaches to stop hypertension (DASH) diets and breast cancer among women: a case control study. *BMC Cancer.* (2020) 20:708. doi: 10.1186/s12885-020-07209-1

59. Toorang F, Sasanfar B, Esmaillzadeh A, Zendehdel K. Adherence to the DASH Diet and risk of breast cancer. *Clin Breast Cancer.* (2022) 22:244–51. doi: 10.1016/j.clbc.2021.07.010

60. Aghamohammadi V, Salari-Moghaddam A, Benisi-Kohansal S, Taghavi M, Azadbakht L, Esmaillzadeh A. Adherence to the MIND diet and risk of breast cancer: a case-control study. *Clin Breast Cancer.* (2021) 21:E158–64. doi: 10.1016/j.clbc.2020.09.009

61. Fereidani S, Eini-Zinab H, Heidari Z, Jalali S, Sedaghat F, Rashidkhani B. Nutrient patterns and risk of breast cancer among Iranian women: a case- control study. *Asian Pac J Cancer Prev.* (2018) 19:2619–24.

62. Lu S, Qian Y, Huang X, Yu H, Yang J, Han R, et al. The association of dietary pattern and breast cancer in Jiangsu, China: a population-based case-control study. *PLoS One.* (2017) 12:e0184453. doi: 10.1371/journal.pone.0184453

63. Guinter M, McLain A, Merchant A, Sandler D, Steck S. A dietary pattern based on estrogen metabolism is associated with breast cancer risk in a prospective cohort of postmenopausal women. *Int J Cancer.* (2018) 143:580–90. doi: 10.1002/ijc.31387

64. Karavasiloglou N, Pestoni G, Faeh D, Rohrmann S. Post-diagnostic diet quality and mortality in females with self-reported history of breast or gynecological cancers: results from the third national health and nutrition examination survey (NHANES III). *Nutrients.* (2019) 11:2558. doi: 10.3390/nu11112558

65. Ergas I, Cespedes Feliciano E, Bradshaw P, Roh J, Kwan M, Cadenhead J, et al. Diet quality and breast cancer recurrence and survival: the pathways study. *JNCI Cancer Spectr.* (2021) 5:kab019. doi: 10.1093/jncics/pkab019

66. Wang F, Cai H, Gu K, Shi L, Yu D, Zhang M, et al. Adherence to dietary recommendations among long-term breast cancer survivors and cancer outcome associations. *Cancer Epidemiol Biomark Prev.* (2020) 29:386–95. doi: 10.1158/1055-9965.EPI-19-0872

67. Lei Y, Ho S, Kwok C, Cheng A, Cheung K, Lee R, et al. Dietary pattern at 18-month post-diagnosis and outcomes of breast cancer among Chinese women with early-stage breast cancer. *Cancer Manag Res.* (2021) 13:4553–65. doi: 10.2147/cmar.S298619

68. Di Maso M, Dal Maso L, Augustin L, Puppo A, Falcini F, Stocco C, et al. Adherence to the Mediterranean diet and mortality after breast cancer. *Nutrients.* (2020) 12:3649. doi: 10.3390/nu12123649

69. Chlebowski R, Aragaki A, Anderson G, Thomson C, Manson J, Simon M, et al. Low-fat dietary pattern and breast cancer mortality in the women's health initiative randomized controlled trial. *J Clin Oncol.* (2017) 35:2919–26. doi: 10.1200/jco.2016.72.0326

70. Pan K, Luo J, Aragaki A, Chlebowski R. Weight loss, diet composition and breast cancer incidence and outcome in postmenopausal women. *Oncotarget.* (2019) 10:3088–92. doi: 10.18632/oncotarget.26864

71. Xu L, Peterson L. The impact of diet on breast cancer outcomes [review]. *Curr Nutr Rep.* (2019) 8:212–21. doi: 10.1007/s13668-019-00278-0

72. Chlebowski R, Aragaki A, Anderson G, Simon M, Manson J, Neuhouser M, et al. Association of low-fat dietary pattern with breast cancer overall survival: a secondary analysis of the women's health initiative randomized clinical trial. *JAMA Oncol.* (2018) 4:e181212. doi: 10.1001/jamaoncol.2018.1212

73. Anyene I, Ergas I, Kwan M, Roh J, Ambrosone C, Kushi L, et al. Plant-based dietary patterns and breast cancer recurrence and survival in the pathways study. *Nutrients.* (2021) 13:3374. doi: 10.3390/nu13103374

74. Jang H, Chung M, Kang S, Park Y. Association between the dietary inflammatory index and risk for cancer recurrence and mortality among patients with breast cancer. *Nutrients.* (2018) 10:1095. doi: 10.3390/nu10081095

75. Lei Y, Ho S, Kwok C, Cheng A, Cheung K, Lee R, et al. Association of high adherence to vegetables and fruits dietary pattern with quality of life among Chinese women with early-stage breast cancer. *Qual Life Res.* (2022) 31:1371–84. doi: 10.1007/s11136-021-02985-0

76. Liu X. *Evaluation of the Effect of Dietary Pattern on Metastasis of Breast Cancer Based on in Vivo Capture of Circulating Tumor Cells*. Jinan: Shandong Normal University (2020).

77. Lorenzo P, Izquierdo A, Diaz Lagares A, Carreira M, Macias Gonzalez M, Cueva J, et al. An epigenetic signature of obesityrelated breast cancer is reflected in leucocytes and associated with Mediterranean dietary pattern [conference abstract]. *Obes Rev.* (2020) 21(Suppl. 1):e13118. doi: 10.1111/obr.13118

78. Lorenzo P, Izquierdo A, Diaz-Lagares A, Carreira M, Macias-Gonzalez M, Sandoval J, et al. ZNF577 methylation levels in leukocytes from women with breast cancer is modulated by adiposity, menopausal state, and the Mediterranean diet. *Front Endocrinol.* (2020) 11:245. doi: 10.3389/fendo.2020.00245

79. Schembre S, Jospe M, Giles E, Sears D, Liao Y, Basen-Engquist K, et al. A low-glucose eating pattern improves biomarkers of postmenopausal breast cancer risk: an exploratory secondary analysis of a randomized feasibility trial. *Nutrients.* (2021) 13:4508. doi: 10.3390/nu13124508

80. Cao S, Lu S, Zhou J, Zhu Z, Li W, Su J, et al. Association between dietary patterns and risk of breast cancer in Chinese female population: a latent class analysis. *Public Health Nutr.* (2021) 24:4918–28. doi: 10.1017/s1368980020004826

81. Sheikhhossein F, Imani H, Amini M, Hosseini F, Shab-Bidar S. The association between adherence to MIND diet and risk of breast cancer: a case-control study. *Int J Clin Pract.* (2021) 75:e14780. doi: 10.1111/ijcp.14780

82. Guinter M, Sandler D, McLain A, Merchant A, Steck S. An estrogen-related dietary pattern and postmenopausal breast cancer risk in a cohort of women with a family history of breast cancer. *Cancer Epidemiol Biomark Prev.* (2018) 27:1223–6. doi: 10.1158/1055-9965.Epi-18-0514

83. Haraldsdottir A, Torfadottir J, Valdimarsdottir U, Adami H, Aspelund T, Tryggvadottir L, et al. Dietary habits in adolescence and midlife and risk of breast cancer in older women. *PLoS One.* (2018) 13:e0198017. doi: 10.1371/journal.pone.0198017

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 26 January 2023
DOI 10.3389/fnut.2023.1024849

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Nahla Al-Bayyari,
Al-Balqa' Applied University, Jordan
William B. Grant,
Sunlight Nutrition and Health Research Center, United States

*CORRESPONDENCE
Lisong Shen
✉ lisongshen@hotmail.com
Ping Wang
✉ pink_wangping@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 22 August 2022
ACCEPTED 06 January 2023
PUBLISHED 26 January 2023

CITATION
Ma Y, Deng L, Huangfu Y, Zhou Y, Wang P and Shen L (2023) Adequate vitamin D level associated with reduced risk of sporadic colorectal cancer.
Front. Nutr. 10:1024849.
doi: 10.3389/fnut.2023.1024849

Adequate vitamin D level associated with reduced risk of sporadic colorectal cancer

Yanhui Ma†, Lin Deng†, Yuchan Huangfu, Yunlan Zhou, Ping Wang* and Lisong Shen*

Department of Laboratory Medicine, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Purpose: The effect of vitamin D level pertinent to colorectal cancer incidence, progression, or mortality risk is complicated, and study findings are mixed. Therefore, we evaluated whether serum vitamin D [25-hydroxyvitamin D, 25(OH)D] is associated with the incidence of sporadic colorectal cancer (CRC).

Methods: This study is a retrospective analysis of the relationship between serum 25(OH)D level and the risk of CRC. Age, sex, body mass index, history of polyp, disease conditions (i.e., diabetes), medications, and other eight vitamins were used as confounding factors. A total of 389 participants were enrolled in this study, including comprising 83 CRC patients without a family history and 306 healthy controls, between January 2020 and March 2021 at the Department of Colorectal Surgery and Endoscope Center at the Xinhua Hospital, Shanghai Jiao Tong University School of Medicine. Adjusted smoothing spline plots, subgroup analysis, and multivariate logistic regression analysis were conducted to estimate the relative risk between serum 25(OH)D and sporadic CRC risk.

Results: After fully adjusting the confounding factors, it was found that circulating 25(OH)D played a protective role in patients with CRC (OR = 0.76 [0.63, 0.92], p = 0.004) and that an adequate vitamin D level was significantly associated with a reduced CRC risk compared to vitamin D deficiency or sufficiency (OR = 0.31 [0.11, 0.9], p = 0.03). According to this study, statins did not affect the potential protective effects of vitamin D (OR = 1.02 [0.97, 1.08], p = 0.44) and may account for the inverse association between serum 25(OH)D and colorectal cancer.

Conclusion: An adequate level of serum 25(OH)D was associated with a reduced CRC risk, especially for the elderly. The finding on the absence of protective effect of vitamin D in the statin use subgroup, suggests it may be one of the substantial contributing confounders, and warrants further investigation.

KEYWORDS

vitamin D, 25(OH)D, sporadic colorectal cancer, risk factor, nutrition

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide (1), while most CRC cases are sporadic and non-inherited, which is influenced by the local gut environment and accumulation of mutations and epigenetic changes. In addition, genetic predisposition is a risk of CRC, and there are several other risk factors strongly associated

with colorectal cancer, such as being overweight or obese, smoking, heavy alcohol use, being older, having a history of adenomatous polyps, and having type 2 diabetes (2). Nutrients such as vitamins are considered to play an important role in the development and prevention of colorectal cancer (3, 4). Vitamin D was highlighted as an important player in numerous diseases (5–8). Its anti-inflammatory, immunomodulatory, proapoptotic, and antiangiogenic effects on inhibiting carcinogenesis and curbing tumor growth are outstanding both *in vivo* and *in vitro* (9, 10). DINOMIT (including seven phases: disjunction, initiation, natural selection, overgrowth, metastasis, involution, and transition), a new model of cancer pathogenesis, is strongly linked to vitamin D deficiency (11).

However, the evidence on whether vitamin D intake or serum levels affect cancer incidence, progression, or mortality is mixed in observational studies and clinical trials. A large number of studies reported that higher intake or circulating vitamin D was associated with a decreased CRC risk (12–14). Conversely, these are null findings from randomized trials and systematic reviews (15–18). In the most recent meta-analysis of RCTs including 10 randomized clinical trials (the Vitamin D and Omega-3 Trial [VITAL] trial), results demonstrated that vitamin D supplementation does not affect cancer incidence but does significantly reduce total cancer mortality rates up to 13% (19). In some cases, the absence of vitamin D effects could be due to incompletely following guidelines for designing and analyzing nutritional clinical studies (20), or maybe driven by unknown confounders. In addition, few studies are focusing on the joint effects of multiple vitamin co-exposure in CRC. One prospective cohort study found the associations between circulating concentrations of six common vitamins (viz., VA, VD, VE, VC, VB12, and VB9) and all-cause and cause-specific mortality risks depending on different exposure patterns (21). A growing body of evidence indicated that vitamin D might exert its biological functions in concert with drugs that are linked with vitamin D absorption and/or metabolism pathway like statins (22). After multivariable adjustment, whether increasing levels of vitamin D were associated with reduced risk of CRC is worth studying.

Herein, we aim to figure out the substantial relationship between serum 25(OH)D and CRC risk in the Chinese population. Furthermore, we explored whether the association varies according to several CRC confounding factors, including sex, age, lifestyle, multivitamin status, medication, and polyp history. This allows us to better understand the experimental and observational results on the association between circulation 25(OH)D and a low risk of CRC.

2. Materials and methods

2.1. Subject recruitment

This retrospective analysis of serum 25(OH)D enrolled 83 CRC cases and 306 controls who underwent endoscopy procedures for disease screening and/or the periodic health examination between January 2020 and March 2021 from the Department of Colorectal Surgery and Endoscope Center at the Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China). All the participants were continuously enrolled for over 1 year. According to their medical records, 83 CRC cases who underwent radical resection with histopathologic or cytologic specimens available were confirmed by one or two pathologists. Other 306 subjects without any other cancer history, such as breast cancer and lung cancer, autoimmune disease, inflammatory bowel disease, severe infectious diseases, and a BMI < 30 are defined as controls. Controls were randomly selected with respect to age. Clinical and laboratory characteristics of patients with CRC and controls are presented in **Supplementary Table 1**. Demographic characteristics and other vitamin results of patients with CRC and controls according to clinical cutoff concentrations of serum 25(OH)D are presented in **Supplementary Tables 2, 3**, respectively. Serological examination records before surgery and/or colonoscopy were chosen to analyze.

2.2. Serum samples and biochemical analyses

For the analyses, 5 ml of fasting blood from all participants was collected 1 or 2 days before surgery and/or colonoscopy. The peripheral blood was collected in a serum separator tube, and samples could clot for 30 min before centrifugation at 1000*g* for 5 min. All peripheral blood samples were processed within 2 h of collection. Serum thiamine (VB1), riboflavin (VB2), pyridoxine (VB6), folic acid (VB9), cobalamin (VB12), vitamin C, vitamin A, and vitamin E were analyzed by using an automatic electrochemistry analyzer (LK3000VI, Lanbiao, Tianjin, China) using commercially available kits. Serum 25(OH)D was measured using the Architect i2000 chemiluminescence immunoassay analyzer (Abbott, Illinois, USA). Inter-assay coefficients of variation (CV%) of vitamin D were less than 6%, and others were less than 10%.

2.3. Statistical analysis

Sample characteristics for the participants were compared using descriptive statistics and tested for significance using the Kruskal–Wallis rank sum test for continuous variables and proportions for categorical variables. If the variable number was less than 10, Fisher's exact probability test was used. For logistic regression analysis, a minimum of 10 outcome events per predictor variable (EPV) is recommended. Considering the Chinese population, judgment criteria for vitamin D levels are as follows: serum 25(OH)D of <25 nmol/L is defined as vitamin D deficiency, 25(OH)D of 25–50 nmol/L is considered vitamin D insufficiency, 25(OH)D of 50–75 nmol/L is vitamin D adequate, and ≥75 nmol/L is defined as vitamin D sufficiency (23, 24). We applied a single-factor analysis of variables for CRC risk including sex, age, history of polyp, BMI, concomitant diseases (diabetes and hypertension), medications (aspirin, statins, and ACEI), and serum vitamin (VB1, VB2, VB6, VB9, VB12, vitamin C, vitamin A, and vitamin E) as confounding factors. Adjusted smoothing spline plots of serum 25(OH)D by mixed factors were created to study the shape of the relationship of 25(OH)D with risk of CRC based on continuous 25(OH)D and 25(OH)D subgroups, respectively. A subgroup analysis examined

Abbreviations: CRC, colorectal cancer; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; VDR, vitamin D receptor; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitors; VB1, thiamine; VB2, riboflavin; VB6, pyridoxine; VB9, folic acid; VB12, cobalamin; CV, coefficients of variation; 95% CIs, 95% confidence intervals; SD, standard deviation.

the association between 25(OH)D and CRC risk according to sex, history of polyp, BMI, statin use, and age. A logistic regression model was used to test for interaction and compare the odds ratio (OR) and 95% confidence interval (CI) among the analyzed subgroups. Multivariable logistic regression models were used to investigate the effects of 25(OH)D and the other variables on the occurrence of CRC. The multivariable regression model adjusted for factors including age (<45, 45–59, 60–74, and ≥75), polyp history (yes or no), diabetes (yes or no), hypertension (yes or no), currently smoking (yes or no), alcohol (yes or no), aspirin use (yes or no), statin use (yes or no), ACEI use (yes or no), BMI (<18.5, 18.5–24.9, and 25–30), and other eight vitamins. The association analyses were performed in continuous 25(OH)D per 10 nmol/L and 25(OH)D groups, respectively. Stratified analyses and assessment of statistical interaction on the multiplicative scale were also performed in 25(OH)D sub-cohorts defined by sex, history of polyp, BMI, statin use, and age. All statistics were two-tailed, and a *P*-value of <0.05 was considered statistically significant. All data were analyzed and visualized using multiple R packages *via* The R Foundation[1] or SPSS 26.0. In the R package mgcv, the gam function was used to fit the generalized additive model on each tile separately.

3. Results

In this retrospective analysis, participants were classified into four categories, namely, deficient, insufficient, adequate, and sufficient, according to the serum 25(OH)D level, as described in the Section "2. Materials and methods." Supplementary Figure 1 is a flowchart for participant recruitment. Table 1 describes the characteristics of the subjects, including demographic characteristics and other vitamin results. Individuals with higher serum 25(OH)D were less likely to have tumors than those with low serum 25(OH)D (16 vs. 34%, $p = 0.13$). Figure 1A presents an overall smoothing spline plot of continuous 25(OH)D and the risk of CRC. As serum 25(OH)D concentration increased, the incidence of CRC significantly declined. The reanalysis result was consistent when data were modified into four groups: vitamin D deficiency, insufficiency, adequate, and sufficiency (Figure 1B).

As a result of a single-factor analysis of CRC risk based on continuous 25(OH)D per 10 nmol/L, several factors, such as sex, age (<45, 45–59, 60–74, and ≥75), BMI (<18.5, 18.5–24.9, and 25–30), polyp history, and medications, were identified to have a strong relationship with CRC (Supplementary Table 4). As another step, we conducted a separate regression analysis using continuous 25(OH)D values stratified by sex, age, polyp history, BMI, concomitant diseases, smoking, alcohol, statin, and aspirin use. The associations of these exposures with CRC are presented in Figure 2 and Supplementary Table 5. After stratification by all confounding factors, the risk of CRC was decreased in all subgroups with elevated 25(OH)D, other than those who used statins (Figure 3; Supplementary Figure 2). There was no significant heterogeneity among analyzed subgroups based on sex, age, polyp history, BMI, concomitant diseases, smoking, alcohol consumption, and statin use, except for aspirin use.

It was noteworthy that our results indicated that 25(OH)D did not act as a protective factor but promoted the risk of CRC in participants receiving statins (OR = 1.02 [0.97, 1.08], $p = 0.44$) (Figure 3D). The remaining data showed that men had a much higher risk of CRC, and vitamin D had a stronger protective effect on men (OR = 0.97 vs. 0.98, $p = 0.002$) (Figure 3A). It was found that participants with a polyp history were more likely to report CRC, and the risk declined with higher serum vitamin D levels (Figure 3B). In the elderly (over 75 years old), vitamin D could have a significant effect on the prevalence of CRC (OR = 0.94 [0.89, 0.99], $p = 0.02$) as the CRC incidence was depicted as a U shape. In the other three age subgroups, the incidence decreased likewise (Figure 3C). Participants under aspirin medication at a low range of serum 25(OH)D were more likely to have CRC (Figure 3E). Consistent trends between 25(OH)D

TABLE 1 Characteristics of the study participants according to clinical cutoff concentrations of serum 25(OH)D.

Clinical cutoffs		25(OH)D (nmol/L)			*P*-value
	<25	25–50	50–75	≥75	
No. of participants (%)	41 (11%)	212 (55%)	111 (29%)	25 (6.4%)	
CRC, N (%)	14 (34%)	46 (22%)	19 (17%)	4 (16%)	0.13
Age	66 ± 17	63 ± 13	62 ± 11	63 ± 11	0.40
Sex					0.30
Female	20 (49%)	91 (43%)	38 (34%)	9 (36%)	
Male	21 (51%)	121 (57%)	73 (66%)	16 (64%)	
BMI	22 ± 2.7	23 ± 2.7	23 ± 2.7	23 ± 2.5	0.04
Vitamins					
VB1 (nmol/mL)	59 ± 13	58 ± 8	61 ± 9	60 ± 9	0.03
VB2 (ng/mL)	241 ± 45	240 ± 41	240 ± 41	247 ± 37	0.87
VB6 (μmol/mL)	20 ± 4.8	20 ± 5.0	20 ± 5.3	20 ± 4.3	0.82
VB9 (nmol/mL)	14 ± 6.3	13 ± 5.5	14 ± 5.5	15 ± 6.1	0.31
VB12 (pg/mL)	269 ± 125	272 ± 99	271 ± 83	282 ± 107	0.96
Vitamin A (μmol/mL)	0.71 ± 0.22	0.80 ± 0.24	0.83 ± 0.24	0.91 ± 0.27	0.005
Vitamin C (μmol/mL)	43 ± 7.4	39 ± 5.2	40 ± 4.9	39 ± 4.1	< 0.001
Vitamin E (μg/mL)	11 ± 1.0	11 ± 1.0	12 ± 1.2	11 ± 1.2	0.001
Diseases and medications					
Polyp history	4 (9.8%)	40 (19%)	27 (24%)	7 (28%)	0.16
Diabetes	5 (12%)	42 (20%)	21 (19%)	3 (12%)	0.56
Hypertension	28 (68%)	115 (54%)	50 (45%)	11 (44%)	0.06
Smoke	4 (9.8%)	22 (10%)	20 (1%)	4 (16%)	0.22
Alcohol	2 (4.9%)	17 (8.0%)	14 (13%)	3 (12%)	0.39
Aspirins	9 (22%)	29 (14%)	6 (5.4%)	2 (8%)	0.02
Statins	4 (9.8%)	27 (13%)	11 (9.9%)	3 (12%)	0.87
ACEI	6 (14.6%)	4 (1. 9%)	3 (2.7%)	1 (4%)	< 0.001

BMI, body mass index; ACEI, angiotensin converting enzyme inhibitors.
Values are means (SD) or numbers (%), otherwise specified.

1 http://www.r-project.org; version 3.4.3.

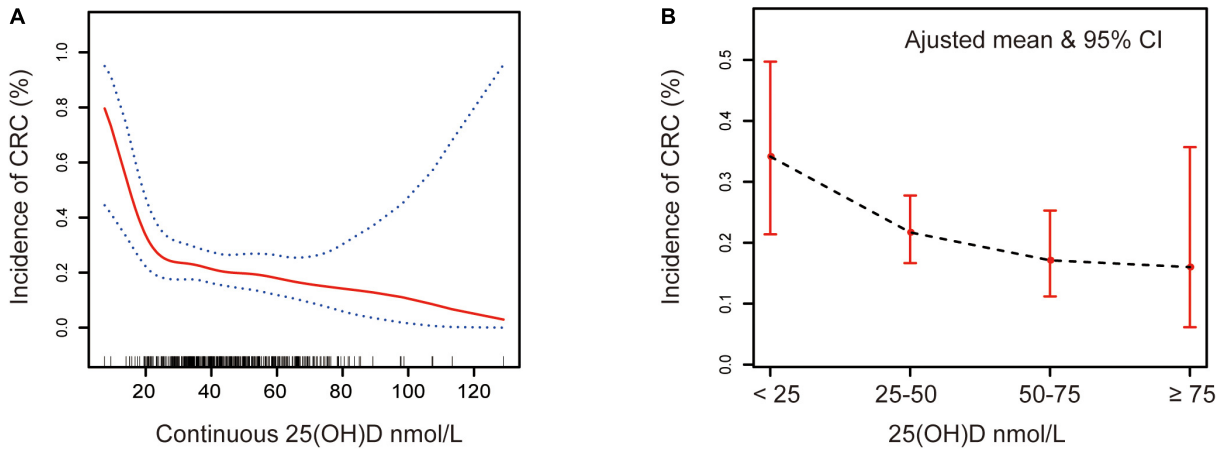


FIGURE 1
Association between serum 25(OH)D and CRC. Adjusted for sex, age, polyp history, diabetes, hypertension, smoking, alcohol, aspirin, statins, ACEI, VB1, VB2, VB6, VB9, VB12, VC, VE, VA, and BMI. **(A)** Red solid line represents the spline plots of continuous 25(OH)D concentration, and the blue dotted line represent the 95% confidence intervals of the spline plots. **(B)** The bar plot of four-level serum 25(OH)D groups with adjusted mean and 95% CIs. Vitamin D deficiency: 25(OH)D < 25 nmol/L, vitamin D insufficiency: 25(OH)D 25–50 nmol/L, vitamin D adequate: 25(OH)D 50–75 nmol/L, and vitamin D sufficiency: 25(OH)D ≥ 75 nmol/L.

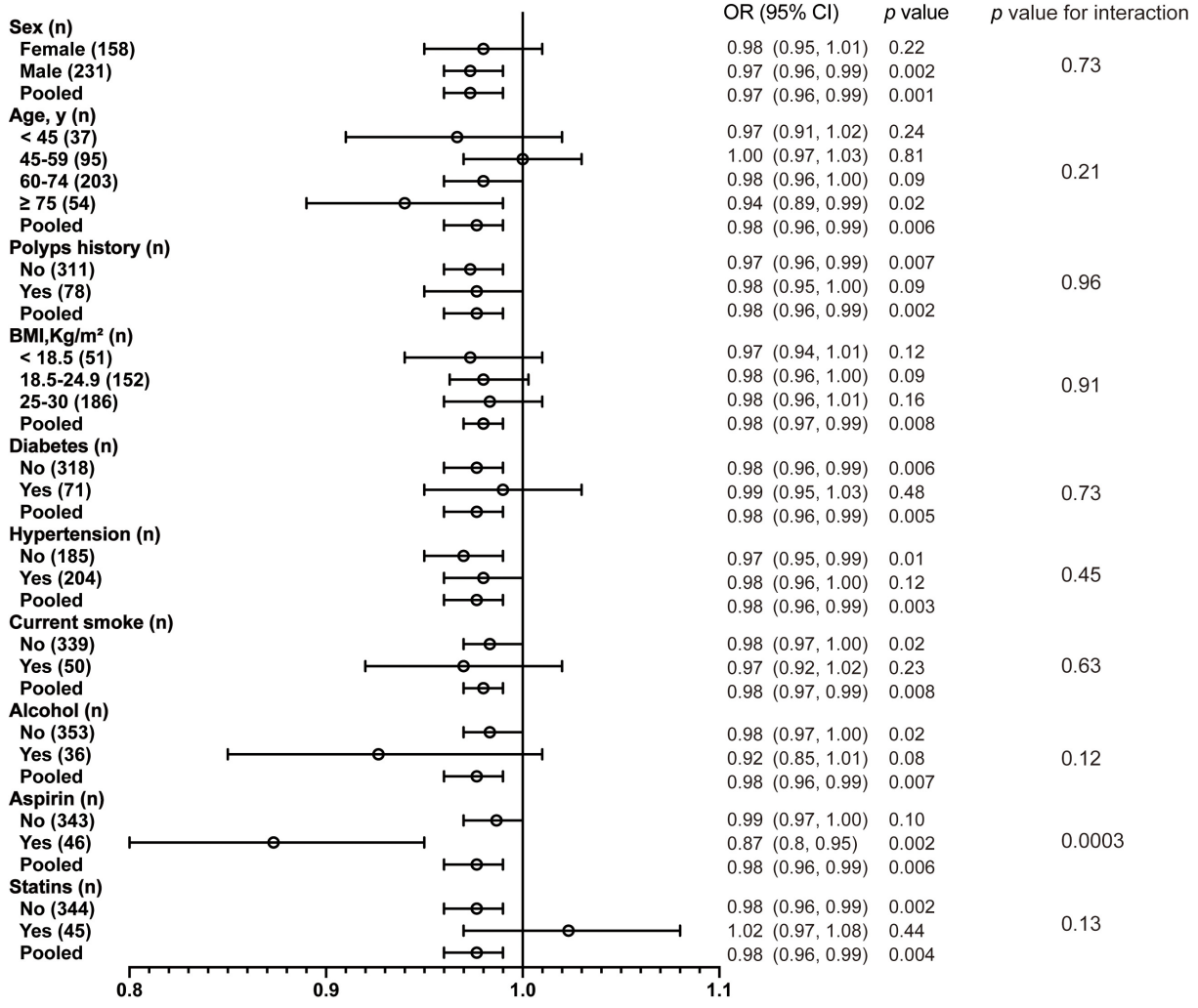


FIGURE 2
Association between 25(OH)D per 10 nmol/L and CRC according to baseline characteristics. BMI, body mass index.

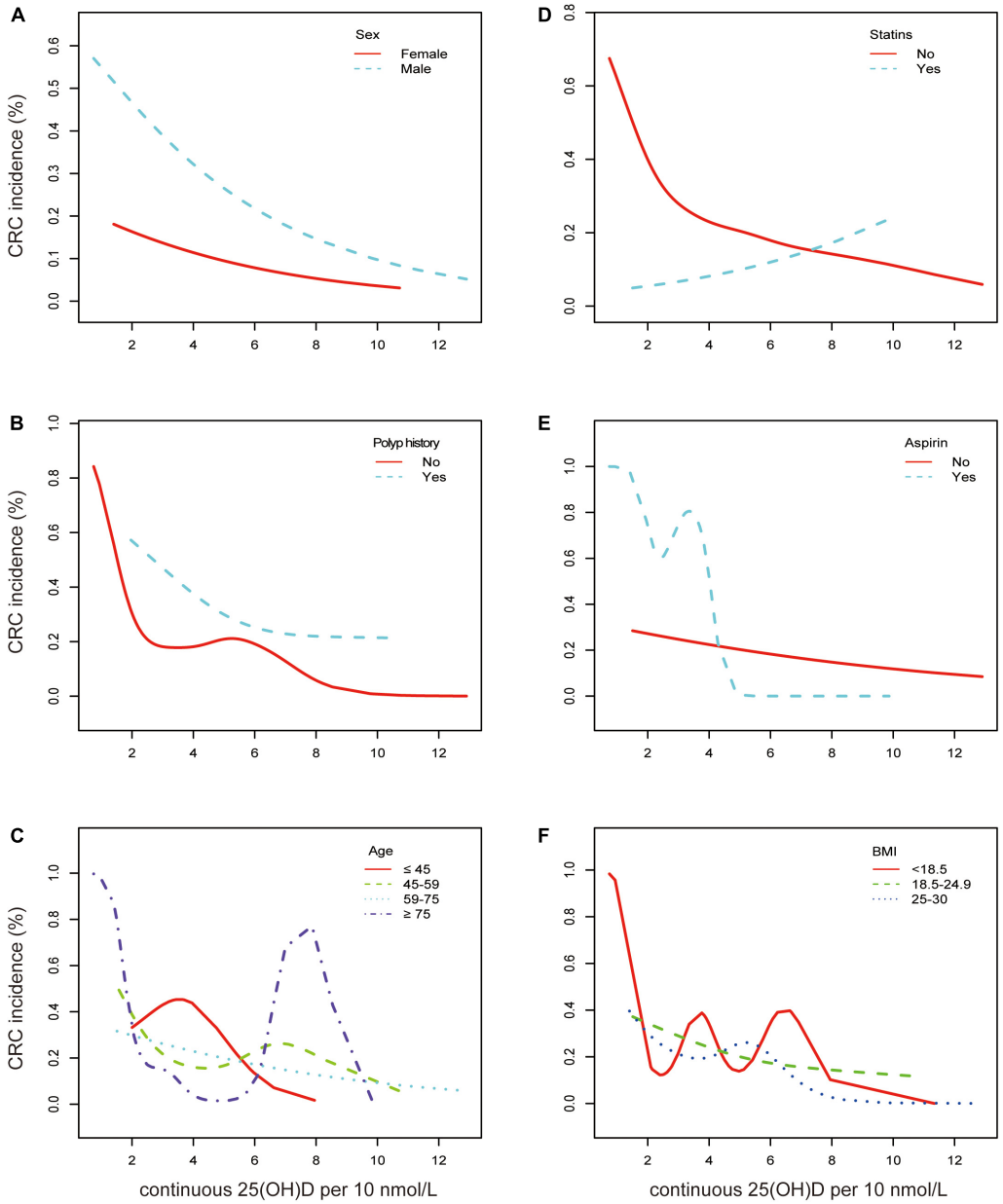


FIGURE 3
Association between continuous 25(OH)D per 10 nmol/L and CRC according to baseline characteristics. Smooth fitting curve adjusted for sex, age, polyps history, diabetes, hypertension, smoking, alcohol, aspirin, statins, ACEI, VA, VB1, VB6, VB9, VB12, VC, VE, VD, and BMI. **(A)** Aqua dashed line represents the spline plots of men and the red solid line represents those of women. **(B)** Aqua dashed line represents the spline plots of polyp history and red solid line represents participants without polyp. **(C)** Red solid line represents the spline plots of age < 45 years, green dashed line represents age between 45 and 59 years, aqua dotted line represents age between 60 and 75 years, and the purple dash-dotted line represents age ≥ 75 years. **(D)** Aqua dashed line represents the spline plots of statin treatment and red solid line represents participants without statin treatment. **(E)** Aqua dashed line represents the spline plots of aspirin use and red solid line represents participants without aspirin. **(F)** Red solid line represents the spline plots of BMI < 18.5, green dashed line represents BMI between 18.5 and 24.9, and blue dotted line represents BMI between 25 and 30.

and CRC incidence in BMI categories, diabetes, hypertension, smoking, and alcohol consumption were found (**Supplementary Figure 2**).

Furthermore, a multivariate regression analysis was used to investigate the effects of serum 25(OH)D on CRC incidence (**Table 2**). When confounding factors are not taken into account, 25(OH)D can lead to a 40–50% reduction in CRC risk. After fully adjusting the confounding factors that may influence CRC occurrence, an adequate level of 25(OH)D is protective against CRC, based on subdivided vitamin D categories (OR = 0.31[0.11, 0.92], $p = 0.03$).

4. Discussion

There is strong evidence that supports the UVB–vitamin D–cancer hypothesis that arose from an inspection of the geographic distribution of colon cancer deaths in the United States (25). In this study, we found that an adequate serum 25(OH)D level protected against sporadic CRC in the Chinese population and that this association was significantly modified by major factors, i.e., age, sex, polyp history, concomitant diseases, currently smoking, medications, BMI, and other vitamins. In addition, no significant interaction was

TABLE 2 Individual effect of serum 25(OH)D concentrations on CRC.

Exposure	Incidence, n (%)	Non-adjusted		Adjust I		Adjust II		Adjust III	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Continuous 25(OH)D per 10 nmol/L	83 (21%)	0.8 (0.7, 0.9)	0.005	0.8 (0.7, 0.9)	0.002	0.8 (0.6, 0.9)	0.004	0.76 (0.63, 0.92)	0.004
Clinical cutoffs									
<25 nmol/L	14 (34%)	Reference		Reference		Reference		Reference	
25–50 nmol/L	46 (22%)	0.5 (0.3, 1.1)	0.09	0.5 (0.2, 1.1)	0.09	0.5 (0.2, 1.2)	0.13	0.56 (0.22, 1.42)	0.22
50–75 nmol/L	19 (17%)	0.4 (0.2, 0.9)	0.03	0.3 (0.1, 0.8)	0.02	0.3 (0.1, 0.9)	0.03	0.31 (0.11, 0.92)	0.03
≥75 nmol/L	4 (16%)	0.4 (0.1, 1.3)	0.12	0.3 (0.1, 1.2)	0.09	0.3 (0.1, 1.2)	0.10	0.32 (0.07, 1.42)	0.14

Adjust I model was adjusted for sex, BMI grade, and age grade.
Adjust II model was adjusted for sex, BMI grade, age grade, polyp history, diabetes, hypertension, smoking, alcohol, aspirin, statins, and ACEI.
Adjust III model was adjusted for sex, BMI grade, age grade, polyp history, diabetes, hypertension, smoking, alcohol, aspirin, statins, ACEI, VB1, VB2, VB6, VB9, VB12, VC, VA, and VE.

found across each factor, except for aspirin. Furthermore, our results suggested that vitamin D was not a protective factor for the subgroup of statins and may contribute to an increased risk of CRC, which requires further investigation.

Several factors contribute to the pathogenesis of sporadic CRC, including genetics and environment, as well as diet and malfunctional gut microbiota, which is regarded as a key point (26, 27). Nutrients and foods also may cooperate, as a dietary pattern, to influence colorectal cancer risk. Rather than nutrition, vitamin D was considered to be a hormone. It may directly or indirectly mediate 3–5% of the human gene expression and had been confirmed in a wide spectrum of anticancer activities: anti-proliferation, induction of differentiation and apoptosis, anti-inflammation, inhibition of invasion and metastasis, and suppression of angiogenesis in experimental studies (9, 28).

It appeared that vitamin D has an inconsistent and intricate association with CRC risk. Low levels of 25(OH)D have been associated with increased cancer incidence and mortality in several observational studies (21, 29). In a meta-analysis of 16 prospective cohort studies with a large population (30), a 50 nmol/L (20 ng/mL) increase in 25(OH)D levels led to a reduction of 11% in cancer incidence rates and a 24% reduction in cancer mortality rates in women. Another meta-analysis of eight prospective studies on the association between serum 25(OH)D levels and cancer incidence and mortality found that cancer risk decreased by 7% and cancer mortality rates decreased by 2% with each increase in serum 25(OH)D levels of 20 nmol/L (8 ng/mL) (31). A Japanese prospective study found higher vitamin D concentration was associated with a lower risk of total cancer (32). The findings of these studies are consistent with the notion that vitamin D may have protective effects against cancer, but not all observational studies showed an association between higher vitamin D status and cancer prevention. There are null findings between vitamin D and CRC risk as well. A systematic review plus meta-analysis did not find evidence to suggest that vitamin D supplementation alone reduces the incidence of cancer or cancer mortality, even after including long-term follow-up results (15). A randomized, placebo-controlled trial found supplementation with vitamin D did not result in a lower incidence of invasive cancer than a placebo (17). Cumulating evidence reported a U-shaped effect of vitamin D on the risk relationship with diseases (33, 34). For standardization of serum total of 25(OH)D values above 100 nmol/L, a higher value than we observed, the risks did not continue to decrease (33). In this study, our results agreed with the conclusion that an adequate level, not the highest vitamin D concentration, led to the most beneficial outcome. However, the optimal serum 25(OH)D for colorectal cancer for the population of Asia may be different from international public health recommendations. Our findings suggested an adequate level of vitamin D (50–75 nmol/L) was preferred according to a Chinese consensus on bone health. Therefore, solid evidence from large population studies is needed to relate to determining nutrient recommendations.

It is important to understand the physiology of vitamin D because about half of the population is diagnosed with deficiency following clinical guidelines based on observational studies. Sources of vitamin D hormones included both endogenous sources, i.e., ultraviolet light, and exogenous sources, i.e., certain foods and dietary supplements. For both sources, the D3 carried in the bloodstream on either DBP or lipoproteins underwent a two-step sequential hydroxylation (25-hydroxylase and 1-alpha–hydroxylase) to produce an active metabolite, 1,25(OH)2D3 (also referred to as calciferol) (35). For dietary vitamin D3, it depended on the cytochrome P450 enzyme CYP27B1 polymorphism as well (36). Downstream vitamin D functioned by binding to and activating the nuclear VDR. A randomized clinical trial demonstrated that the effectiveness of vitamin D3 supplementation on advanced adenomas, but not on adenoma, varied according to genotype at two VDR SNPs (rs7968585 and rs731236). For rs7968585 with the AA genotype, vitamin D3 supplementation reduced risk by 64%. While for G or GG alleles, vitamin D3 supplementation increased the risk by 41% (37). In the meantime, the extrarenal production of 1,25(OH)2D3, likely for paracrine or autocrine uses, was recognized wildly in many tissues, including the epidermis and other epithelial tissues, bone, placenta, and tumors (38). The main reason was that CYP27B1 expression was induced in these extrarenal cells like colorectal carcinoma cells (39). However, the enzyme CYP24A1 or 24-hydroxylase, which degraded 1,25(OH)2D3 to inactive calcitroic acid, was reported upregulated in tumor cells or other cells. Some studies might not find any 1,25 (OH)2D3 effects after longer follow-up periods due to its degradation over time (10, 40). Meta-analyses of cancer incidence with respect to dietary intake had limited success (10). The effect of vitamin D supplementation at a given dose was presumably based on the baseline 25(OH)D level of the study population and the achieved vitamin D status after treatment (34). Clinical guidelines recommend measuring circulating 25(OH)D as a marker of vitamin D deficiency

(41). Therefore, we accessed the association between circulating 25(OH)D and CRC risk rather than dietary vitamin D intake.

Over the past several decades, chemoprevention has been extensively studied as a strategy for reducing the risk of CRC. Aspirin has the strongest evidence that it can lower the risk of CRC (42). Although studies of aspirin prevention of CRC have produced mixed results, reporting both significant (43) and non-significant results (44), most evidence supported an association with decreased risk of CRC (45). In addition, the Aspirin in Reducing Events in Elderly (ASPREE) trial found that aspirin use increased mortality due to all causes and cancer-related mortality, as well as CRC risk (HR 1.77, CI [1.02–3.06]) (46). There were few studies on drug interactions between vitamin D and aspirin. Herein, in the aspirin subgroup, our results supported the beneficial role of aspirin and high-level vitamin D. We still have to work on knowledge gaps such as molecular mechanisms and the application of genomic tools to understand interaction better.

Statin is another important chemoprevention agent that is usually applied to lower cholesterol for the primary prevention of cardiovascular disease (CVD) events. Vitamin D supplements may interact with statin medications because cholecalciferol, the endogenous vitamin D precursor, is derived from cholesterol. Statins may reduce vitamin D synthesis downstream and increase the concentration of vitamin D in the blood (22, 47). Statins and vitamin D appear to compete for the same metabolizing Cytochrome P450 enzyme (48), so high intakes of vitamin D, especially from supplements, may reduce the potency of statins (47, 49). In addition, there is evidence that dysregulation of cholesterol and vitamin D metabolism is associated with age-related diseases (50). Here, we did not focus on the underlying mechanism between vitamin D and statins. But it is worth noting that the protective effect of vitamin D was absent in the statin use subgroup. Alternatively, it showed a significant association between statin use and increased risk of CRC. It supported the interaction and/or competition of vitamin D and statin metabolism existed and proposed an explanation for inconsistent results produced by epidemiological and clinical studies of statins and colorectal neoplasia.

Studies have suggested that a higher BMI greatly raises CRC risk among both men and women (51, 52). In our study, primary data analysis indicated an association between BMI and CRC risk, and serum vitamin D protected against CRC when BMI was $\leq$30 (data not shown). This assumed certain confounding factors existed, such as adiposity-associated metabolites, genetic variants, etc. The main VITAL study showed a possible reduction of total cancer incidence for individuals with normal BMI, but not for individuals with overweight or obesity (18). Body fat distribution and impaired adipose tissue function, rather than BMI, might be better indicators of risk. As reported that polyps were highly associated with CRC (53, 54), we also found that individuals with no polyp history and higher serum 25(OH)D appeared to be at lower risk for CRC.

Older adults were at increased risk of developing vitamin D deficiency, and vitamin D metabolism became impaired. Age-related decline in kidney function associated with progressive structural deterioration of the kidney could affect vitamin D metabolism, leading to the suppression of 1,25(OH)2D3 synthesis (55). One cohort research showed a higher dietary intake of vitamin D was associated with a reduced CRC risk in older adults in the framework of the PREDIMED cohort (12). As previously reported, among randomized VITAL participants (mean [SD] age: 67.1 [7.1] years), no significant differences in cancer incidence by vitamin D treatment were observed (18). We found a U-shaped correlation between serum 25(OH)D and the incidence of CRC in the elderly subgroup, indicating that an adequate level of vitamin D was more important for the elderly. Despite this, we should exercise caution when using high doses of vitamin D in older (19). Overall, we need a population-based study to explore the effect of each exposure of CRC incidence or recurrence.

Vitamin D plays a critical role in calcium and phosphate metabolism as well. A 4-year randomized clinical trial showed that supplementing with vitamin D3 and calcium did not significantly reduce all-type cancer risk among healthy postmenopausal women (56). Studies found that healthy women who took vitamin D and calcium supplements for an average of 7 years did not have a reduced incidence of colorectal cancer (57). A clinical trial based on an ancillary study of data from the VITAL trial revealed that colorectal adenomas or serrated polyps did not appear linked to vitamin D supplementation, but calcium and vitamin D together almost quadruple the risk (58). Moreover, as we all know, vitamins cannot be consumed separately in a daily diet. A growing body of evidence suggests that vitamin interactions are related to diseases (21). We are aware of fewer studies taking any single vitamin as a confounder factor to access the relationship between vitamin D and CRC risk. In view of the interaction with other metabolites like calcium and statins, vitamin D analogs were developed. Chemicals with similar structures and anticancer properties to vitamin D, but with fewer potential side effects (59).

In general, the population of our study for factors affecting CRC incidence was relatively small; therefore, a large population-based study would be needed to investigate the effects of each exposure on CRC. There are also several potential limitations in this retrospective study. First, as a retrospective analysis of observational studies with a limited population, we cannot rule out another residual or unknown confounding as a potential explanation for the observed findings. Nevertheless, we conducted consistent results based on two modeling data [continuous 25(OH)D per 10 ng/mL and 25(OH)D subdivided groups] that overall higher serum 25(OH)D was inversely related to sporadic CRC. Second, cohort studies are less susceptible to selective bias compared with case–control studies. As for case–control studies, the selection of cases may not be representative of all cases within the population. Herein, we obtained laboratory and clinical data of cases and controls before clinical diagnosis, which would be less susceptible to selective bias. Third, our study only performed one single serum 25(OH)D assessment before surgery. This assessment would be compromised if any changes occurred such as dietary habits influenced by diseases. Thus, we applied appropriate inclusion criteria and conducted subgroup and sensitivity analysis, we did not find serum 25(OH)D had significant interaction with other major exposures except for aspirin use.

5. Conclusion

This retrospective study indicated that an adequate serum 25(OH)D is associated with a lower CRC risk. The association between vitamin D and CRC risk was modified by sex, age, polyp history, disease conditions, medications, BMI, and other CRC-related vitamin levels. Our findings supported the hypothesis that vitamin D may grant protection against the risk of cancer. Nonetheless, the

lower risk associated with higher circulating vitamin D concentration seemed to show a U-shaped effect, suggesting the highest 25(OH)D level may not provide optimal benefits, especially for the elderly (≥75 years old). The role of serum 25(OH)D and its interaction with other nutrition, genetic variants, cancer subsites, prognosis, and mortality on CRC should be subject to further studies.

Data availability statement

The datasets presented in this article are not readily available for ethical reasons. Requests to access the datasets should be directed to the corresponding authors.

Ethics statement

This present study conformed to the principles of the Declaration of Helsinki. Approval was obtained from the Research Ethics Committee of the Xinhua Hospital Affiliated to Jiao Tong University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YM designed the study and performed the statistical analysis. YM, LD, and YH collected the data. YM and YZ wrote the manuscript. PW and LS critically revised the manuscript. All authors contributed to the data interpretation and edited, reviewed, and approved the final manuscript.

Funding

This study was supported by the Program for Shanghai Rising Stars of Youth Medical Talents-Clinical Laboratory Practitioner Program (No. [2021]99). The funders had no role in the design or conduct of the study, the collection, analysis, or interpretation of the data, or the preparation, review, or approval of the manuscript.

Acknowledgments

We would like to thank the participants and staff of the Xinhua Hospital for their valuable contributions, as well as Dr. Chao-Yan Yue for her advice and help with statistical analysis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1024849/full#supplementary-material

References

1. Siegel R, Miller K, Goding Sauer A, Fedewa S, Butterly L, Anderson J, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin.* (2020) 70:145–64. doi: 10.3322/caac.21601

2. Lawler M, Johnston B, Van Schaeybroeck S, Salto-Tellez M, Wilson R, Dunlop M, et al. 74 - Colorectal cancer. Sixth ed. In: Niederhuber J, Armitage J, Kastan M, Doroshow J, Tepper J, editors. *Abeloff's Clinical Oncology*. Philadelphia: Elsevier (2020). p. 1219–80.e15.

3. Song M, Chan A, Sun J. Influence of the gut microbiome, diet, and environment on risk of colorectal cancer. *Gastroenterology.* (2020) 158:322–40. doi: 10.1053/j.gastro.2019.06.048

4. Yang W, Ma Y, Smith-Warner S, Song M, Wu K, Wang M, et al. Calcium intake and survival after colorectal cancer diagnosis. *Clin Cancer Res.* (2019) 25:1980–8. doi: 10.1158/1078-0432.CCR-18-2965

5. Bouillon R, Manousaki D, Rosen C, Trajanoska K, Rivadeneira F, Richards J. The health effects of vitamin D supplementation: evidence from human studies. *Nat Rev Endocrinol.* (2022) 18:96–110. doi: 10.1038/s41574-021-00593-z

6. Zhou A, Selvanayagam J, Hypponen E. Non-linear mendelian randomization analyses support a role for vitamin D deficiency in cardiovascular disease risk. *Eur Heart J.* (2022) 43:1731–9. doi: 10.1093/eurheartj/ehab809

7. Jolliffe D, Camargo C Jr., Sluyter J, Aglipay M, Aloia J, Ganmaa D, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol.* (2021) 9:276–92. doi: 10.1016/S2213-8587(21)00051-6

8. Gall Z, Szekely O. Role of vitamin D in cognitive dysfunction: new molecular concepts and discrepancies between animal and human findings. *Nutrients.* (2021) 13:3672. doi: 10.3390/nu13113672

9. Feldman D, Krishnan A, Swami S, Giovannucci E, Feldman B. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer.* (2014) 14:342–57. doi: 10.1038/nrc3691

10. Munoz A, Grant W. Vitamin D and cancer: an historical overview of the epidemiology and mechanisms. *Nutrients.* (2022) 14:1448. doi: 10.3390/nu14071448

11. Garland C, Gorham E, Mohr S, Garland F. Vitamin D for cancer prevention: global perspective. *Ann Epidemiol.* (2009) 19:468–83. doi: 10.1016/j.annepidem.2009.03.021

12. Hernandez-Alonso P, Canudas S, Boughanem H, Toledo E, Sorli J, Estruch R, et al. Dietary vitamin D intake and colorectal cancer risk: a longitudinal approach within the PREDIMED study. *Eur J Nutr.* (2021) 60:4367–78. doi: 10.1007/s00394-021-02585-1

13. McCullough M, Zoltick E, Weinstein S, Fedirko V, Wang M, Cook N, et al. Circulating vitamin D and colorectal cancer risk: an international pooling project of 17 cohorts. *J Natl Cancer Inst.* (2019) 111:158–69. doi: 10.1093/jnci/djy087

14. Cruz-Pierard S, Nestares T, Amaro-Gahete F. Vitamin D and calcium as key potential factors related to colorectal cancer prevention and treatment: a systematic review. *Nutrients.* (2022) 14:4934. doi: 10.3390/nu14224934

15. Goulao B, Stewart F, Ford J, MacLennan G, Avenell A. Cancer and vitamin D supplementation: a systematic review and meta-analysis. *Am J Clin Nutr.* (2018) 107:652–63. doi: 10.1093/ajcn/nqx047

16. Keum N, Giovannucci E. Vitamin D supplements and cancer incidence and mortality: a meta-analysis. *Br J Cancer.* (2014) 111:976–80. doi: 10.1038/bjc.2014.294

17. Manson J, Cook N, Lee I, Christen W, Bassuk S, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med.* (2019) 380:33–44. doi: 10.1056/NEJMoa1809944

18. Chandler P, Chen W, Ajala O, Hazra A, Cook N, Bubes V, et al. Effect of vitamin D3 supplements on development of advanced cancer: a secondary analysis of the VITAL randomized clinical trial. *JAMA Netw Open.* (2020) 3:e2025850. doi: 10.1001/jamanetworkopen.2020.25850

19. Keum N, Lee D, Greenwood D, Manson J, Giovannucci E. Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. *Ann Oncol.* (2019) 30:733–43. doi: 10.1093/annonc/mdz059

20. Grant W, Boucher B, Al Anouti F, Pilz S. Comparing the evidence from observational studies and randomized controlled trials for nonskeletal health effects of vitamin D. *Nutrients.* (2022) 14:3811. doi: 10.3390/nu14183811

21. Cui Y, Zhou H, Wei M, Song W, Di D, Zhang R, et al. Multiple vitamin co-exposure and mortality risk: a prospective study. *Clin Nutr.* (2022) 41:337–47. doi: 10.1016/j.clnu.2021.12.010

22. Warren T, McAllister R, Morgan A, Rai T, McGilligan V, Ennis M, et al. The interdependency and co-regulation of the vitamin D and cholesterol metabolism. *Cells.* (2021) 10:2007. doi: 10.3390/cells10082007

23. Rusinska A, Pludowski P, Walczak M, Borszewska-Kornacka M, Bossowski A, Chlebna-Sokol D, et al. Vitamin D Supplementation guidelines for general population and groups at risk of vitamin D deficiency in poland-recommendations of the polish society of pediatric endocrinology and diabetes and the expert panel with participation of national specialist consultants and representatives of scientific societies-2018 update. *Front Endocrinol.* (2018) 9:246. doi: 10.3389/fendo.2018.00246

24. Xiangpeng L, Cengli Z, Honghong Z, Hanmin Z, Jianlie Z, Siren H, et al. Application guideline for vitamin D and bone health in adult Chinese (2014 Starter Edition). *Chin J Osteoporos.* (2014) 20:1011–30.

25. Garland C, Garland F. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol.* (1980) 9:227–31. doi: 10.1093/ije/9.3.227

26. Flemer B, Lynch D, Brown J, Jeffery I, Ryan F, Claesson M, et al. Tumour-associated and non-tumour-associated microbiota in colorectal cancer. *Gut.* (2017) 66:633–43. doi: 10.1136/gutjnl-2015-309595

27. Vernia F, Longo S, Stefanelli G, Viscido A, Latella G. Dietary factors modulating colorectal carcinogenesis. *Nutrients.* (2021) 13:143. doi: 10.3390/nu13010143

28. Deeb K, Trump D, Johnson C. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer.* (2007) 7:684–700. doi: 10.1038/nrc2196

29. Mondul A, Weinstein S, Layne T, Albanes D. Vitamin D and cancer risk and mortality: state of the science, gaps, and challenges. *Epidemiol Rev.* (2017) 39:28–48. doi: 10.1093/epirev/mxx005

30. Yin L, Ordonez-Mena J, Chen T, Schottker B, Arndt V, Brenner H. Circulating 25-hydroxyvitamin D serum concentration and total cancer incidence and mortality: a systematic review and meta-analysis. *Prev Med.* (2013) 57:753–64. doi: 10.1016/j.ypmed.2013.08.026

31. Han J, Guo X, Yu X, Liu S, Cui X, Zhang B, et al. 25-Hydroxyvitamin D and total cancer incidence and mortality: a meta-analysis of prospective cohort studies. *Nutrients.* (2019) 11:2995. doi: 10.3390/nu11102295

32. Budhathoki S, Hidaka A, Yamaji T, Sawada N, Tanaka-Mizuno S, Kuchiba A, et al. Plasma 25-hydroxyvitamin D concentration and subsequent risk of total and site specific cancers in Japanese population: large case-cohort study within Japan public health center-based prospective study cohort. *BMJ.* (2018) 360:k671. doi: 10.1136/bmj.k671

33. Durazo-Arvizu R, Dawson-Hughes B, Kramer H, Cao G, Merkel J, Coates P, et al. The reverse J-shaped association between serum total 25-Hydroxyvitamin D concentration and all-cause mortality: the impact of assay standardization. *Am J Epidemiol.* (2017) 185:720–6. doi: 10.1093/aje/kww244

34. Pilz S, Trummer C, Theiler-Schwetz V, Grubler M, Verheyen N, Odler B, et al. Critical appraisal of large vitamin D randomized controlled trials. *Nutrients.* (2022) 14:303. doi: 10.3390/nu14020303

35. Demer L, Hsu J, Tintut Y. Steroid hormone vitamin D. *Circ Res.* (2018) 122:1576–85. doi: 10.1161/CIRCRESAHA.118.311585

36. Fedirko V, Mandle H, Zhu W, Hughes D, Siddiq A, Ferrari P, et al. Vitamin D-related genes, blood vitamin D levels and colorectal cancer risk in Western European populations. *Nutrients.* (2019) 11:1954. doi: 10.3390/nu11081954

37. Barry E, Peacock J, Rees J, Bostick R, Robertson D, Bresalier R, et al. Vitamin D receptor genotype, vitamin D3 supplementation, and risk of colorectal adenomas: a randomized clinical trial. *JAMA Oncol.* (2017) 3:628–35. doi: 10.1001/jamaoncol.2016.5917

38. Bikle D. The endocrine society centennial: extrarenal production of 1,25 Dihyroxyvitamin D is now proven. *Endocrinology.* (2016) 157:1717–8. doi: 10.1210/en.2016-1186

39. Jacobs E, Van Pelt C, Forster R, Zaidi W, Hibler E, Galligan M, et al. CYP24A1 and CYP27B1 polymorphisms modulate vitamin D metabolism in colon cancer cells. *Cancer Res.* (2013) 73:2563–73. doi: 10.1158/0008-5472.CAN-12-4134

40. Henn M, Martin-Gorgojo V, Martin-Moreno J. Vitamin D in cancer prevention: gaps in current knowledge and room for hope. *Nutrients.* (2022) 14:4512. doi: 10.3390/nu14214512

41. Bikle D, Malmstroem S, Schwartz J. Current controversies: are free vitamin metabolite levels a more accurate assessment of vitamin D status than total levels? *Endocrinol Metab Clin North Am.* (2017) 46:901–18. doi: 10.1016/j.ecl.2017.07.013

42. Drew D, Cao Y, Chan A. Aspirin and colorectal cancer: the promise of precision chemoprevention. *Nat Rev Cancer.* (2016) 16:173–86. doi: 10.1038/nrc.2016.4

43. Rothwell P, Price J, Fowkes F, Zanchetti A, Roncaglioni M, Tognoni G, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet.* (2012) 379:1602–12. doi: 10.1016/S0140-6736(11)61720-0

44. Chubak J, Whitlock E, Williams S, Kamineni A, Burda B, Buist D, et al. Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. preventive services task force. *Ann Intern Med.* (2016) 164:814–25. doi: 10.7326/M15-2117

45. Cao Y, Nishihara R, Wu K, Wang M, Ogino S, Willett W, et al. Population-wide impact of long-term use of aspirin and the risk for cancer. *JAMA Oncol.* (2016) 2:762–9. doi: 10.1001/jamaoncol.2015.6396

46. McNeil J, Nelson M, Woods R, Lockery J, Wolfe R, Reid C, et al. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med.* (2018) 379:1519–28. doi: 10.1056/NEJMoa1803955

47. Robien K, Oppeneer S, Kelly J, Hamilton-Reeves J. Drug-vitamin D interactions: a systematic review of the literature. *Nutr Clin Pract.* (2013) 28:194–208. doi: 10.1177/0884533612467824

48. Bhattacharyya S, Bhattacharyya K, Maitra A. Possible mechanisms of interaction between statins and vitamin D. *QJM.* (2012) 105:487–91. doi: 10.1093/qjmed/hcs001

49. Aloia J, Li-Ng M, Pollack S. Statins and vitamin D. *Am J Cardiol.* (2007) 100:1329. doi: 10.1016/j.amjcard.2007.05.024

50. Veldurthy V, Wei R, Oz L, Dhawan P, Jeon Y, Christakos S. Vitamin D, calcium homeostasis and aging. *Bone Res.* (2016) 4:16041. doi: 10.1038/boneres.2016.41

51. Recalde M, Davila-Batista V, Diaz Y, Leitzmann M, Romieu I, Freisling H, et al. Body mass index and waist circumference in relation to the risk of 26 types of cancer: a prospective cohort study of 3.5 million adults in Spain. *BMC Med.* (2021) 19:10. doi: 10.1186/s12916-020-01877-3

52. Bull C, Bell J, Murphy N, Sanderson E, Davey Smith G, Timpson N, et al. Adiposity, metabolites, and colorectal cancer risk: mendelian randomization study. *BMC Med.* (2020) 18:396. doi: 10.1186/s12916-020-01855-9

53. Song M, Emilsson L, Roelstraete B, Ludvigsson J. Risk of colorectal cancer in first degree relatives of patients with colorectal polyps: nationwide case-control study in Sweden. *BMJ.* (2021) 373:n877. doi: 10.1136/bmj.n877

54. Rutter M, East J, Rees C, Cripps N, Docherty J, Dolwani S, et al. British society of gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. *Gut.* (2020) 69:201–23. doi: 10.1136/gutjnl-2019-319858

55. Weinstein J, Anderson S. The aging kidney: physiological changes. *Adv Chronic Kidney Dis.* (2010) 17:302–7. doi: 10.1053/j.ackd.2010.05.002

56. Lappe J, Watson P, Travers-Gustafson D, Recker R, Garland C, Gorham E, et al. Effect of vitamin D and calcium supplementation on cancer incidence in older women: a randomized clinical trial. *JAMA.* (2017) 317:1234–43. doi: 10.1001/jama.2017.2115

57. Wactawski-Wende J, Kotchen J, Anderson G, Assaf A, Brunner R, O'Sullivan M, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med.* (2006) 354:684–96. doi: 10.1056/NEJMoa055222

58. Song M, Lee I, Manson J, Buring J, Dushkes R, Gordon D, et al. No association between vitamin D supplementation and risk of colorectal adenomas or serrated polyps in a randomized trial. *Clin Gastroenterol Hepatol.* (2021) 19:128–35.e6. doi: 10.1016/j.cgh.2020.02.013

59. Pereira F, Larriba M, Munoz A. Vitamin D and colon cancer. *Endocr Relat Cancer.* (2012) 19:R51–71. doi: 10.1530/ERC-11-0388

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 26 January 2023
DOI 10.3389/fnut.2023.988632

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Sara Pilotto,
University of Verona, Italy
Jinluan Li,
Fujian Medical University, China

*CORRESPONDENCE
Yongheng Li
✉ yonghenglee@163.com
Ziyu Li
✉ ziyu_li@hsc.pku.edu.cn
Weihu Wang
✉ wangweihu88@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 07 July 2022
ACCEPTED 04 January 2023
PUBLISHED 26 January 2023

CITATION
Ming J, Du R, Geng J, Li S, Liu Z, Cai Y, Zhu X, Zhang Y, Wang H, Wang Z, Tang L, Zhang X, Peng Z, Wu A, Bu Z, Peng Y, Yan Y, Li Z, Li Y, Li Z and Wang W (2023) Prognostic impact of sarcopenia in patients with locally advanced adenocarcinoma of the esophagogastric junction treated with neoadjuvant chemoradiotherapy.
Front. Nutr. 10:988632.
doi: 10.3389/fnut.2023.988632

Prognostic impact of sarcopenia in patients with locally advanced adenocarcinoma of the esophagogastric junction treated with neoadjuvant chemoradiotherapy

Jiao Ming[1], Rongxu Du[1], Jianhao Geng[1], Shuai Li[1], Zhiyan Liu[1], Yong Cai[1], Xianggao Zhu[1], Yangzi Zhang[1], Hongzhi Wang[1], Zhilong Wang[2], Lei Tang[2], Xiaotian Zhang[3], Zhi Peng[3], Aiwen Wu[4], Zhaode Bu[4], Yifan Peng[4], Yan Yan[5], Zhongwu Li[6], Yongheng Li[1*†], Ziyu Li[4*†] and Weihu Wang[1*†]

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Radiation Oncology, Peking University Cancer Hospital and Institute, Beijing, China, [2]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Medical Imaging, Peking University Cancer Hospital and Institute, Beijing, China, [3]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Gastrointestinal Oncology, Peking University Cancer Hospital and Institute, Beijing, China, [4]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Gastrointestinal Surgery, Peking University Cancer Hospital and Institute, Beijing, China, [5]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Endoscopy Center, Peking University Cancer Hospital and Institute, Beijing, China, [6]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Pathology, Peking University Cancer Hospital and Institute, Beijing, China

Background: Few studies have evaluated the significance of sarcopenia in predicting the outcomes of patients with adenocarcinoma of the esophagogastric junction (AEG), especially those who received neoadjuvant chemoradiotherapy (NCRT). We aimed to identify the sarcopenic status and its impact on the outcomes of patients with locally advanced AEG who received NCRT followed by radical surgery or systemic therapy.

Materials and methods: Patients with T3-4N+M0 AEG with accessible abdominal computed tomography (CT) before and after NCRT were retrospectively analyzed. Body composition parameters, particularly the skeletal muscle index (SMI), were assessed using a CT-based method, and sarcopenia was defined using a predetermined SMI cutoff value. Survival analysis was conducted using the Kaplan–Meier method. A Cox proportional hazards regression model was used to identify independent prognostic factors. Receiver operating characteristic curve analysis was carried out, and the area under the curve (AUC) was calculated to test the prognostic accuracy of different factors.

Results: A total of 63 patients were enrolled, 65.1 and 79.4% of whom developed pre- and post-NCRT sarcopenia, respectively. Patients with pre-NCRT sarcopenia had lower radical surgery rates (70.7 *vs*. 95.5%, $p = 0.047$) than those without sarcopenia; however, sarcopenic status did not affect other short-term outcomes, including treatment-related toxicity and efficacy. Pre-NCRT sarcopenia was identified as an independent predictive factor for poor overall survival (OS) [adjusted hazard ratio

(HR), 6.053; p = 0.002] and progression-free survival (PFS) (adjusted HR, 2.873; p = 0.031). Compared with nutritional indices such as the Nutritional Risk Screening 2002, weight loss during NCRT, and post-NCRT sarcopenia, pre-NCRT sarcopenia was regarded as the best predictive index for the 5-year OS (AUC = 0.735) and PFS rates (AUC = 0.770).

Conclusion: Pre-NCRT sarcopenia may be an independent predictive factor for OS and PFS rates in patients with locally advanced AEG receiving multimodal treatment.

KEYWORDS

sarcopenia, adenocarcinoma of the esophagogastric junction, neoadjuvant chemoradiotherapy, prognosis, nutritional indices

1. Introduction

The incidence of adenocarcinoma of the esophagogastric junction (AEG) has increased in Western and Asian countries in the past few decades (1, 2). AEG is highly aggressive, and most patients with this condition are at an advanced stage and have poor survival (3). Multimodal treatment, especially neoadjuvant chemoradiotherapy (NCRT) followed by surgery, has improved the overall survival (OS) of patients with AEG and is recommended as the standard treatment for locally advanced AEG (4). The results of our previous study also confirmed the efficacy of NCRT both in terms of downstaging and improving pathological response in patients with AEG (5).

Patients with locally advanced AEG typically present with progressive dysphagia, odynophagia, satiety, and unintentional weight loss (6), which usually leads to malnutrition. Most patients treated with neoadjuvant therapy (NAT) experience gastrointestinal toxicities such as anorexia, nausea, and emesis, which may aggravate malnutrition. Furthermore, malnutrition is considered a risk factor for adverse clinical outcomes in multiple tumors (7–9). In patients with gastric cancer and AEG, those who were at nutritional risk as assessed by the Nutritional Risk Screening 2002 (NRS 2002) and experienced weight loss, had more severe postoperative complications and poorer survival (7, 10, 11).

Recently, sarcopenia, defined as a loss of skeletal muscle mass and function, has been confirmed as a prognostic nutritional factor for poor outcomes in several types of cancer (12–15). In patients with upper gastrointestinal tract cancer who received NAT, emerging evidence has shown that sarcopenia affected NAT-related toxicity (16, 17), the clinical and pathological response to NAT (18, 19), postoperative complications (19, 20), and long-term survival (16). Sarcopenia is determined by skeletal muscle mass in body composition parameters which can be easily obtained from computed tomography (CT) images. As CT scan objectively demonstrates body composition and is performed routinely in patients with cancer, sarcopenia evaluated by CT method is an objective and reproducible nutritional parameter.

The significance of sarcopenia in predicting the outcomes of patients with AEG, especially those who received NCRT, has not been sufficiently evaluated in previous studies. Therefore, the aim of the present study was to identify the sarcopenic status before and after NCRT and its impact on severe treatment-related toxicity, efficacy of treatment, and survival outcomes in patients with locally advanced AEG who received NCRT.

2. Materials and methods

2.1. Patients

The study population included patients who received NCRT for locally advanced AEG at the Peking University Cancer Hospital between March 2011 and October 2017. The detailed inclusion criteria were as follows: (1) histologically proven AEG; (2) clinical diagnosis of T3-4N+M0 stage *via* endoscopic ultrasound or CT in accordance with the 8th edition American Joint Committee on Cancer (AJCC) Staging Manual; (3) chemoradiotherapy as the initial antitumor therapy; (4) a score of 0 or 1 in Eastern Cooperative Oncology Group performance status before treatment; and (5) accessible CT images of the abdomen before and after NCRT within 1 month or 1 to 2 months, respectively. Exclusion criteria were as follows: (1) combination with other malignant tumors; (2) incomplete clinical or pathological data; (3) no SOX or S-1 chemotherapy regimens during NCRT. Demographic, disease-related, and treatment information was obtained from the patients' medical records.

All patients signed informed consent forms before antitumor therapy, including radiotherapy, chemotherapy, and surgery. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Peking University Beijing Cancer Hospital and Institute (approval number: 2014KT74).

2.2. Treatment strategy

Details of the NCRT treatment strategy have been described in our previous study (5). In brief, all patients received RT with a total dose of 50 Gy to gross tumor and 45 Gy to high-risk lymphatic drainage area in 25 fractions along with concurrent SOX or S-1 chemotherapy. After completion of NCRT, patients without progression were candidates for radical surgery with total gastrectomy and D2 lymphadenectomy by experienced surgeons (21). Thereafter, postoperative adjuvant chemotherapy was considered based on the patient's pathological results and physical tolerance. A multidisciplinary team provided accurate diagnoses

and individualized therapy to patients who did not undergo radical surgery.

2.3. Short-term outcomes

The completion status of NCRT was recorded. NCRT-related toxicities were assessed weekly according to the Common Terminology Criteria for Adverse Events version 4.0, in which severe toxicity was defined as more severe than two grades. Within 1 to 2 months of the completion of NCRT, patients were evaluated for CT-based clinical response in accordance with the RECIST 1.1 criteria (22). The radical surgery rate was calculated. For patients who received surgery, the D2 lymphadenectomy rate, R0 resection rate, and severe complications of surgery, were collected. The pathological response evaluation was recorded using the tumor regression grade (TRG) per the NCCN guidelines (23).

2.4. Follow-up and long-term outcomes

All patients were followed up every 3 months for the first 2 years after the completion of treatment, every 6 months for the next 3 years, and annually thereafter. Follow-up evaluation included medical history, physical examination, cancer biomarker blood tests, thoracic X-rays or CT, and abdominopelvic CT or ultrasonography.

Overall survival (OS) was defined as the time from the date of histological diagnosis to the last date of follow-up or death, whereas progression-free survival (PFS) was defined as the time from the date of histological diagnosis to the date of the progression at primary tumor or metastatic lymph nodes after NCRT, any relapse at local or regional sites after radical surgery, new distant metastasis, the last date of follow-up, or death.

2.5. Assessment of body composition parameters and other nutritional indices

Unenhanced CT images of the abdomen before and after NCRT within 1 month and 1 to 2 months, respectively, were retrieved for analysis. A single CT image of the third lumbar vertebra (L3) with visible transverse and spinous processes was used to measure the cross-sectional area of skeletal muscle and subcutaneous adipose tissue (24) using Varian's Eclipse software (version 15.6), as shown in **Figure 1**. The specific CT Hounsfield unit (HU) range used to identify and demarcate skeletal muscle was −29 to +150 and that for subcutaneous adipose tissue was −190 to −30 (25). The boundaries of the structures were manually corrected if necessary. Body composition parameters were assessed by one investigator (S Li) who was blinded to the patients' information to eliminate measurement bias. The cross-sectional area (cm^2) and radiation attenuation (HU) of the structures were then obtained. The muscle and tissue areas were normalized to the patient's height to calculate the skeletal muscle index (SMI, cm^2/m^2) and subcutaneous adipose tissue index (SATI, cm^2/m^2). Sarcopenia was defined as SMI < 52.4 cm^2/m^2 for men and < 38.5 cm^2/m^2 for women, based on the cutoff value used by Prado et al. (26), which has been proven applicable to AEG (16, 27). The mean HU for skeletal muscle was defined as skeletal muscle density (SMD).

Two other nutritional indices, the NRS 2002 score and weight loss during NCRT, were also evaluated in this study. NRS 2002 is a nutritional screening tool, proposed by the European Society for Clinical Nutrition and Metabolism, to investigate the status of nutrition risk for patients in hospital. It consists of three parts: (1) nutritional status (score 0–3 points), which is evaluated according to the indicators of weight loss, food intake, and body mass index (BMI); (2) severity of disease (score 0–3 points); (3) age (score 0–1 points). The above three parts are added together to get the total score (0–7 points), in which patients scoring 3 or more are at risk nutritionally (28). All patients received the evaluation of NRS 2002 by a trained nurse at initial diagnosis. We also collected patients' weight before and after NCRT in order to calculate the percentage of weight change during NCRT.

2.6. Statistical analysis

The normality of continuous data was determined using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation (SD) and were compared using independent-samples or paired *t*-tests. Variables with a skewed distribution are presented as median (interquartile range) and were compared using the Mann–Whitney *U* test or Wilcoxon signed-rank test. Categorical data are presented as numbers and percentages and were compared using the χ^2 test, Fisher's exact test, or Mann–Whitney *U* test. X-tile program was used to determine the optimal cutoff value of weight loss for predicting OS by selecting the highest χ^2 value (version 3.6.1; Yale University) (29). Survival analysis was conducted using the Kaplan–Meier method, and the results were compared using the log-rank test. Univariate and multivariate survival analyses were performed using Cox proportional hazards regression models. Clinical, pathological, and nutritional factors (age, gender, differentiation, Lauren type, cTNM stage, concurrent chemotherapy regimen, NRS 2002 score, weight loss during NCRT, pre- and post-sarcopenia, and radical surgery) that may influence the survival outcomes were included in the univariate analysis. All variables with p values < 0.10 in the univariate analysis were included in the multivariate analysis. Statistical significance was set at $p < 0.05$. Data were analyzed using IBM SPSS software (version 25.0; Chicago, IL, USA). The prognostic accuracy of factors was tested using the receiver operating characteristic (ROC) curve and compared with the area under the curve (AUC) value using R software (version 4.1.2).

3. Results

3.1. Clinicopathological characteristics and body composition parameters

A total of 63 patients with locally advanced AEG who received NCRT were enrolled in our study. Among them, 41 (65.1%) and 50 (79.4%) had pre- and post-NCRT sarcopenia, respectively, showing an increased incidence of sarcopenia during NCRT ($\chi^2 = 20.661$, $p < 0.001$). The clinicopathological characteristics classified by pre- and post-NCRT sarcopenia status are summarized in **Table 1**. Our data showed that compared to patients without sarcopenia, patients with pre-NCRT sarcopenia were associated with older age (64.4 ± 5.5 *vs.* 59.9 ± 6.5 years, $p = 0.005$) and had a lower

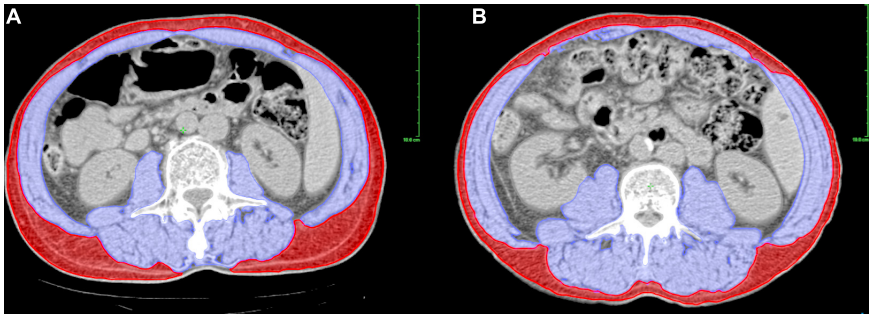


FIGURE 1
Assessment of body composition parameters using a CT-based method at L3 level. The picture shows different sarcopenic statuses in patients with the same BMI, in which blue and red zones represent the skeletal muscle and subcutaneous adipose tissue, respectively. **(A)** A male patient with sarcopenia (SMI = 46.52 cm^2/m^2, BMI = 22.50 kg/m^2). **(B)** A male patient without sarcopenia (SMI = 56.19 cm^2/m^2, BMI = 22.50 kg/m^2). BMI, body mass index; CT, computed tomography; L3, third lumbar vertebra; SMI, skeletal muscle index.

proportion of Lauren intestinal type (48.8 *vs.* 77.3%, $p = 0.029$). The other clinicopathological characteristics did not differ significantly between patients with and without sarcopenia, both pre- and post-NCRT.

In addition, we investigated the relationship between the body composition parameters and sarcopenia. The results indicated that patients with pre-NCRT sarcopenia had lower weight (66.9 ± 10.9 *vs.* 77.2 ± 11.6 kg, $p = 0.001$) and SATI values (34.6 ± 18.1 *vs.* 52.2 ± 21.9 cm^2/m^2, $p = 0.001$) than those of non-sarcopenia patients. Post-NCRT sarcopenia patients also tended to have lower weight (65.6 ± 10.6 *vs.* 78.7 ± 9.8 kg, $p < 0.001$), SATI values (31.9 ± 14.6 *vs.* 53.8 ± 18.4 cm^2/m^2, $p < 0.001$), and SMD values (35.9 ± 6.7 *vs.* 40.0 ± 6.2 HU, $p = 0.048$) than those without sarcopenia.

3.2. Short-term outcomes

Among the 63 patients, 48 (76.2%) completed NCRT as expected. The vast majority (56, 88.9%) experienced benefits due to NCRT in the clinical response evaluation; among them, six patients did not undergo surgery (two were unsuitable for surgery and four refused surgery). In addition, seven patients had disease progression and received systemic therapy instead. Ultimately, 50 (79.4%) patients underwent radical surgery. Patients with pre-NCRT sarcopenia had lower radical surgery rates (70.7 *vs.* 95.5%, $p = 0.047$) than those without sarcopenia. However, completion status, severe toxicity, and clinical response distribution associated with NCRT did not differ significantly between patients with and without sarcopenia. There were also no significant differences in surgical outcomes in terms of D2 lymphadenectomy rate, R0 resection rate, severe complications, and the pathological response evaluation among patients with different sarcopenic statuses (**Supplementary Table 1**).

3.3. Long-term outcomes

The median follow-up time was 59.6 months (95% CI 54.1–65.1) for all patients. As shown in **Figure 2**, patients with pre-NCRT sarcopenia had significantly poorer OS rates among all patients: the 1-, 3-, and 5-year OS rates for patients with pre-NCRT sarcopenia were 85.3, 47.7, and 45.2%, respectively, whereas those for patients without sarcopenia were 100, 80.0, and 80.0%, respectively ($p = 0.003$). Additionally, patients with pre-NCRT sarcopenia had poor PFS rates: the 1-, 3-, and 5-year PFS rates for patients with pre-NCRT sarcopenia were 70.6, 45.4, and 40.0%, respectively, whereas those for patients without sarcopenia were 95.2, 75.6, and 75.6%, respectively ($p = 0.014$). Patients with post-NCRT sarcopenia had a significantly poorer OS rate ($p = 0.026$) and tended to have a poorer PFS rate ($p = 0.051$) than those without sarcopenia.

3.4. Prognostic accuracy of nutritional indices

As sarcopenia was proven to be a significant predictive factor for survival, we tried to identify whether other nutritional indices, including the NRS 2002 score and weight loss during NCRT, could also predict the prognosis and, if so, their accuracy. The cutoff value for weight loss was 8%, calculated using the X-tile program, and the patients were classified into two groups according to the cutoff value. Patients with NRS 2002 scores of ≥ 3 had significantly lower OS ($p = 0.008$) and PFS rates ($p = 0.029$) than those with NRS 2002 scores of < 3. Patients with $\geq 8\%$ weight loss during NCRT had significantly lower OS ($p = 0.003$) and PFS rates ($p = 0.012$) than those who did not meet this criterion. We then tested the prognostic accuracy of these indices using AUC models (**Figure 3**). The results indicated that pre-NCRT sarcopenia was the best predictive index for 5-year OS and PFS rate, with AUC values of 0.735 and 0.770, respectively.

3.5. Univariate and multivariate analyses for OS and PFS

We performed univariate and multivariate analyses in all patients who received NCRT to identify the independent predictive factors for OS and PFS (**Figure 4**). Univariate analysis showed that cTNM stage, NRS 2002 score, weight loss during NCRT, pre- and post-NCRT sarcopenia, and radical surgery were predictive factors of OS and PFS. Among these factors, multivariate analysis further identified that cTNM stage IVA [hazard ratio (HR) 25.647, 95% CI 1.786–368.300, $p = 0.017$], NRS 2002 score ≥ 3 (HR 5.398, 95% CI 1.963–14.844, $p = 0.001$), and pre-NCRT sarcopenia (HR 6.053, 95% CI 1.890–19.388, $p = 0.002$) were independent predictive factors for poor OS.

10.3389/fnut.2023.988632

TABLE 1 Clinicopathological characteristics of patients according to pre- and post-NCRT sarcopenic status (n = 63).

Characteristics		Pre-NCRT			Post-NCRT		
	Total (n = 63)	Sarcopenia (n = 41)	Non-sarcopenia (n = 22)	P-value	Sarcopenia (n = 50)	Non-sarcopenia (n = 13)	P-value
Age (years), mean ± SD	62.8 ± 6.2	64.4 ± 5.5	59.9 ± 6.5	**0.005**§*	63.5 ± 6.3	60.2 ± 5.1	0.084§
Male gender, n (%)	60 (95.2)	38 (95.1)	21 (95.5)	>0.999	48 (96.0)	12 (92.3)	0.506‡
ECOG, n (%)				0.979			0.888
0	50 (79.4)	32 (78.0)	18 (81.8)		39 (78.0)	11 (84.6)	
1	13 (20.6)	9 (22.0)	4 (18.2)		11 (22.0)	2 (15.4)	
NRS 2002 score, n (%)				>0.999			0.631
<3	53 (84.1)	34 (82.9)	19 (86.4)		41 (82.0)	12 (92.3)	
≥3	10 (15.9)	7 (17.1)	3 (13.6)		9 (18.0)	1 (7.7)	
Differentiation, n (%)				0.493			0.592
Well to moderately	25 (39.7)	15 (36.6)	10 (45.5)		19 (38.0)	6 (46.2)	
Poorly	38 (60.3)	26 (63.4)	12 (54.5)		31 (62.0)	7 (53.8)	
Siewert type, n (%)				0.598†			0.771†
Siewert II	37 (58.7)	23 (56.1)	14 (63.6)		30 (60.0)	7 (53.8)	
Siewert III	20 (31.7)	14 (34.1)	6 (27.3)		15 (30.0)	5 (38.5)	
Unavailable	6 (9.5)	4 (9.8)	2 (9.1)		5 (10.0)	1 (7.7)	
Lauren type				**0.041**†*			0.279†
Intestinal type	37 (58.7)	20 (48.8)	17 (77.3)		27 (54.0)	10 (76.9)	
Diffuse type	11 (17.5)	9 (22.0)	2 (9.1)		11 (22.0)	0 (0.0)	
Mixed type	11 (17.5)	9 (22.0)	2 (9.1)		9 (18.0)	2 (15.4)	
Unavailable	4 (6.3)	3 (7.3)	1 (4.5)		3 (6.0)	1 (7.7)	
Clinical T category, n (%)				>0.999			>0.999
T3	14 (22.2)	9 (22.0)	5 (22.7)		11 (22.0)	3 (23.1)	
T4	49 (77.8)	32 (78.0)	17 (77.3)		39 (78.0)	10 (76.9)	
Clinical N category, n (%)				0.106†			0.078†
N1	18 (28.6)	9 (22.0)	9 (40.9)		12 (24.0)	6 (46.2)	
N2	32 (50.8)	22 (53.7)	10 (45.5)		26 (52.0)	6 (46.2)	
N3	13 (20.6)	10 (24.4)	3 (13.6)		12 (24.0)	1 (7.7)	
Clinical TNM stage, n (%)				0.538‡			>0.999‡
III	61 (96.8)	39 (95.1)	22 (100.0)		48 (96.0)	13 (100.0)	
IVA	2 (3.2)	2 (4.9)	0 (0)		2 (4.0)	0 (0)	
Concurrent chT, n (%)				0.116			0.566
S-1	16 (25.4)	13 (31.7)	3 (13.6)		14 (28.0)	2 (15.4)	
SOX	47 (74.6)	28 (68.3)	19 (86.4)		36 (72.0)	11 (84.6)	

chT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NCRT, neoadjuvant chemoradiotherapy; NRS, Nutritional Risk Screening; SD, standard deviation; SOX, S-1 and oxaliplatin.
*Statistically significant values are given in bold.
†Mann-Whitney U test.
‡Fisher's exact test.
§t-test. χ^2 test was used unless otherwise specified.

The cTNM IVA stage (HR 8.739, 95% CI 1.476–51.745, p = 0.017), NRS 2002 score ≥ 3 (HR 3.614, 95% CI 1.446–9.032, p = 0.006), pre-NCRT sarcopenia (HR 2.873, 95% CI 1.099–7.510, p = 0.031), and absence of radical surgery (HR 2.940, 95% CI 1.190–7.262, p = 0.019) were proven to be independent predictive factors for poor PFS.

4. Discussion

In this study, we assessed sarcopenic status using a CT-based method before and after NCRT and determined the significance of sarcopenia in predicting poor OS and PFS rates in patients with

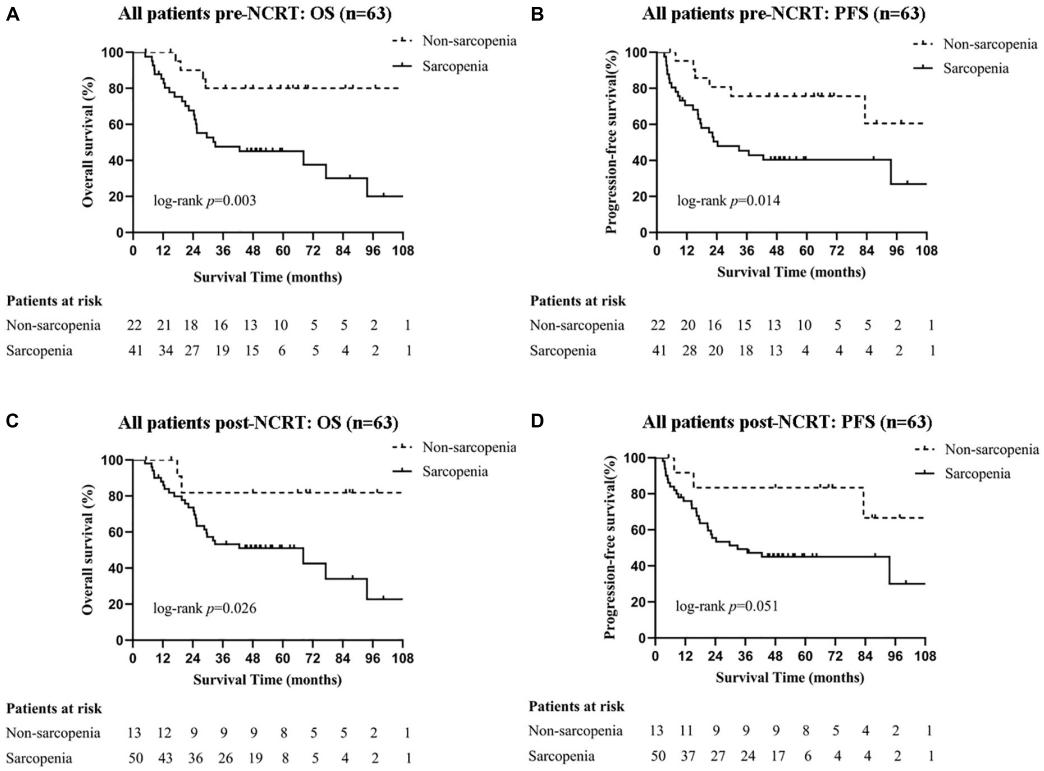


FIGURE 2
Survival curves of all patients with different sarcopenic statuses. Pre-NCRT **(A)** OS and **(B)** PFS. Post-NCRT **(C)** OS, and **(D)** PFS. NCRT, neoadjuvant chemoradiotherapy; OS, overall survival; PFS, progression-free survival.

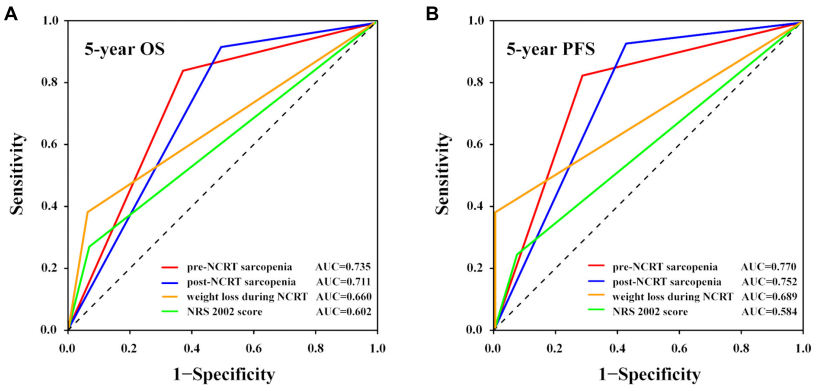


FIGURE 3
Prognostic accuracy of different nutritional indices compared using ROC curves with AUC values. The **(A)** 5-year OS and **(B)** 5-year PFS rates. AUC, area under the curve; NCRT, neoadjuvant chemoradiotherapy; NRS 2002, nutritional risk screening 2002; OS, overall survival; PFS, progression-free survival; ROC, receiver operating characteristic.

locally advanced AEG. We also tested the prognostic accuracy of different nutritional indices to predict survival, of which pre-NCRT sarcopenia was the best predictive factor for 5-year OS and PFS rates. To the best of our knowledge, this is the first study to investigate the sarcopenic status before and after NCRT and identify its impact on outcomes in patients with multimodally treated AEG.

The impact of sarcopenia on poor survival has been determined in multiple cancers (12–15). However, there is a paucity of literature on patients with AEG, and inconsistent results have been obtained in some studies that involved patients with AEG (16, 17, 27). In the present study, pre-NCRT sarcopenia was demonstrated to be an independent predictive factor for OS ($p = 0.002$) and PFS ($p = 0.031$) in multivariate analysis, which may be related to the low proportion of the Lauren intestinal type ($p = 0.029$) and low radical surgery rate ($p = 0.047$). Studies have identified that the intestinal type is associated with favorable prognosis in gastric and AEG patients (30); patients who received NCRT plus radical surgery also had better prognoses than those who did not undergo radical surgery. However, considering the complexity of surgical decision making, which is not only related to complete resectability but also the patient's physical condition including tolerance to surgery and willingness to undergo surgery, the results should be interpreted cautiously. In

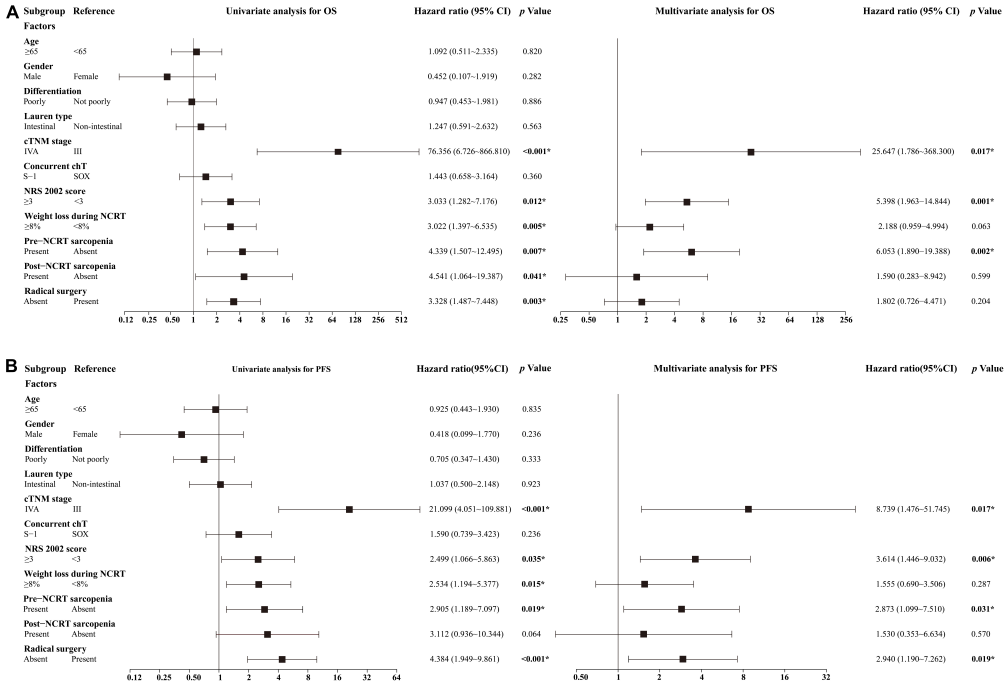


FIGURE 4
Results of univariate and multivariate analyses for **(A)** OS and **(B)** PFS. *Statistically significant values are given in bold. chT, chemotherapy; NCRT, neoadjuvant chemoradiotherapy; OS, overall survival; PFS, progression-free survival; SOX, S-1 and oxaliplatin.

line with our study, Tan et al. also reported the prognostic impact of sarcopenia on poor OS in patients with esophagogastric cancer who underwent NAT and radical surgery (median OS: sarcopenia, 569 days *vs*. non-sarcopenia, 1,013 days; $p = 0.04$), in which 18% of patients had gastroesophageal junction cancers (16). Järvinen et al. also identified that patients with a reduction in SMI during NAT had poor survival (27). Conversely, other studies found no correlation between sarcopenia and survival outcome (17).

In addition, our study demonstrated that pre-NCRT sarcopenia had prognostic superiority in predicting the 5-year OS and PFS rates in patients with locally advanced AEG compared to NRS 2002 score and weight loss. The assessment of sarcopenic status using CT-based methods is objective, quantitative, timely, repeatable, non-invasive and does not require additional medical resources as CT examinations are performed routinely at initial diagnosis. Therefore, we can routinely assess sarcopenic status in all AEG patients receiving multimodal therapy. In comparison, NRS 2002 is a quick and convenient tool to perform initial screening for nutritional risk in hospitalized patients, and previous research has shown that it has prognostic value in postoperative complications and survival in esophageal, gastric, and other cancers (7–9). However, as a rapid nutritional screening method, NRS 2002 depends on patients' self-reported value of weight loss and food intake, and it is only the first step in determining patients' nutritional status (28). Therefore, its accuracy as a prognostic indicator may be limited. To further determine the nutritional status of patients, a comprehensive and detailed nutritional assessment is required. As for weight loss, it has been found that excessive weight loss during NAT or after surgery is associated with severe postoperative complications and worse survival in multiple cancers (10, 11, 31). Nevertheless, weight is affected by many factors. For example, weight gain can result from malignant pleural effusion or ascites due to tumor progression or hypoproteinemia, and weight loss can be caused by dehydration due to acute diarrhea. Therefore, weight loss may not accurately reflect the nutritional status of patients. In addition, only through weight monitoring over a period of time can weight loss be determined, so the nutritional status of patients cannot be assessed timely through weight loss.

In contrast to the generally accepted notion of poor survival in sarcopenic patients, limited studies have reported inconsistent conclusions on the short-term outcomes in patients receiving NAT (16–20, 32, 33). As for the NAT-related toxicity, Panje et al. observed an increased percentage of grade ≥ 3 toxicities during NCRT in pre-NCRT sarcopenic patients (83.3 *vs*. 52.4%, $p = 0.04$) (17), while our study and other studies revealed negative results (32). We also observed no effect of sarcopenia on clinical or pathological responses to NAT, consistent with several previous studies (20, 34). However, others studies found that sarcopenic patients had lower clinical and pathological response rates (18, 19). In addition, neither previous studies (17, 32, 33) nor our study could demonstrate a relationship between sarcopenia and postoperative complications. Although some other studies reported that post-NAT sarcopenia was associated with an increased occurrence of postoperative complications, especially pneumonia (19, 20). Further research is needed to clarify the role of sarcopenia in predicting toxicity and efficacy of multimodal treatment in patients with AEG.

The relationship between clinicopathological characteristics, body composition parameters, and sarcopenia in AEG patients was also investigated in our study. Our cohort was predominantly male (95.2%), with a mean age of 62.8 years, which is consistent with data from a larger group in a Chinese study (35). Post-NCRT sarcopenia was related to reduced SMD ($p = 0.048$), suggesting that NCRT may cause a reduction in the quality of skeletal muscles

(34). Sarcopenia is associated with aging and usually occurs in older individuals (11). Our results also showed that pre-NCRT sarcopenia was associated with older age ($p = 0.005$), consistent with the results of other studies (20, 27, 33). Moreover, along with other studies, we found associations between sarcopenia and lower weight both before and after NCRT (27).

The underlying mechanisms by which sarcopenia develops and influences survival in patients with cancer remain obscure. Various candidate mechanisms, driven by multiple factors related to metabolism and inflammation, have been described (36). First, imbalances in protein metabolism lead to the overall loss of skeletal muscle and development of sarcopenia (36, 37). Imbalances in protein metabolism are associated with malnutrition which is a risk factor for poor survival in cancer patients (7). Whether nutritional supplementation could improve sarcopenic status and improve prognoses, however, requires further investigation. Second, proinflammatory mediators such as tumor necrosis factor-α and interleukin-6 play a pivotal role in the development and progression of sarcopenia (38). Some studies have shown that systemic inflammation is related to poor survival in several cancers (39, 40), and it is also among the most prominent features of sarcopenia (41). Third, cancer treatment, particularly chemotherapy, can cause direct damage to muscle tissue *via* molecular pathways (36). Additionally, other factors related to aging, such as reduced physical activity and a decline in anabolic hormones, may lead to sarcopenia (36). Further studies are required to confirm the hypotheses.

The current study has some limitations. First, owing to the retrospective nature of this study, many patients were excluded due to the lack of available CT images, which might have caused selection bias. In addition, differences in the timing of CT examinations among patients may contribute to the reduced prediction accuracy of sarcopenia on survival. Next, the study's sample size was relatively small, and it was conducted in a single institution, which might have confined its external validity and affected the results, especially for short-term outcomes. Lastly, given few patients had changes in sarcopenia status before and after NCRT, we were not able to assess the impact of changes in sarcopenia status (i.e., patients with sarcopenia before NCRT but without after NCRT and vice versa) on outcomes, although it would be meaningful to conduct such studies. Thus, further prospective studies involving larger sample sizes and multiple institutions are required to confirm our results.

5. Conclusion

Pre-NCRT sarcopenia may be an independent predictive factor for poor OS and PFS rates in patients with locally advanced AEG treated with NCRT and had prognostic superiority in predicting the 5-year OS and PFS rates compared with other nutritional indices. Our findings imply that early screening for sarcopenic status and timely nutritional intervention for patients with sarcopenia may improve their survival outcomes.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Peking University Beijing Cancer Hospital and Institute (approval number: 2014KT74). The patients/participants provided their written informed consent to participate in this study.

Author contributions

WW, ZiL, and YL contributed equally in designing and supervising this study. JM analyzed the data and wrote this manuscript. RD and JG made contributions in collecting the data. SL assessed the body composition parameters in CT images. XgZ, YZ, and HW assisted in data interpretation and manuscript revision. ZyL, YC, XtZ, ZP, AW, ZB, and YP provided clinical data and contributed to the patient management. ZW and LT provided medical imaging data and diagnosis. YY and ZwL provided endoscopic data, pathological data, and diagnosis. All authors read and approved the final manuscript.

Funding

This study was supported by the following programs: Capital's Funds for Health Improvement and Research (No. 2020-2-1027), Beijing Municipal Science and Technology Commission (No. Z181100001718192), and National Natural Science Foundation (No. 82073333).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.988632/full#supplementary-material

References

1. Manabe N, Matsueda K, Haruma K. Epidemiological review of gastroesophageal junction adenocarcinoma in Asian countries. *Digestion.* (2022) 103:29–36. doi: 10.1159/000519602

2. Thrift A, Whiteman D. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. *Ann Oncol.* (2012) 23:3155–62. doi: 10.1093/annonc/mds181

3. Imamura Y, Watanabe M, Oki E, Morita M, Baba H. Esophagogastric junction adenocarcinoma shares characteristics with gastric adenocarcinoma: literature review and retrospective multicenter cohort study. *Ann Gastroenterol Surg.* (2021) 5:46–59. doi: 10.1002/ags3.12406

4. Shapiro J, van Lanschot J, Hulshof M, van Hagen P, van Berge Henegouwen M, Wijnhoven B, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol.* (2015) 16:1090–8.

5. Du R, Ming J, Geng J, Zhu X, Zhang Y, Li S, et al. Establishment of prognostic models for adenocarcinoma of oesophagogastric junction patients with neoadjuvant chemoradiotherapy: a real-world study. *Radiat Oncol.* (2022) 17:45. doi: 10.1186/s13014-022-02016-3

6. Kurtom S, Kaplan B. Esophagus and gastrointestinal junction tumors. *Surg Clin North Am.* (2020) 100:507–21.

7. Choi W, Kim J. Nutritional care of gastric cancer patients with clinical outcomes and complications: a review. *Clin Nutr Res.* (2016) 5:65–78.

8. Trestini I, Paiella S, Sandini M, Sperduti I, Elio G, Pollini T, et al. Prognostic impact of preoperative nutritional risk in patients who undergo surgery for pancreatic adenocarcinoma. *Ann Surg Oncol.* (2020) 27:5325–34.

9. Noh J, Na H, Kim Y, Song H, Kim H, Choi K, et al. Influence of preoperative nutritional status on patients who undergo upfront surgery for esophageal squamous cell carcinoma. *Nutr Cancer.* (2022) 74:2910–9. doi: 10.1080/01635581.2022.2042573

10. Wiwitkeyoonwong J, Jiarpinitnun C, Hiranyatheb P, Ngamphaiboon N. Impact of weight loss on patients with locally advanced esophageal and esophagogastric junction cancers treated with chemoradiotherapy. *Asian Pac J Cancer Prev.* (2021) 22:3847–55. doi: 10.31557/APJCP.2021.22.12.3847

11. Kubo H, Komatsu S, Ichikawa D, Kawaguchi T, Kosuga T, Okamoto K, et al. Impact of body weight loss on recurrence after curative gastrectomy for gastric cancer. *Anticancer Res.* (2016) 36:807–13.

12. Paireder M, Asari R, Kristo I, Rieder E, Tamandl D, Ba-Ssalamah A, et al. Impact of sarcopenia on outcome in patients with esophageal resection following neoadjuvant chemotherapy for esophageal cancer. *Eur J Surg Oncol.* (2017) 43:478–84. doi: 10.1016/j.ejso.2016.11.015

13. Sakurai K, Kubo N, Tamura T, Toyokawa T, Amano R, Tanaka H, et al. Adverse effects of low preoperative skeletal muscle mass in patients undergoing gastrectomy for gastric cancer. *Ann Surg Oncol.* (2017) 24:2712–9.

14. Choi M, Yoon S, Lee K, Song M, Lee I, Lee M, et al. Preoperative sarcopenia and post-operative accelerated muscle loss negatively impact survival after resection of pancreatic cancer. *J Cachexia Sarcopenia Muscle.* (2018) 9:326–34. doi: 10.1002/jcsm.12274

15. Imai K, Takai K, Watanabe S, Hanai T, Suetsugu A, Shiraki M, et al. Sarcopenia impairs prognosis of patients with hepatocellular carcinoma: the role of liver functional reserve and tumor-related factors in loss of skeletal muscle volume. *Nutrients.* (2017) 9:1054. doi: 10.3390/nu9101054

16. Tan B, Brammer K, Randhawa N, Welch N, Parsons S, James E, et al. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. *Eur J Surg Oncol.* (2015) 41:333–8. doi: 10.1016/j.ejso.2014.11.040

17. Panje C, Höng L, Hayoz S, Baracos V, Herrmann E, Garcia Schüler H, et al. Skeletal muscle mass correlates with increased toxicity during neoadjuvant radiochemotherapy in locally advanced esophageal cancer: a SAKK 75/08 substudy. *Radiat Oncol.* (2019) 14:166. doi: 10.1186/s13014-019-1372-3

18. Ozawa Y, Nakano T, Taniyama Y, Sakurai T, Onodera Y, Kamiya K, et al. Evaluation of the impact of psoas muscle index, a parameter of sarcopenia, in patients with esophageal squamous cell carcinoma receiving neoadjuvant therapy. *Esophagus.* (2019) 16:345–51. doi: 10.1007/s10388-019-00670-3

19. Ishida T, Makino T, Yamasaki M, Tanaka K, Miyazaki Y, Takahashi T, et al. Impact of measurement of skeletal muscle mass on clinical outcomes in patients with esophageal cancer undergoing esophagectomy after neoadjuvant chemotherapy. *Surgery.* (2019) 166:1041–7.

20. Elliott J, Doyle S, Murphy C, King S, Guinan E, Beddy P, et al. Sarcopenia: prevalence, and impact on operative and oncologic outcomes in the multimodal management of locally advanced esophageal cancer. *Ann Surg.* (2017) 266:822–30. doi: 10.1097/SLA.0000000000002398

21. Li Z, Li S, Bu Z, Zhang L, Wu X, Shan F, et al. The effect of preoperative treatments on lymph node counts after total gastrectomy in esophagogastric adenocarcinoma. *J Surg Oncol.* (2018) 118:657–63. doi: 10.1002/jso.25188

22. Eisenhauer E, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* (2009) 45:228–47.

23. The National Comprehensive Cancer Network. *Gastric Cancer (Version 2.2022). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines§).* Plymouth Meeting, PA: The National Comprehensive Cancer Network (2022).

24. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol.* (2004) 97:2333–8.

25. Mitsiopoulos N, Baumgartner R, Heymsfield S, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol.* (1998) 85:115–22.

26. Prado C, Lieffers J, McCargar L, Reiman T, Sawyer M, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol.* (2008) 9:629–35. doi: 10.1016/S1470-2045(08)70153-0

27. Järvinen T, Ilonen I, Kauppi J, Salo J, Räsänen J. Loss of skeletal muscle mass during neoadjuvant treatments correlates with worse prognosis in esophageal cancer: a retrospective cohort study. *World J Surg Oncol.* (2018) 16:27.

28. Kondrup J, Allison S, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* (2003) 22:415–21.

29. Camp R, Dolled-Filhart M, Rimm D. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res.* (2004) 10:7252–9. doi: 10.1158/1078-0432.CCR-04-0713

30. Jiménez Fonseca P, Carmona-Bayonas A, Hernández R, Custodio A, Cano J, Lacalle A, et al. Lauren subtypes of advanced gastric cancer influence survival and response to chemotherapy: real-world data from the AGAMENON National Cancer Registry. *Br J Cancer.* (2017) 117:775–82. doi: 10.1038/bjc.2017.245

31. Aoyama S, Motoori M. The impact of weight loss during neoadjuvant chemotherapy on postoperative infectious complications and prognosis in patients with esophageal cancer: exploratory analysis of OGSG1003. *Esophagus.* (2022). [Preprint]. doi: 10.1007/s10388-022-00975-w

32. Miyata H, Sugimura K, Motoori M, Fujiwara Y, Omori T, Yanagimoto Y, et al. Clinical assessment of sarcopenia and changes in body composition during neoadjuvant chemotherapy for esophageal cancer. *Anticancer Res.* (2017) 37:3053–9.

33. Hagens E, Feenstra M, van Egmond M, van Laarhoven H, Hulshof M, Boshier P, et al. Influence of body composition and muscle strength on outcomes after multimodal oesophageal cancer treatment. *J Cachexia Sarcopenia Muscle.* (2020) 11:756–67. doi: 10.1002/jcsm.12540

34. Ishibashi Y, Tsujimoto H, Hiraki S, Kouzu K, Tsuchiya S, Itazaki Y, et al. Predictive value of immuno-inflammatory and nutritional measures modulated by neoadjuvant chemotherapy on the response of neoadjuvant chemotherapy and long-term outcomes in patients with esophageal cancer. *Oncol Lett.* (2020) 19:487–97. doi: 10.3892/ol.2019.11122

35. Liu K, Yang K, Zhang W, Chen X, Chen X, Zhang B, et al. Changes of esophagogastric junctional adenocarcinoma and gastroesophageal reflux disease among surgical patients during 1988-2012: a single-institution, high-volume experience in China. *Ann Surg.* (2016) 263:88–95. doi: 10.1097/SLA.0000000000001148

36. Williams G, Dunne R, Giri S, Shachar S, Caan B. Sarcopenia in the older adult with cancer. *J Clin Oncol.* (2021) 39:2068–78.

37. Cruz-Jentoft A, Sayer A. Sarcopenia. *Lancet.* (2019) 393:2636–46.

38. Moreira-Pais A, Ferreira R, Oliveira P, Duarte J. Sarcopenia versus cancer cachexia: the muscle wasting continuum in healthy and diseased aging. *Biogerontology.* (2021) 22:459–77. doi: 10.1007/s10522-021-09932-z

39. Muhammed A, Fulgenzi C, Dharmapuri S, Pinter M, Balcar L, Scheiner B, et al. The systemic inflammatory response identifies patients with adverse clinical outcome from immunotherapy in hepatocellular carcinoma. *Cancers.* (2021) 14:186. doi: 10.3390/cancers14010186

40. Richards C, Leitch E, Horgan P, Anderson J, McKee R, McMillan D. The relationship between patient physiology, the systemic inflammatory response and survival in patients undergoing curative resection of colorectal cancer. *Br J Cancer.* (2010) 103:1356–61.

41. Yoon H, Oh D, Ahn Y, Noh J, Pyo H, Cho W, et al. Prognostic impact of sarcopenia and skeletal muscle loss during neoadjuvant chemoradiotherapy in esophageal cancer. *Cancers.* (2020) 12:925.

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 01 February 2023
DOI 10.3389/fnut.2023.1076589

OPEN ACCESS

EDITED BY
Paula Ravasco,
Catholic University of Portugal, Portugal

REVIEWED BY
Guoliang Ye,
The Affiliated Hospital of Medical School of Ningbo University, China
Xu Sheng,
People's Hospital of Guangxi Zhuang Autonomous Region, China

*CORRESPONDENCE
Jialiang Gan
✉ gjl5172@163.com
Shuangyi Tang
✉ tshy369@sina.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 21 October 2022
ACCEPTED 05 January 2023
PUBLISHED 01 February 2023

CITATION
Xie H, Wei L, Gao S, Liu M, Liang Y, Yuan G, Wang Q, Xu Y, Tang S and Gan J (2023) Prognostic significance of sarcopenia diagnosed based on the anthropometric equation for progression-free survival and overall survival in patients with colorectal cancer. *Front. Nutr.* 10:1076589. doi: 10.3389/fnut.2023.1076589

Prognostic significance of sarcopenia diagnosed based on the anthropometric equation for progression-free survival and overall survival in patients with colorectal cancer

Hailun Xie[1,2†], Lishuang Wei[3†], Shunhui Gao[1,2†], Mingxiang Liu[1,2], Yanren Liang[1,2], Guanghui Yuan[1,2], Qiwen Wang[1,2], Yansong Xu[4], Shuangyi Tang[5*] and Jialiang Gan[1,2*]

[1]Department of Colorectal and Anal Surgery, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China, [2]Guangxi Key Laboratory of Enhanced Recovery After Surgery for Gastrointestinal Cancer, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China, [3]Department of Geriatric Respiratory Disease Ward, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China, [4]Department of Emergency Surgery, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China, [5]Department of Pharmacy, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China

Background: The purpose of this study was to investigate the prognostic significance of sarcopenia diagnosed based on anthropometric equations for progression-free survival (PFS) and overall survival (OS) in patients with colorectal cancer (CRC).

Methods: A total of 1,441 CRC patients who underwent surgical treatment between January 2012 and December 2016 were enrolled in this study. Sarcopenia was diagnosed according to validated anthropometric equations. The Kaplan–Meier method with the log-rank test was used to estimate the survival curve. Cox proportional hazards regression models with forward selection were used to evaluate risk factors affecting the prognosis of CRC patients. R package "survival" was used to build the prognostic nomograms to predict 1–5 years of PFS and OS in CRC patients. The concordance index (C-index) and calibration curve were used to evaluate the prognostic accuracy of the prognostic nomogram.

Results: Two hundred and seventy-one patients (18.8%) were diagnosed with sarcopenia. Sarcopenia was significantly associated with advanced age, large tumor size, and high mortality. Compared with the non-sarcopenia patients, the PFS of sarcopenia patients was worse (5-year PFS, 48.34 vs. 58.80%, $p = 0.003$). Multivariate survival analysis showed that patients with sarcopenia had a higher risk (23.9%) of adverse PFS (HR, 1.239; 95%CI: 1.019–1.505, $p = 0.031$) than patients without sarcopenia. The OS of patients with sarcopenia was significantly worse than that of patients without sarcopenia (5-year OS: 50.92 vs. 61.62%, $p = 0.001$). In CRC patients, sarcopenia was independently associated with poor OS (HR: 1.273, 95%CI: 1.042–1.556, $p < 0.001$). Moreover, sarcopenia effectively differentiated the OS of CRC patients in the normal carcinoembryonic antigen (CEA) subgroup but not in the high CEA subgroup. Notably, sarcopenia can provide effective prognostic stratification in CRC patients at different pathological stages. Nomograms

that integrated prognostic features were built to predict the risk of adverse outcomes in CRC patients. The C-index and calibration curves showed that these nomograms had good prediction accuracy. Internal validation confirmed that our nomogram has wide application potential.

Conclusion: Sarcopenia diagnosed based on anthropometric equations is an independent risk factor for PFS and OS in CRC patients.

KEYWORDS

sarcopenia, malnutrition, progression-free survival, overall survival, colorectal cancer

1. Introduction

Colorectal cancer (CRC) is a common malignancy of the digestive system. Previous reports have stated that CRC is the third most common cancer in men and the second most common cancer in women, accounting for 10.6 and 9.4%, respectively. Furthermore, CRC is the third leading cause of cancer-related death in men and women, accounting for more than 510,000 deaths in men and more than 420,000 deaths in women (1). In China, the incidence and mortality of CRC are on the rise. The incidence and mortality of CRC ranked second and fifth among all malignancies, respectively (2). Therefore, early identification of poor prognostic factors in CRC patients and timely interventions are urgently needed to improve the prognosis in these patients.

CRC is often accompanied by low food intake, malabsorption of nutrients, and high systemic inflammation, which transform the body into a state of high catabolic and low synthetic malnutrition. Particularly, these patients often present with progressive loss of body mass, including reduced muscle mass, strength, and muscle function, leading to sarcopenia and even cachexia. Sarcopenia significantly affects the prognosis of patients with malignancies. It is a well-known independent risk factor for poor prognosis in malignancies (3–6). There is a 12–60% prevalence of sarcopenia in CRC patients (7, 8). Early detection of sarcopenia and maintenance of skeletal muscle mass and function are important goals for diagnosing and treating cancer patients. The main methods to diagnose sarcopenia include Dual Energy X-Ray Absorptiometry (DXA), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Bioelectrical Impedance Analysis (BIA) (9–11). These diagnostic methods are expensive, time-consuming, cumbersome, or radioactive, so they are poorly used in clinical practice. It is, therefore, necessary to develop a simple, convenient, and reliable diagnostic method to diagnose sarcopenia.

Recently, Wen et al. (12) developed an anthropometric equation for appendicular skeletal muscle (ASM) based on the Chinese population. It is a simple and practical diagnostic tool for sarcopenia. The accuracy of this tool was verified in several studies (13–15). However, there are few studies focused on the correlation between using this equation to diagnose sarcopenia and the prognosis of CRC patients. The purpose of this study was to investigate the prognostic value of sarcopenia diagnosed based on the anthropometric equation in progression-free survival (PFS) and the overall survival (OS) of CRC patients. Therefore, this study aims to become a reference point for the clinical diagnosis, treatment, and research of sarcopenia in CRC patients.

2. Patients and methods

2.1. Study population and data collection

This study included CRC patients who underwent surgical treatment in the Department of Colorectal and Anal Surgery, the First Affiliated Hospital of Guangxi Medical University, between January 2012 and December 2016. The inclusion criteria were as follows: (1) pathological analysis confirmed that the primary lesion was CRC; (2) patients who had not received preoperative neoadjuvant chemoradiotherapy; and (3) patients who had undergone surgical resection for CRC. The exclusion criteria were as follows: (1) patients with unclear primary tumor sites or multi-site tumors; (2) patients <18 years old; and (3) patients who refused to participate in this study. This study was conducted in strict accordance with the provisions of the Declaration of Helsinki. In addition, written informed consent was obtained from all patients or their close relatives. The Ethics Review Board of the First Affiliated Hospital of Guangxi Medical University approved this study, with the approval number: 2021 (KY-E-043).

Clinicopathological information of CRC patients was retrospectively collected. The information included sex, age, height, weight, body mass index (BMI), history of hypertension, diabetes, serum carcinoembryonic antigen (CEA) level, *T* stage, *N* stage, preoperative metastasis, tumor-node-metastasis (TNM) stage, perineural invasion, vascular invasion, pathological type, differentiation, tumor location, tumor size, surgical approach, postoperative radiotherapy, and postoperative chemotherapy.

2.2. Diagnosis of sarcopenia

Sarcopenia is a syndrome primarily characterized by a progressive, generalized reduction in skeletal muscle mass and functional decline. In this study, we estimated the ASM based on the anthropometric equation, which was calculated as follows: 0.193 × weight (kg) + 0.107 × height (cm) −4.157 × sex (male = 1, female = 2) −0.037 × age (year) −2.631. The Skeletal Muscle Index (SMI) was defined as ASM/height squared (m^2), that is, SMI = ASM/Ht squared (Kg/m^2). The updated consensus on the diagnosis and treatment of sarcopenia published by the Asian Working Group on Sarcopenia (AWGS) in 2019 is widely used as the diagnostic criteria for sarcopenia in the Asian population. That is, SMI < 6.92 Kg/m^2 in a man, and SMI < 5.13 Kg/m^2 in a woman is considered sarcopenia (16).

2.3. Follow-up and outcomes

Patients who recovered well were discharged from the hospital. After this, regular visits and telephone follow-ups were performed in the outpatient or inpatient departments. Patients were followed up every 3–6 months in the first year and every 6–12 months from the second year until death. The primary purpose of follow-up was to record the patients' survival status, serum tumor markers, abdominal CT, and electronic fiber colonoscopy. PFS was defined as the interval between surgery and disease recurrence, death, or last follow-up. OS was defined as the interval between surgery and death from any cause or the last follow-up. The date of the last follow-up was February 4, 2021.

2.4. Statistical analysis

Data were expressed as mean ± standard deviation. An independent sample *t*-test was used to compare the measurement data, and the Chi-square test was used to compare categorical data. The Kaplan–Meier method was used to estimate the survival curve, and the log-rank test was used to compare survival rates. Cox proportional hazards regression models with forward selection were used to evaluate risk factors affecting the prognosis of CRC patients. R package "survival" was used to build the prognostic nomograms to predict 1–5 years of PFS and OS in CRC patients. The concordance index (C-index) and calibration curve were used to evaluate the prognostic accuracy of the prognostic nomograms. The total population was randomly divided into two internal validation datasets at a ratio of 7:3 to evaluate the practicability of the nomograms. Differences were considered statistically significant at two-sided *p*-values of <0.05. Statistical analyses were performed using the R software (Version 4.0.2).

3. Results

3.1. Clinicopathologic characteristics

A total of 1,441 CRC patients were enrolled in this study. According to the diagnostic criteria for sarcopenia, 271 patients (18.8%) were diagnosed with sarcopenia. Among the 904 enrolled male patients, 162 were diagnosed with sarcopenia, with an incidence of 17.9%. Among the 537 enrolled female patients, 109 were diagnosed with sarcopenia, with an incidence of 20.3%. The incidence of sarcopenia in female patients was slightly higher than that in male patients; however, there was no significant difference between the two groups ($p = 0.295$). The mean age of sarcopenia patients was 64.6 ± 13.4 years old, and the mean age of non-sarcopenia patients was 56.6 ± 12.6 years old. The mean age of patients with sarcopenia was significantly higher than that of patients without sarcopenia; there was a significant statistical difference between the two groups ($p < 0.001$). There were 705 patients with colon cancer, including 143 who were diagnosed with sarcopenia (20.3%), and 736 patients with rectal cancer, including 82 who were diagnosed with sarcopenia (17.4%). There was no significant difference in the incidence of sarcopenia among CRC patients with different tumor sites ($p = 0.181$). Interestingly, the tumor size in patients with sarcopenia was significantly larger than that in patients without sarcopenia (5.0 vs. 4.5 cm, $p = 0.001$). In addition, patients with sarcopenia also had a higher mortality risk than those without sarcopenia (49.1 vs. 38.4%, $p = 0.002$) (Table 1).

3.2. The relationship between sarcopenia and PFS

Based on the last follow-up, 400 patients had a recurrence, including 84 patients diagnosed with sarcopenia (31.0%) and 316 patients not diagnosed with sarcopenia (27.00%). The 5-year PFS of stage I-IV CRC patients were 78.52, 69.17, 47.04, and 7.30%, respectively. Compared with non-sarcopenia patients, the PFS of sarcopenia patients was worse (5-year PFS, 48.34 vs. 58.80%, $p = 0.003$) (Figure 1A). In the normal CEA subgroup, patients with sarcopenia had a significantly lower PFS than those without sarcopenia (Supplementary Figure S1A). However, no significant difference was observed in the high-CEA group (Supplementary Figure S1C). Notably, sarcopenia can provide effective prognostic stratification for CRC patients at different pathological stages (Figures 2A, B). In the univariate survival analysis, sarcopenia was associated with poor PFS in CRC patients (HR, 1.329; 95%CI: 1.101–1.605, $p = 0.003$). Multivariate survival analysis showed that, compared with non-sarcopenia patients, sarcopenia patients had a 23.9% higher risk of adverse PFS (HR, 1.239; 95%CI: 1.019–1.505, $p = 0.031$) (Table 2). Subgroup multivariate survival analysis showed that sarcopenia was an independent risk factor for PFS in most subgroups of CRC patients (Supplementary Figure S2A).

3.3. The relationship between sarcopenia and OS

A total of 582 patients died, including 133 (49.08%) with sarcopenia and 449 (38.38%) without sarcopenia. The 5-year OS of stage I-IV CRC patients were 81.34, 71.67, 50.37, and 8.76%, respectively. The Kaplan-Meier curve showed that the OS of patients with sarcopenia was significantly lower than that of patients without sarcopenia (5-year OS, 50.92 vs. 61.62%, $p = 0.001$) (Figure 1B). In the early stages of CRC (TNM stage I-II), the OS of patients with sarcopenia was significantly poorer than that of patients without sarcopenia (Figure 2C). In the advanced stage, sarcopenia was still effective in the prognostic differentiation of CRC patients (Figure 2D). Additionally, the subgroup survival analysis showed that sarcopenia could effectively differentiate the OS of CRC patients in the normal CEA subgroup (Supplementary Figure S1B). However, it could not significantly differentiate the prognosis of patients in the high CEA subgroup (Supplementary Figure S1D). Multivariate adjustment survival analysis showed that sarcopenia was independently associated with poor OS (HR: 1.273, 95%CI: 1.042–1.556, $p < 0.001$) in CRC patients (Table 3). Sarcopenia was subsequently discovered as an independent risk factor for OS in most subgroups (Supplementary Figure S2B).

TABLE 1 The relationships between the sarcopenia and clinicopathological factors of CRC patients.

Clinicopathological characteristics	Overall (n = 1,441)	Sarcopenia		P-value
		No (n = 1,170)	Yes (n = 271)	
Sex (Man)	904 (62.7)	742 (63.4)	162 (59.8)	0.295
Age [mean (SD)]	58.1 (13.2)	56.6 (12.6)	64.6 (13.4)	<0.001
BMI [median (IQR)]	22.04 (19.95, 24.31)	22.84 (21.09, 24.98)	18.03 (17.02, 19.13)	<0.001
Hypertension (Yes)	241 (16.7)	208 (17.8)	33 (12.2)	0.033
Diabetes (Yes)	90 (6.2)	77 (6.6)	13 (4.8)	0.34
T stage				0.834
T1	50 (3.5)	39 (3.3)	11 (4.1)	
T2	318 (22.1)	262 (22.4)	56 (20.7)	
T3	770 (53.4)	621 (53.1)	149 (55.0)	
T4	303 (21.0)	248 (21.2)	55 (20.3)	
N stage				0.831
N0	808 (56.1)	655 (56.0)	153 (56.5)	
N1	398 (27.6)	321 (27.4)	77 (28.4)	
N2	235 (16.3)	194 (16.6)	41 (15.1)	
M stage (Yes)	137 (9.5)	107 (9.1)	30 (11.1)	0.391
TNM stage (III–IV)	677 (47.0)	549 (46.9)	128 (47.2)	0.981
Perineural invasion (Yes)	149 (10.3)	126 (10.8)	23 (8.5)	0.317
Vascular invasion (Yes)	247 (17.1)	210 (17.9)	37 (13.7)	0.109
Macroscopic type				0.067
Protrude type	406 (28.2)	318 (27.2)	88 (32.5)	
Infiltrating type	113 (7.8)	87 (7.4)	26 (9.6)	
Ulcerative type	922 (64.0)	765 (65.4)	157 (57.9)	
Differentiation (Poor)	190 (13.2)	156 (13.3)	34 (12.5)	0.806
Tumor location (Rectal)	736 (51.1)	608 (52.0)	128 (47.2)	0.181
Tumor size [median (IQR)]	4.5 (3.5, 6.0)	4.5 (3.5, 6.0)	5.0 (3.6, 6.0)	0.001
CEA (High)	594 (41.2)	472 (40.3)	122 (45.0)	0.180
Surgical method (Open)	604 (41.9)	463 (39.6)	141 (52.0)	<0.001
Radiotherapy (Yes)	134 (9.3)	120 (10.3)	14 (5.2)	0.013
Chemotherapy (Yes)	657 (45.6)	573 (49.0)	84 (31.0)	<0.001
Death (Yes)	582 (40.4)	449 (38.4)	133 (49.1)	0.002
HOS [median (IQR)]	17.0 (11.0, 21.0)	17.0 (11.0, 21.0)	17.0 (12.0, 21.5)	0.077
Hospitalization cost [median (IQR)]	49,539.2 (44,565.3, 55,986.4)	49,399.3 (44,628.5, 55,673.4)	50,069.5 (44,036.4, 56,940.0)	0.519

3.4. Prognostic nomograms

In the multivariate survival analysis, sarcopenia, vascular invasion, CEA, age, *N* stage, and *M* stage were independent factors affecting PFS in CRC patients. Therefore, we used these features to build a PFS nomogram to predict the 1–5 years of PFS in CRC patients (Figure 3A). The PFS nomogram showed that with the increase in CEA, the appearance of vascular invasion, the progress of *N* stage and *M* stage, the increase in age, and the emergence of sarcopenia, the predictive score increased, indicating that the risk of adverse PFS also increased. The C-index of the PFS nomogram was 0.717 (95%CI: 0.696–0.738). In addition, the calibration curves of the PFS nomogram at 3 and 5 years showed consistency between the predicted survival probability and the actual observation value (Supplementary Figures S3A, B).

Similarly, in the multivariate survival analysis of OS, sarcopenia, vascular invasion, differentiation, CEA, age, *N* stage, and *M* stage were all independently associated with OS in CRC patients. Therefore, the OS nomogram, which incorporates these clinicopathological features, was built to facilitate predicting the 1–5 years of OS in CRC patients (Figure 3B). The C-index of the OS nomogram was 0.724 (95%CI: 0.702–0.746). In addition, the

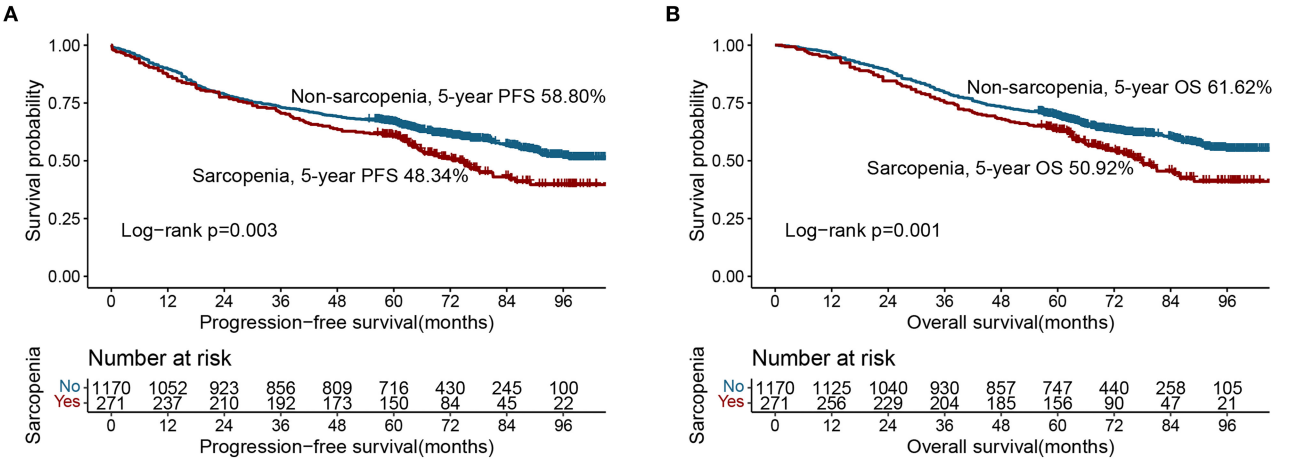


FIGURE 1
Kaplan-Meier curve of sarcopenia in CRC patients. **(A)** Progression-free survival; **(B)** Overall survival.

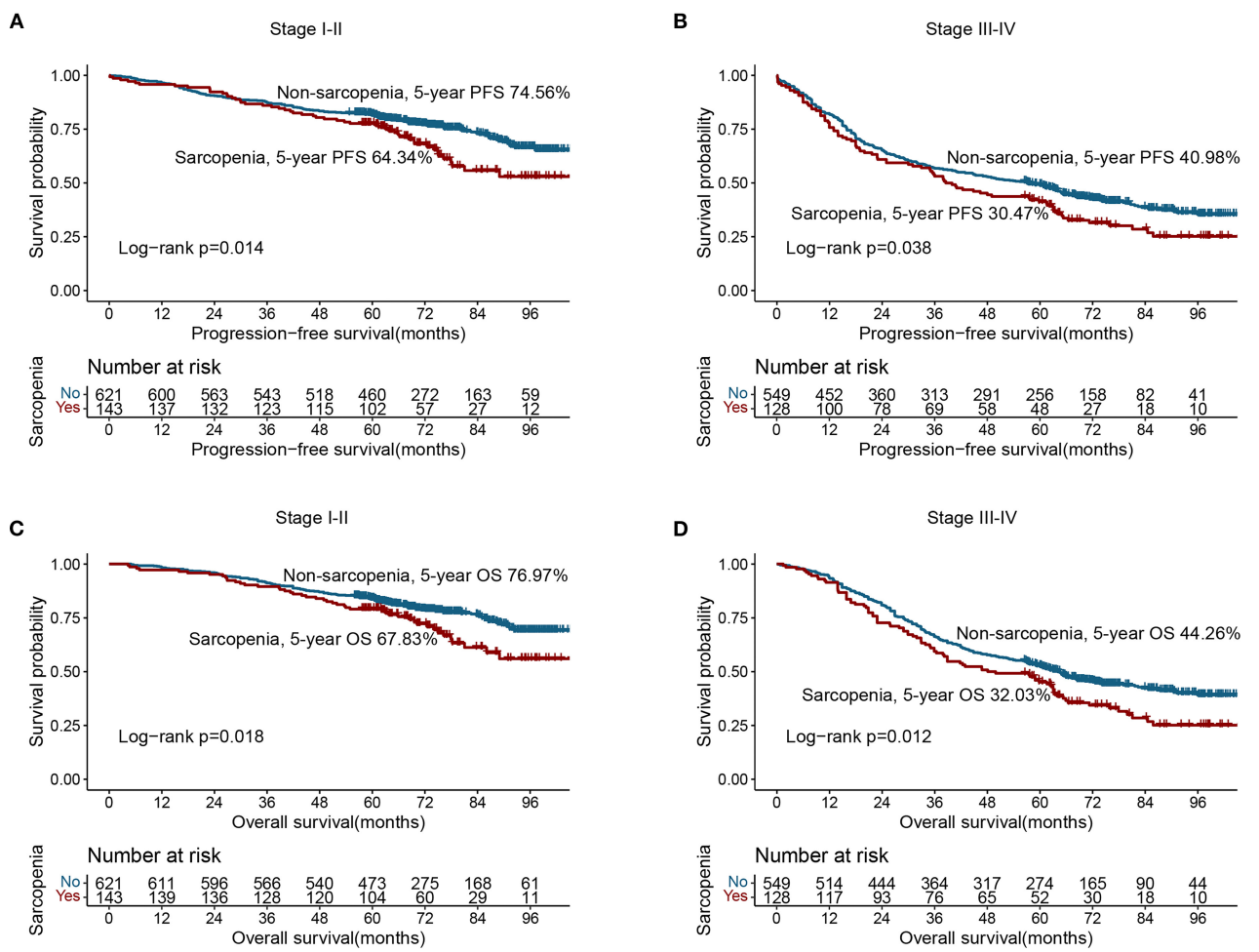


FIGURE 2
Stratified survival analysis of sarcopenia based on different TNM stage. **(A)** Progression-free survival of stage I–II; **(B)** Progression-free survival of stage III–IV; **(C)** Overall survival of stage I–II; **(D)** Overall survival of stage III–IV.

TABLE 2 Univariate and multivariate Cox regression analysis of clinicopathological characteristics associated with disease-free survival in CRC patients.

Clinicopathological characteristics	Progression-free survival			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age	1.280 (1.093–1.499)	0.002	1.287 (1.091–1.519)	0.003
T stage				
T1	Ref.			
T2	1.058 (0.564–1.986)	0.860	0.955 (0.506–1.800)	0.886
T3	2.281 (1.251–4.157)	0.007	1.337 (0.722–2.473)	0.355
T4	3.085 (1.676–5.679)	<0.001	1.479 (0.789–2.772)	0.222
N stage		<0.001		
N0	Ref.			
N1	1.872 (1.553–2.257)	<0.001	1.519 (1.251–1.844)	<0.001
N2	4.055 (3.338–4.927)	<0.001	2.754 (2.223–3.412)	<0.001
M stage	5.384 (4.411–6.572)	<0.001	3.292 (2.661–4.071)	<0.001
Perineural invasion (Positive)	1.951 (1.584–2.403)	<0.001	1.077 (0.839–1.381)	0.561
Vascular invasion (Positive)	1.755 (1.403–2.195)	<0.001	1.259 (1.019–1.556)	0.033
Pathological type				
Protrude type				
Infiltrating type	1.466 (1.075–1.998)	0.016	1.258 (0.918–1.723)	0.153
Ulcerative type	1.366 (1.129–1.653)	0.001	1.143 (0.939–1.393)	0.183
Differentiation (High–medium)	0.700 (0.563–0.869)	0.001	0.847 (0.676–1.060)	0.147
Size (≥5 cm)	1.192 (1.019–1.395)	0.028	0.983 (0.834–1.158)	0.835
CEA (≥5 ng/ml)	1.988 (1.698–2.328)	<0.001	1.484 (1.254–1.757)	<0.001
Sarcopenia (Yes)	1.329 (1.101–1.605)	0.003	1.239 (1.019–1.505)	0.031

calibration curves of the 3- and 5-year OS showed that the nomogram had good prediction accuracy (Supplementary Figures S3C, D).

In addition, according to a ratio of 7:3, we divided the total population into validation cohorts A (1,009) and B (432) for internal validation (Supplementary Table S1). The C-Index of PFS nomogram in validation cohort A and B was 0.710 (95% CI: 0.686–0.735) and 0.737 (95% CI: 0.701–0.773), respectively. In the OS nomogram, the C-index in validation cohorts A and B were 0.721 (95%CI: 0.696–0.746) and 0.733 (95%CI: 0.695–0.771), respectively. Calibration curves for the 3- and 5-year PFS and OS showed consistency between the predicted survival probability and the actual observation value in both validation A (Supplementary Figure S4A) and validation B (Supplementary Figure S4B).

5. Discussion

Sarcopenia is associated with poor clinical outcomes, including increased postoperative complications, postoperative hospitalization duration, increased inpatient costs, and even increased mortality (5, 6, 17–19). A Korean retrospective analysis showed that sarcopenia was associated with poor prognosis and increased chemotherapy toxicity in patients with stage III CRC who received preoperative neoadjuvant therapy (20). Nakanishi et al. (21) found that sarcopenia was significantly associated with disease progression and was an independent risk factor for poor outcomes in CRC patients. Malietzis et al. (22) retrospectively analyzed 805 CRC patients undergoing surgery and found that sarcopenia increased the risk of recurrence by 1.5 times and the risk of death by 1.7 times. Feliciano et al. (4) found that systemic inflammation was associated with sarcopenia in CRC patients. In addition, sarcopenia combined with systemic inflammation almost doubled the risk of death in CRC patients. The above evidence suggests that early screening, diagnosis, and intervention for sarcopenia in CRC patients have important clinical significance.

There are several ways to assess skeletal muscle mass. CT and MRI are more direct measurements of body composition. Their reliability has become the gold standard for estimating skeletal muscle mass (23). DXA is an accurate, reproducible, and widely used imaging modality for assessing body composition and is a commonly used radiological tool for diagnosing sarcopenia in clinical practice (9, 24). However, these measurement methods are limited in application because of the different degrees of radioactive radiation, high inspection costs, increased staffing, measurement tools and software, and operational complexity. BIA is a noninvasive, safe, simple, and radiation-free muscle mass determination method, but its accuracy has recently been questioned (25, 26). Recently, the newly developed anthropometric equation of skeletal muscle mass has gradually attracted much attention (12).

TABLE 3 Univariate and multivariate Cox regression analysis of clinicopathological characteristics associated with overall survival in CRC patients.

Clinicopathological characteristics	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age	1.344 (1.141–1.583)	<0.001	1.315 (1.108–1.561)	0.002
***T* stage**				
T1	Ref.			
T2	1.008 (0.520–1.954)	0.981	0.868 (0.446–1.691)	0.678
T3	2.293 (1.223–4.302)	0.010	1.264 (0.663–2.409)	0.477
T4	3.162 (1.669–5.991)	<0.001	1.396 (0.723–2.697)	0.320
***N* stage**		<0.001		
N0	Ref.			
N1	1.875 (1.544–2.277)	<0.001	1.511 (1.235–1.848)	<0.001
N2	4.079 (3.339–4.983)	<0.001	2.624 (2.103–3.275)	<0.001
M stage	5.609 (4.581–6.866)	<0.001	3.411 (2.748–4.234)	<0.001
Perineural invasion (Positive)	1.713 (1.359–2.159)	<0.001	1.018 (0.786–1.319)	0.890
Vascular invasion (Positive)	2.039 (1.691–2.459)	<0.001	1.317 (1.060–1.637)	0.013
Pathological type				
Protrude type				
Infiltrating type	1.448 (1.050–1.997)	0.024	1.225 (0.884–1.698)	0.223
Ulcerative type	1.366 (1.120–1.665)	0.002	1.148 (0.935–1.408)	0.188
Differentiation (High–medium)	0.648 (0.521–0.807)	<0.001	0.768 (0.611–0.965)	0.023
Size (≥5 cm)	1.308 (1.112–1.539)	0.001	1.096 (0.925–1.298)	0.289
CEA (≥5 ng/ml)	2.036 (1.730–2.397)	<0.001	1.483 (1.246–1.767)	<0.001
Sarcopenia (Yes)	1.374 (1.132–1.667)	0.001	1.273 (1.042–1.556)	0.018

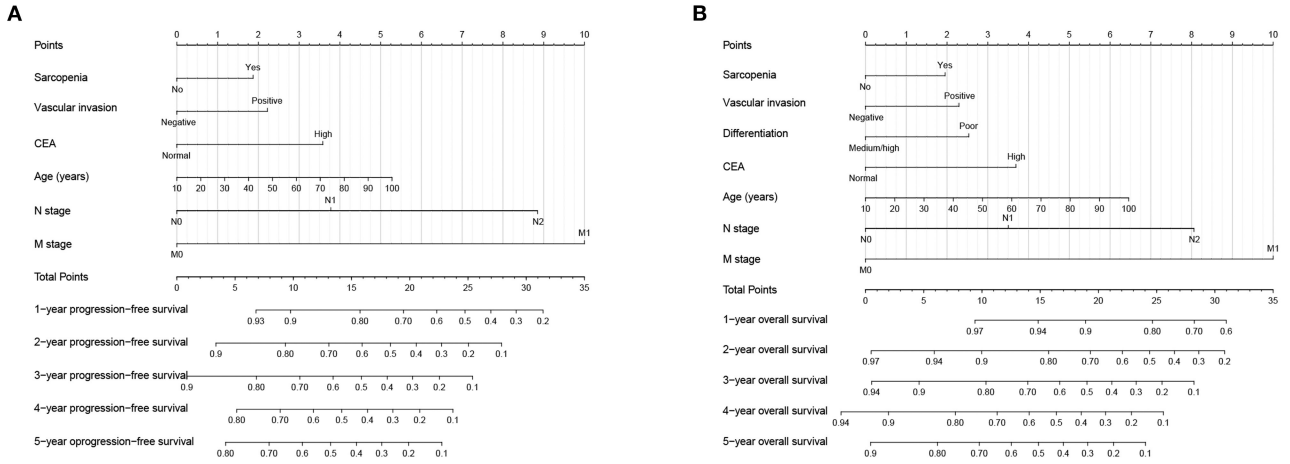


FIGURE 3
Construction prognostic nomograms in CRC patients. **(A)** The Progression-free survival nomogram; **(B)** The overall survival nomogram.

In this study, we found that sarcopenia, diagnosed based on anthropometric equations, is an independent risk factor for PFS and OS in CRC patients. Compared with patients without sarcopenia, those with sarcopenia had a 23.9 and 27.3% higher risk of developing poor PFS and OS, respectively. Sarcopenia also provides an excellent prognostic stratification for CRC patients with normal CEA levels. Moreover, sarcopenia was significantly associated with poor prognosis in most subgroups of CRC patients. TNM staging

is an important tool for evaluating the prognosis of CRC patients, but the prognosis of patients with the same pathological stage is still different. We found that sarcopenia can effectively differentiate prognosis for patients with the same pathological stage; this indicates that additional assessment of sarcopenia can provide a more refined and accurate prognostic assessment for CRC patients.

In the correlation analysis, we noticed that older CRC patients were more likely to develop sarcopenia than younger CRC patients. Related studies also reported that the incidence of sarcopenia gradually increases with age; CRC patients older than 70 years have a sarcopenic incidence as high as 50% (27). With the aging population worldwide, sarcopenia has become an increasingly important issue that endangers public health (28). In addition, we found that CRC patients with tumor size >5 cm were more likely to develop sarcopenia. Patients with a large tumor burden were more likely to have complications, such as intestinal obstruction and bleeding, resulting in an increased risk of malnutrition. In addition, patients with a large tumor burden were often staged late and were in a state of high catabolism, low synthesis, and high inflammation. As a result, these patients have a significantly increased risk of developing sarcopenia. Overall, sarcopenia is both a phenotype that reflects disease progression and a predictor of adverse long-term outcomes in CRC patients.

Previous studies have shown that the 5-year OS of CRC patients was significantly different among stages. Research by Kittrongsiri et al. (29) showed the 5-year OS of stage I–IV CRC patients were 79.67, 67.50, 44.77, and 11.02%, respectively. Mangone et al. (30) found that the 5-year survival of colon cancer was 96.7, 83.4, 70.8, and 16.2%. In our study, the 5-year PFS/OS of stage I–IV CRC patients were (PFS: 78.52, 69.17, 47.04, and 7.30%; OS: 81.34, 71.67, 50.37, and 8.76%). The 5-year survival of CRC patients in this study was in the normal range. The differences in these studies may be affected by the heterogeneity of other pathological factors (such as histological types and differentiation, etc.), as well as the treatment level in different institutions and different periods.

We developed personalized prognostic nomograms to predict the 1–5 years of PFS/OS and OS in CRC patients. These prognostic nomograms integrated general information, sarcopenia, and pathological information and effectively evaluated the prognostic risk of CRC patients. The C-index and calibration curves showed that these nomograms had good prognostic accuracy. Subsequent internal validation cohorts confirmed the application value of these nomograms. These results indicate that our nomogram has wide application potential.

This study had some limitations. First, it adopted a cross-sectional retrospective analysis and failed to conduct multiple monitoring and evaluations. Second, this was a single-center study, and the sample size was relatively limited. In addition, the method for diagnosing sarcopenia was too single, and other skeletal muscle measurement methods were lacking in this study. Multicenter prospective studies are needed in the future to address these issues. Finally, the anthropometric equation also has certain limitations, because it is calculated based on algorithms. Although it has been verified by many queues, there may still be some heterogeneity due to individual differences. However, compared with CT, DXA and BIA, it does not require special equipment, does not cause radiation damage, is simple to calculate, and has strong operability, so it has a wide range of application prospects, suitable for popular grass-roots applications.

6. Conclusion

Sarcopenia diagnosed based on anthropometric equations is an independent risk factor for PFS and OS in CRC patients. The prognostic nomogram based on sarcopenia can provide a personalized reference for prognostic judgment and clinical decision-making of CRC patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University, with the approval number: 2021 (KY-E-043). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JG conception and design. JG and ST management support. SG, ML, YL, GY, QW, and YX data collection. HX data analysis and professional drafting. HX and LW manuscript writing. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Guangxi Medical and Health Appropriate Technology Development and Application Project (No. S2021095) and the Guangxi Medical and Health Committee Self-prepared Project (No. Z20210188).

Acknowledgments

We would like to thank all authors for their substantial work on data collecting and follow-up.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of

their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1076589/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660

2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* (2016) 66:115–32. doi: 10.3322/caac.21338

3. Park IK, Yang SS, Chung E, Cho ES, Lee HS, Shin SJ, et al. Skeletal muscle gauge as a prognostic factor in patients with colorectal cancer. *Cancer Med.* (2021) 10:8451–61. doi: 10.1002/cam4.4354

4. Feliciano EMC, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, et al. Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. *JAMA Oncol.* (2017) 3:e172319. doi: 10.1001/jamaoncol.2017.2319

5. Xie H, Wei L, Liu M, Yuan G, Tang S, Gan J. Preoperative computed tomography-assessed sarcopenia as a predictor of complications and long-term prognosis in patients with colorectal cancer: a systematic review and meta-analysis. *Langenbecks Arch Surg.* (2021) 406:1775–88. doi: 10.1007/s00423-021-02274-x

6. Xie H, Gong Y, Kuang J, Yan L, Ruan G, Tang S, et al. Computed tomography-determined sarcopenia is a useful imaging biomarker for predicting postoperative outcomes in elderly colorectal cancer patients. *Cancer Res Treat.* (2020) 52:957–72. doi: 10.4143/crt.2019.695

7. Vergara-Fernandez O, Trejo-Avila M, Salgado-Nesme N. Sarcopenia in patients with colorectal cancer: a comprehensive review. *World J Clin Cases.* (2020) 8:1188–202. doi: 10.12998/wjcc.v8.i7.1188

8. Huang DD, Wang SL, Zhuang CL, Zheng BS, Lu JX, Chen FF, et al. Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. *Colorectal Dis.* (2015) 17:O256–64. doi: 10.1111/codi.13067

9. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* (2019) 48:16–31. doi: 10.1093/ageing/afy169

10. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* (2011) 12:489–95. doi: 10.1016/S1470-2045(10)70218-7

11. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. *Clin Nutr.* (2022) 41:990–1000. doi: 10.1016/j.clnu.2021.11.014

12. Wen X, Wang M, Jiang CM, Zhang YM. Anthropometric equation for estimation of appendicular skeletal muscle mass in Chinese adults. *Asia Pac J Clin Nutr.* (2011) 20:551–6. doi: 10.3316/ielapa.688409051529343

13. Yang M, Hu X, Wang H, Zhang L, Hao Q, Dong B. Sarcopenia predicts readmission and mortality in elderly patients in acute care wards: a prospective study. *J Cachexia Sarcopenia Muscle.* (2017) 8:251–8. doi: 10.1002/jcsm.12163

14. Hu X, Zhang L, Wang H, Hao Q, Dong B, Yang M. Malnutrition-sarcopenia syndrome predicts mortality in hospitalized older patients. *Sci Rep.* (2017) 7:3171. doi: 10.1038/s41598-017-03388-3

15. Xie H, Ruan G, Wei L, Zhang Q, Ge Y, Song M, et al. Prognostic value of the modified advanced lung cancer inflammation index in overweight or obese patients with lung cancer: results from a multi-center study. *J Parent Enteral Nutr.* (2023) 47:120–9. doi: 10.1002/jpen.2441

16. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc.* (2020) 21:300–7.e2. doi: 10.1016/j.jamda.2019.12.012

17. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg.* (2012) 99:550–7. doi: 10.1002/bjs.7823

18. Besson A, Deftereos I, Gough K, Taylor D, Shannon R, Yeung JM. The association between sarcopenia and quality of life in patients undergoing colorectal cancer surgery: an exploratory study. *Support Care Cancer.* (2021) 29:3411–20. doi: 10.1007/s00520-021-06025-y

19. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. *Eur J Cancer.* (2016) 57:58–67. doi: 10.1016/j.ejca.2015.12.030

20. Jung HW, Kim JW, Kim JY, Kim SW, Yang HK, Lee JW, et al. Effect of muscle mass on toxicity and survival in patients with colon cancer undergoing adjuvant chemotherapy. *Support Care Cancer.* (2015) 23:687–94. doi: 10.1007/s00520-014-2418-6

21. Nakanishi R, Oki E, Sasaki S, Hirose K, Jogo T, Edahiro K, et al. Sarcopenia is an independent predictor of complications after colorectal cancer surgery. *Surg Today.* (2018) 48:151–7. doi: 10.1007/s00595-017-1564-0

22. Malietzis G, Currie AC, Athanasiou T, Johns N, Anyamene N, Glynne-Jones R, et al. Influence of body composition profile on outcomes following colorectal cancer surgery. *Br J Surg.* (2016) 103:572–80. doi: 10.1002/bjs.10075

23. Baracos V, Kazemi-Bajestani SM. Clinical outcomes related to muscle mass in humans with cancer and catabolic illnesses. *Int J Biochem Cell Biol.* (2013) 45:2302–8. doi: 10.1016/j.biocel.2013.06.016

24. Guglielmi G, Ponti F, Agostini M, Amadori M, Battista G, Bazzocchi A. The role of DXA in sarcopenia. *Aging Clin Exp Res.* (2016) 28:1047–60. doi: 10.1007/s40520-016-0589-3

25. Achamrah N, Colange G, Delay J, Rimbert A, Folope V, Petit A, et al. Comparison of body composition assessment by DXA and BIA according to the body mass index: a retrospective study on 3655 measures. *PLoS ONE.* (2018) 13:e0200465. doi: 10.1371/journal.pone.0200465

26. Herda AA, Cleary CJ. Agreement between multifrequency BIA and DXA for assessing segmental appendicular skeletal muscle mass in older adults. *Aging Clin Exp Res.* (2021) 34:2789–95. doi: 10.1007/s40520-021-02000-z

27. Broughman JR, Williams GR, Deal AM Yu H, Nyrop KA, Alston SM, et al. Prevalence of sarcopenia in older patients with colorectal cancer. *J Geriatr Oncol.* (2015) 6:442–5. doi: 10.1016/j.jgo.2015.08.005

28. Lenchik L, Boutin RD. Sarcopenia: beyond muscle atrophy and into the new frontiers of opportunistic imaging, precision medicine, and machine learning. *Semin Musculoskelet Radiol.* (2018) 22:307–22. doi: 10.1055/s-0038-1641573

29. Kittrongsiri K, Wanitsuwan W, Prechawittayakul P, Sangroongruangsri S, Cairns J, Chaikledkaew U. Survival analysis of colorectal cancer patients in a Thai hospital-based cancer registry. *Expert Rev Gastroenterol Hepatol.* (2020) 14:291–300. doi: 10.1080/17474124.2020.1740087

30. Mangone L, Marinelli F, Bisceglia I, Braghiroli MB, Damato A, Pinto C. Five-year relative survival by stage of breast and colon cancers in northern Italy. *Front Oncol.* (2022) 12:982461. doi: 10.3389/fonc.2022.982461

frontiers | Frontiers in Nutrition

TYPE Clinical Trial
PUBLISHED 02 February 2023
DOI 10.3389/fnut.2023.1094081

OPEN ACCESS

EDITED BY
Paula Ravasco,
Catholic University of Portugal,
Portugal

REVIEWED BY
Melih Simsek,
Bezmiâlem Foundation University,
Türkiye
Susmita Barman,
University of Nebraska Medical Center,
United States

*CORRESPONDENCE
Zixiong Zhang
✉ mail_zhxs@163.com
Lin Lai
✉ 303805138@qq.com
Chuying Huang
✉ huangchuying2008@126.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 09 November 2022
ACCEPTED 19 January 2023
PUBLISHED 02 February 2023

CITATION
Yang M, Pei B, Hu Q, Li X, Fang X, Huang X, Yang Z, Chen J, He D, Sun G, Lv P, Wang L, Zhang Z, Lai L and Huang C (2023) Effects of selenium supplementation on concurrent chemoradiotherapy in patients with cervical cancer: A randomized, double-blind, placebo-parallel controlled phase II clinical trial. *Front. Nutr.* 10:1094081. doi: 10.3389/fnut.2023.1094081

Effects of selenium supplementation on concurrent chemoradiotherapy in patients with cervical cancer: A randomized, double-blind, placebo-parallel controlled phase II clinical trial

Mei Yang[1,2†], Bo Pei[1,3†], Qiancheng Hu[4†], Xiaoying Li[5†], Xiping Fang[1], Xue Huang[1], Zunjing Yang[1], Jiaquan Chen[1], Du He[1], Guogen Sun[5], Peng Lv[1], Li Wang[5], Zixiong Zhang[5]*, Lin Lai[1]* and Chuying Huang[1,5,6]*

[1]Department of Oncology, The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, Enshi Clinical College of Wuhan University, Enshi, China, [2]Department of Oncology, Yunfu People's Hospital, Yunfu, China, [3]Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University, Wuhan, China, [4]Department of Abdominal Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [5]Hubei Selenium and Human Health Institute, The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, Enshi, China, [6]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Objective: Selenium (Se) is an essential trace element and may affect cervical cancer occurrence and progression. The association between selenium supplementation and acute toxic reactions and clinical outcomes in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy remains unclear. The aim of this study was to determine the safety profile of add-on Se yeast and assess the potential of Se to ameliorate the hematologic toxicity of concurrent chemoradiotherapy in patients with cervical cancer.

Methods: Patients with Federation International of Gynecology and Obstetrics (FIGO) stage IIB cervical cancer who met all inclusion criteria were randomly assigned to either the experimental group or the control group. The experimental group received Se yeast tablets (100μg Se, twice daily), while the control group received placebos (twice daily) for 5weeks in total. All patients in both groups received standard treatment, including pelvic external irradiation, concurrent five cycles of chemotherapy, and brachytherapy. Measures included the incidence of myelosuppression, impairment of liver and kidney function, objective response rate (ORR), and blood Se concentrations before, during and after the treatment of the two groups.

Results: A total of 104 eligible patients were enrolled in the experimental group (n=50) or the control group (n=54). The ORR in the experimental group and control group were 96 and 94%, respectively (p=0.47). The baseline levels of blood Se before treatment in the experimental and control groups were similar (58.34±17.63μg/L and 60.21±18.42μg/L, p=0.60), but the concentrations became significantly different after course completion between the two groups (76.16±24.47μg/L and 57.48±14.92μg/L, respectively, p<0.01). Se dramatically decreased the incidence of grade 3 myelosuppression (48% vs. 63%, p=0.034) compared to the control group. In the subgroup of patients with moderately well-differentiated cervical cancer, the incidence of thrombocytopenia induced by concurrent chemoradiotherapy was lower in the experimental group than in the control group (53.8% vs. 78.9%, p<0.01).

However, no difference was observed in liver and kidney injuries between the two groups.

Conclusion: Supplementation with Se effectively increased blood Se levels in Se-inadequate cervical cancer patients. As an add-on to standard treatment, Se-yeast significantly decreased the hematologic toxicity of concurrent chemoradiotherapy.

KEYWORDS

cervical cancer, chemoradiotherapy, clinical trial, hematologic toxicity, selenium

1. Introduction

Cervical cancer is one of the most common gynecological malignant tumors, with 604,000 new cases and 342,000 deaths worldwide reported in 2020 (1). The standard treatment mode of early-stage (FIGO stage IA-IB1) patients is radical hysterectomy, lymph node dissection, and/or radiotherapy, and locally advanced stage (FIGO stage IB2-IVA) patients mainly receive platinum-based concurrent chemoradiotherapy (2). The overall incidence of genitourinary complications is reported to be between 17 and 40% in patients with concurrent chemoradiotherapy, while acute toxicity of grades 3–4 occurs in 17.1% of patients with concurrent chemoradiotherapy (3). Acute toxic reactions caused by concurrent chemoradiotherapy often require dose modifications or radiotherapy treatment suspension, which could potentially impair the curative effects of concurrent chemoradiotherapy and prolong the length of stay in the hospital. Previous studies demonstrated that intensity modulation radiotherapy significantly reduced the level of gastrointestinal and hematological toxicity in patients with cervical cancer in comparison to conventional radiotherapy (4, 5). It is imperative to search for an effective strategy to decrease the incidence of acute side effects during concurrent chemoradiotherapy in patients with cervical cancer.

Selenium is an essential trace element and has extremely important biological functions in human health. Previous studies have demonstrated that selenium compounds can enhance the effect of radiotherapy and chemotherapy (6–8). Several studies have revealed that selenium supplementation may decrease the toxicity of chemotherapy and radiotherapy (9–11). However, these studies have been constrained by the limited number of patients included and the lack of randomized controlled clinical trials, and the association between selenium supplementation and acute toxic reactions and clinical outcomes in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy remains unclear. Therefore, we conducted a randomized, placebo-controlled trial to assess whether adding selenium yeast to platinum-based concurrent chemoradiotherapy would decrease acute side effects during treatment and improve efficacy compared with placebo for patients with stage IIB cervical cancer.

2. Patients and methods

We conducted a randomized, double-blind, and placebo-parallel controlled clinical trial to evaluate the effects and safety of Se supplementation on concurrent chemoradiotherapy in patients with stage IIB cervical cancer. This study was approved by the Ethics Committee of the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, and all patients signed informed consent forms to participate in the study. The trial was registered at https://www.chictr.org.cn/listbycreater.aspx (ChiCTR2100043379).

2.1. Patient eligibility

The inclusion criteria were as follows: (1) aged from 18 to 70 years old; (2) histologically or cytologically confirmed cervical cancer and diagnosed with stage IIB cervical cancer according to the 2014 International Association of Obstetrics and Gynecology (FIGO) recommendations; (3) treatment-naïve and eligible to receive first-line concurrent chemoradiotherapy; (4) performance status (PS) score 0–1 points; (5) basically normal functions of major organs (hemogram, heart, liver and kidney), white blood count $\geq 3.5*10^9$/L with neutrophils $\geq 1.5*10^9$/L, platelet count $\geq 100*10^9$/L, and hemoglobin ≥90 g/L. Total bilirubin ≤1.5 times upper limit of normal (ULN) range; alkaline phosphatase (ALP) ≤2.5 times ULN, Transaminases AST and ALT ≤2.5 times ULN, serum creatinine ≤1.2 times ULN; and (6) Patients must read and understand Chinese language, adhere to the study protocol, and must provide written informed consent. The exclusion criteria were as follows: (1) complications with other serious medical diseases; (2) allergy or intolerance to cisplatin or selenium yeast; and (3) pregnancy or lactation.

2.2. Treatment

This double-blind trial was conducted in our hospital. Patients were randomly assigned in a 1:1 ratio to receive selenium yeast tablets (100 μg Se) or placebo twice a day. Randomization was performed using a computer-generated table of random numbers. A table of random numbers was placed in sequentially sealed envelopes. Both investigators and patients were blinded to the treatment allocation. The placebo was prepared by the pharmacy and supplied to the department of cancer labeled with the predetermined coding scheme.

All patients received pelvic external irradiation with six MV X-ray at prescribed doses of PGTV 60Gy/25F and PCTV 50Gy/25F, five times a week, and five cycles of concurrent chemotherapy: intravenous infusion of cisplatin with 30 mg/m^2, once a week. At the later stage of radiotherapy, brachytherapy was performed twice a week using the radioactive source Iridium-192. The dose at point A was 6 or 7Gy, and the total dose reached 28Gy/4F or 30Gy/5F. Treatment was continued until unacceptable toxic effects, such as grade 3 radiation proctitis and radiation cystitis according to the Radiation Therapy Oncology Group (RTOG) classification or grade 3–4 hematological toxicities during concurrent chemoradiotherapy according to the National Cancer Institute Common Toxicity Criteria

(version 3.0). Investigators could interrupt or discontinue individual trial agents to manage treatment-related toxic effects.

2.3. Outcomes

The primary outcome of this study was concurrent chemoradiotherapy-related hematologic toxicity. The secondary outcomes were the objective response rate and safety profile, including liver and renal toxicity.

2.4. Evaluation

Imaging studies (magnetic resonance imaging) were performed before and after the entire treatment to evaluate the therapeutic effects according to Response Evaluation Criteria in Solid Tumor guidelines (RECIST1.1) (12). Therapeutic effects were evaluated by complete response (*CR*), partial response (*PR*), stable disease rates (*SD*) and progressive disease (*PD*). The objective response rate (ORR) was calculated as $ORR = (CR + PR)/\text{total cases} \times 100\%$.

Routine blood tests, routine urine tests, and serum biochemistry tests were taken once a week during the treatment to evaluate the adverse effects according to the National Cancer Institute Common Toxicity Criteria (version 3.0). The main observational items were red blood cell count, white blood cell count, neutrophil count, platelet count, bilirubin, alanine aminotransferase and alkaline phosphatase, urea nitrogen, creatinine, and proteinuria. Whole blood selenium levels were measured before, during and at the end of treatment.

2.5. Measurement of whole blood selenium

Blood samples from the patients with cervical cancer were drawn between 7 am and 8 am after an overnight fast. A 2–3 ml blood sample was drawn from each patient, and the blood sample was immediately frozen at 4°C until analysis. In this study, the selenium level we measured was the whole blood selenium concentration, and we used the microwave digestion method.

2.6. Statistical analysis

All data were analyzed using SPSS Statistics (IBM SPSS Statistics for Windows, Version 22.0). Continuous variables were described as the mean and standard deviation for normally distributed variables. Categorical variables were described as numbers and percentages. Two-sample independent-groups *t*-tests were carried out to compare differences in means between two groups, and Pearson's Chi-square test (χ^2) or Fisher's exact test was used to compare differences between categorical variables. A two-sided p value <0.05 was considered statistically significant.

3. Results

3.1. Patients

From July 2018 to May 2021, a total of 124 patients were enrolled and randomly assigned to the experimental group ($n = 62$) and control group ($n = 62$), but 20 patients were excluded due to withdrawal of consent and noncompliance. Finally, 104 patients were included in the final analysis (Figure 1). There were no significant differences between the two groups in characteristics (Table 1) at baseline.

3.2. Efficacy outcomes

During treatment, patients have different degrees of toxicity effects related to chemoradiotherapy. Se dramatically decreased the incidence of grade 3 myelosuppression compared to the control group (48% vs. 63%, $p = 0.034$; Table 2). The incidence of grade 1–2 myelosuppression in the experimental group was 26 (92%) compared to 25 (92.59%) in the control group ($p = 0.695$). We found no significant difference between the groups for any type of adverse events, including leukopenia, neutropenia, anemia, diarrhea, thrombocytopenia, and liver damage. There was no damage to the kidney noticed in the study (Table 2). We subsequently conducted subgroup analysis of efficacy indicators according to the degree of tumor differentiation. We found that the incidence of platelet toxicity related to chemotherapy in the experimental group was lower than that in the control group ($p < 0.01$; Table 3). The secondary efficacy outcomes of ORR between the experimental group and control group were 96 and 94%, respectively ($p = 0.47$; Table 4).

3.3. Whole blood selenium level

There was no significant difference between the baseline blood selenium level and the blood selenium level in the third week of treatment between the two groups ($p > 0.05$). However, after treatment, the blood selenium concentration of the experimental group was significantly higher than that of the control group ($p < 0.01$; Table 5).

4. Discussion

Selenium is an essential trace element that is fundamentally important to human health. Epidemiological studies demonstrated that salt fortified with selenium as sodium selenite decreased the incidence of hepatocellular cancer by 35% compared to the control group (13). The Nutritional Prevention of Cancer Trial was the first double-blind, placebo-controlled intervention trial to assess whether selenium supplementation could reduce the risk of cancer. Selenium supplementation showed effects of 50% lower total cancer mortality ($p = 0.002$) and 37% lower total cancer incidence ($p = 0.001$) (14). Selenium deficiency also increases the risk of cervical cancer (15). On the other hand, selenium can reduce the harmful toxicities of radiotherapy and chemotherapy without compromising efficacy (8). In this study, we found that selenium supplementation decreased the incidence of grade 3 myelosuppression ($p = 0.034$) but had no effect on the incidence of grade 0–1 myelosuppression, with 26 (52%) in the experimental group and 25 (46.3%) in the control group ($p = 0.695$). Selenium supplementation did not decrease the incidence of thrombocytopenia in patients with cervical cancer between the two groups. However, in a subgroup of patients with highly differentiated cervical cancer, a significant difference in platelet toxicity was observed, with 7 of 13 (53.8%) in the experimental group and 15/19 (78.9%) in the control group ($p < 0.01$). An earlier *in vitro* study showed that supplementation with Se yeast alone or in combination with chemotherapeutic drugs could induce apoptosis in several tumor cell lines (16). In our study, the ORR between the experimental group and the control

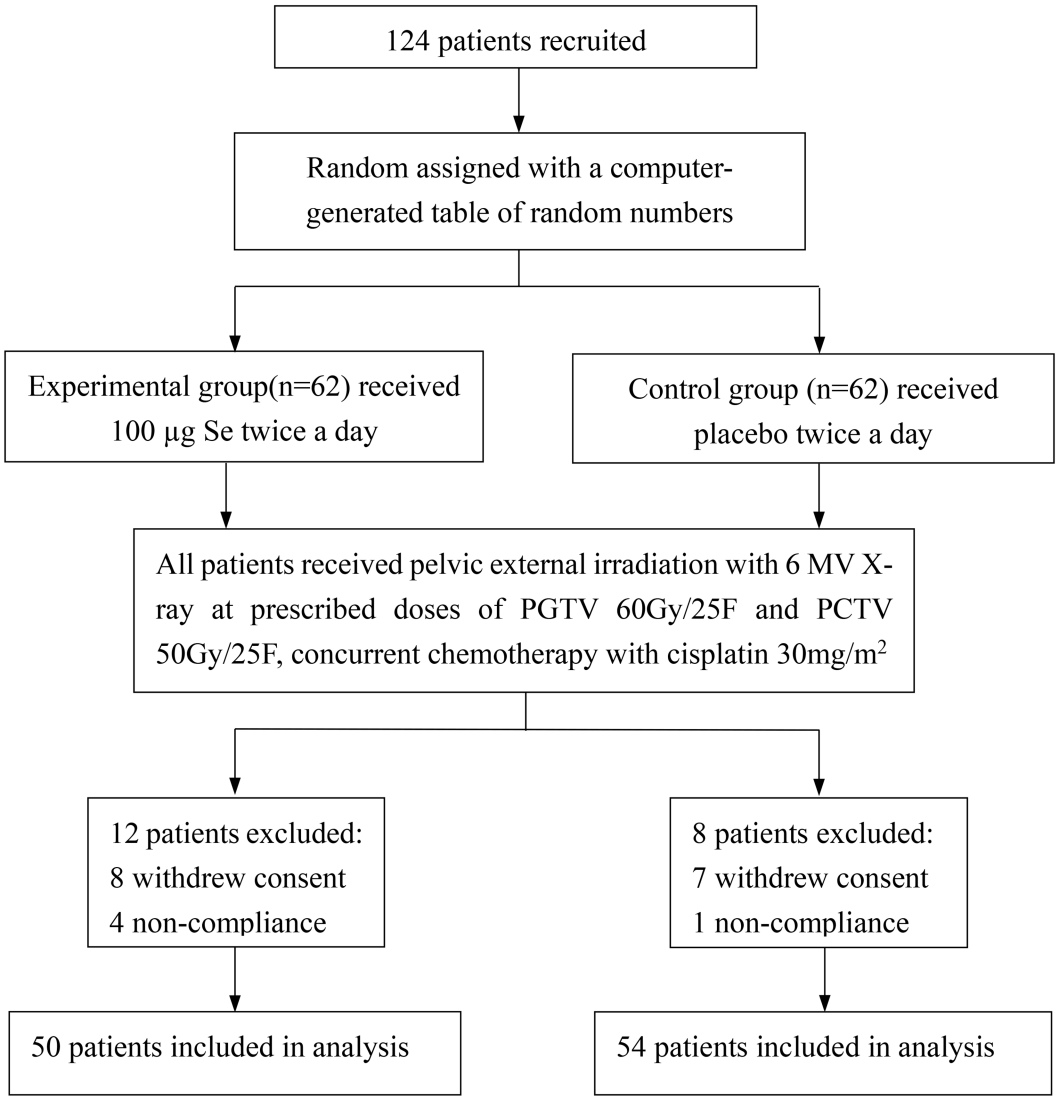


FIGURE 1
Trial profile. PGTV, planning gross tumor volume; PCTV, planning clinical target volume; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

TABLE 1 Baseline demographic and clinical characteristics between the two groups.

Characteristic	Experimental group	Control group	*p*-Value
No. of patients enrolled	50	54	
Median age (±SD)	58 ± 9.26	56.5 ± 9.54	0.72
Time of pregnancy	3.24 ± 1.51	3.41 ± 1.61	0.59
Number of births	2.44 ± 0.99	2.56 ± 1.22	0.60
Mean hospital stay	55.58 ± 7.61	56.00 ± 6.20	0.76
Nation			0.17
Han	22	31	
Ethnic minorities	28	23	
Education background			0.77
Illiteracy	12	10	
Primary school	29	30	
Junior high school	8	13	
Senior high school	1	1	
Pathological types			1
Squamous cell carcinoma	48	52	
Others	2	2	
Degree of differentiation			0.31
Poor	37	35	
Moderately well	13	19	

10.3389/fnut.2023.1094081

TABLE 2 Adverse events with concurrent chemoradiotherapy.

Characteristic	Experimental group (n=50)	Control group (n=54)	p
Myelosuppression			
Grade 1–2	26	25	0.695
Grade 3	24	37	0.034
Grade 4	4	3	0.708
Leukopenia			0.10
Grade 0	7	1	
Grade 1	5	5	
Grade 2	20	21	
Grade 3	18	27	
Grade 4	0	0	
Neutropenia			0.83
Grade 0	9	10	
Grade 1	14	17	
Grade 2	15	18	
Grade 3	12	9	
Grade 4	0	0	
Anemia			0.32
Grade 0	12	6	
Grade 1	16	16	
Grade 2	17	22	
Grade 3	3	8	
Grade 4	2	2	
Thrombocytopenia			0.53
Grade 0	25	26	
Grade 1	11	19	
Grade 2	9	6	
Grade 3	3	2	
Grade 4	2	1	
Liver damage			0.15
Grade 0	26	37	
Grade 1	16	14	
Grade 2	7	2	
Grade 3	1	1	
Grade 4	0	0	
Bilirubin			0.83
Grade 0	47	51	
Grade 1	3	2	
Grade 2	0	0	
Grade 3	0	0	
Grade 4	0	1	
Increased alanine aminotransferase			0.26
Grade 0	39	47	
Grade 1	4	4	
Grade 2	6	2	
Grade 3	0	1	
Grade 4	1	0	
Increased alkaline phosphatase			0.26
Grade 0	29	37	
Grade 1	17	15	
Grade 2	4	1	
Grade 3	0	0	
Grade 4	0	1	
Creatinine increased			
Grade 0–4	0	0	
Urea nitrogen increased			
Grade 0–4	0	0	
Proteinuria			
Grade 0–4	0	0	
Diarrhea	5	4	0.735

TABLE 3 The incidence of thrombocytopenia in patients with moderately well-differentiated cervical cancer between the two groups.

Characteristic	Experimental group (*n*=13)	Control group (*n*=19)	*p*
Thrombocytopenia			<0.01
Grade 0	6	4	
Grade 1	1	14	
Grade 2	4	0	
Grade 3	1	1	
Grade 4	1	0	

TABLE 4 Response rate to first-line concurrent chemoradiotherapy treatment.

Characteristic	Experimental group (*n*=50)	Control group (*n*=54)	*p*
Short-term effects			
CR	10	6	
PR	38	45	
SD	2	2	
PD	0	1	
ORR	96%	94%	0.47

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rates.

TABLE 5 Selenium levels (μg/L) between the two groups.

Characteristic	Experimental group (*n*=50)	Control group (*n*=54)	*p*
Baseline Se level	58.34 ± 17.63	60.21 ± 18.41	0.6
During of RT	63.98 ± 17.68	58.88 ± 17.29	0.14
End of RT	76.16 ± 24.47	57.48 ± 14.92	<0.01

RT, radiation therapy.

group was not significantly different (96% vs. 94%, $p=0.47$), indicating that selenium supplementation has a negligible impact on the efficiency of chemoradiotherapy in cervical cancer. To the best of our knowledge, this is the first clinical trial exploring the role of the addition of selenium in the treatment of patients with cervical cancer. Although several studies have confirmed that selenium supplementation enhances the efficacy of radiotherapy and chemotherapy (17), another phase II clinical trial revealed the opposite result in patients with stage III and stage IV head and neck squamous cell carcinoma treated with selenomethionine combined with concurrent chemoradiotherapy and simple concurrent chemoradiotherapy. It was found that there was no significant difference in CR, overall survival, and progression-free survival between the two groups (17). Although the short-term efficacy of selenium yeast combined with concurrent chemoradiotherapy for cervical cancer has not improved, our data showed that the incidence of myelosuppression in the experimental group was lower than that in the control group. Similar effects have been observed by Katya's team, who noticed that there was no increase in the toxicity of platelets, white blood cell count, neutrophils, hematocrit, and hemoglobin during the selenium supplementation period in leukemia/lymphoma patients (18). Moreover, another study has shown that the addition of 500 μg/day sodium selenite during radiotherapy can reduce the number and severity of diarrhea caused by radiotherapy (10). Recently, a Japanese study revealed that serum selenium predicts achievement of full-dose cisplatin in concurrent chemoradiotherapy for locally advanced head and neck squamous cell carcinoma. Selenium deficiency before treatment was independently associated with poor compliance with cisplatin (19). Collectively, these studies support our findings that selenium supplementation ameliorates the toxic effects of chemoradiotherapy without extra gastrointestinal side effects, providing a new strategy to improve the tolerance and compliance of patients to chemoradiotherapy.

Current studies indicate that radiation therapy and cisplatin induce lipid peroxidation and ferroptosis in cancer cell lines, human cancer samples, and the renal proximal tubules of mice (20, 21). Polyunsaturated fatty acids participate in the formation of essential lipid products that play a crucial role in activating or inhibiting platelet function (22). The platelet membrane structure is very complex with a large number of lipids, making it very sensitive to radiation-induced lipid peroxidation. Recently, a study indicated that although the exposure dose was below the limit, medical workers exposed to low-dose ionizing radiation for a short period of time might have increased first and then decreased platelets (23). Hemoglobin, heme, and hemin produced by old red blood cells trigger ferroptosis in platelets (24). GPX4 is a selenoprotein that utilizes reduced glutathione to convert lipid hydroperoxides to lipid alcohols, thereby alleviating lipid peroxidation and inhibiting ferroptosis. Selenium supplementation can activate GPX4 activity and alleviate ferroptosis inducer RSL3 and erastin-induced lipid oxidation in the retina and heart samples of mice (unpublished data). Hence, we hypothesize that selenium supplementation ameliorates the toxic effects of chemoradiotherapy on platelets by activating GPX4 and mitigates lipid peroxidation, which needs further study in the future.

Although we have provided evidence demonstrating that selenium supplementation can reduce side effects but does not compromise the therapeutic effect of chemoradiotherapy, the molecular mechanism remains unknown. Our trial had several limitations, including that the sample size was limited and the dosage and duration of selenium supplementation were not optimized but can be improved by longer and larger trials in the future. We will continue to follow up with our participants for a much longer time to observe the effect of selenium supplementation on the survival time and gastrointestinal side effects of our patients with cervical cancer.

5. Conclusion

This prospective study demonstrated that selenium supplementation could alleviate the hematologic toxicity of concurrent chemoradiotherapy, but no adverse effects were observed in the treatment of cervical cancer. Selenium supplementation does not compromise the therapeutic effect of chemoradiotherapy and could be a promising therapeutic strategy to protect against chemoradiotherapy-induced side effects.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LL, CH, and ZZ: conception and design. QH, MY, XL, and PL: administrative support. BP, XF, XH, ZY, JC, DH, GS, and LW: provision of study materials or patients. QH and MY: data analysis and interpretation. MY, BP, QH, and CH: manuscript writing. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81660503, 82160490); Health Commission of Hubei Province Scientific Research Project (WJ2021F095); Natural Science Foundation of Enshi Tujia and Miao Autonomous Prefecture Government (E20170002, D20210033).

Acknowledgments

We are grateful to the volunteers for their participation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sung, H, Ferlay, J, Siegel, RL, Laversanne, M, Soerjomataram, I, Jemal, A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2021) 71:209–49. doi: 10.3322/caac.21660
2. Cohen, PA, Jhingran, A, Oaknin, A, and Denny, L. Cervical cancer. *Lancet*. (2019) 393:169–82. doi: 10.1016/S0140-6736(18)32470-X
3. Viswanathan, AN, Lee, LJ, Eswara, JR, Horowitz, NS, Konstantinopoulos, PA, Mirabeau-Beale, KL, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer*. (2014) 120:3870–83. doi: 10.1002/cncr.28849
4. Klopp, AH, Yeung, AR, Deshmukh, S, Gil, KM, Wenzel, L, Westin, SN, et al. Patient-reported toxicity during pelvic intensity-modulated radiation therapy: NRG oncology-RTOG 1203. *J Clin Oncol*. (2018) 36:2538–44. doi: 10.1200/JCO.2017.77.4273
5. Gandhi, AK, Sharma, DN, Rath, GK, Julka, PK, Subramani, V, Sharma, S, et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. *Int J Radiat Oncol Biol Phys*. (2013) 87:542–8. doi: 10.1016/j.ijrobp.2013.06.2059
6. Song, M, Kumaran, MN, Gounder, M, Gibbon, DG, Nieves-Neira, W, Vaidya, A, et al. Phase I trial of selenium plus chemotherapy in gynecologic cancers. *Gynecol Oncol*. (2018) 150:478–86. doi: 10.1016/j.ygyno.2018.07.001
7. Mix, M, Ramnath, N, Gomez, J, de Groot, C, Rajan, S, Dibaj, S, et al. Effects of selenomethionine on acute toxicities from concurrent chemoradiation for inoperable stage III non-small cell lung cancer. *World J Clin Oncol*. (2015) 6:156–65. doi: 10.5306/wjco.v6.i5.156
8. Lobb, RJ, Jacobson, GM, Cursons, RT, and Jameson, MB. The interaction of selenium with chemotherapy and radiation on normal and malignant human mononuclear blood cells. *Int J Mol Sci*. (2018) 19:3167. doi: 10.3390/ijms19103167
9. Saif-Elnasr, M, Abdel-Aziz, N, and El-Batal, AI. Ameliorative effect of selenium nanoparticles and fish oil on cisplatin and gamma irradiation-induced nephrotoxicity in male albino rats. *Drug Chem Toxicol*. (2019) 42:94–103. doi: 10.1080/01480545.2018.1497050
10. Muecke, R, Schomburg, L, Glatzel, M, Berndt-Skorka, R, Baaske, D, Reichl, B, et al. Multicenter, phase 3 trial comparing selenium supplementation with observation in gynecologic radiation oncology. *Int J Radiat Oncol Biol Phys*. (2010) 78:828–35. doi: 10.1016/j.ijrobp.2009.08.013
11. Gurgen, SG, Erdogan, D, Elmas, C, Kaplanoglu, GT, and Ozer, C. Chemoprotective effect of ascorbic acid, alpha-tocopherol, and selenium on cyclophosphamide-induced toxicity in the rat ovarium. *Nutrition*. (2013) 29:777–84. doi: 10.1016/j.nut.2012.11.004
12. Eisenhauer, EA, Therasse, P, Bogaerts, J, Schwartz, LH, Sargent, D, Ford, R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer*. (2009) 45:228–47. doi: 10.1016/j.ejca.2008.10.026
13. Yu, SY, Zhu, YJ, and Li, WG. Protective role of selenium against hepatitis B virus and primary liver cancer in Qidong. *Biol Trace Elem Res*. (1997) 56:117–24. doi: 10.1007/BF02778987
14. Clark, LC, Combs, GF Jr, Turnbull, BW, Slate, EH, Chalker, DK, Chow, J, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA*. (1996) 276:1957–63. doi: 10.1001/jama.276.24.1957
15. Abulizi, G, Zhang, YY, Mijiti, P, Li, H, Abuduxikuer, G, Cai, J, et al. Serum Se, Ni, and As are associated with HPV infection and CIN2+ among Uyghur women in rural China. *BMC Cancer*. (2018) 18:925. doi: 10.1186/s12885-018-4734-6
16. Vadgama, JV, Wu, Y, Shen, D, Hsia, S, and Block, J. Effect of selenium in combination with Adriamycin or Taxol on several different cancer cells. *Anticancer Res*. (2000) 20:1391–414.
17. Mix, M, Singh, AK, Tills, M, Dibaj, S, Groman, A, Jaggernauth, W, et al. Randomized phase II trial of selenomethionine as a modulator of efficacy and toxicity of chemoradiation in squamous cell carcinoma of the head and neck. *World J Clin Oncol*. (2015) 6:166–73. doi: 10.5306/wjco.v6.i5.166
18. Rocha, KC, Vieira, ML, Beltrame, RL, Cartum, J, Alves, SI, Azzalis, LA, et al. Impact of selenium supplementation in neutropenia and immunoglobulin production in childhood cancer patients. *J Med Food*. (2016) 19:560–8. doi: 10.1089/jmf.2015.0145
19. Ohkoshi, A, Ishii, R, Wakamori, S, Nakayama, Y, Yoshida, T, Higashi, K, et al. Serum selenium predicts achievement of full-dose cisplatin in concurrent chemoradiotherapy for locally advanced head and neck squamous cell carcinoma: a prospective, observational study. *Oral Oncol*. (2021) 121:105475. doi: 10.1016/j.oraloncology.2021.105475
20. Lei, G, Zhang, Y, Koppula, P, Liu, X, Zhang, J, Lin, SH, et al. The role of ferroptosis in ionizing radiation-induced cell death and tumor suppression. *Cell Res*. (2020) 30:146–62. doi: 10.1038/s41422-019-0263-3
21. Deng, F, Sharma, I, Dai, Y, Yang, M, and Kanwar, YS. Myo-inositol oxygenase expression profile modulates pathogenic ferroptosis in the renal proximal tubule. *J Clin Invest*. (2019) 129:5033–49. doi: 10.1172/JCI129903
22. Dukanovic, N, Obradovic, S, Zdravkovic, M, Durasevic, S, Stojkovic, M, Tosti, T, et al. Lipids and antiplatelet therapy: important considerations and future perspectives. *Int J Mol Sci*. (2021) 22:3180. doi: 10.3390/ijms22063180
23. Liu, N, Peng, Y, Zhong, X, Ma, Z, He, S, Li, Y, et al. Effects of exposure to low-dose ionizing radiation on changing platelets: a prospective cohort study. *Environ Health Prev Med*. (2021) 26:14. doi: 10.1186/s12199-021-00939-z
24. Imoto, S, Kono, M, Suzuki, T, Shibuya, Y, Sawamura, T, Mizokoshi, Y, et al. Haemin-induced cell death in human monocytic cells is consistent with ferroptosis. *Transfus Apher Sci*. (2018) 57:524–31. doi: 10.1016/j.transci.2018.05.028

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 27 February 2023
DOI 10.3389/fnut.2023.1062117

OPEN ACCESS

EDITED BY
Paula Ravasco,
Catholic University of Portugal,
Portugal

REVIEWED BY
Hirotaka Tashiro,
National Hospital Organization Kure Medical Center, Japan
Sabrina Alves Fernandes,
Federal University of Health Sciences of Porto Alegre, Brazil

*CORRESPONDENCE
Han-Ping Shi
shihp@ccmu.edu.cn
Li Deng
dengli070@foxmail.com
Xin Wang
winsun2011@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 05 October 2022
ACCEPTED 08 February 2023
PUBLISHED 27 February 2023

CITATION
Chen Y, Ruan G-T, Shi J-Y, Liu T, Liu C-A, Xie H-L, Song M-M, Wang Z-W, Hu C-L, Zhang H-Y, Zhang X-W, Tian H-Y, Ge Y-Z, Yang M, Liu Y-Y, Lin S-Q, Liu X-Y, Zheng X, Wang K-H, Cong M-H, Shen X, Wang X, Deng L and Shi H-P (2023) The combination of hand grip strength and modified Glasgow prognostic score predicts clinical outcomes in patients with liver cancer.
Front. Nutr. 10:1062117.
doi: 10.3389/fnut.2023.1062117

The combination of hand grip strength and modified Glasgow prognostic score predicts clinical outcomes in patients with liver cancer

Yue Chen[1,2†], Guo-Tian Ruan[1,2†], Jin-Yu Shi[1,2†], Tong Liu[1,2], Chen-An Liu[1,2], Hai-Lun Xie[1,2], Meng-Meng Song[1,2], Zi-Wen Wang[1,2], Chun-Lei Hu[1,2], He-Yang Zhang[1,2], Xiao-Wei Zhang[1,2], Hai-Ying Tian[1,2], Yi-Zhong Ge[1,2], Ming Yang[1,2], Yu-Ying Liu[1,2], Shi-Qi Lin[1,2], Xiao-Yue Liu[1,2], Xin Zheng[1,2], Kun-Hua Wang[3,4], Ming-Hua Cong[5], Xian Shen[6], Xin Wang[1,2]*, Li Deng[1,2]* and Han-Ping Shi[1,2]*

[1]Department of Gastrointestinal Surgery, Department of Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University, Beijing, China, [2]Key Laboratory of Cancer FSMP for State Market Regulation, Beijing, China, [3]Clinical Medical College, Yunnan University, Kunming, China, [4]General Surgery Clinical Medical Center of Yunnan Province, Kunming, China, [5]Comprehensive Oncology Department, National Cancer Center, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [6]The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

Purpose: Previous studies have shown that both hand grip strength (HGS) and the modified Glasgow Prognostic Score (mGPS) are associated with poor clinical outcomes in patients with liver cancer. In spite of this, no relevant studies have been conducted to determine whether the combination of HGS and mGPS can predict the prognosis of patients with liver cancer. Accordingly, this study sought to explore this possibility.

Methods: This was a multicenter study of patients with liver cancer. Based on the optimal HGS cutoff value for each sex, we determined the HGS cutoff values. The patients were divided into high and low HGS groups based on their HGS scores. An mGPS of 0 was defined as low mGPS, whereas scores higher than 0 were defined as high mGPS. The patients were combined into HGS-mGPS groups for the prediction of survival. Survival analysis was performed using Kaplan–Meier curves. A Cox regression model was designed and adjusted for confounders. To evaluate the nomogram model, receiver operating characteristic curves and calibration curves were used.

Results: A total of 504 patients were enrolled in this study. Of these, 386 (76.6%) were men (mean [SD] age, 56.63 [12.06] years). Multivariate analysis revealed that patients with low HGS and high mGPS had a higher risk of death than those with neither low HGS nor high mGPS (hazard ratio [HR],1.50; 95% confidence interval [CI],1.14–1.98; p=0.001 and HR, 1.55; 95% CI, 1.14–2.12, p=0.001 respectively). Patients with both low HGS and high mGPS had 2.35-fold increased risk of death (HR, 2.35; 95% CI, 1.52–3.63; p<0.001). The area under the curve of HGS-mGPS was 0.623. The calibration curve demonstrated the validity of the HGS-mGPS nomogram model for predicting the survival of patients with liver cancer.

Conclusion: A combination of low HGS and high mGPS is associated with poor prognosis in patients with liver cancer. The combination of HGS and mGPS can predict the prognosis of liver cancer more accurately than HGS or mGPS alone. The nomogram model developed in this study can effectively predict the survival outcomes of liver cancer.

KEYWORDS

hand grip strength, inflammation, mGPS, liver cancer, nomogram

Introduction

Globally, primary liver cancer is the fifth most common cancer and the third leading cause of cancer death (1). In 2018, the global mortality rate for liver cancer reached about 8.5 per 100,000 individuals (2). There is a high incidence of liver cancer in East Asia (3).

Patients with liver cancer are often malnourished because the liver is involved in nutrient metabolism. The poor prognosis of liver cancer has also been linked to impaired nutritional status in some studies (4). The poor nutritional status associated with liver cancer affects a patient's quality of life, the intensity of treatment, and the outcome of disease. Therefore, it is critical to identify nutritional indicators that are easily measured in clinical settings for predicting the prognosis of liver cancer.

Muscle mass is a common nutritional indicator and is often expressed in terms of skeleton muscle mass (SMM). However, SMM is assessed using computed tomography, which is expensive and exerts a significant financial burden on the patient (4). Hand grip strength (HGS) is another indicator that is often used to evaluate muscle mass and is easily measured in clinical settings. Complication-free survival is significantly worse in patients with low HGS, according to previous studies (5). A recent study suggested that HGS is a biomarker for aging and predisposition to various diseases that lead to death (6). A study based on the UK Biobank showed that HGS is associated with mortality from cancer and other disease (7). Victoria et al. found that HGS is a useful tool for diagnosing malnutrition and has a predictive value for six-month mortality in inpatients with cancer (8). Therefore, we speculated that HGS could reflect muscle mass and play a role in predicting the prognosis of liver cancer.

Using a combination of C-reactive protein and albumin levels, the modified Glasgow Prognostic Score (mGPS) provides a prognostic score for patients who have cancer. The mGPS reflects the nutritional and inflammatory status of a patient. It has been shown to have prognostic value for lung, gastrointestinal, and renal cancers, independent of the tumor stage (9). In addition, the mGPS has been found to be significantly associated with sarcopenia in patients with gastric and esophageal cancers (10). Some studies have shown that the systemic inflammatory response evidenced by the mGPS is common in large patient cohorts. Compared with other biochemical parameters, mGPS is a strong prognostic factor, independent of tumor site (9). It has also been suggested that the mGPS may be an independent prognostic factor for liver cancer (11).

Several studies on the prognostic values of HGS and mGPS have been conducted. To our knowledge, there have been no studies to investigate whether liver cancer outcomes can be predicted by combining HGS and mGPS. Therefore, the aim of this study was to investigate the roles of HGS, mGPS, and HGS-mGPS in predicting the prognosis of liver cancer.

Methods

Study population and design

A retrospective analysis of liver cancer patient data from multiple Chinese clinical centers from April 2013 to September 2019 was conducted in this study. The inclusion criteria for this study were as follows: age ≥ 18 years old; the primary tumor was diagnosed as hepatocellular carcinoma; duration of hospitalization ≥2 days; and provision of a signed consent form. A minimum of 18 years old, a hospital stay of 2 days, refusal to sign the consent form, and admission to the intensive care unit at the beginning of the recruitment process were the exclusion criteria. In accordance with the principles of the Declaration of Helsinki, the study was approved by the medical ethical review committee of the hospital where it was conducted.

Patient characteristics

The following information were extracted from the patient records: sex; age; tumor stage; surgery, chemotherapy, and radiotherapy data; HGS; trigeminal skinfold thickness (TSF); body mass index (BMI); and total protein, albumin, C-reactive protein (CRP), aspartate aminotransferase, and alanine transaminase levels.

Laboratory and anthropometric measurements

All blood tests were conducted within 48 h of hospitalization after patients had fasted for at least 9 hours.

Hand grip strength was measured using an electronic hand-held dynamometer (CAMRY, EH101 model, Guangdong, China). Patients were instructed to stand comfortably and perform three maximal isometric contractions with the nondominant hand 30 s apart. BMI was calculated as follows: BMI (kg/m^2) = weight (kg)/height^2 (m^2). TSF involves creating a skinfold by grasping the patient's skin 2 cm above the midpoint of the right upper arm with the thumb and index finger. Calipers were then placed at the midpoint of the skinfold for the measurement of TSF (12).

Definition of variables and evaluation of outcomes

We used the log-rank method to determine the HGS cutoff values for men and women separately. The optimal HGS cutoff values for men and women were 28.3 and 18.6, respectively (Supplementary Figure S2). The patients were classified into low or high HGS groups based on these cutoff values.

An mGPS of 0 is determined as a CRP level < 10 mg/L and an albumin level > 35 g/L, a score of 1 as a CRP level > 10 mg/L or an albumin level < 35 g/L, and a score of 2 as a CRP level > 10 mg/L and an albumin level < 35 g/L (13). An mGPS of 0 was defined as a low mGPS, whereas scores higher than 0 were defined as a high mGPS.

Our method for gathering follow-up records was to obtain them strictly according to the established content from all telephone consultations and follow-ups in outpatient clinics. Observed outcomes were overall survival (OS), which is the time between the first diagnosis of cancer and death, withdrawal from study, or last follow-up.

Statistical analysis

When a variable has a normal distribution, the mean + standard deviation is calculated, while variables with a non-normal distribution are calculated by median (interquartile range). The categorical baseline characteristics of the patients were compared using the chi-squared test and are expressed as numbers (percentages). The independent Student's *t*-test or rank test and the χ^2 test were used for the comparison of continuous variables and categorical data, respectively, between the two groups.

For the survival analyses, we cross-classified the low or high HGS and low or high mGPS groups into four categories (only low HGS, only high mGPS, both, and neither [reference]). A Kaplan–Meier survival curve was calculated using the Kaplan–Meier method. To assess the risk of mortality and value reliability, we calculated hazard ratios (HRs) and 95% confidence intervals (CIs). In the multivariate Cox regression model for the risk of mortality, model 0 was an unadjusted model, model 1 was adjusted for age, sex, and tumor stage, and model 2 was adjusted for age, sex, tumor stage, surgery, radiotherapy, chemotherapy, TSF, smoking, and alcohol consumption. The nomogram was used to establish a prediction model based on HGS-mGPS and survival probability. Nomogram accuracy was evaluated using the area under the curve (AUC) and calibration curves. All statistical analyses were performed by the R Studio statistical software (version 4.2.0). Two-sided *p*-values <0.05 were considered statistically significant.

Results

Patients characteristics

A total of 798 patients with liver cancer were identified in INSCOC database. After excluding patients with missing data, 504 patients were included in this study (Supplementary Figure S1). The study population comprised 386 men (76.6%) and 118 women (23.4%), and their mean age was 56.63 ± 12.06 years (Table 1).

TABLE 1 Baseline characteristics of patients with liver cancer (*N*=504).

	Patients (504)
Sex, *n* (%)	
Men	386 (76.6)
Women	118 (23.4)
Age (year)	56.63 ± 12.06
Tumor stage, *n* (%)	
I	77 (15.3)
II	93 (18.5)
III	102 (20.2)
IV	232 (45.9)
Surgery, *n* (%)	
Yes	204 (40.5)
No	300 (59.5)
Chemotherapy, *n* (%)	
Yes	86 (17.1)
No	419 (83.0)
Radiotherapy, *n* (%)	
Yes	18 (3.6)
No	487 (96.4)
Liver cirrhosis, *n* (%)	
Yes	107 (21.2%)
No	397 (78.8%)
Smoking *n* (%)	
Yes	122 (24.2)
No	106 (21.0)
Other	276 (54.8)
Alcohol *n* (%)	
Yes	130 (25.8)
No	374 (74.2)
BMI (kg/m^2)	22.37 ± 3.23
Total protein (g/L)	68.36 ± 8.09
Albumin (g/L)	37.02 ± 6.14
TSF (mm)	14.00 [10.00, 20.00]
HGS (kg)	26.30 [20.60, 32.00]
CRP (mg/L)	16.82 [4.40, 34.70]
AST (U/L)	40.00 [27.00, 75.40]
ALT (U/L)	35.00 [23.10, 58.80]

Continuous variables are presented as mean ± standard deviation (SD). Meanwhile, TSF, HGS, CRP, AST and ALT are presented as the median (interquartile range). Categorical variables are presented as numbers and percentages. Differences in normally and non-normally distributed baseline characteristics were compared using the chi-square test or *t*-test and Wilcoxon rank sum test, respectively. TSF, triceps skinfold thickness; HGS, handgrip strength; BMI, body mass index; CRP, C reactive protein; AST, aspartate aminotransferase; ALT, Alanine aminotransferase.

Supplementary Table S1 summarizes the baseline characteristics of the patients as determined by their HGS and mGPS categories. The results showed that low HGS was significantly associated with increased CRP level ($p < 0.001$). In addition, the results indicated that mGPS was

associated with HGS ($p < 0.001$). HGS and mGPS were both associated with tumor stage ($p = 0.001$ and $p < 0.001$, respectively).

Relationship between hand grip strength, modified Glasgow prognostic score, hand grip strength-Glasgow prognostic score, and overall survival

Based on Cox regression models adjusted for potential confounders, Table 2 shows the association between each indicator and OS in patients with liver cancer. Death risk was 50% higher in the low HGS group than in the high HGS group (adjusted HR = 1.50; 95% CI: 1.14–1.98; adjusted $p = 0.004$). Continuous HGS, however, did not significantly affect OS (adjusted HR = 0.99; 95% CI: 0.97–1.01; adjusted $p = 0.197$). There was a higher risk of death in the high mGPS group compared to the low mGPS group in regards to mGPS (adjusted HR = 1.55; 95% CI: 1.14–2.12; adjusted $p = 0.001$). HGS-mGPS showed that patients with both low HGS and high mGPS had a significantly higher mortality risk than those with neither (adjusted HR = 2.35; 95% CI: 1.52–3.63; adjusted $p < 0.001$).

Figure 1 shows the Kaplan–Meier curves for patients in different HGS, mGPS, and risk groups. The OS of patients with high HGS was significantly better than that of patients with low HGS ($p < 0.001$). Patients with a high mGPS had worse OS than those with a low mGPS ($p < 0.001$). Patients in the high-risk group (both low HGS and high mGPS) had the worst OS, whereas those in the low-risk group (neither low HGS nor high mGPS) had the best OS ($p < 0.001$).

Stratified analysis

Stratified analyses were conducted to evaluate the relationship between HGS-mGPS and the HR of OS in various subgroups (Table 3). Among liver cancer patients, the association between OS and HGS-mGPS was not modified by age, stage, alcohol intake, or BMI (Table 3). Among patients with both low HGS and high mGPS, even younger patients (<65 years; adjusted HR, 2.16; 95% CI, 1.30–3.60, adjusted $p = 0.003$) with no history of no alcohol consumption (adjusted HR, 2.44; 95% CI, 1.45–4.13, adjusted $p = 0.001$) had more than a two-fold increased risk of death compared with patients with similar characteristics but with neither low HGS nor high mGPS. Subgroup analyses revealed no previous interaction between these factors and HGS-mGPS.

Nomogram and evaluation

COX regression analysis was used to investigate the prognostic factors of liver cancer patients. The result showed that age and tumor

TABLE 2 Association of each indicator and overall survival in patients with liver cancer according to cox regression models adjusted for potential confounders.

	N	Model 0		Model 1		Model 2	
		HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
HGS							
As continues	504	**0.98 (0.96–0.99)**	**<0.001**	0.99 (0.97–1.00)	0.073	0.99 (0.97–1.01)	0.197
High HGS	256	Ref.		Ref.		Ref.	
Low HGS	248	**1.90 (1.48–2.44)**	**<0.001**	**1.57 (1.20–2.04)**	**0.001**	**1.50 (1.14–1.98)**	**0.004**
mGPS							
0	148	Ref.		Ref.		Ref.	
1	202	**1.88 (1.36–2.61)**	**<0.001**	**1.42 (1.02–1.98)**	**0.040**	1.40 (1.00–1.97)	0.055
2	154	**2.48 (1.77–3.47)**	**<0.001**	**1.93 (1.37–2.70)**	**<0.001**	**1.84 (1.30–2.61)**	**0.001**
Low mGPS (mGPS = 0)	148	Ref.		Ref.		Ref.	
High mGPS (mGPS = 1 or 2)	356	**2.12 (1.57–2.86)**	**<0.001**	**1.58 (1.16–2.14)**	**0.004**	**1.55 (1.14–2.12)**	**0.001**
HGS-mGPS							
Low risk (Neither)	95	Ref.		Ref.		Ref.	
Median risk 1 (Only low HGS)	53	**2.13 (1.25–3.64)**	**0.006**	**2.07 (1.21–3.56)**	**0.008**	**2.01 (1.16–3.47)**	**0.013**
Median risk 2 (Only high mGPS)	161	**2.19 (1.42–3.37)**	**<0.001**	**1.86 (1.20–2.86)**	**0.005**	**1.84 (1.19–2.85)**	**0.006**
High risk (Both)	195	**3.60 (2.38–5.44)**	**<0.001**	**2.49 (1.63–3.81)**	**<0.001**	**2.35 (1.52–3.63)**	**<0.001**

Data are presented as hazard ratios (95% confidence intervals). Model 0: unadjusted. Model 1: Adjusted for age, sex, tumor stage. Model 2: Adjusted for age, sex tumor stage, surgery, radiotherapy, chemotherapy, TSF, smoking and alcohol. HGS, hand grip strength; mGPS, modified Glasgow Prognostic Score; HGS-mGPS, the combination of hand grip strength and modified Glasgow Prognostic Score. Bold values indicate statistically significant level ($p < 0.05$).

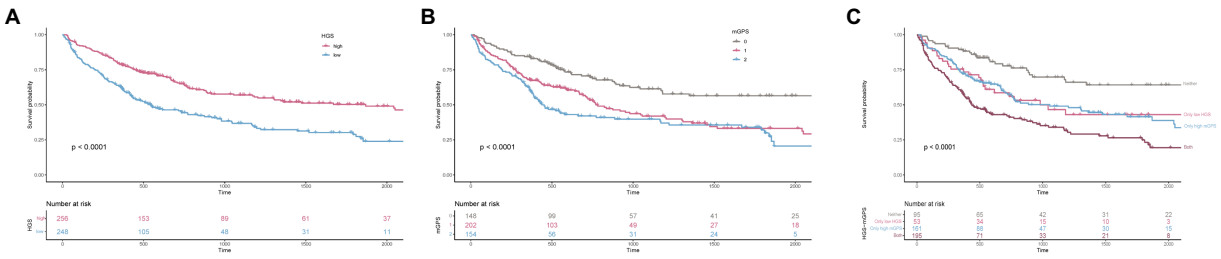


FIGURE 1
The Kaplan–Meier survival curves of HGS, mGPS, and HGS-mGPS. **(A)** HGS; **(B)** mGPS; **(C)** HGS-mGPS. HGS, hand grip strength; mGPS, modified Glasgow Prognosis Score.

TABLE 3 HGS, mGPS, and liver cancer overall survival stratified by body mass index, tumor stage, age, sex, smoking, and alcohol consumption.

Stratification variable	Univariate analysis		Multivariate analysis		*p* for interaction
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	
Tumor stage					0.478
I	3.81 (0.92–15.74)	0.065	4.01 (0.79–20.37)	0.094	
II	2.96 (1.18–7.43)	0.021	3.26 (1.10–9.66)	0.033	
III	2.70 (1.03–7.06)	0.043	2.94 (1.11–7.77)	0.030	
IV	2.66 (1.45–4.90)	0.002	2.26 (1.19–4.29)	0.013	
Age					0.936
<65	3.17 (1.95–5.13)	<0.001	2.16 (1.30–3.60)	0.003	
≥65	3.98 (1.57–10.09)	0.004	3.48 (1.31–9.19)	0.012	
Sex					0.207
Man	3.23 (2.04–5.11)	<0.001	1.99 (1.22–3.25)	0.006	
Woman	5.47 (2.08–14.39)	0.001	4.04 (1.46–11.17)	0.007	
Smoking					0.637
Yes	2.26 (1.10–4.66)	0.027	2.00 (0.89–4.52)	0.095	
No	3.50 (0.83–14.78)	0.088	2.90 (0.61–13.68)	0.179	
Other	4.72 (2.69–8.28)	<0.001	2.59 (1.43–4.72)	0.002	
Alcohol consumption					0.327
Yes	2.36 (1.09–5.12)	0.029	2.01 (0.91–4.46)	0.084	
No	4.12 (2.52–6.74)	<0.001	2.44 (1.45–4.13)	0.001	
BMI					1.000
<18.5	1.45 (0.43–4.85)	0.550	1.39 (0.31–6.32)	0.669	
18.5–24.9	3.46 (2.12–5.65)	<0.001	2.28 (1.36–3.82)	0.002	
≥25	1.77 (1.28–2.44)	0.001	1.55 (1.08–2.22)	0.017	

Cox proportional hazards multiple models adjust for BMI categories (<18.5,18.5–24.9,≥25), at-diagnosis values of age (years), sex (man or woman), tumor stage (I, II, III or IV), surgery (yes or no), chemotherapy (yes or no), radiotherapy, smoking (yes or no), alcohol (yes or no) and TSF, unless stratified by those variables. All HRs compare patients with low HGS and high mGPS vs patients with high HGS and low mGPS.

stage were independent risk factors for them (Supplementary Table S2). The nomogram was constructed using independent prognostic factors (age, tumor stage, and HGS-mGPS; Figure 2). The AUC for HGS-mGPS was 0.623 (Supplementary Figure S3). This result indicated that HGS-mGPS has predictive value for liver cancer. Based on the nomogram, the probability of survival in liver cancer patients is predicted in Figure 2. The total score was determined based on the individual scores calculated using the nomogram. The total risk points of most patients in the present study ranged from 0 to 240. The calibration curves reflected good agreement between 1-year and 5-year OS and the predictions from the nomogram (Supplementary Figure S4).

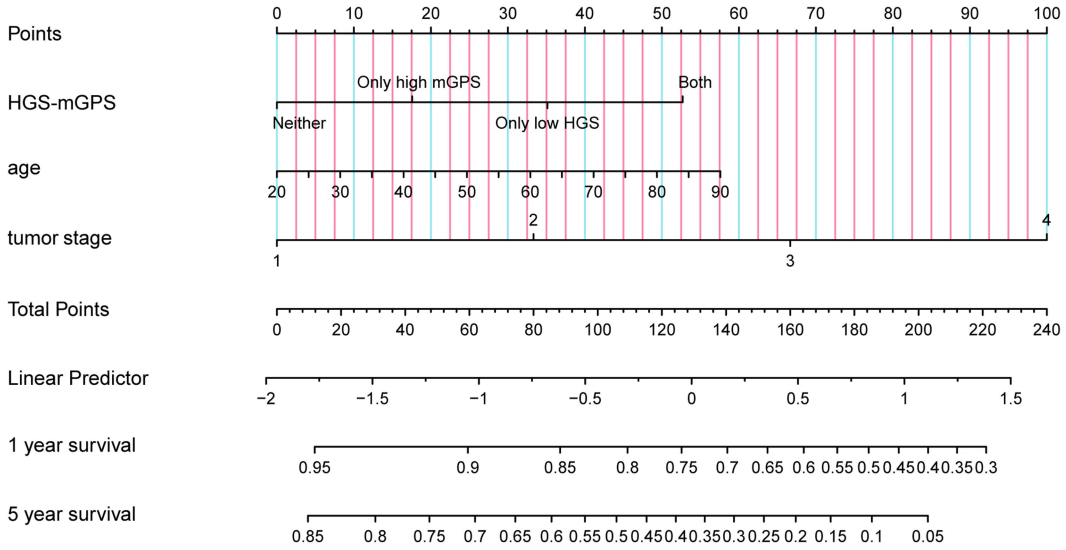


FIGURE 2
A proposed Nomogram for predicting 1year and 5year survival probability of patients with liver cancer. HGS-mGPS, the combination of HGS and mGPS.

TABLE 4 Sensitive analysis (Excluded patients who died in 180days) (n=413).

	N	Model 0		Model 1		Model 2	
		HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
HGS							
As continues	413	0.98 (0.97–1.00)	0.051	0.99 (0.97–1.01)	0.236	0.99 (0.97–1.01)	0.192
High HGS	227	Ref.		Ref.		Ref.	
Low HGS	186	**1.71 (1.26–2.31)**	**<0.001**	**1.44 (1.05–1.98)**	**0.023**	**1.55 (1.11–2.17)**	**0.010**
mGPS							
0	113	Ref.		Ref.		Ref.	
1	163	**1.94 (1.31–2.86)**	**0.001**	**1.47 (0.99–2.19)**	**0.056**	1.36 (0.91–2.04)	0.132
2	117	**2.42 (1.61–3.64)**	**<0.001**	**1.93 (1.28–2.90)**	**0.002**	**1.99 (1.31–3.02)**	**0.001**
Low mGPS (mGPS = 0)	133	Ref.		Ref.		Ref.	
High mGPS (mGPS = 1 or 2)	280	**2.13 (1.49–3.04)**	**<0.001**	**1.65 (1.14–2.37)**	**0.007**	**1.86 (1.29–2.68)**	**0.001**
HGS-mGPS							
Low risk (Neither)	89	Ref.		Ref.		Ref.	
Median risk 1 (Only low HGS)	44	**1.91 (1.01–3.61)**	**0.046**	1.86 (0.98–3.54)	0.057	**2.02 (1.05–3.87)**	**0.035**
Median risk 2 (Only high mGPS)	138	**2.23 (1.36–3.63)**	**0.001**	**1.87 (1.14–3.06)**	**0.013**	**1.79 (1.09–2.94)**	**0.022**
High risk (Both)	142	**3.26 (2.02–5.27)**	**<0.001**	**2.30 (1.40–3.87)**	**0.001**	**2.34 (1.42–3.87)**	**0.001**

Data are presented as hazard ratios (95% confidence intervals). Model 0: unadjusted. Model 1: Adjusted for age, gender, tumor stage. Model 2: Adjusted for age, sex tumor stage, surgery, radiotherapy, chemotherapy, TSF, smoking and alcohol. HGS, handgrip strength; mGPS, modified Glasgow Prognostic Score; HGS-mGPS, combination of HGS and mGPS; HR, hazard ratio; CI, confidence interval; *p*, probability. Bold values indicate statistically significant level ($p < 0.05$).

Sensitivity analysis

Given that HGS-mGPS has prognostic value for liver cancer, a sensitivity analysis was performed (Table 4). Table 4 shows the results of the sensitivity analysis after patients who died less than 6 months from the start of the first investigation were excluded. High-risk groups of HGS-mGPS had a significantly greater risk of death than low-risk groups (adjusted HR = 2.34; 95% CI: 1.42–3.87; adjusted $p = 0.001$).

Discussion

In this multicenter study, we investigated the prognosis values of HGS, mGPS, and HGS-mGPS for liver cancer. According to the results, HGS and mGPS are independently associated with liver cancer prognoses, but their combination negatively correlates with OS. In addition, the nomogram model we developed that incorporated HGS-mGPS and other factors. The model effectively predicted the survival outcomes of liver cancer.

A previous study showed that absolute HGS is associated with liver cancer (14). This study showed, however, that continuous HGS values in liver cancer patients are not significantly associated with all-cause mortality, especially after taking into account confounding variables. We calculated the HGS cutoff values for men and women separately to define low HGS. Low HGS was associated with poor survival probability compared to high HGS based on Cox regression analysis and Kaplan–Meier curves. HGS is strongly correlated with leg muscle strength and is a valid marker of overall limb muscle strength across all age groups. It has also been suggested that HGS is a marker of nutritional status (15, 16). According to a review published in the Lancet, muscle function is important for the diagnosis of sarcopenia, and HGS is one of the commonly used measures (17). However, HGS can only reflect muscle condition and still has limitations. HGS is easily affected by other factors when predicting prognosis. The 2016 Global Leadership Initiative on Malnutrition criteria states that at least one phenotypic criterion and one etiological criterion are required in the diagnosis of malnutrition (18). Therefore, we included inflammatory factors in the present study.

The three-scale mGPS is based on a combination of C-reactive protein and albumin levels and is graded from 0 to 2. The mGPS has been validated worldwide, and has been proven to have an independent prognostic value for various types and stages of cancer (19). The mGPS has also proven useful as a prognostic tool at the time of diagnosis, as well as in patients with a possible ongoing malignancy. The present study showed that mGPS was significantly linked to liver cancer mortality overall. Patients with an mGPS of 3 had a higher risk of death than those with an mGPS of 1. However, in the survival analysis, the risk of death in patients with an mGPS of 2 was not significantly different from that in patients with an mGPS of 3. Therefore, we defined patients with mGPS of 2 or 3 as those with high mGPS.

We combined the HGS and mGPS groups to form a new index, HGS-mGPS. The HGS-mGPS categories included the low-risk, median-risk, and high-risk groups. The risk of death was significantly different among the four groups. As a result of Cox regression and survival analyses, it was found that patients in the high-risk group were at the greatest risk of death. The combination of HGS and mGPS can predict the prognosis of liver cancer more accurately than HGS or mGPS alone. We speculate that the underlying mechanism for this finding is the synergistic effect of muscle loss and a high inflammatory load. A review suggested that the prevalence of sarcopenia is approximately 39% in patients with hepatocellular carcinoma. The mechanism is complex, but it is well established that chronic liver disease can trigger muscle atrophy and structural changes in skeletal muscle, and skeletal muscle compartments contribute to the progression of liver disease (20). In addition, muscle loss leads to insulin resistance and increases the activity of IGF-1, which can regulate hepatocyte proliferation (21). No matter what stage of cancer a patient is at, low muscle mass negatively impacts physical function, quality of life, surgical complications, cancer progression, and reduced possibility of survival (22). Reduced muscle mass increases the inflammatory burden, which further promotes muscle loss. Inflammatory markers in the blood have been shown to exacerbate the loss of muscle strength in previous studies (23). Our study found that lower HGS was significantly associated with higher CRP levels. This result is consistent with previous study (24). CRP changes the expression of proto-oncogenes and suppressor genes and immune regulation through different pathways, affecting cancer cell proliferation, migration, invasion, chemotherapy resistance and immune system resistance (25). Researchers have previously shown a link between higher CRP levels and lower walking speeds and grip strength (26). CRP and albumin may be active mediators of both hepatocellular cancer development and a more aggressive phenotype, rather than merely passive reflections of inflammatory processes. In addition, CRP level seems to reflect mechanism of hepatocellular cancer development (27). Muscle and inflammation are both related to the prognosis of liver cancer, and they interact with each other. Therefore, the combination of HGS and mGPS can predict the outcome of liver cancer more accurately than HGS and mGPS alone and is not susceptible to other confounding factors. In addition, the acquisition of HGS, CRP, and albumin data is simpler and more economical than other expensive examinations.

Malnutrition is a significant risk for patients with liver cancer since the liver is the organ responsible for nutrient metabolism. Malnutrition is common in patients with liver cirrhosis and is associated with mortality and a reduced quality of life (28). Poor nutrition further exacerbates muscle loss which in turn activates the inflammation cascade. Therefore, it is important to pay sufficient attention to malnutrition in patients with liver cancer and note that nutritional status is closely related to their clinical performance. A meta-analysis showed that nutritional intervention can significantly improve the nutritional statuses of patients with gastric cancer (29). However, only 33.9% of physicians follow the recommendations in the oncology section of the ESPEN guidelines (30). A recent review showed that in patients at risk of developing liver cancer, the chance of progression to cachexia is as high as 50% (31). Therefore, more attention should be paid to the nutritional statuses of patients with liver cancer who show low HGS or increased blood inflammatory markers. In addition, it should be noted that improving muscle mass and systemic inflammation can improve the prognosis of patients with liver cancer.

This study has some limitations. First, the study only included Asians, in addition to having a small sample size. It is therefore necessary to conduct future studies with patient samples from diverse ethnicities in order to confirm the findings of the present study. Second, no additional treatment modalities were analyzed in this study. Thirdly, there was a lack of specific assessment of cirrhosis. Finally, the nomogram developed in this study requires further external validation.

Despite these limitations, this study demonstrated the clinical value of HGS-mGPS and its correlation with the outcomes of

liver cancer. To our knowledge, this is the first multicenter study in which the value of the combination of HGS and mGPS for predicting the survival of patients with liver cancer was explored.

Conclusion

This study showed that low HGS and high mGPS are associated with poor prognosis in patients with liver cancer. Furthermore, patients with both low HGS and high mGPS have a higher mortality risk than those with neither low HGS nor high mGPS. The nomogram model developed in the present study can effectively predict the outcomes of liver cancer.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study followed the Helsinki declaration. All participants signed an informed consent form, and this study was approved by the Institutional Review Board of each hospital (Registration number: ChiCTR1800020329).

Author contributions

YC wrote the manuscript. YC, G-TR, and J-YS analyzed and interpreted the patient data. YC, G-TR, J-YS, C-AL, TL, and H-PS made substantial contributions to the conception, design, and intellectual content of the studies. All authors read and approved the final manuscript.

Funding

This work was supported by the National Key Research and Development Program [grant number 2017YFC1309200, 2022YFC2009600] and the Beijing Municipal Science and Technology Commission [grant number SCW2018-06].

Acknowledgments

We would like to thank Editage (www.editage.cn) for English language editing. We are grateful to all the participants who have been part of the project and to the many members of the study teams at different study centers who have enabled this research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1062117/full#supplementary-material

References

1. El-Serag, HB, and Rudolph, KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. (2007) 132:2557–76. doi: 10.1053/j.gastro.2007.04.061

2. Shi, J-F, Cao, M, Wang, Y, Bai, F-Z, Lei, L, Peng, J, et al. Is it possible to halve the incidence of liver cancer in China by 2050? *Int J Cancer*. (2021) 148:1051–65. doi: 10.1002/ijc.33313

3. Wallace, MC, Preen, D, Jeffrey, GP, and Adams, LA. The evolving epidemiology of hepatocellular carcinoma: a global perspective. *Expert Rev Gastroenterol Hepatol*. (2015) 9:765–79. doi: 10.1586/17474124.2015.1028363

4. van Dijk, AM, Coppens, BJP, van Beers, MA, Bruins Slot, AS, Verstraete, CJR, de Bruijne, J, et al. Nutritional status in patients with hepatocellular carcinoma: potential relevance for clinical outcome. *Eur J Intern Med*. (2022) 104:80–8. doi: 10.1016/j.ejim.2022.07.002

5. Lanza, E, Masetti, C, Messana, G, Muglia, R, Pugliese, N, Ceriani, R, et al. Sarcopenia as a predictor of survival in patients undergoing bland transarterial embolization for unresectable hepatocellular carcinoma. *PLoS One*. (2020) 15:e0232371. doi: 10.1371/journal.pone.0232371

6. Leong, DP, Teo, KK, Rangarajan, S, Lopez-Jaramillo, P, Avezum, A, Orlandini, A, et al. Prognostic value of grip strength: findings from the prospective urban rural epidemiology (PURE) study. *Lancet*. (2015) 386:266–73. doi: 10.1016/S0140-6736(14)62000-6

7. Celis-Morales, CA, Welsh, P, Lyall, DM, Steell, L, Petermann, F, Anderson, J, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK biobank participants. *BMJ*. (2018) 361:k1651. doi: 10.1136/bmj.k1651

8. Contreras-Bolívar, V, Sánchez-Torralvo, FJ, Ruiz-Vico, M, González-Almendros, I, Barrios, M, Padín, S, et al. GLIM criteria using hand grip strength adequately predict six-month mortality in cancer inpatients. *Nutrients*. (2019) 11:2043. doi: 10.3390/nu11092043

9. Proctor, MJ, Morrison, DS, Talwar, D, Balmer, SM, O'Reilly, DSJ, Foulis, AK, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow inflammation outcome study. *Br J Cancer*. (2011) 104:726–34. doi: 10.1038/sj.bjc.6606087

10. Hacker, UT, Hasenclever, D, Baber, R, Linder, N, Busse, H, Obermannova, R, et al. Modified Glasgow prognostic score (mGPS) is correlated with sarcopenia and dominates the prognostic role of baseline body composition parameters in advanced gastric and esophagogastric junction cancer patients undergoing first-line treatment from the phase III EXPAND trial. *Ann Oncol*. (2022) 33:685–92. doi: 10.1016/j.annonc.2022.03.274

11. Chen, H, Hu, N, Chang, P, Kang, T, Han, S, Lu, Y, et al. Modified Glasgow prognostic score might be a prognostic factor for hepatocellular carcinoma: a meta-analysis. *Panminerva Med*. (2017) 59:302–7. doi: 10.23736/S0031-0808.16.03236-5

12. Santos, DA, Dawson, JA, Matias, CN, Rocha, PM, Minderico, CS, Allison, DB, et al. Reference values for body composition and anthropometric measurements in athletes. *PLoS One*. (2014) 9:e97846. doi: 10.1371/journal.pone.0097846

13. McMillan, DC. The systemic inflammation-based Glasgow prognostic score: a decade of experience in patients with cancer. *Cancer Treat Rev*. (2013) 39:534–40. doi: 10.1016/j.ctrv.2012.08.003

14. Parra-Soto, S, Pell, JP, Celis-Morales, C, and Ho, FK. Absolute and relative grip strength as predictors of cancer: prospective cohort study of 445 552 participants in UK biobank. *J Cachexia Sarcopenia Muscle*. (2022) 13:325–32. doi: 10.1002/jcsm.12863

15. Bohannon, RW, Magasi, SR, Bubela, DJ, Wang, Y-C, and Gershon, RC. Grip and knee extension muscle strength reflect a common construct among adults. *Muscle Nerve*. (2012) 46:555–8. doi: 10.1002/mus.23350

16. Norman, K, Stobäus, N, Gonzalez, MC, Schulzke, J-D, and Pirlich, M. Hand grip strength: outcome predictor and marker of nutritional status. *Clin Nutr*. (2011) 30:135–42. doi: 10.1016/j.clnu.2010.09.010

17. Cruz-Jentoft, AJ, and Sayer, AA. Sarcopenia. *Lancet*. (2019) 393:2636–46. doi: 10.1016/S0140-6736(19)31138-9

18. Bossi, P, Delrio, P, Mascheroni, A, and Zanetti, M. The Spectrum of malnutrition/cachexia/sarcopenia in oncology according to different cancer types and settings: a narrative review. *Nutrients*. (2021) 13:1980. doi: 10.3390/nu13061980

19. Dupré, A, and Malik, HZ. Inflammation and cancer: what a surgical oncologist should know. *Eur J Surg Oncol*. (2018) 44:566–70. doi: 10.1016/j.ejso.2018.02.209

20. Nachit, M, and Leclercq, IA. Emerging awareness on the importance of skeletal muscle in liver diseases: time to dig deeper into mechanisms! *Clin Sci (Lond)*. (2019) 133:465–81. doi: 10.1042/CS20180421

21. Jiang, C, Wang, Y, Fu, W, Zhang, G, Feng, X, Wang, X, et al. Association between sarcopenia and prognosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Front Nutr*. (2022) 9:978110. doi: 10.3389/fnut.2022.978110

22. Prado, CM, Purcell, SA, and Laviano, A. Nutrition interventions to treat low muscle mass in cancer. *J Cachexia Sarcopenia Muscle*. (2020) 11:366–80. doi: 10.1002/jcsm.12525

23. Ferrucci, L, Penninx, BWJH, Volpato, S, Harris, TB, Bandeen-Roche, K, Balfour, J, et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc*. (2002) 50:1947–54. doi: 10.1046/j.1532-5415.2002.50605.x

24. Tuttle, CSL, Thang, LAN, and Maier, AB. Markers of inflammation and their association with muscle strength and mass: a systematic review and meta-analysis. *Ageing Res Rev*. (2020) 64:101185. doi: 10.1016/j.arr.2020.101185

25. Socha, MW, Malinowski, B, Puk, O, Wartęga, M, Bernard, P, Nowaczyk, M, et al. C-reactive protein as a diagnostic and prognostic factor of endometrial cancer. *Crit Rev Oncol Hematol*. (2021) 164:103419. doi: 10.1016/j.critrevonc.2021.103419

26. Gabay, C, and Kushner, I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med*. (1999) 340:448–54. doi: 10.1056/NEJM199902113400607

27. Akkiz, H, Carr, BI, Bag, HG, Karaoğullarından, Ü, Yalçın, K, Ekin, N, et al. Serum levels of inflammatory markers CRP, ESR and albumin in relation to survival for patients with hepatocellular carcinoma. *Int J Clin Pract*. (2021) 75:e13593. doi: 10.1111/ijcp.13593

28. Schütte, K, Tippelt, B, Schulz, C, Röhl, F-W, Feneberg, A, Seidensticker, R, et al. Malnutrition is a prognostic factor in patients with hepatocellular carcinoma (HCC). *Clin Nutr*. (2015) 34:1122–7. doi: 10.1016/j.clnu.2014.11.007

29. Rinninella, E, Cintoni, M, Raoul, P, Pozzo, C, Strippoli, A, Bria, E, et al. Effects of nutritional interventions on nutritional status in patients with gastric cancer: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr ESPEN*. (2020) 38:28–42. doi: 10.1016/j.clnesp.2020.05.007

30. Kirbiyik, F, and Ozkan, E. Knowledge and practices of medical oncologists concerning nutrition therapy: a survey study. *Clin Nutr ESPEN*. (2018) 27:32–7. doi: 10.1016/j.clnesp.2018.07.004

31. Anker, MS, Holcomb, R, Muscaritoli, M, von Haehling, S, Haverkamp, W, Jatoi, A, et al. Orphan disease status of cancer cachexia in the USA and in the European Union: a systematic review. *J Cachexia Sarcopenia Muscle*. (2019) 10:22–34. doi: 10.1002/jcsm.12402

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 01 March 2023
DOI 10.3389/fnut.2023.1063279

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Ismael Martínez Guardado,
Nebrija University, Spain
Barbara Strasser,
Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Austria

*CORRESPONDENCE
Peter E. Ballmer
✉ peter.ballmer@hispeed.ch

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 06 October 2022
ACCEPTED 06 February 2023
PUBLISHED 01 March 2023

CITATION
Storck LJ, Uster A, Gafner L, Ruehlin M, Gaeumann S, Gisi D, Schmocker M, Meffert PJ, Imoberdorf R, Pless M and Ballmer PE (2023) Effect of combined therapies including nutrition and physical exercise in advanced cancer patients: A pooled analysis. *Front. Nutr.* 10:1063279. doi: 10.3389/fnut.2023.1063279

Effect of combined therapies including nutrition and physical exercise in advanced cancer patients: A pooled analysis

Lena J. Storck[1,2], Alexandra Uster[3], Lucia Gafner[1], Maya Ruehlin[1], Sabine Gaeumann[1], David Gisi[4], Martina Schmocker[4], Peter J. Meffert[5], Reinhard Imoberdorf[6], Miklos Pless[7] and Peter E. Ballmer[8]*

[1]Zentrum für Allgemeine Innere Medizin, Ernährungstherapie/-Beratung, Kantonsspital Winterthur, Winterthur, Switzerland, [2]Medizinische Kliniken, Klinikum Konstanz, Konstanz, Germany, [3]Division of Research, Innovation, and Development, Swiss Cancer League, Bern, Switzerland, [4]Institut für Therapien und Rehabilitation, Kantonsspital Winterthur, Winterthur, Switzerland, [5]Corvus, Statistical Analysis Consulting, Altkalen, Germany, [6]Zentrum für Allgemeine Innere Medizin, Klinik für Innere Medizin, Kantonsspital Winterthur, Winterthur, Switzerland, [7]Klinik für Medizinische Onkologie und Hämatologie, Kantonsspital Winterthur, Winterthur, Switzerland, [8]Past President GESKES-SSNC, Winterthur, Switzerland

Background and aims: Although many cancer patients suffer from malnutrition or cancer cachexia, there is no standard of care so far due to limited intervention trials. Pooled data from two combined trials were analyzed regarding nutritional status and survival time.

Materials and methods: Data from two trials with advanced cancer patients were included. In both trials, patients in the intervention group received at least three times nutritional counseling and supervised training sessions. Patients in the control group continued being treated according to usual care. Nutritional status was measured using BMI, body composition and handgrip strength. Survival time was analyzed using the Cox proportional hazard model with the period between the beginning of the trial and death as underlying time scale.

Results: 68 men (61.8%) and 42 women (38.2%) were randomized either to the intervention (n = 56) or the control (n = 54) group. The inter-group difference for changes in BMI and body composition was not statistically significant after 3 months. Handgrip strength improved significantly from 34.4 ± 10.2 kg to 36.3 ± 9.9 kg at 3 months in the intervention compared to 33.9 ± 9.2 kg to 34.9 ± 9.1 kg in the control group (p = 0.006). The analysis of survival time showed no inter-group difference for all patients. A detailed analysis for different diagnoses showed that in patients with lung cancer, the covariates "CRP value," "days from first diagnosis to randomization" as well as "gender" were significantly associated with survival time. Patients with higher CRP value had a shorter survival time and female patients had a shorter survival time than male patients in our analysis. In addition, patients with pancreatic cancer randomized to the control group had a 20% shorter survival time than those in the intervention group (p = 0.048).

Conclusion: The pooled analysis showed a significant improvement of handgrip strength in advanced cancer patients through the implementation of a combined therapy. Handgrip strength is of prognostic significance in hospitalized patients due to its association with mortality and morbidity. However, no improvements

in further tests were detected. There is great need for further investigations examining the effect of nutritional and exercise therapy on survival time with focus on different cancer diagnoses.

KEYWORDS

cancer, cachexia, malnutrition, dietary counseling, physical exercise

1. Introduction

Approximately half of all tumor patients experience involuntarily weight loss during or even before their disease and suffer from malnutrition or cancer cachexia, especially patients with gastrointestinal cancer (1–3). Cancer cachexia is defined as "a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (4). Therefore, the consequences of malnutrition and cachexia are a substantial impact on quality of life (QoL), impaired functional status, reduced therapy tolerance, and an increased number of unplanned hospital admissions (5, 6).

Although many patients are affected by malnutrition or cachexia, there is no therapy and no standard of care so far (7). Since the pathophysiology of cachexia is complex, therapeutic approaches are intensely studied with a research focus on combined or multimodal therapy (8, 9). In recent years, research activity on this topic has increased significantly, which is also evident in numerous systematic reviews. For example, Prado et al. (10) conducted a review about the effect of nutrition interventions on muscle status in cancer patients. They summarized that "given the positive findings and theoretical benefits of combining nutrition with other treatments, it is likely that such interventions would be beneficial for individuals with cancer at risk for losing muscle" (10).

In 2014, Grande et al. published a Cochrane Analysis on "exercise for cancer cachexia in adults" with the conclusion that there were no studies to make a qualified statement on effectiveness, acceptability, and safety of multimodal interventions (11). Continued research activity allowed Grande et al. to publish an update of their Cochrane Analysis, including four new trials. But due to bias in most domains, i.e., selection bias or blinding, they were still uncertain to make a statement, referring to another update in the future (12). Further reviews regarding exercise in patients with cancer include those by Allan et al. (13), focusing on exercise and energy regulation in cancer cachexia and Avancini et al. (14), investigating physical activity in patients with lung cancer (13, 14). Both emphasized positive effects of physical activity on, for example, fatigue, QoL, pulmonary function, muscle mass, strength and psychological status. However, Allan et al. pointed out that exercise could increase the gap between energy need and energy intake in patients with cancer cachexia, emphasizing the importance of supporting those patients with nutritional counseling and individual exercise advice (13).

Several reviews about multimodal interventions in advanced cancer patients pointed out that there are positive effects on single components like endurance or depression scores as well as lean mass. The reviews concluded that further high-quality studies are needed in order to give clear recommendations (15, 16).

In recent years, we conducted several combined intervention studies in advanced cancer patients and were not able to achieve the calculated sample size in some of them (17, 18). The reasons for this problem were manifold. For example, many patients could not participate in our trials because they did not meet the inclusion and exclusion criteria. For other candidates, the intervention was too strenuous or not feasible in addition to their cancer disease and treatment. Other researchers made the same experience. A two-arm, open-label, randomized multicenter controlled phase II trial conducted by Pascoe et al. (19) was terminated early due to slow recruitment rates. In this study for patients with advanced lung cancer, all patients received structured nutritional, exercise and symptom control advice. Patients in the intervention group additionally received a nutritional supplement to improve the management of cancer cachexia. The calculated sample size was n = 96 and only n = 38 patients could be recruited in five centers within 1 year. In the intervention group, 9 of 19 patients withdrew from the trial or died of tumor progression (19). In another clinical trial investigating the effect of nutrition and electromyostimulation on gait parameters and physical function in advanced cancer patients, data from only n = 26 patients out of n = 58 in the intervention group could be analyzed. The main reasons for drop-out were a fast deterioration in clinical status, lack of time, death, therapy side effects, surgery or mental stress (20).

For the study at hand we pooled data from two clinical studies to obtain a larger sample size and thus more robust results (17, 18). Using similar methodologies, we had investigated in both trials the effect of a combined therapy including nutritional counseling and physical exercise on nutritional status, QoL, and clinical course in advanced cancer patients.

2. Patients and materials and methods

This study used a pooled database of advanced cancer patients prospectively enrolled in two clinical trials. The two trials were designed to investigate the effect of a combined therapy including nutritional counseling and physical exercise on physical performance, nutritional status, body composition, fatigue and QoL. Both studies have been previously published (17, 18). The study protocols were approved by the Cantonal Ethics Committee Zurich (Switzerland) and registered at http://clinicaltrials.gov (NCT01540968 and NCT0285362). Written informed consent was obtained from all patients before study inclusion.

2.1. Procedures

Eligibility criteria for the two trials included in this pooled analysis were as follows: patients with metastatic or locally advanced lung or gastrointestinal cancer, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2 and a life expectancy greater than 6 months as judged by the responsible physician. Patients were considered ineligible if they (i) were on artificial nutrition, (ii) had symptomatic brain metastases or bone metastases or (iii) had had an ileus within the last month.

In the second of the two studies, patients with the following tumor sites were also eligible for inclusion: breast, ovarian, prostate, renal cell, and urothelial. In addition, palliative breast and prostate patients had to be receiving chemotherapy. In the same trial, patients were ineligible if they (iv) had a milk protein allergy and (v) consumed supplements with branched-chain amino acids.

In both trials, the primary investigator enrolled patients and conducted the baseline assessment after written informed consent. After that, patients were randomized using block sizes of six respectively eight. Patients were assigned to either the intervention or the control group at a 1:1 ratio. Patients in the intervention group participated in a nutrition and physical exercise program, while patients in the control group were treated according to the cancer center's standard medical therapy, following good clinical practice. All parameters were evaluated first at baseline, then 3 months later at the end of the intervention and again 3 months post intervention.

2.2. Intervention

2.2.1. Physical exercise

In both trials, the patients in the intervention group conducted two training sessions per week in the hospital's training facilities. Patients exercised in groups of two to six patients under the supervision of an experienced physiotherapist. One training unit of 90 min included a cardio-pulmonary endurance training either on bicycle-ergometers or on treadmills, and a strength training circuit covering different stations to train all larger muscle groups. The endurance intensity corresponded to a Borg scale-value of four to six (on a scale from zero to ten). When patients were receiving chemotherapy the same day, the intensity was set to a maximum of three on the Borg scale. For the strength part, the training goal was three sets of 10 to 15 repetitions. The strength training workload was adjusted at each session according to the individual patients' fitness, and participants were instructed to increase resistance as soon as they were able to complete more than 15 repetitions. The second training session at the hospital consisted of a gym training of 60 min with focus on strength, endurance, balance and coordination. The training intensity corresponded to a Borg scale-value of four to five. In the second study, an additional third training session was conducted at home. According to their specific goals, patients could either choose to do an additional strength session with strength bands or an endurance training with walking or cycling for 30 min.

2.2.2. Nutritional counseling

The nutritional intervention by a registered dietitian comprised an extensive initial nutritional assessment followed by individual nutritional measures, i.e., enrichment of foods or energy- and protein-rich snacks. The patients' nutritional situations were reassessed after 6 weeks and 3 months after the baseline-assessment. Further visits could be arranged as required throughout this period, depending on the clinical and nutritional course. The main objective of the nutritional intervention was for patients to meet protein requirements set at 1.2 g of protein per kg of actual body weight. The energy requirement was calculated according to the Harris-Benedict formula, taking into account factors for disease severity and activity (21). In case of a BMI > 28 kg/m^2, the energy requirement was calculated using the adjusted body weight. In both trials, nutritional supplements were given to the patients in the intervention group: protein-dense oral nutritional supplements in the first and a leucine-rich whey protein supplement in the second study.

2.3. Assessment

2.3.1. Nutritional status

Patients were weighed without shoes and in light clothing. Body composition was assessed using bioelectrical impedance analysis (Body Composition Monitor, Fresenius Medical Care, Switzerland respectively BIA, Akern STA, Florence, Italy). In addition, the nutritional risk screening 2002 (NRS-2002) (22) was conducted. Handgrip strength was measured in the dominant hand using a hydraulic dynamometer (Jamar, Smith and Nephew, Memphis, TN, USA). The test was performed with patients in sitting position holding the elbow flexed at 90° and the forearm and wrist in neutral position. The test was repeated three times with a 1-min rest period between each repetition. The best result of the three measurements was recorded in kilograms (kg) (23, 24).

2.3.2. Dietary intake

After each study assessment, patients were asked to keep a non-consecutive 3-day food diary, including one weekend day, and to record the amount of all ingested foods, beverages, food fortifications, and supplements. The diary was explained with the help of a detailed manual. Volumes and portion sizes were estimated using a photo catalog containing several pictures of serving sizes, which was also handed out to the patients. Portion size was classified into three categories: small, medium, or large. All dietary records were analyzed by the same person, using the software "PRODI 6.2 basis" in the first respectively "6.7 swiss" in the second study (Nutri-Science GmbH, Hausach, Germany).

2.3.3. QoL

Quality of life (QoL) was determined with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC QLQ-C30). The EORTC QLQ-C30 is a 30-item cancer-specific questionnaire including six function scales (physical, emotional, cognitive, social, role and global health status), three symptom scales (fatigue, pain, nausea/vomiting), and six single items assessing the symptoms and financial impact of the disease. Results of the EORTC QLQ-C30 were translated into scores corresponding to a scale of 0 to 100. Higher scores on the function scales indicate better functioning, whereas higher scores on the symptom scales denote impaired functioning (25, 26).

10.3389/fnut.2023.1063279

TABLE 1 Baseline characteristics of study patients, given are means ± standard deviation, or number with proportion in percent, respectively.

	Total (*n* = 110)	Intervention (*n* = 56)	Control (*n* = 54)
Age (years)	63.0 (± 10.2)	63.0 (± 11.1)	63.0 (± 9.2)
BMI (kg/m^2)	25.3 (± 4.8)	25.0 (± 4.6)	25.8 (± 4.9)
Days since diagnosis	592.6 (± 847.9)	419.7 (± 535.5)	772.0 (± 1056.7)
Gender			
Male	68 (61.8%)	36 (64.3%)	32 (59.3%)
Female	42 (38.2%)	20 (35.7%)	22 (40.7%)
Site of primary tumor			
Lung	42 (38.2%)	23 (41.1%)	19 (35.2%)
Colorectal	25 (22.7%)	14 (25.0%)	11 (20.4%)
Pancreatic	20 (18.2%)	9 (16.1%)	11 (20.4%)
Others	23 (20.9%)	10 (17.9%)	13 (24.1%)
Laboratory parameters			
CRP (mg/l)	12.0 (± 23.0)	12.8 (± 23.3)	10.9 (± 23.3)
Albumin (g/l)	40.1 (± 4.1)	40.5 (± 4.4)	39.6 (± 3.8)
Performance status (WHO)			
0	11 (10.0%)	7 (12.5%)	4 (7.4%)
1	75 (68.2%)	38 (67.9%)	37 (68.5%)
2	21 (19.1%)	11 (19.6%)	10 (18.5%)
Unavailable	3 (2.7%)		

2.3.4. Clinical data

C-reactive protein (CRP), adverse and serious adverse events and unplanned hospital admissions were evaluated based on computerized patient hospital records.

2.4. Statistical analysis

Statistical analyses were performed using the programming language R version 3.6.0 (R Foundation, Vienna, Austria). We used Student's *t*-test to compare changes in values within the 3 and 6 month period, respectively. If variable distribution were not approximately of Gaussian distribution, we applied the Mann-Whitney *U* test. To be able to use all datasets as sensitivity analyses, and since the missing values were assumed not to be completely at random, we used 20-fold multiple imputation by chained equations to estimate the missing values (27) implemented in the package "mice." The number of imputations was chosen as the maximum percentage of missing variables according to recommendations of White et al. (28). For the imputation, 99 relevant variables were used. *T*-tests for imputed data were done using the packages "MKmisc" and "mitools." Since numbers within the intervention and control group were small, we also applied regression models to adjust for covariables. Mortality was analyzed using the Cox proportional hazard model with the period between beginning of the trial and death as underlying time-scale.

3. Results

In total, 110 patients were included in the pooled analysis (58 from the first and 52 from the second study). The baseline characteristics are shown in Table 1. 68 men (61.8%) and 42 women (38.2%) were randomized either in the intervention (n = 56) or control (n = 54) group. The mean age was 63.0 ± 10.2 years, and the average body mass index (BMI) was 25.3 kg/m^2. Patients with lung cancer constituted the largest group with (n = 42, 38.2%), followed by patients with colorectal (n = 25, 22.7%) and pancreatic cancer (n = 20, 18.2%). At study inclusion, the groups were well-balanced with regard to demographics, medical characteristics, nutritional status and physical function. Groups were different, though, regarding the days that had passed from first tumor diagnosis to trial start: 419.7 ± 535.5 days for intervention and 772.0 ± 1056.7 days for control patients.

The inter-group difference for changes in BMI, body compartments, NRS, dietary intake, global health status and all symptoms of the EORTC were not statistically significant after 3 and 6 months (Table 2). The inter-group difference for changes in phase angle after 6 months was significant after *t*-test (p = 0.025), but not anymore after adjustment for covariates (Table 2).

Importantly, handgrip strength improved significantly from 34.4 ± 10.2 kg at baseline to 36.3 ± 9.9 kg at 3 months in the intervention group compared to 33.9 ± 9.2 kg at baseline to 34.9 ± 9.1 kg at 3 months in the control group (p = 0.006), both after *t*-test as well as after adjustment for covariates (Tables 2, 3).

Patients in the intervention group joined a mean of 16.3 ± 6.3 of 24 training sessions at the hospital (67.9%). The mean number of individual nutritional counseling sessions was 3.5 ± 1.1 (116.7%). No serious adverse events relating to the nutrition and physical exercise program occurred. There was neither a significant inter-group difference in the average of unplanned hospital admissions nor in the survival time (Table 4).

The covariates "CRP" and "days from first diagnosis to randomization" were significantly associated with survival time. Patients with higher CRP value had a shorter survival time. A detailed analysis of survival time for the three main diagnoses (lung, colorectal, and pancreatic cancer) showed that in patients with lung cancer, the covariates "CRP value," "days from first diagnosis to randomization," and "gender" were significantly associated with survival time. Female patients had a shorter survival time than male patients in our analysis. The analysis for patients with colorectal cancer showed no significant associations at all. Patients with pancreatic cancer randomized to the control group had a 20% shorter survival time than patients in the intervention group (p = 0.048), though.

4. Discussion

Data from two randomized intervention trials with advanced cancer patients were included in a pooled analysis regarding nutritional status and survival time. Handgrip strength, as an indicator for muscle strength and associated with short- and long-term mortality and morbidity (24, 29, 30), was the only parameter that showed significant improvement through the implementation of a combined therapy. No significant changes were detected in

TABLE 2 Changes of nutritional status and quality of life after 3 and 6 months.

	Baseline		Δ 3 months				Δ 6 months			
	Intervention	Control	Intervention	Control	*p*	95% CI	Intervention	Control	*p*	95% CI
BMI (kg/m^2)	24.8 ± 4.1	25.9 ± 5.4	0.55	0.28	0.355	−0.83, 0.30	0.64	0.60	0.908	−0.74, 0.66
NRS	2.0 ± 1.0	1.9 ± 1.1	−0.28	0.09	0.092	−0.06, 0.81	−0.34	−0.14	0.241	−0.14, 0.54
Phase angle (°)	5.1 ± 1.0	5.3 ± 0.8	0.06	−0.12	0.199	−0.46, 0.10	**0.12**	**−0.20**	**0.025**	**−0.61, −0.04**
Lean tissue mass (kg)	54.1 ± 21.2	56.2 ± 19.9	−0.10	0.18	0.740	−1.39, 1.95	−0.75	0.26	0.356	−1.16, 3.19
Hand strength (kg)	34.4 ± 10.2	33.9 ± 9.2	**1.79**	**−0.53**	**0.006**	**−3.93, −0.69**	1.25	0.55	0.422	−2.44, 1.03
Energy intake (kcal)	2213.8 ± 689.4	2098.6 ± 738.5	30.14	−142.73	0.251	−470.25, 124.53	−145.41	−229.41	0.560	−370.96, 202.96
Energy intake (%)	97.6 ± 30.9	90.7 ± 33.7	−0.27	−6.89	0.318	−19.71, 6.48	−6.93	−8.32	0.818	−13.41, 10.64
Protein intake (g)	87.8 ± 25.9	79.6 ± 29.9	6.07	−3.65	0.082	−20.69, 1.25	−4.68	−11.24	0.311	−19.43, 6.31
Protein intake (%)	110.7 ± 41.3	95.6 ± 47.2	−10.82	−11.37	0.958	−20.92, 19.83	−23.20	−34.58	0.360	−35.99, 13.24
Carbohydrate intake (g)	241.5 ± 87.9	233.0 ± 91.0	3.56	−0.20	0.845	−41.81, 34.29	−15.12	−12.72	0.895	−33.83, 38.63
Fat intake (g)	90.8 ± 36.5	85.9 ± 34.6	−2.02	−14.45	0.124	−28.33, 3.48	−7.66	−13.24	0.484	−21.45, 10.29
Global health status	65.8 ± 21.0	58.2 ± 19.8	2.16	5.00	0.463	−4.81, 10.50	5.03	4.52	0.913	−9.91, 8.88

NRS, nutritional risk screening; CI, confidence interval; bold = significant.

TABLE 3 Regression analysis of change of handgrip strength (kg) after 3 months.

	β	*p*
Handgrip strength baseline	**−0.221**	**0.002**
Intervention group	**2.702**	**0.002**
Female	**−3.672**	**0.005**
Age (years)	**−0.101**	**0.025**
CRP (mg/l)	**−0.775**	**0.046**

R^2 = 0.190, *p*-value of F-statistic = 0.001, 95% CI = −1.945, 2.107, bold = significant.

any of the other parameters, such as BMI, NRS, lean body mass, phase angle, energy, and protein intake, as well as QoL, though. In addition, we observed associations between survival time and several parameters, such as CRP. In our analysis, patients with pancreatic cancer randomized to the intervention group had a 20% longer survival time.

Our results for nutritional status and QoL concur with the results of other trials investigating combined or multimodal therapies in advanced cancer patients (7, 31–33). In line with our results, an improvement in handgrip strength was observed (31) but further effects on muscle mass (7, 32) or QoL could not be detected (34). In contrast to our results, Henke et al. (33) described a clear improvement in physical function (33), and both Schink et al. (34) and Stuecher et al. (35) observed a significantly higher muscle mass (34, 35). Our results emphasize that muscle strength can be affected by a combined therapy including physical exercise due to muscular adaptation, which can lead to a greater increase in muscle strength than in muscle mass (36).

The reasons why multimodal interventions seldom effect significant changes could be multifaceted. Dhillon et al. (32) described the possibility of contamination or selection bias, when patients who were highly motivated to participate in an exercise program started to exercise more, even though they were randomized to the control group. This effect may have a high impact on the results by minimizing inter-group differences (32).

A second reason could be the heterogeneity of our study population. To achieve our sample size, we had to include patients with different diagnoses. Albeit focusing on patients with cancer types that are commonly associated with malnutrition (such as lung or pancreatic cancer), the state of malnutrition or cancer cachexia was no inclusion criteria. Jain et al. (37) investigated "the impact of baseline nutritional and exercise status on toxicity and outcomes in phase I and II oncology clinical trials" and found that patients with baseline malnutrition had poor outcomes. Hence, to strengthen trial results, the baseline nutritional and exercise status should be taken into consideration (37).

A third reason could be a particular imbalance between the study arms in both our trials: for patients in the control group, a substantially longer period had passed between diagnosis and study randomization than for those in the intervention group. Regarding this variable, the randomization inexplicably did not ensure a balanced distribution. On the one hand, it could be speculated that patients who have suffered from their tumor disease for a longer time could be in a worse general condition. On the other hand, these patients could have achieved a more stable general condition. Ultimately, the effect of this imbalance remains unclear.

Fourth, advanced cancer patients are dealing with a dynamic disease situation. Thus, potential positive effects of the intervention on QoL or other aspects might be overridden by the negative impact of disease progression (38).

Fifth, caloric intake and coverage of energy and protein requirements presented a small positive trend for the intervention, but no statistical significance. The large scatter in the data could be one reason for the failed significance. Since the intervention patients showed good adherence to the training and nutritional counselling sessions and adequately implemented the nutritional recommendations, we can rather exclude bad adherence to the study program as a principal reason for the wide scattering of the

10.3389/fnut.2023.1063279

TABLE 4 Analysis of survival time for different tumor diagnoses.

		Parameter estimate	Risk ratio	*p*-value
Lung cancer patients (n = 40, events n = 33)	Intervention group	0.281	1.325	0.501
	Female	**−1.000**	**0.368**	**0.016**
	Age (years)	0.005	1.005	0.813
	Days since diagnosis*	**−0.506**	**0.603**	**0.002**
	CRP (mg/l)*	**0.567**	**1.764**	**0.002**
Colorectal cancer patients (n = 21, events n = 16)	Intervention group	−0.316	0.729	0.667
	Female	−0.037	0.964	0.959
	Age (years)	0.042	1.043	0.149
	Days since diagnosis*	−0.553	0.593	0.175
	CRP (mg/l)*	0.255	1.290	0.407
Pancreatic cancer patients (n = 18, events n = 18)	**Intervention group**	**−1.191**	**0.304**	**0.048**
	Female	1.047	2.848	0.196
	Age (years)	**−0.089**	**0.915**	**0.027**
	Days since diagnosis*	0.395	1.485	0.303
	CRP (mg/l)*	**0.844**	**2.326**	**0.026**

Survival time was analyzed using the Cox propotion hazard model with period between beginning of the trial and death/censoring as underlying time scale, *log-transformed, bold = significant.

data. Ester et al. (39) conducted a feasibility trial of a "multimodal exercise, nutrition and palliative care intervention in advanced lung cancer patients." While they could not find a significant change in energy and protein intake, either, they observed a 75% class attendance, which is in line with our results (39).

In the follow-up analysis after 6 months, no parameter changed significantly between the two groups in comparison to the baseline level. The results of the intervention group seem to converge with the control group, although they have not yet reached the same level. A statement on possible long-term effects cannot be made with our study results.

Even though our nutrition and exercise program showed no significant positive effect on unplanned hospital admissions, adverse events and survival time in our pooled analysis, no negative inter-group impact could be observed, either. This is an important finding with regard to the safety of combined or multimodal programs and in line with several other trials. Combined trials including nutritional and physical therapy seem to be safe and feasible for advanced cancer patients (7, 15, 19, 40).

The patients' survival time was analyzed depending on the three main diagnoses lung, pancreatic and colorectal cancer in this pooled analysis. We observed a significant association between survival time and the combined intervention in patients with pancreatic cancer. To date, survival has only been analyzed in few studies, and in particular, the impact of a combined program on different tumor diagnoses has not yet been conclusively investigated. Bargetzi et al. (41) conducted "a secondary analysis of a prospective randomized trial, comparing the effect of protocol-guided individualized nutritional support to standard hospital food on the mortality of hospitalized cancer patients." They found significant improvements in mortality and other outcomes in the intervention group in the short-term. However, interaction tests did not show any significant differences in mortality across the cancer type subgroups (41). In the future, more studies should be conducted with a research focus on survival, as it is undeniably an important outcome.

Three intervention studies are currently ongoing in which multimodal therapy options in cancer patients are investigated: First, the "Multimodal–Exercise, Nutrition and Antiinflammatory medication for Cachexie trial (MENAC)" (7), second, the "Nutrition and Exercise in elderly patients with advanced non-small cell lung or pancreatic cancer study (NEXTAC TWO)" (42) and third, the "Multimodal intervention care on cachexia in patients with advanced cancer (MIRACLE)" (43). We are eagerly awaiting the results of these studies to further discuss our own results, especially because disability free survival is the primary endpoint in the NEXTAC TWO trial (42, 44).

Our pooled analysis has some limitations. First, only two trials could be included, and in both studies, the calculated sample size could not be reached. Notably, the problem of not achieving the sample size and the reasons why patients decline study participation – especially in trials with advanced cancer patients – should get addressed in future studies. Bland et al.'s qualitative study (2022) focused on how people with advanced cancer and cachexia perceive exercise and identified barriers that keep them from exercising, such as, for example, fatigue. They concluded that cancer patients should get offered a combination of home-based and supervised options for exercise: "Combining unsupervised home-based with supervised exercise, which may include incorporating telehealth, may help balance patient exercise preferences that we identified in the current study" (45).

Second, the nutrition and exercise interventions in the two studies were not identical. In the second study, patients were instructed to perform an additional, third exercise session at home, and a leucine-rich supplement was used as part of the nutritional intervention.

The third and main limitation is the imbalance between the two groups. For patients in the control group, a longer period had passed between diagnosis and study randomization than for

those in the intervention group, and the influence of this imbalance remains unclear.

In conclusion, the pooled analysis showed a significant improvement in handgrip strength in advanced cancer patients that had participated in a combined therapy. An impaired handgrip strength is an indicator of increased complications during hospital stays and decreased physical status (24). Hence, handgrip strength is associated with mortality and morbidity and is consequently of prognostic significance in hospitalized patients. However, no improvements in further tests were detected. There is great need for further investigations examining the effects of nutritional and exercise therapy, especially on survival time with focus on different cancer diagnoses.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Kantonale Ethikkommission Zürich, Stampfenbachstrasse 121, 8090 Zürich. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PB was the principal investigator in both studies. AU and LS were in charge of the study and data collection. LS and LG were in charge of writing the manuscript. PM conducted statistical analysis. All authors contributed to the analysis of the data, writing of the manuscript, and read and approved the final manuscript.

Funding

Both studies were funded by grants provided by the Krebsforschung Schweiz (Swiss Cancer Research), Number: KFS-2833-08-2011 and KFS-3495-08-2014. In addition, one study received financial support by the Werner und Hedy Berger-Janser Stiftung.

Acknowledgments

We thank all the physicians of the cancer center for helping to identify and recruit patients for both studies. We also thank the staff of the Nutrition and Dietetics team and the Institute of Physical Therapy for supporting the two trials.

Conflict of interest

PM was employed by company Corvus, Statistical Analysis Consulting, Altkalen, Germany.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Argiles J, Busquets S, Felipe A, Lopez-Soriano F. Molecular mechanisms involved in muscle wasting in cancer and ageing: cachexia versus sarcopenia. *Int J Biochem Cell Biol.* (2005) 37:1084–104. doi: 10.1016/j.biocel.2004.10.003

2. Bozzetti F, Group S. Screening the nutritional status in oncology: a preliminary report on 1,000 outpatients. *Support Care Cancer.* (2009) 17:279–84. doi: 10.1007/s00520-008-0476-3

3. Dewys W, Begg C, Lavin P, Band P, Bennett J, Bertino J, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern cooperative oncology group. *Am J Med.* (1980) 69:491–7. doi: 10.1016/S0149-2918(05)80001-3

4. Fearon K, Strasser F, Anker S, Bosaeus I, Bruera E, Fainsinger R, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* (2011) 12:489–95. doi: 10.1016/S1470-2045(10)70218-7

5. Pirlich M, Schutz T, Norman K, Gastell S, Lubke H, Bischoff S, et al. The German hospital malnutrition study. *Clin Nutr.* (2006) 25:563–72. doi: 10.1016/j.clnu.2006.03.005

6. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. *Clin Nutr.* (2008) 27:5–15. doi: 10.1016/j.clnu.2007.10.007

7. Solheim T, Laird B, Balstad T, Stene G, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. *J Cachexia Sarcopenia Muscle.* (2017) 8:778–88. doi: 10.1002/jcsm.12201

8. Bosaeus I. Nutritional support in multimodal therapy for cancer cachexia. *Support Care Cancer.* (2008) 16:447–51. doi: 10.1007/s00520-007-0388-7

9. Fearon K. Cancer cachexia: developing multimodal therapy for a multidimensional problem. *Eur J Cancer.* (2008) 44:1124–32. doi: 10.1016/j.ejca.2008.02.033

10. Prado C, Purcell S, Laviano A. Nutrition interventions to treat low muscle mass in cancer. *J Cachexia Sarcopenia Muscle.* (2020) 11:366–80. doi: 10.1002/jcsm.12525

11. Grande A, Silva V, Riera R, Medeiros A, Vitoriano S, Peccin M, et al. Exercise for cancer cachexia in adults. *Cochrane Database Syst Rev.* (2014) 11:CD010804. doi: 10.1002/14651858.CD010804.pub2

12. Grande A, Silva V, Sawaris Neto L, Teixeira Basmage J, Peccin M, Maddocks M. Exercise for cancer cachexia in adults. *Cochrane Database Syst Rev.* (2021) 3:CD010804. doi: 10.1002/14651858.CD010804.pub3

13. Allan J, Buss L, Draper N, Currie M. Exercise in people with cancer: a spotlight on energy regulation and cachexia. *Front Physiol.* (2022) 13:836804. doi: 10.3389/fphys.2022.836804

14. Avancini A, Sartori G, Gkountakos A, Casali M, Trestini I, Tregnago D, et al. Physical activity and exercise in lung cancer care: will promises be fulfilled? *Oncologist.* (2020) 25:e555–69. doi: 10.1634/theoncologist.2019-0463

15. Hall C, Cook J, Maddocks M, Skipworth R, Fallon M, Laird B. Combined exercise and nutritional rehabilitation in outpatients with incurable cancer: a systematic review. *Support Care Cancer.* (2019) 27:2371–84. doi: 10.1007/s00520-019-04749-6

16. Barnes O, Wilson R, Gonzalo-Encabo P, Kang D, Christopher C, Bentley T, et al. The effect of exercise and nutritional interventions on body composition in patients with advanced or metastatic cancer: a systematic review. *Nutrients.* (2022) 14:2110. doi: 10.3390/nu14102110

17. Uster A, Ruehlin M, Mey S, Gisi D, Knols R, Imoberdorf R, et al. Effects of nutrition and physical exercise intervention in palliative cancer patients: a randomized controlled trial. *Clin Nutr.* (2018) 37:1202–9. doi: 10.1016/j.clnu.2017.05.027

18. Storck L, Ruehlin M, Gaeumann S, Gisi D, Schmocker M, Meffert P, et al. Effect of a leucine-rich supplement in combination with nutrition and physical exercise in advanced cancer patients: a randomized controlled intervention trial. *Clin Nutr.* (2020) 39:3637–44. doi: 10.1016/j.clnu.2020.04.008

19. Pascoe J, Jackson A, Gaskell C, Gaunt C, Thompson J, Billingham L, et al. Beta-hydroxy beta-methylbutyrate/arginine/glutamine (HMB/Arg/Gln) supplementation to improve the management of cachexia in patients with advanced lung cancer: an open-label, multicentre, randomised, controlled phase II trial (NOURISH). *BMC Cancer.* (2021) 21:800. doi: 10.1186/s12885-021-08519-8

20. Schink K, Gassner H, Reljic D, Herrmann H, Kemmler W, Schwappacher R, et al. Assessment of gait parameters and physical function in patients with advanced cancer participating in a 12-week exercise and nutrition programme: a controlled clinical trial. *Eur J Cancer Care.* (2020) 29:e13199. doi: 10.1111/ecc.13199

21. Harris J, Benedict FG. A biometric study of human basal metabolism. *Proc Natl Acad Sci USA.* (1918) 4:370–3. doi: 10.1073/pnas.4.12.370

22. Kondrup J, Allison S, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* (2003) 22:415–21. doi: 10.1016/S0261-5614(03)00098-0

23. Roberts H, Denison H, Martin H, Patel H, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing.* (2011) 40:423–9. doi: 10.1093/ageing/afr051

24. Norman K, Stobaus N, Gonzalez M, Schulzke J, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. *Clin Nutr.* (2011) 30:135–42. doi: 10.1016/j.clnu.2010.09.010

25. Aaronson N, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N, et al. The european organization for research and treatment of cancer qlq-c30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* (1993) 85:365–76. doi: 10.1093/jnci/85.5.365

26. Kaasa S, Bjordal K, Aaronson N, Moum T, Wist E, Hagen S, et al. The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. *Eur J Cancer.* (1995) 31A:2260–3. doi: 10.1016/0959-8049(95)00296-0

27. Van Buuren S, Brand J, Groothuis-Oudshoorn C, Rubin D. Fully conditional specification in multivariate imputation. *J Stat Comput Simul.* (2006) 76:1049–64. doi: 10.1080/10629360600810434

28. White I, Royston P, Wood A. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med.* (2011) 30:377–99. doi: 10.1002/sim.4067

29. Kim J. Handgrip strength to predict the risk of all-cause and premature mortality in Korean adults: a 10-year cohort study. *Int J Environ Res Public Health.* (2021) 19:39. doi: 10.3390/ijerph19010039

30. McGrath R, Johnson N, Klawitter L, Mahoney S, Trautman K, Carlson C, et al. What are the association patterns between handgrip strength and adverse health conditions? a topical review. *SAGE Open Med.* (2020) 8:2050312120910358. doi: 10.1177/2050312120910358

31. Oldervoll L, Loge J, Lydersen S, Paltiel H, Asp M, Nygaard U, et al. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. *Oncologist.* (2011) 16:1649–57. doi: 10.1634/theoncologist.2011-0133

32. Dhillon H, Bell M, van der Ploeg H, Turner J, Kabourakis M, Spencer L, et al. Impact of physical activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. *Ann Oncol.* (2017) 28:1889–97. doi: 10.1093/annonc/mdx205

33. Henke C, Cabri J, Fricke L, Pankow W, Kandilakis G, Feyer P, et al. Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. *Support Care Cancer.* (2014) 22:95–101. doi: 10.1007/s00520-013-1925-1

34. Schink K, Herrmann H, Schwappacher R, Meyer J, Orlemann T, Waldmann E, et al. Effects of whole-body electromyostimulation combined with individualized nutritional support on body composition in patients with advanced cancer: a controlled pilot trial. *BMC Cancer.* (2018) 18:886. doi: 10.1186/s12885-018-4790-y

35. Stuecher K, Bolling C, Vogt L, Niederer D, Schmidt K, Dignass A, et al. Exercise improves functional capacity and lean body mass in patients with gastrointestinal cancer during chemotherapy: a single-blind RCT. *Support Care Cancer.* (2019) 27:2159–69. doi: 10.1007/s00520-018-4478-5

36. Chen L, Nelson D, Zhao Y, Cui Z, Johnston J. Relationship between muscle mass and muscle strength, and the impact of comorbidities: a population-based, cross-sectional study of older adults in the United States. *BMC Geriatr.* (2013) 13:74. doi: 10.1186/1471-2318-13-74

37. Jain R, Handorf E, Khare V, Blau M, Chertock Y, Hall M. Impact of baseline nutrition and exercise status on toxicity and outcomes in phase I and II oncology clinical trial participants. *Oncologist.* (2020) 25:161–9. doi: 10.1634/theoncologist.2019-0289

38. Steindorf K, Clauss D, Tjaden C, Hackert T, Herbolsheimer F, Bruckner T, et al. Quality of life, fatigue, and sleep probelms in pancreatic cancer patients - a randomized trial on the effects of exercise. *Dtsch Arztebl Int.* (2019) 116:471–8. doi: 10.3238/arztebl.2019.0471

39. Ester M, Culos-Reed S, Abdul-Razzak A, Daun J, Duchek D, Francis G, et al. Feasibility of a multimodal exercise, nutrition, and palliative care intervention in advanced lung cancer. *BMC Cancer.* (2021) 21:159. doi: 10.1186/s12885-021-07872-y

40. Heywood R, McCarthy A, Skinner T. Efficacy of exercise interventions in patients with advanced cancer: a systematic review. *Arch Phys Med Rehabil.* (2018) 99:2595–620. doi: 10.1016/j.apmr.2018.04.008

41. Bargetzi L, Brack C, Herrmann J, Bargetzi A, Hersberger L, Bargetzi M, et al. Nutritional support during the hospital stay reduces mortality in patients with different types of cancers: secondary analysis of a prospective randomized trial. *Ann Oncol.* (2021) 32:1025–33. doi: 10.1016/j.annonc.2021.05.793

42. Miura S, Naito T, Mitsunaga S, Omae K, Mori K, Inano T, et al. A randomized phase II study of nutritional and exercise treatment for elderly patients with advanced non-small cell lung or pancreatic cancer: the NEXTAC-TWO study protocol. *BMC Cancer.* (2019) 19:528. doi: 10.1186/s12885-019-5762-6

43. Maeng C, Kim B, Chon J, Kang W, Kang K, Woo M, et al. Effect of multimodal intervention care on cachexia in patients with advanced cancer compared to conventional management (MIRACLE): an open-label, parallel, randomized, phase 2 trial. *Trials.* (2022) 23:281. doi: 10.1186/s13063-022-06221-z

44. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. *J Cachexia Sarcopenia Muscle.* (2019) 10:73–83. doi: 10.1002/jcsm.12351

45. Bland K, Krishnasamy M, Parr E, Mulder S, Martin P, van Loon L, et al. "I want to get myself as fit as I can and not die just yet" - Perceptions of exercise in people with advanced cancer and cachexia: a qualitative study. *BMC Palliat Care.* (2022) 21:75. doi: 10.1186/s12904-022-00948-x

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 02 March 2023
DOI 10.3389/fnut.2023.1000326

OPEN ACCESS

EDITED BY
Clelia Madeddu,
University of Cagliari, Italy

REVIEWED BY
Xiaojing Zheng,
Sun Yat-sen University Cancer Center (SYSUCC), China
Denisse Castro-Eguiluz,
National Council of Science and Technology (CONACYT), Mexico

*CORRESPONDENCE
Xin Jin
✉ jinxinrd@alumni.hust.edu.cn

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 22 July 2022
ACCEPTED 13 February 2023
PUBLISHED 02 March 2023

CITATION
Wang H-B, Xu X-T, Tian M-X, Ding C-C, Tang J, Qian Y and Jin X (2023) Prognostic values of the prognostic nutritional index, geriatric nutritional risk index, and systemic inflammatory indexes in patients with stage IIB–III cervical cancer receiving radiotherapy. *Front. Nutr.* 10:1000326. doi: 10.3389/fnut.2023.1000326

Prognostic values of the prognostic nutritional index, geriatric nutritional risk index, and systemic inflammatory indexes in patients with stage IIB–III cervical cancer receiving radiotherapy

Hong-Bing Wang[1], Xin-Tian Xu[2], Meng-Xing Tian[3], Chen-Chen Ding[3], Jing Tang[4], Yu Qian[5] and Xin Jin[3]*

[1]Department of Gynecology and Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, [2]Department of Pharmacy, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, [3]Department of Clinical Nutrition, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, [4]Department of Lymphoma Medicine, Breast Cancer and Soft Tissue Tumor Medicine, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, [5]Department of Thoracic Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Background: Growing evidence suggests that nutritional status and inflammation are associated with survival in various cancers. This study aimed to evaluate the prognostic value of the prognostic nutritional index (PNI), geriatric nutritional risk index (GNRI), and systemic inflammatory indexes (neutrophil/lymphocyte ratio [NLR], monocyte/lymphocyte ratio [MLR], and platelet/lymphocyte ratio [PLR]) in patients with stage IIB–III cervical cancer receiving radiotherapy.

Results: The ideal cutoff values for the PNI, GNRI, NLR, MLR, and PLR were 48.3, 97.04, 2.8, 0.41, and 186.67, respectively. Low PNI and GNRI scores were associated with poor OS and PFS. High NLR, MLR, and PLR also predicted inferior 5-year OS and PFS rates in patients with stage IIB–III cervical cancer. Multivariate Cox regression analysis identified tumor size, histological type, stage, number of metastatic lymph nodes, PNI, GNRI, NLR, PLR, and MLR as significant prognostic factors for OS and PFS.

Conclusions: The current findings suggest that the PNI, GNRI, NLR, PLR, and MLR are essential parameters for predicting prognosis in patients with stage IIB–III cervical cancer receiving radiotherapy.

KEYWORDS

prognostic nutritional index, geriatric nutritional risk index, systemic inflammatory indexes, cervical cancer, overall survival

1. Introduction

Although largely preventable, cervical cancer is the fourth most common cancer in women in the USA and worldwide (1). In 2020, approximately 604,000 new cases and 341,000 deaths were reported due to cervical cancer (2). Unfortunately, more than two-thirds of women with cervical cancer are diagnosed at advanced stages in developing countries (3, 4). In patients with locally advanced cervical cancer, survival is worse, and the recurrence

rate is higher than that in those with early-stage cancer. The 5-year survival rate ranges from 31 to 55% in patients with locally advanced cervical cancer undergoing optimal treatment such as chemoradiotherapy (5). Staging, nodal involvement, and human papillomavirus infection affect local control and survival and have been used to predict treatment outcomes in patients with cervical cancer (6–8). However, the existing staging systems and other prognostic factors are not perfect to predict prognosis (9). For example, although some patients have the same International Federation of Gynecology and Obstetrics (FIGO) stage, their prognosis is disparate because of their different pathological types (10, 11). In addition, nutrition status is recognized as a critical determinant of quality of life in patients with cancer (12). It is inherently inaccurate to predict the prognosis using only the existing system if the patient is malnourished. Accordingly, several novel prognostic parameters, a model with the existing system, and novel markers are required to predict life expectancy.

Nutritional status is recognized as a critical determinant of quality of life in patients with cancer (12). Several studies have verified that malnutrition, sarcopenia, and cancer cachexia are associated with higher rates of post-treatment complications, lower rates of clinical response, longer hospital stays, and shorter survival times (13–17). In recent studies, several parameters, including nutritional and inflammatory indicators, have been shown to predict the prognosis of different tumors (18–20). PNI, an easily obtained index for evaluating nutritional status by calculating serum albumin levels and absolute lymphocyte counts, was first introduced to predict operative risk in gastrointestinal surgery (21). Several retrospective studies have indicated that the prognostic nutritional index (PNI) is associated with clinical outcomes in many types of cancer (22, 23). The geriatric nutritional risk index (GNRI) is calculated using serum albumin levels and ideal body weight. A low GNRI has also been verified as an independent prognostic factor affecting overall survival (OS) in patients with cancer (24).

Many studies have demonstrated the value of inflammatory cells in the blood and systemic inflammatory responses in the prognosis of patients with various types of tumors (25). A series of systemic inflammatory indexes, such as the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR), can be obtained in an easily available and inexpensive manner. The prognostic roles of NLR, PLR, and MLR have been verified in lung cancer, colorectal cancer, and hepatocellular carcinoma (26–28). For patients with operable cervical cancer, the prognostic value of NLR, PLR, and MLR has been investigated after surgery (29–32). Some studies have also reported the prognostic value of systemic inflammatory indexes in patients with non-surgical cervical cancer. One study reported that NLR and MLR predicted poor OS in patients with cervical cancer; however, only patients with stage IIB cancer were analyzed (33). A retrospective study found that pretreatment NLR and PNI were significant predictors of prognosis in patients with cervical cancer treated with concurrent chemoradiotherapy (34). However, many patients with stage I and IV disease were also included in the aforementioned study, and the prognosis of these patients was significantly different from that of patients with stage II–III disease. Moreover, survival curves and log-rank tests for different PNI/NLR/PLR values were not performed in Haraga et al.'s research. To date, there have been no reports on the impact of PNI, GNRI, NLR, PLR, and MLR on predicting survival time in patients with stage IIB–III disease undergoing radiotherapy (RT). Therefore, this study aimed to retrospectively analyze whether these factors are significantly associated with the prognosis of patients with stage IIB–III disease treated with RT.

2. Methods and materials

2.1. Study population

Data from patients with cervical cancer who underwent RT were collected at the Hubei Cancer Hospital of Huazhong University of Science and Technology. A total of 178 patients were enrolled in this retrospective study from September 2013 to September 2015. Patients with incomplete medical records were excluded. As this was a retrospective study and the data were anonymous, the requirement for informed consent was waived. This study was approved by the Ethics Committee of Hubei Cancer Hospital of Huazhong University of Science and Technology (LLHBCH2021YN-049).

2.2. Data collection

The demographic characteristics, clinical characteristics, and laboratory results of the 178 patients were obtained from medical records. Data on age, body weight, tumor size, tumor stage, serum levels of squamous cell carcinoma (SCC) antigen, number of metastatic lymph nodes, serum albumin, and platelet, neutrophil, lymphocyte, and monocyte counts were collected. The International Federation of Gynecology and Obstetrics (FIGO) 2009 clinical staging system was used for tumor staging. Blood samples were collected before RT. Routine blood tests were performed using the Sysmex XN-9000 Hematology System (Sysmex Corporation, Shanghai, China). Biochemical tests were performed using an ADVIA 2400 Clinical Chemistry System (Siemens Healthineers, Erlangen, Germany). Serum SCC antigen tests were performed using a Cobas e 801 analytical unit (Roche Diagnostics International AG, Rotkreuz, Switzerland) and body weight was measured before treatment. The PNI and GNRI were calculated using the following formulas: PNI = serum albumin (g/L) + 5 × absolute lymphocyte count (10^9/L) and GNRI = [14.89 × serum albumin level (g/dL)] + [41.7 × actual body weight/ideal body weight]. NLR, PLR, and MLR were calculated as neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratios, respectively.

2.3. RT procedures

Patients with cervical cancer (FIGO stages IIB–III) were treated with RT. If possible, after the initiation of RT, cisplatin at a dose of 40 mg/m^2 on the body surface was also administered. A total of 105 patients underwent intensity-modulated RT (IMRT). The gross, clinical, and planned tumor volumes for patients who received IMRT were defined according to the Radiation Therapy Oncology

TABLE 1 The baseline characteristics of 178 patients with cervical cancer.

Patients features	PNI ≤ 48.3	PNI > 48.3	*P*-value	GNRI ≤ 97.04	GNRI > 97.04	*P*-value	NLR ≤ 2.8	NLR> 2.8	*P*-value	MLR ≤ 0.41	MLR > 0.41	*P*-value	PLR ≤ 186.67	PLR> 186.67	*P*-value
No. of patients	78	100		37	141		110	68		141	37		136	42	
Age [mean (SD)]	52.46 (9.06)	54.93 (9.59)		52.57 (9.22)	54.18 (9.47)		54.81 (9.02)	52.29 (9.90)		54.52 (8.89)	51.27 (10.97)		55.55 (9.22)	48.33 (7.88)	
≤55 [n, (%)]	54 (69.23)	47 (47.00)	0.005	26 (70.27)	75 (53.19)	0.093	58 (52.73)	43 (63.24)	0.223	76 (53.90)	25 (67.57)	0.191	66 (48.53)	35 (83.33)	<0.001
>55 [n, (%)]	24 (30.77)	53 (53.00)		11 (29.73)	66 (46.81)		52 (47.27)	25 (36.76)		65 (46.10)	12 (32.43)		70 (51.47)	7 (16.67)	
No. of metastatic lymph nodes															
≤2 [*n*, (%)]	62 (79.49)	86 (86.00)	0.342	27 (72.97)	121 (85.82)	0.107	92 (83.64)	56 (82.35)	0.987	121 (85.82)	27 (72.97)	0.107	115 (84.56)	33 (78.57)	0.503
>2 [*n*, (%)]	16 (20.51)	14 (14.00)		10 (27.03)	20 (14.18)		18 (16.36)	12 (17.65)		20 (14.18)	10 (27.03)		21 (15.44)	9 (21.43)	
Size of metastatic lymph nodes															
≤1 cm [*n*, (%)]	10 (12.82)	11 (11.00)	0.411	2 (5.41)	19 (13.48)	0.024	11 (10.00)	10 (14.71)	0.409	14 (9.93)	7 (18.92)	0.072	13 (9.56)	8 (19.05)	0.035
>1 cm [*n*, (%)]	24 (30.77)	23 (23.00)		16 (43.24)	31 (21.99)		27 (24.55)	20 (29.41)		34 (24.11)	13 (35.14)		32 (23.53)	15 (35.71)	
No metastatic lymph nodes [*n*, (%)]	44 (56.41)	66 (66.00)		19 (51.35)	91 (64.54)		72 (65.45)	38 (55.88)		93 (65.96)	17 (45.95)		91 (66.91)	19 (45.24)	
Size of tumor															
≤4 cm [*n*, (%)]	31 (39.74)	57 (57.00)	0.033	14 (37.84)	74 (52.48)	0.161	64 (58.18)	24 (35.29)	0.005	74 (52.48)	14 (37.84)	0.161	73 (53.68)	15 (35.71)	0.063
>4 cm [*n*, (%)]	47 (60.26)	43 (43.00)		23 (62.16)	67 (47.52)		46 (41.82)	44 (64.71)		67 (47.52)	23 (62.16)		63 (46.32)	27 (64.29)	
Type to radiotherapy															
IMRT [*n*, (%)]	42 (53.85)	63 (63.00)	0.281	19 (51.35)	86 (60.99)	0.382	70 (63.64)	35 (51.47)	0.148	80 (56.74)	25 (67.57)	0.315	78 (57.35)	27 (64.29)	0.536
RT [*n*, (%)]	36 (46.15)	37 (37.00)		18 (48.65)	55 (39.01)		40 (36.36)	33 (48.53)		61 (43.26)	12 (32.43)		58 (42.65)	15 (35.71)	
Pathology															
Squamous cell carcinoma [*n*, (%)]	69 (88.46)	93 (93.00)	0.432	35 (94.59)	127 (90.07)	0.594	101 (91.82)	61 (89.71)	0.834	128 (90.78)	34 (91.89)	1.000	123 (90.44)	39 (92.86)	0.865
Adenocarcinoma [*n*, (%)]	9 (11.54)	7 (7.00)		2 (5.41)	14 (9.93)		9 (8.18)	7 (10.29)		13 (9.22)	3 (8.11)		13 (9.56)	3 (7.14)	
FIGO stage															
II [*n*, (%)]	36 (46.15)	58 (58.00)	0.156	15 (40.54)	79 (56.03)	0.135	63 (57.27)	31 (45.59)	0.173	81 (57.45)	13 (35.14)	0.025	76 (55.88)	18 (42.86)	0.193
III [*n*, (%)]	42 (53.85)	42 (42.00)		22 (59.46)	62 (43.97)		47 (42.73)	37 (54.41)		60 (42.55)	24 (64.86)		60 (44.12)	24 (57.14)	

(Continued)

10.3389/fnut.2023.1000326

10.3389/fnut.2023.1000326

TABLE 1 (Continued)

Patients features	PNI ≤ 48.3	PNI > 48.3	*P*-value	GNRI ≤ 97.04	GNRI > 97.04	*P*-value	NLR ≤ 2.8	NLR> 2.8	*P*-value	MLR ≤ 0.41	MLR > 0.41	*P*-value	PLR ≤ 186.67	PLR> 186.67	*P*-value
SCC antigen															
≤ 1.5 [*n*, (%)]	19 (24.36)	28 (28.00)	0.707	7 (18.92)	40 (28.37)	0.342	32 (29.09)	15 (22.06)	0.39	41 (29.08)	6 (16.22)	0.171	39 (28.68)	8 (19.05)	0.3
> 1.5 [*n*, (%)]	59 (75.64)	72 (72.00)		30 (81.08)	101 (71.63)		78 (70.91)	53 (77.94)		100 (70.92)	31 (83.78)		97 (71.32)	34 (80.95)	
Chemoradiotherapy															
No [*n*, (%)]	2 (2.56)	5 (5.00)	0.659	1 (2.70)	6 (4.26)	1	3 (2.73)	4 (5.88)	0.512	5 (3.55)	2 (5.41)	0.966	6 (4.41)	1 (2.38)	0.89
Yes [*n*, (%)]	76 (97.44)	95 (95.00)		36 (97.30)	135 (95.74)		107 (97.27)	64 (94.12)		136 (96.45)	35 (94.59)		130 (95.59)	41 (97.62)	
Height (cm) [mean (SD)]	157.06 (4.80)	157.22 (4.06)	0.815	156.49 (4.90)	157.33 (4.24)	0.301	156.88 (4.38)	157.59 (4.39)	0.298	157.11 (4.49)	157.32 (4.03)	0.789	156.88 (4.30)	158.02 (4.59)	0.141
Bodyweight (Kg) [mean (SD)]	56.06 (8.01)	58.33 (7.97)	0.062	50.47 (6.00)	59.13 (7.54)	<0.001	58.24 (8.00)	55.87 (7.95)	0.056	57.43 (7.82)	56.96 (8.96)	0.753	57.86 (7.84)	55.62 (8.54)	0.115
ALB (g/L) [mean (SD)]	38.29 (3.30)	43.58 (2.68)	<0.001	36.41 (3.58)	42.54 (2.94)	<0.001	41.84 (3.48)	40.33 (4.51)	0.013	41.79 (3.50)	39.24 (4.91)	<0.001	41.62 (4.14)	40.12 (3.06)	0.031

IMRT, Intensity-modulated radiotherapy; SCC, Squamous cell carcinoma; PNI, Prognostic nutritional index; GNRI, Geriatric nutritional risk index; NLR, Neutrophil/lymphocyte ratio; MLR, Monocyte/lymphocyte ratio; PLR, Platelet/lymphocyte ratio.

Group guidelines. The prescribed dose was 45.0–50.4 Gy. IMRT was delivered at 1.8 Gy per fraction once daily for 5 days per week. A total of 73 patients underwent conventional RT (CRT). CRT was planned using the Eclipse Planning System and was conducted using a Varian 23EX. Conventional RT was delivered using anterior and posterior opposing techniques at a dose of 45.0–50.4 Gy (1.8 Gy per day, 5 days per week). All patients underwent a high dose of ^{192}Ir brachytherapy after whole-pelvic irradiation at a dose of up to 36 Gy.

2.4. Follow-up strategy

Patients were followed up *via* outpatient examinations or telephone calls. The deadline for follow up was December 2019. OS was defined as the time from the start of RT to the date of death or last follow up. Progression-free survival (PFS) was defined as the initiation of RT, occurrence of tumor progression, death from any cause, or the last follow up.

2.5. Statistical analysis

Receiver operating characteristic (ROC) curves were used to determine the optimal PNI, GNRI, PLR, MLR, and NLR cutoff points using MedCalc (MedCalc Software Ltd., Belgium). R software version 4.1.3 (The R Foundation, Vienna, Austria) was used for statistical analysis. For the baseline characteristics of the patients, means and standard deviations are used to express continuous variables. Numbers and percentages are used to express categorical variables. Descriptive analysis using the chi-square test or Fisher's exact test was performed to compare differences between the two groups. Survival curves were calculated using the Kaplan–Meier method, and the log-rank test was used for comparison. Univariate and multivariate analyses were performed for each marker using the Cox proportional hazards model. Variables that were significant in the univariate analysis with P-values < 0.20 were included in multivariate analysis. We applied the nomogram in this study and visualized the prognostic strengths of different factors in predicting OS.

3. Results

3.1. Patient characteristics

The patient characteristics are presented in Table 1. A total of 178 patients with cervical cancer were enrolled in this retrospective study. The mean age was 53.85. Thirty patients out of 178 (16.9%) had more than two positive metastatic lymph nodes. Ninety-four patients (52.8%) had stage II tumors and 84 (47.2%) had stage III tumors, according to the FIGO 2009 clinical staging system. The mean body mass index (BMI) was 23.19 ± 2.88 kg/m^2 with 3.4% of patients being underweight. By setting survival status as an endpoint, ROC curves were used to determine the cutoff values. The cutoff values for the PNI, GNRI, NLR, MLR, and PLR were 48.3, 97.04, 2.8, 0.41, and 186.67, respectively (Figures 1, 2). The mean PNI, GNRI, NLR, MLR, and PLR were 49.37, 102.74, 2.77,

0.3, and 159.26, respectively. Low PNI and GNRI scores were observed in 78 (43.8%) and 37 (20.8%) patients, respectively. Low NLR, MLR, and PLR values were observed in 110 (61.8%), 141 (79.2%), and 136 (76.4%) patients, respectively (Table 1).

3.2. Prognostic value of PNI and GNRI

In this retrospective cohort study, the 5-year OS rate of the entire population was 75.7%. The effect of nutritional status, as determined using the PNI and GNRI, on the prognosis of patients with cervical cancer was evaluated. Kaplan–Meier analysis showed that patients with a low PNI had shorter OS and PFS (low PNI vs. high PNI, 5-year OS, 64.1% vs. 84.9%, $P < 0.001$; 5-year PFS, 62.8% vs. 84.9%, $P < 0.001$) (Figures 3A, 4A). Similar results were obtained for the relationship between a low GNRI and the survival time of patients with cervical cancer (5-year OS, 48.5 vs. 82.2%, $P<0.001$; 5-year PFS, 53.3 vs. 80.9%, $P < 0.001$) (Figures 3B, 4B). Survival analysis stratified by chemoradiotherapy (CRT) showed that patients with low PNI and GNRI values had shorter OS (low PNI vs. high PNI, $P < 0.01$; low GNRI vs. high GNRI, $P < 0.001$) and PFS (low PNI vs. high PNI, $P < 0.001$; low GNRI vs. high GNRI, $P < 0.001$) (Supplementary Figures 1, 2). Patients with a low GNRI had shorter OS ($P < 0.05$) and PFS ($P < 0.05$) than patients with a high GNRI in the survival analysis stratified by RT alone. There was no significant association between low PNI and OS/PFS in the survival analysis stratified by RT alone (Supplementary Figures 3, 4).

3.3. Prognostic value of NLR, MLR, and PLR

The Kaplan–Meier results indicated that survival time differed depending on the NLR, MLR, and PLR. Patients with low NLR, MLR, and PLR had higher OS than patients in the other groups (5-year OS, low NLR vs. high NLR, 85.4 vs. 59.9%, $P < 0.001$; low MLR vs. high MLR, 82.9 vs. 49.9%, $P < 0.001$; low PLR vs. high PLR: 81.5 vs. 57.5%, $P < 0.001$) (Figure 5). We also analyzed the prognostic relationship between the systemic inflammatory indexes and PFS. Similar results were obtained (5-year PFS: low NLR vs. high NLR, 85.3 vs. 59.0%, $P < 0.001$; low MLR vs. high MLR, 82.8% vs. 47.4%, $P < 0.001$; low PLR vs. high PLR, 81.5 vs. 5.6%, $P < 0.001$) (Figure 6). A significant association between low NLR/MLP/PLR and higher OS/FPS was also found in the survival analysis stratified by CRT (OS, $P < 0.001$; PFS $P < 0.001$) (Supplementary Figures 1, 2). In the survival analysis stratified by RT alone, there was no significant association between low NLR/MLP/PLR and OS/PFS (Supplementary Figures 3, 4).

3.4. Univariate and multivariate analyses for patients with cervical cancer

Univariate and multivariate analyses of the baseline characteristics of OS and PFS are shown in Tables 2, 3. In univariate analysis, tumor size, histological type, stage, number of metastatic lymph nodes, PNI, GNRI, NLR, PLR, and MLR were significantly associated with poor OS and PFS. Other factors, including age, type of RT, SCC antigen levels, and body weight, had no effect on cervical cancer prognosis. In univariate Cox regression analysis, the number of metastatic lymph nodes, tumor size, histological type, stage, GNRI, NLR, and MLR were the most significant predictors of OS and PFS, with hazards ratios (HR) higher than 3 or <0.33.

In the multivariate Cox regression analysis, histological type remained the most significant predictor of OS (HR = 3.33; 95% confidence interval [CI], 1.59–7.00; $P = 0.001$) The multivariate analysis identified that PNI (HR = 0.47; 95% CI, 0.25–0.88; $P < 0.01$), GNRI (HR = 0.35; 95% CI, 0.18–0.68; $P = 0.002$), NLR (HR = 2.60; 95% CI, 1.36–4.97; $P = 0.004$), PLR (HR = 2.12; 95% CI, 1.09–4.13; $P = 0.028$), and MLR (HR = 3.21; 95% CI, 1.66–6.23, $P < 0.001$) were also significantly associated with OS. When the follow-up period was changed to PFS, PNI (HR = 0.47; 95%CI, 0.28–0.87; $P = 0.017$), GNRI (HR = 0.34; 95%CI, 0.17–0.65; $P = 0.001$), NLR (HR = 2.66; 95%CI, 1.42–4.97; $P = 0.002$), PLR (HR = 2.05; 95%CI, 1.10–3.80; $P = 0.023$), and MLR (HR = 3.36; 95%CI, 1.76–6.41; $P < 0.001$) were prognostic indicators for PFS, according to the multivariate analyses. In univariate and multivariate Cox regression analyses stratified by CRT, the GNRI, NLR, PLR, and MLR were also prognostic indicators for OS and PFS (Supplementary Tables 1, 2).

3.5. Prognostic nomograms of PNI, GNRI, and systemic inflammatory indexes

To predict the 3-year and 5-year OS of patients with cervical cancer, nomograms were constructed. Based on the results of the multivariate Cox analysis, the prognostic nomogram included tumor size, histological type, stage, number of metastatic lymph nodes, and PNI/GNRI/systemic inflammatory indexes (Figures 7, 8).

4. Discussion

For patients with stage IIB–III cervical cancer, RT and a combination of chemotherapy and RT are the suggested treatment options. The present study demonstrated that a low PNI, low GNRI, high NLR, high MLR, and high PLR were negative prognostic factors for survival in patients with stage IIB–III disease treated with RT.

Similar to other types of cancers, there is a high prevalence of malnutrition among patients with cervical cancer (35). The incidence of malnutrition was reported as high as 38.79% in patients undergoing cervical cancer surgery before treatment (36). Additionally, a higher stage grade indicates a higher incidence of malnutrition in cervical cancer (37). Poor nutritional status at baseline is also associated with poor quality of life and chemotherapy interruption in patients with cervical cancer (38). In clinical practice, the GNRI and PNI are easily obtained, objective, simple, efficient, and applicable tools to reflect nutritional status compared with other methods, such as patient-generated subjective global assessment and mini nutritional assessment. Our results also showed that poor status, as determined by the PNI and GNRI, was

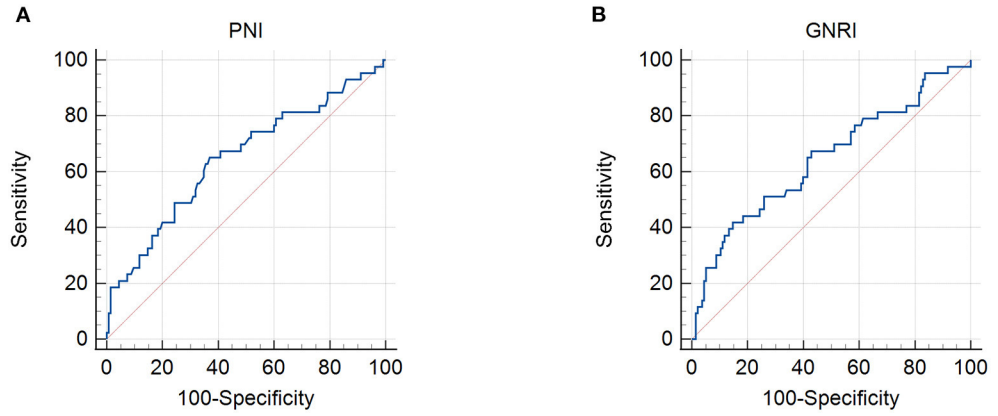


FIGURE 1
Receiver operating characteristic curves for the use of nutritional indicators to predict life expectancy in patients with stage IIB–III cervical cancer receiving radiotherapy based on: **(A)** prognostic nutritional index (PNI) and **(B)** geriatric nutritional risk index (GNRI). Cut-off points with the highest combined sensitivity and specificity were used.

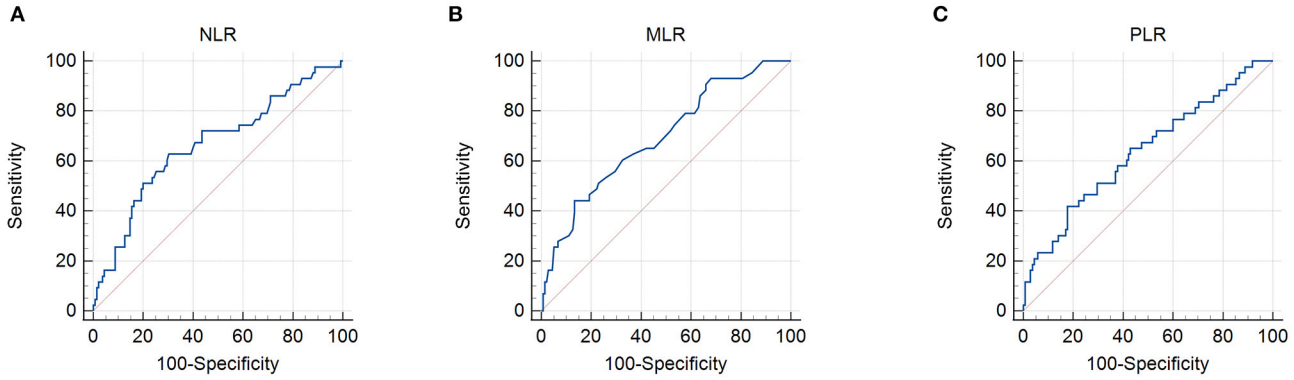


FIGURE 2
Receiver operating characteristic curves for the use of inflammatory indicators to predict life expectancy in patients with stage IIB–III cervical cancer receiving radiotherapy based on: **(A)** neutrophil/lymphocyte ratio (NLR), **(B)** monocyte/lymphocyte ratio (MLR), and **(C)** platelet/lymphocyte ratio (PLR). Cut-off points with the highest combined sensitivity and specificity were used.

associated with shorter OS and PFS. Robust and consistent evidence has shown that cancer-related malnutrition plays a negative role in the prognosis of patients (39–42). Studies have shown that the prevalence of malnutrition in patients with cancer is as high as 80.4% before treatment, and that nutritional status worsens with the progression of anticancer therapies (43, 44). Due to clinically distinct causes, such as dysphagia, stomatitis, bowel obstruction caused by the tumor, and gastrointestinal disorders induced by anticancer therapies, the nutrient intake of patients with cancer is generally reduced (45). In addition, altered metabolism-induced by excess catabolism, anabolic resistance, inflammation caused by tumors, and cancer therapy significantly affect nutritional status (46). These factors lead to weight loss and skeletal muscle depletion in patients with cancer, which are independent risk factors for an unfavorable prognosis. Studies have demonstrated that unintentional weight loss is associated with poor post-operative survival and increased mortality risk in patients with cancer (47–49). The patients with locally advanced cervical cancer receiving primary chemoradiation who had unintentional weight loss $\geq$10% also had a higher risk of death (HR = 2.37) (50). Decreased skeletal muscle mass, widely known as sarcopenia, has also been closely associated with a poor quality of life and short life expectancy (51). Additionally, the common side effects of cytotoxic chemotherapy and RT directly affect the nutritional status of patients, and a poor nutritional status may aggravate these side effects (52). Moreover, the decreased clearance of antitumor drugs in the tissues of patients with malnutrition with a higher drug concentration in the tissue may also lead to a higher rate of treatment toxicity (53). The deterioration of nutritional status can lead to decreased treatment completion (54). Furthermore, loss of body weight with a specific loss of skeletal muscle combined with systemic inflammation caused by tumors results in cancer cachexia (55). Patients with cancer with cachexia have an impaired quality of life, high mortality, and increased treatment costs (46) and currently no effective medical intervention has been confirmed to completely reverse cachexia (56).

An increasing number of studies have shown that cancer-associated systemic inflammatory markers, such as NLR, PLR, and

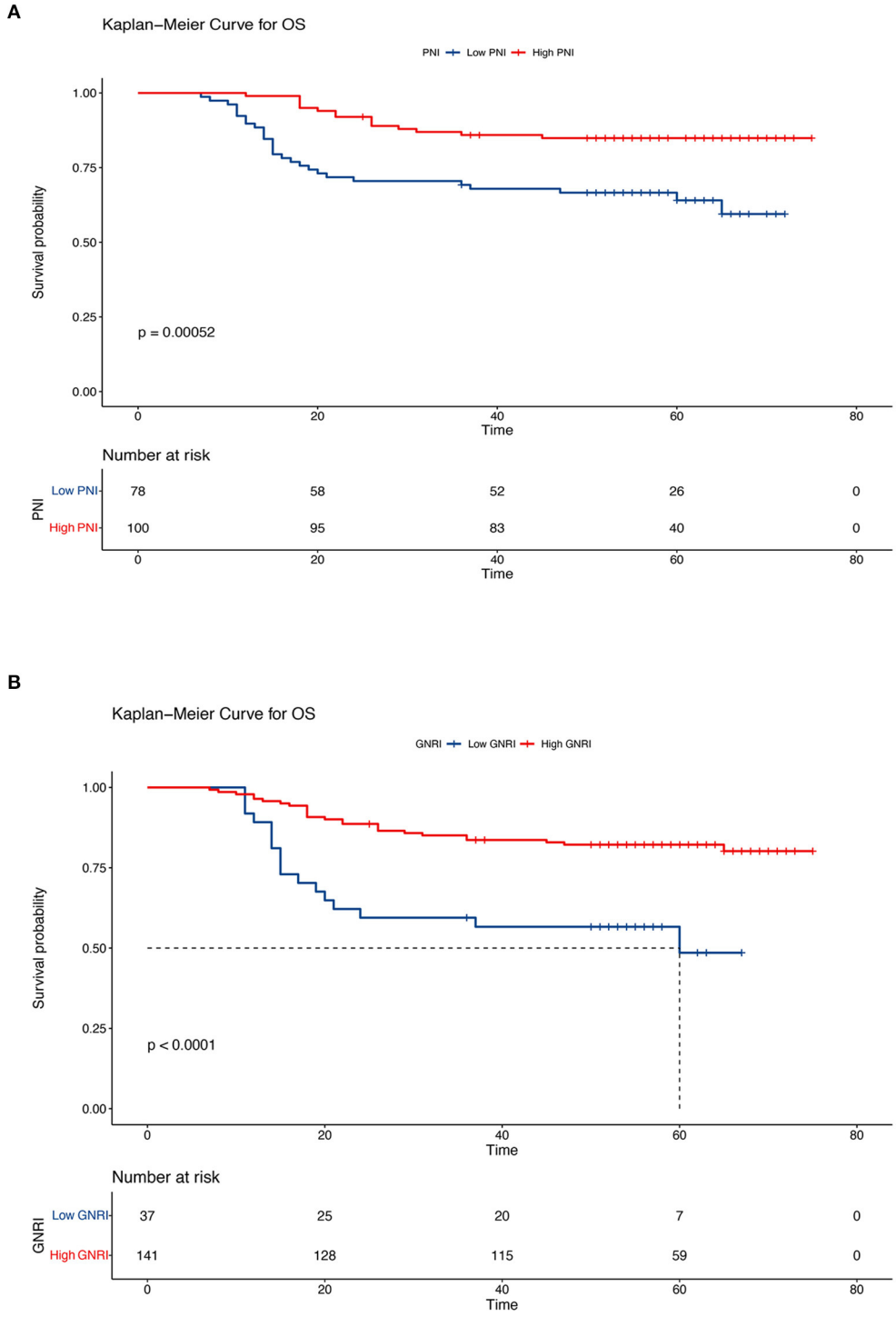


FIGURE 3
Kaplan–Meier curves of overall survival according to the nutritional indicators. **(A)** Low prognostic nutritional index (PNI) vs. high PNI (low PNI: ≤ 48.3, high PNI: > 48.3) and **(B)** low geriatric nutritional risk index (GNRI) vs. high GNRI (low GNRI: ≤ 97.04, high GNRI: > 97.04). The Kaplan–Meier method was used to calculate the survival rate, and the log-rank test was used to compare survival distributions between the groups.

MLR, can be useful in predicting tumor progression. These markers are easily obtained, noninvasive, and inexpensive. Recently, three studies have demonstrated that systemic inflammatory markers are novel independent prognostic factors for predicting post-operative survival in patients with cervical cancer. High NLR, PLR, and MLR are closely related to poor prognosis (29–31). Similarly, our results showed that patients with stage IIB–III cervical cancer who underwent RT with high NLR, PLR, and MLR had shorter OS times. The close relationship between NLR/MLR and tumor prognosis involves tumor-induced inflammation and immune

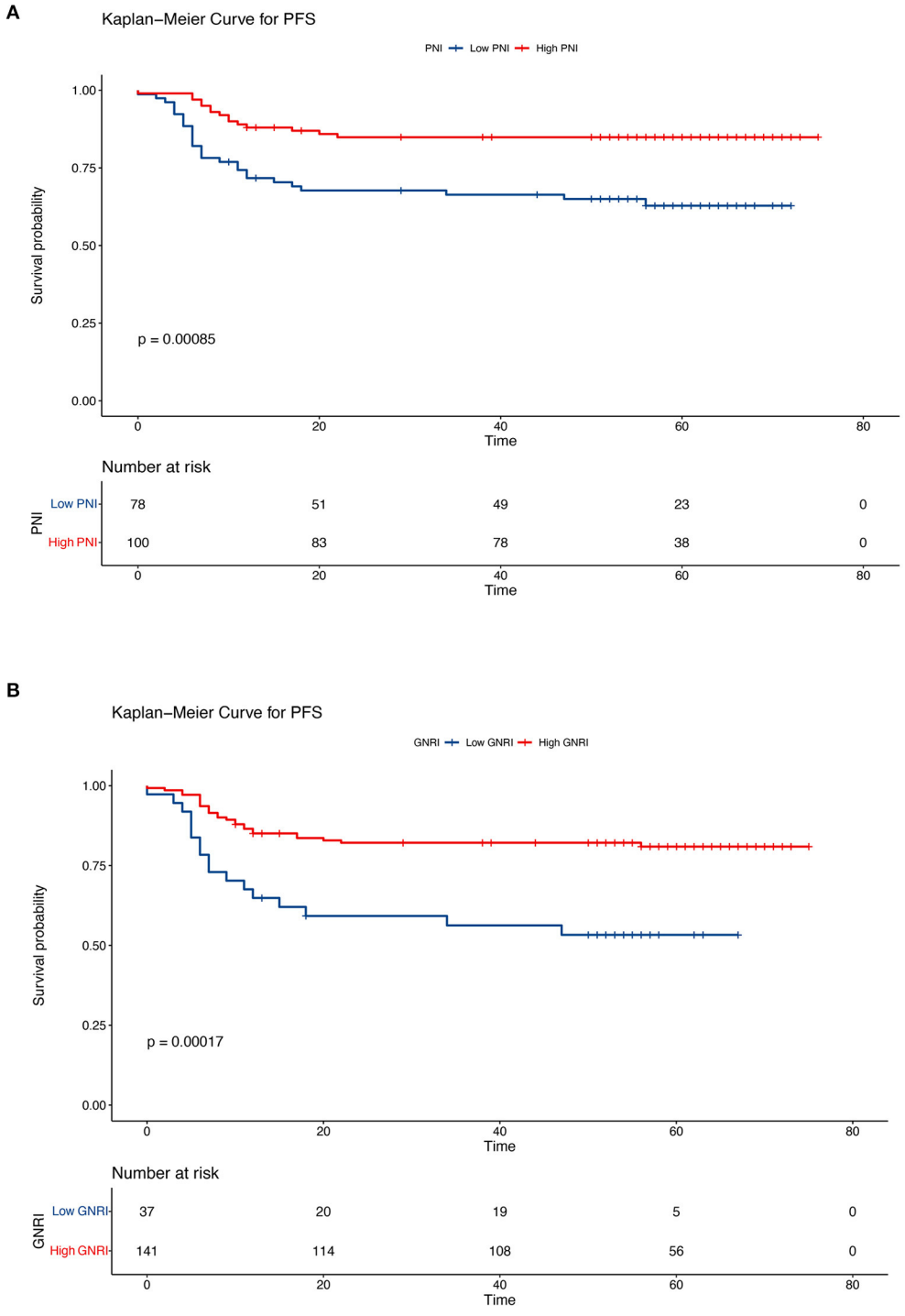


FIGURE 4
Kaplan–Meier curves of progression-free survival according to the nutritional indicators. **(A)** Low prognostic nutritional index (PNI) vs. high PNI (low PNI: ≤ 48.3, high PNI: > 48.3) and **(B)** low geriatric nutritional risk index (GNRI) vs. high GNRI (low GNRI: ≤ 97.04, high GNRI: > 97.04). The Kaplan–Meier method was used to calculate the survival rate, and the log-rank test was used to compare survival distributions between the groups.

function changes. The systemic inflammatory response in patients with tumors is often accompanied by an increase in circulating neutrophil counts (57). Recent studies have found that neutrophils not only exert an anti-tumor effect, but also promote tumor progression (58). Most studies suggest that elevated neutrophil levels lead to tumor progression. The possible mechanisms by which neutrophils promote tumor progression include changes in the microenvironment shaped by cancer cells and release of some growth factors, such as epidermal growth factor and hepatocyte growth factor (59). Monocytes also have diverse functions in

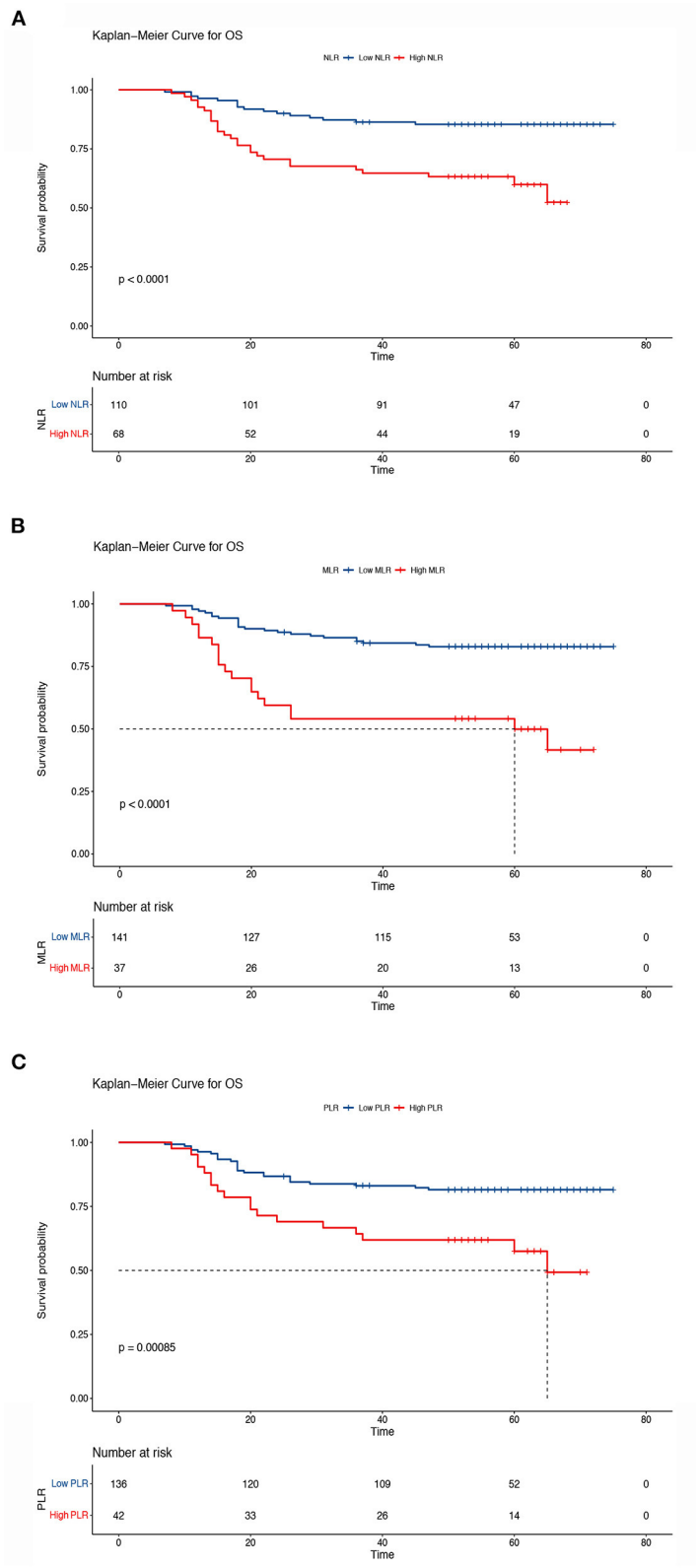


FIGURE 5
Kaplan–Meier curves of overall survival according to the inflammatory indicators. **(A)** Low neutrocyte/lymphocyte ratio (NLR) vs. high NLR (low NLR: ≤ 2.8, high NLR: > 2.8), **(B)** low monocyte/lymphocyte ratio (MLR) vs. high MLR (low MLR: ≤ 0.41, high MLR: > 0.41), and **(C)** low platelet lymphocyte ratio (PLR) vs. high PLR (low PLR: ≤ 186.67, high PLR: > 186.67). The Kaplan–Meier method was used to calculate the survival rate, and the log-rank test was used to compare survival distributions between the groups.

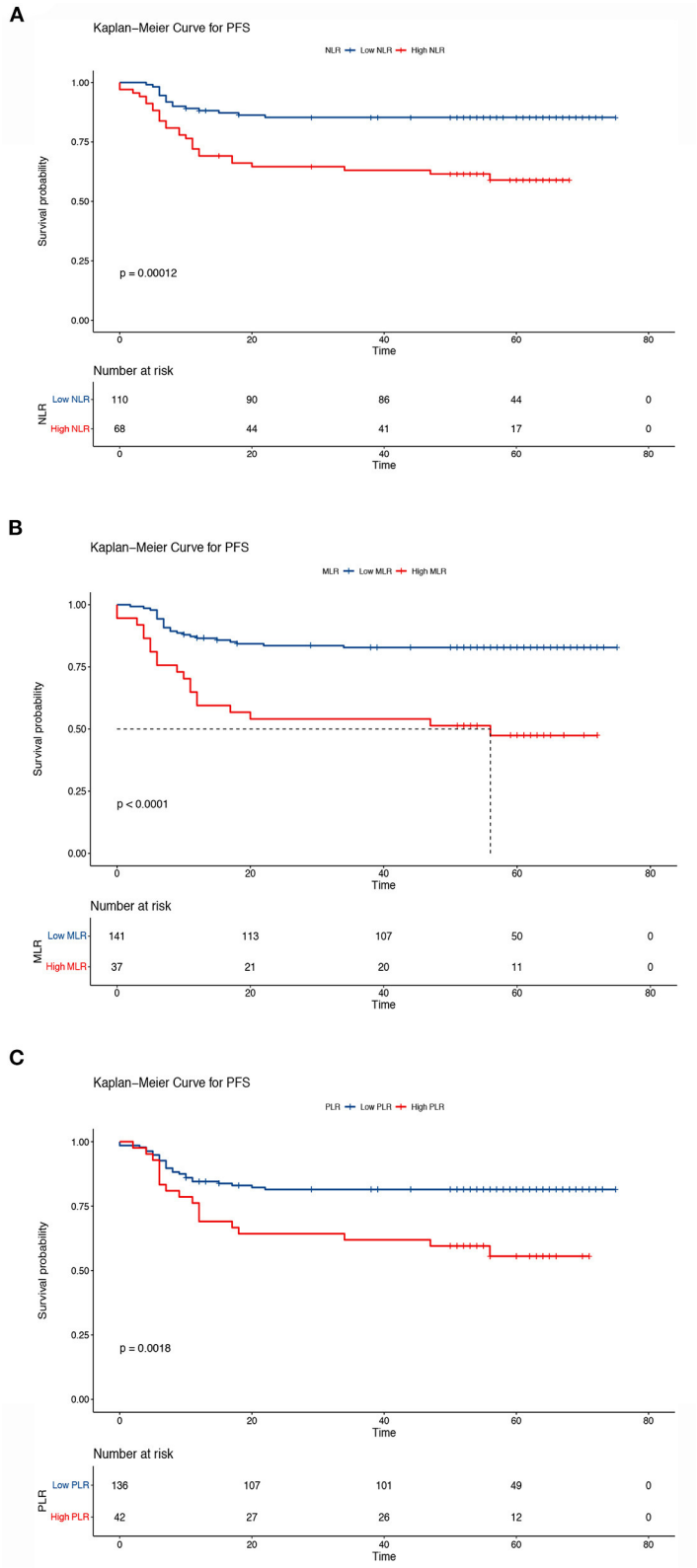


FIGURE 6
Kaplan–Meier curves of progression-free survival according to the inflammatory indicators. **(A)** Low neutrocyte/lymphocyte ratio (NLR) vs. high NLR (low NLR: ≤ 2.8, high NLR: > 2.8), **(B)** low monocyte/lymphocyte ratio (MLR) vs. high MLR (low MLR: ≤ 0.41, high MLR: > 0.41), and **(C)** low platelet/lymphocyte ratio (PLR) vs. high PLR (low PLR: ≤ 186.67, high PLR: > 186.67). The Kaplan–Meier method was used to calculate the survival rate, and the log-rank test was used to compare survival distributions between the groups.

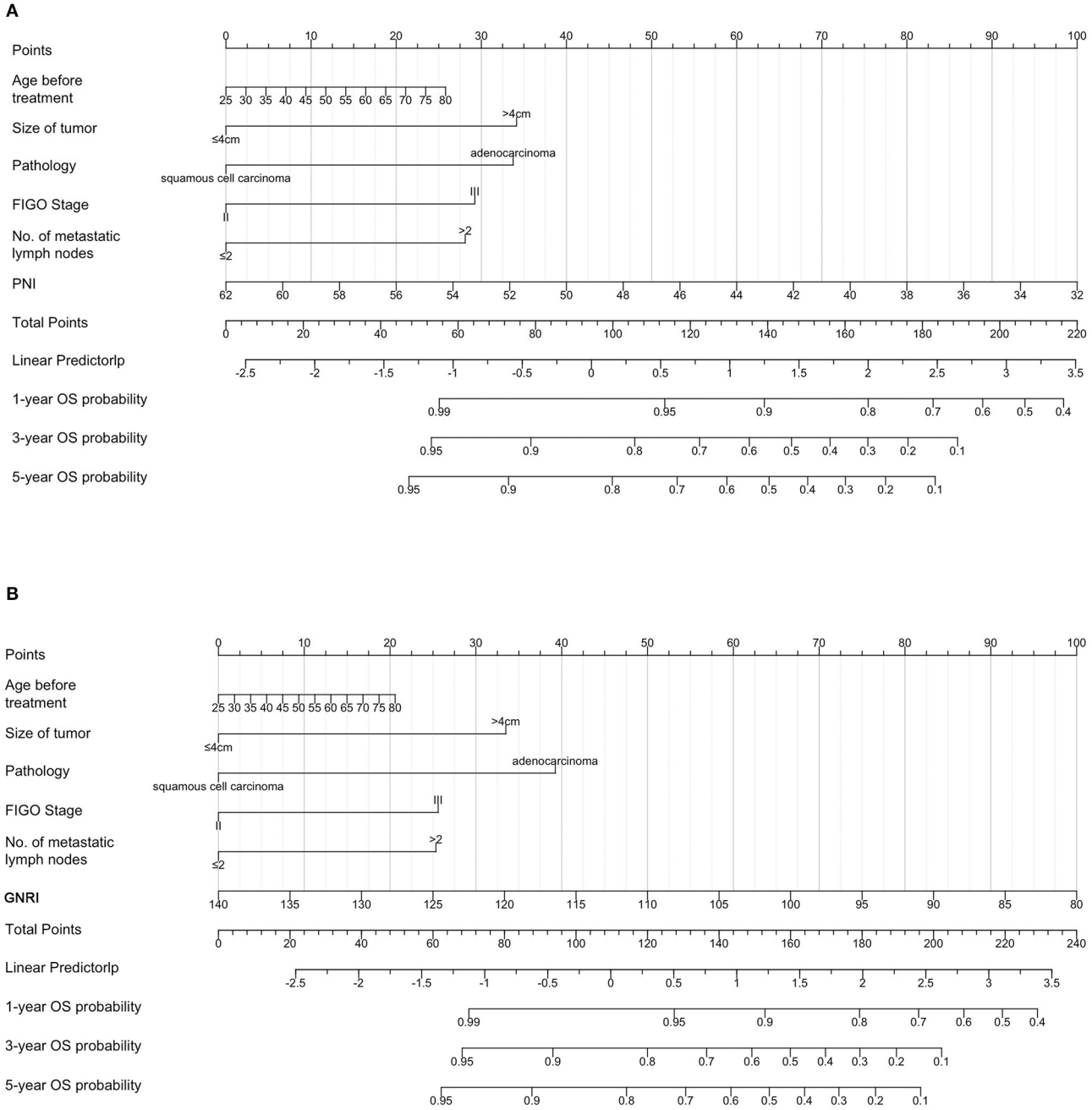


FIGURE 7
Prognostic nomograms for overall survival prediction according to the prognostic nutritional index (PNI) **(A)** and geriatric nutritional risk index (GNRI) **(B)**. Points were assigned for age before treatment, and for tumor size, histological type, stage, number of metastatic lymph nodes, and nutritional indicators. The score of each predictor was determined by drawing a vertical line from the value to the score scale. The total score was summed up by the scores of these predictors, which correspond to overall survival rate.

different types and stages of the tumor (60). The direct tumoricidal functions of monocytes result from cytokine-mediated induction of cell death and phagocytosis and effects on the components of the tumor microenvironment (61). Interestingly, our study also suggests that low PLR is associated with cervical cancer prognosis. This result was inconsistent with Li's finding that PLR was not a significant independent prognostic factor in patients with stage IIB cervical cancer (33). Another study also found that PLR was not associated with OS in gynecological cancer (62). The inconsistent results may be due to the different stages of patients included in the different studies, which could affect the prognosis of cervical cancer. As an essential component of the blood, platelets play an important role in the inflammatory response in patients with cancer with chronic inflammation (63). Angiogenesis is facilitated by the release of pro-angiogenic proteins, such as vascular epidermal growth factor and transforming growth

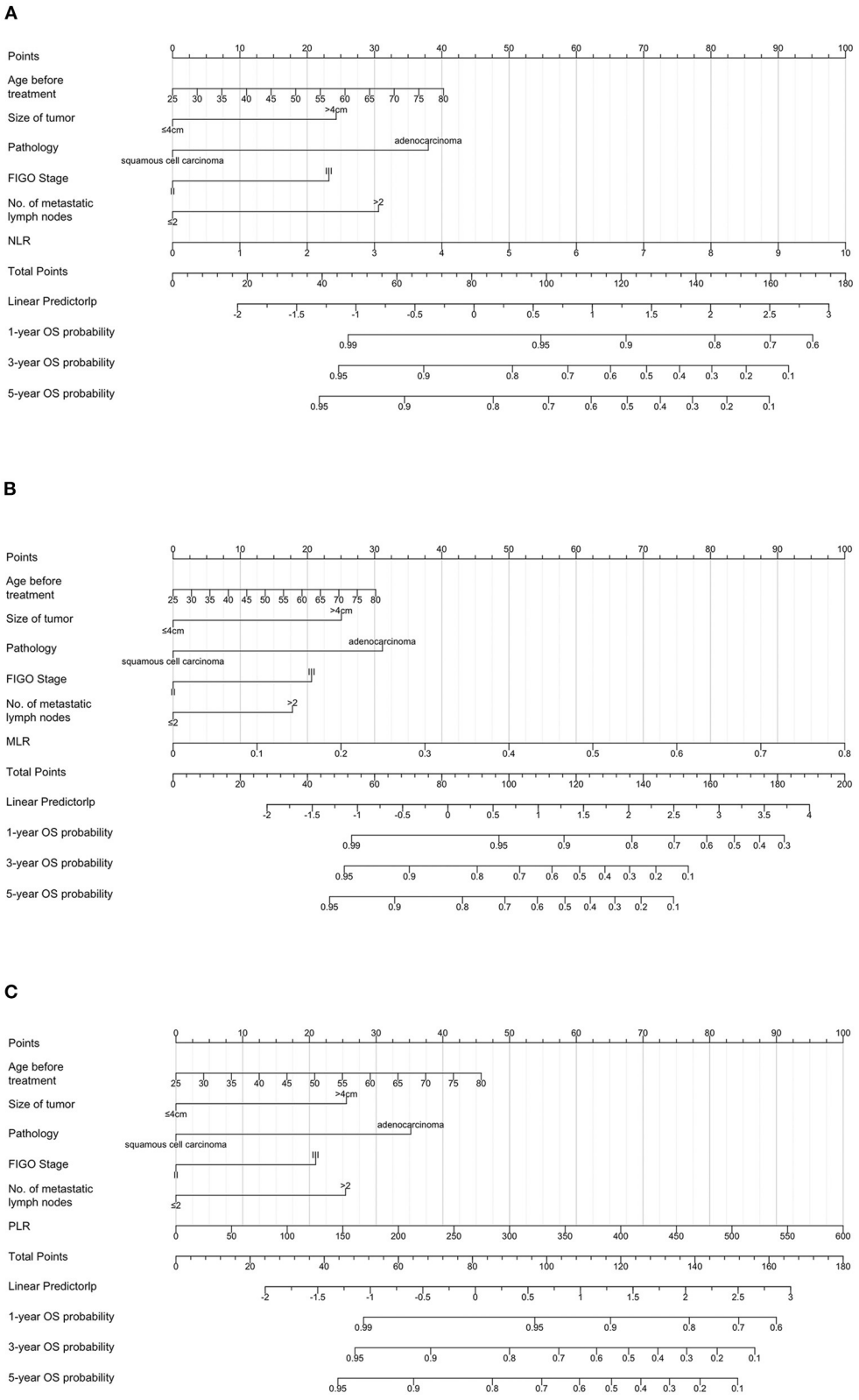


FIGURE 8
Prognostic nomograms for overall survival prediction according to the neutrophil/lymphocyte ratio (NLR) **(A)**, monocyte/lymphocyte ratio (MLR) **(B)**, and platelet/lymphocyte ratio (PLR) **(C)**. Points were assigned for age before treatment, and for tumor size, histological type, stage, number of metastatic lymph nodes, and inflammatory indicators. The score of each predictor was determined by drawing a vertical line from the value to the score scale. The total score was summed up by the scores of these predictors, which correspond to overall survival rate.

TABLE 2 Univariate and multivariate analysis for overall survival.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age				
≤55 vs. >55	0.65 (0.35–1.23)	0.185	0.71 (0.37–1.37)	0.309
No. of metastatic lymph nodes				
≤2 vs. >2	3.11 (1.66–5.83)	<0.001	2.04 (1.04–3.98)	0.036
Size of tumor				
≤4 cm vs. >4 cm	3.34 (1.68–6.63)	0.001	2.34 (1.15–4.74)	0.019
Type of radiotherapy				
IMRT vs. RT	1.21 (0.66–2.21)	0.54	–	–
Chemoradiotherapy				
Yes vs. NO	0.51 (0.16–1.65)	0.26		
Pathology				
squamous cell carcinoma vs. adenocarcinoma	3.7 (1.82–7.52)	<0.001	3.33 (1.59–7.00)	0.001
FIGO Stage				
II vs. III	3.25 (1.67–6.33)	0.001	2.33 (1.17–4.64)	0.016
SCC				
≤ 1.5 vs. > 1.5	1.24 (0.61–2.52)	0.547	–	–
PNI				
≤ 48.3 vs. > 48.3	0.35 (0.19–0.65)	0.001	0.47 (0.25∼0.88)	0.019
GNRI				
≤ 97.04 vs. > 97.04	0.31 (0.17–0.57)	<0.001	0.35 (0.18–0.68)	0.002
NLR				
≤ 2.8 vs. > 2.8	3.26 (1.75–6.06)	<0.001	2.60 (1.36–4.97)	0.004
MLR				
≤ 0.41 vs. > 0.41	3.86 (2.11–7.05)	<0.001	3.21 (1.66–6.23)	<0.001
PLR				
≤ 186.67 vs. > 186.67	2.69 (1.47–4.93)	0.001	2.12 (1.09–4.13)	0.028

IMRT, Intensity-modulated radiotherapy; SCC, Squamous cell carcinoma; PNI, Prognostic nutritional index; GNRI, Geriatric nutritional risk index; NLR, Neutrophil/lymphocyte ratio; MLR, Monocyte/lymphocyte ratio; PLR, Platelet/lymphocyte ratio.

factor, in the tumor microenvironment. The cytokines released by platelets can induce cancer-related inflammation and promote tumor growth and invasion (57).

Many studies have demonstrated that concurrent chemoradiotherapy provides therapeutic benefits over RT alone (64). To explore the prognostic value of the PNI, GNRI, and systemic inflammatory indexes in patients who underwent CRT and RT alone, we performed survival analyses, univariate and multivariate analyses stratified by RT or CRT. The results showed that low GNRI, high NLR, high MLR, and high PLR predicted worse prognosis in patients treated with CRT. However, similar results were not observed in the patients who received RT alone. These inconsistent results may be explained by the small number of patients who underwent RT alone. Although there was an association between low PNI and poor OS/PFS in the multivariate cox analysis for all the patients, this association was not statistically significant in the multivariate analyses stratified by CRT. The possible reason is that patients who can only receive radiotherapy alone have poorer nutritional status than those who can receive concurrent chemotherapy.

Our study has several limitations. First, this was a retrospective study, and all data were collected from a single center. Second, the inflammatory state induced by infection before treatment may have an impact on the outcome. Third, we were not able to evaluate all covariates that might have affected prognosis, even though we included all likely covariates. Moreover, the sample size in this study was small. Additional prospective cohort studies are needed to determine the effects of GNRI, PNI, and systemic inflammatory indexes in patients with stage IIB–III cervical cancer.

TABLE 3 Univariate and multivariate analysis for progression-free survival.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age				
≤55 vs. >55	0.66 (0.35–1.24)	0.201	–	–
No. of metastatic lymph nodes				
≤2 vs. >2	3.03 (1.62–5.67)	0.001	2.12 (1.10–4.09)	0.024
Size of tumor				
≤4 cm vs. >4 cm	3.28 (1.65–6.51)	0.001	2.31 (1.14–4.69)	0.020
Type of radiotherapy				
IMRT vs. RT	1.17 (0.64–2.14)	0.610	–	–
Chemoradiotherapy				
Yes vs. NO	0.46 (0.14–1.47)	0.20		
Pathology				
squamous cell carcinoma vs. adenocarcinoma	4.36 (2.14–8.88)	<0.001	3.62 (1.75–7.49)	<0.001
FIGO Stage				
II vs. III	3.28 (1.68–6.39)	<0.001	2.34 (1.18–4.64)	0.015
SCC antigen				
≤ 1.5 vs. > 1.5	1.19 (0.59–2.41)	0.631	–	–
PNI				
≤ 48.3 vs. > 48.3	0.36 (0.19–0.67)	0.001	0.47 (0.28–0.87)	0.017
GNRI				
≤ 97.04 vs. > 97.04	0.33 (0.18–0.6)	<0.001	0.34 (0.17–0.65)	0.001
NLR				
≤ 2.8 vs. > 2.8	3.15 (1.69–5.84)	<0.001	2.66 (1.42–4.97)	0.002
MLR				
≤ 0.41 vs. > 0.41	3.73 (2.04–6.81)	<0.001	3.36 (1.76–6.41)	<0.001
PLR				
≤ 186.67 vs. > 186.67	2.55 (1.39–4.67)	0.002	2.05 (1.10–3.80)	0.023

IMRT, Intensity-modulated radiotherapy; SCC, Squamous cell carcinoma; PNI, Prognostic nutritional index; GNRI, Geriatric nutritional risk index; NLR, Neutrophil/lymphocyte ratio; MLR, Monocyte/lymphocyte ratio; PLR, Platelet/lymphocyte ratio.

5. Conclusions

Pretreatment GNRI, PNI, and systemic inflammatory indexes might be novel prognostic predictors for patients with stage II–III cervical cancer treated with RT. Low PNI, low GNRI, high NLR, high MLR, and high PLR predicted a worse prognosis. These markers can be incorporated into pretreatment evaluations and act as factors for decision-making in patients with cervical cancer receiving radiotherapy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Hubei Cancer Hospital of Huazhong University of Science and Technology. The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

XJ: conceptualization, methodology, software, investigation, and writing-original draft. H-BW: data collection and writing-review and editing. X-TX: methodology, software, and investigation. M-XT: resources, data curation, and investigation.

C-CD, JT, and YQ: writing-review and editing. All authors revised and approved the final manuscript.

Acknowledgments

We would like to thank Jun-Zhe Bao, Wen-Zhen Jiang, and Ren-Chong Hu for great help.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1000326/full#supplementary-material

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2018) 68:394–424. doi: 10.3322/caac.21492

2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660

3. Vizcaino AP, Moreno V, Bosch FX, Munoz N, Barros-Dios XM, Borras J, et al. International trends in incidence of cervical cancer: Ii. *Squamous-Cell Carcinoma Int J Cancer.* (2000) 86:429–35. doi: 10.1002/(SICI)1097-0215(20000501)86:3<429::AID-IJC20>3.0.CO;2-D

4. Shrivastava S, Mahantshetty U, Engineer R, Tongaonkar H, Kulkarni J, Dinshaw K. Treatment and outcome in cancer cervix patients treated between 1979 and 1994: a single institutional experience. *J Cancer Res Ther.* (2013) 9:672–9. doi: 10.4103/0973-1482.126480

5. Manders DB, Moron A, McIntire D, Miller DS, Richardson DL, Kehoe SM, et al. Locally advanced cervical cancer: outcomes with variable adherence to treatment. *Am J Clin Oncol.* (2018) 41:447–51. doi: 10.1097/COC.0000000000000300

6. Ditto A, Martinelli F, Lo Vullo S, Reato C, Solima E, Carcangiu M, et al. The role of lymphadenectomy in cervical cancer patients: the significance of the number and the status of lymph nodes removed in 526 cases treated in a single institution. *Ann Surg Oncol.* (2013) 20:3948–54. doi: 10.1245/s10434-013-3067-6

7. Huang Y, Zou D, Guo M, He M, He H, Li X, et al. Hpv and radiosensitivity of cervical cancer: a narrative review. *Ann Transl Med.* (2022) 10:1405. doi: 10.21037/atm-22-5930

8. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the Cervix Uteri. *Int J Gynaecol Obstet.* (2018) 143 Suppl 2:22–36. doi: 10.1002/ijgo.12611

9. Cho O, Chun M. Management for locally advanced cervical cancer: new trends and controversial issues. *Radiat Oncol J.* (2018) 36:254–64. doi: 10.3857/roj.2018.00500

10. Williams NL, Werner TL, Jarboe EA, Gaffney DK. Adenocarcinoma of the cervix: should we treat it differently? *Curr Oncol Rep.* (2015) 17:17. doi: 10.1007/s11912-015-0440-6

11. Hu K, Wang W, Liu X, Meng Q, Zhang F. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma of cervix after definitive radiotherapy or concurrent chemoradiotherapy. *Radiat Oncol.* (2018) 13:249. doi: 10.1186/s13014-018-1197-5

12. Cong M, Zhu W, Wang C, Fu Z, Song C, Dai Z, et al. Nutritional status and survival of 8247 cancer patients with or without diabetes mellitus-results from a prospective cohort study. *Cancer Med.* (2020) 9:7428–39. doi: 10.1002/cam4.3397

13. Fujiya K, Kawamura T, Omae K, Makuuchi R, Irino T, Tokunaga M, et al. Impact of malnutrition after gastrectomy for gastric cancer on long-term survival. *Ann Surg Oncol.* (2018) 25:974–83. doi: 10.1245/s10434-018-6342-8

14. Santos I, Mendes L, Mansinho H, Santos CA. Nutritional status and functional status of the pancreatic cancer patients and the impact of adjacent symptoms. *Clin Nutr.* (2021) 40:5486–93. doi: 10.1016/j.clnu.2021.09.019

15. Kubrak C, Martin L, Gramlich L, Scrimger R, Jha N, Debenham B, et al. Prevalence and prognostic significance of malnutrition in patients with cancers of the head and neck. *Clin Nutr.* (2020) 39:901–9. doi: 10.1016/j.clnu.2019.03.030

16. Zhang X, Tang M, Zhang Q, Zhang KP, Guo ZQ, Xu HX, et al. The glim criteria as an effective tool for nutrition assessment and survival prediction in older adult cancer patients. *Clin Nutr.* (2021) 40:1224–32. doi: 10.1016/j.clnu.2020.08.004

17. Xu XT, He DL, Tian MX, Wu HJ, Jin X. Prognostic value of sarcopenia in patients with diffuse large B-Cell lymphoma treated with R-chop: a systematic review and meta-analysis. *Front Nutr.* (2022) 9:816883. doi: 10.3389/fnut.2022.816883

18. Kim SI, Kim SJ, Kim SJ, Cho DS. Prognostic nutritional index and prognosis in renal cell carcinoma: a systematic review and meta-analysis. *Urol Oncol.* (2021) 39:623–30. doi: 10.1016/j.urolonc.2021.05.028

19. Bullock AF, Greenley SL, McKenzie GAG, Paton LW, Johnson MJ. Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis and meta-analysis. *Eur J Clin Nutr.* (2020) 74:1519–35. doi: 10.1038/s41430-020-0629-0

20. Wang D, Hu X, Xiao L, Long G, Yao L, Wang Z, et al. Prognostic nutritional index and systemic immune-inflammation index predict the prognosis of patients with Hcc. *J Gastrointest Surg.* (2021) 25:421–7. doi: 10.1007/s11605-019-04492-7

21. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg.* (1980) 139:160–7. doi: 10.1016/0002-9610(80)90246-9

22. Yan L, Nakamura T, Casadei-Gardini A, Bruixola G, Huang YL, Hu ZD. Long-term and short-term prognostic value of the prognostic nutritional index in cancer: a narrative review. *Ann Transl Med.* (2021) 9:1630. doi: 10.21037/atm-21-4528

23. Park S, Ahn HJ, Yang M, Kim JA, Kim JK, Park SJ. The prognostic nutritional index and post-operative complications after curative lung cancer resection: a retrospective cohort study. *J Thorac Cardiovasc Surg.* (2020) 160:276–85 e1. doi: 10.1016/j.jtcvs.2019.10.105

24. Karayama M, Inoue Y, Yasui H, Hozumi H, Suzuki Y, Furuhashi K, et al. Association of the geriatric nutritional risk index with the survival of patients with non-small-cell lung cancer after platinum-based chemotherapy. *BMC Pulm Med.* (2021) 21:409. doi: 10.1186/s12890-021-01782-2

25. Kumarasamy C, Sabarimurugan S, Madurantakam RM, Lakhotiya K, Samiappan S, Baxi S, et al. Prognostic significance of blood inflammatory biomarkers Nlr, Plr, and Lmr in cancer-a protocol for systematic review and meta-analysis. *Medicine.* (2019) 98:e14834. doi: 10.1097/MD.0000000000014834

26. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-lymphocyte ratio (Nlr) and platelet-to-lymphocyte ratio (Plr) as prognostic markers in patients with non-small cell lung cancer (Nsclc) treated with nivolumab. *Lung Cancer.* (2017) 111:176–81. doi: 10.1016/j.lungcan.2017.07.024

27. Kang Y, Zhu X, Lin Z, Zeng M, Shi P, Cao Y, et al. Compare the diagnostic and prognostic value of mlr, Nlr and Plr in Crc patients. *Clin Lab.* (2021) 67:9. doi: 10.7754/Clin.Lab.2021.201130

28. Cho SH, Hwang JE, Bae WK, Chung IJ. The prognostic role of Pd-L1 expression according to Msi status in stage Iii colon cancer after curative resection. *J Clin Oncol.* (2019) 37:555. doi: 10.1200/JCO.2019.37.4_suppl.555

29. Huang H, Liu Q, Zhu L, Zhang Y, Lu X, Wu Y, et al. Prognostic value of preoperative systemic immune-inflammation index in patients with cervical cancer. *Sci Rep.* (2019) 9:3284. doi: 10.1038/s41598-019-39150-0

30. Chao B, Ju X, Zhang L, Xu X, Zhao Y, A. Novel prognostic marker systemic inflammation response index (Siri) for operable cervical cancer patients. *Front Oncol.* (2020) 10:766. doi: 10.3389/fonc.2020.00766

31. Deng Q, Long Q, Liu Y, Yang Z, Du Y, Chen X. Prognostic value of preoperative peripheral blood mean platelet volume/platelet count ratio (Mpv/Pc) in patients with resectable cervical cancer. *BMC Cancer.* (2021) 21:1282. doi: 10.1186/s12885-021-09016-8

32. Jiang Y, Gu H, Zheng X, Pan B, Liu P, Zheng M. Pretreatment C-reactive protein/albumin ratio is associated with poor survival in patients with 2018 Figo Stage Ib-Iia Hpv-positive cervical cancer. *Pathol Oncol Res.* (2021) 27:1609946. doi: 10.3389/pore.2021.1609946

33. Li YX, Chang JY, He MY, Wang HR, Luo DQ Li FH, et al. Neutrophil-to-lymphocyte ratio (Nlr) and monocyte-to-lymphocyte ratio (Mlr) predict clinical outcome in patients with stage Iib cervical cancer. *J Oncol.* (2021) 2021:2939162. doi: 10.1155/2021/2939162

34. Haraga J, Nakamura K, Omichi C, Nishida T, Haruma T, Kusumoto T, et al. Pretreatment prognostic nutritional index is a significant predictor of prognosis in patients with cervical cancer treated with concurrent chemoradiotherapy. *Mol Clin Oncol.* (2016) 5:567–74. doi: 10.3892/mco.2016.1028

35. Bossi P, Delrio P, Mascheroni A, Zanetti M. The spectrum of malnutrition/cachexia/sarcopenia in oncology according to different cancer types and settings: a narrative review. *Nutrients.* (2021) 13:1980. doi: 10.3390/nu13061980

36. Tian M, Fu H, Du J. Application value of Nrs2002 and Pg-Sga in nutritional assessment for patients with cervical cancer surgery. *Am J Transl Res.* (2021) 13:7186–92.

37. Flores-Cisneros L, Cetina-Perez L, Castillo-Martinez L, Jimenez-Lima R, Luvian-Morales J, Fernandez-Loaiza M, et al. Body composition and nutritional status according to clinical stage in patients with locally advanced cervical cancer. *Eur J Clin Nutr.* (2021) 75:852–5. doi: 10.1038/s41430-020-00797-y

38. Aredes MA, Garcez MR, Chaves GV. Influence of chemoradiotherapy on nutritional status, functional capacity, quality of life and toxicity of treatment for patients with cervical cancer. *Nutr Diet.* (2018) 75:263–70. doi: 10.1111/1747-0080.12414

39. Laviano A, Di Lazzaro L, Koverech A. Nutrition support and clinical outcome in advanced cancer patients. *Proc Nutr Soc.* (2018) 77:388–93. doi: 10.1017/S0029665118000459

40. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. Espen guidelines on nutrition in cancer patients. *Clin Nutr.* (2017) 36:11–48. doi: 10.1016/j.clnu.2016.07.015

41. Aaldriks AA, van der Geest LG, Giltay EJ. le Cessie S, Portielje JE, Tanis BC, et al. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. *J Geriatr Oncol.* (2013) 4:218–26. doi: 10.1016/j.jgo.2013.04.001

42. Fukuda Y, Yamamoto K, Hirao M, Nishikawa K, Maeda S, Haraguchi N, et al. Prevalence of malnutrition among gastric cancer patients undergoing gastrectomy and optimal preoperative nutritional support for preventing surgical site infections. *Ann Surg Oncol.* (2015) 22:S778–85. doi: 10.1245/s10434-015-4820-9

43. Baracos VE. Cancer-associated malnutrition. *Eur J Clin Nutr.* (2018) 72:1255–9. doi: 10.1038/s41430-018-0245-4

44. Guo ZQ Yu JM, Li W, Fu ZM, Lin Y, Shi YY, et al. Survey and analysis of the nutritional status in hospitalized patients with malignant gastric tumors and its influence on the quality of life. *Support Care Cancer.* (2020) 28:373–80. doi: 10.1007/s00520-019-04803-3

45. Martin L, Kubrak C. How much does reduced food intake contribute to cancer-associated weight loss? *Curr Opin Support Palliat Care.* (2018) 12:410–9. doi: 10.1097/SPC.0000000000000379

46. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers.* (2018) 4:17105. doi: 10.1038/nrdp.2017.105

47. Hue JJ, Sugumar K, Kyasaram RK, Shanahan J, Lyons J, Ocuin LM, et al. Weight loss as an untapped early detection marker in pancreatic and periampullary cancer. *Ann Surg Oncol.* (2021) 28:6283–92. doi: 10.1245/s10434-021-09861-8

48. Paixao EMS, Gonzalez MC, Nakano EY, Ito MK, Pizato N. Weight loss, phase angle, and survival in cancer patients undergoing radiotherapy: a prospective study with 10-year follow-up. *Eur J Clin Nutr.* (2021) 75:823–8. doi: 10.1038/s41430-020-00799-w

49. Hendifar AE, Petzel MQB, Zimmers TA, Denlinger CS, Matrisian LM, Picozzi VJ, et al. Pancreas cancer-associated weight loss. *Oncologist.* (2019) 24:691–701. doi: 10.1634/theoncologist.2018-0266

50. Jou J, Coulter E, Roberts T, Binder P, Saenz C, McHale M, et al. Assessment of malnutrition by unintentional weight loss and its implications on oncologic outcomes in patient with locally advanced cervical cancer receiving primary chemoradiation. *Gynecol Oncol.* (2021) 160:721–8. doi: 10.1016/j.ygyno.2020.12.009

51. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by special interest groups (Sig) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr.* (2010) 29:154–9. doi: 10.1016/j.clnu.2009.12.004

52. Laura FC, Lucely CP, Tatiana GC, Roberto JL, Dulce GI, Arturo PS, et al. Handgrip strength, overhydration and nutritional status as a predictors of gastrointestinal toxicity in cervical cancer patients. A prospective study. *Nutr Cancer.* (2022) 74:2444–50. doi: 10.1080/01635581.2021.2012209

53. Prado CM, Lima IS, Baracos VE, Bies RR, McCargar LJ, Reiman T, et al. An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. *Cancer Chemother Pharmacol.* (2011) 67:93–101. doi: 10.1007/s00280-010-1288-y

54. Hamaker ME, Oosterlaan F, van Huis LH, Thielen N, Vondeling A, van den Bos F. Nutritional status and interventions for patients with cancer—a systematic review. *J Geriatr Oncol.* (2021) 12:6–21. doi: 10.1016/j.jgo.2020.06.020

55. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* (2011) 12:489–95. doi: 10.1016/S1470-2045(10)70218-7

56. Jin X, Xu XT, Tian MX Dai Z. Omega-3 polyunsaterated fatty acids improve quality of life and survival, but not body weight in cancer cachexia: a systematic review and meta-analysis of controlled trials. *Nutr Res.* (2022) 107:165–78. doi: 10.1016/j.nutres.2022.09.009

57. Yamamoto T, Kawada K, Obama K. Inflammation-related biomarkers for the prediction of prognosis in colorectal cancer patients. *Int J Mol Sci.* (2021) 22:8002. doi: 10.3390/ijms22158002

58. Kargl J, Busch SE, Yang GH, Kim KH, Hanke ML, Metz HE, et al. Neutrophils dominate the immune cell composition in non-small cell lung cancer. *Nat Commun.* (2017) 8:14381. doi: 10.1038/ncomms14381

59. Xiong S, Dong L, Cheng L. Neutrophils in cancer carcinogenesis and metastasis. *J Hematol Oncol.* (2021) 14:173. doi: 10.1186/s13045-021-01187-y

60. Olingy CE, Dinh HQ, Hedrick CC. Monocyte heterogeneity and functions in cancer. *J Leukoc Biol.* (2019) 106:309–22. doi: 10.1002/JLB.4RI0818-311R

61. Robinson A, Han CZ, Glass CK, Pollard JW. Monocyte regulation in homeostasis and malignancy. *Trends Immunol.* (2021) 42:104–19. doi: 10.1016/j.it.2020.12.001

62. Abu-Shawer O, Abu-Shawer M, Hirmas N, Alhouri A, Massad A, Alsibai B, et al. Hematologic markers of distant metastases and poor prognosis in gynecological cancers. *BMC Cancer.* (2019) 19:141. doi: 10.1186/s12885-019-5326-9

63. Wagner DD. New Links between inflammation and thrombosis. *Arterioscler Thromb Vasc Biol.* (2005) 25:1321–4. doi: 10.1161/01.ATV.0000166521.90532.44

64. Datta NR, Stutz E, Liu M, Rogers S, Klingbiel D, Siebenhuner A, et al. Concurrent chemoradiotherapy vs. radiotherapy alone in locally advanced cervix cancer: a systematic review and meta-analysis. *Gynecol Oncol.* (2017) 145:374–85. doi: 10.1016/j.ygyno.2017.01.033

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 24 April 2023
DOI 10.3389/fnut.2023.1115026

OPEN ACCESS

EDITED BY
Kalliopi-Anna Poulia,
Agricultural University of Athens, Greece

REVIEWED BY
Bin Lu,
Chinese Academy of Medical Sciences and Peking Union Medical College, China
Yihui Wang,
Shanghai Jiao Tong University, China
Amrendra Mandal,
Upstate Medical University, United States

*CORRESPONDENCE
Min He
✉ hemin19910306@wchscu.cn
Zhongwei Zhang
✉ 716461751@qq.com

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 03 December 2022
ACCEPTED 31 March 2023
PUBLISHED 24 April 2023

CITATION
Shi L, Li P, Wang L, Wan D, Wang D, Yan X, He M and Zhang Z (2023) CONUT score is associated with short-term prognosis in patients with severe acute pancreatitis: a propensity score matching cohort study. *Front. Nutr.* 10:1115026. doi: 10.3389/fnut.2023.1115026

CONUT score is associated with short-term prognosis in patients with severe acute pancreatitis: a propensity score matching cohort study

Lvyuan Shi[1], Ping Li[1], Lietao Wang[1], Dingyuan Wan[1], Daojin Wang[2], Xin Yan[1], Min He[1]* and Zhongwei Zhang[1]*

[1]Department of Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China, [2]Department of Radiology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

Background: The Controlling Nutritional Status (CONUT) score was designed to assess the immune-nutritional status in patients. This study aimed to investigate the role of the CONUT score in the short-term prognosis of severe acute pancreatitis.

Methods: This was a retrospective cohort study. 488 patients with severe acute pancreatitis at the Department of Critical Care Medicine of the West China Hospital of Sichuan University (Chengdu, China) were enrolled in the study. Baseline data were collected from the West China Hospital of Sichuan University database. The primary outcome during follow-up was all-cause mortality. The secondary outcomes were 28day mortality, renal insufficiency, length of stay (LOS) in the ICU, and length of stay (LOS) in the hospital. Patients were divided into two groups based on a median CONUT score of 7, and baseline differences between the two groups were eliminated by propensity matching. Univariate Cox regression analyses were performed to estimate the association between CONUT score and outcomes. The Kaplan–Meier method was used to estimate the survival rate of patients.

Results: CONUT score was an independent predictor of all-cause mortality (hazard ratio [HR]:2.093; 95%CI: 1.342–3.263; $p<0.001$) and 28day mortality (hazard ratio [HR]:1.813; 95%CI: 1.135–2.896; $p<0.013$). CONUT score was not statistically significant in predicting the incidence of renal insufficiency. The high CONUT group had significantly higher all-cause mortality ($p<0.001$), and 28day mortality ($p<0.011$) than the low CONUT group.

Conclusion: The CONUT score is an independent predictor of short-term prognosis in patients with severe acute pancreatitis, and timely nutritional support is required to reduce mortality in patients with severe acute pancreatitis.

KEYWORDS

severe acute pancreatitis, CONUT score, short-term prognosis, mortality, ICU

Introduction

Acute pancreatitis is a common clinical emergency abdomen, with a complex and variable condition that is easily treatable in mild cases and often life-threatening in heavy cases (1). The revised Atlanta classification defines acute pancreatitis with acute pancreatitis manifestations and biochemical changes, accompanied by continuous (>48 h) organ failure as severe acute pancreatitis (2). Severe acute pancreatitis has a fatality rate of up to 30%, and if it is accompanied by infection, the mortality rate will be higher (3). The current standard of care for treating severe acute pancreatitis includes an early, thorough approach with an intensive care unit (ICU) as the cornerstone, non-surgical treatment, and organ function protection as the primary emphasis (4). Among them, nutritional support therapy not only provides energy to the organism, but also prevents the evolution of the pathophysiological process of the disease, protects the barrier function of the intestinal mucosa, and is an important way to prevent infection (5–7).

However, for the assessment of a patient's nutritional status, traditional methods include BMI, triceps skinfold thickness, and upper arm circumference (8), all of which have limitations and are susceptible to various effects such as age, gender, and race, as well as problems of measurement error. In addition, there are SGA, PG-SGA assessment forms, and NRS2002 risk screening forms (9–11), currently the NRS2002 risk screening form is commonly used in clinical practice (12). Although these assessment forms can comprehensively assess the nutritional status of patients, there are more contents to be evaluated, and the implementation is more time-consuming and energy-consuming, resulting in a decline in the execution of medical staff and non-cooperation of patients, and there are many subjective problems in the assessment content, which is easy to cause errors.

The Controlling Nutritional Status (CONUT) score, a variable based on serum albumin, total cholesterol, and total peripheral lymphocyte count (13), was originally designed to assess perioperative nutritional and immunological risk in patients undergoing gastrointestinal surgery (14). The CONUT score is easier to perform, more objective, and accurate (15). More recently, the CONUT score has also been validated for prognostic value in many other diseases (16–19). However, there are currently no studies demonstrating that CONUT scores are associated with the prognosis of severe acute pancreatitis, and we hypothesize that CONUT scores are associated with prognosis in patients with SAP. Therefore, we assessed the prognostic value of CONUT scores for short-term outcomes in patients with SAP.

We hypothesized that the CONUT score is associated with short-term prognosis in patients with severe acute pancreatitis. Therefore, we designed a retrospective cohort study to investigate the role of the CONUT score in the short-term prognosis of severe acute pancreatitis.

Abbreviations: CONUT, Controlling Nutritional Status; SAP, Severe Acute Pancreatitis; LOS, length of stay; ICU, Intensive Care Unit; WBC, white blood cell; M, macrophages; L, lymphocyte; ALB, albumin; TC, total cholesterol; Cr, creatinine; TB, total bilirubin; PSM, propensity score matching.

Materials and methods

Study design

The present investigation was a retrospective cohort study. All patients with severe acute pancreatitis at the Department of Critical Care Medicine of the West China Hospital of Sichuan University (Chengdu, China) from December 2015 to December 2019 were eligible for inclusion in the study. Patients younger than 10 years old, incomplete data, non-cooperation with follow-up (non-cooperation, communication difficulties, mental disorders, impaired consciousness, etc.), rescue status, chronic malnutrition and immune deficiency were excluded. Finally, we included a total of 488 severe acute pancreatitis patients in the study.

Human subject protection

The study was approved by the Ethics Committee of the West China Hospital of Sichuan University (no: 2021-1,694), and written informed consent was obtained from all participants.

Data collection

Data on baseline characteristics, comorbidities, and laboratory test results were collected from the West China Hospital of Sichuan University database. Clinical indicators included the patient's surgery and infection. Laboratory variables were obtained from the results of the SAP patients' first examination when the patients were first admitted to the ICU, including white blood cells, macrophages, lymphocytes, albumin, total cholesterol, triglycerides, serum creatinine, and total bilirubin. The CONUT score was calculated based on 3 laboratory variables: serum albumin concentration, total cholesterol concentration, and total peripheral lymphocyte count. The CONUT score was shown in Supplementary Table S1.

Clinical outcomes

The primary outcome was all-cause mortality. The secondary outcomes were 28 day mortality, renal insufficiency, LOS in ICU, and LOS in the hospital. All-cause mortality was defined as the death of a patient due to various causes. The definition of 28 day mortality was death from various causes 28 days after admission. The definition of renal insufficiency was the 2012 version of KDIGO (20).

Statistical analysis

Analyses were conducted using SPSS (version 25.0). All data were first checked for normality of distribution using the Kolmogorov–Smirnov test. Normally distributed data were presented as the mean ± standard deviation. Non-normally distributed data were represented as the median (inter-quartile range). Differences among the CONUT score groups were evaluated using the chi-square test for categorical variables, the *t*-test for normally distributed continuous variables, and the Mann–Whitney U test for asymmetrically distributed continuous variables. CONUT score was divided into the

low CONUT (≤7) and high CONUT (>7) groups according to the median 7. The low CONUT and high CONUT groups were compared by propensity score matching (PSM). We matched each patient from the low CONUT group with a counterpart from the high CONUT group. The propensity score was the predicted probability to be in the low CONUT group, derived from a given multivariable logistic regression value of covariates. The covariates included in the propensity score calculation were age, sex, serum creatinine, and macrophages count. The matching was processed using a greedy nearest neighbor algorithm with a calliper of 0.1 times the SD of the logit of propensity score and without replacement and with random matching order. We then performed the chi-square test and Mann–Whitney U test on the matched variables, and $p > 0.05$ considered the difference between the two groups negligible. The proportional hazard assumption had to be tested before the univariate Cox regression analysis is conducted. The independent relationships between CONUT score and all-cause mortality, 28 day mortality, and renal insufficiency in the study were investigated by univariate Cox regression analyses. Univariate and multivariate COX regression analyses were performed for all-cause mortality and 28 day mortality. The Kaplan–Meier method and the log-rank test were used to estimate the survival rate of patients. A two-sided value of p of <0.05 was considered to indicate statistical significance.

Results

A total of 488 patients with severe acute pancreatitis who were initially admitted to the ICU between December 2015 and December 2019 (Figure 1) were categorized into the low CONUT ($n = 301$) and high CONUT ($n = 187$) groups. Table 1 presented the baseline characteristics of the study groups. The median age was 47 (37, 55) years. Most patients were men (371 cases, 65%). The median CONUT score was 7. The median of LOS in the ICU was 14.5 (7.0, 27.0) days. The median of LOS in the hospital was 24.0 (15.0, 38.0) days. During the 28 day hospital stay, 108 (22.1%) patients died. Of the outcomes at discharge, 125 (25.6%) patients died and 151 (30.9%) developed renal insufficiency. During ICU treatment, 328 (67.2%) patients underwent surgery and 318 (65.2%) patients developed co-infections. A significant difference was found in several variables between the two groups before PSM, with a two-sided p-value of <0.05. However, the group difference was trivial after PSM.

Equal proportion risk assumptions were made before COX regression, and Supplementary Figure S1 shows that the survival risk of the two curves of CONUT ≤ 7 and CONUT > 7 group changes in equal proportions, and this risk ratio does not change with time, so the PH condition of COX regression is valid. The results of after-matching groups of univariate COX regression analyses showed that the CONUT score was an independent predictor of all-cause mortality (hazard ratio [HR]: 2.093;95%CI:1.342–3.263; $p < 0.001$) and 28 day mortality(hazard ratio [HR]: 1.813;95%CI: 1.135–2.896; $p < 0.013$). CONUT score was not statistically significant in predicting the incidence of renal insufficiency (Table 2). Univariate and multivariate COX regression analyses were performed for all-cause mortality and 28 day mortality (Supplementary Tables S2, S3).

The Kaplan–Meier curve comparing the outcomes of the patients according to the median CONUT score is shown in Figures 2A,B. The high CONUT group had significantly higher all-cause mortality

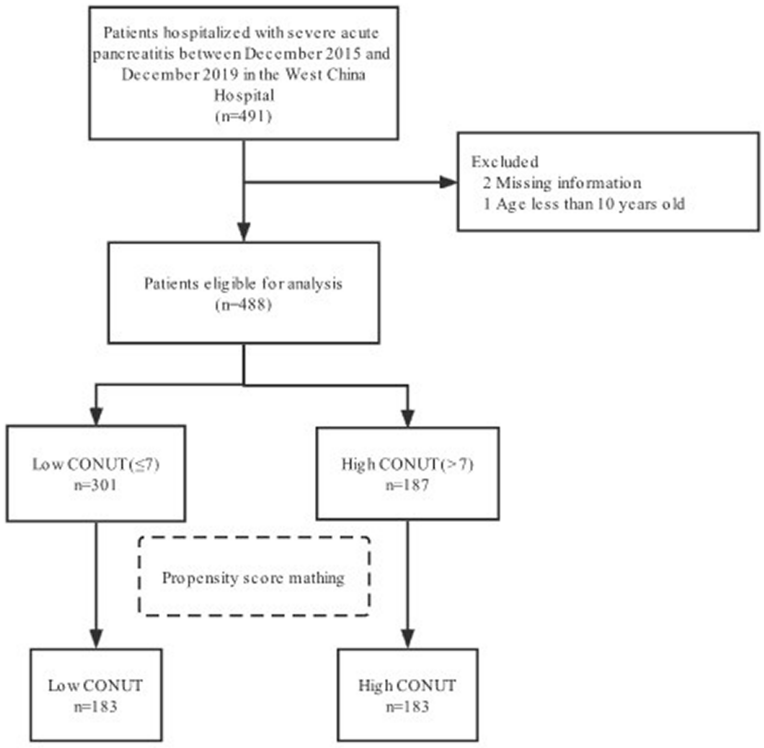


FIGURE 1
The inclusion of the study patients.

TABLE 1 Demographic and baseline characteristics of patients with severe acute pancreatitis.

Characteristics	Before matching			p value	After matching			p value
	All *n* =488	Low CONUT (≤7) *n* =301	High CONUT (>7) *n* =187		All *n* =366	Low CONUT *n* =183	High CONUT *n* =183	
Ages (years)	47 (37, 55)	47.0 (36.0, 55.0)	49 (37, 55)	0.267	48.0 (37.0, 56.0)	47.0 (37.0, 58.0)	49.0 (37.0, 56.0)	0.308
Male gender (%)	317 (65%)	199 (66.1%)	118 (63.1%)	0.498	231 (63.1%)	115 (62.8%)	116 (63.4%)	0.914
All-cause mortality (%)	125 (25.6%)	63 (20.9%)	62 (33.2%)	0.003	89 (24.3%)	29 (15.8%)	60 (32.8%)	0.000
28 day mortality (%)	108 (22.1%)	57 (18.9%)	51 (27.3%)	0.031	77 (21.0%)	27 (14.8%)	50 (27.3%)	0.003
LOS in ICU (days)	14.5 (7.0,27.0)	13.0 (6.0,24.0)	16.0 (9.0,29.0)	0.006	16.0 (7.8,28.3)	15.0 (6.0,27.0)	16.0 (9.0,29.0)	0.131
LOS in hospital (days)	24.0 (15.0, 38.0)	23.0 (14.0, 38.5)	24.0 (16.0, 38.0)	0.358	25.0 (16.0, 41.3)	26.0 (15.0, 42.0)	24.0 (16.0, 38.0)	0.757
Renal insufficiency (%)	151 (30.9%)	81 (26.9%)	70 (37.4%)	0.014	123 (33.6%)	55 (30.1%)	68 (37.2%)	0.150
Surgery (%)	328 (67.2%)	203 (67.4%)	125 (66.8%)	0.891	223 (60.9%)	101 (55.2%)	122 (66.7%)	0.024
Infection (%)	318 (65.2%)	183 (60.8%)	135 (72.2%)	0.010	235 (64.2%)	103 (56.3%)	132 (72.1%)	0.002
WBC (*10^9)	12.0 (8.5, 16.8)	11.9 (8.5, 16.9)	12.1 (8.5, 16.6)	0.907	11.9 (8.3, 16.7)	11.8 (8.2, 16.7)	12.2 (8.5, 16.8)	0.740
M (*10^9)	0.5 (0.3, 0.7)	0.5 (0.4, 0.8)	0.5 (0.3, 0.6)	0.006	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)	0.5 (0.3, 0.6)	0.270
L (*10^6)	975.0 (650.0, 1407.5)	1130.0 (830.0, 1665.0)	740.0 (550.0, 1010.0)	0.000	930.0 (620.0, 1337.5)	1130.0 (830.0, 1740.0)	760.0 (550.0, 1010.0)	0.000
ALB (g/dL)	3.3 (2.9, 3.8)	3.6 (3.3, 4.2)	2.9 (2.6, 3.0)	0.000	3.2 (2.8, 3.8)	3.9 (3.4, 4.4)	2.9 (2.6, 3.0)	0.000
TC (mg/dL)	3.3 (2.9, 3.8)	60.3 (44.3, 96.8)	42.6 (32.6, 62.7)	0.000	51.7 (36.0, 72.9)	61.1 (43.2, 101.3)	43.0 (32.6, 62.7)	0.000
Triglycerides (mg/dL)	2.6 (1.5, 5.3)	2.6 (1.4, 7.3)	2.6 (1.6, 4.1)	0.267	2.7 (1.5, 5.3)	2.7 (1.5, 9.3)	2.7 (1.6, 4.1)	0.125
Cr (umol/L)	89.0 (57.0, 184.0)	79.0 (57.0, 157.5)	108.0 (58.0, 240.0)	0.010	98.5 (58.0, 192.0)	83.0 (58.0, 181.0)	107.0 (58.0, 236.0)	0.203
TB (umol/L)	18.1 (11.9, 30.4)	17.6 (11.8, 28.6)	18.8 (12.1, 33.7)	0.241	18.2 (12.0, 31.7)	17.6 (12.0, 30.5)	18.8 (12.1, 33.7)	0.612

TABLE 2 Short-term complications and outcomes in the propensity score matched cohort.

Outcomes	All patients (*n* =366)	Low CONUTS group (*n*=183)	High CONUTS group (*n*=183)	HR (95%CI)	p value
		CONUTS < 7	CONUTS ≥ 7		
All-cause mortality (%)	89 (24.3%)	29 (15.8%)	60 (32.8%)	2.093 (1.342, 3.263)	0.001
28 day mortality (%)	77 (21.0%)	27 (14.8%)	50 (27.3%)	1.813 (1.135, 2.896)	0.013
Renal insufficiency (%)	123 (33.6%)	55 (30.1%)	68 (37.2%)	1.346 (0.941, 1.926)	0.104

($p<0.001$), and 28 day mortality ($p<0.011$) than the low CONUT group.

Discussion

Mortality in severe acute pancreatitis can reach 30%, and mortality is higher if co-infected (3). There is an important relationship between nutritional status and SAP patients. Nutritional support therapy can not only provide energy for the body, but also inhibit the pathophysiological process evolution of the disease, protect the barrier function of the intestinal mucosa, and is an important way to prevent infection (5–7). To our knowledge, no studies have shown a relationship between CONUT scores and short-term outcomes in patients with acute severe pancreatitis (4). Our results suggest that the CONUT score can be used as a clinical predictor of all-cause mortality and 28 day mortality in patients with SAP. In this study, the higher the CONUT score of SAP patients when admitted to the ICU, the higher the risk of death. SAP patients have a high CONUT score (CONUT score > 7), and patients with a high CONUT score have a risk ratio of 2.093 for death compared to patients with a low CONUT score.

The Controlling Nutritional Status (CONUT) score, is a variable based on serum albumin, total cholesterol, and total peripheral

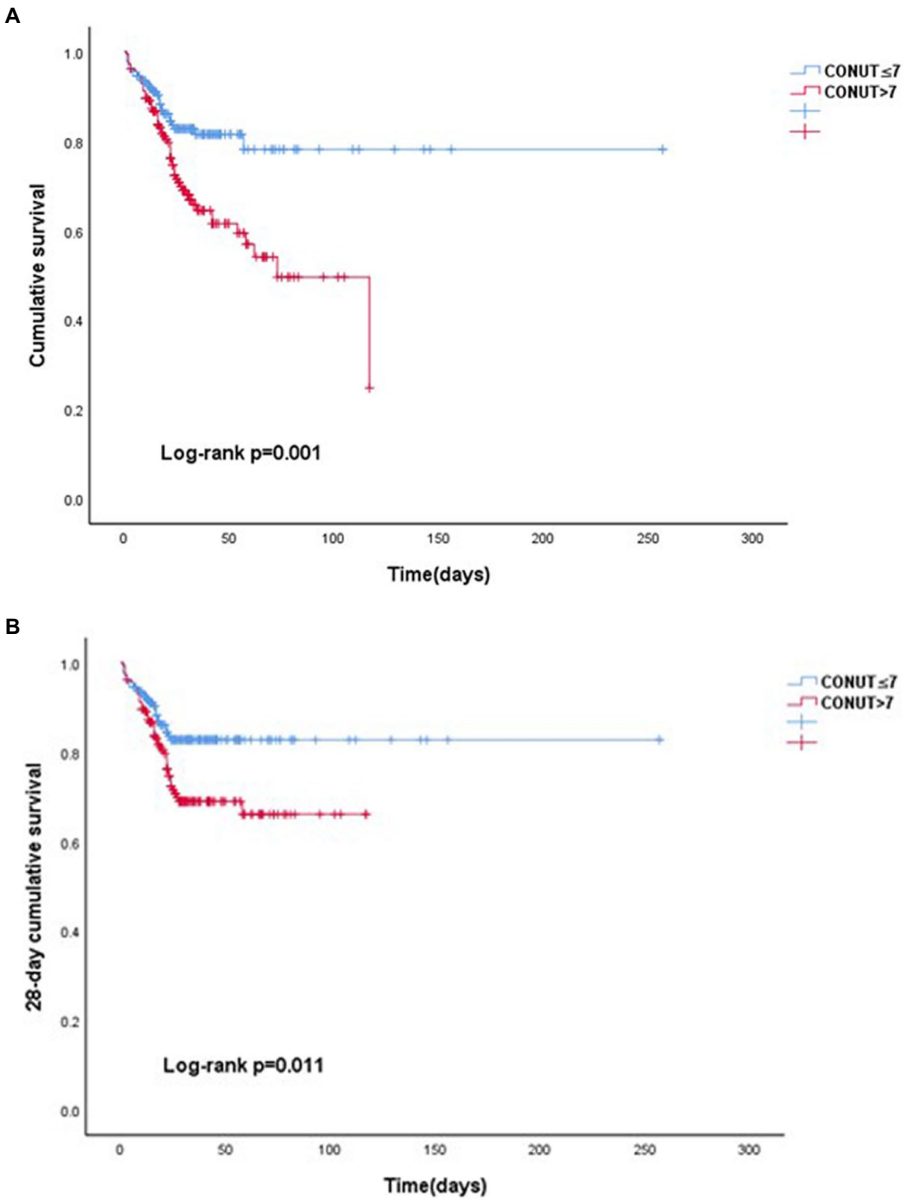


FIGURE 2
Kaplan–Meier curves for outcomes in patients with severe acute pancreatitis. **(A)**. All-cause mortality and **(B)**. 28day mortality.

lymphocyte count (13). Studies have shown that both low albumin and cholesterol are associated with in-hospital mortality in patients with SAP (21, 22). Albumin is the most abundant protein in plasma, and in the event of a disorder of nitrogen metabolism, albumin can serve as a nitrogen source to provide nutrients to tissues (23). Cholesterol is an important component of cell membranes and is also the raw material for the synthesis of many important substances in the body (24). Lymphocytes play an important role in cellular immunity (25). However, prealbumin is more sensitive to acute protein changes (26), and there is no optimal cut-off for serum albumin, cholesterol, and total lymphocyte count. In the CONUT score, the combination of these three components may better reflect the balance of immune-trophic status than univariate markers and enhance the ability to accurately predict outcomes.

The CONUT score was originally designed to assess perioperative nutritional and immunological risk in patients undergoing gastrointestinal surgery (14). In our current study, the CONUT score can also be used as an independent predictor of short-term prognosis in patients with severe acute pancreatitis, with the risk of death in the group with a high CONUT score being 2.093 times higher than the group with a low score and the 28 day risk of death being 1.913 times higher than the group with a low score. SAP patients in the group with a high CONUT score have poor nutritional status. On the one hand, SAP patients have an increased need for nutrients due to the high metabolic characteristics of the disease itself (27, 28), and mortality increases tenfold when the nitrogen balance is negative compared to patients with a positive nitrogen balance (29). On the other hand, when the patient's nutritional status is poor, the intestinal mucosal barrier is blocked, leading to endotoxin displacement, and increasing the risk of infection (30, 31). All of this gives us reason to suspect that the CONUT score can affect the short-term prognosis of patients with SAP.

Therefore, the CONUT score can help us better monitor the nutritional status of SAP patients and prevent malnutrition and affect

prognosis (15). The CONUT score can also help clinicians provide better nutritional support to patients and reduce the incidence of death in SAP patients (32, 33). For patients with severe acute pancreatitis, we should pay close attention to the nutritional status of patients, give nutritional support early, reduce the risk of malnutrition and improve the survival rate of patients (34, 35). Patients with non-severe acute pancreatitis should also be concerned about their nutritional status to prevent progression to severe acute pancreatitis (36).

On the one hand, the CONUT score evaluates the patient's serum albumin level, total cholesterol level, and total lymphocyte count, which is simple and efficient in assessing the patient's nutritional status and has the advantages of low cost and comprehensiveness. Moreover, it also has the advantages of objectivity and feasibility, which can be used for long-term monitoring of nutritional status, timely detection of malnutrition, and the adoption of intervention methods (32). However, on the other hand, studies have shown that CONUT, although very specific, is not very sensitive (37). And the CONUT score has its limitations because it consists of only a few laboratory indicators and lacks basic nutritional indicators, such as recent weight and appetite loss (38).

There are several limitations to this study. First, we included a small sample size in our study, and the data came from a single center in China, with a possible selection bias and a center-specific effect. Second, we did not have data on the patient's pre-illness nutritional status, which may have existed before the disease. Also, we did not study the effect of patient overnutrition on outcomes. Finally, we did not have data on patients' daily CONUT scores.

Conclusion

We conclude that the CONUT score is an independent predictor of short-term prognosis in patients with severe acute pancreatitis, and timely nutritional support is required to reduce mortality in patients with severe acute pancreatitis.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by The ethics committee of the West China Hospital of Sichuan University (no: 2021-1,694). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

LS and MH designed this study. LS carried out the study, performed statistical analyses, and drafted the article. MH and ZZ communicated with patients' families and got their approval and critically reviewed the paper. PL, LW, DaW, XY, and DiW collected data. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by Sichuan Science and Technology Program (Project number: 2021YFS0184 and 2022YFH0002) and Project funded by China Postdoctoral Science Foundation (Project number: 2021M692298).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1115026/full#supplementary-material

References

1. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, et al. Acute pancreatitis. *Lancet*. (2020) 396:726–34. doi: 10.1016/S0140-6736(20)31310-6

2. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. (2013) 62:102–11. doi: 10.1136/gutjnl-2012-302779

3. Werge M, Novovic S, Schmidt PN, Gluud LL. Infection increases mortality in necrotizing pancreatitis: a systematic review and meta-analysis. *Pancreatology*. (2016) 16:698–707. doi: 10.1016/j.pan.2016.07.004

4. Position Paper of the Italian Association for the Study of the LiverPezzilli R, Zerbi A, Campra D, Capurso G, Golfieri R, et al. Consensus guidelines on severe acute pancreatitis. *Dig Liver Dis*. (2015) 47:532–43. doi: 10.1016/j.dld.2015.03.022,

5. Blackburn GL, Bistrian BR, Maini BS, Schlamm HT, Smith MF. Nutritional and metabolic assessment of the hospitalized patient. *JPEN J Parenter Enteral Nutr*. (1977) 1:11–21. doi: 10.1177/014860717700100101

6. van Bokhorst-de MA, van der Schueren PR, Guaitoli EPJ, de Vet HC. Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting. *Clin Nutr*. (2014) 33:39–58. doi: 10.1016/j.clnu.2013.04.008

7. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr*. (2003) 22:415–21. doi: 10.1016/S0261-5614(03)00098-0

8. Bauer J, Capra S, Ferguson M. Use of the scored patient-generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr*. (2002) 56:779–85. doi: 10.1038/sj.ejcn.1601412

9. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewell J, et al. Nutritional assessment: a comparison of clinical judgement and objective measurements. *N Engl J Med*. (1982) 306:969–72. doi: 10.1056/NEJM198204223061606

10. Ignacio de Ulíbarri J, González-Madroño A, de Villar N, González P, González B, Mancha A, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp*. (2005) 20:38–45.

11. Iseki Y, Shibutani M, Maeda K, Nagahara H, Ohtani H, Sugano K, et al. Impact of the preoperative controlling nutritional status (CONUT) score on the survival after curative surgery for colorectal cancer. *PLoS One*. (2015) 10:e0132488. doi: 10.1371/journal.pone.0132488

12. Cañamares-Orbis P, Bernal-Monterde V, Sierra-Gabarda O, Casas-Deza D, Garcia-Rayado G, Cortes L, et al. Impact of liver and pancreas diseases on nutritional status. *Nutrients*. (2021) 13:1650. doi: 10.3390/nu13051650

13. Elghiaty A, Kim J, Jang WS, Park JS, Heo JE, Rha KH, et al. Preoperative controlling nutritional status (CONUT) score as a novel immune-nutritional predictor of survival in non-metastatic clear cell renal cell carcinoma of ≤7 cm on preoperative imaging. *J Cancer Res Clin Oncol*. (2019) 145:957–65. doi: 10.1007/s00432-019-02846-x

14. Ryo S, Kanda M, Ito S, Mochizuki Y, Teramoto H, Ishigure K, et al. The controlling nutritional status score serves as a predictor of short-and long-term outcomes for patients with stage 2 or 3 gastric cancer: analysis of a multi-institutional data set. *Ann Surg Oncol*. (2019) 26:456–64. doi: 10.1245/s10434-018-07121-w

15. Takahashi T, Watanabe T, Otaki Y, Kato S, Tamura H, Nishiyama S, et al. Prognostic significance of the controlling nutritional (CONUT) score in patients with acute coronary syndrome. *Heart Vessel*. (2021) 36:1109–16. doi: 10.1007/s00380-021-01792-4

16. Li W, Li M, Wang T, Ma G, Deng Y, Pu D, et al. Controlling nutritional status (CONUT) score is a prognostic factor in patients with resected breast cancer. *Sci Rep*. (2020) 10:6633. doi: 10.1038/s41598-020-63610-7

17. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. (2012) 158:825–30. doi: 10.7326/0003-4819-158-11-201306040-00007

18. Eckerwall G, Olin H, Andersson B, Andersson R. Fluid resuscitation and nutritional support during severe acute pancreatitis in the past: what have we learned and how can we do better? *Clin Nutr*. (2006) 25:497–504. doi: 10.1016/j.clnu.2005.10.012

19. Kumar A, Singh N, Prakash S, Saraya A, Joshi YK. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *J Clin Gastroenterol*. (2006) 40:431–4. doi: 10.1097/00004836-200605000-00013

20. Greenberg JA, Hsu J, Bawazeer M, Marshall J, Friedrich JO, Nathens A, et al. Clinical practice guideline: management of acute pancreatitis. *Can J Surg J Can Chirurgie*. (2016) 59:128–40. doi: 10.1503/cjs.015015

21. Wang X, Cui Z, Li H, Saleen AF, Zhang D, Miao B, et al. Nosocomial mortality and early prediction of patients with severe acute pancreatitis. *J Gastroenterol Hepatol*. (2010) 25:1386–93. doi: 10.1111/j.1440-1746.2010.06376.x

22. Hong W, Zimmer V, Basharat Z, Zippi M, Stock S, Geng W, et al. Association of total cholesterol with severe acute pancreatitis: a U-shaped relationship. *Clin Nutr*. (2020) 39:250–7. doi: 10.1016/j.clnu.2019.01.022

23. Gounden V., Vashisht R., Jialal I., Hypoalbuminemia, *StatPearls, StatPearls Publishing Copyright © 2022*, StatPearls Publishing LLC, Treasure Island (FL), (2022).

24. Cortes VA, Busso D, Maiz A, Arteaga A, Nervi F, Rigotti A. Physiological and pathological implications of cholesterol. *Front Bioscience*. (2014) 19:416–28. doi: 10.2741/4216

25. Zhou H, Chao W, Cui L, Li M, Zou Y, Yang M. Controlling nutritional status (CONUT) score as immune-nutritional predictor of outcomes in patients undergoing peritoneal dialysis. *Clin Nutr*. (2020) 39:2564–70. doi: 10.1016/j.clnu.2019.11.018

26. Mittman N, Avram MM, Oo KK, Chattopadhyay J. Serum prealbumin predicts survival in hemodialysis and peritoneal dialysis: 10 years of prospective observation. *Am J Kidney Diseases*. (2001) 38:1358–64. doi: 10.1053/ajkd.2001.29256

27. Windsor JA, Hammodat H. Metabolic management of severe acute pancreatitis. *World J Surg*. (2000) 24:664–72. doi: 10.1007/s002689910108

28. Al-Omran M, Albalawi ZH, Tashkandi MF, Al-Ansary LA. Enteral versus parenteral nutrition for acute pancreatitis. *Cochrane Database Syst Rev*. (2010) 2010:CD002837. doi: 10.1002/14651858.CD002837

29. Sitzmann JV, Steinborn PA, Zinner MJ, Cameron JL. Total parenteral nutrition and alternate energy substrates in treatment of severe acute pancreatitis. *Surg Gynecol Obstet*. (1989) 168:311–7.

30. Meier RF, Beglinger C. Nutrition in pancreatic diseases. *Best Pract Res Clin Gastroenterol*. (2006) 20:507–29. doi: 10.1016/j.bpg.2006.01.004

31. Flint RS, Windsor JA. The role of the intestine in the pathophysiology and management of severe acute pancreatitis. *HPB (Oxford)*. (2003) 5:69–85. doi: 10.1080/13651820310001108

32. Takagi K, Buettner S, Ijzermans JNM. Prognostic significance of the controlling nutritional status (CONUT) score in patients with colorectal cancer: a systematic review and meta-analysis. *Int J Surgery*. (2020) 78:91–6. doi: 10.1016/j.ijsu.2020.04.046

33. Jabłońska B, Mrowiec S. Nutritional support in patients with severe acute pancreatitis-current standards. *Nutrients*. (2021) 13:1498. doi: 10.3390/nu13051498

34. Mederos MA, Reber HA, Girgis MD. Acute pancreatitis: a review. *JAMA*. (2021) 325:382–90. doi: 10.1001/jama.2020.20317

35. Cañamares-Orbís P, García-Rayado G, Alfaro-Almajano E. Nutritional support in pancreatic diseases. *Nutrients*. (2022) 14:4570. doi: 10.3390/nu14214570

36. Oláh A, Romics L Jr. Early enteral nutrition in acute pancreatitis – benefits and limitations. *Langenbeck's Arch Surg*. (2008) 393:261–9. doi: 10.1007/s00423-008-0291-9

37. Gascón-Ruiz M, Casas-Deza D, Torres-Ramón I, Zapata-García M, Alonso N, Sesma A, et al. Comparation of different malnutrition screening tools according to GLIM criteria in cancer outpatients. *Eur J Clin Nutr*. (2022) 76:698–702. doi: 10.1038/s41430-021-01021-1

38. Chávez-Tostado M, Cervantes-Guevara G, López-Alvarado SE, Cervantes-Pérez G, Barbosa-Camacho FJ, Fuentes-Orozco C, et al. Comparison of nutritional screening tools to assess nutritional risk and predict clinical outcomes in Mexican patients with digestive diseases. *BMC Gastroenterol*. (2020) 20:79. doi: 10.1186/s12876-020-01214-1

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 12 May 2023
DOI 10.3389/fnut.2023.1080181

OPEN ACCESS

EDITED BY
Paula Ravasco,
Catholic University of Portugal, Portugal

REVIEWED BY
Zailin Yang,
Chongqing University, China
Salvatrice Mancuso,
University of Palermo, Italy

*CORRESPONDENCE
Xiangxiang Zhou
xiangxiangzhou@sdu.edu.cn
Xin Wang
xinw007@126.com

†These authors have contributed equally to this work

RECEIVED 26 October 2022
ACCEPTED 05 April 2023
PUBLISHED 12 May 2023

CITATION
Lu T, Shi X, Ge X, Li Y, Cai Y, Chen X, Hu S, Ding M, Fang X, Liu F, Zhou X and Wang X (2023) Derivation and validation of a nutrition-covered prognostic scoring system for extranodal NK/T-cell lymphoma. *Front. Nutr.* 10:1080181. doi: 10.3389/fnut.2023.1080181

Derivation and validation of a nutrition-covered prognostic scoring system for extranodal NK/T-cell lymphoma

Tiange Lu[1,2,3†], Xue Shi[4†], Xueling Ge[2,5,6,7], Ying Li[4], Yiqing Cai[1,2,3], Xiaomin Chen[1,2,3], Shunfeng Hu[1,2,3], Mei Ding[2,5,6,7], Xiaosheng Fang[2,5,6,7], Fang Liu[8], Xiangxiang Zhou[2,5,6,7*] and Xin Wang[1,2,3,5,6,7*]

[1]Department of Hematology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China, [2]Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China, [3]School of Medicine, Shandong University, Jinan, Shandong, China, [4]Department of Hematology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China, [5]Shandong Provincial Engineering Research Center of Lymphoma, Jinan, Shandong, China, [6]Branch of National Clinical Research Center for Hematologic Diseases, Jinan, Shandong, China, [7]National Clinical Research Center for Hematologic Diseases, The First Affiliated Hospital of Soochow University, Suzhou, China, [8]Department of Psychiatry, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

Introduction: Patients with aggressive lymphomas are at high risk of losing body resources, resulting in malnutrition, immunodeficiency and inferior outcomes. Nutritional status is closely associated with survival, but often neglected in the prognostic assessment. This study aimed to explore the significance of nutritional status in extranodal NK/T-cell lymphoma (ENKTL).

Methods: Univariate and multivariate Cox regression analyses were conducted to examine the significance of nutritional index on overall survival (OS) and progression-free survival (PFS). A nutrition-incorporated score system was constructed based on the multivariate results, and its calibration, discrimination and clinical utility were tested in the training and validation cohort.

Results: Multivariate analysis revealed controlling nutritional status (CONUT) score could independently predict OS (HR 10.247, P=0.001) and PFS (HR 5.587, P=0.001) in addition to prognostic index of natural killer lymphoma plus EBV (PINK-E). Herein, a reformative model, CONUT-PINK-E, was developed and further verified in external validation cohort. CONUT-PINK-E classified patients into three risk grades with significant survival differences ($P < 0.001$). Compared with the current models, CONUT-PINK-E presented superior discrimination, calibration and clinical benefit.

Discussion: In this study, we firstly verified that CONUT score was efficient to screen prognosis-related malnutrition in ENKTL. Moreover, we developed the first nutritional assessment-covered scoring system, CONUT-PINK-E, which might be a promising tool to provide references for clinical decision-making of ENKTL patients.

KEYWORDS

nutrition, CONUT score, extranodal NK/T-cell lymphoma (ENKTCL), prognosis, model

Introduction

Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTL), derived from NK cells or cytotoxic T cells, is a unique and uncommon clinicopathological entity of non-Hodgkin lymphoma (NHL), more prevalent in East Asia and Latin America (1, 2). ENKTL is distinguished by Epstein–Barr virus (EBV) infection and upper aerodigestive tract (UADT) involvement, and is highly aggressive with poor survival outcomes (1, 3, 4).

Since body resources are consuming, malnutrition is a common phenomenon in patients with advanced malignancies, accompanied with compromised immune competence, degressive physical activity and worsened clinical outcomes (5). Even though the prevalence and severity in ENKTL remain unclear, ENKTL patients are at high malnutrition risk due to the primary location and tumor burden (6, 7). Nevertheless, nutritional status assessment has often been neglected in prognosis evaluation.

Nutritional status closely affects the response to antineoplastic therapy, tightly associated with therapy intensity and treatment-related toxicity (8, 9). Either reduced intensity or unbearable toxicity badly impairs the treatment benefits and shortens patients' survival (10). Since cure remains less promising for most ENKTL patients in advanced stage, optimal supportive care is essential to tolerate long-term treatments and achieve a prolonged survival (5). The supportive care relies on the accurate nutritional status assessment, so it is urgent to explore the applicable nutritional index for ENKTL patients.

In last few decades, nutrition-related indices constantly spring up and nutritional status evaluation attracts increasing attention in multiple cancers, such as head and neck cancers and gastric cancer (11, 12). Prognostic nutritional index (PNI) and controlling nutritional status (CONUT) score, two emerging nutritional indices, have been verified possessing greater prognostic significance (13, 14) than the traditional nutritional parameters, such as body weight, triceps skin fold thickness, mid-arm muscle circumference and body mass index (BMI) (15, 16). PNI is calculated as serum albumin level (ALB, g/L) + 0.005 × absolute lymphocyte count (ALC, per mm^3) (17) and CONUT score is calculated from the serum ALB, ALC and total cholesterol (TC) (12), both reflecting the long-term nutritional and immune response status (12, 18).

Nevertheless, the association between PNI, CONUT score and the survival outcomes of ENKTL remains undiscovered. This study aimed to examine the potential of PNI and CONUT score serving as a prognostic marker in ENKTL and further establish a nutrition evaluation-incorporated risk stratification system. The performance of the reformative model would be verified from multiple dimensions and tested in an external validation cohort.

Patients and methods

Study population

We retrospectively analyzed newly diagnosed ENKTL patients in two centers of China, patients hospitalized at Shandong Provincial Hospital from January 2011 to June 2020 constituting the training cohort and patients treated at the Affiliated Hospital of Qingdao University from January 2013 to June 2020 forming the external validation cohort. Two cohorts followed the same inclusion and exclusion criteria. The inclusion criteria were extranodal NK/T-cell lymphoma diagnosed by biopsy based on the WHO 2016 Classifications of mature lymphoid, histiocytic and dendritic neoplasms (19) and treatment-naïve. The key exclusion criteria were with incomplete clinical data and follow-up information or a history of other malignancies or major disease.

Data collection

The baseline data, such as gender, age, extranodal sites, bone marrow involvement, local lymph node involvement, distant lymph node involvement, primary site, primary tumor invasion, Eastern Cooperative Oncology Group (ECOG) score, Ann Arbor stage, B symptoms, international prognostic index (IPI), Korean Prognostic Index (KPI), Prognostic index of natural killer lymphoma (PINK) and PINK plus EBV (PINK-E) were gathered. Laboratory examinations, including serum lactate dehydrogenase (LDH), β2-microglobulin (β2-MG), ALB, ALC, TC and EBV DNA copies were collected.

Criteria of CONUT score

CONUT score criteria were shown in Supplementary Table 1.

Follow-up

The follow-up data, including therapeutic regimens and survival outcomes, were prospectively collected and retrospectively analyzed. The primary observation endpoint was overall survival (OS), followed by progression-free survival (PFS). OS was defined as the period from the date of diagnosis to the date of last follow-up or all-cause death. PFS was calculated as the interval from diagnosis to the first disease progression or last follow-up.

Statistical analyses

Continuous variables that did not fit the normal distribution were reported as medians [interquartile range (IQR)] and compared using the Mann–Whitney *U*-test. Normally distributed variables, reported as mean ± (standard deviation), were compared using the Student t test. Categorical data, presented as frequency (%), were compared using the Chi-squared test or Fisher's exact test. The dichotomous cutoff values of PNI were determined by receiver operating characteristic (ROC) curves according to the maximal associated J statistic (Youden's index). Cox proportional hazards regression model was used in univariate analyses (UVA) and multivariate analyses (MVA) and the results were presented as hazard ratio (HR) and 95% confidence interval (CI). Variables significantly associated with survival in the univariate analysis ($p < 0.05$) were brought into MVA and the further screened independent variables constituted the novel model, whose point assignment was defined according to the rounded regression coefficients (B). Harrell's C-statistic was calculated to reflect the predictive discriminability and calibration curves were plotted to estimate the performance of the proposed model. OS and PFS

10.3389/fnut.2023.1080181

estimated curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Alluvial plot shows the frequency and relationship between the risk grades of the novel model and its included risk factors in the total population of training and validation cohort. Time-dependent ROC curve analysis, decision curve analysis (DCA), net reclassification index (NRI) and integrated discrimination improvement (IDI) were performed to compare the predictive superiority of the novel model and the current scoring systems. $p < 0.05$ was considered statistically significant and all tests were two-tailed. Statistical analyses were executed by SPSS 25.0 (SPSS, Chicago, IL, United States) and R program (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria). Several packages were used in the R environment, including "rms," "forestplot," "CsChange," "Time-ROC," "stdca," "survIDINRI," "survival," "survminer," and "ggalluvial."

Results

Baseline clinical characteristics of cohorts

A total of 160 patients were included in the study, 80 patients in the training cohort and 80 patients in the external validation cohort. The baseline clinical characteristics in two cohorts were presented in Table 1. Most features between the two cohorts were comparable, including onset age ($p = 0.379$), sex distribution ($p = 0.177$), performance status ($p = 0.205$), bone marrow involvement ($p = 0.786$), involved extranodal sites ($p = 0.088$) and UADT involvement ($p = 0.256$). Nevertheless, some differences still existed in some characteristics between the training and validation cohort, such as Ann Arbor stage (III–IV stage, 27.5% vs. 48.8%, $p = 0.006$), LDH level (227.1 vs. 276.2 U/L, $p = 0.016$), IPI grades ($p = 0.001$), KPI grades ($p = 0.004$) and therapy schedules ($p = 0.012$). Patients in advanced stage accounted for a higher proportion in the validation cohort, which might explain the corresponding higher LDH level, more high-risk patients and more patients receiving chemotherapy alone in the validation cohort.

Association between nutritional indices and survival outcomes of ENKTL patients

We further conducted UVA and MVA to investigate the prognostic significance of PNI and CONUT score in ENKTL. UVA illustrated that PNI was an predictive factor to OS (HR [95% CI] = 2.275 [1.184–4.369], $p = 0.014$) but not to PFS (HR [95% CI] =1.653 [0.926–2.954], $p = 0.089$) while CONUT score was a significant predictor to both OS (HR [95% CI] =29.385 [9.583–90.102], $p < 0.001$) and PFS (HR [95% CI] =12.516 [5.899–26.558], $p < 0.001$; Table 2). Then all the significant variables ($p < 0.05$) in UVA were brought into MVA excluding PINK out of the consideration that PINK and PINK-E might have collinearity and PINK-E is a more integrated index. As shown in forest plot (Figure 1), MVA revealed that CONUT score could independently predict OS (HR [95% CI] =10.247 [2.589–40.554], $p = 0.001$) and PFS (HR [95% CI] =5.587 [2.087–14.953], $p = 0.001$) of ENKTL. The CONUT score-estimated Kaplan–Meier survival curves differentiated patients into two groups with distinct OS ($p < 0.001$) and PFS ($p < 0.001$; Supplementary Figure 1), verifying that CONUT score

TABLE 1 Basic clinical characteristics of the training and validation cohorts.

Variables	Training cohort (*n*=80)	Validation cohort (*n*=80)	*P*-value
Basic results			
Age, years	51.5 (41.5,60.0)	48.0 (37.3,57.8)	0.379
Sex (%)			
Female	22 (27.5%)	30 (37.5%)	0.177
Male	58 (72.5%)	50 (62.5%)	
ECOG score (%)			
<2	63 (78.8%)	56 (70.0%)	0.205
≥2	17 (21.2%)	24 (30.0%)	
BM involvement (%)			
Absence	72 (90.0%)	73 (91.3%)	0.786
Presence	8 (10.0%)	7 (8.7%)	
Extranodal sites (%)			
< 2	60 (75%)	50 (62.5%)	0.088
≥2	20 (25%)	30 (37.5%)	
Ann Arbor stage (%)			
I/II	58 (72.5%)	41 (51.2%)	0.006
III/IV	22 (27.5%)	39 (48.8%)	
Primary site (%)			
UADT	59 (73.8%)	65 (81.3%)	0.256
Non-UADT	21 (26.2%)	15 (18.7%)	
B symptoms (%)			
Absence	47 (58.8%)	40 (50.0%)	0.267
Presence	33 (41.2%)	40 (50.0%)	
Serological results			
LDH, U/L	227.1 (176.0, 305.5)	276.2 (198.7, 457.6)	0.016
β2-MG, mg/L	2.6 (2.2, 3.6)	2.3 (1.7, 3.1)	0.006
TC, mmol/L	4.4 (3.5, 5.1)	4.1 (3.4, 4.8)	0.079
ALB, g/L	37.3 (32.8, 39.9)	36.2 (32.2, 39.6)	0.354
ALC, 10^9/L	1.4 (0.8, 1.8)	1.3 (0.9, 1.6)	0.582
PNI	45.4 (41.2, 51.0)	45.4 (39.5, 48.2)	0.261
CONUT score	3.0 (1.0, 5.0)	4.0 (2.0, 5.0)	0.164
Clinical scoring systems			
IPI (%)			
Low risk (0/1)	46 (57.5%)	26 (32.5%)	0.001
Low-intermediate risk (2)	17 (21.3%)	13 (16.3%)	
Intermediate-high risk (3)	8 (10.0%)	18 (22.5%)	
High risk (4/5)	9 (11.3%)	23 (28.7%)	

(Continued)

TABLE 1 (Continued)

Variables	Training cohort (*n*=80)	Validation cohort (*n*=80)	*P*-value
KPI (%)			
Group1 (0)	13 (16.3%)	16 (20.0%)	0.004
Group2 (1)	29 (36.2%)	18 (22.5%)	
Group3 (2)	21 (26.2%)	10 (12.5%)	
Group4 (3/4)	17 (21.3%)	36 (45.0%)	
PINK (%)			
Low risk (0)	24 (30.0%)	12 (15.0%)	0.073
Intermediate risk (1)	25 (31.3%)	32 (40.0%)	
High risk (2/3/4)	31 (38.7%)	36 (45.0%)	
PINK-E (%)			
Low risk (0/1)	39 (48.8%)	35 (43.8%)	0.536
Intermediate risk (2)	16 (20.0%)	22 (27.5%)	
High risk (3/4/5)	25 (31.2%)	23 (28.7%)	
Therapy (%)			
CT alone	30 (37.5%)	48 (60.0%)	0.012
RT alone	12 (15.0%)	5 (6.3%)	
CRT	38 (47.5%)	27 (33.8%)	

ECOG, Eastern Cooperative Oncology Group; BM, bone marrow; UADT, upper aerodigestive tract; LDH, lactate dehydrogenase; β2-MG, beta-2 microglobulin; TC, serum total cholesterol; ALB, serum albumin; ALC, absolute lymphocyte count; PNI, Prognostic Nutritional Index; CONUT, Controlling Nutritional Status score; IPI, international prognostic index; KPI, Korean Prognostic Index; PINK, Prognostic index of natural killer lymphoma; PINK-E, PINK plus Epstein–Barr virus (EBV); CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy.

could serve as a competent index to screen prognosis-related malnutrition in ENKTL.

Derivation of a reformative stratification model, CONUT-PINK-E

Since the prognostic capacity of CONUT score has been verified, we attempted to establish a CONUT score-included prognostic model for ENKTL. MVA hinted that PINK-E was another independent predictive marker to OS (PINK-E = 2, HR [95% CI] =3.842 [1.108–13.325], $p = 0.034$; PINK-E = 3/4/5, HR [95% CI] =9.185 [1.888–44.688], $p = 0.006$) and PFS (PINK-E = 2, HR [95% CI] =2.308 [0.964–5.526], $p = 0.06$; PINK-E = 3/4/5, HR [95% CI] =4.535 [1.613–12.751], $p = 0.004$). Meanwhile, PINK-E-estimated survival curves also reverified its qualification as a prognostic marker (Supplementary Figure 1).

Based on the above findings, we reformed PINK-E through incorporating with CONUT score and established an integrated prognostic model, CONUT-PINK-E. The reformative model contains six risk factors, including age ≥ 60 years old, Ann Arbor stage III/IV, distant lymph node involvement, non-nasal type, detectable EBV-DNA in blood and moderate/severe malnutrition (CONUT score ≥ 5). We need to collect 8 variables to get a point of CONUT-PINK-E, including age, Ann Arbor stage, distant lymph node involvement, non-nasal type, detectable EBV-DNA, ALB, TC and ALC. Based on CONUT score, ALB concentrations of ≥3.50 g/dL, 3.00–3.49 g/dL, 2.50–2.99 g/dL, and <2.50 g/dL were scored as 0, 2, 4, and 6 points, TC levels of ≥180 mg/dL, 140–179 mg/dL, 100–139 mg/dL, and <100 mg/dL were endowed with 0, 1, 2, and 3 points, and ALC of ≥1,600/mm^3, 1,200–1,599/mm^3, 800–1,199/mm^3, and <800/mm^3 were scored as 0, 1, 2, and 3 points, separately. Once the sum of CONUT score arrived 5, it would be regarded as an unfavorable risk factor in the CONUT-PINK-E scoring system. In the novel model, CONUT score ≥ 5 was endowed with two points, PINK-E = 2 with one point and PINK-E = 3/4/5 with two points in accordance with their rounded regression coefficients (B; Figure 1). CONUT-PINK-E was calculated as a sum of points and differentiated patients into five groups: 0 point (no or just one risk factor of PINK-E), 1 point (two risk factors of PINK-E), 2 points (CONUT score ≥ 5 or over 3 risk factors of PINK-E), 3 points (CONUT score ≥ 5 and 2 risk factors of PINK-E), and 4 points (CONUT score ≥ 5 and over 3 risk factors of PINK-E).

Capacity of CONUT-PINK-E in survival prediction of ENKTL patients

To Figure out the predictive ability of CONUT-PINK-E, we assessed its discrimination and calibration in the training cohort and verified them in the external validation cohort. In the training cohort, the Harrell's C-statistic for OS and PFS prediction was 0.860 (95% CI, 0.821–0.899) and 0.808 (95% CI, 0.760–0.856; Supplementary Table 2), and the calibration plots for the probability of 1-, 2-, and 3-year OS and PFS showed great consistence between the prediction and actual observation (Figures 2A,B). Similarly, in the validation cohort, the Harrell's C-statistic for OS and PFS prediction was 0.848(95% CI, 0.799–0.897) and 0.811(95% CI, 0.762–0.859), and the calibration plots presented that 1-, 2-, and 3-year prediction perfectly coincided with the actual observation (Figures 2C,D). The results indicated that the predictive capacity of CONUT-PINK-E was encouraging and reliable.

Prognostic performance of CONUT-PINK-E in survival risk stratification

The overall median OS was 51 (95% CI, 29.3–72.7) months and the 3- and 5-year OS rates were 50.9% and 38.2%, while the median PFS was 23 (95% CI, 17.1–28.9) months and the 3-year PFS rate was 23.2% in the training cohort. The corresponding data of the validation cohort was 48 (95% CI, 34.2–61.8) months, 57.4, 35.3% and 20 (95% CI, 13.0–27.0) months, 30.4%, respectively (Supplementary Table 3). The survival outcomes of two cohorts were close.

Kaplan–Meier curves were plotted to examine the survival outcomes of patients with different CONUT-PINK-E scores. In the training cohort, the OS of patients with 0, 1, 2, 3, 4 points of CONUT-PINK-E was 74.0 (95%CI, 50.2–97.8), 51.0 (95%CI, 12.8–89.2), 36.0 (95%CI, NA-NA), 14.0 (95%CI, 9.6–18.4), and 4.0 (95%CI, 2.6–5.4), respectively. The corresponding data of PFS was separately 32.0 (95%CI, 26.6–37.4), 26.0 (95%CI, 18.5–33.5), 14.0 (95%CI, 0–29.5), 6.0 (95%CI, 3.9–8.1), and 2.0 (95%CI, 0–5.1). As shown in Supplementary Figure 3A, no significant difference was

TABLE 2 Univariate analysis of OS and PFS in the training cohort.

Basic results	OS				PFS			
	B	SE	HR (95%CI)	*P*-value	B	SE	HR (95%CI)	*P*-value
Age, ≥60 vs. < 60, years	0.668	0.393	1.951 (0.903–4.217)	0.089	0.411	0.342	1.508 (0.771–2.951)	0.230
Sex, male vs. female	−0.218	0.370	0.804 (0.390–1.659)	0.555	−0.069	0.319	0.933 (−0.500–1.742)	0.828
ECOG score, ≥2 vs. < 2	0.820	0.362	2.271 (1.117–4.620)	**0.024**	0.618	0.322	1.855 (0.986–3.489)	0.055
BM involvement, presence vs. absence	0.876	0.450	2.401 (0.995–5.797)	0.051	0.471	0.437	1.601 (0.680–3.772)	0.282
Extranodal sites, ≥2 vs. < 2	0.623	0.364	1.864 (0.913–3.804)	0.087	0.464	0.313	1.590 (0.861–2.938)	0.139
Ann Arbor Stage, III/IV vs. I/II	0.651	0.334	1.917 (0.996–3.692)	0.052	0.554	0.290	1.740 (0.985–3.074)	0.057
B symptoms, presence vs. absence	0.341	0.335	1.407 (0.730–2.712)	0.308	0.412	0.279	1.510 (0.874–2.610)	0.140
LDH, ≥250 vs. < 250, U/L	0.850	0.353	2.340 (1.171–4.675)	**0.016**	0.664	0.302	1.942 (1.074–3.513)	**0.028**
β2-MG, ≥3 vs. < 3, mg/L	0.970	0.346	2.639 (1.339–5.198)	**0.005**	0.771	0.288	2.161 (1.229–3.802)	**0.007**
PNI, ≤45 vs. > 45	0.822	0.333	2.275 (1.184–4.369)	**0.014**	0.503	0.296	1.653 (0.926–2.954)	0.089
CONUT score, 5–12 vs. 0–4	3.380	0.572	29.385 (9.583–90.102)	**<0.001**	2.527	0.384	12.516 (5.899–26.558)	**<0.001**
IPI				**<0.001**				**<0.001**
0–1	Reference				Reference			
2	1.205	0.427	3.336 (1.445–7.704)	**0.005**	0.820	0.357	2.270 (1.128–4.566)	**0.022**
3	2.217	0.578	9.182 (2.958–28.505)	**<0.001**	1.473	0.522	4.364 (1.570–12.130)	**0.005**
4–5	2.267	0.521	9.651 (3.476–26.794)	**<0.001**	1.630	0.427	5.105 (2.210–11.789)	**<0.001**
KPI				**<0.001**				**<0.001**
0	Reference				Reference			
1	0.156	0.520	1.169 (0.422–3.242)	0.764	0.107	0.386	1.113 (0.522–2.370)	0.782
2	0.553	0.536	1.739 (0.608–4.973)	0.302	0.360	0.421	1.434 (0.628–3.273)	0.393
3–4	2.338	0.559	10.356 (3.459–31.006)	**<0.001**	1.627	0.428	5.090 (2.198–11.786)	**<0.001**
PINK				**<0.001**				**<0.001**
0	Reference				Reference			
1	0.368	0.517	1.445 (0.524–3.980)	0.477	0.003	0.362	1.003 (0.494–2.039)	0.993
2–4	2.661	0.551	14.309 (4.857–42.158)	**<0.001**	1.709	0.362	5.522 (2.719–11.216)	**<0.001**
PINK-E				**<0.001**				**<0.001**
0–1	Reference				Reference			
2	1.382	0.466	3.984 (1.598–9.934)	**0.003**	0.992	0.362	2.695 (1.325–5.484)	**0.006**
3–5	2.709	0.482	15.022 (5.837–38.661)	**<0.001**	2.036	0.346	7.657 (3.884–15.096)	**<0.001**
Therapy								
RT alone	Reference			**0.059**	Reference			**0.402**
CT alone	1.152	0.757	3.163(0.717–13.948)	**0.128**	0.109	0.461	1.115(0.452–2.751)	**0.813**
CRT	0.297	0.769	1.346(0.298–6.077)	**0.699**	0.407	0.304	1.503(0.828–2.727)	**0.180**

ECOG, Eastern Cooperative Oncology Group; BM, bone marrow; LDH, lactate dehydrogenase; β2-MG, beta-2 microglobulin; PNI, prognostic nutritional index; CONUT score, Controlling Nutritional Status score; IPI, international prognostic index; KPI, Korean Prognostic Index; PINK, Prognostic index of natural killer lymphoma; PINK-E, PINK plus Epstein–Barr virus (EBV); OS, overall survival; PFS, progression-free survival; B, coefficient; SE, standard error; HR, Hazard ratio; CI, confidence interval. The bold values mean statistically significant.

observed in OS of patients with 0 or 1 point ($p = 0.118$) and patients with 3 or 4 points ($p = 0.466$). While gradual widening of the survival gap between patients with 1 point or 2 points was observed over time, although the sample size of subgroup limited its statistical significance. Patients with 2 or 3 points exhibited significant survival differences ($p = 0.034$). The survival curve of PFS showed a similar trend (Supplementary Figure 3B). Therefore, we divided patients into three risk layers according to survival differences (Figure 3). Patients with 0 or 1 point were included in the low-risk group due to the relatively superior survival, while

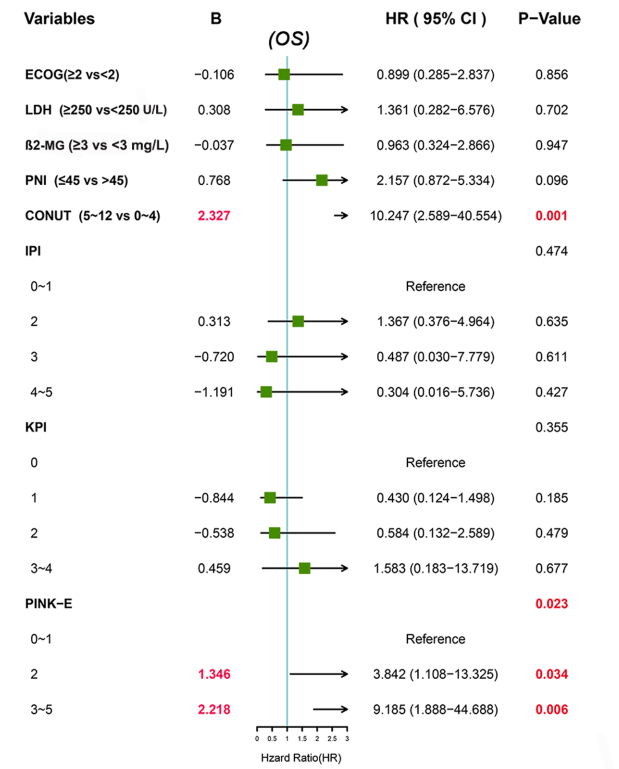


FIGURE 1
Forest plots of multivariate analysis for OS and PFS.

patients with 2 points were assigned to the intermediate-risk group and patients with 3 or 4 points were classified as high-risk group due to sequentially-shorten survival.

In the training cohort, the median OS of the low-risk group was 74.0 (95%CI, 55.0–93.0) months, significantly superior than 36.0 (NA-NA) and 5.0 (0.3–9.7) months of intermediate- and high-risk group, respectively ($p < 0.001$, Figure 3A; Supplementary Table 4). Afterwards, we further examined the performance of the stratifying rules in the external validation cohort. Significant OS differences ($p < 0.001$) also existed among three risk grades, and the median OS was 72.0 (95%CI, 49.0–95.0), 26.0 (95%CI, 9.6–42.4), and 7.0 (95%CI, 4.7–9.3) months for low-, intermediate- and high-risk, respectively (Figure 3B; Supplementary Table 4). The 3-year OS rate was 77.7 and 85.4% for the low-risk group, while 9.9% and 0 for high-risk group in the training and validation cohort. In addition, the performance of CONUT-PINK-E in PFS risk stratification was equally impressing (Figures 3C,D; Supplementary Table 4). The 2-year PFS rate was 71.5% and 72.6%, 0 and 0 for low- and high-risk group, respectively (Supplementary Table 4). These indicate that CONUT-PINK-E has strong correlation with patients' survival and can effectively stratify patients.

Alluvial plot exhibited the frequency and relationship between the CONUT-PINK-E and its constituent factors, CONUT and PINK-E, in the total 160 patients. The gray blocks represented the detailed scores and the colorful blocks symbolized the risk groups, while the width of the ribbons corresponded to the percentage of patients who had the same CONUT score, PINK-E and risk group assigned. In the total population, patients in the CONUT-PINK-E low risk group accounted for the majority and no patients with CONUT score < 5 were divided into CONUT-PINK-E high risk group (Figure 3E).

Performance comparison between CONUT-PINK-E and the current scoring systems

CONUT-PINK-E has been proved capable of serving as an outstanding prognostic model for ENKTL. Naturally, we will compare its performance with the present scoring systems, including IPI, KPI, PINK and PINK-E. Primarily, the discrimination parameter, Harrell's C-statistic of CONUT-PINK-E was 0.860 (95% CI, 0.821–0.899), significantly higher than 0.744 (95% CI, 0.672–0.816) of IPI ($p = 0.001$), 0.748 (95% CI, 0.681–0.814) of KPI ($p = 0.001$), 0.792 (95% CI, 0.745–0.838) of PINK ($p = 0.001$) and 0.809 (95% CI, 0.762–0.857) of PINK-E ($p = 0.001$) for OS prediction in the training cohort (Supplementary Table 2). The similar superiority in discrimination for OS prediction in the validation cohort and PFS prediction in both training and validation cohort were also confirmed (Supplementary Table 2).

Time-dependent AUC, a more precise parameter reflecting discrimination, was further measured. The 1- to 5-year time-dependent AUCs with a range for CONUT-PINK-E, IPI, KPI, PINK and PINK-E were ordinally 0.832–0.961, 0.710–0.785 ($p < 0.001$),

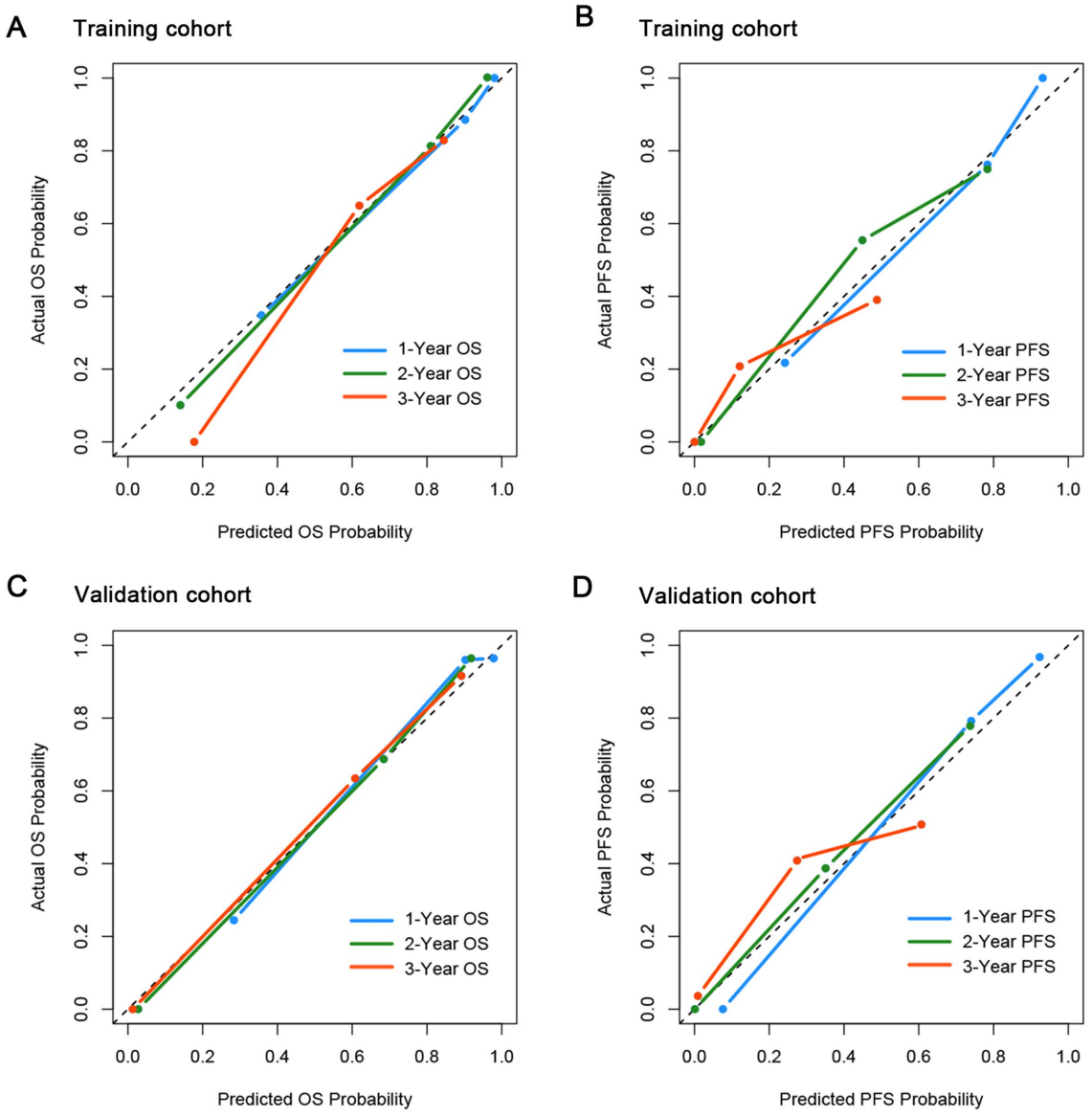


FIGURE 2
Calibration curves for the probability of OS and PFS in the training and validation cohort. **(A)** for OS in the training cohort; **(B)** for PFS in the training cohort; **(C)** for OS in the validation cohort; **(D)** for PFS in the validation cohort.

0.659–0.826 ($p < 0.001$), 0.802–0.883 ($p < 0.001$) and 0.815–0.902 ($p < 0.001$) in the training cohort (Figure 4A; Supplementary Table 5). The corresponding data in the validation cohort were 0.773–0.937, 0.646–0.840 ($p < 0.001$), 0.623–0.691 ($p < 0.001$), 0.663–0.842 ($p < 0.001$) and 0.741–0.894 ($p < 0.001$, Figure 4B; Supplementary Table 5). The time-dependent AUCs of CONUT-PINK-E in PFS prediction were consistently higher than those of IPI, KPI, PINK and PINK-E in both training and validation cohort (Supplementary Figure 4; Supplementary Table 5). The above results demonstrated that CONUT-PINK-E possessed higher discrimination than the existing models in stratifying ENKTL patients.

The IDI and NRI were calculated to examine the amelioration after incorporating CONUT score with PINK-E and reclassifying the risk grades. CONUT-PINK-E possessed positive IDI and NRI in 1-, 2-, and 3-year OS and PFS prediction in two cohorts, suggesting that CONUT-PINK-E achieved significant improvements compared with the current prognostic tools, which simultaneously indicated that nutritional status played a vital role in the prognosis of ENKTL (Supplementary Tables 6, 7).

DCA was conclusively performed to examine the clinical utility of CONUT-PINK-E, since decision curve could graphically present the clinical value of a prognostic tool based on a continuum of potential thresholds for risk of death (the x-axis) and the net benefit of using the model to stratify patients relative to the assumption that no patient would be dead (the y-axis). The result demonstrated CONUT-PINK-E brought higher net benefits than IPI, KPI, PINK and PINK-E in forecasting OS and PFS of ENKTL patients (OS: Figures 4C,D; PFS: Supplementary Figure 4).

10.3389/fnut.2023.1080181

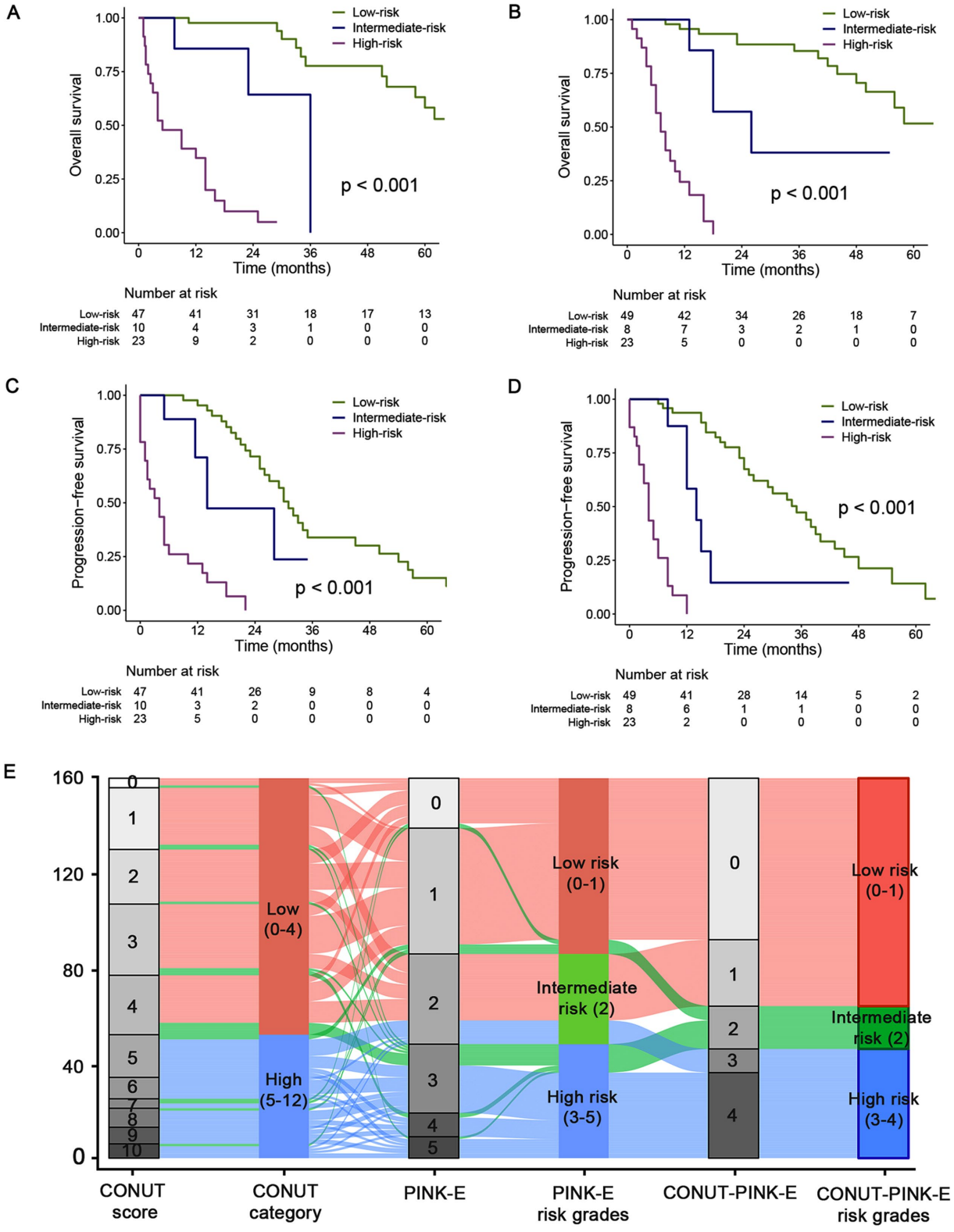


FIGURE 3
Kaplan–Meier estimated OS and PFS curves of CONUT-PINK-E grades and alluvial plot in the training and validation cohorts. Low risk group with CONUT-PINK-E=0/1; Intermediate risk group with CONUT-PINK-E=2; High risk group with CONUT-PINK-E=3/4. **(A,C)** For OS and PFS in training cohort; **(B,D)** For OS and PFS in the external validation cohort; **(E)** the alluvial plot shows the frequency and relationship between the CONUT-PINK-E risk stratifications and the included risk factors in the total population of training and validation cohort. The width of the ribbons corresponds to the percentage of patients who had the same CONUT score, PINK-E and risk group assigned.

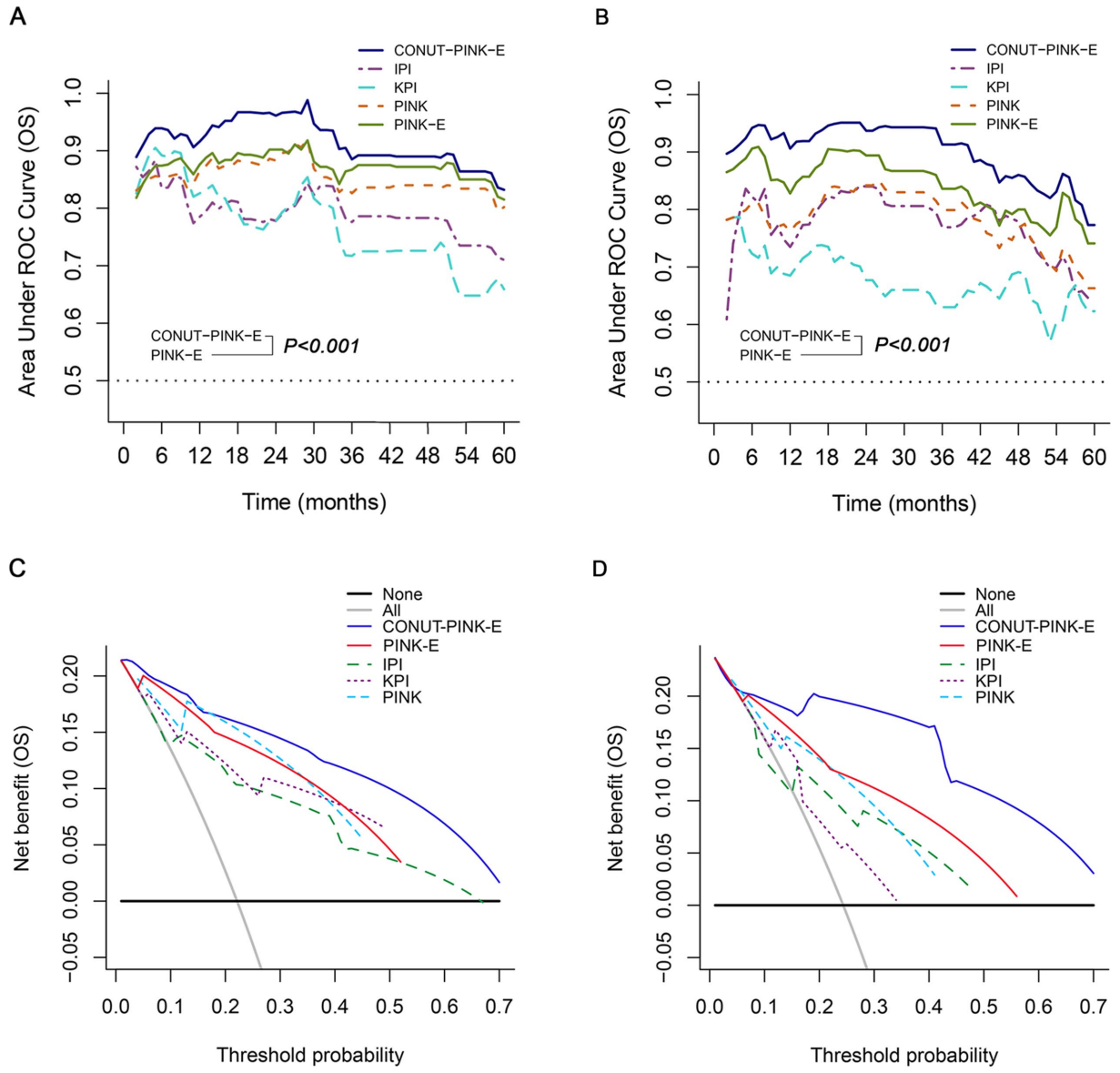


FIGURE 4
Performance of CONUT-PINK-E in predicting OS in the training and external validation cohorts. Comparison of time-dependent AUCs among CONUT-PINK-E and IPI, KPI, PINK, PINK-E **(A)** in the training cohort, **(B)** in the external validation cohort; Decision curve contrasts of CONUT-PINK-E and IPI, KPI, PINK, PINK-E **(C)** in the training cohort, **(D)** in the external validation cohort.

Discussion

In this study, we provided new arguments to support the correlation between malnutrition and lymphoma, where malnutrition was strongly associated with inferior survival outcomes of patients with ENKTL. CONUT score, as an index reflecting long-term nutritional status, was a powerful tool to screen prognosis-related malnutrition in ENKTL, outperforming the PNI score. Additionally, CONUT score ≥ 5 served as an independent marker indicating unfavorable outcomes, which further confirmed the critical role of malnutrition in ENKTL and hinted us that combining CONUT score with another independent factor, PINK-E, might get better stratifying performance. Thus, the first nutrition evaluation-incorporated risk stratifying system for ENKTL patients, CONUT-PINK-E, was delivered. CONUT-PINK-E was composed of simple laboratorial and imaging parameters, reliable and accessible, might provide helpful reference for individualized nutritional and metabolic care.

Nutrition has been gradually regarded as a critical factor involved in the progression of malignancies (20), since nutrition could change drug metabolic pathways and interfere the expression of drug transporters, resulting in slower clearance of anticancer drugs and enhancive treatment-related toxicities (21). Nutrition status can be assessed by various indicators, including but not limited to body weight, triceps skin fold thickness, mid-arm muscle circumference, BMI, ALB, ALC, transferrin and creatinine to height ratio (15, 22). Nonetheless, previous studies verified that parameters, like BMI, ALC and ALB, were not significant enough to serve as independent survival indicators against the CONUT score in various cancers (14, 23, 24).

PNI, a serology-derived nutrition parameter, was originally developed for perioperative patients and afterwards generalized into patients with malignancies, which was also found less valuable than CONUT score in survival prediction for multiple malignancies (25, 26). Consistent with fore-mentioned reports, our study also found that CONUT score was a more comprehensive and efficient tool to detect malnutrition for survival prediction in ENKTL, of which ALB mainly reflects the patient's nutritional status, ALC serves as a marker of nutrition and immune response and TC has been verified significantly associated with the long-term prognosis of mature T- and NK-cell neoplasms in our previous report (27).

Previously, numerous prognostic tools have been proposed for ENKTL, such as IPI (28), KPI (29) developed in CHOP or CHOP-like era (30) and PINK or PINK-E (31) derived in non-anthracycline-based chemotherapy era. However, IPI and KPI became less useful with the abandonment of anthracycline-containing regimen (32). PINK and PINK-E behaved well but presented limitations in guiding the suitable therapeutic regimens (33). Our study also showed that PINK-E performed best among the existing prognostic systems. Nevertheless, the performance of PINK-E acquired further amelioration by incorporating with CONUT score. CONUT-PINK-E behaved better in discrimination, calibration and clinical net benefit than IPI, KPI, PINK and PINK-E. The high-risk patients identified by CONUT-PINK-E presented worse survival than those identified by the existed models, hinting us their treatment schedules should be more deliberative. The treatment landscape for ENKTL has evolved in last decades, with accumulating evidence supporting systemic L-Asparaginase incorporated non-anthracycline-based chemotherapy was an optimal choice for advanced-stage and relapsed or refractory ENKTL (2, 31). Despite this, a portion of advanced patients face the dilemma aborting the treatment schedules due to the intolerable toxicities (34). The CONUT-PINK-E score targeted this challenge and provided vital theoretical guidance for clinical decision-making. Although few nutrition interventional studies for specific types of hematological tumors were being conducted (7), suggestions from clinical nutritionists and multidisciplinary consultations can favor to develop more rational treatment schedules, helping patients to endure long-term intensive chemotherapy. Furthermore, with the awareness of the relationship between malnutrition and malignancies, increasing number of nutrition interventional studies would be conducted and nutrition intervention schemes would be listed in the guidelines of cancer treatment.

Nevertheless, the limitations should be addressed. First, CONUT-PINK-E was derived from retrospective study, which had its inherent biases. Second, the sample size was relatively modest, although independent external validation was performed to increase the credibility. Third, fewer patients in this study experienced immunotherapy or HSCT, making it impossible to compare the prognostic influence of different therapies for patients under the same risk stratification.

In future, with the increasement of sample size and therapy options, subgroup analysis of different therapies for patients under the same risk stratification might be conducted, which could help to identify the specific subgroups who would benefit most from CONUT-PINK-E system.

In conclusion, it is the first time that CONUT score was recognized to act as an independent prognostic parameter in newly diagnosed ENKTL patients. More importantly, the first risk stratification system covering nutritional status assessment for ENKTL patients, CONUT-PINK-E, was derived from the data of two centers in China. The data in our study, including treatment therapies and survival outcomes, were consistent with the precedent large-scale, real-world reports. Based on that, CONUT-PINK-E presented better discrimination, calibration, prognostic performance, stability than the existed prognostic models, suggesting that it would provide convinced guidance for ENKTL patients' clinical decision-making.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors on a reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethical Committee of Shandong Provincial Hospital Affiliated to Shandong University and the Medical Ethical Committee of Affiliated Hospital of Qingdao University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

TL: study concept and design, data analysis, and writing the manuscript. XS and YL: data collection of the external validation cohort. XG, MD, and XF: data acquisition of the training cohort. YC, XC, and SH: patients' follow-up. FL: study concept and design. XW and XZ: study supervision and manuscript revision. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by National Natural Science Foundation (nos. 82170189, 82070203, 81800194, and 81770210), Key Research and Development Program of Shandong Province (no. 2018CXGC1213), Development Project of Youth Innovation Teams in Colleges and Universities of Shandong Province (no. 2020KJL006), China Postdoctoral Science Foundation (nos. 2021T140422 and 2020M672103), Translational Research Grant of NCRCH (nos. 2021WWB02 and 2020ZKMB01), Shandong Provincial Natural Science Foundation (nos. ZR2021YQ51 and ZR2020MH124), Technology Development Project of Jinan City (no. 202134034), Taishan Scholars Program of Shandong Province, Shandong Provincial Engineering Research Center of Lymphoma, and Academic Promotion Programme of Shandong First Medical University (nos. 2019QL018 and 2020RC006).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1080181/full#supplementary-material

References

1. Chen SY, Yang Y, Qi SN, Wang Y, Hu C, He X, et al. Validation of nomogram-revised risk index and comparison with other models for extranodal nasal-type NK/T-cell lymphoma in the modern chemotherapy era: indication for prognostication and clinical decision-making. *Leukemia*. (2021) 35:130–42. doi: 10.1038/s41375-020-0791-3

2. Fox CP, Civallero M, Ko YH, Manni M, Skrypets T, Pileri S, et al. Survival outcomes of patients with extranodal natural-killer T-cell lymphoma: a prospective cohort study from the international T-cell project. *Lancet Haematol*. (2020) 7:e284–94. doi: 10.1016/S2352-3026(19)30283-2

3. Marchi E, O'Connor OA. The rapidly changing landscape in mature T-cell lymphoma (MTCL) biology and management. *CA Cancer J Clin*. (2020) 70:47–70. doi: 10.3322/caac.21589

4. Kim H, Jeong H, Yamaguchi M, Sohn I, Yoon SE, Byeon S, et al. Prediction and prevention of central nervous system relapse in patients with extranodal natural killer/T-cell lymphoma. *Blood*. (2020) 136:2548–56. doi: 10.1182/blood.2020005026

5. Arends J. Struggling with nutrition in patients with advanced cancer: nutrition and nourishment-focusing on metabolism and supportive care. *Ann Oncol*. (2018) 29:ii27–34. doi: 10.1093/annonc/mdy093

6. Ravasco P, Monteiro Grillo I, Camilo M. Cancer wasting and quality of life react to early individualized nutritional counselling! *Clin Nutr*. (2007) 26:7–15. doi: 10.1016/j.clnu.2006.10.005

7. Mancuso S, Mattana M, Santoro M, Carlisi M, Buscemi S, Siragusa S. Host-related factors and cancer: malnutrition and non-Hodgkin lymphoma. *Hematol Oncol*. (2022) 40:320–31. doi: 10.1002/hon.3002

8. Ureshino H, Kusaba K, Kidoguchi K, Sano H, Nishioka A, Itamura H, et al. Clinical impact of the CONUT score and mogamulizumab in adult T cell leukemia/lymphoma. *Ann Hematol*. (2019) 98:465–71. doi: 10.1007/s00277-018-3502-7

9. Van der Schueren MAE D, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. *Ann Oncol*. (2018) 29:1141–53. doi: 10.1093/annonc/mdy114

10. Wang Z, Wang Y, Zhang X, Zhang T. Pretreatment prognostic nutritional index as a prognostic factor in lung cancer: review and meta-analysis. *Clin Chim Acta*. (2018) 486:303–10. doi: 10.1016/j.cca.2018.08.030

11. Kubrak C, Martin L, Gramlich L, Scrimger R, Jha N, Debenham B, et al. Prevalence and prognostic significance of malnutrition in patients with cancers of the head and neck. *Clin Nutr*. (2020) 39:901–9. doi: 10.1016/j.clnu.2019.03.030

12. Kuroda D, Sawayama H, Kurashige J, Iwatsuki M, Eto T, Tokunaga R, et al. Controlling nutritional status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. *Gastric Cancer*. (2018) 21:204–12. doi: 10.1007/s10120-017-0744-3

13. Xiao H, Zhou H, Zhang P, Xiao H, Liu K, Chen X, et al. Association among the prognostic nutritional index, completion of adjuvant chemotherapy, and cancer-specific survival after curative resection of stage II/III gastric cancer. *Eur J Clin Nutr*. (2020) 74:555–64. doi: 10.1038/s41430-019-0502-1

14. Kheirouri S, Alizadeh M. Prognostic potential of the preoperative controlling nutritional status (CONUT) score in predicting survival of patients with cancer: a systematic review. *Adv Nutr*. (2021) 12:234–50. doi: 10.1093/advances/nmaa102

15. Jiang K, Singh Maharjan SR, Slee A, Davenport A. Differences between anthropometric and bioimpedance measurements of muscle mass in the arm and hand grip and pinch strength in patients with chronic kidney disease. *Clin Nutr*. (2021) 40:320–3. doi: 10.1016/j.clnu.2020.04.026

16. Palleschi M, Scarpi E, Casadei C. Body mass index (BMI) and benefit from adjuvant chemotherapy in breast cancer: is it enough? *Breast Cancer Res Treat*. (2021) 185:255–6. doi: 10.1007/s10549-020-05923-9

17. Okadome K, Baba Y, Yagi T, Kiyozumi Y, Ishimoto T, Iwatsuki M, et al. Prognostic nutritional index, tumor-infiltrating lymphocytes, and prognosis in patients with esophageal cancer. *Ann Surg*. (2020) 271:693–700. doi: 10.1097/SLA.0000000000002985

18. Li Y, Zhang C, Ji R, Lu H, Zhang W, Li LL, et al. Prognostic significance of the controlling nutritional status (CONUT) score in epithelial ovarian cancer. *Int J Gynecol Cancer*. (2020) 30:74–82. doi: 10.1136/ijgc-2019-000865

19. Cazzola M. Introduction to a review series: the 2016 revision of the WHO classification of tumors of hematopoietic and lymphoid tissues. *Blood*. (2016) 127:2361–4. doi: 10.1182/blood-2016-03-657379

20. Zhou X, Sun X, Zhao W, Fang X, Wang X. Prognostic significance of peripheral blood absolute lymphocyte count and derived neutrophil to lymphocyte ratio in patients with newly diagnosed extranodal natural killer/T-cell lymphoma. *Cancer Manag Res*. (2019) 11:4243–54. doi: 10.2147/CMAR.S193397

21. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. (2014) 15:e493–503. doi: 10.1016/S1470-2045(14)70263-3

22. Tarantino G, Vinciguerra M, Ragosta A, Citro V, Conforti P, Salvati G, et al. Do transferrin levels predict Haemodialysis adequacy in patients with end-stage renal disease? *Nutrients*. (2019) 11:1123. doi: 10.3390/nu11051123

23. Harimoto N, Yoshizumi T, Inokuchi S, Itoh S, Adachi E, Ikeda Y, et al. Prognostic significance of preoperative controlling nutritional status (CONUT) score in patients undergoing hepatic resection for hepatocellular carcinoma: a multi-institutional study. *Ann Surg Oncol*. (2018) 25:3316–23. doi: 10.1245/s10434-018-6672-6

24. Harimoto N, Yoshizumi T, Sakata K, Nagatsu A, Motomura T, Itoh S, et al. Prognostic significance of preoperative controlling nutritional status (CONUT) score in patients undergoing hepatic resection for hepatocellular carcinoma. *World J Surg*. (2017) 41:2805–12. doi: 10.1007/s00268-017-4097-1

25. Takagi K, Buettner S, Ijzermans JNM. Prognostic significance of the controlling nutritional status (CONUT) score in patients with colorectal cancer: a systematic review and meta-analysis. *Int J Surg*. (2020) 78:91–6. doi: 10.1016/j.ijsu.2020.04.046

26. Mao YS, Hao SJ, Zou CF, Xie ZB, Fu DL. Controlling nutritional status score is superior to prognostic nutritional index score in predicting survival and complications in pancreatic ductal adenocarcinoma: a Chinese propensity score matching study. *Br J Nutr*. (2020) 124:1190–7. doi: 10.1017/S0007114520002299

27. Lu T, Shi L, Shi G, Cai Y, Hu S, Liu J, et al. Derivation and validation of a lipid-covered prognostic model for mature T-cell lymphomas. *Cancer Cell Int*. (2021) 21:348. doi: 10.1186/s12935-021-02042-3

28. Au WY, Weisenburger DD, Intragumtornchai T, Nakamura S, Kim WS, Sng I, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the international peripheral T-cell lymphoma project. *Blood*. (2009) 113:3931–7. doi: 10.1182/blood-2008-10-185256

29. Lee J, Suh C, Park YH, Ko YH, Bang SM, Lee JH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. *J Clin Oncol*. (2006) 24:612–8. doi: 10.1200/JCO.2005.04.1384

30. Yang Y, Zhang YJ, Zhu Y, Cao JZ, Yuan ZY, Xu LM, et al. Prognostic nomogram for overall survival in previously untreated patients with extranodal NK/T-cell lymphoma, nasal-type: a multicenter study. *Leukemia*. (2015) 29:1571–7. doi: 10.1038/leu.2015.44

31. Kim SJ, Yoon DH, Jaccard A, Chng WJ, Lim ST, Hong H, et al. A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. *Lancet Oncol*. (2016) 17:389–400. doi: 10.1016/S1470-2045(15)00533-1

32. Tse E, Kwong YL. The diagnosis and management of NK/T-cell lymphomas. *J Hematol Oncol*. (2017) 10:85. doi: 10.1186/s13045-017-0452-9

33. Tse E, Kwong YL. Diagnosis and management of extranodal NK/T cell lymphoma nasal type. *Expert Rev Hematol*. (2016) 9:861–71. doi: 10.1080/17474086.2016.1206465

34. Tobberup R, Thoresen L, Falkmer UG, Yilmaz MK, Solheim TS, Balstad TR. Effects of current parenteral nutrition treatment on health-related quality of life, physical function, nutritional status, survival and adverse events exclusively in patients with advanced cancer: a systematic literature review. *Crit Rev Oncol Hematol*. (2019) 139:96–107. doi: 10.1016/j.critrevonc.2019.04.014

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 24 July 2023
DOI 10.3389/fnut.2023.1043550

OPEN ACCESS

EDITED BY
Paula Ravasco,
Catholic University of Portugal, Portugal

REVIEWED BY
Xudong Liu,
Guangdong Pharmaceutical University, China
Aparna Gangopadhyay,
Other, India

*CORRESPONDENCE
Xiaohua Li
✉ xjyylixiaohua@163.com

†These authors have contributed equally to this work

RECEIVED 13 September 2022
ACCEPTED 23 June 2023
PUBLISHED 24 July 2023

CITATION
Wei J, Lu J, Jia H, Yang X, Guo X, Liu J and Li X (2023) Value of a preoperative prognostic nutritional index for the prognostic evaluation of gastric neuroendocrine carcinoma patients. *Front. Nutr.* 10:1043550. doi: 10.3389/fnut.2023.1043550

Value of a preoperative prognostic nutritional index for the prognostic evaluation of gastric neuroendocrine carcinoma patients

Jiangpeng Wei†, Ju Lu†, Hanxiang Jia†, Xisheng Yang, Xin Guo, Jinqiang Liu and Xiaohua Li*

Department of Gastrointestinal Surgery, Xijing Hospital, Air Force Military Medical University, Xi'an, Shaanxi, China

Objective: To study the value of Onodera's prognostic nutrition index (PNI) in patients with gastric neuroendocrine cancer (G-NEC).

Methods: The clinical data on 148 cases of G-NEC presented between March 2010 and April 2022 were retrospectively analyzed. The relationship between the clinical characteristics of the patients and PNI was analyzed. Optimal PNI cutoff values for G-NEC prognosis prediction were calculated using the X-tile software. The survival curves were created using the Kaplan–Meier method. A Cox proportional hazards model was also established to identify independent prognostic factors that impact the prognosis of patients with G-NEC.

Results: The median overall survival (OS) rate was 30 months (range 6–127 months), and the OS rates at 1, 3 and 5 years were 89.2, 71.6 and 68.2%, respectively. The mean PNI of the 148 patients before the operation was 49.5±8.0. The mean PNI of patients with anemia ($p<0.001$) and abnormal carcinoembryonic antigen ($p=0.039$) was significantly lower than that of patients without such comorbidities. The mean PNI of patients with Stage III tumors ($p<0.001$) and postoperative complications was significantly lower ($p=0.005$). PNI optimal cutoff values were 50 ($p<0.001$). Based on the cut-off value of the PNI, these patients were divided into a PNI-high group (PNI≥50.0, $n=77$) and a PNI-low group (PNI<50.0, $n=71$). The PNI-high group had a significantly better 5-years OS rate compared with the PNI-low group (76.6% vs. 59.2%, $\chi^2=14.7$, $p<0.001$). Multivariate analysis demonstrated that PNI and pathological stage were independent prognostic factors for patients with G-NEC. In the subgroup analysis, OS rates were significantly lower in the PNI-low group than in the PNI-high group among patients with stage I and stage III of the disease.

Conclusion: The PNI is a simple and useful marker for predicting long-term outcomes in G-NEC patients regardless of tumor stage. Based on our results, we suggest that PNI should be included in routine assessments of patients with G-NEC.

KEYWORDS

Onodera's prognostic nutrition index, radical gastrectomy, gastric neuroendocrine cancer, adverse events, overall survival

1. Introduction

Despite progress in early detection, surgical techniques, and adjuvant treatment of gastric neuroendocrine carcinoma (G-NEC), this disease is still a health problem worldwide (1). Surgery is the main method of treatment (2). Even after R0 resection has been achieved, certain G-NEC patients still experience postoperative recurrence. Currently, the prognosis of patients with G-NEC is usually determined based on the pTNM stage, but there are still certain defects (such as whether the operation and pathological examination were standardized) in using this method. Therefore, indicators with a higher accuracy rate are needed to determine the prognosis. G-NEC has complex clinical manifestations and its differentiation is closely associated with the endocrine system and metabolism (3). Therefore, these patients require comprehensive multidisciplinary management, with nutritional evaluation of importance for the evaluation and management of these patients (4).

Nutrition and immune status have also been reported to affect the long-term prognosis of patients with malignant tumors (5, 6). Since serum albumin expression is associated with nutritional status and lymphocyte count is associated with immune status, Onodera's prognostic nutrition index (PNI) can be used to evaluate the nutritional and immune status of patients. Since the 2010s, Onodera's PNI has been widely used as a predictor of survival in patients with various malignant tumors, including gastrointestinal (7–9) and non-gastrointestinal cancers (10, 11). However, to our knowledge, no study has been conducted to explore the clinical significance and prognostic value of PNI in G-NEC. Therefore, we retrospectively studied the relationship between PNI and clinicopathological factors, as well as the predictive value of PNI for overall survival (OS) in patients with G-NEC.

2. Patients and methods

2.1. Patients

We retrospectively collected clinical data on 148 patients who had undergone radical resection for G-NEC at the Department of Gastrointestinal Surgery of the First Affiliated Hospital of Air Force Military Medical University from March 2010 to April 2022. Inclusion criteria: a pathological diagnosis of G-NEC after surgery; complete clinical and follow-up data; complete radical operation. Exclusion criteria: previous or preoperative use of chemotherapy drugs; incomplete clinical data; poor compliance and treatment not completed as instructed by the doctor (Figure 1). This study was approved by the hospital's ethics committee and written informed consent was obtained from all patients enrolled for the use of their data.

Abbreviations: PNI, prognostic nutrition index; G-NEC, gastric neuroendocrine cancer; BMI, body mass index; ASA, American Association of Anesthesiologists; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; WBC, white blood cell count; AFP, alpha-fetoprotein; CA, carbohydrate antigen; OS, overall survival; DFS, disease-free survival.

2.2. Data collection

The results of the preoperative blood test, which included the level of serum albumin and total lymphocyte count in peripheral blood, were obtained by reviewing the electronic medical record system of our hospital. The PNI was calculated based on serum albumin (g/L) +5 lymphocyte count (10^9/L). The basic characteristics of the patients, including age, body mass index (BMI), tumor location, method of operation, tumor depth, lymph node metastasis, postoperative adjuvant therapy, and tumor node metastasis classification (TNM) were also recorded. The incidence of postoperative complications also was evaluated in the present study. The severity of complications was defined according to the Clavien-Dindo classification. The stage of TNM was defined according to the American Joint Committee on Cancer 8th edition. The relationship in PNI, clinicopathological characteristics, postoperative complications, and prognosis was analyzed.

2.3. Follow-Up

After discharge, regular telephone interviews or outpatient follow-up visits began 1 month after the operation. In addition to physical examination, follow-up also includes gastroscopy, liver, and lung imaging examination, and serum alpha-fetoprotein (AFP).

Carbohydrate antigen 199 (CA199), carbohydrate antigen 125 (CA125), and carcinoembryonic antigen (CEA) monitoring to determine whether there is distant metastasis and local recurrence. Follow-up was conducted every three months within the first three years and every six months thereafter. Follow-up information on patients was collected from tumor registries and hospital records or was obtained from patients and family members. In our research study, we used OS and disease-free survival (DFS) as the endpoint of the study, as OS is considered the most suitable event for survival analysis. The DFS was defined as the time from the operation to tumor recurrence or death, whichever occurred first. The OS was defined as the time from the operation to death.

2.4. Statistical analysis

Count data were summarized using frequencies and percentages and processed using SPSS 22.0 statistical software (Version 22.0, IBM, New York). The appropriate cut-off points of PNI for the prediction of the prognosis of G-NEC were calculated using X-tile software. The PNI and clinicopathological characteristics were analyzed using the Chi-square test or Fisher's exact test. The Kaplan–Meier method and the log-rank test were performed to compare OS between groups. Significant prognostic risk factors identified through a univariate analysis were further assessed through a multivariate analysis using Cox's proportional hazards regression model. Hazard ratio (HR) and 95% confidence interval (95% CI) were used as correlation measurements in our research study. A value of p of <0.05 was considered to indicate statistical significance.

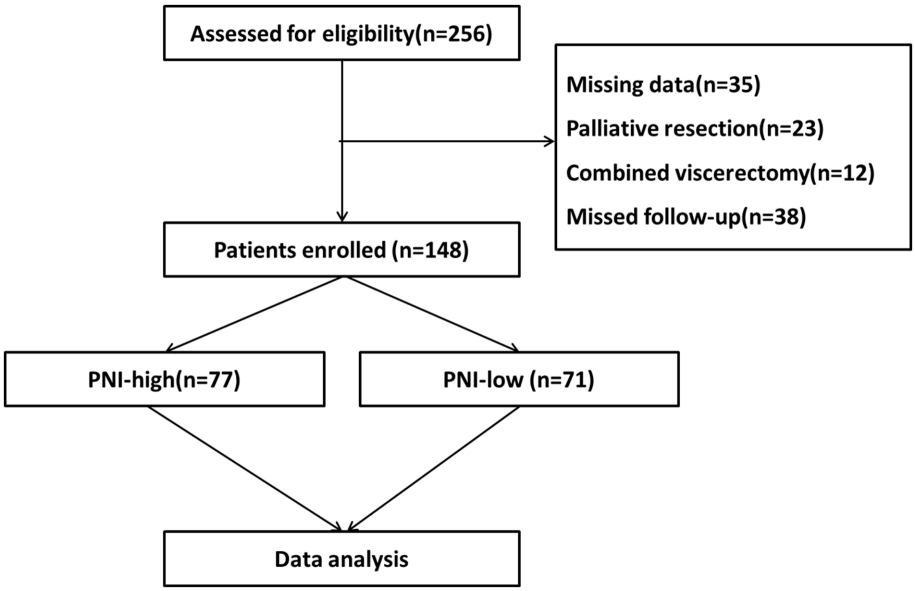


FIGURE 1
The flowchart of patient selection.

3. Results

3.1. Characteristics of the study population

A total of 148 patients were included in this study. The baseline characteristics of the enrolled patients are shown in Table 1. The mean age of the patients enrolled was 60.0 years and 84.5% of the patients were male. The average PNI of the patients before the operation was 49.5 ± 8.0, while the average PNI of patients ≥65 years old was 46.8 ± 8.0, and the average PNI of patients <65 years old was 50.9 ± 7.6. The difference between the two groups was statistically significant ($p = 0.003$). The mean PNI of patients with Stage III of the disease was significantly lower than that of Stage I and II patients ($p = 0.046$). The mean PNI of patients with anemia ($p < 0.001$) and abnormal CEA ($p = 0.039$) was significantly lower than those without such comorbidities. The mean PNI of patients with postoperative complications was lower than that of patients without postoperative complications ($p = 0.005$). In the subgroup analysis, patients with Clavien I-II complications ($p = 0.001$) and infectious ($p = 0.001$) had a lower mean PNI (Table 1).

3.2. Clinical characteristics of patients based on preoperative PNI

As shown in Figure 2, the optimal cut-off value of the PNI was 50.0, with sensitivity = 0.646, and specificity = 0.358, corresponding to the maximum Youden index (= 0.349) for the prediction of 5-years OS in the ROC analysis. Based on the cut-off value of the PNI, these patients were divided into a PNI-high group (PNI ≥ 50.0, $n = 77$) and a PNI-low group (PNI <50.0, $n = 71$). Unlike the PNI-low group, the PNI-high group had a significantly higher OS at 1, 3, and 5 years (83.1% vs. 94.8, 60.6% vs. 81.8 and 59.2% vs. 76.6%, respectively, $p < 0.001$) (Figure 3).

The average BMI of the high PNI group was (23.3 ± 2.7) and the low PNI group was (22.1 ± 3.2), with the difference between the two groups being statistically significant ($p = 0.010$). The average hemoglobin level of the high PNI group was (143.1 ± 19.0) and the low PNI group was (119.7 ± 26.1), with the difference between these two groups being statistically significant ($p < 0.001$). The incidence of postoperative complications in patients with high PNI was lower than that of patients with low PNI ($p = 0.004$), while the incidence of infections in patients with high PNI was lower than that of patients with low PNI, and showed a statistically significant difference ($p = 0.002$). The incidence of Clavien I-II events in the low PNI group was higher than that of the high PNI group ($p = 0.007$), while there was no significant difference according to adverse events. Meanwhile, the high PNI groups had tumors of a smaller size ($p < 0.001$), less blood loss ($p = 0.032$), and lower surgical costs ($p = 0.031$) (Table 2).

3.3. Prognosis of patients based on preoperative PNI

The median OS rate was 30 months (range 6–127 months), and the OS rates at 1, 3, and 5 years were 89.2%, 71.6%, and 68.2%, respectively. The PNI-high group had a significantly better 5-years OS rate (70.5% vs. 42.1%, $\chi^2 = 14.745$, $p < 0.001$), compared to the PNI-low group. The 5-year DFS rate was 69.2% in the PNI-high group and 49.0% in the PNI-low group ($\chi^2 = 8.374$, $p = 0.004$, Figure 3B). Our results showed that a low PNI was associated with a poor OS and DFS in G-NEC patients (Figure 3). Univariate analysis showed that patient age, BMI, anemia, PNI, and pathological stage were associated with prognosis (Table 3). However, only the pathological stage and PNI were independent prognostic predictors (Table 3). Then, we analyzed the predictive value of PNI in patients at different pathological stages. Low PNI was associated with the poor prognosis of patients with stage

10.3389/fnut.2023.1043550

TABLE 1 The relationship between the clinicopathological factors and the PNI values are expressed as means and standard deviations.

Clinicopathological		*N* (%)	PNI	Statistical value	*p* value
Sex	Male	125 (84.5)	49.5 ± 8.1	$t = -0.252$	0.801
	Female	23 (15.5)	49.9 ± 7.5		
Age (years)	<65	98 (65.1)	50.9 ± 7.6	$t = 3.018$	0.003
	≥65	50 (34.9)	46.8 ± 8.0		
BMI (Kg/m^2)	<18	10 (6.8)	47.0 ± 4.3	$t = -1.036$	0.302
	≥18	138 (93.2)	49.7 ± 8.2		
Tumor location	upper	63 (42.6)	50.0 ± 7.7	$\chi 2 = 0.583$	0.559
	lower-middle	56 (37.8)	49.7 ± 7.8		
	Mixed	29 (19.6)	48.1 ± 8.9		
Operation mode	Open	122 (82.4)	49.7 ± 8.1	$t = 0.386$	0.700
	Laparoscopy	26 (17.6)	48.9 ± 7.4		
CEA (ng/ml)	<5	117 (17.6)	50.2 ± 7.9	$t = 2.087$	0.039
	≥5	31 (17.6)	46.9 ± 7.5		
AFP (ng/ml)	<7	130 (87.8)	49.7 ± 8.0	$t = 0.574$	0.567
	≥7	18 (12.2)	48.5 ± 8.0		
CA199 (U/ml)	<18	131 (88.5)	49.8 ± 7.9	$t = 1.225$	0.223
	≥18	17 (11.5)	47.3 ± 8.4		
CA125 (U/ml)	<18	134 (90.5)	49.9 ± 7.7	$t = 1.944$	0.054
	≥18	14 (9.5)	45.6 ± 9.7		
WBC count (*109/L)	Normal	98 (66.2)	50.2 ± 8.0	$t = 1.463$	0.146
	Abnormal	50 (33.8)	48.2 ± 7.8		
Hypohemia	Yes	43 (29.1)	51.1 ± 7.9	$t = 3.757$	<0.001
	No	105 (70.9)	45.9 ± 6.9		
ASA score	I	122 (82.4)	49.9 ± 8.1	$t = 1.237$	0.218
	II-III	26 (17.6)	47.8 ± 7.4		
Tumor depth	T1, T2	33 (22.3)	50.8 ± 6.5	$t = 1.006$	0.316
	T3, T4	115 (77.7)	49.2 ± 8.3		
Lymph node metastasis	Negative	57 (38.5)	49.4 ± 6.7	$t = -0.223$	0.824
	Positive	91 (61.5)	49.7 ± 8.7		
Pathological stage	Stage I, II	105 (70.9)	50.4 ± 7.5	$t = 2.017$	0.046
	Stage III	43 (29.1)	47.5 ± 8.8		
Postoperative complications	Yes	24 (16.2)	45.3 ± 7.8	$t = -2.878$	0.005
	NO	124 (83.8)	50.3 ± 7.7		
Infectious	Yes	15 (10.1)	42.9 ± 8.8	$t = -3.536$	0.001
	NO	133 (89.9)	50.3 ± 7.6		
Surgical	Yes	9 (6.1)	47.7 ± 7.5	$t = -0.701$	0.484
	NO	139 (93.9)	49.7 ± 8.0		
Clavien I–II	Yes	16 (10.8)	43.6 ± 8.9	$t = -3.250$	0.001
	NO	132 (89.2)	50.3 ± 7.6		
Clavien IIIa or greater	Yes	8(5.4)	47.4 ± 8.0	$t = -0.776$	0.439
	NO	140 (94.6)	49.7 ± 7.9		

BMI, body mass index; ASA, American association of anesthesiologists; HR, hazard ratio; CI, confidence interval; PNI, prognostic nutritional index; CEA, carcinoembryonic antigen; WBC, white blood cell count; AFP, alpha-fetoprotein; CA, carbohydrate antigen. (a: anemia is defined as male HB ≤ 120 g/L and female HB ≤ 110 g/L; b: hypoalbuminemia is defined as ≤ 35 g/L). Abnormal: White blood cell count<4*109/L or >10*109/L.

I and III G-NEC (Figure 4). However, PNI was not associated with a poor prognosis in stage II G-NEC patients (Figure 4).

4. Discussion

Studies have shown that, as an important function of the inflammatory response, immunity is closely associated with nutrition and the occurrence and metastasis of tumors (12, 13), and gastrointestinal tumors, in particular, can significantly affect the nutritional (14) and immune status (15) of patients. Therefore, an increasing number of studies have focused on the role of inflammation and nutrition in patients with gastrointestinal tumors. The PNI is calculated based on lymphocyte count and serum albumin level. Lymphocytes release TNF, interferon-γ, and other cytokines, which can inhibit the growth and metastasis of cancer cells. The reduction in its number leads to weakening of the immune function of the body, making cancer cells more prone to immune escape (16, 17), and leading to the poor prognosis of cancer patients (18). Serum albumin is an important nutritional index of the human body. However, in advanced gastrointestinal tumors, there is often insufficient intake and excessive loss, leading to a decrease in albumin levels and an increase in perioperative risk, further affects clinical outcomes (9). Therefore, many studies have found that PNI plays an important role in the development and prognosis of gastrointestinal tumors (19–22). However, no relevant studies have been conducted on G-NEC. At present, there is no unified definition scheme for PNI, but the differences in the data calculated using each different scheme are small, while PNI is obtained through ROC curve analysis (8, 10, 20, 22). The ROC curve analysis showed that 50.0 was the best cut-off point, and patients were accordingly divided into a PNI-high group (PNI ≥ 50) and a PNI-low group (PNI < 50). We found for the first time that PNI can predict the prognosis of patients with gastric neuroendocrine carcinoma and is an independent risk factor for OS of patients with gastric neuroendocrine carcinoma.

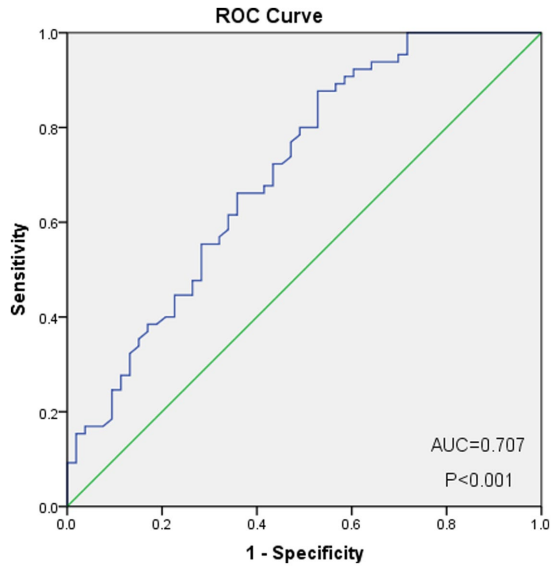


FIGURE 2
ROC curve for determination of the cut-off value of PNI.

The results of our study showed that the mean PNI of patients with a higher pathological stage, as well as anemia and abnormal CEA, was lower than that of patients without such comorbidities. The results may be associated with an increase in tumor biochemical indicators and chronic blood loss when gastric tumors are at the advanced stage. This suggests the necessity of early prevention and supportive therapy (23).

The postoperative complications recorded in our study confirmed that a low immune status before G-NEC surgery was closely associated with postoperative complications. The PNI of patients with postoperative complications was significantly lower than that of patients without complications. At the same time, it was found that the incidence of infections was higher in the low PNI group, which may be associated with a low level of immunity and malnutrition. In the group with complications and Clavien grade I-II, the difference in

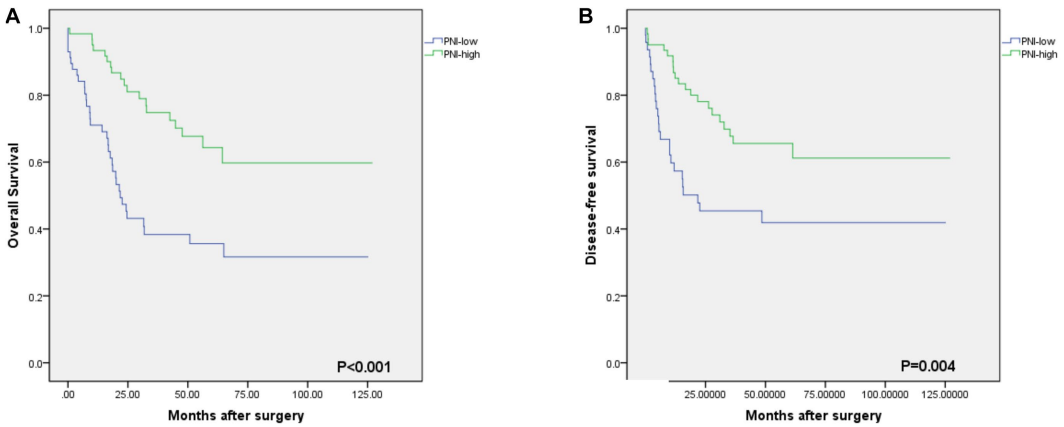


FIGURE 3
Kaplan–Meier estimates of the overall survival (OS) and disease-free survival (DFS) according to the PNI. **(A)** the OS rate of the PNI-low group was significantly lower than that of the PNI-high group (p<0.001). **(B)** the DFS rate of the PNI-low group was significantly lower than that of the PNI-high group (p=0.004).

TABLE 2 Demographic and clinical characteristics of the enrolled patients according to preoperative prognostic nutritional index.

Clinicopathological	PNI-low (*n* =71)	PNI-high (*n* =77)	Statistical value	*p* value
Sex			$\chi^2 = 0.193$	0.661
Male	59	66		
Female	12	11		
Age (year)	60.2 ± 8.0	59.8 ± 8.4	$t = 0.303$	0.762
BMI (Kg/m^2)	22.1 ± 3.2	23.3 ± 2.7	$t = -2.596$	0.010
Tumor location			$\chi^2 = 0.918$	0.632
Upper	28	35		
Lower-middle	27	29		
Mixed	16	13		
CEA (ng/ml)	7.0 ± 14.5	7.4 ± 27.2	$t = -0.104$	0.917
AFP (ng/ml)	56.8 ± 36.2	59.7 ± 42.9	$t = -0.443$	0.658
CA199 (U/ml)	27.5 ± 4.9	28.6 ± 17.4	$t = -0.710$	0.479
CA125 (U/ml)	14.8 ± 14.3	11.2 ± 5.2	$t = 1.950$	0.055
WBC count (*109/L)	6.6 ± 4.7	6.3 ± 3.7	$t = 0.315$	0.754
Hemoglobin (g/L)	119.7 ± 26.1	143.1 ± 19.0	$t = -6.178$	<0.001
Tumor depth			$\chi^2 = 1.252$	0.263
T1, T2	13	20		
T3, T4	58	57		
Lymph node metastasis			$\chi^2 = 0.313$	0.576
Negative	29	28		
Positive	42	49		
Pathological stage			$\chi^2 = 0.176$	0.675
Stage I, II	40	46		
Stage III	31	31		
Postoperative complications			$\chi^2 = 8.383$	0.004
Yes	18	6		
No	53	71		
Surgical			$\chi^2 = 0.221$	0.738*
Yes	5	4		
No	66	73		
Infectious			$\chi^2 = 10.950$	0.002*
Yes	13	2		
No	58	75		
Clavien-Dindo classification				
Clavien I-II			$\chi^2 = 8.439$	0.007*
Yes	13	3		
No	58	72		
Clavien IIIa or greater			$\chi^2 = 0.719$	0.481*
Yes	5	3		
No	66	74		
Tumor size (cm)	6.4 ± 2.2	4.7 ± 2.0	$t = 4.757$	<0.001
Blood loss (ml)	173.9 ± 129.8	151.3 ± 86.9	$t = 1.237$	0.211
Hospital stay (days)	8.6 ± 3.0	7.7 ± 2.4	$t = 2.142$	0.032
Surgery costs (CNY)	68937.4 ± 18912.1	61994.7 ± 19771.6	$t = 2.179$	0.031

*Using Fisher's exact test. BMI, body mass index; ASA, American association of anesthesiologists; HR, hazard ratio; CI, confidence interval; PNI, prognostic nutritional index; CEA, carcinoembryonic antigen; WBC, white blood cell count; AFP, alpha-fetoprotein; CA, carbohydrate antigen.

TABLE 3 Univariate and multivariate Cox regression analysis for overall survival in patients with gastric neuroendocrine carcinoma.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Gender			0.136			0.257
Male	1.00	Reference		1.00	Reference	
Female	2.170	0.783–6.019		1.952	0.615–6.197	
Age (years)			0.003			0.090
<60	1	Reference		1.00	Reference	
≥60	2.483	1.364–4.518		0.542	0.268–1.099	
ASA score			0.557			0.905
	1	Reference		1.00	Reference	
II–III	1.212	0.637–2.308		0.954	0.438–2.076	
BMI (Kg/m^2)			0.021			0.074
<18	1	Reference		1	Reference	
≥18	0.389	0.174–0.867		2.649	1.014–6.919	
Tumor size (cm)			0.384			0.151
≤5	1	Reference		1.00	Reference	
>5	1.292	0.725–2.302		1.704	0.824–3.525	
Tumor location			0.387			0.052
Upper	1.00	Reference		1.00	Reference	0.294
Lower-middle	1.425	0.692–2.935		1.446	0.591–3.537	
Multiple	0.960	0.431–2.141		0.816	0.330–2.015	
CEA (ng/ml)			0.128			0.173
<5	1.00	Reference		1.00	Reference	
≥5	1.577	0.877–2.836		0.624	0.317–1.230	
AFP (ng/ml)			0.735			0.456
<7	1.00	Reference		1.00	Reference	
≥7	0.864	0.369–2.021		0.671	0.235–1.915	
WBC count ($*10^9/L$)			0.902			0.714
Normal	1.00	Reference		1.00	Reference	
Abnormal	1.037	0.582–1.847		1.140	0.566–2.298	
Hypohemia			0.001			0.461
No	1.00	Reference		1.00	Reference	
Yes	1.259	0.682–2.324		3.730	1.681–8.277	
Tumor depth			0.288			0.374
T1, T2	1.00	Reference		1.00	Reference	
T3, T4	0.288	0.708–3.194		1.551	0.589–4.089	
Lymph node metastasis			0.273			0.507
Negative	1.00	Reference		1.00	Reference	
Positive	0.273	1.389		1.313	0.587–2.936	
Pathological stage			0.001			0.006
Stage I, II	1.00	Reference		1.00	Reference	
Stage III	0.314	0.138–0.714		2.601	1.503–4.504	
PNI			<0.001			<0.001
High	1.00	Reference		1	Reference	
Low	2.876	1.636–5.057		5.955	2.916–12.162	
Chemotherapy			0.837			0.892
Not performed	1.00	Reference		1.00	Reference	
Performed	1.064	0.591–1.915		1.049	0.524–2.102	

BMI, body mass index; ASA, American association of anesthesiologists; HR, hazard ratio; CI, confidence interval; PNI, prognostic nutritional index; CEA, carcinoembryonic antigen; WBC, white blood cell count; AFP, alpha-fetoprotein; CA, carbohydrate antigen.

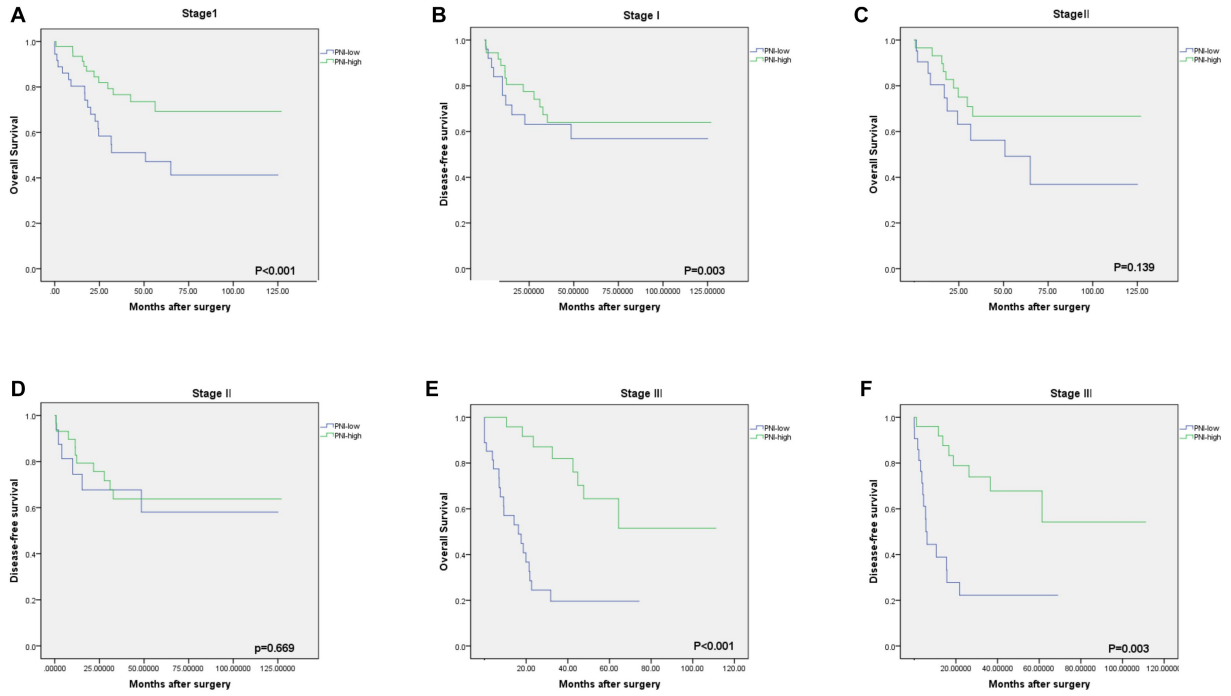


FIGURE 4
Kaplan–Meier estimates of the overall survival (OS) and disease-free survival (DFS) according to the PNI among patients with stage I [**(A)** OS, $p<0.001$; **(B)** DFS, $p=0.003$], stage II [**(C)** OS, $p=0.139$; **(D)** DFS, $p=0.669$], stage III [**(E)** OS, $p<0.001$; **(F)** DFS, $p=0.003$].

PNI between the two groups was obvious, but there was no difference in complications in patients with Clavien grade IIIa or greater. This may be because infection-related complications were mostly mild infections, while more serious complications were mostly associated with surgery itself, which is similar to the results of our study.

Currently, several studies conducted on GC have suggested that there is a correlation between PNI and OS, but the mechanism by which it changes according to the stage of the disease is still unknown. Previous reports have found that a low PNI is a predictor of a poor prognosis in patients with stage I and III GC patients, but not at stage II and IV (9). Unlike previous studies, the study by Sakurai (22) found that low PNI could not predict the prognosis of patients at stage III and was a poor predictor of the prognosis of patients at stage I and II. Similarly, we also explored the prognostic value of PNI in patients with G-NEC at different stages. The results showed that in patients with G-NEC stages I and III, a low PNI was significantly associated with poor OS, but a similar result was not obtained for stage II. Since there may be many differences in disease progression between GC and G-NEC, in addition to PNI, the survival rate of patients with stage II G-NEC may also be affected by other clinicopathological factors. Some studies have shown that PNI is of the greatest prognostic value in patients with advanced GC (stage II and III) (21, 24), but it is unclear whether it has the same value in patients with G-NEC. Therefore, more large-scale studies are needed to confirm these results.

Currently, the mechanism of association between PNI and the survival of G-NEC patients is unclear. We speculate that cancer progression is affected by both cancer cells and the immune system. First, albumin can protect cells against tumorigenesis by helping stabilize cell growth and DNA replication (25) and is an independent prognostic factor in ESCC patients (26). Second, lymphocytes inhibit tumor cell proliferation and invasion through cytokine-mediated cytotoxicity (27), in which neutrophils can promote tumor angiogenesis and metastasis, and promote tumor progression by inhibiting *T* cells (28), with an increase in neutrophils associated with poor cancer prognosis (29). Finally, malnutrition and the immune system can interact with each other to promote tumor proliferation and reduce the treatment response (30) and may jointly affect the prognosis of patients with G-NEC.

Our study also has certain limitations. First, since the incidence rate of G-NEC is relatively low, the sample size included in this study is small and the study was retrospective. Therefore, multicenter and large sample clinical studies are needed in the future to obtain more accurate PNI values and better predict the prognosis of patients with G-NEC. Second, due to different sample sizes and patient selection criteria, the optimal PNI values varied between studies, resulting in research bias. Third, many of the G-NEC patients included in our study have just been diagnosed and an evaluation of relevant endocrine indicators was not included. There may be deviations caused by different treatment strategies. In summary, PNI is a simple, practical and effective biomarker, since it can be determined by performing simple blood and liver function tests in patients with G-NEC. For patients with lower PNI values, early intervention may help improve the prognosis and prolong the survival of patients with G-NEC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Ethics Committee of First Affiliated Hospital of Air Force Military Medical University. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JW, JL, and HJ: data curation, formal analysis, project administration, software, and writing – original draft. XL: funding acquisition and supervision. XY: investigation. JL and HJ: visualization. JW and XL: writing – review and editing. All authors contributed to the article and approved the submitted version.

Funding

This work is supported by grants from the National Natural Science Foundation of China (Key Program 82100680) by Gang JI and the Shaanxi Innovation Team (2021-TD-43) by XL and Gang JI.

Acknowledgments

The authors thank the support of all the medical staff of the Department of Gastrointestinal Surgery, Xijing Hospital.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. (2017) 3:1335–42. doi: 10.1001/jamaoncol.2017.0589

2. Vitale G, Barrea L, Aversa A. Neuroendocrine neoplasms: what we have learned and what the future holds in the pharmacological treatment. *Minerva Med*. (2021) 112:315–7. doi: 10.23736/S0026-4806.21.07450-4

3. Santos AP, Castro C, Antunes L, Henrique R, Cardoso MH, Monteiro MP. Disseminated well-differentiated gastro-Entero-pancreatic tumors are associated with metabolic syndrome. *J Clin Med*. (2019) 8:1479. doi: 10.3390/jcm8091479

4. Laing E, Kiss N, Michael M, Krishnasamy M. Nutritional complications and the Management of Patients with Gastroenteropancreatic neuroendocrine tumors. *Neuroendocrinology*. (2020) 110:430–42. doi: 10.1159/000503634

5. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: clinical nutrition in cancer. *Clin Nutr*. (2021) 40:2898–913. doi: 10.1016/j.clnu.2021.02.005

6. Wiseman MJ. Nutrition and cancer: prevention and survival. *Br J Nutr*. (2019) 122:481–7. doi: 10.1017/S0007114518002222

7. Watanabe J, Otani S, Sakamoto T, Arai Y, Hanaki T, Amisaki M, et al. Prognostic indicators based on inflammatory and nutritional factors after pancreaticoduodenectomy for pancreatic cancer. *Surg Today*. (2016) 46:1258–67. doi: 10.1007/s00595-016-1308-6

8. Jian-Hui C, Iskandar EA, Cai S, Chen CQ, Wu H, Xu JB, et al. Significance of Onodera's prognostic nutritional index in patients with colorectal cancer: a large cohort study in a single Chinese institution. *Tumour Biol*. (2016) 37:3277–83. doi: 10.1007/s13277-015-4008-8

9. Migita K, Takayama T, Saeki K, Matsumoto S, Wakatsuki K, Enomoto K, et al. The prognostic nutritional index predicts long-term outcomes of gastric cancer patients independent of tumor stage. *Ann Surg Oncol*. (2013) 20:2647–54. doi: 10.1245/s10434-013-2926-5

10. Kwon WA, Kim S, Kim SH, Joung JY, Seo HK, Lee KH, et al. Pretreatment prognostic nutritional index is an independent predictor of survival in patients with metastatic renal cell carcinoma treated with targeted therapy. *Clin Genitourin Cancer*. (2017) 15:100–11. doi: 10.1016/j.clgc.2016.07.025

11. Mohri T, Mohri Y, Shigemori T, Takeuchi K, Itoh Y, Kato T. Impact of prognostic nutritional index on long-term outcomes in patients with breast cancer. *World J Surg Oncol*. (2016) 14:170. doi: 10.1186/s12957-016-0920-7

12. Schmitt M, Greten FR. The inflammatory pathogenesis of colorectal cancer. *Nat Rev Immunol*. (2021) 21:653–67. doi: 10.1038/s41577-021-00534-x

13. Wang D, Cabalag CS, Clemons NJ, DuBois RN. Cyclooxygenases and prostaglandins in tumor immunology and microenvironment of gastrointestinal Cancer. *Gastroenterology*. (2021) 161:1813–29. doi: 10.1053/j.gastro.2021.09.059

14. Rinninella E, Cintoni M, Raoul P, Pozzo C, Strippoli A, Bria E, et al. Effects of nutritional interventions on nutritional status in patients with gastric cancer: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr ESPEN*. (2020) 38:28–42. doi: 10.1016/j.clnesp.2020.05.007

15. Adiamah A, Skorepa P, Weimann A, Lobo DN. The impact of preoperative immune modulating nutrition on outcomes in patients undergoing surgery for gastrointestinal Cancer: a systematic review and Meta-analysis. *Ann Surg*. (2019) 270:247–56. doi: 10.1097/SLA.0000000000003256

16. Farhood B, Najafi M, Mortezaee K. CD8(+) cytotoxic T lymphocytes in cancer immunotherapy: a review. *J Cell Physiol*. (2019) 234:8509–21. doi: 10.1002/jcp.27782

17. Khan U, Ghazanfar H. T lymphocytes and autoimmunity. *Int Rev Cell Mol Biol*. (2018) 341:125–68. doi: 10.1016/bs.ircmb.2018.05.008

18. Hirahara T, Arigami T, Yanagita S, Matsushita D, Uchikado Y, Kita Y, et al. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. *BMC Cancer*. (2019) 19:672. doi: 10.1186/s12885-019-5903-y

19. Ryo S, Kanda M, Ito S, Mochizuki Y, Teramoto H, Ishigure K, et al. The controlling nutritional status score serves as a predictor of short-and long-term outcomes for patients with stage 2 or 3 gastric Cancer: analysis of a multi-institutional data set. *Ann Surg Oncol*. (2019) 26:456–64. doi: 10.1245/s10434-018-07121-w

20. Hirahara N, Tajima Y, Fujii Y, Yamamoto T, Hyakudomi R, Taniura T, et al. Preoperative prognostic nutritional index predicts long-term outcome in gastric Cancer: a propensity score-matched analysis. *Anticancer Res*. (2018) 38:4735–46. doi: 10.21873/anticanres.12781

21. Jiang N, Deng JY, Ding XW, Ke B, Liu N, Zhang RP, et al. Prognostic nutritional index predicts postoperative complications and long-term outcomes of gastric cancer. *World J Gastroenterol*. (2014) 20:10537–44. doi: 10.3748/wjg.v20.i30.10537

22. Sakurai K, Tamura T, Toyokawa T, Amano R, Kubo N, Tanaka H, et al. Low preoperative prognostic nutritional index predicts poor survival post-gastrectomy in elderly patients with gastric Cancer. *Ann Surg Oncol*. (2016) 23:3669–76. doi: 10.1245/s10434-016-5272-6

23. Jin XF, Spampatti MP, Spitzweg C, Auernhammer CJ. Supportive therapy in gastroenteropancreatic neuroendocrine tumors: often forgotten but important. *Rev Endocr Metab Disord*. (2018) 19:145–58. doi: 10.1007/s11154-018-9443-6

24. Sun KY, Xu JB, Chen SL, Yuan YJ, Wu H, Peng JJ, et al. Novel immunological and nutritional-based prognostic index for gastric cancer. *World J Gastroenterol*. (2015) 21:5961–71. doi: 10.3748/wjg.v21.i19.5961

25. Ouyang X, Dang Y, Zhang F, Huang Q. Low serum albumin correlates with poor survival in gastric Cancer patients. *Clin Lab*. (2018) 64:239–45. doi: 10.7754/Clin.Lab.2017.170804

26. Zhu X, Chen D, Li S, Zhang W, Li Y, Wang X, et al. Albumin-to-alkaline phosphatase ratio as a novel and promising prognostic biomarker in patients undergoing

Esophagectomy for carcinoma: a propensity score matching study. *Front Oncol*. (2021) 11:764076. doi: 10.3389/fonc.2021.764076

27. Ray-Coquard I, Cropet C, Van Glabbeke M, Sebban C, Le Cesne A, Judson I, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. *Cancer Res*. (2009) 69:5383–91. doi: 10.1158/0008-5472.CAN-08-3845

28. Hao S, Andersen M, Yu H. Detection of immune suppressive neutrophils in peripheral blood samples of cancer patients. *Am J Blood Res*. (2013) 3:239–45.

29. Wang TT, Zhao YL, Peng LS, Chen N, Chen W, Lv YP, et al. Tumour-activated neutrophils in gastric cancer foster immune suppression and disease progression through GM-CSF-PD-L1 pathway. *Gut*. (2017) 66:1900–11. doi: 10.1136/gutjnl-2016-313075

30. Nakamura I, Shibata M, Gonda K, Yazawa T, Shimura T, Anazawa T, et al. Serum levels of vascular endothelial growth factor are increased and correlate with malnutrition, immunosuppression involving MDSCs and systemic inflammation in patients with cancer of the digestive system. *Oncol Lett*. (2013) 5:1682–6. doi: 10.3892/ol.2013.1231

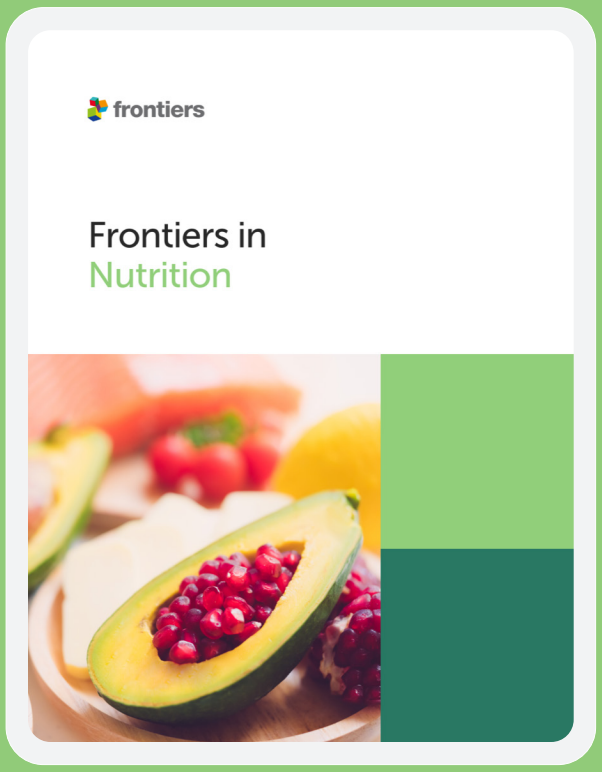
Frontiers in Nutrition

Explores what and how we eat in the context of health, sustainability and 21st century food science

A multidisciplinary journal that integrates research on dietary behavior, agronomy and 21st century food science with a focus on human health.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact