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Clinical nutrition and oncologic outcomes - volume 1

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ORIGINAL RESEARCH
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Pre-diagnosis Dairy Product Intake and Ovarian Cancer Mortality: Results From the Ovarian Cancer Follow-Up Study (OOPS)

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Background: Dairy product consumption is associated with ovarian cancer (OC) incidence. However, limited evidence is available on its influence on OC mortality.

Methods: The association between pre-diagnostic dairy product intake and OC mortality was investigated in the OC follow-up study, which included a hospital-based cohort (n = 853) of women diagnosed with epithelial OC between 2015 and 2020. Pre-diagnosis diet information was collected using a validated food frequency questionnaire. Deaths were ascertained up to March 31, 2021 via death registry linkage. Cox proportional hazards model was used to estimate the adjusted hazard ratio (HR) and 95% confidence interval (CI) for the aforementioned association.

Results: A total of 130 women died during the median follow-up of 37.2 months (interquartile: 24.7–50.2 months). Comparisons of highest to lowest tertile intake showed that pre-diagnosis dairy product use was associated with total OC mortality (HR = 2.03, 95% CI = 1.21–3.40, p trend = 0.06). In addition, short survival was separately associated with protein (HR = 2.09, 95% CI = 1.25–3.49, p trend < 0.05), fat (HR = 2.16, 95% CI = 1.30–3.61, p trend < 0.05), and calcium (HR = 2.03, 95% CI = 1.21–3.4, p trend = 0.06) from dairy intake. Similar positive magnitudes were observed for menopausal status, residual lesions, histological type, and body mass index, although not all of these factors showed statistical significance.

Conclusion: Pre-diagnosis dairy product consumption, including protein, fat, and calcium from dairy intake, was associated with higher mortality among OC survivors.

Keywords: cohort, dairy, mortality, ovarian cancer, prognosis, survival

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INTRODUCTION

Ovarian cancer (OC) is one of the most fatal gynecological malignancies, with an estimated 313,959 new cases and 207,252 new deaths globally in 2020 (1). In China, OC is the second leading cause of gynecological malignancy death, with ∼25,000 new cases and 22,000 new deaths in 2015 (2). Since there are few early specific symptoms, a high proportion of women are diagnosed at advanced stages

when the therapeutic effect is poor and the fatality rate is high (3). Although the 5-year survival rate has increased in recent years, it was still <50% in China (4), which seriously threatens women's health. Evidence suggests that several factors can influence the OC prognosis, including histotype, stage of disease at diagnosis, volume of residual disease after primary debulking surgery, parity, and number of ovulatory cycles (3, 5, 6). However, most of these factors are difficult to modify. In the last decade, increasing evidence has suggested that diet is a feasible intervention target, which might affect survival in OC patients (7–9).

Dairy products are an important and common part of daily diet. Dairy products are rich in protein, fat, and calcium. The fat in dairy products may be related to high levels of circulating estrogen and insulin-like growth factor-1, which may be associated with poor OC prognosis (10–14). Several studies have investigated the relationship between pre-diagnosis consumption of milk or dairy products and OC prognosis (7–9, 15, 16). Among them, three studies have reported a null association (8, 9, 16). However, some investigations have generated different results. For example, Nagle et al. found a modest relationship between pre-diagnosis dairy intake and poor survival for 609 Australian OC patients (15). Only one prospective cohort study conducted in the U.S. has reported a significant negative association between all types of milk consumption and OC survival (7). This inconsistent evidence might be attributed to different study design, population, exposure assessment, and adjustment for potential confounders. Furthermore, none of these studies has further analyzed the association between main nutrients in pre-diagnosis dairy product consumption and OC mortality. To the best of our knowledge, no study has explored the effect of dairy products on the survival of Chinese women with OC who may have different daily intake and consume different types of dairy compared to the American and European population.

Therefore, a prospective follow-up study was conducted to investigate the association between pre-diagnosis consumption of dairy products and related nutrients, including protein, fat, and calcium, and OC prognosis in China.

MATERIALS AND METHODS

Study Population

The OC follow-up study (OOPS) is a prospective longitudinal cohort study of newly diagnosed OC patients. Participants were recruited for the purpose of collecting demographic, clinical, and lifestyle data in order to assess their associations with cancer-related outcomes. The study was approved by the Institutional Review Board of the Ethics Committee of Shengjing Hospital of China Medical University. All women provided signed consent to participate. Based on traditional statistics and previous published studies, we set $\alpha = 0.05$, $Z_{1-0.05/2} = 1.96$, $Z_{\beta} = 1.28$, $P_0 = 0.30$, $RR = 1.40$, $P_1 = 0.42$. And, we calculated the sample size is 662. Actually, a total of 853 women aged 18–79 years who were newly diagnosed with OC were identified between January 2015 and December 2020. Of these, 796 women agreed to participate and 744 (93%) returned the completed study questionnaire. After excluding participants who reported significantly abnormal caloric intake (<500 or > 3,500 calories per day; $n = 17$) or left 11 (10%) or more food items blank ($n = 24$), dietary data were available for 703 women with OC (**Figure 1**), which reached the statistical power.

Data Collection

Information on demographic and lifestyle factors was collected in person using a self-administered questionnaire, which included information on diet, smoking status, alcohol intake status, tea intake status, menopausal status, parity, education, income, and amount of physical activity. Anthropometrics, including weight and height [used to calculate body mass index (BMI)], were measured at baseline. In addition, clinically relevant covariates included age at diagnosis, histological type, histopathologic grade, International Federation of Gynecology and Obstetrics (FIGO) stage, residual lesions, and comorbidities. Information on these covariates was collected from the electronic medical records of the Shengjing hospital information system.

Dietary Exposure Assessment

Dietary intake was assessed at recruitment via a 111-item food frequency questionnaire (FFQ), which was an extended version of a previously validated FFQ (with an addition of 11 food items) used in the Tianjin Chronic Low-grade Systemic Inflammation and Health cohort study (17, 18). Participants were required to recall their accustomed intake of these food items during the year prior to OC diagnosis. Seven response categories were provided for each food item (i.e., almost never, less than once a week, once a week, two to three times a week, four to six times a week, once a day, and two or more times a day). Total dairy product intake was calculated by summing up intake amounts of whole milk, low-fat dairy, yogurt, and cheese. Intakes of different dairy products in grams/day were computed by multiplying consumption frequencies per day and fitted portion sizes (g/time). In addition, consumption of protein, fat, and calcium was computed from the above dairy products. Nutrient intake was determined by multiplying the frequency of consumption of each food by the nutrient content of the specified portions. Nutrient intake was estimated based on the Chinese Food Composition Tables (19).

Follow-Up and Outcome

Information on the vital status of participants was determined using data extracted from the medical records every 6 months and by active follow-up. All-cause mortality was the endpoint for follow-up. Survival time was defined as the interval between histologic diagnosis and date of death from any cause or the date of last follow-up (March 31, 2021) for patients who were still alive.

Statistical Analysis

Differences in general and clinical characteristics across dairy product intake categories were assessed using one-way ANOVA or the Kruskal–Wallis test for continuous variables, and the χ^2 test for categorical variables. The Kaplan–Meier technique was used to plot crude survival curves and estimate crude overall survival probabilities. Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence

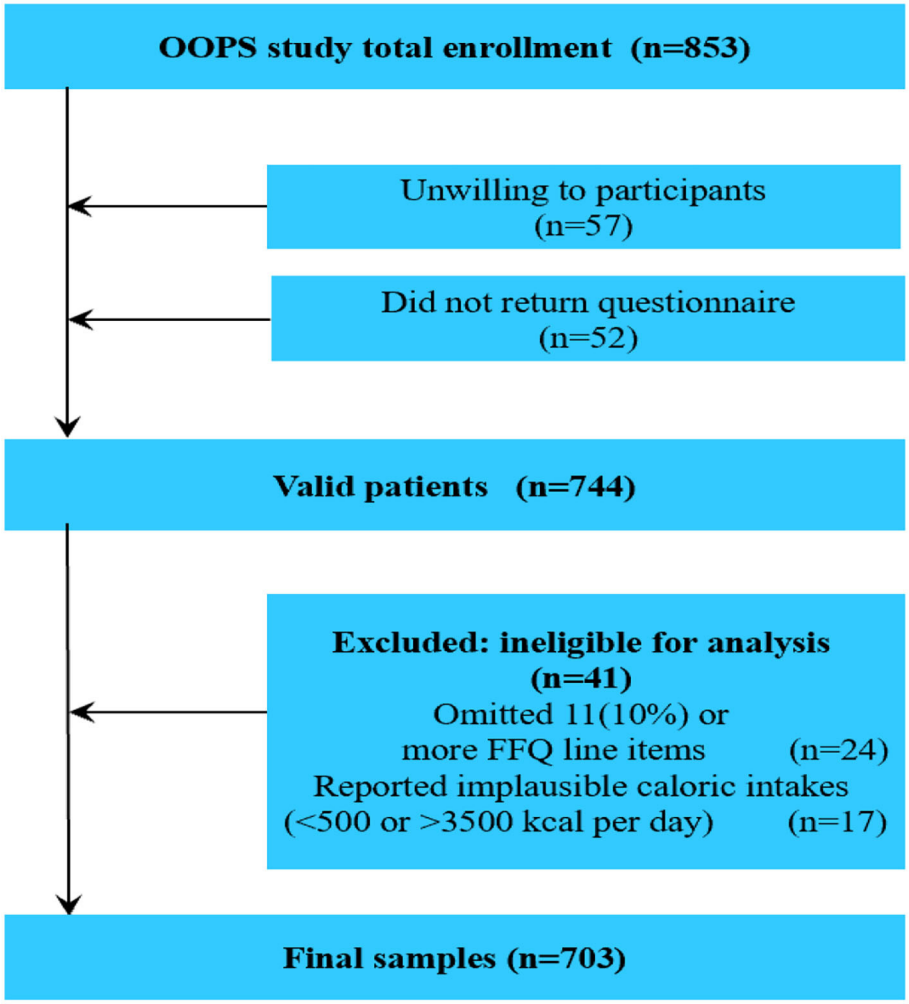

FIGURE 1 | Flow of participants through study.

interval (CI) for the association of baseline dairy products and relative nutrient intake with overall survival. The proportional hazards assumption was evaluated by including an interaction term between each activity variable and log survival time. No violations were observed (all $p > 0.05$). Dairy product intake was categorized by tertile distribution, where the lowest tertile served as the reference group. Tests for linear trends were carried out by assigning the median value of consumption for each tertile of dairy products and relative nutrients and treating it as a continuous variable in the respective regression model. To control for confounding factors, the model was adjusted for age at diagnosis (<50, ≥50 years), total energy intake (continuous, kcal), BMI (continuous, kg/m^2), comorbidities (yes or no), diet change (yes or no), dietary pattern (derived using principal components for factor analysis), education (junior secondary or below, senior high school/technical secondary school, and junior college/university or above), FIGO stage (I–II, III–IV, and unknown), histological type (serous, non-serous), histopathologic grade (well, moderate, and poorly differentiated), menopausal status (yes or no), parity (≤1, ≥2), physical activity (continuous), residual lesions (none, <1, ≥1 cm), and smoking status (yes or no). Selection of covariates for the final model was based on clinical significance, previous studies, and degree of correlation with the exposure.

Stratified exploratory analyses were also performed using categories of menopausal status ("no" compared to "yes"), residual lesions ("no" compared to "yes"), histological type (serous compared to non-serous), and BMI (<25 compared to ≥25 kg/m^2). Respective multiplicative interaction terms in the multivariable-adjusted models were tested by including the cross product of the dairy products or relative nutrients as a continuous variable and the potential effect modifier as a continuous or categorical variable, as appropriate. In addition, the association between pre-diagnosis dairy product intake and overall survival in stage III or IV OC patients was analyzed. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Two-sided *P*-values of < 0.05 were considered statistically significant.

TABLE 1 | General characteristics of ovarian cancer patients according to dairy products ($N = 703$).

Variables	Total dairy products consumption (g/day)			*P*-value
	T1 (<17.46)	T2 (17.46–90.00)	T3 (≥90.00)	
No. of patients	232	235	237	
Age at diagnosis (years), Median (IQR)	53.00 (48.00–60.00)	53.50 (47.00–60.00)	53.00 (48.00–61.00)	0.56
Follow–up time (m), Median (IQR)	33.83 (23.25–47.30)	30.92 (19.77–47.87)	29.60 (17.63–45.23)	0.23
Body mass index (kg/m^2), Median (IQR)	23.30 (21.30–25.25)	23.30 (20.70–25.00)	23.30 (20.80–25.00)	0.70
Physical activity (MET/hours/days), Median (IQR)	14.15 (6.15–21.55)	14.10 (7.30–22.00)	13.60 (6.10–22.90)	0.85
Diet intake (Mean ± SD)				
Total energy (kcal/d)	1,168.06 ± 394.29	1,406.47 ± 472.09	1,786.04 ± 585.62	<0.05
Meat (g/day)	27.76 ± 22.76	36.70 ± 28.23	44.49 ± 33.91	<0.05
Eggs (g/day)	31.83 ± 26.23	34.71 ± 26.34	46.56 ± 26.65	<0.05
Fish and seafood (g/day)	22.60 ± 31.63	27.43± 24.66	35.39 ± 32.70	<0.05
Beans and bean products (g/day)	68.45 ± 68.97	85.45 ± 77.06	101.55 ± 85.11	<0.05
Vegetables (g/day)	192.81 ± 122.42	202.72 ± 108.51	246.53 ± 127.06	<0.05
Fruits (g/day)	153.73 ± 132.59	189.81 ± 152.41	239.45 ± 173.92	<0.05
Diet change (*n*, %)				0.07
No	188 (81.03)	169 (72.22)	178 (75.11)	
Yes	44 (18.97)	69 (27.78)	59 (24.89)	
Smoke status (*n*, %)				0.15
No	203 (87.50)	212 (90.60)	220 (92.83)	
Yes	29 (12.50)	22 (9.40)	17 (7.17)	
Alcohol intake (*n*, %)				0.08
No	194 (83.62)	181 (77.35)	179 (75.53)	
Yes	38 (16.38)	53 (22.65)	58 (24.47)	
Tea drinking (*n*, %)				0.60
No	161 (69.40)	161 (68.80)	155 (65.40)	
Yes	71 (30.60)	73 (31.20)	82 (34.60)	
Menopausal status (*n*, %)				0.48
No	58 (25.0)	66 (28.21)	71 (29.96)	
Yes	174 (75.0)	168 (71.79)	166 (70.04)	
Parity (*n*, %)				<0.05
≤1	144 (62.07)	172 (73.50)	189 (79.75)	
≥2	88 (37.93)	62 (26.50)	48 (20.25)	
Educational level (*n*, %)				0.09
Junior secondary or below	140 (60.34)	112 (47.86)	123 (51.90)	
Senior high school/technical secondary school	42 (18.11)	52 (22.22)	53 (22.36)	
Junior college/university or above	50 (21.55)	70 (29.92)	61 (25.74)	
Income per month (Yuan), (*n*, %)				0.44
<5,000	145 (62.50)	144 (61.54)	132 (55.70)	
5,000 to <10,000	59 (25.43)	59 (25.21)	76 (32.07)	
≥10,000	28 (12.07)	31 (13.25)	29 (12.23)	

IQR, interquartile range; MET, metabolic equivalent task; SD, standard deviation; T, tertile.

RESULTS

General characteristics of 703 OC patients organized by tertiles of total dairy consumption are listed in **Table 1**. Patients with a higher total dairy product intake were more likely to consume total energy, meat, eggs, fish and seafood, beans and bean products, vegetables, and fruits, and had less parity. No differences in other listed variables were observed. Among the 703 OC patients included in the analysis, 130 deaths occurred during a median follow-up of 37.17 months (interquartile: 24.73–50.17 months). Non-serous histological subtype, later-stage disease, and greater residual disease were statistically significantly associated with worse survival in this cohort (**Table 2**).

Table 3 represents the associations between total dairy and relative nutrient intake and overall survival of OC. Patients with total dairy product intake in the highest tertile had worse overall survival compared to those in the lowest tertile (HR = 2.03, 95% CI = 1.21–3.40), though a linear trend was not evident (*p*

TABLE 2 | Selected clinical characteristics and associations with all-cause mortality among women diagnosed with ovarian cancer ($N = 703$).

Characteristic	No. of deaths/total (%)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Age at diagnosis			
≤50	45/258 (17.44)	1.00 (ref)	1.00 (ref)
>50	85/445 (19.10)	1.18 (0.82–1.70)	1.24 (0.85–1.79)
Histological type			
Serous	92/479 (19.21)	1.00 (ref)	1.00 (ref)
Non-serous	38/224 (16.96)	0.87 (0.59–1.27)	1.71 (1.11–2.66)
Histopathologic grade			
Well-differentiated	5/56 (8.93)	1.00 (ref)	1.00 (ref)
Moderately differentiated	7/48 (14.58)	1.44 (0.46–4.57)	1.12 (0.35–3.57)
Poorly differentiated	118/599 (19.70)	2.32 (0.95–5.67)	1.76 (0.70–4.43)
FIGO stage			
I–II	41/342 (11.99)	1.00 (ref)	1.00 (ref)
III–IV	89/338 (26.33)	2.75 (1.89–4.00)	2.54 (1.65–3.91)
Residual lesions			
No	82/553 (14.83)	1.00 (ref)	1.00 (ref)
<1 cm	31/106 (29.25)	2.22 (1.47–3.36)	1.73 (1.11–2.68)
≥1 cm	17/44 (38.64)	3.18 (1.89–5.37)	2.41 (1.39–4.16)
Comorbidities			
No	74/393 (18.83)	1.00 (ref)	1.00 (ref)
Yes	56/310 (18.06)	0.82 (0.58–1.16)	0.97 (0.68–1.38)

[a] *Mutually adjusted for all other variables listed in the table.*
CI, confidence interval; HR, hazard ratio; Ref, reference.

trend = 0.06). A similar pattern was observed for calcium from dairy intake ($HR_{T3VS.T1} = 2.03$, 95% CI = 1.21–3.40, p trend = 0.06). Moreover, worse survival was evident for the highest tertile compared to the lowest tertile of protein from dairy intake (HR = 2.09, 95% CI = 1.25–3.49, p trend < 0.05) and for the highest tertile compared to the lowest tertile of fat from dairy intake (HR = 2.16, 95% CI = 1.30–3.61, p trend < 0.05). **Figure 2** represents the association between total dairy intake and overall survival for OC. Compared to the lowest tertile of total dairy intake, survival was lower in patients in the highest intake tertile. Similar results for protein, fat, and calcium from dairy were observed (**Supplementary Figures 1–3**).

The influence of total dairy intake on overall survival in OC was examined across potential effect-modifying variables. Of note, the higher mortality risk associated with the highest total dairy intake was present only in menopausal patients, patients with no residual lesions, non-serous patients, or patients with BMI of <25 (**Figure 3**). Nevertheless, statistical power to adequately examine the differences was limited by the sample size in the above stratified analyses. Such analyses should be considered exploratory. Similar results were obtained for the protein, fat, and calcium from dairy products (**Supplementary Figures 4–6**). Results among patients with stage III-IV OC were consistent with the main findings, although they were attenuated (data not shown).

TABLE 3 | Hazard ratio (95% CI) for overall survival among ovarian cancer patients according to total dairy and relative nutrients intake.

Dietary variables	T1	T2	T3	P for trend[d]
Total dairy (g/day)				
Rang of intake	<17.46	17.46–90.00	≥90.00	
Deaths, *N* (% of total deaths)	29 (22.31)	51 (39.23)	50 (38.46)	
Model 1[a] (95% CI)	1.00 (ref)	1.78 (1.13–2.81)	1.84 (1.16–2.91)	<0.05
Model 2[b] HR (95% CI)	1.00 (ref)	1.85 (1.16–2.95)	2.04 (1.23–3.39)	<0.05
Model 3[c] HR (95% CI)	1.00 (ref)	2.00 (1.24–3.22)	2.03 (1.21–3.40)	0.06
Protein from dairy (g/day)				
Rang of intake	<0.49	0.49–3.00	≥3.00	
Deaths, *N* (% of total deaths)	29 (22.31)	51 (39.23)	50 (38.46)	
Model 1[a] (95% CI)	1.00 (ref)	1.76 (1.11–2.78)	1.86 (1.18–2.94)	<0.05
Model 2[b] HR (95% CI)	1.00 (ref)	1.83 (1.15–2.92)	2.07 (1.25–3.45)	<0.05
Model 3[c] HR (95% CI)	1.00 (ref)	1.97 (1.22–3.17)	2.09 (1.25–3.49)	<0.05
Fat from dairy (g/day)				
Rang of intake	<0.39	0.39–2.78	≥2.78	
Deaths, *N* (% of total deaths)	29 (22.31)	49 (37.69)	52 (40.00)	
Model 1[a] (95% CI)	1.00 (ref)	1.73 (1.09–2.74)	1.93 (1.22–3.04)	<0.05
Model 2[b] HR (95% CI)	1.00 (ref)	1.81 (1.14–2.9)	2.18 (1.31–3.61)	<0.05
Model 3[c] HR (95% CI)	1.00 (ref)	1.94 (1.20–3.13)	2.16 (1.30–3.61)	<0.05
Calcium from dairy (mg/day)				
Rang of intake	<15.79	15.79–100.89	≥100.89	
Deaths, N (% of total deaths)	29 (22.31)	52 (40.00)	49 (37.69)	
Model 1[a] (95% CI)	1.00 (ref)	1.81 (1.14–2.85)	1.81 (1.15–2.87)	0.06
Model 2[b] HR (95% CI)	1.00 (ref)	1.87 (1.18–2.98)	2.00 (1.20–3.34)	<0.05
Model 3[c] HR (95% CI)	1.00 (ref)	2.00 (1.25-3.22)	2.03 (1.21–3.40)	0.06

CI, confidence interval; HR, hazard ratio; Ref, reference; T, tertile.
[a] *Model 1 unadjusted.*
[b] *Model 2 adjusted for age at diagnosis and total energy.*
[c] *Model 3 same as Model 2 and further adjusted for body mass index, comorbidities, diet change, dietary pattern, education, FIGO stage, histological type, histopathologic grade, menopausal status, parity, physical activity, residual lesions, and smoke status.*
[d] *P-value for linear trend calculated from category median values.*

DISCUSSION

In this prospective cohort of 853 women diagnosed with OC, pre-diagnosis dairy product intake was positively associated with total mortality. Similar magnitudes of the mortality increase

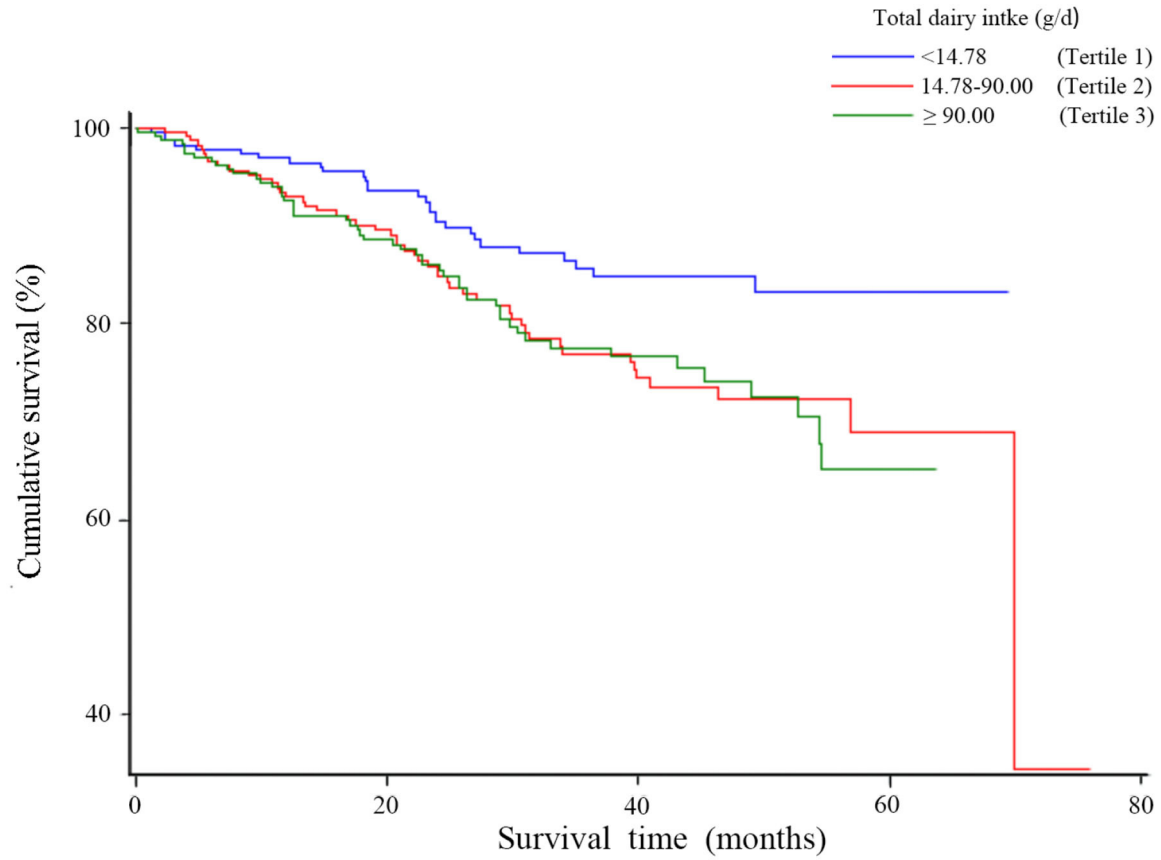

FIGURE 2 | Kaplan-Meier survival curves for total dairy productions consumption.

were observed for pre-diagnosis protein, fat, and calcium from dairy intake.

Findings from prior studies on the association between pre-diagnosis consumption of dairy products and OC survival were limited and inconsistent (**Supplementary Table 1**). The present findings are in line with a previous longitudinal follow-up study of 341 U.S. women diagnosed with OC, where higher pre-diagnosis intake of all types of milk was associated with worse survival (7). In addition, an earlier cohort study of 609 Australian epithelial OC cases reported a modest relationship between pre-diagnosis dairy intake and poor survival (15). However, results from the three follow-up cohort studies were inconsistent with the present findings (8, 9, 16). Playdon et al. found that pre-diagnosis intake of low-fat or high-fat dairy was not associated with OC survival among 811 Australian women with OC (9). A study conducted by Thomson et al. among 636 U.S. OC patients indicated no correlation between milk consumption and OC survival (8). In Japan, a large and prospective study by Sakauchi et al. followed 64,327 women for an average of 13.3 years, where a total of 77 of them died of OC. This study also showed no association between consumption of milk and dairy products and the survival of OC patients (16). The reason for this inconsistency might be attributable to different ways used to assess the exposure to dairy products. Exposure assessment in study by Playdon et al. was based on the dairy servings. The Thomson et al. study was based on the points of the Healthy Eating Index 2005, while the Sakauchi et al. study was based on the frequency of dairy intake. Exposure assessment in the present study was based on the quantity of dairy intake, which might be more accurate than that in other studies. Moreover, the proportion of advanced stage patients in the present study (III–IV: 48.1%) was obviously smaller than that in the study by Playdon et al. (III–IV: 71.0%). The ethnic composition of the population of the present study (Asian) differed from that of the study by Thomson et al. (mainly white: 88.1%). The study evidence suggested that consumption of dairy products was also different between Chinese and American patients (20). In our study, only 38 (5.4%) OC patients reached Dietary guidelines for Chinese residents recommend intake (300 g/d), and the mean dairy products intake was 84 g/d. This is lower than American patients (20).

Although the current research on the underlying biological mechanisms of dairy product intake and OC prognosis has been scarce, the present study considered the possible effects from the aspects of fat, protein, and calcium content. Dietary fat has been indicated to be related to high levels of circulating estrogen. The present evidence suggests that elevated levels of

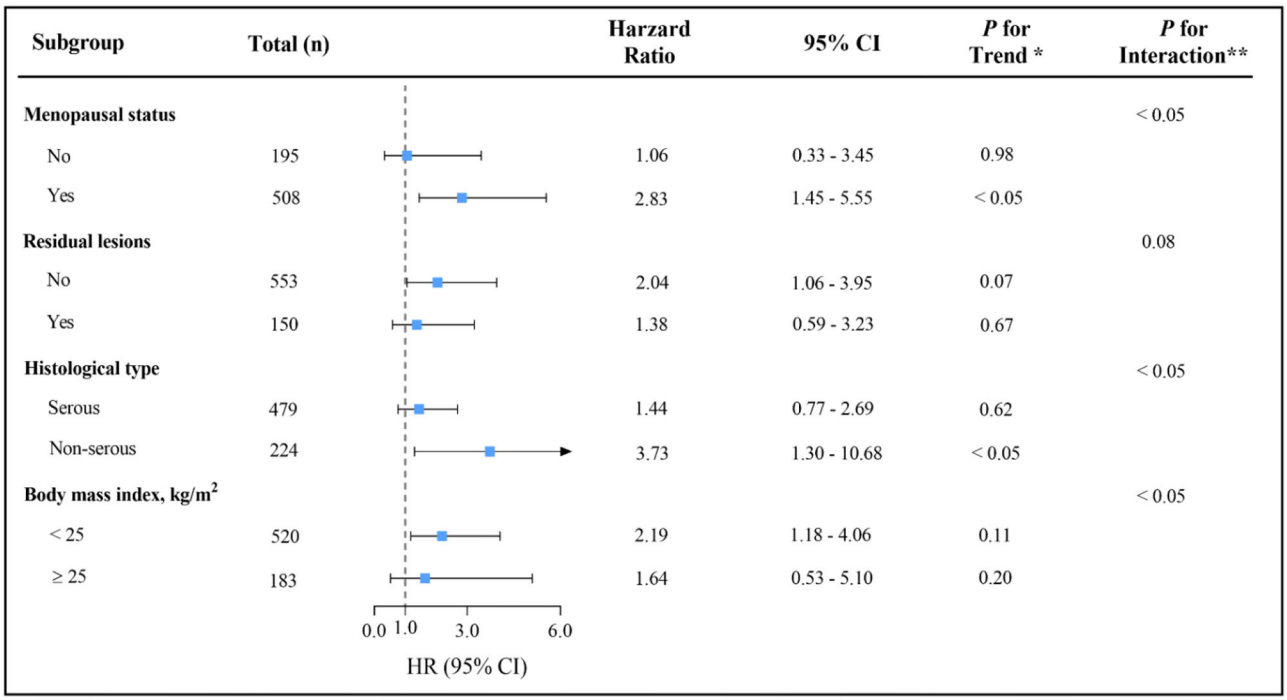

FIGURE 3 | Multivariable hazard ratios (HRs) and 95% CIs for overall survival among ovarian cancer patients across strata of various factors. The analyses used three categories of total dairy intake (T_1 < 14.76, T_2 14.76-90.00 and T_3 ≥ 90.00g/d). The forest plot represents the HRs of the comparison of the highest versus the lowest of dairy intake. Cox model stratified by menopausal status, residual lesions, histological type and body mass index, with additional adjustments for age at diagnosis, comorbidities, diet change, dietary pattern, education, FIGO stage, histopathologic grade, parity, physical activity, smoke status and total energy.* indicates P for trend across levels of total dairy intake.** indicates P for interaction between strata and total dairy intake.

estrogen may promote growth and proliferation of OC (13). Furthermore, fat and protein dairy product components may be positively implicated in elevating the level of insulin-like growth factor-1 (11, 14). Insulin-like growth factor-1 receptor overexpression can increase the proliferation of OC cells, restrain OC cell apoptosis, or induce malignant transformation of OC cells (10, 12). The receptor-interacting protein kinase 1 might regulate the mitochondrial Ca2+ uptake to promote cancer cell proliferation (21).

The present study had strengths that are worth mentioning. The originality of the work is the principal strength of the present research, because this is the first study to investigate the relationship between pre-diagnostic diary product intake and OC prognosis in China. The prospective and high follow-up rates (93%) reduce the potential for recall and selection bias. A further strength is that the study was rigorously controlled for the majority of potential prognosis-related confounding factors, such as comorbidities, FIGO stage, histological type, and residual lesions. In addition, the potential impact of nutrients, such as fat, calcium, and protein, in dairy products on the prognosis of OC was further explored.

Nevertheless, several limitations exist in the current study. First, since we directly collected the frequency of dairy product intake rather than intake in the questionnaire, the assessment of dairy product intake may be imprecise. However, well-trained investigators as well as validated FFQs were utilized to collect dietary information for OC patients in the study, which might reduce deviation. Second, since the dietary intake of OC patients was obtained using FFQ measurements prior to diagnosis, it may not reflect the intake after diagnosis. However, dairy products constitute a key part of the daily diet. It is possible that the intake of dairy products may not change before and after diagnosis because recent studies have provided limited or weak evidence of the potential effect of dairy products on OC (22). Third, we failed to examine whether associations with OC prognosis and dairy product type differed by subtype, such as skim/low-fat milk, cheese, and yogurt, due to lower intakes of these dairy products in the present study as well as in China (23). In addition, although the impact of pre-diagnostic dairy product intake on progression-free survival of OC patients was not examined, evidence suggested that OC patients might have short post-progression survival because of the high mortality rate and progression-free survival similarity to overall survival (24, 25). Fourth, the pre-diagnosis daily dairy product consumption in the present study (mean: 84.00 g/day) was close to the estimates made by the Shanghai Women's Health Study of 64,191 adult Chinese women (mean: 62.25 g/day) (26). Conversely, the mean intake of dairy products in the U.S. is estimated to be 268.8 g/day (20). Therefore, the present study findings should be interpreted with caution. Fifth, residual confounding factors are a possible concern in any observational study. Although we comprehensively adjusted for the majority of potential

confounders to minimize their influence, there was no way to exclude the impact of unknown or unmeasured confounders.

In conclusion, high pre-diagnosis dairy product intake was strongly associated with worse survival in OC patients. This prognostic effect was similar in the analyses of protein, fat, and calcium from dairy. Further studies with longer follow-up periods, as well as analyses of different dairy products, are warranted in the future.

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 Shengjing Hospital of China Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

T-TG, X-QL, and Q-JW: study design. SG, X-QL, and SY: collection of data. F-HL and Y-FW: analysis of data. LJ, F-HL, Z-YW, Y-FW, and, RH: drafting the manuscript. LJ, T-TG, F-HL, Z-YW, Y-FW, LJ, and Q-JW: revision of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.750801/full#supplementary-material

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Meta-analysis of Glutamine on Immune Function and Post-Operative Complications of Patients With Colorectal Cancer

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The aim of this meta-analysis was to evaluate the clinical significance of glutamine in the management of patients with colorectal cancer (CRC) after radical operation. Electronic databases, including PubMed, EMBASE, MEDLINE, Cochrane Library, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), VIP medicine information system (VIP), and Wanfang electronic databases were comprehensively searched from inception to 30, July 2021. Prospective randomized trials with glutamine vs. routine nutrition or blank therapy were selected. The immune function related indicators (including IgA, IgG, IgM, CD4+, CD8+, and the ratio of CD4+/CD8+), post-operative complications [including surgical site infection (SSI), anastomotic leakage, and length of hospital stay (LOS)], and corresponding 95% confidence intervals (CIs) were assessed in the pooled analysis. Subsequently, the heterogeneity between studies, sensitivity, publication bias, and meta-regression analysis were performed. Consequently, 31 studies which contained 2,201 patients (1,108 in the glutamine group and 1,093 in the control group) were included. Results of pooled analysis indicated that glutamine significantly improved the humoral immune function indicators [including IgA (SMD = 1.15, 95% CI: 0.72–1.58), IgM (SMD = 0.68, 95% CI: 0.48–0.89), and IgG (SMD = 1.10, 95% CI: 0.70–1.50)], and the T cell immune function indicators [including CD4+ (SMD = 0.76, 95% CI: 0.53–0.99) and the ratio of CD4+/CD8+ (SMD = 0.92, 95% CI: 0.57–1.28)]. Meanwhile, the content of CD8+ was decreased significantly (SMD = −0.50, 95% CI: −0.91 to −0.10) followed by glutamine intervention. Pooled analysis of SSI (RR = 0.48, 95% CI: 0.30–0.75), anastomotic leakage (RR = 0.23, 95% CI: 0.09–0.61), and LOS (SMD = −1.13, 95% CI: −1.68 to −0.58) were decreased significantly in glutamine group compared with control group. Metaregression analysis revealed that the covariate of small-sample effects influenced the robustness and reliability of IgG outcome potentially. Findings of the present work demonstrated that

glutamine ought to be applied as an effective immunenutrition therapy in the treatment of patients with CRC after radical surgery. The present meta-analysis has been registered in PROSPERO (no. CRD42021243327).

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO, Identifier: CRD42021243327.

Keywords: colorectal cancer, humoral immunity, T cell immunity, post-operative complications, meta-analysis

INTRODUCTION

Colorectal cancer (CRC) is the most malignant tumors in digestive system and has become a serious threat to human health. Statistically, the global data showed that newly increased patients with CRC ∼1,880,725 (including 1,148,515 cases of colon cancer and 732,210 cases of rectum cancer), and the fatality rate of CRC was estimated to be ∼9.4% (1). Furthermore, the death rate from CRC is predicted to increase by 60% (colon cancer) and 71.5% (rectum cancer), respectively, in 2035 (2). Data from the American Cancer Society indicates that CRC is the third most common cancer diagnosed in both men and women in the United States. The number of CRC cases in the US for 2021 are: 1,04,270 new cases of colon cancer and 45,230 new cases of rectal cancer (3). From 2012 through 2016, CRC increased every year by 2% in people younger than 50 and 1% in people 50–64 in the US (3).

Surgical treatment in the management of non-metastatic or resectable CRC is irreplaceable and recommended as the first-line for radical treatment by the National Comprehensive Cancer Network (NCCN) Guidelines (4, 5) and European Society for Medical Oncology (ESMO) Guidelines (6, 7). However, due to the long-term consumption of tumor before the radical resection of CRC, insufficient nutritional intake, and the stress responses caused by surgical trauma the patients are most likely to suffer from malnutrition, decreased immune function, intestinal dysfunction, and post-operative complications. Previous studies have reported that malnutrition prevalence has been widely reported to reach 15–40% in patients with cancer at the time of diagnosis, and up to 80–90% in advanced cases of the disease (8). The prevalence of malnutrition in CRC patients also ranged from 45 to 60% (9) and these rates significantly increased followed by radical surgery (10). In addition, immune dysfunction or immunosuppression caused by surgery acted as the main inducement of post-operative complications. Many studies have attributed post-operative complications such as surgical site infection (SSI), anastomotic leak, ureteral injury, intraabdominal abscess, enteric fistula, bleeding, and post-operative bowel obstruction to immune dysfunction and malnutrition (11–14). Consequently, these complications not only significantly affected the short-term outcomes, such as the prolonging length of hospital stay (LOS) and increasing associated health costs, but it also deteriorated the long-term oncological results, including declining patients' quality of life and cancer recrudescence (15, 16).

Increasing evidences from clinical researches demonstrated that immunonutrition therapy was very likely to improve the immune function and decrease complications or recrudescence in patients after CRC surgery (17–20). Glutamine, a critical substance of immunenutrition, is an important source of energy for the intestinal tract and could improve intestinal function. Many studies have revealed the positive role of glutamine in CRC patients who underwent radical surgery (21–23). Furthermore, glutamine levels in serum could affect overall survival (OS) and progression-free survival (PFS) significantly, and serum glutamine levels may be applied as a prognostic indicator in patients with CRC (24, 25). However, other studies indicated that glutamine applied in CRC patients did not significantly improve the survival outcomes or post-operative complications (26–28).

These evidences were hard to match due to the heterogeneity of study designs, study populations, sample quantities, and systematic approaches based upon current clinical studies. To address those ambiguities and to evaluate the actual clinical significance of glutamine in patients with CRC, a meta-analysis of randomized, prospective clinical trials about glutamine applied in CRC patients who underwent radical surgery was conducted. This meta-analysis provided essential evidence of the effects of glutamine on immune functions and post-operative complications of patients with CRC.

MATERIALS AND METHODS

Protocol Registration

We have registered this protocol previously in PROSPERO in April 2021 (number: CRD42021243327, https://www.crd.york.ac.uk/PROSPERO).

Eligibility Criteria

The Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA statement was referred by this study and the "PICOS" principles was employed for developing the inclusion and exclusion criteria. Studies that meet the following inclusion criteria were included: (1) the design of study was a prospectively randomized controlled trial (RCT); (2) patients with CRC (including colon cancer and rectal cancer) and undergone radical surgery; (3) glutamine was set as experiment group and routine nutrition or blank therapy (fluid supporting therapy) as control group; (4) at least one of the investigated outcomes was reported in original researches. The exclusion criteria were as follows: (i) irrelevant studies and duplicated literatures; (ii) unavailable data literatures; (iii) letters, reviews, comments, case-report, laboratory studies, and meta-analysis.

Search Methodology

The PubMed, EMBASE, MEDLINE, Cochrane Library, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), VIP medicine information system (VIP), and Wanfang electronic databases were comprehensively searched up to July 30, 2021. The search terms were in the combination of medical subject headings (MeSH) terms and the following free words: (Colon/Rectal/colorectal/cancer/tumor/carcinoma/neoplasm) AND (glutamine/nutrition/immunenutrition) AND (complication/infection/leakage) AND (immune/immunity/IgA/IgG/IgM/CD4+/CD8+/CD4+/CD8+) AND (random/randomized/RCTs/clinical trial). In addition, potentially relevant references were also obtained manually. The language of all the publications was not limited.

Study Selection

All search results were combined in Endnote™, Version X8 (Thompson Reuters). Duplicates were removed manually. Two investigators (Tao Yang and Xuhong Yan) filtered the original studies independently. If the literature meets the eligibility criteria, the two investigators will further read the full text to screen the study. Any discrepancies were tackled by discussion or third-party consensus.

Data Extraction and Analysis

All data were collected independently by two investigators (Tao Yang and Yibo Cao) from eligible RCTs using a standardized form. The following information were extracted including: (i) Study ID, including the name of the first author and publication year; (ii) study subjects, number of participants, and their ages; (iii) treatment regimens for the treatment and control groups; and (iv) the primary endpoint, the immune function related indicators (including IgA, IgG, IgM, CD4+, CD8+, and the ratio of CD4+/CD8+) and the secondary endpoint, the post-operative complications (including SSI, anastomotic leakage, and LOS). If insufficient details were reported, we would contact authors for further information. Disagreements between two investigators were tackled by discussion and consensus.

Quality Assessment

The Cochrane Collaboration's tool for assessing risk of bias were employed for quality evaluation. Any disagreements during assessment were resolved by iteration, discussion, and consensus.

Statistical Analysis

All data were analyzed using Stata version 14.0 (Stata Corporation). Heterogeneity amongst studies was assessed using a Q-test and an I^2-test before determining the pooled effect. A

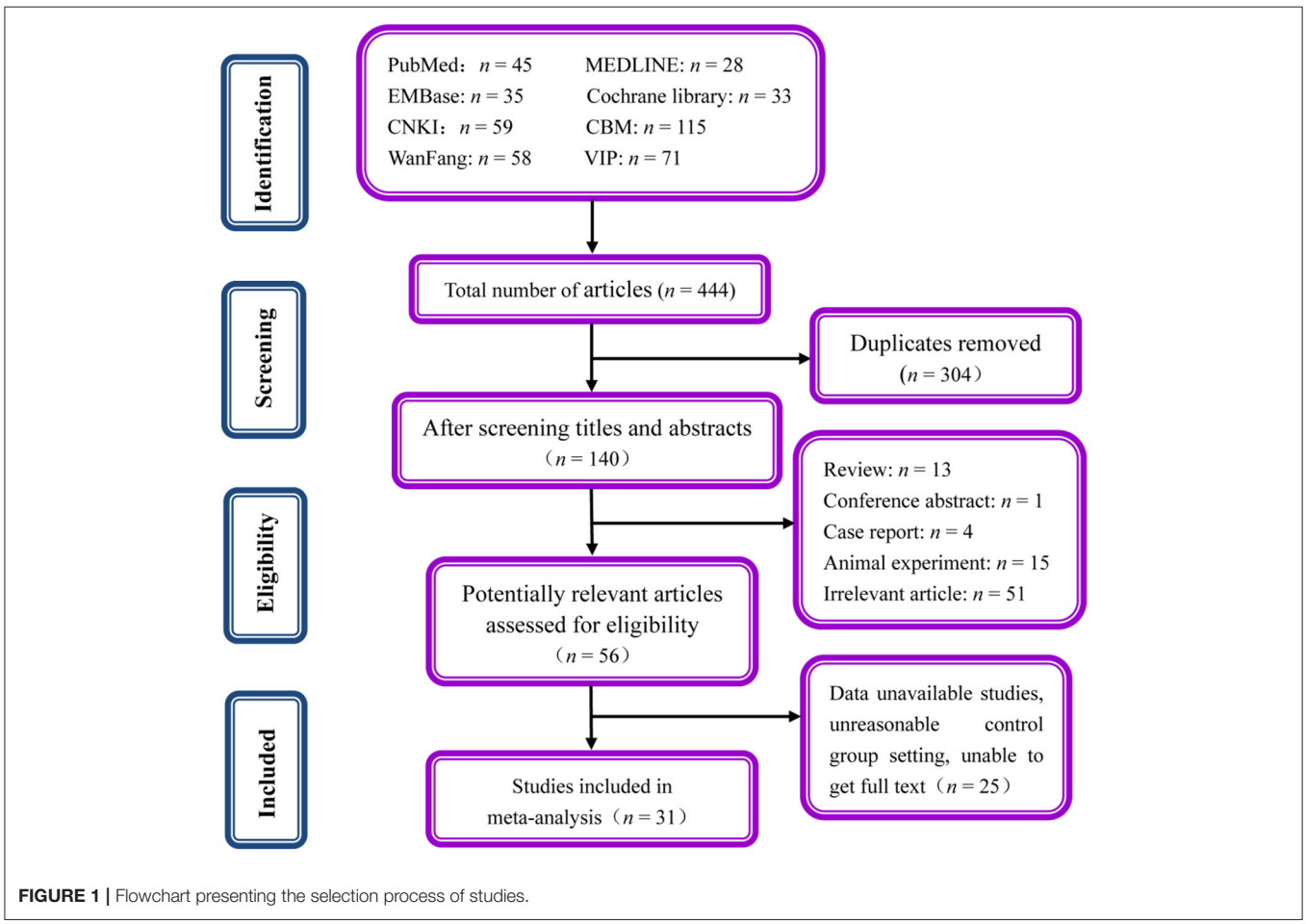

FIGURE 1 | Flowchart presenting the selection process of studies.

fixed effects model or a random effects model was based on the results of the Q-test and I^2-test. A fixed effects model was adopted if $I^2 < 50\%$ and $p > 0.1$. Otherwise, a random effects model was used. The primary endpoint was immune function related indicators (IgA, IgG, IgM, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$) and LOS was a continuous variable. The pooled analysis of these indicators was expressed as standard mean difference (SMD). The SSI and anastomotic leakage were dichotomous variables, and the pooled analysis of these complications was expressed as relative risks (RR). The significance of pooled effects was determined using a Z-test; $p < 0.05$ was considered to indicate a statistically significant difference. Sensitivity analysis was utilized to investigate the influence of a high-risk study on overall meta-analysis. Possible publication bias and the detailed reasons underlying publication bias were determined by contour-enhanced funnel plot. Possible source of heterogeneity was explored by metaregression performing via random effect model, and the restricted maximum likelihood (REML) estimation method proposed by Harbord et al. (29) was applied in metaregression.

RESULTS

Study Selection Outcome

A total of 444 relevant articles were retrieved ultimately. Among these, 304 were repeated articles. Totally, 84 literatures were excluded by screening the titles and abstracts due to reviews, conference abstract, animal experiments, case report, with 56 articles remaining. Then 25 articles were excluded by examining

TABLE 1 | Main information of included studies in the meta-analysis.

Study ID	Sample size (*n*)		Ages (year)		Dose of glutamine	Route of administration	Tumor types	Outcomes
	Treatment	Control	Treatment	Control				
Morlion et al. (21)	15	13	Mean: 67.1	Mean: 68.2	0.3 g/(kg•d)	PN	CRC	⑨
Oguz et al. (23)	57	52	Mean: 52	Mean: 57	1 g/(kg•d)	PN	CRC	⑦⑧⑨
Cui et al. (55)	20	20	Mean: 55	Mean: 56	0.5 g/(kg•d)	PN	CC	⑨
van Barneveld et al. (22)	61	62	Mean: 64	Mean: 65	11.9 g/d	EN	RC	⑦⑧
Chen (38)	22	22	58.7 ± 6.7		30 g/d	EN	CRC	①②③④⑤⑥⑨
Chen et al. (31)	50	50	64.22 ± 5.89	63.57 ± 6.5	60 g/d	EN	RC	①②③④⑥
Chen and Lin (39)	24	24	66.84 ± 5.52	68.12 ± 4.46	0.4 g/(kg•d)	PN	CC	④⑤⑥⑦⑧
Chen et al. (40)	42	42	62.1 ± 10.6	62.7 ± 11.3	0.5 g/kg•d	PN	CC	④⑤⑥⑧
Cheng and Huang (41)	50	50	NR		100 ml/d	PN	CC	①②③⑦⑧
De et al. (57)	52	52	53.54 ± 11.57	53.24 ± 11.38	100 ml/d	EN	CC	④⑤⑥
Huang et al. (42)	63	63	Range: 32–69	Range: 35–67	100 ml/d	PN	CC	①②③
Huang et al. (43)	15	15	57.0 ± 4.7	56.8 ± 3.5	0.4 g/(kg•d)	PN	CRC	②③④⑤
Huang et al. (35)	11	11	Range: 41–70		100 ml/d	PN	CRC	①②③⑦⑧
Jiang et al. (44)	31	31	56.8 ± 10.2	58.2 ± 9.5	0.4 g/(kg•d)	PN	CRC	①②③④⑤⑥
Li et al. (36)	20	20	57.81 ± 3.75	58.02 ± 4.63	NR	PN	CRC	⑧⑨
Li and Jia (45)	32	32	62.6 ± 9.6	65.5 ± 9.0	0.5 g/(kg•d)	EN	CRC	⑦⑧⑨
Li and Li (30)	30	30	50.1 ± 4.6	50.5 ± 4.9	0.4 g/(kg•d)	EN	RC	④⑤
Liu et al. (46)	40	40	61.4 ± 7.0	59.1 ± 7.5	100 ml/d	EN	CC	⑧⑨
Liu et al. (47)	43	42	57.1 ± 9.8	58.2 ± 10.1	0.4 g/(kg•d)	PN	CRC	①②③④⑤⑥
Luo et al. (48)	23	23	Range: 38–69		0.5 g/(kg•d)	PN	CC	①②③⑨
Shao et al. (34)	51	51	Range: 35–75		NR	EN	CRC	②③④⑤⑥
Song et al. (49)	20	20	Range: 28–80		0.4 g/(kg•d)	PN	CRC	①②③④⑤⑥
Ya et al. (50)	24	24	NR		20 g/d	PN	CRC	①②③④⑤⑥
Wang et al. (32)	30	30	58.7 ± 3.6	60.3 ± 4.5	0.3 g/(kg•d)	PN	RC	①②③⑧
Yang and Li (51)	24	20	Mean: 60.2	Mean: 61.1	100 mL/d	PN	CC	⑦⑧
Tasheng et al. (33)	70	70	59.3 ± 8.2	55.3 ± 9.1	0.4 g/(kg•d)	PN	CRC	④⑤⑥
Zhang et al. (37)	47	47	57.35 ± 16.4		100 mL/d	PN	CRC	①②③④⑤⑥
Zhang and Li (52)	30	30	Range: 28–80		0.4 g/(kg•d)	PN	CC	②③④⑤⑥
Zhao (53)	32	28	56.75 ± 5.60	54.42 ± 5.21	50 mL/d	PN	CRC	⑧
Zheng (54)	55	55	NR		100 mL/d	PN	CC	①②③
Bu et al. (56)	24	24	70.5 ± 10.6	66.8 ± 10.9	0.5 g/kg•d	PN	CRC	①②③④⑤⑥

NR, not report; PN, parenteral nutrition; EN, enteral nutrition; ①, CD4+; ②, CD8+; ③, the ratio of CD4+/CD8+; ④, IgA; ⑤, IgG; ⑥, IgM; ⑦, anastomotic leakage; ⑧, SSI; ⑨, LOS.

FIGURE 2 | Methodological quality graph and summary of the included studies: **(A)** Risk of bias summary; **(B)** Risk of bias graph.

the abstracts or full-texts. Finally, this meta-analysis included 31 studies that fulfilled the inclusion criteria (**Figure 1**).

Study Characteristics

Totally, 2,201 patients were involved in 31 studies (21–23, 30–57). Among these, 1,108 were allocated to the glutamine group and 1,093 patients were allocated to the control group. **Table 1** displayed the main characteristics of the included 31 studies. Overall, 31 studies were published between 1998 and 2019 years. Eight trials (22, 30, 31, 34, 38, 45, 46, 57) administrated glutamine through enteral nutrition (EN) and 23 trials (21, 23, 32, 33, 35–37, 39–44, 47–56) administrated through parenteral nutrition (PN). With regards to the outcomes of humoral immune function, 14 trials (31, 32, 37, 38, 41–44, 47–50, 54, 56) reported IgA indicator, 17 trials (31, 32, 34, 35, 37, 38, 41–44, 47–50, 52, 54, 56) reported IgM indicator, and 17 trials (31, 32, 34, 35, 37, 38, 41–44, 47–50, 52, 54, 56) reported IgG indicator. In addition, the outcomes of T cell immune function, including CD4+ content, was reported by 16 trials (30, 31, 33, 34, 37–40, 43, 44, 47, 49, 50, 52, 56, 57), CD8+ content, was reported by 15 trials (30, 33, 34, 37–40, 43, 44, 47, 49, 50, 52, 56, 57), and the ratio of CD4+/CD8+ was reported by 13 trials (31, 33, 34, 37, 38, 40, 44, 47, 49, 50, 52, 56, 57). Furthermore, the outcome of anastomotic leakage was reported by seven trials (22, 23, 35, 39, 41, 45, 51), SSI was reported by 12 trials (22, 23, 32, 35, 36, 39–41, 45, 46, 51, 53), and the LOS was reported by eight trials (21, 23, 36, 38, 45, 46, 48, 55). The main characteristics of the included studies are presented in **Table 1**.

Study Quality Assessment

Methodological quality assessment and outline of the included 31 studies were presented in **Figures 2A,B**. The generation of randomized sequence was identified adequately in all trials. The allocation concealment was unclear according to all trials. These trials were neither single nor double blinding design.

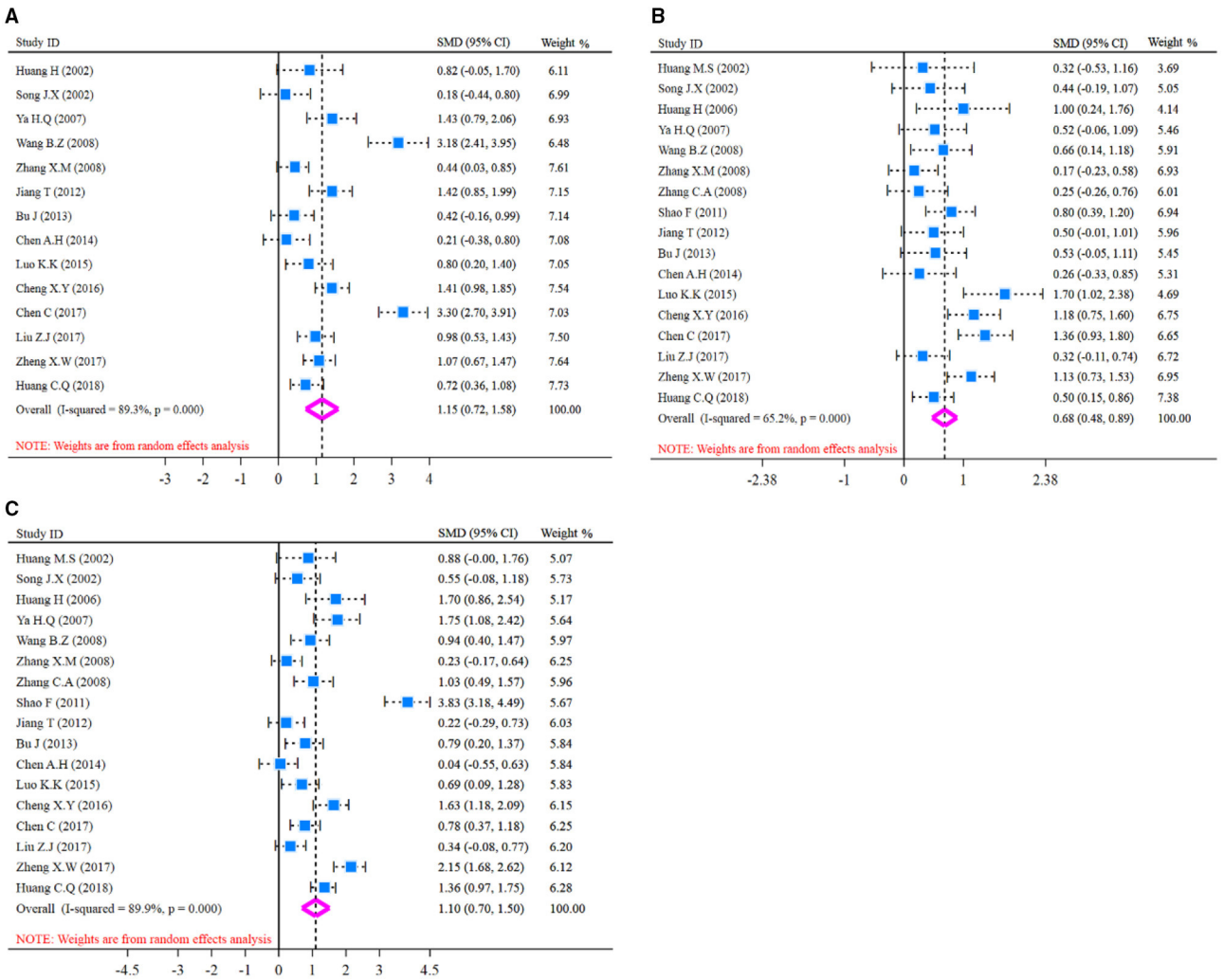

FIGURE 3 | Forest plot of standard mean difference (SMD) for IgA, IgM, and IgG. **(A)** Forest plot of IgA; **(B)** Forest plot of IgM; **(C)** Forest plot of IgG. All pooled analysis applied a random effect model.

Consequently, the evaluation of detection bias was high risk (**Figure 2B**). Incomplete outcomes and selective reporting were not detected in all studies. Conclusively, the methodological quality of all included trials stayed at a lower level due to the lack of blinding.

Results of Meta-analysis

Glutamine on Humoral Immune Function of Patients With CRC

The pooled analysis of humoral immune function indicators (IgA, IgM, IgG) is presented in **Figure 3** and SMD presentation. Heterogeneity was examined firstly before pooled analysis of these indicators. Test results revealed that there was a significant heterogeneity for IgA (I^2-test = 89.3% and Q-test p = 0.000, **Figure 3A**), moderate heterogeneity for IgM (I^2-test = 65.2% and Q-test p = 0.000, **Figure 3B**), and significant heterogeneity for IgG (I^2-test = 89.9% and Q-test p = 0.000, **Figure 3C**) between included studies. Thus, a random effect model was selected for pooled analysis. Results revealed that IgA content was significantly increased (Z = 5.27, p = 0.000; SMD = 1.15, 95% CI: 0.72–1.58; **Figure 3A**) in the glutamine group compared with the control group. Meanwhile, the indicator of IgM was also increased (Z = 6.47, p = 0.000; SMD = 0.68, 95% CI: 0.48–0.89; **Figure 3B**) in glutamine group. In addition, the indicator of IgG was significantly increased (Z = 5.34, p = 0.000; SMD = 1.10, 95% CI: 0.70–1.50; **Figure 3C**) in glutamine group compared with control group. These results demonstrated that glutamine improved the humoral immune function effectively for patients with CRC after radical operation.

Glutamine on T Cell Immune Function of Patients With CRC

Before pooled analysis of T cell immune function indicators (CD4+, CD8+, CD4+/CD8+), heterogeneity across studies was

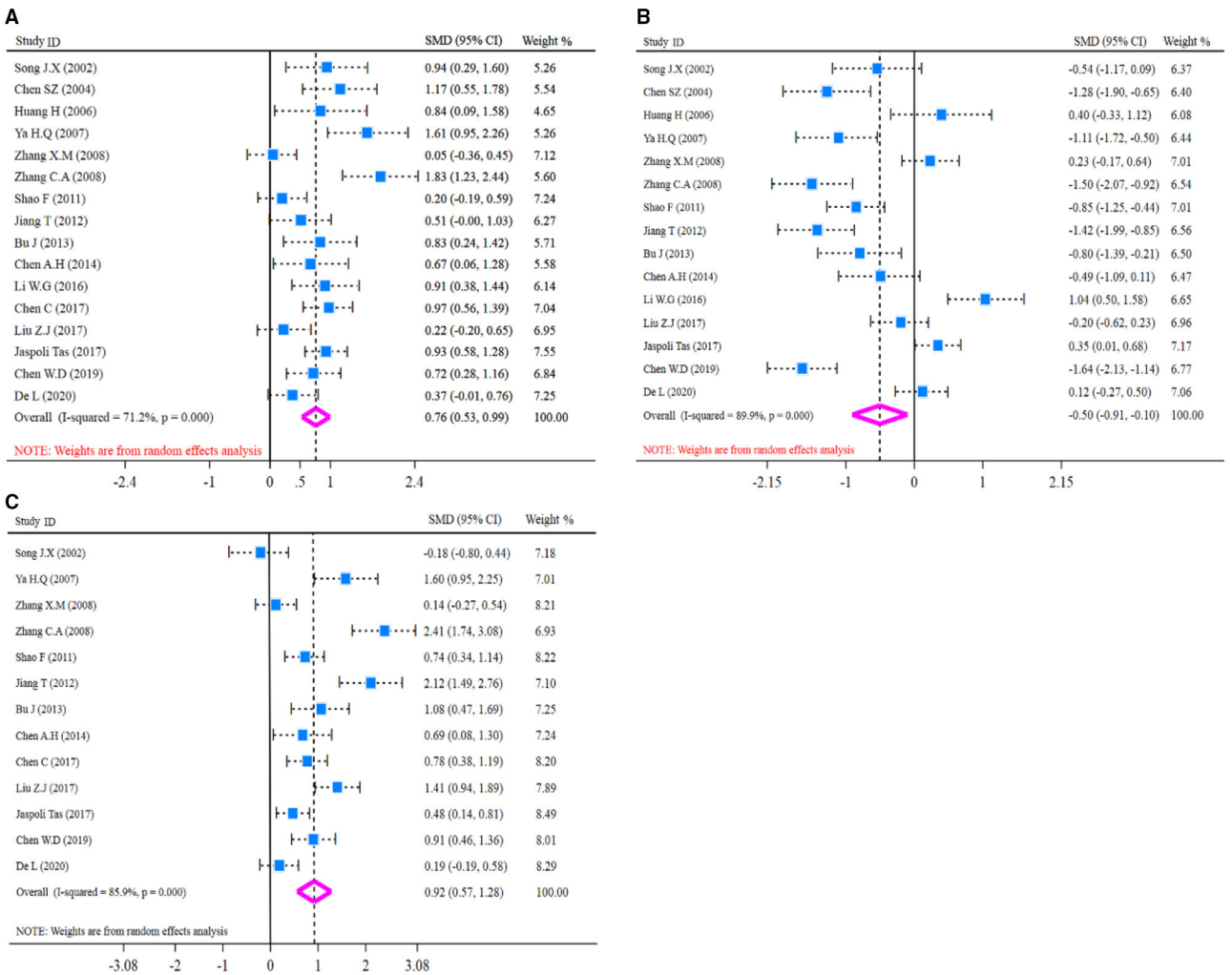

FIGURE 4 | Forest plot of standard mean difference (SMD) for CD4+, CD8+, and CD4+/CD8+. **(A)** Forest plot of CD4+; **(B)** Forest plot of CD8+; **(C)** Forest plot of CD4+/CD8+. All pooled analysis applied a random effect model.

tested conventionally. Heterogeneity test results revealed there was moderate heterogeneity for CD4+ (I^2-test = 71.2% and Q-test $p = 0.000$, **Figure 4A**), significant heterogeneity for CD8+ (I^2-test = 89.9% and Q-test $p = 0.000$, **Figure 4B**), and significant heterogeneity for CD4+/CD8+ (I^2-test = 85.9% and Q-test $p = 0.000$, **Figure 4C**). So, a random effect model was selected for pooled analysis. In the pooled meta-analysis, the content of CD4+ was increased significantly ($Z = 6.47$, $p = 0.000$; SMD = 0.76, 95% CI: 0.53–0.99; **Figure 4A**) in the glutamine group compared with the control group. On the contrary, the content of CD8+ was decreased significantly ($Z = 2.44$, $p = 0.015$; SMD = −0.50, 95% CI: −0.91 to −0.10; **Figure 4B**) in the glutamine group. Meanwhile, the ratio of CD4+/CD8+ was increased significantly ($Z = 5.07$, $p = 0.000$; SMD = 0.92, 95% CI: 0.57–1.28; **Figure 4C**) in the glutamine group compared with the control group. Results are shown in **Figure 4** and SMD presentation.

Glutamine on Post-Operative Complications of Patients With CRC

Heterogeneity was examined prior to pooled analysis of SSI, anastomotic leakage, and LOS. Test results revealed there were no significant heterogeneity across 12 studies (I^2-test = 0.0% and Q-test $p = 0.909$, **Figure 5A**) that reported SSI outcome, seven studies (I^2-test = 0.0% and Q-test $p = 0.944$, **Figure 5B**) that reported anastomotic leakage. Thus, a fixed effects model was applied for the pooled analysis. However, results revealed there was significant heterogeneity for LOS outcome (I^2-test = 85.6% and Q-test $p = 0.000$, **Figure 5C**). So, a random effect model was employed for pooled analysis. In the pooled meta-analysis, the rates of SSI were decreased significantly ($Z = 3.18$, $p = 0.001$; RR = 0.48, 95% CI: 0.30–0.75; **Figure 5A**) in glutamine group compared with the control group. Meanwhile, the rates of anastomotic leakage were decreased significantly ($Z = 2.98$, $p = 0.003$; RR = 0.23, 95% CI: 0.09–0.61; **Figure 5B**)

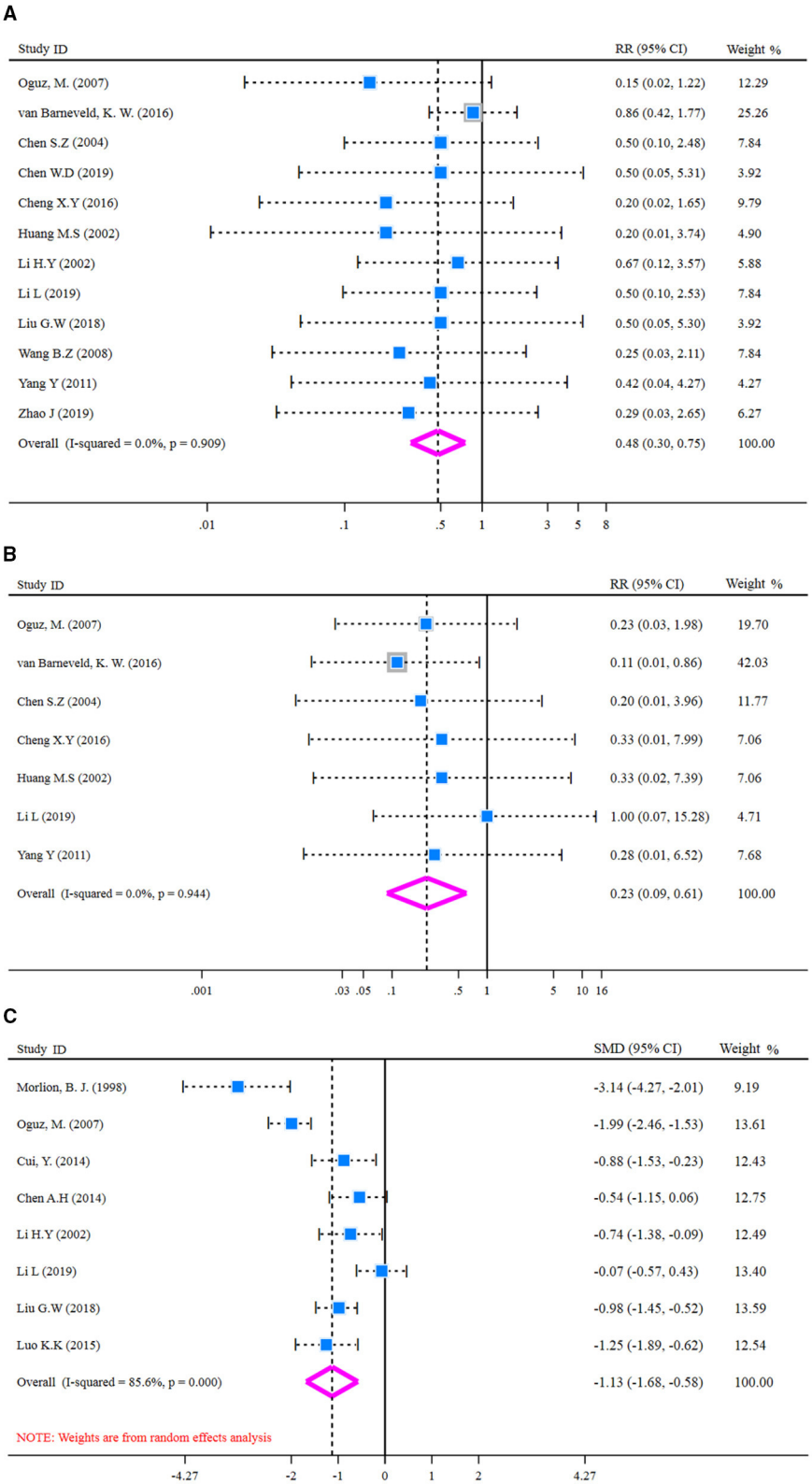

FIGURE 5 | Forest plot of for SSI, anastomotic leakage, and LOS. **(A)** Forest plot of SSI applied a fixed effect model; **(B)** Forest plot of anastomotic leakage applied a fixed effect model; **(C)** Forest plot of LOS applied a random effect model. SSI, surgical site infection; LOS, length of hospital stay.

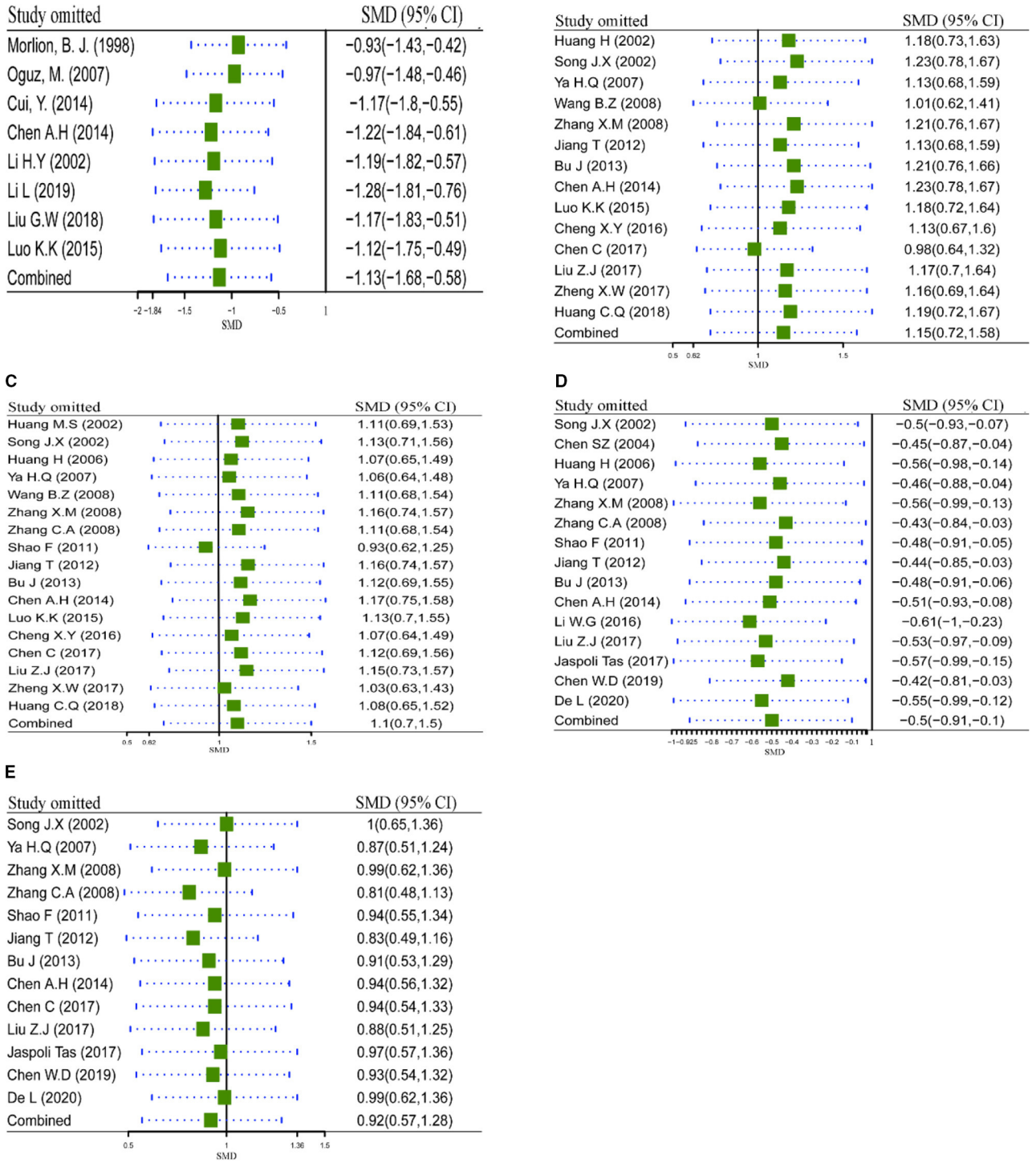

FIGURE 6 | Sensitivity analysis via leave-one-out procedure each time. **(A)** Sensitivity analysis of LOS; **(B)** Sensitivity analysis of IgA; **(C)** Sensitivity analysis of IgG; **(D)** Sensitivity analysis of CD8+; **(E)** Sensitivity analysis of CD4+/CD8+. LOS, length of hospital stay.

in the glutamine group. Furthermore, the LOS outcome was decreased significantly ($Z = 4.03$, $p = 0.000$; SMD = −1.13, 95% CI: −1.68 to −0.58; **Figure 5C**) in the glutamine group compared with the control group. These results showed that glutamine could reduce post-operative complications of patients with CRC.

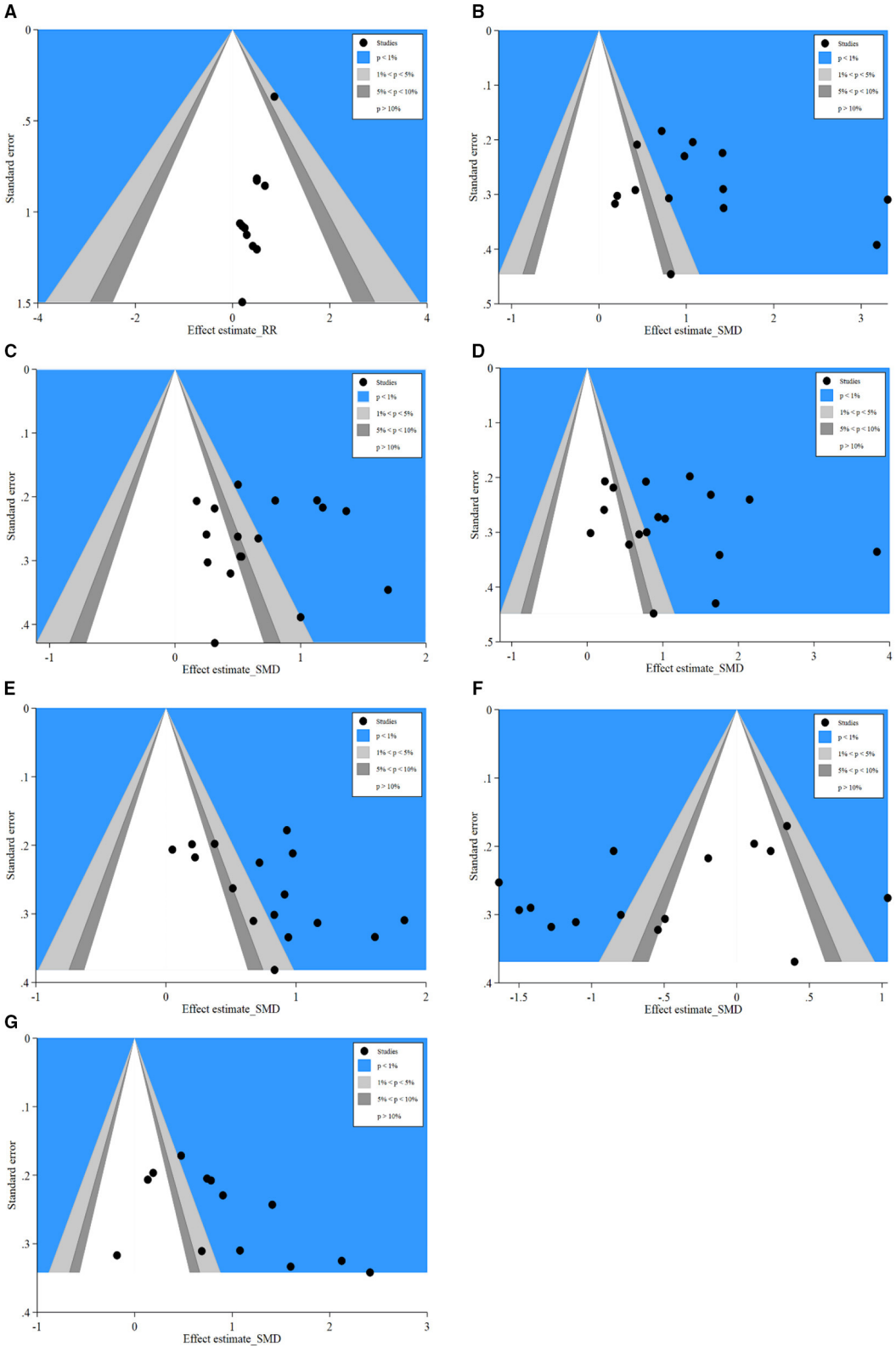

FIGURE 7 | Contour-enhanced funnel plots of SSI, IgA, IgM, IgG, CD4+, CD8+, and CD4+/CD8+. **(A)** Contour-enhanced funnel plot of SSI; **(B)** Contour-enhanced funnel plot of IgA; **(C)** Contour-enhanced funnel plot of IgM; **(D)** Contour-enhanced funnel plot of IgG; **(E)** Contour-enhanced funnel plot of CD4+; **(F)** Contour-enhanced funnel plot of CD8+; **(G)** Contour-enhanced funnel plot of CD4+/CD8+. SSI, surgical site infection.

TABLE 2 | Results of Meta-regression analysis.

Covariates	Univariate analysis				Multivariate analysis		
	Exponentiated coefficient	95% CI	*P*	Tau^2	Exponentiated coefficient	95% CI	*P*
Administration route (PN/EN)							
SSI (12 studies)	1.48	0.51 to 4.29	0.43	0.00	1.43	0.37 to 5.43	0.56
IgA (14 studies)	2.00	0.40 to 10.0	0.37	0.82	1.93	0.29 to 12.8	0.46
IgM (17 studies)	1.22	0.68 to 2.18	0.48	0.12	1.24	0.65 to 2.38	0.49
IgG (17 studies)	1.66	0.47 to 5.80	0.41	0.77	0.75	0.20 to 2.85	0.66
$CD4^+$ (16 studies)	0.80	0.46 to 1.39	0.40	0.17	0.79	0.40 to 1.58	0.48
$CD8^+$ (15 studies)	1.86	0.69 to 5.02	0.20	0.55	1.82	0.57 to 5.81	0.28
$CD4^+/CD8^+$ (13 studies)	0.62	0.23 to 1.64	0.30	0.47	0.79	0.20 to 3.16	0.71
Tumor type (Colon/rectal/colorectal cancer)							
SSI (12 studies)	0.99	0.48 to 2.05	0.97	0.00	0.97	0.45 to 2.07	0.93
IgA (14 studies)	0.78	0.41 to 1.48	0.42	0.84	0.86	0.28 to 2.61	0.77
IgM (17 studies)	0.80	0.63 to 1.00	0.05	0.09	0.83	0.61 to 1.13	0.21
IgG (17 studies)	0.84	0.49 to 1.45	0.51	0.77	1.27	0.69 to 2.35	0.41
$CD4^+$ (16 studies)	0.84	0.63 to 1.13	0.23	0.15	0.82	0.60 to 1.12	0.20
$CD8^+$ (15 studies)	1.28	0.77 to 2.14	0.32	0.58	1.33	0.79 to 2.24	0.26
$CD4^+/CD8^+$ (13 studies)	0.90	0.51 to 1.58	0.69	0.52	0.84	0.46 to 1.52	0.53
Total sample size (<100/ ≥100)							
SSI (12 studies)	1.31	0.45 to 3.79	0.58	0.00	1.07	0.28 to 4.06	0.91
IgA (14 studies)	1.88	0.56 to 6.29	0.28	0.79	1.37	0.15 to 12.2	0.75
IgM (17 studies)	1.59	1.06 to 2.39	**0.03**	0.07	1.23	0.67 to 2.27	0.47
IgG (17 studies)	3.20	1.38 to 7.44	**0.01**	0.47	4.45	1.26 to 15.7	**0.02**
$CD4^+$ (16 studies)	0.82	0.46 to 1.46	0.47	0.17	0.91	0.45 to 1.84	0.76
$CD8^+$ (15 studies)	1.62	0.53 to 4.93	0.37	0.59	1.23	0.35 to 4.33	0.72
$CD4^+/CD8^+$ (13 studies)	0.57	0.22 to 1.47	0.22	0.44	0.63	0.16 to 2.48	0.46

NA, Not applicable; SSI, surgical site infection. Significant results are in bold and underlined presentation.

Sensitivity Analysis for Robustness of Pooled Analysis

Sensitivity analysis *via* leave-one-out procedure each time was carried out to verify robustness of pooled results (LOS, IgA, IgG, CD8+, and CD4+/CD8+) with significant heterogeneity (≥80%) across included studies. Results are shown in **Figure 6**. Sensitivity analysis of LOS outcome (**Figure 6A**) indicated that exclusion of any study did not account for heterogeneity significantly, which demonstrated the pooled result of LOS was robust to some extent. Meanwhile, the same conclusions were retrieved from the sensitivity analysis of IgA (**Figure 6B**), IgG (**Figure 6C**), CD8+ (**Figure 6D**), and CD4+/CD8+ (**Figure 6E**). All results of sensitivity analysis demonstrated that the pooled results were robust to some extent.

Contour-Enhanced Funnel Plot for Potential Source of Publication Bias

Contour-enhanced funnel plot, which added conventional milestones in levels of statistical significance ($p < 0.01$, $p < 0.05$, $p < 0.1$ or $p > 0.1$) to funnel plots, was utilized to distinguish detail reasons of publication bias. Results of SSI (**Figure 7A**) indicated many studies were in areas of none-statistical significance ($p > 0.1$), which suggested that the origin of asymmetry may be more likely due to publication bias. Furthermore, results of IgA (**Figure 7B**), IgM (**Figure 7C**), IgG (**Figure 7D**), CD4+ (**Figure 7E**), CD8+ (**Figure 7F**), and CD4+/CD8+ (**Figure 7G**) presented that a great majority of missing studies were in areas of higher statistical significance ($p < 0.01$), which indicated the origin of asymmetry was most likely to be due to undetected factors rather than publication bias. Subsequently, we traced the original researches again, speculating that studies with a small sample size, ITT analysis, and missing blinding in many studies may account for those undetected bias. These factors may influence our conclusions potentially.

Metaregression Analysis

Metaregression was performed to assess the effect of underlying confounding factors on pooled effect estimation and to seek the sources of heterogeneity. The following covariates were predicted as potential factors premeditatedly: ① Administration route (PN or EN) of glutamine; ② Tumor type (Colon/rectal/CRC); ③ Total sample size (<100 or ≥100). Overall, univariate analysis indicated the administration route (PN or EN) of glutamine (**Table 2**, **Figure 8A**) and type of tumor (**Table 2**, **Figure 8B**) had no significant influence on the results of SSI, IgA, IgM, IgG, CD4+, CD8+, and CD4+/CD8+ outcomes ($p > 0.05$). The remaining variable of total sample size had significant influences on the pooled effects of IgM ($p = 0.03$, **Table 2**,

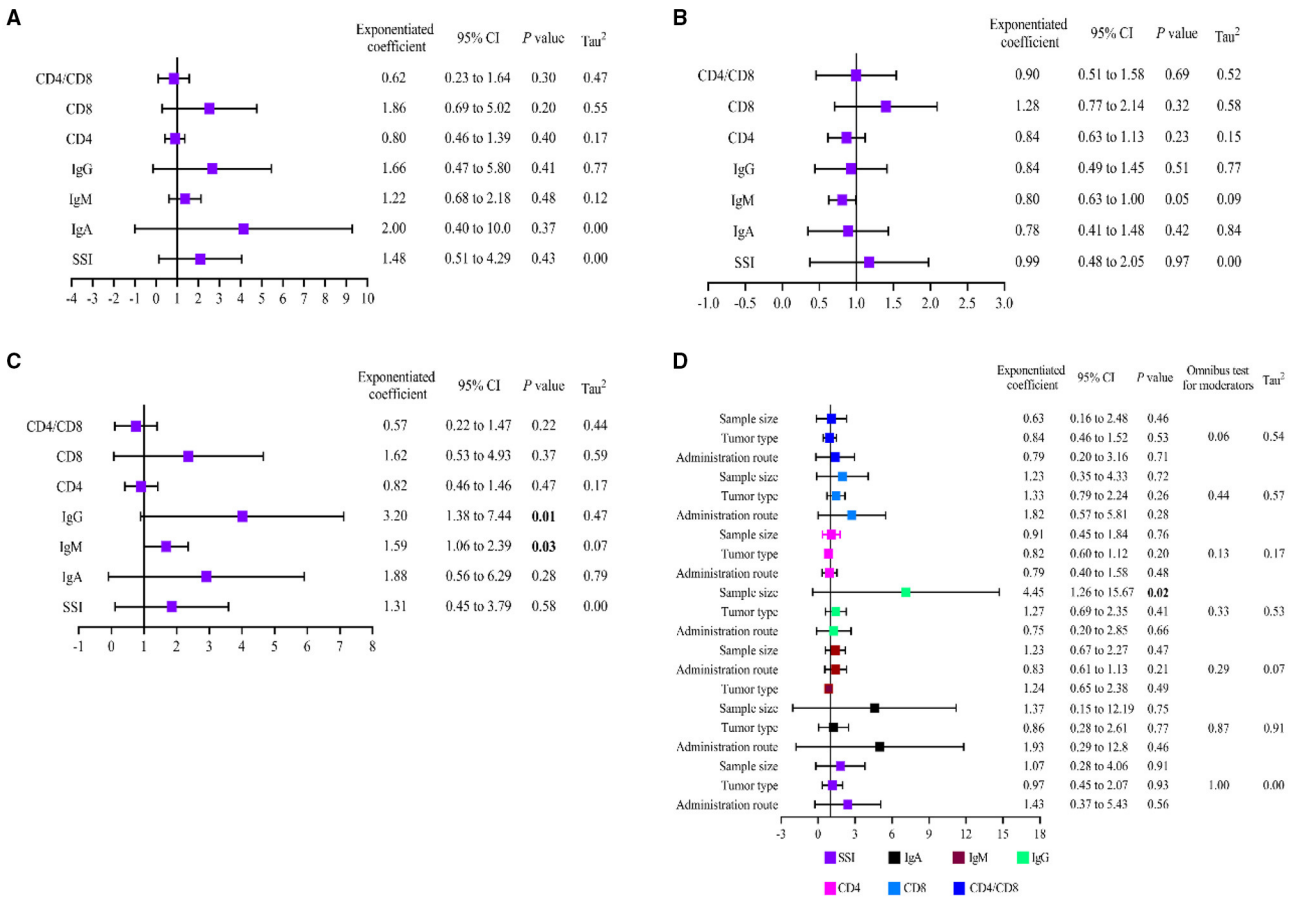

FIGURE 8 | Results of metaregression analysis. **(A)** Univariate analysis of administration route; **(B)** Univariate analysis of tumor type; **(C)** Univariate analysis of total sample size; **(D)** Multivariate analysis of all covariates. SSI, surgical site infection.

Figure 8C) and IgG ($p = 0.01$, **Table 2**, **Figure 8C**). Then, multivariate metaregression was utilized to evaluate the impact of multicovariates on the pooled effects. Three mentioned covariates (administration route of glutamine, tumor type, and total sample size) did not affect the pooled effects of SSI, IgA, IgM, CD4+, CD8+, and CD4+/CD8+, and the heterogeneity did not stem from this model ($p > 0.05$, **Table 2**, **Figure 8D**). However, multivariate analysis revealed that the endpoint of IgG was influenced by the covariate of total sample size ($P = 0.02$, **Table 2**, **Figure 8D**), which indicated the heterogeneity may originate from this covariate.

DISCUSSION

Overall, findings from this study illustrated that immune functions (including humoral immune function and T cell immune function) can be improved significantly with glutamine in sufferers with CRC. Meanwhile, the main post-operative complications also reduced by glutamine in patients with CRC after surgery. The certainty of conclusion from current study is mainly reflected in the following three aspects. First of all, the critical indicators of humoral immune function, including IgA, IgM, IgG, were significantly increased followed by glutamine intervention. The results of integrated analysis revealed that IgA content (SMD = 1.15, 95% CI: 0.72–1.58) was increased significantly in glutamine group compared with the control group. Meanwhile, the indicator of IgM (SMD = 0.68, 95% CI: 0.48–0.89) and IgG were also significantly increased (SMD = 1.10, 95% CI: 0.70–1.50) in glutamine group. These results demonstrated that glutamine was able to improve the humoral immune function effectively for patients with CRC after radical operation. Secondly, results of integrated analysis revealed that glutamine could regulate T cell immune function effectively of CRC patients after radical surgery. On one hand, the content of CD4+ (SMD = 0.76, 95% CI: 0.53–0.99) and index of CD4+/CD8+ (SMD = 0.92, 95% CI: 0.57–1.28) were increased significantly in glutamine group compared with control group. On the other hand, the content of CD8+ was decreased significantly (SMD = −0.50, 95% CI: −0.91 to −0.10) in glutamine group. These results indicated that glutamine could regulate the disordered immune function of T cell. Thirdly, all indicators of post-operative complications were decreased by glutamine in patients with

CRC after surgery. Pooled analysis of SSI (RR = 0.48, 95% CI: 0.30–0.75), anastomotic leakage (RR = 0.23, 95% CI: 0.09–0.61), and LOS (SMD = −1.13, 95% CI: −1.68 to −0.58) were decreased significantly in glutamine group compared with control group. All supporting evidence mentioned above demonstrated that glutamine should be applied as an effective immunenutrition therapy in the treatment of CRC patients after radical surgery.

Immunenutrition support for patients who underwent radical surgery for CRC is widely accepted for reducing the incidence and severity of post-operative complications. However, appropriate assessment and application of immunenutrition therapies were largely neglected (58). Until to now, immunenutrition support is generally recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) for malnourished patients with cancer (59), and it also coincided with the program of enhanced recovery after surgery (ERAS) (60). Glutamine, a substance of immunenutrition, as the major fuel source for macrophages, lymphocytes, and enterocytes, could increase the immune cell responses and decrease inflammations evidently (61, 62). For lymphocytes, glutamine activates the expression of T cell surface markers CD25, CD45RO, and CD71, promotes directly the proliferation of CD3+ (marker for mature lymphocytes) and T regulatory cells (T-reg) (63, 64). Furthermore, glutamine also reduces lymphokine-activated killer cell activity (64, 65). For monocytes and macrophages, glutamine stimulates antigen presentation, increases expression of surface antigens, and improves antioxidant defenses (66, 67). Due to the high rates of glutamine utilization in lymphocytes, macrophages, and neutrophils, the deficiency of glutamine is mostly like to arise immune dysfunction (68, 69). Previous study has indicated that glutamine could promote T cells differentiated into three subsets (Th1, Th17, and Treg). Meanwhile, glutaminase (GLS), which converts glutamine to glutamate, can promote Th17 but constrain Th1 and CTL effector cell differentiation (70). In addition, a clinical trial reported that glutamine and omega-3 fatty acids not only increased the total lymphocyte count, CD4+, CD8+, complement C3, IgG, IgA in all patients, but also decreased C-reactive protein (CRP) and the rates of wound infection (71). Thus, we come to the conclusion that deficiency of glutamine may lead to impaired immune function and ampliative inflammatory responses of CRC patients after radical surgery. On the contrary, glutamine supplementation could improve immune function and decrease complications after radical surgery in CRC patients.

This current work exerts more attention to the clinical benefits of glutamine in CRC patients after radical surgery. However, it is noteworthy that potential limitations of this integrated analysis should be emphasized. Thirty-one included trials were neither single nor double blinding design, which increases the risk of detection bias. Meanwhile, undetected bias predicted by contour-enhanced funnel plot showed studies with a small sample size and missing ITT analysis may account for potential bias. These factors may have a potential impact on final conclusions. Metaregression by univariate and multivariate analysis found sample size included in original studies was a potential covariate causing significant heterogeneity, and deescalating validity of results in this pooled analysis.

All in all, this meta-analysis with 2,201 patients from 31 RCTs provide pivotal evidence that glutamine supplementation could improve immune function and decrease post-operative complications of CRC patients after radical surgery effectively. When accepting the conclusions of this study, the methodological limitations should be noticed at the same time. It is widely recognized that the management CRC in pre- or post-operative stages is very much needed in the participation of multiple disciplinary team (MDT) and requires long-term medication. Thus, increasing RCTs with larger scale and multidimensional efficacy and nutritional status assessment are extensively required to balance the risk-benefit profile of glutamine in the management of CRC.

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.

AUTHOR CONTRIBUTIONS

TY, XY, and YC performed the search and drafted the manuscript. TY and XY performed the data extraction and analyzed the data. YC, TB, and TX designed the study and amended the original draft. GL, SG, and KX equally involved and contributed into the study conduction. All authors contributed to the article and approved the submitted version.

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Nutritional Risk Index Predicts Survival in Patients With Breast Cancer Treated With Neoadjuvant Chemotherapy

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Nutritional risk index (NRI) is an index based on ideal body weight that aims to present body weight and serum albumin levels. It has been utilized to discriminate patients at risk of postoperative complications and predict the postoperative outcome of major surgeries. However, this index remains limited for breast cancer patients treated with neoadjuvant chemotherapy (NACT). The research explores the clinical and prognostic significance of NRI in breast cancer patients. This study included 785 breast cancer patients (477 cases received NACT and 308 cases did not) were enrolled in this retrospective study. The optimal NRI cutoff value was evaluated by receiver operating characteristic (ROC) curve, then reclassified as low NRI group (<112) and high NRI group (≥112). The results demonstrated that NRI independently predicted survival on disease-free survival (DFS) and overall survival (OS) by univariate and multivariate Cox regression survival analyses [$P = 0.019$, hazard ratio (HR): 1.521, 95% CI: 1.071–2.161 and $P = 0.004$, HR: 1.415, 95% CI: 1.119–1.789; and $P = 0.026$, HR:1.500, 95% CI: 1.051–2.143 and $P < 0.001$, HR: 1.547, 95% CI: 1.221–1.959]. According to the optimal cutoff value of NRI, the high NRI value patients had longer mean DFS and OS time in contrast to those with low NRI value patients (63.47 vs. 40.50 months; 71.50 vs. 56.39 months). Furthermore, the results demonstrated that the high NRI score patients had significantly longer mean DFS and OS time than those with low NRI score patients in early-stage breast cancer ($\chi^2 = 9.0510$, $P = 0.0026$ and $\chi^2 = 9.2140$, $P = 0.0024$) and advanced breast cancer ($\chi^2 = 6.2500$, $P = 0.0124$ and $\chi^2 = 5.8880$, $P = 0.0152$). The mean DFS and OS values in patients with high NRI scores were significantly longer in contrast to those with low NRI scores in different molecular subtypes. The common toxicities after NACT were hematologic and gastrointestinal reactions, and the NRI had no statistically significant effects on toxicities, except in nausea ($\chi^2 = 9.2413$, $P = 0.0024$), mouth ulcers ($\chi^2 = 4.8133$, $P = 0.0282$), anemia ($\chi^2 = 8.5441$, $P = 0.0140$), and leukopenia

($\chi^2 = 11.0951$, $P = 0.0039$). NRI serves as a minimally invasive, easily accessible and convenient prognostic tool for evaluating breast cancer prognoses and treatment efficacy, and may help doctors in terms of selecting measures of greater efficiency or appropriateness to better treat breast cancer.

Keywords: nutritional risk index, breast cancer, nutrition, neoadjuvant chemotherapy, prognosis

INTRODUCTION

Breast cancer is among the most frequently diagnosed cancers in women globally, and seriously endangers their health (1). Although breast cancer often yields relatively more satisfactory prognoses compared to other types of cancer (e.g., lung cancer), the survival outcomes of patients with aggressive pathological breast cancer or distant metastasis remain to be alarmingly poor—about 90% of breast cancer deaths are caused by the occurrence of distant metastasis (2). As scientific evidence accumulates, treatment strategies, such as surgery, hormone therapy, targeted therapy, and immunotherapy, have forged a comprehensive network of promising treatments with varying degrees of curative effects (3). Aside from the differences in disease conditions, nutritional status also plays an essential role in shaping patients' prognosis as well as treatment efficacy and outcomes.

Decreased appetite with weight loss and cachexia, for instance, can be commonly found in cancer patients (4, 5). As a complicated and multifactorial syndrome, cachexia affects ∼50–80% of cancer patients, and is correlated with 20–40% of cancer deaths (6). It is important to note that poor nutritional status not only accelerates the progression of cancer, but also hinders the treatment of the disease, effectively creating a vicious circle that impacts both cancer care and treatment (7, 8). Previous studies found that malnutrition could cause patients' poor response to antitumor therapy, increase the incidence of postoperative complications, and subsequently, result in unsatisfactory survival prognosis (9, 10). In addition, cachexia may be a direct cause of death for cancer patients (11). In one retrospective autopsy study, for instance, the results show that ∼1% of 486 patients with cancer died from no other cause but cachexia (11). While some emerging evidence suggests that response rates of chemotherapy were lower among weight-losing patients, limited research on this relationship in breast cancer patients is available (12). Hence, it is of vital significance to discover more convenient indicators to evaluate the effect of nutritional status on disease prognosis and treatment efficacy in breast cancer patients.

Currently known indicators that reflect patients' nutritional status range from the assessment of patients' total body weight (TBW), globulin (GLB), albumin to globulin ratio (AGR), body mass index (BMI), to the prognostic nutritional index (PNI). For instance, previous studies show that malnutrition was related to poor treatment outcomes among patients with various types of cancers (13–15). Nevertheless, people know little about the relationship between nutritional status, cancer prognosis, and treatment efficacy in breast cancer patients (16). Existing evidence often suggests that breast cancer might be related to overnutrition, as opposed to malnutrition (17), effectively contradicting what is known about the predictive role of nutritional status in cancer patients.

To further cloud the research field, research indicates that factors such as BMI might be an unstable indicator of breast cancer patients' nutrition status-the relationship between BMI and the risk of women developing breast cancer differs by patients' menopausal status: in premenopausal women, most studies found either no association or a weak inverse correlation (18); however, in postmenopausal women, greater levels of BMI often increase women's likelihood of receiving a breast cancer diagnosis (19). One way to better shed light on the relationship between nutritional status, cancer prognosis, and treatment efficacy in breast cancer patients is via close examinations of less-studied factors such as the Nutritional Risk Index (NRI).

NRI is one of the most promising assessment tools in gauging the impact of nutritional status on cancer patients' morbidity and mortality rates (20). It is a composite index that factors in changes in patients' ideal body weight, present body weight, and serum albumin levels, and could serve as a convenient screening mechanism to predict the incidence rate of nutrition-related morbidity and mortality in cancer patients (21). For instance, current evidence suggests that low preoperative NRI was associated with poor prognosis and increased postoperative complications and can serve as an indicator in elderly colorectal cancer patients (22). However, this index remains limited for breast cancer patients treated with neoadjuvant chemotherapy. Therefore, to bridge the research gap, the current study aims to evaluate the clinical and prognostic significance of NRI in breast cancer patients, and the correlation between NRI and the treatment efficacy.

MATERIALS AND METHODS

Study Population

The retrospective study included a total of 785 participants-477 patients with breast cancer undergoing NACT (NACT group) and 308 breast cancer patients as control (non-NACT group). All patients received surgery at a large national hospital located in Beijing, China between January 1998 and December 2016. Anthracyclines-based and/or taxanes-based chemotherapy regimens were used for 477 breast cancer patients received NACT treatment. The detailed clinicopathological data were obtained from the patients' electronic medical records. This study was covered under Institutional Review Board (IRB) approved of Cancer Hospital Chinese Academy of Medical Sciences and Tongji Hospital, and it adheres to the standards of the Declaration of Helsinki and its subsequent amendments. All

of the patients provided written consent before participating in the study.

Participants were considered as eligible if they were breast cancer patients who had: (1) Confirmed by pathology; (2) Undergone primary tumor resection; (3) Performance Status (Zubrod-ECOG-WHO, ZPS) between 0 and 2 scores, and Karnofsky Performance Scores (KPS) $\geq$80 scores; (4) complete clinical recorded and follow-up data for all patients; (5) Expected to survive over 3 months; (6) Admission examination showed no obvious abnormalities in liver and renal function. Exclusion criteria were: (1) Patients received relevant anti-tumor therapy, such as chemotherapy, radiotherapy; (2) With serious complications, for instance, infection, pneumonia, skin ulcer; (3) Patients with chronic inflammatory diseases or autoimmune disease, for example, liver cirrhosis, systemic lupus erythematosus (SLE); (4) With distant organ metastasis; (5) Blood product transfusion within 1 month before treatment.

Pre-treatment Evaluation and TNM Classification

The 8th edition American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) were used to evaluate TNM stage classification (23, 24). The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were performed to evaluate the response rates of patients who received NACT (25). The Miller and Payne grade (MPG) framework was used to assess the histological response of the participants (26). The National Cancer Institute Common Toxicity Criteria (NCI-CTC) was used to assess the chemotherapy toxicity and adverse effects (27). Molecular classification of breast cancer was triple-negative type, HER2-enriched type, Luminal B HER2-negative type, Luminal B HER2-positive type, and Luminal A type, respectively (28).

Peripheral Venous Blood Parameters and Nutritional Factors

All of patients' blood samples were taken within 7 days before treatment. NRI is calculated as follows: 1.519 $\times$ serum albumin level (g/l) + 41.7 $\times$ (present/ideal body weight). And the ideal weight (Wlo) was calculated using the following formula: Height-100-[(Height-150)/2.5].

Follow-Up

Follow-up modalities included clinical examination, laboratory tests (routine blood test and blood biochemical), imaging examination (ultrasonography, mammography, and computed tomography of the chest). Follow-up evaluations were performed: (1) every 3 months for the first to second year postoperatively, (2) every 6 months for the third to fifth year postoperatively, (3) then yearly thereafter. Disease-free survival (DFS) was the duration from date of surgery to tumor recurrence, distant metastases, the date of death from any cause or last follow-up. Overall survival (OS) was the duration from the date of surgery to the date of death from any cause or last follow-up. Follow-up data were obtained from medical records, both inpatients and outpatients.

Statistical Analysis

The optimal cutoff values of related variables were utilized receiver operating characteristic (ROC) curves. The qualitative data was presented as the number of cases (%), and with intergroup comparisons performed in Chi-square test or Fisher's exact test. Survival curves, including DFS and OS, were generated using the Kaplan-Meier method coupled with the Log-rank test. The univariate and multivariate Cox proportional hazards regression model was used to discern potential prognostic factors. The association between patients' NRI and prognosis was performed using hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were carried out by SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and GraphPad prism 8.0 (GraphPad Inc., La Jolla, CA, USA). Alpha was set at the 0.05 level, and a two-tailed $P < 0.05$ was interpreted to achieve statistically significant.

RESULTS

Demographic and Clinicopathologic Features

The ROC curve was used to confirm the optimal cutoff value of NRI, and the value was 112. Two NRI groups were formed by the optimal NRI cutoff value: low NRI group (NRI < 112) and high NRI group (NRI $\geq$ 112). Of all patients, in the results demonstrated that age ($\chi^2 = 4.2272$, $P = 0.0398$), menopause ($\chi^2 = 12.6300$, $P = 0.0004$), US-LNM ($\chi^2 = 6.6599$, $P = 0.0099$), total lymph nodes ($\chi^2 = 8.7863$, $P = 0.0030$), total axillary lymph nodes ($\chi^2 = 6.9193$, $P = 0.0085$) were statistically significant differences between the two NRI groups. Other parameters were not statistically significant differences between the two NRI groups ($P > 0.05$) (see **Table 1**).

Nutritional Parameters and Hematological Parameters

Of all enrolled patients, there were significant differences in weight ($\chi^2 = 165.5080$, $P < 0.0001$), Body Mass Index (BMI) ($\chi^2 = 189.1500$, $P < 0.0001$), Alanine aminotransferase (ALT) ($\chi^2 = 14.2711$, $P = 0.0002$), Aspartate aminotransferase (AST) ($\chi^2 = 8.6402$, $P = 0.0033$), Lactate dehydrogenase (LDH) ($\chi^2 = 19.1932$, $P < 0.0001$), γ-glutamyl transpeptidase (GGT) ($\chi^2 = 22.926$, $P < 0.001$), Alkaline phosphatase (ALP) ($\chi^2 = 12.861$, $P = 0.0003$), Blood glucose (GLU) ($\chi^2 = 13.713$, $P < 0.001$), Immunoglobulin G (IgG) ($\chi^2 = 15.8213$, $P < 0.0001$), Albumin (ALB) ($\chi^2 = 135.2380$, $P < 0.0001$), White blood cell (W) ($\chi^2 = 6.9193$, $P = 0.0085$), Red blood cell (R) ($\chi^2 = 34.5983$, $P < 0.0001$), Hemoglobin (Hb) ($\chi^2 = 30.5623$, $P < 0.0001$), Neutrophil (N) ($\chi^2 = 12.2538$, $P = 0.0005$), Eosinophils (E) ($\chi^2 = 5.6190$, $P = 0.0178$), Platelet (P) ($\chi^2 = 13.8379$, $P = 0.0002$), respectively. The results were shown in **Table 2**.

Univariate and Multivariate Cox Regression Survival Analyses for Survival Analysis

The univariate and multivariate Cox proportional-hazards models with time-varying NRI were used to analyze the independent prognostic factors. Through univariate and

TABLE 1 | Demographic and clinicopathologic characteristics of the study's 785 breast cancer participants.

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	Low NRI 291	High NRI 494	χ^2	*P*-value	Low NRI 174	High NRI 303	χ^2	*P*-value	Low NRI 117	High NRI 191	χ^2	*P*-value
Age (years)			4.2272	0.0398			7.2047	0.0073			0.0037	0.9514
<47	157 (53.95%)	229 (46.36%)			98 (56.32%)	132 (43.56%)			59 (50.43%)	97 (50.79%)		
≥47	134 (46.05%)	265 (53.64%)			76 (43.68%)	171 (56.44%)			58 (49.57%)	94 (49.21%)		
Family history			0.5565	0.4557			3.3583	0.0669			1.4663	0.2259
No	217 (74.57%)	380 (76.92%)			118 (67.82%)	229 (75.58%)			99 (84.62%)	151 (79.06%)		
Yes	74 (25.43%)	114 (23.08%)			56 (32.18%)	74 (24.42%)			18 (15.38%)	40 (20.94%)		
Menopause			12.6300	0.0004			8.2428	0.0041			4.2263	0.0398
No	206 (70.79%)	287 (58.10%)			117 (67.24%)	163 (53.80%)			89 (76.07%)	124 (64.92%)		
Yes	85 (29.21%)	207 (41.90%)			57 (32.76%)	140 (46.20%)			28 (23.93%)	67 (35.08%)		
ABO blood type			0.3976	0.9827			2.0368	0.7290			1.8269	0.7676
A	76 (26.12%)	138 (27.94%)			42 (24.14%)	90 (29.70%)			34 (29.06%)	48 (25.13%)		
B	97 (33.33%)	165 (33.40%)			58 (33.33%)	87 (28.71%)			39 (33.33%)	78 (40.84%)		
O	89 (30.58%)	145 (29.35%)			54 (31.03%)	92 (30.36%)			35 (29.91%)	53 (27.75%)		
AB	29 (9.97%)	46 (9.31%)			20 (11.49%)	34 (11.22%)			9 (7.69%)	12 (6.28%)		
Tumor site			0.8458	0.3578			0.0358	0.8500			3.0094	0.0828
Right	143 (49.14%)	226 (45.75%)			84 (48.28%)	149 (49.17%)			59 (50.43%)	77 (40.31%)		
Left	148 (50.86%)	268 (54.25%)			90 (51.72%)	154 (50.83%)			58 (49.57%)	114 (59.69%)		
US-Primary tumor site			5.1400	0.2732			6.7210	0.1514			3.3700	0.4979
Upper outer quadrant	190 (65.29%)	299 (60.53%)			116 (66.67%)	189 (62.38%)			74 (63.25%)	110 (57.59%)		
Lower outer quadrant	21 (7.22%)	60 (12.15%)			9 (5.17%)	35 (11.55%)			12 (10.26%)	25 (13.09%)		
Lower inner quadrant	13 (4.47%)	24 (4.86%)			9 (5.17%)	9 (2.97%)			4 (3.42%)	15 (7.85%)		
Upper inner quadrant	46 (15.81%)	74 (14.98%)			23 (13.22%)	38 (12.54%)			23 (19.66%)	36 (18.85%)		
Central	21 (7.22%)	37 (7.49%)			17 (9.77%)	32 (10.56%)			4 (3.42%)	5 (2.62%)		
US-Tumor size (cm)			3.5999	0.1653			3.0109	0.2219			1.7944	0.4077
≤2cm	105 (36.08%)	205 (41.50%)			44 (25.29%)	91 (30.03%)			61 (52.14%)	114 (59.69%)		
>2 and <5 cm	153 (52.58%)	249 (50.40%)			99 (56.90%)	174 (57.43%)			54 (46.15%)	75 (39.27%)		
≥5 cm	33 (11.34%)	40 (8.10%)			31 (17.82%)	38 (12.54%)			2 (1.71%)	2 (1.05%)		
US-LNM			6.6599	0.0099			4.3998	0.0359			2.1557	0.1421
No	230 (79.04%)	349 (70.65%)			125 (71.84%)	189 (62.38%)			105 (89.74%)	160 (83.77%)		
Yes	61 (20.96%)	145 (29.35%)			49 (28.16%)	114 (37.62%)			12 (10.26%)	31 (16.23%)		

(Continued)

TABLE 1 | Continued

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	**Low NRI 291**	**High NRI 494**	**χ^2**	***P*-value**	**Low NRI 174**	**High NRI 303**	**χ^2**	***P*-value**	**Low NRI 117**	**High NRI 191**	**χ^2**	***P*-value**
US-BIRADS			0.2781	0.8702			0.7660	0.6818			0.2191	0.8963
4	27 (9.28%)	51 (10.32%)			18 (10.34%)	36 (11.88%)			9 (7.69%)	15 (7.85%)		
5	118 (40.55%)	202 (40.89%)			64 (36.78%)	119 (39.27%)			54 (46.15%)	83 (43.46%)		
6	146 (50.17%)	241 (48.79%)			92 (52.87%)	148 (48.84%)			54 (46.15%)	93 (48.69%)		
Clinical T stage			1.1766	0.8819			0.7925	0.9395			2.3854	0.6653
T1	59 (20.27%)	109 (22.06%)			25 (14.37%)	40 (13.20%)			34 (29.06%)	69 (36.13%)		
T2	154 (52.92%)	259 (52.43%)			80 (45.98%)	146 (48.18%)			74 (63.25%)	113 (59.16%)		
T3	53 (18.21%)	78 (15.79%)			45 (25.86%)	70 (23.10%)			8 (6.84%)	8 (4.19%)		
T4	25 (8.59%)	48 (9.72%)			24 (13.79%)	47 (15.51%)			1 (0.85%)	1 (0.52%)		
Clinical N stage			6.8947	0.1416			3.2495	0.5170			4.8157	0.3067
N0	125 (42.96%)	174 (35.22%)			31 (17.82%)	42 (13.86%)			94 (80.34%)	132 (69.11%)		
N1	75 (25.77%)	158 (31.98%)			56 (32.18%)	108 (35.64%)			19 (16.24%)	50 (26.18%)		
N2	53 (18.21%)	107 (21.66%)			50 (28.74%)	101 (33.33%)			3 (2.56%)	6 (3.14%)		
N3	38 (13.06%)	55 (11.13%)			37 (21.26%)	52 (17.16%)			1 (0.85%)	3 (1.57%)		
Clinical TNM stage			1.0040	0.6053			0.6262	0.7312			0.5983	0.7415
I	34 (11.68%)	58 (11.74%)			6 (3.45%)	8 (2.64%)			28 (23.93%)	50 (26.18%)		
II	148 (50.86%)	234 (47.37%)			64 (36.78%)	104 (34.32%)			84 (71.79%)	130 (68.06%)		
III	109 (37.46%)	202 (40.89%)			104 (59.77%)	191 (63.04%)			5 (4.27%)	11 (5.76%)		
Neoadjuvant Chemotherapy (PRE)							3.9810	0.4085				
AC/ACF					6 (3.45%)	22 (7.26%)						
CT/ACT					11 (6.32%)	16 (5.28%)						
AT					86 (49.43%)	137 (45.21%)						
TP					48 (27.59%)	93 (30.69%)						
Others					23 (13.22%)	35 (11.55%)						
Chemotherapy times (PRE)							0.4359	0.5091				
<6					52 (29.89%)	82 (27.06%)						
≥6					122 (70.11%)	221 (72.94%)						
Response							4.0382	0.4009				
CR					3 (1.72%)	4 (1.32%)						
PR					110 (63.22%)	202 (66.67%)						
SD					56 (32.18%)	95 (31.35%)						

(Continued)

TABLE 1 | Continued

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	**Low NRI 291**	**High NRI 494**	**χ^2**	***P*-value**	**Low NRI 174**	**High NRI 303**	**χ^2**	***P*-value**	**Low NRI 117**	**High NRI 191**	**χ^2**	***P*-value**
PD					5 (2.87%)	2 (0.66%)						
Miller and Payne grade							5.3440	0.2538				
1					7 (4.02%)	15 (4.95%)						
2					40 (22.99%)	86 (28.38%)						
3					63 (36.21%)	114 (37.62%)						
4					30 (17.24%)	32 (10.56%)						
5					34 (19.54%)	56 (18.48%)						
Pathological response							0.0382	0.8450				
pCR					27 (15.52%)	45 (14.85%)						
non-pCR					147 (84.48%)	258 (85.15%)						
Post-chemotherapy regimen			0.9129	0.9693			2.5610	0.7673			2.9160	0.7129
AC/ACF	47 (16.15%)	78 (15.79%)			13 (7.47%)	30 (9.90%)			34 (29.06%)	48 (25.13%)		
CT/ACT	48 (16.49%)	77 (15.59%)			12 (6.90%)	18 (5.94%)			36 (30.77%)	59 (30.89%)		
AT	38 (13.06%)	59 (11.94%)			17 (9.77%)	20 (6.60%)			21 (17.95%)	39 (20.42%)		
TP	24 (8.25%)	37 (7.49%)			15 (8.62%)	24 (7.92%)			9 (7.69%)	13 (6.81%)		
Others	37 (12.71%)	71 (14.37%)			30 (17.24%)	51 (16.83%)			7 (5.98%)	20 (10.47%)		
NO	97 (33.33%)	172 (34.82%)			87 (50.00%)	160 (52.81%)			10 (8.55%)	12 (6.28%)		
Operative time (min)			0.7026	0.4019			0.1904	0.6626			0.4766	0.4900
<90	123 (42.27%)	224 (45.34%)			90 (51.72%)	163 (53.80%)			33 (28.21%)	61 (31.94%)		
≥90	168 (57.73%)	270 (54.66%)			84 (48.28%)	140 (46.20%)			84 (71.79%)	130 (68.06%)		
Type of surgery			0.4121	0.5209			2.6578	0.1030			0.5543	0.4566
Mastectomy	221 (75.95%)	385 (77.94%)			142 (81.61%)	264 (87.13%)			79 (67.52%)	121 (63.35%)		
Breast-conserving surgery	70 (24.05%)	109 (22.06%)			32 (18.39%)	39 (12.87%)			38 (32.48%)	70 (36.65%)		
Tumor size			0.6829	0.7108			1.4411	0.4865			8.8906	0.0117
≤2 cm	157 (53.95%)	280 (56.68%)			102 (58.62%)	161 (53.14%)			55 (47.01%)	119 (62.30%)		
>2 and <5 cm	114 (39.18%)	185 (37.45%)			57 (32.76%)	115 (37.95%)			57 (48.72%)	70 (36.65%)		
≥5 cm	20 (6.87%)	29 (5.87%)			15 (8.62%)	27 (8.91%)			5 (4.27%)	2 (1.05%)		
Histologic type			1.7407	0.4188			4.1249	0.1271			0.3858	0.8246
Ductal	284 (97.59%)	474 (95.95%)			172 (98.85%)	289 (95.38%)			112 (95.73%)	185 (96.86%)		
Lobular	4 (1.37%)	9 (1.82%)			1 (0.57%)	6 (1.98%)			3 (2.56%)	3 (1.57%)		
Others	3 (1.03%)	11 (2.23%)			1 (0.57%)	8 (2.64%)			2 (1.71%)	3 (1.57%)		

(Continued)

TABLE 1 | Continued

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	**Low NRI 291**	**High NRI 494**	χ^2	***P*-value**	**Low NRI 174**	**High NRI 303**	χ^2	***P*-value**	**Low NRI 117**	**High NRI 191**	χ^2	***P*-value**
Histologic grade			1.3423	0.5111			3.0411	0.2186			13.3849	0.0012
I	52 (17.87%)	81 (16.40%)			34 (19.54%)	74 (24.42%)			18 (15.38%)	7 (3.66%)		
II	164 (56.36%)	267 (54.05%)			98 (56.32%)	146 (48.18%)			66 (56.41%)	121 (63.35%)		
III	75 (25.77%)	146 (29.55%)			42 (24.14%)	83 (27.39%)			33 (28.21%)	63 (32.98%)		
Pathological T stage			2.5200	0.6411			5.7720	0.2169			4.1800	0.3822
Tis/T0	35 (12.03%)	57 (11.54%)			32 (18.39%)	56 (18.48%)			3 (2.56%)	1 (0.52%)		
T1	113 (38.83%)	189 (38.26%)			76 (43.68%)	114 (37.62%)			37 (31.62%)	75 (39.27%)		
T2	114 (39.18%)	212 (42.91%)			44 (25.29%)	105 (34.65%)			70 (59.83%)	107 (56.02%)		
T3	21 (7.22%)	24 (4.86%)			16 (9.20%)	18 (5.94%)			5 (4.27%)	6 (3.14%)		
T4	8 (2.75%)	12 (2.43%)			6 (3.45%)	10 (3.30%)			2 (1.71%)	2 (1.05%)		
Pathological N stage			3.2307	0.5200			2.0263	0.7309			6.1693	0.1869
N0	124 (42.61%)	202 (40.89%)			67 (38.51%)	109 (35.97%)			57 (48.72%)	93 (48.69%)		
N1	56 (19.24%)	119 (24.09%)			35 (20.11%)	66 (21.78%)			21 (17.95%)	53 (27.75%)		
N2	51 (17.53%)	71 (14.37%)			32 (18.39%)	45 (14.85%)			19 (16.24%)	26 (13.61%)		
N3	60 (20.62%)	102 (20.65%)			40 (22.99%)	83 (27.39%)			20 (17.09%)	19 (9.95%)		
Pathological TNM stage			2.8211	0.5882			5.8386	0.2115			3.7345	0.4431
Tis/T0	28 (9.62%)	46 (9.31%)			26 (14.94%)	45 (14.85%)			2 (1.71%)	1 (0.52%)		
I	64 (21.99%)	93 (18.83%)			39 (22.41%)	44 (14.52%)			25 (21.37%)	49 (25.65%)		
II	87 (29.90%)	175 (35.43%)			36 (20.69%)	82 (27.06%)			51 (43.59%)	93 (48.69%)		
III	112 (38.49%)	180 (36.44%)			73 (41.95%)	132 (43.56%)			39 (33.33%)	48 (25.13%)		
Total lymph nodes			8.7863	0.0030			3.9425	0.0471			4.9253	0.0265
<21	165 (56.70%)	226 (45.75%)			84 (48.28%)	118 (38.94%)			81 (69.23%)	108 (56.54%)		
≥21	126 (43.30%)	268 (54.25%)			90 (51.72%)	185 (61.06%)			36 (30.77%)	83 (43.46%)		
Positive lymph nodes			0.3660	0.5452			0.5296	0.4668			0.0127	0.9101
<1	126 (43.30%)	203 (41.09%)			69 (39.66%)	110 (36.30%)			57 (48.72%)	93 (48.69%)		
≥1	165 (56.70%)	291 (58.91%)			105 (60.34%)	193 (63.70%)			60 (51.28%)	98 (51.31%)		
Total axillary lymph nodes			6.9193	0.0085			5.2727	0.0217			1.6639	0.1971

(Continued)

TABLE 1 | Continued

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	**Low NRI 291**	**High NRI 494**	χ^2	***P*-value**	**Low NRI 174**	**High NRI 303**	χ^2	***P*-value**	**Low NRI 117**	**High NRI 191**	χ^2	***P*-value**
<20	162 (55.67%)	227 (45.95%)			83 (47.70%)	112 (36.96%)			79 (67.52%)	115 (60.21%)		
≥20	129 (44.33%)	267 (54.05%)			91 (52.30%)	191 (63.04%)			38 (32.48%)	76 (39.79%)		
Positive axillary lymph nodes			0.0160	0.8993			0.2612	0.6093			0.2575	0.6118
<1	128 (43.99%)	215 (43.52%)			69 (39.66%)	113 (37.29%)			59 (50.43%)	102 (53.40%)		
≥1	163 (56.01%)	279 (56.48%)			105 (60.34%)	190 (62.71%)			58 (49.57%)	89 (46.60%)		
Post-operative complications			0.7944	0.3728			4.4512	0.0349			0.6359	0.4252
No	273 (93.81%)	455 (92.11%)			169 (97.13%)	280 (92.41%)			104 (88.89%)	175 (91.62%)		
Yes	18 (6.19%)	39 (7.89%)			5 (2.87%)	23 (7.59%)			13 (11.11%)	16 (8.38%)		
Post-operative chemotherapy			0.1792	0.6721			0.3484	0.5550			0.5609	0.4539
No	97 (33.33%)	172 (34.82%)			87 (50.00%)	160 (52.81%)			10 (8.55%)	12 (6.28%)		
Yes	194 (66.67%)	322 (65.18%)			87 (50.00%)	143 (47.19%)			107 (91.45%)	179 (93.72%)		
Post-operative chemotherapy times			0.1528	0.6959			0.0100	0.9205			0.1177	0.7316
<4	136 (46.74%)	238 (48.18%)			124 (71.26%)	216 (71.29%)			12 (10.26%)	22 (11.52%)		
≥4	155 (53.26%)	256 (51.82%)			50 (28.74%)	87 (28.71%)			105 (89.74%)	169 (88.48%)		
Post-operative radiotherapy			0.0034	0.9534			0.3244	0.5690			0.3721	0.5419
No	73 (25.09%)	123 (24.90%)			46 (26.44%)	73 (24.09%)			27 (23.08%)	50 (26.18%)		
Yes	218 (74.91%)	371 (75.10%)			128 (73.56%)	230 (75.91%)			90 (76.92%)	141 (73.82%)		
Post-operative endocrine therapy			0.0968	0.7557			0.5481	0.4591			0.1384	0.7099
No	114 (39.18%)	188 (38.06%)			79 (45.40%)	127 (41.91%)			35 (29.91%)	61 (31.94%)		
Yes	177 (60.82%)	306 (61.94%)			95 (54.60%)	176 (58.09%)			82 (70.09%)	130 (68.06%)		
Post-operative targeted therapy			2.3758	0.1232			2.8104	0.0937			0.1659	0.6838
No	207 (71.13%)	376 (76.11%)			113 (64.94%)	219 (72.28%)			94 (80.34%)	157 (82.20%)		
Yes	84 (28.87%)	118 (23.89%)			61 (35.06%)	84 (27.72%)			23 (19.66%)	34 (17.80%)		

TABLE 2 | The correlation between nutritional parameters/blood parameters and NRI.

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	**Low NRI 291**	**High NRI 494**	χ^2	***P*-value**	**Low NRI 174**	**High NRI 303**	χ^2	***P*-value**	**Low NRI 117**	**High NRI 191**	χ^2	***P*-value**
Weight (Kg)			165.5080	<0.0001			114.6400	<0.0001			52.3078	<0.0001
<62.00	229 (78.69%)	154 (31.17%)			142 (81.61%)	93 (30.69%)			87 (74.36%)	61 (31.94%)		
≥62.00	62 (21.31%)	340 (68.83%)			32 (18.39%)	210 (69.31%)			30 (25.64%)	130 (68.06%)		
Height (m)			0.0191	0.8900			0.2239	0.6361			0.5970	0.4397
<1.60	124 (42.61%)	213 (43.12%)			82 (47.13%)	136 (44.88%)			42 (35.90%)	77 (40.31%)		
≥1.60	167 (57.39%)	281 (56.88%)			92 (52.87%)	167 (55.12%)			75 (64.10%)	114 (59.69%)		
BMI			189.1500	<0.0001			124.4900	<0.0001			65.9453	<0.0001
<24.00	238 (81.79%)	153 (30.97%)			148 (85.06%)	97 (32.01%)			90 (76.92%)	56 (29.32%)		
≥24.00	53 (18.21%)	341 (69.03%)			26 (14.94%)	206 (67.99%)			27 (23.08%)	135 (70.68%)		
ALT (U/L)			14.2711	0.0002			6.3387	0.0118			8.0961	0.0044
<15	163 (56.01%)	207 (41.90%)			89 (51.15%)	119 (39.27%)			74 (63.25%)	88 (46.07%)		
≥15	129 (44.33%)	287 (58.10%)			85 (48.85%)	184 (60.73%)			44 (37.61%)	103 (53.93%)		
AST (U/L)			8.6402	0.0033			4.4634	0.0346			4.0702	0.0437
<18	160 (54.98%)	218 (44.13%)			88 (50.57%)	123 (40.59%)			72 (61.54%)	95 (49.74%)		
≥18	131 (45.02%)	276 (55.87%)			86 (49.43%)	180 (59.41%)			45 (38.46%)	96 (50.26%)		
LDH (U/L)			19.1932	<0.0001			11.6302	0.0007			7.5377	0.0060
<167	169 (58.08%)	207 (41.90%)			88 (50.57%)	105 (34.65%)			81 (69.23%)	102 (53.40%)		
≥167	122 (41.92%)	287 (58.10%)			86 (49.43%)	198 (65.35%)			36 (30.77%)	89 (46.60%)		
GGT (U/L)			22.9262	<0.0001			9.4150	0.0022			14.3058	0.0002
<17	168 (57.73%)	198 (40.08%)			90 (51.72%)	113 (37.29%)			78 (66.67%)	85 (44.50%)		
≥17	123 (42.27%)	296 (59.92%)			84 (48.28%)	190 (62.71%)			39 (33.33%)	106 (55.50%)		
ALP (U/L)			12.8606	0.0003			8.3752	0.0038			4.4880	0.0341
<64	164 (56.36%)	213 (43.12%)			98 (56.32%)	129 (42.57%)			66 (56.41%)	84 (43.98%)		
≥64	127 (43.64%)	281 (56.88%)			76 (43.68%)	174 (57.43%)			51 (43.59%)	107 (56.02%)		
GLU (mmol/L)			13.7133	0.0002			20.6972	<0.0001			0.0934	0.7599
<5.33	170 (58.42%)	221 (44.74%)			114 (65.52%)	133 (43.89%)			56 (47.86%)	88 (46.07%)		
≥5.33	121 (41.58%)	273 (55.26%)			60 (34.48%)	170 (56.11%)			61 (52.14%)	103 (53.93%)		
IgA (g/L)			0.5835	0.4450			0.6877	0.4069			0.0467	0.8289
<2.30	149 (51.20%)	239 (48.38%)			93 (53.45%)	150 (49.50%)			56 (47.86%)	89 (46.60%)		
≥2.30	142 (48.80%)	255 (51.62%)			81 (46.55%)	153 (50.50%)			61 (52.14%)	102 (53.40%)		
IgG (g/L)			15.8213	<0.0001			7.1034	0.0077			9.1460	0.0025
<11.70	170 (58.42%)	216 (43.72%)			99 (56.90%)	134 (44.22%)			71 (60.68%)	82 (42.93%)		
≥11.70	121 (41.58%)	278 (56.28%)			75 (43.10%)	169 (55.78%)			46 (39.32%)	109 (57.07%)		
IgM (g/L)			2.8698	0.0903			1.7770	0.1825			1.0348	0.3090
<1.10	132 (45.36%)	255 (51.62%)			82 (47.13%)	162 (53.47%)			50 (42.74%)	93 (48.69%)		
≥1.10	159 (54.64%)	239 (48.38%)			92 (52.87%)	141 (46.53%)			67 (57.26%)	98 (51.31%)		

(Continued)

TABLE 2 | Continued

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	**Low NRI 291**	**High NRI 494**	χ^2	***P*-value**	**Low NRI 174**	**High NRI 303**	χ^2	***P*-value**	**Low NRI 117**	**High NRI 191**	χ^2	***P*-value**
ALB (g/L)			135.2380	<0.0001			74.2045	<0.0001			61.3788	<0.0001
<45.2	224 (76.98%)	168 (34.01%)			131 (75.29%)	104 (34.32%)			93 (79.49%)	64 (33.51%)		
≥45.2	67 (23.02%)	326 (65.99%)			43 (24.71%)	199 (65.68%)			24 (20.51%)	127 (66.49%)		
CRP (mg/dl)			0.6978	0.4035			0.0235	0.8783			1.0375	0.3084
<0.02	148 (50.86%)	236 (47.77%)			69 (39.66%)	118 (38.94%)			79 (67.52%)	118 (61.78%)		
≥0.02	143 (49.14%)	258 (52.23%)			105 (60.34%)	185 (61.06%)			38 (32.48%)	73 (38.22%)		
CA125 (U/ml)			2.7964	0.0945			2.1107	0.1463			0.8742	0.3498
<13.35	134 (46.05%)	258 (52.23%)			73 (41.95%)	148 (48.84%)			61 (52.14%)	110 (57.59%)		
≥13.35	157 (53.95%)	236 (47.77%)			101 (58.05%)	155 (51.16%)			56 (47.86%)	81 (42.41%)		
CA153 (U/ml)			0.0620	0.8033			0.3039	0.5814			0.9651	0.3259
<11.63	147 (50.52%)	245 (49.60%)			73 (41.95%)	135 (44.55%)			74 (63.25%)	110 (57.59%)		
≥11.63	144 (49.48%)	249 (50.40%)			101 (58.05%)	168 (55.45%)			43 (36.75%)	81 (42.41%)		
CEA (ng/ml)			0.0378	0.8459			0.0651	0.7986			0.0081	0.9285
<1.66	144 (49.48%)	248 (50.20%)			76 (43.68%)	136 (44.88%)			68 (58.12%)	112 (58.64%)		
≥1.66	147 (50.52%)	246 (49.80%)			98 (56.32%)	167 (55.12%)			49 (41.88%)	79 (41.36%)		
D-D (mg/L)			0.9341	0.3338			0.9454	0.3309			0.0537	0.8167
<0.29	150 (51.55%)	237 (47.98%)			78 (44.83%)	122 (40.26%)			72 (61.54%)	115 (60.21%)		
≥0.29	141 (48.45%)	257 (52.02%)			96 (55.17%)	181 (59.74%)			45 (38.46%)	76 (39.79%)		
FIB (g/L)			1.8362	0.1754			0.6464	0.4214			1.2150	0.2704
<2.85	153 (52.58%)	235 (47.57%)			83 (47.70%)	133 (43.89%)			70 (59.83%)	102 (53.40%)		
≥2.85	138 (47.42%)	259 (52.43%)			91 (52.30%)	170 (56.11%)			47 (40.17%)	89 (46.60%)		
INR			0.1167	0.7326			0.0951	0.7578			0.1161	0.7333
<0.93	133 (45.70%)	232 (46.96%)			63 (36.21%)	114 (37.62%)			70 (59.83%)	118 (61.78%)		
≥0.93	158 (54.30%)	262 (53.04%)			111 (63.79%)	189 (62.38%)			47 (40.17%)	73 (38.22%)		
FDP (ug/ml)			0.2037	0.6518			1.5777	0.2091			0.1936	0.6599
<1.40	133 (45.70%)	234 (47.37%)			44 (25.29%)	93 (30.69%)			89 (76.07%)	141 (73.82%)		
≥1.40	158 (54.30%)	260 (52.63%)			130 (74.71%)	210 (69.31%)			28 (23.93%)	50 (26.18%)		
Before chemotherapy												
White blood cell (W) ($\times 10^9$/L)			6.9193	0.0085			2.2118	0.1370			5.5383	0.0186
<6.01	162 (55.67%)	227 (45.95%)			95 (54.60%)	144 (47.52%)			67 (57.26%)	83 (43.46%)		
≥6.01	129 (44.33%)	267 (54.05%)			79 (45.40%)	159 (52.48%)			50 (42.74%)	108 (56.54%)		

(Continued)

TABLE 2 | Continued

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	**Low NRI 291**	**High NRI 494**	χ^2	***P*-value**	**Low NRI 174**	**High NRI 303**	χ^2	***P*-value**	**Low NRI 117**	**High NRI 191**	χ^2	***P*-value**
Red blood cell (R) ($\times 10^{12}$/L)			34.5983	<0.0001			24.9932	<0.0001			10.0475	0.0015
<4.40	184 (63.23%)	205 (41.50%)			112 (64.37%)	123 (40.59%)			72 (61.54%)	82 (42.93%)		
≥4.40	107 (36.77%)	289 (58.50%)			62 (35.63%)	180 (59.41%)			45 (38.46%)	109 (57.07%)		
Hemoglobin (Hb) ($\times 10^9$/L)			30.5623	<0.0001			15.0049	0.0001			16.4623	<0.0001
<132	179 (61.51%)	203 (41.09%)			109 (62.64%)	134 (44.22%)			70 (59.83%)	69 (36.13%)		
≥132	112 (38.49%)	291 (58.91%)			65 (37.36%)	169 (55.78%)			47 (40.17%)	122 (63.87%)		
Neutrophil (N) ($\times 10^9$/L)			12.2538	0.0005			5.6323	0.0176			6.7928	0.0092
<3.68	169 (58.08%)	223 (45.14%)			96 (55.17%)	133 (43.89%)			73 (62.39%)	90 (47.12%)		
≥3.68	122 (41.92%)	271 (54.86%)			78 (44.83%)	170 (56.11%)			44 (37.61%)	101 (52.88%)		
Lymphocyte (L) ($\times 10^9$/L)			0.0043	0.9477			0.3036	0.5816			0.3575	0.5499
<1.76	145 (49.83%)	246 (49.80%)			97 (55.75%)	161 (53.14%)			48 (41.03%)	85 (44.50%)		
≥1.76	146 (50.17%)	248 (50.20%)			77 (44.25%)	142 (46.86%)			69 (58.97%)	106 (55.50%)		
Monocyte (M) ($\times 10^9$/L)			0.1913	0.6619			0.0532	0.8175			0.1483	0.7002
<0.35	139 (47.77%)	228 (46.15%)			80 (45.98%)	136 (44.88%)			59 (50.43%)	92 (48.17%)		
≥0.35	152 (52.23%)	266 (53.85%)			94 (54.02%)	167 (55.12%)			58 (49.57%)	99 (51.83%)		
Eosinophils (E) ($\times 10^9$/L)			5.6190	0.0178			1.2650	0.2607			5.5256	0.0187
<0.06	116 (39.86%)	240 (48.58%)			82 (47.13%)	159 (52.48%)			34 (29.06%)	81 (42.41%)		
≥0.06	175 (60.14%)	254 (51.42%)			92 (52.87%)	144 (47.52%)			83 (70.94%)	110 (57.59%)		
Basophils (B) ($\times 10^9$/L)			2.6581	0.1030			3.1246	0.0771			0.1668	0.6830
<0.02	93 (31.96%)	131 (26.52%)			58 (33.33%)	78 (25.74%)			35 (29.91%)	53 (27.75%)		
≥0.02	198 (68.04%)	363 (73.48%)			116 (66.67%)	225 (74.26%)			82 (70.09%)	138 (72.25%)		
Platelet (P) ($\times 10^9$/L)			13.8379	0.0002			9.6383	0.0019			4.1917	0.0406
<243	169 (58.08%)	219 (44.33%)			98 (56.32%)	126 (41.58%)			71 (60.68%)	93 (48.69%)		
≥243	122 (41.92%)	275 (55.67%)			76 (43.68%)	177 (58.42%)			46 (39.32%)	98 (51.31%)		

TABLE 3 | Univariate and multivariate cox regression survival analyses of the NRI for the prediction of DFS and OS in the participants.

	Univariate analysis	DFS	Multivariate analysis		Univariate analysis	OS	Multivariate analysis	
Parameters	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Cases (*n*)								
Age (years)		0.6653				0.9316		
<47	1 (reference)				1 (reference)			
≥47	0.926 (0.654–1.311)				1.015 (0.717–1.437)			
Weight (Kg)		0.3371				0.3594		
<62.00	1 (reference)				1 (reference)			
≥62.00	1.212 (0.819–1.793)				1.209 (0.806–1.814)			
Height (m)		0.5863				0.5458		
<1.60	1 (reference)				1 (reference)			
≥1.60	0.926 (0.700–1.223)				0.915 (0.687–1.220)			
BMI		0.0696				0.1769		
<24.00	1 (reference)				1 (reference)			
≥24.00	0.690 (0.462–1.030)				0.754 (0.500–1.136)			
Family history		0.3081				0.7330		
No	1 (reference)				1 (reference)			
Yes	0.855 (0.633–1.155)				0.948 (0.700–1.285)			
Menopause		0.0210		0.0037		0.1971		
No	1 (reference)		1 (reference)		1 (reference)			
Yes	1.531 (1.066–2.199)		1.412 (1.119–1.782)		1.274 (0.882–1.841)			
ALT (U/L)		0.9828				0.4137		
<15	1 (reference)				1 (reference)			
≥15	1.003 (0.740–1.361)				0.880 (0.648–1.196)			
AST (U/L)		0.3652				0.7735		
<18	1 (reference)				1 (reference)			
≥18	0.867 (0.636–1.181)				0.955 (0.696–1.309)			
LDH (U/L)		0.2055				0.3921		
<167	1 (reference)				1 (reference)			
≥167	1.198 (0.906–1.586)				1.131 (0.853–1.499)			
GGT (U/L)		0.8440				0.9701		
<17	1 (reference)				1 (reference)			
≥17	1.029 (0.773–1.370)				1.006 (0.751–1.347)			
ALP (U/L)		0.0780				0.0714		
<64	1 (reference)				1 (reference)			
≥64	1.293 (0.972–1.721)				1.306 (0.977–1.745)			
GLU (mmol/L)		0.0022		0.0032		0.0142		0.0019
<5.33	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥5.33	0.647 (0.490–0.855)		0.713 (0.569–0.893)		0.694 (0.519–0.930)		0.683 (0.536–0.869)	
IgA		0.5811				0.3024		
<2.30	1 (reference)				1 (reference)			
≥2.30	1.074 (0.834–1.384)				1.146 (0.885–1.483)			
IgG		0.7248				0.7598		
<11.70	1 (reference)				1 (reference)			
≥11.70	0.956 (0.745–1.227)				0.962 (0.748–1.237)			
IgM		0.6205				0.7928		
<1.10	1 (reference)				1 (reference)			
≥1.10	0.939 (0.732–1.205)				0.966 (0.748–1.249)			
ALB		0.2803				0.7265		
<45.2	1 (reference)				1 (reference)			
≥45.2	1.172 (0.879–1.564)				0.949 (0.707–1.273)			

(Continued)

TABLE 3 | Continued

	Univariate analysis	DFS	Multivariate analysis		Univariate analysis	OS	Multivariate analysis	
Parameters	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
CRP		0.1714				0.4541		
<0.02	1 (reference)				1 (reference)			
≥0.02	0.822 (0.620–1.089)				0.894 (0.666–1.199)			
CA125		0.0174		0.0248		0.1988		
<13.35	1 (reference)		1 (reference)		1 (reference)			
≥13.35	1.372 (1.057–1.781)		1.298 (1.034–1.630)		1.188 (0.914–1.543)			
CA153		0.0040		0.0180		0.0042		0.0033
<11.63	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥11.63	1.516 (1.143–2.012)		1.302 (1.046–1.620)		1.514 (1.140–2.011)		1.390 (1.116–1.732)	
CEA		0.4982				0.8598		
<1.66	1 (reference)				1 (reference)			
≥1.66	0.914 (0.705–1.186)				1.024 (0.786–1.334)			
D–D (mg/L)		0.1937				0.2868		
<0.29	1 (reference)				1 (reference)			
≥0.29	1.200 (0.911–1.581)				1.166 (0.879–1.546)			
FIB (g/L)		0.8146				0.2548		
<2.85	1 (reference)				1 (reference)			
≥2.85	0.969 (0.745–1.261)				1.167 (0.895–1.522)			
INR		0.6036				0.0448		0.0107
<0.93	1 (reference)				1 (reference)		1 (reference)	
≥0.93	0.936 (0.728–1.203)				1.296 (1.006–1.671)		1.335 (1.069–1.667)	
FDP (ug/ml)		0.5275				0.3305		
<1.40	1 (reference)				1 (reference)			
≥1.40	1.102 (0.815–1.492)				0.859 (0.633–1.166)			
ABO blood type		0.0874				0.1258		
A	1 (reference)				1 (reference)			
B	0.950 (0.695–1.299)				0.898 (0.649–1.243)			
O	0.718 (0.517–0.997)				0.745 (0.531–1.044)			
AB	1.175 (0.746–1.850)				1.238 (0.770–1.992)			
White blood cell (W)		0.0901				0.2279		
<6.01	1 (reference)				1 (reference)			
≥6.01	1.406 (0.948–2.086)				1.289 (0.853–1.947)			
Red blood cell (R)		0.8669				0.7343		
<4.40	1 (reference)				1 (reference)			
≥4.40	0.974 (0.716–1.325)				1.055 (0.774–1.438)			
Hemoglobin (Hb)		0.6310				0.3908		
<132	1 (reference)				1 (reference)			
≥132	0.928 (0.683–1.261)				0.877 (0.649–1.184)			
Neutrophil (N)		0.8081				0.8474		
<3.68	1 (reference)				1 (reference)			
≥3.68	0.956 (0.667–1.371)				0.964 (0.661–1.405)			
Lymphocyte (L)		0.1995				0.7082		
<1.76	1 (reference)				1 (reference)			
≥1.76	0.828 (0.620–1.105)				0.946 (0.707–1.265)			
Monocyte (M)		0.3330				0.0030		0.0030
<0.35	1 (reference)				1 (reference)		1 (reference)	
≥0.35	0.875 (0.668–1.146)				0.657 (0.497–0.868)		0.701 (0.556–0.884)	

(Continued)

TABLE 3 | Continued

	Univariate analysis	DFS	Multivariate analysis		Univariate analysis	OS	Multivariate analysis	
Parameters	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Eosinophils (E)		0.0141		0.0197		0.0005		0.0234
<0.06	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥0.06	0.715 (0.546–0.934)		0.766 (0.613–0.958)		0.613 (0.466–0.807)		0.775 (0.622–0.966)	
Basophils (B)		0.3230				0.2915		
<0.02	1 (reference)				1 (reference)			
≥0.02	1.156 (0.867–1.543)				1.172 (0.873–1.572)			
Platelet (P)		0.1400				0.2032		
<243	1 (reference)				1 (reference)			
≥243	0.829 (0.646–1.064)				0.847 (0.657–1.094)			
Nutritional risk index (NRI)		0.0191		0.0038		0.0257		0.0003
<112	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥112	1.521 (1.071–2.161)		1.415 (1.119–1.789)		1.500 (1.051–2.143)		1.547 (1.221–1.959)	
Tumor site		0.1413				0.1316		
Right	1 (reference)				1 (reference)			
Left	1.208 (0.939–1.553)				1.218 (0.942-1.575)			
US-Primary tumor site		0.2583				0.2737		
Upper outer quadrant	1 (reference)				1 (reference)			
Lower outer quadrant	1.267 (0.852–1.885)				1.256 (0.832–1.895)			
Lower inner quadrant	1.399 (0.809–2.420)				1.747 (1.011–3.017)			
Upper inner quadrant	1.351 (0.964–1.891)				1.190 (0.841–1.686)			
Central	1.397 (0.798–2.447)				1.216 (0.692–2.137)			
US-Tumor size		0.5810				0.8227		
≤2 cm	1 (reference)				1 (reference)			
>2 and <5 cm	0.899 (0.657–1.228)				0.980 (0.713–1.346)			
≥5 cm	1.131 (0.616–2.077)				0.827 (0.445–1.537)			
US-LNM		0.9629				0.4328		
No	1 (reference)				1 (reference)			
Yes	0.992 (0.699–1.406)				1.152 (0.809–1.640)			
US-BIRADS		0.7120				0.5340		
4 (4a 4b 4c)	1 (reference)				1 (reference)			
5	0.828 (0.517–1.325)				0.766 (0.459–1.279)			
6	0.875 (0.540–1.419)				0.837 (0.494–11.419)			
Clinical stage								
Clinical T stage		0.0810				0.0403		0.0200
T1	1 (reference)				1 (reference)		1 (reference)	
T2	2.060 (1.190–3.568)				2.218 (1.241–3.964)		2.102 (1.181–3.740)	
T3	2.040 (1.026–4.055)				2.619 (1.285–5.341)		2.496 (1.227–5.079)	
T4	2.006 (0.901–4.464)				2.730 (1.177–6.332)		2.693 (1.167–6.212)	
Clinical *N* stage		0.1683				0.4248		
N0	1 (reference)				1 (reference)			
N1	0.957 (0.637–1.440)				1.051 (0.679–1.629)			
N2	0.976 (0.488–1.951)				0.998 (0.490–2.031)			
N3	1.676 (0.784–3.585)				1.552 (0.693–3.477)			

(Continued)

TABLE 3 | Continued

	Univariate analysis	DFS	Multivariate analysis		Univariate analysis	OS	Multivariate analysis	
Parameters	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Clinical TNM stage		0.1995				0.3053		
I	1 (reference)				1 (reference)			
II	0.581 (0.310–1.091)				0.601 (0.308–1.172)			
III	0.693 (0.287–1.677)				0.662 (0.260–1.685)			
Operative time (min)		0.2776				0.0618		
<90	1 (reference)				1 (reference)			
≥90	0.855 (0.645–1.134)				0.760 (0.569–1.014)			
Type of surgery		0.1932				0.4770		
Mastectomy	1 (reference)				1 (reference)			
Breast-conserving surgery	0.788 (0.550–1.128)				1.144 (0.790–1.656)			
Histologic type		0.0200		0.0190		0.0083		0.0060
Ductal	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Lobular	2.682 (1.175–6.119)		2.718 (1.187–6.223)		2.638 (1.099–6.334)		2.562 (1.229–5.341)	
Others	2.230 (1.067–4.660)		2.074 (1.005–4.284)		2.552 (1.149–5.672)		2.162 (1.050–4.448)	
Histologic grade		0.1184				0.1867		
I	1 (reference)				1 (reference)			
II	0.784 (0.490–1.255)				0.811 (0.502–1.310)			
III	0.625 (0.379–1.030)				0.655 (0.391–1.097)			
Pathological T stage		0.0100		0.0099		0.0184		0.0380
Tis/T0	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
T1	1.573 (0.897–2.758)		1.573 (0.897–2.758)		0.625 (0.204–1.916)		0.605 (0.197–1.854)	
T2	1.981 (1.126–3.486)		1.981 (1.126–3.486)		0.512 (0.161–1.629)		0.498 (0.158–1.572)	
T3	1.485 (0.732–3.014)		1.485 (0.732–3.014)		0.420 (0.117–1.505)		0.397 (0.111–1.426)	
T4	3.324 (1.557–7.096)		3.324 (1.557–7.096)		1.537 (0.392–6.027)		1.320 (0.334–5.221)	
Pathological *N* stage		0.0103		0.0140		<0.0001		<0.0001
N0	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
N1	2.592 (0.865–7.767)		2.550 (0.841–7.734)		1.818 (0.619–5.344)		1.400 (1.047–1.872)	
N2	3.603 (0.923–14.063)		3.726 (0.947–14.660)		4.966 (1.444–17.085)		1.685 (1.192–2.381)	
N3	5.998 (1.535–23.435)		6.016 (1.527–23.694)		9.131 (2.615–31.877)		2.384 (1.717–3.311)	
Pathological TNM stage		0.0030		0.0170		0.0110		0.0005
Tis/T0	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
I	1.998 (0.584–6.839)		1.322 (0.658–2.655)		2.671 (0.738–9.663)		2.849 (0.786–10.320)	
II	2.282 (0.634–8.210)		1.558 (0.778–3.121)		3.727 (0.969–14.331)		3.963 (1.044–15.046)	
III	2.025 (0.420–9.760)		0.631 (0.261–1.526)		1.258 (0.274–5.771)		1.215 (0.265–5.575)	
Total lymph nodes		0.8118				0.6789		
<21	1 (reference)				1 (reference)			
≥21	0.935 (0.536–1.629)				0.882 (0.487–1.598)			
Positive lymph nodes		0.3806				0.6448		
<1	1 (reference)				1 (reference)			
≥1	0.564 (0.157–2.028)				0.742 (0.209–2.638)			
Total axillary lymph nodes		0.2165				0.3777		
<20	1 (reference)				1 (reference)			
≥20	0.704 (0.404–1.228)				0.767 (0.425–1.383)			

(Continued)

TABLE 3 | Continued

	Univariate analysis	DFS	Multivariate analysis		Univariate analysis	OS	Multivariate analysis	
Parameters	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Positive axillary lymph nodes		0.6622				0.6196		
<1	1 (reference)				1 (reference)			
≥1	0.822 (0.342–1.978)				0.788 (0.307–2.020)			
Molecular subtype		0.0520				0.0581		
Luminal A	1 (reference)				1 (reference)			
Luminal B HER2+	0.264 (0.097–0.720)				0.226 (0.080–0.638)			
Luminal B HER2–	0.630 (0.366–1.082)				0.514 (0.296–0.893)			
HER2 enriched	0.187 (0.063–0.558)				0.247 (0.081–0.753)			
Triple negative	0.581 (0.286–1.177)				0.547 (0.266–1.124)			
ER status		0.2301				0.9455		
Negative	1 (reference)				1 (reference)			
Positive	0.735 (0.444–1.215)				1.018 (0.616–1.680)			
PR status		0.2885				0.2090		
Negative	1 (reference)				1 (reference)			
Positive	1.237 (0.835–1.833)				1.269 (0.875–1.839)			
HER2 status		0.1047				0.1166		
Negative (0—-++)	1 (reference)				1 (reference)			
Positive (+ + +)	2.109 (0.856–5.196)				2.041 (0.837–4.975)			
Ki-67 status		0.0020		0.0370		0.0041		0.0380
Negative (≤14%)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Positive (>14%)	1.731 (1.223–2.450)		1.332 (1.018–1.742)		1.664 (1.175–2.357)		1.329 (1.016–1.738)	
AR status		0.4306				0.9714		
Negative	1 (reference)				1 (reference)			
Positive	0.835 (0.534–1.307)				0.991 (0.607–1.618)			
CK5/6 status		0.0170		0.0007		0.0238		0.0002
Negative	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Positive	1.725 (1.103–2.699)		1.756 (1.271–2.428)		1.713 (1.074–2.732)		1.870 (1.349–2.593)	
E-cad status		0.1380				<0.0001		<0.0001
Negative	1 (reference)				1 (reference)		1 (reference)	
Positive	1.297 (0.920–1.830)				2.566 (1.765–3.728)		2.667 (2.002–3.553)	
EGFR status		0.2977				0.9685		
Negative	1 (reference)				1 (reference)			
Positive	0.805 (0.535–1.211)				1.009 (0.655–1.554)			
P53 status		0.0840				0.0729		
Negative	1 (reference)				1 (reference)			
Positive	0.783 (0.593–1.033)				0.774 (0.585–1.024)			
TOP2A status		0.4136				0.3998		
Negative	1 (reference)				1 (reference)			
Positive	1.159 (0.814–1.651)				1.173 (0.809–1.700)			
Lymph vessel invasion		0.0329		0.0002		0.0321		0.0011
Negative	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Positive	1.423 (1.029–1.966)		1.585 (1.245–2.018)		1.429 (1.031–1.981)		1.523 (1.182–1.962)	
Neural invasion		0.7620				0.5040		
Negative	1 (reference)				1 (reference)			
Positive	0.937 (0.613–1.432)				1.152 (0.761–1.742)			

(Continued)

TABLE 3 | Continued

	Univariate analysis	DFS	Multivariate analysis		Univariate analysis	OS	Multivariate analysis	
Parameters	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Post-operative chemotherapy		<0.0001		0.0001		0.0001		0.0006
No	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Yes	0.458 (0.314–0.670)		0.523 (0.376–0.725)		0.475 (0.324–0.697)		0.575 (0.420–0.789)	
Post-operative radiotherapy		0.2115				0.1298		
No	1 (reference)				1 (reference)			
Yes	1.236 (0.886–1.723)				1.303 (0.925–1.834)			
Post-operative endocrine therapy		0.0105		0.0300		0.0210		0.0280
No	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Yes	0.631 (0.444–0.898)		0.771 (0.609–0.975)		0.752 (0.590–0.958)		0.764 (0.602–0.971)	
Post-operative targeted therapy		<0.0001		<0.0001		<0.0001		<0.0001
No	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Yes	0.507 (0.390–0.658)		0.457 (0.356–0.587)		0.590 (0.457–0.763)		0.556 (0.432-0.716)	

multivariate Cox regression analysis, menopause, GLU, Cancer antigen 125 (CA125), Cancer antigen 153 (CA153), eosinophils, NRI, histologic type, pathological T/N/TNM stage, Ki-67 status, Cytokeratin 5/6 (CK5/6) status, lymph vessel invasion (LVI), post-operative chemotherapy, post-operative endocrine therapy, post-operative targeted therapy were the significant prognostic factors for DFS. Moreover, GLU, CA153, International normalized ratio (INR), monocyte, eosinophils, NRI, clinical T stage, histologic type, pathological T/N/TNM stage, Ki-67 status, CK5/6 status, E-cadherin (E-cad) status, LVI, post-operative chemotherapy, post-operative endocrine therapy, post-operative targeted therapy were the significant prognostic factors for OS (see **Table 3**).

DFS and OS by NRI

As seen in **Table 3**, the NRI was the important prognostic factors DFS and OS using the cutoff value of 112. The results performed that high NRI was associated with prolonged DFS and OS ($P = 0.019$, HR: 1.521, 95% CI: 1.071–2.161 and $P = 0.004$, HR: 1.415, 95% CI: 1.119–1.789; and $P = 0.026$, HR: 1.500, 95% CI: 1.051–2.143 and $P < 0.001$, HR: 1.547, 95% CI: 1.221–1.959, respectively), on both univariate and multivariate analyses.

Of all breast cancer patients, patients with low NRI scores had mean DFS and OS time of 40.50 and 63.47 months, while patients with high NRI scores were 56.39 and 71.50 months, respectively. Furthermore, the mean DFS and OS survive time of NRI in the high group were remarkably longer in contrast to for those of NRI in the low group by the log-rank analysis ($\chi^2 = 13.9500$, $P = 0.0002$ and $\chi^2 = 4.4660$, $P = 0.0346$, respectively; **Figures 1A,B**). In the NACT group, the mean DFS and OS survive time of NRI in the high group were remarkably longer in contrast to those of NRI in the low group ($\chi^2 = 4.9440$, $P = 0.0262$ and $\chi^2 = 5.3210$, $P = 0.0211$, respectively; **Figures 1C,D**). In the non-NACT group, the mean DFS and OS survive time of NRI in the high group were remarkably longer in contrast to those of NRI in the low group ($\chi^2 = 8.3230$, $P = 0.0039$ and $\chi^2 = 7.9940$, $P = 0.0047$, respectively; **Figures 1E,F**).

The Association Between Pathologic Stage and NRI in Breast Cancer Patients

The results shown that pathologic TNM stage was the significant predictor via the univariate and multivariate analyses (see **Table 3**). In order to further study the efficiency of prediction of NRI, and the NRI was analyzed by the pathologic TNM stage. Of all breast cancer patients, the results shown that patients with high NRI scores had notably longer DFS and OS survive time than those with low NRI scores in early-stage breast cancer (included pathologic Tis/T0 and pathologic I stage) ($\chi^2 = 9.0510$, $P = 0.0026$ and $\chi^2 = 9.2140$, $P = 0.0024$). Similarly, patients with high NRI scores had remarkably longer DFS and OS survive time than those with low NRI scores in advanced stage breast cancer (pathologic II and pathologic III stage) ($\chi^2 = 6.2500$, $P = 0.0124$ and $\chi^2 = 5.8880$, $P = 0.0152$). In the NACT group, the results also indicated that patients with high NRI scores had longer DFS and OS survive time than those with low NRI scores in early-stage breast cancer ($\chi^2 = 3.0700$, $P = 0.0798$ and $\chi^2 = 3.9210$, $P = 0.0477$). Meanwhile, patients with high NRI scores had longer DFS and OS survive time than those with low NRI scores in advanced stage breast cancer ($\chi^2 = 2.2330$, $P = 0.1351$ and $\chi^2 = 2.0160$, $P = 0.1557$). In the non-NACT group, the results demonstrated that patients with high NRI scores had remarkably longer DFS and OS survive time than those with low NRI scores in early-stage breast cancer ($\chi^2 = 7.3580$, $P = 0.0067$ and $\chi^2 = 5.1700$, $P = 0.0230$). Furthermore, patients with high NRI scores had longer DFS and OS than

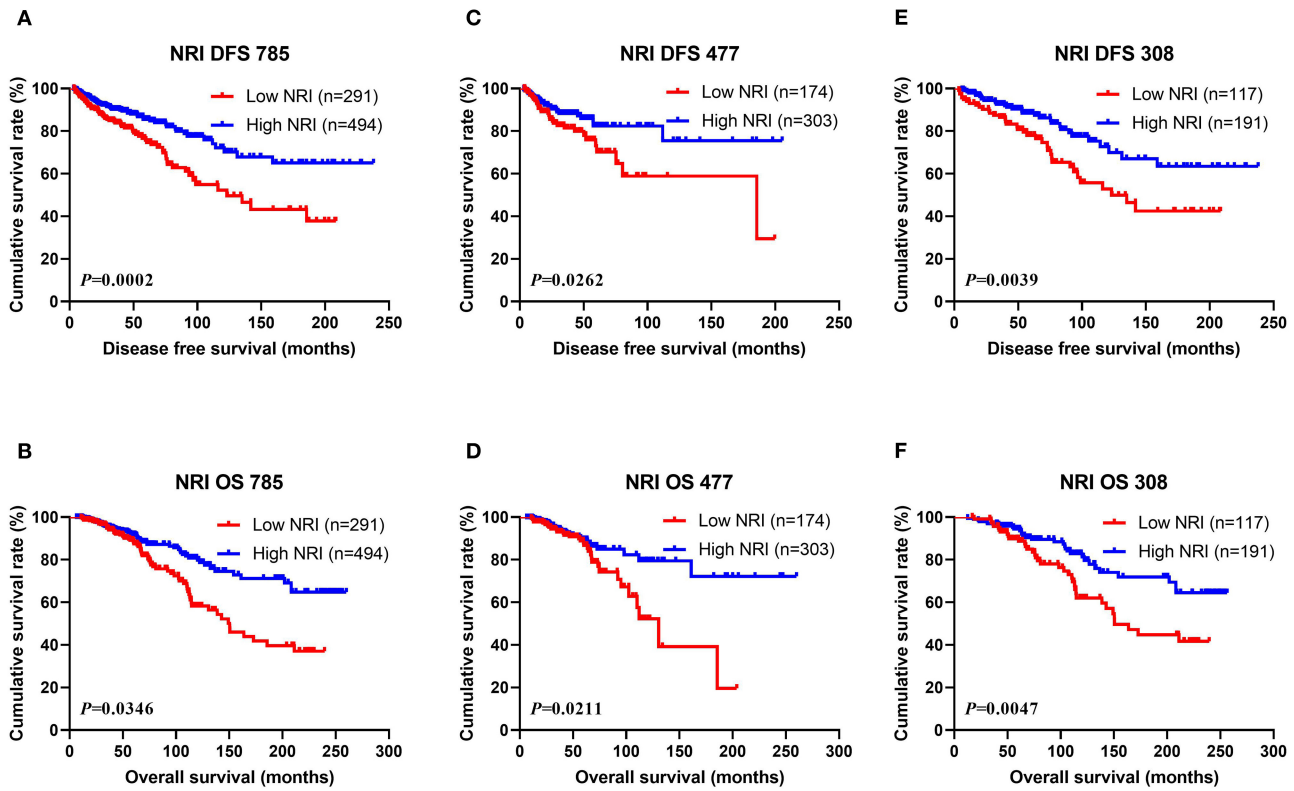

FIGURE 1 | DFS and OS of patients with breast cancer. **(A)** Kaplan-Meier analysis of DFS for the NRI of all breast cancer patients. **(B)** Kaplan-Meier analysis of OS for the NRI of all breast cancer patients. **(C)** Kaplan-Meier analysis of DFS for the NRI of breast cancer patients in NACT group. **(D)** Kaplan-Meier analysis of OS for the NRI of breast cancer patients in NACT group. **(E)** Kaplan-Meier analysis of DFS for the NRI of breast cancer patients in non-NACT group. **(F)** Kaplan-Meier analysis of OS for the NRI of breast cancer patients in non-NACT group.

those with low NRI scores in advanced stage breast cancer ($\chi^2 = 3.7450$, $P = 0.0530$ and $\chi^2 = 3.7570$, $P = 0.0526$). See in **Figure 2**.

The Association Between Pathology Parameters and NRI in Patients With Breast Cancer

The results performed that statistically significant differences were found in TOP2A status ($\chi^2 = 4.0108$, $P = 0.0452$), and no statistically significant differences were observed in the other pathology parameters in all cases ($P > 0.05$). These findings were shown in **Table 4**. We also analyzed that the different molecular subtypes by NRI. Of all enrolled patients, the mean DFS and OS survive time for patients with high NRI by the log-rank test were longer than in those with low NRI in Luminal A subtype ($\chi^2 = 0.0496$, $P = 0.8238$ and $\chi^2 = 0.1107$, $P = 0.7394$), Luminal B HER2-positive subtype ($\chi^2 = 0.4465$, $P = 0.5040$ and $\chi^2 = 0.2313$, $P = 0.6305$), Luminal B HER2-negative subtype ($\chi^2 = 3.4830$, $P = 0.0620$ and $\chi^2 = 3.8280$, $P = 0.0504$), HER2-enriched subtype ($\chi^2 = 6.1510$, $P = 0.0131$ and $\chi^2 = 5.6560$, $P = 0.0174$), triple-negative subtype ($\chi^2 = 5.8120$, $P = 0.0159$ and $\chi^2 = 6.9300$, $P = 0.0085$; **Figure 3A**). Moreover, we also analyzed the molecular subtypes by NRI in the NACT group and the non-NACT group (**Figures 3B,C**).

The Association Between LVI and NRI in Breast Cancer Patients

Through univariate and multivariate analyses, LVI was the significant predictor (**Table 3**). The ability of NRI to determine breast cancer prognosis was further assessed by examining the relationship between LVI and NRI. Among the patients without LVI, patients who had high NRI scores had remarkably longer DFS and OS survive time than those had low NRI scores ($\chi^2 = 13.6600$, $P = 0.0002$ and $\chi^2 = 12.1500$, $P = 0.0005$). Among the patients with LVI, patients who had high NRI scores had longer DFS and OS survive time than those had low NRI scores ($\chi^2 = 0.8332$, $P = 0.3613$ and $\chi^2 = 1.4780$, $P = 0.2241$). In the NACT group, patients who had high NRI scores had notably longer DFS and OS survive time than those had low NRI scores without LVI ($\chi^2 = 6.4450$, $P = 0.0111$ and $\chi^2 = 6.9200$, $P = 0.0085$). Furthermore, patients who had high NRI scores had longer DFS and OS survive time than those had low NRI scores with LVI ($\chi^2 = 0.07560$, $P = 0.7833$ and $\chi^2 = 0.1831$, $P = 0.6687$). In the non-NACT group, patients who had high NRI values had remarkably longer DFS and OS survive time than those had low NRI values

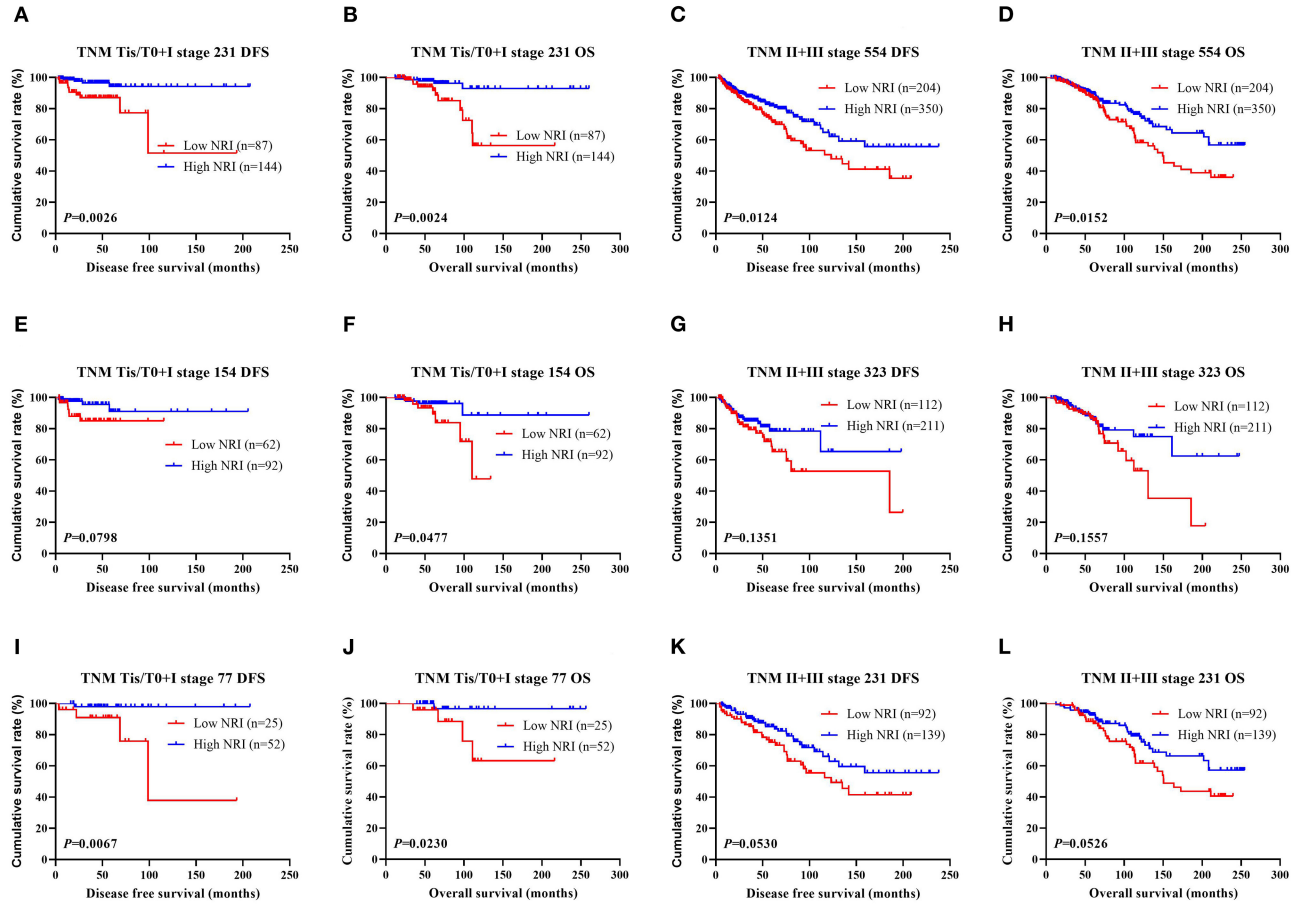

FIGURE 2 | DFS and OS for the NRI of breast cancer patients in different pathologic stages. **(A)** Kaplan-Meier analysis of DFS for the NRI scores of early-stage breast cancer (Tis/T0+I stage) patients in all enrolled breast cancer patients. **(B)** Kaplan-Meier analysis of OS for the NRI values of early-stage breast cancer (Tis/T0+I stage) patients in all enrolled breast cancer patients. **(C)** Kaplan-Meier analysis of DFS for the NRI values of advanced stage breast cancer (II+III stage) patients in all enrolled breast cancer patients. **(D)** Kaplan-Meier analysis of OS for the NRI levels of advanced stage breast cancer (II + III stage) patients in all enrolled breast cancer patients. **(E)** Kaplan-Meier analysis of DFS for the NRI values of early-stage breast cancer (Tis/T0 + I stage) patients in NACT group. **(F)** Kaplan-Meier analysis of OS for the NRI scores of early-stage breast cancer (Tis/T0 + I stage) patients in NACT group. **(G)** Kaplan-Meier analysis of DFS for the NRI values of advanced stage breast cancer (II + III stage) patients in NACT group. **(H)** Kaplan-Meier analysis of OS for the NRI values of advanced stage breast cancer (II + III stage) patients in NACT group. **(I)** Kaplan-Meier analysis of DFS for the NRI scores of early-stage breast cancer (Tis/T0 + I stage) patients in non-NACT group. **(J)** Kaplan-Meier analysis of OS for the NRI scores of early-stage breast cancer (Tis/T0 + I stage) patients in non-NACT group. **(K)** Kaplan-Meier analysis of DFS for the NRI values of advanced stage breast cancer (II + III stage) patients in non-NACT group. **(L)** Kaplan-Meier analysis of OS for the NRI of advanced stage breast cancer (II + III stage) patients in non-NACT group.

without LVI ($\chi^2 = 6.4910$, $P = 0.0108$ and $\chi^2 = 5.8110$, $P = 0.0159$). At the same time, patients who had high NRI values had longer DFS and OS survive time than those had low NRI values with LVI ($\chi^2 = 1.3370$, $P = 0.2476$ and $\chi^2 = 2.5280$, $P = 0.1118$; **Figure 4**).

The Association Between NRI and Response in Breast Cancer Patients Received NACT

In the NACT group, all enrolled received neoadjuvant chemotherapy, and the effect of chemotherapy was evaluated after two chemotherapy cycles. After surgery, the degree of pathological remission was evaluated by MPG. So, we analyzed the MPG by NRI, and the results indicated that there was no difference in MPG grade 1 ($\chi^2 = 0.5520$, $P = 0.4575$ and $\chi^2 = 0.0136$, $P = 0.9071$), MPG grade 3 ($\chi^2 = 0.4711$, $P = 0.4925$ and $\chi^2 = 0.1296$, $P = 0.7189$), MPG grade 4 ($\chi^2 = 0.6459$, $P = 0.4216$ and $\chi^2 = 1.9650$, $P = 0.1610$), MPG grade 5 ($\chi^2 = 1.6620$, $P = 0.1973$ and $\chi^2 = 1.7820$, $P = 0.1819$), except in MPG grade 2 ($\chi^2 = 10.9100$, $P = 0.0010$ and $\chi^2 = 9.5030$, $P = 0.0021$; **Figure 5**). Furthermore, we analyzed the relationship between response and NRI, and the results indicated that there was no difference in CR ($\chi^2 = 0.0000$, P>0.9999 and $\chi^2 = 0.0000$, P>0.9999), PR ($\chi^2 = 0.7815$, $P = 0.3767$ and $\chi^2 = 0.6523$, $P = 0.4193$), SD ($\chi^2 = 2.5450$, $P = 0.1107$ and $\chi^2 = 3.1730$, $P = 0.0749$), except in PD ($\chi^2 = 3.8460$, $P = 0.0499$ and $\chi^2 = 2.7400$, $P = 0.0979$; **Figure 6**).

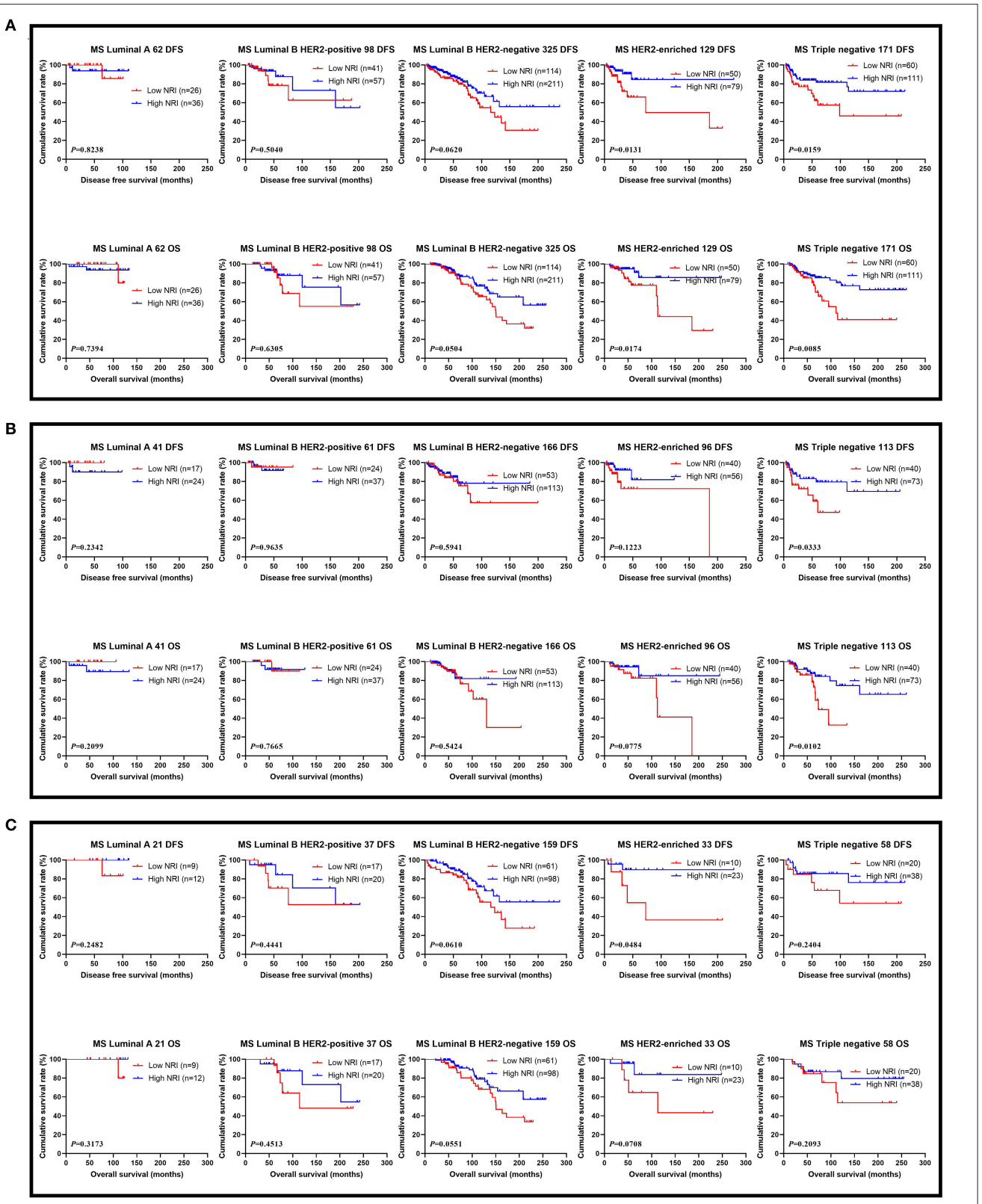

FIGURE 3 | DFS and OS for the NRI of breast cancer patients in different molecular subtypes. **(A)** DFS and OS for the NRI of breast cancer patients in different molecular subtypes in all patients; **(B)** DFS and OS for the NRI of breast cancer patients in different molecular subtypes in NACT group; **(C)** DFS and OS for the NRI of breast cancer patients in different molecular subtypes in non-NACT group.

TABLE 4 | The association between molecular subtype and NRI in patients with breast cancer.

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	**Low NRI 291**	**High NRI 494**	χ^2	***P*-value**	**Low NRI 174**	**High NRI 303**	χ^2	***P*-value**	**Low NRI 117**	**High NRI 191**	χ^2	***P*-value**
Core needle biopsy ($N = 477$)												
Molecular subtype							4.0360	0.4012				
Luminal A					12 (6.90%)	13 (4.29%)						
Luminal B HER2+					23 (13.22%)	44 (14.52%)						
Luminal B HER2–					62 (35.63%)	124 (40.92%)						
HER2 enriched					39 (22.41%)	52 (17.16%)						
Triple negative					38 (21.84%)	70 (23.10%)						
ER status							0.2041	0.6515				
Negative					72 (41.38%)	119 (39.27%)						
Positive					102 (58.62%)	184 (60.73%)						
PR status							0.0337	0.8544				
Negative					68 (39.08%)	121 (39.93%)						
Positive					106 (60.92%)	182 (60.07%)						
HER2 status							0.6994	0.4030				
Negative (0−++)					110 (63.22%)	203 (67.00%)						
Positive (+ + +)					64 (36.78%)	100 (33.00%)						
Ki-67 status							0.3469	0.5559				
Negative (≤14%)					33 (18.97%)	51 (16.83%)						
Positive (>14%)					141 (81.03%)	252 (83.17%)						
Postoperative pathology (IHC)												
Molecular subtype			2.9300	0.5696			5.1830	0.2690			2.9020	0.5743
Luminal A	26 (8.93%)	36 (7.29%)			17 (9.77%)	24 (7.92%)			9 (7.69%)	12 (6.28%)		
Luminal B HER2+	41 (14.09%)	57 (11.54%)			24 (13.79%)	37 (12.21%)			17 (14.53%)	20 (10.47%)		
Luminal B HER2–	111 (38.14%)	214 (43.32%)			50 (28.74%)	116 (38.28%)			61 (52.14%)	98 (51.31%)		
HER2 enriched	50 (17.18%)	79 (15.99%)			41 (23.56%)	55 (18.15%)			9 (7.69%)	24 (12.57%)		
Triple negative	63 (21.65%)	108 (21.86%)			42 (24.14%)	71 (23.43%)			21 (17.95%)	37 (19.37%)		
ER status			0.1729	0.6775			0.8871	0.3463			3.3940	0.0654
Negative	107 (36.77%)	189 (38.26%)			76 (43.68%)	119 (39.27%)			31 (26.50%)	70 (36.65%)		
Positive	184 (63.23%)	305 (61.74%)			98 (56.32%)	184 (60.73%)			86 (73.50%)	121 (63.35%)		
PR status			0.7569	0.3843			0.0058	0.9395			2.1254	0.1449
Negative	111 (38.14%)	204 (41.30%)			77 (44.25%)	133 (43.89%)			34 (29.06%)	71 (37.17%)		
Positive	180 (61.86%)	290 (58.70%)			97 (55.75%)	170 (56.11%)			83 (70.94%)	120 (62.83%)		

(Continued)

TABLE 4 | Continued

Parameters	NRI 785				NRI 477				NRI 308			
Cases (*n*)	**Low NRI 291**	**High NRI 494**	χ^2	***P*-value**	**Low NRI 174**	**High NRI 303**	χ^2	***P*-value**	**Low NRI 117**	**High NRI 191**	χ^2	***P*-value**
HER2 status			0.7958	0.3724			1.3451	0.2461			0.0172	0.8956
Negative (0−++)	201 (69.07%)	356 (72.06%)			111 (63.79%)	209 (68.98%)			90 (76.92%)	147 (76.96%)		
Positive (+ + +)	90 (30.93%)	138 (27.94%)			63 (36.21%)	94 (31.02%)			27 (23.08%)	44 (23.04%)		
Ki-67 status			3.7906	0.0515			2.7846	0.0952			1.2634	0.2610
Negative (≤14%)	93 (31.96%)	126 (25.51%)			64 (36.78%)	89 (29.37%)			29 (24.79%)	37 (19.37%)		
Positive (>14%)	198 (68.04%)	368 (74.49%)			110 (63.22%)	214 (70.63%)			88 (75.21%)	154 (80.63%)		
AR status			2.1484	0.1427			1.7504	0.1858			0.2902	0.5901
Negative	254 (87.29%)	412 (83.40%)			138 (79.31%)	224 (73.93%)			116 (99.15%)	188 (98.43%)		
Positive	37 (12.71%)	82 (16.60%)			36 (20.69%)	79 (26.07%)			1 (0.85%)	3 (1.57%)		
CK5/6 status			0.2902	0.5901			0.0007	0.9786			0.9001	0.3428
Negative	256 (87.97%)	428 (86.64%)			148 (85.06%)	258 (85.15%)			108 (92.31%)	170 (89.01%)		
Positive	35 (12.03%)	66 (13.36%)			26 (14.94%)	45 (14.85%)			9 (7.69%)	21 (10.99%)		
E-cad status			0.0005	0.9831			0.1598	0.6894			0.1258	0.7228
Negative	131 (45.02%)	222 (44.94%)			60 (34.48%)	110 (36.30%)			71 (60.68%)	112 (58.64%)		
Positive	160 (54.98%)	272 (55.06%)			114 (65.52%)	193 (63.70%)			46 (39.32%)	79 (41.36%)		
EGFR status			2.1847	0.1394			0.9965	0.3182			1.1764	0.2781
Negative	227 (78.01%)	362 (73.28%)			127 (72.99%)	208 (68.65%)			100 (85.47%)	154 (80.63%)		
Positive	64 (21.99%)	132 (26.72%)			47 (27.01%)	95 (31.35%)			17 (14.53%)	37 (19.37%)		
P53 status			0.2789	0.5974			0.0668	0.7960			0.2816	0.5957
Negative	150 (51.55%)	245 (49.60%)			90 (51.72%)	153 (50.50%)			60 (51.28%)	92 (48.17%)		
Positive	141 (48.45%)	249 (50.40%)			84 (48.28%)	150 (49.50%)			57 (48.72%)	99 (51.83%)		
TOP2A status			4.0108	0.0452			0.0014	0.9699			9.6194	0.0019
Negative	124 (42.61%)	175 (35.43%)			60 (34.48%)	105 (34.65%)			64 (54.70%)	70 (36.65%)		
Positive	167 (57.39%)	319 (64.57%)			114 (65.52%)	198 (65.35%)			53 (45.30%)	121 (63.35%)		
Lymph vessel invasion			0.3940	0.5302			0.1226	0.7263			0.4555	0.4998
Negative	203 (69.76%)	355 (71.86%)			115 (66.09%)	205 (67.66%)			88 (75.21%)	150 (78.53%)		
Positive	88 (30.24%)	139 (28.14%)			59 (33.91%)	98 (32.34%)			29 (24.79%)	41 (21.47%)		
Neural invasion			1.2591	0.2618			0.2483	0.6183			2.7576	0.0968
Negative	243 (83.51%)	427 (86.44%)			138 (79.31%)	246 (81.19%)			105 (89.74%)	181 (94.76%)		
Positive	48 (16.49%)	67 (13.56%)			36 (20.69%)	57 (18.81%)			12 (10.26%)	10 (5.24%)		

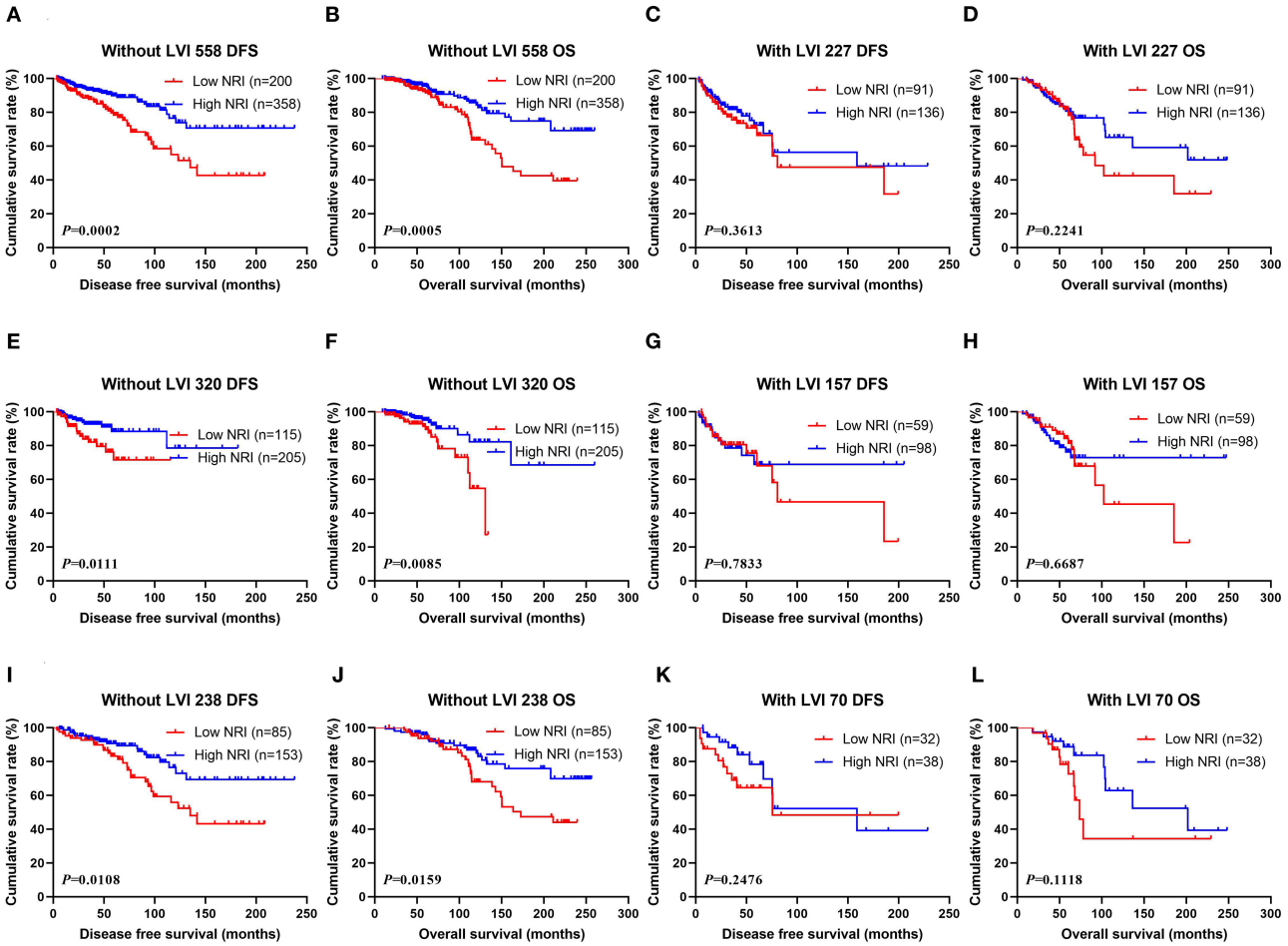

FIGURE 4 | (A) Kaplan-Meier analysis of DFS of patients without LVI by NRI in all breast cancer patients, **(B)** Kaplan-Meier analysis of OS of patients without LVI by NRI in all breast cancer patients, **(C)** Kaplan-Meier analysis of DFS of patients with LVI by NRI in all breast cancer patients, **(D)** Kaplan-Meier analysis of OS of patients LVI by NRI in all breast cancer patients; **(E)** Kaplan-Meier analysis of DFS of patients without LVI by NRI in NACT group, **(F)** Kaplan-Meier analysis of OS of patients without LVI by NRI in NACT group, **(G)** Kaplan-Meier analysis of DFS of patients with LVI by NRI in NACT group, **(H)** Kaplan-Meier analysis of OS of patients with LVI by NRI in NACT group; **(I)** Kaplan-Meier analysis of DFS of patients without LVI by NRI in non-NACT group, **(J)** Kaplan-Meier analysis of OS of patients without LVI by NRI in non-NACT group, **(K)** Kaplan-Meier analysis of DFS of patients with LVI by NRI in non-NACT group, **(L)** Kaplan-Meier analysis of OS of patients with LVI by NRI in non-NACT group.

The Relationship Between NRI and Toxicity and Adverse Effects

In the NACT group, the common toxicities after NACT were hematologic and gastrointestinal reactions. The results shown that the nausea ($\chi^2 = 9.2413$, $P = 0.0024$), mouth ulcers ($\chi^2 = 4.8133$, $P = 0.0282$), anemia ($\chi^2 = 8.5441$, $P = 0.0140$), and leukopenia ($\chi^2 = 11.0951$, $P = 0.0039$) were statistically different between the two groups (see **Table 5**).

DISCUSSION

Breast cancer is a major public health threat globally (29). In women around the world, breast cancer is a very common female malignant tumor and the leading cause of cancer-related deaths (2). Although promising treatment options are emerging, recurrence and metastasis are still the driving causes for breast cancer fatality (30). Evidence shows that approximately 30%-40% of patients who suffer from invasive breast cancer will eventually progress to metastatic breast cancer, whose 5-year survival rate could be poorer than 30% (31, 32). Additionally, research also suggests that probabilities of recurrence and progression could occur in some breast cancer patients even after radical resection and neoadjuvant/adjuvant therapy (33). Therefore, to address these issues, there is an urgent need to develop assessment strategies based on non-invasive, reproducible, and convenient biomarkers to estimate the curative effects and the prognosis of breast cancer, as well as to better pair treatment options with patient characteristics (e.g., ascertain those breast cancer patients who get a profit from neoadjuvant chemotherapy).

Prior studies have identified a limited number of screening tools to evaluate nutritional risks that have the potential to

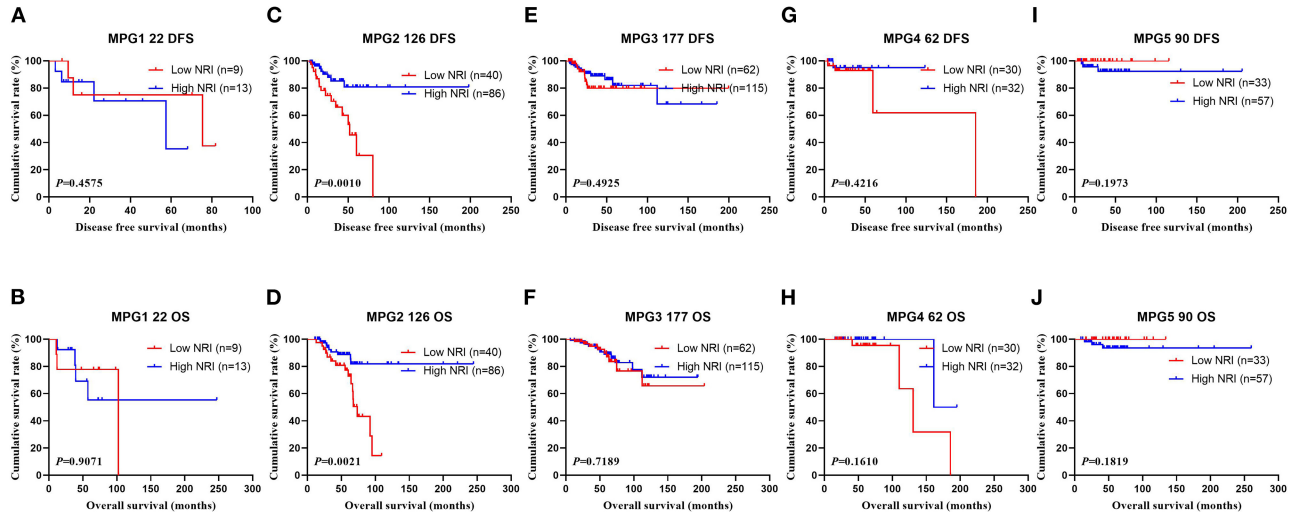

FIGURE 5 | DFS and OS for the NRI of breast cancer patients in Miller and Payne grade (MPG) in NACT group. **(A)** Kaplan-Meier analysis of DFS of patients with MPG 1, **(B)** Kaplan-Meier analysis of OS of patients with MPG 1, **(C)** Kaplan-Meier analysis of DFS of patients with MPG 2, **(D)** Kaplan-Meier analysis of OS of patients with MPG 2, **(E)** Kaplan-Meier analysis of DFS of patients with MPG 3, **(F)** Kaplan-Meier analysis of OS of patients with MPG 3, **(G)** Kaplan-Meier analysis of DFS of patients with MPG 4, **(H)** Kaplan-Meier analysis of OS of patients with MPG 4, **(I)** Kaplan-Meier analysis of DFS of patients with MPG 5, **(J)** Kaplan-Meier analysis of OS of patients with MPG 5.

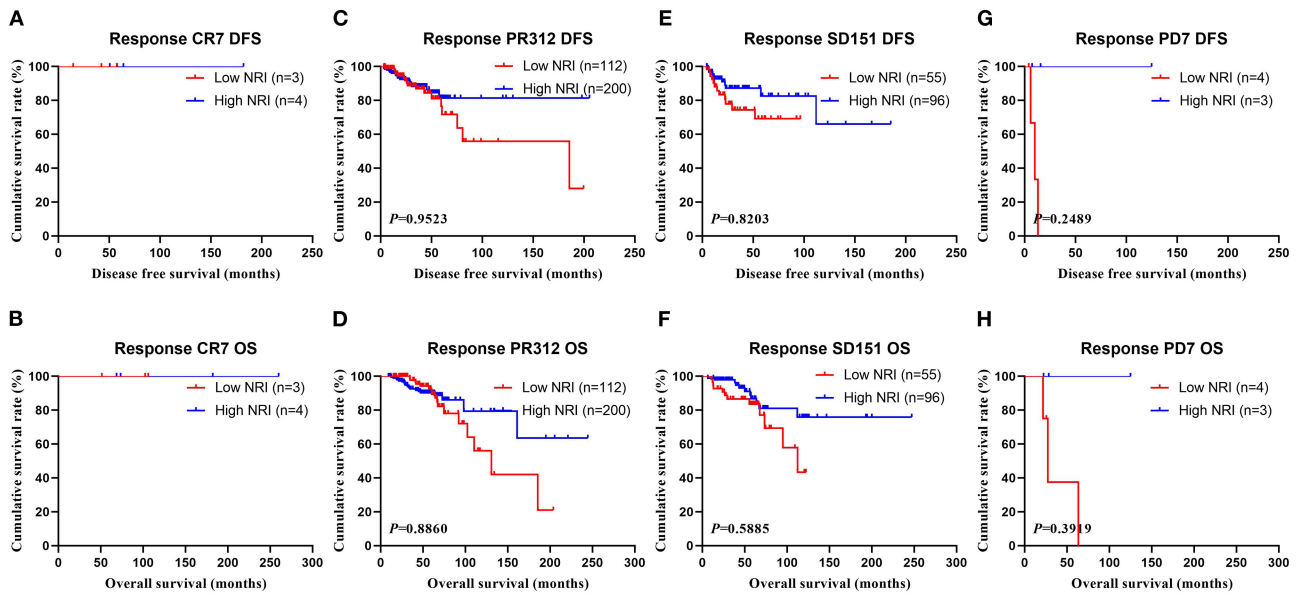

FIGURE 6 | DFS and OS for the NRI of breast cancer patients in response in NACT group. **(A)** Kaplan-Meier analysis of DFS of patients with response CR, **(B)** Kaplan-Meier analysis of OS of patients with response CR, **(C)** Kaplan-Meier analysis of DFS of patients with response PR, **(D)** Kaplan-Meier analysis of OS of patients with response PR, **(E)** Kaplan-Meier analysis of DFS of patients with response SD, **(F)** Kaplan-Meier analysis of OS of patients with response SD, **(G)** Kaplan-Meier analysis of DFS of patients with response PD, **(H)** Kaplan-Meier analysis of OS of patients with response PD.

predict prognosis in cancer patients, ranging from Subjective Global Assessment (SGA), Nutritional Risk Screening 2002 (NRS 2002), Mini Nutritional Assessment-Screening Form (MNA-SF), and Malnutrition Universal Screening Tool (MUST), as well as several nutritional status markers such as the neutrophil-to-lymphocyte ratio, prognostic nutritional index, BMI, serum albumin, total lymphocyte count, and indicators such as patients' cholesterol levels (34–38). Among them, BMI and serum albumin level are usually used as makers of patients' nutritional status in routine clinical practice (39), largely due to their abilities to predict cancer patients' survival rates, as indicated in recent studies (40–42). While these tools play an important role in

TABLE 5 | The correlation between NRI and toxicity assessment.

Parameters	NRI 477			
Cases (*n*)	Low NRI 174	High NRI 303	χ^2	*P*-value
Decreased appetite			2.2133	0.1368
No	20 (11.49%)	50 (16.50%)		
Yes	154 (88.51%)	253 (83.50%)		
Nausea			9.2413	0.0024
No	11 (6.32%)	48 (15.84%)		
Yes	163 (93.68%)	255 (84.16%)		
Vomiting			2.5293	0.1118
No	77 (44.25%)	157 (51.82%)		
Yes	97 (55.75%)	146 (48.18%)		
Diarrhea			0.5410	0.4620
No	160 (91.95%)	284 (93.73%)		
Yes	14 (8.05%)	19 (6.27%)		
Mouth ulcers			4.8133	0.0282
No	165 (94.83%)	298 (98.35%)		
Yes	9 (5.17%)	5 (1.65%)		
Alopecia			0.0350	0.8516
No	80 (45.98%)	142 (46.86%)		
Yes	94 (54.02%)	161 (53.14%)		
Peripheral neurotoxicity			0.1828	0.6690
No	144 (82.76%)	246 (81.19%)		
Yes	30 (17.24%)	57 (18.81%)		
Anemia			8.5441	0.0140
Grade 0	79 (45.40%)	178 (58.75%)		
Grade 1–2	92 (52.87%)	123 (40.59%)		
Grade 3–4	3 (1.72%)	2 (0.66%)		
Leukopenia			11.0951	0.0039
Grade 0	35 (20.11%)	103 (33.99%)		
Grade 1–2	92 (52.87%)	141 (46.53%)		
Grade 3–4	47 (27.01%)	59 (19.47%)		
Neutropenia			5.3754	0.0680
Grade 0	41 (23.56%)	102 (33.66%)		
Grade 1–2	71 (40.80%)	108 (35.64%)		
Grade 3–4	62 (35.63%)	93 (30.69%)		
Thrombocytopenia			3.8748	0.1441
Grade 0	128 (73.56%)	244 (80.53%)		
Grade 1–2	44 (25.29%)	54 (17.82%)		
Grade 3–4	2 (1.15%)	5 (1.65%)		
Gastrointestinal reaction			4.2926	0.1169
Grade 0	8 (4.60%)	30 (9.90%)		
Grade 1–2	164 (94.25%)	269 (88.78%)		
Grade 3–4	2 (1.15%)	4 (1.32%)		
Myelosuppression			2.2843	0.3191
Grade 0	27 (15.52%)	63 (20.79%)		
Grade 1–2	64 (36.78%)	111 (36.63%)		
Grade 3–4	83 (47.70%)	129 (42.57%)		
Hepatic dysfunction			2.8849	0.2364
Grade 0	129 (74.14%)	242 (79.87%)		
Grade 1–2	45 (25.86%)	60 (19.80%)		
Grade 3–4	0 (0.00%)	1 (0.33%)		

nutritional assessment, the fact that they rely on subjective assessments that could be easily varied and swayed by individual examiners makes these screening mechanisms incomparable and unsatisfactory. Additionally, some non-nutritional factors such as inflammation, fluid status, renal dysfunction, and hepatic congestion also exert diverse effects on indicators like serum albumin and BMI (43, 44), effectively exposing these tools to additional noises. Thus, it is neither sufficient nor precise to evaluate patients' nutritional risk with regard to their cancer prognosis and treatment efficacy only by their BMI or albumin status.

Fortunately, NRI values measured by a combination of factors such as ideal body weight, serum albumin, and present body weight may overcome the shortcomings of individual indicators. In other words, creating patients' NRI score as a combined index of their ideal body weight, present body weight, and serum albumin levels has the potential to minimize the effects of fluid status, and in turn, distinguish nutritional risk better than individual indexes. As demonstrated in previous studies, one of the indexes under the NRI umbrella that could appraise forecasting risk of malnutrition-related incidence rate and mortality in advanced-age patients was the Geriatric Nutritional Risk Index (GNRI) (45). GNRI has been associated with poor treatment outcomes in many diseases, including cancer (46–50). Moreover, previous research also illustrated that in patients with new metastatic gastric adenocarcinoma and esophageal adenocarcinoma, pretreatment NRI and change of NRI in that were significant prognostic factors for OS.

Emerging evidence further suggests that evaluate NRI at baseline and during treatment can not only indicate patients' nutrition status but also provide useful prognostic information (51). Nevertheless, while meaningful insights are procurable, little is known about the association between NRI, prognosis, and treatment efficacy in breast cancer patients. To bridge the research gap, by analyzing the clinical and demographic attributes of 785 participants, our study demonstrated the clinical significance of using NRI to assess nutritional risk assessment in breast cancer patients. Our results indicated that high levels of NRI were significantly associated with more indicative clinicopathologic characteristics (age, menopause, US-LNM, total lymph nodes, and total axillary lymph nodes), nutritional parameters, and blood parameters (weight, BMI, ALT, AST, LDH, GGT, ALP, GLU, IgG, W, ALB, Hb, R, N, E, and P) of all breast cancer patients.

Through the univariate and multivariate Cox regression survival analyses, the preoperative NRI was an independent predictor of DFS and OS survive time. And the average DFS and OS survive time for patients who had high NRI scores were longer than for those who had low NRI scores by the log-rank analysis in the NACT group and the non-NACT group. Similar conclusions have been reached in many published studies focusing on other malignancies (52, 53). For instance, 143 patients with localized esophageal cancer treated with definitive concurrent chemoradiotherapy in a retrospective study conducted by Clavier and associates, multivariable analyses indicated that the NRI was an independent predictor for patients' overall survival (52). Moreover, Cox and colleagues retrospectively analyzed patients

with esophageal cancer included chemoradiotherapy with or without cetuximab in the SCOPE1 clinical trial, reporting that NRI<100 in a baseline was significantly related to decreased overall survival in cancer patients (53).

Previous studies suggest that patients' NRI values were prognostic in a range of localized as well as metastatic tumors like esophageal cancer (54, 55). However, there is a dearth of research on the effects of NRI on prognosis and treatment efficacy in breast cancer patients. To bridge the research gap, we analyzed the relationship between pathologic stage and NRI in patients with breast cancer, and observed that patients who had high NRI scores had longer DFS and OS survive time than those who had low NRI values in both patients with early-stage breast cancer and advanced stage breast cancer. Furthermore, patients who had high NRI levels had longer DFS and OS survive time in contrast to those who had low NRI scores in molecular subtypes of breast cancer. Moreover, the results also performed the mean DFS and OS survive time in breast cancer patients who had high NRI scores were longer than in those patients who had low NRI scores with LVI status. Furthermore, we also analyzed the relationship between NRI and MPG/Response, and the results also shown that patients who had high NRI scores had longer DFS and OS survive time than those who had low NRI scores in different MPG grades, especially in MPG grade 2; and patients who had high NRI values had longer DFS and OS survive time in contrast to those who had low NRI scores in different responses.

All breast cancer patients could tolerate the neoadjuvant chemotherapy toxicities and adverse effects. The hematologic and gastrointestinal reactions were the common toxicities and adverse effects, and the results shown that there was no difference using the optimal NRI cutoff value of 112 in toxicity assessment, except in nausea, mouth ulcers, anemia, leukopenia, which should get doctors' as well as patients' attention. Using NRI as a prognostic marker and monitoring response to treatment make it possible to start timely interventions to reduce the risk of these complications.

As far as we know, this study is the first to illustrate the clinical and prognostic significance of NRI in a large cohort of breast cancer patients. Additionally, we also demonstrate that the change of NRI during treatment is a predictor for DFS and OS in different molecular subtypes and different lymph vessel invasion levels, as well as the relationship between NRI status and neoadjuvant chemotherapy toxicities.

However, the presented study is not without limitations. Firstly, our study evaluated the research topic from a retrospective perspective and was underway in a single-center with a relatively restricted number of breast cancer patients. To further enrich the literature, multicenter-based research that draws insights from large study populations should be encouraged. Secondly, as common in studies that adopt similar research methods (e.g., utilize eligibility criteria to screen patients), selection bias in our study could be difficult to eliminate. Thirdly, as NRI is a non-specific tumor marker, additional validation of the association between NRI, cancer prognosis, and treatment efficacy in large prospective studies should be conducted in the future.

CONCLUSION

NRI is described as the significant predictor for breast cancer patients, and may forecast the survival and prognosis for breast cancer. The minimally invasive, easily accessible and convenient indicators should be help doctors in terms of selecting measures, evaluating the curative effect, and estimating the prognosis of breast 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 was approved by the Ethics Committee of Cancer Hospital Chinese Academy of Medical Sciences and Tongji Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC and YQ: writing—original draft and writing—review & editing. XK and ZS: formal analysis. ZW, XW, and YD: data curation and investigation. YF and XL: methodology and supervision. XL and JW: resources, funding acquisition, and project administration. All authors contributed to the article and approved the submitted version.

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Prognostic Significance of Modified Advanced Lung Cancer Inflammation Index in Patients With Renal Cell Carcinoma Undergoing Laparoscopic Nephrectomy: A Multi-Institutional, Propensity Score Matching Cohort Study

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Background: We conducted a multi-institutional clinical study to assess the prognostic value of the advanced lung cancer inflammatory index (ALI) and modified ALI (mALI) in patients with renal cell carcinoma (RCC).

Methods: We collected 440 patients who underwent laparoscopic nephrectomy at three centers from 2014 to 2019. ALI was defined as body mass index (BMI) × serum albumin (ALB)/neutrophil-to-lymphocyte ratio (NLR) and mALI as L3 muscle index × ALB/NLR. Kaplan-Meier curves, receiver operating characteristic (ROC) curves and Cox survival analysis were used to assess the effect of ALI and mALI on overall survival (OS). In addition, we performed 1:1 propensity score matching (PSM) for the high mALI and low mALI groups to further explore the impact of mALI on survival in RCC patients.

Results: The optimal cut-off values for ALI and mALI were 40.6 and 83.0, respectively. Based on the cut-off values, we divided the patients into high ALI and low ALI groups, high mALI and low mALI groups. ALI and mALI were significantly associated with the AJCC stage, Fuhrman grade, T stage, and M stage. Low ALI ($p = 0.002$) or low mALI ($p < 0.001$) was associated with poorer prognosis. ROC curves showed that mALI was a better predictor of OS than ALI. Multivariate Cox regression analysis showed that low mALI (aHR = 2.22; 95% CI 1.19–4.13, $p = 0.012$) was an independent risk factor for OS in RCC patients who underwent nephrectomy, while ALI (aHR = 1.40; 95% CI 0.73–2.66, $p = 0.309$) was not significantly associated. Furthermore, after PSM analysis, we found

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that mALI remained an independent risk factor for OS (aHR = 2.88; 95% CI 1.33–6.26, $p = 0.007$) in patients with RCC.

Conclusions: For RCC patients undergoing laparoscopic nephrectomy, low ALI and low mALI were associated with poor prognosis, and preoperative mALI can be used as a potential independent prognostic indicator for RCC patients.

Keywords: renal cell carcinoma, advanced lung cancer inflammatory index, modified advanced lung cancer inflammatory index, overall survival, biomarker

INTRODUCTION

Renal cancer, also known as renal cell carcinoma (RCC), is a malignant tumor originating from the urinary tubular epithelium of the renal parenchyma, and its incidence accounts for 2.2% of adult malignancies worldwide (1). Approximately 25–30% of RCC patients have developed locally advanced or metastatic lesions at the time of initial diagnosis (2, 3). For patients with locally advanced and metastatic renal cancer, although targeted drug therapy has achieved certain efficacy and more clinical trials of drugs are ongoing, the overall prognosis is still poor (4, 5). The preferred treatment for early stage non-metastatic RCC remains radical nephrectomy or partial nephrectomy. Early recurrence or metastasis is still found in 20–30% of patients treated with surgery at follow-up (6). Therefore, the search for better prognostic predictors can be of great help in developing individualized follow-up and treatment plans.

A growing number of studies have confirmed the importance of systemic inflammatory response, local immune response and nutritional status in the progression of malignancy and patient prognosis (7–9). Several blood indicators, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR), have been shown correlate with the prognosis of patients with RCC (10, 11). In addition, indicators reflecting nutritional status, such as serum albumin (ALB), hemoglobin and sarcopenia have been identified as postoperative prognostic factors in patients with RCC (12, 13). Jafri et al. (14) developed the advanced lung cancer inflammation index (ALI) to assess the degree of systemic nutrition and inflammation in patients with metastatic non-small cell lung cancer (NSCLC). The ALI combines body mass index (BMI, kg/m^2), serum ALB (g/dL) and NLR and is defined as BMI × ALB/NLR. In addition, Kim et al. (15) replaced BMI with L3 muscle index (cm^2/m^2) to construct a modified ALI (mALI) score and found that low mALI was an independent prognostic risk factor for shorter overall survival (OS).

In this study, we aimed to assess the prognostic value of ALI and mALI on OS in patients undergoing laparoscopic nephrectomy in a multicenter clinical study.

Abbreviations: RCC, renal cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; ALB, albumin; ALI, advanced lung cancer inflammatory index; mALI, modified advanced lung cancer inflammatory index; BMI, body mass index; OS, overall survival; ROC, receiver operating characteristic; AUC, area under the curve; aHR, adjusted hazard ratio; CI, confidence interval; PSM, propensity score matching; SMI, skeletal muscle index.

MATERIALS AND METHODS

Study Design and Patients

In this multi-institutional study, we collected 590 patients with RCC who underwent partial or radical nephrectomy between January 2014 and December 2019 at the Department of Urology, Zhongda Hospital Southeast University, the Department of Urology, Shanghai Tenth People's Hospital, and the Department of Urology, Shidong Hospital. All patients were operated by the most experienced urologists in that hospital. Exclusion criteria were as follows: patients combined with other malignancies; patients received other anticancer treatments before surgery; patients lacked complete medical records or were lost to follow-up; patients lacked preoperative laboratory test data. We excluded 150 patients, resulting in 440 patients included in the final study. The methodology of this study followed the criteria in the Declaration of Helsinki (revised in 2013) and received ethical approval from the Ethics Committee of Zhongda Hospital Southeast University (ZDKYSB077) and Ethics Committee of Shanghai Tenth People's Hospital of Tongji University (SHSY-IEC-BG/02.04/04.0-81602469).

Clinical Data Collection and Follow-Up

Clinicopathological features, laboratory test data, and imaging results for all patients were available from the electronic medical record. Laboratory test data were measured 2 days prior to surgery or closest to the time of surgery, and laboratory data included serum ALB (g/dL), neutrophils, and lymphocytes. The L3 muscle index (cm^2/m^2) in the imaging results was determined based on our previous study (13). In addition, we included gender, age, BMI [weight (kg)/height^2 (m^2)], cardiovascular disease, diabetes, hypertension, smoking, type of surgery, laterality, AJCC stage, T stage, N stage, M stage, and Fuhrman grade. OS was calculated from the date of surgical treatment to the date of last follow-up or death.

Statistical Analysis

Categorical variables were expressed as numbers and percentages and analyzed with chi-square tests. As previously described, ALI = BMI × ALB/NLR, and mALI = L3 muscle index × ALB/NLR. Optimal cut-off values for ALI and mALI were determined using X-tile software (version 3.6.1). Kaplan-Meier curves were used to assess the effect of ALI and mALI on OS. Receiver operating characteristic (ROC) curves were used to compare the effect of ALI and mALI's predictive ability on OS and was calculated using the area under the curve (AUC). Univariate and

multivariate Cox regression were used to assess the relationship between ALI, mALI and OS, and the associated adjusted hazard ratio (aHR) and 95% confidence interval (CI) were calculated. In multivariate Cox regression analysis, three models were constructed to further assess the relationship between ALI, mALI and OS. Base model: adjusted for age, gender, BMI, hypertension, cardiovascular diseases, diabetes and smoking; core model: base model variables plus surgery type and laterality; extended model: core model variables plus AJCC stage, T stage, N stage, M stage and Fuhrman grade.

Based on the optimal cut-off value of mALI determined by the X-tile software, we divided the patients into a high mALI group ($n = 216$) and a low mALI group ($n = 214$). Considering the differences in some variables between the two groups, we used the "Matching" package in R software to perform 1:1 propensity score matching (PSM) for the high mALI and low mALI groups, adjusting for gender, age, BMI, cardiovascular disease, diabetes, hypertension, smoking, surgery type, laterality, AJCC stage, T stage, N stage, M stage, and Fuhrman grade to further explore the effect of mALI on OS in patients with RCC. Statistical analyses were performed using SPSS software (version 26.0), Graphpad Prism (version 8.3.0), and R software (version 3.6.2). P value < 0.05 was considered statistically significant.

RESULTS

According to the X-tile software, the optimal cut-off values for ALI and mALI were 40.6 and 83.0, respectively (**Figure 1**). Based on the cut-off values, we divided the patients into high ALI and low ALI groups, and high mALI and low mALI groups. The clinicopathological characteristics of all patients were shown in **Table 1**. Chi-square testing showed that ALI was associated with BMI, hypertension, surgery type, AJCC stage, T stage, M stage and Fuhrman grade, whereas mALI was statistically associated with BMI, surgery type, AJCC stage, T stage, M stage and Fuhrman grade. A higher proportion of patients with BMI $\geq$ 25kg/m^2, underwent partial nephrectomy, AJCC I/II stage, T1/T2 stage, M0 stage, and Fuhrman I/II grade were in the high ALI and high mALI groups compared with the low ALI and low mALI groups. In addition, we found that higher T stage, M stage, AJCC stage and Fuhrman grade were associated with lower ALI and lower mALI (**Figure 2**).

We performed survival analysis for the high ALI and low ALI groups, as well as for the high mALI and low mALI groups. Kaplan-Meier curves showed that low ALI ($p = 0.002$) and low mALI ($p < 0.001$) were associated with worse prognosis (**Figure 3**). Subsequently, we used ROC curves to assess the predictive ability of ALI and mALI for OS. We

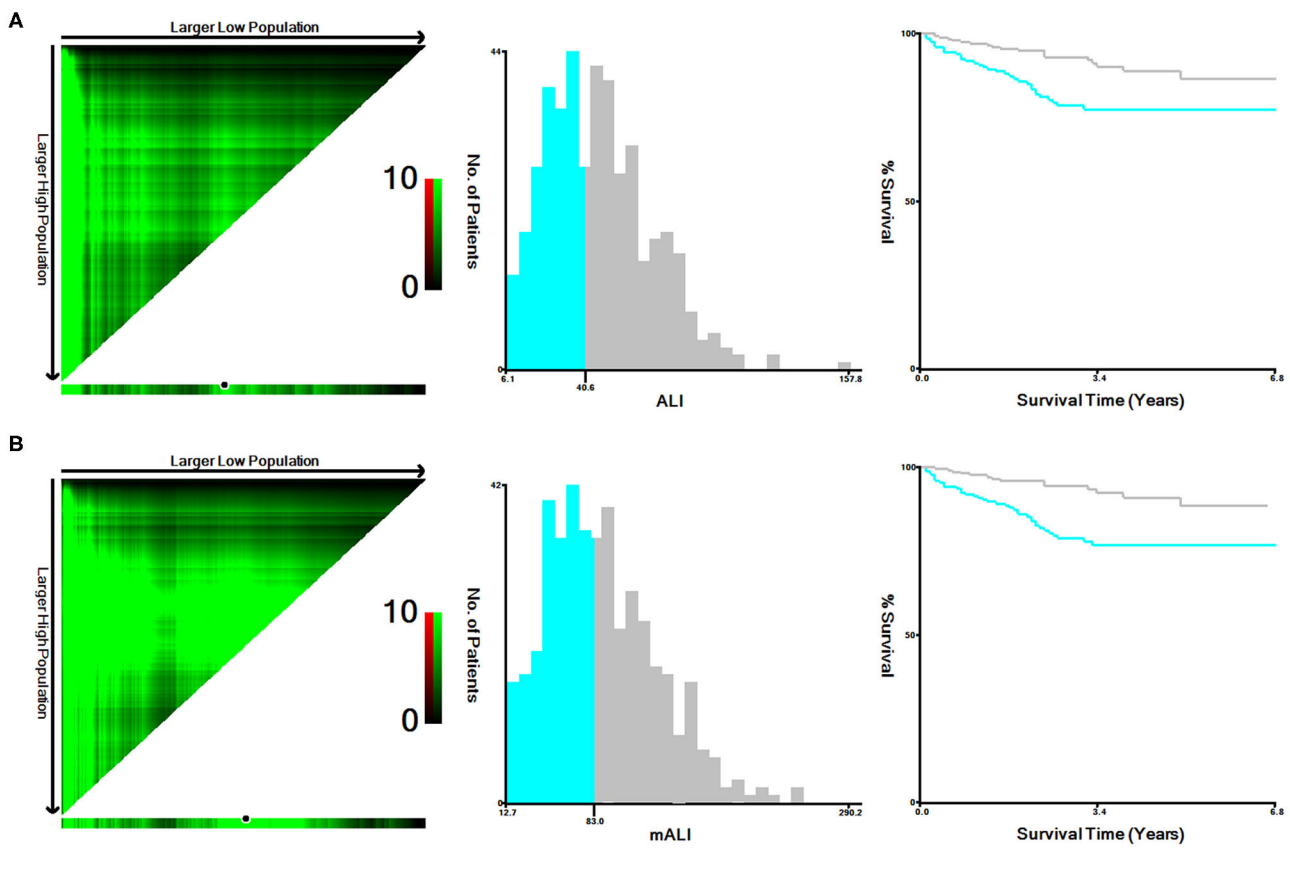

FIGURE 1 | X-tile stratified analysis of ALI and mALI. **(A)** ALI; **(B)** mALI. ALI, advanced lung cancer inflammation index; mALI, modified advanced lung cancer inflammation index.

TABLE 1 | Clinical characteristics of the patients according to ALI and mALI before PSM.

Characteristic	All	ALI		*P* value	mALI		*P* value
	patients *N* = 440	Low ALI *N* = 196	High ALI *N* = 244		Low ALI *N* = 224	High ALI *N* = 216	
Age categorized, y				0.964			0.613
≤65	317 (72.0)	141 (71.9)	176 (72.1)		159 (71.0)	158 (73.1)	
>65	123 (28.0)	55 (28.1)	68 (27.9)		65 (29.0)	58 (26.9)	
Gender				0.994			0.177
Male	294 (66.8)	131 (66.8)	163 (66.8)		143 (63.8)	151 (69.9)	
Female	146 (33.2)	65 (33.2)	81 (33.2)		81 (36.2)	65 (30.1)	
BMI categorized, kg/m^2				<0.001			<0.001
<25	249 (56.6)	138 (70.4)	111 (45.5)		148 (66.1)	101 (46.8)	
≥25	191 (43.4)	58 (29.6)	133 (54.5)		76 (33.9)	115 (53.2)	
Hypertension				0.039			0.137
No	250 (56.8)	122 (62.2)	128 (52.5)		125 (60.3)	115 (53.2)	
Yes	190 (43.2)	74 (37.8)	116 (47.5)		89 (39.7)	101 (46.8)	
Diabetes				0.567			0.924
No	370 (84.1)	167 (85.2)	203 (83.2)		188 (83.9)	182 (84.3)	
Yes	70 (15.9)	29 (14.8)	41 (16.8)		36 (16.1)	34 (15.7)	
Cardiovascular diseases				0.933			0.758
No	389 (88.4)	173 (88.3)	216 (88.5)		197 (87.9)	192 (88.9)	
Yes	51 (11.6)	23 (11.7)	28 (11.5)		27 (12.1)	24 (11.1)	
Smoking				0.369			0.467
No	367 (83.4)	160 (81.6)	207 (84.8)		184 (82.1)	183 (84.7)	
Yes	73 (16.6)	36 (18.4)	37 (15.2)		40 (17.9)	33 (15.3)	
Surgery type				<0.001			<0.001
Partial nephrectomy	266 (60.5)	90 (45.9)	176 (72.1)		105 (46.9)	161 (74.5)	
Radical nephrectomy	174 (39.5)	106 (54.1)	68 (27.9)		119 (53.1)	55 (25.5)	
Laterality				0.405			0.151
Right	217 (49.3)	101 (51.5)	116 (47.5)		118 (52.7)	99 (45.8)	
Left	223 (50.7)	95 (48.5)	128 (52.5)		106 (47.3)	117 (54.2)	
AJCC stage				<0.001			0.003
I	328 (74.5)	128 (65.3)	200 (82.0)		151 (67.4)	177 (81.9)	
II	26 (5.9)	17 (8.7)	9 (3.7)		19 (8.5)	7 (3.2)	
III	61 (13.9)	33 (16.8)	28 (11.5)		36 (16.1)	25 (11.6)	
IV	25 (5.7)	18 (9.2)	7 (2.9)		18 (8.0)	7 (3.2)	
T-stage				<0.001			0.001
T1	335 (76.1)	131 (66.8)	204 (83.6)		154 (68.8)	181 (83.8)	
T2	30 (6.8)	19 (9.7)	11 (9.4)		21 (9.4)	9 (4.2)	
T3	64 (14.5)	41 (20.9)	23 (9.4)		44 (19.6)	20 (9.3)	
T4	11 (2.5)	5 (2.6)	6 (2.5)		5 (2.2)	6 (2.8)	
N-stage				0.227			0.506
N0	423 (96.1)	186 (94.9)	237 (97.1)		214 (95.5)	209 (96.8)	
N1	17 (3.9)	10 (5.1)	7 (2.9)		10 (4.5)	7 (3.2)	
M-stage				<0.001			0.003
M0	421 (95.7)	180 (91.8)	241 (98.8)		208 (92.9)	213 (98.6)	
M1	19 (4.3)	16 (8.2)	3 (1.2)		16 (7.1)	3 (1.4)	
Fuhrman grade				0.017			0.020
I	74 (16.8)	27 (13.8)	47 (19.3)		28 (12.5)	46 (21.3)	
II	274 (62.3)	117 (59.7)	157 (64.3)		141 (62.9)	133 (61.6)	
III	82 (18.6)	44 (22.4)	38 (15.6)		47 (21.0)	35 (16.2)	
IV	10 (2.3)	8 (4.1)	2 (0.8)		8 (3.6)	2 (0.9)	
Urea nitrogen (mean, SD)	6.46, 4.45	6.77, 3.43	6.21, 5.12	0.190	6.62, 3.31	6.29, 5.38	0.433
Creatinine (mean, SD)	112.28, 88.72	123.55, 90.12	103.29, 86.73	0.018	119.82, 85.72	104.50, 91.27	0.071
Uric acid (mean, SD)	277.54, 102.81	281.14, 106.17	274.69, 100.19	0.517	277.33, 107.74	277.76, 97.73	0.965

PSM, propensity score matching; ALI, advanced lung cancer inflammation index; mALI, modified advanced lung cancer inflammation index; BMI, body mass index; AJCC, american joint committee on cancer; SD, standard deviation.

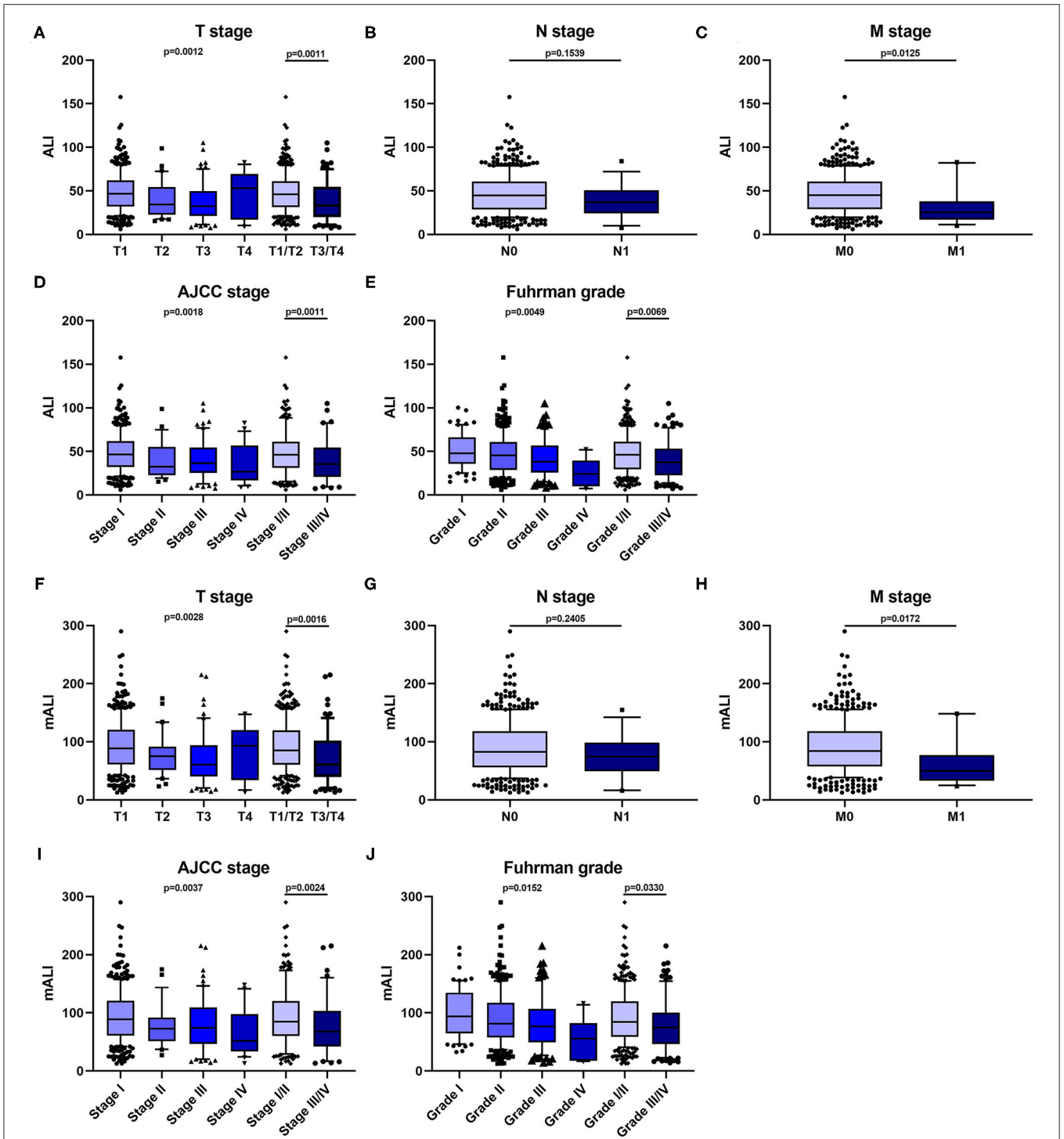

FIGURE 2 | Relationship between patients' clinical characteristics and ALI, mALI. **(A–E)** Levels of ALI in different T-stage **(A)**, N-stage **(B)**, M-stage **(C)**, AJCC stage **(D)**, and Fuhrman grade **(E)**. **(F–J)** Levels of ALI in different T-stage **(F)**, N-stage **(G)**, M-stage **(H)**, AJCC stage **(I)**, and Fuhrman grade **(J)**. ALI, advanced lung cancer inflammation index; mALI, modified advanced lung cancer inflammation index.

found that mALI had a better ability to predict OS than ALI (**Supplementary Figure 1**). In addition, univariate Cox regression analysis showed that low ALI and low mALI were associated with poorer OS (**Table 2**). Multivariate Cox regression analysis showed that mALI was consistently an independent risk factor for OS, whether in the basic model (low mALI vs. high

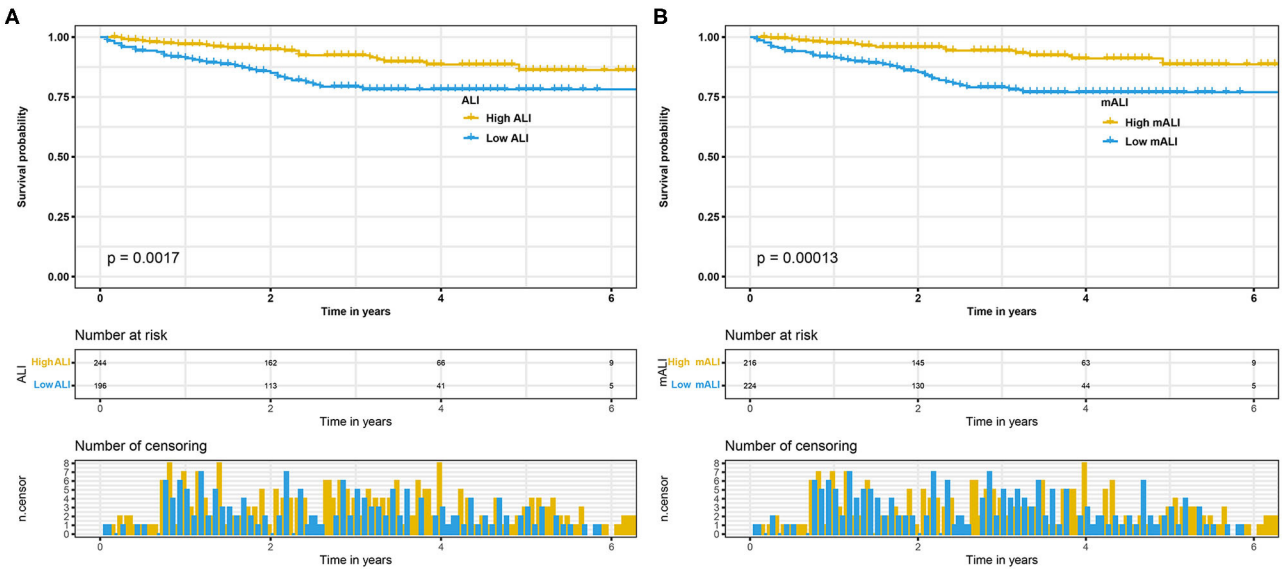

FIGURE 3 | Kaplan-Meier curves for OS stratified by ALI and mALI before PSM. **(A)** ALI OS; **(B)** mALI OS. OS, overall survival; ALI, advanced lung cancer inflammation index; mALI, modified advanced lung cancer inflammation index; PSM, propensity score matching.

TABLE 2 | Relative risk of overall survival (OS) was calculated according to ALI and mALI [a].

Characteristic	Univariate analysis		Basic model		Core model		Extended model	
	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
BEFORE PSM								
ALI								
High	Reference		Reference		Reference		Reference	
Low	2.36 (1.36–4.10)	0.002	2.22 (1.25–3.93)	0.007	1.62 (0.89–2.96)	0.117	1.40 (0.73–2.66)	0.309
mALI								
High	Reference		Reference		Reference		Reference	
Low	3.09 (1.68–5.68)	<0.001	3.09 (1.68–5.69)	<0.001	2.20 (1.17–4.14)	0.014	2.22 (1.19–4.13)	0.012
AFTER PSM								
mALI								
High	Reference		Reference		Reference		Reference	
Low	2.16 (1.04–4.48)	0.039	2.26 (1.09–4.70)	0.029	2.26 (1.08–4.70)	0.030	2.88 (1.33–6.26)	0.007

[a] *Adjusted covariates: Basic model: age, gender, BMI, hypertension, diabetes, cardiovascular diseases, and smoking; Core model: basic model plus surgery type and laterality; Extended model: core model plus AJCC stage, T stage, N stage, M stage, and fuhrman grade. PSM, propensity score matching; BMI, body mass index; AJCC, american joint committee on cancer; aHR, adjusted hazard ratio; CI, confidence interval; mALI, modified advanced lung cancer inflammation index.*

mALI: aHR = 3.09; 95% CI 1.68–5.69, $p < 0.001$), core model (low mALI vs. high mALI: aHR = 2.20; 95% CI 1.17–4.14, $p = 0.014$) or extended model (low mALI vs. high mALI: aHR = 2.22; 95% CI 1.19–4.13, $p = 0.012$), while ALI was statistically significant only in the basic model (**Table 2**).

Considering the effect of other confounding variables, we performed a 1:1 PSM analysis for the high mALI and low mALI groups and adjusted for the 14 variables of gender, age, BMI, cardiovascular disease, diabetes, hypertension, smoking, surgery type, laterality, AJCC stage, T stage, N stage, M stage, and Fuhrman grade (**Figure 4**). After the PSM analysis, 154 patients were included in the high mALI and low mALI groups, respectively. Clinicopathological characteristics of 308 patients after PSM were shown in **Supplementary Table 1**. We performed survival analysis in 308 patients and Kaplan-Meier curves still showed that low mALI ($p = 0.034$) was associated with a poorer prognosis (**Figure 5**). Univariate and multivariate Cox regression analyses showed that low mALI was associated with a higher risk and that low mALI was associated with a 188% higher risk compared to high mALI in the extended model (aHR = 2.88; 95% CI 1.33–6.26, $p = 0.007$) (**Table 2**).

DISCUSSION

Our study is the first study assessing the prognostic value of ALI and mALI in RCC. In this multi-institutional retrospective

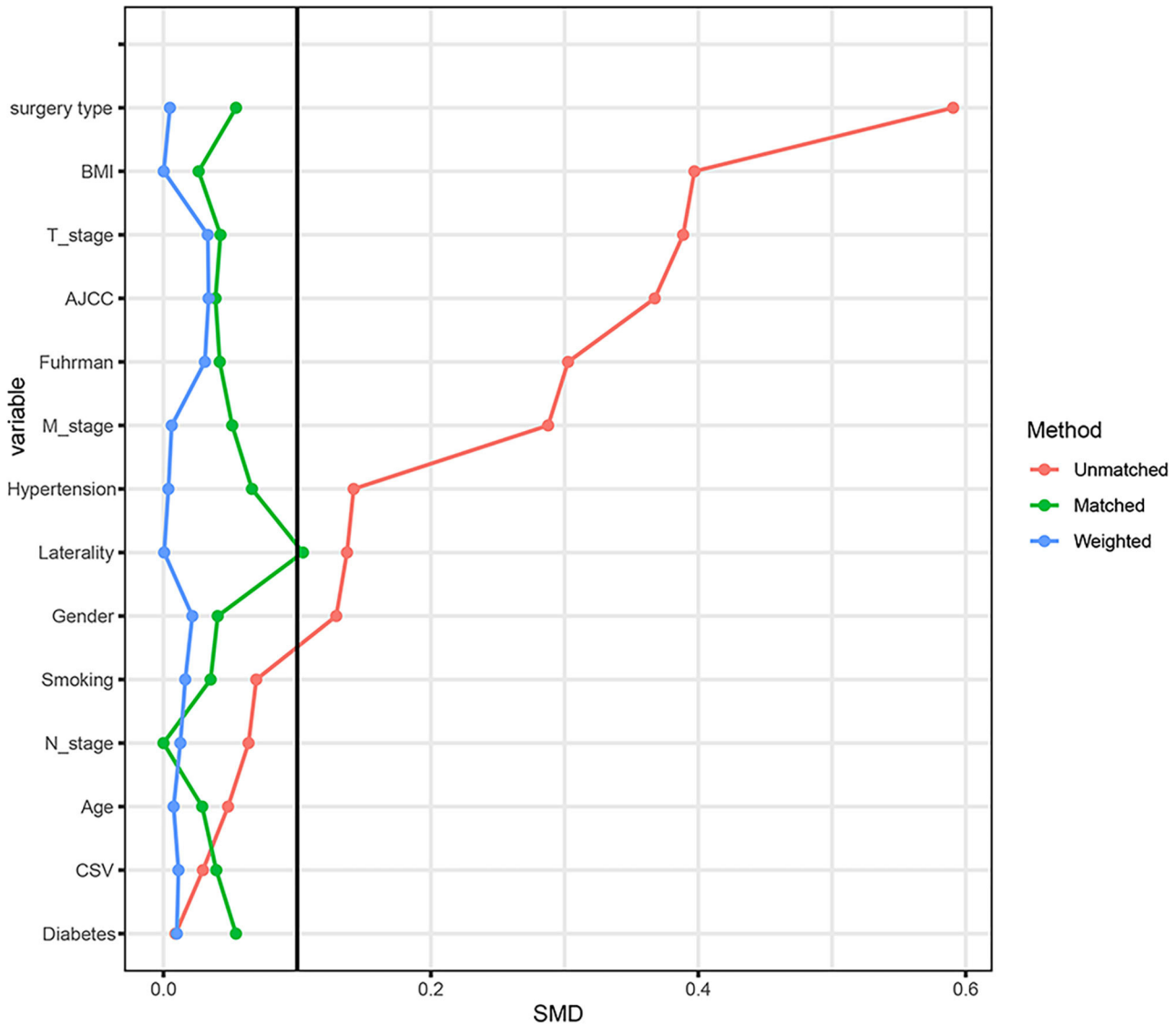

FIGURE 4 | The standardized mean difference (SMD) results of different variables after PSM. PSM, propensity score matching.

study, we included clinical data from 440 patients who underwent nephrectomy and used Kaplan-Meier curves, ROC curves, and univariate and multivariate Cox regression analyses to explore the correlation between ALI, mALI, and OS. We found that low ALI and low mALI were correlated with poor prognosis, mALI was an independent risk factor for OS, and mALI was a better predictor of OS in RCC patients than ALI. In addition, we further performed 1:1 PSM on patients in the low mALI and high mALI groups and found that mALI was still an independent risk factor for OS.

L3 muscle index is a common indicator of sarcopenia. Sarcopenia is an age-related syndrome and is considered an emerging indicator that can reflect nutritional status (16). Sarcopenia is defined as an age-related syndrome of reduced skeletal muscle mass, decreased muscle strength and/or decreased physical performance (17). Currently, sarcopenia can be assessed by measuring the L3 lumbar skeletal muscle index (SMI) (18). In recent years, there were increasing evidences that oncology patients often had comorbid sarcopenia. The prevalence of sarcopenia ranged from 20 to 70% in different tumors (19). Studies have shown that as SMI decreases, oncology patients have a poorer prognosis and an increased risk of complications (20). Our previous studies found that sarcopenia was a risk factor for survival time in patients with bladder cancer and RCC (13, 21). Sarcopenia played an important role in the treatment prognosis of oncology patients, and nutritional, exercise and pharmacological interventions for patients with sarcopenia could reduce the occurrence of post-treatment

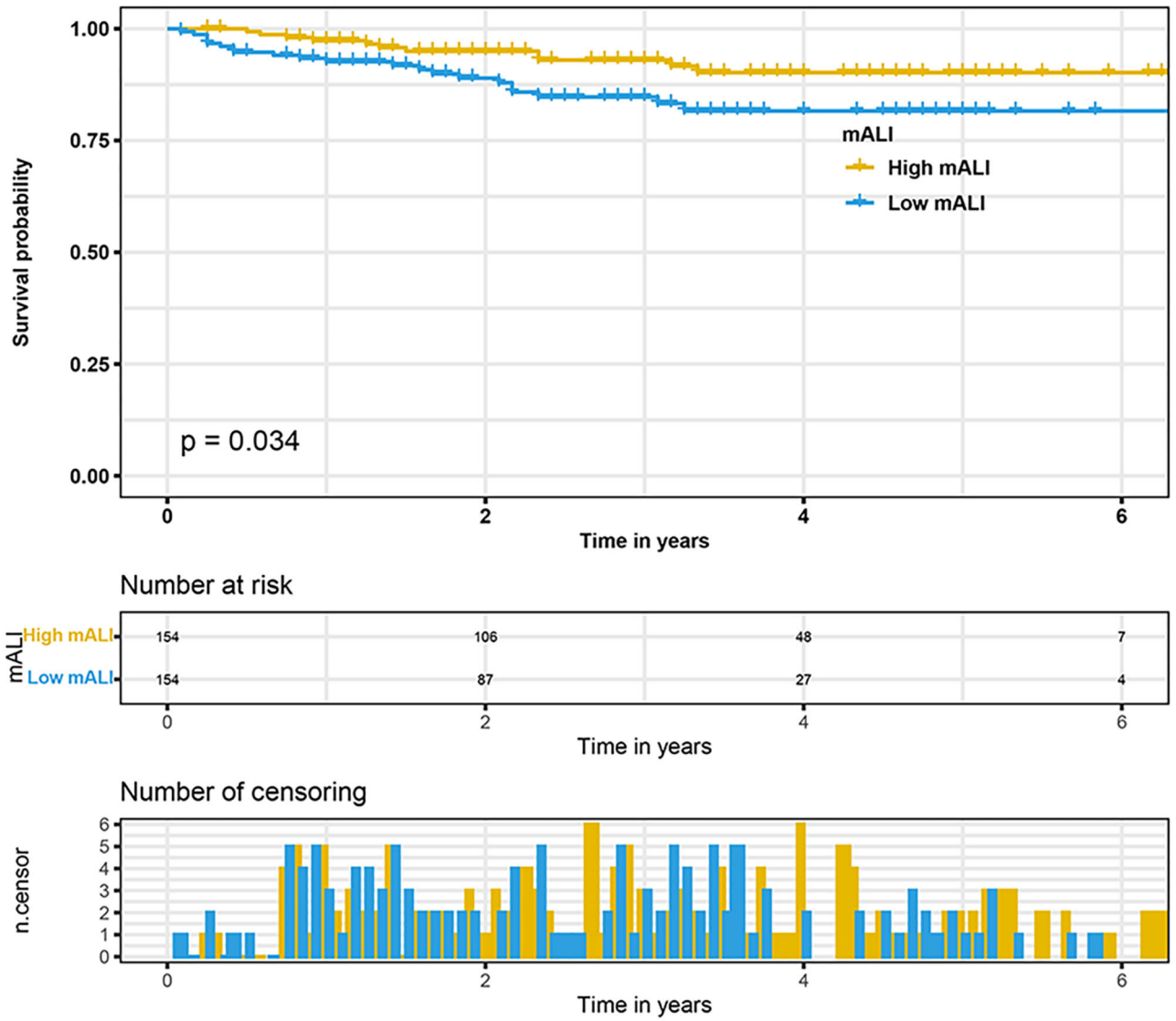

FIGURE 5 | Kaplan-Meier curves for OS stratified by mALI after PSM. OS, overall survival; mALI, modified advanced lung cancer inflammation index; PSM, propensity score matching.

complications and improve the prognosis of patients with oncology (22).

ALB is a product synthesized by the liver and is an important component of human serum protein, which has an important role in the transport and synthesis of substances in the organism. Serum ALB is a common marker used to assess the nutritional status of patients, and low serum ALB level indicates that the patient is malnourished (23). In addition to being an indicator of nutritional status, serum ALB may also be associated with mechanisms of inflammatory response (24). Studies have demonstrated that preoperative low serum ALB levels may be considered as a marker of systemic inflammation and a poor prognostic indicator of survival outcome in cancer patients (25, 26).

Many studies have shown that the development of malignant tumors is closely related to the tumor microenvironment (27). Inflammatory cells, such as neutrophils, lymphocytes, and monocytes, are important components of the tumor microenvironment, and their mediated inflammatory responses can promote tumor cell proliferation, invasion, metastasis, and immune escape (7, 28). The combination of multiple inflammatory cells, such as NLR, PLR and LMR, has been shown to correlate with the prognosis of various cancers (29, 30). NLR is an evaluation indicator reflecting the systemic inflammatory response and is one of the earliest and most classical inflammatory indicators found. The literature reports that preoperative NLR levels are significantly associated with postoperative tumor survival in a variety of solid tumors (31).

In order to better assess patient prognosis, Jafri et al. (14) developed an index (ALI) that could reflect the degree of systemic nutrition and inflammation in patients based on three indicators: BMI, ALB and NLR, and found that low ALI was a poor prognostic indicator for patients with advanced NSCLC. In addition, subsequent studies have shown that low ALI can be used to assess the prognosis of various malignancies, such as small cell lung cancer (SCLC), colorectal cancer and pancreatic carcinoma (32, 33). Considering that BMI cannot directly measure body fat and skeletal muscle content, Kim et al. (15) replaced BMI with L3 muscle index to construct a modified ALI (mALI) score and found that low mALI was an independent prognostic risk factor for SCLC patients OS shortening. In the present study, we compared the predictive ability of ALI and mALI for OS, and found that mALI better predicted OS in RCC patients and that mALI was an independent risk factor for OS.

Despite the positive results obtained in this study, there are several limitations to this study. First, although this study was a three-institution multicenter study, it was still a retrospective study and required an expanded sample for prospective studies. Second, we did not assess patients' quality of life or postoperative nutritional status. Final, we did not include other treatments in the study, which may also have an impact on prognosis.

CONCLUSION

In general, we found that both ALI and mALI were associated with poor prognosis in patients with RCC, but mALI was a better predictor of OS than ALI, and mALI was an independent prognostic factor for OS in patients with RCC undergoing laparoscopic nephrectomy.

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 Zhongda Hospital Southeast University (ZDKYSB077) and Ethics Committee of Shanghai Tenth People's Hospital of Tongji University (SHSY-IEC-BG/02.04/04.0-81602469). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WM, JG, SC, and MC: conception and design. JG, SC, and MC: administrative support. WM, KW, YW, and JN: Provision of study materials or patients and manuscript writing. WM, HZ, YW, ZW, and RL: collection and assembly of data. WM and KW: data analysis and interpretation. All authors contributed to the article, final approval of manuscript, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.781647/full#supplementary-material

Supplementary Figure 1 | Comparison of area under ROC curves for ALI and mALI in predicting OS. ROC, receiver operating characteristic; OS, overall survival; ALI, advanced lung cancer inflammation index; mALI, modified advanced lung cancer inflammation index.

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Progressive Skeletal Muscle Loss After Surgery and Adjuvant Radiotherapy Impact Survival Outcomes in Patients With Early Stage Cervical Cancer

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The effect of skeletal muscle loss associated with surgery and adjuvant radiotherapy on survival outcomes in patients with early-stage cervical cancer remains unclear. We analyzed the data of 133 patients with early-stage cervical cancer who underwent surgery and adjuvant radiotherapy between 2013 and 2018 at two tertiary centers. Skeletal muscle changes were measured using computed tomography scans at baseline, at simulation for radiotherapy, and at 3 months post-treatment. A decrease of ≥5% in the skeletal muscle was defined as "muscle loss." The Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) was used to assess gastrointestinal toxicity. The Patient-Generated Subjective Global Assessment (PG-SGA) was used for nutritional assessment. Predictors of overall survival were identified using the Cox regression models. The median follow-up period was 3.7 years. After treatment, 32 patients (24.1%) experienced muscle loss. The rate of muscle loss was higher in patients with PRO-CTCAE score ≥3 or PG-SGA score ≥4 at the end of radiotherapy than in patients with PRO-CTCAE score ≤2 or PG-SGA score 0–3 (75.0 vs. 10.5%, $p < 0.001$; 71.4 vs. 2.2%, $p < 0.001$). The 3-year overall survival was significantly lower in patients with muscle loss than in those with muscle preserved (65.6 vs. 93.9%, $p < 0.001$). Multivariate analysis showed that muscle loss was independently associated with poor overall survival (hazard ratio, 4.55; 95% confidence interval: 1.63–12.72; $p < 0.001$). Muscle loss after surgery and adjuvant radiotherapy was associated with poor overall survival in patients with early-stage cervical cancer. Muscle loss is associated with patient-reported gastrointestinal toxicity and deterioration in nutritional status.

Keywords: skeletal muscle loss, pelvic radiotherapy, cervical cancer, nutrition, clinical outcome

INTRODUCTION

Cervical cancer is the fourth most commonly occurring cancer and the fourth leading cause of cancer-related deaths in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020 (1). Radical hysterectomy with bilateral pelvic lymph node dissection is the primary treatment for patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB-IIA cervical cancer. Despite favorable outcomes after surgery, patients with risk factors for recurrence are administered adjuvant pelvic radiotherapy to reduce the risk of pelvic recurrence, although no significant improvement in overall survival due to adjuvant pelvic radiotherapy has been reported (2–4). Consideration of treatment-related morbidity is important.

Pelvic radiotherapy is associated with gastrointestinal (GI) toxicities that can be challenging for the patients, interfere with the quality of life, and lead to deterioration of nutritional status (5–14). Patients who experience a high symptom burden and deterioration of nutritional status might develop adverse changes in body composition, such as skeletal muscle loss (15–17). The skeletal muscle acts as an endocrine organ that produces and releases myokines, which play a role in regulating the metabolism and inflammation in the entire body (18). Studies have reported that skeletal muscle loss during chemoradiotherapy is associated with poor survival outcomes in patients with locally advanced cervical cancer (7–13). However, the effect of skeletal muscle loss associated with surgery and adjuvant radiotherapy on survival outcomes in patients with early-stage cervical cancer remains unclear.

Skeletal muscle mass can be evaluated by a variety of techniques and reported as total body skeletal muscle mass, as appendicular skeletal muscle mass, or as muscle cross-sectional area of specific muscle groups or body locations (19). Computed tomography (CT) images are widely performed in cancer patients for routine cancer care and can provide objective skeletal muscle measurement. The cross-sectional areas of the skeletal muscle at the level of the third lumbar vertebra (L3) are strongly correlated with the total body skeletal muscle (20–22). The prognostic value of CT-based body composition measurement had also been evaluated and validated in various malignancies (23). Longitudinal analysis of CT images of cancer patients may help evaluate skeletal muscle changes during cancer treatments and their associations with clinical outcomes (**Figure 1**).

We hypothesized that skeletal muscle loss after surgery and adjuvant radiotherapy would affect survival outcomes in patients with early-stage cervical cancer. This study aimed to evaluate skeletal muscle using CT scans performed during routine cancer care and determine whether skeletal muscle loss is associated with survival outcomes in patients with early-stage cervical cancer.

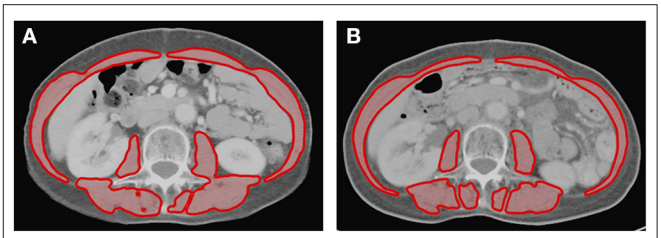

FIGURE 1 | Axial cross-sectional areas of skeletal muscle (red) on CT images at the L3 vertebral level **(A)** before and **(B)** after treatment in one patient. The skeletal muscle areas of this patient were 81.6 and 77.3 cm^2 before and after treatment, respectively. This patient had a reduction of 5.3% of skeletal muscle after treatment.

PATIENTS, MATERIALS, AND METHODS

Patients

This study was approved by the Institutional Review Board. The need for informed consent was waived because of the retrospective and observational nature of the study. The data of patients with FIGO stage IB-IIA cervical cancer with indications for postoperative radiotherapy after hysterectomy between 2013 and 2018 were reviewed at two tertiary centers. The inclusion criteria were as follows: (a) adequate clinical data, GI toxicity data, and nutritional assessment data, (b) CT scans performed before surgery and within 3 months after adjuvant radiotherapy. Patients were excluded from the analysis if they had a history of other malignancies.

Treatments

Pre-treatment CT scans were routinely performed for the pre-surgical workup. The surgeries were performed by accredited gynecologic oncologists, and included hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. After surgery, the patients were recommended adjuvant pelvic radiotherapy considering the pathological risk factors (tumor size, depth of cervical stromal invasion, and invasion of the lymphovascular space). For patients with pelvic lymph node metastasis, parametrial involvement, or positive surgical margins, adjuvant pelvic radiotherapy concurrent with cisplatin-based chemotherapy was indicated. After surgical wound healing, a CT scan was performed for planning radiotherapy. Pelvic radiotherapy was administered using intensity-modulated radiotherapy (IMRT) up to 45–50.4 Gy. The clinical target volume encompassed the obturator, internal iliac, external iliac, common iliac, and presacral nodal regions, and the upper vagina. Vaginal cuff brachytherapy was considered at the discretion of the treating physicians after the completion of pelvic IMRT. High-dose rate brachytherapy at 5 Gy for 4 fractions was delivered. Post-treatment CT scans were performed within 3 months after completion of radiotherapy.

GI Toxicity Assessment

GI toxicities were assessed weekly using the Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). The PRO-CTCAE questionnaires included the severity of abdominal pain, interference of abdominal pain with daily activities, and frequency of diarrhea, were administered to patients (24). Patients scored these three PRO-CTCAE items at home or recorded whenever severe or bothersome symptoms occurred. The PRO-CTCAE questionnaires were provided by patients

to nurses in the health education room before weekly clinic appointments. The PRO-CTCAE scores toxicity on a 5-point Likert scale, with 0 indicating none, not at all, and never, respectively. We analyzed the highest score for each item during 3–5 weeks of radiotherapy because radiotherapy-induced GI toxicities generally become symptomatic at 3 weeks and reach a maximum at 5 weeks (25).

Physicians also graded the GI toxicity every week using CTCAE version 4.0. Previous studies reported that PRO-CTCAE could evaluate the treatment-related toxicity more accurately than the physician-graded CTCAE (6, 15). In this study, PRO-CTCAE data were used for analysis.

Nutritional Assessment

We evaluated the nutritional status of patients using Patient-Generated Subjective Global Assessment (PG-SGA) at the beginning and end of radiotherapy. The PG-SGA provides a score (higher score indicates a higher risk of malnutrition) and categorizes patients into three distinct classes of nutritional status: A, well-nourished; B, suspected malnutrition or moderately malnourished; and C, severely malnourished. In this analysis, patients were categorized into two groups: well-nourished (PG-SGA score 0–3) and malnourished (PG-SGA score $\geq$4) (15, 26–28).

Skeletal Muscle Measurement

The CT scans at three timepoints were retrieved for analysis (**Figure 2**). The cross-sectional area (cm^2) of the skeletal muscle was measured on a single slice of the CT scan at the third lumbar vertebral level. One researcher, blinded to the patient information, measured the skeletal muscle using the Varian Eclipse software (Varian Medical Systems Inc., Palo Alto, CA, USA) (20–22, 29–31). Skeletal muscle was defined based on Hounsfield unit (HU) thresholds ranging from −29 to +150 HU. The skeletal muscle index (SMI) was calculated as the cross-sectional muscle area divided by height in square meters (cm^2/m^2) (32). The cut-off values for sarcopenia were set at the lowest tertile for SMI based on previous studies (33–36). The body mass index (BMI) within 2 weeks of the CT scans was obtained from medical records.

The current definition of cachexia is weight loss >5% over the past 6 months (17). Based on this cut-off value, several studies have reported that weight or muscle loss >5% during cancer treatment is associated with poor survival outcomes in cancer patients (35–38). In this study, patients with a decrease in BMI or SMI $\geq$5% after surgery and adjuvant radiotherapy were categorized as having weight loss or muscle loss, and those with a gain or decrease of <5% in BMI or SMI were categorized as "preserved".

Statistical Analysis

Continuous variables are expressed as medians and interquartile range (IQR) or mean ± standard deviation. The comparisons of continuous variables were analyzed using independent *t*-tests or Mann–Whitney *U* tests, as appropriate. Categorical data are expressed as frequency (%) and were analyzed using the chi-square test or Fisher's exact test. Changes in BMI and SMI were analyzed by repeated-measures ANOVA with Bonferroni adjustment for the *post-hoc* tests. Paired *t*-tests were used to assess changes in PG-SGA score between the start and the end of radiotherapy. McNemar's test was used to test for significant differences in the paired categorical data. Spearman's correlation coefficient was used to evaluate the correlations.

Overall survival (OS) and disease-free survival (DFS) were measured from the date of surgery to the date of death/last follow-up and the date of disease recurrence, death, or last follow-up, respectively. Univariate and multivariate analyses of OS and DFS were performed using the Cox proportional hazards model, and the results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Multivariate models were selected by backward elimination with a significance level of 0.05. The data were analyzed using IBM SPSS software (version 21.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Patient Characteristics

We reviewed the data of 181 patients with cervical cancer who underwent hysterectomy and adjuvant pelvic radiotherapy. Patients with a history of other malignancy ($n = 4$), missing PG-SGA data ($n = 11$), missing PRO-CTCAE data ($n = 25$),

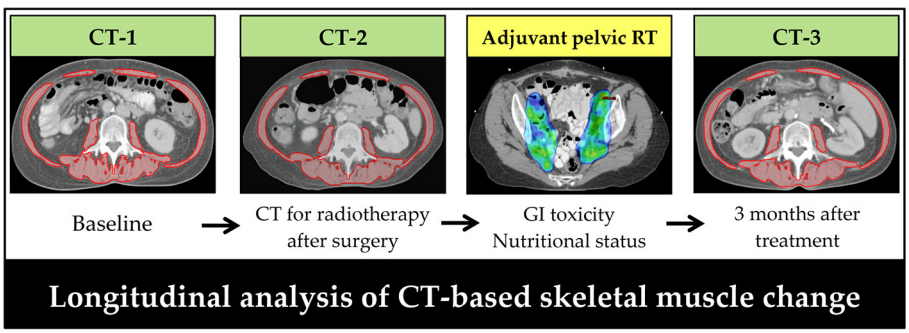

FIGURE 2 | Timeline of computed tomography scans for patients with early-stage cervical cancer receiving surgery and post-operative pelvic radiotherapy. Skeletal muscle was assessed on a transversal computed tomography slice at the level of L3. Red: skeletal muscle area. CT, computed tomography; RT, radiotherapy.

TABLE 1 | Patient and tumor characteristics.

Characteristics	Overall ($n = 133$)
Age (years)	53 (46–61)
Stage (FIGO 2018)	
IB1	16 (12.0)
IB2	58 (43.6)
IB3	23 (17.3)
IIA1	26 (19.5)
IIA2	10 (7.5)
Histology	
Squamous cell carcinoma	104 (78.2)
Adenocarcinoma	29 (21.8)
Pathological cervical tumor size	
<4 cm	92 (69.2)
≥4 cm	41 (30.8)
Pathological risk factors	
Pelvc lymph node metastasis	41 (30.8)
Parametrial invasion	16 (12.0)
Positive surgical margin	8 (6.0)
Lymphovascular space invasion	103 (77.4)
Deep one-third cervical stromal invasion	97 (72.9)
Adjuvant treatment	
Radiotherapy only	71 (53.4)
CCRT	62 (46.6)

CCRT, concurrent chemoradiotherapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range.
Data are median (IQR) or n (%).

and in whom CT was not performed after treatment ($n = 8$) were excluded. The final analysis was included the data of 133 patients. The patient and tumor characteristics are summarized in **Table 1**. The median follow-up period was 3.7 years (IQR: 2.6–5.7), during which 22 (16.5%) patients experienced recurrence, and 17 (12.8%) patients died.

GI Toxicity and Nutritional Status During Pelvic Radiotherapy

All patients completed the planned pelvic radiotherapy with a median duration of radiotherapy of 39 days (IQR: 37–41). Overall, 28 (21.1%) patients reported PRO-CTCAE score ≥3 for abdominal pain or diarrhea. In all, 14 (10.5%) patients reported severe or very severe abdominal pain, 16 (12.0%) reported that their abdominal pain interfered with their activities quite a bit or very much, and 27 (20.3%) patients reported frequent or almost constant diarrhea.

The nutritional status deteriorated during pelvic radiotherapy with an increase in the PG-SGA score from the start to the end of radiotherapy (1.4 to 3.3, $p < 0.001$). The number of malnourished patients was 13 (9.8%) at the start of radiotherapy and increased to 42 (31.6%) at the end of radiotherapy. Patients with PRO-CTCAE scores ≥3 had significantly higher PG-SGA scores at the end of radiotherapy than those reporting PRO-CTCAE ≤2 (7.6 vs. 2.1%, $p<0.001$). At the end of radiotherapy, the proportion of malnourished patients was higher in the PRO-CTCAE score ≥3 group than in the PRO-CTCAE score ≤2 group (85.7 vs. 17.1%, $p < 0.001$).

Skeletal Muscle Changes After Surgery and Adjuvant Radiotherapy

The median duration from pre-treatment CT to simulation CT for radiotherapy and post-treatment CT was 23 days (IQR: 21–25) and 137 days (IQR: 126–144), respectively. The cut-off value for sarcopenia was set at SMI <38.5 cm^2/m^2, which corresponds to the lowest tertile. Changes in the BMI and SMI were seen across the three time points ($p = 0.004$ and $p = 0.02$, respectively). BMI decreased from the baseline level by 1.0% post-surgery (23.94 vs. 23.69 kg/m^2, a decrease of 0.25 kg/m^2; 95% CI: −0.33 to −0.18; $p < 0.001$), and returned to the baseline level 3 months post-radiotherapy (23.94 vs. 23.95 kg/m^2, an increase of 0.01 kg/m^2; 95% CI: −0.17 to 0.18; $p = 0.95$). SMI decreased from the baseline level by 0.4% post-surgery (38.7 vs. 38.5 cm^2/m^2, a decrease of 0.2 cm^2/m^2; 95% CI: −0.2 to −0.1; $p < 0.001$) and by 1.1% 3 months post-radiotherapy (38.7 vs. 38.3 cm^2/m^2, a reduction of 0.4 cm^2/m^2; 95% CI: −0.7 to −0.1; $p = 0.007$). The changes in BMI and SMI were correlated ($\rho = 0.59$; $p < 0.001$) (**Supplementary Figure 1**). After surgery and adjuvant pelvic radiotherapy, 23 (17.3%) and 32 (24.1%) patients developed ≥5% loss of weight and muscle, respectively.

The changes in BMI and SMI after treatment were not significantly different between patients with or without concurrent chemotherapy (BMI: 0.06% vs. −0.03%, $p = 0.91$; SMI: −0.9 vs. −1.3%, $p = 0.70$).

Skeletal Muscle Change Based on Patient-Reported GI Toxicity or Nutritional Status

The changes in BMI and SMI after treatment according to the PRO-CTCAE and PG-SGA scores are summarized in **Table 2**. The frequency of patients experiencing weight or muscle loss was significantly higher in the PRO-CTCAE score ≥3 group than PRO-CTCAE score ≤2 group. Nutritional status at the beginning of radiotherapy was not associated with a change in BMI or SMI after treatment. In contrast, malnourished status at the end of radiotherapy was associated with weight or muscle loss after treatment.

The longitudinal changes in BMI and SMI according to PRO-CTCAE or PG-SGA scores are presented in **Figure 3**. Patients with PRO-CTCAE score ≥3 showed a greater reduction in SMI after surgery (BMI: −1.4 vs. −0.9%, $p = 0.26$; SMI: −0.9 vs. −0.3%, $p = 0.04$) and in BMI and SMI after radiotherapy (BMI: −3.7 vs. 1.0%, $p < 0.001$; SMI: −6.6 vs. 0.4%, $p < 0.001$) than patients with PRO-CTCAE score ≤2. Patients who were malnourished at the end of radiotherapy had reduced BMI and SMI after surgery (BMI: −1.7 vs. −0.7%, $p = 0.003$; SMI: −1.0 vs. −0.2%, $p < 0.001$) and showed a further decrease in BMI and SMI after radiotherapy (BMI: −4.0 vs. 1.9%, $p < 0.001$; SMI: −5.9 vs. 1.1%, $p < 0.001$) compared to well-nourished patients.

TABLE 2 | Body mass index and skeletal muscle index changes by PRO-CTCAE and PG-SGA.

	PRO-CTCAE score			PG-SGA at the start of radiotherapy[a]			PG-SGA at the end of radiotherapy[a]		
Variable	**≤2 (*n* = 105)**	**≥3 (*n* = 28)**	***p*-value**	**0–3 (*n* = 120)**	**≥4 (n=13)**	***p*-value**	**0–3 (*n* = 91)**	**≥4 (*n* = 42)**	***p*-value**
BMI change, *n* (%)									
Gain or loss <5%	93 (88.6)	17 (60.7)	0.001	99 (82.5)	11 (84.6)	1.00	88 (96.7)	22 (52.4)	<0.001
Loss ≥5%	12 (11.4)	11 (39.3)		21 (17.5)	2 (15.4)		3 (3.3)	20 (47.6)	
SMI change, *n* (%)									
Gain or loss <5%	94 (89.5)	7 (25.0)	<0.001	93 (77.5)	8 (61.5)	0.30	89 (97.8)	12 (28.6)	<0.001
Loss ≥5%	11 (10.5)	21 (75.0)		27 (22.5)	5 (38.5)		2 (2.2)	30 (71.4)	

BMI, body mass index; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; PG-SGA, Patient-Generated Subjective Global Assessment; SMI, skeletal muscle index.

[a]*Malnourished defined as PG-SGA score ≥4.*

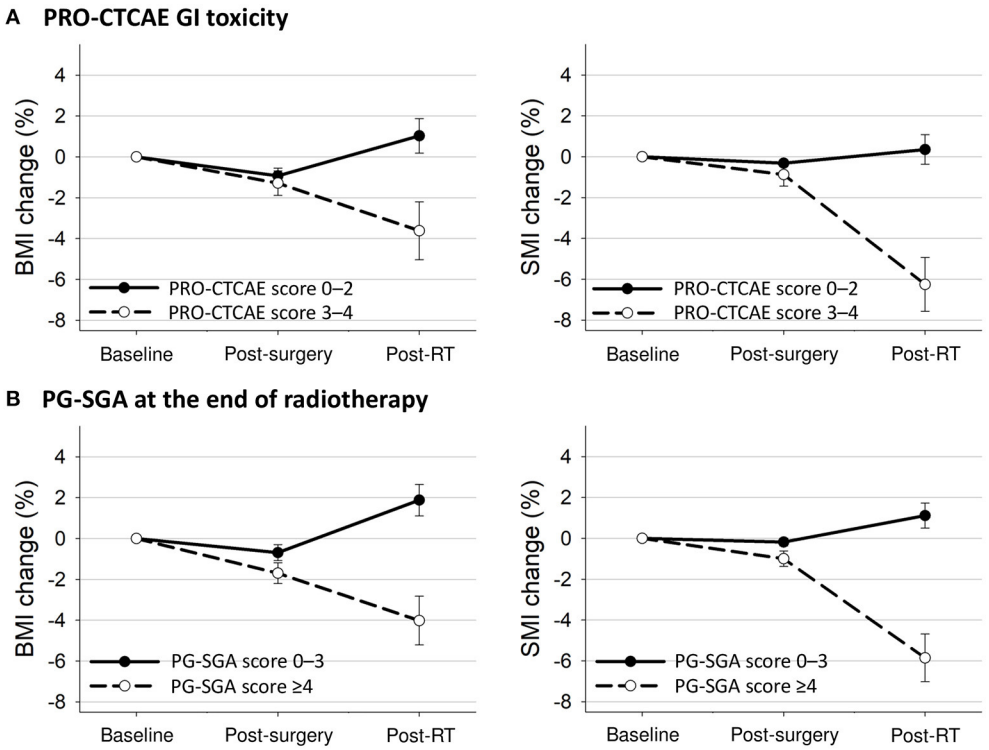

FIGURE 3 | Mean changes with 95% confidence interval bars in BMI and SMI from baseline to 3 months after treatment completion according to **(A)** PRO-CTCAE GI toxicity and **(B)** PG-SGA at the end of radiotherapy. BMI, body mass index; GI, gastrointestinal; PG-SGA, Patient-Generated Subjective Global Assessment; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; RT, radiotherapy; SMI, skeletal muscle index.

Prognostic Impact of Skeletal Muscle on Survival

The 3-year OS and DFS for the entire cohort were 86.8 and 83.2%, respectively. The 3-year OS was 65.6 and 93.9% in the groups with muscle loss and muscle preserved, respectively ($p < 0.001$); the corresponding 3-year DFS rates were 62.5 and 89.9%, respectively ($p < 0.001$; **Figure 4A**). The 3-year OS was 78.3 and 88.6% in the weight loss and weight preserved groups, respectively ($p = 0.18$); the corresponding 3-year DFS was 73.9 and 85.2%, respectively ($p = 0.19$; **Figure 4B**).

On univariate analysis, adenocarcinoma, malnourishment at the end of radiotherapy, pre-treatment sarcopenia, and muscle loss were associated with poor OS and DFS (**Table 3**). Multivariate analysis showed that adenocarcinoma and muscle loss were independently associated with poor OS and DFS. Malnourishment at the beginning of radiotherapy, pre-treatment BMI, and weight loss after treatment were not associated with OS or DFS. In a subgroup analysis of patients with squamous cell carcinoma ($n = 104$), pre-treatment sarcopenia and muscle loss after treatment were independently associated with poor OS. Muscle loss was independently associated with poor DFS;

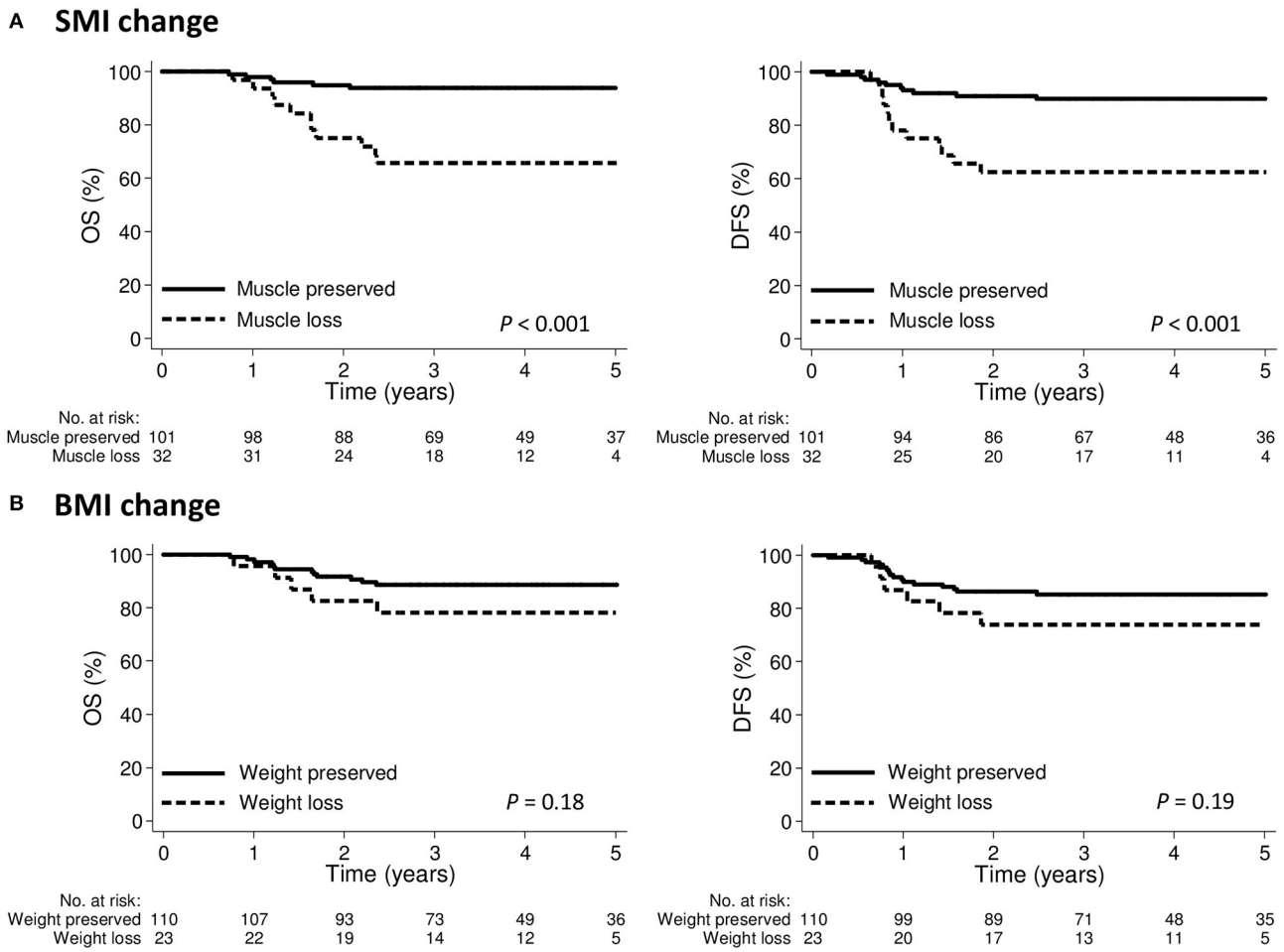

FIGURE 4 | Kaplan-Meier curve demonstrating overall survival and disease-free survival according to **(A)** SMI change or **(B)** BMI change groups. BMI, body mass index; SMI, skeletal muscle index.

however, pre-treatment sarcopenia was not associated with DFS (**Supplementary Table 1**).

DISCUSSION

This study found that skeletal muscle loss after surgery and adjuvant pelvic radiotherapy was associated with poor survival outcomes in patients with early-stage cervical cancer. However, pre-treatment sarcopenia, BMI, and weight loss after treatment were not independently associated with survival outcomes. In addition, skeletal muscle loss was associated with patient-reported GI toxicity and deterioration of nutritional status during pelvic radiotherapy.

The current role of adjuvant pelvic radiotherapy is to decrease the risk of pelvic recurrence in patients with early-stage cervical cancer; however, the outcomes of previous randomized trials indicate that pelvic radiotherapy may not have a benefit of better overall survival (2–4). Pelvic radiotherapy can cause GI toxicity in these patients and deteriorate their nutritional status and quality of life. We found that patients with severe GI toxicities were malnourished at the end of radiotherapy. Severe GI toxicity or malnourishment at the end of radiotherapy was also associated with significant muscle loss after treatment. Notably, patients with muscle loss had significantly poorer OS than those with preserved muscle. Considering the role of adjuvant pelvic radiotherapy mentioned above, we suggest that preservation of muscle mass should be a treatment goal to optimize the OS in these patients.

Skeletal muscle loss is associated with a higher risk of recurrence and overall and cancer-specific mortality in locally advanced cervical cancer (9–11). Although the patients in this study had early-stage cervical cancer, muscle loss was also associated with a higher risk of recurrence and mortality. Moreover, the most common histological type of cervical cancer is squamous cell carcinoma, and its clinical behavior is less aggressive than that of adenocarcinoma (39). In a subgroup analysis of patients with squamous cell carcinoma, muscle loss was associated with a higher risk of recurrence and mortality. This might be because skeletal muscle, as an endocrine organ, regulates the metabolism and inflammation in the entire body.

TABLE 3 | Univariate and multivariate analyses of factors associated with overall survival and disease-free survival.

		Overall survival				Disease-free survival			
		Univariate		Multivariate*		Univariate		Multivariate*	
Characteristics		**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age	continuous	0.99 (0.94–1.03)	0.55			0.99 (0.95–1.03)	0.64		
FIGO stage	IIA vs. IB	1.09 (0.38–3.08)	0.88			0.78 (0.29–2.12)	0.63		
Histology	AC vs. SCC	4.50 (1.73–11.67)	0.002	3.96 (1.50–10.43)	0.005	2.79(1.19–6.54)	0.02	2.44 (1.04–5.75)	0.04
Pelvc lymph node metastasis	Yes vs. No	0.70 (0.23–2.16)	0.54			1.06 (0.43–2.59)	0.91		
Parametrial involvement	Yes vs. No	1.58 (0.46–5.51)	0.47			1.20 (0.35–4.04)	0.77		
Positive surgical margin	Yes vs. No	2.42 (0.55–10.58)	0.24			1.87 (0.44–8.00)	0.40		
Lymphovascular space invasion	Yes vs. No	0.67 (0.24–1.89)	0.45			0.91 (0.32–2.59)	0.86		
Deep cervical stromal invasion	Yes vs. No	0.91 (0.32–2.59)	0.86			1.02 (0.40–2.62)	0.96		
Adjuvant treatment	CCRT vs. RT	0.81 (0.31–2.13)	0.67			0.96 (0.41–2.22)	0.92		
Malnourished at the start of RT**	Yes vs. No	1.98 (0.57–6.88)	0.29			2.10 (0.71–6.22)	0.18		
Malnourished at the end of RT**	Yes vs. No	3.15 (1.20–8.28)	0.02			2.25 (0.98–5.19)	0.06		
Pre-treatment BMI	continuous	0.89 (0.78–1.02)	0.10			0.97 (0.87–1.08)	0.53		
Weight loss ≥5% after treatment	Yes vs. No	2.01 (0.71–5.71)	0.19			1.87 (0.73–4.77)	0.19		
Pre-treatment sarcopenia	Yes vs. No	3.04 (1.16–7.99)	0.02	2.67 (0.99–7.17)	0.051	2.13 (0.92–4.92)	0.08		
Muscle loss ≥5% after treatment	Yes vs. No	6.26 (2.31–16.94)	<0.001	4.55 (1.63–12.72)	0.004	4.27 (1.84–9.89)	0.001	3.94 (1.69–9.19)	0.001

AC, adenocarcinoma; BMI, body mass index; CCRT, concurrent chemoradiotherapy; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; RT, radiotherapy; SCC, squamous cell carcinoma; SMI, skeletal muscle index.

** Multivariable analysis using a backward selection method.*

*** Malnourished defined as PG-SGA score ≥4.*

Changes in the metabolic and inflammatory status caused by muscle loss might create a favorable environment for cancer cell growth and disease recurrence (40–42). However, the mechanisms linking muscle loss, recurrence, and cancer-specific mortality need to be investigated in further studies.

Many factors can contribute to muscle loss, including malnutrition, treatment-related toxicity, systemic inflammation, physical inactivity, and aggressiveness of cancer itself (16). In this study, patients with severe GI toxicity or malnourished status at the end of radiotherapy had considerable muscle loss after treatment. Although supportive care such as medication or nutritional counseling was provided to these patients when GI toxicity or malnutrition occurred, there is a need for more effective interventions to preserve skeletal muscle, particularly for patients with PRO-CTCAE score ≥3 or malnourished status at the end of pelvic radiotherapy. Considering that the pathophysiology of muscle loss is multifactorial (43), multimodal interventions (nutrition, exercise, and anabolic medication) might help preserve skeletal muscle. The timing and duration of interventions should also be considered because it can take months to restore rapid muscle loss during cancer treatment (44–46). Moreover, our previous study reported that bowel radiation dose-volume is associated with muscle loss during pelvic radiotherapy (8). It is interesting to classify patients into a lower or higher risk of muscle loss based on patients' conditions and bowel radiation dose-volume and may design targeted multimodal supportive care for patients with a higher risk of muscle loss. Future studies are needed.

Skeletal muscle loss may not be detected by measuring body weight during cancer care. Although the changes in BMI were moderately correlated with changes in SMI in this study, evidence has revealed that changes in the adipose tissue could confound the interpretation of the changes in BMI and mask the detection of muscle loss (18). Moreover, pre-treatment BMI or weight loss after treatment was not associated with survival outcomes in our patients. In previous studies that evaluated patients with locally advanced cervical cancer, the prognostic role of BMI was debatable, while muscle loss was associated with poorer survival outcomes (9–12). These findings suggest the relevance of integrating muscle measurements into clinical practice. In this study, we used CT scans acquired during cancer care to measure skeletal muscle. However, CT scans might not be available for all patients with cervical cancer. This is because MRI might be preferred due to its higher ability to evaluate the

local invasion of cervical cancer. The interchangeability of CT- and MRI-derived measurements of the cross-sectional area at superior mesenteric artery level has been reported, suggesting that it might be feasible to evaluate skeletal muscle using MRI (47). Further studies are needed to evaluate the interchangeability of CT and MRI-derived skeletal muscle measurement at the level of L3 in cervical cancer. Our findings also need to be validated in future studies.

This study had some limitations. This is a retrospective investigation with a small number of patients and limited follow-up duration. The sample size of this study was inadequate to draw a firm conclusion (48, 49). Longer follow-up is also needed to provide a more comprehensive view of the effects of skeletal muscle loss on outcomes. Information such as quality of life was not available for analysis owing to the retrospective design of the study. Selection bias and residual and unmeasured confounding factors are also potential limitations of this retrospective study. Despite these limitations, the strength of our study is that patients received very similar treatments, and there were patient-reported outcomes of GI toxicity assessment and nutritional assessment. The treatment outcomes were comparable to those reported in previous studies (4–6).

In summary, our findings showed that skeletal muscle loss after surgery and adjuvant pelvic radiotherapy was independently associated with poor survival outcomes in patients with early-stage cervical cancer. Muscle loss is also associated with GI toxicity and deterioration of nutritional status. While adjuvant pelvic radiotherapy can reduce the risk of pelvic recurrence, it is important to preserve the muscle to optimize survival outcomes for these patients. Future studies are necessary to evaluate whether early multimodal interventions can preserve the muscle in these patients.

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 MacKay Memorial Hospital and Changhua Christian Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JL, J-BL, and M-HW designed the research. JL and J-BL analyzed data and wrote this manuscript. T-CC contributed in performing the research. Y-TJ contributed in performing the image data analysis. F-JS conducted the statistical analysis. Y-JC revised this manuscript critically for important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.773506/full#supplementary-material

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Impact of Body Composition During Neoadjuvant Chemoradiotherapy on Complications, Survival and Tumor Response in Patients With Locally Advanced Rectal Cancer

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Background: To explore the impact of body composition before neoadjuvant chemoradiotherapy (pre-NCRT) and after neoadjuvant chemoradiotherapy (post-NCRT) on complications, survival, and tumor response in patients with locally advanced rectal cancer (LARC).

Methods: Patients with LARC who underwent radical surgery after NCRT between Ja 22nuary 2012 and March 2019 were studied. Body composition parameters, including skeletal muscle area (SMA), muscle density (MD), visceral fat area (VFA), total abdominal fat area (TAFA), and subcutaneous fat area (SFA), was identified at the third lumbar vertebra level on computed tomography (CT). The patients were divided into two groups based on the sex-specific quartile values of SMA, MD, VFA, TAFA, SFA, and body composition change. Patient characteristics, short- and long-term postoperative complications, survival, and tumor response were analyzed.

Results: A total of 122 eligible patients were enrolled. Body composition parameters, except MD, were strongly correlated with BMI ($p < 0.001$). Pre-NCRT low MD ($p = 0.04$) and TAFA loss ($p = 0.02$) were significantly correlated with short- and long-term ileus, respectively. Pre-NCRT low SMA was a significant prognostic factor for both disease-free survival (DFS) (HR 2.611, 95% CI 1.129–6.040, $p = 0.025$) and cancer-specific survival (CSS) (HR 3.124, 95% CI 1.030–9.472, $p = 0.044$) in the Cox regression multivariate analysis. Multivariate logistic regression analysis identified post-NCRT SFA (OR 3.425, 95% CI 1.392–8.427, $p = 0.007$) and SFA loss (OR 3.358, 95% CI 1.214–9.289, $p = 0.02$) as independent risk factors for tumor regression grade (TRG) and downstaging, respectively.

Conclusion: Pre-NCRT low MD and TAFA loss were related to a high incidence of short- and long-term ileus, respectively. Pre-NCRT low SMA was a significant prognostic factor for CSS and DFS. Post-NCRT SFA and SFA loss were independent risk factors for TRG and downstaging, respectively.

Keywords: body composition, rectal cancer, complications, prognosis, tumor response

BACKGROUND

Colorectal cancer is one of the most common cancers worldwide and is the second leading cause of cancer-related deaths (1). Rectal cancer accounts for nearly 30% of all colorectal cancers (2). Despite progress in standard treatment for locally advanced rectal cancer (LARC) and neoadjuvant chemoradiotherapy (NCRT) with total mesorectal excision, LARC patients are still burdened by considerable risks of morbidity and metastasis (3–5). Moreover, tumor response after NCRT is a critical reference index for the subsequent treatment and prognosis of patients (6, 7). Hence, preoperative modifiable risk factors that could potentially identify complications, survival prospects, and tumor response in LARC patients are needed to stratify patients with high-risk status and guide tailored treatment.

Cancer-related inflammation and malnutrition are highly prevalent in cancer patients and are essential predictors of complications, survival, and tumor response (8, 9). Patients with cancer-related inflammation and malnutrition are more prone to obtaining a reduced therapeutic effect and experiencing increased chemotherapy toxicity (10–13). Previous studies indicated that a scoring system combining inflammatory and nutritional parameters plays an essential role in predicting outcomes, cancer treatment results and survival (14, 15). Body composition identified from computed tomography (CT) at the third lumbar cross-section of skeletal muscle and fat area is considered an essential biomarker that reflects both inflammatory and nutritional statuses, and its association with cancer outcomes is gaining attention (16, 17). In addition, unlike body mass index (BMI), which neglects the role of sex and is unable to differentiate between muscle mass and fat mass or to characterize the distribution of adipose tissue, body composition could reflect the "real" status of cancer patients more precisely (18–20).

Recently, several meta-analyses have shown the value of CT-based specific profiles of the muscle and adipose parameters (body composition) in predicting short- and long-term outcomes in several cancers (21–23). Skeletal muscle depletion was identified as an independent risk factor for survival in non-metastatic colorectal cancer (13). In rectal cancer, CT-quantified adipose tissue distribution was strongly associated with postoperative complications (24). Furthermore, Chung et al. (25) analyzed 93 LARC patients and found that the change in muscle mass might be a promising parameter to predict overall survival. Notwithstanding, several studies have assessed the relationship between CT-based body composition and LARC, but these studies did not thoroughly assess pre- and post-NCRT body composition and the change in body composition or determine which specific parameters might be risk factors for postoperative morbidity, long-term oncological outcome, and tumor response.

Hence, our study aimed to analyze pre- and post-NCRT body composition parameters and the change in body composition during NCRT to assess the relationship between nutritional status and body composition parameters and to identify whether different body composition parameters could be predictive of short- and long-term complications, survival, and tumor response in a homogenous group of patients with LARC.

METHODS

Study Population

A total of 122 patients with LARC with prospective follow-up data treated at the Department of General Surgery at Peking University Third Hospital were retrospectively analyzed between January 2012 and March 2018. The inclusion criteria were as follows: (1) pre-NCRT colonoscopy pathology confirming the diagnosis of adenocarcinoma; (2) diagnosis of LARC through pre-NCRT CT and magnetic resonance imaging (MRI); (3) all patients underwent NCRT followed by radical surgery; and (4) complete inpatient data, including pre- and post-NCRT CT scans and follow-up data. The exclusion criteria were as follows: (1) presence of other cancers in addition to rectal adenocarcinoma; (2) presence of lumbar metal implants; and (3) management by a watch and wait strategy after NCRT. Ethical approval was obtained from Peking University Third Hospital (IRB00006761-M2019387), and this study adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board of Peking University Third Hospital.

NCRT Treatment

All patients were treated with the same NCRT treatment scheme. The decision to administer NCRT or conduct radical resection was made by a multidisciplinary team, which consisted of surgeons, oncologists, pathologists, and radiologists. Radiation doses ranged from 45 to 50 Gy given across 25 fractions. Radiation was given according to institutional protocols. The oral capecitabine dosage during the whole course of radiotherapy (RT) was 1,650 mg/m^2 per day. The American Joint Committee on Cancer (AJCC) eighth edition classification standard recommended by the National Comprehensive Cancer Network (NCCN) guidelines was adopted for the pathological staging of the patients. The AJCC tumor regression grade (TRG) definitions were as follows: TRG0, no sign of tumor cells; TRG1, single tumor cell or small groups of tumor cells; TRG2, residual cancer with a desmoplastic response (mild regression); and TRG3, no tumor cells killed. In this study, TRG0-1 was defined as a good response, while TRG2-3 was defined as a poor response. A decline in postoperative staging compared to clinical staging was defined as downstaging.

Measurement and Definition of Body Composition

We retrospectively measured pre-NCRT (before starting NCRT) and post-NCRT (8–12 weeks after the cessation of NCRT) cross-sectional CT images in the supine position, taken at the level of the third lumbar vertebra (L3). A Java-based open-source image processing software, ImageJ software v1.47i (National Institutes of Health, Bethesda, MD), was used to determine skeletal muscle and fat tissue areas (26). The following tissue Hounsfield unit (HU) thresholds were employed:−29 to 150 HU for skeletal muscle, and −190 to −30 HU for adipose tissue (**Supplementary Figure 1**) (26). Muscle density (MD) was calculated through the mean HU of the skeletal muscle area (SMA). SMA, visceral fat area (VFA), total

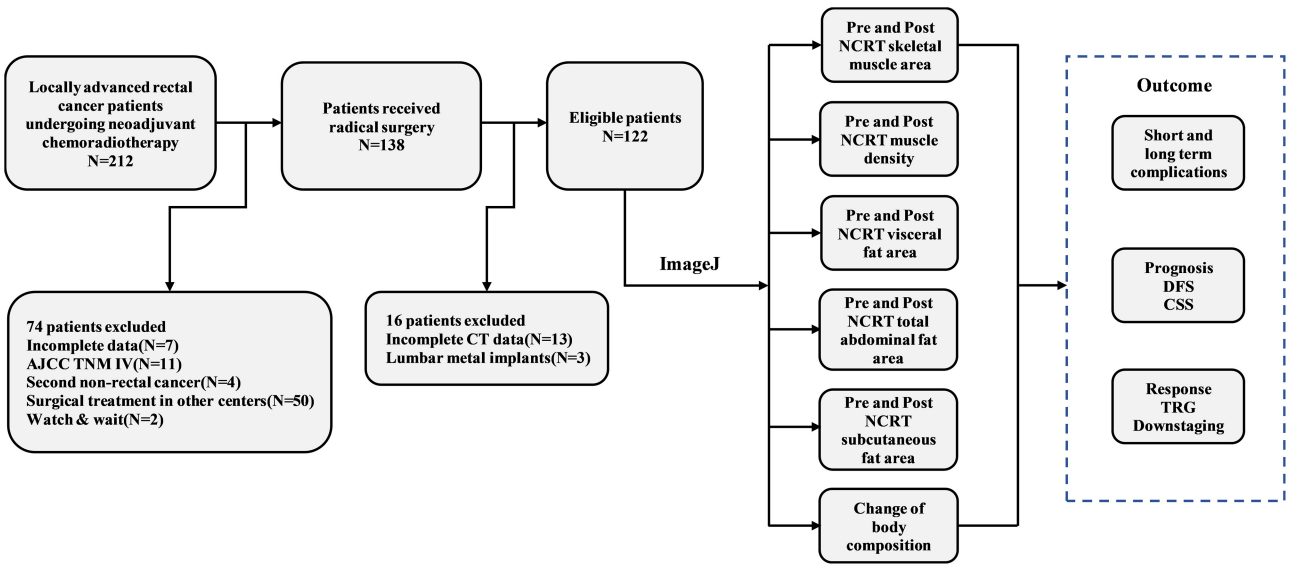

FIGURE 1 | Flow chart of the study.

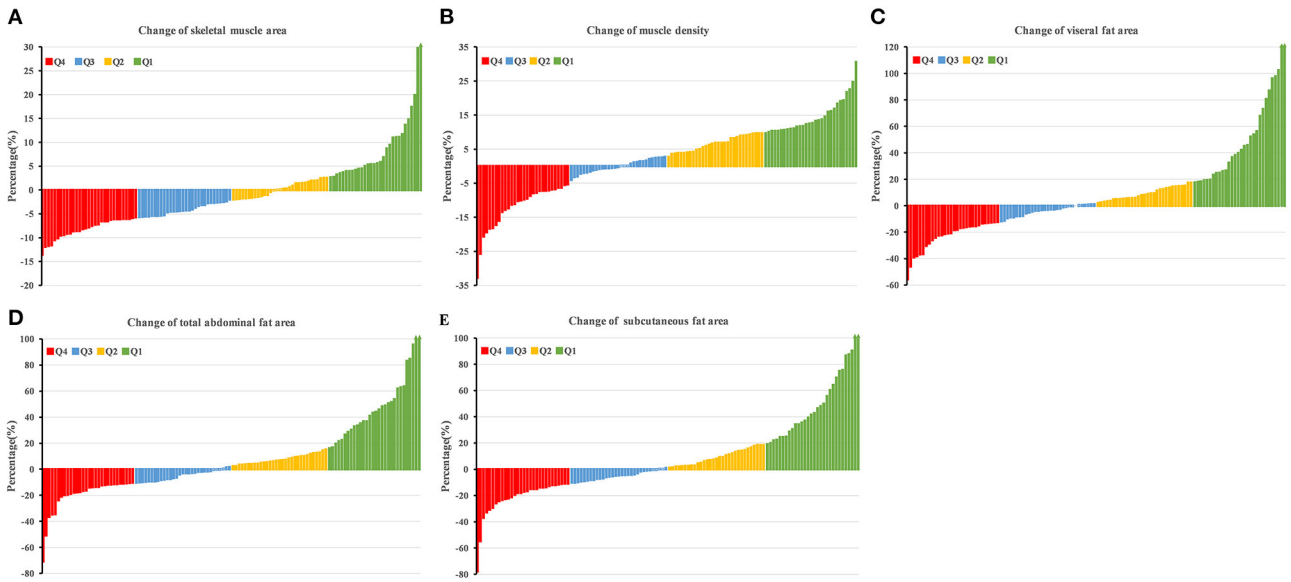

FIGURE 2 | Change of skeletal muscle area **(A)**, muscle density **(B)**, visceral fat area **(C)**, total abdominal fat area **(D)**, subcutaneous fat area **(E)** during NCRT. Q1, Q2, Q3, and Q4 have represented the highest quartile, 50–75%, 25–50%, and lowest quartile, respectively.

abdominal fat area (TAFA), and subcutaneous fat area (SFA) were normalized by the square of height (m^2). SMA and MD were divided into low and normal groups according to the lowest sex-specific quartile cutoff values, and VFA, TAFA and SFA were divided into high and normal groups according to the highest sex-specific quartile cutoff values (27). The change in body composition was initially expressed as a percentage calculated by (post-NCRT body composition–pre-NCRT body composition)/pre-NCRT body composition × 100. We dichotomized our patients into a body composition loss group and a normal group according to the lowest quartile cutoff values (25).

Outcome Parameters

Short-term complications included overall complications, ileus, surgical site infection (SII), unplanned reoperation, and Clavien-Dindo (CD) classification of complications (28). Long-term complications included ileus, delayed reversal, reversal failure, radiation proctitis, and anastomotic stricture. Survival outcomes included cancer-specific survival (CSS) and disease-free survival

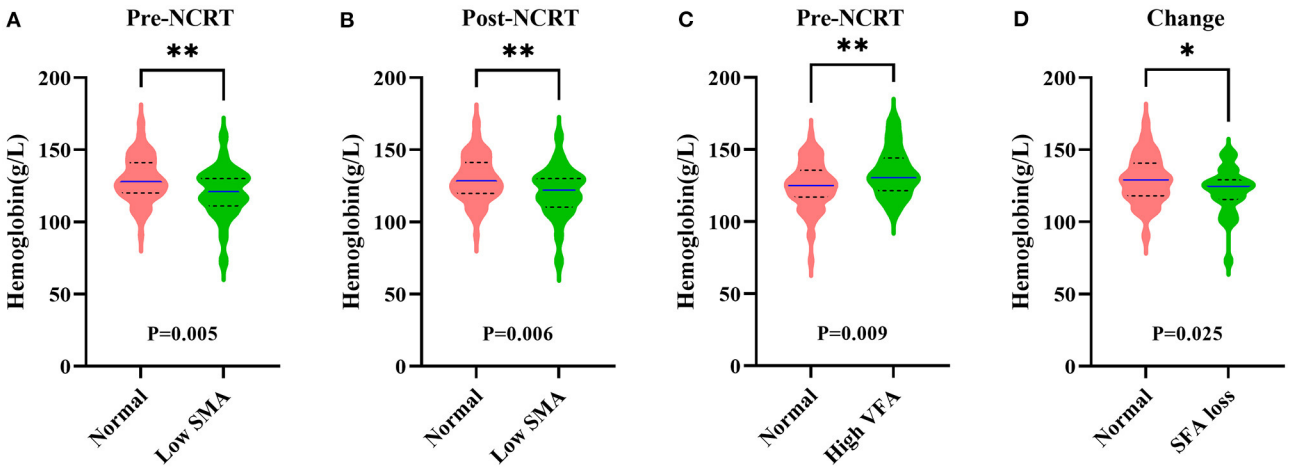

FIGURE 3 | Correlation among hemoglobin and pre-NCRT skeletal muscle area **(SMA) (A)**, post-NCRT SMA **(B)**, pre-NCRT visceral fat area **(VFA) (C)**, subcutaneous fat area **(SFA)** loss **(D)**. The *symbol indicates $p < 0.05$ and **symbol indicates $p < 0.01$.

(DFS). CSS was defined as the period from surgical treatment to the date of death caused by rectal cancer. DFS was defined as the period from surgical treatment to tumor recurrence. Tumor response included TRG and tumor downstaging.

Statistical Analysis

The Kolmogorov–Smirnov method was used to determine the normality of the data. Normally distributed data are expressed as the means ± standard deviations and were analyzed using independent sample *t*-test, while skewed data are expressed as the medians (interquartile ranges) and were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Factors that influenced tumor response were assessed using logistic regression, and factors that influenced DFS and CSS were assessed using Cox regression. Potential risk factors ($p < 0.1$) were adopted for the multivariate analysis with the backward stepwise method, following the results of the univariate analysis. Survival curves were drawn using the Kaplan–Meier method owing to the significant difference observed in the follow-up time of the patients; thus, all survival analyses were targeted at the cumulative survival rate of the patients. Time-dependent receiver operating characteristic (ROC) analysis to compare the prognostic values of the markers for DFS and CSS was performed by the "timeROC" package in R version 3.5.2. All statistical analyses were conducted using SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA). A *p*-value of < 0.05 was recognized as statistically significant.

RESULTS

Patient Characteristics

According to the inclusion and exclusion criteria, 122 patients were eventually enrolled in the study. A detailed flow chart of the patient selection process and outcomes is shown in **Figure 1**. Among the study population, 88 patients were male (71.5%), with a mean age of 60 years (range 22–82). The mean BMI was 23.9 kg/m^2 (range 15.2–32.9) for men and 24.4 kg/m^2 (range 19.1–30.1) for women. Sixty-three (43.7%) patients had tumor size > 4 cm, while 75 (54.3%) had tumor size ≤ 4 cm. Thirty-nine (32.0%) patients had tumors in the lower rectum, while the remaining 83 (68.0%) patients had tumors in the mid-high rectum. A total of 24 (19.7%) patients had clinical stage T4 disease, and 91 (74.6%) patients had clinically positive lymph nodes. Eighteen (14.8%) patients achieved ypT0N0M0 after NCRT, and 89 (76.6%) patients achieved downstaging after NCRT. According to the four-tier AJCC-TRG system, 72 (59%) patients were TRG0-1, while 50 (41%) patients were TRG2-3. The detailed baseline clinicopathological characteristics of the patients are shown in **Supplementary Table 1**.

Impact of Neoadjuvant Therapy on Body Composition

The median pre-NCRT SMA, MD, VFA, TAFA, and SFA were 46.47 cm^2/m^2, 37.04 HU, 48.99 cm^2/m^2, 103.12 cm^2/m^2, and 43.46 cm^2/m^2, respectively, while the median of post-NCRT SMA, MD, VFA, TAFA, and SFA were 45.88 cm^2/m^2, 37.75 HU, 46.93 cm^2/m^2, 104.20 cm^2/m^2, and 45.35 cm^2/m^2. No statistically significant difference was observed between pre-NCRT and post-NCRT body composition ($p > 0.05$). The median changes in SMA, MD, VFA, TAFA, and SFA were −0.65, 2.29, 9.4, 8.24, and 9.67%, respectively. Overall, the distribution of % change in body composition during NCRT is shown in **Figure 2**. The detailed body composition parameters and the change in body composition of LARC patients are shown in **Supplementary Table 2**.

Body Composition and Nutritional Status (BMI, ALB, FIB, and HB)

We further explored the relationship between body composition and nutrition status. Except for pre- and post-NCRT MD, BMI was strongly correlated with pre- and post-NCRT body

TABLE 1 | Correlation of body composition and short- and long-term complications.

Variable	Short-term complications					Long-term complications				
	Complications *N* = 26	**Ileus *N* = 11**	**SSI *N* = 12**	**Unplanned reoperation *N* = 5**	**CD > III *N* = 10**	**Ileus *N* = 10**	**Reversal delayed *N* = 54**	**Reversal failure *N* = 8**	**Radiation proctitis *N* = 7**	**Anastomotic stricture *N* = 7**
	***P*-value[a]**	***P*-value[b]**	***P*-value[b]**	***P*-value[b]**	***P*-value[b]**	***P*-value[b]**	***P*-value[a]**	***P*-value[b]**	***P*-value[b]**	***P*-value[b]**
Pre-NCRT										
Low SMA	0.758	1.000	1.000	0.419	0.430	1.000	0.537	1.000	0.607	1.000
Low MD	0.755	**0.040**	0.750	1.000	0.975	0.425	0.409	0.781	1.000	1.000
High VFA	0.474	1.000	0.750	0.178	0.975	0.462	0.368	0.315	0.386	1.000
High TAFA	0.840	0.376	0.698	0.774	0.975	0.462	0.368	0.315	0.344	1.000
High SFA	0.755	0.880	1.000	1.000	0.975	0.975	1.000	1.000	0.949	0.949
Post-NCRT										
Low SMA	0.360	1.000	1.000	1.000	0.926	0.511	0.465	1.000	0.800	1.000
Low MD	0.928	0.659	0.808	1.000	1.000	0.511	1.000	0.618	0.371	1.000
High VFA	0.840	1.000	1.000	1.000	1.000	0.462	0.625	1.000	0.307	0.949
High TAFA	0.840	1.000	1.000	0.439	0.462	0.462	1.000	0.963	0.307	0.949
High SFA	0.064	0.559	0.698	1.000	0.975	0.462	1.000	1.000	0.386	1.000
Change										
SMA loss	0.680	0.659	0.255	0.845	1.000	0.159	0.683	1.000	1.000	0.720
MD loss	0.409	1.000	0.274	0.774	0.975	0.462	0.138	1.000	1.000	1.000
VFA loss	0.474	0.880	0.750	0.178	0.425	0.118	0.845	1.000	0.949	1.000
TAFA loss	0.474	1.000	0.750	0.178	0.425	**0.020**	1.000	0.700	0.872	0.872
SFA loss	0.219	1.000	0.306	1.000	1.000	1.000	0.611	1.000	1.000	1.000

SSI, surgical site infection; CD, Clavien-Dindo classification; SMA, skeletal muscle area; MD, muscle density; VFA, visceral fat area; TAFA, total abdominal fat area; SFA, subcutaneous fat area.

[a] *Chi-square test.*

[b] *Fisher's exact test.*

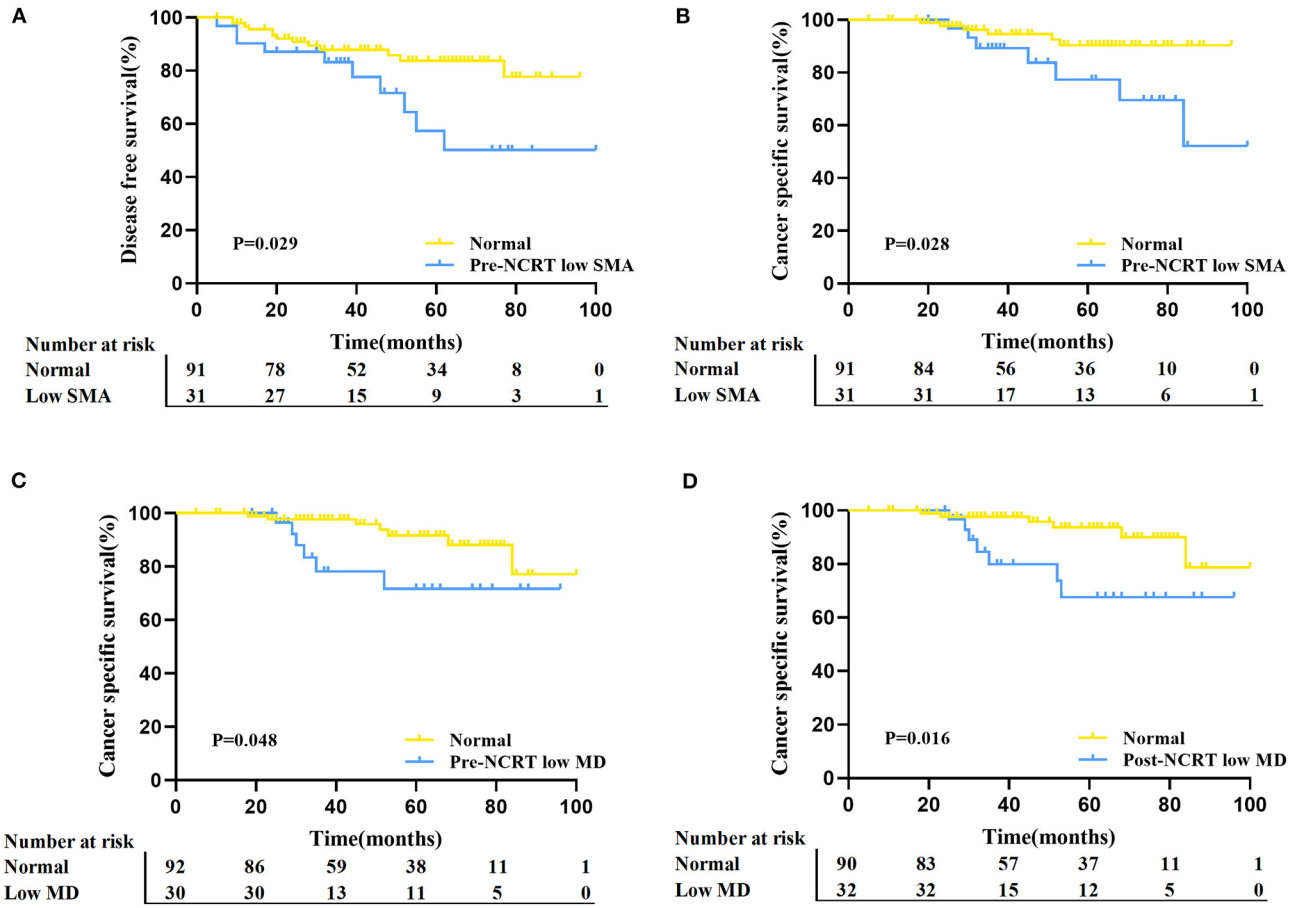

FIGURE 4 | Comparison of DFS and CSS between the different status of body composition in LARC patients. **(A)** Kaplan–Meier analysis for DFS rate between normal and pre-NCRT low SMA groups in LARC patients ($p = 0.029$). **(B)** Kaplan–Meier analysis for the CSS rate between normal and pre-NCRT low SMA groups in LARC patients ($p = 0.028$). **(C)** Kaplan–Meier analysis for CSS rate between normal and pre-NCRT low MD groups in LARC patients ($p = 0.048$). **(D)** Kaplan–Meier analysis for the CSS rate between normal and post-NCRT low MD in LARC patients ($p = 0.016$).

composition ($p < 0.001$; **Supplementary Table 3**) and weakly correlated with the change in body composition ($p > 0.05$). There was no significant difference in albumin (ALB) for body composition and change in body composition. Fibrinogen (FIB) was only associated with pre-NCRT SMA ($p = 0.041$). With regard to hemoglobin (HB), there were significant differences in the pre- and post-NCRT low SMA groups ($p = 0.005$; $p = 0.006$), pre-NCRT high VFA group ($p = 0.009$), SFA loss group ($p = 0.025$) and normal group according to the Mann-Whitney U test (**Figure 3**).

Short- and Long-Term Complications and Body Composition

A chi-square test was conducted to determine whether body composition was closely correlated with short- and long-term complications. All short- and long-term complication outcomes are included in **Table 1**. Twenty-six (21.3%) patients experienced a short-term complication, and the rates of ileus, SSI, unplanned reoperation, and CD>III were 9% (11 cases), 9.8% (12 cases), 4.1% (5 cases), and 8.2% (10 cases), respectively. Among all body composition parameters, pre-NCRT low MD (p = 0.04) was related to short-term ileus. The other indicators were not associated with short-term complications. Concerning long-term complications, 10 (8.2%) of 122 patients experienced long-term ileus, while 7 (10.3%) of 68 patients who underwent Dixon operation suffered from radiation proctitis and anastomotic stricture. Of the 63 patients who underwent preventive diverting stoma, 8 (12.7%) failed to undergo reversal. A total of 54 patients underwent stoma reversal, and 37 (68.5%) patients' reversal later than 6 months after surgery was considered delayed. Only TAFA loss ($p = 0.02$) was associated with long-term ileus.

Time-Dependent ROC Curve of Body Composition and Change in Body Composition

Time-dependent ROC analysis was conducted to compare the ability of body composition to predict DFS and CSS. In the first, third, fourth, fifth, and sixth years after surgery, the AUCs of pre-NCRT SMA for predicting DFS continued to be superior to those

TABLE 2 | Cox proportion independent predictors of DFS and CCS in LARC patients.

	DFS		CSS					
	Univariate HR (95%CI)	Multivariate *P*-value	Univariate HR (95%CI)	Multivariate *P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Gender (male vs. female)	0.600 (0.222–1.623)	0.314	-	-	0.324 (0.071–1.486)	0.147	-	-
Age, years	1.008 (0.976–1.042)	0.617	-	-	1.022 (0.976–1.070)	0.358	-	-
BMI (kg/m^2)	0.945 (0.831–1.074)	0.387	-	-	0.884 (0.774–1.052)	0.165	-	-
Tumor size (>4 vs. ≤4 cm)	2.915 (0.865–9.826)	0.084	-	-	4.844 (0.628–37.383)	0.130	-	-
Surgery procedure	-	0.592	-	-	-	0.270	-	-
Miles vs. hartmann	0.574 (0.168–1.962)		-	-	0.588 (0.140–2.474)	0.469	-	-
Dixon vs. hartmann	0.567 (0.183–1.758)		-	-	0.310 (0.073–1.323)	0.114	-	-
Tumor location			-	-	-	-	-	-
Low vs. mid-high	0.774 (0.305–1.965)	0.589	-	-	0.737 (0.203–2.681)	0.643	-	-
cT (cT4 vs. cT2-3)	3.066 (1.291–7.283)	**0.011**	2.811 (1.165–6.780)	**0.021**	2.966 (0.956–9.197)	0.060	2.944 (0.940–9.226)	0.064
cN (negative vs. positive)	4.539 (1.062–19.400)	**0.041**	3.820 (0.888–16.437)	0.072	34.598 (0.217–5513.741)	0.171	-	-
ypTNM (0 vs. I–III)	0.457 (0.107–1.956)	0.291	-	-	0.431 (0.56–3.349)	0.421	-	-
CEA (>5 vs. ≤5 ng/L)	2.404 (0.947–6.105)	0.065	-	-	2.488 (0.755–8.204)	0.134	-	-
Pre-NCRT low SMA vs. normal	2.429 (1.063–5.549)	**0.035**	2.611 (1.129–6.040)	**0.025**	3.200 (1.072–9.558)	**0.037**	3.124 (1.030–9.472)	**0.044**
Pre-NCRT low MD vs. normal	2.070 (0.895–4.789)	0.089	-	-	2.880 (0.963–8.619)	0.059	-	-
Post-NCRT low MD vs. normal	-	-	-	-	3.532 (1.181–10.557)	**0.024**	3.006 (1.003–9.008)	**0.049**

HR, hazard ratio; CI, cofidence interval; cT, clinical T stage; cN, clinical N status; ypTNM, post neoadjuvant pathological TNM stage; CEA, carcinoembryonic antigen; SMA, skeletal muscle area; MD, muscle density. The bold values represent P<0.05.

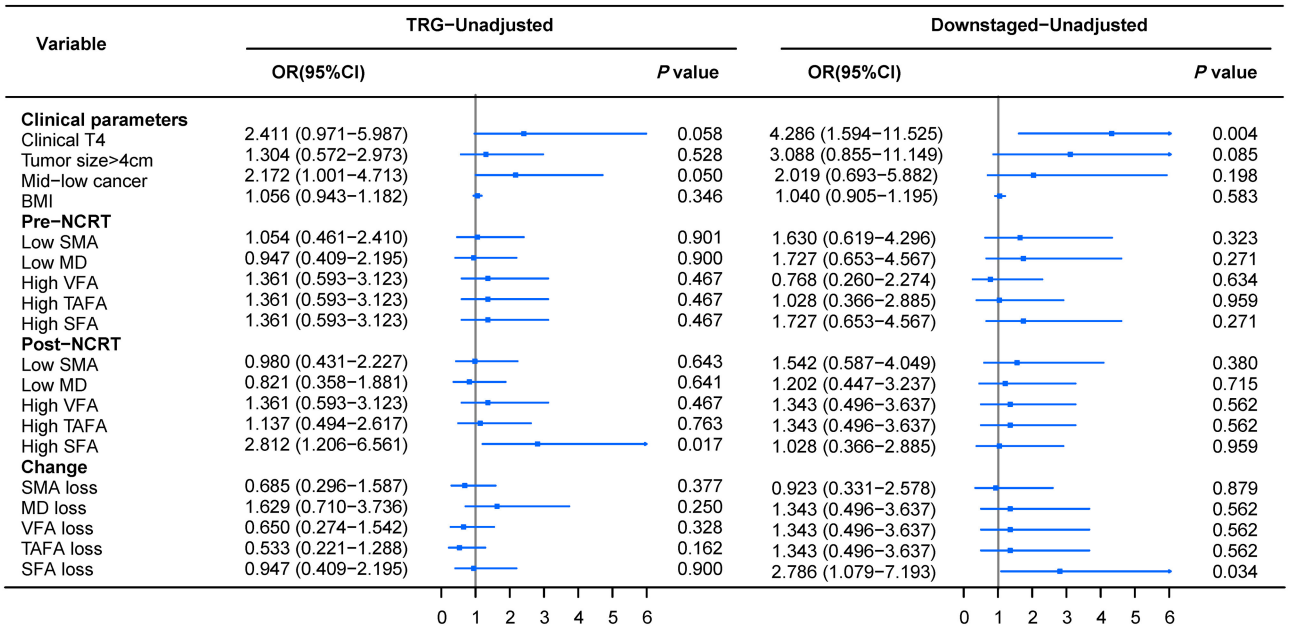

FIGURE 5 | Forrest plot of unadjusted logistic regression to assess the discrimination ability of body composition for tumor TRG and downstaging.

of other parameters (**Supplementary Figure 2A**). Meanwhile, the time-dependent ROC curve for CSS showed that pre-NCRT SMA has a relatively stable ability in predicting CSS (**Supplementary Figure 2B**). The AUCs of pre-NCRT SMA for predicting 1-, 2-, 3-, 4-, 5-, and 6-year DFS were 0.678, 0.549, 0.544, 0.621, 0.64, and 0.626, respectively. Meanwhile, the AUCs of pre-NCRT SMA for predicting 2-, 3-, 4-, 5-, 6- and 7-year CSS were 0.537, 0.593, 0.649, 0.608, 0.15, and 0.744, respectively.

Long-Term Outcomes and Body Composition

The follow-up time ranged from 5 to 100 months, and the median follow-up time was 46.5 months. Thirteen (10.7%) patients had died at the last follow-up, and local recurrence with or without metastasis occurred in 23 (18.9%) patients among the 122 enrolled patients. With regard to DFS, pre-NCRT low SMA ($p = 0.029$) was significantly correlated with poor DFS according to Kaplan-Meier analysis (**Figure 4A**), and the cumulative 5-year DFS rate of pre-NCRT low SMA was 57.3%. Regarding CSS, pre-NCRT SMA and pre- and post-NCRT MD could distinguish patients with poor CSS (**Figures 4B–D**), and the cumulative 5-year DFS rates were 77.3, 71.7, and 67.6%, respectively. The other body composition parameters failed to differentiate survival in LARC patients (**Supplementary Figures 3, 4**).

Cox regression analysis was conducted further to demonstrate the prognostic value of body composition. Univariate analysis showed that clinical T stage, clinical lymph node status, and pre-NCRT SMA were significantly associated with DFS (**Table 2**). Multivariate analysis indicated that both pre-NCRT low SMA (HR 2.611, 95% CI 1.129–6.040, $p = 0.025$) and clinical stage T4 (HR 2.811, 95% CI 1.165–6.780, $p = 0.021$) were independent prognostic factors of poor DFS in LARC patients undergoing radical surgery following NCRT. Meanwhile, univariate analysis showed that pre-NCRT SMA and post-NCRT MD were also significantly associated with CSS (**Table 2**). Subsequent multivariate analysis showed that pre-NCRT low SMA (HR 3.124, 95% CI 1.030–9.472, $p = 0.044$) and post-NCRT low MD (HR 3.532, 95% CI 1.181–10.557, $p = 0.024$) were independent risk factors for CSS (**Table 2**).

Tumor Response and Body Composition

Finally, logistic regression analysis was performed based on TRG and downstaging to further determine the clinical utility of body composition in predicting tumor response to NCRT. In the univariate logistic regression analysis of TRG, post-NCRT high SFA was associated with a poor response, while the other body composition parameters were not (**Figure 5**). Concerning downstaging, cT4 and SFA loss were strongly correlated with poor downstaging (**Figure 5**). In multivariate logistic regression analysis, post-NCRT low SFA (OR 3.425, 95% CI 1.392–8.427, $p = 0.007$) and SFA loss (OR 3.358, 95% CI 1.214–9.289, $p = 0.02$) remained significantly associated with TRG and downstaging, respectively. Detailed data are shown in **Tables 3**, **4**.

DISCUSSION

We used CT-based pre- and post-NCRT body composition and change in body composition to explore potential markers to predict short- and long-term complications, survival, and tumor response. First, no significant change was observed in body composition during NCRT. Second, we found a strong correlation between nutritional status and specific body

TABLE 3 | Multivariate logistic regression analysis for TRG in LARC patients.

Variables	Score	*N*	Multivariate OR (95%CI)	*P*-value
cT	cT2-3	98	1 (-)	-
	cT4	24	3.801 (1.413–10.224)	**0.008**
Tumor location	Mid-High	83	1 (-)	-
	Low	39	2.666 (1.153–6.163)	**0.022**
Post-High SFA	Low	92	1 (-)	-
	High	30	3.425 (1.392–8.427)	**0.007**

OR, odds ratio; CI, confidence interval; cT, clinical T stage; SFA, subcutaneous fat area. The bold values represent P<0.05.

TABLE 4 | Multivariate logistic regression analysis for downstaged LARC patients.

Variables	Score	*N*	Multivariate OR (95%CI)	*P*-value
cT	cT2-3	98	1 (-)	-
	cT4	24	5.003 (1.765–14.188)	**0.002**
Tumor size	≤4 cm	33	1 (-)	-
	>4 cm	89	0.205 (0.112–1.600)	0.205
SFA change	Normal	92	1 (-)	-
	Loss	30	3.358 (1.214–9.289)	**0.020**

OR, odds ratio; CI, confidence interval; cT, clinical T stage; SFA, subcutaneous fat area. The bold values represent P<0.05.

composition parameters. Third, we found that pre-NCRT MD and TAFA loss significantly correlated with short- and long-term ileus, respectively. Fourth, we found that pre-NCRT low SMA was an independent risk factor for both DFS and CSS through Cox regression analysis. Finally, through logistic regression, we found that subcutaneous fat tissue and its change during NCRT were independent risk factors for TRG and downstaging, respectively. This study demonstrated that specific indicators of body composition are promising predictors of specific types of complications, survival, and tumor response in LARC patients.

In previous studies, BMI was widely adopted to predict the postoperative short- and long-term outcomes of cancer patients because it is relatively easy to collect in large studies; however, it is also well known to be a less effective measure of body composition, overlooking the role of sex and the proportions of muscle and fat tissue (18–20). Our findings also reflect the same phenomenon as previous studies, as BMI showed weak correlations with survival and tumor response. Conversely, in our study, body composition showed a good ability to predict postoperative complications, survival, and tumor response in LARC patients. Additionally, abdominal CT examinations are routinely performed pre- and post-NCRT, confirming that body composition is a better standard parameter for LARC patients. CT-based body composition analyses have been performed in the clinic in the European population for decades, and a common cutoff value for body composition is well defined. However, the body composition of the Asian population is significantly different from that of the European population. The optimal cutoff value for body composition in the Asian population is still unclear. Miyamoto et al. found that the sex-specific quartile cutoff value of body composition was suitable for the Asian population, and skeletal muscle depletion according to this cutoff value was closely correlated with high mortality in colorectal cancer (27). For practical reasons to improve discrimination, we dichotomized our patients into different groups according to the sex-specific quartile value.

Sheikhbahaei et al. reported that prostate cancer patients suffer from a significant reduction in muscle mass and an increase in subcutaneous adiposity during NCRT (29). Interestingly, no apparent change in body composition was observed in our study, which is consistent with the findings of Chung et al.'s and De Nardi et al.'s study in LARC patients (25, 30). This is probably due to the difference in the timing of post-NCRT imaging. In Chung et al.'s, De Nardi et al.'s and our study, all patients underwent post-NCRT imaging 4–12 weeks after NCRT compared with 3–12 months in Sheikhbahaei et al.'s study. This finding indicates no significant difference in body composition in the population receiving neoadjuvant therapy in a short period.

Recently, a study of 1,630 stage I to III colon cancer patients indicated that low SMA and low MD were associated with a longer length of stay and a higher risk of postsurgical complications (31). A published study by Heus et al. that measured visceral obesity at L3-L4 of the preoperative CT scan demonstrated that VFA $\geq$100 cm^2 was associated with a higher occurrence of complications in patients with advanced ovarian cancer undergoing cytoreductive surgery (32). These studies all suggested that body composition parameters might be promising predictors of postsurgical complications in cancer patients. However, these findings were restricted to complications within 30 days after surgery, and the correlation between long-term postoperative morbidity and body composition remains unclear. Hence, we comprehensively analyzed the relationship between body composition and short- and long-term complications. Pre-NCRT low MD was correlated with a higher incidence of short-term ileus in LARC patients, while TAFA loss was correlated with a higher incidence of long-term ileus. However, we did not find an association between muscle mass and short- and long-term complications. In line with our results, Chung et al. and De Nardi et al. also showed no association between skeletal muscle and postoperative complications, and explained that due to the shorter gap between CT scans and surgery (25, 30). The change in muscle mass was not been observed in that short gap, thus significant impact on muscle mass in complications could not be observed.

To explore the relationship between body composition and prognosis in LARC, we conducted a multivariate analysis of DFS and CSS. Pre-NCRT low SMA was an independent risk factor for both DFS (HR 2.611, 95% CI 1.129–6.040, $p = 0.025$) and CSS (HR 3.124, 95% CI 1.030–9.472, $p = 0.044$). Patients with pre-NCRT low SMA had a significantly lower DFS and CSS than normal patients, which was consistent with the findings of previous studies on body composition (25, 33, 34).

However, other adipose-based indicators did not show the same phenomenon in our study, which indicated that obesity might cause some difficulty in surgery and lead to a higher complication rate (35), but obesity does not cause a decline in survival. For patients with muscle depletion, it may be challenging to tolerate the whole process of radiotherapy and chemotherapy, resulting in a decrease in the treatment intensity of patients (10–13). Furthermore, in our study, patients with pre-NCRT low SMA were strongly correlated with low HB levels and high FIB levels, indicating that pre-NCRT low SMA is closely associated with malnutrition and inflammation in LARC patients. Cancer-related inflammation and malnutrition are highly prevalent in cancer patients and serve as vital survival predictors (8, 9). In addition, skeletal muscle depletion underlines insulin resistance and chronic inflammation in breast cancer, leading to cancer progression and poor survival (36). The above situation may be the reason why pre-NCRT low SMA was associated with unfavorable survival in our study.

To our knowledge, tumor response plays an essential role in treating LARC patients (6), but there is still a lack of research on the relationship between body composition and tumor response in LARC. Recently, some researchers have started to focus on this issue. Lin et al. established a novel model using pre-NCRT MD and SMA loss that was proposed to predict the tumor response in locally advanced gastric cancer with an area under the curve of 0.764 (37). Omarini et al. reported that visceral adiposity was closely involved in chemosensitivity in breast cancer, and high VFA was a negative predictive factor for pathological complete response (38). However, De Nardi et al. reported that both SMA, SFA and VFA variation after NCRT did not correlated to TRG in LARC (30). The lack of significative in this study might be caused by the small sample size, only 52 patients were included. Our results suggest that post-NCRT SFA (OR 3.425, 95% CI 1.392–8.427, $p = 0.007$) was an independent risk factor for TRG, while SFA loss (OR 3.358, 95% CI 1.214–9.289, $p = 0.02$) was an independent risk factor for downstaging. The unfavorable impact of SFA on TRG might be attributed to the following reasons. Fat tissue, previously thought to only store and mobilize lipids, is now gradually being recognized as a complex secretory organ that can produce cytokines (interleukin-1, interleukin-6, and tumor necrosis factor-α) (39), cause a systemic inflammatory response and regulate FIB levels to cause NCRT resistance (40). SFA loss reflects a rare condition called lipodystrophy, which is associated with secondary metabolic resistance syndrome, including hyperlipidemia and insulin resistance, and patients with lipodystrophy are more prone to a reduced therapy effect (41). This indicates that significant SFA loss may be a mechanism underlying poor downstaging in patients with LARC who underwent NCRT.

Some limitations exist in this study. First, this study was a single-center retrospective study, so some selection bias inevitably exists. Second, due to this study's relatively small sample size, some research endpoints only showed a tendency related to body composition but did not show a significant difference. More patients should be included in the future, and the follow-up time should be extended to verify these findings. Third, this study explored body composition at only two time points, pre-NCRT and post-NCRT, without considering the postoperative time point. Body composition changes over time. It would be necessary to determine which specific time point may accurately reflect the outcome of patients. Finally, we chose sex-specific quartiles as a cutoff value according to a previous study. Further studies may be needed to confirm our results to clarify that this cutoff value is suitable for the Asian population.

In summary, this study is the first to comprehensively analyze pre- and post-NCRT body composition parameters and the change in body composition during NCRT and to assess their relationships with short- and long-term complications, survival, and tumor response in a homogenous group of patients with LARC. A better understanding of CT-based body composition may be key to optimizing patient conditions and allowing more accurate preoperative risk stratification.

CONCLUSION

In conclusion, CT-based body composition parameters could predict short- and long-term complications, long-term survival, and tumor response in LARC. Of importance, pre-NCRT SMA status has significant prognostic value for individuals with LARC.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical approval was obtained from Peking University Third Hospital (IRB00006761-M2019387), and this study adhered to the tenets of the Declaration of Helsinki. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZL, SL, and YW collected and analyzed data and wrote the manuscript. XL and PR contributed to data collection. YW and HW contributed to follow-up. XZ and HW provided intellectual contributions. HW, XZ, and WF supervised the project, discussed data analysis, and reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.796601/full#supplementary-material

Supplementary Figure 1 | CT-based cross-sectional image of the third lumbar (L3) measured for SMA **(A)**, VFA **(B)**, TATA **(C)**, and SFA **(D)** using ImageJ software v1.47i (National Institutes of Health, Bethesda, MD). The area delineated by the yellow solid line represents the region of interest.

Supplementary Figure 2 | Time-dependent ROC of body composition and the change of body composition for DFS **(A)** and CSS **(B)**.

Supplementary Figure 3 | Kaplan-Meier analysis for DFS according to body composition and change of body composition.

Supplementary Figure 4 | Kaplan-Meier analysis for CSS according to body composition and change of body composition.

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Postoperative Loss of Skeletal Muscle Mass Predicts Poor Survival After Gastric Cancer Surgery

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Background: Skeletal muscle mass deterioration is common in gastric cancer (GC) patients and is linked to poor prognosis. However, information regarding the effect of skeletal muscle mass changes in the postoperative period is scarce. This study was to investigate the link between postoperative loss of skeletal muscle mass and survival following GC surgery.

Methods: Patients who underwent GC surgery between January 2015 and December 2016 were recruited into the study. Computed tomography at L3 vertebral level was used to examine skeletal muscle index prior to surgery and about 6 months after surgery. Skeletal muscle index changes were categorized as presence or absence of ≥5% loss. Overall survival (OS) and disease-free survival (DFS) were analyzed, and Cox proportional hazard models used to identify their predictors.

Results: The study comprised of 318 gastric cancer patients of which 63.5% were male. The group's mean age was 58.14 ± 10.77 years. Sixty-five patients experienced postoperative skeletal muscle index loss ≥5% and had poorer OS ($P = 0.004$) and DFS ($P = 0.020$). We find that postoperative skeletal muscle index loss ≥ 5% predicts OS [hazard ratio (HR): 2.769, 95% confidence interval (CI): 1.865–4.111; $P < 0.001$] and DFS (HR: 2.533, 95% CI: 1.753–3.659; $P < 0.001$).

Conclusions: Loss of skeletal muscle mass postoperatively is linked to poor survival following GC surgery. Further studies are needed to determine whether stabilizing or enhancing skeletal muscle mass after surgery improves survival.

Keywords: muscle loss, gastric cancer, surgery, survival, prognosis

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INTRODUCTION

While its incidence rate continues to decrease in most parts of the world, gastric cancer (GC) accounts for the fifth common cancer and become the third leading cause of cancer-related death worldwide (1, 2). GC is mostly diagnosed after it has progressed to an advanced stage, and as such, has a low 5-year survival (3). Surgical resection is the most effective therapeutic intervention against GC (4). However, despite advances in operative techniques and perioperative care, GC prognosis after surgery remains poor (5). Numerous studies have shown that cancer prognosis is

conditioned not only by non-modifiable tumor-specific factors such as histology and stage but also modifiable patient-individual factors such as performance status (i.e., patients' physical functioning associated with activities of daily life) and body composition (6–8). Thus, timely identification of these modifiable factors is needed for effective targeted interventions and improved prognosis.

Examination of body composition and its influence on cancer outcomes has drawn growing interest in surgical oncology. Notably, loss of skeletal muscle mass has cancer prognostic value (6–8). Preoperative reduction in skeletal muscle mass is related to poor prognosis after surgical treatment of various cancers, including GC (9–11). Identifying skeletal muscle mass preoperative loss is prognostic and may allow timely therapeutic intervention for better GC outcomes. However, GC patients are often malnourished before surgery, and their malnutrition is often worsened by various factors like postoperative chemotherapy and reduced stomach volume (12). Significant postoperative weight loss has been reported after GC surgery (13, 14), suggesting that muscle wasting might occur in the postoperative period. We have recently reported that after GC surgery, reduced skeletal muscle mass occurs in 3 months after hospital discharge (15). Postoperative skeletal muscle mass has also been reported to negatively impact survival after digestive tract cancer surgeries, including pancreatic, colorectal, and esophageal cancer (7, 16, 17). However, as far as we know, earlier studies mainly concentrated on the influence of preoperative skeletal muscle mass loss on postsurgical GC prognosis. Thus, it is unclear whether the loss of skeletal muscle postoperatively is a risk factor for poor GC prognosis after surgery. If this were the case, then serial assessment of skeletal muscle mass postoperatively may guide efficient interventions.

Here, we aimed to assess postoperative changes in skeletal muscle mass using computed tomography (CT) after GC surgery and to determine whether these changes affect overall and disease-free survival.

MATERIALS AND METHODS

Study Population

Patients aged > 18 years, who underwent GC surgery between January 2015 and December 2016 at the Department of General Surgery/Shanghai Clinical Nutrition Research Center, Zhongshan Hospital, Fudan University, China, were recruited into the study from our prospective clinical database. Patients under palliative or emergency surgery were excluded from the study. Our institutional ethics committee provided ethical approval for the study, which was conducted based on the Declaration of Helsinki ethical standards.

Assessment of Skeletal Muscle Mass

We utilized routine patient abdominal CT scans to examine skeletal muscle mass, as we previously described (18). The CT images used were either contrast-enhanced or unenhanced multiphase acquisitions, 5 mm thick. Two adjacent CT images at L3 vertebral levels in the same series were chosen in the non-contrast phase. Next, total skeletal muscle area (SMA) was quantified using ImageJ2 software (The National Institutes of Health, Washington, MD, USA) between −29 to +150 Hounsfield units (HU) for skeletal muscle on both slices, and the average SMA reported. Skeletal muscle index (SMI) was computed using the formula: SMI = SMA/height^2, expressed in cm^2/m^2. Anonymized CT images were analyzed by an experienced study evaluator who was not aware of the order of images. All included patients underwent abdominal CT scans within 7 days before surgery and about 6 months after surgery, and SMI changes were calculated. Because skeletal muscle losses $\geq$ 5% have previously been associated with poor clinical outcomes, including short survival in cancer treatment (19), we used this cutoff threshold to define the postoperative loss of skeletal muscle mass by grouping patients as SMI loss $\geq$ 5% or SMI loss < 5%.

Data Collection

The clinical data collected included demographics, preoperative characteristics [including BMI (body mass index), ECOG (eastern cooperative oncology group) performance status, serum hemoglobin and albumin level, and comorbidities], operative and pathologic features [including tumor location, type of resection, type of reconstruction, histology, and cancer stage based on the 8th AJCC (American joint committee on cancer) edition], postoperative characteristics (postoperative hospital stay, postoperative complications examined based on the Dindo and Clavien classification), number of patients needing chemotherapy, and chemotherapy tolerance (defined as chemotherapy modification including dose reduction, delay, or termination, and evaluated using a dichotomous scale of absent vs. present) (20). Data on overall survival (OS) and disease-free survival (DFS) were collected. In our prospective clinical database, the follow-up period for all patients was 1st-month post-surgery and after every 3 months, until June 2020.

Statistical Analysis

Statistical analysis was done on SPSS 23.0 software (SPSS Inc., Chicago, IL, USA). Continuous data are expressed as mean ± standard deviation (SD), whereas categorical data are shown as percentages and numbers. Independent-samples *t*-test or Mann-Whitney *U* test was employed to analyze continuous variables. χ^2 test or the Fisher exact test was used to compare categorical data. Kaplan-Meier analyses were used to generate OS and DFS curves. Variations in survival were analyzed using the log-rank test. The impact of postoperative skeletal muscle mass loss on survival was investigated using Cox proportional hazard models. First, univariate analyses were performed respectively for all potential variables that were chosen based on clinical information. Multivariate analysis was then done using Cox proportional backward stepwise procedure, including all variables with $P < 0.05$ in the univariate analysis. $P < 0.05$ indicates statistical significance.

TABLE 1 | Patient demographic and clinical characteristics according to postoperative skeletal muscle mass loss.

Characteristics	Total ($n = 318$)	SMI loss ≥ 5% ($n = 65$)	SMI loss < 5% ($n = 253$)	*P*-value
Gender				0.284
Male	202 (63.5)	45 (69.2)	157 (62.1)	
Female	116 (36.5)	20 (30.8)	96 (37.9)	
Age (years), mean ± SD	58.14 ± 10.77	60.86 ± 10.73	57.45 ± 10.68	**0.022**
Diabetes	21 (6.6)	6 (9.2)	15 (5.9)	0.399
Respiratory comorbidity	17 (5.3)	3 (4.6)	14 (5.5)	1.000
Cardiovascular comorbidity	58 (18.2)	13 (20)	45 (17.8)	0.680
Serum albumin (g/L), mean ± SD	38.46 ± 4.79	37.54 ± 4.47	38.69 ± 4.85	0.083
Serum hemoglobin (g/L), mean ± SD	122.72 ± 23.58	119.46 ± 21.77	123.56 ± 23.99	0.212
Preoperative BMI (kg/m^2), mean ± SD	22.29 ± 3.38	21.61 ± 3.29	22.47 ± 3.38	0.067
Preoperative SMI (cm^2/m^2), mean ± SD	42.60 ± 5.23	41.71 ± 5.34	42.82 ± 5.18	0.124
Preoperative ECOG performance status				0.549
0	261 (82.1)	55 (84.6)	206 (81.4)	
1	57 (17.9)	10 (15.4)	47 (18.6)	
Tumor location				0.816
Upper	70 (22.0)	15 (23.1)	55 (21.7)	
Not upper	248 (78.0)	50 (76.9)	198 (78.3)	
Type of resection				0.596
Total gastrectomy	99 (31.1)	22 (33.8)	77 (30.4)	
Subtotal gastrectomy	219 (68.9)	43 (66.2)	176 (69.6)	
Type of reconstruction				0.741
Billroth I	121 (38.1)	26 (40.0)	95 (37.5)	
Billroth II	69 (21.7)	11 (16.9)	58 (22.9)	
Roux-en-Y	117 (36.8)	26 (40.0)	91 (36.0)	
Other	11 (3.5)	2 (3.1)	9 (3.6)	
Histology				0.793
Undifferentiated	113 (35.5)	24 (36.9)	89 (35.2)	
Differentiated	205 (64.5)	41 (63.1)	164 (64.8)	
AJCC stage				**0.010**
I	79 (24.8)	12 (18.5)	67 (26.5)	
II	115 (36.2)	17 (26.2)	98 (38.7)	
III	124 (39.0)	36 (55.4)	88 (34.8)	
Postoperative any complication	56 (17.6)	17 (26.2)	39 (15.4)	**0.043**
Postoperative hospital stay (days), mean ± SD	9.48 ± 2.17	9.72 ± 2.50	9.42 ± 2.08	0.314
Postoperative chemotherapy	216 (67.9)	51 (78.5)	165 (65.2)	**0.041**
Chemotherapy modification	73 (23.0)	23 (35.4)	50 (19.8)	**0.008**

Values are presented as n (%) unless otherwise stated. Bold values indicate statistical significant.
SD, standard deviation; BMI, body mass index; SMI, skeletal muscle index; AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group.

RESULTS

Patient Characteristics

Of the 363 patients who consecutively underwent curative GC surgery from January 2015 to December 2016, 318 patients (63.5% male, mean age 58.14 years) met the inclusion criteria. 65 patients exhibited SMI losses ≥ 5%, while 253 had SMI losses < 5%. Participant characteristics are shown on **Table 1**. The groups with ≥ 5% SMI loss and the one with < 5% SMI loss were similar with regards to gender, diabetes, respiratory and cardiovascular comorbidity, serum albumin and hemoglobin, preoperative BMI, preoperative SMI, preoperative ECOG performance status, tumor location, type of resection, type of reconstruction, histology, and postoperative hospital stay ($P > 0.05$). However, ≥ 5% loss significantly correlated with advanced age (60.86 ± 10.73 vs. 57.45 ± 10.68 years, $P = 0.022$), higher incidence of postoperative complications (26.2 vs. 15.4%; $P = 0.043$), higher rates of postoperative chemotherapy (78.5 vs. 65.2%; $P = 0.041$), and chemotherapy modification including dose reduction, delay, or termination (35.4 vs. 19.8%; $P = 0.008$). Moreover, AJCC stage differed significantly between the two groups ($P = 0.010$).

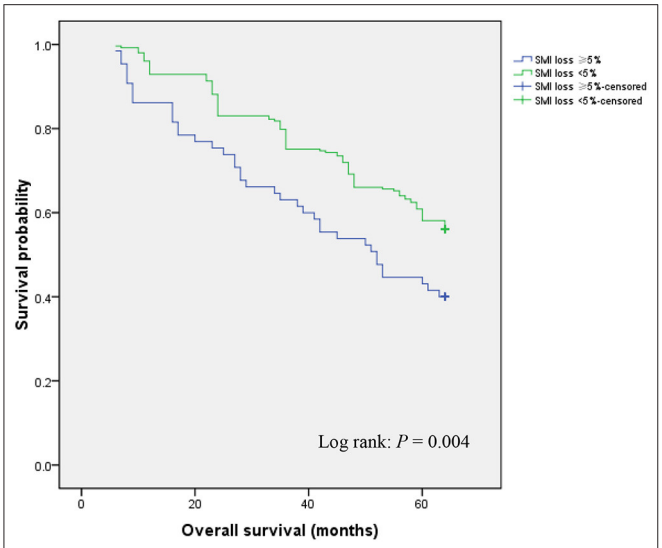

FIGURE 1 | Overall survival according to postoperative skeletal muscle mass loss.

Effects of Postoperative Skeletal Muscle Mass Loss on Overall Survival

During follow-up, patients who exhibited ≥ 5% SMI loss showed significantly lower OS relative to those with < 5% SMI loss (40.0 vs. 56.1%; $P = 0.004$) (**Figure 1**). Univariate and multivariate analyses were used to identify factors influencing OS following GC curative surgery (**Table 2**). Univariate analysis revealed the following factor as significantly-associated with poor OS: age ≥ 65 years [hazard ratio (HR) = 1.638, 95% confidence interval (CI) = 1.160–2.314; $P = 0.005$], hypoproteinemia (HR = 1.501, 95% CI = 1.035–2.328; $P = 0.043$), preoperative SMI (HR = 2.546, 95% CI = 1.774–3.653; $P < 0.001$), histology (HR = 1.500, 95% CI = 1.083–2.078; $P = 0.015$), AJCC stage (II vs. I: HR = 6.355, 95% CI = 3.719–10.859; $P < 0.001$; III vs. I: HR = 6.930, 95% CI = 4.200–11.435; $P < 0.001$), postoperative any complication (HR = 1.494, 95% CI = 1.011–2.209; $P = 0.044$), postoperative chemotherapy (HR = 1.619, 95% CI = 1.117–2.348; $P = 0.011$), chemotherapy modification (HR = 1.545, 95% CI = 1.081–2.207; $P = 0.017$), and SMI loss ≥ 5% (HR = 1.693, 95% CI = 1.175–2.439; $P = 0.005$). Multivariate analysis identified the following factors as independently correlating with poor OS: age ≥65 years (HR = 1.616, 95% CI = 1.130–2.311; $P = 0.009$), preoperative SMI (HR = 2.187, 95% CI = 1.491–3.208; $P < 0.001$), AJCC stage (II vs. I: HR = 6.106, 95% CI = 3.504–10.641; $P < 0.001$; III vs. I: HR = 8.840, 95% CI = 5.231–14.938; $P < 0.001$), chemotherapy modification (HR = 1.498, 95% CI = 1.079–2.325; $P = 0.032$), and SMI loss ≥ 5% (HR = 2.769, 95% CI = 1.865–4.111; $P < 0.001$).

Effects of Postoperative Loss of Skeletal Muscle Mass on Disease-Free Survival

In the course of follow-up, patients who exhibited ≥ 5% SMI loss showed considerably lower DFS rates relative to those with < 5% SMI loss (33.8 vs. 46.2%; $P = 0.020$) (**Figure 2**). Univariate and multivariate analyses were used to identify factors influencing DFS following GC curative surgery (**Table 3**). Univariate analysis revealed the following factors as significantly correlating with poor DFS: hypoproteinemia (HR = 1.401, 95% CI = 1.022–1.922; $P = 0.036$), preoperative SMI (HR = 2.348, 95% CI = 1.675–3.290; $P < 0.001$), histology (HR = 1.774, 95% CI = 1.319–2.388; $P < 0.001$), AJCC stage (II vs. I: HR = 12.511, 95% CI = 7.524–20.804); $P < 0.001$; III vs. I: HR = 8.525, 95% CI = 5.237–13.878; $P < 0.001$), postoperative any complication (HR = 1.854, 95% CI = 1.307–2.629; $P = 0.001$), chemotherapy modification (HR = 1.513, 95% CI = 1.032–1.975; $P = 0.019$), and ≥ 5% SMI loss (HR = 1.492, 95% CI = 1.058–2.102; $P = 0.022$). Multivariate analysis identified preoperative SMI (HR = 1.953, 95% CI = 1.369–2.786; $P < 0.001$), AJCC stage (II vs. I: HR = 11.726, 95% CI = 6.983–19.690; $P < 0.001$; III vs. I: HR = 10.096, 95% CI = 6.091–16.735; $P < 0.001$), chemotherapy modification (HR = 1.403, 95% CI = 1.006–1.879; $P = 0.041$), and SMI loss ≥ 5% (HR = 2.533, 95% CI = 1.753–3.659; $P < 0.001$) as independently correlated with poor DFS.

DISCUSSION

To our best knowledge, this study was the first report suggesting that postoperative loss of skeletal muscle mass negatively influences OS and DFS in patients following GC surgery. These findings may guide clinicians on the optimal use of prophylactic strategies to reduce postoperative skeletal muscle mass loss, aiming to improve GC outcomes after surgery.

Even though there has been a significant advancement in nutritional support therapy, surgical techniques, and increased recovery rates following surgery, GC surgery is still associated with high malnutrition risk as a result of gastrointestinal complications and reduced food intake. These problems are exacerbated by chronic comorbidities, unintentional weight loss prior to surgery, and postoperative chemotherapy (12). Poor nutrition is linked to poor clinical outcomes, which mainly include increased morbidity and mortality, as well as decreased survival (21–23). Thus, the management of malnutrition is critical for GC treatment and prognosis. Recently, loss of skeletal muscle mass emerged as a prognostic indicator in various cancers during surgery (6–11). However, studies conducted previously primarily focused on the effects of preoperative skeletal muscle mass loss after gastric cancer surgery, and it is unclear whether postoperative skeletal muscle mass loss affects post-GC surgery prognosis. Additionally, postoperative skeletal muscle mass loss negatively impacts survival after digestive tract surgery due to the pancreatic, colorectal, and esophagus cancers (7, 16, 17). Here, we sought to examine skeletal muscle mass postoperative changes after GC surgery and to determine whether these changes affect OS and DFS.

A standard technique for measuring skeletal muscle mass is lacking. Different methods like dual-energy X-ray absorptiometry and CT scanning, are applied to quantitatively measure skeletal muscle mass in clinical practice and research (24). Of the widely used techniques, CT scan has emerged

TABLE 2 | Univariate and multivariate analyses of prognostic factors for overall survival.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Gender				
Male vs. female	1.118 (0.763–1.639)	0.567		
Age, years				
≥ 65 vs. < 65	1.638 (1.160–2.314)	0.005	1.616 (1.130–2.311)	**0.009**
Diabetes				
Yes vs. no	1.572 (0.890–2.777)	0.120		
Respiratory comorbidity				
Yes vs. no	1.329 (0.587–3.008)	0.495		
Cardiovascular comorbidity				
Yes vs. no	1.066 (0.714–1.591)	0.754		
Hypoproteinemia				
Yes vs. no	1.501 (1.035–2.328)	0.043	1.432 (0.975–1.072)	0.097
Anemia				
Yes vs. no	1.188 (0.783–1.802)	0.417		
Preoperative BMI, kg/m^2				
< 18.5 vs. 18.5–25	1.138 (0.704–1.839)	0.598		
> 25 vs. 18.5–25	1.052 (0.700–1.582)	0.808		
Preoperative SMI, cm^2/m^2				
< 43.13 for men or < 37.81 for women vs. ≥ 43.13 for men or ≥ 37.81 for women[a]	2.546 (1.774–3.653)	< 0.001	2.187 (1.491–3.208)	**< 0.001**
Preoperative ECOG performance status				
1 vs. 0	1.223 (0.887–1.687)	0.220		
Tumor location				
Upper vs. not upper	1.066 (0.721–1.575)	0.750		
Type of resection				
Total vs. subtotal	1.230 (0.874–1.730)	0.235		
Histology				
Undifferentiated vs. differentiated	1.500 (1.083–2.078)	0.015	1.098 (0.773–1.559)	0.601
AJCC stage				
II vs. I	6.355 (3.719–10.859)	< 0.001	6.106 (3.504–10.641)	**< 0.001**
III vs. I	6.930 (4.200–11.435)	< 0.001	8.840 (5.231–14.938)	**< 0.001**
Postoperative any complication				
Yes vs. no	1.494 (1.011–2.209)	0.044	1.193 (0.797–1.786)	0.390
Postoperative chemotherapy				
Yes vs. no	1.619 (1.117–2.348)	0.011	1.229 (0.823–1.836)	0.314
Chemotherapy modification				
Yes vs. no	1.545 (1.081–2.207)	0.017	1.498 (1.079–2.325)	**0.032**
SMI loss				
≥ 5% vs. < 5%	1.693 (1.175–2.439)	0.005	2.769 (1.865–4.111)	**< 0.001**

Bold values indicate statistical significant.

HR, hazard ratio; CI, confidence interval; BMI, body mass index; SMI, skeletal muscle index; ECOG, Eastern Cooperative Oncology Group.

[a]*This cut point was based on the recent study showing that SMI < 43.13 cm^2/m^2 for men or < 37.81 cm^2/m^2 for women was associated with poor surgical and oncologic outcomes after gastrointestinal cancer surgery (18).*

as a reliable method of skeletal muscle mass measurement (25–27). Cross-sectional areas of skeletal muscle tissue on single CT slices at L3 vertebral levels have been shown to strongly correlate with total body skeletal muscle tissue. CT images provide objective quantitative measures of skeletal muscle mass via SMI calculation (28–30). Thus, the assessment of skeletal muscle mass using CT scan at L3 vertebral levels combined with SMI calculation is increasingly used to examine the impact of preoperative skeletal muscle mass changes on clinical outcomes after digestive tract cancer surgery (18, 31, 32). Here, we used CT scan to measure skeletal muscle mass before and approximately 6 months after surgery and calculated SMI changes. We considered ≥ 5% skeletal muscle loss indicative of significant postoperative skeletal muscle mass loss, since

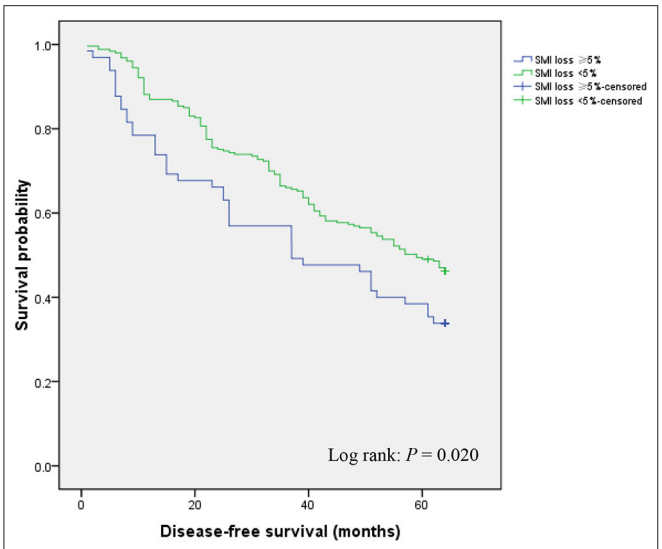

FIGURE 2 | Disease-free survival according to postoperative skeletal muscle mass loss.

it has been previously associated with poor clinical outcomes, including short survival with cancer treatment. Our data revealed 65 of 318 patients as having ≥ 5% SMI loss in the 6 months after GC surgery. ≥ 5% SMI loss significantly correlated with older age, higher incidence of postoperative complications, and higher postoperative chemotherapy and chemotherapy modification (like dose reduction, delay/termination). There was a significant difference in AJCC stage between the two groups. However, the ≥ 5% SMI loss group was comparable to the < 5% SMI loss group with regards to gender, diabetes, respiratory and cardiovascular comorbidity, serum albumin and hemoglobin, preoperative BMI, preoperative SMI, preoperative ECOG performance status, tumor location, type of resection, type of reconstruction, histology, and postoperative hospital stay. These indicate that the ≥ 5% SMI loss criteria used in this study represents significant postoperative skeletal muscle mass loss after GC surgery. Moreover, skeletal muscle mass measurement using abdominal CT scans can be employed to postoperatively evaluate patients, as abdominal CT scans are regularly used, inexpensive, and easy to execute during follow up after GC surgery.

Regarding the survival following cancer surgery, it always receives a significant concern for the prognostic gain following oncologic surgery. Studies have mainly evaluated the association between skeletal muscle mass loss and survival postoperatively. Here, we primarily assessed the effect of postoperative skeletal muscle mass loss on OS and DFS after GC surgery. Our data show that postoperative skeletal muscle mass loss significantly correlates with lower OS and DFS following GC surgery. Multivariate analyses reveal that it is an unfavorable prognostic indicator of disease-free survival. These findings are consistent with previous reports on surgical treatment of other gastrointestinal cancers (7, 16, 17, 33, 34), indicating independent relationship between skeletal muscle mass loss postoperatively and cancer endpoints. Although we did not examine the reasons underlying the strong link between postoperative skeletal muscle mass loss and survival, we speculate that it may be due to multiple factors, including poor tolerability of systemic chemotherapy. Previous studies, including our recent one on digestive cancer surgery, show that loss of skeletal muscle mass may reduce the ability to tolerate systemic chemotherapy. Thus, patients exhibiting low skeletal muscle mass are more likely to experience extreme treatment-associated toxicities, leading to fewer completed chemotherapy cycles (18, 26, 35). Here, postoperative skeletal muscle mass loss was related to more chemotherapy modifications, like dose reduction, delay/termination, and was identified as a risk factor for poor OS and DFS following GC surgery. This could lead to poorer disease control and low survival. Nevertheless, these findings highlight the importance of identifying skeletal muscle mass loss after surgery because it allows prophylactic strategies including the use of proper nutritional support therapy and physical exercise aiming to reduce postoperative skeletal muscle mass loss.

We acknowledge the following limitations in our study. First, our analysis did not examine nutritional intake and physical activity, which are linked to skeletal muscle mass and may affect survival (36). The inclusion of these data would more comprehensively highlight the causal link between skeletal muscle mass loss and poor survival. Secondly, being a single-center study, it may exaggerate the impact of postoperative skeletal muscle mass loss on survival. Thus, there is a need to conduct international multicenter studies to verify these findings. Thirdly, recent evidence indicates that both low skeletal muscle mass and decreased skeletal muscle function influence clinical outcomes (37, 38). However, our study did not capture data on skeletal muscle functions like grip strength/walking speed because of the retrospective design of the study cohort. Further research should evaluate both skeletal muscle mass and function, to evidently reveal the effect of skeletal muscle changes on cancer patients post-surgery. Finally, there were apparent differences in participant characteristics between the two groups, such as AJCC stage, which may affect OS and DFS. The Propensity Score Matching will be conducted to comprehensively answer the question regarding the impact of postoperative loss of skeletal muscle mass on survival after GC surgery. In addition, the univariate and multivariate analyses of risk factors affecting OS and DFS in our study are of great significance, and due to the confounding factors, the significance of OS and DFS in patients with different skeletal muscles is unclear and unreliable. Thus, we will include the related analysis in our future studies in this field of research.

In this study, our data show that postoperative skeletal muscle mass loss negatively affects survival and that it has a strong, independent, prognostic value after GC surgery. Identification of postoperative skeletal muscle mass loss by abdominal CT imaging after GC surgery and targeted approaches to reduce postoperative skeletal muscle mass loss may improve GC outcomes.

TABLE 3 | Univariate and multivariate analyses of prognostic factors for disease-free survival.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Gender				
Male vs. female	1.217 (0.861–1.721)	0.265		
Age, years				
≥ 65 vs. < 65	1.327 (0.679–1.875)	0.158		
Diabetes				
Yes vs. no	1.641 (0.967–2.785)	0.067		
Respiratory comorbidity				
Yes vs. no	1.358 (0.717–2.570)	0.348		
Cardiovascular comorbidity				
Yes vs. no	1.045 (0.722–1.512)	0.816		
Hypoproteinemia				
Yes vs. no	1.401 (1.022–1.922)	0.036	1.225 (0.879–1.709)	0.231
Anemia				
Yes vs. no	1.371 (0.926–2.0292)	0.115		
Preoperative BMI, kg/m^2				
< 18.5 vs. 18.5–25	1.021 (0.648–1.609)	0.928		
> 25 vs. 18.5–25	0.994 (0.685–1.442)	0.975		
Preoperative SMI, cm^2/m^2				
< 43.13 for men or < 37.81 for women vs. ≥ 43.13 for men or ≥ 37.81 for women[a]	2.348 (1.675–3.290)	< 0.001	1.953 (1.369–2.786)	**< 0.001**
Preoperative ECOG performance status				
1 vs. 0	1.111 (0.827–1.493)	0.485		
Tumor location				
Upper vs. not upper	1.063 (0.745–1.516)	0.735		
Type of resection				
Total vs. subtotal	1.316 (0.964–1.794)	0.083		
Histology				
Undifferentiated vs. differentiated	1.774 (1.319–2.388)	< 0.001	1.307 (0.962–1.776)	0.087
AJCC stage				
II vs. I	12.511 (7.524–20.804)	< 0.001	11.726 (6.983–19.690)	**< 0.001**
III vs. I	8.525 (5.237–13.878)	< 0.001	10.096 (6.091–16.735)	**< 0.001**
Postoperative any complication				
Yes vs. no	1.854 (1.307–2.629)	0.001	1.371 (0.954–1.970)	0.088
Postoperative chemotherapy				
Yes vs. no	1.314 (0.948–1.822)	0.101		
Chemotherapy modification				
Yes vs. no	1.513 (1.032–1.975)	0.019	1.403 (1.006–1.879)	**0.041**
SMI loss				
≥ 5% vs. < 5%	1.492 (1.058–2.102)	0.022	2.533 (1.753–3.659)	**< 0.001**

Bold values indicate statistical significant.

HR, hazard ratio; CI, confidence interval; BMI, body mass index; SMI, skeletal muscle index; ECOG, Eastern Cooperative Oncology Group.

[a]*This cut point was based on the recent study showing that SMI < 43.13 cm^2/m^2 for men or < 37.81 cm^2/m^2 for women was associated with poor surgical and oncologic outcomes after gastrointestinal cancer surgery (18).*

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 Zhongshan Hospital Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GW supervised the entire project and ST designed the study. QZ, ZZ, SL, JX, JW, YZ, QX, QM, and YJ performed data collection. QZ and ZZ conducted data analyses. ST wrote and revised the

manuscript. All authors critically reviewed and approved the final manuscript.

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Relationship Between Nutritional Status and Clinical Outcome in Patients With Gastrointestinal Stromal Tumor After Surgical Resection

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Background: Currently, gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors in the gastrointestinal tract, and surgical resection is the main treatment. Malnutrition after gastrointestinal surgery is not uncommon, which may have adverse effects on postoperative recovery and prognosis. However, the nutritional status of GIST patients after surgical resection and its impact on clinical outcomes have received less attention. Therefore, the aim of this study was to dynamically evaluate the nutritional status of GIST patients undergoing surgical resection, and to analyze the correlation between nutritional status and clinical outcomes.

Methods: We retrospectively analyzed the clinical data of GIST patients who underwent surgical resection in the Fourth Hospital of Hebei Medical University from January 2016 to January 2020. Nutritional risk screening 2002 (NRS2002) and Patient-Generated Subjective Global Assessment (PG-SGA) were used to assess the nutritional status of all patients at admission and discharge, and the correlation between nutritional risk and clinical outcomes was analyzed.

Results: A total of 413 GIST patients were included in this study, among which 114 patients had malnutrition risk at admission (NRS2002 score $\geq$ 3), and 65 patients had malnutrition (PG-SGA score $\geq$ 4). The malnutrition risk rate (27.60 vs. 46.73%, $p < 0.001$) and malnutrition incidence (15.73 vs. 37.29%, $p < 0.001$) at admission were lower than those at discharge. Compared with the laboratory results at admission, the albumin, prealbumin, and total protein of the patients at discharge were significantly lower (all $p < 0.05$). And there was a negative correlation between PG-SGA and clinical outcome (all $p < 0.05$).

Conclusion: The nutritional status of GIST patients after surgical resection at discharge was worse than that at admission, and malnutrition is an important risk factor leading to poor clinical outcomes.

Keywords: gastrointestinal stromal tumors, surgical resection, nutrition status, NRS2002, PG-SGA

INTRODUCTION

Presently, gastrointestinal stromal tumors (GIST) are increasing rapidly worldwide, mostly due to mutations in KIT and PDGFRA genes (1, 2). In recent years, with the advancement of molecular biology research on GIST, the treatment mode has made breakthrough progress, but surgical resection is still the mainstay and most effective treatment for GIST (3–5). However, some patients experienced nutritional deterioration after surgery, especially in patients undergoing gastrointestinal resection, which often resulted in reduced food intake and weight loss. Numerous studies have demonstrated that malnutrition is consistently associated with negative outcomes, such as high perioperative infection rates, long hospitalization time, and short survival time (6–8).

However, until now, numerous studies focused on the nutritional status of patients such as gastric cancer and other malignant cancer, while few people pay attention to the nutritional status of GIST patients, especially those with surgical resection at discharge (9–11). Our previous study has found that 77.76% of newly diagnosed GISTs were at risk of malnutrition (Nutritional risk screening 2002 score $\geq$ 3), and the incidence of malnutrition was 10.09% (Patient-Generated Subjective Global Assessment score $\geq$ 4) at admission (12). This suggests that malnutrition is common in newly diagnosed GIST patients on admission. Similarly, the nutritional status assessment of GIST patients after surgical resection at discharge is equally important and requires attention. Meanwhile, there are a large number of published studies showing that malnutrition in surgical patients after discharge, which will affect the quality of life of patients and lead to delayed postoperative treatment and increased mortality (13–15). However, the relationship between nutritional status and clinical outcomes of GIST patients after surgical resection is also unclear. Therefore, attention to malnutrition in GIST patients will be particularly important for improving the quality of life and significantly prolonging the survival period.

Currently, many nutritional guidelines recommend standardized nutritional supports, including nutritional screening, assessment, intervention, and monitoring. Among them, the nutritional screening is the first step, and NRS2002 is the recommended screening tool (16–22). Meanwhile, PG-SGA is a nutritional assessment method developed on the basis of Subjective Global Assessment (SGA) designed specifically for cancer patients (23). It has been confirmed by clinical studies in various countries that it can be used for nutritional assessment of tumor patients and is an effective tool for evaluating the specific nutritional status of tumor patients (24). In addition, the physical measurement indexes including body weight, body mass index (BMI), and grip strength, as well as blood biochemical parameters including lymphocytes, albumin, and prealbumin,

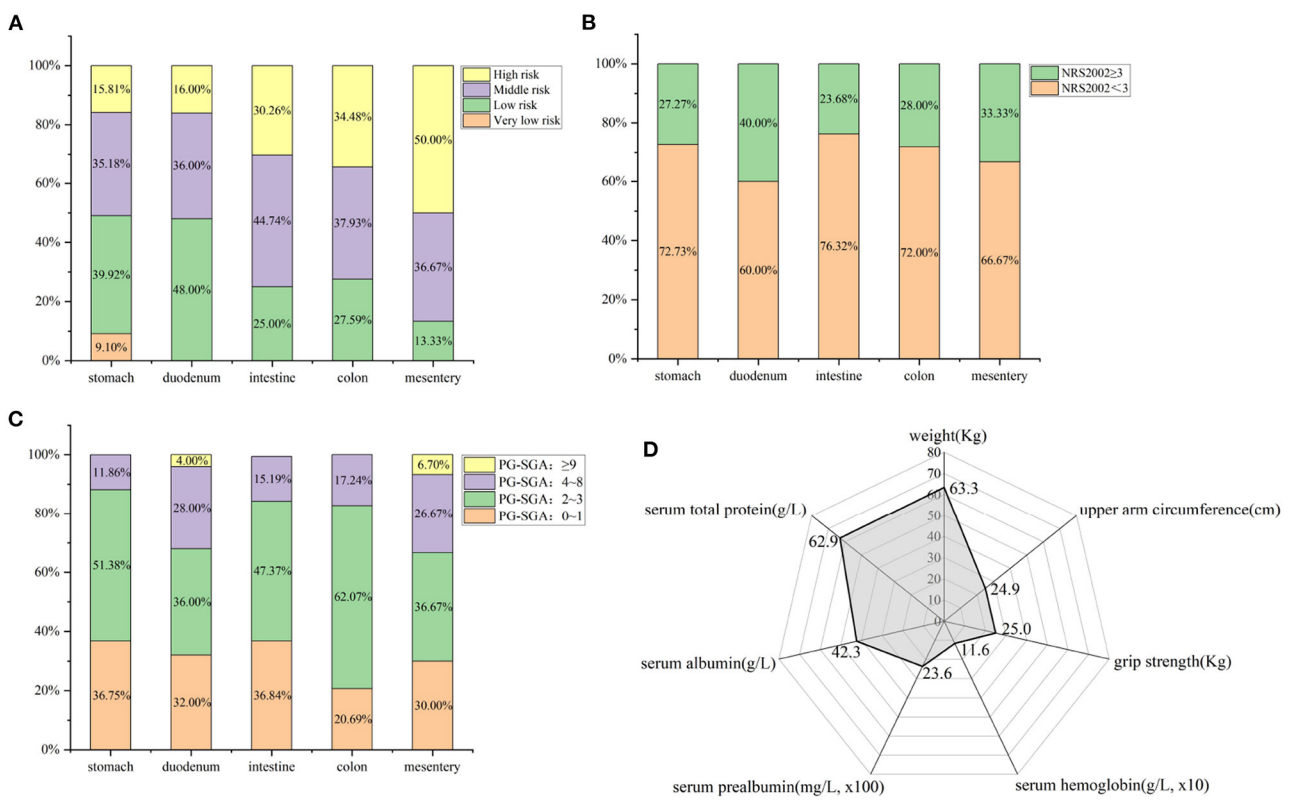

FIGURE 1 | Baseline data of 413 GIST patients at admission. **(A)** Disease distribution according to different tumors; **(B)** NRS2002 nutritional risk screening; **(C)** PG-SGA nutritional assessment; **(D)** Other nutrition-related indicators (Mean).

are also commonly used to evaluate the nutritional status of patients (25, 26).

At present, there is no standard nutritional evaluation method for GIST patients undergoing surgical resection, and there is no consensus on which evaluation method will be the best choice. Moreover, there are few studies on the application of NRS2002 combined with PG-SGA in the perioperative assessment of GIST patients. Therefore, in the present study, we used NRS2002 combined with PG-SGA and other nutritional indicators to evaluate the nutritional status of patients with GIST after surgical resection, in order to clarify whether postoperative nutritional status is related to adverse clinical outcomes.

METHODS AND MATERIALS

Patient Section

This study retrospectively analyzed the medical data of 413 GIST patients who underwent surgical resection in our hospital from January 2016 to January 2020. Inclusion criteria were as follows: (1) pathological diagnosis was GIST; (2) radical surgical resection; (3) without preoperative anti-tumor treatment; (4) completion of Quality of Life Questionnaire; and (5) detailed and complete clinical data. Exclusion criteria were as follows: (1) the patient had accepted antitumor therapies before surgery; (2) patients with cognitive impairment or other acute psychological problems; (3) those without complete medical records and laboratory results; (4) inpatients who were admitted due to surgical emergency; (5) patients who refused to accept assessment or do not sign informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was tested and approved by the ethics committee of The Fourth Hospital of Hebei Medical University, and the patients provided informed consent.

Assessment Method

All patients completed anthropometry, NRS2002 screening, PG-SGA assessment, and blood biochemical parameters examination within 24 h after admission and 24 h before discharge, and NRS2002 screening and PG-SGA evaluation were evaluated by the same group of physicians. The anthropometry of patients included weight, upper arm circumference, and grip strength. The blood biochemical parameters examination included serum hemoglobin, albumin, prealbumin, and total protein, etc. All patients were screened by NRS2002 score after admission, and the score was $\geq$3, indicating that there was a risk of malnutrition in patients. PG-SGA score includes patient self-assessment and medical staff assessment, which includes seven areas (27). Patients' self-assessment includes weight changes, dietary intake, eating symptoms, and physical activity and function. Medical staff assessment includes nutrition-related disease status, metabolic status, and physical examination. Each of these seven areas is given a score of 0–4, and the sum of scores obtained in each area is divided into quantitative and qualitative evaluations, thus providing guidance on the level of nutrition and drug intervention required by each patient. Quantitative evaluation results are as follows: PG-SGA score of 0–1 indicates that nutritional support not required and treatment in the future based on routine re-evaluation, 2–3 points indicate malnutrition or suspected malnutrition, 4–8 points indicate moderate malnutrition, and $\geq$9 points indicate severe malnutrition (27).

Quality of Life Assessment

The quality of life of patients was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) 3.0 version, which was composed of 30 items, including five functional scales (physical, role, emotional, cognitive and social functioning functions), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/quality of life domain and six single symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems) (28). The functional and symptom scale score was divided into four grades, and the direct score was 1 (no) to 4 (very). The global health scale score was divided into seven grades, and the score was 1 (very poor) to 7 (very good) according to the patient's response options. The mean value of each subscale was linearly converted to the range of 0–100 scores. Higher scores in global health status and functional scales indicate better quality of life, whereas higher scores in the symptom scales indicate more severe symptoms. In this study, all patients were investigated by EORTC-QLQ-C30 questionnaire 1 month after discharge.

TABLE 1 | Patient baseline demographic and clinical characteristics at admission.

Variables	*N* (Percentage)
Age (years)	59.7 ± 10.3 *
Sex (male)	201 (48.32%)
Tumor location	
Stomach	253 (61.26%)
Duodenum	25 (6.05%)
Intestine	76 (18.40%)
Colon	29 (7.02%)
Mesentery	30 (7.26%)
Tumor size (cm)	5.3 ± 4.8*
Nuclear mitotic figure (50HPF)	
<5	149 (36.08%)
6~10	236 (57.14%)
>10	28 (6.78%)
c-kit exons	
Positive	268 (64.89%)
Negative	145 (35.11%)
PDGFRA exons	
Positive	112 (27.12%)
Negative	301 (72.88%)

*Mean ± SD.

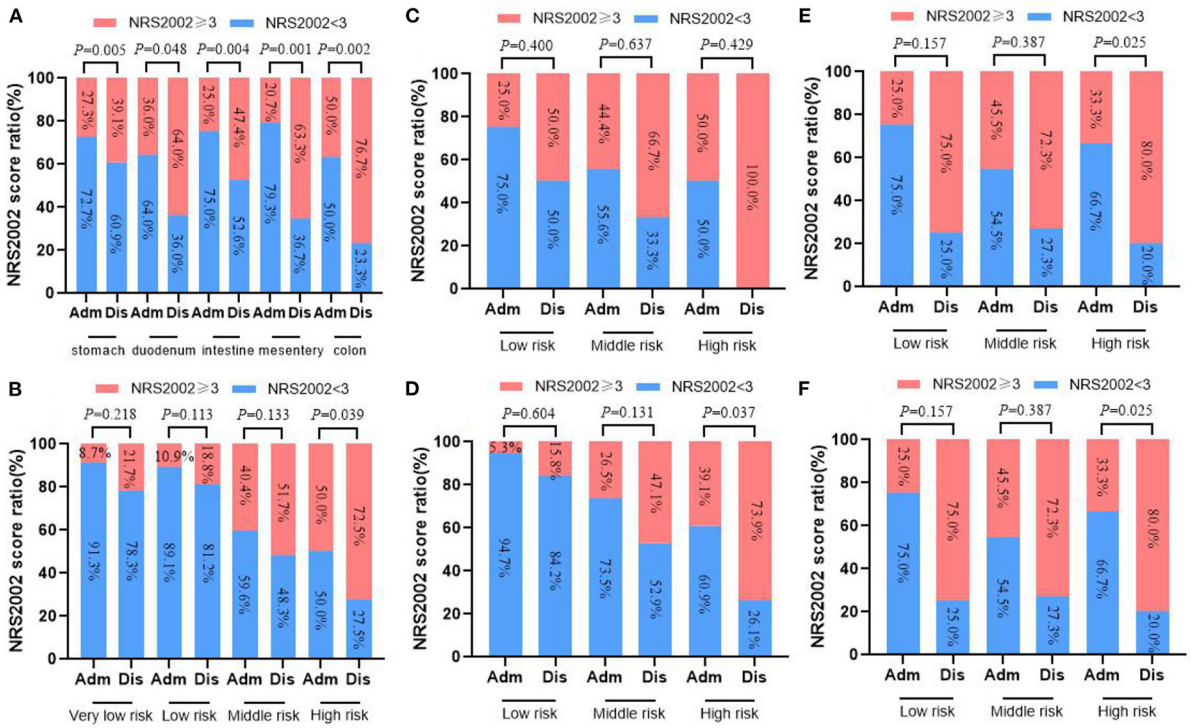

FIGURE 2 | Changes of NRS2002 screening at admission and discharge in 413 GIST patients. **(A)** Total; **(B)** stomach; **(C)** duodenum; **(D)** intestine; **(E)** colorectal; **(F)** mesentery.

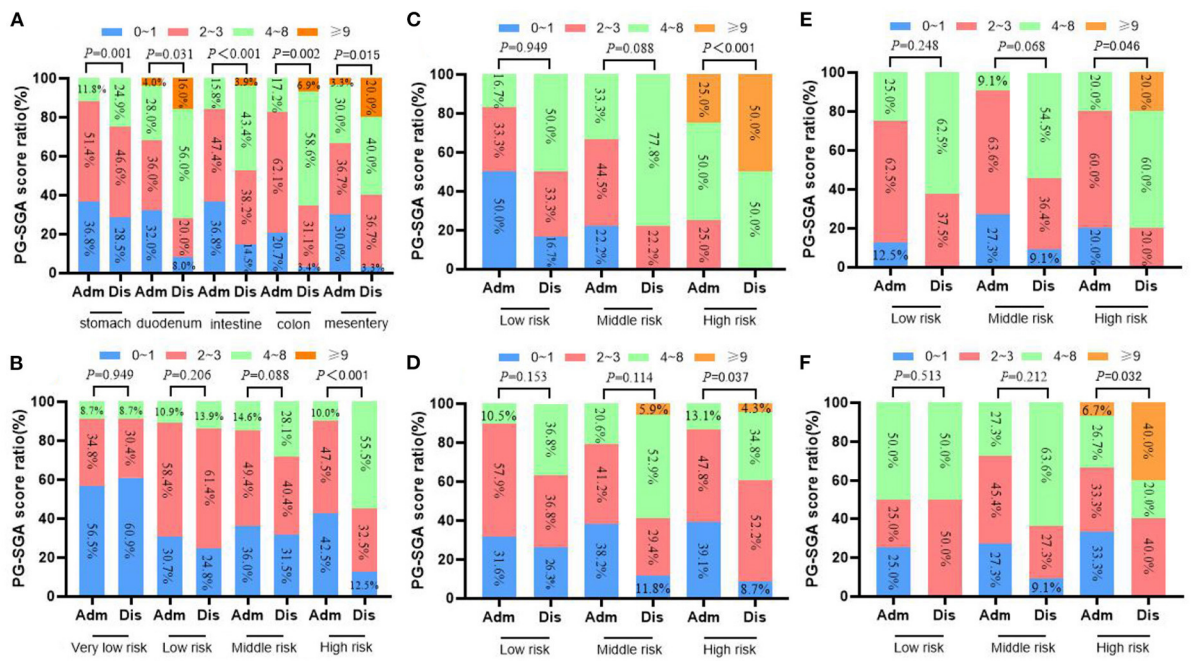

FIGURE 3 | Changes of PG-SGA nutritional assessment in 413 GIST patients at admission and discharge. **(A)** Total; **(B)** stomach; **(C)** duodenum; **(D)** intestine; **(E)** colorectal; **(F)** mesentery.

Clinicopathological Parameters and Definitions

We collected the basic data of newly diagnosed GIST patients including gender, age, weight, etc. Laboratory tests include routine blood tests and biochemical tests. Preoperative examination included abdominal computed tomography (CT), nuclear magnetic resonance imaging (MRI), and gastrointestinal endoscopy. Pathology and gene detection included tumor location, tumor size, mitotic count, immunohistochemistry, risk classification, c-kit exons 9, 11, 13 and 17, and PDGFRA exons 12 and 18. The risk classification standard we adopted is the 2008 version of the improved National Institutes of Health (NIH) classification (29).

Meanwhile, the clinical related outcome indicators were recorded, including hospitalization time, complications, and expenses. The hospitalized complications included infectious complications and other complications. Infectious complications are defined as the presence of pathogens in the body's original sterile tissues and confirmed by pathogen culture results, or there are clinical symptoms and signs, imaging or hematological evidence related to infection (30). The discharge standard is as follows: patients can live self-care, normal urination, normal body temperature, and no need for intravenous infusion (31).

Statistical Analyses

All statistical analyses were performed using SPSS 21.0 software (IBM, Armonk, NY, USA) and GraphPad Prism 8.01 (GraphPad Software, San Diego, California). All continuous variables are tested for normal distribution by Kruskal-Wallis test. The variable of normal distribution is represented by mean ± standard deviation, and the variable of non-normal distribution is represented by median. The classification variables were compared by χ^2 or Fisher exact test, and the continuous variables were compared by independent *t*-test or Mann-Whitney *U*-test. Logistic regression analysis was used for multivariate analysis of the risk of postoperative complications. According to the potential confounding factors, multiple linear regression analysis was used to evaluate the correlation between nutritional indicators (NRS2002, PG-SGA, weight, upper arm circumference, grip strength, serum hemoglobin, albumin, prealbumin, and total protein) and EORTC-QLQ-C30 scale. *P*-value < 0.05 was regarded as statistical difference significantly.

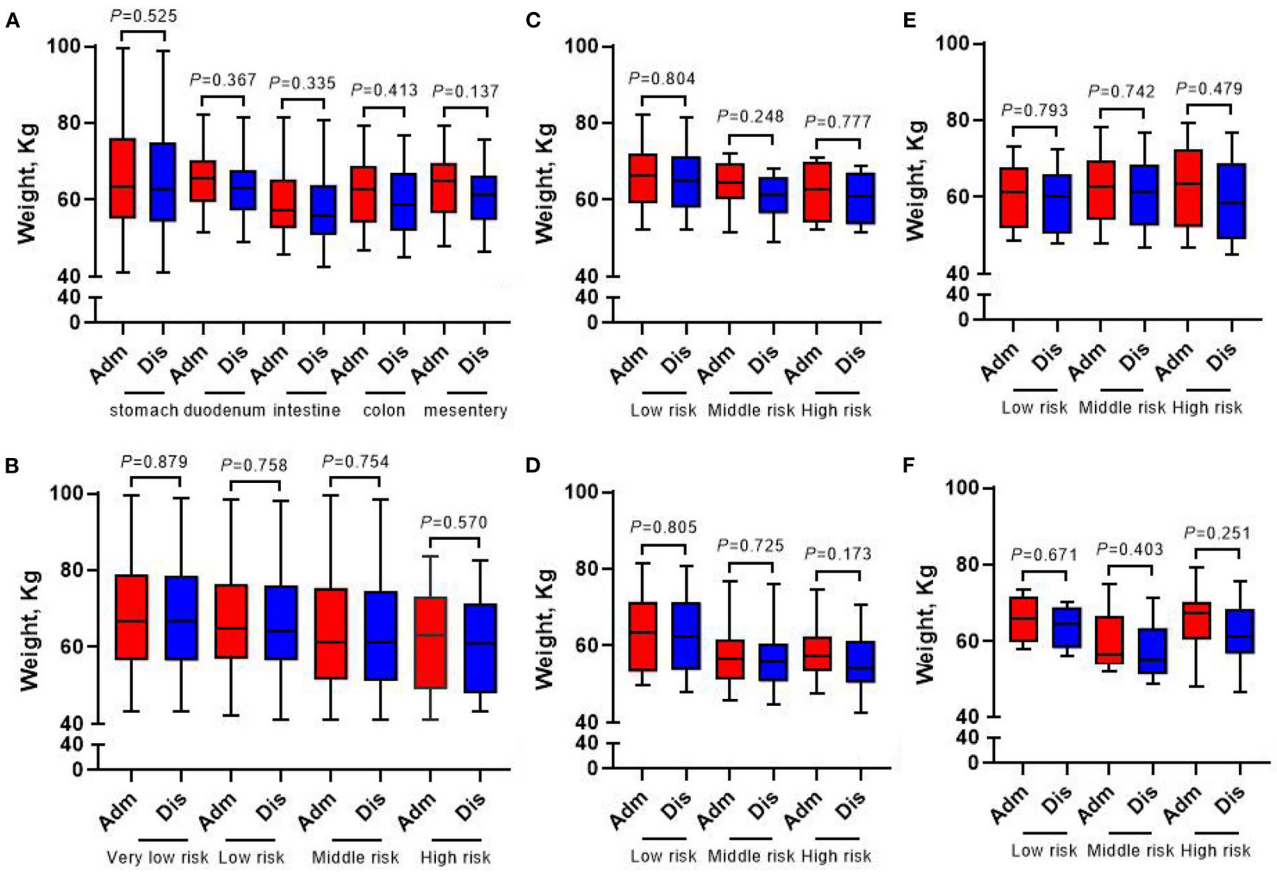

FIGURE 4 | Changes of weight in 413 GIST patients at admission and discharge. **(A)** Total; **(B)** stomach; **(C)** duodenum; **(D)** intestine; **(E)** colorectal; **(F)** mesentery.

RESULTS

Patient Characteristics

Between January 2016 to January 2020, 413 GIST patients were screened for inclusion. According to the 2008 version of NIH stromal tumor risk classification standard, 92 cases (22.28%) of high risk group, tumor location is mostly mesentery; there were 154 cases (37.29%) in the middle risk group, and 144 cases (34.86%) in the low risk group, while 23 cases (5.57%) in the very low risk group were all located in the stomach (**Figure 1A**). All GIST patients were confirmed by pathology and underwent R0 resection, including 23 cases of combined organ resection. Among these 23 patients, there were 8 cases of combined splenectomy, 6 cases of partial hepatectomy, 5 cases of pancreatic tail resection, 2 cases of cholecystectomy, 1 case of oophorectomy, and 1 case of partial bladder resection. After surgical resection, 413 patients with postoperative pathology of high-risk group (22.28%) and medium-risk group (37.29%) were treated with oral targeted drug imatinib, while patients in low-risk group and extremely low-risk group were regularly reviewed. Other baseline demographic and clinical features of the whole group are shown in **Table 1**.

All patients underwent NRS2002 screening and PG-SGA assessment at admission, and **Figures 1B,C** show the nutritional risk and assessment of 413 GIST patients on admission. Among them, 114 patients (27.60%) had the risk of malnutrition (NRS2002 score ≥ 3), and 65 patients (15.74%) had malnutrition (PG-SGA score ≥ 4). Meanwhile, the average weight of all patients at admission was 63.3 Kg, and the average grip strength was 25.0 Kg. The average values of laboratory-related nutritional indicators such as serum albumin, prealbumin and total protein were 42.3 g/L, 236.0 mg/L, and 62.9 g/L, respectively (**Figure 1D**).

Changes of NRS2002 Score and PG-SGA Score at Admission and Discharge

All patients completed NRS2002 screening and PG-SGA assessment at admission and upon discharge. At admission, 299 cases (72.40%) had NRS2002 score < 3, and 114 cases (27.60%) had NRS2002 score ≥ 3. However, 193 cases (46.73%) had nutritional risk at discharge (NRS2002 score ≥ 3), and the difference was statistically significant ($p < 0.001$). Meanwhile, based on the different tumor locations, the proportion of NRS2002 score ≥ 3 at discharge was also higher than that at admission (all $p < 0.05$). Moreover, for patients at the same tumor location, NRS2002 scores had no difference between admission and discharge for those with risk grade below middle risk (all p

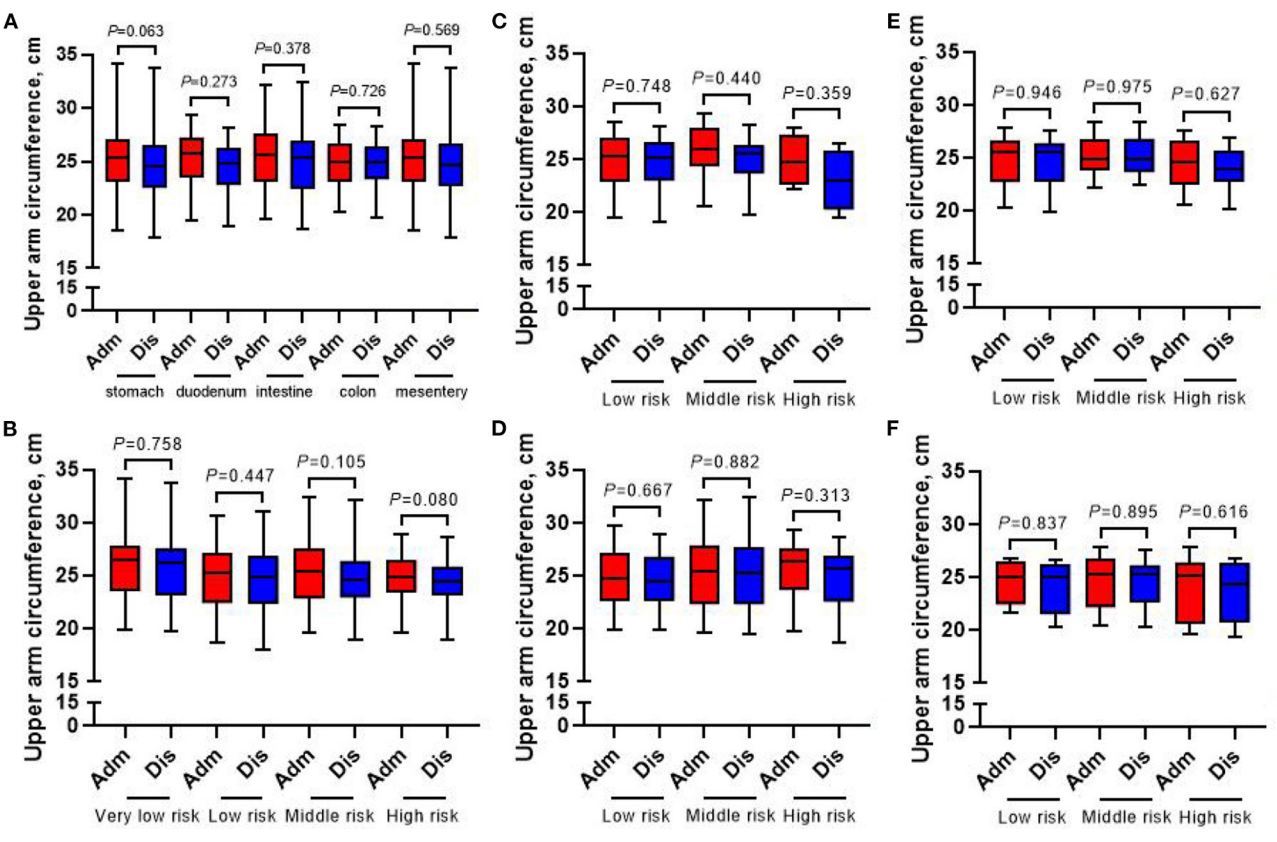

FIGURE 5 | Changes of upper arm circumference in 413 GIST patients at admission and discharge. **(A)** Total; **(B)** stomach; **(C)** duodenum; **(D)** intestine; **(E)** colorectal; **(F)** mesentery.

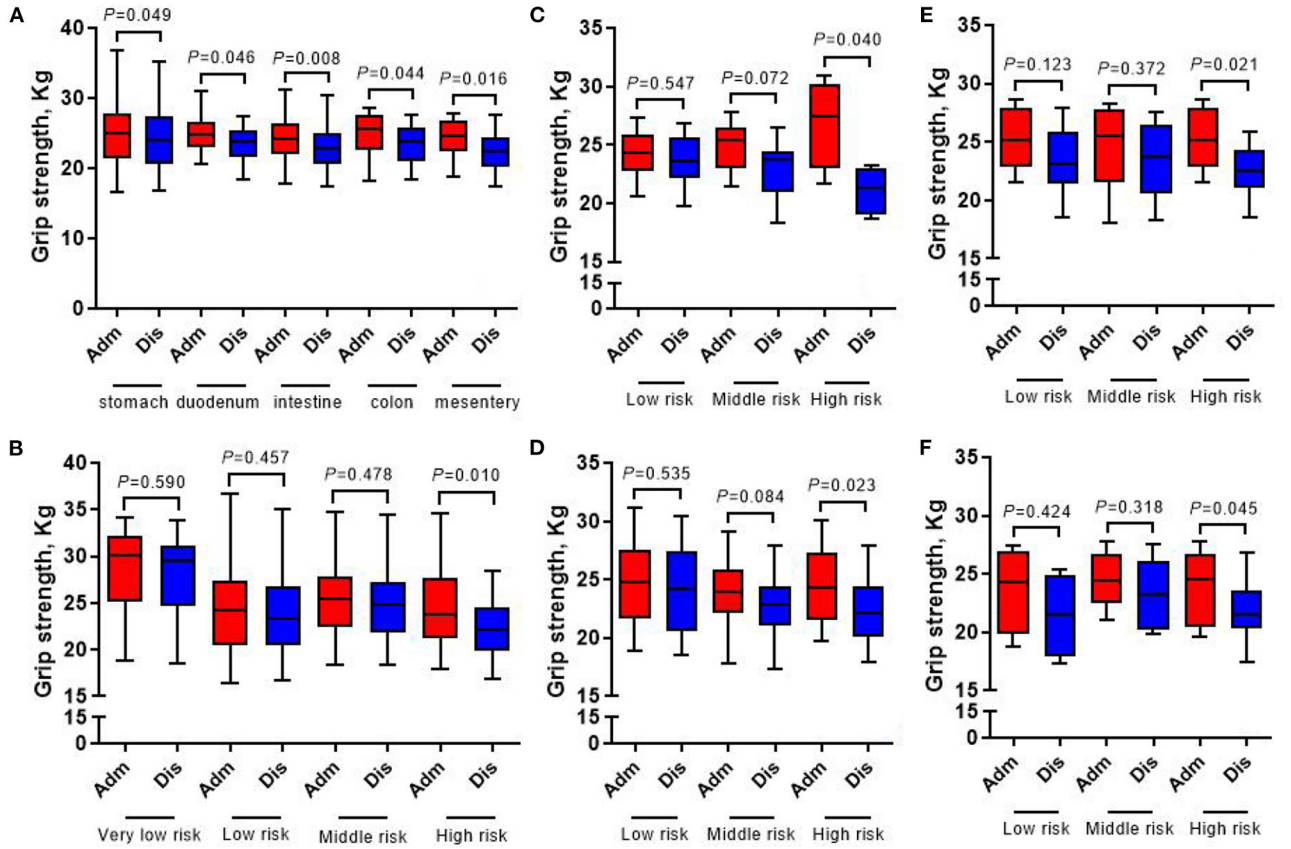

FIGURE 6 | Changes of grip strength in 413 GIST patients at admission and discharge. **(A)** Total; **(B)** stomach; **(C)** duodenum; **(D)** intestine; **(E)** colorectal; **(F)** mesentery.

> 0.05), but the difference was significant only among high-risk patients (all $p < 0.05$) (**Figure 2**).

Furthermore, only 65 patients had malnutrition at admission (PG-SGA score ≥ 4), while the proportion increased significantly at discharge (15.73 vs. 37.29%, $p < 0.001$). There were 154 patients with PG-SGA score ≥ 4 points at discharge, of which PG-SGA score ≥ 9 accounted for 3.15%. In addition, the number of patients at different tumor locations with PG-SGA score ≥ 4 at discharge was higher than at admission (all $p < 0.05$). Subgroup analysis of GIST patients at the same tumor site showed that especially for patients at high risk, they are more likely to suffer from malnutrition than before admission (PG-SGA score ≥ 4) (all $p < 0.05$) (**Figure 3**).

Figures 4, **5** show that compared with the time of admission, whether GIST patients located at different tumor sites or patients with different risk grades at the same tumor site, there was no difference in their body weight and upper arm circumference at the time of discharge (all $p > 0.05$). However, in terms of patient grip strength, we found that there were significant differences between GIST patients with different tumor sites at admission and at discharge. Further analysis showed that for patients with different risk grades, only high-risk GIST patients have such obvious differences (**Figure 6**).

Changes of Laboratory Examination Indexes at Admission and Discharge

The whole group of patients underwent nutrition-related peripheral blood laboratory tests at admission and at discharge, and the change in hemoglobin level was not statistically significant (all $p > 0.05$) (**Figure 7**). In terms of changes in other laboratory indicators, whether in accordance with the different tumor locations or the different risk grades for subgroup analysis, the albumin, prealbumin, and total protein of all patients at discharge were lower than those at admission (all $p < 0.05$) (**Figures 8–10**).

Nutritional Support and Postoperative Complications

Analysis of nutritional support based on different PG-SGA scores showed that 65 patients needed nutritional intervention at admission (PG-SGA score ≥ 4). However, only 49 patients (75.38%) received nutritional support 1 week before treatment, of which 9.52% received parenteral nutrition (PN) support, 50.77% received enteral nutrition (EN) support, and 15.38% received both EN and PN support. In addition, we also found that the proportion of patients who needed nutritional intervention at

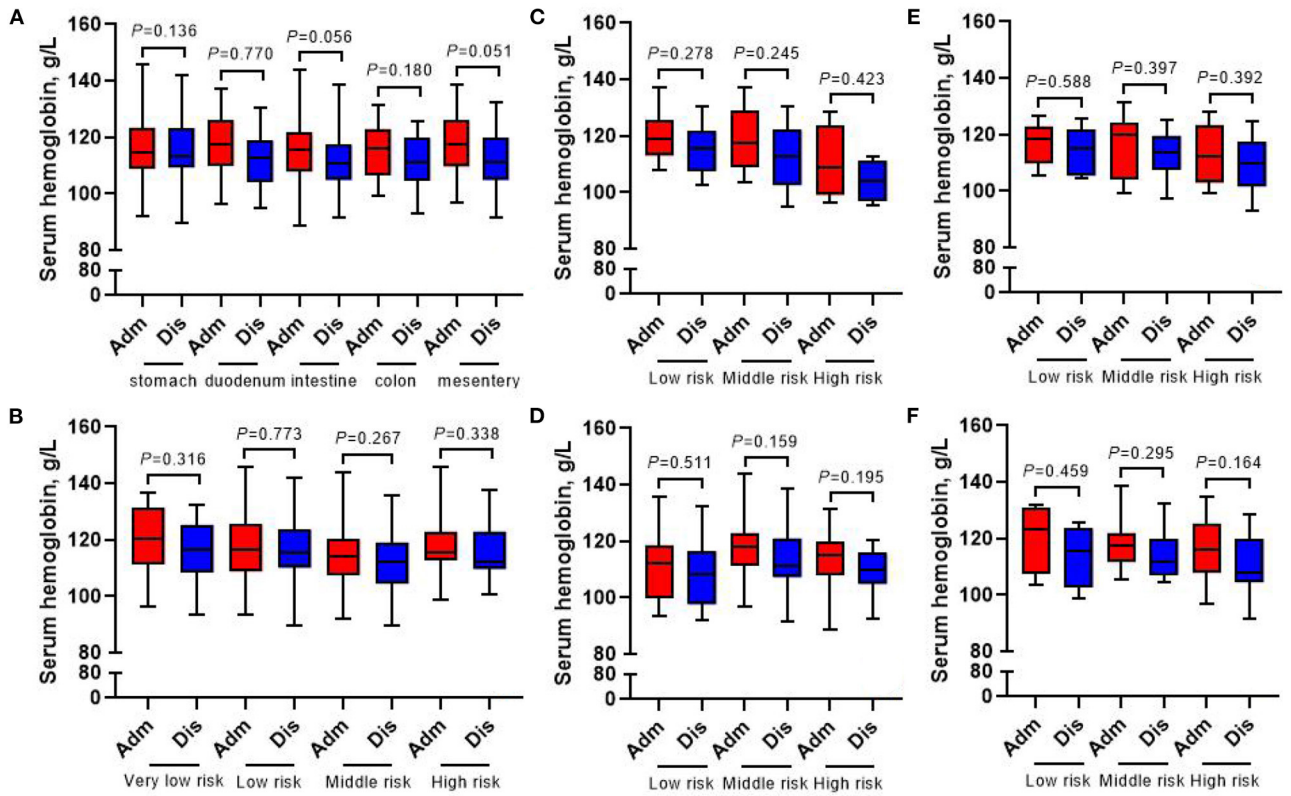

FIGURE 7 | Changes of serum hemoglobin in 413 GIST patients at admission and discharge. **(A)** Total; **(B)** stomach; **(C)** duodenum; **(D)** intestine; **(E)** colorectal; **(F)** mesentery.

discharge (PG-SGA score ≥ 4) was higher than that at admission, but only 62 cases (40.26%) received nutritional support at discharge (**Table 2**).

Among the 413 patients, 82 cases (19.85%) had postoperative complications, including 24 cases of surgical-related complications, 55 cases of respiratory complications, and 3 cases of cardiovascular complications. The patients were divided into two groups based on the PG-SGA score at admission. The incidence of complications in the PG-SGA ≥ 4 group was 29.23% (19/65), which was significantly higher than that in the PG-SGA < 4 group (18.10%, 63/348) ($p = 0.039$). In order to reduce the interference of nutritional support on the incidence of postoperative complications, the comparison between group B and group D without nutritional support showed that the incidence of postoperative complications in the group without malnutrition (PG-SGA < 4) was lower than that in the group with malnutrition (PG-SGA ≥ 4) (18.02 vs. 56.25%, $p < 0.001$). Further subgroup analysis of group C and group D with simultaneous malnutrition (PG-SGA ≥ 4) showed that the incidence of postoperative complications in group C with preoperative nutritional support was significantly lower than that in group D without nutritional support (20.41 vs. 56.25%, $p = 0.006$, **Table 3**).

Meanwhile, we conducted a multivariate analysis of the risk factors that may affect postoperative complications in patients with GIST, and found that the age of patients (≥ 60 years) ($p = 0.004$, OR = 10.552, 95%CI: 2.114∼52.683), intraoperative combined organ resection ($p = 0.012$, OR = 14.917, 95%CI: 1.827∼121.808), and preoperative malnutrition (PG-SGA$\geq$4) ($p = 0.001$, OR = 33.228, 95%CI: 4.060∼271.970) were all independent risk factors for postoperative complications in this group of patients.

The Relationship Between Nutritional Status and Quality of Life in GIST Patients

As an indicator of quality of life, the average score of global health status of patients was 75.7. In terms of the scores of the five functional scales, the average scores of patients' social function and emotional function were the highest, but the score of role function was the lowest (**Figure 11A**). Among the nine medical symptoms, economic problems scored the highest, followed by insomnia and fatigue. Only a few patients reported nausea, vomiting, and dyspnea (**Figure 11B**).

In addition, we analyzed the correlation between the nutritional indicators of patients at discharge and the quality of life of patients, and found that the NRS2002 score (−2.769, 95%CI: −3.992∼-1.546, $p < 000.1$) and PG-SGA (−4.826, 95%CI: −6.685∼-1.034, $p < 000.1$) score of patients at discharge were closely related to the global health indicators of patients. Moreover, patients with good nutritional status at discharge had

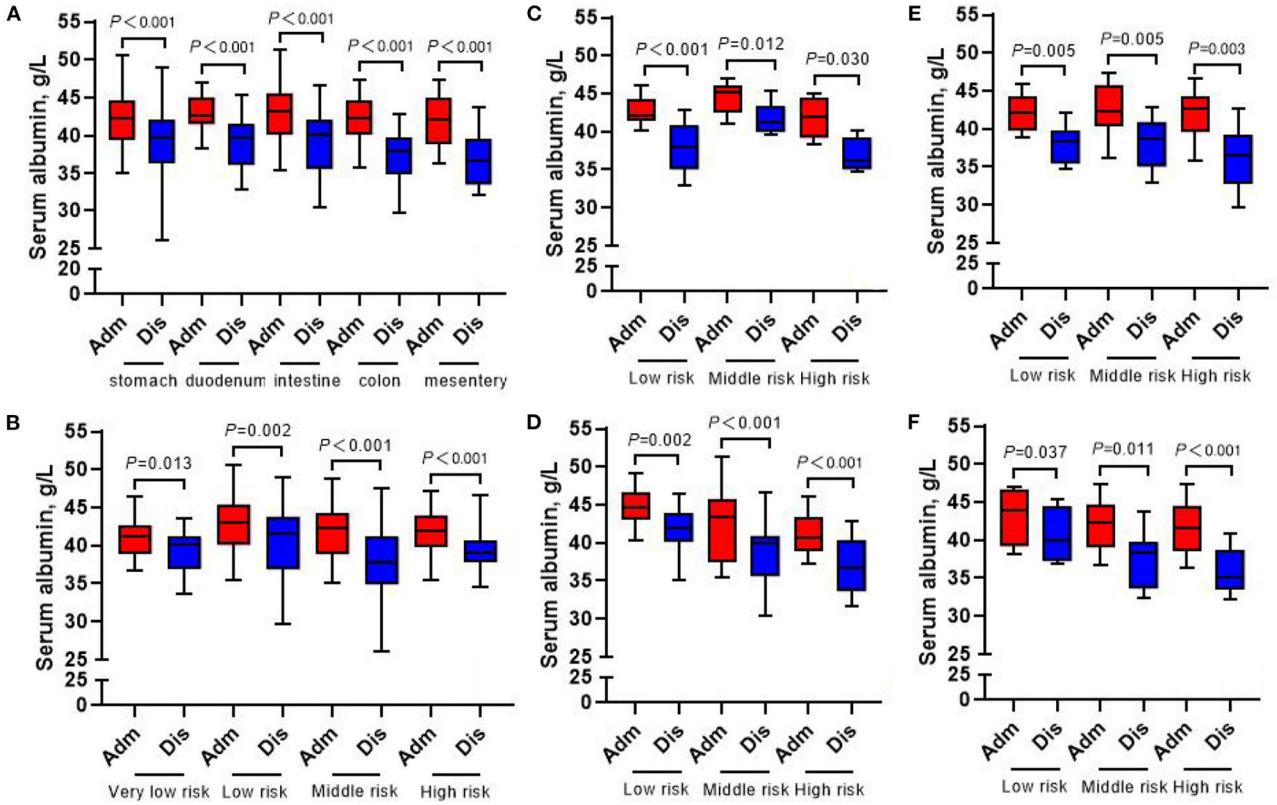

FIGURE 8 | Changes of serum albumin in 413 GIST patients at admission and discharge. **(A)** Total; **(B)** stomach; **(C)** duodenum; **(D)** intestine; **(E)** colorectal; **(F)** mesentery.

good HRQoL scores in other symptoms and functional scores (**Table 4**).

DISCUSSION

In recent years, numerous surveys have shown that the incidence of malnutrition in cancer patients is 32%, and it is even more common in digestive tract tumors (32, 33). Currently, most studies mainly investigate the nutritional status of cancer patients during hospitalization, while few studies focus on the nutritional status of patients at discharge (34, 35). A multicenter cross-sectional survey showed that the incidence of nutritional risk (NRS 2002 $\geq$ 3) at discharge was significantly higher than that at hospitalization (42.82 vs. 40.12%), and the incidence of malnutrition (PG-SGA $\geq$ 4) was 30.47%, which was also significantly higher than 26.45% at hospitalization (36). Meanwhile, surgical resection is the most important treatment for GIST patients, but it will lead to gastrointestinal dysfunction, which will worsen the nutritional status of patients and increase the incidence of postoperative complications. Deterioration of nutritional status in discharged patients will further affect compliance with subsequent anti-tumor therapy, cause decline in quality of life, and increase readmission rate within 6 months. However, there are few reports on the changes in postoperative nutritional status of GIST patients and its impact on clinical outcomes. Our retrospective study was the first to investigate the nutritional status changes of GIST patients during perioperative period and their effects on postoperative complications and quality of life through NRS2002 nutritional risk screening combined with PG-SGA score and laboratory nutritional indicators.

By dynamically observing the nutritional status changes of GIST patients during perioperative period, we found that the body weight, grip strength, and upper arm circumference at discharge were significantly lower than those at admission, but the decrease was more obvious only in the high-risk group. This may be due to the fact that patients in the high-risk group had larger size and larger surgical trauma than those in other groups, resulting in slow recovery of gastrointestinal function and insufficient postoperative nutritional intake. Moreover, we also found that serum albumin, prealbumin, and total protein were significantly lower than those at admission, which may be related to the increase of protein catabolism caused by traumatic stress stimulation after surgical treatment, thus causing the deterioration of nutritional status. This is similar to the results of Zhu et al. (36). Furthermore, our results also discovered that nutritional risk and malnutrition were common in GIST patients during perioperative period, especially

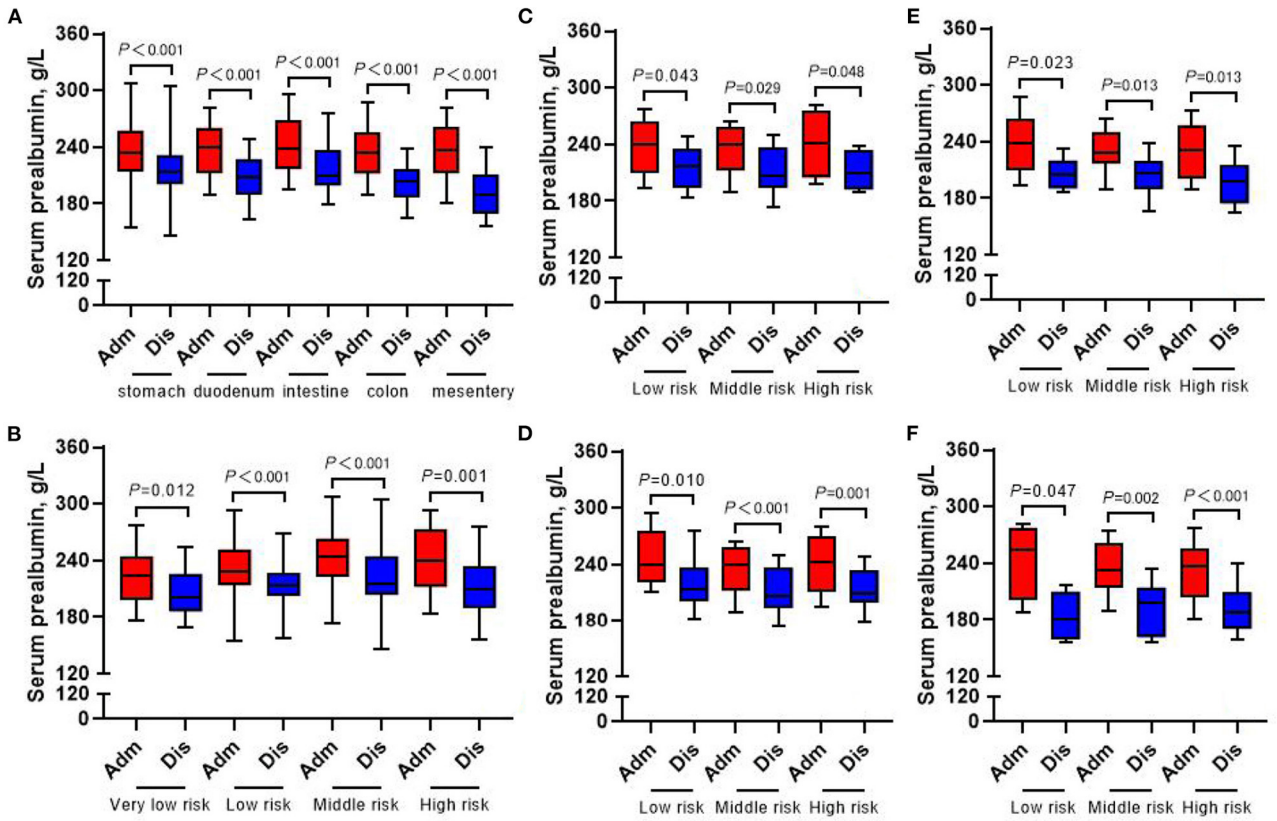

FIGURE 9 | Changes of serum prealbumin in 413 GIST patients at admission and discharge. **(A)** Total; **(B)** stomach; **(C)** duodenum; **(D)** intestine; **(E)** colorectal; **(F)** mesentery.

when patients were discharged after surgery. Through NRS2002 screening and PG-SGA assessment within 24 h after admission and 24 h before discharge, it was found that the incidence of nutritional risk and malnutrition at discharge was 27.60 and 15.73%, respectively, which was significantly higher than 46.73 and 37.29% at admission. Interestingly, our further stratified analysis found that risk of malnutrition in patients in the high-risk group and in patients which located in the mesentery was significantly higher than that in other groups. This suggests that we need to pay more attention to the nutritional status changes, nutritional monitoring, and treatment of GIST patients during perioperative period, especially when the patients are discharged.

We further analyzed the effect of perioperative nutritional status on clinical outcomes of GIST patients, and found that the incidence of surgical-related complications in patients with malnutrition (PG-SGA score $\geq$ 4) (29.23%) was significantly higher than that in patients without malnutrition (18.10%). In addition, the study also showed that patients with nutritional risk had lower incidence of complications than patients without nutritional support ($p = 0.006$), but patients without nutritional risk could not benefit from nutritional support ($p > 0.05$). Moreover, we found that preoperative malnutrition (PG-SGA score $\geq$ 4) was one of the independent risk factors for postoperative complications. Numerous studies have also confirmed that the incidence of postoperative complications in patients receiving preoperative nutritional support is significantly reduced. Jie et al. found that for patients with PG-SGA $\geq$ 4, 50% of patients without nutritional support had complications, but the incidence of complications in patients receiving nutritional support was reduced to 26% (37, 38). The results of this study are consistent with the above studies, which suggests that it is necessary to provide preoperative nutritional support for patients with malnutrition, so as to reduce the incidence of postoperative complications.

This retrospective study was the first to investigate the relationship between postoperative quality of life and nutritional status of GIST patients at discharge. Interestingly, we found that the nutritional status of patients at discharge is closely related to the quality of life. Most importantly, the NRS2002 score and PG-SGA score of patients at discharge were closely related to the global health indicators of patients. These findings have also been supported by other studies, which also found the relationship between nutritional status

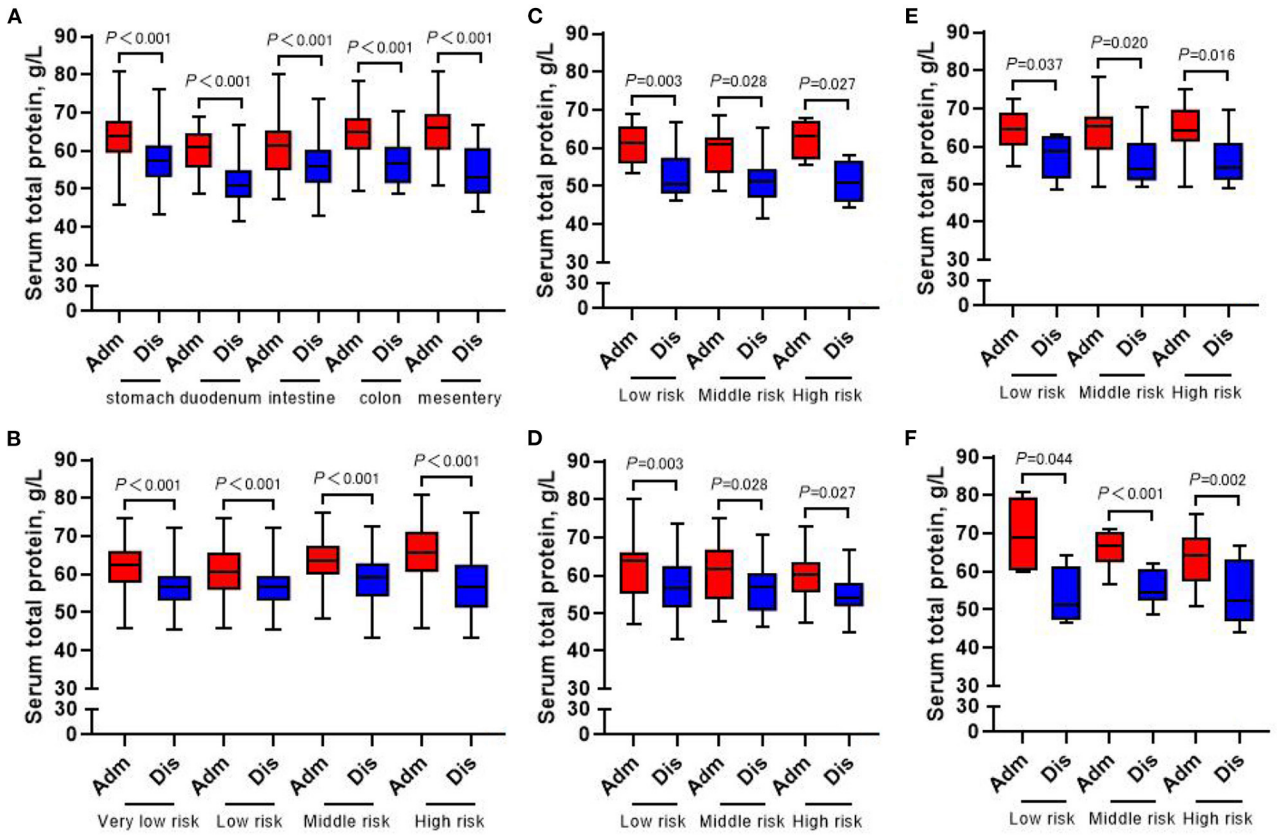

FIGURE 10 | Changes of serum total protein in 413 GIST patients at admission and discharge. **(A)** Total; **(B)** stomach; **(C)** duodenum; **(D)** intestine; **(E)** colorectal; **(F)** mesentery.

TABLE 2 | Patient-generated subjective global assessment classification and nutritional support situation [*n* (%)].

Nutrition support	Admission PG-SGA				Discharge PG-SGA			
	0∼1 (*N* = 144)	2∼3 (*N* = 204)	4∼8 (*N* = 63)	≥9 (*N* = 2)	0∼1 (*N* = 87)	2∼3 (*N* = 172)	4∼8 (*N* = 139)	≥9 (*N* = 15)
No	140 (97.22)	193 (94.08)	16 (25.40)	0 (0)	80 (89.89)	151 (87.79)	87 (62.59)	5 (33.33)
Yes								
PN	0 (0)	1 (0.49)	6 (9.52)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
EN	4 (2.78)	10 (4.90)	32 (50.79)	1 (50.00)	7 (10.11)	21 (12.21)	52 (37.41)	10 (66.67)
EN and PN	0 (0)	0 (0)	9 (14.29)	1 (50.00)	0 (0)	0 (0)	0 (0)	0 (0)

PN, parenteral nutrition; EN, enteral nutrition; PG-SGA, patient-Generated Subjective Global Assessment.

and quality of life in cancer patients. Zhang et al. found that the nutritional status of patients with gastrointestinal cancer determines the quality of life during subsequent treatment (39). Moreover, other scholars also found that the nutritional status of patients may be a decisive factor affecting the quality of life of patients with advanced cancer after discharge, especially in patients with upper gastrointestinal cancer (40, 41). In view of these results, we speculated that the nutritional status of patients at discharge, especially NRS2002 score and PG-SGA score may play a more important role in evaluating the quality of life of patients with GIST after surgery.

There are still some limitations of this study that need to be addressed. First, this study is a single-center retrospective study with limited number of cases. Second, we only investigated the postoperative complications and the quality of life at

TABLE 3 | Comparison of postoperative complications based on PG-SGA score [*n* (%)].

Variable	PG-SGA<4		*P*	Total 1	PG-SGA ≥4		*P*	Total 2	*P**	*P***
	Support (A) (*N* = 15)	No support (B) (*N* = 333)			Support (C) (*N* = 49)	No support (D) (*N* = 16)				
Total	3 (20.00)	60 (18.02)	1.000[b]	63 (18.10)	10 (20.41)	9 (56.25)	0.006	19 (29.23)	<0.001	0.039
Wound infection	1 (6.67)	3 (0.90)	0.417[b]	4 (1.15)	1 (2.04)	1 (6.25)	0.990[b]	2 (3.08)	0.446[b]	0.530[b]
Anastomotic leakage	0 (0)	4 (1.20)	–	4 (1.15)	1 (2.04)	0 (0)	–	1 (1.54)	–	1.000[b]
Lymphatic leakage	0 (0)	0 (0)	–	0 (0)	0 (0)	1 (6.25)	–	1 (1.54)	–	–
Abdominal infection	0 (0)	1 (0.30)	–	1 (0.29)	0 (0)	1 (6.25)	–	1 (1.54)	0.166	1.000[b]
Abdominal bleeding	0 (0)	3 (0.90)	–	3 (0.86)	0 (0)	1 (6.25)	–	1 (1.54)	0.446[b]	1.000[b]
Anastomotic bleeding	0 (0)	2 (0.60)	–	2 (0.57)	0 (0)	0 (0)	–	0 (0)	–	–
intestinal obstruction	0 (0)	3 (0.90)	–	3 (0.86)	0 (0)	1 (6.25)	–	1 (1.54)	0.446[b]	1.000[b]
Respiratory complications	2 (13.33)	42 (12.61)	1.000[b]	44 (12.64)	7 (14.29)	4 (25.00)	0.543[b]	11 (16.92)	0.293[b]	<0.001
Cardiovascular complications	0 (0)	2 (0.60)	–	2 (0.57)	1 (2.04)	0 (0)	–	1 (1.54)	–	0.965[b]

*Note: *B vs. D; **Total 1 vs. Total 2; [b]Continuity correction; PG-SGA, patient-Generated Subjective Global Assessment.*

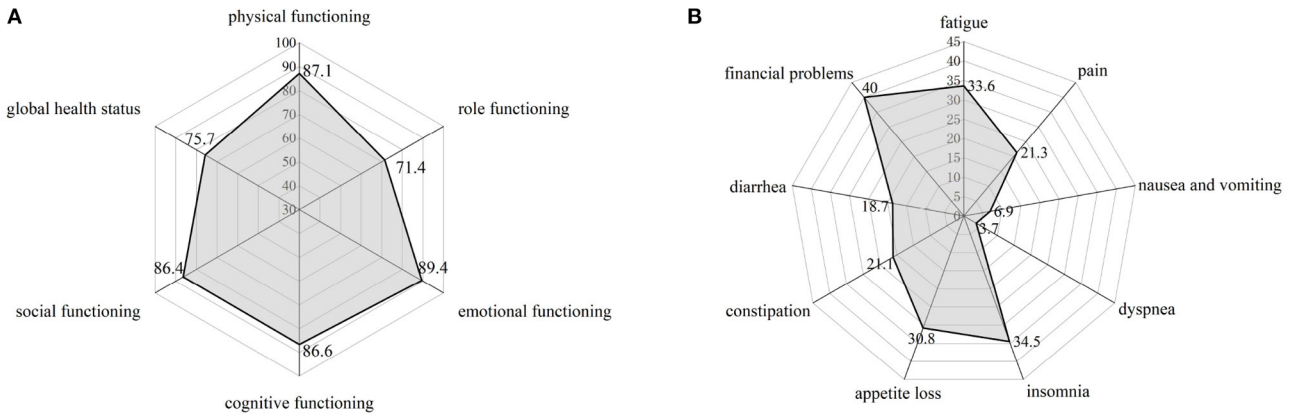

FIGURE 11 | HRQoL score according to overall global health status **(A)**, sub-domains of functioning **(A)** and symptoms **(B)**.

1 month after surgery, but lacked the long-term dynamic assessment of quality of life after surgery. Third, we did not follow up the survival status of patients, so it was impossible to assess the impact of postoperative nutritional status on the long-term prognosis of patients. Therefore, it is necessary to further carry out multi-center prospective studies to assess the impact of perioperative nutritional status changes in GIST patients on long-term clinical outcomes such as prognosis, quality of life, and subsequent treatment tolerance.

CONCLUSION

In this study, NRS2002 nutritional risk screening combined with PG-SGA nutritional assessment and other nutritional related indicators were used for the first time to dynamically assess the nutritional status changes of GIST patients during perioperative period. Studies have shown that the proportion of nutritional risk (27.60%) and malnutrition (15.73%) in GIST patients at admission is high, but the nutritional status is further deteriorated at discharge, and the nutritional risk and malnutrition rates are 46.73 and 37.29%, respectively. Most importantly, poor perioperative nutritional status is also closely related to poor clinical outcomes. Therefore, NRS2002 nutritional screening, PG-SGA nutritional assessment and other nutrition-related indicators (weight, grip strength, upper arm circumference, serum hemoglobin, albumin, prealbumin, and total protein) should be dynamically monitored in patients with GIST during perioperative period, and necessary nutritional support should be given to patients with malnutrition.

TABLE 4 | Multivariable linear regression model on quality of life, symptom scales, and functional scales from the EORTC QLQ-C30.

Factors[#]	Quality of life and functional scales from the EORTC QLQ-C30 questionnaire[a]					
	Physical functioning	**Role functioning**	**Emotional functioning**	**Cognitive functioning**	**Social functioning**	**Global QoL**
NRS2002	−1.888 (−2.915; −0.862)*	−3.885 (−5.808; −1.962)*	−2.812 (−3.945; −1.679)*	−0.851 (−2.426;0.725)	−0.970 (−2.561; 0.621)	−2.769 (−3.992; −1.546)*
PG–SGA	−2.276 (−2.997; −1.555)*	−2.948 (−4.299; −1.597)*	−0.837 (−1.634; −0.041)*	−1.404 (−2.511; −0.297)*	−0.919 (−2.037;0.199)	−4.826 (−6.685; −1.034)*
Weight	−0.028 (−0.178; 0.121)	−0.096 (−0.376; 0.183)	0.112 (−0.053; 0.277)	−0.243 (−0.472; −0.013)*	0.047 (−0.185; 0.278)	−0.015 (−0.193; 0.163)
Upper arm circumference	0.104 (−0.427; 0.636)	−0.546 (−1.542; 0.450)	−0.216 (−0.803; 0.370)	0.106 (−0.709; 0.922)	0.033 (−0.791; 0.856)	−0.404 (−1.037; 0.230)
Grip strength	0.42 2(−0.035; 0.878)	0.673 (−0.182; 1.528)	0.358 (−0.146; 0.861)	0.562 (−0.138; 1.263)	0.338 (−0.369; 1.045)	0.550 (0.007; 1.094)*
Serum hemoglobin	0.078 (−0.050; 0.206)	0.138 (−0.102; 0.378)	0.038 (−0.103; 0.179)	0.187 (−0.010; 0.383)	0.118 (−0.081; 0.316)	0.098 (−0.055; 0.250)
Serum albumin	0.326 (0.018; 0.635)	0.320 (−0.258; 0.898)	0.286 (−0.055; 0.627)	0.378 (−0.096; 0.852)	0.071 (−0.408; 0.549)	0.366 (−0.002; 0.734)
Serum prealbumin	0.046 (−0.004; 0.635)	0.028 (−0.065; 0.121)	0.010 (−0.045; 0.064)	0.076 (0.000; 0.153)*	0.031 (−0.047; 0.108)	0.045 (−0.014; 0.105)
Serum total protein	−0.050 (−0.254; 0.154)	−0.079 (−0.461; 0.304)	−0.159 (−0.384; 0.067)	−0.037 (−0.350; 0.277)	−0.237 (−0.554; 0.079)	−0.135 (−0.378; 0.109)

Factors[#]	Symptom scales from the EORTC QLQ–C30 questionnaire[b]								
	Fatigue	**Nausea /vomiting**	**Pain**	**Dyspnea**	**Insomnia**	**Appetite loss**	**Constipation**	**Diarrhea**	**Financial problem**
NRS2002	1.518 (0.441; 2.595)*	0.170 (−0.465; 0.804)	2.843 (1.260; 4.426)*	−0.173 (−0.980; 0.635)	0.449 (−1.945; 2.843)	−3.066 (−5.720; −0.412)*	0.538 (−1.487; 1.679)*	−0.641 (−2.130; 0.848)	−0.300 (−2.464; 1.864)
PG–SGA	0.971 (0.215; 1.728)*	0.265 (−0.180; 0.711)	−0.379 (−1.492; 0.733)	0.39 (−0.177; 0.958)*	0.344 (−1.338; 2.026)	0.187 (−1.678; 2.052)	−0.024 (−1.136; 1.088)	0.415 (−0.632; 1.461)	−0.057 (−1.578; 1.463)
Weight	−0.067 (−0.224; 0.090)	−0.015 (−0.108; 0.077)	−0.033 (−0.264; 0.197)	−0.098 (−0.216; 0.019)	0.241 (−0.107; 0.590)	−0.142 (−0.528; 0.245)	−0.008 (−0.238; 0.223)	0.064 (−0.153; 0.281)	−0.209 (−0.524; 0.105)
Upper arm circumference	0.144 (−0.414; 0.702)	0.006 (−0.322; 0.334)	0.063 (−0.757; 0.883)	−0.002 (−0.421; 0.416)	0.800 (−0.440; 2.039)*	1.333 (−0.041; 2.707)*	−0.366 (−1.185; 0.454)	0.358 (−0.413; 1.129)	−0.691 (−1.812; 0.429)
Grip strength	−0.145 (−0.624; 0.334)	0.101 (−0.181; 0.383)	−0.108 (−0.812; 0.596)	0.101 (−0.258; 0.460)	−0.580 (−1.645; 0.484)	−0.225 (−1.4051; 0.955)	−0.053 (−0.757; 0.650)	−0.470 (−1.132; 0.192)	0.417 (−0.546; 1.379)
Serum hemoglobin	−0.084 (−0.218; 0.051)	0.092 (0.012; 0.171)	0.026 (−0.171; 0.224)	−0.047 (−0.148; 0.054)	−0.075 (−0.374; 0.223)	−0.074 (−0.405; 0.257)	0.030 (−0.168; 0.227)	0.038 (−0.148; 0.224)	0.138 (−0.132; 0.408)
Serum albumin	−0.319 (−0.642; 0.005)	−0.105 (−0.296; 0.086)	−0.240 (−0.716; 0.236)	0.027 (−0.216; 0.270)	−0.036 (−0.756; 0.684)	−0.507 (−1.305; 0.291)	−0.076 (−0.552; 0.400)	0.246 (−0.202; 0.693)	0.441 (−0.210; 1.092)
Serum prealbumin	−0.026 (−0.079; 0.026)	0.020 (−0.010; 0.051)	−0.025 (−0.101; 0.052)	0.025 (−0.014; 0.064)	−0.035 (−0.151; 0.080)	−0.063 (−0.192; 0.065)	0.015 (−0.062; 0.092)	0.010 (−0.062; 0.082)	−0.058 (−0.162; 0.047)
Serum total protein	−0.059 (−0.273; 0.156)	−0.024 (−0.150; 0.102)	0.422 (0.107; 0.736)*	0.030 (−0.131; 0.190)	0.171 (−0.306; 0.647)	0.010 (−0.518; 0.538)	−0.080 (−0.395; 0.234)	−0.056 (−0.352; 0.241)	0.384 (−0.047; 0.814)

Note: Scores are presented as linear regression coefficients, with 95% confidence intervals between brackets. During stepwise backward linear regression, the weakest associated variables are excluded from the model (–).
*#The relevant factors analyzed are all nutritional indicators measured at discharge. [a]Higher scores represent better quality of life or functioning. [b]Higher scores represent more symptoms. *Indicate significant variables ($p < 0.05$).*

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 study design was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (Approval Number: 2018088). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QZ: conception and design and administrative support. PD, PY, YT, HG, YoL, CS, ZZ, DW, XZ, BT, and YuL: provision of study materials or patients. PD, PY, YT, HG, and YaL: collection and assembly of data. PD, HG, and CS: data analysis and interpretation. All authors contributed to the article and approved the submitted version.

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Association Between Red and Processed Meat Consumption and Risk of Prostate Cancer: A Systematic Review and Meta-Analysis

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Background: Debate on the potential carcinogenic effects of meat intake is open and the relationship between meat consumption and risk of prostate cancer remains uncertain. This meta-analysis was conducted to summarize earlier prospective studies on the association of meat consumption with risk of prostate cancer.

Methods: Relevant studies were identified by exploring PubMed/Medline, Scopus, Web of Science, EMBASE, and Google Scholar databases up to December 2020. Fixed-effects and random-effects meta-analyses were used for pooling the relative risks (RRs). Heterogeneity across studies was evaluated using the Q-statistic and *I*-square (I^2). A funnel plot and Egger's test was used to detect publication bias. Linear and non-linear dose-response analyses were performed to estimate the dose-response relations between meat intake and risk of prostate cancer.

Results: Twenty-five prospective studies were included in this meta-analysis. Totally, 1,900,910 participants with 35,326 incident cases of prostate cancer were investigated. Pooling the eligible effect sizes, we observed that high consumption of processed meat might be associated with an increased risk of "total prostate cancer" (RR: 1.06; 95% CI: 1.01, 1.10; $I^2 = 1.5\%$, $P = 0.43$) and "advanced prostate cancer" (1.17; 1.09, 1.26; $I^2 = 58.8\%$, $P = 0.01$). However, the association between processed meat and "advanced prostate cancer" was not significant in the random-effects model: 1.12 (95% CI: 0.98, 1.29). A linear dose-response analysis indicated that an increment of 50 grams per day of processed meat intake might be related to a 4% greater risk of "total prostate cancer" (1.04; 1.00, 1.08; $I^2 = 0.0\%$, $P = 0.51$). "Total meat intake" was marginally associated with all outcomes of prostate cancer risk (1.04; 1.01, 1.07; $I^2 = 58.4\%$, $P < 0.001$).

Conclusions: This systematic review and meta-analysis of prospective studies indicated that increased consumption of "total meat" and "processed meat" might be associated with a higher risk of prostate cancer.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=230824, identifier: CRD42021230824.

Keywords: red meat, processed meat, total meat, prostate cancer, meta-analysis

INTRODUCTION

Prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men worldwide (1, 2). It is the most commonly diagnosed cancer in 12 regions of the world in men with an incidence rate of 13.5%, globally (2).

Older age, African-American descent, and family history are the established risk factors for prostate cancer. Diet is one of the most modifiable risk factors for prostate cancer (3). Consumption of some food groups has been positively or inversely associated with the risk of prostate cancer (4, 5). The most interesting food group in this regard is the consumption of meat and meat products. The relation between meat intake and risk of prostate cancer has been widely investigated; however, findings are controversial (6, 7). Red and processed meat contain heme iron and other compounds including heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and N-nitroso compounds (NOCs) that are produced by high-temperature or prolonged cooking (8, 9). These compounds were reported to be carcinogenic in animal studies (10). Earlier studies have shown a positive association between red and processed meat consumption with prostate cancer risk (6, 11). However, previous two meta-analyses of prospective cohort studies did not find a relationship between red or processed meat consumption and risk of developing prostate cancer (12, 13), except for a weak positive association between processed meat intake and total prostate cancer risk (13). In a pooled analysis of 15 cohort studies in 2016, total red meat, unprocessed red meat, and processed meat consumption were not associated with risk of all prostate cancer (14). Five new big cohort studies were published since the release of the last meta-analysis. Furthermore, no previous study had examined the non-linear dose-response association between meat consumption and risk of prostate cancer. In the current study, we did an updated systematic review and a comprehensive dose-response meta-analysis of previous studies on the relationship between red and processed meat consumption and risk of prostate cancer.

METHODS AND MATERIALS

Search Strategy

This systematic review and meta-analysis presented based on PRISMA guideline (15). The protocol for this review was registered at PROSPERO (registration no. CRD42021230824). We investigated the electronic databases of PubMed/Medline, Scopus, Web of Science, EMBASE, and Google Scholar systematically to find relevant studies. In this search, we used keywords including the following terms: ("prostatic neoplasms" OR "prostate cancer" OR "prostatic neoplasms" OR "prostate") AND ("red meat" OR "meat" OR "meat products" OR "pork meat" OR "meat" OR "meat products" OR "red meat" OR "minced meat" OR "beef" OR "mutton" OR "pork" OR "veal" OR "lamb" OR "processed meat" OR "hamburger" OR "salami" OR "hot dog" OR "bacon" OR "sausage"). No restriction was used when searching the databases. To avoid missing any relevant study, we reviewed the reference lists of all related publications. Duplicate citations were then removed. All potentially relevant studies identified from the literature search were screened by two independent investigators (SNM and AA) based on the study title and abstract. Any disagreements were resolved in consultation with the principal investigator (AE).

Inclusion Criteria

Studies were included in this systematic review and meta-analysis if they met the following criteria: (1) publications done on men > 18 years old; (2) those that assessed consumption of red or processed meat as the exposure; (3) examined high vs. low meat consumption; (4) investigated risk of prostate cancer as the outcome; and (5) nested case-control, case-cohort, and prospective cohort studies.

Exclusion Criteria

We excluded duplicate citations and those that did not meet our inclusion criteria. Studies that assessed consumption of meat, chicken, or fish intake together were excluded (some studies that considered white meat as part of the processed meat were not excluded). We also did not include studies that investigated the incident symptomatic benign prostatic hyperplasia as the outcome. In addition, case-control, cross-sectional, ecological design, reviews, editorials, commentaries, and letters were not included as well.

Data Extraction

The following information was extracted with a standardized data collection form by two reviewers (SNM and AA): the first author's last name, name of the study cohort, country, participants' age (mean or range), number of participants, number of cases, years of follow up (mean, median, or maximum number of follow up), method of assessment of meat intake, the main exposure and outcome of interest, comparisons, the relevant effect size [including odds ratios (ORs), risk ratios or relative risks (RRs), and hazard ratios (HRs)] and 95% confidence intervals (CIs), and covariates used for adjustment. Any disagreements in data extraction between the two reviewers were consulted with the leading investigator (AE).

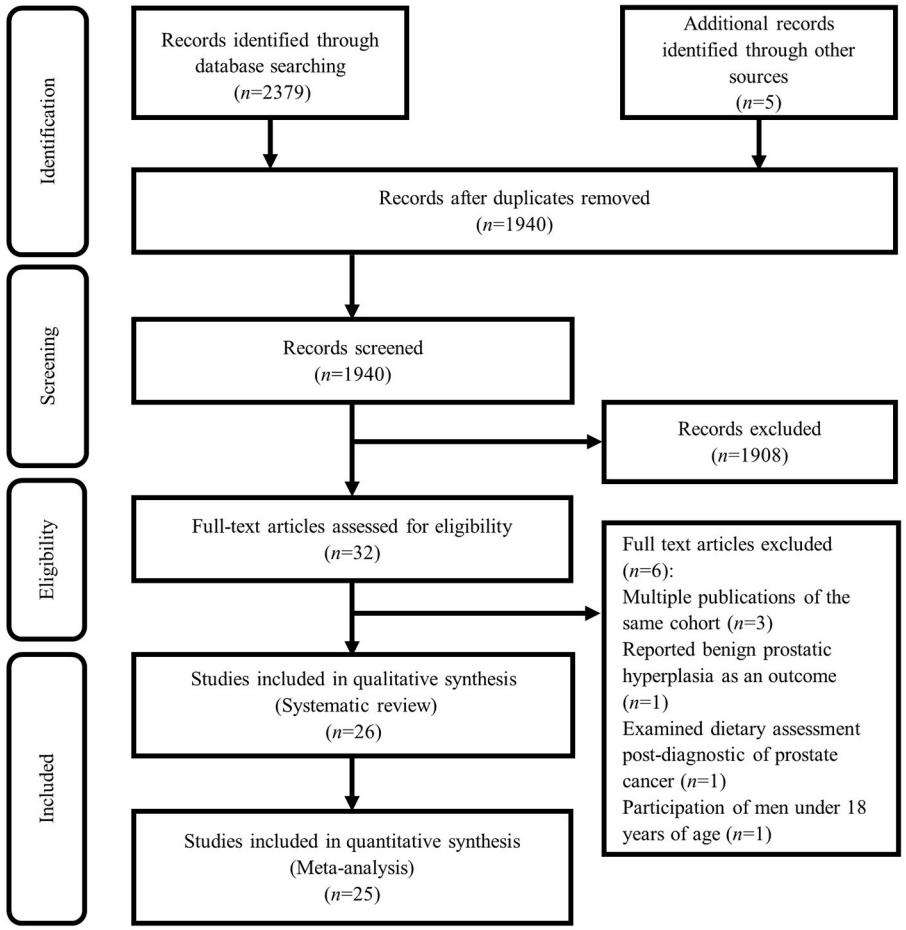

FIGURE 1 | Flowchart of the study selection process.

"Red meat" was defined as the consumption of red meat and unprocessed red meat. "Processed meat" was defined as the consumption of sausages, bacon, hamburger, ham, lunch meat, hot dogs, cured meat, cold meat, smoked beef, and processed poultry, poultry sausage. "Red and processed meat" was considered as the sum of red meat and processed meat. In addition, "total meat" was defined as the sum of red meat, processed meat, and meat (in publications where meat consumption had not been defined to be red or white meat). The studies had defined the outcome in different ways. In the current meta-analysis, studies with the outcome of prostate cancer, total prostate cancer, all prostate cancer, and prostate cancer diagnosis were included in the category of "total prostate cancer." In addition, "advanced prostate cancer" in this study was defined as advanced prostate cancer, high-stage prostate cancer, lethal prostate cancer, fatal prostate cancer, non-localized or high-grade cancer, and metastatic prostate cancer.

Excluded Articles

Based on our initial search, 1,940 studies were found. Based on screening for title and abstract, a total of 1,908 articles were excluded and 32 articles remained to be assessed for eligibility. After evaluation, 6 further studies were excluded due to the following reasons: three cohort studies with the same population in other publications including NIH-AAPR cohort (16, 17), and ATBC cohort (18), in which we considered the most comprehensive publication (19). In other words, among studies published from the NIH-AAPR cohort, we included the study of Sinha et al. and excluded the studies of Major et al. and Cross et al. because the study of Sinha et al. had considered a larger sample size. Also, among studies published from the ATBC cohort, we included the study of Wright et al. because had considered a more follow-up duration. The study of Kristal et al. was excluded because of considering incident symptomatic benign prostatic hyperplasia as the outcome, rather than prostate cancer (20). In addition, we excluded the study of Richman et al. because of considering post-diagnostic dietary intakes (21). Also, the study of Veierød et al. was excluded due to the participation of men under 18 years of age (22). Therefore, a total of 26 studies remained for the current systematic review. In the meta-analysis, we included 25 (6, 7, 11, 23–44), out of these 26 studies, because the study of Orenstein et al. did not report the required effect sizes (45). The details of the study selection process are shown in **Figure 1**.

Quality Assessment of Studies

The quality of each study was assessed using the Newcastle-Ottawa Scale (NOS). To ensure that the scoring of studies is unbiased, scoring was done by two independent investigators (SNM and AA). This scale includes three parameters for quality assessment: selection, comparability, and outcomes for cohort study. Each study can receive a maximum of four stars for selection, two stars for comparability, and three stars for the outcome. Therefore, in total, each study can achieve a maximum of 9 stars (46). We defined studies with NOS scores of ≥7 as high-quality studies and those with a score of <7 as low-quality studies.

Statistical Analysis

In this meta-analysis, we included ORs, RRs, and HRs for the nested case-control, case-cohort, and prospective cohort studies. Given that random-effects meta-analysis might result in some bias for small studies (47, 48), we applied a fixed-effects model to compute RRs estimates and 95% CIs in this analysis. However, random-effects model was also applied. Q-statistic and I-square (I^2) were used to evaluate heterogeneity across the studies. Significant heterogeneity between studies was indicated if $I^2 > 50\%$. Subgroup analyses were used to find the possible sources of heterogeneity. Between-study heterogeneity was assessed using a fixed-effects model. These analyses were done based on predefined criteria, including country, study quality, and adjustment for energy intake, smoking, alcohol consumption, and family history of cancer. For one study (26) that reported risk estimates for the lowest vs. highest categories of processed meat intake, the risk estimates were computed for the highest vs. the lowest categories of processed meat intake using the Orsini method (49). We conducted a sensitivity analysis to evaluate the influence of a single study on the overall meta-analysis estimate. The possibility of publication bias among included studies was examined by visual evaluation of a funnel plot and the Egger's test. For the egger's test, P values < 0.10 were considered as statistically significant. If there was a significant publication bias, we examined the influence of a publication bias on the findings using the "trim and fill" method (50). A random-effects linear dose-response meta-analysis was performed to estimate the pooled RRs and 95% CIs of prostate cancer for each additional 50 g/day red and processed meat consumption. To do this, the generalized least squares trend estimation method was used, as suggested by Orsini et al., and Greenland and Longnecker (49, 51). Primarily, study-specific slope lines were estimated, followed by combining these lines to obtain an overall average slope. In the dose-response analysis, if the total number of participants or cases in each category was not reported, we divided the total number by the number of categories (52). The median or mean amount of meat intake in each category was allocated to the corresponding RR for each study. For studies that stated the intake as ranges, we estimated the midpoint in each category by calculating the mean of the lower and upper bound. If the highest category was open-ended, the length of the open-ended interval was assumed to be the same as that of the adjacent interval. For studies that reported meat intake as serving or time, we considered 120 grams of red meat, 50 grams of processed meat, and 85 grams of total red and processed meat as a serving, as used in previous studies (53). For studies that stated grams per 1,000 kcal, we calculated the reported intakes using the mean energy intake or 2,000 kcal daily intake. We also examined the non-linear dose-response association between meat intake and prostate cancer risk. Meat consumption was modeled by using restricted cubic splines with 3 knots at percentiles of 10, 50, and 90% of the distribution. The correlation within reported risk estimates was considered and the study-specific RRs were combined using a one stage linear mixed effects meta-analysis. Considering the null hypothesis testing, the significance for non-linearity was computed assuming the coefficient of the second spline equal to zero. Statistical analyses were performed using STATA version 14. P values < 0.05 were considered statistically significant.

RESULTS

Study Characteristics

Characteristics of included studies are provided in **Supplementary Table 1**. Sixteen studies were reported from the United States (US) (6, 11, 26, 28, 31–36, 38, 40–44), seven from Europe (7, 23, 25, 27, 29, 30, 39), and two from East Asia (24, 37). The number of participants in these studies ranged from 240 to 1,179,172. Totally, 1,900,910 participants with 35,326 incident cases of prostate cancer were investigated in these publications. Participants were followed up for 6 to 23 years. Participants aged over 18 years old. Assessment of meat consumption was mostly done using a food frequency questionnaire (FFQ), except for three studies that used dietary records (7, 23, 25), and four studies that used an unidentified questionnaire (24, 31, 40, 42). Most studies had controlled for age ($n = 23$), smoking ($n = 14$), energy intake ($n = 13$), body mass index (BMI) ($n = 13$), family history of cancer ($n = 9$), and education ($n = 7$). Out of 25 studies, 11 studies were of high quality (NOS ≥ 7) (7, 11, 23, 25, 27, 28, 34–36, 38, 44) and other articles were of low quality (NOS < 7, $n = 14$) (6, 24, 26, 29–33, 37, 39–43). For studies that reported the effect sizes for different types of red or processed meat separately (31, 34, 40, 43), we combined the effect sizes using a fixed-effects model and then included the final effect size in the meta-analysis. This was also the case for studies that had reported effect sizes separately for different age (35) or race groups (11).

Considering red meat consumption as the exposure, we found that four studies reported a positive association with risk of total prostate cancers (6, 23, 29, 40). However, in one study, a significant relationship was observed only with beef (40). No significant relationship was found in the remaining 12 studies (7, 11, 25, 27, 30, 31, 33, 34, 36, 37, 41, 45). In terms of advanced prostate cancer, one study found a significant positive association with red meat intake (6), but there was no significant relationship in 8 studies (11, 27, 29, 31, 33–36). About processed meat consumption, a significant association was found between processed meat intake and total prostate cancer in four studies (6, 11, 34, 39). However, in one study this association was seen only in African Americans (11). In another study, it was significant for ham/lunch meat intake (34). No significant relationship was observed in 10 studies (7, 23, 25, 27, 30, 31, 33, 36, 40, 44).

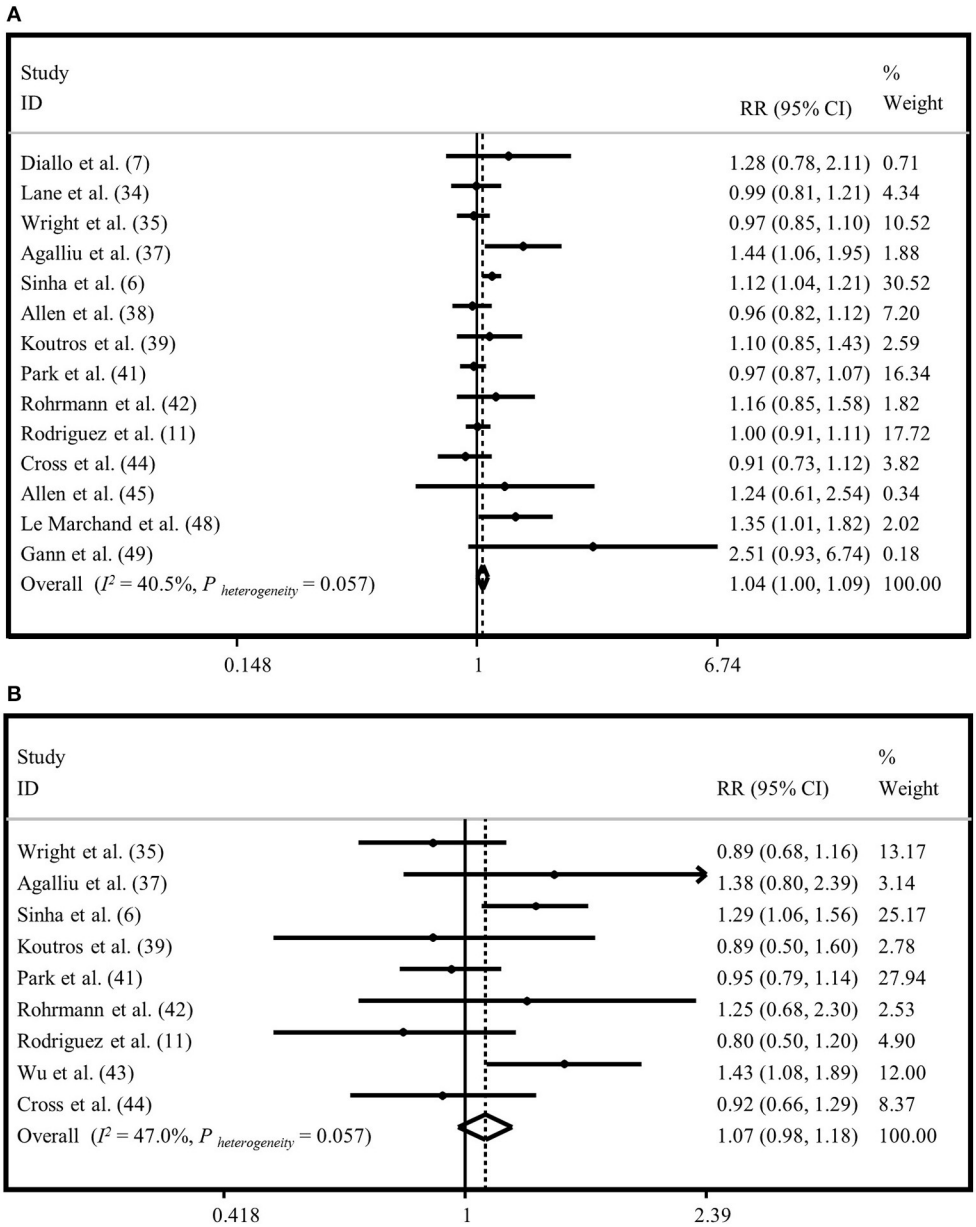

FIGURE 2 | Forest plot derived from fixed-effects meta-analysis investigating the association between red meat intake and risk of total prostate cancer **(A)** and advanced prostate cancer **(B)**. RR, relative risk; CI, confidence intervals; I^2, I-square.

Three studies found a significant association between processed meat consumption and advanced prostate cancer (6, 26, 34). Among these studies, one study found this association only for sausage intake (34). Five studies reached no significant association between processed meat intake and risk of advanced prostate cancer (11, 27, 31, 33, 36).

Findings From the Meta-Analysis

Twenty-five articles were included in this meta-analysis. We performed the analysis based on red meat, processed meat, red and processed meat, and total meat (all meat, red and processed meat) consumption separately. In addition, in each group, the analyses were done separately for total prostate cancer and advanced prostate cancer. However, a pooled analysis for all outcomes of prostate cancer was also performed.

Meta-Analysis on "Red Meat Intake" and Risk of "Total Prostate Cancer"

Fourteen studies assessed the association between red meat intake and risk of total prostate cancer (6, 7, 11, 25, 27, 29–31, 33, 34, 36, 37, 40, 41). The summary risk estimate based on fixed-effects model for "total prostate cancer," comparing

the highest vs. lowest "red meat intake" was 1.04 (95% CI: 1.00, 1.09) (**Figure 2A**). When we applied random-effects model, this finding became non-significant (1.05; 95% CI: 0.98, 1.12) (**Supplementary Figure 1A**). Heterogeneity was moderate (I^2 = 40.5%, P = 0.05). There was no evidence of publication bias (Egger's test P = 0.173). The results from the subgroup analyses revealed that adjustment for energy intake, alcohol consumption, and family history of cancer had influenced the association of "red meat intake" and risk of "total prostate cancer" (**Supplementary Table 2**).

Meta-Analysis on "Red Meat Intake" and "Advanced Prostate Cancer"

Totally, nine publications examined the association between consumption of "red meat" and risk of "advanced prostate cancer" (6, 11, 27, 29, 31, 33–36). Comparing extreme categories, no significant association was found between "red meat intake" and risk of "advanced prostate cancer" based on fixed-effects model (RR = 1.07, 95% CI: 0.98, 1.18) (**Figure 2B**). The same findings were obtained when we applied random-effects meta-analysis (RR = 1.07, 95% CI: 0.92, 1.24) (**Supplementary Figure 1B**). The results of heterogeneity and publication bias analysis revealed no significant between-study heterogeneity (I^2 = 47.0%, P = 0.05) and no evidence of publication bias (Egger's test P = 0.857). Findings from subgroup analyses are provided in **Supplementary Table 2**.

Meta-Analysis on "Processed Meat Intake" and "Total Prostate Cancer"

To investigate the association between "processed meat intake" and risk of "total prostate cancer," 13 studies were included (6, 7, 11, 25, 27, 30, 31, 33, 34, 36, 39, 40, 44). A significant relationship was observed when the highest category of "processed meat intake" was compared to the lowest intake based on both random and fixed-effects analyses (RR = 1.06, 95% CI: 1.01, 1.10). No evidence of heterogeneity was seen between studies (I^2 = 1.5%, P = 0.43) (**Figure 3A**; **Supplementary Figure 2A**). Publication bias was seen by Egger's test (P = 0.06). The influence of a publication bias on the findings was examined using the 'trim and fill' analysis. After imputing four hypothetically missing effect sizes in this analysis, the results were still statistically significant in the fixed-effects model (RR = 1.04, 95% CI: 1.00, 1.08), but not in the random-effects model (1.04; 95% CI: 0.99, 1.09). Findings from subgroup analyses are provided in **Supplementary Table 2**.

Meta-Analysis on "Processed Meat Intake" and "Advanced Prostate Cancer"

Eight publications were included to assess the association between "processed meat intake" and the risk of "advanced prostate cancer" (6, 11, 26, 27, 31, 33, 34, 36). High intake of "processed meat" was positively associated with the risk of "advanced prostate cancer" in the fixed-effects model (RR=1.17, 95% CI: 1.09, 1.26), with a moderate heterogeneity between studies (I^2 = 58.8%, P = 0.01) (**Figure 3B**). However, there was no significant association between "processed meat intake" and the risk of "advanced prostate cancer" in the random-effects model (RR = 1.12, 95% CI: 0.98, 1.29) (**Supplementary Figure 2B**). Egger's regression test revealed no statistical evidence of publication bias (P = 0.569). Subgroup analyses were conducted to find the sources of between-study heterogeneity (**Supplementary Table 2**). Subgroup analyses revealed that adjustment for energy intake and family history of cancer might provide some reasons for between-study heterogeneity.

Meta-Analysis on "Red and Processed Meat Intake" and "Total Prostate Cancer"

The relationship between "red and processed meat intake" and "total prostate cancer" risk was investigated using thirteen studies (6, 7, 11, 25, 27, 30, 31, 33, 34, 36, 38, 40, 43). The association was not significant between "red and processed meat intake" and risk of "total prostate cancer," comparing the highest and lowest categories in the fixed-effects model (RR = 1.02, 95% CI: 0.99, 1.05) (**Supplementary Figure 3A**) and random-effects model (RR = 1.01, 95% CI: 0.96, 1.05) (**Supplementary Figure 4A**). Heterogeneity was not significant between studies (I^2 = 42.1%, P = 0.05). We found no evidence of publication bias among the included studies (Egger's test P = 0.551). Based on subgroup analyses, we found that country and adjustment for alcohol consumption might explain between-study heterogeneity (**Supplementary Table 2**).

Meta-Analysis on "Red and Processed Meat Intake" and "Advanced Prostate Cancer"

Nine studies were included to investigate the relationship between "red and processed meat intake" and risk of "advanced prostate cancer" (6, 11, 27, 31, 33–36, 42). The summary risk estimate for "advanced prostate cancer," comparing the highest and lowest categories of "red and processed meat intake," was 1.05 (95% CI: 0.97, 1.12) in the fixed-effects model (**Supplementary Figure 3B**), and 1.00 (95% CI: 0.87, 1.15) in the random-effects analysis (**Supplementary Figure 4B**), indicating that there was no significant association between "total red and processed meat intake" and risk of "advanced prostate cancer." Heterogeneity between studies was 63.3% (P = 0.005). No evidence of publication bias was observed by Egger's test (P = 0.292). We performed subgroup analyses to assess sources of between-study heterogeneity. In the subgroup analyses, we found that country and adjustment for alcohol consumption might describe between-study heterogeneity (**Supplementary Table 2**).

Meta-Analysis on "Total Meat Intake" and "Total Prostate Cancer"

Twenty studies were used to evaluate the association between "total meat intake" (total meat, meat, red meat, processed meat, and red and processed meat intake) and risk of "total prostate cancer" (6, 7, 11, 24, 25, 27, 29–34, 36–41, 43, 44). We found a marginal positive relationship between "total meat intake" and risk of "total prostate cancer" in the fixed-effects model (1.03; 95% CI: 1.00, 1.06; I^2 = 42.2%, P = 0.01) (**Figure 4A**), but not in the random-effects analysis (RR=1.03, 95% CI: 0.98, 1.08) (**Supplementary Figure 5A**). Results of Egger's test

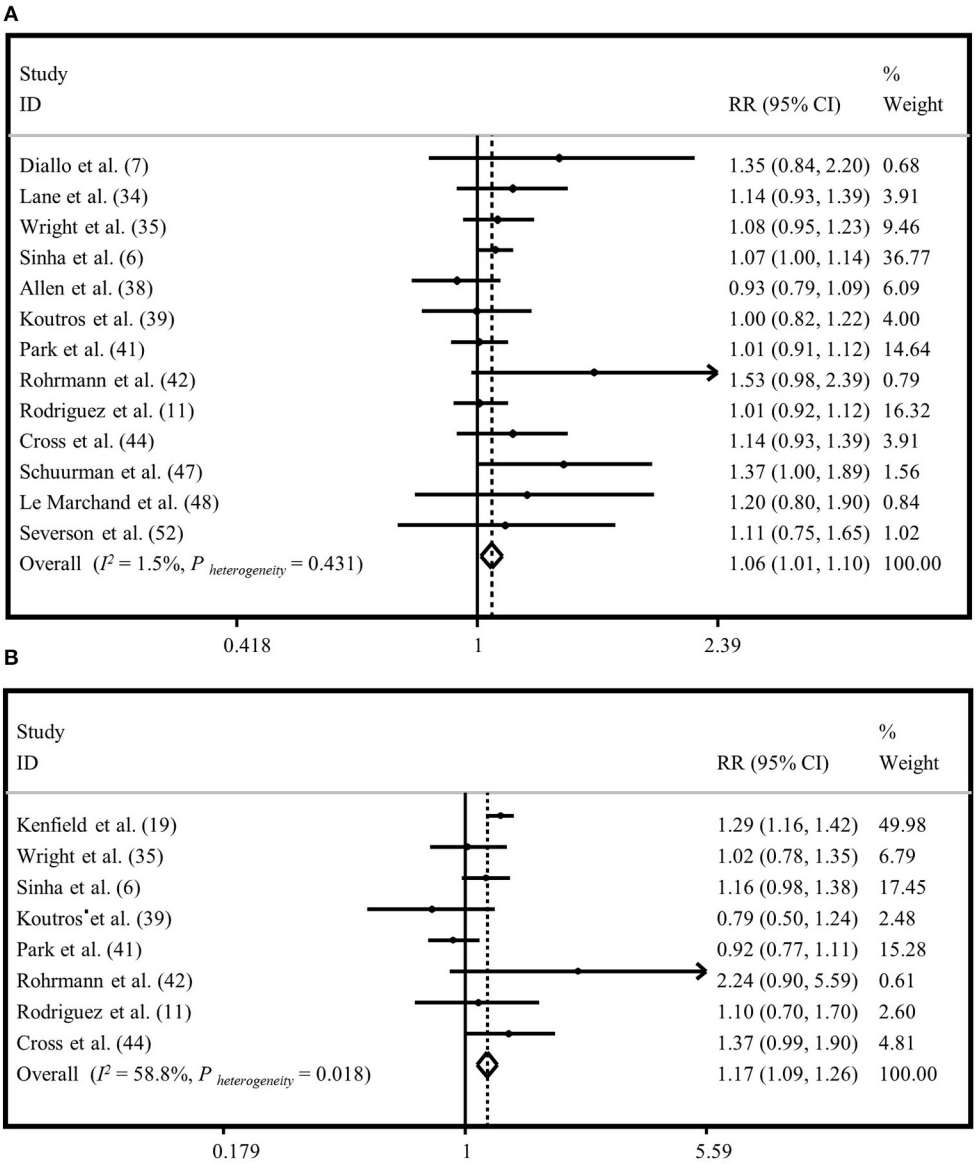

FIGURE 3 | Forest plot derived from fixed-effects meta-analysis investigating the association between processed meat intake and risk of total prostate cancer **(A)** and advanced prostate cancer **(B)**. RR, relative risk; CI, confidence intervals; I^2, I-square.

indicated no publication bias (Egger's test = 0.413). Based on subgroup analyses, adjustment for energy intake and alcohol consumption, and study quality score might be potential sources of heterogeneity (**Supplementary Table 2**).

Meta-Analysis on "Total Meat Intake" and "Advanced Prostate Cancer"

Twelve studies were included to examine the association between "total meat intake" and risk of "advanced prostate cancer" (6, 11, 26, 27, 29, 31–36, 42). Generally, we observed a significant association between "total meat intake" and risk of "advanced prostate cancer" with a summary risk estimate of 1.09 for the highest vs. lowest categories in the fixed-effects model (95% CI: 1.02, 1.16; I^2 = 63.3%, P = 0.002) (**Figure 4B**); however, this relationship was not significant in the random-effects model (RR = 1.05, 95% CI: 0.93, 1.18) (**Supplementary Figure 5B**). The Egger's test did not show evidence of publication bias (P = 0.269). Based on subgroup analyses, we observed that adjustment for alcohol consumption and family history of cancer influenced the association between "total meat intake" and risk of "advanced prostate cancer." When we did subgroup analysis based on studies that did or did not control for alcohol consumption, we found an increased risk of "advanced prostate cancer" with "total meat consumption" in studies that did adjustment for alcohol intake

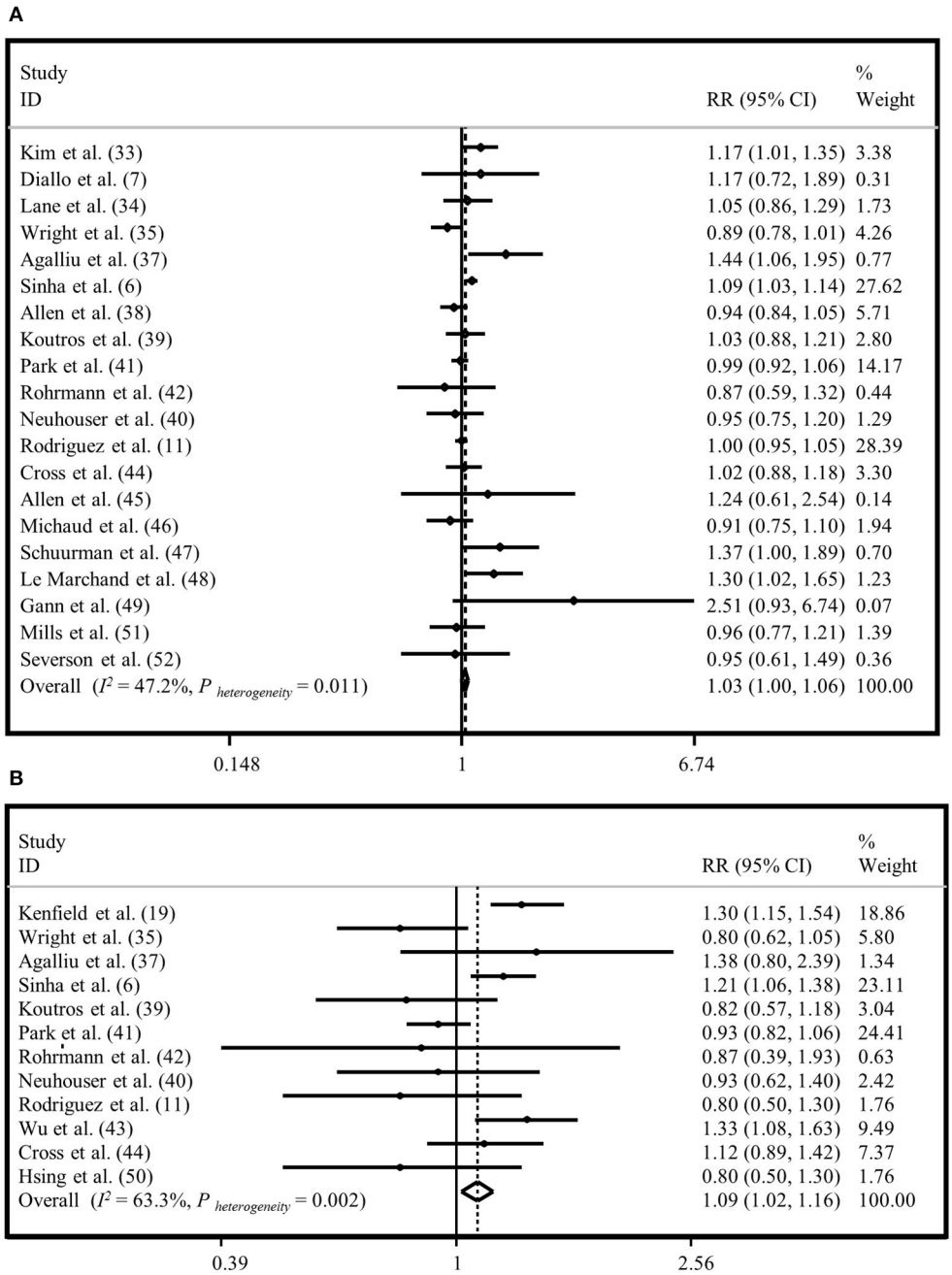

FIGURE 4 | Forest plot derived from fixed-effects meta-analysis investigating the association between total meat intake and risk of total prostate cancer **(A)** and advanced prostate cancer **(B)**. RR, relative risk; CI, confidence intervals; I^2, I-square.

(RR = 1.24, 95% CI: 1.11, 1.39), while in other studies, there was no significant association (RR = 1.02, 95% CI: 0.95, 1.10). In addition, analysis based on studies that controlled for family history of cancer revealed no significant association in studies that did adjustment for this variable (RR = 1.01, 95% CI: 0.92, 1.11), while others reached a significant positive association between "total meat intake" and risk of "advanced prostate cancer" (RR = 1.17, 95% CI: 1.07, 1.28) (**Supplementary Table 2**).

Meta-Analysis on "Total Meat Intake" and "All Outcomes of Prostate Cancer"

Twenty-two studies had investigated the association between "total meat intake" and "all outcomes of prostate cancer" (6, 7, 11, 24–27, 29–37, 39–44). The summary risk estimate for "all outcomes of prostate cancer" risk, comparing the highest and lowest "total meat intake," was 1.04 (95% CI: 1.01, 1.07; $I^2 = 58.4\%$, $P < 0.001$) in the fixed-effects (**Figure 5**), and 1.06 (95% CI: 1.01, 1.12) in the random-effects analyses

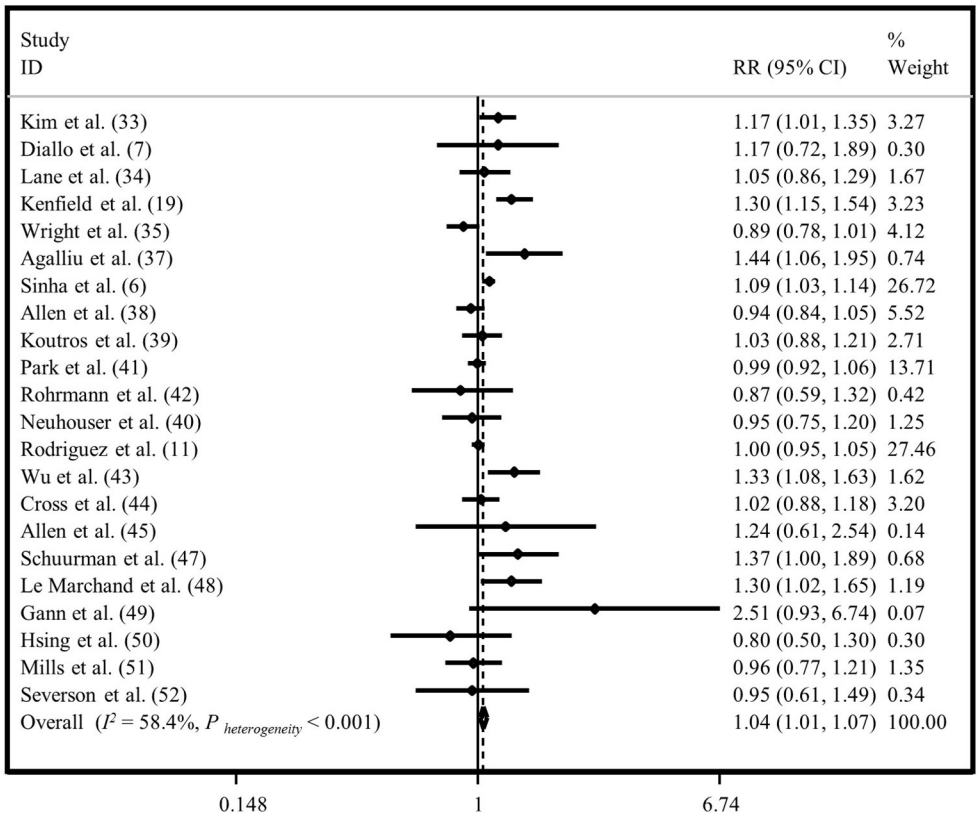

FIGURE 5 | Forest plot derived from fixed-effects meta-analysis investigating the association between total meat intake and all outcomes of prostate cancer. RR, relative risk; CI, confidence intervals; I^2, I-square.

(**Supplementary Figure 6**), indicating that increased intake of "total meat" may be positively associated with an increased risk of "all outcomes of prostate cancer." Publication bias was not documented by Egger's test ($P = 0.240$).

Subgroup analyses were done to investigate possible sources of heterogeneity. We observed that adjustment for energy intake and alcohol consumption, and study quality score were the possible sources of heterogeneity (**Supplementary Table 2**).

Sensitivity Analysis

Findings from sensitivity analyses in each of the above-mentioned meta-analyses revealed that none of the single studies had a significant effect on the pooled effect size.

Linear and Non-linear Dose-Response Analyses

Overall, four studies from the linear (27, 35, 40, 41) and seven studies from the non-linear dose-response analysis (23, 26, 27, 35, 38, 40, 41) were excluded and finally, 21 publications in the linear (6, 7, 11, 17, 23–26, 28–34, 37–39, 42–44), and 18 studies in the non-linear analysis (6, 7, 11, 17, 24, 25, 28–34, 37, 39, 42–44) were included. Findings from the linear dose-response analysis for "processed meat intake" and "total prostate cancer" based on twelve prospective studies revealed that consumption of additional 50 grams per day of processed meat might be associated with a 4% increased risk of "total prostate cancer" (RR = 1.04, 95% CI: 1.00, 1.08; $I^2 = 0.0\%$, $P = 0.51$) (**Supplementary Figure 8A**). No other significant associations were seen between different exposures and study outcomes, either in linear or in non-linear analyses (**Figure 6**; **Supplementary Figures 7**, **8B**, **9**–**15**).

DISCUSSION

In this systematic review and meta-analysis of prospective studies, we found that total meat intake was marginally associated with all outcomes of prostate cancer risk. This association was more evident about processed meat consumption. Although a significant weak relationship was observed between red meat consumption and risk of total prostate cancer in the fixed-effects model, there was no such significant association between red meat consumption and risk of advanced prostate cancer.

There were an estimated 1.3 million new cases of prostate cancer and 3,59,000 deaths worldwide in 2018 (1). In the present systematic review and meta-analysis, we found that dietary intake of processed meat might be associated with a greater risk of total prostate cancer. Although such a significant positive relationship was observed with advanced prostate cancer in the fixed-effects

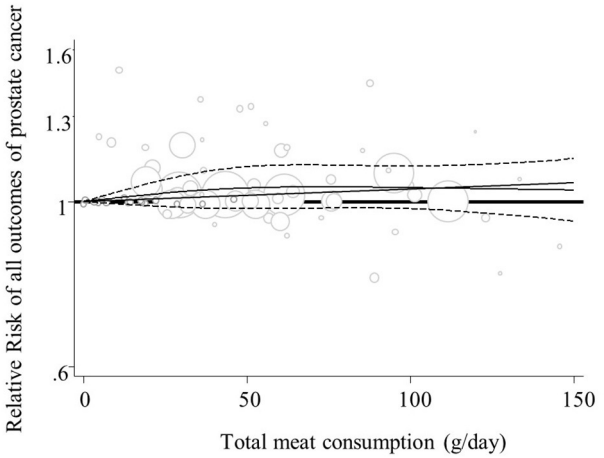

FIGURE 6 | Non-linear dose-response relation between total meat intake and all outcomes of prostate cancer (P-nonlinearity = 0.37; $n = 18$ studies).

analysis, it was not significant in the random-effects analysis. Moreover, we observed a weak significant linear dose-response association between processed meat intake and total prostate cancer. Three earlier studies have previously investigated the association between processed meat consumption and risk of prostate cancer (12–14). In line with our study, a marginally significant dose-response association between processed meat intake and total prostate cancer was reported by Alexander et al. (12). Also Bylsma and Alexander have reported a significant positive relationship between consumption of processed meat and risk of total prostate cancer in their meta-analysis (13). However, no significant relationship was observed between processed meat intake and risk of advanced prostate cancer in that meta-analysis (13). In addition, in a pooled analysis of 15 prospective cohort studies (14) and a meta-analysis of Alexander et al., no significant relationship was found between processed meat consumption and risk of prostate cancer (12). Different findings might be explained by some reasons. For example, in the present study, we included three additional studies that were not included in previous publications (7, 25, 26). Furthermore, prior studies had not combined data on fatal prostate cancer and advanced prostate cancer, while we considered all as advanced prostate cancer.

Although we did not observe a significant association between red meat intake and risk of advanced prostate cancer, a significant weak relationship between red meat consumption and risk of total prostate cancer was seen in the fixed-effects analysis. Previous studies reported no significant association between red meat intake and risk of total and advanced prostate cancer (12–14). Discrepant findings might be originated from the inclusion of two new studies in our analysis (7, 25). In addition, we excluded the study of Veierød et al., which was done on men aged under 18 years (22), while it was included in the previous meta-analysis. Moreover, we included the study of Neuhouser et al. (32), in which type of meat was not specified, in the category of "total meat" analysis, while earlier studies had considered this study in their analysis on "total red meat intake."

When we combined red and processed meat intake, no significant association was found with total and advanced prostate cancer. This might be attributed to the inclusion of studies that examined both red meat and processed meat intakes, and lack of inclusion of studies that examined only red meat or processed meat consumption.

The present meta-analysis has several strengths overs previous meta-analyses. This study pooled effect sizes from 22 papers to investigate the link between total meat intake and risk of all outcomes of prostate cancer for the first time. In addition, we included five new big cohort studies in this meta-analysis. Furthermore, additional studies were included in the linear and non-linear dose-response analyses in the current study. Moreover, both random-effects and fixed-effects models were done in this study to investigate more accurate association between meat intake and prostate cancer. Also, further subgroup analyses, as compared with earlier studies, was performed in this analysis. Finally, in additional to linear dose-response analysis, we did non-linear dose-response analysis in this study as well, while previous studies have only performed linear dose-response analysis.

The relationship between meat consumption and risk of prostate cancer can be explained by several potential mechanisms. Heme iron in red and processed meat (54) and N-nitroso compounds (NOCs) in processed meat are considered as DNA damaging factors (55). Heme iron, which is carried by hemoglobin or directly via the bloodstream throughout the body, is able to catalyze the oxidative reactions that might cause DNA, protein, and lipid oxidations in multiple organs including prostate (55). NOCs in processed meat are formed by the reaction between nitrites or nitrates and amines or amides (56), and the presence of NOCs in processed meat may increase the risk of cancers (8). The presence of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) in cooked foods, particularly meat, and their excessive consumption may increase the risk of some types of cancer (57). HCAs are part of a family of mutagenic compounds and are believed to play an important role in the etiology of human cancers. It has been shown that 2-Amino-1-methyl-6-phenylimiazo[4,5-b]pyridine (PhIP), but not other prominent HCAs existing in cooked meats, forms DNA adducts in the human prostate, which can, in turn, led to abnormal prostate cells (58). Also, excess fat in meat increases the production of hormones such as estrogens, which may further increase the risk of hormone-related cancers such as breast and prostate cancer (59). As shown in previous publications, high dietary intake of red and processed meat was associated with increased risk of depression (60), which can in turn elevate the risk of prostate cancer (61).

This study has several strengths. For the first time, we performed a non-linear dose-response association between meat intake and risk of prostate cancer. We included only prospective studies in this meta-analysis. Therefore, the probability of recall and selection bias is minimized, however, one should consider lost to follow-up in each individual study. In the current analysis a few studies have reported number of people lost to follow-up. This should be considered in the interpretation of our findings. In the sensitivity analysis, our findings were stable and robust.

Most included studies had controlled for confounders such as age, energy intake, and smoking. We had some limitations in this meta-analysis as well. In most studies, FFQ has been used to assess food intake, therefore, measurement error and misclassification of study subjects was possible. We did not examine the association between cooking methods of meat and prostate cancer. In some studies, processed poultry was also included in total processed meat.

In conclusion, we found that total meat intake might be poorly associated with all outcomes of prostate cancer. Consumption of processed meat might be associated with an increased risk of total and advanced prostate cancer. Also, we observed a weak relationship between red meat consumption and risk of total prostate cancer, but not with advanced prostate cancer. Given some significant, albeit weak, associations between meat consumption and risk of different types of prostate cancer, recommendations on the consumption of meat should be done cautiously. In addition, consumption of processed meat intake, due to its detrimental effects on human health, should be reduced. Policymakers might use the current findings to make policies about reducing the production and availability of processed meats. In addition, it seems that subsidizing red and processed meats should be shifted toward healthier animal protein options such as white meat and dairy products. In order to increase consumer awareness, the possible risks of consuming processed meat could be mentioned in nutrition labels.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

SN-M, AS-M, and AA contributed to the conception, design, literature search, statistical analyses, data interpretation, and manuscript drafting. BL contributed to the conception, design, and manuscript drafting. AE contributed to the conception, design, statistical analyses, data interpretation, manuscript drafting, and supervised the study. All authors approved the final manuscript for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.801722/full#supplementary-material

Supplementary Figure 1 | Forest plot derived from random-effects meta-analysis investigating the association between red meat intake and risk of total prostate cancer **(A)** and advanced prostate cancer **(B)**. RR, relative risk; CI, confidence intervals; I^2, I-square.

Supplementary Figure 2 | Forest plot derived from random-effects meta-analysis investigating the association between processed meat intake and risk of total prostate cancer **(A)** and advanced prostate cancer **(B)**. RR, relative risk; CI, confidence intervals; I^2, I-square.

Supplementary Figure 3 | Forest plot derived from fixed-effects meta-analysis investigating the association between red and processed meat intake and risk of total prostate cancer **(A)** and advanced prostate cancer **(B)**. RR, relative risk; CI, confidence intervals; I^2, I-square.

Supplementary Figure 4 | Forest plot derived from random-effects meta-analysis investigating the association between red and processed meat intake and risk of total prostate cancer **(A)** and advanced prostate cancer **(B)**. RR, relative risk; CI, confidence intervals; I^2, I-square.

Supplementary Figure 5 | Forest plot derived from random-effects meta-analysis investigating the association between total meat intake and risk of total prostate cancer **(A)** and advanced prostate cancer **(B)**. RR, relative risk; CI, confidence intervals; I^2, I-square.

Supplementary Figure 6 | Forest plot derived from random-effects meta-analysis investigating the association between total meat intake and all outcomes of prostate cancer. RR, relative risk; CI, confidence intervals; I^2, I-square.

Supplementary Figure 7 | Summary of relative risk of total prostate cancer **(A)** and advanced prostate cancer **(B)** for each 50 g/day increase in red meat intake. CI, confidence intervals; I^2, I-square.

Supplementary Figure 8 | Summary of relative risk of total prostate cancer **(A)** and advanced prostate cancer **(B)** for each 50 g/day increase in processed meat intake. CI, confidence intervals; I^2, I-square.

Supplementary Figure 9 | Summary of relative risk of total prostate cancer **(A)** and advanced prostate cancer **(B)** for each 50 g/day increase in red and processed meat intake. CI, confidence intervals; I^2, I-square.

Supplementary Figure 10 | Summary of relative risk of total prostate cancer **(A)** and advanced prostate cancer **(B)** for each 50 g/day increase in total meat intake. CI, confidence intervals; I^2, I-square.

Supplementary Figure 11 | Summary of relative risk of all outcomes of prostate cancer for each 50 g/day increase in total meat intake. CI, confidence intervals; I^2, I-square.

Supplementary Figure 12 | Non-linear dose-response relation between red meat intake and total prostate cancer **(A)** (P-non-linearity = 0.76; $n = 11$ studies) and advanced prostate cancer **(B)** (P-non-linearity = 0.40; $n = 8$ studies).

Supplementary Figure 13 | Non-linear dose-response relation between processed meat intake and total prostate cancer **(A)** (P-non-linearity = 0.13; $n = 11$ studies) and advanced prostate cancer **(B)** (P-nonlinearity = 0.81; n = 7 studies).

Supplementary Figure 14 | Nonlinear dose-response relation between red and processed meat intake and total prostate cancer **(A)** (P-non-linearity = 0.35; $n = 10$ studies) and advanced prostate cancer **(B)** (P-non-linearity = 0.86; $n = 8$ studies).

Supplementary Figure 15 | Non-linear dose-response relation between total meat intake and total prostate cancer **(A)** (P-nonlinearity = 0.41; $n = 16$ studies) and advanced prostate cancer **(B)** (P-non-linearity = 0.26; $n = 10$ studies).

Supplementary Table 1 | Characteristics of included studies in the systematic review on meat consumption and risk of prostate cancer.

Supplementary Table 2 | Results of subgroup analyses on the association of meat consumption and risk of prostate cancer.

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Association Between Systemic Inflammation and Malnutrition With Survival in Patients With Cancer Sarcopenia—A Prospective Multicenter Study

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Objective: Systemic inflammation and malnutrition are correlated with cancer sarcopenia and have deleterious effects on oncological outcomes. However, the combined effect of inflammation and malnutrition in patients with cancer sarcopenia remains unclear.

Methods: We prospectively collected information on 1,204 patients diagnosed with cancer sarcopenia. the mean (SD) age was 64.5 (11.4%) years, and 705 (58.60%) of the patients were male. The patients were categorized into the high advanced lung cancer inflammation index (ALI) group (≥18.39) and the low ALI group (<18.39) according to the optimal survival cut-off curve. We selected the optimal inflammation marker using the C-index, decision curve analysis (DCA), and a prognostic receiver operating characteristic curve. Univariate and multivariate survival analyses were performed to determine the prognostic value of the optimal inflammation indicator. We also analyzed the association between inflammation and malnutrition in patients with cancer.

Results: The C-index, DCA, and prognostic area under the curve of ALI in patients with cancer sarcopenia were higher or better than those of neutrophil-lymphocyte ratio (NLR), prognostic nutritional index (PNI), systemic immune-inflammation index (SII), and *platelet-lymphocyte* ratio (PLR). The prognosis for patients in the low ALI group was worse than that of patients in the high ALI group [HR (95%CI) = 1.584 (1.280–1.959), $P<0.001$]. When the ALI was divided into quartiles, we observed that decreased ALI scores strongly correlated with decreased overall survival (OS). Patients with both a low ALI and severe malnutrition (vs. patients with high ALI and well-nourished) had a 2.262-fold death risk ($P < 0.001$). Subgroup analysis showed a significant interactive association between the ALI and death risk in terms of TNM stage (P for interaction = 0.030).

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Conclusions: The inflammation indicator of the ALI was better than those of the NLR, PNI, SII, and PLR in patients with cancer sarcopenia. Inflammation combined with severe malnutrition has a nearly 3-fold death risk in patients with cancer sarcopenia, suggesting that reducing systemic inflammation, strengthening nutritional intervention, and improving skeletal muscle mass are necessary.

Keywords: ALI, systemic inflammation, malnutrition, cancer sarcopenia, overall survival

INTRODUCTION

The European Working Group on Sarcopenia in Older People (EWGSOP) (1) and the Asian Working Group for Sarcopenia (AWGS) (2) have recommended that in the definition of skeletal sarcopenia, the loss of muscle strength and functional impairment should be increased on the basis of the loss of muscle mass. Cancer-related sarcopenia is considered part of cancer cachexia syndrome and is caused by a negative balance of protein and energy due to metabolic abnormalities and reduced food intake (3). Sarcopenia can cause contractile dysfunction, metabolic and endocrine abnormalities, and affect the systemic metabolism and immune and inflammatory responses (4).

Sarcopenia is a condition caused by systemic inflammation, commonly found in malignancy. As part of the tumor's systemic inflammatory response, pro-inflammatory cytokines and growth factors have a profound catabolic effect on the host's metabolism, leading to muscle failure (5). Low muscularity may lead to local muscle inflammation, and further to damage driving systemic inflammation (6). This inflammatory cycle, in turn, can enhance tumor aggressiveness or reduce response to treatment, impairing the transition to survival (7). Additionally, systemic inflammation is related to anorexia and insufficient nutrient intake, which in turn leads to accelerated loss of skeletal muscle and adipose tissue (4). Remarkably, cancer sarcopenia is an aspect of cancer-related malnutrition and is thought to have a negative impact on the survival of patients with cancer patients (8, 9). Accordingly, a low nutritional status is usually associated with sarcopenia. Early detection of malnourished patients and nutritional interventions is essential. The Patient-Generated Subjective Global Assessment (PG-SGA) nutrition evaluation tool is based on the SGA and is specifically developed for patients with cancer. The scored PG-SGA further develops the PG-SGA concept, which includes a numerical score and provides a global rating for good, moderate, or suspected malnutrition or severe malnutrition (10).

To our knowledge, no relevant study has investigated the combined association of the systemic inflammatory response and cancer malnutrition in patients with cancer sarcopenia survival. Systemic inflammatory response (SIR) markers, such as Serum C-reactive protein (CRP), hypoalbuminemia, absolute white blood cell count (WBC), and their components have been shown to play essential roles in the development and progression of cancer (11). At present, the predictive ability of inflammation-related cancer prognostic indexes such as the neutrophil-lymphocyte ratio (NLR), advanced lung cancer inflammation index (ALI), prognostic nutritional index (PNI), systemic immune-inflammation index (SII), and platelet-lymphocyte ratio (PLR) in patients with cancer sarcopenia is unknown. The purpose of this study was to identify an optimal inflammation indicator among these indicators and to investigate the combined prognostic effects of inflammation and malnutrition in patients with cancer sarcopenia.

MATERIALS AND METHODS

Study Population

The Investigation on Nutrition Status and its Clinical Outcome of Common Cancers ("INSCOC") was a prospective cohort gathered from multiple clinical centers for patients with cancer in China (June 2012 to December 2019). The inclusion criteria were: age $\geq$18 years, hospitalization $\geq$48 h, and pathological diagnosis of cancer. The protocol was approved by the local ethics committee of the participating clinical centers, and all patients provided signed informed consent (Registration Number: ChiCTR1800020329).

Data Collection and Definitions

This study mainly included common population baseline characteristics, inflammation-related indicators, body measurements, laboratory examinations, and nutrition-related evaluation indicators. Body measurements were performed in strict accordance with the patient's admission with light inpatient clothing and socks in a relaxed state. Laboratory indicators were obtained without intervention before admission, and nutritional assessment was performed by specially trained professionals. Eleven major cancer types were included: lung, gastric, colorectal, esophageal, hepatobiliary, pancreatic, breast, uterine ovarian, nasopharyngeal, and urological cancer, and other cancer subtypes.

Body mass index (BMI, kg/m^2) was calculated by dividing the weight by the square of the height. The BMI classification was based on Chinese standards. The included inflammation indexes included: the NLR (neutrophil count/ lymphocyte count), PLR (platelet count/lymphocyte count), PNI [10 $\times$ albumin (g/dl) + 0.005 $\times$ lymphocyte count], SII (platelet count $\times$ neutrophil count/lymphocyte count), ALI [BMI (kg/m^2) $\times$ albumin (g/dl)/NLR]. The nutritional status of patients was assessed using the PG-SGA criteria, including patient self-evaluation and professional evaluation. According to the PGSGA score, the patients were classified into three different nutritional statuses: well-nourished (0–3), moderately malnourished (4–8), and severely malnourished ($\geq$9).

Assessment of Cancer Sarcopenia

According to the 2019 AWGS sarcopenia diagnosis consensus, the diagnosis of sarcopenia is based on a combination of a low appendicular skeletal muscle index (ASMI) and low muscle strength (handgrip strength, HGS) (12). For the HGS measurement, the handle was individually adjusted according to the size of the patient's hand. During the measurement, the surveyor guided or helped the patient to sit upright, with the arm resting on the armrest and the elbow bend 90°. Demonstrate the operation steps first and then instructed the patient to hold the handle with maximum strength within 3 s. The test was carried out thrice, and the maximum hand strength was recorded as the result. ASM was estimated using an equation that has been described and validated for the Chinese population: ASM = 0.193 × body weight + 0.107 × height (cm)−4.157 × sex−0.037 × age−2.631 (13). Bodyweight, height, and age were measured in kg, cm, and years, respectively. Male sex was coded as 1 and female sex as 2 (13–15). The ASM equation model is in good agreement with double X-ray absorptiometer measurements (adjusted $R^2 = 0.90$, standard error of estimate = 1.63 kg) (13). After estimating the ASM values, ASMI was calculated as follows: SMI = ASM/height^2 (m^2) (14, 15).

The cut-off value that defined low muscle mass was based on the ASMI of the lowest 20% percentile in the study population (14, 15). The low ASMI classification criterion was: male <6.946 kg/m^2 and female <5.421 kg/m^2. The classification standard for low grip strength was male <28 kg and female <18 kg (12).

Outcomes

The primary observational endpoint of this study was the patient's overall survival (OS), that is, the patient's survival time from the time of cancer diagnosis to the time of death, the time of withdrawal from the study, or the last follow-up time. A professional follow-up team conducted the clinical follow-up *via* telephone and outpatient or hospitalization records.

Statistical Analysis

In this study, the inflammation indicators were divided into high- and low-groups, as calculated using log-rank statistics with R software to obtain the best survival cut-off value, namely high NLR (≥3.13) vs. low NLR (<3.13), high PLR (≥250.57) vs. low PLR (<250.57), high PNI (≥42.4) vs. low PNI (<42.4), high SII (≥968.33) vs. low SII (<968.33), and high ALI (≥18.39) vs. low ALI (<18.39) (**Supplementary Figure S1**). Additionally, the ALI score was stratified into quartiles based on baseline ALI score. Continuous variables are presented as the mean ± standard deviation (SD); the median (interquartile range) was used if necessary, and the unpaired Student's *t*-test was used for comparison between groups. Discontinuous variables are presented as percentiles (%), and comparisons between groups were performed using the chi-square test.

The selection of the best prognostic index was determined by using the prognostic receiver operator characteristic curve (ROC), decision curve analysis (DCA), and Harrell's concordance index (C-index). Pearson's correlations between the ALI and potential clinical parameters were computed. OS was calculated using the Kaplan-Meier method. To evaluate the risk ratios (HRs) and 95% confidence intervals (CIs) of OS, multivariate Cox survival regression analysis was performed using different adjustment models to reduce clinical deviation. Model 0: unadjusted; Model 1: adjusted for age, sex, and TNM stage; Model 2: adjusted for age, sex, radical resection, TNM stage, the European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Karnofsky Performance Status (KPS), neoadjuvant chemoradiotherapy, post-operative chemoradiotherapy, lymphocytes, neutrophils, WBC, aspartate aminotransferase, alanine transaminase, serum albumin, comorbid disease (s), family history of cancer, tea consumption, alcohol consumption, smoking, platelet count, hemoglobin, total serum protein, PGSGA, nutritional intervention, 30-day mortality, HGS, and tumor types. The sensitivity analysis was performed by excluding patients who died within 6 months and those with TNM stage IV, respectively. We also constructed cube plots to estimate the relationship between the ALI and HRs of OS. Models were adjusted for model 2.

All statistical analyses were performed using the R platform (version 4.0.3, https://www.r-project.org/), and a two-tailed $P < 0.05$, was regarded statistically significant. The R packages we used in this study included: "survminer," "survival," "rms," "foreign," "timeROC," and "ggplot2."

RESULTS

Baseline Characteristics

A total of 9,727 patients with cancer were included in the cohort study, of whom 1,204 patients were diagnosed with sarcopenia (**Supplementary Figure S2**). In the baseline data, the mean age of the patients was 64.5 ± 11.4 years and there were 705 male patients (58.60%). Among the main common cancer types, there were 239 (19.90%) cases of lung cancer, 245 (20.30%) of gastric cancer, 270 (22.40%) of colorectal cancer, and 145 (12.00%) of esophageal cancer. Additionally, 1,000 patients were diagnosed with malnutrition, including 398 (33.10%) cases of moderate malnutrition and 602 (50.00%) of severe malnutrition. However, only 328 (27.20%) patients received nutritional intervention (**Table 1**).

During the 43.7 months median follow-up period, with an estimated median OS of 25.7 months, we observed 572 deaths. We also observed the total mortality of this population from 1 to 5 years, namely, 36.4% (95% CI 60.9–66.4%) at 1 year, 48.7% (95% CI 48.4–54.3%) at 2 years, 54.6% (95% CI 42.4–48.5%) at 3 years, 57.1% (95% CI 39.9–46.2%) at 4 years, and 58.2% (95% CI 38.7–45.2%) at 5 years, amounting to a rate of 270 events per 1,000 patient-years.

Comparison of Inflammation Indicators

Five inflammatory indicators were analyzed and compared in terms of prognostic prediction and distinguishing ability in patients with cancer sarcopenia, namely the NLR, PLR, PNI, SII, and ALI. The C-index showed that the ALI [0.629 (0.606–0.652)] was superior to other inflammatory indexes [NLR (C-index 95%CI) = 0.614 (0.590–0.637), $P < 0.001$; PNI (C-index 95%CI) = 0.618 (0.594–0.642), $P = 0.251$; SII (C-index 95%CI) =

TABLE 1 | Demographic and clinical characteristics.

	Overall
Characteristics	Patients (*n*, %) ($n = 1,204$)
Age, years, [mean (SD)]	64.51 (11.42)
Sex, *n* (%)	
Male	705 (58.60)
Female	499 (41.40)
Sites of cancer, *n* (%)	
Lung cancer, *n* (%)	239 (19.90)
Gastric cancer, *n* (%)	245 (20.30)
Colorectal cancer, *n* (%)	270 (22.40)
Esophageal cancer, *n* (%)	145 (12.00)
Hepatobiliary cancer, *n* (%)	31 (2.60)
Pancreatic cancer, *n* (%)	42 (3.50)
Breast cancer, *n* (%)	64 (5.30)
Utero ovarian cancer, *n* (%)	65 (5.40)
Nasopharyngeal cancer, *n* (%)	55 (4.60)
Urological cancer, *n* (%)	17 (1.40)
Other cancer subtypes, *n* (%)	31 (2.60)
Comorbid disease(s), yes, *n* (%)	
0	755 (62.70)
1	320 (26.60)
2	87 (7.20)
3 or more	42 (3.50)
Family history of cancer, yes, *n* (%)	159 (13.20)
Smoking, yes, *n* (%)	572 (47.50)
Alcohol consumption, yes, *n* (%)	242 (20.10)
Tea consumption, *n* (%)	280 (23.30)
BMI, kg/m^2 [mean (SD)]	18.42 (1.78)
TNM stage, *n* (%)	
I	107 (8.90)
II	249 (20.70)
III	303 (25.20)
IV	545 (45.30)
Radical resection, yes, *n* (%)	347 (28.80)
Neoadjuvant chemoradiotherapy, yes, *n* (%)	46 (3.80)
Postoperative chemoradiotherapy, yes, *n* (%)	560 (46.50)
EORTC QLQ-C30	49.80 (9.280)
KPS [mean (SD)]	79.95 (17.39)
Serum total protein (g/L) [mean (SD)]	65.30 (8.19)
Serum albumin (g/L) [mean (SD)]	36.29 (5.78)
AST (U/L) [median (IQR)]	21.90 (17.00, 29.93)
ALT (U/L) [median (IQR)]	17.00 (11.18, 30.88)
Hemoglobin (g/L) [mean (SD)]	113.36 (21.20)
WBC ($\times 10^9$/L) [mean (SD)]	7.05 (3.72)
Neutrophils ($\times 10^9$/L) [mean (SD)]	4.92 (3.57)
Lymphocytes ($\times 10^9$/L) [mean (SD)]	1.41 (0.87)
Platelet ($\times 10^9$/L) [mean (SD)]	231.35 (97.95)
30-day death, yes, *n* (%)	32 (2.70)
PGSGA, *n* (%)	
Well-nourished	204 (16.90)
Moderately malnourished	398 (33.10)
Severely malnourished	602 (50.00)
Nutritional intervention, yes, *n* (%)	328 (27.20)
HGS [mean (SD)], (Kg)	16.55 (6.41)
ALI [median (IQR)]	21.26 (10.84, 32.26)
NLR [median (IQR)]	3.13 (1.85, 5.59)
PNI [median (IQR)]	43.50 (38.40, 48.30)
SII [median (IQR)]	679.00 (363.03, 1,132.47)
PLR [median (IQR)]	171.25 (114.96, 256.39)

BMI, Body Mass Index; EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer (EORTC), Quality of Life Questionnaire-Core 30 (QLQ-C30); KPS, Karnofsky Performance Status; AST, Aspartate Aminotransferase; ALT, Alanine Transaminase; WBC, White Blood Cells; ALI, Advanced Lung Cancer Inflammation Index; NLR, Neutrophil-Lymphocyte Ratio; PNI, Prognostic Nutritional Index; SII, Systemic Immune-Inflammation Index; PLR, Platelet-Lymphocyte Ratio; HGS, Hand grip strength; PGSGA, Patient-Generated Subjective Global Assessment.

0.613 (0.5890.636), $P = 0.013$; and PLR (C-index 95%CI) = 0.575 (0.5500.599), $P = 0.038$], and the DCA curve suggested that the prognostic distinguishing ability and clinical application value of the ALI were superior to those of the other inflammatory indexes. The prognostic ROC curve indicated consistent results; that is, the area under the curve (AUC) of ALI was larger than that of other inflammation indicators (**Figure 1**).

Distribution, Correlation, and Prognostic Analysis Based on the ALI

Based on the total cohort ($n = 9,727$), we analyzed the distribution of the ALI in different cancer types, TNM stages, ages, and sexes, finding that the ALI scores of the patients with cancer sarcopenia were significantly lower than those of patients with non-cancer sarcopenia (all $P < 0.001$) (**Figure 2**).

Baseline data based on ALI stratification showed that sex, cancer type, BMI, TNM stage, EORTC QLQ-C30, KPS, total serum protein, serum albumin, hemoglobin, WBS, neutrophils, lymphocytes, platelets, 30-day mortality, PGSGA, and nutritional intervention were significantly different between the high and low ALI groups (**Supplementary Table S1**). We further analyzed the EORTC QLQ-C30 scores among the different ALI groups, and found that the functional status score and quality of life scores of patients with cancer sarcopenia in the low ALI group were significantly lower than those of corresponding patients in the high ALI group (all $P < 0.001$), but the symptom score of the low ALI group was significantly higher than that of the high ALI group ($P < 0.001$; **Supplementary Table S2**).

The calibration curve showed that the ALI had good predictive ability in patients with cancer sarcopenia at 1, 3, and 5-years (**Supplementary Figure S3**). The survival curve showed that the survival of patients with low ALI was worse than that of patients

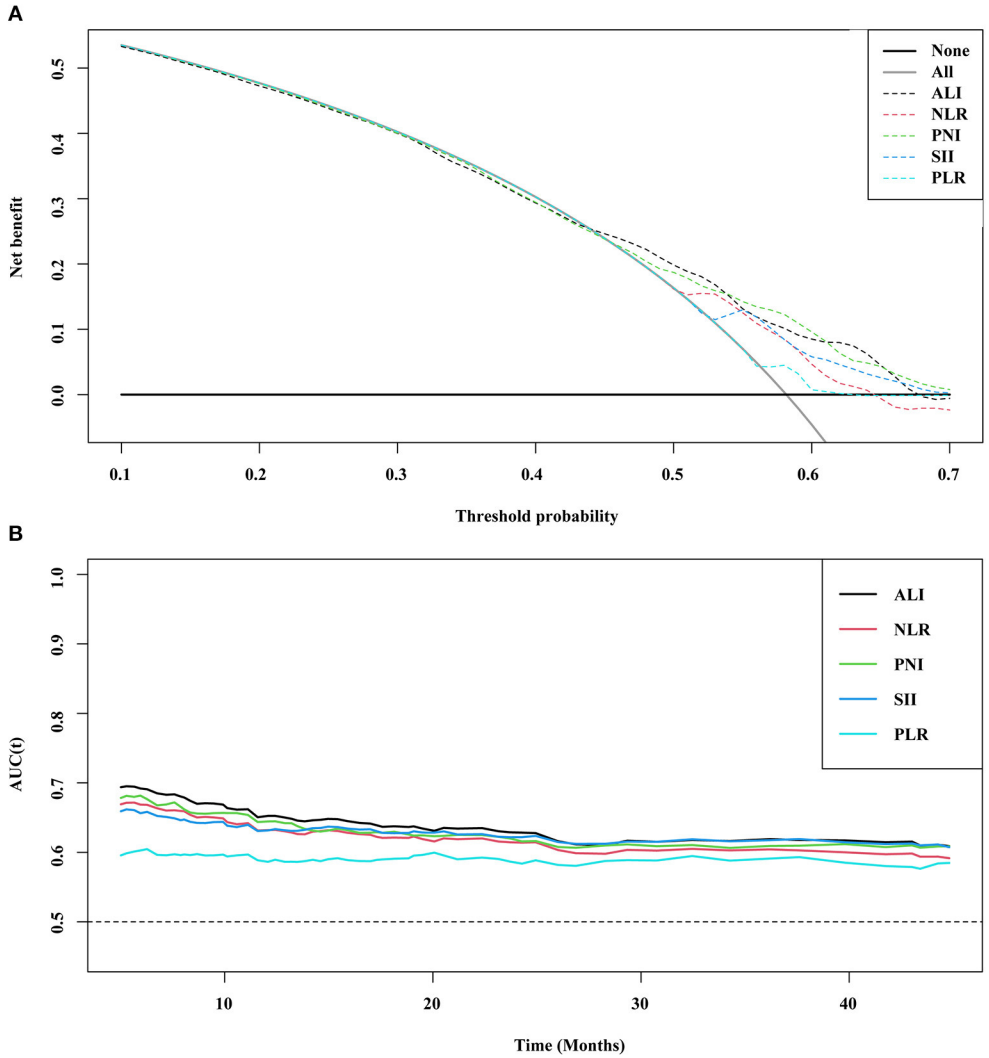

FIGURE 1 | DCA and prognostic ROC of different inflammation markers **(A)** DCA; **(B)** ROC. ALI, Advanced Lung Cancer Inflammation Index; NLR, Neutrophil-Lymphocyte Ratio; PNI, Prognostic Nutritional Index; SII, Systemic Immune-Inflammation Index; PLR, Platelet-Lymphocyte Ratio; ROC, Receiver Operating Characteristic Curve; DCA, Decision Curve Analysis.

with high ALI ($P < 0.0001$; **Supplementary Figure S4A**). The restricted cubic spline curves showed that the HR of patients decreased with an increase in the ALI, showing an "L-shaped" linear relationship (**Figures 3A–C**). Similarly, as the ALI decreased, the risk of death increased (**Figure 3D**). Multivariate survival analysis showed that when the ALI was used as a continuous variable, the risk of death in patients decreased as the ALI increased [model 2: adjusted HR (95%CI) = 0.776 (0.562–1.072), $P = 0.124$]. When ALI was used as a binary variable, the prognosis of patients with low ALI was significantly worse than that of patients with high ALI [model 2: adjusted HR (95%CI) = 1.584 (1.280–1.959), $P < 0.001$]. When ALI was divided into quartiles, compared with the quartile 1 group (>37.94), the risk of death of patients in quartile 2–4 groups was significantly increased [model 2: P for trends <0.001; quartile 2 group (21.26–37.94): 1.330 (1.021–1.734), $P = 0.035$; quartile 3 group (10.84–21.26): 1.870 (1.423–2.458), $P < 0.001$; quartile 4 group (<10.84): 2.145 (1.511–3.044), $P < 0.001$] (**Table 2**). Sensitivity analysis was performed by excluding patients who died within 6 months and those whose TNM stage was IV. The results were consistent with the previously described findings (**Supplementary Table S3**). The prognostic analysis results of different tumor subgroups showed that a low ALI was associated with significantly worse prognosis in patients with colorectal cancer when compared with those patients with high ALI [model 2: adjusted HR (95%CI) = 2.347 (1.286–4.284), $P = 0.005$] (**Supplementary Table S4**).

Combined Effect of the ALI and Malnutrition

First, we calculated the prognostic value of the PGSGA in patients with cancer sarcopenia (**Supplementary Figure S4B**). Univariate

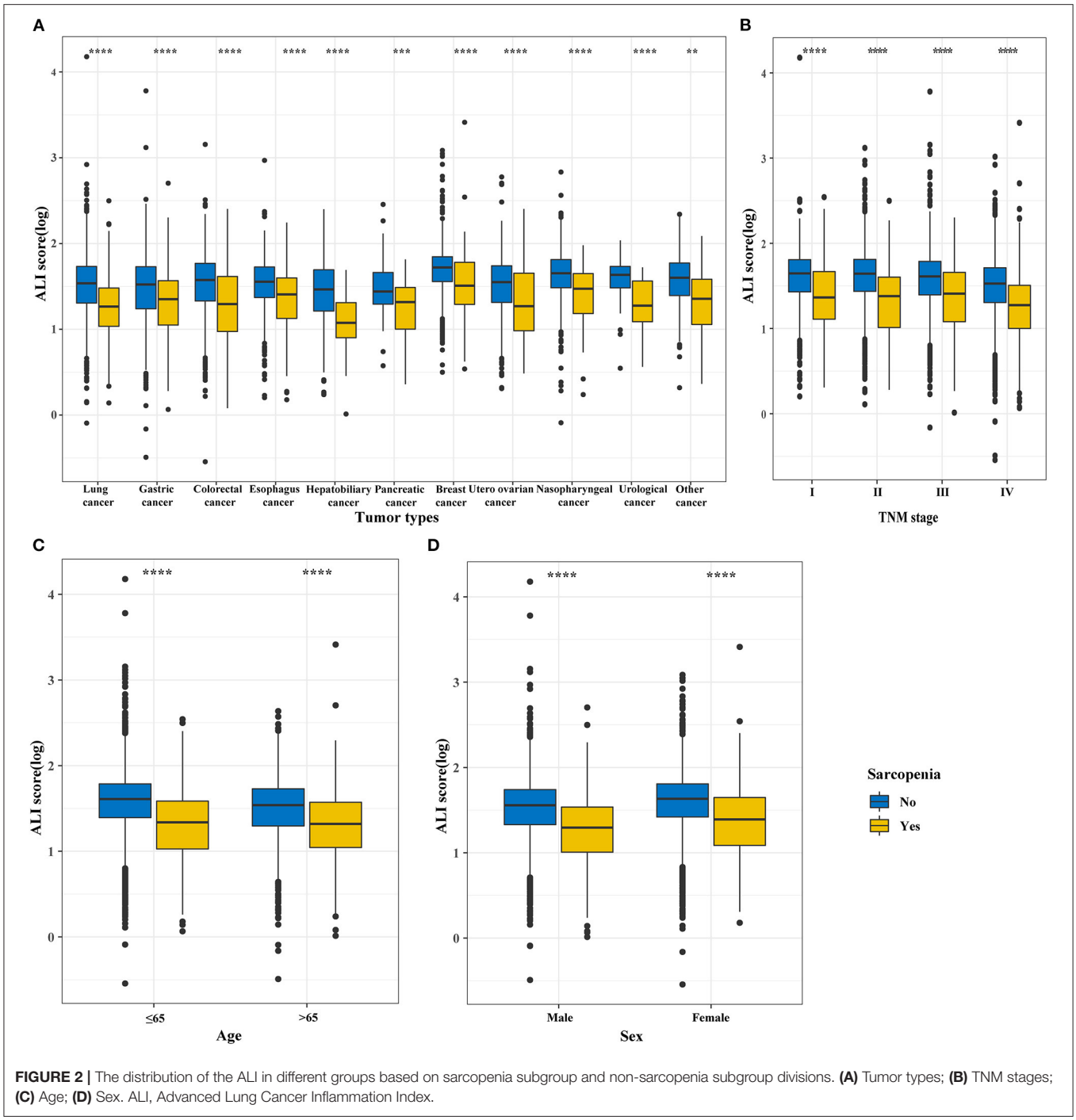

FIGURE 2 | The distribution of the ALI in different groups based on sarcopenia subgroup and non-sarcopenia subgroup divisions. **(A)** Tumor types; **(B)** TNM stages; **(C)** Age; **(D)** Sex. ALI, Advanced Lung Cancer Inflammation Index.

and multivariate survival analyses showed that compared with well-nourished patients, moderately malnourished patients (Adjusted HR = 1.207, 95%CI = 0.886–1.646, $P = 0.233$) and severely malnourished patients (Adjusted HR = 1.561, 95%CI = 1.148–2.123, $P = 0.004$) had a worse prognosis (**Table 3**; **Figure 4**). Additionally, we performed a combined survival analysis of the ALI and PGSGA in patients with cancer sarcopenia, and the results showed that compared with patients with high ALI and who were well-nourished, the risk of death in patients with low ALI who had severe malnutrition was 2.262-fold (95%CI = 1.527–3.351, $P < 0.001$) (**Table 3**).

Subgroup Analysis

Subgroup analysis was performed to assess the association between the ALI and the risk of death in different subgroups. A significantly interactive association between the ALI (high ALI, ≥18.39 vs. low ALI, <18.39) and death risk was observed in the TNM stage (P for interaction = 0.030). However, no other

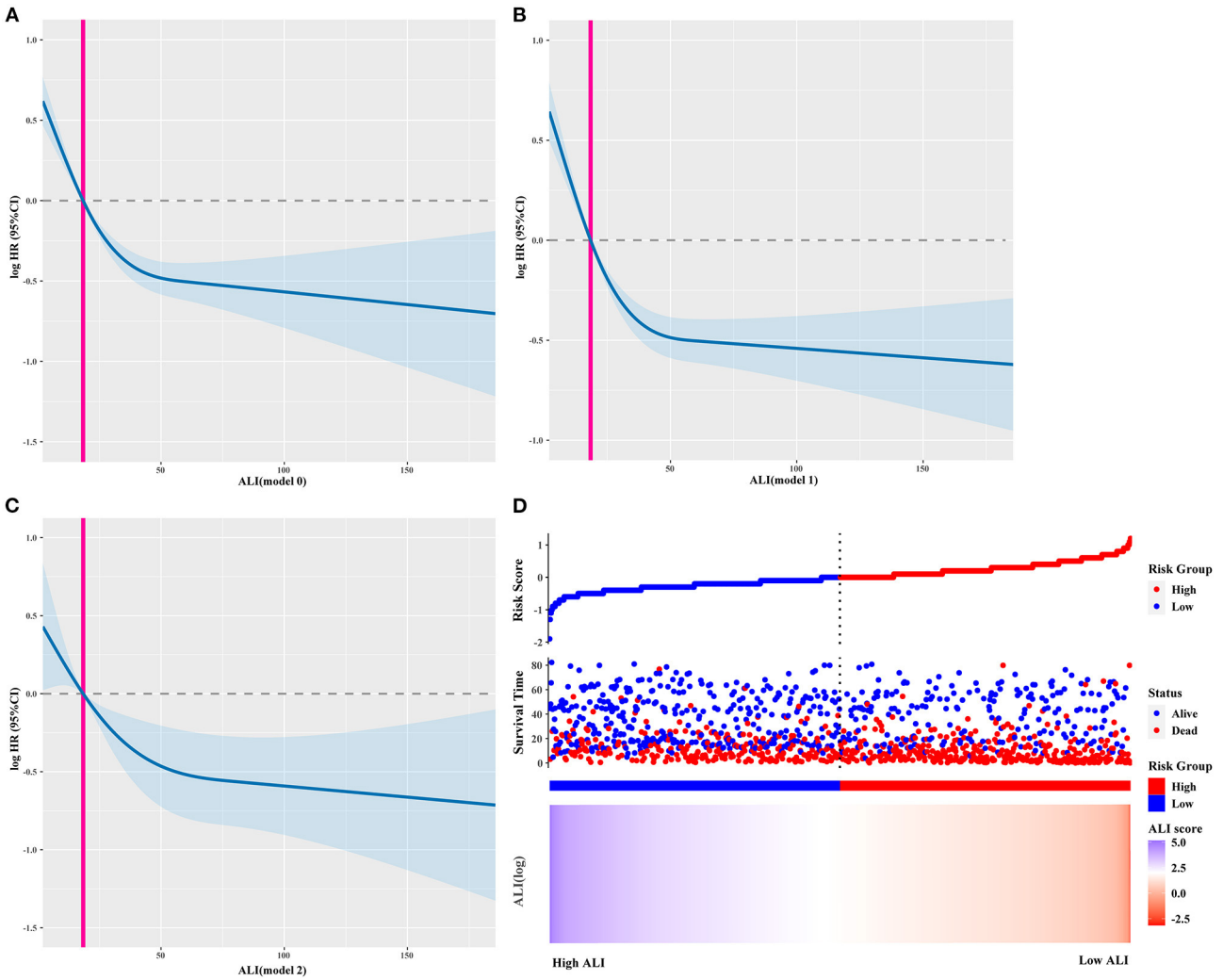

FIGURE 3 | The restricted cubic spline curves and ALI risk model curve. **(A–C)** The restricted cubic spline curves of different adjusted models, **(A)** model 0: Unadjusted; Model 1: Adjusted for Age, Sex and TNM stage; Model 2: Adjusted for Age, Sex, Radical resection, TNM stage, EORTC QLQ-C30, KPS, Neoadjuvant chemoradiotherapy, Postoperative chemoradiotherapy, Lymphocytes, Neutrophils, WBC, AST, ALT, Serum albumin, Comorbid disease (s), Family history of cancer, Tea consumption, Alcohol consumption, Smoking, Platelet, Hemoglobin, Serum total protein, PGSGA, Nutritional intervention, 30-day mortality, HGS; **(D)** ALI risk model curve. ALI, Advanced Lung Cancer Inflammation Index; WBC, White Blood Cells; AST, Aspartate Aminotransferase; ALT, Alanine Transaminase; HGS, Hand grip strength; BMI, Body Mass Index; EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer (EORTC), Quality of Life Questionnaire-Core 30 (QLQ-C30); PGSGA, Patient-Generated Subjective Global Assessment; KPS, Karnofsky Performance Status.

significant association was found for the subgroup variables (P for interaction > 0.05) (**Figure 5**).

DISCUSSION

To our knowledge, this was the first study to investigate the combined effects of systemic inflammatory indicators and malnutrition on the prognosis of patients with cancer sarcopenia. In our study, the C-index, DCA, and prognostic AUC of the ALI in patients with cancer sarcopenia were higher or better than those of the NLR, PNI, SII, and PLR. Accordingly, we chose the ALI score as the optimal inflammation-related index for prognosis-related analysis. When we compared the ALI in patients with cancer sarcopenia and non-cancer sarcopenia, we found that the ALI in different tumor types, TNM stage, age, and sex showed that the ALI in patients with cancer sarcopenia was lower than that in patients with non-cancer sarcopenia. This further demonstrates the distinguishing ability of the ALI in patients with cancer sarcopenia. The physical function score and quality of life score of patients with high ALI were higher than those of patients with low ALI, while the symptom score showed the opposite result. In other words, patients with low ALI have a worse quality of life than patients with high ALI, and this often indicates a poor prognosis. Systemic inflammation is often activated in cancer patients and is associated with the development of anorexia, fatigue, impaired physical activity, and

TABLE 2 | Univariate and multivariate analysis of the OS in patients with cancer sarcopenia.

Variables	OS (model 0)		OS (model 1)		OS (model 2)	
	Crude HR (95%CI)	Crude *P*	Adjusted HR (95%CI)	Adjusted *P*	Adjusted HR (95%CI)	Adjusted *P*
ALI						
As continuous	0.679 (0.503–0.916)	0.011	0.755 (0.570–1.001)	0.051	0.776 (0.562–1.072)	0.124
By cut-off						
ALI ≥ 18.39	1		1		1	
ALI < 18.39	2.063 (1.763–2.413)	<0.001	2.058 (1.757–2.412)	<0.001	1.584 (1.280–1.959)	<0.001
By Interquartile						
Q1 (37.94∼)	1		1		1	
Q2 (21.26∼37.94)	1.566 (1.215–2.019)	0.001	1.356 (1.051–1.750)	0.019	1.330 (1.021–1.734)	0.035
Q3 (10.84∼21.26)	2.412 (1.896–3.068)	<0.001	2.088 (1.639–2.660)	<0.001	1.870 (1.423–2.458)	<0.001
Q4 (∼10.84)	2.745 (2.163–3.484)	<0.001	2.749 (2.162–3.496)	<0.001	2.145 (1.511–3.044)	<0.001
P for trends		<0.001		<0.001		<0.001

Model 0: Unadjusted; Model 1: Adjusted for Age, Sex and TNM stage; Model 2: Adjusted for Age, Sex, Radical resection, TNM stage, EORTC QLQ-C30, KPS, Neoadjuvant chemoradiotherapy, Postoperative chemoradiotherapy, Lymphocytes, Neutrophils, WBC, AST, ALT, Serum albumin, Comorbid disease(s), Family history of cancer, Tea consumption, Alcohol consumption, Smoking, Platelet, Hemoglobin, Serum total protein, PGSGA, Nutritional intervention, 30-day mortality, and tumor types, HGS. OS, Overall Survival; HR, Hazards Ratio; CI, Confidence Interval; BMI: Body Mass Index; EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer (EORTC), Quality of Life Questionnaire-Core 30 (QLQ-C30); KPS, Karnofsky Performance Status; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; WBC: White Blood Cells; HGS: Hand grip strength; ALI: Advanced Lung Cancer Inflammation Index; PGSGA: Patient-Generated Subjective Global Assessment.

TABLE 3 | Combined effect survival analysis.

Variables	OS		OS*	
	Crude HR (95%CI)	Crude *P*	Adjusted HR (95%CI)	Adjusted *P*
PGSGA[a]				
Well-nourished	1		1	
Moderately malnourished	1.651 (1.233–2.211)	0.001	1.207 (0.886–1.646)	0.233
Severely malnourished	2.922 (2.226–3.835)	<0.001	1.561 (1.148–2.123)	0.004
PGSGA and ALI[b]				
High ALI and Well-nourished	1		1	
High ALI and Moderately malnourished	1.408 (0.980–2.021)	0.064	1.081 (0.741–1.578)	0.687
High ALI and Severely malnourished	2.397 (1.701–3.377)	<0.001	1.448 (0.812–2.584)	0.210
Low ALI and Well-nourished	1.480 (0.852–2.571)	0.164	1.558 (1.079–2.250)	0.018
Low ALI and Moderately malnourished	2.837 (1.957–4.112)	<0.001	2.097 (1.383–3.178)	<0.001
Low ALI and Severely malnourished	4.118 (2.967–5.715)	<0.001	2.262 (1.527–3.351)	<0.001

OS, Overall Survival; HR, Hazards Ratio; CI, Confidence Interval; BMI, Body Mass Index; EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer (EORTC), Quality of Life Questionnaire-Core 30 (QLQ-C30); KPS, Karnofsky Performance Status; AST, Aspartate Aminotransferase; ALT, Alanine Transaminase; WBC, White Blood Cells; HGS, Hand grip strength; ALI, Advanced Lung Cancer Inflammation Index; PGSGA, Patient-Generated Subjective Global Assessment.

[*] Adjusted model.

[a] Adjusted for Age, Sex, Radical resection, TNM stage, EORTC QLQ-C30, KPS, Neoadjuvant chemoradiotherapy, Postoperative chemoradiotherapy, Lymphocytes, Neutrophils, WBC, AST, ALT, Serum albumin, Comorbid disease(s), Family history of cancer, Tea consumption, Alcohol consumption, Smoking, Platelet, Hemoglobin, Serum total protein, Nutritional intervention, 30-day mortality, HGS, and tumor types.

[b] Adjusted for Age, Sex, Radical resection, TNM stage, EORTC QLQ-C30, KPS, Neoadjuvant chemoradiotherapy, Postoperative chemoradiotherapy, Lymphocytes, Neutrophils, WBC, AST, ALT, Serum albumin, Comorbid disease(s), Family history of cancer, Tea consumption, Alcohol consumption, Smoking, Platelet, Hemoglobin, Serum total protein, Nutritional intervention, 30-day mortality, HGS, and tumor types.

weight loss (16). These are well-related to the composition of the ALI, and also reflect the inflammatory directional and physical function activities of the ALI in patients with cancer sarcopenia.

The ALI is composed of BMI, albumin, and NLR, which can reflect the inflammatory status of the host (17, 18). In previous studies, BMI was reported to be associated with skeletal sarcopenia, which is an important component of cancer cachexia syndrome and an important prognostic factor for patients with cancer (19). Additionally, serum albumin levels were affected by the SIR[12]. A study by Evans et al. recommended that an abnormal serum albumin should be considered a chronic disease characterized by inflammation and correlates well with the risk of

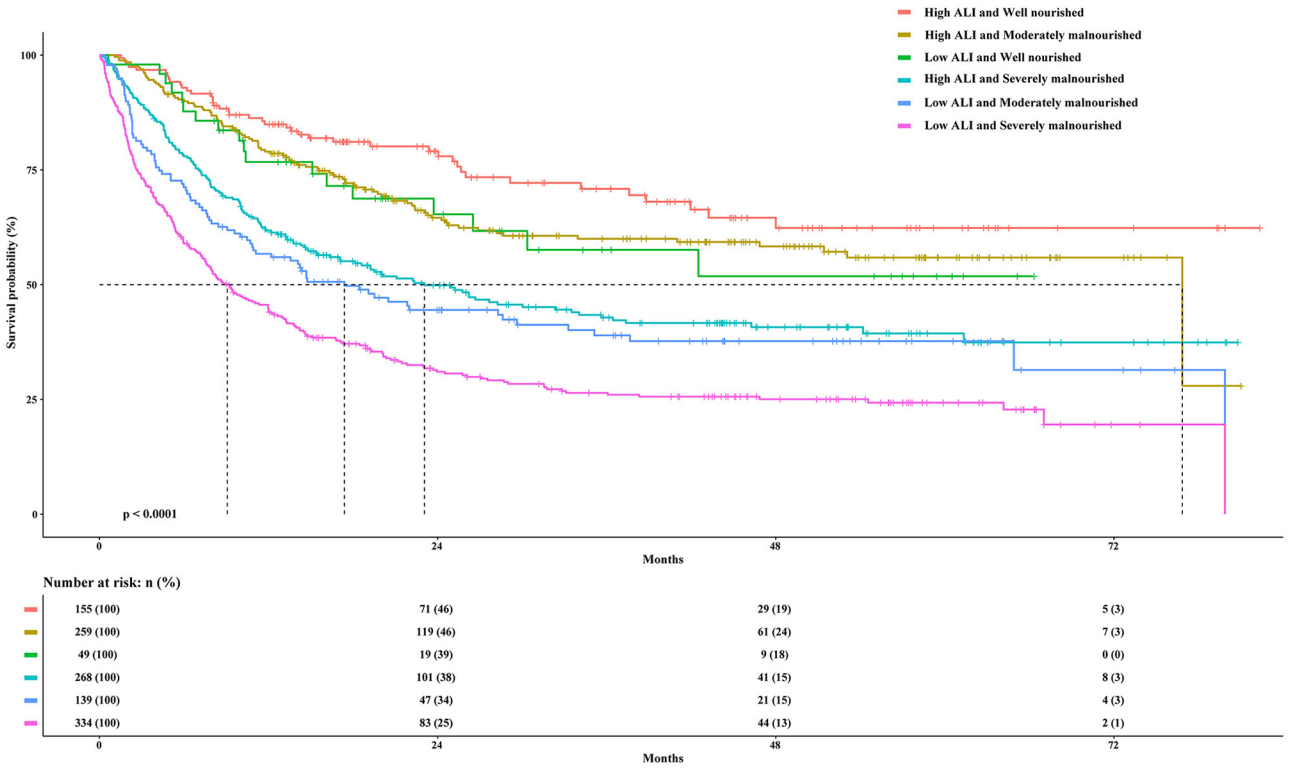

FIGURE 4 | The Kaplan-Meier survival curves of the ALI combined with the PGSGA for the OS of patients with sarcopenia. ALI, Advanced Lung Cancer Inflammation Index; PGSGA, Patient-Generated Subjective Global Assessment; OS, overall survival.

adverse patient outcomes, and the serum albumin concentration decreased when inflammation was present (20). Inflammation is involved in carcinogenesis and cancer development (21), and SIR is considered the seventh hallmark of cancer through host tumor interaction (22). Consistent with this evidence, the potential of the SIR status as a prognostic marker of various cancers has also been confirmed, and the NLR is a reliable SIR marker. The NLR is composed of the neutrophil and lymphocyte counts. The tumor microenvironment is rich in neutrophils. The role of neutrophils in promoting inflammation and providing an appropriate environment for tumor growth explains that neutrophils activate various inflammatory markers, such as vascular endothelial growth factor and anti-apoptosis factors, such as the nuclear factor kappa light chain enhancer of activated B cells, promoting extracellular matrix remodeling and tumor progression (21, 23).

In contrast, the lymphocyte count reflects the activation of the immune system and its inhibitory effect on tumor proliferation and migration (17). A lower ALI score is associated with decreased BMI and serum albumin levels accompanied by increase in the NLR levels, representing a higher level of inflammation. In our baseline data analysis, we also found that the BMI and serum albumin levels of patients with a low ALI were lower than those of patients with a high ALI. As cancer sarcopenia results from chronic systemic inflammation, the combination of BMI, serum albumin, and inflammation markers (NLR) can more accurately assess cancer sarcopenia. In addition, the ALI seems to have better prognostic value in advanced stages of cancer (24). Our baseline data also showed that most patients with cancer sarcopenia were at an advanced stage. Therefore, the ALI has excellent prognostic value for patients with cancer sarcopenia.

When analyzing the prognostic value of the ALI, it was found that the risk of death increased with decrease in the ALI. The ALI score is an independent prognostic factor for patients with cancer. Tumor stage was closely related to the ALI. It has been reported that the degree of systemic inflammation is related to tumor progression. However, even at the same stage, the degree of inflammation may vary depending on the type of cancer (25). Additionally, we also found that the co-occurrence of a low ALI and severe malnutrition was associated with 2.262-fold mortality risk among patients with cancer sarcopenia compared with those with high ALI who were well-nourished. In malignant tumors, the systemic inflammatory response and nutritional status are both definite prognostic factors. Increasing evidence has shown that SIR was closely related to the nutritional status of various types of cancer (26). The ALI is a new malignant tumor index recently described, and the potential of the ALI as a prognostic factor for various types of cancer has gradually been revealed, such as for lung cancer (27, 28), gastric cancer (18, 29), colorectal cancer (25, 30), pancreatic cancer (31, 32), esophageal cancer (33), head and neck squamous

Variables	High ALI(≥18.39) Deaths/Patients	Low ALI (<18.39) Deaths/Patients	Adjusted HR(95%CI)	Adjusted P	P for interaction
Age (years)					0.103
≤65	114/323	153/244	1.858 (1.313-2.628)	<0.001	
>65	173/359	192/278	1.415 (1.064-1.884)	0.017	
Sex					0.458
Male	175/368	238/337	1.519 (1.157-1.995)	0.003	
Female	112/314	107/185	1.723 (1.189-2.498)	0.004	
BMI					0.193
<18.5	129/278	198/284	1.452 (1.040-2.027)	0.028	
≥18.5	158/404	147/238	1.941 (1.431-2.631)	<0.001	
Radical resection					0.439
No	237/483	279/374	1.526 (1.203-1.934)	<0.001	
Yes	50/199	66/148	1.206 (0.833-1.745)	0.321	
Preoperative chemoradiotherapy					0.630
No	276/658	336/500	1.563 (1.258-1.941)	<0.001	
Yes	11/24	9/22	2.5*10^11 (4.2*10^9-1.5*10^13)	<0.001	
Postoperative chemoradiotherapy					0.698
No	120/353	165/291	1.460 (1.015-2.100)	0.041	
Yes	167/329	180/231	1.751 (1.315-2.330)	<0.001	
TNM stage					0.030
I	13/67	7/40	436.96 (139.19-1371.72)	<0.001	
II	37/147	34/102	1.373 (0.639-2.950)	0.417	
III	57/190	79/113	3.146 (1.915-5.167)	<0.001	
IV	180/278	225/267	1.400 (1.073-1.827)	0.013	
PGSGA					0.294
Well nourished	42/155	18/49	2.085 (0.776-5.606)	0.145	
Moderately malnourished	98/259	83/139	1.916 (1.421-2.583)	<0.001	
Severely malnourished	147/268	244/334	1.431 (1.087-1.884)	0.011	
Nutritional intervention					0.659
No	225/553	207/323	1.569 (1.219-2.019)	<0.001	
Yes	62/129	138/199	1.410 (0.900-2.208)	0.134	

FIGURE 5 | The stratification analysis of the ALI. Adjusted for model 2: Age, Sex, Radical resection, TNM stage, EORTC QLQ-C30, KPS, Neoadjuvant chemoradiotherapy, Post-operative chemoradiotherapy, Lymphocytes, Neutrophils, WBC, AST, ALT, Serum albumin, Comorbid disease (s), Family history of cancer, Tea consumption, Alcohol consumption, Smoking, Platelet, Hemoglobin, Serum total protein, PGSGA, Nutritional intervention, 30-day death, HGS. ALI, Advanced Lung Cancer Inflammation Index; WBC, White Blood Cells; AST, Aspartate Aminotransferase; ALT, Alanine Transaminase; HGS, Hand grip strength; BMI, Body Mass Index; EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer (EORTC), Quality of Life Questionnaire-Core 30 (QLQ-C30); PGSGA, Patient-Generated Subjective Global Assessment; KPS, Karnofsky Performance Status.

cell carcinoma (34), nasopharyngeal carcinoma (35), thymic epithelial tumors (36), and melanoma (37). We hypothesize that the systemic inflammation reflected by the ALI is the basis of sarcopenia. The cytokine concentration in the inflammatory environment increases. The cytokines secreted by the tumor and surrounding cells can promote protein degradation (38), inhibit the differentiation of skeletal muscle cells, promote muscle wasting (39), and promote insulin resistance (40).

Increased cytokine concentrations in the circulation can activate the ubiquitin-proteasome proteolytic pathway, leading to insulin resistance and muscle wasting, thereby further aggravating sarcopenia (41). On the other hand, local muscle inflammation can further promote systemic inflammation and muscle interpretation (6, 7). Skeletal sarcopenia may also be caused by malnutrition (42). Nutritional and metabolic disorders are very common in patients with advanced cancer and can lead to weight loss, reduced quality of life, and poor treatment outcomes (43). The degree of malnutrition is affected by several factors, including anorexia and reduced nutritional intake (44). Insufficient energy and protein intake were independent risk factors for skeletal sarcopenia (42). A poor nutritional status can lead to immune dysfunction and muscle atrophy (45). Systemic inflammation is related to anorexia and insufficient nutrient intake, which in turn lead to accelerated loss of skeletal muscle. In some patients, inflammation causes anorexia and is accompanied by decrease in skeletal muscle (4). Malnutrition can also

impair the immune response and damage host defenses against cancer (46). In short, systemic inflammation, malnutrition and sarcopenia are closely related, forming a vicious circle. In our study, the number of malnourished patients diagnosed with the PCSGA was as high as 83.1% (including 50% of severely malnourished patients), but only 27.2% of patients received a nutritional intervention. Adequate nutrition and resistance exercise are the basis for the management of sarcopenia, and multimodal interventions are often associated with the best outcomes. Systemic inflammation and malnutrition are problems that patients with cancer cannot avoid. Therefore, strengthening the comprehensive treatment of patients to prevent muscle consumption and improve physical condition, strength and quality of life is urgently needed (47).

To our knowledge, this was the first study to investigate the combined effects of systemic inflammation and malnutrition in patients with cancer. Although ours was a multicenter cohort study of patients with cancer sarcopenia, we acknowledge some potential limitations. Regardless of the systemic inflammation indicators examined and the subgroups defined according to age, BMI, sex, and tumor stage, the results were basically the same. Other indicators of inflammation, such as interleukin-6, TNF-α and CRP should be collected in our cohort in the future. Notably, a study with a larger sample size and more participating centers is needed to verify the conclusions. In addition, it is imperative to conduct prospective clinical trials of comprehensive treatment, including anti-inflammatory and nutritional interventions.

CONCLUSION

In summary, our study found that the ability of the ALI to distinguish and predict the prognosis of patients with cancer sarcopenia was better than that of the NLR, PNI, SII, and PLR. Low ALI levels are associated with a worse prognosis in patients with cancer and sarcopenia. We also found that patients with both a low ALI who were severe malnutrition had a nearly three-fold higher risk of mortality compared to patients with a high ALI and well-nourished. Systemic inflammation, malnutrition, and sarcopenia affect each other. For patients with cancer sarcopenia, it is necessary to develop comprehensive treatment with the aim of reducing systemic inflammation, strengthening nutritional intervention, and improving skeletal muscle mass.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study followed the tenets of 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

G-TR wrote the manuscript. G-TR, Y-ZG, and H-LX analyzed and interpreted the patient data. G-TR, Y-ZG, H-LX, and H-PS made substantial contributions to the conception, design, and intellectual content of the studies. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.811288/full#supplementary-material

Supplementary Figure S1 | Optimal cut-off value of inflammation markers according to the results of the standardized log-rank statistic.

Supplementary Figure S2 | Flowchart of patient selection for this study.

Supplementary Figure S3 | The 1-, 3-, and 5-year calibration curves of the ALI in patients with cancer sarcopenia. ALI, advanced lung cancer inflammation index.

Supplementary Figure S4 | The Kaplan-Meier survival curves of ALI and PGSGA in the OS of patients with sarcopenia. ALI, advanced lung cancer inflammation index; OS, overall survival; PG-SGA, Patient-Generated Subjective Global Assessment.

Supplementary Table S1 | Demographic and clinical characteristics stratified by ALI.

Supplementary Table S2 | The EORTC QLQ-C30 of overall patients and different ALI group.

Supplementary Table S3 | Sensitivity analysis of the OS in patients with cancer sarcopenia.

Supplementary Table S4 | Univariate and multivariate analysis of the OS in patients with cancer sarcopenia.

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The Association Between Metabolic Status and Risk of Cancer Among Patients With Obesity: Metabolically Healthy Obesity vs. Metabolically Unhealthy Obesity

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Background: Controversial evidence about the association between cancer risk and metabolic status among individuals with obesity has been reported, but pooled data remain absent. This study aims to present pooled data comparing cancer risk between patients with metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO).

Methods: The current study systematically searched pieces of literature on January 4, 2021, of prospective cohorts that compare the incidence of cancer between MHO and MUO. The quality of included studies was assessed using Newcastle–Ottawa scale, and publication bias was evaluated using funnel plots.

Results: Eleven high-quality studies were eventually selected. Quantitative analysis indicates that a lower cancer incidence exists for MHO phenotype than that for MUO (odds ratio [OR], 0.71; 95% confidential interval [CI], 0.61–0.84). Consistent outcomes are presented by subgroup analyses, which are grouped by cohort region (western population: [OR, 0.84; 95% CI, 0.75–0.93]; Asian population: [OR, 0.64; 95% CI, 0.54–0.77]); definition of metabolic unhealthiness (≥3 metabolic abnormalities: [OR, 0.62; 95% CI, 0.54–0.71]; ≥1 metabolic abnormality: [OR, 0.76; 95% CI, 0.62–0.94]); and definition of obesity (body mass index (BMI), ≥30 kg/m^2: [OR, 0.84; 95% CI, 0.73–0.98]; BMI, ≥25 kg/m^2: [OR, 0.53; 95% CI, 0.52–0.55]).

Conclusion: In conclusion, this study suggests a reduced cancer risk for MHO compared to MUO regardless of population heterogeneity, or the definitions of obesity and metabolic status.

Keywords: metabolically healthy obesity (MHO), metabolically unhealthy obesity (MUO), risk of cancer, meta-analysis, pan-cancer

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HIGHLIGHTS

The correlation of metabolic status and cancer risk among individuals with obesity remains controversial. This systematic review and meta-analysis, for the first time, suggests a reduced cancer risk for patients with metabolically healthy obesity compared to those with metabolically unhealthy obesity [OR 0.71, 95% CI 0.61–0.84]. Our findings promote the understanding of the association between metabolic status and cancer risk and also provide further clinical implication of malignancy prevention for individuals with obesity plus metabolic abnormalities.

INTRODUCTION

Obesity, currently prevalent in over 10% of mankind, has tripled since the 1970s and has been a global pandemic for decades' (1, 2). Adequate evidence has reported the increased risk of cardiovascular disease (3), type 2 diabetes (4), cancers (5), and reduced life expectancy (6, 7) for the population with obesity, causing enormous health and socioeconomic burden. Obesity is defined by the World Health Organization as abnormal or excessive fat accumulation. However, observation data have revealed that a proportion of individuals with obesity have less chance of developing metabolic abnormalities and related cardiometabolic diseases (8–11), which implies that the extent of adiposity cannot comprehensively explain the risk of developing obesity-related comorbidities. Therefore, this obesity subgroup is prescribed as metabolically healthy obesity (MHO) (12).

With age- and gender-dependent prevalence of 10–30% (13), MHO is not rare even though the variation of prevalence is high across cohort studies (14, 15), which is mostly caused by the different MHO criteria. Notably, although harmonized criteria have recently been raised (16), no current standard MHO criteria exist. Individuals with obesity are usually referred to as MHO when normal levels of glucose and lipid parameters as well as the absence of hypertension are reported. Otherwise, they are classified as the metabolically unhealthy obesity (MUO) phenotype. For the last two decades, multiple studies have investigated the impact of the metabolic status difference between MHO and MUO on the risk of cardiovascular disease and type 2 diabetes (4, 17).

In recent years, the biological mechanisms underlying obesity, metabolism and tumor have been reported (18–20). Thus, several cohorts have also been conducted to investigate the correlation between metabolic status and cancer risk among individuals with obesity by comparing MHO vs. MUO (21–23). However, controversies of the conclusions from those cohorts still remain, and a lack of collaborative and pooled evidence is noted. Although a previous meta-analysis reported the association between MHO and cancer risk (24), they focus on obesity rather than metabolic status, by comparing MHO with metabolically healthy individuals with normal weight (MHNW). Therefore, this study, for the first time to our knowledge, aims to explore the association between cancer risk and metabolic status among individuals diagnosed with obesity by presenting pooled evidence comparing the cancer incidence between MHO and MUO phenotypes.

Abbreviations: MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; MHNW, metabolically healthy normal weight; OR, odds ratio; CI, confidential interval; BMI, body mass index.

METHODS

Search Strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (25) to systematically search articles that compare the cancer incidence of MHO and MUO in PubMed, Embase, ClinicalTrial.gov, and Cochrane Library Central Register of Controlled Trials database regardless of publication language or date. These terms were used: metabolically healthy obesity, metabolically unhealthy obesity, metabolically healthy obese, MHO, MUO, metabolically obese, metabolically abnormal obesity, metabolically abnormal obese, tumor, cancer, malignancy, and neoplasm.

Inclusion and Exclusion Criteria

Studies were included if the following inclusion criteria are fulfilled: (1) patients must be divided into different body size-related phenotypes (normal weight or obese), and they were further classified according to their metabolic health status (metabolically healthy or metabolically unhealthy/abnormal); (2) comparative studies of the cancer incidence between MHO and MUO; (3) cohorts focused on malignancies only, excluding benign tumors; and (4) studies providing data that are available for quantitative analysis. The exclusion criteria are as follows: (1) reviews, meta-analysis, case report, or basic science; (2) studies that are MHO-related but without comparison between MHO and MUO were performed; (3) cohorts that do not separate benign and malignant tumors; (4) studies reporting incidence of advanced cancer only rather than any type of cancer; and (5) data not available for quantitative analysis. Two authors have independently selected the articles and resolved the discrepancies through discussion.

Data Extraction and Quality Assessment

The information including publication year, country, malignant tumor types, cohort size, follow-up duration, cancer incidence rate (per 1,000 person-years), and definition of obesity and metabolic status were collected. The number of events (diagnosis of cancer) and total patients with MHO and MUO phenotypes, respectively, were extracted.

The Newcastle–Ottawa Assessment Scale (NOS) was used to assess the quality of included studies which contains the aspects of selection, comparability, and exposure (26). Studies scored seven or more are ranked as low risk of bias. The funnel plots were used to evaluate publication bias. Publication bias is low when a funnel plot is symmetrical, and the circles representing included studies gathered around the tip of the funnel plot.

Statistical Analysis

Odds ratio (OR) with 95% confidential interval (CI) was calculated following the number of events of cancer and

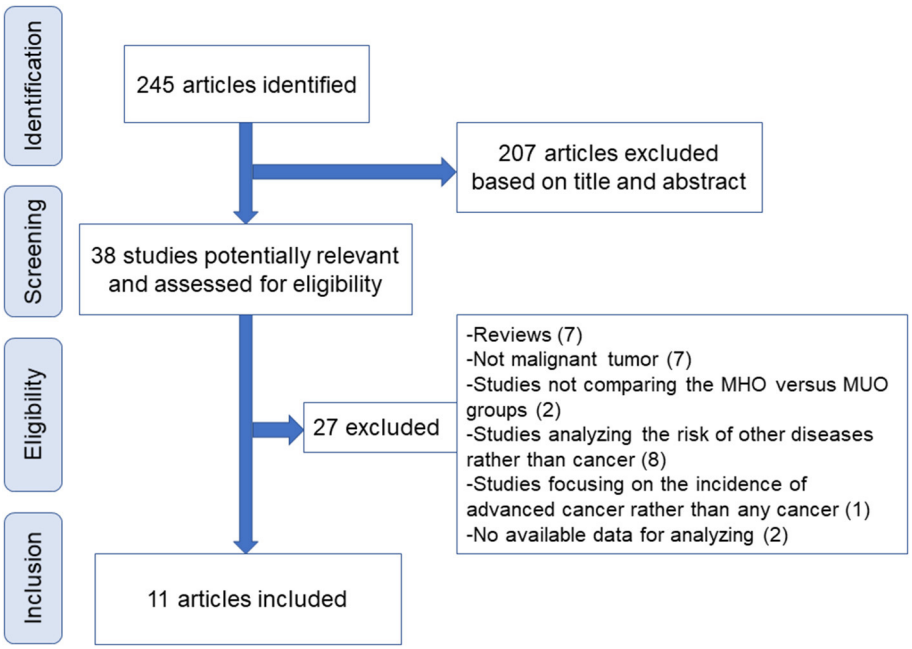

FIGURE 1 | Flowchart of study screening. MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.

total patients. A random-effects model was used when the heterogeneity was high. Otherwise, a fixed-effects model was used. Heterogeneity among studies was assessed using I^2 or Q tests. An I^2 of >50% or Q test reporting $P < 0.1$ indicated that heterogeneity was high. A heterogeneity test was conducted by removing each study in the quantitative analysis to evaluate the possible origins of the heterogeneity. Subgroup analyses were also conducted to investigate the impact of possible confounding (e.g., region and different MHO definitions) by dividing the studies into different subgroups. All the above analyses and plots were conducted using Review Manager (version 5.3).

RESULTS

Characteristics of the Included Studies

Figure 1 displays the flowchart of screening eligible studies. Moreover, 245 articles were identified after searching, and 207 were excluded on the basis of titles and abstracts. The other 38 publications were further assessed for eligibility via full-text review, and 11 articles were eventually selected for meta-analysis (21, 22, 27–35). Notably, of the 27 excluded articles, seven studies compared the incidence of colorectal neoplasm (benign tumor included) between MHO and MUO with the overlapped database. One study reported the incidence of pan-cancer using UK Biobank data that do not provide available data for quantitative analysis, whereas another study focused on the incidence of advanced cancer rather than any cancer (**Supplementary Table 1**).

Table 1 presents the characteristics of the 11 included studies. Five and six studies were conducted in western countries and Asia, respectively. The study by Arnlov reported pan-cancer incidence with a limited number of MHO and MUO patients, and the other 10 studies focused on six types of cancers including breast, colorectal, thyroid, gastric, prostate, and bladder cancers with a maximum of 4,383,392 patients involved. The follow-up duration of those studies generally exceeds 5 years (median) except that the EPIC Study has a median follow-up of 3.7 years. Importantly, the definition of body mass index (BMI) and metabolic status varies among those studies. All of the Asian population-based cohorts consistently define BMI of >25 kg/m^2 as obesity according to the International Diabetes Federation criteria for the Asian population (1), whereas the western population-based cohorts use BMI of >30 kg/m^2 to define obesity. However, notably, two western country-based studies by Murphy and Park categorize participants with overweight or obesity as the same group (normal weight vs. overweight and obesity). Metabolic unhealthiness is defined as a diagnosis of three or more metabolic abnormalities regarding triglyceride, high-density lipoprotein cholesterol, fasting glucose, and blood pressure in six studies. However, the other five studies defined metabolic unhealthiness as a diagnosis of one or more metabolic abnormalities. In **Supplementary Table 2**, the quality of included studies is assessed. All of the studies are ranked as high quality with a NOS score no <7.

Comparison of Cancer Incidence Between MHO and MUO Phenotypes

In **Figure 2**, the incidence of cancer is compared between MHO and MUO phenotypes. Except for Arnlov's study, all the other studies show favorable MHO outcomes, although statistical significance is not reached in five studies. Notably, because Kown

TABLE 1 | Characteristics of included studies.

References	Region	Data source	Cancer type	Number of patients		Follow-up duration	Definition of obese	Definition of metabolically unhealthy (MU) and metabolically health (MH)
				MHO	MUO			
Arnlov et al. (21)	Sweden	Swedish cancer register	Pan-cancer	30	66	Median: 30 years	BMI >30	MU if ≥3 of the following criteria is fulfilled, otherwise MH: • Fasting blood glucose ≥5.6 mmol/l (100 mg/dl) • BP ≥130/85 mmHg or treatment • TG ≥1.7 mmol/l (150 mg/dl) • High density lipoprotein cholesterol <1.04 mmol/l (40 mg/dl) • BMI ≥29.4 kg/m^2
Murphy et al. (22)	Europe	EPIC study	Colorectal cancer	214	737	Median: 3.7 years	BMI ≥25 (overweight, obese)	C-peptide concentration tertile cut-points: 2.96 ng/ml and 4.74 ng/ml, MHO if below the first tertile of C-peptide and MUO if above the first tertile
Kabat et al. (28)	USA	Women's health initiative memory study	Breast cancer	3,347	4,902	15 years (Overall)	BMI ≥30	MU if ≥3 of the following criteria is fulfilled, otherwise MH: WC ≥88 cm, TG ≥150 mg/dL, HDL-C <50 mg/dL, glucose ≥100 mg/dL, and systolic/diastolic BP ≥130/85 mmHg or treatment for hypertension
Park et al. (29)	USA	Sister study	Breast cancer	6,014	20,966	Mean: 6.4 years	BMI ≥25 (overweight, obese)	MU if ≥1 of the following criteria is fulfilled, otherwise MH: WC ≥88 cm, TG ≥150 mg/dL, HDL-C <50 mg/dL, glucose ≥100 mg/dL, and systolic/diastolic BP ≥130/85 mmHg or treatment for hypertension
Kabat et al. (30)	USA	Women's health initiative memory study	Colorectal cancer	4,038	4,931	15 years (Overall)	BMI ≥30	MU if ≥3 of the following criteria is fulfilled, otherwise MH: WC ≥88 cm, TG ≥150 mg/dL, HDL-C <50 mg/dL, glucose ≥100 mg/dL, and systolic/diastolic BP ≥130/85 mmHg or treatment for hypertension
Kwon et al. (34)	Korea	Kangbuk samsung health study	Thyroid cancer	15,402	58,884	Median: 5.3 years	BMI ≥25	MU if ≥1 of the following criteria is fulfilled, otherwise MH: Fasting glucose level ≥ 100 mg/dL or current use of glucose-lowering agents, BP ≥ 130/85 mmHg or current use of BP-lowering agents, elevated TG level (≥ 150 mg/dL) or current use of lipid-lowering agents, low HDL-C (< 40 mg/dl in men or < 50 mg/dl in women), or insulin resistance, defined as an HOMA-IR score ≥ 2.5
Hashimoto and Hamaguchi (35)	Japan	NAGALA study	Gastric cancer	653	3,425	Median: 5.5 years	BMI ≥25	MU if ≥1 of the following criteria is fulfilled, otherwise MH: Impaired fasting plasma glucose and/or diabetes was defined as fasting plasma glucose > 5.6 mmol/L and/or current medical treatment. Hypertension was defined as systolic BP > 130 mmHg and/or diastolic BP > 85 mmHg or current medical treatment. Elevated TG were defined as TG > 1.7 mmol/L or treatment for hyperlipidemia. Low HDL-cholesterol was defined as < 1.0 mmol/L in men and < 1.3 mmol/L in women.

(Continued)

TABLE 1 | Continued

References	Region	Data source	Cancer type	Number of patients		Follow-up duration	Definition of obese	Definition of metabolically unhealthy (MU) and metabolically health (MH)
				MHO	MUO			
Cho et al. (31)	Korea	NHIS-HEALS	Colorectal cancer	28,557	86,238	2009–2015	BMI ≥25	MU if ≥1 of the following criteria is fulfilled, otherwise MH: (1) systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg and/or taking antihypertensive medications; (2) TG level ≥150 mg/dl and/or taking lipid-lowering medications; (3) FPG level ≥100 mg/dl and/or taking antidiabetic medications; and (4) HDL-C levels <40 mg/dl in men and <50 mg/dl in women
Chung et al. (32)	Korea	NHIS-HEALS	Pancreatic cancer	65,983	54,349	median: 6.1 years	BMI ≥25	MU if ≥3 of the following criteria is fulfilled, otherwise MH: Fasting glucose levels ≥5.6 mmol/L (100 mg/dL) or the current use of glucose-lowering agents under the ICD-10 codes E10–E14; BP ≥130/85 mmHg or the use of antihypertensive agents under the ICD-10 codes I10–15; serum TG levels ≥1.7 mmol/L (≥150 mg/dL) or the current use of lipid-lowering agents under the ICD-10 code E78; HDL-C levels <1.0 mmol/L (40 mg/dL) in men or <1.3 mmol/L (50 mg/dL) in women or the current use of lipid-lowering agents under the ICD-10 code E78; and (WC) WC >90 cm for men or ≥85 cm for women, based on the International Diabetes Federation criteria for the Asian population.
Kim (27)	Korea	NHC databases	Bladder cancer	2,313,991	2,069,401	Median: 5.4 years	BMI ≥25	MU if ≥3 of the following criteria is fulfilled, otherwise MH: TG level ≥150 mg/dL, HDL-C level <40 mg/dL, fasting glucose level ≥100 mg/dL (or taking anti-diabetic medications), BP ≥ 130/85 mmHg (or taking antihypertensive drugs), or WC ≥ 90 cm, according to the Asian-specific waist circumference cut-off
Kim (33)	Korea	NHC database	Prostate cancer	2,312,838	2,067,004	Median: 5.4 years	BMI ≥25	MU if ≥3 of the following criteria is met, otherwise MH: TG ≥ 150 mg/dL, HDL-C < 40 mg/dL, fasting glucose ≥ 100 mg/dL, BP ≥ 130/85 mmHg (or taking antihypertensive drug treatment), or WC > 90 cm, according to the International Diabetes Federation criteria for Asian countries.

MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; BMI, body mass index (kg/m^2); BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; WC, waist circumference.

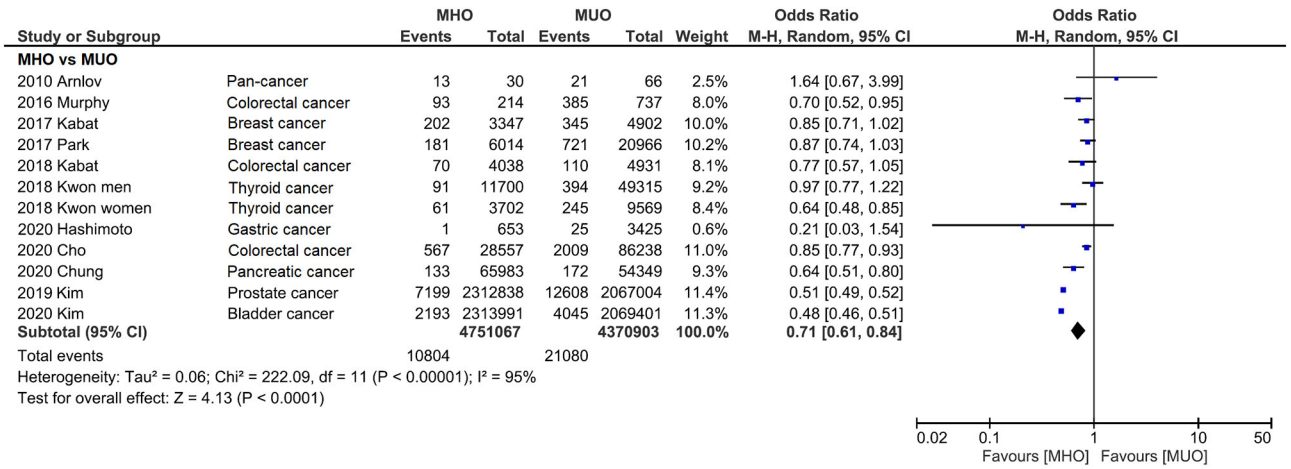

FIGURE 2 | Forest plot that compares cancer incidence between metabolically healthy obesity and metabolically unhealthy obesity. Cancer incidence is significantly lower for metabolically healthy obesity.

reported the data of men and women (34), those data were also separately presented in the present study.

Consistently, pooled outcome indicates that cancer incidence is 29% lower in MHO than that in MUO (OR, 0.71; 95% CI, 0.61–0.84), despite the interstudy heterogeneity remaining high (I^2 = 95%). The funnel plot indicates that the publication bias of this quantitative analysis is insignificant with a symmetrical funnel plot, and *P* value of 0.671 and 0.115 for Egger's test and Begg's test, respectively (**Figure 3** and **Supplementary Figure 1**). Further analyses excluded different studies in quantitative analysis to rule out the reasons for heterogeneity. **Supplementary Figure 2** shows that the heterogeneity drops to I^2 = 45% and I^2 = 28% after removing two (27, 33) and three (27, 32, 33) studies.

Subgroup analyses were also conducted to reveal the potential confounding effects of the present study findings. **Figure 4** displays the outcome categorized by population. Quantitative analyses of both western (OR, 0.84; 95% CI, 0.75–0.93; I^2 = 0%) and Asian (OR, 0.64; 95% CI, 0.54–0.77; I^2 = 96%) populations indicate that MHO phenotype has lower cancer incidence. Likewise, subgroup analysis by the definition of metabolic unhealthiness shows favorable MHO evidence (**Figure 5**). Pooled OR (MHO versus MUO) is 0.62 (95% CI, 0.54–0.71; I^2 = 90%) and 0.76 (95% CI, 0.62–0.94; I^2 = 67%) for studies defining metabolic unhealthiness as three or more and one or more metabolic abnormalities, respectively. Moreover, the present study further conducted subgroup analysis according to the definition of obesity (**Supplementary Figure 3**) and MHO phenotype has a lower incidence of cancer in two subgroups either defining BMI of ≥30 kg/m^2 as obesity (OR, 0.84; 95% CI, 0.73–0.98; I^2 = 19%) or BMI of ≥25 kg/m^2 as obesity (OR, 0.53; 95% CI, 0.52–0.55; I^2 = 96%).

The present study also compared MHNW with MHO, MUO, and metabolically unhealthy normal weight (MUNW) to more comprehensively investigate the impact of different phenotypes on cancer incidence. Moreover, MHNW phenotype has consistently lower cancer incidence compared with MUNW (OR, 1.19; 95% CI, 1.13–1.25; I^2 = 55%), MHO (OR, 1.29; 95% CI, 1.23–1.35; I^2 = 56%), and MUO (OR, 1.09; 95% CI, 1.07–1.11; I^2 = 26%; **Supplementary Figure 4**).

DISCUSSION

The investigation of the impact of MHO on cardiovascular diseases and type 2 diabetes has been an ongoing effort ever since the MHO concept was raised in the 1950's by Dr. Jean Vague' (12). In recent years, researchers have started to focus on the correlation between MHO and the risk of cancer. Although a previous meta-analysis compares the risk of cancer between MHO and MHNW (24), their study is mostly about the impact of obesity on the risk of cancer among patients without metabolic abnormalities. Compared to metabolically healthy population with normal weight, they claimed, MHO had a significantly increased chance of developing cancer (OR 1.14, 95% CI 1.05–1.23), which was independent from the modification by age, sex, ethnicity, smoking, sample size or length of follow-up. Hence, their study found an increased risk of cancer related to obesity itself. Nevertheless, evidence that presents the correlation between metabolic status and cancer risk among patients with obesity is still lacking. The present study, therefore, investigated cancer incidence between MHO and its comparative phenotype—MUO. Our meta-analysis indicates that there is a reduced risk of cancer for MHO phenotype compared with MUO phenotype. Subgroup analyses show consistent outcomes after cohorts from different regions or using different definitions of obesity and metabolic status are distinguished.

The impact of MHO on diseases (e.g., cardiovascular diseases and cancer) has remained debated. The disagreement may be originated from multiple confounding. Ununified MHO definition is believed to be an important confounding factor that limits the interpretation of relevant studies. Although the MHO concept was raised decades ago, more than 30

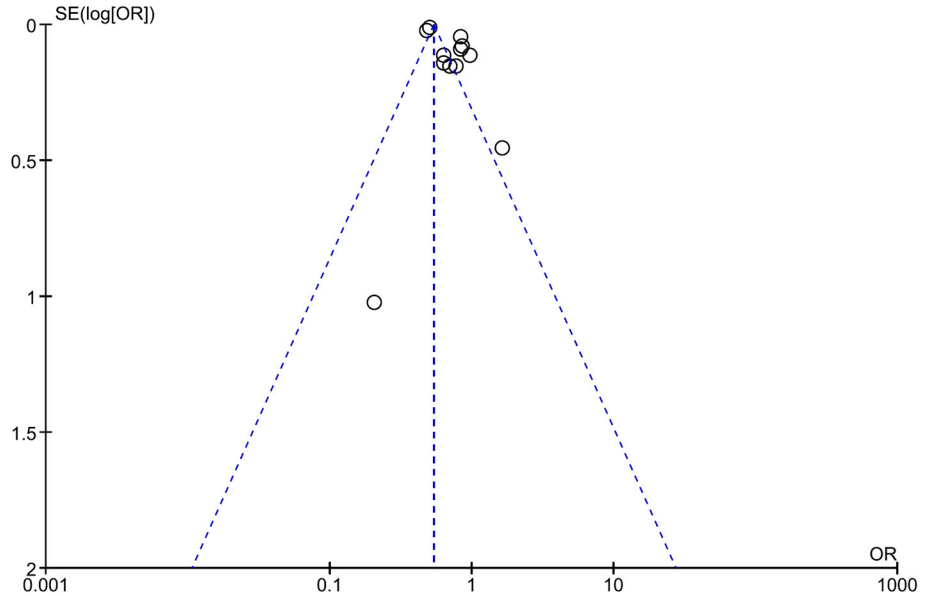

FIGURE 3 | Funnel plot of analysis comparing cancer incidence between metabolically healthy obesity and metabolically unhealthy obesity.

Study or Subgroup	MHO Events	MHO Total	MUO Events	MUO Total	Weight	Odds Ratio M-H, Random, 95% CI
Western country population						
2010 Arnlov	13	30	21	66	1.4%	1.64 [0.67, 3.99]
2016 Murphy	93	214	385	737	11.8%	0.70 [0.52, 0.95]
2017 Kabat	202	3347	345	4902	34.3%	0.85 [0.71, 1.02]
2017 Park	181	6014	721	20966	40.4%	0.87 [0.74, 1.03]
2018 Kabat	70	4038	110	4931	12.1%	0.77 [0.57, 1.05]
Subtotal (95% CI)		**13643**		**31602**	**100.0%**	**0.84 [0.75, 0.93]**
Total events	559		1582			
Heterogeneity: Tau² = 0.00; Chi² = 3.96, df = 4 (P = 0.41); I² = 0%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Asian population						
2018 Kwon men	91	11700	394	49315	14.8%	0.97 [0.77, 1.22]
2018 Kwon women	61	3702	245	9569	13.2%	0.64 [0.48, 0.85]
2020 Hashimoto	1	653	25	3425	0.8%	0.21 [0.03, 1.54]
2020 Cho	567	28557	2009	86238	18.3%	0.85 [0.77, 0.93]
2020 Chung	133	65983	172	54349	14.8%	0.64 [0.51, 0.80]
2019 Kim	7199	2312838	12608	2067004	19.2%	0.51 [0.49, 0.52]
2020 Kim	2193	2313991	4045	2069401	19.0%	0.48 [0.46, 0.51]
Total (95% CI)		**4737424**		**4339301**	**100.0%**	**0.64 [0.54, 0.77]**
Total events	10245		19498			
Heterogeneity: Tau² = 0.05; Chi² = 147.21, df = 6 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 4.72 (P < 0.00001)						

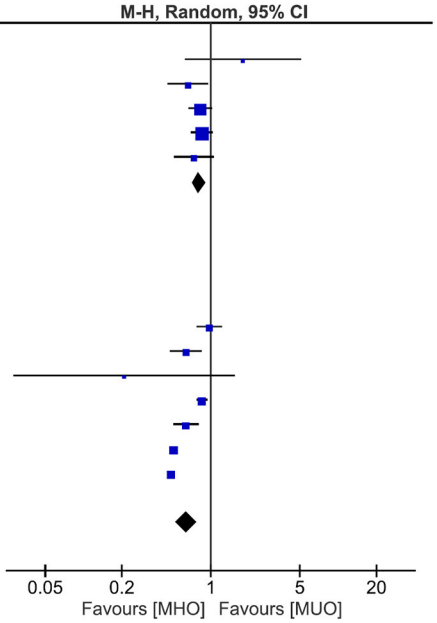

FIGURE 4 | Subgroup analysis grouped by the region of cohorts. Lower cancer incidence for metabolically healthy obesity phenotype is found in both western population and Asian population.

different definitions of metabolic health have been used (36). Moreover, the heterogeneity among those definitions may lead to a significantly different MHO prevalence. For instance, Bluher reviewed the MHO prevalence in the National Health and Nutrition Examination Survey III program (13) and found that 40% of the participants are classified as MHO using the National Cholesterol Education Program Adult Treatment Panel III criteria (37). However, the MHO proportion drops to 20% when more strict insulin sensitivity parameter cutoffs are used (38). Similarly, a Chinese cohort reported that the MHO prevalence varies between 4.2 and 13.6% when different definitions are used (14). Thus, the present study distinguished the definition of metabolic health and obesity to perform subgroup analyses. Notably, although consistent outcomes between subgroups were

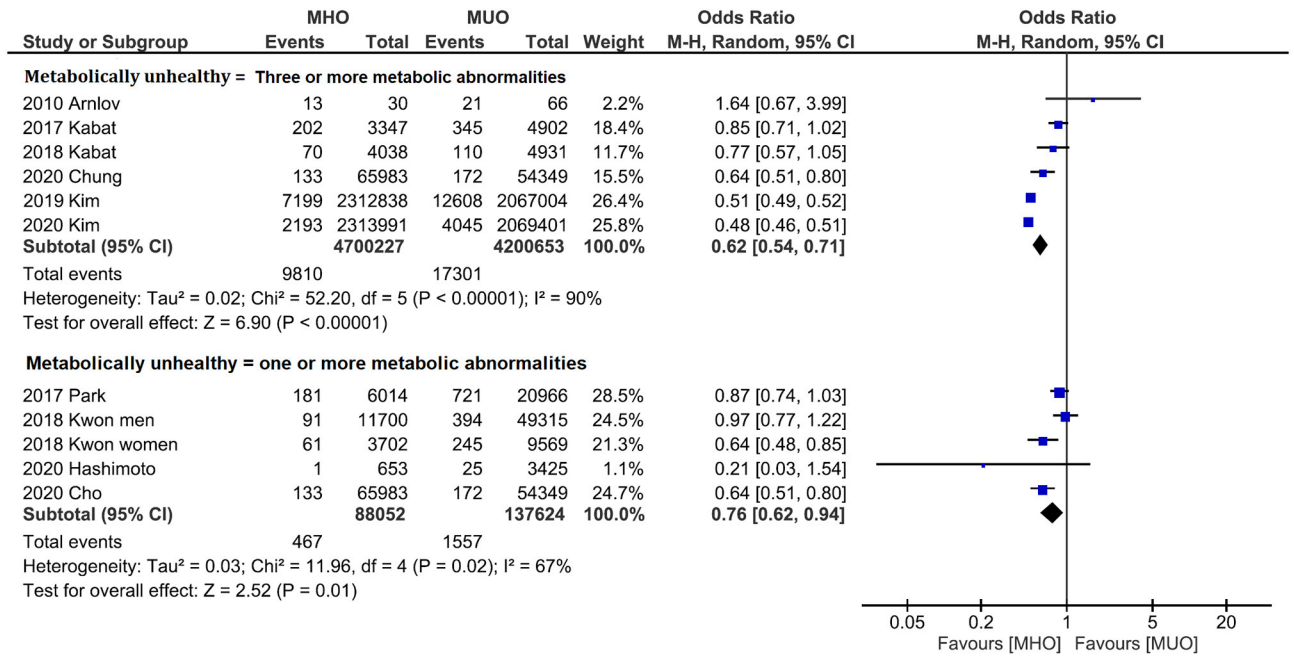

FIGURE 5 | Subgroup analysis grouped by the definition of metabolically status. Lower cancer incidence for metabolically healthy obesity phenotype is found in both studies defining three or more metabolic abnormalities as metabolically unhealthy and studies defining one or more metabolic abnormalities as metabolically unhealthy.

found in the present analyses, the need for standardized MHO criteria should still be addressed. Additionally, subgroup analysis was also conducted based on the regions of the included cohorts, given that the significant regional difference of MHO prevalence that was previously reported (39, 40). MHO was also found to have a lower risk of cancer compared with MUO in either western or Asian countries, which necessitates multiregional studies in the future to compare the risk of cancer between MHO and MUO.

The limitation of this study is that the analysis of the impact of demographic characteristics (e.g., age and gender) on the association between MHO and cancer incidence is absent because of the lack of available data from the included studies. Previous evidence shows that MHO persistence is correlated with younger age and consistently decreases with increasing age (40). Moreover, the general variation of MHO prevalence between males and females is also indicated across a collaborative study of 10 European cohorts (15). Nevertheless, Lin et al. conducted a metaregression and revealed that age and gender (also ethnicity and smoking status) do not significantly affect the cancer risk among individuals with MHO (24), although the study by Kwon indicates an incidence that is twice higher in rate (per 1,000 person-years) of thyroid cancer in females than in males with MHO (34). However, the incidence rate of cancer between females and males should be appropriately interpreted. Most of the cohorts included in the present study emphasized the incidence of a single cancer type for patients with MHO. However, the variation of cancer incidence could be substantial among different cancer types. For instance, some types of cancer can be hormone-related (e.g., breast and thyroid cancers), and the hormone level between genders is distinct. Some cancer types have even been well-recognized to be more prevalent between gender [e.g., bladder cancer, whose incidence of men to women is roughly 4:1 (41)]. This potential bias, therefore, warrants future studies to investigate the association more comprehensively between cancer risk and MHO individuals. Analyzing pan-cancer risk using a similar cohort with adequate follow-up duration would be a feasible strategy. Additionally, the pan-cancer analysis within a single cohort may also more objectively and accurately present the true cancer incidence rate of individuals with MHO. Previously, although Arnlov and Cao conducted pan-cancer analysis among MHO individuals, their studies either have a small sample size (<100 participants with MHO and MUO individuals combined) (21) or do not provide cancer incidence rate of MHO individuals (23).

In terms of the biological differences, MHO is believed to have greater insulin sensitivity, better insulin secretion, normal inflammatory markers and normal adipose tissue function, while MUO is more likely to show insulin resistance, higher markers of inflammation and adipose tissue dysfunction (13). Insulin sensitive MHO is associated with less immune cell infiltration into visceral fat depots, lower mean adipocyte size and a favorable adipokine secretion pattern, while a pro-inflammatory, diabetogenic and atherogenic secretion pattern may contribute to the development of MUO (42). Another critical debate over MHO is whether it represents a *stable condition*, which may also influence the interpretation of the present findings. Bluher's review proposed that individuals in long-term obesity treatment programs may undergo cycles of weight loss and regain accompanied by changing their phenotype from MUO to MHO

and back to MUO (13). Multiple longitude studies have also demonstrated that an proportion of MHO defined at the baseline will undergo the transition to MUO when the follow-up is long enough, although this transition is not necessarily a one-way road (39, 43–45). The gender difference behind MHO-MUO transition still maintains controversial (40, 46), and the lower MHO prevalence in postmenopausal than in premenopausal women suggests that changes in sex hormones may promote this transition (47).

This study is believed to be the first systematic review and meta-analysis combining the evidence comparing the risk of cancer between MHO and MUO. Another strength of the present study is the subgroup analyses investigating the influence of potential confounding on the outcomes. Nevertheless, limitations need to be indicated. Besides the aforementioned potential bias caused by ununified MHO definitions, demographic characteristics (e.g., age, gender, and region), study design flaw, and transition between MHO and MUO, the definition of obesity (waist circumstance or BMI) is not discussed in the present study. Moreover, the heterogeneity is substantial in the present analyses, and some of the included studies are using different big registry cohorts from the same country, which may also produce overlapping data. Last but not the least, although all of the included studies are prospective and of high-quality, randomized-controlled trials on this topic are not feasible (24) and limit the causality investigation.

In conclusion, this study suggests a reduced cancer risk for MHO compared to MUO regardless of population heterogeneity, or the definitions of obesity and metabolic status. In the future, several key factors in designing the studies should be paid attention to. First, a standardized concept of MHO should be employed across the studies to avoid unnecessary bias. Second, the multicenter prospective observational cohorts should be conducted across different regions to reduce the heterogeneity of cancer risk among different races. Moreover, the future study should avoid reporting the incidence of a single type of cancer but reporting all the types of cancer that are observed. Importantly, the proportion of female and male participants should be balanced so that the bias caused by gender and hormone levels could be much avoided. Lastly, experimental assays are required to further explore the underlying mechanism between metabolic status and cancer risk among patients with obesity.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

XZ, JA, and LY: conceptualization. XZ, HX, RP, TL, and SQ: search and screening. XZ, HX, RP, and TL: data extraction, data validation, and quality assessment. XZ, HX, and RP: statistical analysis, interpreted the results, and writing (original draft preparation). XZ, JA, LY, and QW: writing (review and editing). All authors have approved the final version and submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.783660/full#supplementary-material

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frontiers in Nutrition

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Prognostic Value of Sarcopenia in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP: A Systematic Review and Meta-Analysis

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Objective: Several studies have reported conflicting results regarding the association between sarcopenia and outcomes in patients with diffuse large B-cell lymphoma (DLBCL). This meta-analysis aimed to evaluate the prognostic value of sarcopenia in patients with DLBCL.

Methods: PubMed, Embase, and Cochrane Library databases were searched to identify trials exploring the association between sarcopenia and prognosis in patients with DLBCL treated with chemotherapy. A meta-analysis of overall survival (OS), progression-free survival (PFS), treatment completion, and rate of complete response (CR) was performed.

Results: Twelve studies that involved 2,324 patients with DLBCL were included. Sarcopenia was associated with poor OS and PFS in patients with DLBCL, even after adjusting for confounders. Patients with sarcopenia had lower rates of CR and treatment completion than patients without sarcopenia.

Conclusions: Sarcopenia is a negative predictor of prognosis in patients with DLBCL. Additional and prospective studies investigating the diagnostic criteria for sarcopenia are warranted.

Keywords: sarcopenia, diffuse large B-cell lymphoma, overall survival, complete response, meta-analysis

INTRODUCTION

Lymphomas are solid tumors in the immune system. Non-Hodgkin lymphoma accounts for ∼90% of all lymphomas (1). Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma in the United States and worldwide (2, 3). Compared to the chemotherapy regimen of cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP), the combination of immunotherapy with rituximab (R-CHOP) has been found to significantly improve outcomes. Although progression-free survival (PFS) and overall survival (OS) have improved as validated by many randomized controlled trials, ∼40% of patients experience relapse or progression (4). Clinicians and researchers have found that the prognosis of DLBCL is not only related to age,

disease stage, and extranodal involvement but also closely to the patients' nutritional status and skeletal muscle loss.

Sarcopenia is defined as a progressive and generalized skeletal muscle disorder associated with an increased likelihood of adverse outcomes, including falls, fractures, physical disability, and mortality (5). Sarcopenia is prevalent in patients with cancer: 15–50% had skeletal muscle loss (6), while 38–70% were diagnosed with sarcopenia (6). Sarcopenia can increase the risk of death (7), reduce chemotherapy tolerance (8), increase the risk of postoperative complications, and reduce the quality of life (9) and survival (8, 10). Furthermore, several meta-analyses have also verified the prognostic role of sarcopenia in patients with lung cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, and head and neck cancer (11–15).

Recent studies have explored sarcopenia as a prognostic factor for patients with DLBCL. However, the results were inconsistent and controversial. One meta-analysis reported that sarcopenia predicted OS in patients with malignant hematological diseases, while only four studies on patients with DLBCL were included in the meta-analysis (16). Importantly, several recently published studies, which were not included in the above meta-analysis, further explored the prognostic role of sarcopenia in patients with DLBCL. To fill this knowledge gap, we conducted a comprehensive systematic review and meta-analysis of these studies. The impact of sarcopenia on clinical outcomes in patients with DLBCL undergoing immunochemotherapy was evaluated.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. We searched all the published articles in the PubMed, Embase, and Cochrane Library databases until July 2021 for all references using the keywords, MeSH terms "sarcopenia" and "diffuse large B-cell lymphoma," and other related words. The complete search used for PubMed was {[sarcopenia (MeSH Term)] OR muscle OR cachexia OR body composition} AND {[diffuse large B-cell lymphoma (MeSH Term)] OR [non-Hodgkin lymphoma (MeSH Term)]}. Unpublished studies and original data were not included. To avoid oversights in the literature search, two independent researchers searched for the relevant trials twice.

Study Selection and Data Extraction

Studies were included if (1) the study was designed as a prospective cohort study or a retrospective study; (2) patients diagnosed with DLBCL were treated with chemotherapy; (3) skeletal muscle mass or function was measured before treatment; and (4) outcomes included OS, PFS, treatment completion, and rate of complete response (CR). Studies published as abstracts and case reports were excluded. Studies in which participants were not diagnosed with DLBCL and the diagnosis of sarcopenia was not clearly defined were also excluded.

Data from the included studies were extracted by two authors and checked by another author. The following data were collected: name of the first author, year of publication, characteristics of the study participants, number of participants, definition of sarcopenia, method to measure muscle, muscle measurement time, prevalence of sarcopenia, and anti-tumor therapy method for DLBCL and outcomes.

Quality Assessment

The quality of the included trials was evaluated using the Quality In Prognostic Studies (QUIPS) tool by two reviewers independently—study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting were assessed. If more than four of these six criteria had a low risk of bias, the study was considered to have a low risk of bias, and if two or more criteria had a high risk of bias, the study was considered to have a high risk of bias. The remaining studies were classified as having a moderate risk of bias (17).

Data Synthesis and Statistical Analysis

Stata software (version 15.0, StataCorp., College Station, TX, USA) was used for statistical analyses. A heterogeneity test was performed for each analysis, and $I^2 > 50\%$ indicated heterogeneity. When heterogeneity across studies was identified ($I^2 > 50\%$), the random-effects model was used to calculate the pooled hazard ratio (HR) and corresponding 95% confidence intervals (CIs). If studies were homogeneous, a fixed-effects model was used for the analysis. Most of the HR values were extracted from the univariate and multivariate Cox regression analyses, and a few were calculated using the Kaplan–Meier curves. If several methods were used to diagnose sarcopenia, such as skeletal muscle index (SMI) and skeletal muscle density (SMD), SMI was used in the meta-analysis for OS and PFS. A predefined subgroup analysis based on the anti-tumor treatment, skeletal muscle measurement method, and rate of sarcopenia was performed to identify the potential sources of heterogeneity and further explore the prognostic role of sarcopenia. Publication bias was assessed using. The funnel plots and Egger's regression intercept analysis.

RESULTS

Study Selection and Characteristics

A total of 659 related studies were extracted from the above-mentioned databases; 12 met the eligibility criteria and were thus included in the meta-analysis (**Figure 1**). The sample size ranged from 80 to 522 in the 12 studies. All included studies were retrospective cohort studies. The 12 included studies included 2,324 participants, among whom 996 were diagnosed with sarcopenia (18, 19). Seven studies used SMI at the third lumbar vertebra level (L3) on computed tomography (CT) (CT-L3-SMI) for the measurement of skeletal muscle mass (18–24). In the other three studies, SMD at the L3 level on CT imaging (CT-L3-SMD) was used for the measurement of skeletal muscle mass (18, 21, 25). In the two studies, skeletal muscle mass measured using SMI at the psoas level (CT-PM-SMI) (26) and fourth thoracic levels (CT-T4-SMI) (27) were used as the representative skeletal muscle mass of the whole body. One study used muscle mass at the L3 level on CT (CT-L3-muscle mass) as a diagnostic criterion

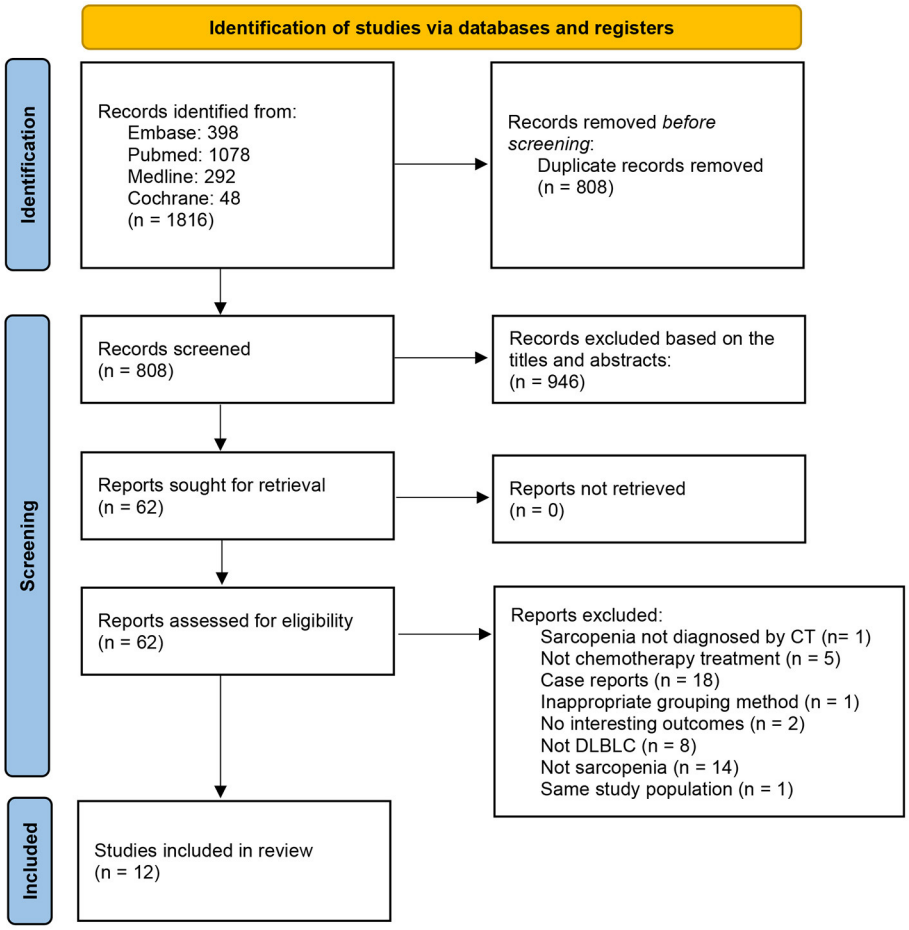

FIGURE 1 | Flow diagram of the selection process in the meta-analysis.

for sarcopenia (28), while another study used a combination of CT-PM-SMI and CT-L3-SMI to diagnose sarcopenia (29). Eleven studies reported the OS and FPS. Five studies evaluated the impact of sarcopenia on treatment completion, and five studies assessed the rate of CR of anti-tumor therapy. The characteristics of the trials included in this meta-analysis are presented in **Table 1**.

Risk of Bias of Individual Studies

Table 2 presents an assessment of the risk of bias in the trials. According to the QUIPS checklist, five included studies had an overall low risk of bias, six trials had an overall moderate risk of bias, and one study had an overall high risk of bias.

Association Between Pretreatment Sarcopenia and OS

In total, 11 studies reported OS as an outcome (**Figure 2A**). A fixed-effect model indicated moderate heterogeneity between studies ($I^2 = 47.7\%$), in which patients with sarcopenia tended to have a shorter OS than those without sarcopenia (HR = 2.25; 95% CI = 1.90–2.67, $P < 0.01$). According to the multivariate analysis of eight trials, the association between pretreatment sarcopenia and poor OS was significant (HR = 1.90; 95% CI = 1.52–2.37, $P < 0.01$; $I^2 = 38.4\%$) (**Figure 2B**).

To comprehensively evaluate the association between sarcopenia and OS in DLBCL, subgroup analysis was performed based on the anti-tumor treatment, skeletal muscle measurement, and rate of sarcopenia. In most subgroup meta-analyses, the pooled data indicated an association between sarcopenia and shorter OS in patients with DLBCL. Subgroup analysis also showed that sarcopenia had no significant impact on OS of patients with DLBCL treated with multiple treatment methods (HR = 1.21; 95% CI = 0.73–2.02, $P > 0.05$; $I^2 = 39.8\%$; **Table 3**).

Association Between Pretreatment Sarcopenia and PFS

Eleven studies reported an association between pretreatment sarcopenia and PFS in patients with DLBCL. The crude pooled HR of skeletal muscle mass loss for PFS was 2.00 (95% CI = 1.72–2.32, $P < 0.01$), while low, non-significant heterogeneity was detected ($I^2 = 26.4\%$; $P = 0.08$). The adjusted summary HR

TABLE 1 | Characteristics of the trials included in the meta-analysis.

References	Study design	*n* (Male/female)	Age	Method to measure muscle	Definition of sarcopenia	Muscle measurement time	Prevalence of sarcopenia	Treatment	Outcomes
Besutti et al. (18)	RS	60/56	63.7	CT-L3-SMI/CT-L3-SMD	L3-SMI: ♂ <43 cm^2/m^2 (BMI<25), ♂ <53 cm^2/m^2(BMI≥25), ♀ <41 cm^2/m^2, L3-SMD: <41 HU (BMI<25), <33 HU (BMI≥25)	Prior to treatment	25% (L3-SMI)	chemoimmunotherapy	OS, PFS (Univariate and multivariate analysis) Treatment completion
Camus et al. (19)	RS	35/45	78.66	CT-L3-SMI	♂ <55.8 cm^2/m^2, ♀ <38.9 cm^2/m^2	Prior to treatment	55%	R-CHOP/R-miniCHOP	OS FPS (Univariate and multivariate analysis) Treatment completion
Chu et al. (25)	RS	125/99	62	CT-L3-SMD	<41 HU (BMI<25), <33 HU (BMI≥25)	Within 1 months prior to treatment	51.8%	R-CHOP	OS FPS (Univariate and multivariate analysis) Treatment response
Go et al. (27)	RS	112/75	66.5/60	CT-T4-SMI	lowest quartile of T4 SMI	Prior to treatment	24.6%	R-CHOP	OS FPS (Univariate and multivariate analysis) Treatment completion Treatment response
Go et al. (20)	RS	112/81	NR	CT-L3-SMI	♂ <52.4 cm^2/m^2, ♀ <38.5 cm^2/m^2;	Prior to treatment	26.9%	R-CHOP	OS FPS Treatment response Treatment completion
Guo et al. (21)	RS	114/87	56.9	CT-L3-SMI/CT-L3-SMD	L3-SMI : <27.55 cm^2/m^2 L3-SMD: ≤36.86 HU	Within 4 months prior to treatment	23.9% (L3-SMI)	R-CHOP	OS FPS (Univariate and multivariate analysis)
Iltar et al. (26)	RS	66/54	59.11	CT-PM-SMI	♂ < 440.4 mm^2/m^2 ♀ <306.87 mm^2/m^2	Prior to treatment	54.2%	R-CHOP	OS FPS (Univariate and multivariate analysis) Treatment response
Lanic et al. (22)	RS	36/46	78	CT-L3-SMI	♂ <55.8 cm^2/m^2, ♀ <38.9 cm^2/m^2;	Prior to treatment	54.9%	R-CHOP/R-miniCHOP	OS FPS (Univariate and multivariate analysis) Treatment completion
Nakamura et al. (23)	RS	121/86	60	CT-L3-SMI	♂ <47.1 cm^2/m^2, ♀ <34.4 cm^2/m^2	Prior to treatment	55.6%	R-CHOP/R-THP-COP	OS FPS (Univariate and multivariate analysis)
Rier et al. (28)	RS	80/84	64.5	CT-L3-muscle mass	Z-score< −1	Within 3 months prior to treatment	48.8%	R-CHOP	OS FPS (Univariate and multivariate analysis) Treatment response
Go et al. (29)	RS	130/98	64	CT-PM-SMI + CT-L3-SMI	L3-SMI: ♂ <52.4 cm^2/m^2, ♀ <38.5 cm^2/m^2, PM-SMI: ♂ <4.4 cm^2/m^2, ♀ <3.1 cm^2/m^2	Prior to treatment	43.9%	R-CHOP	OS FPS
Xiao et al. (24)	RS	510/12	68.1/61.2	CT-L3-SMI	♂ <53 cm^2/m^2, ♀ <41 cm^2/m^2	Within 3 months prior to treatment	49%	CHOP +/− R	Treatment completion

♂:male; ♀: female; RS: retrospective study; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-THP-COP: rituximab, cyclophosphamide, tetrahydropyranyladriamycin, vincristine, prednisone.

TABLE 2 | Quality assessment of individual studies using the QUIPS instrument.

References	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall risk of bias
Besutti et al. (18)	M	L	L	L	L	M	M
Camus et al. (19)	M	L	L	L	L	M	M
Chu et al. (25)	L	M	L	L	L	L	L
Go et al. (27)	M	L	M	L	L	L	M
Go et al. (20)	M	L	L	L	H	L	M
Guo et al. (21)	M	L	L	L	L	M	M
Iltar et al. (26)	L	L	L	L	L	M	L
Lanic et al. (22)	L	L	L	L	L	M	L
Nakamura et al. (23)	L	L	L	L	L	M	L
Rier et al. (28)	M	L	L	L	L	M	M
Go et al. (29)	M	M	M	L	H	H	H
Xiao et al. (24)	M	M	L	L	L	L	L

L, Low-risk; M, Moderate-risk; H, High-risk.

from eight selected trials was 1.64 (95% CI = 1.32–2.03, $P < 0.01$), in which low, non-significant heterogeneity was detected ($I^2 = 0.0\%$) (**Figure 3**).

Subgroups analysis based on the anti-tumor treatments suggested that sarcopenia predicted negative PFS in patients with DLBCL treated with R-CHOP (HR = 2.17; 95% CI = 1.85–2.56, $P < 0.01$; $I^2 = 0\%$) but not in those treated with multiple treatment methods (HR = 1.25; 95% CI = 0.85–1.85, $P = 0.250$; $I^2 = 0\%$). The other subgroup analyses showed an association between sarcopenia and poor PFS (**Table 3**).

Sarcopenia and Treatment Completion

Five studies assessed the association between sarcopenia and treatment completion. The pooled results from the fixed model indicated that sarcopenia decreased the rate of treatment completion [odds ratio (OR) = 0.50; 95% CI = 0.37–0.65, $P < 0.01$]. Heterogeneity between studies was low ($I^2 = 21.1\%$) (**Figure 4**).

Sarcopenia and Rate of CR

Five studies analyzed the relationship between sarcopenia and the rate of CR in DLBCL. As shown in **Figure 5**, sarcopenia predicted a low rate of CR (OR = 0.47; 95% CI = 0.24–0.93, $P < 0.01$). Howev er, there was significant heterogeneity between studies ($I^2 = 72.3\%$).

Publication Bias

The Begg's funnel plots and Egger's publication bias plots were used to assess the potential publication bias for OS in the univariate analysis. No publication bias was detected using the Egger's test ($P = 0.344$) (**Figure 6**).

DISCUSSION

Our meta-analysis showed that sarcopenia was associated with poor survival, even after adjustment for confounders. Furthermore, the meta-analysis outcomes showed a low rate of CR in patients with sarcopenia after R-CHOP therapy. In addition, patients with sarcopenia tended to fail to complete the treatment plan compared to patients without sarcopenia. These results are consistent with a recently published meta-analysis study, which demonstrated that overall mortality of hematopoietic cancer was significantly associated with sarcopenia. However, only two studies that involved patients with DLBCL were included, and several recently updated researches were not (30).

In our study, the incidence of sarcopenia ranged from 23.9 to 55.6%, which was consistent with the previous study involving United States veterans with DLBCL, which was >30% based on CT diagnosis before chemotherapy (24). The significant differences in the incidence of sarcopenia among patients with DLBCL were due to the lack of uniform diagnostic criteria and cut-off values. Additionally, patients with DLBCL also experience further muscle loss during chemotherapy, with skeletal muscle area decreasing by ∼2.8% after treatment (24).

The mechanism of sarcopenia is complex. Aging is a crucial risk factor for sarcopenia. The aging process breaks the balance between muscle protein synthesis and catabolism, eventually leading to gradual loss of skeletal muscle loss (31). The mechanism of aging related sarcopenia also involves negative protein turnover characterized by reduction of myofibrillar and mitochondrial protein synthesis and increased proteolysis via the ubiquitin proteasome and calcium-dependent activation of proteases (32, 33). The decreased number of type II fiber satellite cells and the intramuscular and intermuscular fat infiltration (myosteatosis) caused by aging contribute to sarcopenia at the cellular level (31, 34). Systemic inflammation is also crucial for the pathogenesis of muscle loss in later life. The chronic pro-inflammatory state caused by increased production of pro-inflammatory cytokines is a possible underlying cause of muscle loss (35). The high incidence of sarcopenia in patients with DLBCL can be explained by the average age of the study cohort included in this meta-analysis, which ranged from 60 to 70

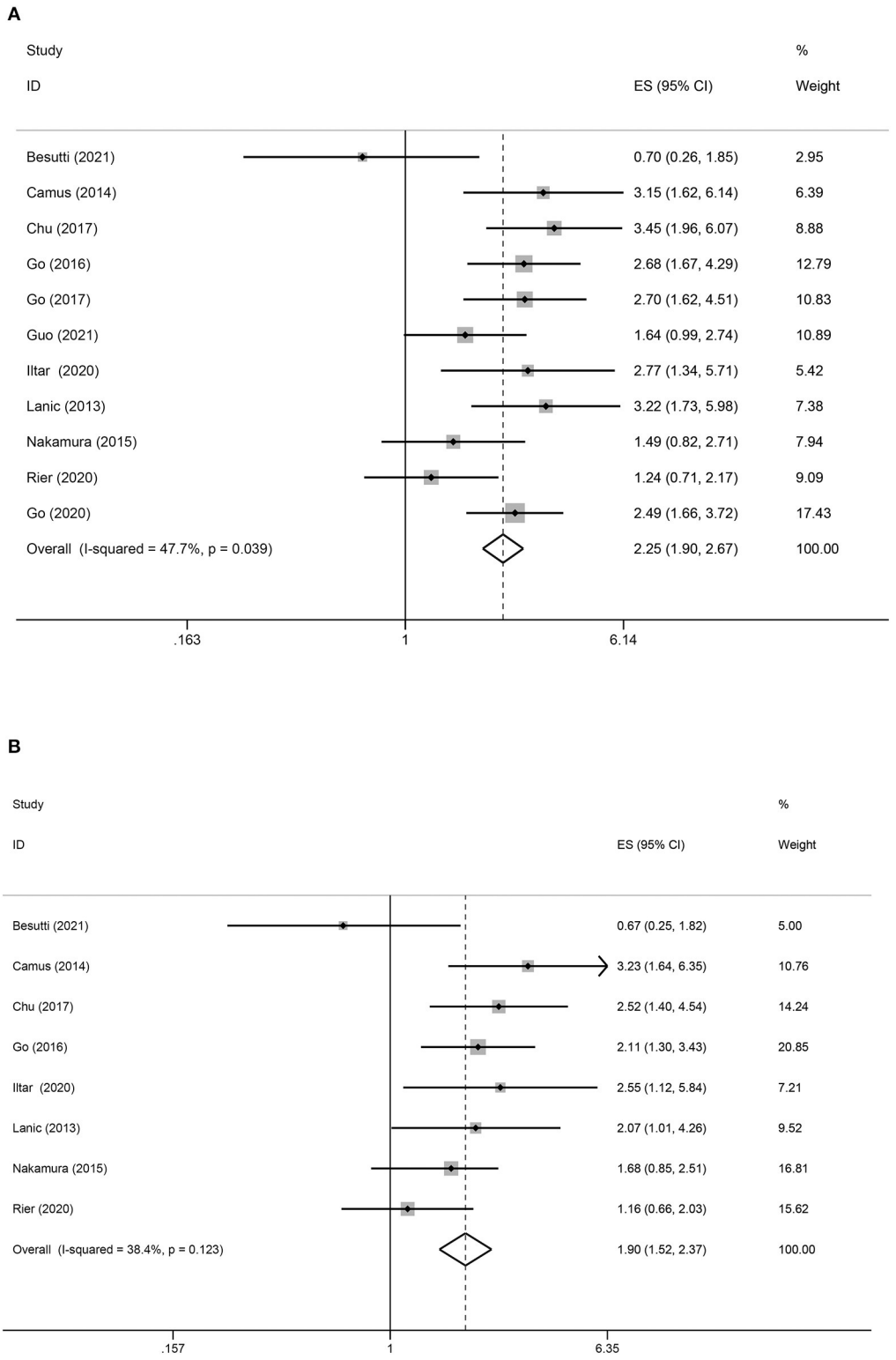

FIGURE 2 | Forest plots of the association between sarcopenia and OS in patients with DLBCL undergoing chemotherapy. **(A)** Univariate analysis **(B)** Multivariate analysis. **(A)** Univariate analysis of pooled results of the association between sarcopenia and OS. The pooled HR was 2.25 (95% CI = 1.90–2.67, $p < 0.01$, $I^2 = 47.7\%$). **(B)** Multivariate analysis of pooled results of the association between sarcopenia and OS from. The pooled adjusted HR was 1.90 (95% CI = 1.52–2.37, $p < 0.01$; $I^2 = 38.4\%$).

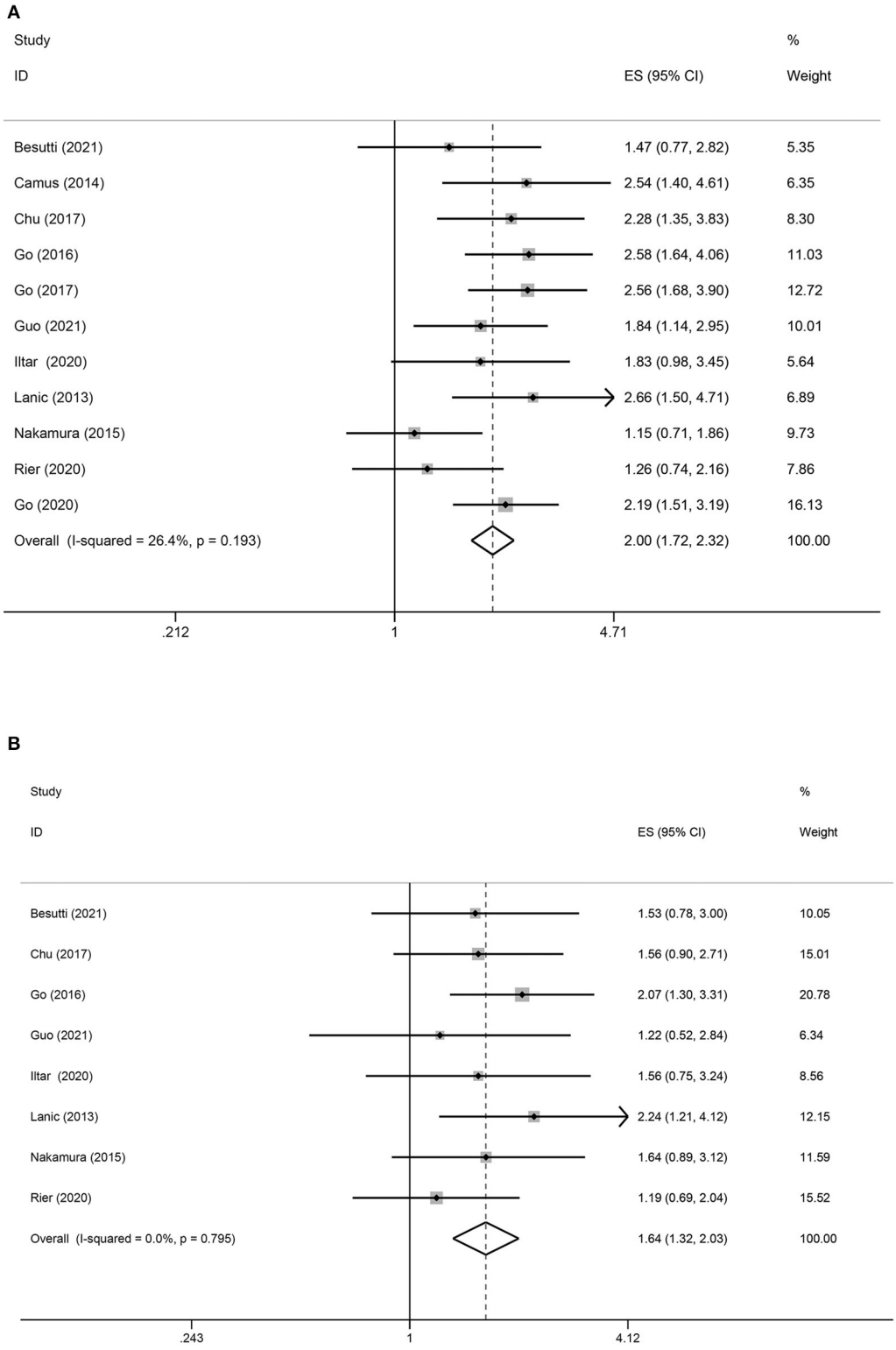

FIGURE 3 | Forest plots of the association between sarcopenia and PFS in patients with DLBCL undergoing chemotherapy. **(A)** Univariate analysis **(B)** Multivariate analysis. **(A)** Univariate analysis of pooled results of the association between sarcopenia and PFS. The pooled HR was 2.00 (95% CI = 1.72–2.32, $p < 0.01$, $I^2 = 26.4\%$). **(B)** Multivariate analysis of pooled results of the association between sarcopenia and OS. The pooled adjusted HR in total was 1.64 (95% CI = 1.32–2.03, $p < 0.01$; $I^2 = 0.0\%$).

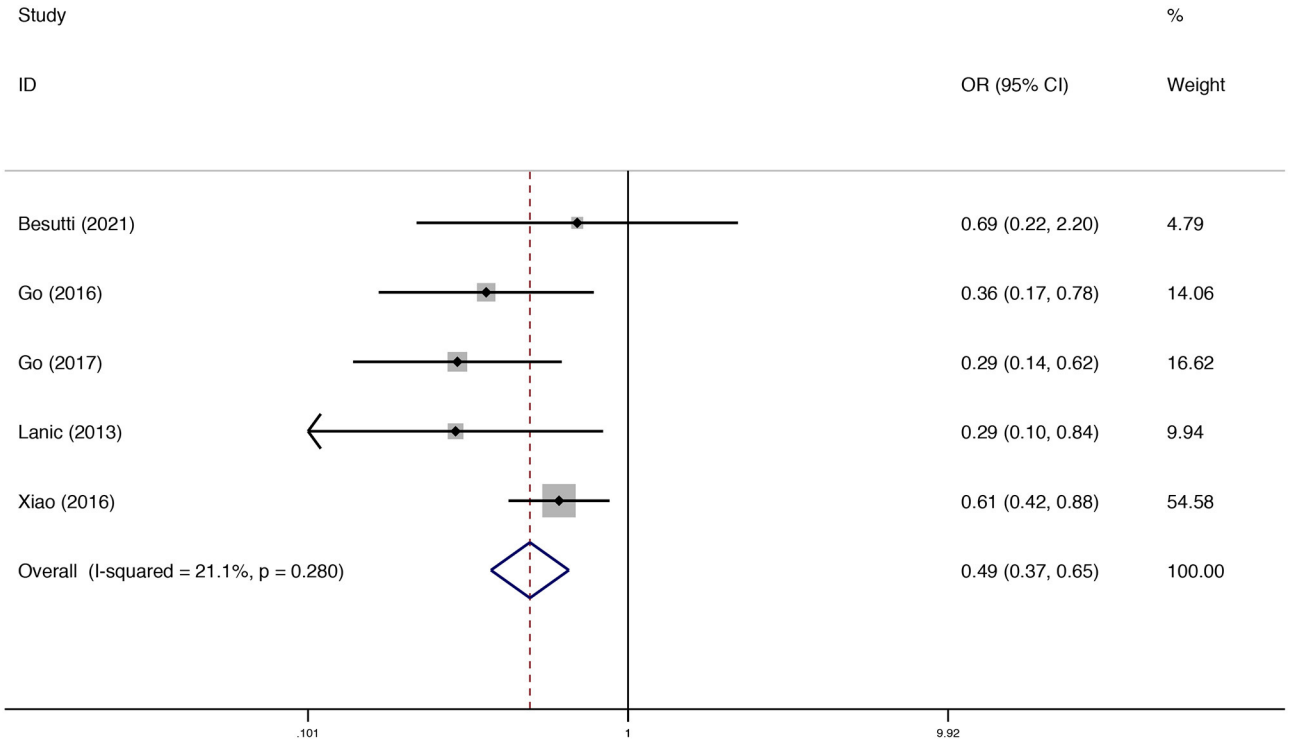

FIGURE 4 | Forest plots of the meta-analysis of the effect of sarcopenia on treatment completion in patients with DLBCL undergoing chemotherapy. Pooled results of the OR of the rate of treatment completion in patients with DLBCL. The pooled OR of patients with DLBCL was 0.49 (95% CI = 0.37–0.65, $I^2 = 21.1\%$).

TABLE 3 | Subgroup analysis of the association between sarcopenia and survival of patients with DLBCL treated with chemotherapy.

Subgroup	Methods	Heterogeneity	HR	95% CI	*p*
OS					
Anti-tumor treatments					
R-CHOP	Fixed	28.2%	2.43	(2.03–2.91)	$p < 0.001$
R-CHOP + others	Fixed	39.8%	1.21	(0.73–2.02)	$p = 0.456$
Measurement of skeletal muscle					
CT-L3-SMI	Random	55.1%	2.03	(1.39–2.97)	$p = 0.001$
CT-L3-SMD	Random	0%	3.51	(2.47–4.98)	$p = 0.029$
Other measurement methods	Random	45.1%	2.20	(1.55–3.13)	$P < 0.001$
Rate of sarcopenia					
<30%	Random	60.8%	1.93	(1.22–3.06)	$p = 0.005$
>40%	Random	45.7%	2.36	(1.76–3.18)	$p < 0.001$
PFS					
Anti-tumor treatments					
R-CHOP	Fixed	0%	2.17	(1.85–2.56)	$p < 0.001$
R-CHOP + others	Fixed	0%	1.25	(0.85–1.85)	$p = 0.250$
Measurement of skeletal muscle					
CT-L3-SMI	Random	43.8%	1.95	(1.58–2.41)	$p < 0.001$
CT-L3-SMD	Random	0%	2.48	(1.84–3.36)	$p = 0.001$
Other measurement methods	Random	31.6%	2.01	(1.59–2.54)	$p < 0.001$
Rate of sarcopenia					
<30%	Fixed	0.5%	2.19	(1.72–2.78)	$p < 0.001$
>40%	Fixed	38.2%	1.89	(1.56–2.29)	$p < 0.001$

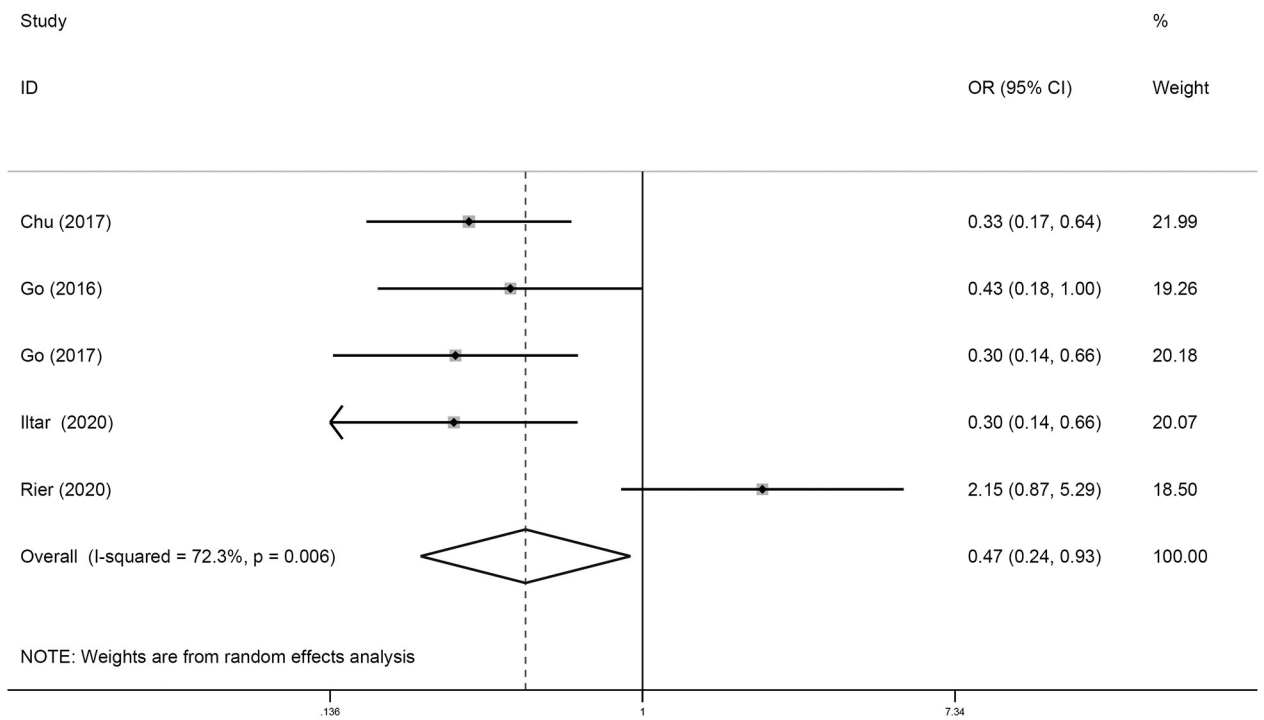

FIGURE 5 | Forest plots of the meta-analysis of the effect of sarcopenia on the rate of CR in patients with DLBCL undergoing chemotherapy. Pooled results of OR of rate of CR in patients with DLBCL. The pooled OR of patients with DLBCL was 0.47 (95% CI = 0.24–0.93, $I^2 = 72.3\%$).

years. These patients are susceptible to sarcopenia. Moreover, various pro-inflammatory cytokines, including prostaglandins, interleukin-6, interleukin-1, tumor necrosis factor, interferon gamma, and leukemia inhibitory factor, secreted by the tumors also elicit catabolism in the skeletal muscles and accelerate muscle loss (36, 37). In addition, the abnormal metabolism of proteins and amino acids caused by the tumor exacerbates muscle loss. Malnutrition due to the tumor and anti-tumor therapy also affects muscle mass in patients with DLBCL (38). Furthermore, physical activity is also greatly limited in patients with cancer.

Our findings suggested an overall negative effect of sarcopenia in the rate of CR. However, this result was inconsistent with the previous studies. In the study by Rier, when low muscle mass (LMM) was used as the diagnostic criteria for sarcopenia, there was no difference in the rate of CR between the sarcopenia and non-sarcopenia groups (28). Another study showed that there was no difference in the rate of CR between the groups in patients whose chemotherapy treatment was uninterrupted (29). Upon reviewing the literature, we found the decreased clearance of the anti-tumor drugs in the tissues of patients with muscle reduction may improve the therapeutic effect while accompanying side effects, including increased toxicity (39). The study by Guo confirmed that grade 3–4 toxicity during or after immunochemotherapy was associated with poor body composition. For every 5 cm^2/m^2 decrease in SMI, the risk of any grade 3–4 toxicity increased by 34% (21). Another study also confirmed that the sarcopenia group had more frequent grade 3 anemia, grade 3–4 and 4 thrombocytopenia, and grade 4–5 non-hematologic toxicity (21). Increased toxicity may lead to early discontinuation of treatment, which may be a reason for the reduction in the rate of CR. The pooled data from this meta-analysis also indicated that sarcopenia was associated with the inability to complete the standard number of treatment cycles due to toxicity. Moreover, the association between lower SMG, SMD, SMI, and lean body mass (LBM) and the increasing risk of dose delay/reduction was also demonstrated in the study by Guo (21).

Most importantly, the meta-analysis provided convincing evidence that sarcopenia was associated with low OS and PFS. The association between sarcopenia and prognosis was independent of other prognostic factors, such as age, sex, prognostic index, and hypoalbuminemia. The pathogenesis of poor survival in patients with cancer and sarcopenia is unclear. A commonly postulated mechanism is that greater drug toxicity results in decreased treatment tolerance and reduction in effective drug doses (15, 40). Another potential explanation is that decreased levels of insulin-like growth factor-1 (IGF-1) are secreted by the smaller skeletal muscle and that both insulin-like growth factor-1 receptor (IGF-1R) density and signaling are impaired in the aged skeletal muscle (41). Recent studies have suggested that the IGF-1/IGF-1R signaling pathway may contribute to the progression of DLBCL and other

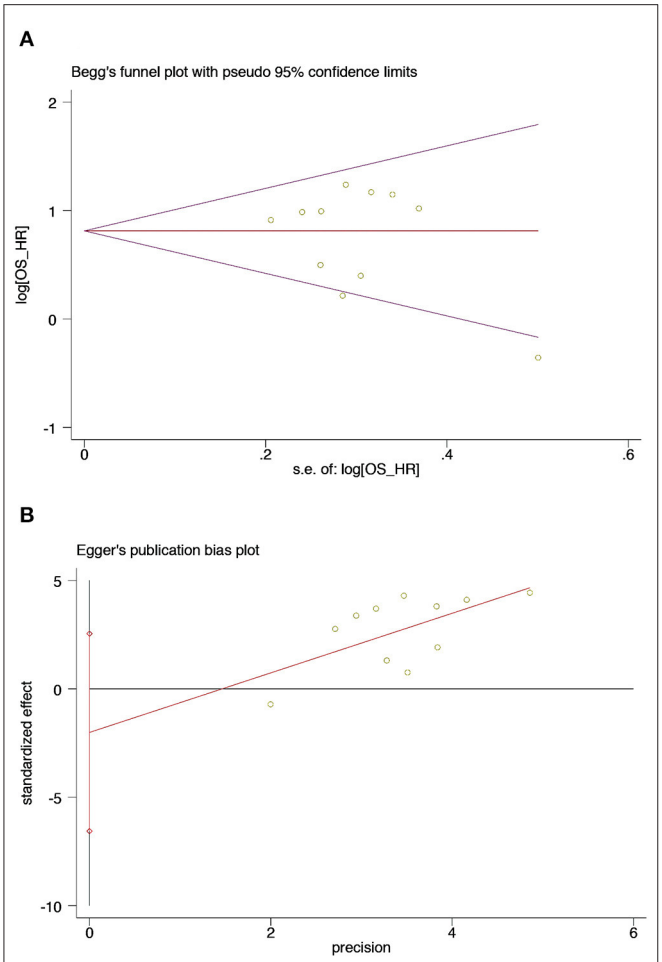

FIGURE 6 | Begg's test and Egger's test of sarcopenia and OS from univariate analysis in patients with DLBCL undergoing chemotherapy **(A)** Begg's test **(B)** Egger's test. **(A)** Begg's funnel plots of publication bias for the association between sarcopenia and OS from univariate analysis ($p = 0.755$). **(B)** Egger's test of publication bias for the association between sarcopenia and OS from univariate analysis ($p = 0.344$).

cancers (42–44). In addition, muscle loss is a manifestation of malnutrition. Malnutrition encountered in patients with DLBCL also leads to increased incidence of treatment-related toxicity, which influences the occurrence of poor survival outcomes (38). Sarcopenia is also a hallmark of cancer cachexia. Poor OS and PFS may be a consequence of cancer cachexia rather than sarcopenia. Patients with cancer cachexia tend to have progressive functional impairment and worse clinical outcomes due to the profound systemic inflammation associated with cancer.

Although sarcopenia was associated with poor survival in patients with DLBCL, the prognostic value of low body mass index (BMI) in the included studies remains controversial. Two studies showed that low BMI was associated with poor OS and PFS (19, 22). However, in the four studies, underweight was not significantly associated with poor survival (20, 26, 27, 29). In Besutti's study, no significant difference was observed between different the BMI groups (<25, 25–30, ≥30) in terms of OS and PFS. However, sarcopenia in patients with obesity have the worst survival after further stratifying patients into sarcopenia and obesity group (18). As a result, the prognostic value of sarcopenia in DLBCL cancer patients with obesity, normal weight, and underweight should be further studied.

Our study has some limitations. All included trials were retrospective studies. There was considerable heterogeneity in the meta-analysis with respect to patient cohorts as a result of using different diagnostic criteria for sarcopenia. Although the muscle mass in all included studies was measured on CT, the scan level of CT used in each study was different, and the cut-off values varied. In addition, the various treatment strategies used in the studies were also likely to contribute to heterogeneity. Another limitation of our meta-analysis is the different definitions of OS and PFS in the studies. Further, the lack of measurement of relevant indicators of muscle function is a limitation. The included studies were retrospective and evaluated muscle mass only on CT, but not by muscle function. The definition of sarcopenia includes not only the reduction of muscle mass but also the degeneration of muscle function. Moreover, gene mutations also play a key role in determining the prognosis of patients with DLBCL. However, none of the included articles investigated the effect of sarcopenia on prognosis in patients with DLBCL with different gene mutations. Therefore, further studies using rigorous design are warranted to verify the strength of prognostic role of sarcopenia in patients with DLBCL.

CONCLUSION

The prevalence of sarcopenia is higher in patients with DLBCL than in the general population. Loss of skeletal mass is associated with poor survival in patients with DLBCL. Sarcopenia also negatively affects the rate of treatment completion and CR to immunochemotherapy. Identification of consensus diagnostic criteria for sarcopenia and design of prospective studies that incorporate measurements of muscle strength and physical function are the areas for further research.

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.

AUTHOR CONTRIBUTIONS

XJ: conceptualization, methodology, software, investigation, and writing—original draft. X-TX: methodology, software, and investigation. M-XT: resources, data curation, and investigation. D-LH and H-JW: writing—review and editing. All authors revised and approved the final manuscript.

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Effects of Immunonutrition in Head and Neck Cancer Patients Undergoing Cancer Treatment – A Systematic Review

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Background and Aims: Malnutrition is prevalent among head and neck cancer (HNC) patients and leads to undesirable outcomes such as reduced treatment response and increased treatment-related side effects. This systematic review summarizes the recent evidence regarding the effect of immunonutrition in HNC patients undergoing radiotherapy and chemotherapy.

Methods: A literature search was conducted of the CENTRAL, ProQuest, MEDLINE, EBSCOhost, Web of Science and CINAHL databases; and further supplemented with internet and manual searches. Studies published between January 2011 and May 2021 were identified, screened, retrieved, and data extraction was performed.

Results: Twenty studies involving 1535 patients were included, 15 were randomized controlled trials (RCTs), three were retrospective study and two were comparative cohort studies. Five out of seven studies reported improvement or maintenance of nutrition status with continuous supplementation using immunonutrient-enriched formula. Three studies reported functional status as an outcome, with one study reporting significant improvement, one study reporting maintenance, and another study reporting no difference in the functional status of patients supplemented with immunonutrient-enriched formulas. Supplementation with glutamine did not reduce the overall incidence of mucositis but delayed the onset of oral mucositis and had significantly less incidence of severe oral mucositis.

Conclusion: Supplementation with immunonutrient-enriched formulas in HNC patients during radiotherapy and chemotherapy may improve or maintain nutrition status. Supplementation with glutamine during HNC radiotherapy and chemotherapy may delay the onset of oral mucositis and reduce incidences of severe oral mucositis. Further investigations are required, focusing on the timing, dosage, and duration of immunonutrition.

Systematic Review Registration: PROSPERO, identifier CRD42021241817.

Keywords: immunonutrition, glutamine, arginine, omega 3 fatty acid, radiotherapy, cancer treatment, head and neck (H&N) cancer

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INTRODUCTION

Head and neck cancer refers to neoplasms occurring in the head and neck region, including the pharynx, nasal, and oral cavity, metastasising to cervical neck nodes. The curative treatment of HNC includes concurrent chemoradiotherapy, radiotherapy alone, or postoperative radiotherapy.

Malnutrition in cancer patients is associated with weight loss, reduced immune competence, increased risk of infections, increased treatment toxicities, and greater mortality risk. The prevalence of malnutrition is very high in cancer patients undergoing treatment (1–3). Patients with primary cancers involving the gastrointestinal tract, head and neck, liver, and lung are exceptionally at high risk of malnutrition (1). In HNC, the prevalence of malnutrition is at an alarming 22–56% upon diagnosis (4–6). Malnutrition in cancer patients can be attributed to inadequate nutritional intake, likely due to primary anorexia or secondary causes (e.g., mucositis, xerostomia, intestinal obstruction, malabsorption, nausea, vomiting, pain, etc.). Additionally, metabolic derangements such as increased metabolism and catabolism further reduce cancer patients' nutrition status. For cancer patients undergoing cancer treatment, malnutrition increases the risk of treatment-related toxicities, resulting in treatment withdrawal and eventual reduction in treatment response.

Immunonutrition can be defined as modulation of either the immune system activity or modulation of the consequences of activation of the immune system by nutrients or specific food items fed in amounts above those typically encountered in the diet (7). Immunonutrients identified and studied are omega-3 fatty acids, glutamine, arginine, branched-chain amino acids, and nucleotides (8–10). Immunonutrition can be provided in the form of immunonutrient-enriched formula, single immunonutrient, or combination of immunonutrients. Immunonutrition was found to reduce the severity of treatment-related toxicities such as oral mucositis, diarrhea, oesophagitis, and weight loss (11, 12). However, the variability in the type, dose, and duration of immunonutrition led to inconsistent outcomes among available evidence.

This systematic review summarizes the recent evidence regarding the effect of immunonutrition in HNC patients undergoing radiotherapy and chemotherapy.

MATERIALS AND METHODS

This systematic review was designed according to the PICOS criteria outlined in **Table 1** and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement guidelines. The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number: CRD42021241817.

Search Strategy

A literature search was conducted of six databases: Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, ProQuest, MEDLINE (Pubmed), EBSCOhost, Web of Science and CINAHL. The literature search was further supplemented with internet searches (e.g., Google Scholar) and a manual search of the reference lists of relevant studies and previously published systematic reviews. Studies published from January 2011 to May 2021 were included in the search. There were no language restrictions for the studies.

The search strategy included three groups of keywords and Medical Subject Headings (MeSH) terms that describe immunonutrition, head and neck cancer patients, and cancer treatment. Search terms of the same group, such as "immunonutrition," "immune-enhancing nutrition," "immune-modulating nutrition," "glutamine," "arginine," omega 3 fatty acid," "fish oil," "nucleotides" were combined using Boolean operator OR. Search terms for the three different groups were then combined with the Boolean operator AND (refer to **Supplementary Material**).

Eligibility Criteria

The inclusion criteria for studies to be considered for this review were (1) primary research involving adult (above 18 years) HNC patients undergoing radiotherapy and or chemotherapy either as primary treatment modality or post-operatively; (2) comparing immunonutrition (combination of immunonutrients or involve at least one immunonutrient – glutamine, arginine, omega 3 fatty acid) vs. standard nutrition (polymeric nutrition formula that is nutritionally complete), or placebo or no nutrition intervention; (3) reported nutrition status, functional status and treatment-related toxicities as outcomes.

Studies that did not meet the inclusion criteria were excluded: involving participants <18 years old, involving participants who did not undergo radiotherapy or chemotherapy, and involving nutrition supplementation via parenteral nutrition. Duplicate and irrelevant studies were also excluded in case reports, letters, reviews, animal or *in vitro* studies.

Study Selection and Data Collection

The selection of articles involved three stages: (1) selection based on title, (2) abstract consideration, (3) assessing the full text. Two reviewers independently assessed the potentially relevant articles for eligibility. Disagreements are resolved through discussion until consensus is reached. A third reviewer was consulted in the event that no consensus was reached.

Database searches and reference lists were imported into EndNote™ 20, Clarivate Analytics (US) LLC. Data extraction was performed using a data extraction table that collects information such as bibliography information (title, author, publication year, journal, country/institution where the study was conducted), study design, study duration, study population (inclusion/exclusion criteria, sample size, type of cancer, type of treatment), intervention, comparison, outcomes, etc. Study investigators were contacted to clarify or obtain more information when necessary. Two reviewers independently extracted the data. Discrepancies are resolved through discussion until consensus is reached. A third reviewer was consulted in the event no consensus was reached.

TABLE 1 | PICOS Criteria.

Criteria	Description
Participants	HNC patients undergoing radiotherapy and/or chemotherapy
Intervention/Exposure	Supplementation with immunonutrition -including arginine, glutamine, omega-3 fatty acids, nucleotides; isolated or combined; administered via oral supplementation or enteral route
Comparison	Any parallel group with similar clinical properties, receiving standard care, with or without nutrition supplementation
Outcomes	Nutrition status, functional status, treatment-related toxicities
Study Design	RCT, non-RCT (e.g., controlled clinical trial)

Outcomes

The primary outcome specified was nutrition status, which included: changes in weight and BMI, body composition, Subjective Global Assessment (SGA), and Nutritional Risk Index (NRI).

Secondary outcomes that were specified were functional status and treatment-related toxicities. Functional status is measured by handgrip strength or performance scores such as ECOG, Kondrup, or Karnofsky Performance Index. Incidences and severity of treatment-related toxicities are graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Quality and Risk of Bias Assessment

Two reviewers performed the quality and Risk of Bias assessment independently, using the Jadad Scale (13) and Cochrane Risk of Bias Tool (14) for randomized, controlled trials. Results were compared, and any discrepancies were resolved through discussion; a third reviewer was consulted on the occasion where consensus could not be reached. The methodological quality of controlled trials was scored according to three areas – randomisation, masking and accountability. The bias of the studies was rated as High, Low or Unclear; on five specified domains (Selection, Performance, Attrition, Reporting, and Other).

Data Synthesis

Narrative synthesis of the information gathered in the data extraction form is structured around the type of intervention, target population characteristics, type of outcome, and intervention content. Summary of intervention effects were tabulated.

RESULTS

The literature search identified 1,519 articles. Nine other articles were identified through reference list and citation search. Duplicate articles and ineligible articles were removed via automation tools or manual identification. The remaining 243 articles were screened based on title and abstract. The full texts of 62 articles were then retrieved and assessed. Thirty-six studies were excluded because they did not meet the eligibility criteria, and two studies were excluded because of duplication. Three studies published as abstracts were excluded because retrieval of the full manuscript was unsuccessful as there was no reply from the authors (15–17). Finally, a total of 20 studies were included in this systematic review. The study selection process is outlined in **Figure 1**.

Characteristics of the studies included are summarized in **Table 2**. The sample size of the studies ranges between 26 and 262, with an accumulative total of 1,535 patients, of which 805 received immunonutrition while 730 received standard nutrition or placebo or no treatment. The studies are categorized according to the type of intervention, including supplementation using immunonutrient-enriched formula, or supplementation using a single immunonutrient or combination of immunonutrients. Ten studies involved supplementation using immunonutrient-enriched formula (18–27), while nine studies involved the supplementation of a single immunonutrient (glutamine) (28–36), and one study involved supplementation of immunonutrients (glutamine and arginine) with hydroxy-beta-methylbutarate (37). Majority of the studies involved only HNC on radiotherapy with or without chemotherapy, except for five studies that involved HNC and oesophageal cancer patients in their study population (19, 23, 25, 36, 38).

Most of the studies involved immunonutrition as oral nutrition supplements and are only administered via a feeding tube when the subjects were unable to tolerate it orally. For the three studies that involved oesophageal cancer patients, the immunonutrient-enriched formula was administered via a feeding tube upon initiation of intervention (19, 23, 25).

Quality and Risk of Bias Assessment

The risk of bias of the included studies was evaluated using the Cochrane Risk of Bias Tool for Randomized Control Trials and summarized in **Figure 2**. Out of the 15 studies that were evaluated, seven were classified under low risk of bias, four were classified as high risk of bias, and four were judged to have raised some concerns of risk of bias. The most common source of bias was performance bias (i.e., blinding of participants and personnel). Seven studies were non-blinded as they were either open-label studies or the control group did not receive any treatment. For selection bias, four studies did not describe in detail the randomisation process or participant allocation. Therefore, the risk of bias was unclear. In terms of detection bias, five studies did not describe if the outcome assessors were blinded to the intervention allocation or not. Hence the risk of bias was unclear. Finally, for attrition bias, five studies were classified as high risk as there was more than 10% dropout or loss of sample.

The quality of the clinical trials was also assessed using the Jadad scale and summarized in **Table 3**. Twelve studies were of high quality (score between 3 and 5), whereas three were low quality (score between 0 and 2).

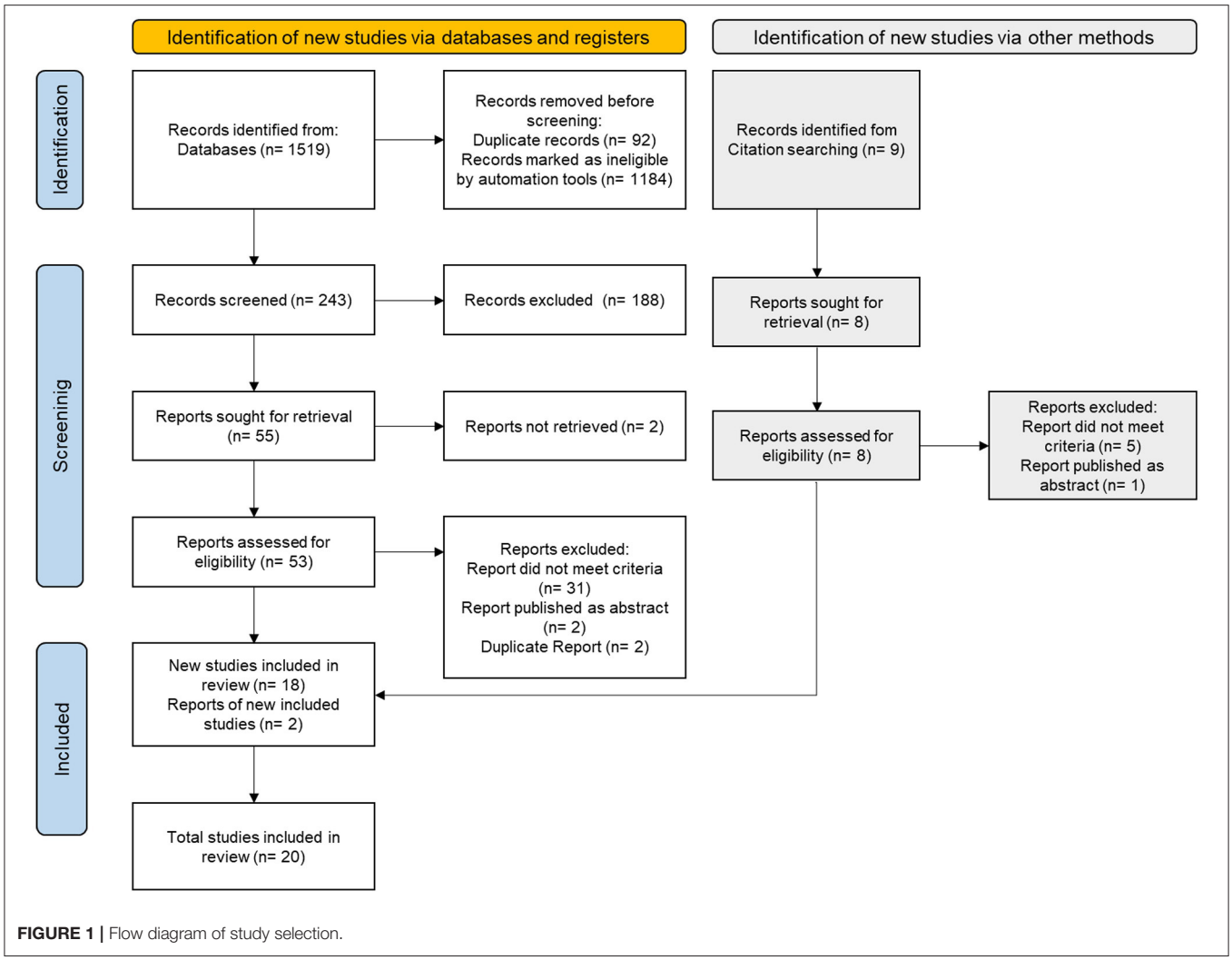

FIGURE 1 | Flow diagram of study selection.

Immunonutrient-Enriched Nutrition Formula

Ten studies evaluated the effects of immunonutrient-enriched nutrition formulas. Of these, three involved nutrition formula enriched with arginine and omega-3 fatty acids (18, 23, 27); two involved nutrition formula enriched with omega-3 fatty acids (24, 25); two involved nutrition formula enriched with arginine, glutamine and omega-3 fatty acids (19, 21); one involved nutrition formula enriched with glutamine and arginine (22); one involved elemental nutrition formula containing glutamine (20); and one involved nutrition formula enriched with glutamine and omega-3 fatty acids (26). In terms of methodological quality, seven out of 10 of the studies were of good quality.

Most studies involved continuous supplementation during and throughout the radiotherapy and chemotherapy treatment, except for Boisselier et al. that provided immunonutrient-enriched formula in intervals (5 days before each chemotherapy cycle) (18); Roca-Rodriguez et al. that started immunonutrient-enriched formula 14 days after initiation of radiotherapy and continued up to 90 days post-radiotherapy treatment (24); and Yeh et al. that continued the immunonutrient-enriched formula until one-month post-radiotherapy treatment (26).

In terms of nutritional status, five studies found significant improvements in the nutrition status for patients in the intervention group (21, 23, 25–27). On the other hand, two studies observed no difference between the intervention and control groups (20, 24). For treatment-related toxicities, three studies reported reduced incidence and severity of oral mucositis in the intervention group (20–22), while three other studies found no difference between groups (18, 23, 24). Hematological toxicities were reported to be higher in the control group by two studies (19, 21), while one study reported no difference between groups (24). Only three studies measured functional status as an outcome. Fietkau et al. reported significantly improved functional status (improved Karnofsky Performance Index score) in the intervention group (25), Vasson et al. reported maintenance of functional status in the intervention group compared to the control group who had deterioration of functional status (increased WHO Performance Status score and decreased Karnofsky Index score) (23), while Roca-Rodriguez et

TABLE 2 | Summary of studies included in the systematic review.

ID	Study and country	Study design	Type of cancer, treatment	*N* = (IG,CG)	Duration of supplementation and Intervention
Immunonutrient-enriched Formulas					
1	Boisselier (18) 2020 France	Prospective, randomized, controlled, double-blind, multicenter	HNC, RTx/CTx	172 (86, 86)	Interval (5 days before each CTx cycle) IG: IN (Oral Impact – L-arginine, n-3 FAs, ribonucleic acids) CG: SN (isocaloric, isonitrogenous) 3 servings/day
2	Chitapanarux (19) 2019 Thailand	Prospective, randomized, controlled, not blinded, multicenter	HNC, oesophageal & cervical ca, RTx/CTx	88 (44, 44)	Continuous throughout treatment (5–7 weeks) IG: regular diet + IN (Neo-Mune - arginine, glutamine, fish oil) 2 servings/day or enteral IN before and after RTx CG: regular diet or enteral SN
3	Harada (20) 2019 Japan	Prospective, randomized, not blinded, single center	Oral SCC, RTx/CTx	50 (25, 25)	Continuous throughout treatment (6–7 weeks) IG: IN (Elental – elemental formula with glutamine), throughout treatment 1bottle/day CG: no treatment
4	Chitapanarux (21) 2016 Thailand	Prospective, randomized, not blinded, single center	HNC, RTx/CTx	40 (20, 20)	Continuous throughout treatment (7 weeks) IG: nutrition counseling + IN (Neo-mune – arginine, glutamine, MCT, fish oil) 2 servings/day before and after RTx CG: nutrition counseling only
5	Vasson (23) 2014 France	Prospective, randomized, controlled, double-blind, multicenter	HNC & oesophageal ca, RTx/CTx	28 (15, 13)	Continuous, 5 days before initiation of RTx until end of treatment (5–7 weeks) IG: enteral IN (Impact – arginine, EPA & DHA, ribonucleotides) CG: SN (Isosource – isocaloric, isonitrogenous, polymeric)
6	Roca-Rodriguez (24) 2014 Spain	Prospective, randomized, controlled, not blinded, single center	ENT ca, RTx	26 (13, 13)	Continuous, 14 days after initiation of RTx until 90 days post RTx IG: IN (Prosure – 3 servings/day, add on with standard formula CG: SN (Isosource – standard, polymeric)
7	Fietkau (25) 2013 Germany	Prospective, randomized, controlled, double-blind, multicenter	HNC & oesophageal ca, RTx/CTx	69 (38, 31)	Continuous throughout treatment (up till 14 weeks) IG: SN + IN (Supportan – high fat, high protein, fish oil) 500ml via PEG feeding CG: SN (Fresubin Energy Fibre) via PEG feeding allowed orally
8	Yeh (26) 2013 Taiwan	Prospective, randomized, controlled, not blinded, single center	HNC, RTx/CTx	68 (31, 37)	Continuous throughout treatment until 1 month post treatment (3 months) IG: IN (Ethanwell – protein & energy-densed, n-3 FAs, glutamine, selenium, CoQ10; Ethanzyme - probiotics) CG: SN (Isocal)
9*	Chao (27) 2020 Taiwan	Retrospective, single center	HNC & oesophageal ca, RTx/CTx	88 (44, 44)	Continuous throughout treatment (> 7 days supplementation) IG: IN (Oral Impact – L-arginine, n-3 FAs, ribonucleic acids) CG: SN (isocaloric, isonitrogenous) 3 servings/day
10*	Yuce Sari (22) 2016 Turkey	Prospective, Not randomized, not blinded, single center	HNC, RTx/CTx	29 (15, 14)	Continuous throughout treatment (5–7 weeks) IG: IN (Abound – glutamine, arginine) throughout treatment CG: no treatment

(Continued)

TABLE 2 | Continued

ID	Study and country	Study design	Type of cancer, treatment	*N* = (IG,CG)	Duration of supplementation and Intervention
Immunonutrients					
11	Huang (29) 2019 Taiwan	Prospective, randomized, controlled, double-blind, single center	HNC, RTx/CTx	59 (30, 29)	Continuous, 1 week before initiation of RTx until 2 weeks post RTx (8 weeks) IG: L-glutamine 10g + maltodextrin 5g CG: placebo – maltodextrin 15g 3x/day
12	Pathak (28) 2019 India	Prospective, randomized, controlled, not blinded, single center	Oropharynx & larynx ca, RTx/CTx	56 (28, 28)	Continuous, 5 days/week during treatment (7 weeks) IG: glutamine 10 g 2 h before RTx CG: no treatment
13	Lopez-Vaquero (32) 2017 Spain	Prospective, randomized, controlled, double-blind, single center	HNC, RTx/CTx	49 (25, 24)	Continuous throughout RTx (6 weeks) IG: glutamine 10 g CG: maltodextrin 10 g 3x/day
14	Pattanayak (33) 2016 India	Prospective, randomized, controlled, not blinded, single center	HNC, RTx/CTx	162 (81, 81)	Continuous throughout RTx (7 weeks) IG: glutamine 15 g 2x/day CG: no treatment
15	Tsujimoto (34) 2015 Japan	Prospective, randomized, controlled, double-blind, single center	HNC, RTx/CTx	40 (20, 20)	Continuous throughout RTx (6–7 weeks) IG: glutamine 10 g CG: placebo 10 g 3x/day
16	Imai (37) 2014 Japan	Prospective, randomized, controlled, not blinded, single center	HNC, RTx/CTx	34 (16, 18)	Continuous throughout RTx until 1 week post RTx (7–8 weeks) IG: HMB+Arg/Gln (Abound – beta-hydroxy-beta-methylbutarate, L-arginine, L-glutamine) 2x/day CG: no intervention active prophylactic enteral tube feeding
17	Chattopadhyay (35) 2014 India	Prospective, randomized, not blinded, case control, single center	HNC, RTx/CTx	70 (35, 35)	Continuous, 5 days/week during treatment IG: glutamine 10 g 2 h before RTx CG: no treatment
18*	Akmansu (30) 2018 Turkey	Retrospective, single center	HNC, RTx/CTx	28 (18,10)	Continuous throughout treatment (5–7 weeks) IG: L-glutamine 10 g 3x/day CG: no treatment
19*	Pachon Ibanez (31) 2018 Spain	Prospective, non-randomized, comparative, cohort, single center	HNC, RTx/CTx	262 (131,131)	Continuous throughout RTx (7 weeks) IG: glutamine 10g 3x/day CG: no treatment
20*	Vidal-Casariego (36) 2013 Spain	Retrospective, non-randomized, cohort	HNC, lung, oesophageal ca RTx to head and neck and chest area	117 (32, 58, 27)	Up to 6 weeks Glutamine 30 g/day IG A: Early treatment - received glutamine before initiating and during RTx IG B: Delayed treatment - received glutamine when RTx had already begun CG: Not treated - did not receive any glutamine during RTx

Arg, arginine; CG, control group; CTx, chemotherapy; DHA, docosahexaenoic acid; EPA, eicosapentanoiec acid; FA, fatty acid; Gln, glutamine; HMB, beta-hydroxy beta-methylbutyric acid; IG, intervention group; IN, immunonutrition formula; RTx, radiotherapy, SN, standard nutrition formula
**Non-RCT studies.*

al. reported no difference in the functional status between control and the intervention group (24). The results of the studies are summarized in **Tables 4**, **5**.

Glutamine

Nine studies evaluated the effects of supplementation with single immunonutrient (glutamine) vs. placebo or no treatment (28–36). All studies involved continuous supplementation with 10 to 30 grams of glutamine per day and supplementation period ranging between five to eight weeks. One study involved continuous supplementation until one-week post-treatment with a combination of immunonutrients (arginine and glutamine) with HMB (37). However, only five studies were classified as having good methodological quality, with a Jadad score between

	Selection bias – random sequence generation	Selection bias – allocation concealment	Reporting bias – selective reporting	Other bias – other sources of bias	Performance bias – blinding (participant and personnel)	Detection bias – blinding (outcome assessment)	Attrition bias – incomplete outcome data	**Overall risk of- bias judgement**
Boisselier 2020	low	low	low	low	low	low	low	**Low risk**
Chao 2020	Non-RCT - retrospective study							
Chitapanarux 2019	low	low	low	low	high	unclear	low	**Some concerns**
Harada 2019	unclear	unclear	low	low	high	unclear	low	**High risk**
Chitapanarux 2016	low	low	low	low	high	unclear	low	**Some concerns**
Yuce Sari 2016	Non-RCT – comparative cohort study							
Vasson 2014	low	low	low	low	low	low	high	**Low risk**
Roca-Rodriguez 2014	unclear	unclear	low	low	high	unclear	low	**High risk**
Fietkau 2013	low	low	low	low	low	low	high	**Some concerns**
Yeh 2013	low	low	low	low	high	low	low	**Low risk**
Huang 2019	low	low	low	low	low	low	high	**Low risk**
Pathak 2019	low	low	low	low	high	unclear	low	**Some concerns**
Akmansu 2018	Non-RCT - retrospective study							
Pachon Ibanez 2018	Non-RCT – comparative cohort study							
Lopez-Vaquero 2017	low	low	low	low	low	low	low	**Low risk**
Pattanayak 2016	low	low	low	low	unclear	low	low	**Low risk**
Tsujimoto 2015	low	low	low	low	low	low	high	**Low risk**
Imai 2014	unclear	unclear	low	low	low	low	high	**High risk**
Chattopadhyay 2014	unclear	unclear	low	low	high	low	low	**High risk**
Vidal-Casariego 2013	Non-RCT - retrospective study							

FIGURE 2 | Summary of risk of bias assessment using the Cochrane Risk of Bias Tool for Randomized Control Trails.

3 and 5. Two studies were of poor methodological quality, and three other studies were non-randomized controlled trials.

Three studies found no difference in the overall incidence of oral mucositis between the control and intervention groups (31, 32, 35). One study found no difference between groups for the onset of mucositis and mucositis duration (34). However, four studies reported delayed onset of oral mucositis in patients supplemented with glutamine (28, 30, 33, 35). Furthermore, four studies reported a lower incidence of severe oral mucositis in the intervention group than in the control group (29, 30, 33, 35). The severity of oral mucositis was also reported to be significantly lower in the intervention group (28, 34).

Significantly later onset of dysphagia and less severe dysphagia (28) were observed in patients receiving glutamine compared to those who received placebo or no treatment. There were also reports of lower incidences of dermatitis (32, 37) and a shorter duration of dermatitis in the intervention group (37). However, another study found no difference in the development of dermatitis between the two groups (29). Significant weight loss was reported by two studies in the control group compared to the intervention group (28, 34), while two studies reported no difference between the two groups (30, 32). Tsujimoto et al. reported lower NRS scores in patients receiving glutamine supplementation (34).

TABLE 3 | Summary of methodological quality assessment using the Jadad Score.

	Study described as randomized	Method to generate the sequence of randomisation described and appropriate	Study described as double-blind	Method of double-blinding described and appropriate	Description of withdrawals and dropouts	Overall score
Boisselier 2020	1	1	1	1	1	5
Chao 2020	Non-RCT - retrospective study					
Chitapanarux 2019	1	1	0	0	1	3
Harada 2019	1	0	0	0	1	2
Chitapanarux 2016	1	1	0	0	1	3
Yuce Sari 2016	Non-RCT - comparative cohort study					
Vasson 2014	1	1	1	1	1	5
Roca-Rodriguez 2014	1	1	0	0	1	3
Fietkau 2013	1	1	1	1	1	5
Yeh 2013	1	1	0	0	1	3
Huang 2019	1	1	1	1	1	5
Pathak 2019	1	1	0	0	1	3
Akmansu 2018	Non-RCT - retrospective study					
Pachon Ibanez 2018	Non-RCT – comparative cohort study					
Lopez-Vaquero 2017	1	1	1	1	1	5
Pattanayak 2016	1	1	0	0	1	3
Tsujimoto 2015	1	0	1	1	1	4
Imai 2014	1	0	0	0	1	2
Chattopadhyay 2014	1	0	0	0	1	2
Vidal-Casariego 2013	Non-RCT - retrospective study					

Interestingly, Vidal-Casariego et al. evaluated the effects of early supplementation with glutamine against delayed supplementation with glutamine and no supplementation (36). There was a significant difference in the development of oral mucositis, whereby 75% of those with early supplementation, 94.7% of those with delayed supplementation, and 100% of those without supplementation developed oral mucositis. Less severe oral mucositis was also observed in patients who received early supplementation of glutamine. The same study also reported lower incidence and a smaller degree of weight loss in patients with early supplementation of glutamine, followed by delayed supplementation and no supplementation.

DISCUSSION

This systematic review summarizes recent evidence regarding the effect of immunonutrition in HNC patients undergoing radiotherapy and chemotherapy in nutrition status, functional status, and treatment-related toxicities.

Radiotherapy with or without chemotherapy is the most common mode of treatment for HNC as primary treatment or postoperative treatment (39). Even though current cancer treatment modalities are effective for tumor control; they are also associated with acute and late toxicities. Radiotherapy to the head and neck region is site-specific and localized, causing direct damage to cells in that area. This can damage nearby food consumption or digestion structures, such as taste buds and salivary glands. This will affect the early digestion process and taste changes, eventually leading to a loss of appetite and desire to consume food. Chemotherapy side effects can also lead to gastrointestinal symptoms, loss of appetite, and exacerbate radiotherapy side effects. Previous literature reported that HNC patients are at exceptionally high risk of malnutrition before initiation of radiotherapy and chemotherapy, and their nutrition status deteriorate further as the treatment progresses (6, 40–43).

Glutamine is a conditionally essential amino acid during metabolic stress. It is the primary fuel for the proliferation of lymphocytes, production of cytokines, and macrophage phagocytic and secretory activities (44). It is also the precursor for amino acids, proteins, nucleotides synthesis, and ammoniagenesis in the kidneys (45). Hence, glutamine may be beneficial in reducing mucosal damage during cancer treatment, including mucositis, stomatitis, pharyngitis, esophagitis and enteritis; and promote mucosal healing during and post-cancer treatment (46, 47). Arginine is involved in nucleotides, polyamines, nitric oxide, ornithine, citrulline and proline synthesis. Therefore, arginine has an essential role in the modulation of immune function, regulation of blood flow, angiogenesis and wound healing (46, 48). Omega-3 fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), modulates the immune system by reducing the production of pro-inflammatory arachidonic acid (AA) and competes with AA for cyclooxygenase and lipoxygenase enzymes

TABLE 4 | Summary of results.

ID	Study	Results	Improvement or Maintenance of Nutrition Status	Improvement or Maintenance of Functional Status	Incidence and Severity of Treatment-related Toxicities
Immunonutrient-enriched Formulas					
1	Boisselier (18) 2020	Nutrition Status: - Functional Status: - Treatment-related toxicities: no difference in severe oral mucositis rate – IG 33.7%, CG 34.9% Overall survival and progression free survival 3 years post treatment improved in IG 77% & 70%, CG 68% & 59%	NA	NA	↔
2	Chitapanarux (19) 2019	Nutrition Status: - Functional Status: - Treatment-related toxicities: Higher incidences of hematological toxicities in CG than IG ($p = 0.03$) Higher percentage of grade 3–4 non-hematological toxicities in CG than IG, but not significant ($p = 0.2$)	NA	NA	-
3	Harada (20) 2019	Nutrition status: No significant difference in body weight between groups Functional Status: - Treatment-related toxicities: Significantly lower grade of mucositis in IG ($p = 0.0006$) Significantly lower rates of severe mucositis during chemoradiation in IG 4.76% than CG 77.8% ($p < 0.0001$)	↔	NA	-
4	Chitapanarux (21) 2016	Nutritional status: Significant weight loss in CG 56.3–47.0kg ($p < 0.001$), maintained in IG 60.0–53.0 kg ($p = 0.109$) Functional Status: - Treatment-related toxicities: Non-hematological toxicities - oral mucositis 20% in CG, 5% in IG; radiation dermatitis 5% in CG, 0% in IG Severe hematological toxicities - significantly higher incidences in CG than IG ($p = 0.035$) Alb and pre-alb reduced in both groups, but median alb in IG significantly higher in IG ($p = 0.028$) at end of treatment	+	NA	-

(Continued)

TABLE 4 | Continued

ID	Study	Results	Improvement or Maintenance of Nutrition Status	Improvement or Maintenance of Functional Status	Incidence and Severity of Treatment-related Toxicities
5	Vasson (23) 2014	Nutritional status: Weight – significantly increased in IG (+1.8 ± 2.7kg) BMI - significantly increased in IG (+10.7 ± 0.9kg/m^2) lean body mass - significantly increased in IG (+2.1 ± 3.2kg) Functional status: Deterioration of functional capacities in CG – increased WHO PS score and decreased Karnofsky Index Upper arm muscular strength maintained in both IG & CG – no significant difference Treatment-related toxicities: no significant difference for mucositis QOL: EORTC-QLQ C30, QOL-H&N35 – no significant difference between groups	+	+	↔
6	Roca-Rodriguez (24) 2014	Nutrition status: BMI decreased during treatment, then recovered post treatment, no significant difference between groups Functional status: No significant difference between groups for Karnofsky Performance Index during treatment and post treatment Treatment-related toxicities: No significant difference between groups for haematologic/mucosal/skin toxicity	↔	↔	↔
7	Fietkau (25) 2013	Nutritional status: improved NRS score, body cell mass, body weight, BMI, MAC in IG, but not significant Kondrup score – significant improvement in IG compared with CG ($p = 0.0165$) SGA score – IG 28.6% improvement and 71.4% no change; CG 3.3% improvement, 86.7% no change, 10% deteriorate ($p = 0.0065$) Functional status: Significant improvement of Karnofsky Performance Index in IG (p=0.04), less decreased in hand grip strength in IG but not statistically significant Treatment-related toxicities: - QOL: EORTC-QLQ C30 – no significant difference between groups	+	+	NA

(Continued)

TABLE 4 | Continued

ID	Study	Results	Improvement or Maintenance of Nutrition Status	Improvement or Maintenance of Functional Status	Incidence and Severity of Treatment-related Toxicities
8	Yeh (26) 2013	Nutritional status: Weight – IG+BMI<19 weight gain 9.0%; CG+BMI<19 weight loss 7.3% ($p<0.05$) maintenance and improved alb & pre-alb levels in IG where BMI <19 Functional Status: - Treatment-related toxicities: -	+	NA	NA
9*	Chao (27) 2020	Nutritional status: Significant increase in weight (0.97 ± 2.7 kg) in IG, but significant decrease in CG (-0.90 ± 1.49 kg) Significant increase in BMI (0.35±1.02 kg/m^2) in IG, but significant decrease in CG (−0.33 ± 0.54 kg/m^2) Significant increase in MAMC (0.26 ± 0.72 cm) in IG, but significant decrease in CG (−0.27 ± 0.70 cm) Better PG-SGA score for IG compared to CG ($p = 0.048$) NRI significantly increased in IG (0.67 ± 1.85), but decreased in CG Functional Status: - Treatment-related toxicities: -	+	NA	NA
10*	Yuce Sari (22) 2016	Nutrition Status: - Functional Status: - Treatment-related toxicities: Significantly higher stomatitis scores, oral mucositis scores, oral pain scores, dysphagia scores in CG compared to IG QOL: No significant difference between groups for global health score, functional scale. Significant lower social function score, and higher symptom scale score in CG	NA	NA	-
Immunonutrients					
11	Huang (29) 2019	Nutrition status: Decrease of BMI strongly correlated with severe oral mucositis Functional Status: - Treatment-related toxicities: Significantly lower incidence of severe oral mucositis in IG ($p = 0.045$) Significant difference between groups for mean maximum mucositis grade, IG 1.6 ± 0.6 compared to CG 2.1 ± 0.8 ($p = 0.009$) No difference between groups for development of dermatitis ($p = 0.221$)	NA	NA	-

(Continued)

TABLE 4 | Continued

ID	Study	Results	Improvement or Maintenance of Nutrition Status	Improvement or Maintenance of Functional Status	Incidence and Severity of Treatment-related Toxicities
12	Pathak (28) 2019	Nutrition status: Significant weight loss >3 kg, CG 100% compared to IG 71% Functional Status: - Treatment-related toxicities: Significantly later time to onset and less severity of oral mucositis and dysphagia in IG compared to CG	+	NA	-
13	Lopez-Vaquero (32) 2017	Nutrition status: No significant difference between groups for weight loss Functional Status: - Treatment-related toxicities: Incidence and severity of oral mucositis – no significant difference between groups Significantly lower incidence and severity of dermatitis in IG compared to CG ($p = 0.038$ and $p = 0.032$)	↔	NA	-^
14	Pattanayak (33) 2016	Nutrition Status: - Functional Status: - Treatment-related toxicities: Onset of oral mucositis – 55% of CG at week 3, 55% of IG at week 5 Severity of mucositis – 92% CG developed grade 3 mucositis, none of IG developed grade 3 mucositis Less incidence of pain/dysphagia/nausea/cough in IG	NA	NA	-
15	Tsujimoto (34) 2015	Nutrition status: NRS score significantly lower in IG ($p<0.05$) Mean % weight change – IG 3.6%, control 6.0% Functional Status: - Treatment-related toxicities: Maximal mucositis grade and mean mucositis grade significantly lower in IG 2.9 ± 0.3, CG 3.3 ± 0.4 ($p = 0.005$) Mean time to mucositis onset and mucositis duration no significant difference between groups ($p = 0.663$ and $p = 0.6717$)	+	NA	-
16	Imai (37) 2014	Nutrition Status: - Functional Status: - Treatment-related toxicities: Incidence of >grade 2 dermatitis significantly lower in IG 62.6% compared to CG 94.4% ($p = 0.029$) Duration of dermatitis significantly shorter in IG 44.8% compared to 56.7% ($p = 0.009$)	NA	NA	-

(Continued)

TABLE 4 | Continued

ID	Study	Results	Improvement or Maintenance of Nutrition Status	Improvement or Maintenance of Functional Status	Incidence and Severity of Treatment-related Toxicities
17	Chattopadhyay (35) 2014	Nutrition Status: - Functional Status: - Treatment-related toxicities: No significant difference between groups in development of oral mucositis Significantly lower incidence of severe mucositis (grade 3 & 4) in IG ($p = 0.02$ and $p = 0.04$) Significantly less mean duration of severe oral mucositis in IG 6.6 days compared to CG 9.2 days ($p < 0.001$) Significantly earlier onset of oral mucositis in CG ($p < 0.001$)	NA	NA	-
18*	Akmansu (30) 2018	Nutrition status: No significant difference between groups for weight changes Functional Status: - Treatment-related toxicities: No significant difference between groups for incidence of oral mucositis (42.1% and 44.4%), but significantly lower incidence for severe mucositis >grade 3 in IG 5.3% compared to CG 55.6% ($p = 0.008$) CG significantly earlier onset of mucositis at 14th day compared to IG at 18th day	↔	NA	-
19*	Pachon Ibanez (31) 2018	Nutrition Status: - Functional Status: - Treatment-related toxicities: Incidence of oral mucositis lower in IG 50.4% compared to CG 59.5%, but not significant ($p = 0.55$) Incidence of odynophagia lower in IG 55.7% compared to CG 77.9% ($p = 0.0001$)	NA	NA	-^
20*	Vidal-Casariego (36) 2013	Nutrition status: Occurrence of weight loss – IG A 6.6%, IG B 9.2%, CG 13.1%, significant difference between groups ($p = 0.008$) Significantly less weight loss in IG A 5.6 kg, IG B 11.3 kg, CG 13.4 kg (0.009) Functional Status: - Treatment-related toxicities: Development of oral mucositis – IG A 75%, IG B 94.7%, CG: 100%, significant difference between IG A and CG Severity of oral mucositis lower in IG A Risk of mucositis for patients receiving glutamine −14%, 95% CI	+	NA	-

+Indicates significant improvement or maintenance of nutritional status or functional status in the intervention group compared to control group ($p < 0.05$).

↔Indicates non-significant results ($p > 0.05$).

-Indicates significant lower incidence or severity of treatment-related toxicities in the intervention group compared to control group ($p < 0.05$).

NA outcome not being studied or reported^ no significant difference for severity and incidence of oral mucositis, but significantly lower incidence and severity of dermatitis in one study and lower incidence of odynophagia in another.

**non-RCT studies.*

TABLE 5 | Summary of results according to types of formulas or immunonutrients.

	Number of studies	Outcomes	Positive results ($p < 0.05$)	Non-significant results ($p > 0.05$)
Immunonutrient-enriched Formulas				
Nutrition formula with omega-3 fatty acids	2	Nutritional status	1	1
		Functional status	1	1
		Treatment-related toxicities		1
Nutrition formula with omega-3 fatty acids + arginine and/or glutamine	6	Nutritional status	4[#]	
		Functional status	1	
		Treatment-related toxicities	2	2
Nutrition formula with arginine and glutamine	2	Nutritional status		1
		Treatment-related toxicities	1[#]	
Immunonutrients				
Glutamine	9	Nutritional status	3[#]	2[#]
		Treatment-related toxicities (oral mucositis)	7[#]	2[*#]
Glutamine + Arginine with HMB	1	Treatment-related toxicities (dermatitis)	1	

Nutrition status is measured by changes in weight and BMI, body composition, Subjective Global Assessment (SGA), and Nutritional Risk Index (NRI).
-Functional status is measured by handgrip strength or performance scores such as ECOG score, Kondrup score or Karnofsky Performance Index.
-Positive results depicts improvement or maintenance of nutritional status and functional status, or lower incidence or severity of treatment-related toxicities.
[*]*No significant difference for severity and incidence of oral mucositis, but significantly lower incidence and severity of dermatitis in one study and lower incidence of odynophagia in another.*
[#]*Contains references that are non-RCT studies.*

(49). Past literature suggests that omega-3 fatty acids may be associated with anticatabolic and antilipolytic activities (50).

The present systematic review found that overall, continuous supplementation with immunonutrient-enriched formulas may improve or maintain the nutrition status of HNC patients undergoing radiotherapy and chemotherapy. Six out of seven studies that implemented supplementation with immunonutrient-enriched formula during chemoradiation reported significant positive results in the intervention group compared to the control group receiving isocaloric, isonitrogenous nutrition supplementation or standard nutrition care. Maintenance or improvement in nutrition status is observed in subjects supplemented with formulas enriched with different combinations of omega-3 fatty acids with arginine and or glutamine. Even though nutrition status plays an essential role in the tolerance to treatment, treatment outcomes and survival, only 13 studies reported nutrition status as an outcome. It is also observed that the indicators used to measure nutritional status differ vastly among the studies. The most common indicator is weight or percentage of weight loss, while indicators like body composition or mid-arm circumference are less commonly used to measure nutrition status.

Changes in the functional status of HNC patients during cancer treatment is an important area in cancer management that have been of interest in the past two decades. Radiotherapy and chemotherapy treatment-related side effects such as oral pain, swallowing difficulty and nausea, can impair patients' quality of life significantly. However, the present systematic review only identified three studies that reported changes in the functional status of patients as an outcome of supplementation with immunonutrition. Two out of three studies reported improved functional status (Karnofsky Index scores) in the intervention group receiving immunonutrient-enriched formulas.

Studies that implemented supplementation with glutamine mostly reported treatment-related toxicities as the primary outcome, namely oral mucositis. Mucositis is the most common treatment side effect that occurs in HNC patients undergoing radiotherapy. In the present systematic review, three studies reported that there was no difference between groups being observed in terms of overall incidence (all grades) of oral mucositis. However, delayed onset of oral mucositis, less severe oral mucositis and lower incidence of severe oral mucositis was reported in eight other studies. Nutrition status was reported as a secondary outcome in seven studies. However, only three studies found significant positive results (less weight loss than the control group), while another two studies did not find any significant difference between the control and intervention groups. Even though glutamine was given in a modular supplementation, there were still positive outcomes in the nutrition status. This may be due to less severe oral mucositis in the intervention group, allowing for adequate intake of regular diet and oral nutrition supplement.

The present systematic review has several limitations. Due to the broad inclusion criteria, this systematic review included varied study designs, supplementation regimes and duration, and outcome measurements. The variability is high among studies that have been conducted in terms of timing and duration of supplementation, type of formula or combinations

of immunonutrients, and dosage of immunonutrients or immunonutrient-enriched nutrition formula. Some studies included other primary cancer sites besides HNC, such as oesophageal, cervical and lung. Hence the outcomes were also inconsistent between studies. There were also very few RCTs with a large sample size. Furthermore, methodological quality and risk of bias were also of varying degrees, making it difficult to perform a more robust analysis or draw conclusions from the limited evidence available.

Even though our findings may not be conclusive, the positive effects of immunonutrition in HNC patients, whether in immunonutrient-enriched formula, or supplementation of single immunonutrient, or combination of immunonutrients; is still worth being investigated in future studies. Based on the systematic review findings, future studies should focus on well-designed, randomized controlled trials to investigate the effects of different dosages and combinations of immunonutrients in nutritional and functional status. Finally, future trials should also be more progressive, looking into the impact of timing and duration of immunonutrition, including supplementation prior to cancer treatment and continuation of nutrition supplementation post-treatment, which may further optimize the nutrition status of HNC patients and lead to better treatment outcomes.

CONCLUSION

In conclusion, the present review found that supplementation with immunonutrient-enriched formulas in HNC patients during radiotherapy and chemotherapy may improve or maintain nutrition status. Supplementation with glutamine during HNC radiotherapy and chemotherapy may delay the onset of oral mucositis and reduce the incidence of severe oral mucositis. However, these findings are not conclusive, given the studies heterogeneity. Therefore, further investigations are encouraged in the future, focusing on the timing, dosage and duration of immunonutrition required for nutrition optimisation.

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.

AUTHOR CONTRIBUTIONS

ST and HM contributed equally to the conception and design of the manuscript amd critical appraised the data selected. ST conducted the data collection and analysis and drafted the manuscript. All authors critically revised the manuscript, agree to be accountable for all aspects of work ensuring the integrity and accuracy of the manuscript, and read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.821924/full#supplementary-material

Supplementary Material 1 | Search Strategy for the Systematic Review.

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Effects of Diabetes on Inflammatory Status and Prognosis in Cancer Patients

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Background: Cancer and diabetes mellitus (DM) are prevalent, but there still a lack of convinced evidence clearly explaining the extent of the effect of diabetes in cancer.

Data and Methods: Clinical data of 2,929 cancer patients were collected. Diabetes were diagnosed according to the Diabetes Diagnosis and Treatment Criteria. BMI was classified by the BMI standards for Chinese adults published by the Working Group on Obesity. All involved patients were classified into the non-DM group and DM group. The Kaplan–Meier curve, log-rank test and Cox regression analyses were used to perform survival analysis.

Results: Compared with non-DM patients, OS in DM patients was significant shorter in lung cancer (HR = 2.076, $P = 0.001$ in early stage; HR = 2.118, $P < 0.001$ in advanced stage), digestive tract cancer (HR = 1.768, $P = 0.020$ in early stage; HR = 2.454, $P = 0.005$ in advanced stage), leukemia (HR = 2.636, $P < 0.001$), breast cancer (HR = 2.495, $P = 0.047$ in early stage; HR = 2.929, $P = 0.019$ in advanced stage) and liver cancer (HR = 3.086, $P < 0.001$ in early stage; HR = 2.219, $P = 0.049$ in advanced stage). DM negatively influenced OS when the BMI was within the normal range in overall cancer (HR = 2.468, $P < 0.001$), lung cancer (HR = 2.297, $P < 0.001$), digestive tract cancer (HR = 2.354, $P < 0.001$), liver cancer (HR = 2.406, $P = 0.001$), leukemia (HR = 4.039, $P < 0.001$) and breast cancer (HR = 4.222, $P = 0.008$). Among those with BMI $\geq$ 24 kg/m^2, DM played a role only in lung cancer (HR = 1.597, $P = 0.037$).

Conclusions: Patients with diabetes tend to combine worse body composition and inflammation status, and that glycemic control can ameliorate the impairment of diabetes to some extent.

Keywords: cancer, diabetes, inflammation, prognosis, BMI

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INTRODUCTION

Cancer is currently one of the major diseases that threaten the health of residents (1), and 8–18% cancer patients have diabetes as a comorbid medical condition (2). According to the epidemiological survey conducted by the Chinese Medical Association, the total number of people with diabetes in mainland China is 129.8 million (3). China has become the country with the highest incidence of diabetes in the world (4). Diabetes were significantly related with higher cancer occurrence and mortality in many cancer types (5). Overall cancer risk was found significantly elevated with a standardized increased ratio of 1.15 (95% CI 1.12–1.19) and 1.25 (95% CI 1.21–1.30)

in males and females, respectively (6). A systemic review of 23 studies demonstrated a 41% increased risk for long-term, all-cause mortality for diabetic patients compared with those without diabetes (7). Diabetes and associated metabolic disorders contribute directly or indirectly to cancer progression (8). Anaerobic glycolysis, known as Warburg, is classic in cancer. But Warburg does not mean glucose is unimportant. In contrast, hyperglycemia stimulates cancer proliferation (9). Most cancers predominantly express the glucose transporter 1, which has a high affinity for glucose. The increased glycolysis in cancer cells provides the materials necessary for nucleotide, amino acid, and lipid synthesis. Besides, advanced glycation end products (AGRs) due to hyperglycemia, and its receptors (RAGRs) have been reported to lead to oxidative stress and increased inflammation, which promotes cancer growth, angiogenesis, and metastases (10). Obesity, also a prevalence worldwide, is a risk factor of both diabetes and cancer (11, 12). Excessive adipose tissue generates oxidative stress by increased production of pro-inflammatory adipokines. And BMI is regarded as a typical measurement of obese. There have been numerous studies on the relationship between diabetes and cancer. However, at present, barely convinced evidence clearly explains the extent of the effect of diabetes in different cancer types, stages and body mass indices (BMI), which remains to be further investigated (13–15). In addition, as a wasting disease, the nutritional status of patients gradually deteriorates with the development of cancers (16). Therefore, this large-scale retrospective cohort study is to investigate the impact of diabetes on the prognosis of tumor patients.

DATA AND METHODS

Clinical Data Collection

Clinical data of cancer patients from November 2011 to December 2018 in the Department of Oncology, Cancer Center, First Hospital of Jilin University were collected. No specific selection criteria were established for cancer type or demographic characteristics, except for patients who declined to participate in the study. All patients were regularly followed up by telephone interviews or outpatient visits.

Main Inclusion Criteria

(1) Clear diagnosis of malignancy in pathological specimens. (2) Age ≥18 years. (3) No nutritional support treatment prior to nutritional assessment and laboratory testing.

Major Exclusion Criteria

(1) Those who were unwilling to keep blood specimens. (2) Combination of other types of tumors. (3) Combination of other metabolic or immunological diseases. (4) Those who had incomplete records of necessary indexes. Clinical-pathological variables including age, sex, BMI, tumor types, TNM stages (AJCC 7th edition), alcohol consumption, smoking status. Scales including Karnofsky Performance Status (KPS), the Patient-Generated Subjective Global Assessment (PG-SGA) and the Nutritional Risk Screening-2002 score (NRS-2002), and quality of life (QoL-C30). Laboratory examinations including total protein(TP), albumin, prealbumin (PAB), transferrin (TFN), C-reaction protein(CRP), neutrophil to lymphocyte ratio (NLR) and platelets to lymphocyte ratio (PLR). Anthropometric indices including hand-grip strength (HGS) and visceral fat area (VFA) by bioelectrical impedance analysis.

TABLE 1 | Patient characteristics stratified by diabetes.

Characteristics	Groups		Total	*P*-value
	Non-DM (*n*%)	DM (*n*%)		
Age (year)				
<65	2,038 (80.5)	287 (72.5)	2,325 (79.4)	<0.001
≥65	495 (19.5)	109 (27.5)	604 (20.6)	
Sex				
Male	1,102 (43.5)	169 (42.7)	1,271 (43.4)	0.757
Female	1,431 (56.5)	227 (57.3)	1,658 (56.6)	
Smoking				
No	1,519 (60.0)	249 (62.9)	1,768 (60.4)	0.271
Yes	1,014 (40.0)	147 (37.1)	1,161 (39.6)	
Alcohol consumption				
No	2,050 (80.9)	327 (82.6)	2,377 (81.2)	0.437
Yes	483 (19.1)	69 (17.4)	552 (18.8)	
Tumor types				
Lung	773 (30.5)	125 (31.6)	898 (30.7)	0.001
Digestive tract	507 (20.0)	91(23.0)	598 (20.4)	
Liver	136 (5.4)	41 (10.4)	177 (6.0)	
Leukemia	284 (11.2)	31 (7.8)	315 (10.8)	
Breast	625 (24.7)	76 (19.2)	701(23.9)	
Others	208 (8.2)	32 (8.1)	240(8.2)	
TNM stages				
I	448 (18.6)	51 (13.3)	499 (17.9)	<0.001
II	569 (23.7)	86 (22.5)	655 (23.5)	
III	594 (24.7)	131 (34.2)	725 (26.0)	
IV	475 (19.8)	85 (22.2)	560 (20.1)	
Leukemia	318 (13.2)	30 (7.8)	348 (12.5)	
PG-SGA				
0–1	1,035 (40.9)	133 (33.6)	1,168 (39.9)	0.002
2–3	437 (17.3)	62 (15.7)	499 (17.1)	
4–8	744 (29.4)	130 (32.8)	874 (29.9)	
≥9	314 (12.4)	71 (17.9)	385 (13.2)	
NRS-2002				
<3	2,077 (90.7)	328 (92.7)	24,05 (90.9)	0.224
≥3	214 (9.3)	26 (7.3)	240 (9.1)	
QoL-C30				
<60	795 (31.5)	140 (35.4)	935 (32.0)	0.117
≥60	1,730 (68.5)	255 (64.6)	1,985 (68.0)	
VFA (cm^2)				
<90	1,352 (53.4)	188 (47.5)	1,540 (52.6)	0.029
≥90	1,181 (46.6)	208 (52.5)	1,389 (47.4)	

DM, diabetes mellitus; PG-SGA, the Patient-Generated Subjective Global Assessment; NRS-2002, the Nutritional Risk Screening-2002 score; QoL-C30, quality of life; VFA, visceral fat area.

TABLE 2 | Basic clinical information for all involved patients stratified by DM.

Parameters	Lung Cancer (*N* = 898)			Digestive tract Cancer (*N* = 598)			Liver Cancer (*N* = 177)			Leukemia (*N* = 315)			Breast Cancer (*N* = 701)			Others (*N* = 240)		
	Non-DM	DM	*P*	Non-DM	DM	*P*	Non-DM	DM	*P*	Non-DM	DM	*P*	Non-DM	DM	*P*	Non-DM	DM	*P*
NRS2002	0.64	0.89	0.027	0.85	0.64	0.106	0.67	0.62	0.813	0.29	0.38	0.603	0.21	0.42	0.034	0.74	0.59	0.564
KPS	89.43	88.88	0.554	86.49	87.69	0.425	88.82	86.83	0.347	89.79	86.77	0.251	91.95	92.24	0.780	89.09	88.75	0.874
TP (g/L)	67.78	67.99	0.724	64.02	66.09	0.032	65.38	64.90	0.716	64.17	59.36	<0.001	69.12	70.36	0.069	68.11	69.56	0.282
Albumin (g/L)	39.26	38.62	0.151	37.15	37.41	0.664	36.90	35.20	0.084	37.81	35.42	0.014	41.73	41.76	0.961	39.50	38.60	0.370
PAB (g/L)	0.21	0.21	0.257	0.19	0.19	0.794	0.18	0.17	0.971	0.22	0.21	0.765	0.23	0.24	0.562	0.21	0.19	0.082
TFN (g/L)	4.18	2.20	0.669	2.41	2.48	0.696	2.33	2.29	0.801	10.21	3.33	0.728	2.72	2.47	0.412	2.37	2.32	0.786
CRP (mg/L)	15.12	22.39	0.072	24.37	20.46	0.431	12.18	18.23	0.375	26.70	22.52	0.614	5.80	9.57	0.340	26.43	16.22	0.494
Height (cm)	1.65	1.65	0.211	1.67	1.65	0.068	1.66	1.65	0.349	166.60	167.65	0.505	158.83	157.68	0.073	1.61	1.61	0.696
Weight (kg)	63.91	65.33	0.204	61.82	63.60	0.181	63.52	61.29	0.239	64.87	67.72	0.214	62.87	62.49	0.749	60.83	62.19	0.480
BMI (kg/m^2)	23.15	23.92	0.016	22.15	23.24	0.007	22.89	22.36	0.328	23.30	24.07	0.258	24.90	25.10	0.641	23.43	23.84	0.513
HGS (kg)	26.34	25.11	0.197	25.94	23.89	0.068	27.04	22.85	0.031	25.61	26.69	0.580	20.38	18.29	0.004	21.15	20.40	0.616
VFA (cm^2)	90.49	99.31	0.009	79.57	91.94	0.003	85.69	85.83	0.981	78.07	95.98	0.004	100.26	106.25	0.148	91.79	89.74	0.758
NLR	3.23	5.88	0.003	4.38	6.80	0.089	4.15	4.55	0.686	2.89	2.82	0.934	2.22	5.98	<0.001	3.87	3.01	0.059
PLR	171.55	174.12	0.839	180.08	216.81	0.050	147.52	185.18	0.074	174.68	184.85	0.795	146.04	168.90	0.022	188.54	173.66	0.611

DM, diabetes mellitus; NRS-2002, the nutritional risk screening-2002 score; KPS, karnofsky performance status; TP, total protein; PAB, prealbumin; TFN, transferrin; CRP, C-reaction protein; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio; HGS, hand-grip strength; VFA, visceral fat area.

TABLE 3 | Basic clinical information of E-DM vs. non-DM patients.

Parameters	Lung Cancer (*N* = 898)			Digestive tract Cancer (*N* = 598)			Liver Cancer (*N* = 177)			Leukemia (*N* = 315)			Breast Cancer (*N* = 701)			Others (*N* = 240)		
	Non-DM	E-DM	*P*	Non-DM	E-DM	*P*	Non-DM	E-DM	*P*	Non-DM	E-DM	*P*	Non-DM	E-DM	*P*	Non-DM	E-DM	*P*
NRS2002	0.64	1.07	0.004	0.85	0.71	0.513	0.67	0.92	0.478	0.29	0.80	0.069	0.21	0.64	0.001	0.75	0.57	0.540
KPS	89.41	88.85	0.636	86.63	86.88	0.901	88.82	85.00	0.254	89.79	87.14	0.341	91.97	91.72	0.877	89.01	88.70	0.899
TP (g/L)	67.78	66.99	0.345	64.16	66.18	0.072	65.38	64.29	0.607	64.17	56.00	<0.001	69.13	69.65	0.625	68.02	69.03	0.521
Albumin (g/L)	39.26	38.29	0.114	37.23	37.59	0.652	36.90	34.89	0.191	37.81	33.76	0.004	41.74	41.02	0.348	39.47	38.64	0.475
PAB (g/L)	0.21	0.21	0.529	0.19	0.18	0.465	0.18	0.15	0.270	0.22	0.18	0.127	0.23	0.22	0.251	0.21	0.18	0.092
TFN (g/L)	4.19	2.08	0.748	2.42	2.39	0.910	2.33	2.20	0.577	2.49	2.40	0.891	2.72	2.58	0.738	2.37	2.27	0.649
CRP (mg/L)	15.16	17.41	0.618	23.40	23.26	0.983	12.18	9.08	0.774	10.21	5.63	0.321	5.80	12.00	0.246	26.66	17.36	0.579
Height (cm)	1.66	1.64	0.098	1.67	1.66	0.453	1.66	1.63	0.097	1.67	1.69	0.250	1.59	1.57	0.140	1.61	1.61	0.949
Weight (kg)	63.81	62.69	0.457	61.79	63.39	0.362	63.52	60.01	0.240	64.87	64.48	0.907	62.87	60.42	0.185	60.77	61.03	0.907
BMI(kg/m^2)	23.12	23.14	0.963	22.16	22.97	0.128	22.89	22.66	0.785	23.30	22.49	0.406	24.91	24.38	0.435	23.37	23.48	0.881
HGS (kg)	26.32	24.27	0.119	26.00	24.12	0.203	27.04	18.02	0.003	25.61	24.21	0.622	20.38	17.33	0.008	21.21	19.64	0.363
VFA (cm^2)	90.22	94.22	0.384	79.45	84.93	0.319	85.69	83.10	0.788	78.07	79.29	0.891	100.28	99.47	0.901	91.25	88.44	0.710
NLR	3.23	4.31	0.014	4.34	9.06	0.017	4.15	4.50	0.822	2.89	2.73	0.892	2.22	3.40	<0.001	3.88	2.85	0.047
PLR	171.69	182.99	0.529	179.75	234.08	0.032	147.52	210.40	0.051	174.68	194.66	0.727	146.10	183.39	0.011	188.47	178.58	0.775

DM, diabetes mellitus; E-DM, euglycemia diabetes mellitus; NRS-2002, the nutritional risk screening-2002 score; KPS, karnofsky performance status; TP, total protein; PAB, prealbumin; TFN, transferrin; CRP, C-reaction protein; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio; HGS, hand-grip strength; VFA: visceral fat area.

Diabetes Diagnosis Criteria

According to the Diabetes Diagnosis and Treatment Criteria established by the American Diabetes Association (ADA), (1) Fasting blood glucose ≥7.0 mmol/L (overnight blood glucose without food for at least 8–10 h); (2) Oral glucose tolerance test (OGTT) two-hour blood glucose ≥11.1 mmol/L; (3) Hemoglobin A1c (HbA1c) ≥6.5%; (4) Random blood glucose ≥11.1 mmol/L, along with symptoms related to diabetes such as polydipsia, polyphagia, polyuria and emaciation. Meeting any one of the above four conditions can be diagnosed with diabetes mellitus.

Classification of BMI

The BMI ranges were reclassified into normal (18.5 kg/m²-23.9 kg/m²), overweight (24.0 kg/m²-27.9 kg/m²) and obese (≥28 kg/m²) according to the BMI standards for Chinese adults published by the Working Group on Obesity (WGO).

Operation Rules of Anthropometric Indices

HGS was examined in all subjects using a Jamar hydraulic grip dynamometer (Sammons Preston Rolyan, Illinois, USA). Patients were comfortably seated in an upright position with the shoulders tucked in, neutral rotation, 90°elbow flexion, and the forearms and wrists in a neutral position. The patient gripped the dynamometer with maximum strength. The test is performed three times in a row, with a 1-min rest at the end of each set, and the maximum grip strength is recorded.

VFA is assessed by the Inbody S10 (Biospace Co.®), a multi-frequency bioelectrical impedance body composition analyzer. For analysis on patients in the supine position, electrode pads are attached to the ipsilateral upper and lower extremities and all procedures are performed according to the manufacturer's recommendations.

Statistical Analysis

Data were analyzed by SPSS for Windows version 26.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY) and R version 4.0 (R Foundation for Statistical Computing, Vienna, Austria). All involved patients were classified into the non-DM group and DM group according to the ADA diagnosis criteria. The Kolmogorov–Smirnov test was used to confirm normal distributions of continuous data. Independent *t*-tests were used for normally distributed data. Counting data were examined by using the chi-square test. The Kaplan–Meier curve, log-rank test, and Cox regression analyses were used to perform survival analysis in specific cancer types, stages and BMI and in all participants. $P < 0.05$ was taken to indicate statistical significance.

RESULTS

Among the 2,929 cancer patients recruited, 43.4% were men and 56.6% were women, with a mean age of 55 years. The mean follow-up period was 36.24 months and 791 patients died. According to the ADA criteria for the management of DM, 2,533 patients were included in the non-DM group and 396 patients were included in the DM group. The demographic, clinical and pathological characteristics of patients in the non-DM and DM groups were shown in **Table 1**. DM was significantly associated with age, PG-SGA, VFA, tumor types and stages ($P < 0.05$).

Relationship Between DM and Clinical Parameters

Compared with non-DM patients, NRS-2002 was higher in DM patients with lung cancer (0.89 vs 0.64, $P = 0.027$) and breast cancer (0.42 vs 0.21, $P = 0.034$). BMI (23.92kg/m^2 vs 23.15kg/m^2, $P = 0.016$), VFA (99.31 vs 90.49cm^2, $P = 0.009$), and NLR (5.88 vs 3.23, $P = 0.003$) were higher in patients with lung cancer combined with diabetes than in patients without diabetes. Digestive tract cancer patients with DM had higher BMI (23.24 vs 22.15kg/m^2, $P = 0.007$), PLR (216.81 vs 180.08, $P = 0.050$) and VFA (91.94 vs 79.57cm^2, $P = 0.003$) than non-DM patients. Liver cancer patients with DM had lower HGS compared with non-DM patients (22.85 vs 27.04kg, $P = 0.031$). TP (64.17 vs 59.36g/L, $P < 0.001$) and albumin (37.81 vs 35.42 g/L, $P = 0.014$) were higher, while VFA was lower (78.07 vs 95.98 cm^2, $P = 0.004$) in patients with leukemia combined without diabetes than in patients with diabetes. In addition, HGS was lower (18.29 vs 20.38kg, $P = 0.004$) while NLR (5.98 vs 2.22, $P < 0.001$) and PLR (168.90 vs 146.04, $P = 0.022$) were higher in patients with breast cancer combined with diabetes than in patients without diabetes (**Table 2**).

Relationship Between Glycemic Control and Clinical Indicators in DM Patients

Compared with non-DM patients, NRS-2002 was higher in E-DM patients with lung cancer (1.07 vs 0.64, $P = 0.004$) and breast cancer (0.64 vs 0.21, $P = 0.001$). DM patients with euglycemia

TABLE 4 | Hazard risk for all cancers mortality in patients with diabetes stratified by stages.

Specific tumor types	HR	95% CI	*P*-values
Overall cancer			
Early	2.599	2.024–3.336	<0.001
Advanced	2.427	1.887–3.121	<0.001
Lung cancer			
Early	2.076	1.332–3.236	0.001
Advanced	2.118	1.437–3.121	<0.001
Digestive tract cancer			
Early	1.768	1.093–2.863	0.020
Advanced	2.454	1.316–4.576	0.005
Liver cancer			
Early	3.086	1.668–5.708	<0.001
Advanced	2.219	1.004–4.906	0.049
Leukemia	2.636	1.628–4.269	<0.001
Breast Cancer			
Early	2.495	1.011–6.155	0.047
Advanced	2.929	1.193–7.189	0.019
Others			
Early	4.320	2.103–8.871	<0.001
Advanced	3.691	0.830–16.411	0.086

(E-DM) had higher NLR than non-DM patients in lung cancer (4.31 vs 3.23, $P = 0.014$), gastrointestinal tumors (9.06 vs 4.34, $P = 0.017$), and breast cancer (3.40 vs 2.22, $P = 0.014$) (**Table 3**). Although the differences were not always statistically significant, E-DM patients had lower TFN, lower albumin and lower HGS than non-DM patients. It indicated that good glycemic control can make up the adverse effects of diabetes to some extent.

Prognostic Impact of DM in Different Cancer Types Stratified by Stages

Table 4 and **Figure 1** showed the relationship between DM and OS in specific cancer types stratified by stages. Compared with non-DM patients, OS in DM patients was significant shorter in overall cancer, lung cancer, gastrointestinal tract tumors, leukemia, advanced stage breast cancer and early stage liver cancer. The HR was 2.599 (95% CI: 2.024–3.336, $P < 0.001$) in early stage overall cancer, 2.427 (95% CI: 1.887–3.121, $P < 0.001$) in advanced overall cancer, 2.076 (95% CI: 1.332–3.236, $P = 0.001$) in early stage lung cancer, 2.118 (95% CI: 1.437–3.121, $P < 0.001$) in advanced lung cancer, 1.768 (95% CI: 1.093–2.863, $P = 0.020$), in early stage digestive tract cancer, 2.454 (95% CI: 1.316–4.576, $P = 0.005$) in advanced digestive tract cancer, 3.086 (95% CI: 1.668-5.708, $P < 0.001$) in early stage liver cancer, 2.219 (95% CI: 1.004-4.906, $P = 0.049$) in advanced liver cancer, 2.636 (95% CI: 1.628–4.269, $P < 0.001$) in leukemia, 2.495 (95% CI:

TABLE 5 | Hazard risk for all cancers mortality in patients with diabetes stratified by BMI (kg/m^2).

Specific tumor types	HR	95% CI	*P*-values
Overall Cancer			
18.5 ≤ BMI < 23.9	2.468	2.004 to 3.041	<0.001
BMI ≥ 24	1.898	1.410 to 2.556	<0.001
Lung Cancer			
18.5 ≤ BMI < 23.9	2.297	1.635 to 3.229	<0.001
BMI ≥ 24	1.597	1.029 to 2.479	0.037
Digestive tract Cancer			
18.5 ≤ BMI < 23.9	2.354	1.508 to 3.675	<0.001
BMI ≥ 24	1.220	0.588 to 2.534	0.594
Liver Cancer			
18.5 ≤ BMI < 23.9	2.406	1.414 to 4.092	0.001
BMI ≥ 24	2.203	0.718 to 6.762	0.168
Leukemia			
18.5 ≤ BMI < 23.9	4.039	2.291 to 7.120	<0.001
BMI ≥ 24	1.496	0.580 to 3.858	0.405
Breast Cancer			
18.5 ≤ BMI < 23.9	4.222	1.466 to 12.164	0.008
BMI ≥ 24	1.526	0.447 to 5.210	0.500
Others			
18.5 ≤ BMI < 23.9	2.002	0.760 to 5.271	0.160
BMI ≥ 24	6.747	2.769 to 16.441	<0.001

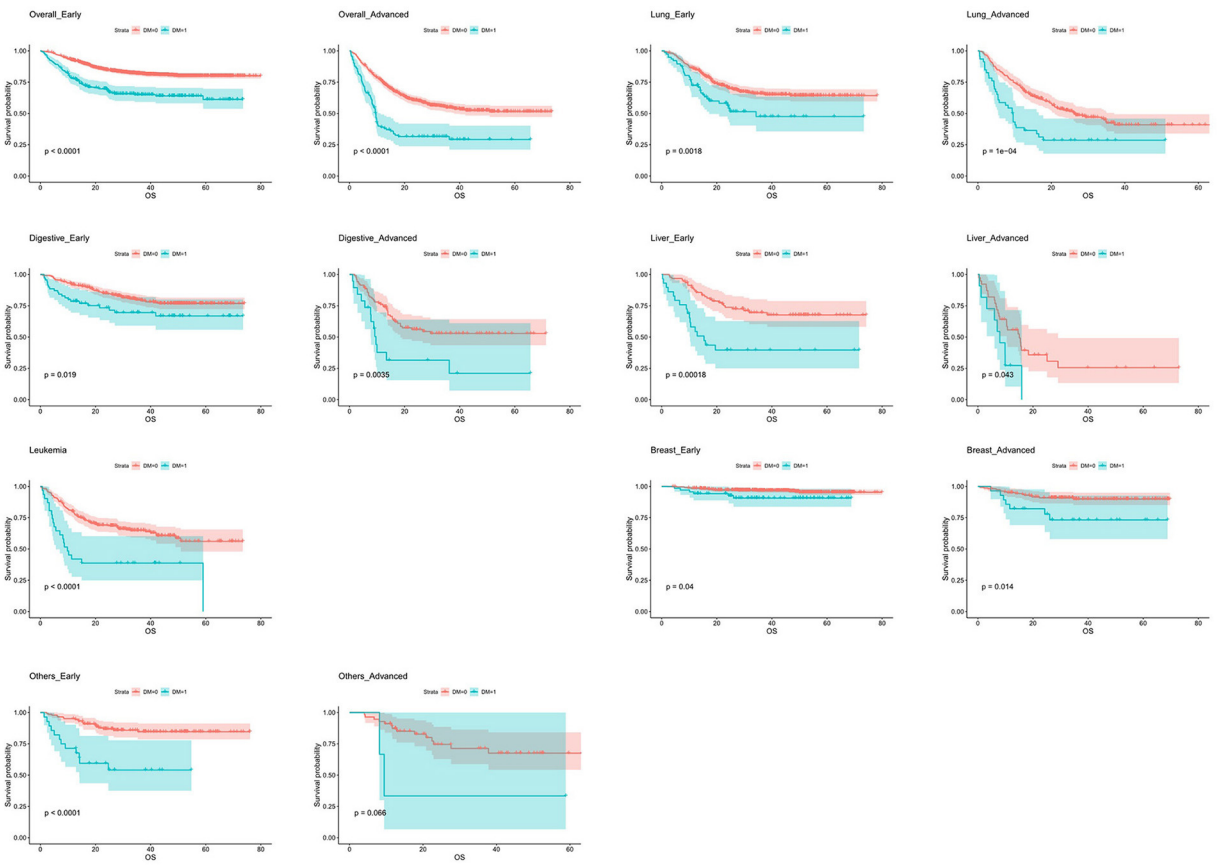

FIGURE 1 | Kaplan–Meier curves of overall survival in different cancer types stratified by stage. DM, diabetes mellitus.

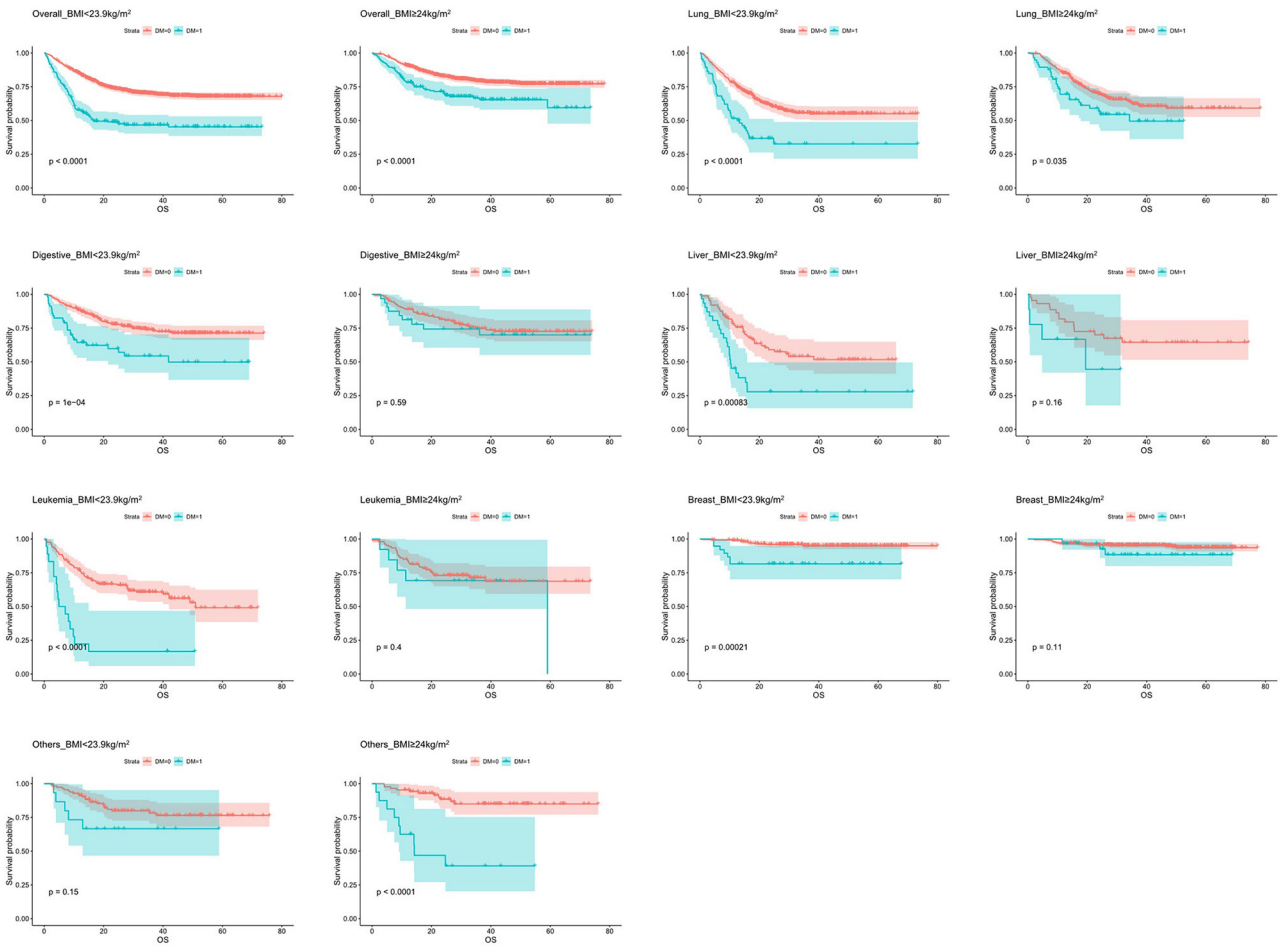

FIGURE 2 | Kaplan–Meier curves of overall survival in different cancer types stratified by BMI.

1.011–6.155, $P = 0.047$) in early stage breast cancer, 2.929 (95% CI: 1.193–7.189, $P = 0.019$) in advanced breast cancer, and 4.320 (95% CI:2.103–8.871, $P < 0.001$) in patients with early stage other tumors (**Figure 1**).

Prognostic Impact of DM in Different Cancer Types Stratified by BMI

Patients was classified by BMI into normal ($18.5 \leq$ BMI < 23.9 kg/m^2) and obese (BMI ≥ 24.0 kg/m^2) categories according to WGO. **Table 5** and **Figure 2** showed the relationship between DM and OS in specific cancer types stratified by BMI. The combination of diabetes had negative impact on OS when the BMI was within the normal range in lung cancer (HR = 2.297, 95% CI: 1.635–3.229, $P < 0.001$), digestive tract cancer (HR = 2.354, 95% CI: 1.508–3.675, $P < 0.001$), liver cancer (HR = 2.406, 95% CI: 1.414–4.092, $P = 0.001$), leukemia (HR = 4.039, 95% CI: 2.291–7.120, $P < 0.001$) and breast cancer (HR = 4.222, 95% CI: 1.466–12.164, $P = 0.008$). In contrast, among those with BMI $\geq$ 24 kg/m^2, DM played a role only in lung cancer (HR = 1.597, 95% CI: 1.029–2.479, $P = 0.037$) and other tumors (HR = 6.747, 95% CI: 2.769–16.441, $P < 0.001$). Furthermore, it was observed that, the HR of DM patients with BMI in normal range (HR = 2.468, 95% CI: 2.004–3.041, $P < 0.001$) was significantly higher than those whose BMI ≥ 24 kg/m^2 (HR = 1.898, 95% CI: 1.410–2.556, $P < 0.001$) in overall tumors.

DISCUSSION

In previous studies, significant differences in inflammatory status, nutritional status, and quality of life between diabetic and non-diabetic patients have been demonstrated (17, 18). But there was no large-scale data on the differences between diabetic and non-diabetic patients and whether effective glycemic control can make up the adverse effects of diabetes in cancer patients. In the present study, we found that body composition and inflammatory parameters in cancer patients with diabetes differed from those without diabetes, suggesting that diabetes exacerbated the systemic inflammatory response of the body (19). For diabetic patients with good glycemic control, there still existed relatively more active inflammatory status compared to patients without diabetes, especially NLR. But quite a few indicators, such as albumin, PAB and CRP were not statistically

different, suggesting that good glycemic control can reduce the adverse effects of diabetes to some extent.

DM has a negative impact on tumor patients in different stages. For most types of tumors, the prognosis of patients with DM is poor (20). Diabetes has a greater impact on patient prognosis in early stage liver cancer patients due to the combination of systemic metabolic changes and the development of systemic inflammation in patients with liver cancer at early stages (21). However, DM behaved as a stronger risk factor in advanced patients compared with those in early stage in colon cancer, lung cancer and breast cancer, which may due to the longer survival period of advanced cancer that allows the risk of DM to unfold. Therefore, the management of blood glucose in cancer patients with relatively longer survivals becomes increasingly important (22). It is worth mentioning that the adverse effects of diabetes were observed in leukemia, which may further illustrate the role of abnormal metabolism in malignant hematologic diseases and provide a theoretical basis for subsequent studies on the mechanisms of hematologic metabolism.

The BMI stratification was also discussed, and the risk of diabetes was more pronounced in patients with normal BMI. Patients with normal BMI and diabetes tend to have a longer disease duration and are less tolerant of treatment, while patients with higher BMI even without diabetes continuously exist a similar systemic inflammatory response as diabetic patients (23), which may account for the differences in diabetes risk across populations with different BMIs.

There is a limitation for choosing blood glucose as a marker of glycemic control mainly for the shortcomings of possibly inaccurate assessment of long term blood glucose control. The reasons are listed following. First, the glycated hemoglobin A1C (HbA1c), a reliable measurement of glycemic control, was not chose in this study as a marker of glycemic control mainly due to the inconvenience. In real clinical settings, HbA1c was mainly tested when DM was newly diagnosed or a DM patient with unsatisfied blood glucose levels. Second, although the cutoff value of HbA1c for DM is clearly defined, the reasonable threshold of HbA1c for predicting the prognosis was not a consensus (24), which may bring bias if HbA1c was chose as a glycemic control marker. Third, measurements of DM which also have an impact on cancer development should be taken into analysis as confounders. Several diabetes medications are reported related with cancer prognosis, typically metformin. To be accurate, the mechanisms are still unclear and the results of metformin in cancer prognosis are not always positive (25, 26). Given the limited patients using metformin (only 1.2%) in this study, the stratified sub-analysis was not committed. This topic should be further investigated.

In summary, we found that patients with diabetes tend to combine worse body composition and inflammatory indicators, and that glycemic control can ameliorate the impairment of diabetes to some extent. The above results suggest the negative influence of hyperglycemia in systemic inflammation metabolism. Besides, the risk posed by diabetes is not the same in patients with different tumor types and stages. Thus, the management of diabetes should be emphasized, especially for patients in early stages, which may bring a more durable disease-free state. Finally, we analyzed patients with different BMI to further analyze the relationship between body composition and diseases, and we believe that more studies should be done in the future.

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

XL, KZ, and WJ conducted and drafted the manuscript. WZ and YL collected and analyzed the data. ML, JC, and WL designed the manuscript. ML, JC, WL, XL, KZ, and WJ revised the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Prognostic Value of Prognostic Nutritional Index in Patients With Colorectal Cancer Undergoing Surgical Treatment

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Background: To investigate the relationship between prognostic nutritional index (PNI) and the survival of patients with colorectal cancer (CRC) undergoing surgical treatment.

Methods: In total 1,014 CRC patients who underwent surgical treatment were enrolled. Logistic regression analysis was used to identify the features that influenced postoperative complications in CRC patients. Restricted cubic spline was used to assess the dose-response relationship between PNI and survival in CRC patients. Kaplan-Meier method and log-rank test were used to compare survival differences between groups of CRC patients. Cox proportional risk regression models was used to assess independent risk factors for progression-free survival (PFS) and overall survival (OS) of CRC patients.

Results: Low PNI was associated with high tumor burden, invasive pathological features, and poor host status. Compared with patients with high PNI, patients with low PNI have a higher incidence of complications and longer hospital stay. Low PNI was an independent risk factor for postoperative complications in CRC patients. for every SD increased in PNI, the risk of poor prognosis for CRC patients was reduced by 2.3% (HR = 0.977, 95%CI = 0.962–0.993, $p = 0.004$) in PFS, and 2.3% (HR = 0.977, 95%CI = 0.962–0.993, $p = 0.004$) in OS. PNI was an independent prognostic factor affecting the PFS and OS of CRC patients. Finally, we constructed the PNI-based nomograms to predict postoperative complications, 1–5 years PFS and OS in CRC patients. Concordance index and calibration curve indicated that the PNI-based nomograms have moderate prediction accuracy.

Conclusion: PNI is an independent risk factor affecting postoperative complications, PFS and OS of CRC patients, and is a useful supplement to the TNM stage.

Keywords: prognostic nutritional index, colorectal cancer, complication, prognosis, nutrition

INTRODUCTION

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancy in the world, ranking third in incidence and second in cancer-related death, according to the latest data. It is estimated that more than 1.93 million new CRC cases and 935,000 death occur globally in 2020, accounting for ∼10% of new cancer cases and cancer-related death worldwide (1). In China, CRC is the fourth most common malignancy (∼388,000 cases) and the fifth most common cause of cancer-related death (∼187,000 cases) (2). With the development of treatment methods such as surgery, radiochemotherapy, immunotherapy, and targeted therapy, the 5- and 10- year survival rate of patients with early CRC can reach 58–65%, but the survival rate of CRC patients with recurrence and metastasis can be reduce to 10% (3). Microvascular invasion, tumor-related factors, tumor-node-metastasis (TNM) stage, microsatellite status, etc. have been reported as prognostic factors for CRC patients. However, effective prognostic factors are still lacking, especially simple and economical biomarkers. Therefore, there is an urgent need to find effective prognostic indicators to help clinicians adopt optimal prevention and treatment strategies to reduce CRC-related mortality.

More and more evidences indicate that the gradual decline of nutritional status is related to disease progression and is one of the main reasons for poor treatment effectiveness. Perioperative malnutrition not only significantly increases the incidence of postoperative complications, but is also associated with poor long-term outcomes (4, 5). In addition, the immune status is also an important factor affecting the clinical outcome of patients (6). Various prognostic indicators calculated from serum parameters have been confirmed to be associated with prognosis of patients with cancer. The evaluation of preoperative immune-nutritional status can predict the risk and survival rate of surgery, which is helpful to determine strategies to prevent postoperative complications and improve the prognosis. The prognostic nutritional index (PNI), which combines nutritional and immune parameters, has been proven to be a good predictor of postoperative complications and survival rates for many malignancy (7–9). Tokunaga et al. (8) conducted a study of 556 cases of CRC in 2015. The results indicated that preoperative PNI could effectively predict severe complications, recurrence and poor prognosis in CRC patients undergoing resection. Noh et al. (10) found that low PNI was associated with increased postoperative complications, long hospital stays, poor prognosis, and aggressive tumor phenotype. A meta-analysis in 2019 also showed that compared with CRC patients with low PNI, the overall survival (OS) of those with high PNI was significantly improved (11).

There are still few studies on the relationship between PNI and postoperative complications and long-term prognosis in CRC patients. In addition, the prognostic prediction efficiency of a single indicator is still low, and the combination of multiple indicators to construct a nomogram may be an effective means to improve the prognostic predictive performance. Therefore, this study aimed to explore the value of PNI in evaluating postoperative complications and long-term prognosis of CRC patients undergoing surgical treatment, and construct PNI-based nomograms to individually predict the prognosis of CRC patients, so as to provide certain guidance for formulating treatment strategies for CRC patients.

PATIENTS AND METHODS

Study Design

This study included CRC patients who underwent surgical treatment at the department of colorectal and anal Surgery of the First Affiliated Hospital of Guangxi Medical University from January 2012 to December 2015. Inclusion criteria are as follows: (1) Histopathologically confirmed colon or rectal cancer; (2) The primary tumor received surgical resection; 3) Complete available clinicopathological data; (4) Complete postoperative follow-up data. The exclusion criteria were as follows: (1) Patients complicated with other primary malignancy during the same period; (2) Patients with autoimmune diseases, blood diseases, obviously abnormal liver function or abnormal kidney function; (3) Patients with obvious clinical evidence of infection or inflammation; (4) Patients who lost follow-up or did not have complete data. This study strictly complied with the Helsinki Declaration during the research process, and was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University, with the approval number: 2021 (KY-E-043).

Data Collection

Clinicopathological features included the following aspects: basic information included sex, age, height, and weight; preoperative basic diseases included hypertension and diabetes; preoperative laboratory serological tests included neutrophil count, lymphocyte count, and albumin (hypoproteinaemia, defined as albumin <35 g/L) and serum CEA level (normal, <5.00 ng/ml; high, ≥5.00 ng/ml), All preoperative laboratory serological tests were performed 1 week before surgery; Pathological characteristics included TNM stage, pathological tumor infiltration depth (pT) stage, pathological lymph node metastasis (pN stage), distant metastasis, perineural invasion, vascular invasion, pathological type, differentiation, tumor location, and tumor size. Surgical information included surgical approach (laparoscopic or open), operating time (median 192 min), and intraoperative bleeding (median 100 mL). Body mass index (BMI) was defined as weight (kg) / square height (m^2) (low: <18.5, normal: 18.5–24, high: ≥24). PNI was defined as: serum albumin (g/L) + 5 × total peripheral lymphocyte count ($\times 10^9$/L). Neutrophil to lymphocyte ratio (NLR) was defined as: neutrophil count (10^9/L) / lymphocyte count (10^9/L). Platelet to lymphocyte ratio (PLR) was defined as: platelet count (10^9/L) / lymphocyte count (10^9/L). The postoperative complications of CRC patients in this study were strictly classified according to the modified Clavien complication classification system (12, 13).

Follow-Up

CRC patients were followed up every 3 months for 2 years after surgery, and every 6 months thereafter. The last follow-up date was February 04, 2021. Progression-free survival (PFS) was defined as the time interval between the date of surgery and the

patient's disease recurrence, death, or the last follow-up; OS was defined as the time interval between the date of surgery and the patient's death or last follow-up.

Statistical Analysis

Continuous data was presented as means with standard deviations (SDs), and classification data was presented as frequencies and percentages. Chi-square test or *t*-test was used to analyze the correlation between PNI and various clinicopathological features. The optimal cutoff value of PNI was determined by the standardized log-rank statistic (R package "survminer") based on the OS. Logistic regression analysis was used to identify the features that influenced postoperative complications in CRC patients. Restricted cubic spline (RCS) was used to assess the dose-response relationship between PNI and survival in CRC patients. Kaplan-Meier method and log-rank test were used to compare survival differences between groups of CRC patients. Cox proportional risk regression models was used to assess independent risk factors for PFS and OS of CRC patients. Receiver operator characteristic curve (ROC) analysis was used to compare the effectiveness of PNI and other prognostic indicators in predicting PFS and OS. In addition, based on the results of multivariate analysis, we constructed the PNI-based nomograms to predict postoperative complications, 1–5 years PFS and OS in CRC patients. Concordance index (C-index) and calibration curve were used to assess the prognostic accuracy of PNI-based nomograms. Finally, time-dependent ROC and decision curve analysis (DCA) were used to compare the ability of the nomogram with the traditional TNM stage in predicting long-term prognosis of CRC patients. A $p < 0.05$

TABLE 1 | The relationships between the PNI and clinicopathological factors of CRC patients.

Features	Total (n = 1,014)	PNI		X^2/t	*P* value
		Low (n = 334)	High (n = 680)		
Gender (Male)	639 (63.0%)	224 (67.1%)	415 (61.0%)	3.502	0.061
Age (Years) (≥60)	482 (47.5%)	197 (59.0%)	285 (41.9%)	26.171	<0.001
Age (Years)	57.33 ± 13.338	59.27 ± 14.219	56.11 ± 12.605	3.700	<0.001
BMI				25.599	<0.001
Low	138 (13.6%)	69 (20.7%)	69 (10.1%)		
Normal	599 (59.1%)	195 (58.4%)	404 (59.4%)		
High	277 (27.3%)	70 (21.0%)	207 (30.4%)		
Hypertension (Yes)	153 (15.1%)	64 (19.2%)	89 (13.1%)	6.449	0.011
Diabetes (Yes)	65 (6.4%)	31 (9.3%)	34 (5.0%)	6.844	0.009
pT stage (T3-4)	765 (75.4%)	250 (74.9%)	515 (75.7%)	0.095	0.758
pN stage				2.439	0.295
N0	551 (54.1%)	191 (57.2%)	358 (52.6%)		
N1	295 (29.1%)	87 (26.0%)	208 (30.6%)		
N2	170 (16.8%)	56 (16.8%)	114 (16.8%)		
Clinical distant metastasis (Yes)	105 (10.8%)	47 (14.1%)	58 (8.5%)	7.412	0.006
TNM stage				10.826	0.013
I stage	184 (18.1%)	68 (20.4%)	116 (17.1%)		
II stage	328 (32.3%)	103 (30.8%)	225 (33.1%)		
III stage	397 (39.2%)	116 (34.7%)	281 (41.3%)		
IV stage	105 (10.4%)	47 (14.1%)	58 (8.5%)		
Tumor location (Colon)	510 (50.3%)	191 (57.2%)	319 (46.9%)	9.457	0.002
Tumor size (≥5 cm)	492 (48.5%)	205 (61.4%)	287 (42.2%)	32.958	<0.001
Perineural invasion (Positive)	90 (8.9%)	32 (9.6%)	58 (8.5%)	0.306	0.580
Vascular invasion (Positive)	151 (14.9%)	47 (14.1%)	104 (15.3%)	0.264	0.607
Macroscopic type				6.885	0.032
Protrude type	250 (24.7%)	94 (28.1%)	156 (22.9%)		
Infiltrating type	95 (9.4%)	38 (11.4%)	57 (8.4%)		
Ulcerative type	669 (66.0%)	202 (60.5%)	467 (68.7%)		
Histological type (Poor)	123 (12.1%)	40 (12.0%)	83 (12.2%)	0.011	0.916
CEA (≥5 ng/ml)	428 (42.2%)	169 (50.6%)	259 (38.1%)	14.372	<0.001
Length of stay	18.00 (16.00, 22.00)	20.00 (17.00, 24.00)	18.00 (16.00, 21.00)	3.854	<0.001
Recurrence and metastasis (Yes)	297 (29.3)	118 (35.3)	179 (26.3)	8.771	0.003
Death (Yes)	444 (43.8)	182 (54.5)	262 (38.5)	23.184	<0.001

CRC, colorectal cancer; BMI, body mass index; PNI, prognostic nutrition index.

was considered statistically significant. All statistical analysis was performed using SPSS 24.0 (IBMSPSS, IBM CorPoration, Armonk, NY) and R software (3.5.3; http://www.r-Project.org).

RESULTS

Characteristics of Clinical Baseline

A total of 1,014 CRC patients were enrolled in this study. The optimal cut-off value of PNI was determined as 44.65 by the standardized log-rank statistic (**Supplementary Figure S1**). Based on this cut-off value, there were 334 (38.9%) patients in the low PNI group and 680 (61.1%) patients in the high PNI group. The characteristics of CRC patients were presented in **Table 1**. There were 639 (63.0%) males and 375 (37.0%) females. 532 (52.5%) patients were $<$ 60 years old, and 482(47.5%) patients were $\geq$ 60 years old, with an average age of 57.33 $\pm$ 13.34. There were 504 (56.1%) cases of rectal cancer and 510 (43.9%) cases of colon cancer. There were 184 (18.1%) TNM stage I, 328 (32.3%) TNM stage II, 397 (38.7%) TNM stage III, and 105 (10.8%) TNM stage IV. The median follow-up time of 67.2 months (1–100.9 months).

Correlation Analysis of PNI and Various Clinical Characteristics

We conducted a correlation analysis between PNI and clinicopathological features. The results showed that low PNI was associated with advanced age, low BMI, preoperative comorbidity (hypertension, diabetes), distant metastasis, advanced TNM stage, colon cancer, large tumor size, macroscopic type, high CEA level, long hospital stay, high recurrence and high mortality (All $p < 0.05$). While there were no statistically significant differences between the high and low PNI groups in terms of gender, pT stage, pN stage, perineural invasion, vascular invasion, differentiation and other tumor-related factors (**Table 1** and **Supplementary Figure S2**).

Relationship Between PNI and Postoperative Complications in CRC Patients

Among 1,014 CRC patients, a total of 180 (17.8%) patients had various postoperative complications, including 18 (1.78%) cases of intestinal obstruction, 30 (2.96%) cases of anastomotic problems, 54 (5.33%) cases of wound problems, 29 (2.86%) cases of pulmonary infection, 13 (1.28%) cases of gastrointestinal problems, 6 (0.59%) cases of abdominal infection and 30 (2.96%) cases of other complications. According to the modified Clavien complication classification system, there are 64 (6.3%) grade I complications, 89 (8.8%) grade II complications, and 18 (1.8%) grade III complications, including grade IIIa 10 (1.0%) cases, 8 (0.8%) cases of grade IIIb complications, 8 (0.8%) cases of grade IV complications, including 5 (0.5%) cases of grade IVa, 3 (0.3%) cases of grade IVb complications, and 1 (0.1%) complication of grade V complications. Compared with those with high PNI, the total postoperative complications ($X^2 = 15.771$, $p < 0.001$) of patients with low PNI significantly increased, especially grade I ($X^2 = 16.074$, $p < 0.001$) and grade III ($X^2 = 4.244$, $p < 0.001$) (**Supplementary Table S1**). The complication rate in the PNI (Q1) group was 6.61%, while the complication rate in the PNI (Q4) group was 3.45%. In addition, the length of hospital stays gradually decreased from 20 days for patients with PNI $<$ 43.40 to 17 days for patients with PNI $>$ 50.70 (**Supplementary Figure S3**). Univariate logistic regression analysis showed that age, hypertension, PNI, surgical approach, operating time, intraoperative bleeding and serum CEA levels were associated with postoperative complications; However, multivariate analysis showed that only age ($\geq$60 years) (OR: 1.677, 95%CI: 1.181–2.380, $p = 0.004$) and low PNI (HR: 1.580, 95%CI: 1.122–2.27, $p = 0.009$), Operating time ($\geq$192 min) (OR: 1.530, 95%CI: 1.104–2.122, $p = 0.044$) and intraoperative bleeding ($\geq$100 mL) (OR: 1.660, 95% CI: 1.109–2.484, $p = 0.014$) were independent risk factors for postoperative complications in CRC patients (**Supplementary Table S2**).

Relationship Between PNI and Survival in CRC Patients

The RCS showed that with the increase of PNI, The PFS (**Figures 1A,C**) and OS (**Figures 1B,D**) of CRC patients increased gradually. After adjusting confounding factors, there was still a negative non-linear relationship between PNI and survival of CRC patients. During follow-up, a total of 297 (29.3%) patients had recurrence and metastasis, including 118 patients in the low PNI group (35.33% of the low PNI group) and 179 patients in the high PNI group (26.32% of the high PNI group). The PFS of the low PNI group was significantly lower than that of the high PNI group (42.5 vs. 59.3%, $p < 0.001$) (**Figure 2A**). By the last follow-up, 444 (43.79%) patients died, including 182 patients in the low PNI group (54.49% of the low PNI group) and 262 patients in the high PNI group (38.53% of the high PNI group). The OS of patients with low PNI was significantly lower than that of the patients with high PNI (45.5 vs. 61.5%, $p < 0.001$) (**Figure 2B**). In addition, stratified analysis showed that for patients with stage I-II CRC, PFS (57.3 vs. 73.9%, $p = 0.002$) and OS (60.2 vs. 76.0%, p = 0.002) in the low PNI group were significantly lower than those in the high PNI group (**Figures 2C,D**). Similarly, for patients with stage III-IV CRC, PFS (27.0 vs. 44.5%, $p < 0.001$) and OS (30.1 vs. 46.9%, $p < 0.001$) in the low PNI group were also significantly lower than those in the high PNI group (**Figures 2E,F**).

Prognostic Factors Affecting PFS and OS in CRC Patients

In univariate analysis, PFS was affected by the following clinicopathological characteristics: Age ($p = 0.002$), BMI ($p = 0.026$), PNI ($p < 0.001$), pT stage ($p < 0.001$), pN stage ($p < 0.001$), distant metastasis ($p < 0.001$), tumor size ($p = 0.021$), perineural invasion ($p < 0.001$), vascular invasion ($p < 0.001$), differentiation ($p = 0.010$), surgical approach ($p < 0.001$), and CEA($p < 0.001$). Subsequently, a multivariate analysis was performed on the 12 significant factors. The results showed that the independent prognostic factors affecting PFS in CRC patients

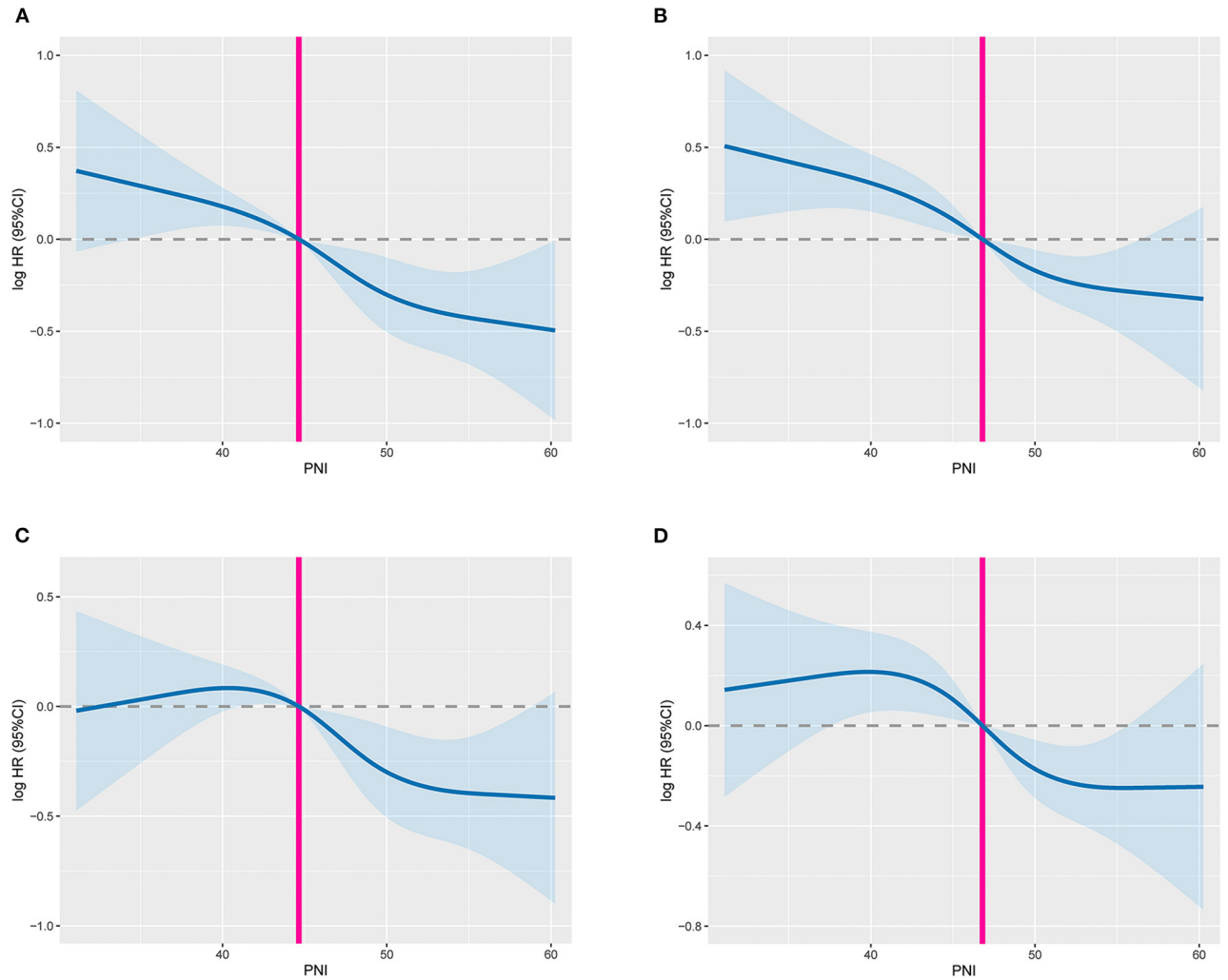

FIGURE 1 | The dose-response relationship between PNI and survival in CRC patients. **(A)** Unadjusted RCS of PFS; **(B)** unadjusted RCS of OS; **(C)** adjusted RCS of PFS; **(D)** adjusted RCS of OS; The model adjusted for gender, age, BMI, hypertension, diabetes, pT stage, pN stage, clinical distant metastasis, tumor location, tumor size, perineural invasion, vascular invasion, macroscopic type, and histological type.

were age (≥60 years) (HR = 1.297, 95%CI = 1.072–1.568, p = 0.007), PNI (HR = 1.359, 95%CI = 1.115–1.656, p = 0.002), pT stage (HR = 1.561, 95% CI = 1.184–2.059, p = 0.002), pN stage (p < 0.001), Distant metastasis (HR = 3.113, 95%CI = 2.420–4.005, p < 0.001), vascular invasion (HR = 1.363, 95%CI = 1.062–1.750, p = 0.015) and CEA (HR = 1.463, 95%CI = 1.203–1.780, p < 0.001) (**Table 2**).

Similarly, univariate analysis showed that the following clinical features were significantly associated with OS: age (p < 0.002), BMI (p = 0.031), PNI (p < 0.001), pT stage (p < 0.001), pN stage (p < 0.001), distant metastasis (p < 0.001), tumor size (p = 0.002), perineural invasion (p < 0.001), vascular invasion (p < 0.001), differentiation (p = 0.002), surgical method (p < 0.001) and CEA (p < 0.001). However, in multivariate analysis, only age (≥60 years)(HR = 1.377, 95%CI = 1.132–1.674, p = 0.001), low PNI(HR = 1.329, 95%CI = 1.085–1.627, p = 0.006), high pT stage (T2-3) (HR = 1.599, 95% CI = 1.199–2.132, p = 0.001), high pN stage (p < 0.001), distant metastasis (HR = 3.325, 95%CI = 2.579–4.287, p < 0.001), vascular invasion (HR = 1.396, 95%CI = 1.083– 1.800, p = 0.010) and high CEA(HR = 1.445, 95%CI = 1.182–1.768, p < 0.001) were independent risk factors for OS in CRC patients (**Table 3**).

The consistency test showed that when PNI was used as a continuous variable, for every SD increased in PNI, the risk of poor prognosis for CRC patients was reduced by 2.3% (HR = 0.977, 95%CI = 0.962–0.993, p = 0.004) in PFS, and 2.3% (HR = 0.977, 95%CI = 0.962–0.993, p = 0.004) in OS. In PFS, when PNI was split into quartiles, Q2, Q3, and Q4 were all positively associated with better prognosis (p < 0.001) with the lowest group (Q1) as a reference. After adjusting for confounders, the HRs of PFS were 0.768 (0.600, 0.984), 0.701 (0.543, 0.903), and 0.651 (0.499, 0.848), respectively (**Supplementary Table S3**,

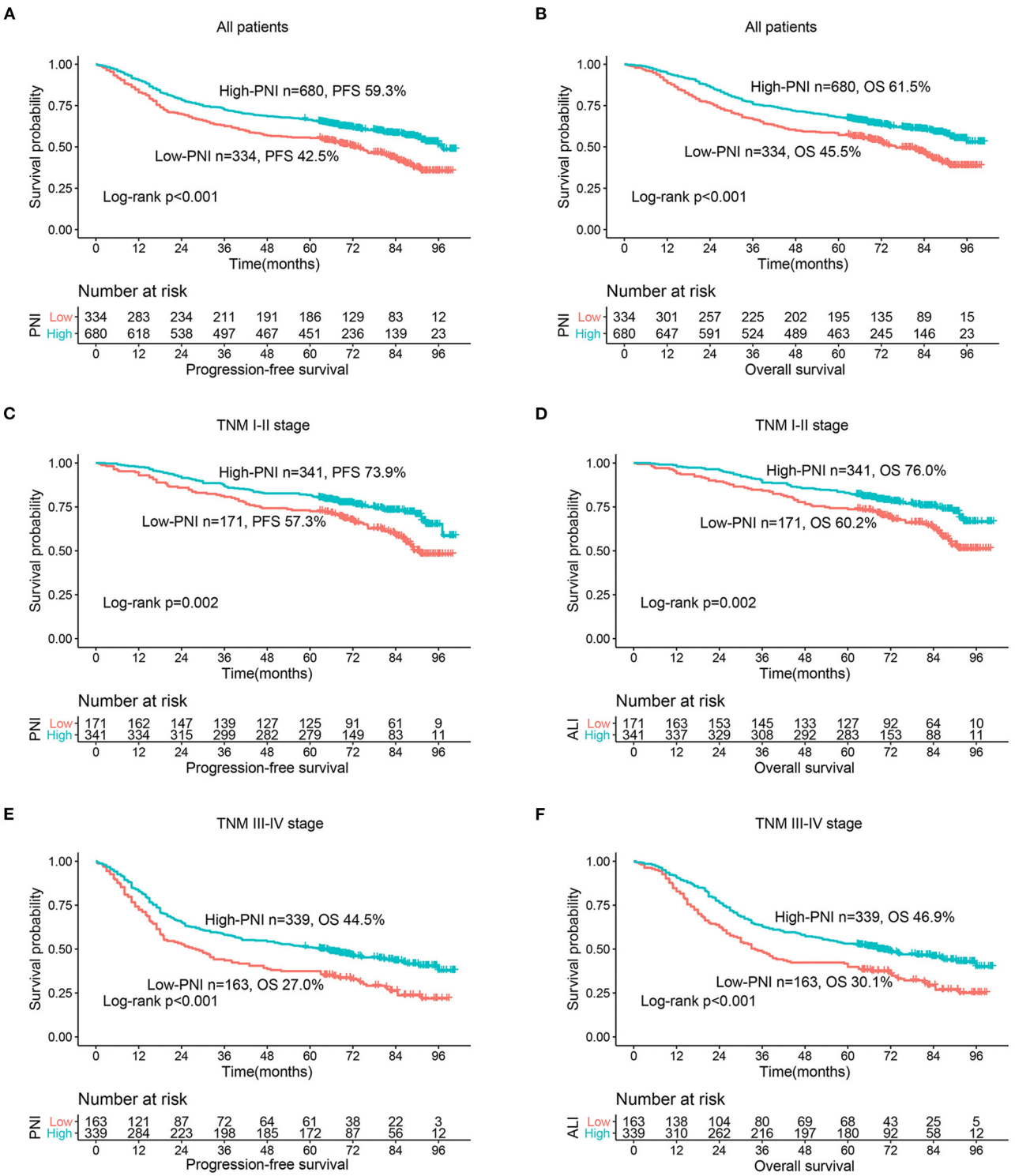

FIGURE 2 | Kaplan-Meier curves of different PNI groups in CRC patients. **(A)** PFS of PNI; **(B)** OS of PNI; **(C)** PFS of PNI based on TNM I-II stage; **(D)** OS of PNI based on TNM I-II stage; **(E)** PFS of PNI based on TNM III-IV stage; **(F)** OS of PNI based on TNM III-IV stage.

PFS). Also in OS, with the increase of PNI, the prognosis of patients gradually increased, and the HR of OS were 0.791 (0.615, 1.018), 0.674 (0.517, 0.877), and 0.666 (0.509, 0.873), respectively (**Supplementary Table S3**, OS). We performed a subgroup analysis using univariate Cox regression based on various clinical features. A total of 19 clinical features and 40 subgroups were

TABLE 2 | Univariate and multivariate Cox regression analysis of clinicopathological characteristics associated with progression-free survival.

Characteristic	Progression-free survival			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Gender (Female)	0.988 (0.819, 1.191)	0.895		
Age (≥60 years)	1.334 (1.113, 1.600)	0.002	1.297 (1.072, 1.568)	0.007
BMI		0.026		0.720
Low	Ref.		Ref.	
Normal	0.831 (0.647, 1.068)	0.148	0.964 (0.743, 1.250)	0.781
High	0.674 (0.504, 0.902)	0.008	0.891 (0.658, 1.207)	0.458
Hypertension (Yes)	1.155 (0.905, 1.475)	0.248		
Diabetes (Yes)	1.188 (0.838, 1.684)	0.334		
PNI (Low)	1.519 (1.264, 1.827)	<0.001	1.359 (1.115, 1.656)	0.002
pT stage (T3-4)	2.458 (1.894, 3.189)	<0.001	1.561 (1.184, 2.059)	0.002
pN stage		<0.001		<0.001
N0	Ref.		Ref.	
N1	1.648 (1.330, 2.042)	<0.001	1.405 (1.124, 1.755)	0.003
N2	3.620 (2.889, 4.534)	<0.001	2.645 (2.077, 3.370)	<0.001
Distant metastasis (Yes)	4.854 (3.869, 6.089)	<0.001	3.113 (2.420, 4.005)	<0.001
Tumor location (Colon)	0.969 (0.808, 1.161)	0.731		
Tumor size (≥5 cm)	1.238 (1.033, 1.484)	0.021	0.938 (0.775, 1.136)	0.514
Perineural invasion (Positive)	1.805 (1.379, 2.363)	<0.001	1.120 (0.829, 1.513)	0.461
Vascular invasion (Positive)	1.982 (1.592, 2.467)	<0.001	1.363 (1.062, 1.750)	0.015
Macroscopic type		0.095		
Protrude type	Ref.			
Infiltrating type	1.396 (0.991, 1.967)	0.057		
Ulcerative type	1.239 (0.988, 1.554)	0.063		
Histological grade (Poor)	1.409 (1.086, 1.829)	0.010	1.180 (0.898, 1.550)	0.235
Surgical approach (Open)	1.533 (1.278, 1.838)	<0.001	1.190 (0.979, 1.447)	0.080
Operating time (median) (≥192 min)	1.080 (0.900, 1.295)	0.408		
Blood loss (median) (≥100 mL)	1.143 (0.938, 1.394)	0.186		
CEA (≥5 ng/ml)	2.010 (1.676, 2.411)	<0.001	1.463 (1.203, 1.780)	<0.001
Postoperative chemoradiotherapy (Yes)	1.084 (0.903, 1.301)	0.389		

CRC, colorectal cancer; BMI, body mass index; PNI, prognostic nutrition index.

included. The results showed that low PNI was a risk factor affecting the prognosis of CRC patients in most subgroups (**Supplementary Figures S4A,B**). In addition, we compared the effectiveness of PNI with other prognostic indicators (NLR and PLR) in predicting the clinical outcome of CRC patients through the ROC curve. The results showed that the ability of PNI was superior to other prognostic indicators in predicting PFS in CRC patients (**Supplementary Figures S5A,B**). Similarly, the ability of PNI was superior to NLR in predicting OS in CRC patients (**Supplementary Figures S5C,D**).

Construction of PNI Based Prediction Model

The nomogram is considered a simple and effective tool to provide personalized risk prediction for patients. We developed a complication nomogram to predict the risk of postoperative complications in CRC patients (**Figure 3A**). The nomogram included operation time, intraoperative bleeding, age and PNI. The C-index of the complication nomogram was 0.646 (95%CI: 0.601–0.691), and the calibration curve showed a good consistency between the probability of complication predicted by the nomogram and the actual results (**Figure 3B**). These results indicated that our complication nomogram had good predictive accuracy in predicting postoperative complications in CRC patients. Similarly, based on prognostic variables identified in multivariate survival analysis (vascular invasion, CEA level, pT stage, pN stage, distant metastasis, age, and PNI), we developed two survival nomograms to predict 1–5-years PFS (**Figure 4A**) and OS (**Figure 4B**) of CRC patients. The C-index of PFS and OS nomogram was 0.723(95%CI: 0.712–0.735) and 0.729(95%CI: 0.705–0.753), and the calibration curves of PFS (**Supplementary Figures S6A,B**) and OS (**Supplementary Figure S6C,D**) all proved the best consistency between the predicted survival probability and the actual observed value. These results indicated that the prognostic

TABLE 3 | Univariate and multivariate Cox regression analysis of clinicopathological characteristics associated with overall survival.

Characteristic	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Gender (Female)	0.994 (0.903, 1.095)	0.910		
Age (≥60 years)	1.421 (1.179, 1.713)	<0.001	1.377 (1.132, 1.674)	0.001
BMI		0.031		0.792
Low	Ref.		Ref.	
Normal	0.841 (0.650, 1.090)	0.190	0.976 (0.746, 1.276)	0.857
High	0.675 (0.500, 0.911)	0.010	0.908 (0.664, 1.243)	0.548
Hypertension (Yes)	1.172 (0.913, 1.504)	0.213		
Diabetes (Yes)	1.250 (0.881, 1.773)	0.212		
PNI (Low)	1.526 (1.263, 1.844)	<0.001	1.329 (1.085, 1.627)	0.006
pT stage (T3-4)	2.536 (1.931, 3.329)	<0.001	1.599 (1.199, 2.132)	0.001
pN stage		<0.001		<0.001
N0	Ref.		Ref.	
N1	1.627 (1.304, 2.030)	<0.001	1.376 (1.094, 1.730)	0.006
N2	3.651 (2.899, 4.598)	<0.001	2.588 (2.021, 3.315)	<0.001
Distant metastasis (Yes)	5.145 (4.092, 6.468)	<0.001	3.325 (2.579, 4.287)	<0.001
Tumor location (Colon)	0.997 (0.827, 1.200)	0.971		
Tumor size (≥5cm)	1.340 (1.112, 1.615)	0.002	1.023 (0.841, 1.246)	0.817
Perineural invasion (Positive)	1.789 (1.357, 2.359)	<0.001	1.079 (0.792, 1.468)	0.630
Vascular invasion (Positive)	2.042 (1.635, 2.551)	<0.001	1.396 (1.083, 1.800)	0.010
Macroscopic type		0.126		
Protrude type	Ref.			
Infiltrating type	1.349 (0.945, 1.927)	0.100		
Ulcerative type	1.248 (0.989, 1.576)	0.062		
Histological grade (Poor)	1.523 (1.173, 1.979)	0.002	1.292 (0.981, 1.701)	0.068
Surgical approach (Open)	1.616 (1.341, 1.949)	<0.001	1.216 (0.994, 1.487)	0.057
Operating time (median) (≥192 min)	1.087 (0.902, 1.311)	0.380		
Blood loss (median) (≥100 mL)	1.183 (0.964, 1.452)	0.108		
CEA (≥5 ng/ml)	2.025 (1.680, 2.441)	<0.001	1.445 (1.182, 1.768)	<0.001
Postoperative chemoradiotherapy (Yes)	1.004 (0.831, 1.212)	0.971		

CRC, colorectal cancer; BMI, body mass index; PNI, prognostic nutrition index.

nomogram we constructed had good predictive accuracy in predicting the prognosis of CRC patients.

We compared our nomograms with traditional TNM stage system through time-dependent ROC. The results showed that compared with TNM stage, our nomogram had better resolution and accuracy in predicting PFS (**Supplementary Figures S7A,B**) and OS (**Supplementary Figures S7C,D**) at 3- and 5- year. In addition, the DCA showed that when the threshold probability of predicting 3- and 5-year PFS was between 10 and 57% and 10 and 76%, respectively, the PFS nomogram showed a net benefit superior to the TNM stage system (**Supplementary Figures S8A,B**). Similar results also appeared on the OS nomogram, when the threshold probability of OS prediction at 3- and 5- year is 10–50% and 10–66%, respectively, the OS nomogram showed a net benefit superior to TNM stage (**Supplementary Figures S8C,D**). The above results indicated that compared with the traditional TNM stage system, the PNI-based nomograms could obtain higher net benefit within a larger threshold probability range.

DISCUSSION

Tumor inflammatory microenvironment plays an important role in cancer progression (14). Virchow et al. first detected the presence of tumor-infiltrating lymphocytes in 1,881 and speculated that the occurrence of tumors might be related to inflammation (15). Hanahan et al. (16) further found that immune and inflammatory cells were an important part of the tumor microenvironment, they could produce cytokines and chemokines through autocrine and paracrine ways to influence tumor growth. Recently, a variety of prognostic indicators based on cancer-related inflammation have been developed to predict surgical risk and tumor prognosis (17, 18). PNI, established by Onodera et al. (19), is a simple and easy parameter to reflect the immune and inflammatory status and has been proved to be

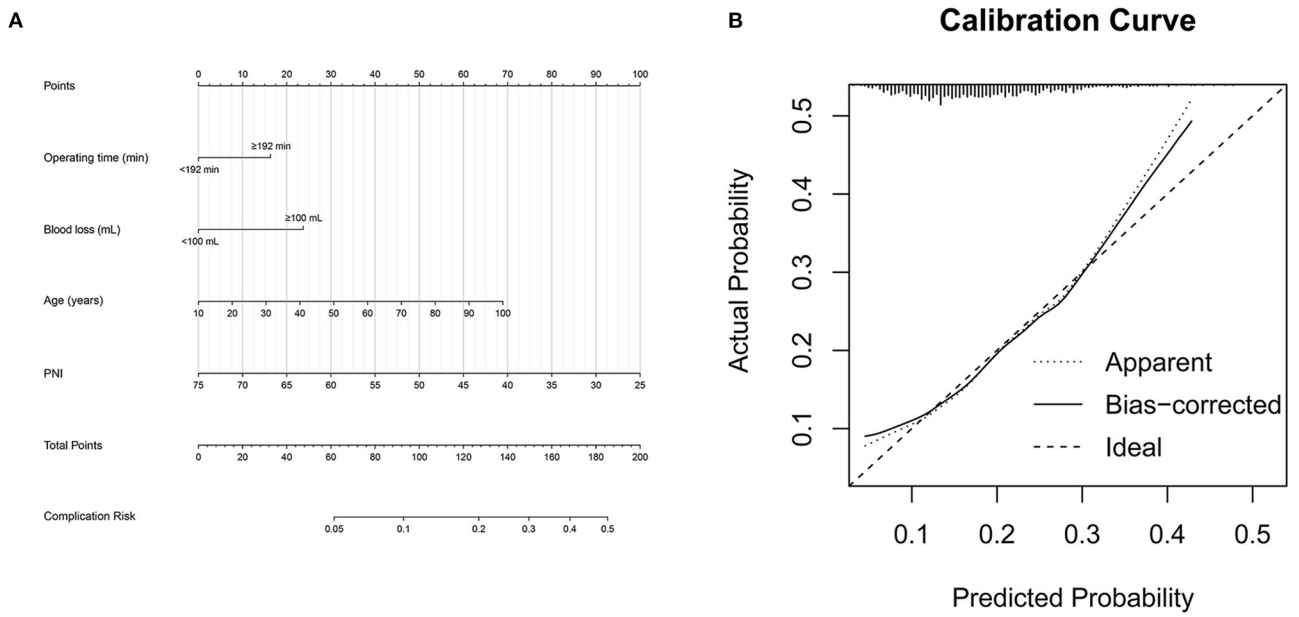

FIGURE 3 | Construction a novel complication nomogram model. **(A)** Complication nomogram; **(B)** calibration curve of complication nomogram.

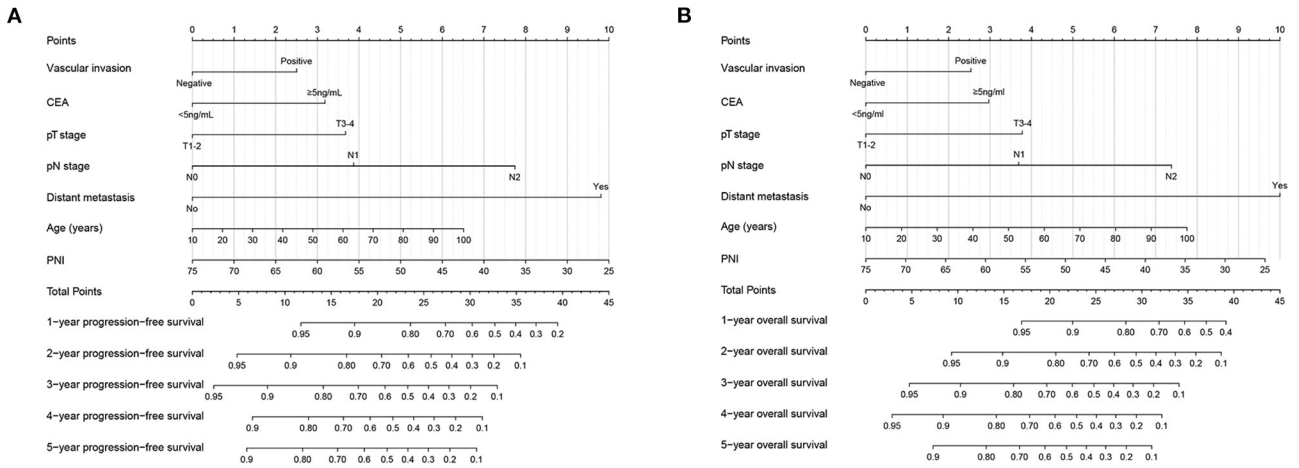

FIGURE 4 | Construction the novel prognostic nomograms in CRC patients. **(A)** PFS nomogram; **(B)** OS nomogram.

an effective prognostic indicator for various malignancy (7–9). The latest research suggested that serum albumin was associated with systemic inflammation. The decrease in serum albumin may be the result of the combined effect of the liver reordering of protein synthesis in the body under high inflammation and the redistribution of albumin inside and outside blood vessels (20). In addition, hypoalbuminemia reflects malnutrition and impaired immune response of patients, which is associated with increased disease severity, high risk of progression, and low survival (21, 22). Lymphocytes play a vital role in cancer immune monitoring, which can inhibit the proliferation and growth of tumor cells by mediating cytotoxic cell death (6). It has been reported that a low peripheral lymphocyte may indicate an inadequate immune response to tumor, which will create a favorable microenvironment for tumor recurrence and lead to poor prognosis (23). Therefore, the PNI can reflect not only the nutritional status of patients, but also the cancer-related immune inflammatory response.

In this study, we demonstrated that preoperative PNI was a useful predictor of postoperative complications and long-term outcome in CRC patients. We found that low PNI was associated with high tumor burden, invasive pathological features, and poor host status, which was consistent with a number of previous studies (10, 24, 25). Notably, PNI was

significantly associated with CEA and TNM stage, suggesting that PNI has similar prognostic value to CEA and TNM stage. That is, PNI calculated based on routine preoperative laboratory data has great potential as a predictor of CRC invasion potential. In addition, we found that PNI was superior to conventional prognostic indicators of inflammation in predicting the prognosis of CRC patients. Malnutrition and hyper-inflammatory status increase the risk of postoperative complications in CRC patients. In our study, approximately 17.8% of CRC patients had postoperative complications of varying degrees. The rate of postoperative complications in the low PNI group reached 24.6%, while that of the high PNI group was only 14.4%. Thus, patients with low PNI were more prone to postoperative complications. In addition, multivariate analysis showed that low PNI was an independent risk factor for postoperative complications in CRC patients. Studies have shown that postoperative complications have a negative impact on the survival of patients, and the severity of complications is related to the survival time of patients with malignancy (26, 27). This may be due to the complications enhance the systemic inflammatory response (28). Perioperative immunonutritional support can reduce postoperative complications in malnourished patients (29, 30). We constructed a simple and effective complication prediction nomogram based on risk factors identified in multivariate analysis, which can provide a scientific basis for the implementation of nutritional support.

The TNM staging system is currently recognized as the most effective tool for predicting disease progression and designing treatment strategies in CRC patients. However, it has been reported that patients with the same TNM stage may still have different clinical outcomes (31). In this study, PNI could effectively stratify the prognosis of CRC patients in each stage, which showed PNI could be used as a useful supplement to TNM stage. In addition, compared with early CRC patients, PNI could more effectively stratify the prognosis of advanced CRC patients. This may be related to the following reasons: advanced tumor have a higher tumor load and are more prone to proliferation, invasion, and neovascularization, leading to high systemic inflammation. In addition, patients with advanced tumors are prone to obstruction, bleeding, and reduced food intake, which leads to decreased nutritional status. In summary, we believed that preoperative PNI is a reliable, objective, reproducible and cheap predictive indicator for CRC patients undergoing surgical treatment, and can be considered as a routine clinical application.

For convenient and intuitive use in clinical practice, we constructed novel and effective prognostic nomograms for personalized prognostic evaluation in CRC patients. These nomograms have the advantage of integrating personal conditions, tumor characteristics, serum tumor markers and nutritional and immune inflammatory-related markers. Compared with TNM stage, the nomograms have better resolution and accuracy in predicting the 3- and 5-year PFS and OS of CRC patients. These nomograms can help to develop individualized risk stratification, individualized follow-up, and treatment strategies for CRC patients. These models can directly help clinicians quantify the prognostic risk of CRC patients, thus making it easier to formulate appropriate treatment strategies for CRC patients.

This study demonstrated that PNI was a useful indicator for predicting postoperative complications and long-term prognosis of CRC patients. Different from previous studies, we evaluated the prognostic value of PNI in CRC patients from multiple perspectives, including postoperative complications, hospital stay, PFS and OS, which provided a favorable reference for comprehensively evaluating the prognostic value and clinical application prospects of PNI in CRC patients. In addition, we have constructed PNI-based nomograms, which can be more personalized and convenient to use in clinical practice. In the era of precision medicine, individualized and specific management of patients is required. These analyses may provide further insights for the nutritional or immunological evaluation of CRC patients. However, there are some limitations to our study. First, this was a retrospective single-center study, so further validation of our results in a large sample, prospective cohort is needed in the future. In addition, since preoperative PNI was assessed only at a single time point, it failed to reflect the impact of PNI trajectory changes on prognosis, which requires further exploration in future studies. Finally, due to the limited samples, PNI-based nomograms could not be further validated. In the future, we expect to be able to further validate the accuracy of nomograms we constructed in large samples and multiple centers.

CONCLUSION

This study demonstrated that PNI was an independent risk factor affecting postoperative complications, PFS and OS in CRC patients, and was a useful supplement to the TNM stage. PNI-based nomograms had good predictive accuracy and could be used to individually assess the prognosis 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 author.

ETHICS STATEMENT

This research strictly complied with the provisions of the Helsinki Declaration and was approved by the institutional review boards of the participating institution.

AUTHOR CONTRIBUTIONS

JG conception and design. JG and ST management support. HX, GY, and ML data collection. HX data analysis and professional drafting. HX and LW manuscript writing. All authors agreed to

publish. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.794489/full#supplementary-material

Supplementary Figure S1 | The optimal cutoff value of PNI was determined by optimal stratification method.

Supplementary Figure S2 | Box plot of clinicopathological features based on low and high PNI group. The boxplots show the 5 and 95% confidence intervals. The box plot lower extreme is the first quartile and the box plot upper extreme is the third quartile. Box plots show the median and whiskers are the minimum and maximum, respectively. The statistical method used for each group was the student's *t*-test. $p > 0.05$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Supplementary Figure S3 | Postoperative complication rate and hospital stay according to preoperative prognostic nutritional index categories.

Supplementary Figure S4 | Subgroup survival analysis based on various clinicopathological features. **(A)** Subgroup PFS analysis; **(B)** Subgroup OS analysis.

Supplementary Figure S5 | Comparison of the ability of PNI and other prognostic indexes in predicting prognosis of CRC patients using ROC curves. **(A)** PFS at 3-year point; **(B)** PFS at 5-year point; **(C)** OS at 3-year point; **(D)** OS at 5-year point.

Supplementary Figure S6 | Calibration curve of novel complication nomograms. **(A)** 3-year PFS; **(B)** 5-year PFS; **(C)** 3-year OS; **(D)** 5-year OS. The X axis presents the predicted probability and the Y axis shows the actual probability. The calibration lines fit along with the 45°reference.

Supplementary Figure S7 | Comparison of the ability of novel prognostic nomograms and TNM classification in predicting prognosis at 3-year and 5-year point. **(A)** 3-year PFS; **(B)** 5-year PFS; **(C)** 3-year OS; **(D)** 5-year OS.

Supplementary Figure S8 | Decision curve analyses of novel prognostic nomograms and TNM classification for **(A)** 3-year PFS; **(B)** 5-year PFS; **(C)** 3-year OS; and **(D)** 5-year OS.

Supplementary Table S1 | Details of postoperative complications according to modified Clavien grading system.

Supplementary Table S2 | Univariate and multivariate Logistic regression analysis of complications in CRC patients.

Supplementary Table S3 | The association between prognostic nutritional index and hazard ratio of CRC patients.

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Comparison of the Index of Nutritional Quality in Breast Cancer Patients With Healthy Women

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Background: The index of nutritional quality (INQ) is derived from the food frequency questionnaire (FFQ) and is a method of quantitative and qualitative analysis of diet. This study aimed to compare the INQ for different dietary components between breast cancer (BC) patients and healthy control.

Methods: This case-control study was performed on 180 women with BC and 360 healthy women. Data on general characteristics, medical history, anthropometric indices, physical activity, alcohol consumption, reproductive history, smoking, and dietary intake were collected. A valid FFQ was used to assess the intake of nutrients and the INQ was calculated based on the daily intake of the nutrients.

Results: There was a significant association between BC and INQ of vitamin A (OR = 0.07, 0.01–0.29), vitamin E (OR = 0.43, 0.20–0.93), vitamin B6 (OR = 0.003, 0.000–0.021), riboflavin (OR = 0.25, 0.11–0.59), vitamin K (OR = 0.58, 0.37–0.90), biotin (OR = 0.07, 0.02–0.26), vitamin B12 (OR = 0.32, 0.18–0.56), vitamin C (OR = 0.72, 0.55–0.95), zinc (OR = 0.020, 0.005–0.083), calcium (OR = 0.14, 0.04–0.54) and magnesium (OR = 0.003, 0.000–0.024). Further adjustment for BMI disappeared the association between INQ of vitamin C and BC. The results did not change after further adjustments for waist circumstance and total calorie intake

Conclusion: A significant association was observed between BC and the INQ of vitamin A, vitamin E, vitamin B6, riboflavin, vitamin K, biotin, vitamin B12, vitamin C, zinc, calcium, and magnesium. The INQ can be used as an indicator in assessing clinical nutrition-related problems. Future longitudinal studies are needed to confirm these results.

Keywords: breast cancer, dietary intake, the index of nutritional quality, cancer, breast

INTRODUCTION

BC is the most frequent cancer among women with an estimated. 2 million new cancer cases diagnosed in 2018 (23% of all cancers) and ranks second overall (10.9% of all cancers). Up to 15 million people were diagnosed with BC by 2020 (1). BC accounts for 23% of all gynecological cancers worldwide (2) and a recent study indicated that incidence and mortality rates of breast cancer are rising (3). In 2008, there were 8 million deaths from malignant diseases, which is estimated to reach 11 million by 2030 (4). BC is influenced by genetics, lifestyle, and environmental factors (1, 2, 4).

Lifestyle including physical activity and nutrition play an important role in cancer. Overweight and obesity were reported to be associated with a higher risk of BC in postmenopausal women (5–7). Higher intakes of saturated fatty acids (8) and alcohol consumption (5, 9) are reported to be associated with an increased risk of BC. On the other hand, a low-fat diet was associated with a 9% reduction in the risk of BC (1). The Mediterranean diet, which is low in red meat and high in fruits and vegetables, is associated with a moderate reduction in the risk of BC in postmenopausal women (10–12).

Some studies reported the positive effect of diets rich in antioxidants, including vitamin E, vitamin A, beta-carotene, vitamin C, folate, unsaturated fatty acids, carbohydrates, vitamin D, carotenoids, phytoestrogens, and fiber on BC. Women who received a healthier diet including antioxidants and low-fat milk were less likely to develop BC than women with a higher intake of fat and red meat (5, 13, 14). A healthy eating pattern with plenty of unrefined grains, vegetables, fruits, nuts, and olive oil and moderate to low intake of saturated fatty acids and red meat may improve overall survival after BC diagnosis. An improper and unbalanced diet increases the risk of BC and nutritional intervention in patients with BC may be an integral part of the treatment approach. Nutritional counseling and supplements may be helpful in reducing BC development (15). However, some studies found no association between nutritional status and BC (16).

Many studies were carried out on the association of dietary components and BC. However, the effect of dietary components in comparison with the recommended dietary allowance (RDA) on the BC risk is not clear. Nutritional quality of diet plays an important role in controlling BC. (INQ) provides a comprehensive list of nutritional components and is a way to qualitatively analyze individual foods, meals, and diets (14, 17). The INQ is derived from a food frequency questionnaire (FFQ) that reflects the frequency of foods received in the past year (18). Few studies with small sample sizes and without adjusting calorie intake were done on the association of INQ and BC (14, 19). So, the aim of this study was to compare the INQ between women with BC and healthy women.

Abbreviations: FFQ, Food frequency questionnaire; INQ, index of nutritional quality; BC, breast cancer; BMI, body mass index; WC, waist circumstance; RDA, Recommended Dietary Allowance; DRI, Dietary Reference Intake.

METHODS

Participants

This case-control study was performed in September 2020 on 180 women with BC and 360 healthy age-matched women referred to the cancer clinic of Shohadaye Tajrish Hospital in Tehran, Iran. Inclusion criteria for the case group were women with BC, age between 35 and 65 years, no more than 1 month after diagnosis of BC, no diseases affecting food intake, and no antioxidant supplements intake. Inclusion criteria in the control group were aged between 35 and 65 years, no more than 1 month after the first diagnosis of BC (regardless of severity and stage of BC), no disease affecting food intake, no use of antioxidant supplements and be Do not have any cancer. Exclusion criteria were the inability to collect the required information and any disease that may affect the diet such as liver disease and diabetes. The written informed consent forms were obtained from all participants prior to the study.

Data on age, demographic characteristics, medical history, daily physical activity (using international physical activity questionnaire), alcohol consumption, reproductive history, smoking, and level of education were collected. Anthropometric indices, including weight, height, body mass index (BMI), and waist circumstance (WC) were measured.

Dietary Intake

A validated semi-quantitative FFQ was used to assess dietary intake over the past year through face-to-face interviews by a trained nutritionist (20). The FFQ can provide useful information about individual food intake over a period of one year (19, 21). All data obtained from FFQ was converted to grams and dietary data were analyzed using Nutritionist IV software.

INQ was used as a tool designed to assess dietary patterns, including an algorithm that represents the properties of micronutrients and macronutrients and shows the weight coefficients of the epidemiological relationship between nutrients and health outcomes. The components of the algorithm indicated the overall quality of nutrition as follows: Nutrients including vitamin A, vitamin D, vitamin C, vitamin E, vitamin B12, vitamin B6, potassium, calcium, zinc, omega-3 fatty acids, magnesium, selenium, vitamin B5, biotin, niacin, thiamin, riboflavin, iron, total carotenoids, and total bioflavonoids were included. The denominator of the fraction included saturated fatty acids, trans fatty acids, sodium, sugar, and cholesterol. All the nutrients were weighed according to the effect on health, according to the available data. The correlation between INQ scores and the average ranking of foods was evaluated and its validity was confirmed (22).

The INQ of each nutrient was assessed based on the Recommended Dietary Amount (RDA) or Adequate Nutrition (AI) using the following formula: INQ is equal to the amount of nutrient consumed per 1,000 kcal/RDA or AI of that nutrient per 1,000 kcal. Then, the information obtained from the FFQ was analyzed to calculate the average daily consumption of energy and nutrients, and the INQ was calculated based on the daily nutrient intake (23).

TABLE 1 | Distribution of characteristics across cases and controls ($n = 540$).

	Controls ($n = 360$)		cases ($n = 180$)		*P*-Value
	Mean ± SD	Min–max	Mean ± SD	Min–max	
Age (year)	58.3 ± 9.7	33–99	49.9 ± 9.4	38–99	0.27
Body mass index (BMI)	27.2 ± 4.4	20.5–43.1	29.2 ± 4.2	17.3–41.7	0.001
Pregnancy numbers	3.7 ± 1.9	0–12	2.9 ± 1.8	0–8	0.001
Abortion numbers	0.45 ± 0.70	0–4	0.38 ± 0.73	0–3	0.32
Breastfeeding duration	59.7 ± 33.5	0–188	33.8 ± 29.4	0–126	0.001
Menopause age	47.1 ± 5.8	30–59	47.3 ± 5.8	38–55	0.88

TABLE 2 | Dietary intake of breast cancer patients and control groups.

	Cases ($n = 180$)		Controls ($n = 360$)		*P*-Value
	Mean ± SD	Min–max	Mean ± SD	Min–max	
Total energy intake (Kcal/day)	2737 ± 925.3	963.3–7684	2315 ± 1066	946.2–4989	0.011
Protein (gram/day)	86.6 ± 41.5	36.5–370.4	84.9 ± 41.7	31.2–255.2	0.80
Carbohydrate (gram/day)	402.1 ± 124.6	119.0–792.6	311.7 ± 170.2	100.8–776.6	0.001
Total fat (gram/day)	92.9 ± 42.2	38.9–325.8	93.3 ± 52.8	27.7–244.7	0.95
Cholesterol intake (milligram/day)	242.1 ± 130.1	59.4–895.5	232.7 ± 161.8	13.2–1124	0.70
Saturate fatty acid (gram/day)	29.3 ± 18.9	10.1–169.0	25.2 ± 13.0	9.1–78.9	0.14
MUFA (gram/day)	30.5 ± 13.3	12.5–78.9	35.1 ± 24.5	9.1–152.7	0.15
PUFA (gram/day)	19.4 ± 8.5	7.3–47.9	19.0 ± 12.3	4.6–60.4	0.82
Sodium (milligram/day)	5661 ± 2559	1688–15375	4935 ± 4288	300.5–21467	0.20
Potassium (milligram/day)	4083 ± 1829	1120–14726	4635 ± 4909	1115–38778	0.34
Vitamin A (microgram/day)	485.1 ± 265.0	105.7–1696	876.8 ± 1950	77.5–15636	0.11
Beta-carotene (microgram/day)	3116 ± 1967	644.8–12144	7271 ± 23168	220.6–184065	0.15
Vitamin C (milligram/day)	150.7 ± 113.9	18.9–938.5	217.9 ± 278.6	11.1–1649	0.07
Calcium (milligram/day)	1277 ± 1011	427.8–9467	1198 ± 674.1	94.1–4462	0.56
Iron (milligram/day)	19.7 ± 6.4	5.9–41.5	15.4 ± 12.1	3.6–83.0	0.011
Vitamin D (microgram/day)	1.05 ± 0.84	0.01–3.5	1.79 ± 1.56	0.11–7.6	0.001
Vitamin E (milligram/day)	17.7 ± 11.4	5.3–66.2	17.4 ± 11.6	3.9–82.2	0.91
Thiamin (milligram/day)	2.3 ± 0.9	0.7–6.8	1.5 ± 0.7	0.3–4.2	0.001
Riboflavin (milligram/day)	2.3 ± 1.4	0.9–12.3	2.1 ± 1.3	0.5–10.5	0.57
Niacin (milligram/day)	24.3 ± 7.9	9.9–51.8	18.2 ± 9.2	4.9–44.6	0.001
Pyridoxine (milligram/day)	1.8 ± 0.7	0.8–6.7	2.1 ± 1.2	0.6–7.9	0.11
Acid folic (microgram/day)	673.5 ± 205.2	230.1–1289	465.4 ± 308.7	166.5–1782	0.001
Vitamin B12 (microgram/day)	4.0 ± 3.7	0.6–32.8	4.6 ± 3.1	0.7–17.5	0.19
Zinc (milligram/day)	11.3 ± 6.0	4.1–44.5	12.8 ± 6.9	4.7–35.5	0.18
Manganese (milligram/day)	5.7 ± 2.6	2.1–23.1	4.9 ± 3.7	1.1–25.1	0.09
Selenium (microgram/day)	98.7 ± 40.8	28.4–283.4	82.6 ± 41.7	25.9–300.6	0.01

Statistical Analysis

Independent *t*-test and Chi-square methods were used to compare the quantitative and qualitative variables between the two groups, respectively. Logistic regression was used to investigate the relationship between dietary antioxidant index and BC after adjusting for age (model 1), age and BMI (model 2), and age, BMI, WC, and total energy intake (model 3). First, the FFQ Half was completed through interviews. All statistical analyses were performed using SPSS software (version 21) and $P < 0.05$ was considered significant.

RESULTS

Significant differences were found between healthy women and women with BC in body mass index (27.2 ± 4.4 vs. 29.2 ± 4.2 m/h^2, $p = 0.001$), pregnancy numbers (4 ± 1.9 vs. 3 ± 1.8, $p = 0.001$), and breastfeeding weeks (59.7 ± 33.5 vs. 33.8 ± 29.4, $p = 0.001$) (**Table 1**).

Regarding to dietary intake, women with BC had higher intake of calorie (2737 ± 925.3 vs. 2315 ± 1066 Kcal/d, $p = 0.01$), carbohydrate (402.1 ± 124.6 vs. 311.7 ± 170.2 g/d, $p = 0.001$), iron (19.7 ± 6.4 vs. 15.4 ± 12.1 mg/d, $p = 0.01$), thiamin (2.3 ±

TABLE 3 | Comparison of the index of nutritional quality (INQ) of breast cancer patients and control group.

	Cases (n = 180)	Controls (n = 360)	P-value
	Mean±SD		
Vitamin A	0.45 ± 0.20	0.87 ± 1.41	0.02
VitC (mg)	1.41 ± 0.93	2.11 ± 2.12	<0.01
Fe (mg)	0.82 ± 0.16	0.71 ± 0.30	<0.01
VitD	0.05 ± 0.04	0.11 ± 0.08	<0.01
VitE (mg)	0.86 ± 0.44	1.03 ± 0.45	0.03
VitK	1.03 ± 0.42	3.07 ± 2.89	0.15
Thiamin (mg)	1.57 ± 0.34	1.25 ± 0.35	<0.01
Riboflavin (mg)	1.49 ± 0.29	1.79 ± 0.72	<0.01
Niacin	1.29 ± 0.26	1.15 ± 0.34	<0.01
B5	0.76 ± 0.16	1.05 ± 0.25	<0.01
Biotin	0.75 ± 0.22	0.96 ± 0.34	<0.01
VitB6 (mg)	0.88 ± 0.15	1.22 ± 0.38	<0.01
Folate (mcg)	1.25 ± 0.25	0.97 ± 0.29	<0.01
VitB12 (mcg)	1.13 ± 0.55	1.91 ± 1.61	<0.01
Magnesium (mg)	0.86 ± 0.15	1.17 ± 0.57	<0.01
Zinc (mg)	1.01 ± 0.25	1.40 ± 0.45	<0.01
Calcium (mg)	0.81 ± 0.22	0.97 ± 0.38	<0.01
Selenium (mcg)	1.31 ± 0.33	1.39 ± 0.58	0.34
Cu (mg)	0.47 ± 0.08	0.50 ± 0.23	0.31
Mn (mg)	2.41 ± 0.90	2.37 ± 1.19	0.85

0.9 vs. 1.5 ± 0.7 mg/d, $p = 0.001$), niacin (24.3 ± 7.9 vs. 18.2 ± 9.2 mg/d, $p = 0.001$), acid folic (673.5 ± 205.2 vs. 465.4 ± 308.7 μg/d, $p = 0.001$), and selenium (98.7 ± 40.8 vs. 82.6 ± 41.7 μg/d, $p = 0.01$), and lower intake of vitamin D (1.05 ± 0.84 vs. 1.79 ± 1.56 μg/d, $p = 0.001$) (**Table 2**).

Regarding to the INQ, women with BC had higher intake of iron (0.82 ± 0.16 vs. 0.71 ± 0.30 mg/d, $p < 0.01$), thiamine (1.57 ± 0.34 vs.1.25 ± 0.35 mg/d, $p < 0.01$), niacin (1.29 ± 0.26 vs.1.15 ± 0.34 mg/d, $p < 0.01$) and folate (1.25 ± 0.25 vs. 0.97 ± 0.29 μg/d, $p < 0.01$), and lower intake of vitamin A (0.45 ± 0.20 vs. 0.87 ± 1.41 μg/d, $p = 0.02$), vitamin C (1.41 ± 0.93 vs. 2.11 ± 2.12 mg/d, $p < 0.01$), vitamin D (0.05 ± 0.04 vs. 0.11 ± 0.08 μg/d, $p < 0.01$), vitamin E (0.86 ± 0.44 vs. 1.03 ± 0.45 mg/d, $p = 0.03$), riboflavin (1.49 ± 0.29 vs. 1.79 ± 0.72 mg/d, $p < 0.01$), vitamin B5 (0.76 ± 0.16 vs. 1.05 ± 0.25 mg/d, $p < 0.01$), biotin (0.75 ± 0.22 vs. 0.96 ± 0.34 mg/d, $p < 0.01$), vitamin B6 (0.88 ± 0.15 vs. 1.22±0.38 mg/d, $p < 0.01$), vitamin B12 (1.13 ± 0.55 vs. 1.91 ± 1.61 μg/d, $p < 0.01$), magnesium (0.86 ± 0.15 vs. 1.17 ± 0.57 mg/d, $p < 0.01$), zinc (1.01 ± 0.25 vs. 1.40 ± 0.45 mg/d, $p < 0.01$), calcium (0.81 ± 0.22 vs. 0.97 ± 0.38 mg/d, $p < 0.01$) (**Table 3**).

There were significant negative associations between BC and INQ of vitamin A (OR = 0.07, $p < 0.01$), vitamin E (OR = 0.43, $p = 0.03$), vitamin B6 (OR = 0.003, $p < 0.01$), riboflavin (OR = 0.25, $p < 0.01$), vitamin K (OR = 0.58, $p < 0.01$), biotin (OR = 0.07, $p < 0.01$), vitamin B12 (OR = 0.32, $p < 0.01$), vitamin C (OR = 0.72, p = 0.02), zinc (OR = 0.020, $p < 0.01$), calcium (OR = 0.14, $p < 0.01$) and magnesium (OR = 0.003, $p < 0.01$). The association between INQ of vitamin C and BC was disappeared after adjustment for BMI. The results did not change after further adjustments for WC and total energy intake (**Table 4**).

DISCUSSION

In the present study, a negative association was observed between BC and the INQ of vitamin A, vitamin E, vitamin B6, riboflavin, vitamin K, biotin, vitamin B12, vitamin C, zinc, calcium, and magnesium. Few studies were performed on the association between the INQ and different types of cancer. For example, one study found an inverse association between the INQ of vitamin A, vitamin D, and vitamin B6, and gastric cancer (19). The INQ is a simple method that can be used in the clinical evaluation of the dietary intake of the patients (14). Standard tools such as INQ may present a more accurate and functional comparison in the association between diet and health outcomes compared to the traditional assessment of dietary intake.

In the present study, energy and carbohydrate intake were higher in women with BC, which was in line with previous studies reporting that consuming more energy increased the risk of cancer by 60 to 70% (24). Many studies were performed on the association of BC and dietary macronutrients. For example, Seiri et al. reported a significant association between BC with dietary fat intake and animal protein (22). However, another study reported that total fat intake was not associated with BC while consuming more olive oil was associated with a reduced risk of BC (23). Another study found no association between overall carbohydrate intake and BC, but a high intake of sweets in sedentary women increases the risk of disease (25). The effects of different types of macronutrients on cancer risk may vary, with some macronutrients having a protective effect and some acting as a risk factor.

Regarding the association between BC and the intake of vitamins, there was a significant association between INQ of vitamin A, vitamin E, vitamin B6, riboflavin, vitamin K, biotin, vitamin B12, and vitamin C with BC. Different micronutrients play crucial roles in cell homeostasis and metabolism and should be received in the recommended amounts. Several studies reported that high consumption of fruits and vegetables reduces the risk of BC due to their antioxidant contents (25–27). For example, the consumption of tomatoes, which is a rich source of lycopene, beta-carotene, vitamin E, and other carotenoids was reported to reduce BC risk by reducing DNA damage and strengthening the immune system. Flavonoids in fruits and vegetables are capable to lower the risk of estrogen-related BC. In addition, a high intake of vitamin C was associated with a lower prevalence of BC in obese women (14, 25–27). Vitamin E induces cancer cell apoptosis that may have a role in the prevention of BC (28). Vitamin D status is also important for protecting against the progression of BC. The biologically active form of vitamin D interacts with the vitamin D receptor (VDR)coordinates the regulation of cancer cell proliferation, differentiation, and survival. So, vitamin D may act as a therapeutic agent for BC through binding and activating the VDRs (29, 30). The protective effect of high folate intake on the risk of BC is more important

TABLE 4 | The association between breast cancer and the index of nutritional quality (INQ).

	ORs and 95%CI	*P*-value[a]	ORs and 95%CI	*P*-value[b]	ORs and 95%CI	*P*-value[f]
INQ vitamin A	0.07 (0.01–0.29)	<0.01	0.06 (0.01–0.33)	<0.01	0.07 (0.01–0.35)	<0.01
INQ vitamin E	0.43 (0.20–0.93)	0.03	0.35 (0.14–0.84)	0.02	0.36 (0.14–0.87)	0.02
INQ vitamin B6	0.003 (0.000–0.021)	<0.01	0.005 (0.001–0.045)	<0.01	0.005 (0.001–0.046)	<0.01
INQ riboflavin	0.25 (0.11–0.59)	<0.01	0.28 (0.10–0.75)	0.01	0.29 (0.11–0.78)	<0.01
INQ vitamin K	0.58 (0.37–0.90)	<0.01	0.61 (0.39–0.95)	0.03	0.62 (0.40–0.97)	0.04
INQ biotin	0.07 (0.02–0.26)	<0.01	0.10 (0.02–0.47)	<0.01	0.11 (0.02–0.49)	<0.01
INQ vitamin B12	0.32 (0.18–0.56)	<0.01	0.33 (0.17–0.64)	<0.01	0.34 (0.17–0.66)	<0.01
INQ vitamin C	0.72 (0.55–0.95)	0.02	0.78 (0.58–1.04)	0.09	0.77 (0.58–1.03)	0.08
INQ zinc	0.020 (0.005–0.083)	<0.01	0.019 (0.003–0.098)	<0.01	0.017 (0.003–0.092)	<0.01
INQ selenium	0.69 (0.33–1.41)	0.31	0.68 (0.28–1.61)	0.38	0.74 (0.30–1.80)	0.51
INQ calcium	0.14 (0.04–0.54)	<0.01	0.11 (0.02–0.54)	<0.01	0.11 (0.02–0.54)	<0.01
INQ cupper	0.35 (0.04–2.9)	0.33	0.35 (0.03–4.2)	0.41	0.35 (0.03–3.9)	0.40
INQ magnesium	0.003 (0.000–0.024)	<0.01	0.003 (0.000–0.036)	<0.01	0.003 (0.000–0.033)	<0.01
INQ manganese	1.01 (0.75–1.4)	0.85	1.04 (0.72–1.49)	0.82	1.06 (0.74–1.54)	0.73

[a] *Age adjusted.*
[b] *Age and BMI adjusted.*
[f] *Age, BMI, WC, and total energy intake adjusted.*

in people who have enough vitamin B12. Folate is essential for nucleotide synthesis, DNA and RNA methylation, and the conversion of homocysteine to methionine by methionine synthetase, and the presence of vitamin B12 as a cofactor is essential for these reactions (31). Some studies found that excess folate stimulates existing neoplasms (32). In the present study, women with BC consumed higher folate than healthy women. Vitamin K3 was also reported to act as an anti-cancer agent against BC through the mitochondrial apoptosis pathway (33). In addition, in the present study, a negative association was found between INQ of vitamin B6 and BC. Vitamin B6 plays an important role in amino acid metabolism and reduces chronic inflammation. Vitamin B6 levels decrease with increasing levels of inflammatory markers such as interleukin-6, C-reactive protein, and the alpha tumor necrosis factor which are involved in cancer (19).

Regarding the association between BC and minerals, there was a significant association between BC and the INQ of zinc, calcium, and magnesium. Magnesium is involved in the metabolism of nucleic acids and impaired magnesium homeostasis may induce tumor progression (34). Zinc is vital for cell function and plays an important role in the etiology of cancer. It has many roles in the onset, progression, and termination of cancer. The interaction between zinc transporter and immune function may be a mechanism for the role of zinc in cancer (35). In one study, serum zinc levels were not associated with the severity of cancer, so more studies are required in this regard (36). In another study on BC patients, they had high serum levels of calcium, magnesium, iron, copper, manganese, and low levels of sodium, potassium, and arsenic (37).

Some studies failed to find any association between micronutrients and BC. Lazar et al. reported no significant association between vitamin C, vitamin A, vitamin E, selenium, and zinc with the risk of BC (38). The relationship between micronutrients and cancer may be affected by the amount of intake of that nutrient as well as the ratio between their intakes to the recommended amount of that nutrient. The INQ is a measure that compares the amount of intake with the dietary reference intake (DRI) of that nutrient. Interestingly, in the present study, vitamin D intake was significantly lower in BC patients. While vitamin D-related INQ was not associated with BC. According to the findings of the present study, there was no association between vitamin D and BC considering the currently recommended amounts of vitamin D. Higher amounts of vitamin D may be needed to have a preventative effect on BC.

On the other hand, dietary intake of folate, iron, and selenium was significantly higher in patients with BC compared to the healthy controls. However, the INQ levels of these two nutrients were not associated with BC risk. It can be inferred that considering the intake of nutrients may be misleading. The INQ compares the mean intake with the recommended amounts of the nutrients and can be preferred for a better understanding of the association between health outcomes and dietary components. Few studies were performed on the association between BC and the INQ. Vahid et al. found that there was an inverse relationship between INQs of vitamins A, C, B1, B2, B12 and selenium and BC risk (14) which was partially in line with the present study. However, this study was based on a smaller sample size compared to the present study which may have significantly influenced the association between INQ of some nutrients and BC.

However, this study had some limitations. Biochemical parameters such as Hb, Hct, MCV, MCH were not measured in the present study and the effects of the nutrients on these biomarkers are unknown. In addition, this case-control study was limited to BC patients, which makes it difficult to generalize the results to other cancers. This study focused on INQ, which is calculated based on DRI and cannot be used for nutrients or dietary components without DRI.

Future prospective studies with larger sample sizes on different cancers are warranted to evaluation the value of the INQ in determining the role of nutrients in reducing cancer risk. The advantage of using INQ is the adjustment of the amount of nutrients based on the amount of calories received and comparison them with the recommended amount of diet.

CONCLUSION

A significant relationship was observed between BC and INQ of vitamin A, vitamin E, vitamin B6, riboflavin, vitamin K, biotin, vitamin B12, vitamin C, zinc, calcium, and magnesium. The INQ can play an important role in the clinical evaluation of the dietary intake of the patients. The use of standard tools and indicators such as INQ compared to the traditional assessment of dietary intake may present a more accurate and functional comparison in the association between diet and different health outcomes. Future longitudinal studies are needed to confirm these results.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IR.MEDSAB.REC.1397.070. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG, SDo, and MEA designed the study involved in the data collection, analysis, and drafting of the manuscript. MB, MAf, MAh, FV, SA, SHD, and NM were involved in the design of the study, analysis of the data, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Prognostic Value of Geriatric Nutritional Risk Index in Esophageal Carcinoma: A Systematic Review and Meta-Analysis

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Esophageal cancer (EC) is one of the most common cancers worldwide. Malnutrition often leads to poor prognosis of patients with EC. Geriatric nutritional risk index (GNRI) was reported as an objective nutrition-related risk index. We intend to comprehensively review evidence of GNRI in predicting EC prognosis. To explore the influence of GNRI on the long-term survival outcome of patients with EC, a meta-analysis was needed. We searched the Web of Science, Medline, Embase, and the Cochrane Library databases. The association between prognosis of patients with EC and GNRI was evaluated by pooling hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). The fixed model or random model method was chosen according to the heterogeneity among the studies. Totally, 11 studies with 1785 patients who met the inclusion criteria were eventually included in our meta-analysis. Comparing the lower level GNRI group and the higher level GNRI group, the pooled results showed that lower GNRI had a negative impact on overall survival (OS) (HR: 1.75, 95% CI: 1.45–2.10, $P < 0.01$) and cancer-specific survival (CSS) (HR: 1.77, 95% CI: 1.19–2.62, $P < 0.01$), indicating that lower GNRI significantly predicted poor OS. In conclusion, lower GNRI could predict the poor prognosis of patients with EC. Meanwhile, more well-designed randomized controlled trials (RCTs) are needed to confirm the findings.

Keywords: geriatric nutritional risk index (GNRI), esophageal carcinoma (EC), prognostic, weight, meta-analysis

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INTRODUCTION

Esophageal cancer (EC) is the tenth most common malignant tumor and also one of the most common causes of cancer death worldwide (1). It consists of two main types of esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Despite advancement in therapies of EC, the 5-year post-esophagectomy survival rate is still low with only approximately 30% (2, 3). Since the symptoms of EC in the early stage are easy to be neglected, patients often lose the optimum opportunity to get surgical therapy, so the survival outcome of patients with EC remains unfavorable (4). In recent years, impaired baseline nutrition has been considered a prognostic factor of cancer, especially gastrointestinal tumors. Malnutrition is common, particularly, in patients with upper digestive tract malignancies due to nutrition loss, increased metabolic demands, and an insufficient oral intake (5). Remarkably, it is reported that 60–80% of patients with EC suffered

from malnutrition. Malnutrition is generally evaluated as low body mass index (BMI) and low level of serum albumin. Meanwhile, malnutrition is reported to be associated with poor short- and long-term clinical outcomes in patients with EC (6). Quantities of relevant studies have been conducted with mixed results. Therefore, the association between the overall survival (OS) of patients with EC and malnutrition remains still controversial.

Geriatric nutritional risk index (GNRI) was first proposed by Bouillanne et al. (7) in 2005, taking both serum albumin and the ratio of present body weight to ideal body weight into consideration. GNRI is regarded as a better indicator of nutrition-related outcomes better than serum albumin level and BMI alone in elderly patients. GNRI is calculated by the formula as follows: GNRI = (1.489 × albumin, g/L) + (41.7 × present/ideal body weight, kg) (7). It has been originally recommended for the assessment of patients, such as elderly patients with high risk for cardiovascular disease (8), hemodialysis (9), and chronic obstructive pulmonary disease (10). To date, several cohort studies but not meta-analysis studies have explored the relationship between GNRI and the OS of patients with EC. Therefore, this meta-analysis is needed to investigate the prognostic value of GNRI in patients with EC and to evaluate whether the GNRI could be used as a prognosis predictor in patients with EC.

MATERIALS AND METHODS

Search Strategies

Systematic literature retrieval of the Embase, Medline, Web of Science, and the Cochrane Library was performed till July 1, 2021, using the following search strategies and terms: (((((((esophagus [Title/Abstract]) OR esophageal [Title/Abstract]) OR oesophagus [Title/Abstract]) OR oesophageal [Title/Abstract])) AND (((tumor [Title/Abstract]) OR cancer [Title/Abstract]) OR carcinoma [Title/Abstract])) AND (((prognostic [Title/Abstract]) OR prognosis [Title/Abstract]) OR survival [Title/Abstract])) AND (GNRI [All Fields]).

Study Selections

The included standards were as follows: (1) study patients were pathologically confirmed EC without evidence of metastasis or recurrence; (2) observational studies or randomized controlled trials (RCTs) were eligible, which explored the effect of GNRI on the survival outcomes of patients with EC; (3) studies clearly illustrate the correlation between GNRI and survival outcomes of patients with EC; (4) the patients in studies had received treatment options such as surgery, radiotherapy, or chemotherapy; (5) the patients were grouped according to the level of GNRI; (6) papers published in English only; and (7) more than 5 points of Newcastle-Ottawa Scale (NOS) score were considered eligible for inclusion. The following studies were excluded: (1) patients with non-esophageal carcinoma; (2) article type such as case report, review, abstract, animal experiment, and conference report; (3) without sufficient data for meta-analysis; and (4) duplicated studies.

Data Extraction and Quality Assessment

Relevant data were extracted from included studies and compared results by two authors (JZ and PF) independently. Adjudication was performed by the third author (XL) to resolve discrepancies and avoid bias. A standardized data extraction

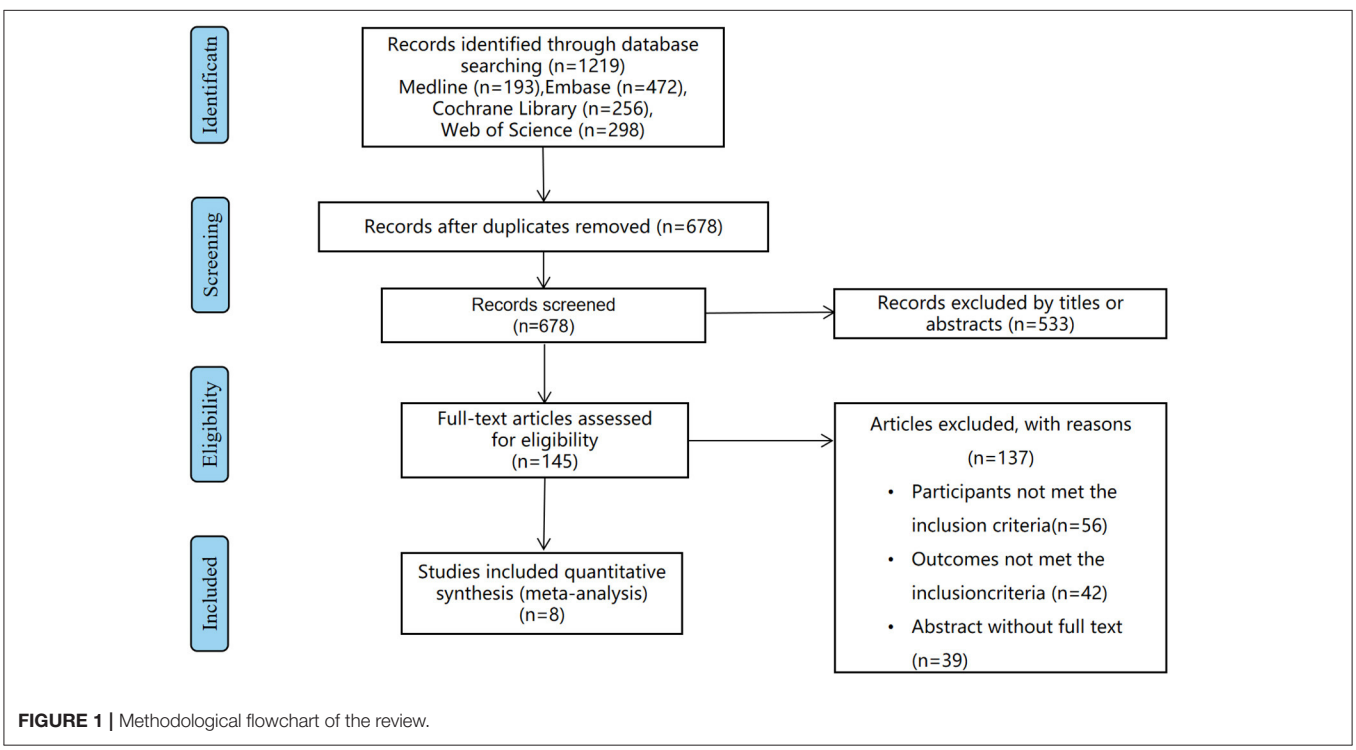

FIGURE 1 | Methodological flowchart of the review.

TABLE 1 | Main characteristics of all the studies included in the meta-analysis.

Study	Year	Population	No. (M/F)	Follow-up (months)	Treatment	Age (years)	Cut-off	Outcome	Stage	Type	HR	NOS score
Bo et al. (14)	2016	Chinese	207(130/77)	120	Radiotherapy	NR	92	OS	I-IV	ESCC	M	7
Bo et al. (14)	2016	Chinese	216(133/83)	120	Radiotherapy	NR	98	OS	I-IV	ESCC	M	7
Kubo et al. (17)	2018	Japanese	240(193/47)	60	Surgery + neoadjuvant therapy	63.4 ± 7.8	92	OS	I-IV	ESCC	M	7
Kubo et al. (17)	2018	Japanese	240(193/47)	60	Surgery + neoadjuvant therapy	63.4 ± 7.8	92	CSS	I-IV	ESCC	M	7
Migita et al. (18)	2018	Japanese	137(116/21)	60	Surgery + chemoradiotherapy	NR	98	OS	I-III	ESCC	M	6
Yamana et al. (21)	2018	Japanese	54(NR)	50	Surgery + neoadjuvant therapy	NR	92	OS	I-IV	ESCC	M	6
Yamana et al. (21)	2018	Japanese	162(NR)	50	Surgery	NR	92	OS	I-IV	ESCC	M	6
Wang et al. (19)	2019	Chinese	52(34/18)	60	Radiotherapy or definitive concurrent chemoradiotherapy	74 (70-83)	92	OS	I-IV	ESCC	M	6
Hirahara et al. (15)	2020	Japanese	191(169/22)	72	Surgery + adjuvant chemotherapy	NR	97.1	CSS	I-III	ESCC	M	7
Kouzu et al. (16)	2020	Japanese	128(113/15)	60	Surgery	73.2 ± 5.5	92	OS	I-IV	EC	U	6
Tan et al. (19)	2021	Chinese	158(126/32)	80	Surgery	70.7 ± 4.49	96.6	OS	I-IV	EC	M	6

OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio, "M" means the HR come from multivariate analysis, "U" means the HR comes from univariate analysis; NR, not reported; ESCC, esophageal squamous cell cancer; EC, esophageal carcinoma; NOS, Newcastle-Ottawa Scale.

procedure was used to retrieve the data from studies. The basic characteristics of studies, including author, publication year, number of the patients, age, study design, cutoff value, treatment, and survival outcomes, were extracted. The NOS (11) was utilized to evaluate the quality and risk-of-bias of observational studies, which consisted of the following three factors: selection of patients, comparability between the groups, and assessment of interesting outcomes. Studies were assigned using a score of 0–9 (allocated as stars), and we defined 0–3, 4–6, and 7–9 as low, medium, and high quality studies, respectively.

Statistical Analysis

Data analyses were based on STATA 12.0 package (StataCorp, College Station, TX, USA) in accordance with PRISMA guidelines (12). The survival outcome rate data were collected from the papers directly or Kaplan-Meier curves. Hazard ratio (HR) with a 95% confidence interval (CI) was adopted for the comparison. The heterogeneity of each study was evaluated by using a chi-square-based Q-test and the I^2 test. If low heterogeneity between studies ($P_Q > 0.05$, $I^2 < 50\%$) was observed, a fixed-effect model would be applied for analysis. Otherwise, random-effects models were used. Sensitivity analysis by sequentially removing one study at a time was performed. The potential publication bias was estimated by a funnel plot, and Begg's test was performed to assess the asymmetry. All P-values were two-sided. A P-value < 0.05 was considered statistically significant (13).

RESULTS

Characteristics of Studies

Based on the criteria mentioned earlier, the search results are shown in **Figure 1**. After the initial search, 1,219 articles were found through 4 databases after the removal of 541 duplicates. Then, there were 533 studies removed after reviewing titles and abstracts. Later, 137 articles were found not meeting the inclusion criteria by further full-text screening. Eventually, 8 articles (14–21) involving 11 studies, containing 1785 patients in total, were included in the meta-analysis. All the included studies had reported the cutoff point of the GNRI, with different fixed values as follows: 92, 96.6, 97.1, and 98. As for survival outcomes, HRs on OS, cancer-specific survival (CSS) could be extracted from 9 and 2 of these studies, respectively. Notably, 448 patients underwent surgery, 862 patients underwent surgery combing oncological treatment, and 475 patients underwent non-surgery treatment. Both patients included were from Asia, China, and Japan. More detailed information and basic characteristics of the included studies in this meta-analysis are summarized in **Table 1**. Based on the NOS, the included studies' scores ranging from 6 to 7, showing the qualities of these studies, were high, which are eligible for the subsequent analysis. In **Table 2**, we specified population, expose, comparison, and outcome (PECO) elements of each study and whether it is an observational study or a secondary observational study in an interventional study.

TABLE 2 | Abstract table summarizing PECO in the studies of GNRI.

Study	Population						Expose	Comparison	Outcome	Research type	NOS scores
	EC stage				Phase of GNRI assessment						
	I	II	III	IV	Pre-treatment	Post-treatment					
Bo et al. (14)	22	138	54	25		NR			OS	Observational study	7
Kubo et al. (17)	70	51	105	14		NR			OS	Observational study	7
Kubo et al. (17)	70	51	105	14		NR			CSS	Observational study	7
Migita et al. (18)	NR	NR	NR	NR	√				OS	Observational study	6
Yamana et al. (21)	NR	NR	NR	NR	√		Low GNRI	High GNRI	OS	Observational study	6
Wang et al. (20)	20		32			NR			OS	Observational study	6
Hirahara et al. (15)	73	41	77	NR		√			CSS	Observational study	7
Kouzu et al. (16)	70		58		√				OS	Observational study	6
Tan et al. (19)	NR	NR	NR	NR	√				OS	Observational study	6

PECO, population, expose, comparison, and outcome; OS, overall survival; CSS, cancer-specific survival; EC, esophageal carcinoma; GNRI, geriatric nutritional risk index; NR, not reported.

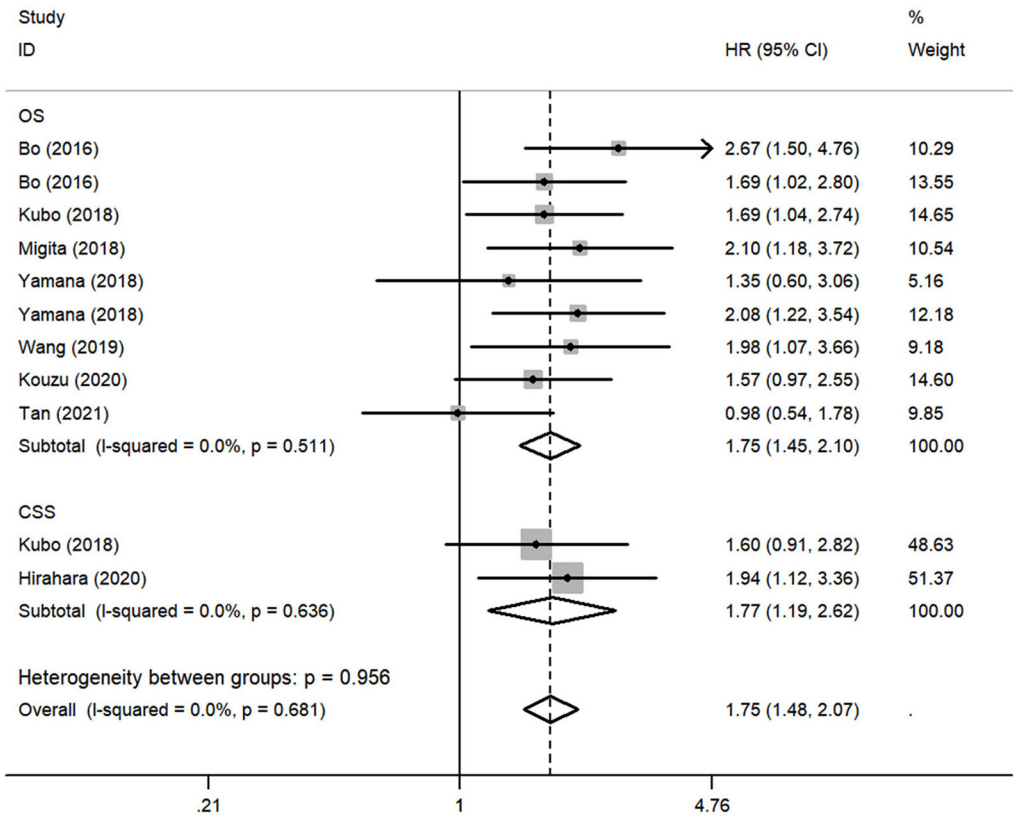

FIGURE 2 | Forest plot of pooled hazard ratio (HR) of geriatric nutritional risk index (GNRI) in predicting survival outcomes in esophageal cancer (EC).

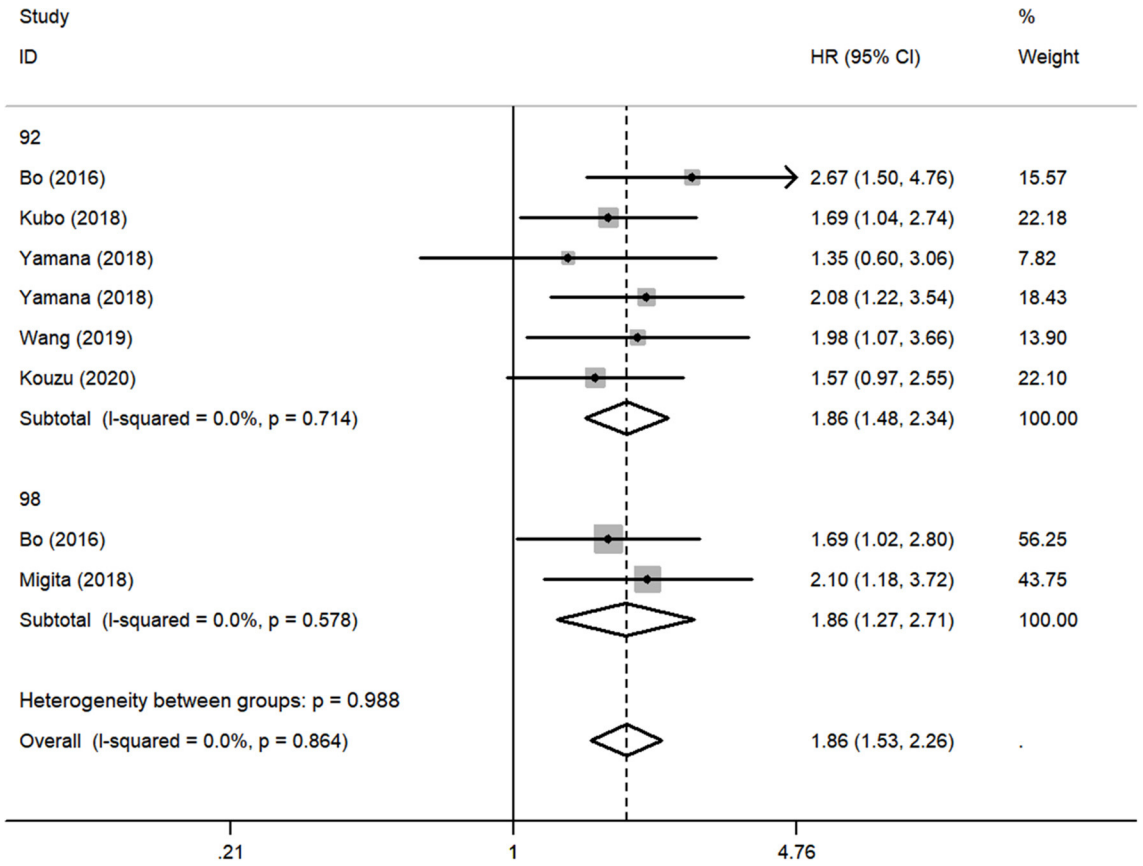

FIGURE 3 | Forest plot showing subgroup analysis of the selected studies about the prognostic significance of GNRI in patients with different cutoff values.

Meta-Analysis

To assess the impact of lower GNRI on OS, a fixed-effects model was conducted to analyze since the heterogeneity was non-significant (I^2 = 0.0%, P = 0.511). Totally, 9 studies contained a number of 1354 patients applying OS as the survival outcome. The pooled HR was 1.75 (95% CI: 1.45–2.10, P < 0.01) (**Figure 2**), indicating that patients with low GNRI had poorer OS than those with high GNRI. To investigate the correlation between GNRI and CSS, 2 studies with a total of 431 patients were included. Heterogeneity was acceptable in the analysis (I^2 = 0%, P = 0.636), a fixed-effects model was used, and the pooled HR was 1.77 (95% CI: 1.19–2.62, P < 0.01) (**Figure 2**), suggesting that low GNRI was significantly associated with worse CSS.

Although there was no obvious heterogeneity among the studies, we still conducted a subgroup analysis to achieve a deeper investigation. The criteria of the subgroups were as follows: cutoff value, therapeutic method, and population. In the subgroup of cutoff value, no heterogeneity was found in studies (I^2 = 0.0%, P = 0.714), and a fixed-effects model was applied to the analysis. We concluded that the low GNRI was significantly associated with the worse OS when the cutoff value was set as 92 (HR: 1.86, 95% CI: 1.48–2.34, P < 0.01). When setting the cutoff value as 98, the low GNRI was also associated with poorer OS (HR: 1.86, 95% CI: 1.27–2.71, P < 0.01), without any heterogeneity (I^2 = 0.0%, P = 0.578) (**Figure 3**). In the subgroup of patient treatment, low GNRI and poor OS were statistically significantly associated with patients who underwent surgical therapy (HR: 1.52, 95% CI: 1.12–2.07, P < 0.05; fixed-effects model), oncological treatment (HR: 2.04, 95% CI: 1.47–2.81, P < 0.05; fixed-effects model), and esophagectomy with oncological treatment (HR: 1.75, 95% CI: 1.25–2.45, P < 0.05; fixed-effects model) (**Figure 4**). In the subgroup of the population, we found that low GNRI significantly related to poor prognosis in both Chinese patients (HR: 1.72, 95% CI: 1.30–2.29, P < 0.01; fixed-effects model) and Japanese patients (HR: 1.77, 95% CI: 1.38–2.26, P < 0.01; fixed-effects model), and there was no heterogeneity in the data (**Figure 5**), so we used the fixed-effects model for analysis. These two subgroup analyses both observed that low GNRI was associated with poor OS regardless of population.

Two of the included studies had investigated the association between GNRI value and postoperative complication rate using odds ratio (OR). The ORs of Kubo et al. (17) and Migita et al. (18) were 1.467 (95% CI: 0.414–5.196, P = 0.550) and 1.660 (95% CI: 0.771–3.576, P = 0.196), respectively. The pooled OR was 1.606 (95% CI: 0.883–3.094, P = 0.157), which indicated that

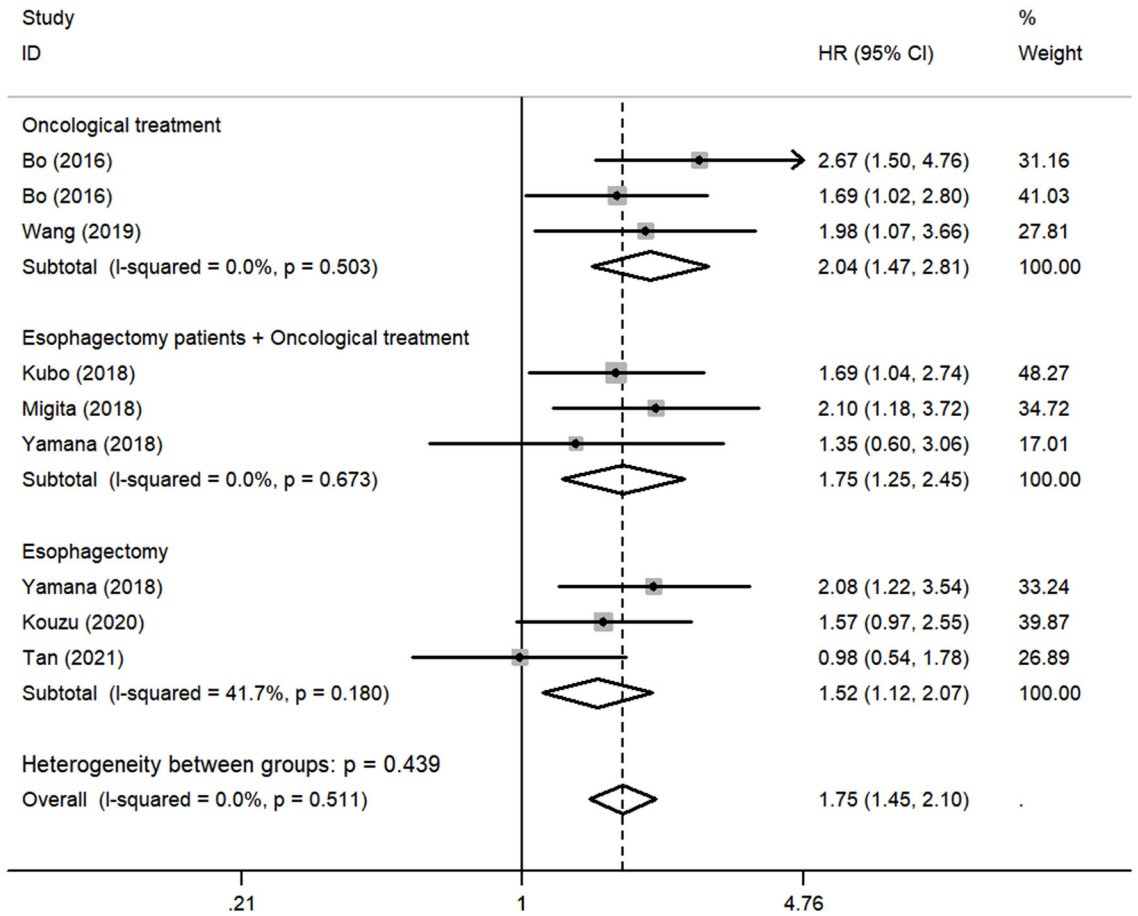

FIGURE 4 | Forest plot showing subgroup analysis of the selected studies about the prognostic significance of GNRI in patients with different treatments.

low GNRI does not increase the risk of postoperative complications (**Table 3**).

Sensitivity Analysis and Publication Bias

To assess the stability and reliability of the primary analysis, sensitivity analysis was utilized through sequential removal of each study. The result showed that the survival outcome of the prime analysis was not influenced by removing any single study, even when drawing the study with relatively low quality (**Figure 6A**). Moreover, the hidden publication bias was tested using Begg's test. A symmetrical appearance was checked in the funnel plot (**Figure 6B**). The *P*-value of Begg's test was 0.759. Therefore, no notable publication bias was found in the meta-analysis.

DISCUSSION

The nutritional risk index (NRI), combining serum albumin and BMI, was described by Buzby (22) for the first time. Patients with EC often have difficulty in per OS nutrition due to postoperative anastomotic stenosis, which is often accompanied by symptoms of malnutrition. The most common manifestations are weight loss and reduced albumin. However, a single nutritional index cannot fully reflect the nutritional status of patients with EC. Recently, various nutritional indexes [such as GNRI and skeletal muscle mass index (23)] have emerged in evaluating the nutritional status of patients with EC, which have better manifestation than traditional NRI. GNRI is a nutritional indicator combined with both serum albumin, present, and ideal body weight, which could accurately reflect the nutritional level of patients and provide more comprehensive nutritional support treatment, thereby improving the accuracy of predicting the prognosis of patients with EC (24). The index has been wildly applied to evaluate the malnutrition status and severity degree of postoperative complications of hospitalized adults. However, patients with EC, especially elderly patients, were usually suffering from malnutrition and weight loss due to insufficient nutritional intake (25). As a result, the concept of GNRI was introduced by Bouillanne et al. for the first time in 2005. GNRI was an omnibus index, which took ideal body weight into consideration at the basis of NRI. Therefore, GNRI was advantaged in evaluating the nutritional status of senile patients. The GNRI score was reported as an independent

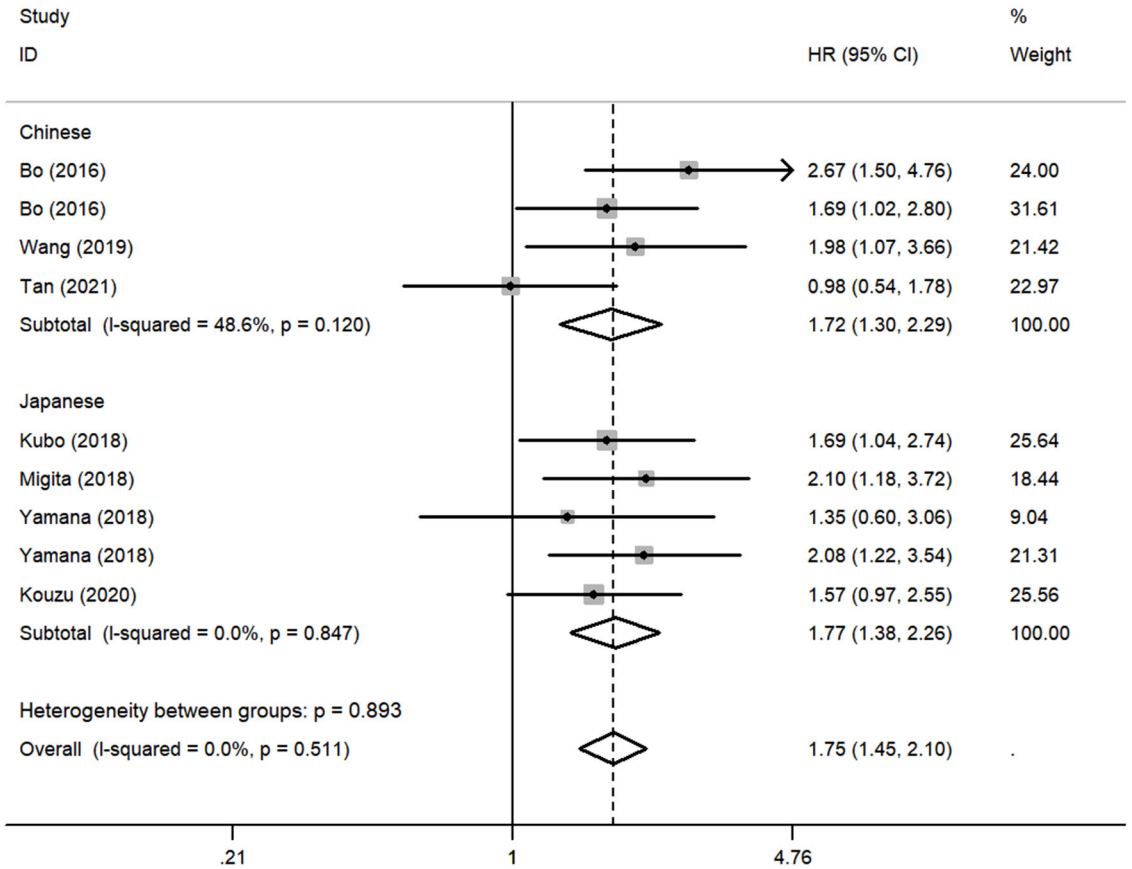

FIGURE 5 | Forest plot showing subgroup analysis of the selected studies about the prognostic significance of GNRI in patients with different populations.

TABLE 3 | The relationships between the GNRI and postoperative complication rate.

Study	Year	GNRI	
		OR (95%CI)	*P*
Kubo et al. (17)	2018	1.467 (0.414–5.196)	0.550
Migita et al. (18)	2018	1.660 (0.771–3.576)	0.196
Pooled OR		1.606 (0.883–3.094)	0.157

OR, odds ratio; GNRI, geriatric nutritional risk index.

indicator of morbidity and mortality in patients with chronic heart failure (26) and sepsis (27) in previous research. In recent years, GNRI was applied to predict the long-term outcomes of upper digestive cancer, such as EC and gastric cancer (28). For EC, the amount of study related to GNRI and OS was limited, and the predictive efficiency of GNRI was not clear. Thus, this meta-analysis was conducted to explore the influence of GNRI on the survival outcomes of EC. To the best of our knowledge, no meta-analysis of this topic has ever been performed before us.

We totally included 11 studies in this meta-analysis, containing 1785 patients. The cutoff value of GNRI in the studies was divided into two categories as follows: GNRI < 92 and GNRI > 98. Only two included studies of Hirahara et al. and Tan et al. set the cutoff value as GNRI $= 97.1$ and GNRI $= 96.6$, lacking studies setting GNRI in the same standard, and we did not include these two studies into subgroup analysis. According to the results of the cutoff value subgroup analysis, the pooled HR showed that a lower level of GNRI had a significant adverse influence on the OS of patients with EC. Meanwhile, we could easily get the same conclusion from the other two subgroups' results according to the pooled HRs. Bo et al. first conducted the study to explore the relationship between GNRI and 5-year OS of EC, indicating that higher HR was related to lower GNRI (1.69 for 92–98 vs. >98; 2.67 for <92 vs. >98) (14). Thereafter, several similar studies were carried out. In the study by Migita

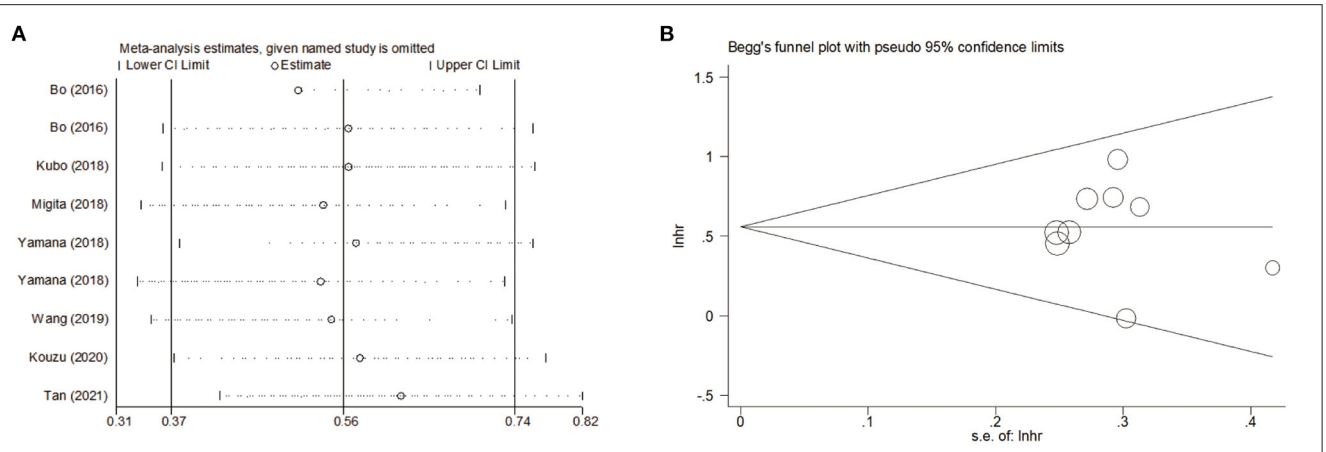

FIGURE 6 | (A) Sensitivity analysis for meta-analysis of GNRI. **(B)** Funnel plots of publication bias for meta-analysis of GNRI.

et al. (18), the HR was 2.10 with 95% CI 1.18–3.72 (<98 vs. >98). For the studies by Kubo et al. (17) and Yamana et al. (21), the HRs were 1.687 (95% CI: 1.038–2.742) and 1.35 (95% CI: 0.59–3.03). In addition, Hirahara et al. (15) used CSS as the survival outcome to evaluate the impact of GNRI on patients with EC in different EC stages. However, the sample sizes of the previous studies were not large enough. Thus, we pooled these studies into this meta-analysis. The result suggested that GNRI was potential to be a prognostic factor of long-term OS of patients with EC.

In past studies, low GNRI has been reported to be associated with the prognosis of colorectal cancer (29), non-small cell lung cancer (30), lymphoma, nasopharyngeal cancer (30), lymphoma, and nasopharyngeal cancer (31, 32). Consistently, our study confirms that GNRI is closely associated with the long-term prognosis of EC. Cancer-associated malnutrition plays an essential and multifaceted role in tumor progression. The exact mechanism between malnutrition and tumor in patients with EC was still undefined. However, it has increasingly been acknowledged that cancer-caused nutritional disorders, such as cachexia and sarcopenia (33, 34), are admitted to be irreversible outcomes of the interaction between host and tumor (35). Moreover, nutritional disorders caused by a tumor also raise the risk of infectious complications in surgery, weaken the efficacy of chemoradiotherapy, and increase the incidence of side effects of adjuvant therapy (36), which are closely related to the patient's prognosis.

This analysis had several limitations. First, no well-designed RCTs but only retrospective cohort studies were brought into the study, probably causing reduced statistical effectiveness. In addition, the total amount of patients in studies was only 1785, the remaining suffering from a limited sample size. Second, most included studies only focus on the OS. This may not comprehensively and systematically reflect the GNRI impact on EC prognosis. Other long-term results, such as recurrence-free survival (RFS), progression-free survival (PFS), and disease-free survival (DFS), should be taken into account. Third, the therapy strategies were not all the same in the included cohort studies, although no apparent heterogeneity was found. Fourth, most researchers have used different cutoff values in their studies to define the GNRI level, lacking uniform criteria for the cutoff value of GNRI in different studies. The pooled survival outcomes may deviate from the actual value. Finally, the patients' population was all from the Asian group; no western research was included, which may lead to a selection bias in the patients' races to some degree. Considering all the limitations listed above, which might affect the validity of the results, the conclusion is not persuasive enough and needs to be refined. Thus, more well-conducted studies with large sample sizes, especially RCTs, were urgently needed to confirm and update our conclusion. Meanwhile, the following studies should complete different survival outcomes, and patients from different races should also be included so that the subgroup analysis could better elucidate the correlation between GNRI and EC prognosis.

CONCLUSION

Overall, a lower level of GNRI was associated with poor survival outcomes. GNRI was a potential independent prognostic indicator for patients with EC. Meanwhile, more high-quality studies are needed to confirm the findings.

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.

AUTHOR CONTRIBUTIONS

YYu conceptualized the study, revised the manuscript, and supervised the study. JZ, PF, and XL conceptualized the study, drafted the manuscript, and made the figures. SL, XX, YG, QS, HZ, YYa, and XZ collected the literature and revised the manuscript. All authors contributed to this study and approved the submitted version.

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Association of Modified Geriatric Nutrition Risk Index and Handgrip Strength With Survival in Cancer: A Multi-Centre Cohort Study

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Background: This study aimed to explore the value of combining the modified geriatric nutrition risk index (mGNRI) and handgrip strength (HGS) in the prognosis assessment of cancer.

Methods: This multicenter, prospective cohort study, enrolled 5,607 cancer patients from 27 medical centers across 17 provinces in China between June 2012 and December 2019. The primary outcome was overall survival. Secondary outcomes included the Karnofsky Performance Scale (KPS) score, Patient-Generated Subjective Global Assessment (PG-SGA) score, cachexia, and admission 90-day outcome. A composite prognostic score (mGNRI-HGS score) was developed based on the mGNRI and HGS. The Kaplan–Meier method was used to draw the survival curve, and log-rank analysis was used to estimate the survival rate. The Cox proportional hazards model was used to investigate the associations of the mGNRI, HGS or mGNRI-HGS score with risk of mortality among the cancer patients, adjusted for potential confounders.

Results: A low mGNRI (HR = 0.99, 95%CI = 0.98–0.99, $p < 0.001$) and low HGS (HR = 0.99, 95%CI = 0.98–0.99, $p = 0.001$) were associated with an increased risk of mortality. A severe mGNRI-HGS score was independently associated with reduced survival. Compared with patients with normal scores, the risk of mortality among the patients with moderate and severe mGNRI-HGS scores was 28.8 and 13.3% higher, respectively. Even within the same pathological stage, it presented significant gradient prognostic stratification. Additionally, a low mGNRI-HGS score was also independently associated with a higher risk of low KPS ($p < 0.001$), high PGSGA ($p < 0.001$), cachexia ($p < 0.001$), and adverse admission 90-day outcome ($p < 0.001$).

Conclusions: The mGNRI and HGS may be useful predictors of long-term prognosis in cancer patients. The combination of the two methods provides effective prognostic stratification for cancer patients and could predict physical frailty, malnutrition, and cachexia.

Keywords: nutrition, inflammation, handgrip strength, cancer, prognostic, modified geriatric nutrition risk index

INTRODUCTION

Cancer is a heavy burden, with morbidity and mortality rapidly increasing worldwide. Currently, it is one of the leading global causes of death, with an estimated 19.3 million new cases and nearly 10 million deaths in 2020. Of these, China ranks first in cancer incidence, with about 4.57 million cases, and first in mortality, with approximately three million deaths (1). The incidence of cancer increases sharply with age. With China's population aging, the burden of cancer will increase correspondingly in the future (2, 3). Therefore, there is an urgent need to find effective, simple, and universal prognostic assessment tools for cancer to help formulate optimal treatment strategies.

Systemic inflammation caused by host-tumor interaction is closely related to the occurrence and development of cancer, and is considered the seventh marker of cancer (4, 5). Also closely related to the development and clinical outcome of the disease is nutritional status. Malnutrition can lead to disease progression and is a main reason for poor treatment effectiveness (6, 7). Recently, a C-reactive protein (CRP)-based modified geriatric nutrition risk index (mGNRI) was developed and proved to be an effective tool for predicting the clinical outcome of esophageal cancer (8). As a combined indicator of systemic inflammation and nutrition, the mGNRI has broad potential for assessing the prognosis of patients with cancer.

Hand grip strength (HGS) of the dominant hand is an economical and effective anthropometric measure of muscle function. Since 2018, the European Working Group on Sarcopenia in Older People (EWGSOP) has recommended HGS as an important indicator for defining sarcopenia in clinical practice (9). In addition, low HGS is recommended as the standard for the definition of cancer cachexia (10). Assessment of HGS provides significant additional prognostic information for patients with cancer, and reduced HGS is considered to be related to deterioration in patient survival (11, 12).

The prognostic value of a single indicator for patients with cancer is still limited, and the combination of multiple indicators may be a good direction for development. The mGNRI represents the inflammatory and nutritional status of patients, and HGS reflects their physical status. Whether the combination of the two can provide further prognostic and therapeutic guidance for cancer patients is unclear. Therefore, this study aimed to explore the value of combining the mGNRI and HGS as a prognostic tool for cancer patients and to provide reference values to optimize prognosis assessment and treatment strategies.

MATERIALS AND METHODS

Study Design and Population

This was a multicenter, prospective cohort study. The patients were part of the Investigation on Nutrition Status and its Clinical Outcome of Common Cancers (INSCOC) project, which included patients with cancer from 27 clinical medical centers across 17 provinces in China, from June 2012 to December 2019. In this study, eligible patients were 18 years of age and older with a histopathological or cytological diagnosis of cancer. We excluded patients who were admitted for <24 h, were younger than 18 years old, were unwilling or unable to participate because of cognitive impairment, or who did not have complete data available on CRP, albumin, height, weight, and HGS. The patients were prospectively followed up by professionals until the last follow-up date (30/10/2020) or the date of death for any reason, and the follow-up outcome was recorded in detail. Follow-up was performed through face-to-face inquiries or telephone interviews. All patient data were analyzed anonymously. All patients provided written consent. This study was approved by the ethics committees of all participating institutions.

Data Acquisition and Definitions

Baseline sociodemographic information was obtained by well-trained professionals when the patients were admitted to the hospital, including age, sex, smoking history, alcohol history, family history of cancer, comorbidities (hypertension and diabetes), and anthropometric measurements [height, weight, body mass index (BMI)]. Blood serological parameters collected at baseline included white blood cell (WBC), neutrophil, lymphocyte, platelet, and red blood cell (RBC) counts, hemoglobin (Hb), CRP, and serum albumin. All serological tests were performed within a week of admission. Tumor information included the tumor site and tumor-node-metastasis (TNM) stage (American Joint Committee on Cancer staging System, 8th Edition). Treatments included surgery, radiotherapy, and chemotherapy.

According to previous measurement methods (13). the electronic Hand Grip Dynamometer (CAMRY, Model EH101, Guagndong, China) was used to measure the HGS of dominant hands. The patients held the dynamometer with maximum strength with the dominant hand, the test was repeated three times, and the maximum HGS was recorded. The HGS of patients was measured before antitumor therapy. The GNRI was calculated using the following formula: 1.489 × albumin (g/dL) + 41.7 × present body weight (kg)/ideal body weight (kg). mGNRI was calculated as: (1.489 / CRP in mg/dL) + [41.7 × present body weight (kg)/ideal body weight (kg)]. Based on previous research, (14) the Lorentz formula was used to calculate the ideal body

weight, as follows: height (cm)-100—{[height (cm)−150]/4} for men and height (cm)-100—{[height (cm)−150]/2.5} for women. The current body weight/ideal body weight was considered to be 1 when the current weight exceeded the ideal weight (15).

The primary outcome was overall survival (OS), defined as the period from the date of pathological diagnosis of cancer to the date of death or the last follow-up. Secondary outcomes included the Karnofsky Performance Scale (KPS) score (≤70 indicating risk), the Patient-Generated Subjective Global Assessment (PG-SGA) score (≥4 indicating risk), cachexia, and admission 90-day outcome. The KPS and PG-SGA were assessed and recorded by trained staff at baseline. The diagnosis of cachexia was based on the internationally recognized definition and diagnostic criteria for cancer cachexia presented by Fearon et al. in the 2011 International Consensus on Cachexia (16), as follows: (1) weight loss >5% of starting body weight in the past 6 months without dieting; (2) BMI <20 kg/m^2 and any degree of weight loss >2%; or (3) Skeletal muscle depletion was evident, as estimated by the mid upper-arm muscle area (men: <32 cm^2, women: <18 cm^2). Patients meeting one or more of the above criteria were diagnosed with cancer cachexia. The admission 90-day outcome was defined as survival outcome within 90 days of hospitalization for anticancer therapy.

Statistical Analysis

Optimal stratification was used to determine the threshold of continuous mGNRI and GNRI using log-rank statistics. Given the significant difference in HGS between men and women, we used sex-specific optimal stratification to determine the optimal threshold of continuous HGS in men and women, respectively. The optimum thresholds for GNRI and mGNRI are 93 and 43, respectively (**Supplementary Figure S2**, GNRI, mGNRI). Low GNRI is defined as <93, while above 93 is considered a high GNRI. Low mGNRI is defined as <43, and an mGNRI above 43 is considered a high mGNRI. The sex-specific optimum thresholds for HGS are 16.1 kg for women and 22.0 kg for men (**Supplementary Figure S2**, HGS). Subsequently, low HGS was defined as HGS for males <22.0 kg, HGS for females <16.1 kg, and otherwise, it was considered high. A composite prognostic score was developed using mGNRI and HGS: mGNRI and HGS were assigned, low mGNRI and low HGS were scored as 1, and high mGNRI and high HGS were scored as 0. The two scores were then summed to construct the mGNRI-HGS score. We classified the mGNRI-HGS score into three groups, namely normal (score of 0), moderate (score of 1), and severe (score of 2). mGNRI-HGS score, mGNRI, and HGS were the exposures for the present analysis.

Baseline characteristics of the study population were presented as mean (standard deviation) or median (interquartile range) for continuous variables, and as number (percentage) for categorical variables. Differences between groups were analyzed using the Chi-square test, *t*-test, or Kruskal–Wallis test, as appropriate. We fitted three statistical models, which were adjusted for potential confounding factors such as sociodemographic, clinical, and pathological features: model (a) did not adjust for any confounding factors; model (b) adjusted for age, sex, BMI, and TNM stage; model (c) controlled for the same factors as model b, plus tumor type, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, and family history. Similar to previous studies (17), we constructed a restricted cubic spline to evaluate the relationship between continuous covariates and mortality in cancer patients in the different models. The time-dependent area under the receiver operating characteristic curve (AUC) was used to compare the predictive capacity of GNRI and mGNRI.

The Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer mortality per standard deviation (SD) change or quartile 2, 3, 4 (compared with quartile (1) in mGNRI and HGS, and was adjusted for potential confounders including age, sex, BMI, TNM stage, tumor type, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, and family history. Meanwhile, we did subgroup analysis by age, sex, BMI, etc., and tested the interaction of the exposure with these factors and their effects on the outcome.

We then used the Cox proportional hazards model to examine the association of per 1-unit change (1 vs. 0, 2 vs. 0) of the mGNRI-HGS score with cancer mortality, and then adjusted for the same covariates. In addition, we did subgroup analysis by tumor types and pathological stages to test the dose response relationship of the exposure on the outcome.

The Kaplan-Meier method and log-rank analysis were used to estimate the differences in outcomes of various mGNRI-HGS score. We conducted subgroup survival analysis based on different pathological stages and tumor types to test the universality of the model. Univariate and multifactor logistic regression models were used to assess the association of mGNRI, HGS, and mGNRI-HGS score with low KPS, high PGSGA, cachexia, and admission 90-day outcome, adjusted for different models. The discriminant index, including C-statistic, continuous net reclassification improvement (cNRI), and integrated discrimination improvement (IDI) were used to compare the prognostic prediction ability of prediction covariates and prognostic gain of the combined pathological stages. Finally, we randomly assigned the total population to "validation a" (3,927 cases) and "validation b" (1,680 cases) in a ratio of 7:3 based on computer-generated random numbers, in order to perform randomized internal validation of the constructed combination score. A two-sided *p*-value of <0.05 was considered statistically significant for all analyses. R software, version 4.0.5 was used for statistical analyses.

RESULTS

Baseline Characteristics

This study included 5,607 cancer patients with complete data from multiple centers (**Supplementary Figure S1**), including 3,378 males and 2,229 females, with a mean age of 59.4 (11.3) years. Based on the established thresholds, there were 70.29% patients with high GNRI, 29.71% with low GNRI, 54.25% with high mGNRI, and 45.75% with low mGNRI. There were 55.68% and 44.32% patients with high and low HGS, respectively. Detailed information on baseline characteristics is presented in **Supplementary Table S1**. Low mGNRI and low HGS were

statistically associated with poor physical condition (high age, low BMI), poor nutritional status (low albumin, low RBC count, and low Hb), high inflammatory status (high WBC, neutrophil, and platelet counts and low lymphocyte count), and advanced pathological stage. In addition, both low mGNRI and low HGS were associated with adverse outcomes, including prolonged hospital stay, high KPS, high PG-SGA, cachexia, and low survival rates.

Comparison of Survival Curves for mGNRI and HGS

We compared the effectiveness of mGNRI and GNRI in assessing the prognosis of cancer patients through AUC analysis (**Supplementary Figure S3A**), and the results showed that mGNRI was more effective than GNRI in predicting the prognosis of cancer patients in the total population and at various stages. In addition, compared to the GNRI, mGNRI performed better in stratifying the prognosis of cancer patients (**Supplementary Figure S3B**). The Kaplan–Meier survival curves revealed that a low mGNRI was associated with an increased risk of mortality in cancer patients. Compared with patients with a high mGNRI, patients with a low mGNRI had an approximately 19.72% (48.23 vs. 67.95%, log-rank $p < 0.001$) increased risk of death (**Figure 1A**). Patients with low HGS had an approximately 14.18% higher risk of death than those with high HGS (65.21 vs. 51.03%, log-rank $p < 0.001$) (**Figure 1B**). We further found that mGNRI and HGS can effectively stratify the prognosis of both male and female patients (**Supplementary Figures S6A,B**). It is worth noting that these differences were significant in different tumor types (lung cancer, gastrointestinal cancer, and non-gastrointestinal cancers) (**Supplementary Figures S7A,B**). In addition, mGNRI and HGS were also effective prognostic predictors in patients in various pathological stages (**Supplementary Figures S8A,B**).

Relationship Between mGNRI and HGS and Survival of Patients

Restricted cubic spline plots suggested that mGNRI (**Supplementary Figure S4A**) and HGS (**Supplementary Figure S4B**) were significantly positively associated with patient prognosis. With decrease in the mGNRI and HGS, the prognosis of patients gradually worsened, and the trend was not affected by confounding factors. Both univariate and multivariable Cox proportional hazards models suggested that low mGNRI and low HGS were independent risk factors for prognosis (**Supplementary Table S2**). After adjusting for confounders, for every SD increase in the mGNRI and HGS, the risk of poor prognosis for cancer patients was reduced by 20% (HR = 0.80, 95% CI = 0.75–0.84, $p < 0.001$) and 16% (HR = 0.84, 95% CI = 0.80–0.88, $p < 0.001$), respectively (**Supplementary Table S3**).

In multivariate subgroup analysis, both the mGNRI and HGS were independent prognostic factors for the 32 patient subgroups (**Supplementary Figures S5A,B**). We found that low mGNRI was independently associated with low KPS (OR = 0.97, 95% CI = 0.96–0.98, $p < 0.001$), high PG-SGA (OR = 0.98, 95% CI = 0.97–0.98, $p < 0.001$), cachexia (OR = 0.99, 95% CI = 0.98–0.99, $p < 0.001$), and adverse admission 90-day outcomes (OR = 0.95, 95% CI = 0.92–0.97, $p < 0.001$), as was the case with low HGS (low KPS, OR = 0.93, 95% CI = 0.92–0.94, $p < 0.001$; high PG-SGA, OR = 0.97, 95% CI = 0.96–0.97, $p < 0.001$; Cachexia, OR = 0.98, 95% CI = 0.97–0.99, $p < 0.001$; adverse admission 90-day outcomes, OR = 0.95, 95% CI = 0.93–0.96, $p < 0.001$) (**Supplementary Table S4**).

Construction of a Novel Score Based on mGNRI and HGS

Our results showed that mGNRI and HGS have marked value and relatively consistent weight in evaluating the adverse prognosis of cancer patients. Therefore, we developed a combination score using the mGNRI and HGS indexes. In the analysis of differences between groups, high mGNRI-HGS scores were closely associated with poor physical condition, poor nutritional status, high inflammatory status, and progressive pathological stage (**Supplementary Table S5**). Compared with patients with normal scores, the mortality risk of patients with moderate and severe scores was 28.8 and 13.3% higher, respectively (**Figure 1C**). In subgroup analysis by sex, higher mGNRI-HGS scores were still associated with reduced survival (**Supplementary Figure S6**). Different types of tumors failed to change the correlation between the mGNRI-HGS score and the prognosis of cancer patients (**Supplementary Figure S7C**). Notably, even in the same pathological stage, the mGNRI-HGS score presented significant gradient prognostic stratification (**Supplementary Figure S8C**), indicating that the score can further predict prognosis and stratify risk in patients at the same pathological stage.

In multivariable Cox regression analysis, the mGNRI-HGS score remained independently associated with reduced survival (**Table 1**). For each change per 1-unit, the corresponding risk of adverse outcome increased by more than 37%. Compared with the normal group, the risk of adverse outcome in the severe group was more than doubled. In subgroup analysis, we found that the mGNRI-HGS score showed significant dose-response effects (**Figures 2A,B**). With increasing mGNRI-HGS scores, the risk of poor prognosis in the normal, moderate, and severe groups gradually increased. On multivariable logistic regression analysis, the severe mGNRI-HGS score was independently associated with an increased risk of low KPS, high PG-SGA, cachexia, and adverse admission 90-day outcome (**Table 2**). In comparative analysis with sub-components, the mGNRI-HGS score showed a great advantage in both prediction accuracy and gain for pathological stage (**Supplementary Table S6**). The randomized internal validation showed that the mGNRI-HGS score could still effectively stratify the prognosis of patients in the total population (**Figure 3A**), different tumor types (**Figures 3B,C**), and different pathological stages (**Figures 3D,E**).

DISCUSSION

In the present study, we found that the mGNRI-HGS score could comprehensively reflect the physical condition, inflammatory

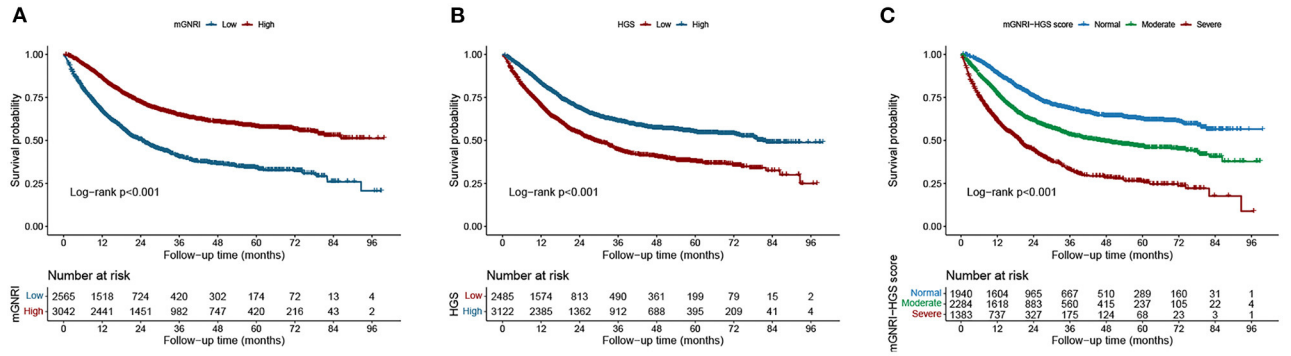

FIGURE 1 | Kaplan-Meier curve of mGNRI, HGS, and mGNRI-HGS score in patients with cancer. **(A)**, mGNRI; **(B)**, HGS; **(C)**, mGNRI-HGS score.

TABLE 1 | Trend test of the relationship between mGNRI-HGS score and survival.

mGNRI-HGS score	Model a	*p*-value	Model b	*p*-value	Model c	*p*-value
Normal	Ref		Ref		Ref	
Moderate	1.744 (1.570, 1.937)	<0.001	1.413 (1.265, 1.578)	<0.001	1.368 (1.224, 1.527)	<0.001
Severe	3.171 (2.842, 3.537)	<0.001	2.203 (1.94, 2.502)	<0.001	2.153 (1.895, 2.447)	<0.001
p for trend		<0.001		<0.001		<0.001

Model a, No adjusted; Model b, Adjusted for age, sex, BMI, TNM stage; Model c, Adjusted for age, sex, BMI, TNM stage, tumor type, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, family history.

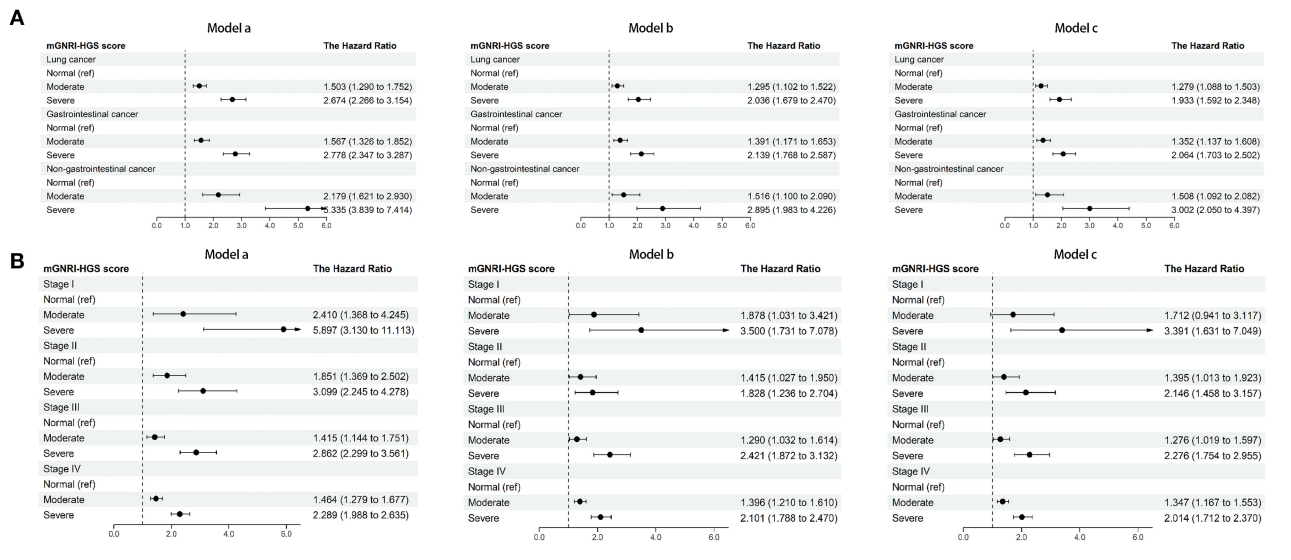

FIGURE 2 | Dose-response effects of mGNRI-HGS score based on subgroup. **(A)**, tumor types; **(B)**, pathological stages. Model a, No adjusted. Model b, Adjusted for age, sex, BMI, TNM stage. Model c, Adjusted for age, sex, BMI, TNM stage, tumor type, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, family history.

state, and pathological characteristics of patients in this cohort. The mGNRI-HGS score proved to be an independent prognostic factor for cancer patients; as the mGNRI-HGS score increased, patient survival showed a step-like decline. The mGNRI-HGS score effectively differentiated outcomes in patients with the same pathological stage and presented a significant dose-response relationship, indicating that the score can be a useful prognostic index for tumor-related factors, independent of pathological stage. In addition, we found that the mGNRI-HGS score was an effective prognostic tool for different tumor types, suggesting that this comprehensive score can be used for prognosis assessment of different cancer populations. To further validate the effectiveness

TABLE 2 | Logistic regression analysis of mGNRI-HGS score associated with secondary outcome.

KPS						
mGNRI-HGS score	**Model a**	***p*-value**	**Model b**	***p*-value**	**Model c**	***p*-value**
Normal	Ref		Ref			
Moderate	3.738 (2.860, 4.885)	<0.001	3.271 (2.476, 4.322)	<0.001	3.275 (2.470, 4.343)	<0.001
Severe	8.581 (6.572, 11.204)	<0.001	6.499 (4.803, 8.793)	<0.001	6.326 (4.651, 8.603)	<0.001
p for trend		<0.001		<0.001		<0.001
PGSGA						
Normal	Ref		Ref		Ref	
Moderate	2.200 (1.945, 2.489)	<0.001	1.797 (1.573, 2.053)	<0.001	1.793 (1.568, 2.051)	<0.001
Severe	5.723 (4.880, 6.713)	<0.001	3.703 (3.088, 4.441)	<0.001	3.702 (3.082, 4.446)	<0.001
p for trend		<0.001		<0.001		<0.001
Cachexia						
Normal	Ref		Ref		Ref	
Moderate	2.252 (1.948, 2.603)	<0.001	1.700 (1.453, 1.988)	<0.001	1.697 (1.450, 1.987)	<0.001
Severe	4.356 (3.725, 5.094)	<0.001	2.448 (2.030, 2.953)	<0.001	2.434 (2.016, 2.939)	<0.001
p for trend		<0.001		<0.001		<0.001
Admission 90 days outcome						
Normal	Ref		Ref			
Moderate	4.381 (2.883, 6.656)	<0.001	3.099 (2.013, 4.770)	<0.001	2.942 (1.907, 4.537)	<0.001
Severe	11.422 (7.586, 17.199)	<0.001	6.301 (4.011, 9.898)	<0.001	5.803 (3.684, 9.140)	<0.001
p for trend		<0.001		<0.001		<0.001

Model a, No adjusted; Model b, Adjusted for age, sex, BMI, TNM stage; Model c, Adjusted for age, sex, BMI, TNM stage, tumor type, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, family history.

of the score, we conducted a randomized internal validation. The results showed that the mGNRI-HGS score was still an independent prognostic predictor for cancer and could effectively stratify the prognosis of cancer patients.

The mGNRI combines serological and anthropometric indicators to comprehensively reflect the patient's inflammatory and nutritional status. It was developed from the GNRI and emphasizes the role of CRP as a indicator of systemic inflammation (8). Systemic inflammation plays a key role in the development and progression of cancer. It stimulates angiogenesis and cell proliferation through induction of reactive oxygen and nitrogen species (18, 19). Serum CRP is the most representative marker of systemic inflammation in clinical practice. With inflammation, the liver inhibits the synthesis of albumin and promotes the synthesis of acute-phase proteins. However, albumin is easily affected by the fluid balance in the body, leading to instability, (20, 21) while CRP is widely regarded as an effective indicator of systemic inflammation given its stability (22). In this study, we found that compared with the GNRI, the mGNRI had a better predictive ability for the prognosis of cancer patients and performed better in stratifying the adverse risks of patients, which may be because of the ability of CRP in reflecting systemic inflammation. Since albumin instability may reduce its prognostic predictive ability in cancer patients, we chose CRP-based mGNRI to construct the prognostic score in this study.

HGS is a simple and effective method to assess the physical status of cancer patients. Low HGS has been shown to reflect poor prognosis in cancer patients (11, 23). Some studies have suggested that decreased muscle function in cancer patients is the result of local muscle inflammation, and that increased inflammatory cytokines can also lead to insulin resistance and muscle depletion by activating the ubiquitin-proteasome proteolytic pathway (24, 25). A decrease in muscle mass and strength can lead to changes in functional status, leading to limitations in daily activities. Low HGS is considered an external sign of decreased muscle function, and a low mGNRI reflects a high level of cancer-related inflammation (8, 26). In this study, we found that patients with both low mGNRI and low HGS had a more than 5-fold higher risk of functional decline compared to patients with normal results. The strong combination of the two may provide a reference for prognostic stratification of cancer and the choice of therapeutic strategies. As mGRNI and HGS have the advantages of simple operation and low price, the mGNRI-HGS score can be routinely measured in clinical practice for prognostic assessment of cancer patients, which has broad clinical application prospects.

The interaction between the tumor and the patient's local response has a profound impact on the patient's general condition, including on daily activities and nutritional status. Nutritional disorders caused by cancer also affect the outcome of cancer treatment, increasing the risk of infection and complications and reducing the efficacy and continuity of chemotherapy and radiotherapy (6, 27). We further found that the mGNRI and HGS were useful indicators of malnutrition, cachexia, and short-term outcomes in cancer patients, and that the combination of the two could significantly enhance prediction of the risk of adverse outcomes.

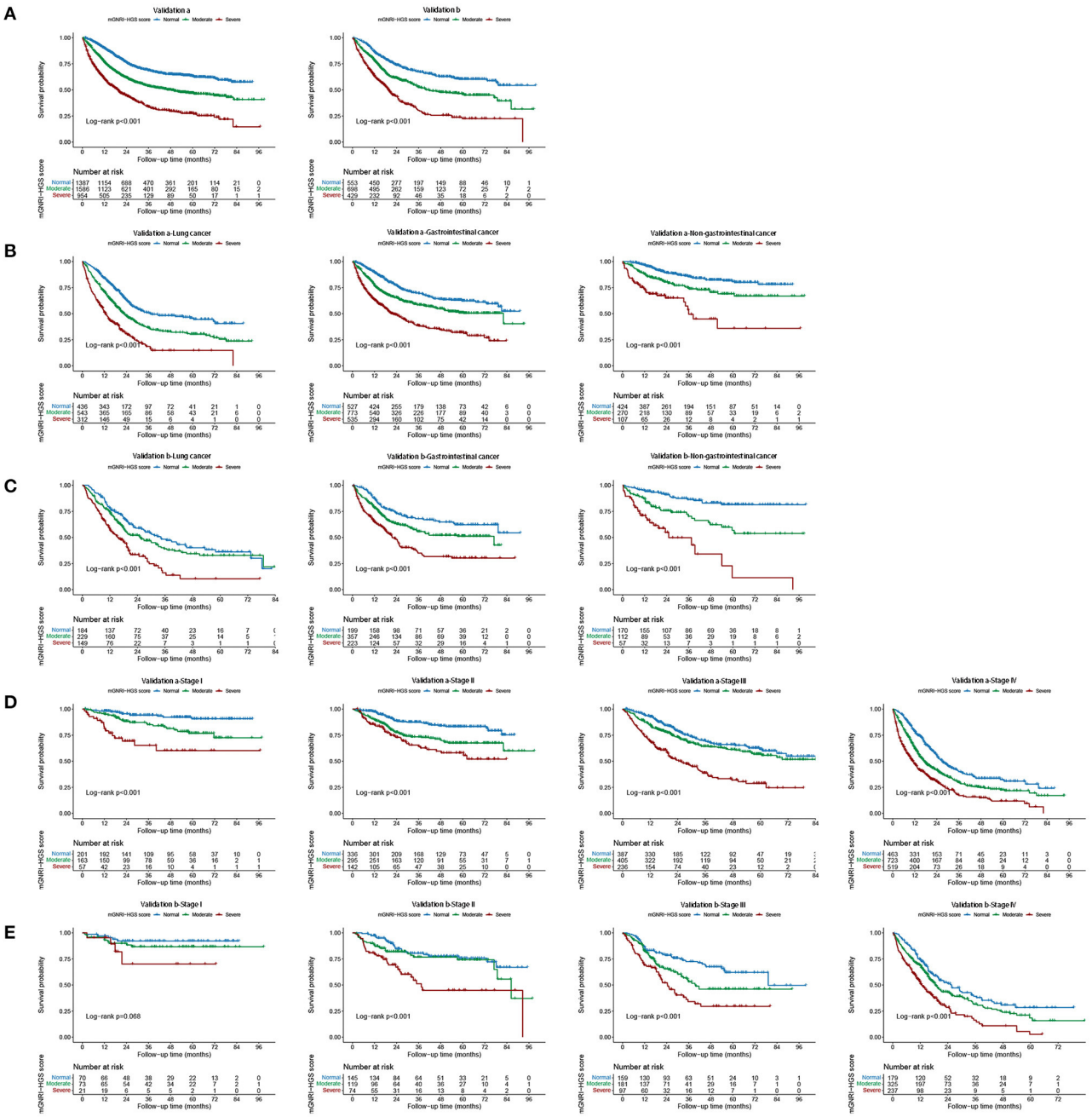

FIGURE 3 | Internal validation of mGNRI-HGS score based different tumor types and pathological stages. **(A)** Internal validation of mGNRI-HGS score; **(B)** Internal validation a of mGNRI-HGS score based on tumor types; **(C)** Internal validation b of mGNRI-HGS score based on tumor types; **(D)** Internal validation a of mGNRI-HGS score based on pathological stages; **(E)** Internal validation b of mGNRI-HGS score based on pathological stages.

The purpose of this study was to provide routes for early detection of the adverse state of cancer patients, evidence on tools for assessing the prognosis of cancer patients, and references for formulating treatment strategies for cancer patients through the comprehensive evaluation of anthropometric measurements and serum biological indicators. However, we note a few limitations that should be considered. First, although internal validation was conducted and good consistency was achieved, it is still necessary to validate our results with a larger sample and multi-center external cohort in the future. Second, the data on inflammatory nutritional indicators and body measurements were only evaluated at a single time point, failing to reflect the impact of their trajectory changes on prognosis, which needs to be further explored in the future. Finally, this study only included Chinese patients, and its extension to populations in other countries remains to be explored.

CONCLUSION

This study demonstrated that the mGNRI is a useful indicator of long-term prognosis in cancer patients. The combination of mGNRI and HGS could provide effective prognostic stratification for cancer patients and predict physical frailty, malnutrition, and cachexia.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of each hospital (Registration Number: ChiCTR1800020329). This study followed the Helsinki declaration. All participants signed an informed consent form to participate in this study.

AUTHOR CONTRIBUTIONS

HS, HX, GR, and HZ conceived and designed the study. HX, QZ, YG, MS, XiZ, XLiu, and SL assisted with the development of the methods. HS, HX, GR, QZ, XiaZ, XLi, and KZ did the data analysis. MY, MT, ZL, and HX drafted the initial manuscript. HS is the guarantor and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors assisted with the interpretation of the findings, commented on drafts of the manuscript, and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.850138/full#supplementary-material

Supplementary Figure S1 | Study design.

Supplementary Figure S2 | The optimum thresholds of mGNRI and HGS.

Supplementary Figure S3 | Comparison the effectiveness of mGNRI and GNRI in predicting the prognosis of cancer patients. **(A)** The AUC of mGNRI and GNRI. **(B)** The survival curve of mGNRI and GNRI.

Supplementary Figure S4 | The association between mGNRI and HGS and all-cause mortality in patients with cancer. **(A)**, Mgnri; **(B)**, HGS. Model a: No adjusted. Model b: Adjusted for age, sex, BMI, TNM stage. Model c: Adjusted for age, sex, BMI, TNM stage, tumor type, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, family history.

Supplementary Figure S5 | The association between mGNRI and HGS and hazard risk of overall survival in various subgroups. (The model adjusted for age, sex, BMI, TNM stage, tumor type, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, family history). **(A)**, mGNRI; **(B)**, HGS.

Supplementary Figure S6 | Stratified survival analysis of mGNRI, HGS, and mGNRI-HGS score based on sex. **(A)**, male; **(B)**, female.

Supplementary Figure S7 | Stratified survival analysis of mGNRI, HGS, and mGNRI-HGS score based on tumor types. **(A)**, mGNRI; **(B)**, HGS; **(C)**, mGNRI-HGS score.

Supplementary Figure S8 | Stratified survival analysis of mGNRI, HGS, and mGNRI-HGS score based on pathological stages. **(A)**, mGNRI; **(B)**, HGS; **(C)**, mGNRI-HGS score.

Supplementary Table S1 | Association between the mGNRI, HGS and clinical characteristics.

Supplementary Table S2 | Cox regression analysis of characteristics associated with overall survival.

Supplementary Table S3 | Trend test of the relationship between mGNRI and HGS and survival.

Supplementary Table S4 | Logistic regression analysis of mGNRI and HGS associated with secondary outcome.

Supplementary Table S5 | Association between the mGNRI-HGS score and clinical characteristics.

Supplementary Table S6 | Comparative analysis of the discrimination of mGNRI, HGS, mGNRI-HGS score for all-cause mortality in patients with cancer.

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REVIEW
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Progress in Applicability of Scoring Systems Based on Nutritional and Inflammatory Parameters for Ovarian Cancer

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Ovarian cancer is a malignancy that seriously endangers women's health; its case fatality rate ranks first among the gynecological malignancies. The status of nutrition of ovarian cancer patients is related to their prognoses. Thus, it is important to evaluate, monitor, and improve the nutritional status of ovarian cancer patients during their treatment. Currently, there are several tools for examining malnutrition and nutritional assessment, including NRI (nutrition risk index), PG-SGA (patient-generated subjective global assessment), and NRS 2002 (nutritional risk screening 2002). In addition to malnutrition risk examination and related assessment tools, the evaluation of muscle mass, C-reactive protein, lymphocytes, and other inflammation status indicators, such as neutrophils to lymphocytes ratio, lymphocyte-to-monocyte ratio, and C-reactive protein-albumin ratio, is of great importance. The nutritional status of ovarian cancer patients undergoing surgery affects their postoperative complications and survival rates. Accurate evaluation of perioperative nutrition in ovarian cancer patients is crucial in clinical settings. An intelligent nutritional diagnosis can be developed based on the results of its systematic and comprehensive assessment, which would lay a foundation for the implementation of personalized and precise nutritional therapy.

Keywords: nutritional support, efficacy evaluation, nutritional screening, inflammatory parameters, ovarian cancer

INTRODUCTION

Ovarian cancer is a gynecological malignancy associated with the highest fatality rate. Approximately 70% of ovarian cancer patients are diagnosed at the advanced clinical stages on their first visit to the doctor. Patients often report ventosity, abdominal pain, intestinal obstruction, decreased appetite, and nausea, which in turn affects their nutritional intake (1). Studies show that the malnutrition incidence among ovarian cancer patients is significantly higher than that in other gynecological diseases; the median survival time of malnourished ovarian cancer patients is also shorter than the of well-nourished patients (2). Multi-mechanism underlies the occurrence of malnutrition and cachexia in ovarian cancer patients. The tumor itself causes metabolic disorders in the body as catabolism is greater than anabolism. Patients with advanced ovarian cancer are prone to malignant intestinal obstruction and gastrointestinal metastasis; tumor enlargement can also lead to mechanical obstruction of the gastrointestinal tract (3). Some non-specific symptoms

caused by huge solid tumors and ascites trigger the loss of appetite. In addition, the activation of inflammatory responses increases the synthesis and the entry of pro-inflammatory factors in the blood. Secretion of acute proteins [such as C-reactive protein (CRP)] can promote tumor cell proliferation and support the growth of primary tumors, leading to the formation of a microenvironment conducive for metastasis and further secondary metastasis (4). At the same time, due to the high immunosuppressive microenvironment, multiple types of cells interact with inflammatory factors to further promote the formation of tumors. When patients are undernourished, they have a low tolerance to surgery, show insensitivity toward radiotherapy and chemotherapy, and decreased immune function, which predisposes them to secondary infections. Therefore, clinical nutritional therapy is of great significance for cancer patients. In addition to traditional nutrition risk screening, clinical nutrition assessment should consider the assessment of muscle mass and function and evaluation of systemic inflammatory state (5). This review aimed to discuss the guiding significance of the scoring system based on nutritional and inflammatory parameters in the prognosis of ovarian cancer. It may provide a reference for further clinical evaluation and development of individualized treatment strategies.

NUTRITIONAL INDICATORS

Nutrition Risk Index

Nutrition risk index (NRI) proposed by the Parenteral Nutrition Research Collaborative Group of the American Veterans Association in 1991, is used to examine the effects of total parenteral nutritional support for patients before major clinical abdominal surgery and thoracic surgery. The primary reference indicators are the percentage of weight loss and serum albumin level (6). A study included 660 patients who had undergone radical gastrectomy showed that malnutrition was significantly associated with postoperative wound complications after gastrectomy. NRI on the fifth day post-surgery could predict postoperative wound complications after gastrectomy (7). Yim et al. (8) conducted an NRI-based study in 213 patients with ovarian cancer. Among them, 78% of the patients had low-to-mild nutritional risk, while the other 22% were in the moderate-to-severe nutritional risk group. The 5-year overall survival (OS) rate in ovarian cancer patients with moderate-to-severe nutritional risk (45.3%) was significantly lower as compared to those at low-to-mild nutritional risk (64.0%), respectively (P = 0.024); the progression-free survival (PFS) period was substantially shortened in the moderate-to-severe nutritional risk group (15 vs. 28 months, P = 0.011). Yoon et al. (9) studied the applicability of NRI to assess the relationship between survival rate and nutritional factors before and after chemotherapy. A total of 212 patients in stage III/IV of ovarian cancer who had undergone surgery along with six courses of chemotherapy with cisplatin and paclitaxel, were enrolled. The results showed that NRI was significantly related to survival time; the survival time of patients with moderate-to-severe malnutrition before chemotherapy (48 months) was significantly shorter as compared to those with mild-to-moderate malnutrition (80 months). The relationship between NRI and the OS rate after treatment was in line with the previous studies. The relative risk of death in patients with moderate-to-severe malnutrition was 3.6 times greater as compared to those with mild-to-moderate malnutrition. Compared with other composite indicators, NRI is simple, easy to use, and has better sensitivity and specificity. However, its main disadvantage is the pre-requisite data of the patient's current and past weights. If the patient develops edema due to the disease, the NRI measurement is affected. In addition, owing to the effect of stress on serum albumin concentration, the use of NRI screening is limited in clinical settings.

Nutritional Risk Screening 2002

The Danish Parenteral and Enteral Nutrition Association has developed NRS 2002 (nutritional risk screening 2002), the first nutritional risk screening tool that relies on evidence-based medicine. It is also recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN).

The core indicators selected to reflect the nutritional risk were derived based on 128 randomized controlled trials (RCTs) (10). It is suitable for nutritional risk evaluation of inpatients and is not only simple but also easy to implement. The scoring method for patients is divided into two parts according to the nutritional status and disease severity; each part is further divided into four levels. When the total score $\geq$3, patients are "at nutritional risk." NRS 2002 has good sensitivity and specificity. Bargetzi reports that NRS is closely related to the patient's 180-day mortality rate. Each point increase in the patient's NRS score is associated with a 37% increase in the risk of all-cause death in cancer patients within 180 days. In addition, NRS is associated with the composite endpoint for adverse outcomes, the average hospitalization time, impairment in quality of life, and functional decline (11). NRS 2002 is mainly used for the evaluation of patients with gastric cancer and esophageal cancer having a high incidence of malnutrition (12, 13). In addition, NRS 2002 nutritional risk screening tool can help in the identification of malnourished patients who need to be given different nutritional support. It provides theoretical support for the formulation of personalized treatment plans and has good guiding and predictive effects on the nutritional screening of patients with colorectal cancer (14). However, NRS is rarely used in patients with gynecological tumors. Hertlein et al. (15), using NRS 2002, performed nutritional risk screening for 47 patients with ovarian cancer and found that 70.2% (33 cases) of total patients were at nutritional risk, which is, NRS 2002 score was $\geq$3 points.

Nutritional risk is also related to the incidence of surgical complications and duration of hospital stay. Another study by Hertlein et al. (16) shows that perioperative immune nutrition supplementation in patients with malnourished ovarian cancer with an NRS 2002 score of $\geq$3 does not significantly improve the complication rate and hospital stay, but it can reduce complications due to infections. Deficiencies were also found during NRS 2002 application. During the screening process, for patients with deviations in their weight change estimates and dietary intake, or those who did not answer the questions, the results were not accurate. Kyle et al. analyzed the relationship

between the NRS 2002 score and the prognoses of 995 inpatients and reported that NRS 2002 could not objectively and accurately reflect the nutritional status of some patients (17). The main reason is that NRS 2002 integrates the patient's nutritional status, disease severity, age along with other factors. Thus, there are more subjective components and individual indicators have significant weights (18). NRS 2002, which gives greater consideration to the complications in nutrition-related diseases, still does not solve the problem of the lack of a unified standard for the evaluation of the nutritional status in patients. Further, its utility for ovarian cancer is less explored.

Subjective Global Assessment and Patient-Generated Subjective Global Assessment

Subjective global assessment (SGA), recommended by the American Society for Parenteral and Enteral Nutrition (AND/ASPEN), is a screening tool that includes detailed medical history and physical evaluation parameters (19). Patient-generated subjective global assessment (PG-SGA) is based on SGA, which consists of two parts: patient self-assessment and medical staff assessment. The self-assessment part further includes four aspects, which include, food intake, weight, symptoms, activity, and physical function. If the PG-SGA score is greater than or equal to 9 points, a comprehensive assessment should be performed, followed by nutritional intervention; anti-tumor treatment should be suspended. Gupta et al. (20) performed an SGA-based evaluation of 98 ovarian cancer patients and found that 47% of patients were A-graded, which implied having good nutrition; 29% were B-graded, which implied mild-to-moderate malnutrition, and 24% were C-graded, indicative of severe malnutrition. At 3 months, the median survival time in the grade A group was significantly longer than that in the B and C groups (19.9 vs. 3.7 months, $P < 0.001$). The patient survival rate due to improved nutritional status after 3 months was significantly higher than that of patients with worsened nutritional status. These findings were independent of age, diagnosis time, treatment history, and CA125. Chantragawee (21) reports that as compared to endometrial cancer and cervical cancer, malnutrition is more common in patients with ovarian cancer based on PG-SGA. Phippen reports that (22) patients who experience febrile neutropenia (FN) have a higher PG-SGA score, and it may be a reasonable predictor of FN in patients with gynecological malignancies receiving multi-drug primary chemotherapy. It may also be beneficial for preventive GCSF. Das et al. (23) used PG-SGA to assess the status of nutrition of 60 patients with gynecological malignancies. A total of 88.33% of patients with gynecological tumors had a certain degree of malnutrition or were at risk of malnutrition. Approximately 5% weight loss in the preceding month could replace the comprehensive score PG-SGA in triage patients. Laky et al. (24) used the SGA and PG-SGA scales for the nutritional assessment of 194 patients with different gynecological tumors. The incidence of malnutrition in ovarian cancer patients was the highest, estimated to be 67%. They found that the evaluation results of SGA and PG-SGA were very similar. However, SGA could not accurately reflect the changes in acute nutritional status and lacked evidential support for screening and clinical outcomes. However, PG-SGA is significantly related to objective and subjective parameters and is widely considered as a relevant method for examining the nutritional status among patients in clinical settings (25).

Prognostic Nutritional Index

Prognostic nutritional index (PNI) is used for the assessment of the nutritional status among patients who have undergone surgery, predicting surgical risks, and for prognostic judgments. It was first established by Onodera et al. (26), a Japanese scholar. Originally, PNI was used for the evaluation of the nutrition and immune status of patients undergoing gastrointestinal surgery. It is determined according to the lymphocyte count and level of serum albumin in the peripheral blood. In recent years, it has been used as a new indicator for prognostic judgment of patients with gastrointestinal malignant tumors, gynecological tumors, and lung cancer (27). PNI reflects preoperative malnutrition and is used to predict the incidence of postoperative complications. It is also a prognostic predictor for the long-term progression of various malignant tumors. Yoshikawa et al. (28) used PNI 46.5 as the critical value for ovarian clear cell carcinoma patients. The OS of the patients in the PNI high group was significantly longer than those in the PNI low group. Multivariate analysis indicated that high PNI could be an important independent potential predictive prognostic factor for a good prognosis. The disease-free survival rate of the two groups was not abnormal, but the postrecurrence survival was significantly higher in the high-PNI group than in the low-PNI group [hazard ratio (HR) = 6.43; 95% CI, 1.09–121.64 months, $P = 0.0383$]. Komura et al. (29) retrospectively analyzed data of 308 patients in stages I–IV of epithelial ovarian cancer. In early ovarian cancer, PNI = 44.7 was used as the cut-off value, and in advanced ovarian cancer, PNI = 42.9 was the threshold. In early ovarian cancer patients, reduced PNI was not significantly correlated with PFS and disease-related survival. However, multivariate analysis for advanced ovarian cancer showed that low PNI could be an independent predictive risk factor for PFS and disease-related survival. In addition, they found that for the prediction of disease-specific survival in patients with epithelial ovarian cancer, the PNI before treatment was a better indicator than the platelet count. Although thrombocytosis before treatment is used as an independent factor for poor prognoses in patients with epithelial ovarian cancer, it usually reflects lower PNI, and no prognostic information is available when adjusting for the PNI values (30). Feng et al. (31) used PNI = 46.2 as the critical value and showed that low preoperative PNI was correlated with the FIGO stage progression, elevated CA125 level, extensive presence of ascites, residual tumors, and platinum resistance. In multivariate analysis, PNI as a continuous variable was an independent predictor of OS. PNI is a validated prognostic predictive parameter for high-grade serous ovarian cancer (HGSC). Miao et al. (32) used PNI = 45 as the cut-off value and found that the AUC of PNI-predicted platinum resistance was 0.688; the sensitivity was 62.50%, and the specificity was 83.47%. The median PFS of patients with a lower PNI (<45) was 12 months (95% CI, 10.62–13.38 months),

whereas the median PFS of patients with a higher PNI (≥45) was 23 months (95% CI, 18.03–27.97 months). PFS and OS in the low-PNI group were significantly lower than those in the high-PNI group (both $P < 0.001$). Multivariate analysis showed that PNI < 45 was an independent risk factor for PFS and OS outcomes. Zhang et al. (33) retrospectively analyzed the data of 237 patients with epithelial ovarian cancer using PNI = 47.2 as the cut-off value. They found that the PFS in the low PNI group was significantly lower than in the high PNI group. For low and high PNI groups of platinum-sensitive patients, PFS was 49.4 and 28.9 months ($P < 0.001$), respectively, and OS was 55.7 and 82.7 months ($P < 0.001$), respectively. However, there were no statistically significant differences in PFS and OS between the two groups of patients demonstrating platinum resistance. The efficacy of PNI in predicting OS and resistance to platinum was higher than CA125. Thus, PNI, owing to its high efficiency and simplicity, has been widely used, in evaluating the pre-treatment status of patients with various malignancies. Although some studies report that PNI is related to the prognosis of ovarian malignant tumors, these studies have some limitations that need to be addressed. The sample size in single-center retrospective studies is limited, and whether the same conclusion applies to different populations and different cancer types needs to be investigated in the future. Currently, there is no uniform standard for the best cut-off value of PNI. Differences in the selection criteria and method selection also need to be addressed (34).

Skeletal Muscle Index

Skeletal muscle index (SMI) is widely used to evaluate sarcopenia. It is measured as the total area of all skeletal muscles (psoas major, erector spinae, quadratus lumborum, transverse abdominis, extra-abdominal; the total area of the oblique muscles and internal oblique muscles) divided by the height squared (35). The area of skeletal muscle is evaluated using several methods, such as bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), and CT scan imaging. Considering the clinical practicality and economic factors, currently, the CT imaging method is being widely used (36). The third lumbar spine SMI is widely used for nutritional assessment and in the assessment of tumor prognosis. However, there is no uniform standard cut-off value (37). Staley, using SMI 41 as the cut-off value, evaluated 201 patients with epithelial ovarian cancer and found that sarcopenia was not associated with poor survival outcomes or chemotherapy toxicity. Prospective studies in the future should focus on interventions to prevent or reverse sarcopenia, improve the survival, performance status, and quality of life of patients with ovarian cancer (38). Kim et al. analyzed the data of 179 patients in stages III–IV of HGSC using SMI 39 as the cut-off value. They found that the PFS and OS of patients in the sarcopenia and control groups were similar. In the subgroup analysis of the sarcopenia group, the OS for high fat-to-muscle ratio (FMR) group patients was significantly lower than that in the low FMR group. High FMR was an independent prognostic factor for poor OS in the sarcopenia group (5-year survival rate, 44.7 vs. 80.0%; $P = 0.046$) (39). Ataseven used SMI along with muscle attenuation [MA; Hounsfield units (HU)] and analyzed 323 cases of advanced epithelial ovarian cancer. They found no statistically significant differences in PFS and OS between the patients in the sarcopenia and control groups. However, low MA was correlated significantly with OS, particularly in patients exhibiting residual tumors. MA assessment can be used for risk stratification after tumor reduction (40). Rutten retrospectively analyzed 216 patients with ovarian cancer who underwent primary debulking surgery (PDS) treatment using SMI 38.73 as the threshold. Patients with sarcopenia had a significant survival disadvantage. However, the skeletal muscle reduction could not predict OS or other grave complications in ovarian cancer patients (41). Yoshino assessed the skeletal muscle area (SMA) at the third lumbar vertebrae in 60 patients at stage III/IV EOC who underwent induction chemotherapy (IC). The cut-off value of SMA-to-SMA ratio (SMAR) before and after IC was determined; SMAR critical value was 0.96 and low SMAR could predict poor prognosis of IC in patients with advanced EOC (42). Ubachs found that SMI reduction in ovarian cancer patients in stage III undergoing neoadjuvant chemotherapy (NACT) was not associated with a worsening prognosis. However, there was a positive correlation between SMI and adverse events (43). Skeletal muscle depletion, which affects the patients' ability to receive treatment. A total of 893 adverse events (70.6%) were reported preoperatively in the decreased SMI group, compared with 372 events (29.4%) in the stable/increased SMI group ($P = 0.008$). The percentage of grade 3–4 events (such as pulmonary embolisms, coagulation disorders with clinical symptoms, gastrointestinal function significantly changed) in the reduced SMI group (5.3%) was higher than that in the stable SMI group or the elevated SMI group (2.6%). Huang conducted a retrospective analysis of 139 ovarian cancer patients in stage III and found that, during treatment, SMI significantly reduced and was independently correlated with poor OS in stage III EOC patients who received adjuvant platinum-based chemotherapy and PDS. The modified Glasgow prognostic score (mGPS) could be a potential predictor of SMI decline during treatment (44). SMI includes skeletal muscles at the caudal level of the third lumbar vertebra from the CT images. This plane has several muscles and is a complex region to perform measurements. Large area inclusion may increase measurement errors. The current knowledge on SMI and ovarian cancer is based on retrospective studies. Thus, future prospective studies will be of great significance for prognostic prediction of skeletal muscle state (45).

Psoas Muscle Index and Psoas Muscle Volume

Psoas muscle index (PMI) is the value obtained from the measurement of the cross-sectional area of the psoas major muscle on either side. It is calculated as the sum of the area divided by the square of the height. Some studies have pointed out that PMI and SMI are not well comparable, and the SMI measured by CT cannot be used interchangeably (46). We speculate that PMI is easier to measure and calculate than SMI. The quality of psoas major muscle, which maintains the stability of body posture and conducts the strength of upper and lower limbs, is easily affected by the patient's own nutritional status and daily activities. The psoas major muscle is located in the abdominal cavity and has a fixed position. In recent years, studies from abroad show that indicators based on the area

TABLE 1 | Comparison of commonly used nutritional indicators for cancer patients.

	NRI	NRS 2002	SGA	PG-SGA	PNI	SMI	PMI	PV
Age	×	✓	×	×	×	×	×	×
BMI	✓	✓	✓	✓	×	×	×	×
Involuntary weight loss	✓	✓	✓	✓	×	×	×	×
Diet-related symptoms	×	×	✓	✓	×	×	×	×
Dietary changes	×	✓	✓	✓	×	×	×	×
Physical activity	×	×	✓	✓	×	×	×	×
Disease severity	×	✓		✓	×	×	×	×
Physical examination	×	×	✓	✓	✓	✓	✓	✓
The laboratory indicators	✓	×	×	×	✓	×	×	×

of the psoas muscle are significantly related to the prognosis of abdominal surgery, and also represent to a certain extent, the skeletal muscle content of the whole body (47). Yoshikawa evaluated the data of 72 patients suffering from epithelial ovarian cancer and undergoing combination therapy with paclitaxel and carboplatin; PMI of 5.4 was the critical value. Compared to the patients with lower PMI, the OS of patients with higher PMI significantly improved. Multivariate analysis of OS showed that low PMI was an independent unfavorable prognostic factor and that PMI may provide a potential prognostic biomarker for epithelial ovarian cancer patients (48). Matsubara et al. enrolled 92 epithelial ovarian cancer patients and calculated the psoas muscle volume (PV) based on their three-dimensional CT (3D-CT) scans. Patients with low PV had significantly worse PFS and OS; PV was found to be better than SMA and psoas area (PA) in predicting prognosis (49). Psoas index (PI) is the main cross-sectional area of the psoas muscle divided by the height squared. Yoshikawa evaluated the median PI of 76 patients with ovarian cancer undergoing first-line chemotherapy. Compared with patients having high PI, those with low PI were more likely to develop peripheral neuropathy (32 vs. 11%; $P = 0.047$). The PI value was independent of other toxicities such as neutropenia and thrombocytopenia. Thus, the median PMI can serve as a potential predictive biomarker for toxicity in ovarian cancer patients (50). Rutten speculates that changes in the psoas muscle area cannot represent alterations in the total muscle area, and that total skeletal muscle cannot be used as a substitute for predicting the survival of patients with ovarian cancer (51). Taken together, studies based on psoas major muscle and ovarian cancer need further prospective validation. The development of a unified evaluation system would be more valuable for studying the prognosis of ovarian cancer. We presented a comparison of commonly used nutritional indicators in cancer patients (**Table 1**).

INFLAMMATORY INDICATORS

Neutrophil-to-Lymphocyte Ratio

Neutrophil-to-lymphocyte ratio (NLR), an inflammation index, reflects the dynamic balance between neutrophils and lymphocytes, and comprehensively represents the patient's immune status. Recent studies report that the prognosis of malignant tumors is closely related to clinicopathological signs, and that chronic inflammation plays a crucial role in tumor invasion and metastasis (52). NLR can predict the prognosis of several solid tumors, including lung cancer, breast cancer, and ovarian cancer (53, 54). Medina Fernández et al. (55) included 122 advanced ovarian cancer patients and found that during a concurrent infection, CRP peaked at 48 h, while NLR peaked at 24 h; NLR was more effective for predicting infection-related complications. Zhou et al. (56) retrospectively analyzed 370 epithelial ovarian cancer cases in FIGO III using NLR = 3.08 as the cut-off value and found that PFS and OS of patients in the NLR high group were substantially lower than those in the NLR low group ($P < 0.05$); NLR and PLT could jointly predict the OS. Feng et al. (57) through factor analysis, reported that high NLR was only related to PFS. Salman et al. (58) found that between the NLR $\geq$ 6.0 and the NLR $<$ 6.0 groups, there was no statistically significant difference in the rates of optimal debulking. However, there was a significant correlation between high NLR and OS. Williams et al. (59) reports that high NLR values are correlated with advanced tumor stage and higher grade, bilateral adnexal masses, presence of ascites, and related risk factors, including greater height, Jewish ethnicity, family history of cancer, more ovulation cycles, and use of talcum powder in premenopausal women. In patients at FIGO stages IIIC and IV, who underwent NACT, Sanna prospectively evaluated the dynamic changes in NLR for patients with HGS advanced epithelial ovarian cancer. The decrease in NLR after three cycles was significantly associated with a better response to NACT; the PFS was significantly higher as compared to patients whose NLR value increased after three cycles of NACT. Thus, the changes in NLR during treatment can be used as a response predictor for NACT in HGS advanced ovarian cancer patients, which means that NLR was elevated and chemotherapy was less effective (60). Marchetti performed retrospective analyses of the NLR and BRCA gene status of 39 epithelial ovarian cancer patients; regardless of BRCA mutant or wild-type, the median progression free survival in the low NLR group was longer than that in the NLR group. Thus, NLR is a validated prognostic marker for OC patients and is independent of the BRCA mutation status (61). Wu et al. collected data for 262 ovarian cancer patients; among them, 258 patients had benign ovarian cancer. A total of 232 healthy controls were also included. The derived neutrophil-to-lymphocyte ratio (dNLR) was evaluated based on parameters of whole blood cells. dNLR was substantially different between ovarian cancer, benign ovarian disease, and the healthy control groups. It was positively correlated with ovarian cancer staging and CA125 (all $P < 0.001$). Thus, dNLR can be used as an effective indicator to differentiate ovarian cancer from benign disease (62). Taken together, NLR is closely associated with the clinical characteristics of ovarian serous epithelial cancer, including FIGO staging, degree of differentiation, and tumor markers. Thus, NLR has a high value for evaluating the prognosis of patients.

Platelet-to-Lymphocyte Ratio

Platelet-to-lymphocyte ratio (PLR) is the ratio of platelets to lymphocytes. Studies show that platelets perform the function of

sensing, monitoring, and transmitting information. Tumor cells cause loss of vascular endothelium, activation of platelets, and formation of platelet-vascular wall-tumor cell interactions. It may be related to the balance between platelet-dependent pro-tumor inflammatory response and lymphocyte-mediated anti-tumor immune response in the tumor microenvironment (63). The release of various inflammatory mediators can induce an increase in the platelet number. Activated platelets secrete platelet-derived growth factor (PDGF), platelet-activating factor (PAF), and vascular endothelial growth factor (VEGF) along with several other cytokines to promote the formation of tumor-related blood vessels and the degradation of extracellular matrix, which in turn enhance tumor growth and distant metastasis (64). PLR is closely related to the recurrence and survival cycle of malignant tumors (65). Asher et al. (66) retrospectively analyzed data from 235 patients with ovarian cancer and found that the OS of patients with PLR <300 and PLR ≥300 were 14.5 and 37.4 months, respectively. Multivariate analysis suggested that high PLR was an independent prognostic factor for ovarian cancer. Badora-Rybicka (67) retrospectively analyzed 315 cases of ovarian cancer. Similarly, high PLR was an independent predictive risk factor for PFS, however, it did not affect OS. Raungkaewmanee et al. (68) found that for PLR ≥200 the AUC of FIGO staging was 0.66, sensitivity was 72.7%, and specificity was 65.7%. The patients whose PLR >200 showed shorter PFS and OS. Single-factor analysis indicated that high PLR was a potential risk factor for OS. Taken together, PLR has potential predictive clinical value in advanced diseases. Compared with thrombocytosis or NLR, PLR is a better prognostic indicator for EOC patients. Zhang et al. (69) performed a multivariate analysis with PLR = 203 as the cut-off value. Unlike CA125, NLR, fibrinogen, CRP, and albumin levels, PLR was an independent risk factor for PFS. Thus, for prognostic prediction of ovarian cancer, preoperative PLR is better than CA125, NLR, fibrinogen, CRP, and albumin levels. Zhao et al. performed a meta-analysis of 13 studies consisting of 3,467 patients with ovarian cancer and found that those with PLR ≥200 had shorter OS and PFS. Therefore, high PLR is correlated to poor prognosis (70).

Lymphocyte-to-Monocyte Ratio

Lymphocytes and monocytes are the key immune cell types mediating the inflammatory response. Lymphocyte-to-monocyte ratio (LMR), a combination of tumor-related inflammatory cells, is related to the prognoses of several tumors (71). Existing immunological studies show that lymphocytes, forming the core of the body's immune response, participate in cellular immunity and humoral immunity. Among them, the T lymphocytes perform the functions of anti-tumor cells and exhibit anti-infection and anti-allogeneic effects. Several studies report an increase in T-lymphocytes in the peripheral blood of ovarian cancer patients (72, 73). Monocytes can produce a variety of cytokines and chemokines, which in turn, promote the occurrence and progression of tumors by immunosuppressive effects and stimulation of tumor angiogenesis. Monocytes can also produce tumor-associated macrophages (74). TAMs can promote the efficacy of tumor angiogenesis by secreting angiogenic factors and regulate the degradation of the extracellular matrix through enzymes and inhibitors, beneficial for tumor migration and progression. However, TAMs also simultaneously exert anti-tumor effects. Their prognostic influence is the result of the interaction between the tumor-promoting and anti-tumor effects. Therefore, the peripheral blood lymphocyte count can reflect a certain degree, the anti-tumor immune response to ovarian cancer. A decrease in the peripheral blood lymphocyte count may lead to a decline in the tumor immune response, thereby promoting tumor progression and metastasis. Monocytes derived from inflammatory chemokines and cytokines can promote tumor progression (75). Yang (76) evaluated the clinical data of a total of 364 newly diagnosed epithelial ovarian cancer patients. The best cut-off for LMR to predict the survival of patients with epithelial ovarian cancer was estimated at 3.84; the median follow-up time was 37 months. The results of multivariate analysis showed that postoperative FIGO stages III–IV, poorly differentiated tumor grade, presence of lymph node metastasis, absence of postoperative adjuvant treatment, and LMR ≤ 3.84, were independent risk factors affecting PFS and OS in epithelial ovarian cancer patients. Kwon et al. (77) included the clinical data of 109 ovarian clear cell carcinoma patients. Using an LMR cut-off of 4.2, high LMR was found to be significantly correlated to high 5-year PFS and OS. FIGO staging, residual disease, and platinum remission were independent prognostic factors for PFS, while FIGO staging, residual disease, platinum remission, and LMR were independent prognostic factors for OS according to the results of multivariate analysis. Thus, LMR is the most reliable independent factor for the OS prognosis in ovarian clear cell carcinoma patients. According to the data for the entire cohort, the optimal LMR threshold selected based on PFS and OS ROC curves was 2.07. Eo et al. (78) collected clinical data of 234 epithelial ovarian cancer patients. The 5-year OS rates in the LMR low and the LMR high groups were 42.2 and 67.2%, respectively; the 5-year PFS rates in the two groups were 40.0 and 62.5%, respectively. According to the multivariate analysis, the most important prognostic factors that influenced PFS were age, FIGO stage, and tumor antigen 125 level; LMR was the most valuable prognostic factor for OS prediction. A meta-analysis of LMR for ovarian cancer patients by Gong confirms that low LMR is associated with worse OS and PFS; it is also significantly related to G2/G3 classification, III–IV staging, CA125, and malignant ascites. The author also discussed elaborately the inconsistency in cut-off values of LMR in the

TABLE 2 | Comparison of commonly used inflammation indicators for cancer patients.

	NLR	PLR	LMR	CAR	GPS
Neutrophils	✓	×	×	×	×
Lymphocytes	✓	✓	✓	×	×
Platelets	×	✓		×	×
Monocyte	×	×	✓	×	×
C-reactive protein				✓	✓
Albumin	×	×	×	✓	✓

included studies, and their retrospective designs, particularly in Asia. These may result in bias and need to be addressed in future investigations (79).

C-Reactive Protein-Albumin Ratio and Glasgow Prognostic Score

C-reactive protein-albumin ratio (CAR) is a recently developed indicator that comprehensively evaluates the level of inflammation and nutritional status of the patient. It is related to the prognosis of several tumors. Tumor-related inflammation plays an important role in the infiltration, proliferation, tumor progression, and metastasis of tumor cells (80). CRP is synthesized by the liver in response to infection, inflammation, and tissue damage, and is regulated by several cytokines. CRP is a highly specific marker of systemic inflammation (81). Patients with ovarian cancer often show elevated serum CRP levels, which indicates that there is a chronic

TABLE 3 | Relationship between inflammatory markers and prognosis.

	Author	*n*	Stage	Mean age	Index significance
NLR					
1	Medina Fernández et al. (55)	122	NA	55.8	NLR ≥ 8 from the beginning, and after having a clear fall in NLR, start exhibiting rising values should have a potential infective complication.
2	Zhou et al. (56)	370	III, *n* = 370	54.3	NLR > 3.08 had shorter PFS (16.9 vs. 19.5 months, HR = 1.3, 95% CI = 1.03–1.63, *P* = 0.022) and OS (33.5 vs. 46.8 months, HR 1.3, 95% CI = 1.01–1.66, *P* = 0.001).
3	Feng et al. (57)	875	(I, II), *n* = 75; (III, IV), *n* = 800	NA	A high NLR (≥ 3.24) was associated with reduced PFS (*P* < 0.001) and OS (*P* < 0.001).
4	Salman et al. (58)	111	IIIC, *n* = 75; IV, *n* = 801	63.3	NLR ≥ 6.0 was associated with significantly worse OS (*P* < 0.05).
5	Williams et al. (59)	519	NA	NA	Higher NLR was associated with significantly worse OS (*P* = 0.003).
6	Sanna et al. (60)	161	IIIC, *n* = 47; IVA, *n* = 76; IVB, *n* = 38	57	NLR > 1.58 had shorter PFS (10 vs. 24 months, HR = 9.3, 95% CI = 4.9–17.7, *P* < 0.0001).
7	Marchetti et al. (61)	397	(I, II), *n* = 136; (III, IV), *n* = 126	43.4	NLR < 4 had a significant 7-month increase in mPFS (26 vs. 19 months, *P* = 0.009).
8	Wu et al. (62)	262	(I, II), *n* = 136; (III, IV), *n* = 127	43.4	dNLR ≤ 2.11, distinguish ovarian cancer from benign ovarian disease (*P* < 0.001); dNLR ≤ 1.9, distinguish ovarian cancer from healthy controls
PLR					
1	Asher et al. (66)	235	I, *n* = 55; II, *n* = 28; III, *n* = 107; IV, *n* = 34; missing, *n* = 11	62	PLR < 300 had longer OS (37.4 vs. 14.5 months, *P* < 0.001)
2	Badora-Rybicka et al. (67)	315	I, *n* = 61; II, *n* = 30; III, *n* = 186; IV, *n* = 38	54	PLR < 62.31 had longer PFS (AUC: 0.665, 95% CI = 0.59–0.73, *P* < 0.0001); PLR < 129.78 had longer OS (AUC: 0.610, 95% CI = 0.55–0.67, *P* = 0.0008).
3	Raungkaewmanee et al. (68)	166	(I, II), *n* = 88; (III, IV), *n* = 78	53	PLR ≥ 200 had shorter PFS (*P* = 0.003) and OS (*P* = 0.002)
4	Zhang et al. (69)	190	I, *n* = 22; II, *n* = 31; III, *n* = 128; IV, *n* = 9	50.6	PLR > 203 had shorter PFS (11 vs. 24 months, *P* < 0.001) and OS (28 vs. 64 months, *P* < 0.001)
LMR					
1	Yang et al. (76)	364	(I, II), *n* = 52; (III, IV), *n* = 312	NA	LMR ≥ 3.84 had longer mPFS (88 vs. 56 months, *P* < 0.01) and mOS (100 vs. 69 months, *P* < 0.01)
2	Kwon et al. (77)	109	(I, II), *n* = 64; (III, IV), *n* = 45	50	LMR ≥ 4.2 had longer 5-year PFS (76.2 vs. 39.8%, *P* = 0.003) and OS rate (90.1 vs. 50.6%, *P* < 0.001)
3	Eo et al. (78)	234	(I, II), *n* = 97; (III, IV), *n* = 137	54	LMR > 2.07 had longer 5-year PFS (40.0 vs. 62.5%, *P* < 0.0001) and OS rate (42.2 vs. 67.2%, *P* < 0.0001)
CAR					
1	Komura et al. (84)	308	(I, II), *n* = 166; (III, IV), *n* = 144	NA	CRP/Alb > 0.048 had shorter OS (HR = 2.35; 95% CI, 1.30–4.48; *P* = 0.0044)
2	Liu et al. (85)	200	I, *n* = 25; II, *n* = 33; III, *n* = 107; IV, *n* = 35	53	Cut-off value = 0.68; CRP/Alb was associated with a more advanced tumor stage (*P* = 0.001), fewer patients with ideal cytoreductive surgery (*P* = 0.049), the presence of ascites (*P* = 0.009) and higher serum CA-125 level (*P* = 0.002).
GPS					
1	Sharma et al. (86)	154	III, *n* = 109; IV, *n* = 43	63.3	OS (months): GPS = 0, 40.9 (29.9–51.9); GPS = 1, 27.5 (23.3–31.8); GPS = 2, 22.4 (12.1–32.6); *P* = 0.02
2	Omichi et al. (87)	216	I, *n* = 87; II, *n* = 15; III, *n* = 88; IV, *n* = 26	61	The higher the GPS score, the shorter the OS and PFS (all *P* < 0.001)
3	Zhu et al. (88)	672	III, *n* = 564; IV, *n* = 108	55	The higher the GPS score, the shorter the OS and PFS (all *P* < 0.001)

NA, not available.

inflammatory response to the progression of ovarian cancer (82, 83). In clinical settings, serum albumin level is primarily used for the assessment of the nutritional status of patients. The malnutrition of patients caused by tumors and the host response to these tumors can alter albumin levels. Decreased albumin levels can lead to undernourishment in patients and affect their prognoses. Komura et al. (84) retrospectively analyzed the data from 308 epithelial ovarian cancer patients and found that regardless of the clinical-stage or the rate of reductive surgery, elevated CRP/Alb remained an independent predictor of short-term disease-specific survival. CRP/Alb was better than CRP for the prediction of disease-specific survival in EOC patients (HR = 1.96; 95% CI, 1.10–3.57; $P = 0.0221$). Liu et al. (85) using CRP/Alb = 0.68 as the critical value, found that elevated CRP/Alb was associated with advanced stage, residual tumor, ascites, elevated CA-125 levels, Glasgow prognostic score (GPS), and mGPS. CRP/Alb was an independent prognostic factor for OS. The AUC values for CRP/Alb at 1-, 3-, and 5-years were higher than those for GPS, mGPS, and PNI.

The GPS scoring system combines CRP and AIb levels. When CRP > 10 mg/L and AIb < 35 g/L, the GPS is considered as two points. When one indicator is abnormal, it is one point. Both indicators are normally scored as 0. Sharma et al. (86) retrospectively analyzed data of 154 ovarian cancer patients in advanced stage and found that GPS was an independent factor of the OS rate ($P < 0.05$). The higher the GPS score, the worse was the prognosis. Omichi et al. (87) analyzed the data of 216 patients with epithelial ovarian cancer and found that in all the stages of ovarian cancer, PFS and OS were shorter when the GPS score was 2 points as compared to 0 and 1 point. According to multivariate analysis, a high GPS score was determined as an independent risk factor for recurrence and OS in all stages of ovarian cancer, regardless of the histological grade. Zhu et al. (88) retrospectively analyzed 672 advanced ovarian cancer patient data and found that high GPS scores were associated significantly with postoperative residual tumor size ($P = 0.007$), histological grade ($P = 0.001$), and histological type of the tumor ($P = 0.013$). High GPS scores reflected a low rate of complete remission post NACT, and the OS rate and disease-free survival time were substantially shortened (all $P < 0.001$). We presented a comparison of commonly used inflammation indicators in cancer patients (**Table 2**).

CONCLUSION

In summary, the clinical significance of nutritional screening tools is not only for the evaluation of the preoperative nutritional status, but more importantly, they predict the patient's clinical outcome and determine whether the patient can benefit from nutritional support, thereby, guiding their rational applicability in clinical settings (89). Understanding the patient's nutritional status and timely implementation of nutritional therapy can improve the patient's quality of life and reduce their risk of malnutrition (90). In recent years, imaging technology has rapidly advanced and also gained popularity in the field of nutritional assessment. CT scan can more directly and objectively assess the body's skeletal muscle and fat content. In addition, it measures the CT value of muscles in an area that indirectly reflects the density of skeletal muscle. Therefore, the content and density of skeletal muscle as new indicators for evaluating nutritional status have attracted widespread scientific attention (91). For the treatment of ovarian cancer in, always we pay too much attention to quality assessment of the operation itself, but most are late ovarian cancer patients, patients constitution is poor, poor nutritional status, therefore, we should as soon as possible before surgery for patients with nutritional screening, such as we mentioned earlier NRS, PG-SGA score, etc., if the malnutrition, to correct as soon as possible, in addition. It is also intuitively important to assess the inflammatory status of muscle mass and function, as well as CRP and other inflammatory systems. Inflammatory responses can promote tumor progression through multiple pathways. **Table 3** shows that the baseline status of city-wide inflammation can be used to predict disease-free survival and total mortality in ovarian cancer patients (**Table 3**). Of course, these studies also have limitations. There are many single-center retrospective studies, and there is a certain risk of bias. The critical values of each indicator of inflammation are not used, and the accuracy and sensitivity cannot meet the needs of clinical biomarkers. However, a "gold standard" is still lacking as the currently commonly used screening tools have their distinct characteristics. We believed that there was a very strong association within these indicators, both within nutritional status, inflammatory indicators, and between the two categories. Because inflammatory state induces catabolism and high protein consumption, with subsequent muscle loss (91). However, as we showed in **Table 3**, all these inflammatory indicators have some significance in the prognostic guidance of ovarian cancer (**Table 3**). However, their optimal cut-off values were different in the different cohorts. Thus, more forward-looking joint index screening approaches need to be developed in the future. The use of a variety of scores and a combination of the nutritional-related inflammation and muscle indicators are currently recommended to screen the nutritional status of patients more accurately with ovarian cancer. Future large-scale prospective studies, including ethnic, regional, and long-term follow-up, are needed to determine which markers are of greater prognostic value. This would further enable the formulation of a corresponding reasonable nutritional support regime. Finally, early detection and controlling of the progression of the disease are crucial to reducing its complications, improving the patients' quality of life, and shortening their length of hospital stay.

AUTHOR CONTRIBUTIONS

JM and YW: topic planning, manuscript development, and writing. CJ and LC: material collection and sorting. JC and DL: critical revision and supervision of the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Preoperative Prognostic Nutritional Index Predict Survival in Patients With Resectable Esophageal Squamous Cell Carcinoma

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Background: Prognostic nutritional index (PNI) is one of the most important factors related to prognosis in many types of cancer. This study aimed to evaluate the PNI on predicting the overall survival (OS) in resectable esophageal squamous cell carcinoma (ESCC).

Methods: A total of 165 patients with resectable ESCC were included in our retrospective study. PNI values before surgery were calculated for each patient [PNI = 10 × albumin (gr/dL) + 0.005 × total lymphocyte count (mm^3)]. PNI cutoff value was selected by drawing receiver operating characteristics (ROC) curve, which used OS time as the endpoint. The Kaplan-Meier method and the Cox regression model of multivariate analysis were used to analyze the prognostic relationship between PNI and OS.

Results: Among the 165 patients, 34 (20.6%) were women and 131 (79.4%) were men. The mean age was 62.67 ± 7.95 years, with the age range from 44 to 85 years. The average PNI was 46.68 ± 8.66. ROC curve showed that the best cutoff value was 43.85. All patients were divided into two groups: 72 patients (43.6%) were in the low PNI group (<43.85), while 93 patients (56.4%) were in the high PNI group (≥ 43.85). Univariate analysis demonstrated that PNI, tumor length, and T-stage and pathological stage were related to the prognosis of patients with ESCC ($P < 0.05$). The Kaplan-Meier curve showed that the high PNI group has significantly increased OS compared to low PNI group ($p = 0.01$). Three-year OS rates were 57.5% in the low PNI group while 77.7% in the high PNI group. Univariate analysis showed that advanced pathological stage, large tumor length, and low PNI (separately, $p < 0.05$) were significant risk factors for shorter OS. Multivariate analysis showed that tumor length ($P = 0.008$) and PNI ($P = 0.017$) were independent prognostic factors in patients with resectable ESCC.

Conclusion: PNI is a simple and useful predictive marker for the OS time in patients with radical esophagectomy.

Keywords: prognostic nutritional index, esophageal squamous cell carcinoma, overall survival, prognosis, radical esophagectomy

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INTRODUCTION

Esophageal cancer (EC) is one of the most common malignant tumors in the world. This disease has a crude mortality rate of 7.8/100,000 in 2020, which represented 5.5% of all cancer deaths and ranked as the sixth most common cause of cancer death (1, 2). In China, EC is the fourth most common cause of mortality, with 30.1 deaths per 100,000 in 2020 (3). Despite advances in the treatment of esophageal squamous cell carcinoma (ESCC), radical surgical operation remains the first choice of treatment, but the overall survival (OS) remains poor. In Japan, the 5-year survival rate of esophageal cancer is 44.1% (4), while in China it is 30.3% in the same period (5). Hence, there is a continuing interest in looking for a simple and useful prognostic maker to identify patients with ESCC who are at greater risk.

Due to dysphagia, swallowing pain, eating obstruction, and tumor consumption, patients with esophageal cancer are prone to malnutrition (6). Recently, the prognostic nutritional index (PNI) has been reported to be a prognostic marker in various gastrointestinal cancer, such as gastric cancer and gastro-esophageal junction cancer (7–10). Until now, there are few studies focused on the relationship between PNI and OS in resectable ESCC. Besides, the best critical value of PNI for predicting cancer prognosis is different in many reports. Thus, the aim of this research was to evaluate the prognostic value of PNI in predicting OS with ESCC and validate the best critical cutoff value of PNI in ESCC.

MATERIALS AND METHODS

Patients

From January 2017 to August 2020, a retrospective analysis was conducted in 165 patients with ESCC that underwent radical esophagectomy at the cancer hospital of Shantou University Medical College (Guangdong, China). All of the patients included in the analysis met the following criteria: (1) have ESCC confirmed by histopathology; (2) had surgery or preceded by adjuvant chemotherapy/radiotherapy before surgery; (3) have curative esophagectomy with R0 resection (*en bloc* resection with margins histologically free of disease); (4) have American Society of Anesthesiology (ASA) grade of 1-2. The ASA grade 1 was among 56 patients, which occupied 33.94% of our study group. The ASA grade 2 was among 109 patients, which occupied 66.06% of our study group.

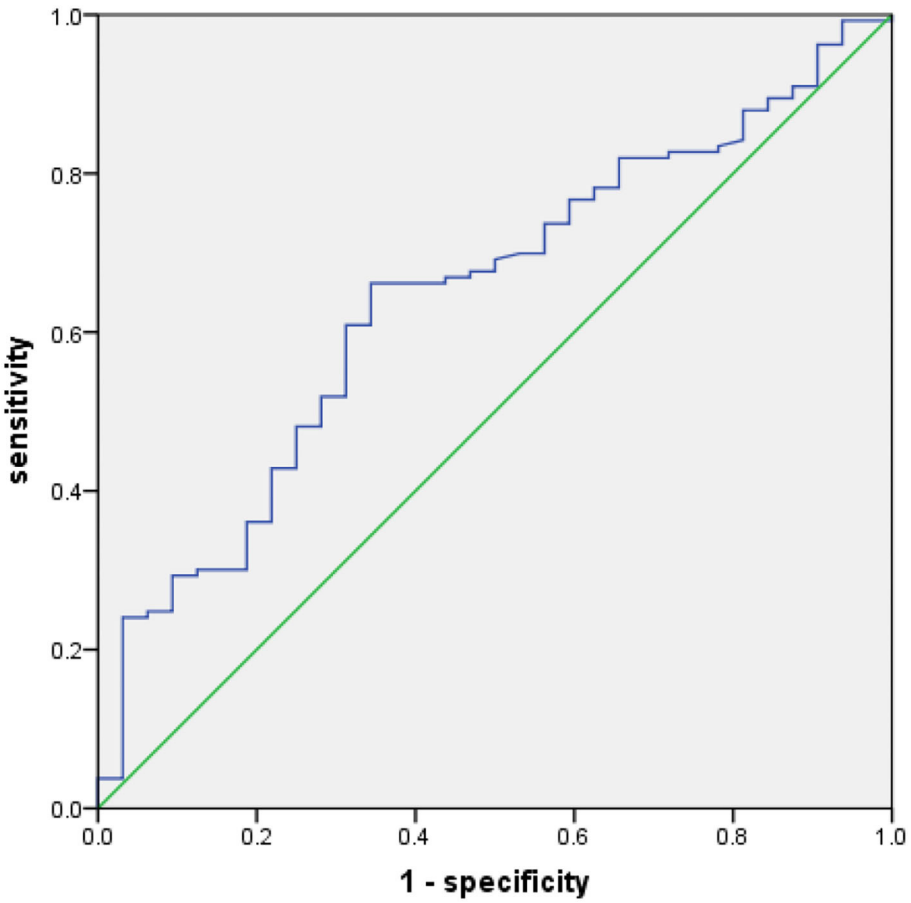

FIGURE 1 | Receiver operating characteristics (ROC) for overall survival (OS) was plotted to calculate the best critical value for prognostic nutritional index (PNI).

Albumin and lymphocyte counts were collected using a routine blood test within one week before surgery. The patients' clinicopathological characteristics and pathological data were obtained from medical records.

Follow-Up and Definitions

At our hospital, patients were followed up through telephone interviews and regularly received follow-up check-ups in the outpatient department. Recording of medical history, physical examination, blood routine, blood biochemistry, and CT scan of the chest were performed every 3 months for the first 2 years after surgery, then annually.

The last follow-up date was September 2021.

Overall survival was defined as the interval from the date of surgery to the date of cancer-related death or last contact.

The PNI was calculated using the following formula: PNI = 10 × albumin (gr/ dL) +0.005 x total lymphocyte count (mm^3). The best cut-off value of PNI was selected by drawing the ROC curve used OS time as the endpoint.

Statistical Analysis

The statistical was performed using IBM SPSS software version 21. The best cut-off value of PNI was selected by drawing the ROC curve, which used OS time as the endpoint. Then, the Youden index (sensitivity + specificity−1) was calculated. Independent sample *T*-test and one-way ANOVA were used for the comparison of measurement data.

Enumeration data were compared by the chi-square test. The Kaplan-Meier method and the Cox regression model of multivariate analysis were used to analyze the prognostic relationship between PNI and OS. $P < 0.05$ was considered statistically significant.

RESULTS

The ROC Curve for an Optimal Cutoff Value

The ROC curve was plotted as shown in **Figure 1**. When the PNI value was 43.85, the Youden index was at its maximum (YI = 0.297), showing that 43.85 was the best critical value for PNI (area under the curve (AUC) of the ROC was 0.644 with a sensitivity of 60.9% and a specificity of 65.6%). Hence, based on the best critical value of PNI, patients were divided the low-PNI group (< 43.85) and the high-PNI group (≥ 43.85).

Relationship Between PNI and Clinicopathological Characteristics

The relationship between PNI and clinicopathological characteristics of 165 patients enrolled in this study is summarized in **Table 1**. Among 165 patients, 34 (20.6%) were women and 131 (79.40%) were men. The mean age was 62.67 ± 7.95 years, with the age ranging from 44 to 85 years. The average PNI of 165 patients with ESCC was 46.68 ± 8.66. ROC curve showed that the best cutoff value was 43.85. All patients were divided into two groups: 72 patients (43.6%) were in the low PNI group (< 43.85), while 93 patients (56.4%) were in the high PNI group (≥ 43.85). Our study showed that PNI value was associated with tumor size ($p = 0.042$), T classification ($p = 0.002$) and pathological stage ($p = 0.014$).

TABLE 1 | Relationships between prognostic nutritional index (PNI) and clinicopathological characteristics in 165 patients with esophageal squamous cell carcinoma (ESCC).

Characteristic	Total patients	PNI		
		PNI <43.5 (*n* = 72)	PNI ≥43.5 (*n* = 93)	*P*-value
Male	131	61	70	0.137
Female	34	11	23	
Age (years)		62.97 ± 8.00	62.44 ± 7.96	0.809
Tumor diameter (cm)		4.66 ± 1.87	3.87 ± 1.34	0.042
Tumor location				0.175
Upper	23	13	10	
Middle	93	35	58	
Lower	49	24	25	
Differentiation				0.668
Well	10	3	7	
Moderate	126	56	70	
Poor	29	13	16	
T classification				0.002
T1	35	8	27	
T2	26	7	19	
T3	93	50	43	
T4	11	7	4	
Lymph node metastasis				0.051
N0	80	30	50	
N1	43	16	27	
N2	25	16	9	
N3	17	10	7	
Pathological stage				0.014
I	30	7	23	
II	61	25	36	
III	74	40	34	

PNI and Overall Survival

Finally, 165 patients were followed up and analyzed in our study. During the last follow-up date of September 2021, 133 patients (80.6%) were alive, while cancer-related death occurred in 32 patients. The Kaplan-Meier analysis and the log-rank test showed that patients with low PNI had a significantly worse prognosis in OS than those with high PNI ($p = 0.01$). To all patients, three-year OS rates were 57.5% in the low PNI group, while 77.7% in the high PNI group (**Figure 2**).

Multivariate Analyses of Independent Prognostic Factors

Among 165 patients, univariate analysis showed that advanced pathological stage ($p = 0.045$), large tumor length ($p < 0.001$), and low PNI ($p = 0.003$) were significant risk factors for shorter OS. Multivariate analysis showed that tumor length ($P = 0.008$)

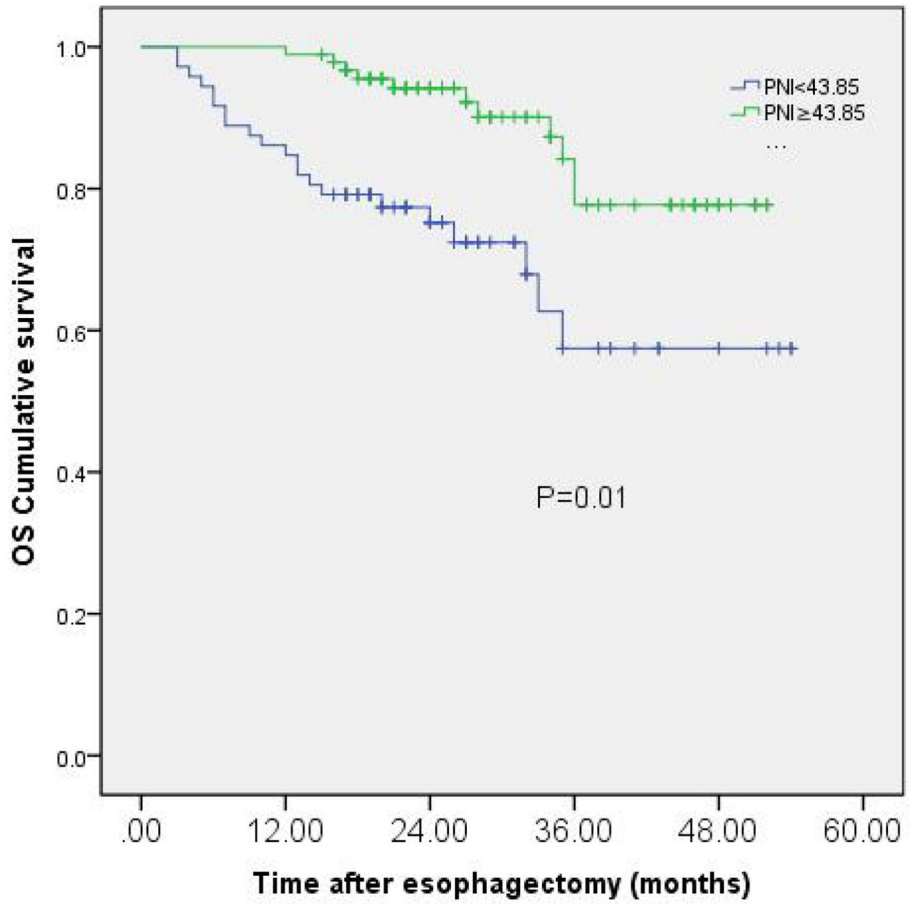

FIGURE 2 | Kaplan-Meier curves of OS based on PNI group in 165 patients with esophageal squamous cell carcinoma (ESCC).

TABLE 2 | Prognostic factors for overall survival (OS) in patients with ESCC.

Variables	Patients ($n = 165$)	Category	Univariate			Multivariate		
			HR	95% CI	*p* value	HR	95% CI	*p* value
Gender	131/34	Female/male	0.388	0.118–1.273	0.118			
Age	98/67	<65/≥65	1.015	0.973–1.060	0.486			
Pathological stage	91/74	I, II/ III	1.698	1.103–2.848	0.045			
Tumor length	59/106	<3 cm/≥3 cm	1.416	1.171–1.712	<0.001	1.313	1.072–1.608	0.008
PNI	72/93	<43.5/≥43.5	0.934	0.893–0.976	0.003	0.948	0.907–0.991	0.017

HR, hazard ratio; CI, confidence interval.

and PNI ($P = 0.017$) were independent prognostic factors in patients with resectable ESCC (**Table 2**).

DISCUSSION

Until now, ESCC treatment strategies included surgery, chemotherapy, and radiation (11). Despite advances in the treatment of ESCC, radical surgical operation remains the modality choice of treatment, but the rate of postoperative recurrence rate is still high (12). Although tumor, nodes, and metastases (TNM) stage, tumor diameter, and lymph node metastasis can evaluate the prognosis of esophageal cancer, the predictive value is still limited for a long time. Therefore, it will become more and more important to find a simple, reliable, and repeatable factor that can accurately predict a patient's prognosis for ESCC. Accumulating studies (13–15) have demonstrated that the nutritional status and immune function are related to the occurrence and development of malignant cancers, while serum protein and lymphocyte count can reflect the nutritional status

of the body. PNI index is a nutritional evaluation index that was put forward by Japanese scholar Onodera (16), which has been widely applied to evaluate the prognosis of cancer (17–19). Until now, there are few studies focused on the relationship between PNI and OS in resectable ESCC. Therefore, this study conducted a retrospective analysis to evaluate the prognostic value of PNI in resectable ESCC.

Prognostic nutritional index involves the values of serum albumin and peripheral blood lymphocyte count two parameters, which are routinely measured in clinical practice, particularly before surgical operation. Serum albumin is produced by hepatocytes, which is an important component of the plasma, and its level can reflect the body's nutritional status (20). Recently, several studies have shown that low serum albumin is a risk factor for malignant tumor prognosis (21–23), although it alone is not sufficient and accurate to predict the final outcome in cancer patients. Another calculated element of PNI is the blood lymphocyte count. Lymphocytes are one of the fundamental components of cell-mediated immunity with inhibitory effects on the proliferation and invasion of tumor cells *via* cytokine-mediated cytotoxicity (24, 25). Lymphocyte is an important part of the body's immunity, in which low lymphocyte indicates that the body's immunity is not good or there is a disorder, thereby making the prognosis of patients worse (26). Therefore, the decrease of PNI reflects the decreased inhibition of inflammatory response and tumor cell invasion, thus affecting the prognosis of tumor patients. However, the mechanism of PNI influencing the prognosis of tumor patients is not clear.

In our present study, we found that PNI, tumor length, and T-stage and pathological stage were related to the prognosis of patients with resectable ESCC. Multivariate analysis showed that tumor length and PNI were independent prognostic factors in patients with resectable ESCC. Patients with low PNI have significantly decreased OS in comparison to those with high PNI. These results suggest that PNI is a simple and useful predictive marker for the overall survival time in patients with radical esophagectomy.

The best critical cutoff value of PNI in predicting OS in patients with malignant tumors is still controversial, and previous studies showed various cutoff values for PNI (27–29). Therefore, another aim of our study was to propose and validate an optimal cutoff value which can predict OS with better accuracy in ESCC. The best cut-off value of PNI in our study was selected by drawing an ROC curve, which used OS time as the endpoint, and then calculating the maximum Youden index, which represented the best sensitivity and accuracy and has a good clinical practicability. However, the cutoff value for PNI in our study seemed to be lower than those reported in lung cancer and gliomas (30, 31). The possible reason may be that due to the location of esophageal cancer, most patients have some degree of swallowing difficulty, which results in poor nutritional status.

Finally, several limitations were considered in our study. First, this was a retrospective study that included a limited number of patients, which may lead to a selection bias. Second, due to the follow-up time, we lack the 5-year survival rate, and only had 3-year survival rate. Therefore, our conclusions may be strengthened by further exploration. On the other way, the long data collection time in this retrospective analysis and advances in surgical technology during this period may influence the clinical outcome.

CONCLUSION

The present study demonstrated that the PNI is a simple and useful predictive marker of the OS time in patients with radical esophagectomy. PNI can be routinely calculated in patients with ESCC before surgery to help clinicians develop effective measures for early 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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Cancer Hospital of Shantou University Medical College. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ZZ and HZ designed the study. ZZ was the main author of the manuscript and they performed data extraction and writing. HC supervised the project, assisted with the statistical analysis, and interpretation of the results. The paper was written by ZZ. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.824839/full#supplementary-material

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BRIEF RESEARCH REPORT
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Long Term Survivals in Aggressive Primary Brain Malignancies Treated With an Adjuvant Ketogenic Diet

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Aggressive primary brain tumors (APBT) glioblastoma multiforme and grade IV astrocytoma are treated with multimodality treatments that include surgery to remove as much tumor as possible without sacrificing neurological function followed by radiation therapy and chemotherapy usually temozolomide. Survivals in adults are in the range of 8–16 months. The addition of a ketogenic diet (KD) to rodents with transplanted brain tumors increased survival in nine of 11 animals to over 299 days compared to survival in untreated controls of 33 days and radiation only controls of 38 days. We treated humans with APBT with standard of care neurosurgery immediately followed by 6 weeks of an adjuvant ketogenic diet concurrent with radiation therapy and temozolomide. Twice daily measurements of blood ketones and glucose were recorded and the patients' diet was modified toward the goal of maintaining blood ketone levels approaching 3 mM. Of the nine patients who completed the protocol three younger patients age 32, 28, and 22 at enrollment are alive and employed with clinically stable disease and brain images 74, 58, and 52 months since diagnosis. All the six older patients mean age 55 have died with disease progression detected on average 8 months after Dx. In conclusion: 1. It is possible to implement and maintain dietary induced ketosis in patients with APBT; 2. The longer survivals observed in younger patients treated with KD need to be confirmed in larger studies that should be focused on younger patients possibly under age 40.

Keywords: glioblastoma multiforme, ketogenic diet, diet therapy, long term survival, verified ketosis

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INTRODUCTION

While treatments for many malignancies have advanced to more targeted therapies, systemic treatments for aggressive primary brain malignancies (glioblastoma multiforme, GBM, also known as WHO grade IV astrocytoma) continue to rely on alkylating agents that can cross the blood brain barrier (usually temozolomide, TMZ) (1). Current therapy includes surgical resection of as much of the tumor as possible without impairing vital brain functions, followed

by radiation therapy and TMZ (2). The addition of TMZ prolongs survival on average 2.5 months (3). Bevacizumab (Avastin®) does not increase survival in patients with newly diagnosed GBM, but is helpful in the treatment of relapsed patients (4). Wearing an "electric hat" for alternating electric field therapy is reported to prolong survival on average by 2.7 months (5). These therapies prolong life incrementally with median survivals in adult patients in the range of 8–16 months (6).

Studies including rodent models suggest that adding a ketogenic diet (KD) to some of the standard treatments used in humans may prolong survival. The addition of KD to radiation therapy markedly prolonged the life of nine of 11 rodents. Histological evaluation 299 days post GBM implantation showed that nine of 11 animals were free of disease. This compared with survival of 33 days in untreated controls, and 38 days in animals treated with just radiation (7). Reports from other investigators also demonstrate increased survival in animals treated with KD, with retarded growth of their brain malignancy (8–11).

We report long term follow up of nine adult patients with aggressive primary brain tumors who, following their initial neurosurgery, were treated with 6 weeks of an adjuvant KD combined with standard of care radiation therapy and chemotherapy with TMZ. The patients' blood ketones were measured twice daily and the results were used to make adjustments in their diets to assure that ketosis was maintained during the entire 6 weeks of the study period.

METHODS

Clinical Protocol

After signing informed consent 12 patients were enrolled in our clinical trial protocol that was IRB approved (11-452s). Two patients (#1 and #2, **Tables 1**, **2**) were studied with the original protocol that stipulated starting the KD after they failed conventional treatments, and 10 were treated with the revised protocol that started the KD at the same time as the initial radiation and chemotherapy treatments, and continued KD for 6 weeks. This protocol had the primary objectives of investigating side effects attributable to the KD, as well as noting tumor response and time to progression. Patient #3 withdrew before completing just 4 weeks of the diet because he had to return to work as a long haul truck driver and could not complete the protocol after the fourth week. Nine patients completed the revised protocol.

The inclusion criteria were participants must be over 16 years of age, had histologically confirmed diagnosis of GBM, had an Eastern Cooperative Oncology Group performance status of $\leq$2, a life expectancy of $>$3 months, could tolerate a high-fat diet, and had the ability to give informed consent. The exclusion criteria were participants may not have diabetes mellitus, may not have had a cholecystectomy within a year prior to entering the study, did not have any malignancy other than the brain cancer, had not participated in another investigational study within 2 weeks prior to this study's entrance, did not have brain metastasis from a non-brain primary tumor, did not have any major comorbidity such as liver, kidney, or heart failure, and were not pregnant.

The protocol KD was caloric balanced, based on the patient's starting weight and was constructed using the KetoDietCalculator software program so that the ratio in grams of fat to combined grams of protein and carbohydrates was 3:1. The calculation ranges used for all subjects in the original protocol was 20–25 kilocalories (kcal)/kilogram (kg) of body weight, considered a mild restriction. The protein was low at 20 kcal/kg body weight so 25 kcal/kg was used to provide minimum of 0.6 gram (g) protein (pro)/kg. Actual meals plan for all subjects started as a range of 23–25 kcal/kg. In that range, with a 3:1 ratio, a 0.6–0.7 g pro/kg was provided. Calculations for an 1,800 kcal daily intake yields the following range of macronutrients: 1,566 fat kilocalories (174 grams of fat) 234 protein and carbohydrate kilocalories (58.5 grams). Protein grams for the meal plan are based on the subject's weight to achieve at least 0.6 gm pro/kg and the remaining kcal from carbohydrates. A gram food scale was given to each participant to ensure the correct measurements of each food item as calculated by the KetoDietCalculator. Other studies have used 1,600 kcal and higher fat ratio of 4:1 but those provide even lower protein so are not sustainable for muscle maintenance.

Before starting and after completing the KD protocol, the patients had a history and physical exam along with complete blood counts, chemistries, lipids, and uric acid. During the 6 weeks of KD, the patients recorded their daily weights, and twice daily measurements of blood glucose and ketones obtained upon waking prior to eating and evenings 2 h after eating. Each patient was given an Omron Model HBF-400 Scale for their daily weights, an Abbot Precision Xtra Meter with test strips to measure their blood ketones and glucose twice daily, a log to record their results and a food scale. Participants received dietary instruction by a registered dietitian who developed a meal plan and menus for each subject. In addition, a dietitian called or visited the patients regularly (at least once a week) to review results of the patients' glucose and ketone measurements as they related to the food logs which were kept by the patients throughout their time on the KD. Follow up examination and imaging were at the discretion of the referring physician.

Protocol Revision, Tolerability, and Side Effects

Our initial protocol stipulated starting of the KD after tumor growth was demonstrated following the patients' initial treatment with surgery, radiation and temozolomide. We revised our protocol based on a report, in a rodent model, that nine of 11 mice with a transplanted primary brain tumor that were treated with a KD simultaneously with radiation therapy survived, whereas all of the control mice and mice treated with only radiation therapy or only KD died (7). The success of this simultaneous dual treatment in animals prompted a revision of our protocol so that patients' initial post-surgery treatment included a KD begun at the same time as radiation therapy and chemotherapy. The enrolled patients maintained ketosis for 6 weeks with support from their family and/or caregivers and our dieticians (MN, and MMN). Participants maintained blood glucoses under 100 mg/dl and blood ketones

around 1–2 mM. All participants lost weight, averaging about 5 lbs. Combining the KD with standard-of-care radiation and chemotherapies did not add any significant side effects to the patients' therapy.

RESULTS

Nine of 10 patients completed the revised protocol (**Figure 1**) with KD therapy initiated at the same time that they started their treatments with radiation therapy and TMZ. Patient #3 had to return to work as a long haul truck driver and could not complete the protocol after the fourth week. Blood glucose and ketone concentrations were measured twice daily, fasting in the morning when the patients first awoke and in the evening before they went to bed. **Table 1** shows the means and standard deviations for each patient's ketone and glucose measurements on days 1 and 14 and averages throughout the study. Aggregate averages for all the patients and lines of linear best fit are depicted in **Figure 2** for the patients' twice daily blood glucose and ketone measurements as well as their daily weights.

Patient outcomes for the 12 patients initiating the KD protocols are presented in **Table 2**. The two patients (Patients # 1 and 2) who were treated with KD after they had progression of their disease following initial standard of care had died as a result of their GBM. Patient #3 failed to complete the required 6 weeks of the protocol. Nine patients (#4 thru 12) completed the protocol and were treated with the KD simultaneously with standard of care radiation and chemotherapies administered following their neurosurgery. Three of these nine patients are progression-free 80, 64, and 62 months since diagnosis. These three long term survivors were younger: 32, 28, and 22 years old at the time of diagnosis. The other six patients were older, mean age 55 at diagnosis, and had progression of their disease 8, 11, 9, 6, 6, and 6 months after their diagnosis. The two patients who are alive 80 and 62 months without progression had GBM that were positive for the isocitrate dehydrogenase-1 R132H mutation (IDH1-R132H). The tumor of the third long-term progression-free patient was grade III astrocytoma (IDH mutation status undetermined).

DISCUSSION

Younger patients with GBM are reported to have a better prognosis (12–17). A recent report documents long term survival in a 26 year old male treated for GBM with only a KD who is alive 80 months post diagnosis with just slow growth of this tumor documented by serial imaging studies (18). Our present study showed three of nine patients treated with an adjuvant ketogenic diet along with standard treatments of surgery and radiation are still alive 80, 62, and 64 months from diagnosis with no evidence of disease advancement. These long-term survivors were all younger (age 32, 28, and 22) when diagnosed as compared to those who died with progression of disease (mean age 55 at diagnosis).

Longer survival in younger patients suggests that aggressive primary brain cancers in these patients may have a biological propensity for slower growth and/or a greater sensitivity to treatment with a ketogenic diet along with radiation and chemotherapy (2, 19). Tumors of two of our patients tested positive for the IDH 131/132 polymorphism associated with longer survival (20). These features at diagnosis suggested that these patients may have had a favorable prognosis. Methylation of the MGMT promoter (21) was not evaluated in our study. The six older patients treated in our study, mean age 55, did not live longer than expected and probably did not benefit from the addition of the ketogenic diet to their therapy. Our results align with previous reports showing that age is a critical factor for survival (22, 23). We suggest that future studies evaluating the addition of a ketogenic diet to GBM therapy should be targeted toward younger patients perhaps 40 years of age or younger (24).

After their initial neurosurgery, radiation, chemotherapy and adjuvant ketogenic diet treatments, all of our patients reported some decrease in mental capacity. One of the surviving patients prior to his GBM diagnosis worked as an investment counselor. After his initial surgeries, radiation and chemotherapy, he could not perform the executive functions quick enough to continue working in that capacity. However, he is able to work in a position that does not require such a high level of executive function. All three of the surviving patients have returned to full employment.

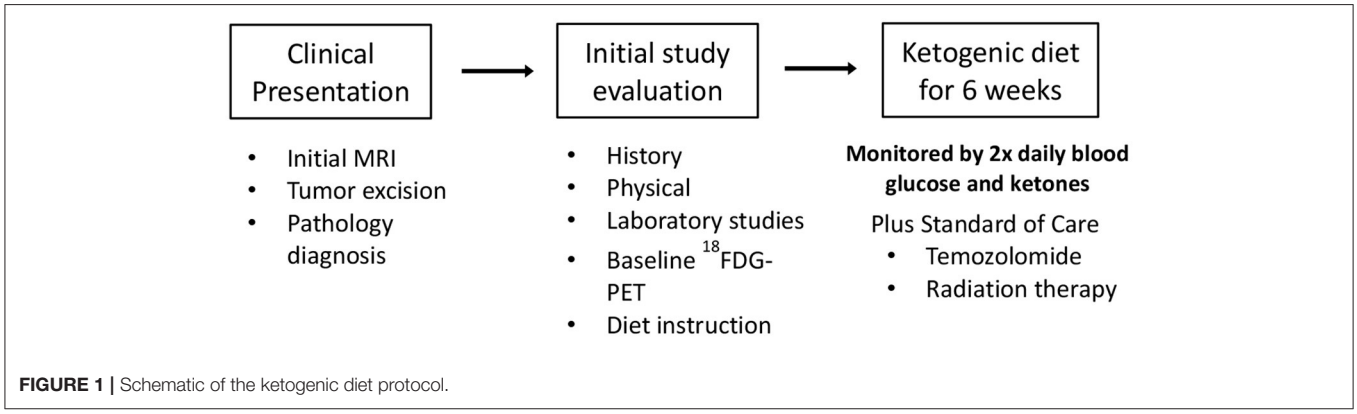

FIGURE 1 | Schematic of the ketogenic diet protocol.

TABLE 1 | Blood glucose and ketones: first and last days and averages.

Averages glucose		Through day 42								
Pt#-Age-Gen		First glucose Ave ± StdDev			Last glucose Ave ± StdDev			Ave-glucose Ave ± StdDev		
1	55 M	90	±	11.1	80.2	±	8.3	85.6	±	11
2	52 M	81.7	±	15	81.7	±	7	81.7	±	11.7
3	71 M	106.8	±	13.7	123.5	±	26.2	114.4	±	21.8
4	32 M	97.9	±	9.3	100.2	±	11.1	98.9	±	10.1
5	57 M	102.6	±	10.7	104.5	±	8.1	103.5	±	9.5
6	35 M	116.5	±	23.5	115.9	±	25.9	116.2	±	24.4
7	37 M	88.9	±	8.8	99.7	±	12	94.2	±	11.8
8	67 M	82.1	±	11	90	±	10.6	85.9	±	11.4
9	28 F	87.1	±	10.2	84.1	±	8.5	85.6	±	9.4
10	22 M	80.4	±	9.8	92	±	15.1	85.3	±	13.4
11	68 M	137.2	±	20.2	146	±	30.5	141.5	±	25.9
12	63 M	97.5	±	8	107.5	±	11.7	102.5	±	11.2
Average ketones		**Through day 42**								
Pt#-Age-Gen		First ketone Ave ± StdDev			Last ketone Ave ± StdDev			Ave- ketone Ave ± StdDev		
1	55 M	2.7	±	0.7	4.1	±	0.7	3.3	±	1
2	52 M	2.9	±	0.9	4	±	1.1	3.5	±	1.1
3	71 M	1.5	±	0.9	2.6	±	1.1	2	±	1.1
4	32 M	1.6	±	1.2	1.8	±	0.8	1.7	±	1
5	57 M	2.1	±	0.5	2.8	±	0.7	2.5	±	0.7
6	35 M	0.9	±	0.7	2	±	1.1	1.4	±	1.1
7	37 M	0.7	±	0.4	2	±	0.9	1.3	±	0.9
8	67 M	1.1	±	0.6	1.2	±	0.6	1.1	±	0.6
9	28 F	3	±	0.8	3.5	±	0.9	3.3	±	0.9
10	22 M	1.5	±	1.1	2.6	±	1.4	2	±	1.3
11	68 M	0.4	±	0.2	1.2	±	0.7	0.8	±	0.6
12	63 M	0.6	±	0.3	1.5	±	0.6	1	±	0.7

The cooperation of the patients, their families and caregivers was essential for preparation of the foods in the ketogenic diet and twice-a-day monitoring and recording of blood glucose and ketone levels. Following neurosurgery, patients may require assistance to check their blood ketones and implement changes in their diet based on their ketone concentrations. It is critical that the patients' ketotic state be verified with twice daily checks of the level of ketones in their blood. Ongoing reinforcement of the protocol was provided by dietitians (MMN or MN) who helped to maintain the patients' ketotic state throughout the 6 weeks study. If needed, dietary modifications were made by the dietitian (MN) to keep the twice daily blood ketone levels approaching 3 mM. Patients and their families agreed that 6 weeks was about as long as they could adhere to the dietary specifications and restrictions stipulated by the ketogenic diet.

It was hypothesized that aggressive primary brain tumors may not be able to metabolize ketones like normal brain tissues depriving the tumor tissue of nutrients required for survival and growth and this was the rationale used to initiate this study (25). However, ketone metabolism in human brain tumors does not differ from metabolism in neighboring normal brain, suggesting that selective ketone metabolic differences between normal and malignant brain cells may not be a plausible mechanism for the proposed antineoplastic effects of dietary induced ketosis (26). β-hydroxybutyrate is the main ketone produced with a ketogenic diet and is known to function as a histone deacetylase inhibitor which affects translation of DNA and this may be part of the mechanism responsible for the significant anti-tumor effects observed in controlled studies using animal models of aggressive primary brain cancers treated with a ketogenic diet (8, 9, 26–29).

Long term survival with aggressive primary brain cancer is possible (30–33). The three younger patients reported here are alive and working with stable brain images and clinical exams following treatment with standard of care neurosurgery followed by radiation, temozolomide and an adjuvant ketogenic diet. The diet was implemented and adjusted over time by

TABLE 2 | Patient outcomes.

Original protocol: **Treated with KD after tumor progression on standard of care treatment**				
Pt#	**Age**	**Sex**		
1	55	M	Tumor progression on ketogenic diet	
2	52	M	Tumor progression on ketogenic diet	
Revised protocol: **Treated with KD at same time as standard of care treatment**				
			Months to progression	**Months of progression free survival**
3*	71	M		
4	32	M		**80**
5	57	M	8	
6	35	M	11	
7	37	M	9	
8	67	M	6	
9	28	F		**62**
10	22	M		**64**
11	68	M	6	
12	63	M	6	

**Patient 3 withdrew before completing just 4 weeks of the diet. The bold values indicates patients alive without disease progression.*

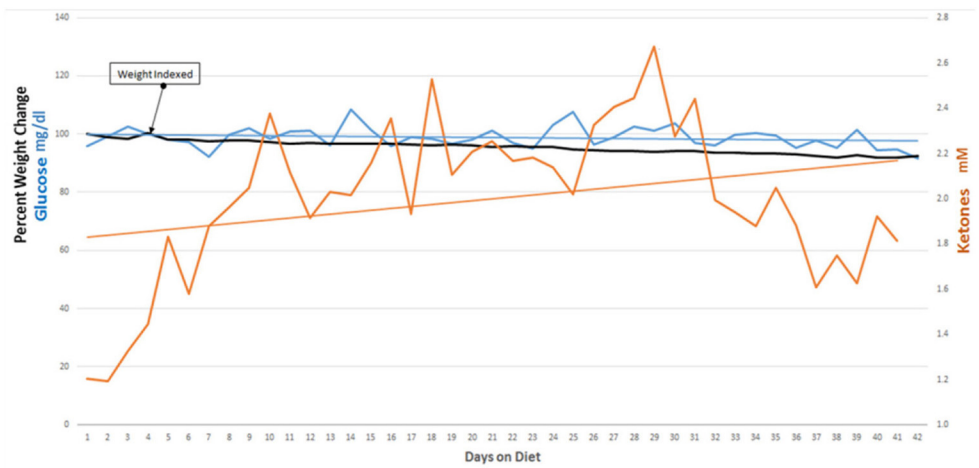

FIGURE 2 | Daily glucose and ketone averages and weight change.

registered dieticians experienced with using the ketogenic diet for patients with intractable seizures (34). Following neurosurgery our patients needed help from family members for executive functions and this included assistance with food preparation and adjustments to their diets based on the results of twice a day measurements of blood glucose and ketones.

Previous studies demonstrated that it is possible to prescribe a ketogenic diet in patients with primary aggressive brain malignancies (35–38). Our study extends these reports by enlisting the cooperation of family members and dietitians to help insure maintenance of the ketotic state. Whether the diet contributed to the longevity in our three surviving patients is a question that can only be answered by larger studies. Since 12 older patients with verified diet induced ketosis, six in our study and six reported by van der Leuw (24) did not appear to benefit from an adjuvant ketogenic diet, we suggest that future evaluations of the ketogenic diet in patients with aggressive primary brain cancer be restricted to younger patients, possibly under 40 years of age.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB), Michigan State University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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A Novel Clinically Prognostic Stratification Based on Prognostic Nutritional Index Status and Histological Grade in Patients With Gallbladder Cancer After Radical Surgery

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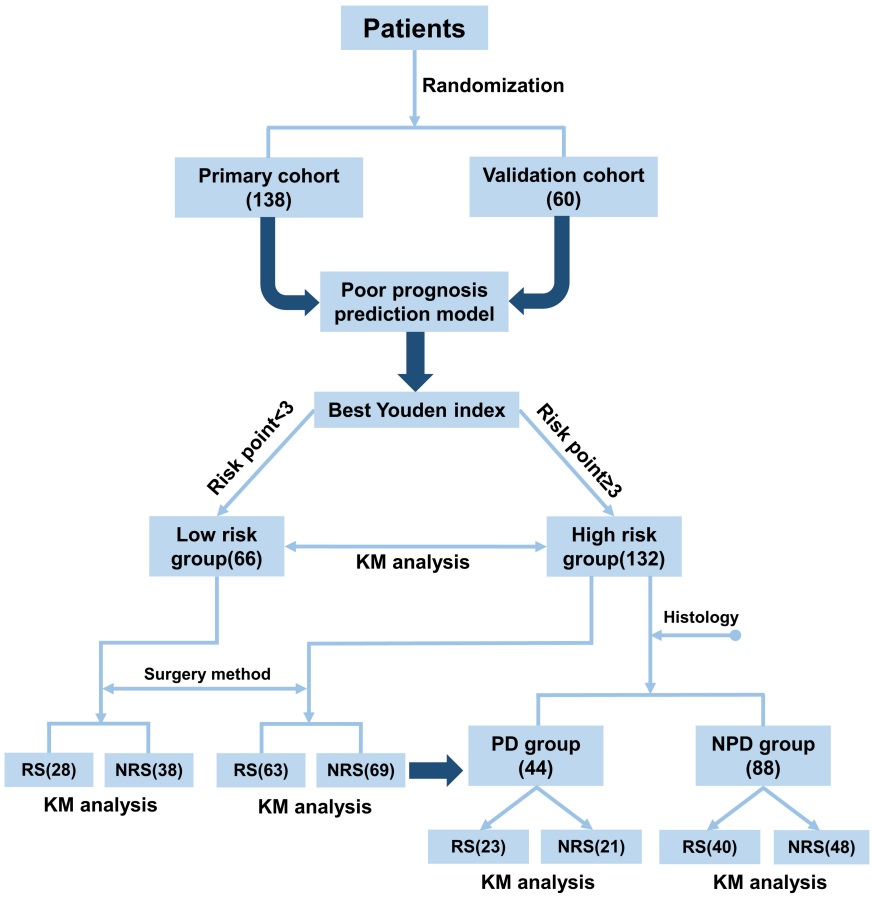
Purpose: Gallbladder carcinoma (GBC) is the most common malignancy of the biliary tract, with a 5-year survival rate of 5%. The prognostic models to predict the prognosis of patients with GBC remain controversial. Therefore, to construct a prognosis prediction of GBC, a retrospective cohort study was carried out to investigate the prognostic nutritional index and histological grade in the long-term outcome of patients with GBC after radical surgery (RS).

Methods: A retrospective study of a total of 198 patients with GBC who underwent surgical treatment were enrolled. The hematological indicators, imageological data, and perioperative clinical data were acquired for statistical analysis and poor prognosis model construction.

Results: Prognostic nutrition index (PNI) < 45.88, maximum tumor diameter (MTD) > 2.24 cm, and jaundice (JD) were all associated with a poor prognosis in multivariate logistic regression analysis. The prognosis prediction model was based on the three risk factors, which indicated a superior predictive ability in the primary cohort [area under the curve (AUC) = 0.951] and validation cohort (AUC = 0.888). In multivariate Cox regression analysis, poorly differentiation (PD) was associated with poor 3-year survival. In addition, Kaplan–Meier (KM) survival analysis suggested that GBC patients with high-risk scores and PD had a better prognosis after RS ($p < 0.05$), but there was no significant difference in prognosis for patients with non-poorly differentiation (NPD) or low-risk scores after RS ($p > 0.05$).

Conclusion: Our prediction model for GBC patients with prognosis evaluation is accurate and effective. For patients with PD and high-risk scores, RS is highly recommended; a simple cholecystectomy can also be considered for acceptance for patients with NPD or low-risk score. The significant findings provide a new therapeutic strategy for the clinical treatment of GBC.

Keywords: gallbladder carcinoma, prognosis, prognostic nutrition index, histological grade, radical resection



SCHEME 1 | Flowchart of manuscript design.

INTRODUCTION

Gallbladder carcinoma (GBC) is the most common malignancy of the biliary tract (1). The surveillance, epidemiology, and end results program estimated that the incidence of GBC was 2.5 per 100,000 persons (2, 3). GBC is difficult to be diagnosed at an early stage due to the symptomless nature. When an accurate diagnosis is made, radical cure often cannot be implemented due to the direct invasion into adjacent structures, such as the hepatic artery or portal vein, as well as metastasis *via* the lymphatic, perineural, and hematogenous routes (4–6). The median overall survival (OS) for GBC was about 6 months, with a 5-year survival rate of 5% (7, 8). Therefore, it is important to improve the early diagnostic rate of patients with GBC and evaluate their prognosis perioperative-operation.

Although various scoring systems are used in clinical practice, the preoperative prognostic models to predict the prognosis of patients with GBC remain controversial (9–11). These models were based on a number of hematological and clinical indicators, such as prognostic nutrition index (PNI), the diameter of tumor, jaundice, and TNM stage (12–15). Numerous clinical pieces of evidence have shown that the PNI was associated with prognosis in patients with digestive tract malignancies, such as hepatocellular carcinoma, gastric carcinoma, pancreatic carcinoma, and colorectal carcinoma (16–19). Moreover, several studies have investigated the relationship between histological grade and prognosis of endometrial and breast cancer (20, 21). However, the PNI and histological grade have not yet been determined in the prediction of prognosis in patients with GBC. Therefore, to construct a poor prognosis prediction of GBC to guide its treatment, we conducted a retrospective cohort study of patients with GBC to investigate the PNI and histological grade indicators in the long-term outcome.

Abbreviations: PNI, prognostic nutrition index; MTD, maximum tumor diameter; LNM, lymph node metastasis; NRS, non-radical surgery; RS, radical surgery; JD, jaundice; PD, poorly differentiation; NPD, non-poorly differentiation.

PATIENTS AND METHODS

Study Population

We conducted a retrospective study on a total of 198 patients with GBC who underwent surgery in the Department of Hepatobiliary Surgery of Fujian Medical University Union Hospital between January 2008 and December 2017. The study was carried out in accordance with the protocol approved by the Ethics Committee

of the Medical Faculty of Fujian Medical University, according to the Declaration of Helsinki.

All the patients included in the present study fit the following criteria: (1) patients with GBC underwent surgery [radical surgery (RS) or non-radical surgery (NRS)]; and (2) neither radiotherapy nor chemotherapy was administered prior to or posterior to the surgery. The histological diagnosis of the tumors was based on the criteria of the World Health Organization (WHO), and the TNM stage was determined according to the American Joint Committee on Cancer (AJCC, 7th). The patients with the following characteristics were excluded: (1) the medical history, operation records, and auxiliary examination are incomplete; (2) death occurred during and after the operation; (3) patients are not willing to cooperate with the investigation during the follow-up; and (4) patients with coexisting or previous cancers. Based on the hospital database, the following data were collected for each patient, such as age, gender, T stage, and other miscellaneous clinical characteristics.

Analysis of Indicators

The prognostic nutrition index was calculated from the baseline clinical peripheral lymphocyte count (PLC) ($*10^9$/L) and serum albumin (ALB) (g/L) within 1 week before surgery as follows (22, 23): PNI = ALB (g/L) + 5 × PLC ($*10^9$/L). Jaundice was defined as yellow staining of the sclera of the patients (serum bilirubin > 34 mmol/L). Patients with postoperative recurrence/metastasis/death time less than 36-months were considered to have poor prognosis. The obtained hematological index and imageological index were established with a receiver operating characteristic (ROC) curve of poor prognosis. The cut-off values of these variables were obtained according to the best Youden index when these areas under the curve (AUC) were more than 0.6, and then classified into two categories; the classification criteria for each potential index were determined through the literature when the AUC was less than 0.6.

Follow-Up Assessments

All of the patients were followed by telephone interviews or outpatient reviews. The duration of follow-up was defined as the time between the date of operation and the last follow-up before the data were analyzed, or the date of death. The patients received follow-ups until December 2020. The patients were followed up every 3 months during the first postoperative years, and every 6 months for the next 2 years. Physical examination, peripheral blood tumor marker measurements (Ca199 and CEA), and pectoral and abdominal computed tomography (CT) or magnetic resonance imaging (MRI) were performed during the follow-up period. The median follow-up duration was 17.5 months (range 1–36 months). The follow-up rate of this study was 87.9%.

Statistical Analysis

The statistical analyses were performed by standard SPSS (version 25.0, IBM, Armonk, NY, United States). The categorical variables were presented as numeric values and percentages, and the continuous variables with normal distributions were presented as means and standard deviations (mean ± SDs). An independent *t*-test was used to compare the groups of continuous, normally distributed variables. Pearson's χ^2 test was used to determine the significance of the differences for the dichotomous variables. Univariate analysis and multivariate analyses with the logistic/Cox regression proportional hazard

TABLE 1 | Baseline characteristics of study patients.

Variable	Primary cohort	Validation cohort	*P*-value
PNI	46.36 ± 5.92	45.67 ± 7.46	0.487
Age (years)	57.37 ± 10.17	57.02 ± 11.68	0.831
Gender			
Female	103(74.64)	45(75.00)	0.957
Male	35(25.36)	15(25.00)	
MTD (cm)	2.41 ± 0.39	2.21 ± 0.45	0.905
CEA (ng/mL)	3.03 ± 0.52	3.15 ± 0.53	0.140
CA199 (kU/L)	158.42 ± 234.06	189.25 ± 227.58	0.391
LNM			
Positive	42(30.43)	19(31.67)	0.863
Negative	96(69.56)	41(68.33)	
TNM staging			0.536
I	21(15.22)	5(8.33)	
II	47(34.06)	20(33.33)	
III	49(35.50)	23(38.34)	
IV	21(15.22)	12(20.00)	
Histological grading			
PD	43(31.16)	21(35.00)	0.622
NPD	95(68.84)	39(65.00)	
Histological type			
Adenocarcinoma	126(91.30)	58(96.67)	0.176
Other types	12(8.70)	2(3.33)	
Jaundice			
Present	19(13.77)	11(18.33)	0.410
Absent	119(86.23)	49(81.67)	
Cholelithiasis			
Present	40(28.99)	21(35.00)	0.400
Absent	98(71.01)	39(65.00)	
Tumor location			
Neck	69(50.00)	26(43.33)	0.388
Others	69(50.00)	34(56.67)	
Liver Invasion			
Present	97(70.29)	39(65.00)	0.461
Absent	41(29.71)	21(35.00)	
Choledoch Invasion			
Present	64(46.38)	27(45.00)	0.858
Absent	74(53.62)	33(55.00)	
Diabetes			
Present	30(21.74)	15(25.00)	0.615
Absent	108(78.26)	45(75.00)	
Hypertension			
Present	25(18.12)	15(25.00)	0.268
Absent	113(81.88)	45(75.00)	
Smoking			
Present	27(19.57)	13(21.67)	0.735
Absent	111(80.43)	47(78.33)	
Poor prognosis			
Present	96(69.57)	41(68.33)	0.868
Absent	43(30.43)	19(31.67)	

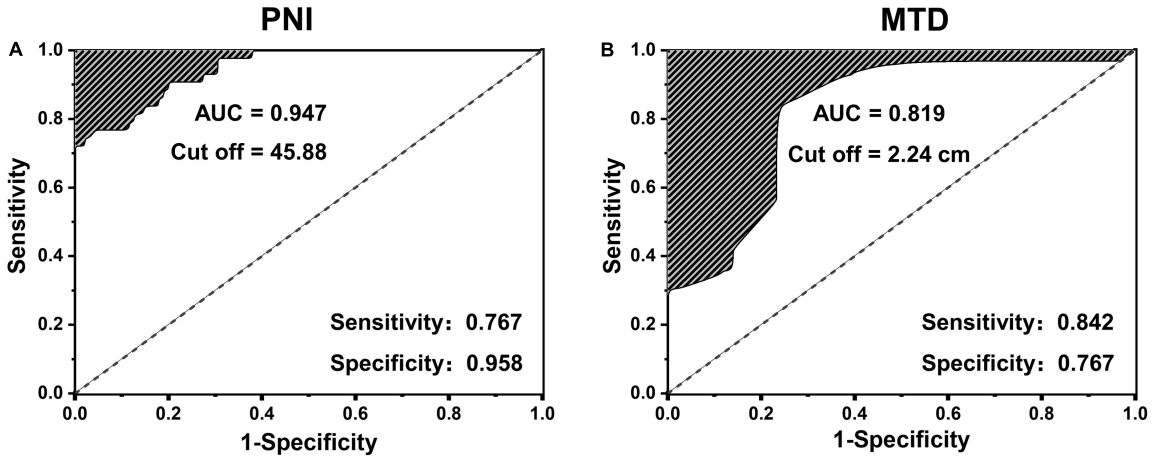


FIGURE 1 | The receiver operating characteristic (ROC) curve of poor prognosis established with the candidate factors of panel **(A)** prognostic nutrition index (PNI) and **(B)** maximum tumor diameter (MTD).

TABLE 2 | Univariable and multivariate regression analyses of factors for the presence of poor prognosis in the primary cohort.

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95%CI**	***P*-value**	**OR**	**95%CI**	***P*-value**
PNI < 45.88	3.508	2.203–5.583	<0.001	3.269	2.026–5.043	<0.001
Gender	0.825	0.365–1.865	0.644			
Age < 60	1.121	0.858–1.856	0.785			
LN metastasis	1.676	0.734–3.827	0.220			
TNM staging	0.561	0.233–1.411	0.056			
MTD > 2.24 cm	1.116	1.049–2.273	<0.001	0.075	1.015–2.374	0.002
CEA < 5 ng/mL	0.768	0.458–1.569	0.485			
CA199 < 40 kU/L	0.895	0.396–1.636	0.652			
PD	5.897	1.225–8.378	0.027	3.288	0.133–8.514	0.467
Pathology	1.115	0.317–3.925	0.865			
Jaundice	3.140	1.839–6.033	0.006	3.059	1.494–5.751	0.021
Cholelithiasis	1.080	0.486–2.401	0.851			
Tumor location	1.610	0.778–3.333	0.200			
Liver Invasion	2.302	1.082–4.894	0.030	1.741	0.454–6.682	0.419
Choledoch Invasion	1.643	0.644–4.188	0.298			
Diabetes	2.027	0.706–5.820	0.189			
Hypertension	2.290	0.804–6.527	0.121			
Smoking	2.374	0.948–5.944	0.065			

model were performed to evaluate the prognostic factors. OS survival and overall recurrence were defined as the time from operation until death or censoring, which were calculated by the Kaplan–Meier (KM) analysis, and the difference in groups was assessed by the log-rank test. All values of ps were two-sided, with statistical significance set at p less than 0.05.

TABLE 3 | Multivariable analysis of risk factors of poor prognosis and measurement of the risk score.

	Multivariate analysis				
Variable	**OR**	**95%CI**	***P*-value**	**B coefficient**	**Points**
PNI < 45.88	3.175	1.929–4.751	<0.001	4.497	4
MTD > 2.24 cm	1.106	1.026–2.431	0.002	2.241	2
Jaundice	2.961	1.037–4.931	0.037	2.403	2

RESULTS

Study Design

The flowchart of the manuscript design is presented in **Scheme 1**. In this study, a total of 198 patients with GBC were enrolled and randomly assigned to the primary cohort (n = 138) and validation cohort (n = 60) in a ratio of 7:3. A poor prognosis prediction model was built and validated based on the clinical and laboratory

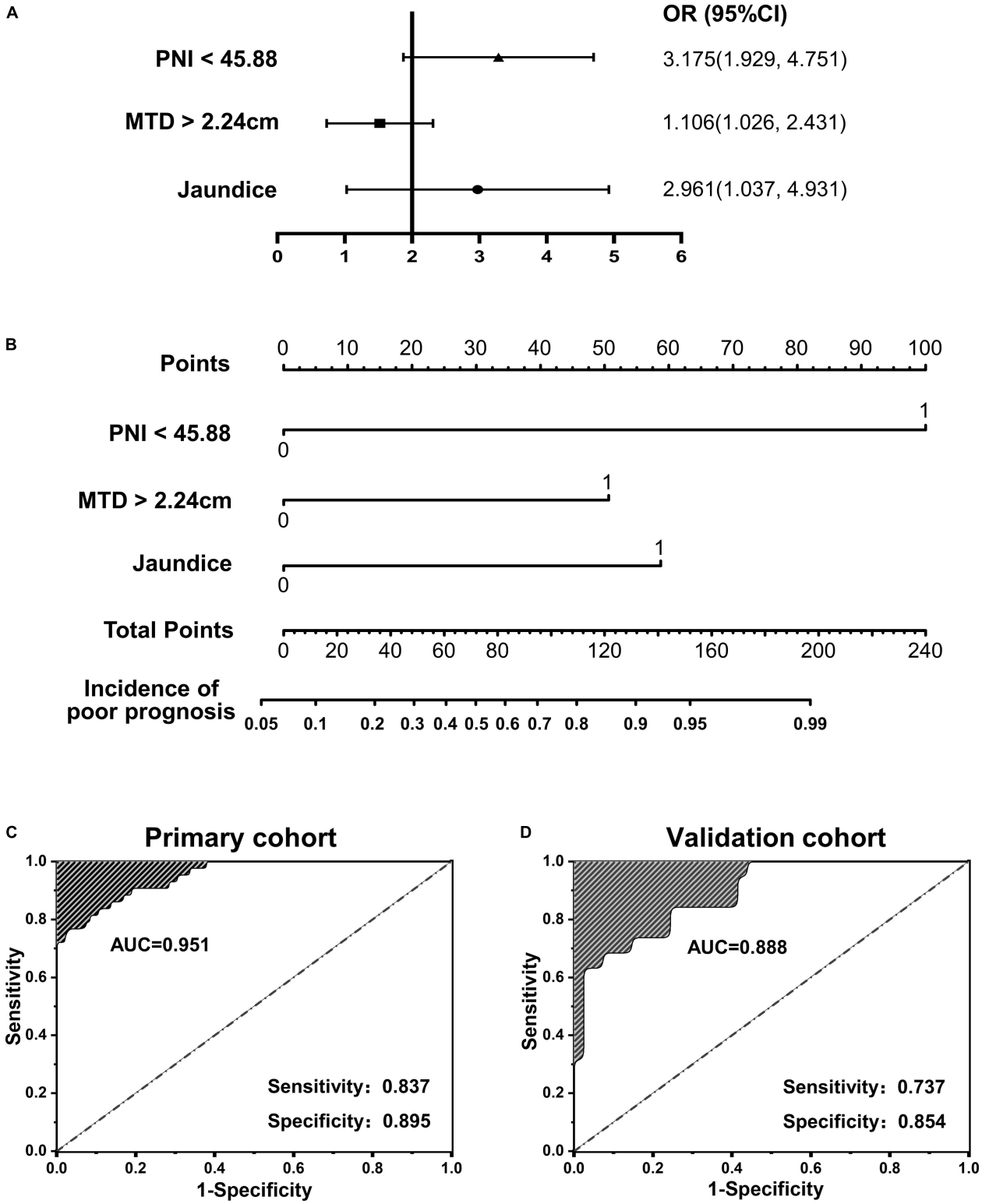


FIGURE 2 | (A,B) Forest plot and nomogram plot of independent predictors of poor prognosis with odds-ratio (*OR*) multivariate regression model; **(C,D)** area under the curve (AUC) in the primary cohort and validation cohort.

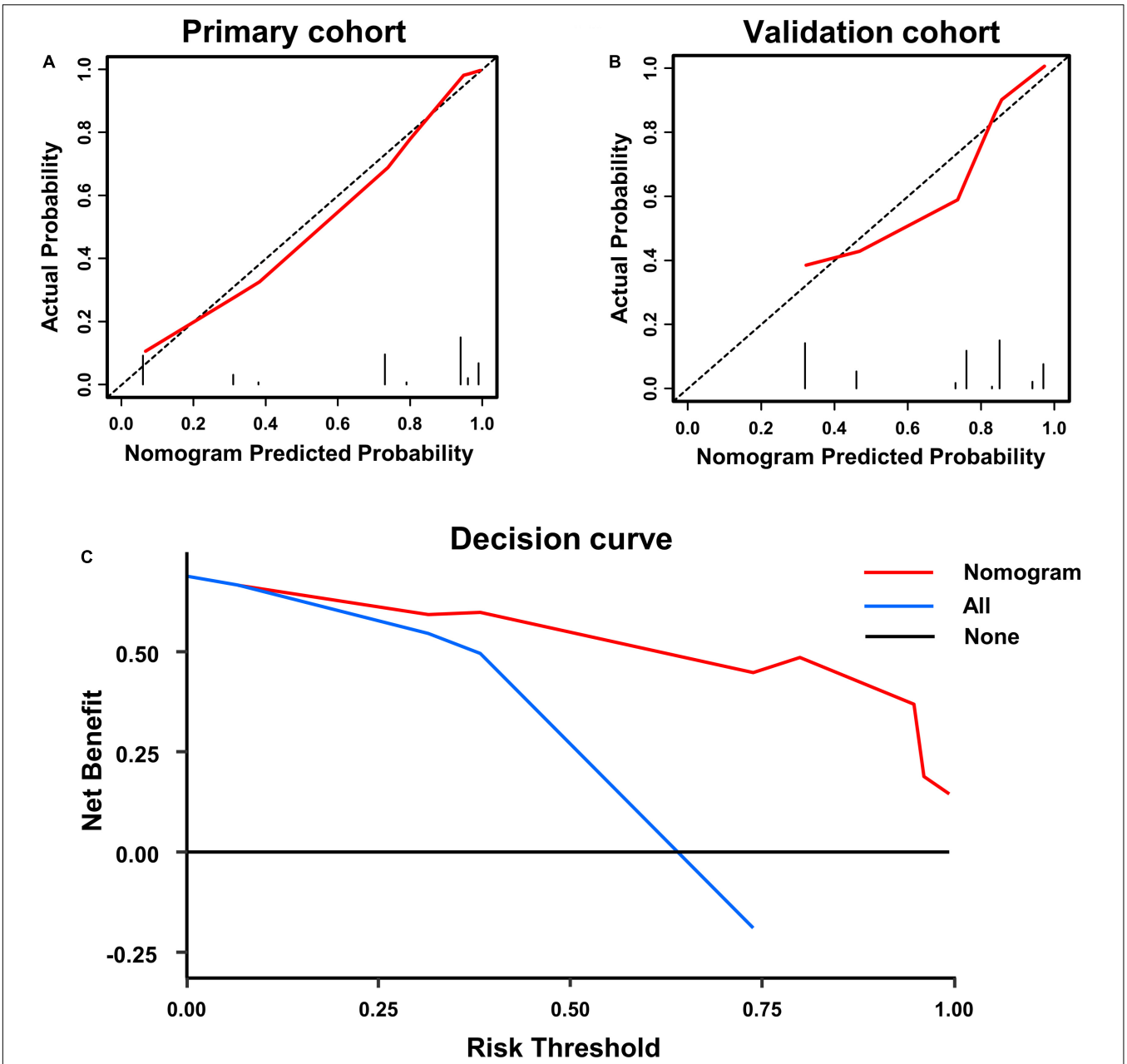


FIGURE 3 | Calibration curve of poor prognosis prediction model in primary cohort **(A)** and validation cohort **(B)**; and **(C)** presents the decision curve for all patients.

indicators. According to the best Youden index, all patients were divided into high-risk and low-risk groups based on an optimal cut-off value. Subsequently, survival analyses were compared between high-risk and low-risk groups and their subgroups.

Patients Characteristics

The baseline hematological, imageological, and pathological characteristics in the primary cohort and validation cohort are shown in **Table 1**. Among the two cohorts, the factors, such as PNI, age, gender, maximum tumor diameter (MTD), CEA, CA199, lymph node metastasis (LNM), TNM staging (I–IV grade), histological grading (poorly differentiation-PD and non-poorly differentiation-NPD), histological type, jaundice, cholelithiasis, tumor location, liver invasion, choledoch invasion, diabetes, hypertension, smoking, and poor prognosis between the two groups, showed no significant difference ($p > 0.05$).

Model Built and Validation

The ROC curve of poor prognosis established with the candidate factors of PNI and MTD is shown in **Figure 1**. The AUC of PNI was 0.947, which was more than 0.6, and the cut-off value was 45.88. The AUC of maximum tumor diameter (MTD) was

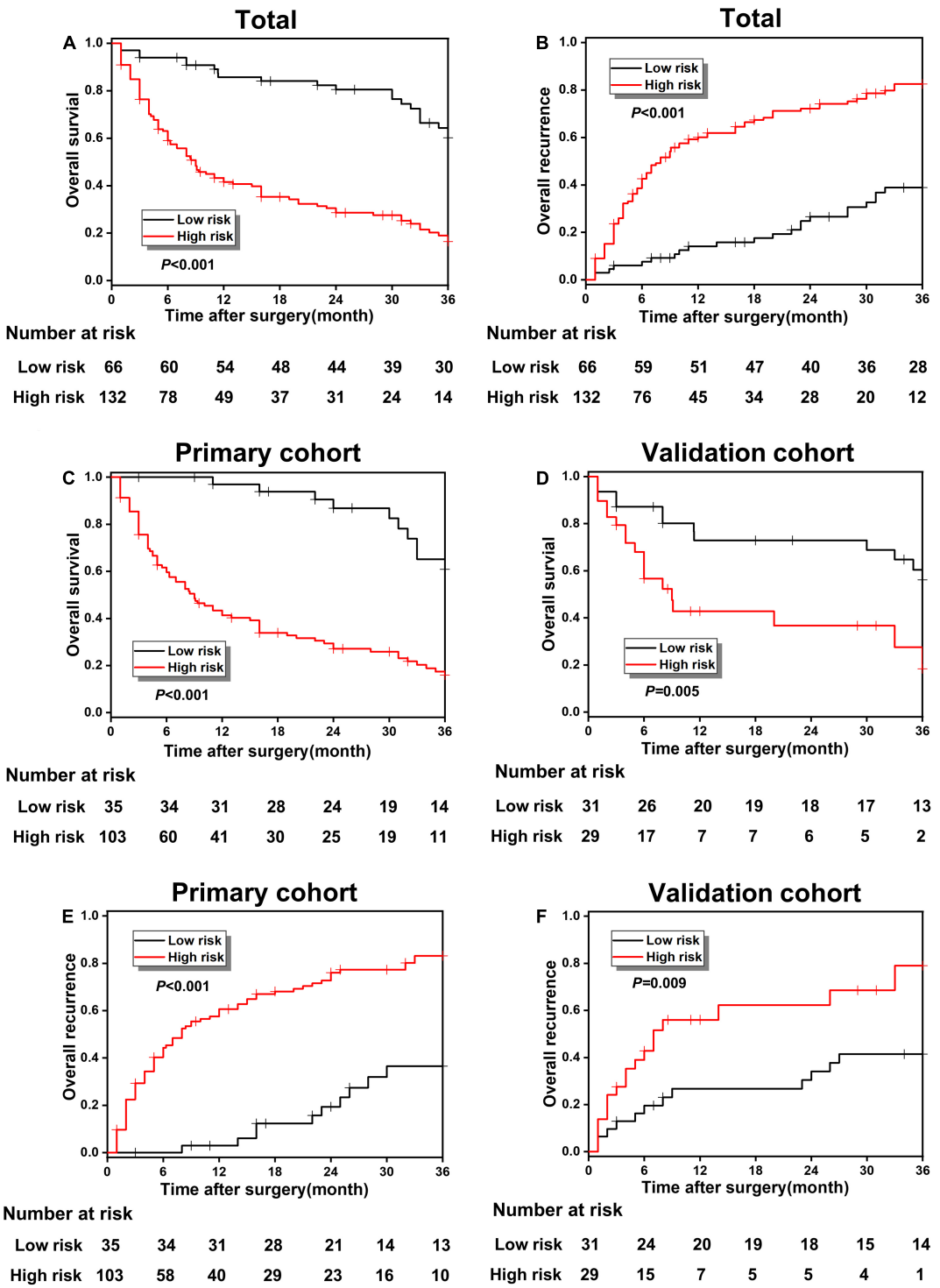


FIGURE 4 | (A,B) The overall survival (OS) and recurrence comparison in the whole cohort between poor prognosis low-risk and high-risk groups; **(B–F)** the OS and recurrence comparison in the primary and validation cohort between the low-risk and high-risk groups.

0.819 and the cut-off value was 2.24 cm. Therefore, these two values were used to classify the classification variables in the next regression analysis.

The eighteen candidate risk factors related to poor prognosis were screened by univariate logistic regression analysis in the primary cohort which are shown in **Table 2**, and the positive

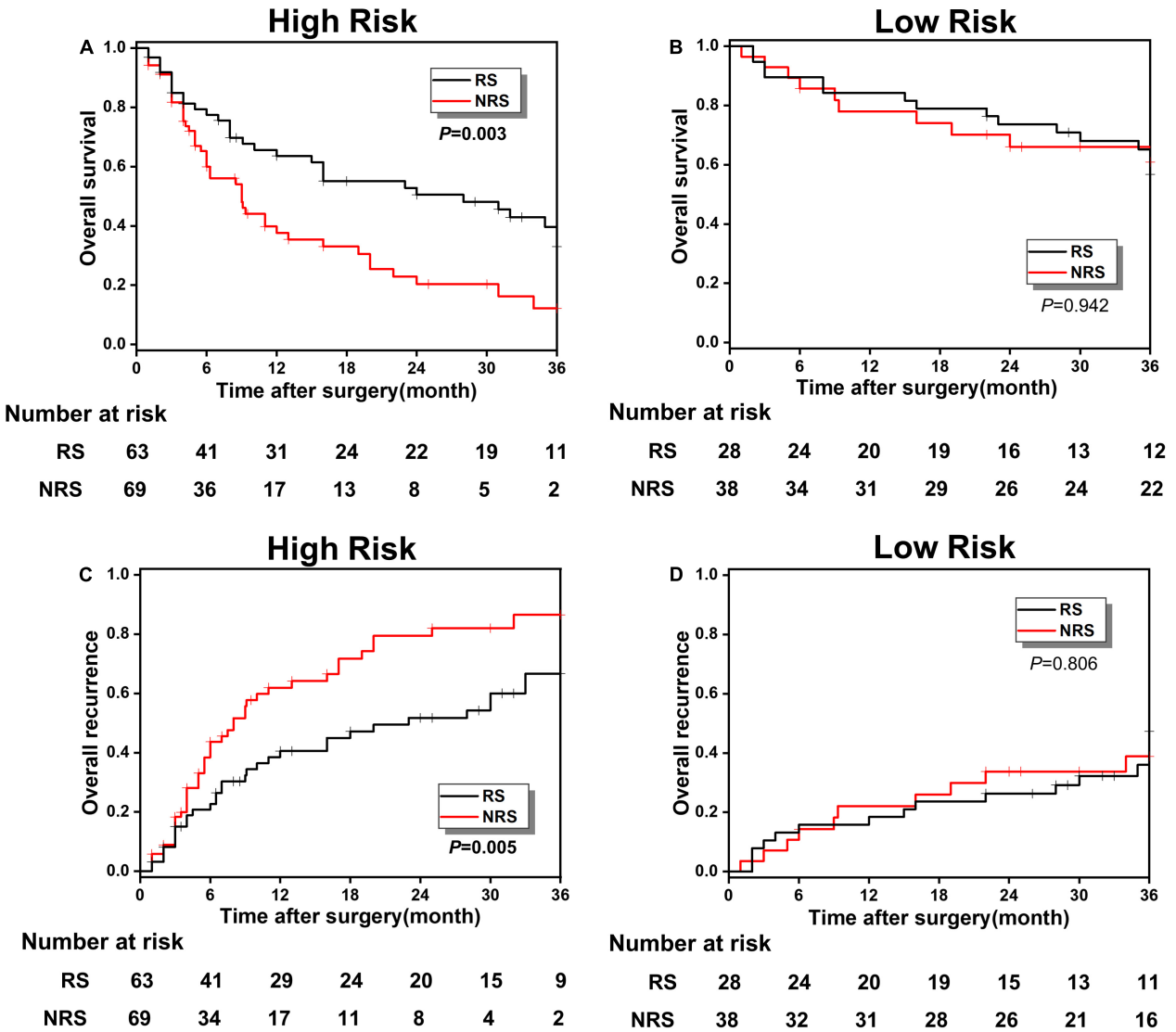


FIGURE 5 | (A,B) The OS comparison between radical surgery (RS) and non-radical surgery (NRS) subgroups in the low-risk and high-risk groups; **(C,D)** the overall recurrence comparison between the RS and NRS subgroups in the low-risk and high-risk groups.

results were, respectively, PNI < 45.88 (odds ratio [*OR*]: 3.508, $p < 0.001$), MTD > 2.24 cm (MTD, *OR*: 1.116, $p < 0.001$), PD (*OR*: 5.897, $p = 0.027$), Jaundice (JD, *OR*: 3.140, $p = 0.006$), liver invasion (*OR*: 2.302, $p = 0.030$). After multivariate analysis, the positive results were, respectively,: PNI < 45.88 (*OR*: 3.269, $p < 0.001$), MTD > 2.24 cm (*OR*: 0.075, $p = 0.002$), JD (*OR*: 3.059, $p = 0.021$). The multivariable analysis of these risk factors of poor prognosis and measurement of the risk scores are presented in **Table 3**. The prognosis prediction model was obtained by adding the total number of points scored in each of the three independent risk factors. The model was: poor prognosis risk = 4 × PNI + 2 × MTD + 2 × JD. The highest score was 8, and the lowest score was 0.

To further verify the validity of this model, a forest plot of independent predictors of poor prognosis with the *OR* and a nomogram plot for predicting poor prognosis risk were presented in **Figures 2A,B**. It can be seen that PNI shows a higher score in predicting the incidence of poor prognosis, followed by MTD and JD. The AUC of the prediction model in the primary cohort was 0.951 (**Figure 2C**), and was 0.888 in the validation cohort (**Figure 2D**). To distinguish the incidence of poor prognosis in the high-risk group and the low-risk group for all study patients, according to the best Youden index of 0.610, we obtained an optimal cutoff value of 3.0.

A calibration analysis of this poor prognosis prediction model was presented in **Figures 3A,B**. The calibration curve and the lack of statistical significance in the H-L test (p was 0.090 in the primary cohort and was 0.192 in the validation cohort) indicate a reliable calibration. The decision curve shown in **Figure 3C** indicates that if the threshold probability is within

TABLE 4 | Univariable and multivariate regression analyses of factors for predicting overall 3-years survival of study patients.

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**95%CI**	***P*-value**	**HR**	**95%CI**	***P*-value**
PNI < 45.88	0.258	0.168–0.396	<0.001	0.269	0.170–0.427	<0.001
MTD > 2.24 cm	0.731	0.513–1.043	0.084			
Gender	1.042	0.707–1.537	0.835			
Age < 60	0.985	0.725–1.539	0.458			
LN metastasis	0.661	0.465–0.941	0.025	0.859	0.556–1.327	0.493
TNM staging	0.449	0.243–0.832	0.011	0.769	0.324–1.822	0.551
CEA < 5 ng/mL	0.689	0.358–1.036	0.582			
CA199 < 40 kU/L	1.052	0.657–1.369	0.268			
PD	2.133	1.515–3.003	0.006	1.731	1.183–2.534	0.005
Pathology	0.958	0.503–1.825	0.896			
Jaundice	0.585	0.400–0.857	0.008	0.784	0.510–1.203	0.265
Cholelithiasis	1.212	0.862–1.704	0.270			
Tumor location	0.803	0.573–1.126	0.204			
Liver invasion	1.139	0.793–1.635	0.482			
Choledoch invasion	0.814	0.581–1.139	0.230			
Diabetes	0.852	0.578–1.256	0.419			
Hypertension	0.974	0.646–1.468	0.900			
Smoking	0.816	0.544–1.224	0.326			

a range from 0.05 to 0.99, the use of the nomogram can bring more net benefit to the patient than complete intervention or no intervention at all.

Overall Survival and Recurrence

According to the optimal cut-off value of 3.0, all study patients were divided into two groups with different risks of poor prognosis, including the low-risk group and high-risk group, and the KM survival analysis was carried out between the two groups to further effectiveness of risk classification based on the prediction model. The OS rate was 60.17% in the low-risk group and 16.43% in the high-risk group, which shows a significant statistical difference ($p < 0.001$; **Figure 4A**). The overall recurrence rate in the low-risk and the high-risk groups were 38.83 and 82.51%, respectively, indicating a significant statistical difference ($p < 0.001$; **Figure 4B**). **Figures 4C,D** has shown a great difference of the OS rate between low-risk and high-risk groups in the primary cohort (60.81 vs. 15.96%, $p < 0.001$) and validation cohort (56.12 vs. 18.34%, $p = 0.005$). The overall recurrence rate between the low-risk and high-risk groups in the primary cohort was 36.50 and 83.19%, respectively, and the difference was statistically significant ($p < 0.001$; **Figure 4E**). In the validation cohort, the overall recurrence rate between the low-risk and high-risk groups also showed a statistical difference (41.41 vs. 79.06%, $p = 0.009$; **Figure 4F**).

According to different surgical methods, such as RS (stands for radical resection) and NRS (stands for simple cholecystectomy), the patients in the poor prognosis low-risk and high-risk groups were classified into RS and NRS subgroups, respectively, and the KM survival analysis was conducted between RS and NRS subgroups. In the high-risk group, the OS rate in the RS and NRS subgroup were, respectively, 32.99 and 12.21%, indicating a significant statistical difference ($p < 0.001$; **Figure 5A**). Meanwhile, the overall recurrence rate between the RS and NRS subgroups also showed statistical difference (66.67 vs. 86.49%, $p = 0.005$; **Figure 5C**). While in the low-risk group, the OS rate and recurrence rate between RS and NRS subgroup indicated no statistical difference ($p > 0.001$; **Figures 5B,D**).

As presented in **Table 4**, after univariable and multivariate regression analyses of the factors for predicting overall 3-years survival of study patients, we detected another risk factor, histological grade, in addition to PNI. Accordingly, its pathological grade could be categorized into PD and NPD (mainly including high and moderate differentiation). To further verify the survival relationship between histological grade and surgical methods, to provide important surgical guidance for the decision-making of patients with GBC, patients in the high-risk group were reclassified into the PD and NPD groups, and the KM survival analysis was conducted between RS and NRS subgroups. **Figures 6A,C** presented the OS and recurrence rate between RS and NRS subgroups in the PD group, which has shown statistical difference ($p < 0.05$). However, no statistical difference existed between RS and NRS subgroups in the NPD group ($p > 0.05$; **Figures 6B,D**).

DISCUSSION

In this study, a poor prognosis prediction model was established and validated by the hematological index, imageological data, and jaundice. With an AUC of 0.951 in the primary cohort and 0.888 in the validation cohort, this model contains PNI, MTD, and JD which demonstrates superior practicability and availability.

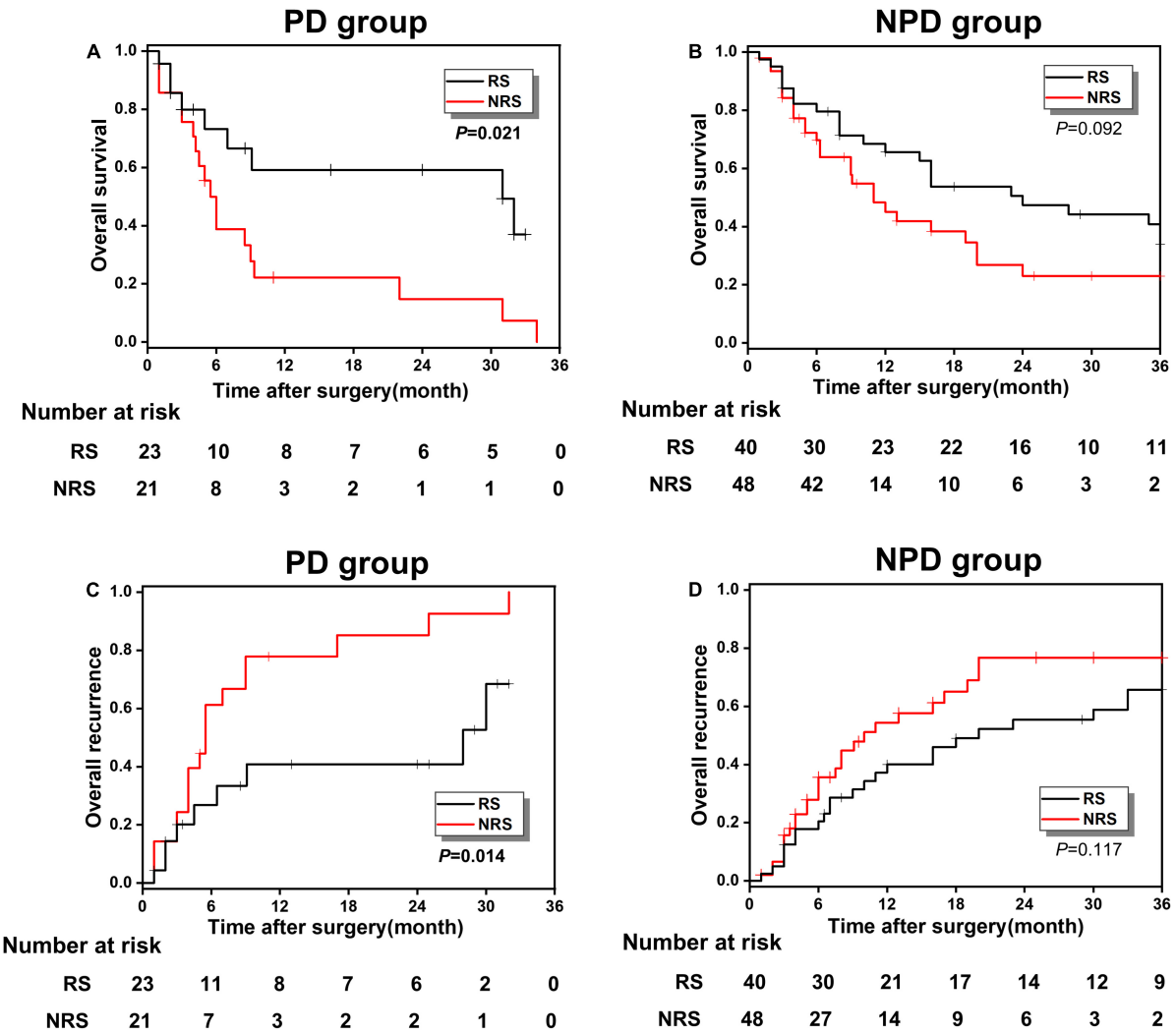


FIGURE 6 | (A,B) The OS comparison between the RS and NRS subgroups in PD and NPD groups; **(C,D)** the overall recurrence comparison between the RS and NRS subgroups in PD and NPD groups.

Moreover, RS is beneficial to the long-term survival of patients with a high-risk of poor prognosis. For the patients with a low-risk of poor prognosis, a single cholecystectomy has little effect on the long-term prognosis. Nevertheless, in the high-risk group, patients with PD, RS is necessary, while for patients with high and moderate differentiation, RS has little effect on the long-term prognosis. Hence, a simple cholecystectomy is suitable to the GBC patients with high and moderate differentiation in the high-risk group instead of radical resection with great trauma. The significant findings provide a new therapeutic strategy for the clinical treatment of patients with GBC.

Low PNI was initially found to be an important predictor of a high risk of short-term postoperative complications in the gastrointestinal tract (24). The PNI can reflect the pretreated host immunological and nutritional status and thus affect postoperative survival. Recently, increasing evidence suggested that PNI was also related to OS in various types of malignancies, such as esophageal cancer and breast cancer (25–27). Our study demonstrated that the GBC patients with PNI < 45.88 were associated with a poor prognosis (AUC = 0.947; sensitivity, 0.767; and specificity, 0.958). In previous studies, the maximum tumor diameter (MTD more than 5 mm) has also been identified as a very important risk factor for poor prognosis for patients with primary hepatic carcinoma (28). The most likely reason is that the larger MTD is usually associated with capsular invasion, non-invasive growth patterns, satellite nodules, or tumor thrombi (29–31). Moreover, larger tumor size stimulates invasive behavior. Our study indicated that the GBC patients with MTD > 2.24 cm were related to a poor prognosis (AUC = 0.819; sensitivity, 0.842; and specificity, 0.767). In addition, some studies have confirmed that jaundice was a risk factor for the poor prognosis of cholangiocarcinoma and pancreatic ductal adenocarcinoma (32, 33). Patients with jaundice have cholestasis, usually associated with biliary tract

infection, and poor surgical tolerance, which was consistent with our findings.

An early prediction of poor prognosis can effectively benefit preoperative or intraoperative individualized surgical plans, which have been verified by some experienced scholars (34–36). Ethun et al. analyzed 262 cases of accidental GBC from multiple centers and added the parameters, such as T stage, degree of differentiation, vascular invasion, and perineural invasion to establish the prediction model of local residual lesions, distant metastasis, and long-term survival (37). However, the evaluation of accidental GBC may be influenced by subjective factors and may have certain limitations. Mochizuki et al. established a risk scoring model for GBC by using the above four indicators (2–3 points for the low-risk group and 6–8 points for the high-risk group), and the scoring results were highly correlated with prognosis (38). This model has certain practicability, but lacks systematic evaluation and external verification, so the accuracy of the model has certain deficiencies. Bai et al. analyzed the data of 142 patients undergoing RS of GBC in Peking Union Medical College Hospital, which found that CA199, jaundice, tumor stage, and resection margin were independent prognostic factors through Cox regression model analysis (39). Then, they established the corresponding nomogram and evaluated the model accuracy through the subject operating characteristic curve and found that the prediction accuracy was good. However, the prediction effect of this model is not the optimal type (0.797–0.803). Established by the hematological, imageological indexes, and clinical manifestation, our prediction model demonstrated good predictive ability, which presented a higher prediction accuracy than single hematology index prediction models or radiomics. Furthermore, the AUC of this model in the primary cohort was 0.951, and in the validation cohort was 0.888, which indicates strong predictive performance.

The occurrence of poor prognosis will result in increased early recurrence rates. In this study, according to the best Yoden index, the patients were divided into a high-risk group and a low-risk group based on an optimal cut-off value. The 3-year survival of the high-risk group was lower than those of the lower-risk group in the primary and validation cohort. Meanwhile, our study found that RS could availably increase the long-term outcome of the high-risk group, which indicates that RS can effectively improve the postoperative OS of patients with GBC and reduce postoperative overall recurrence. Furthermore, the patients with RS or a simple cholecystectomy did not show a significant difference in OS and recurrence in the low-risk group. However, it does not mean that these patients can undergo simple cholecystectomy without RS in clinical practice. Studies have proved that simple cholecystectomy for stage T1b GBC had similar effects to RS, and there was no statistical difference in 5-year and 10-year postoperative survival rates (40, 41). Wang et al. suggested that a simple cholecystectomy was suitable for the GBC patients with T1b stage (AJCC 8th) and MTD < 1 cm (42). Therefore, preoperative comprehensive consideration should be taken from many aspects, such as TNM stage and tumor differentiation.

In addition, our study discovered that in the high-risk group, there was no significant difference of 3-year survival and recurrence in GBC patients with high and moderate differentiation, whether they underwent RS or a simple cholecystectomy. While patients with PD could obtain a long-term survival without recurrence after RS. Hence, for patients with PD and a high-risk score, when preoperative or intraoperative diagnosis of GBC is made, RS is highly recommended. Nonetheless, if the patient is postoperative diagnosed of accidental GBC, due to the few significant difference of 3-year survival and recurrence for the patients with high and moderate differentiation or a low-risk prediction score, rather than a traumatic RS, a simple cholecystectomy can be considered for acceptance.

However, this study has certain limitations. First of all, a single-center retrospective study may not have such a high level of evidence, and the results are not strongly persuasive. Second, the data included in this study are insufficient (only 198 patients), so there may be some deviations in the results. In addition, our prediction model is established by PNI, MTD, and jaundice, but other clinical characteristic parameters, such as tumor margins, invasion, and metastasis, have not been comprehensively evaluated. Hence, the issues mentioned above need to be further verified by more and larger participants, multicenter randomized controlled studies, and this is also the research plan that we need to carry out further in the future.

CONCLUSION

In summary, we have developed and validated a novel poor prognosis prediction model based on PNI, MTD, and jaundice for patients with GBC, which shows superior practicability and availability. Due to a high-risk score of early tumor recurrence, our findings demonstrate that RS is necessary for those preoperative or intraoperative diagnosis of patients with GBC. Nevertheless, for those postoperative accidental diagnosis of GBC, whereas for patients with PD and a high-risk score, RS is highly recommended; while for the patients with high and moderate differentiation or a low-risk score, rather than a traumatic RS, a simple cholecystectomy can be considered for acceptance. These findings demonstrate important guiding significance for the next treatment strategy of accidental GBC which occasionally appears in clinic.

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 Medical Faculty of

Fujian Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SQ and PC contributed to the conception of the study. HH, ZY, and GC contributed to the data collection and audit. SQ and PC performed the data analyses and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Prognostic Roles of Glucose to Lymphocyte Ratio and Modified Glasgow Prognosis Score in Patients With Non-small Cell Lung Cancer

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Background: Non-small cell lung cancer (NSCLC) is among the most prevalent malignancies worldwide. Previous studies have shown that the status of inflammation, nutrition and immune are closely related to overall survival (OS) of patients with NSCLC, but little is known about their interactive and combined roles. Hence, we chose glucose to lymphocyte ratio (GLR) and modified Glasgow Prognosis Score (mGPS) as prognostic factors and assessed the prognostic values of them for patients with NSCLC.

Methods: Baseline clinicopathologic and laboratory characteristics of 862 patients with NSCLC were obtained from a multicenter prospective cohort. The Cox proportional hazard regression models were used to determine prognostic values of the clinical factors. A nomogram was also constructed integrating the clinical factors with clinical significance or independent prognostic values. Concordance index (C-index) was utilized to evaluate the prediction accuracy of the TNM stage and the nomogram.

Results: Multivariate analyses demonstrated that GLR [Hazard ratio (HR) = 1.029, 95% confidence interval (CI) = 1.004–1.056, $P = 0.023$] and mGPS (score of 1: HR = 1.404, 95% CI = 1.143–1.726, $P = 0.001$; score of 2: HR = 1.515, 95% CI = 1.159–1.980, $P = 0.002$) were independent prognostic factors for patients with NSCLC. The C-indexes of the TNM stage and the nomogram were 0.642 (95% CI = 0.620–0.663) and 0.694 (95% CI = 0.671–0.717), respectively.

Conclusion: GLR and mGPS were independent prognostic factors for patients with NSCLC. Moreover, our constructed nomogram might be superior in predicting prognosis of patients with NSCLC compared with the TNM stage.

Keywords: glucose to lymphocyte ratio, modified Glasgow Prognosis Score, non-small cell lung cancer, inflammation, nutrition, immune

INTRODUCTION

Non-small cell lung cancer (NSCLC), which is a common type of lung cancer, is the leading cause of cancer-related death worldwide, bringing a tremendous burden to families and society (1, 2). In previous studies, numerous prognostic factors were identified to better predict survival and inform clinical decisions for patients with NSCLC (3–10). Due to limitations of these studies, however, existing prognostic factors are inadequate to meet the growing needs for better prediction of survival and informing more effective treatment strategies for patients with NSCLC (11, 12). Therefore, development of better prediction models would result in better therapy decisions and would be beneficial to improve outcomes for patients with NSCLC.

Previous studies have shown that inflammation is an important promoting factor for the occurrence and development of lung cancer (13). The risk of death in patients with NSCLC with high levels of inflammation is much higher than those with low levels of inflammation. Elevated fasting blood glucose (FBG) is not only the direct embodiment of insulin resistance caused by inflammation, but also the direct cause of further inflammation. C-reactive protein (CRP), as a common clinical index, is very sensitive to the changes of inflammatory level.

On the other hand, the nutritional and immune status of patients with NSCLC are also crucial to their survival. Some studies suggested that the survival of patients with NSCLC, with poor nutritional and lymphocyte status, is worse than those with good status, and this gap can be corrected by nutritional supplement and immune intervention (14, 15). In addition to being an immune marker, recent studies have reported that lymphocytes are closely related to the nutritional status of the body (16). Moreover, serum albumin (Alb) has been used as a nutritional index in clinic for a long time.

Therefore, we identified glucose to lymphocyte ratio (GLR), which is a parameter that integrates both FBG levels and lymphocyte counts, and the modified Glasgow prognostic score (mGPS), which combines Alb and CRP, to be prognostic factors with high accuracy in patients with NSCLC. GLR and mGPS are previously reported prognostic indicators of a variety of cancers. We reasoned that a combination of both GLR and mGPS would be more promising in prediction of OS for patients with NSCLC. Thus, we established a nomogram model that combined GLR and mGPS. We showed that this nomogram was more accurate and specific in predicting prognosis for patients with NSCLC.

The current study aimed to evaluate the prognostic values of GLR, mGPS and a nomogram model that combined GLR and mGPS in patients with NSCLC.

MATERIALS AND METHODS

Study Population

A total of 2,740 patients with NSCLC, who were diagnosed between 2012 and 2019, were enrolled from a multicenter prospective cohort which included patients from 14 hospitals (**Figure 1**). The inclusion criteria were as following: age $\geq$ 18 years at diagnosis, a pathological diagnosis of NSCLC, willing and able to provide written informed consent, and consciousness throughout treatment with no communication disorders. Patients with any of the following conditions will be excluded: acquired immune deficiency syndrome, mental or cognitive impairment, or receiving organ transplantation. Cases which patients were hospitalized for more than 2 times during the study were considered as single cases. 1,878 patients without reported data for one or more of above variables were excluded. Of these excluded patients, 59 were missing Alb levels, 1,272 were missing CRP levels, 133 were missing FBG levels, 117 were missing lymphocyte counts, 115 were missing age information, and 182 were missing TNM stage data (**Figure 1**). The study was approved by the Ethical Review Committees of the participating hospitals and was conducted in accordance with the guidelines of the Declaration of Helsinki. The study was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn) and the registration number is ChiCTR1800020329.

Patient Characteristics and Outcomes

The following demographic and clinicopathological data were collected within 24 h of admission: sex, age, height, weight, smoking status, alcohol consumption, tea-drinking status, health information (hypertension, diabetes and coronary heart disease), TNM stage, FBG levels, lymphocyte counts, Alb and CRP levels. Smoking more than 20 cigarettes in a lifetime was regarded as smoking. Regular alcohol consumption in the past year was regarded as drinking. Regular tea drinking in the past year was regarded as tea drinking. TNM stages were determined according to the guidelines of the American Joint Committee on Cancer (17). Blood samples were taken at 6 a.m. the next day after the patient's admission. Before that, patients were required to be fasting for at least 8 h. The mGPS was defined as following: arbitrary Alb levels and CRP $\leq$ 10 mg/L were scored as 0; Alb $\geq$ 35 g/L or CRP $>$ 10 mg/L were scored as 1; Alb $<$ 35 g/L and CRP $>$ 10 mg/L were scored as 2. GLR was the level of FBG divided by the lymphocyte counts. Patient death due to NSCLC was defined as the primary endpoint of the clinical trials.

Statistical Analyses

Data were presented as simple percentages or medians and interquartile range (IQR). The Fisher's exact test or chi-square test was used for the assessment of baseline characteristics. Student's *t* test was utilized for the analyses of continuous variables with normal distributions. The Mann-Whitney test was used for the analyses of continuous variables with non-normal distributions.

The prognostic values of different variables were evaluated by the univariate and multivariate Cox proportional hazard regression models. Our proposed nomogram model was constructed based on these identified prognostic factors. Concordance index (C-index) and Area Under the Curve (AUC) were used to evaluate the accuracy of our nomogram model. The Cox regression models were used for hazard ratio (HR) and associated 95% confidence interval (CI). $P < 0.05$ was regarded as statistically significant. For all the analyses, either the R (version 4.0.1) or SPSS (version 26.0) software was employed.

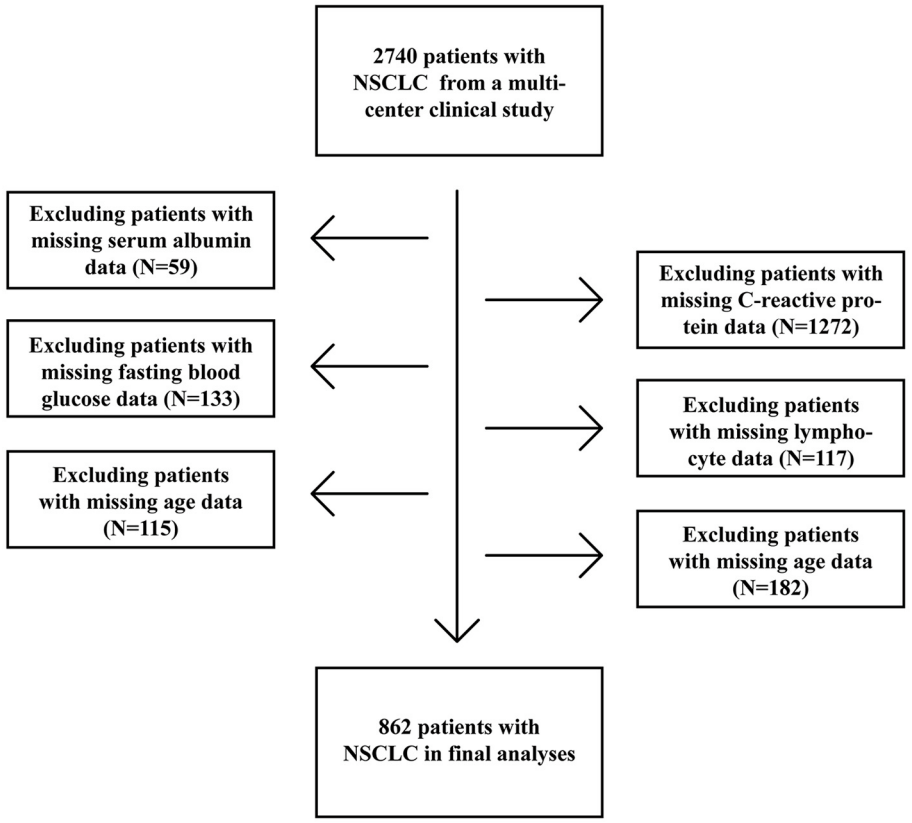

FIGURE 1 | Procedures for selection of study participants with non-small cell lung cancer (NSCLC) from a multi-center clinical database.

RESULTS

Patient Characteristics

Of all the participants, the median age was 61 years (IQR, 54 to 67 years), the median BMI was 22.99 kg/m^2 (IQR, 20.81 to 25.10 kg/m^2), the median GLR was 3.66 (IQR, 2.76 to 5.18). 64.2% (553/862) of the patients were male. 8.0% (69/862), 15.2% (131/862), 23.5% (203/862) and 53.2% (459/862) of them were in stage I, II, III, and IV, respectively. According to the values of mGPS, the baseline characteristics were divided into three groups and were summarized in **Table 1**.

Independent Prognostic Factors for NSCLC

Univariate analyses indicated that sex, BMI, tea drinking status, TNM stage, mGPS and GLR were prognostic factors for patients with NSCLC, while age, smoking status, alcohol consumption, and health status (hypertension, diabetes and coronary heart disease) were not. Multivariate analyses further indicated that sex (HR = 0.814, 95% CI = 0.666–0.995, $P = 0.023$), BMI (HR = 0.939, 95% CI = 0.913–0.966, $P < 0.001$), TNM stage (stage II: HR = 3.718, 95% CI = 1.762–7.847, $P = 0.001$; stage III: HR = 6.466, 95% CI = 3.153–13.258, $P < 0.001$; stage IV: HR = 10.205, 95% CI = 5.048–20.632, $P < 0.001$), mGPS (score of 1: HR = 1.404, 95% CI = 1.143-1.726, $P = 0.001$; score of 2: HR = 1.515, 95% CI = 1.159-1.980, $P = 0.002$) and GLR (HR = 1.029, 95% CI = 1.004–1.056, $P = 0.023$) were independent prognostic factors. The detailed results of these analyses were summarized in **Table 2**.

GLR and mGPS Prognostic Roles

Correlation analyses indicated that the risk of death was positively related to GLR levels (**Table 3**, **Supplementary Figure 1**). Receiver operating characteristic curve (ROC) analyses determined that the optimal cut-off value for GLR was 4.726. Patients with a GLR > 4.726 had a lower OS compared with patients who had a GLR smaller than or equal to 4.726 (HR = 1.501, 95% CI = 1.246–1.808, $P < 0.001$; **Supplementary Figures 2, 3**). When GLR was divided into 4 quartiles (1st quartile: GLR < 2.760; 2nd quartile: 2.760 ≤ GLR < 3.662; 3rd quartile: 3.662 ≤ GLR < 5.194; 4th quartile: GLR ≥ 5.194), patients in the 4th quartile had a significantly higher risk of death (HR = 1.662, 95% CI = 1.292–2.138, $P < 0.001$) compared to those in the 1st quartile. For mGPS, patients with a score of 1 or 2 had a significantly decreased survival time compared to those with a score of 0. Detailed associations between mGPS and OS in patients with NSCLC were presented in **Table 3, Supplementary Figure 4**.

TABLE 1 | Characteristics of patients with different mGPS.

Characteristics	mGPS = 0 (n = 507)	mGPS = 1 (n = 254)	mGPS = 2 (n = 101)	P-value
Sex[a] (male)	300 (59.2)	177 (69.7)	76 (75.2)	0.001
Age in years[b]	59.71 (9.29)	61.22 (9.77)	62.99 (10.76)	0.003
BMI[b] (kg/m^2)	23.38 (3.31)	22.91 (3.15)	21.95 (3.25)	<0.001
Smoking status[ac] (Yes)	282 (55.6)	161 (63.4)	69 (68.3)	0.018
Alcohol consumption[a,d] (Yes)	128 (25.2)	70 (27.6)	31 (30.7)	0.481
Tea drinking status[a,e] (Yes)	107 (21.1)	68 (26.8)	33 (32.7)	0.023
Hypertension[a] (Yes)	91 (17.9)	67 (26.4)	24 (23.8)	0.021
Diabetes[a] (Yes)	43 (8.5)	26 (10.2)	7 (6.9)	0.561
Coronary heart disease[a] (Yes)	29 (5.7)	20 (7.9)	8 (7.9)	0.452
TNM stage[a]				<0.001
I	56 (11.0)	10 (3.9)	3 (3.0)	
II	88 (17.4)	33 (13.0)	10 (9.9)	
III	126 (24.9)	58 (22.8)	19 (18.8)	
IV	237 (46.7)	153 (60.2)	69 (68.3)	
GLR[b]	4.28 (2.91)	4.89 (3.16)	4.84 (3.10)	0.018

mGPS, modified Glasgow prognostic score; BMI, body mass index; GLR, blood glucose to lymphocyte ratio.
[a]*Categorical variables are presented as number (percentage).*
[b]*Continuous variables are presented as mean (standard deviation).*
[c]*The standard is to smoke more than 20 cigarettes in a lifetime.*
[d]*The standard is regular drinking in the past year.*
[e]*The standard is regular drinking tea in the past year.*

TABLE 2 | Associations between clinical variables and OS in patients with NSCLC.

Variables	Univariate analysis		Multivariate analysis[a]	
	HR (95% CIs)	P-value	HR (95% CIs)	P-value
Sex	0.789 (0.655, 0.951)	0.013	0.814 (0.666, 0.995)	0.023
Age	1.009 (0.999, 1.018)	0.066	1.000 (0.990, 1.009)	0.972
BMI	0.927 (0.906, 0.953)	<0.001	0.939 (0.913, 0.966)	<0.001
Smoking status[b]	1.127 (0.941, 1.349)	0.193		
Alcohol consumption[c]	0.954 (0.781, 1.164)	0.640		
Tea drinking status[d]	1.236 (1.013, 1.508)	0.037	1.104 (0.892, 1.367)	0.365
Hypertension	1.064 (0.859, 1.319)	0.568		
Diabetes	0.956 (0.699, 1.306)	0.775		
Coronary heart disease	0.965 (0.674, 1.381)	0.845		
TNM stage				
I	Reference		Reference	
II	3.824 (1.813, 8.066)	<0.001	3.718 (1.762, 7.847)	0.001
III	7.064 (3.449, 14.469)	<0.001	6.466 (3.153, 13.258)	<0.001
IV	11.548 (5.721, 23.310)	<0.001	10.205 (5.048, 20.632)	<0.001
mGPS				
0	Reference		Reference	
1	1.879 (1.550, 2.277)	<0.001	1.404 (1.143, 1.726)	0.001
2	2.174 (1.669, 2.831)	<0.001	1.515 (1.159, 1.980)	0.002
GLR	1.038 (1.013, 1.063)	0.002	1.029 (1.004, 1.056)	0.023

OS, overall survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; CIs, confidence interval; BMI, body mass index; mGPS, modified Glasgow prognostic score; GLR, blood glucose to lymphocyte ratio.
[a]*The variables showed prognosis roles in univariate analysis or considered clinically significant were involved in multivariate analysis.*
[b]*The standard is to smoke more than 20 cigarettes in a lifetime.*
[c]*The standard is regular drinking in the past year.*
[d]*The standard is regular drinking tea in the past year.*

TABLE 3 | Associations between GLR or mGPS and OS in patients with NSCLC.

Variables	Patients (*n*)	Crude HR (95% CIs)	*P*-value	Adjusted HR (95% CIs)	*P*-value
GLR[a]					
Continuous	862	1.038 (1.013, 1.063)	0.002	1.029 (1.004, 1.056)	0.023
Categories[b]					
Low	604	Reference		Reference	
High	258	1.691 (1.408, 2.030)	<0.001	1.501 (1.246, 1.808)	<0.001
Quartiles					
1	215	Reference		Reference	
2	216	1.147 (0.884, 1.487)	0.302	1.122 (0.864, 1.457)	0.388
3	216	1.249 (0.966, 1.615)	0.089	1.185 (0.914, 1.536)	0.199
4	215	1.877 (1.468, 2.400)	<0.001	1.662 (1.292, 2.138)	<0.001
mGPS[c]					
0	507	Reference		Reference	
1	254	1.723 (1.406, 2.111)	<0.001	1.404 (1.143, 1.726)	0.001
2	101	2.021 (1.559, 2.621)	<0.001	1.515 (1.159, 1.980)	0.002
GLR and mGPS[d]					
Low GLR and 0 score	382	Reference		Reference	
High GLR and 0 score	125	1.790 (1.371, 2.336)	<0.001	1.564 (1.220, 2.006)	<0.001
Low GLR and 1 score	157	2.024 (1.590, 2.577)	<0.001	1.499 (1.153, 1.948)	0.002
High GLR and 1 score	97	2.477 (1.878, 3.267)	<0.001	1.910 (1.413, 2.583)	<0.001
Low GLR and 2 score	65	2.077 (1.482, 2.912)	<0.001	1.425 (1.014, 2.003)	0.042
High GLR and 2 score	36	3.686 (2.485, 5.467)	<0.001	2.554 (1.705, 3.824)	<0.001

GLR, blood glucose to lymphocyte ratio; mGPS, modified Glasgow prognostic score; OS, overall survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; CIs, confidence intervals.
[a] *Models were adjusted for sex, age, body mass index, tea drinking status, TNM stage and mGPS.*
[b] *The cut-off point of GLR is 4.726.*
[c] *Model was adjusted for sex, age, body mass index, tea drinking status, TNM stage and GLR (as a continuous variable).*
[d] *Model was adjusted for sex, age, body mass index, tea drinking status and TNM stage.*

Combination Prognostic Roles

Based on different combinations of GLR and mGPS, all patients were assigned into six groups: group 1 (Low GLR and mGPS = 0), group 2 (High GLR and mGPS = 0), group 3 (Low GLR and mGPS = 1), group 4 (High GLR and mGPS = 1), group 5 (Low GLR and mGPS = 2), and group 6 (High GLR and mGPS = 2). Compared with patients in group 1, lower OS was observed for patients in group 2 (HR = 1.564, 95% CI = 1.220–2.006, $P < 0.001$), group 3 (HR = 1.499, 95% CI = 1.153–1.948, $P = 0.002$), group 4 (HR = 1.910, 95% CI = 1.413–2.583, $P < 0.001$), group 5 (HR = 1.425, 95% CI = 1.014–2.003, $P = 0.042$), and group 6 (HR = 2.554, 95% CI = 1.705–3.824, $P < 0.001$). Detailed results were summarized in **Table 2**.

Evaluation of the Constructed Nomogram

Variables, with clinical significance (age) or with independent prognostic value (TNM stage, BMI, GLR, mGPS, sex), were included in the constructed nomogram (**Figure 2**). The calibration curves for 1-, 2- and 3-year OS were in good agreement with prediction from our nomogram (**Supplementary Figure 5**). C-indexes of the TNM stage and the nomogram were 0.642 (95% CI, 0.620–0.663) and 0.694 (95% CI, 0.671–0.717), respectively. Time-dependent ROCs were generated based on the GLR, mGPS, TNM stage and our nomogram. AUCs of ROCs generated from the TNM stage and our nomogram were 68.48 and 74.54% at 1 year, 67.74 and 73.27% at 2 years, 73.16 and 76.82% at 3 years, and 77.59 and 81.69% at 4 years, respectively (**Supplementary Figure 6**). These data suggested that our nomogram model might performs better in predicting OS compared with the classical TNM stage classification in patients with NSCLC (**Supplementary Figure 7**).

DISCUSSION

In the current study, we concluded that GLR and mGPS were negatively correlated with OS in patients with NSCLC. We also confirmed that clinical factors, such as sex, BMI and TNM stage, were independent risk factors for patients with NSCLC. Further, we developed a nomogram model that incorporated NSCLC prognostic factors, which might provide more accurate prediction of OS than the TNM staging system or other traditional indicators included in the nomogram in patients with NSCLC. Using c-indexes and AUC, we showed that our nomogram model was superior in predicting outcomes of patients with NSCLC compared to the classical TNM stage classification method.

GLR, which is the ratio of FBG levels and lymphocyte counts, was shown to be a good predictor of OS in several malignancies, such as pancreatic and gallbladder tumors (18, 19). Level of FBG

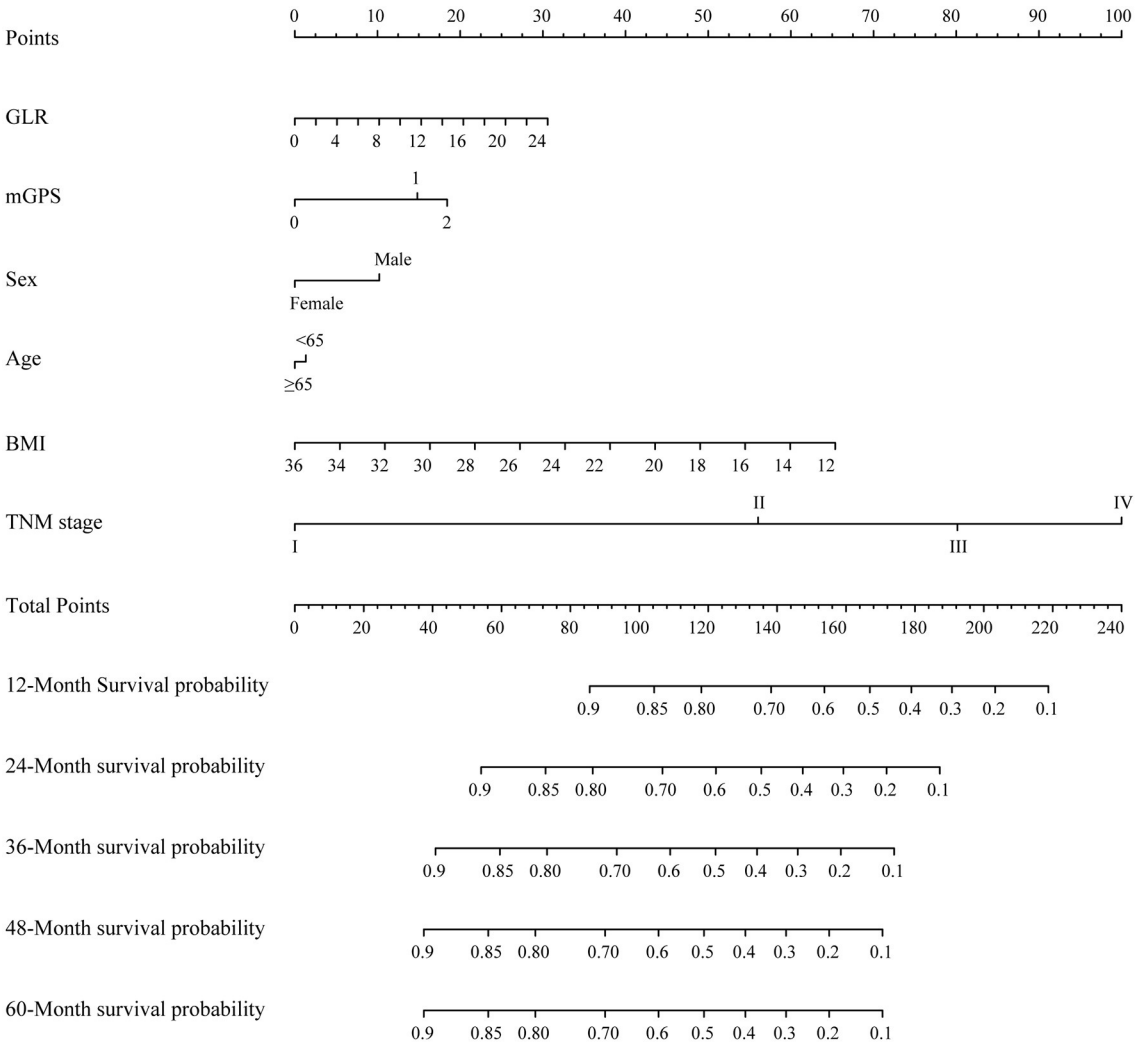

FIGURE 2 | A proposed nomogram for predicting median survival time and survival probability of patients with non-small cell lung cancer (NSCLC). To use the nomogram, a line is drawn upward to the Points axis to determine the number of points received for each variable. Sum of these points makes the total points. For total points, a line is drawn from the Total Points axis downward to the survival axes to determine the estimated median survival time and survival probability.

was also found to be independent predictor for OS in patients with NSCLC (20). Diabetes can lead to hyperinsulinemia and insulin resistance, which can promote tumor growth (21, 22). Moreover, previous studies showed that hyperglycemia, which could form irreversible glycation end-products, could change the tumor microenvironment and contribute to tumor development (23). Previous studies also demonstrated that circulating lymphocytes can contribute to improved outcomes in cancer patients by enhancing cancer immune-surveillance (13, 24). In the tumor microenvironment, lack of T cells indicated impaired anti-tumor immunity (25). More than that, lymphocytes, which are important cells in immunity, also indicate patient's nutritional status (16). Research indicated that nutrition education and oral supplementation can both improve nutritional status as well as the activity of lymphocytes, which will improve the prognosis of patients with NSCLC (14, 15, 26). In conclusion, the elevated GLR, representing hyperglycemia and low lymphocyte count, is closely related to cancer progression and poor prognosis, which is consistent with our results. Interestingly, regulatory T cells were activated under low glucose levels, countering anti-tumor immunity (27–29). Thus, the potential synergism between hypoglycemia and immunosuppression might block cancer progression. Further studies could be carried out to verify this hypothesis and explore the possible mechanisms.

It was reported that mGPS, combining Alb levels and CRP levels, was identified as a prognostic marker for patients with NSCLC (30). As an inflammatory index, decreased Alb levels indicated malnutrition and systemic inflammation (31). Studies had shown that malnutrition and systemic inflammation are closely related to the adverse outcomes of patients with NSCLC (32). Moreover, increased CRP levels

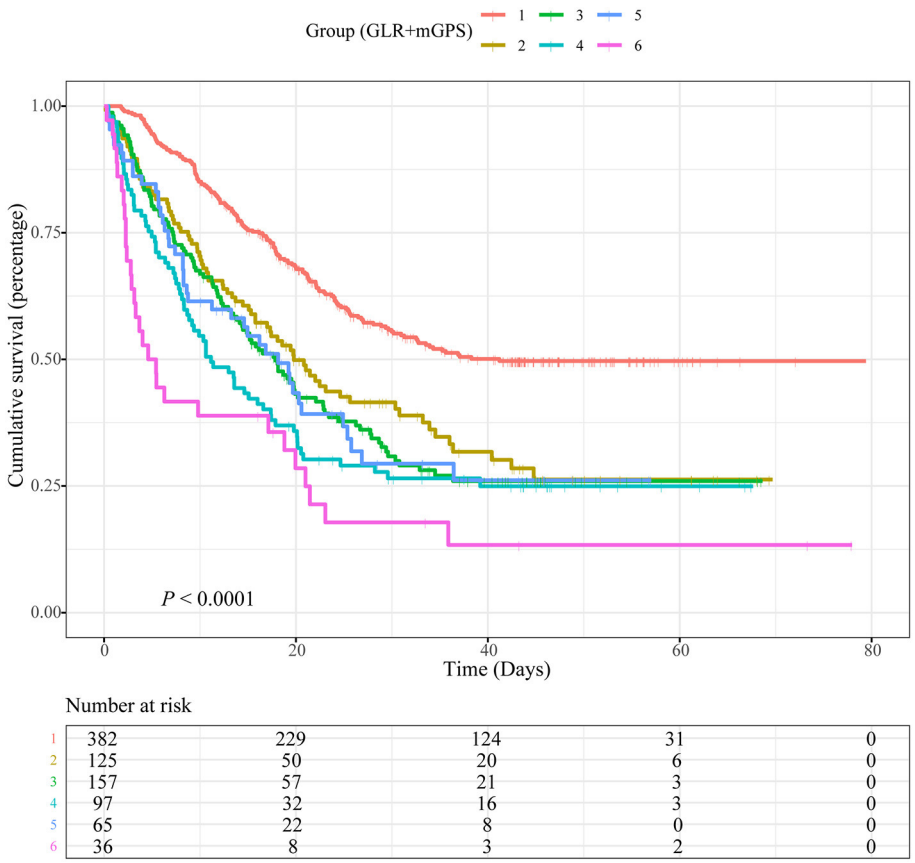

FIGURE 3 | Kaplan-Meier curves showing associations between a combination of blood glucose to lymphocyte ratio (GLR) and modified Glasgow prognostic score (mGPS) and overall survival (OS) in patients with non-small cell lung cancer (NSCLC). Group 1: Low GLR and mGPS = 0; Group 2: High GLR and mGPS = 0; Group 3: Low GLR and mGPS = 1; Group 4: High GLR and mGPS = 1; Group 5: Low GLR and mGPS = 2; Group 6: High GLR and mGPS = 2.

were linked to lymphocytopenia and impaired T cell response in tumors, which can further promote cancer progression (33). It is recognized that ongoing systemic inflammatory responses (indicated by an elevated CRP) in cancer patients can lead to poor survival due to reasons such as increased protein breakdown (34–37). Hence, higher mGPS, meaning hypoalbuminemia and elevated CRP levels, is associated with a poor prognosis in patients with NSCLC, which is consistent with our conclusion.

In this study, we explored how a combination of GLR and mGPS would relate to OS of patients with NSCLC. A higher death risk was found in patients with high GLR and mGPS = 2, compared with those who have a low GLR and mGPS = 0. Higher GLR and mGPS mean higher FBG and CRP levels, and lower lymphocyte count and albumin levels, which are associated with high inflammatory status, malnutrition and immune insufficiency. Studies had shown that systemic inflammation, malnutrition and immune dysfunction are related to the progression of cancer, which will lead to worse survival (38, 39). More than that, these indicators and states will also affect each other. Prior studies identified an association between inflammatory status and the occurrence of diabetes. Inflammatory responses likely contribute to diabetes occurrence by regulating insulin resistance, which in turn intensifies the symptoms of hyperglycemia and further promotes long-term complications of diabetes (40). Moreover, by activating macrophages, hypoalbuminemia can impair the immune response within tumors (41). Hence, we reasoned that integration of systemic inflammatory state, malnutrition and inhibition of immune function could provide a more comprehensive and accurate prediction of OS, compared to any of those single factors.

In conclusion, lowering FBG levels, activating immune system, improving systemic inflammation levels, and maintaining adequate nutrition could improve the prognosis of patients with NSCLC. It should be noted that while parenteral and enteral nutrition was an important way of nutritional support for patients with NSCLC, it could also potentially lead to hyperglycemia (42). Therefore, it would be advisable to maintain an appropriate FBG levels while actively carry out nutritional interventions (43).

In addition to GLR and mGPS, our model also included sex, age, BMI and TNM stage. Previous studies had shown that age, TNM stage and BMI are predictors for OS of patients with

NSCLC (44–46). In this study, we showed that our constructed nomogram might be superior in predicting OS of patients with NSCLC compared with any of above factors included in the nomogram, providing a basis for personalized treatment and clinical applications.

However, our study might have flaws in several ways. The sample sizes were relatively small, which might affect the statistical power. It is worth mentioning that in **Figure 3**, when GLR is higher than 6.25, the association between GLR and risk of death for patients with NSCLC was no longer significant. Based on threshold analyses, piecewise regression analyses and population distribution analyses, we suspected that this was due to the small sample size (**Supplementary Figure 8, Supplementary Table 1**). In addition, laboratory data were determined using standard laboratory tests, which were limited in scope compared to more advanced testing techniques. Studies with larger sample size and more clinical factors should be carried out in the future to further improve OS prediction for patients with NSCLC. Because the records of NSCLC treatment in our database were not detailed enough, such as the interval between admission and operation, chemotherapy or radiotherapy, the operation mode of operation, the scheme and specific dose of chemotherapy, the radiation dose of radiotherapy, etc., we believed that adding these treatment data to the multivariate analysis might affect the reliability and stability of the results. Therefore, we did not adjust for the treatments. In future research, we will improve the deficiencies mentioned above in the database and record the treatment data of patients in more detail.

CONCLUSION

In summary, GLR and mGPS could be used as independent prognostic factors for survival of patients with NSCLC. The proposed nomogram could predict OS of patients with NSCLC with good sensitivity and specificity. Compared to the TNM staging system or other traditional indicators included in the nomogram, our proposed nomogram might provide a more accurate and specific tool for facilitating clinical decisions, personalized treatment, and disease management in patients with NSCLC.

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 Ethical Review Committees of the participating hospitals. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-PS: conceptualization and methodology. MY: data curation and writing- original draft preparation. QZ: visualization, investigation, and data curation. Y-ZG, TL, and K-PZ: software. MT: validation and visualization. C-LH, XZ, M-MS, H-LX, and X-YL: writing-reviewing and editing. Z-WW, G-TR, X-WZ, H-YZ, Q-QL, X-RL, and S-QL: supervision and investigation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.871301/full#supplementary-material

Supplementary Figure 1 | Associations between blood glucose to lymphocyte ratio (GLR) and overall survival (OS) in patients with non-small cell lung cancer (NSCLC). Model was adjusted for sex, age, BMI, tea drinking status, TNM stage and modified Glasgow prognostic score (mGPS).

Supplementary Figure 2 | Receiver operating characteristic curve (ROC) for determining the cut-off point of blood glucose to lymphocyte ratio (GLR).

Supplementary Figure 3 | Kaplan-Meier curves showing associations between blood glucose to lymphocyte ratio (GLR) and overall survival (OS) in patients with non-small cell lung cancer (NSCLC).

Supplementary Figure 4 | Kaplan-Meier curves showing associations between modified Glasgow prognostic score (mGPS) and overall survival (OS) in patients with non-small cell lung cancer (NSCLC).

Supplementary Figure 5 | Calibration curves for predicting survival probability of patients with non-small cell lung cancer (NSCLC).

Supplementary Figure 6 | Area Under the Curves (AUCs) of time-dependent receiver operating characteristic curves (ROCs) generated based on the TNM stage and the nomogram for patients with non-small cell lung cancer (NSCLC).

Supplementary Figure 7 | Area Under the Curves (AUCs) of TNM stage and the nomogram in patients with non-small cell lung cancer (NSCLC).

Supplementary Figure 8 | Associations between blood glucose to lymphocyte ratio (GLR < 6.25 or ≥ 6.25) and OS in patients with non-small cell lung cancer (NSCLC). The models were adjusted for sex, age, BMI, tea drinking status, TNM stage and modified Glasgow prognostic score (mGPS).

Supplementary Table 1 | Associations between GLR and OS in patients with NSCLC. GLR, blood glucose to lymphocyte ratio; OS, overall survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; CIs, confidence intervals. a Models were adjusted for sex, age, body mass index, tea drinking status, TNM stage and mGPS.

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Poor Pre-operative Nutritional Status Is a Risk Factor of Post-operative Infections in Patients With Gastrointestinal Cancer—A Multicenter Prospective Cohort Study

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Objective: This study aimed to assess the prognostic value of the Nutritional Risk Score 2002 (NRS2002) and patient-generated subjective global assessment (PG-SGA) for post-operative infections in patients with gastric cancer (GC) and colorectal cancer (CRC) who underwent curative surgery.

Methods: This prospective study included 1,493 GC patients and 879 CRC patients who underwent curative surgery at 18 hospitals in China between April 2017 and March 2020. The NRS2002 and PG-SGA were performed on the day of admission. The relationship between the nutritional status of patients before surgery and post-surgical incidence of infection was analyzed using univariate and multiple logistic regression analyses.

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Results: According to NRS2002, the prevalence of nutritional risk was 51.1% in GC patients and 63.9% in CRC patients. According to the PG-SGA, 38.9% of GC patients and 54.2% of CRC patients had malnutrition. Approximately 4.4% of the GC patients and 9.9% of the CRC patients developed infectious complications after surgery. The univariate and multiple logistic regression analyses showed that the risk of infections was significantly higher in GC patients with a high nutritional risk score (NRS2002 $\geq$5) than in those with a low score (NRS2002 $<$3), and the PG-SGA score was identified as a predictor of post-operative infection complications of CRC.

Conclusion: The pre-operative nutritional status of patients with GC or CRC has an impact on post-operative infection occurrence. NRS2002 $\geq$5 was a risk factor for post-operative infection in patients with GC, and the PG-SGA B/C was a predictor of infections in patients with CRC.

Keywords: NRS2002, PG-SGA, gastric cancer, colorectal cancer (CRC), post-operation infection

INTRODUCTION

Colorectal cancer (CRC, including anal cancer) and gastric cancer (GC) are within the top five cancer types of all estimated cancer cases and deaths worldwide. CRC and GC represent the two major types of gastrointestinal cancers, accounting for 37.8 and 21.0% of the incidence, respectively (1). As common types of gastrointestinal tumors, CRC or GC in patients often gives rise to nutritional risk or malnutrition, which is exacerbated by surgical stress (2). In some patients with GC, skeletal muscle strength and mass decrease before surgery, which causes a vicious cycle of decline in physical function and further malnutrition, resulting in shortened survival (3, 4). Pre-operative nutrition and frailty have been reported to increase the relative risk of post-operative complications by 2–4 times (5, 6).

Infectious complications are one of the most common complications after surgery and are associated with poor prognosis. Infections after surgery can significantly increase hospitalization costs, prolong the length of hospital stay, and even lead to an increase in infection-related mortality (7). Therefore, the evaluation of perioperative risk factors is of great significance for the prevention and treatment of post-operative infections. In addition to age, BMI, ASA score, diabetes, multiple underlying diseases, and other factors (8, 9), nutritional risk and malnutrition are important risk factors for infections.

To increase awareness and allow for early recognition and treatment, many types of nutritional assessments are used in clinical practice, especially *via* validated nutrition screening tools. For example, the NRS2002 introduced by Kondrup et al., (10) is the preferred tool for screening and assessing hospital patients. The NRS2002 was developed by the Danish Society for Parenteral and Enteral Nutrition in 2003 and was verified in an analysis that included 128 controlled clinical trials (10). It was recommended to screen nutritional risk by the Europe Society for Parenteral and Enteral Nutrition (ESPEN) Guidelines (11). The patient-generated subjective global assessment (PG-SGA) tool, mentioned in the European guidelines, was modified according to the SGA and is a frequently used nutritional assessment tool in cancer patients (11).

However, their role in predicting post-operative infections in patients with gastrointestinal cancer is unknown. It has been shown that nutritional risk and low pre-operative nutritional status in patients with GC are associated with decreased immune function and the development of complications, especially infectious complications (12). However, Pacelli et al. (13) found that pre-operative nutritional status was not correlated with the incidence and mortality of post-operative infection-related complications in patients with GC. Hsueh et al. (14) compared five nutrition assessment tools and found that the PG-SGA performed the poorest and failed to predict any post-operative complications in patients with GC.

Previous studies generally included a range of diseases with a small number of cases, which may have led to inconsistent results. To date, there have been no multi-center studies in China on the relationship between NRS2002, PG-SGA, and post-operative infections in patients with gastrointestinal cancer. Thus, the aim of this study was to assess the prognostic value of NRS2002 and PG-SGA for post-operative infections in patients with GC and CRC who underwent curative surgery.

METHODS

This prospective cohort study was conducted in 18 hospitals in China between April 2017 and March 2020. The research protocol was reviewed and approved by the Ethics Committees of each institution. The National Ethics approval number is 2014ZFYJ-010. All the participants provided written informed consent. The Clinical Trial.gov identification number is NCT03115931.

Patients

The main inclusion criteria were aged 18–80 years, diagnosed with GC or CRC, and scheduled to undergo elective surgical treatment. The main exclusion criteria included the presence of non-cancer inflammatory diseases, a history of malignant tumors, without curative surgery, an inability to complete the NRS2002 or PG-SGA, and a refusal to sign the consent form.

Data Collection

The demographic and clinical characteristics were recorded within an electronic database by one or more trained investigators at each center. The weight and height were measured by two trained evaluators on the day of admission, and the body mass index (BMI) was calculated and classified according to the World Health Organization criteria. The diagnosed comorbidities (hypertension, diabetes), nutritional risk as determined by the NRS2002 at hospital admission, and smoking status (active smoker) were recorded. The PG-SGA was conducted on the day of admission. The Biochemical indexes, such as albumin, prealbumin, fasting plasma glucose, triglycerides, alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen (BUN), serum creatinine, hemoglobin, and white blood cell (WBC), were determined on the day of admission to the hospitals. In the present study, we examined infection complications classified according to the definition raised by the Centers for Disease Control and Prevention (15). This study particularly monitored the infections by the two experienced clinicians in each center. All infections were recorded between post-operative day 1 and hospital discharge.

NRS2002

Nutritional risk was assessed by NRS2002. NRS2002 takes into account impaired nutritional status (low, moderate or severe) and severity of disease (low, moderate or severe), with an adjustment for age of $\geq$70 years (10). The final scoring of NRS2002 ranges from 0 to 7. We use the three categories for the NRS2002: no nutritional risk ($<$3), nutritional risk (3, 4), and high nutritional risk ($\geq$5). The NRS2002 was routinely conducted at admission by routine in the hospitals and recorded in the electronic medical record system. It was assessed by one trained nurse with 1-year nutritional expertise in each center.

PG-SGA

The PG-SGA, a nutritional status assessment method, was modified according to the SGA and designed specifically for cancer patients. This involves patients' self-assessment and medical staff evaluation. The core content includes seven parts: weight, food intake, symptoms, functional capacity, disease and its relation to nutritional requirements, metabolic demand (stress), and physical examination; the first four parts were evaluated by patients themselves and the last three by the medical staff (16). The examination consists of visual inspection and palpation of muscles, subcutaneous fat and edema. Muscle wasting was investigated by visual inspection and palpation of muscles with loss of bulk and tone in temporal areas, deltoids and quadriceps indicating muscle depletion. The triceps and midaxillary line at the level of the lower ribs were investigated with regard to depletion of subcutaneous fat. Ankles were examined for the presence of edema. The degree of muscle and fat depletion was evaluated and rated as 0 (normal) to 3 (severe deficit) (17). Based on the above assessments, patients were classified as well-nourished (PGSGA A), moderately malnourished (PG-SGA B) or severely malnourished (PG-SGA C).

The PG-SGA was carried out by trained registered clinical dietitians in each center, and supervised by one of our researchers. All dietitians underwent training in the PG-SGA procedure, as training has been shown to increase comprehensibility (18). We have provided a lecture explaining the rationale behind the PG-SGA, another lecture demonstrating its use and electronic version. Next, all the dietitians took part in a workshop to practice the PG-SGA, including the physical examination, and discussed the use and interpretation of the PG-SGA.

Statistical Analysis

The continuous variables were described as means (standard deviations, SD) and the categorical variables as numbers (percentages). We preformed Pearson Chi-square test, Fisher's exact test and Cochran-Mantel-Haenszel Statistics on comparison of post-operative infection rates between gastric cancer and colorectal cancer and among different nutritional status. The odds ratios (ORs), 95% confidence intervals (95% CIs), and P for trend of the risk of post-operative infection complications were determined using univariate logistic regression models according to the three categories of the NRS2002 and PG-SGA and the quartiles of the serum biomarkers. Furthermore, the same method was used to calculate the ORs and 95% CIs for the serum biomarkers after log transformation and then dividing by the log transformation SD (per 1-SD increment). For the NRS2002 and PG-SGA, we developed two sets of multivariable-adjusted models: Model 1 adjusted for age and sex and Model 2 adjusted for age, gender, and other possible confounders that were identified in the univariate logistic regression analysis (P for trend $<$0.05). In addition, we performed subgroup analysis stratified by median age and sex for the risk of post-operative infection complications within the NRS2002 and PG-SGA groups. The dataset contains some missing values of the cancer stage and pre-operative chemotherapy. A sensitivity analysis was performed among those who had available information to increase the effect of the statistical analysis and interpret the main analysis. GC and CRC were to be analyzed separately in univariate and multivariable logistic regression and subgroup analysis. Statistical significance was set at $P < 0.05$. All the statistical analyses were performed using the SPSS version 25.0.

RESULTS

A total of 4,279 patients who underwent selective operations in general surgery departments between April 2017 and March 2020 were included. A total of 1,493 GC patients and 879 CRC patients fulfilled the criteria for enrollment in this study (**Figure 1**). Patients ($n = 81$) who had pre-operative non-cancer-related infectious diseases, those who did not undergo curative surgery ($n = 65$), patients who refused to sign consent form ($n = 22$), and patients with other conditions ($n = 1{,}739$) were excluded (**Figure 1**). **Table 1** shows the characteristics of the study population. According to the NRS2002, in GC cohort, there were 48.9% had no nutritional risk, 45.1% had nutritional risk, and 6.0% had high nutritional risk. In CRC cohort, the

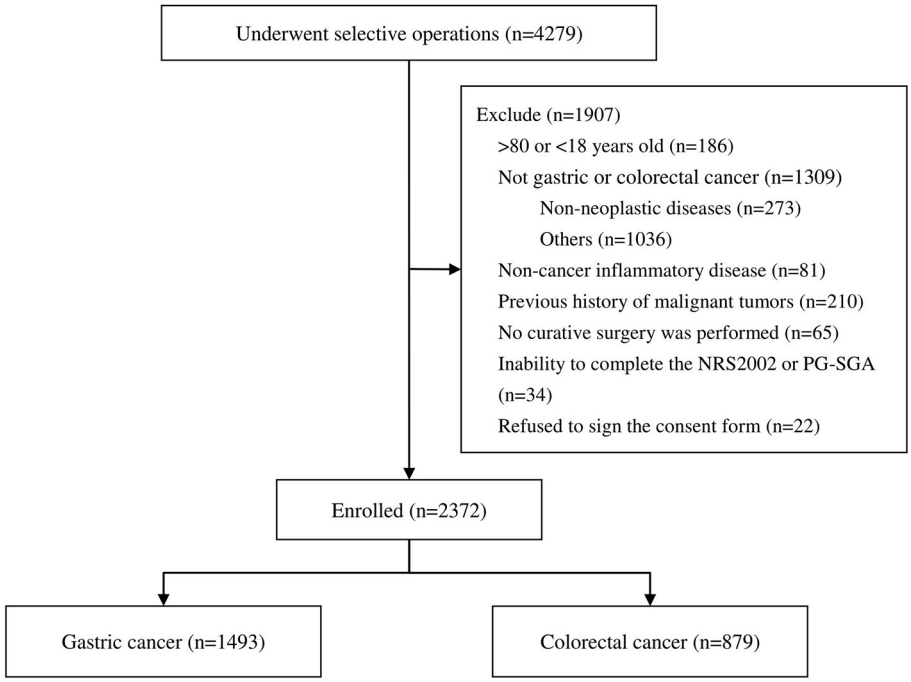

FIGURE 1 | Diagram of patient enrollment in the study.

proportions were 36.1, 56.9, and 7.1%. According to the PG-SGA, the percentages of patients who were well-nourished, moderately malnourished and severely malnourished in GC cohort were 61.1, 34.2, and 4.7%, respectively. And in CRC cohort were 45.8, 51.3, and 2.9%. The mean age of the GC patients was 59.8 ± 10.7 years, 72.5% were male, 2.0% had hypertension, and 8.7% had diabetes. Of the CRC patients, 60.8% were male and 39.2% female, with an average age of 60.2 ± 11.4 years. A total of 2.7% had a history of hypertension and 7.7% diabetes.

The number of post-operative infections per each NRS2002 and PG-SGA category was showed in **Supplementary Table S1**. We observed a gradual increase in the infection rate of CRC patients with the increase of NRS2002 scores, but it was not statistically significant (8.5, 10.4, and 12.9%, $P = 0.485$; **Supplementary Table S1**). A similar result was found in PG-SGA categories in GC patients (4.4, 3.8, and 8.7%, $P = 0.192$; **Supplementary Table S1**). The rates of post-operative infections between GC and CRC were statistically different [65 (4.4%) vs. 87 (9.9%) $P < 0.001$, **Supplementary Table S1**]. And the Test of Homogeneity of Odds Ratio with the NRS2002 categories suggested that the OR values between layers were homogenous ($P = 0.456$). Therefore, after controlling the NRS2002 influence on stratification factor, CRC was found to be a risk factor for the occurrences of infections, with a common-OR = 2.35, 95% CI 1.68–3.30, $P < 0.001$. However, the tests with PG-SGA categories suggested that the OR values between layers were heterogeneous ($P = 0.047$). Therefore, after PG-SGA stratification, CRC was found to be a risk factor for the occurrences of infections in patients with a "B" grade, OR = 3.70, 95% CI 2.16–6.32, $P < 0.001$. Those with an "A" or "C" grade, diagnosis had no effect on the occurrences of infections [OR (A) = 1.46, 95% CI 0.87–2.45, P (A) = 0.147; OR (C) = 2.50, 95% CI 0.69–9.04, P (C) = 0.166; **Supplementary Table S1**].

Univariate Logistic Regression Analysis

In patients with GC, the univariate logistic regression analysis showed that smoking (OR 2.09, 95% CI: 1.26–3.46, $P = 0.005$; **Table 2**) was a significant risk factor for post-operative infections, whereas the NRS2002 scores were not (P for trend = 0.062; **Table 3A**). However, we found a significantly increased risk of post-operative infections in patients with NRS2002 ≥5 compared with those with NRS2002 <3 (OR 2.82, 95% CI: 1.29–6.19). For a per 1-SD increment in total bilirubin, the OR for infection post-operatively was 1.28 (95% CI: 1.01–1.62) and the BUN was 1.46 (95% CI: 1.15–1.86; **Table 2**).

From the univariate logistic regression analysis of the CRC patients, hypertension (OR 3.99, 95% CI: 1.61–9.91, $P = 0.003$; **Table 2**), diabetes (OR 2.62, 95% CI: 1.39–4.95, $P = 0.003$; **Table 2**), and the PG-SGA B/C (P for trend <0.001; **Table 3B**) were predictors of post-operative infection complications, while laparoscopic surgery (OR 0.23, 95% CI: 0.14–0.38, $P < 0.001$; **Table 2**) was a protective factor. In patients with CRC, NRS2002 score <3 category was set as the reference, and the OR for the risk of post-operative infections for patients in the NRS2002 score = 3–4 category and the NRS2002 score ≥5 category was 1.25 (95% CI: 0.77–2.03) and 1.59 (95% CI: 0.69–3.69), respectively (P for trend = 0.232; **Table 3B**). With the increase of NRS2002 score, the upward trend of infection risk was not statistically significant. For a per 1-SD increment in WBC, the OR for post-operative infections was 1.25 (95% CI: 1.01–1.55; **Table 2**).

TABLE 1 | Characteristics of all participants.

	GC (n = 1,493)	CRC (n = 879)	Total (n = 2,372)
Age, year	59.8 (10.7)	60.2 (11.4)	59.9 (11.0)
Gender			
Male	1,082 (72.5)	534 (60.8)	1,616 (68.1)
Female	411 (27.5)	345 (39.2)	756 (31.9)
Height, cm	166.6 (7.3)	164.1 (8.1)	165.7 (7.7)
Weight, kg	64.5 (10.9)	62.8 (10.9)	63.8 (10.9)
BMI, kg/m^2	23.2 (3.2)	23.2 (3.2)	23.2 (3.2)
Hypertension, yes	30 (2.0)	24 (2.7)	54 (2.3)
Diabetes, yes	130 (8.7)	68 (7.7)	198 (8.3)
Smoking, yes	390 (26.1)	172 (19.6)	562 (23.7)
NRS2002			
<3	730 (48.9)	317 (36.1)	1,047 (44.1)
3–4	674 (45.1)	500 (56.9)	1,174 (49.5)
≥5	89 (6.0)	62 (7.1)	151 (6.4)
PG-SGA			
A	895 (61.1)	400 (45.8)	1,295 (55.4)
B	501 (34.2)	448 (51.3)	949 (40.6)
C	69 (4.7)	26 (2.9)	95 (4.1)
Operation type			
Laparotomy	1,068 (71.5)	361 (41.1)	1,429 (60.2)
Laparoscopy	425 (28.5)	518 (58.9)	943 (39.8)
Infection complications, yes	65 (4.4)	87 (9.9)	152 (6.4)
LOS, day	18.2 (8.6)	18.1 (7.9)	18.1 (8.3)
Albumin, g/L	41.5 (5.1)	40.6 (5.2)	41.2 (5.2)
Prealbumin, mg/L	266.0 (81.4)	260.5 (78.6)	263.9 (80.4)
FBG, mmol/L	5.6 (1.3)	5.6 (1.4)	5.6 (1.4)
TG, mmol/L	1.4 (0.8)	1.3 (0.7)	1.4 (0.8)
ALT, U/L	23.3 (20.6)	18.4 (12.4)	21.5 (18.2)
AST, U/L	26.7 (36.1)	20.9 (14.0)	24.5 (30.0)
T-Bil, μmol/L	13.2 (8.7)	13.6 (11.3)	13.3 (9.8)
BUN, mmol/L	5.7 (2.0)	5.2 (2.0)	5.5 (2.0)
Scr, μmol/L	75.4 (21.6)	73.1 (20.9)	74.6 (21.4)
Hemoglobin, g/L	127.4 (23.8)	126.2 (22.8)	126.9 (23.4)
WBC, 10^9/L	5.9 (2.1)	6.7 (2.6)	6.2 (2.3)

Quantitative variables were expressed as means (standard deviations). Categorical variables were expressed as number (percentages).
GC, gastric cancer; CRC, colorectal cancer; BMI, body mass index; NRS2002, Nutrition Risk Screening 2002; PG-SGA, Patient-generated Subjective Global Assessment; LOS, length of stay; FBG, fasting plasma glucose; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-Bil, total bilirubin; BUN, blood urea nitrogen; Scr, serum creatinine; Hb, hemoglobin; WBC, white blood cell.

Multivariable Logistic Regression Analysis

The results of multivariable logistic regression analysis are presented in **Tables 3A**,**B**. In Model 1 of the GC patients, the OR for post-operative infections was 2.75 (95% CI: 1.22–6.19; **Table 3A**) in individuals with NRS2002 ≥5 compared with those with NRS2002 <3. NRS2002 ≥5 was not associated with post-operative infection complications in Model 2 (OR 1.95, 95% CI: 0.81–4.69; **Table 3A**). In both of the models, the PG-SGA B/C remained an important predictor of infection complications in the CRC patients compared with PG-SGA A (P for trend <0.001; **Table 3B**) but was not a significant predictor in the GC patients (P for trend >0.05; **Table 3A**). The results of sensitivity analysis were similar to the main analysis (**Supplementary Tables S3A,B**).

Stratified Analysis

Based on stratified analysis, the OR of NRS2002 ≥5 was higher in the younger subgroup (≤61 years) of GC (OR 3.68, 95% CI: 1.15–11.72, P for interaction = 0.043; **Table 4A**) according to the median age of the patients. In the male population with GC, the OR of NRS2002 ≥5 was statistically significant (OR 3.09, 95% CI: 1.26–7.59, P for trend = 0.045; **Table 4A**). In the stratified analysis of patients with CRC patients, the NRS2002 score remained statistically insignificant; meanwhile, PG-SGA grade was not correlated with post-operative infections in the younger subgroup (≤62 years; P for trend = 0.144, P for interaction = 0.043; **Table 4B**). However, in the older subgroup, the OR of each category of PG-SGA increased (PG-SGA B vs. A: OR 3.23, 95% CI:1.44–7.25; PG-SGA C vs.

TABLE 2 | The association of clinical characteristics and hematologic biomarkers with post-operative infections.

		GC				CRC			
		No. of cases	**OR (95% CI)**	***P*-Value**	**Per 1-SD**	**No. of cases**	**OR (95% CI)**	***P*-Value**	**Per 1-SD**
Age		1,493	1.01 (0.99–1.04)	0.327		879	1.00 (0.99–1.02)	0.679	
Gender		1,493	0.71 (0.39–1.30)	0.271		879	0.80 (0.50–1.27)	0.338	
Smoking		1,493	2.09 (1.26–3.46)	0.005		879	1.26 (0.74–2.14)	0.398	
BMI		1,493	1.02 (0.95–1.10)	0.585		879	0.98 (0.92–1.06)	0.637	
Hypertension		1,493	0	0.998		879	3.99 (1.61–9.91)	0.003	
Diabetes		1,493	0.87 (0.34–2.20)	0.767		879	2.62 (1.39–4.95)	0.003	
Laparoscopy		1,493	2.39 (1.45–3.95)	0.001		879	0.23 (0.14–0.38)	<0.001	
Albumin	Q1	379	1	0.609[†]	0.94 (0.74–1.20)	220	1	0.630[†]	0.84 (0.68–1.03)
	Q2	382	0.99 (0.49–2.01)			236	0.80 (0.43–1.48)		
	Q3	361	1.54 (0.80–2.97)			204	1.04 (0.57–1.90)		
	Q4	371	0.63 (0.28–1.40)			219	0.78 (0.41–1.46)		
Prealbumin	Q1	380	1	0.188[†]	0.84 (0.66–1.07)	220	1	0.161[†]	0.87 (0.71–1.08)
	Q2	375	0.96 (0.50–1.86)			221	0.95 (0.53–1.71)		
	Q3	369	0.92 (0.47–1.79)			223	0.62 (0.32–1.17)		
	Q4	369	0.58 (0.27–1.24)			215	0.72 (0.39–1.35)		
FBG	Q1	376	1	0.479[†]	1.17 (0.93–1.48)	220	1	0.092[†]	1.15 (0.93–1.42)
	Q2	399	1.69 (0.82–3.48)			235	1.16 (0.60–2.23)		
	Q3	353	1.35 (0.62–2.92)			210	1.05 (0.53–2.08)		
	Q4	365	1.48 (0.70–3.15)			214	1.76 (0.95–3.27)		
TG	Q1	378	1	0.933[†]	1.05 (0.82–1.34)	228	1	0.838[†]	1.08 (0.86–1.35)
	Q2	392	0.90 (0.45–1.82)			214	1.07 (0.58–1.98)		
	Q3	350	0.95 (0.47–1.93)			222	0.65 (0.33–1.27)		
	Q4	373	1.01 (0.51–2.02)			215	1.23 (0.68–2.22)		
ALT	Q1	385	1	0.819[†]	1.08 (0.84–1.37)	221	1	0.096[†]	1.21 (0.97–1.50)
	Q2	407	1.51 (0.76–3.00)			227	1.83 (0.93–3.62)		
	Q3	351	1.02 (0.47–2.20)			212	1.80 (0.90–3.60)		
	Q4	350	1.27 (0.61–2.64)			219	1.91 (0.96–3.77)		
AST	Q1	419	1	0.911[†]	1.06 (0.83–1.34)	232	1	0.083[†]	1.17 (0.95–1.43)
	Q2	379	1.25 (0.64–2.44)			229	1.58 (0.82–3.06)		
	Q3	328	0.90 (0.42–1.91)			212	1.56 (0.80–3.06)		
	Q4	367	1.15 (0.58–2.28)			206	1.87 (0.97–3.60)		
T-Bil	Q1	387	1	0.078[†]	1.28 (1.01–1.62)	220	1	0.059[†]	1.15 (0.92–1.42)
	Q2	365	1.62 (0.72–3.64)			221	0.72 (0.35–1.47)		
	Q3	375	2.46 (1.16–5.25)			219	1.49 (0.80–2.76)		
	Q4	366	1.84 (0.83–4.07)			219	1.49 (0.80–2.76)		
BUN	Q1	359	1	0.089[†]	1.46 (1.15–1.86)	206	1	0.818[†]	1.06 (0.84–1.35)
	Q2	358	0.52 (0.23–1.18)			205	1.13 (0.58–2.20)		
	Q3	356	0.70 (0.33–1.49)			202	1.02 (0.52–2.03)		
	Q4	341	1.59 (0.84–3.00)			204	0.95 (0.48–1.9)		
Scr	Q1	369	1	0.756[†]	0.87 (0.72–1.05)	224	1	0.186[†]	0.87 (0.70–1.07)
	Q2	368	1.00 (0.49–2.04)			205	0.96 (0.52–1.76)		
	Q3	373	1.18 (0.60–2.34)			215	0.86 (0.47–1.59)		
	Q4	363	0.82 (0.39–1.73)			214	0.64 (0.33–1.24)		
Hb	Q1	378	1	0.427[†]	1.17 (0.89–1.54)	221	1	0.970[†]	0.97 (0.78–1.21)
	Q2	390	1.26 (0.62–2.57)			227	1.07 (0.58–1.97)		
	Q3	360	1.05 (0.49–2.24)			223	0.84 (0.44–1.60)		
	Q4	365	1.43 (0.71–2.89)			208	1.07 (0.57–2.00)		
WBC	Q1	376	1	0.496[†]	0.97 (0.75–1.24)	221	1	0.058[†]	1.25 (1.01–1.55)
	Q2	376	0.73 (0.36–1.47)			219	1.01 (0.52–1.96)		
	Q3	371	1.01 (0.53–1.95)			221	0.89 (0.45–1.75)		
	Q4	370	0.68 (0.33–1.41)			218	1.83 (1.00–3.34)		

GC, gastric cancer; CRC, colorectal cancer; FBG, fasting plasma glucose; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-Bil, total bilirubin; BUN, blood urea nitrogen; Scr, serum creatinine; Hb, hemoglobin; WBC, white blood cell.

[†] *For trend.*

TABLE 3A | The association of NRS2002 and PG-SGA with post-operative infections (GC).

		OR (95% CI)			*P* for trend	Per 1-SD
		Category 1	Category 2	Category 3		
NRS2002[†]	**No. of cases**	730	674	89		
	Not adjusted	1	1.09 (0.64–1.86)	2.82 (1.29–6.19)	0.062	1.27 (1.00–1.61)
	No. of cases	730	674	89		
	Model 1	1	1.09 (0.63–1.86)	2.75 (1.22–6.19)	0.078	1.26 (0.99–1.60)
	No. of cases	696	639	79		
	Model 2	1	0.99 (0.57–1.73)	1.95 (0.81–4.69)	0.325	1.17 (0.91–1.51)
PG-SGA	**No. of cases**	895	501	69		
	Not adjusted	1	0.87 (0.49–1.51)	2.09 (0.85–5.13)	0.499	1.09 (0.85–1.38)
	No. of cases	895	501	69		
	Model 1	1	0.87 (0.49–1.52)	2.10 (0.85–5.17)	0.499	1.09 (0.85–1.39)
	No. of cases	840	479	69		
	Model 2	1	0.80 (0.45–1.45)	1.86 (0.73–4.77)	0.705	1.05 (0.82–1.35)

Model 1: Adjusted for age and gender. Model 2: Adjusted for age, gender, smoking, hypertension, diabetes, laparoscopy, T-Bil, BUN and WBC. GC, gastric cancer.
[†]NRS2002 was classified as three categories by the criteria of "<3," "3–4," and "≥5" score. PG-SGA was classified as three categories by the criteria of "A," "B," and "C" grade.

TABLE 3B | The association of NRS2002 and PG-SGA with post-operative infections (CRC).

		OR (95% CI)			*P* for trend	Per 1-SD
	Category 1	Category 2	Category 3			
NRS2002[†]	**No. of cases**	317	500	62		
	Not adjusted	1	1.25 (0.77–2.03)	1.59 (0.69–3.69)	0.232	1.29 (1.03–1.61)
	No. of cases	317	500	62		
	Model 1	1	1.26 (0.77–2.05)	1.58 (0.67–3.75)	0.234	1.29 (1.03–1.62)
	No. of cases	303	456	58		
	Model 2	1	1.04 (0.60–1.81)	1.43 (0.57–3.60)	0.550	1.19 (0.93–1.53)
PG-SGA	**No. of cases**	400	448	26		
	Not adjusted	1	2.19 (1.34–3.57)	3.57 (1.24–10.27)	0.001	1.48 (1.19–1.85)
	No. of cases	400	448	26		
	Model 1	1	2.22 (1.36–3.63)	3.57 (1.23–10.33)	<0.001	1.49 (1.19–1.86)
	No. of cases	371	415	26		
	Model 2	1	2.62 (1.48–4.63)	5.29 (1.64–17.10)	<0.001	1.64 (1.27–2.12)

Model 1: Adjusted for age and gender. Model 2: Adjusted for age, gender, smoking, hypertension, diabetes, laparoscopy, T-Bil, BUN, and WBC. CRC, colorectal cancer.
[†]NRS2002 was classified as three categories by the criteria of "<3," "3–4," and "≥5" score. PG-SGA was classified as three categories by the criteria of "A," "B," and "C" grade.

A: OR 6.79, 95% CI:1.79–25.83; P for trend = 0.001, P for interaction <0.001; **Table 4B**).

DISCUSSIONS

Gastric cancer and CRC had the 5th (5.6%) and 3rd (10%) highest incidences among all cancers, respectively, and the 4th (7.7%) and 2nd (9.4%) for mortality, respectively, according to Global Cancer Statistics 2020 (1). Pre-operative nutritional status is associated with short-term and long-term prognosis in gastrointestinal cancer (19–21). The aim of this study was to assess the relationship between the pre-operation nutritional status and post-operation infections in patients with GC and CRC. In our study, 51.1% of the GC patients and 63.9% of the CRC patients were at nutritional risk according to the NRS2002, and 38.9 and 54.2% had moderate or severe malnutrition, respectively, according to the PG-SGA. We found that the PG-SGA B and C was a risk factor for post-operative infections in CRC. In patients with GC, NRS2002 ≥5 was a risk factor.

There are several commonly used nutritional screening tools worldwide, including the NRS2002, malnutrition screening tools (MST), and malnutrition universal screening tools (MUST). The most widely used is NRS2002 because of its low cost, easy application, and wide applicability. In contrast to the previous nutrition score, it assessed the severity of the disease to evaluate nutritional requirements. In addition, age was also taken into account. All of these features enabled the NRS2002 tool to cover a wide range of diseases in hospital, including cancer.

We found that having a high nutritional risk, defined as NRS2002 ≥5, increased the risk of post-operative infections in

TABLE 4A | Stratified analysis of GC (age and gender).

			OR (95% CI)			*P* for trend	Per 1-SD	*P* for interaction
			Category 1	Category 2	Category 3			
NRS2002[†]	Age	**No. of cases**	415	328	28			
		≤61*	1	0.55 (0.24–1.29)	3.68 (1.15–11.72)	0.729	1.19 (0.83–1.71)	0.043
		No. of cases	315	346	61			
		>61*	1	1.87 (0.86–4.06)	2.72 (0.90–8.27)	0.046	1.31 (0.95–1.80)	
	Gender	**No. of cases**	540	479	63			
		Male	1	1.25 (0.68–2.28)	3.09 (1.26–7.59)	0.045	1.31 (1.00–1.71)	0.706
		No. of cases	190	195	26			
		Female	1	0.69 (0.21–2.21)	2.18 (0.43–11.10)	0.792	1.16 (0.70–1.93)	
PG-SGA	Age	**No. of cases**	467	257	33			
		≤61*	1	0.80 (0.34–1.87)	3.44 (1.09–10.83)	0.303	1.20 (0.85–1.69)	0.402
		No. of cases	428	244	36			
		>61*	1	0.92 (0.43–1.93)	1.14 (0.26–5.07)	0.958	0.99 (0.70–1.39)	
	Gender	**No. of cases**	656	354	46			
		Male	1	1.16 (0.63–2.12)	1.51 (0.44–5.15)	0.468	1.11 (0.84–1.46)	0.788
		No. of cases	239	147	23			
		Female	1	0.16 (0.02–1.24)	3.44 (0.87–13.50)	0.859	1.05 (0.63–1.74)	

GC, gastric cancer.
*[†]NRS2002 was classified as three categories by the criteria of "<3," "3–4," and "≥5" score. PG-SGA was classified as three categories by the criteria of "A," "B," and "C" grade. *The median age of the GC patients is 61.*

TABLE 4B | Stratified analysis of CRC (age and gender).

			OR (95% CI)			*P* for trend	Per 1-SD	*P* for interaction
			Category 1	Category 2	Category 3			
NRS2002[†]	Age	**No. of cases**	173	283	14			
		≤62*	1	1.16 (0.60–2.23)	1.76 (0.36–8.59)	0.513	1.20 (0.85–1.69)	0.238
		No. of cases	144	217	48			
		>62*	1	1.37 (0.66–2.83)	1.57 (0.56–4.44)	0.330	1.35 (1.00–1.82)	
	Gender	**No. of cases**	200	300	34			
		Male	1	1.08 (0.60–1.94)	1.55 (0.54–4.46)	0.515	1.22 (0.93–1.62)	0.802
		No. of cases	117	200	28			
		Female	1	1.75 (0.72–4.26)	1.89 (0.46–7.81)	0.231	1.44 (0.98–2.11)	
PG-SGA	Age	**No. of cases**	229	229	10			
		≤62*	1	1.67 (0.88–3.15)	1.39 (0.17–11.59)	0.144	1.26 (0.92–1.72)	<0.001
		No. of cases	171	219	16			
		>62*	1	3.23 (1.44–7.25)	6.79 (1.79–25.83)	0.001	1.76 (1.27–2.44)	
	Gender	**No. of cases**	254	259	16			
		Male	1	1.87 (1.04–3.37)	4.12 (1.21–14.03)	0.008	1.44 (1.10–1.89)	0.094
		No. of cases	146	189	10			
		Female	1	3.23 (1.28–8.16)	2.59 (0.28–23.91)	0.019	1.6 (1.08–2.37)	

CRC, colorectal cancer.
*[†]NRS2002 was classified as three categories by the criteria of "<3," "3–4," and "≥5" score. PG-SGA was classified as three categories by the criteria of "A," "B," and "C" grade. *The median age of the CRC patients is 62.*

patients with GC, which was similar to what was reported in previous studies. Qiu et al. (22) reported that having NRS2002 ≥3 was an independent adverse prognostic factor for overall survival in their study that included 830 patients with GC. In another study that included 880 GC patients who were undergoing a gastrectomy, NRS2002 ≥3 was significantly associated with post-operative complications ($P < 0.001$). However, this association disappeared when the authors performed multivariate analyses adjusting for sex, age, BMI, Charlson comorbidity index, hypohemia, hypoprotein malnutrition, tumor site, laparoscopic surgery, and sarcopenia (23). However, in our study, NRS2002 ≥5 maintained consistent prediction

ability in the multifactor-adjusted models. Therefore, we believe that NRS2002 $\geq$5 is more predictable than NRS2002 $\geq$3 in indicating poor prognosis of the patient underwent radical gastrectomy. In addition, in stratified analysis of NRS2002 $\geq$5, we observed that the risk of post-operative infections was higher in GC patients younger than 61 years and in male GC patients, and it was lower in the patients older than 61 years and in female. However, the results in the age stratification were not statistically significant. Nutritional risk evaluated by the NRS2002 was not identified as a predictor of post-operative infections in patients with CRC. The results of Wang et al. reflected the same view. They found that there were no statistically significant differences in the incidence rates of post-operative complications between patients with and without nutritional risk, according to NRS2002 score ($P = 0.546$) (24). In contrast to the present findings, a previous study performed by Schwegler et al. (25) suggested that the NRS2002 was successful in predicting post-operative complications, including infections, in 186 CRC patients who were undergoing surgery (OR 2.43, $P = 0.004$). Correspondingly, our study was a multi-center study with a large sample size, and our outcome focused on infection complications, which was the advantage of our study compared with the former.

The NRS2002 is a screening tool, which is a fast and simple method that can be used by any healthcare professional to determine whether patients need further comprehensive nutritional assessment and nutritional treatment plan. In the meanwhile, guidelines suggest that objective and quantitative assessments should be applied to patients with abnormal nutritional screening results (11). There are several commonly used nutrition assessment tools, including the PG-SGA, Mini-Nutritional Assessment (MNA), and Global Leadership Initiative on Malnutrition (GLIM). Due to its comprehensiveness and utility, the PG-SGA appears to be one of the most useful methods for the nutritional assessment of cancer patients. As an assessment tool, the PG-SGA should be conducted by nutrition professionals, which includes a comprehensive examination and evaluation of the patients' nutrition metabolism and body function for establishing a nutritional treatment plan.

We observed that the risk of post-operative infections increased in patients with CRC in the PG-SGA B group 2.19 times (95% CI: 1.34–3.57) and the PG-SGA C group 3.57 times (95% CI: 1.24–10.27). The prognostic value of the PG-SGA for post-operative infections maybe attributed to the combination of data such as unconscious weight loss, food intake, gastrointestinal symptoms, active capability, and physical examination of the patient, which were strongly associated with negative outcomes (26, 27). In multivariable logistic regression analysis, the ORs of PG-SGA B/C increased (PG-SGA B vs. A: OR 2.62, 95% CI: 1.48–4.63; PG-SGA C vs. A: OR 5.29, 95% CI: 1.64–17.10; *P* for trend $<$0.001), which means that the prognostic value of the PG-SGA for post-operative infections increased after adjusting for age, gender, smoking, hypertension, diabetes, operation type, total bilirubin, BUN, and WBC. However, when we stratified age, we found that PG-SGA lost its predictive power for people younger than 62 years. This leads us to believe that PG-SGA may be more suitable for predicting post-operative infections in elderly colorectal cancer patients. Our study also suggested that the PG-SGA was unable to predict post-operative infections in patients with GC. Similar to this study, Seo et al. (20) found that the PG-SGA did not predict the adverse events of post-operative chemotherapy in patients with gastrectomy. Esfahani et al. (28) found that there was no significant difference in the PG-SGA scores between metastatic and non-metastatic GC patients. The reason for the weakness of the PG-SGA in predicting poor prognosis of GC patients is unknown. Meanwhile, a more suitable nutritional status assessment tool for patients with GC is still needed.

This study has a few limitations that need to be considered. Although we performed nutritional screening and assessment during the first day of admission, there were no records of NRS2002 score and PG-SGA grade after that. Therefore, we cannot guarantee that the initial NRS2002 score and PG-SGA grade had been unaltered before surgery. Significant improvement in dietitians' perception of difficulty and comprehensibility of the PG-SGA can be achieved by providing short term training. However, a perceived difficulty for the physical examination still remained, which may have affected the classifying the degree of malnutrition. Another limitation is that we did not consider the impact of perioperative nutritional support therapy. In our 18 centers, the medical staff would provide nutritional support therapy for patients with nutritional risk or malnutrition in accordance with the local practices, and there is still no uniform standard. Therefore, we ignored the effects of nutrition support therapy on results in this study. In a subsequent study, we will continue to explore the relationship between nutritional support therapy and the prognosis of cancer.

In conclusion, this study showed that NRS2002 $\geq$5 provided good value for clinicians in the prediction of post-operative infections in patients with GC, enabling advanced interventions. On the other hand, PG-SGA B/C was a good predictor in CRC patients. Simultaneously, this article highlighted the need for a nutritional assessment tool that can better predict clinical outcomes in patients with GC.

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 Clinical Trial Ethics Committee, Jinling Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XWa, LZ, and XG contributed to the conception and design of the study. LZ and SW drafted and revised the manuscript. XWa supervised the entire project and was responsible for the conception and funding. TG collected and collated data. DH contributed to the statistical analysis plan. SW contributed to the collation and analysis of the data. XWa and DH revised the manuscript for important intellectual content. LH, BL, YG, JC,

DG, ZJ, YW, FG, JZ, ZX, ZC, JX, LW, JQ, GD, HH, YN, GaL, ML, HY, WZ, YZ, HQ, XWu, KW, QC, JY, YT, PZ, GJ, BO, and GuL contributed to case enrollment and data collection. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, read, and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.850063/full#supplementary-material

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REVIEW
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Fatty Acids as a Tool to Boost Cancer Immunotherapy Efficacy

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Although immunotherapy represents one of the most potent therapeutic anti-cancer approaches, only a limited number of patients shows clinical benefit. Recent evidence suggests that patients' nutritional status plays a major role in immunotherapy outcome. Fatty acids are essential in a balanced diet and well-known to influence the immune response. Moreover, short-chain fatty acids (SCFAs) show beneficial effects in metabolic disorders as well as in cancer and polyunsaturated fatty acids (PUFAs) contribute to body weight and fat free mass preservation in cancer patients. In line with these data, several studies imply a role for SCFAs and PUFAs in boosting the outcome of immunotherapy. In this review, we specifically focus on mechanistic data showing that SCFAs modulate the immunogenicity of tumor cells and we discuss the direct effects of SCFAs and PUFAs on the immune system in the context of cancer. We provide preclinical and clinical evidence indicating that SCFAs and PUFAs may have the potential to boost immunotherapy efficacy. Finally, we describe the challenges and address opportunities for successful application of nutritional interventions focusing on SCFAs and PUFAs to increase the therapeutic potential of immunotherapeutic approaches for cancer.

Keywords: cancer, immunotherapy, fatty acid, SCFAs, PUFAs

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INTRODUCTION

According to the world health organization (WHO), cancer is the second leading cause of death globally. Worldwide, cancer accounted for nearly 10 million death in 2020 and the cancer burden further continues to grow (1, 2). Immunotherapy, a treatment that utilizes the immune system in order to help the body to fight cancer, represents one of the most promising novel treatment approaches. A variety of different immunotherapeutic strategies are currently being used, including immune checkpoint inhibitors (3), immuno-cytokines (4), monoclonal antibodies (5), adoptive T or NK cell based therapies (6, 7) and cancer vaccines (8). To improve therapeutic outcome, immunotherapy is often combined with other treatments such as chemotherapy or radiation (9).

However, despite long-lasting effects of immunotherapy in some responders (4, 10), disease control occurs in only a small subset of patients (11–13). For example, <13% of the eligible patients for immune checkpoint inhibitor therapy in the U.S. actually benefit from this treatment (11). This low response rate can in part be explained by the fact that a small, but significant

proportion of patients receiving immunotherapy develop immune-related adverse effects that dictate cessation of treatment (14). However, in the majority of the patients, the underlying reasons for the lack of response to immunotherapy are unknown. Various mechanisms have been proposed, such as low programmed death-ligand 1 (PD-L1) expression on tumor cells limiting efficacy of immune checkpoint inhibitors (15) and low mutational burden in combination with downregulation of human leukocyte antigen (HLA) proteins. The latter disrupts the process of antigen presentation of tumor cells, thereby hindering effective T cell recognition, eventually leading to failing of T cell-based immunotherapeutic approaches (16). In addition, the tumor microenvironment (TME) influences immunotherapy responses, e.g., a hypoxic TME impairs anti-tumor immunity and has been suggested to suppress the efficacy of immunotherapy (17). Also, infiltration in the TME of regulatory T cells, myeloid-derived suppressor cells (MDSCs) and M2 tumor-associated macrophages (TAMs) is associated with immunosuppression (16). Moreover, the efficacy of immunotherapy is dependent on a competent immune system, but the latter can be compromised due to multiple host factors, including malnutrition, a problem often encountered in cancer patients (18, 19).

Several epidemiological studies have reported an association between nutritional and metabolic status of cancer patients and responsiveness to immunotherapy. For instance, a low prognostic nutritional index (PNI) has been reported as an independent predictor of short time to treatment failure in lung cancer patients treated with the anti-PD-L1 immune checkpoint inhibitor Atezolizumab (20). In another cohort of lung cancer patients, malnutrition parameters, such as hypoalbuminemia and significant weight loss, have been associated with decreased immunotherapy efficacy (21). Moreover, clinical data from lung cancer and melanoma patients have indicated that cachectic cancer patients appear refractory to immune checkpoint inhibitor therapy (22). In contrast, obesity has been associated with improved responses to immune checkpoint blocking agents in cancer patients (23). Obesity results in increased inflammation and immunosenesence, tumor progression and PD-1-mediated T cell dysfunction which is driven, at least in part, by elevated leptin levels (24). Elevated levels of PD-1 are correlated with increased T cell exhaustion, but also facilitates the success of anti-PD-1 checkpoint therapy, contributing to increased overall survival of obese cancer patients treated with anti-PD-1 antibodies (24). Thus, evidence of an association between nutritional status and immunotherapy efficacy is arising and the underlying mechanisms explaining to what extent the nutritional status is involved in the responsiveness to immunotherapy are becoming increasingly clear.

Fatty acids (**Supplementary Box 1**) are essential in a balanced diet and dietary fatty acids are well-known to influence the nutritional status as well as the immune response of cancer patients (25, 26). Specifically, oral nutritional supplementation containing omega-3 polyunsaturated fatty acids (*n*-3 PUFAs) resulted in preservation of body weight and fat free mass in lung cancer patients (25). Moreover, nutritional intervention with a specific diet rich in *n*-3 PUFAs, reduced serum levels of inflammatory mediators in cancer patients receiving radiotherapy (26). The role of omega-6 PUFAs (*n*-6 PUFAs) on inflammation is more controversial. Although in general high intake of *n*-6 PUFAs has been linked to increased inflammation, some studies also suggest that specific *n*-6 PUFAs can actually decrease inflammation (27). Finally, as a separate class of fatty acids, short-chain fatty acids (SCFAs), formed in the gut upon fermentation of dietary fibers, are known for their anti-inflammatory properties (28) and show beneficial effects in metabolic disorders as well as in cancer (29–31).

Overall, epidemiological evidence associating nutritional status to immunotherapy outcome is increasing and the beneficial effects of specific types of SCFAs and PUFAs on nutritional status, metabolism and the immune response are well-established (25–31). In the next paragraphs, the evidence supporting the potential use of dietary interventions with SCFAs and PUFAs to enhance immunotherapy efficacy will be discussed.

SCFAS AND PUFAS POTENTIALLY ENHANCE IMMUNOTHERAPY EFFICACY

Epidemiological Data Indicate That SCFAs Associate With Response to Immunotherapy

Epidemiological studies specifically investigated the relationship between serum and fecal SCFA concentration and immunotherapy response. In that context, Nomura et al. demonstrated that high concentrations of fecal acetic, propionic, butyric and valeric acids were associated with longer progression-free survival in patients with solid tumors receiving the anti-PD-1 antibodies Nivolumab or Pembrolizumab (32). In line with the data presented by Nomura et al., metabolomics profiling of the gut microbiota from patients with non-small cell lung cancer (NSCLC) receiving Nivolumab showed that propionate and butyrate were significantly associated with long-term beneficial effects (33). However, Coutzac et al. reported an inverse relation between serum SCFA levels and outcome in melanoma patients receiving the anti-CTLA-4 antibodies Ipilimumab; patients with lower serum levels of butyrate and propionate demonstrated longer progression free survival (34). These findings may be

Abbreviations: ARA, arachidonic acid; CRP, C reactive protein; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDAC, histone deacetylase activity; HFD, high fat diet; HIF-1α, hypoxia-induced factor 1α; HLA, human leukocyte antigen; ICAM-1, intercellular adhesion molecule 1; IFNγ, interferon γ; IL, interleukin; LPS, lipopolysaccharide; LFA, lymphocyte function-associated antigen 1; MDSC, myeloid-derived suppressor cells; MHC-1, major histocompatibility complex 1; MICA/B, MHC class I polypeptide-related sequence A/B; NK, natural killer; NKG2D, natural killer group 2D; NSCLC, non-small cell lung cancer; *n*-3 PUFAs, omega 3 polyunsaturated fatty acids; *n*-6 PUFAs, omega 6 polyunsaturated fatty acids; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PNI, prognostic nutritional index; PGE-2, prostaglandin E 2; PUFAs, polyunsaturated fatty acids; SCFAs, short-chain fatty acids; SFAs, saturated fatty acids; TAMs, tumor-associated macrophages; TCR, T cell receptor; TEER, transepithelial electrical resistance; Th1, T helper cell 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TME, tumor microenvironment; TNFα, tumor necrosis factor α; TRAIL, tumor necrosis factor-related apoptosis inducing ligand; WHO, world health organization.

the result of the complex interplay between production and absorption of SCFAs in the gastrointestinal tract. Taken together, the results of these studies suggest that fecal and/or serum SCFAs concentrations associate with response to immunotherapy.

In vitro Data Indicate That SCFAs and *n*-3 PUFAs Enhance Immunotherapy Efficacy

A plethora of *in vitro* studies has indicated the potential of SCFAs to improve immunotherapy efficacy via enhancing the immunogenicity of cancer cells. Already in 1994, it was shown that colon adenocarcinoma cells enhanced the expression of major histocompatibility complex 1 (MHC-1) and intercellular adhesion molecule 1 (ICAM-1) upon butyrate exposure, which makes tumor cells more sensitive to cytotoxic lymphocytes-mediated killing (35). More recently, acetate has been shown to reduce the expression of CD155 on colorectal cancer cells (36). CD155 is a ligand for the inhibitory receptor T cell immunoreceptor with Ig and ITIM domains (TIGIT) expressed on natural killer (NK) cells, T cells and dendritic cells (DCs) and is frequently upregulated in malignant cells (37–39). Downregulation of CD155 on cancer cells has been suggested to enhance CD8+ T cell effector responses toward cancer cells (36). Andresen et al. and Hogh et al. (40, 41) both demonstrated that propionate induced the expression of the natural killer group 2D (NKG2D) ligands MHC class I polypeptide-related sequence A/B (MICA/B) on cancer cells. Activated NK and T cells recognize these MICA/B positive cells via the NKG2D receptor, followed by elimination of the target cell upon ligand-receptor coupling (42). Altogether, these *in vitro* data imply that SCFAs are capable of sensitizing cancer cells to immunogenic responses, potentiating the effects of immunotherapeutic approaches used to combat cancer.

Immunotherapy removes the break on the immune system, potentially causing a range of undesired inflammatory side-effects (43). Inflammation at barrier organs, including the gastrointestinal mucosa, is a common sign of toxicity in patients treated with immune checkpoint blockers (44). The gastrointestinal mucosa has an important role in controlling pathogenic organisms, while maintaining adequate permeability for nutrient absorption (45). A disruptive intestinal barrier can cause microorganisms to translocate into the bloodstream leading to adverse effects (46). In the context of fatty acids, *in vitro* studies have indicated that SCFAs significantly improve intestinal barrier function, measured by transepithelial electrical resistance (TEER) (47). In agreement, Nielson et al. found that butyrate at physiologically relevant concentrations (1-10 mM) significantly improved epithelial barrier function in E12 human colon cells (48) and Peng et al. also confirmed that butyrate (2 mM) improves intestinal barrier function (49). Together, these data indicate that SCFAs can improve gut barrier function and thereby might suppress the immune-mediated toxicities often induced by immunotherapy.

Another possible side effect of immunotherapy is cytokine storm syndrome, which can be harmful as it can interfere with body functions and in severe cases even can lead to organ failure and death (50). Park et al. demonstrated that acetate promotes T cell differentiation into both effector T cells producing IL-17 and interferon γ (IFNγ) or regulatory T cells producing IL-10, depending on the cytokine milieu (51). It has been proposed that butyrate and propionate, but not acetate, modulate cytotoxic T cell activation by inhibiting DC secretion of IL-12. Importantly, butyrate and propionate supported a more tolerogenic immune activation of the innate immune system instead of a pro-inflammatory response in the gut (52). The results of these studies highlight the potential of SCFAs to provide a balance between inflammation and immunity, and it is tempting to speculate that these SCFAs may prevent the cytokine storm syndrome often induced by T cell based immunotherapy.

Similar as for SCFAs, *in vitro* studies have suggested that *n*-3 PUFAs might contribute to suppression of exacerbated inflammatory cytokine production by immune cells. Long chain PUFAs, present in membrane phospholipid, are released by phospholipases and serve as substrate for cyclooxygenase isozymes and 5-lipoxygenase and are precursors for different prostaglandins, leukotrienes, thromboxanes and other eicosanoids. The relative abundance of *n*-3 and *n*-6 PUFAs and the respective lipid species within these categories determine the eicosanoid lipid mediators species and the respective effect on immune function and their pro- or anti-inflammatory potential. Where in general the eicosanoids derived from the *n*-6 fatty acid (arachidonic acid, ARA) have a high pro-inflammatory potential, the species derives from *n*-3 fatty acid (eicosapentaenoic acid, EPA and docosahexaenoic acid, DHA) have low or even anti-inflammatory properties. For instance, Hao et al. showed that EPA treatment reduced lipopolysaccharide (LPS) or prostaglandin E 2 (PGE-2)-induced expression of IL-6 and tumor necrosis factor α (TNFα) and increased the expression of IL-10 in both macrophages and hepatocytes (53). While EPA reduces these inflammatory responses, its direct anti-carcinogenic effects on tumor cells is preserved (53, 54). Hence, *n*-3 PUFA supplementation has been suggested as a useful addition for adoptive T cell therapy (54). These studies propose that dietary interventions focusing on *n*-3 PUFAs could also be beneficial to prevent or diminish the cytokine storm.

The efficacy of immunotherapy has been shown to be dependent on the TME. For instance, a hypoxic TME impairs anti-tumor immunity, induces T cell exhaustion and has been suggested to suppress the efficacy of immunotherapy (17). Moreover, infiltration of immunosuppressive cells, such as regulatory T cells, MDSCs and M2 TAMs into the TME is associated with immunosuppression, potentially affecting immunotherapy efficacy (16) and a recent review highlighted a major role for cancer-associated fibroblasts in the TME in promoting immunotherapy resistance (55). Multiple studies indicate that SCFAs, *n*-3 and *n*-6 PUFAs alter the TME. Specifically, butyrate inhibited the hypoxia-induced induction and activity of hypoxia-induced factor 1α (HIF-1α) in HT1080 human fibrosarcoma cells and butyrate also suppressed HIF-1α and vascular endothelial growth factor (VEGF) expression in vascular endothelial cells in hypoxic conditions *in vitro* (56). Similarly, DHA supplementation *in vitro* resulted in decreased HIF-1α total protein levels and transcriptional activity in the malignant breast cell lines, but not in the non-transformed

cell line (57). Thus, SCFAs and *n*-3 PUFAs may exert relevant anti-cancer effect in a hypoxic TME. In addition, as described before, depending on the cytokine milieu, acetate promotes a pro-inflammatory TME *via* enhancing effector T cell function or suppresses inflammation *via* promoting differentiation of regulatory T cells (51). Also, in general, increased dietary *n*-6 PUFA consumption is associated with a pro-inflammatory TME, while *n*-3 PUFA rich diets suppress inflammation (the effects of dietary PUFAs on immune cells in the TME has been extensively reviewed by Khadge et al.) (58). Furthermore, SCFAs as well as *n*-3 PUFAs have been shown to inhibit fibroblast matrix metalloproteinase secretion into the TME (59, 60). However, it remains to be studied whether SCFAs, *n*-3 and *n*-6 PUFAs influence the outcome of immunotherapy via modulation of the TME.

In addition, specific PUFAs have been described to enhance immunotherapy outcome via other mechanisms. For example, it has been shown that DHA can enhance the anti-proliferative as well as the apoptotic effect of tumor necrosis factor-related apoptosis inducing ligand (TRAIL—an immune-cytokine used as immunotherapy) specifically for cancer cells (61). Kumar et al. demonstrated the potential of ARA to enhance the capacity of DCs to exhibit increased *in vitro* and *in vivo* chemotaxis accompanied with better stimulatory and cytotoxic T cell activity as well as a favorable T helper cell 1 (Th1) cytokine profile. These results highlight the potential of ARA to enhance DC capacity for DC-based vaccines for cancer immunotherapy (62).

Preclinical *in vivo* Data on the Effects of SCFAs and PUFAs on Immunotherapy Outcome Are Inconclusive

Several *in vivo* studies investigated the effects of SCFAs on the efficacy of immunotherapy. One of the earliest observations, in 1994, indicated that intraperitoneally injected butyrate significantly enhanced the immune-mediated effects of recombinant IL-2 treatment in a subcutaneous adenocarcinoma rat model (35). In a more recent study, mice bearing melanoma or pancreatic tumors were treated with an adoptive T cell therapy approach. The results showed that the *in vivo* anti-tumor immunity of transferred cytotoxic T cells was ameliorated when cultured *ex vivo* in presence of butyrate and pentanoate. The improved *in vivo* cytotoxic T cell response was explained by histone deacetylase activity (HDAC) inhibiting capacity of butyrate and pentanoate, which enhanced the expression of effector molecules (TNFα and IFNγ) produced by cytotoxic T cells (63). However, it should be noted that the effect of cytotoxic T cells transferred in tumor bearing mice was absent when pentanoate was administrated *in vivo* via injections (63). The exact mechanism has not yet been elucidated, but one possible explanation might be that *in vivo* pentanoate administration, similarly as butyrate, propionate and acetate (64–66), not only improves the function of effector T cells, but also promotes T cell differentiation into regulatory T cells (51), thereby resulting in no overall beneficial effect of the adoptive T cell therapy approach *in vivo*. Yet, the promoting or suppressing function of SCFAs on anti-cancer T cell mediated cytotoxicity *in vivo* requires further examination, especially since another study did not observe any changes in the frequency of regulatory T cells in tumors upon oral butyrate administration in a subcutaneous colon cancer mouse model (67). Actually, in this study, oral butyrate administration even boosted the anti-tumor responses of CD8+ effector T cells *in vivo* (67). Altogether, from these data it is speculated that SCFAs can push the immune response in 2 direction, either toward enhanced CD8+ effector T cell functioning or toward increased differentiation of immuno-suppressive regulatory T cells. Which direction is activated by the SCFAs most likely depends on the cytokine environment (51). Although these studies did not show directly a beneficial effect of SCFAs on adoptive T cell therapy efficacy *in vivo*, these data imply a role for SCFAs in *ex vivo* culturing of T cells used in adoptive T cell therapies (63). Moreover, several preclinical mouse studies have investigated the combinatory effects of SCFAs and immune checkpoint inhibitors. Han et al. demonstrated that oral administration of inulin, a dietary fiber serving as a nutrient source for the gut bacteria which generate SCFAs, modulates the gut microbiome composition. Consequently, the anti-tumor activity of anti-PD-1 antibodies was amplified in murine models of colon cancer and melanoma (68). In agreement, mice bearing melanoma tumors treated with anti–PD-1 therapy in combination with a fiber-rich diet demonstrated delayed tumor outgrowth compared to mice receiving a fiber-poor diet. The therapeutic gain observed in the mice receiving the fiber-rich diet might partly be explained by the significantly higher levels of propionate observed in the stool samples (69). Furthermore, anti-PD-1 antibody efficacy was largely impaired in MC38-tumor bearing mice receiving fecal microbiota transplantation (FMT) from newly diagnosed colorectal cancer patients compared to mice receiving FMT from healthy controls. Remarkably, dietary pectin, a soluble fiber that is fermented in many metabolites in the gut, including SCFAs, could reverse the poor efficacy of anti-PD-1. Follow-up experiments indicated that supplementation of butyrate (but not acetate) in the drinking water, instead of pectin, was already sufficient to result in synergistic therapeutic effects when combined with immune checkpoint inhibitor therapy (70). Although these studies suggest a role for SCFAs in supporting immune checkpoint inhibitor therapy, it was previously shown that butyrate supplementation reduced the efficacy of anti-CTLA-4 antibodies in multiple tumor mouse models, by inhibiting the upregulation of the co-stimulatory molecules CD80/CD86 on dendritic cells (34). In line, no beneficial effect of anti-PD-1 treatment in combination with pentanoate injections was observed in a subcutaneous mouse model for melanoma (63). The authors did not explore the reason of these negative data, but given the small number of mice and the large variation in the data, the power of this experiment may have been too low to reach statistically significant differences. Overall, currently published *in vivo* studies investigating the effects of SCFAs on the outcome of immunotherapy provide contradictive information. The opposing results obtained in the different studies could be related to differences in the experimental design such as concentrations, route of administration of the SCFAs or different dietary fibers fermentable in SCFAs, different response read-outs as well as different types of immunotherapy treatment.

Therefore, improved standardization of intervention designs, and use of appropriate experimental models will further facilitate systematic evaluation of the effects of SCFAs on the outcome of immunotherapy.

In contrast to SCFAs, preclinical *in vivo* studies on the direct effects of dietary PUFAs on the outcome of immunotherapeutic approaches in cancer are lacking. However, several preclinical cancer models show that these lipids can modulate immune responsiveness. For example, in a mouse model for obesity-associated breast cancer, a high fat diet (HFD) in combination with fish oil resulted in a reduction of inflammatory markers (TNFα, IL-6) and in an increase of the anti-inflammatory marker IL-10, compared to HFD alone (71). Additionally, experimental research in colon cancer tumor bearing cachectic mice has revealed that intervention with a diet rich in *n*-3 PUFAs reduced the inflammatory state and improved immune competence (72). Furthermore, in a mouse model of castrate-resistant prostate cancer, administration of a diet rich in *n*-3 PUFAs inhibited the function of M2 tumor associated macrophages (TAMs) (73). Opposite to *n*-3 PUFAs, diets rich in saturated fatty acids (SFAs) promote an immunosuppressive TME, conceivably via stimulating chronic low-grade inflammation. For example, Liu et al. demonstrated that SFAs enhance the differentiation of pro-tumorigenic TAMs. In this study, breast tumor-bearing mice were fed a high fat diet consisting of either cacao butter (rich in SFAs) or fish oil (rich in *n*-3 PUFAs). Fish oil resulted in uncoupled obesity-associated tumor growth and reduced the number of pro-tumoral TAMs, whereas cacao butter enhanced the differentiation of pro-tumoral TAMs (74). In addition, the *n*-6 PUFA ARA, which can be converted into several prostaglandins including PGE-2, stimulated the accumulation of myeloid-derived suppressor cells (MDSC) inhibiting immunosurveillance in the TME (75). Overall, these data suggest that *n*-3 PUFAs can reduce chronic low-grade inflammation in cancer, while SFAs and *n*-6 PUFAs lead to an immunosuppressive TME via stimulation of chronic low-grade inflammation. Nevertheless, it remains to be addressed whether these SFAs, *n*-3 and *n*-6 PUFAs influence the outcome of immunotherapy. Here as well, standardization of intervention designs, and selection of appropriate experimental models will expedite systematic exploration of the potential of *n*-3 or *n*-6 PUFAs to contribute to clinical efficacy of immunotherapy.

In addition to direct effects of PUFAs on immune cells, PUFAs can also influence the immune response by modulating the gut microbiome. Preclinical evidence has shown that *n*-3 PUFAs, especially EPA and DHA, can modify the gut microbiota composition in several rodent models in a beneficial manner by increasing the intestinal population of Bifidobacteria (76, 77), Akkermansia muciniphila bacteria (77, 78) and Firmicutes bacteria (79). Contrary, a diet high in *n*-6 PUFAs has been shown to induce gut microbiome dysbiosis resulting in a marked reduction of Firmicutes, Clostridia and Lachnospiraceae bacterial presence while stimulating growth of Bacteroidetes and Deferribacteraceae bacteria and the pro-inflammatory Mucispirillum schaedleri and Lactobacillus bacteria (80). In line, supplementation of high-fat diets rich in *n*-6 PUFA to aged mice caused dysbiosis resulting in intestinal inflammation by promoting bacterial overgrowth while depleting microbes from the Bacteroidetes and Firmicutes phyla (81). Although evidence is arising that the microbiota composition is essential for determining immunotherapy outcome, there is currently no consensus what type of microbiota composition or which microbial species are robustly associated with clinical responses; while one study reported an association between high abundance of Bifidobacterium longum, Collinsella aerofaciens, and Enterococcus faecium and improved responses to immunotherapy (82), other studies reported an association between higher abundance of microbes from the Verrucomicrobiota and Firmicutes phyla and enhanced immunotherapy responses (83, 84). Thus, despite recognition of prebiotic properties of PUFAs, the effects of PUFAs on immunotherapy outcome remain ambiguous.

Fermentable Fibers and *n*-3 PUFAs Have the Potential to Enhance Clinical Immunotherapy Efficacy

Data on specific fatty acid tailored dietary intervention studies to explore the effect on immunotherapy responsiveness in cancer patients are not yet available. However, recently, a cohort study investigated whether intake of dietary fiber (fermenting into SCFAs) affects clinical outcome of melanoma patients treated with different immune checkpoint inhibitors. The patients reporting sufficient dietary fiber intake, using the National Cancer Institute Dietary Screener Questionnaire, demonstrated a significantly longer progression-free survival compared to patients reporting insufficient dietary fiber intake (69). To evaluate whether dietary fiber intake and probiotic use may synergistically affect clinical outcomes in these melanoma patients treated with immune checkpoint inhibitors, the study compared levels of fiber intake and probiotic use in this patient population. Strikingly, longest progression-free survival was observed in patients reporting sufficient dietary fiber intake without probiotic use (69). These findings suggest that use of commercially available probiotics consumed by this study population is not beneficial in the setting of immune checkpoint inhibitors, while dietary fiber interventions synergistically enhance immunotherapy efficacy potentially by supporting a diverse microbiome and increasing SCFA content. Along this line, a phase 2 clinical trial (NCT04645680), aiming to investigate the effects of dietary fiber intervention on the structure and function of the gut microbiome in patients with melanoma treated with Pembrolizumab or Nivolumab, is currently recruiting patients.

Although direct clinical evidence regarding the effects of PUFAs on immunotherapy outcome is lacking, multiple clinical intervention studies in cancer patients indicate that *n*-3 PUFAs modulate immune responsiveness by reducing chronic low-grade inflammation (85). For example, the role of EPA and DHA on inflammatory and oxidative status in patients with NSCLC treated with chemotherapy was investigated in a multicenter randomized double-blinded control trial. Results indicated that dietary administration of these *n*-3 PUFAs decreased the levels of oxidative stress as well as the production of the pro-inflammatory

mediators C-reactive protein (CRP) and IL-6 (86). Furthermore, increased concentrations of EPA and DHA, as a result of consumption of a medical food rich in fish oil, protein, and leucine, reduced serum levels of the inflammatory mediator PGE-2 in a randomized clinical trial for patients receiving radiotherapy (26). Overall, these clinical intervention studies indicate that *n*-3 PUFAs have anti-inflammatory effects in cancer patients. However, as indicated before, it remains unclear how these *n*-3 PUFAs influence the outcome of immunotherapy.

Several clinical intervention studies have associated *n*-3 PUFA rich diets with modulation of the gut microbiome in humans. For example, healthy volunteers receiving *n*-3 PUFA rich diets for 8 weeks, reversibly increased the abundance of the SFCA producing bacteria Bifidobacterium, Roseburia and Lactobacillus in the gut (87). In addition, type 2 diabetes patients treated with a diet enriched with 100 g sardines 5 days a week for 6 months demonstrated a decreased Firmicutes/Bacteroidetes ratio at the end of the study compared to standard diet. Both dietary interventions decreased phylum Firmicutes concentrations (88). These clinical studies, similarly as for the *in vivo* animal data, indicate that *n*-3 PUFAs may modulate the gut microbiome beneficially. However, since there currently is no consensus what type of microbiota composition or which microbial species are robustly associated with clinical responses to immunotherapy, the effects of *n*-3 PUFAs on immunotherapy outcome in cancer patients remains uncertain.

CHALLENGES, OPPORTUNITIES AND FUTURE DIRECTIONS

In this review we have described the influence of dietary intervention with SCFAs and dietary fibers that are fermented in SCFAs on immunotherapy efficacy. Proposed mechanisms through which SCFAs enhance immunotherapy efficacy include sensitization of cancer cells to immunogenic responses, improved gut barrier function and enhanced cytotoxic T cell functioning (see **Figure 1**). Moreover, recent clinical data indicate that fiber rich diets are beneficially impacting immunotherapy outcome, potentially via supporting fiber fermentation, which yields increased content of SCFAs or by increasing the gut microbiota diversity. Overall, dietary fiber or SCFA administration holds the potential to improve immunotherapy efficacy. Yet, most evidence is rather speculative and direct proof for an effect of SCFAs on immunotherapy outcome is relatively sparse and sometimes even contradictory. Therefore, to fully understand the mechanisms underlying the effects of different SCFAs on immunotherapy efficacy, more research will be essential.

We have further depicted the impact of dietary intervention with PUFAs on immunotherapy outcome. The currently available data indicate that for cancer patients with elevated systemic chronic low-grade inflammation, e.g., obese patients, a diet rich in *n*-3 PUFAs might be preferred above a *n*-6 PUFA rich diet which promotes an immunosuppressive TME by stimulating chronic low-grade inflammation. Similar to patients with obesity, malnourished patients suffering from sarcopenia or cachexia often have chronic inflammation leading to immune senescence and may also benefit from intervention with *n*-3 PUFAs to reduce chronic inflammation and thereby potentially improve immune competence and immunotherapy efficacy. Nonetheless, whether in these malnourished patients, consumption of anti-inflammatory *n*-3 PUFAs restores, stimulates or actually further inhibit immunotherapy efficacy is currently unknown. One could also argue that elevated *n*-6 PUFA levels, which are regarded as more pro-inflammatory, may support the immune activating properties of immunotherapy in patients with immune senescence. Thus, depending on the nutritional status of cancer patients, either *n*-3 or *n*-6 PUFAs may contribute to enhance immunotherapy efficacy, awaiting further validation in follow-up experiments.

The collective, sometimes contradictive or inconclusive evidence available on the use and influence of dietary intervention with SCFAs or PUFAs to improve therapy outcome, highlights the importance of metabolic profiling and personalized medicine in this context. It will be essential to develop tailored diets: a single recommended diet for all cancer patients treated with immunotherapy most likely not exist due to the variability in metabolism of lipids and immune responses. In that context, nutritional status or patients' body composition should be taken into account. Obese individuals for instance, have significantly higher fecal SCFA concentrations with a similar fiber intake, compared to lean individuals (89). Also, malnourished patients may require a different route of administration of the dietary intervention then obese patients. There are different ways to administer diets according to the patients' needs, including classical oral intake via a dietary regimen, but also supplementation with enriched oral nutritional supplements, capsules or concentrated parenteral emulsions or injections, specifically for patients who cannot adhere to the recommended intake via the classical way. Since personalized nutritional interventions are relatively feasible, this approach holds the potential to extend the clinical benefit of immunotherapeutic approaches to many different populations who currently do not benefit from this treatment. Yet, several challenges need to be overcome before fatty acid focused dietary regimens can be integrated in standard of care. First of all, dietary interventions require sufficient consumption and adherence to the recommended intake, while some diets, e.g., ketogenic diet, are very difficult to comply with. In addition, cancer cells require fatty acids for energy storage, membrane production, and the generation of signaling molecules (90). Hence, it will be complex to balance fatty acid focused dietary interventions in such a manner that they suppresses tumor vitality instead of promoting tumor growth. Moreover, different cancer types vary in their preferred energy source and metabolic activity. For instance, many cancer types overexpress stearoyl-CoA desaturases (SCD) enzymes (91, 92) which prevents SFA lipotoxicity, and has been suggested to reduce ferroptosis triggered by peroxidation of PUFAs (93). Also, cancer cells frequently upregulate enzymes involved in lipid elongation, which appears to promote cancer progression (94). Additionally, although epidemiological, *in vitro* and preclinical data indicate a potentially beneficial effect of dietary fibers that are fermented into SCFAs, further research would be required to better understand the specificity of the

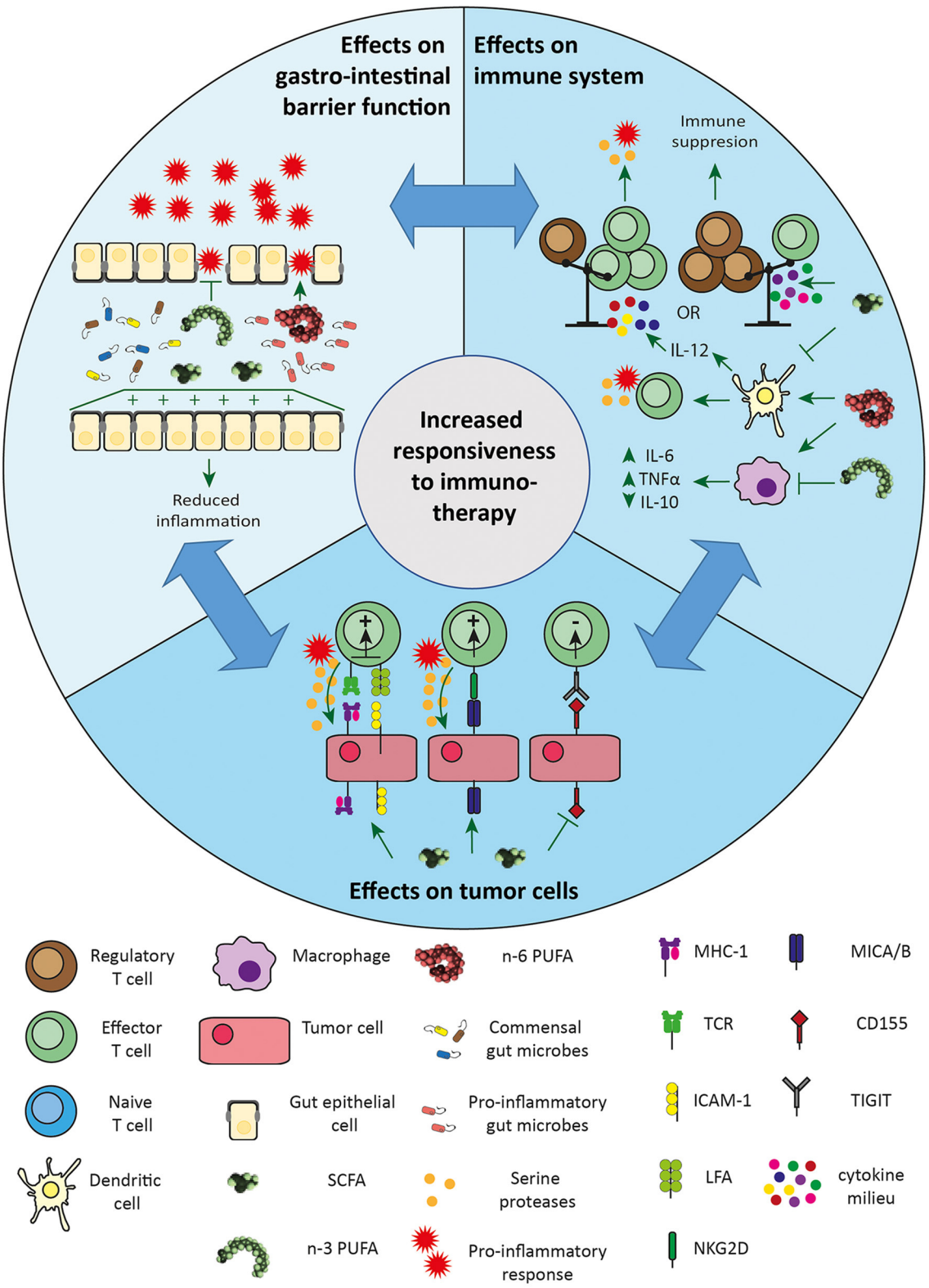

FIGURE 1 | Proposed mechanisms through which SCFAs and PUFAs enhance immunotherapy efficacy. Effects on gastric barrier: SCFAs can improve gut barrier function and have, as well as *n*-3 PUFAs, anti-inflammatory effects. Diets rich in *n*-3 PUFAs have a beneficial effect on the gut microbiome. Both have beneficial effects on gastro-intestinal functioning, thereby reducing immune-mediated toxicity and may enhance to immunotherapy outcome, as the need of cessation of treatment is lower. Diets rich in *n*-6 PUFAs lead to dysbiosis accompanied with pro-inflammatory effects. Effects on immune system: SCFAs promote T cell differentiation in both

(Continued)

FIGURE 1 | effector T cells and regulatory T cells, depending on the cytokine milieu. SCFAs also inhibit IL-12 secretion from dendritic cells modulating effector T cell activation. Contrary, *n*-6 PUFAs enhance dendritic cell capacity to stimulate cytotoxic T cell activity, directly reducing tumor growth. *n*-6 PUFAs' pro-inflammatory effects occur mainly via stimulation of macrophages contributing to chronic low-grade inflammation. In contrast, *n*-3 PUFAs suppress inflammation via reducing IL-6 and TNFα and increasing IL-10 production. Effects on tumor cells: SCFAs enhance the expression of MHC-1 and ICAM-1 on tumor cells, making them more sensitive to cytotoxic lymphocytes-mediated killing. SCFAs also induce the expression of MICA/B on tumor cells, making them a target for effector T cells via the NKG2D receptor. SCFAs reduce the expression of CD155 on tumor cells, inhibiting the interaction with TIGIT expressed on effector CD8+ T cells. ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; IL-10, interleukin 10; IL-12, interleukin 12; LFA, lymphocyte function-associated antigen 1; MHC-1, major histocompatibility complex 1; MICA/B, MHC class I polypeptide-related sequence A/B; NKG2D, natural killer group 2D; *n*-3 PUFAs, omega 3 polyunsaturated fatty acids; *n*-6 PUFAs, omega 6 polyunsaturated fatty acids; SCFAs, short chain fatty acids; TCR, T cell receptor; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TNFα, tumor necrosis factor α.

different SCFAs. Furthermore, it is difficult to reach high levels of SCFAs systemically and in peripheral organs via dietary intake. The gut lumen is the major site of production of SCFAs and there is a strong biological gradient for each SCFA from the gut lumen to peripheral organs, which leads to different exposure of cells and tissues to SCFAs (95). Finally, even if sufficiently high systemic levels of SCFAs are reached, it will be essential to prevent comorbidity-related adverse effects such as hyperphagia, hypertriglyceridemia, ectopic lipid deposition in liver and skeletal muscle, and liver and muscle insulin resistance (96).

To ensure clinical application, the direct effects of SCFAs and PUFAs on the immune system and TME and the effects of dietary interventions on the gut epithelial cells and microbiome should be tested. Crucially, the most favorable ratios between different SCFAs, branched SCFAs, saturated, unsaturated and *n*-3 PUFAs/*n*-6 PUFAs, as well as different dosages of the fatty acids should be explored. Human cohort and clinical intervention studies need to be established. If standardized well, these human studies will reveal reliable correlations between the intake of relevant food components and follow-up data from cancer patients receiving immunotherapy, which will help us to better understand the etiology of the responsiveness in patients with different metabolic profiles. To prevent heterogeneity and create robust data, these human clinical interventions studies will also need standardization of protocols (e.g., timing of dietary interventions, timing and dosages of the immunotherapy and fecal and serum samples collection) in combination with detailed multi-analysis. In such well-controlled human clinical trials, baseline and follow-up measurements regarding tumor progression will proof the impact of diet on the outcome of immunotherapy. Moreover, metabolic and biochemical parameters will contribute to the unraveling of the mechanisms underlying the effects of SCFAs and PUFAs on immunotherapy responsiveness in cancer.

Currently, no nutritional biomarkers to predict which patients will respond to immunotherapy are available. Promising epidemiological data do however indicate an association between the patients' nutritional status and immune checkpoint inhibitor therapy efficacy, pointing toward a potential role for fecal and serum SCFA content as well as gut microbiome diversity as biomarker. These data hold promise for the development of biomarker signatures to predict treatment responses, based on metabolic and biochemical data and validated food frequency/lifestyle questionnaires. Most likely, multiple biomarker signatures will be required taking into account subgroup analysis, e.g., patients with obesity will respond differently compared to malnourished patients and therefore need different biomarker signatures. Finally, it will be crucial to validate the developed biomarker signatures in well-controlled human clinical intervention studies as described above.

In conclusion, dietary regimens that focus on SCFAs and PUFAs to improve the outcome of immunotherapeutic approaches hold great promise. Specifically, SCFAs can sensitize cancer cells to immunogenic responses, improve gut barrier function, reduce the cytokine storm and activate cytotoxic T cells. Furthermore, fibers which are fermented into SCFAs can also indirectly influence the outcome of immunotherapy *via* modulation of the gut microbiome. Similar to SCFAs, *n*-3 PUFAs may also reduce the cytokine storm and inhibit chronic low-grade inflammation potentially creating a TME where immune checkpoint inhibitors work more efficiently, whereas other patients may benefit from a diet rich in pro-inflammatory *n*-6 PUFAs actually supporting the immune activating properties of immunotherapy. Despite all the promising data, several challenges remain to be overcome, highlighting the necessity of more studies before dietary interventions focusing on SCFAs and PUFAs can become standard of care in the clinic.

AUTHOR CONTRIBUTIONS

JT and RS-S conceived the presented idea. AW and LS wrote the manuscript with support from JB, AH, LD, and RL. All authors contributed to the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.868436/full#supplementary-material

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Establish a New Diagnosis of Sarcopenia Based on Extracted Radiomic Features to Predict Prognosis of Patients With Gastric Cancer

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Background: Preoperative sarcopenia is a prognostic risk factor for gastric cancer (GC). This study aimed to determine whether radiomic sarcopenia features on computed tomography (CT) could be used to diagnose sarcopenia preoperatively, and whether they could be used to accurately predict the postoperative survival and complication prognosis of patients with GC.

Methods: We retrospectively analyzed data of 550 patients with GC who underwent radical gastrectomy. The patients were divided into training (2014–2016) and validation (2017–2019) cohorts. We established a radiomics-based diagnosis tool for sarcopenia. Thereafter, univariate and multivariate analyses of diagnostic factors were carried out. Receiver operator characteristic (ROC) curves and area under the curve (AUC) were used to compare different diagnostic models. The Kaplan–Meier method was used to estimate the survival curve.

Results: Radiomic sarcopenia correlated with complications and long-term survival. Skeletal muscle index, grip strength, and walking speed were correlated with postoperative complications in both cohorts (AUCs: 0.632, 0.577, and 0.614, respectively in the training cohort; 0.570, 0.605, 0.546, respectively, in the validation cohort), and original sarcopenia was more accurate than any of these indicators. However, radiomic sarcopenia has a higher AUC in predicting short-term complications than original sarcopenia in both groups (AUCs: 0.646 vs. 0.635 in the training cohort; 0.641 vs. 0.625 in the validation cohort). In the training cohort, the overall survival time of patients with original sarcopenia was shorter than normal patients (hazard ratio, HR = 1.741; 95% confidence interval [CI], 1.044–2.903; p = 0.031). While radiomic sarcopenia had a greater prognostic significance, the overall survival time of patients

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with radiomic sarcopenia was significantly worse than normal patients (HR, 1.880; 95% CI, 1.225–2.885, $p = 0.003$).

Conclusion: Extracted sarcopenia features based on CT can predict long-term survival and short-term complications of GC patients after surgery, and its accuracy has been verified by training and validation groups. Compared with original sarcopenia, radiomic sarcopenia can effectively improve the accuracy of survival and complication prediction and also shorten the time and steps of traditional screening, thereby reducing the subjectivity effects of sarcopenia assessment.

Keywords: radiomics, sarcopenia, gastric cancer, prognosis, diagnosis

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer, the third leading cause of cancer-related deaths worldwide (1), and the most common malignant tumor in China (2). Radical gastrectomy remains the standard of care for curable GC (3). However, gastrectomy may be accompanied by many complications, such as infection, bleeding, anastomotic fistula, or organ dysfunction (4). Therefore, complications will affect functional recovery and may prolong hospital stays, increase economic burden, and deplete medical resources (5).

It is well known that GC is an extremely aggressive malignant tumor of the upper digestive tract. Owing to gastrointestinal insufficiency or failure, patients with GC often have insufficient nutrient intake or malabsorption. Approximately 60.2% of patients with gastroesophageal tumors develop malnutrition, this percentage is higher than that for most other malignant tumors (6). Therefore, patients with GC often experience malnutrition or cachexia before surgery, increasing the chance of postoperative complications and mortality (7, 8). Therefore, an effective tool for predicting postoperative complications and mortality will be helpful.

Sarcopenia is a malnutrition-related syndrome characterized by the gradual and complete loss of skeletal muscle mass and strength (9) and has been shown to be a new predictor of postoperative complications in patients with GC (10). In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) reached a general consensus on the definition of sarcopenia: the loss of skeletal muscle plus low muscle strength and/or poor physical function that appears with age (9). Similarly, sarcopenia was described as an old age-related syndrome by the Asian Working Group for Sarcopenia (AWGS); the AWGS also recommended a definition using Asian cutoff values in 2014 (11). However, the traditional method for diagnosing sarcopenia not only needs to consider the waist muscle mass measured on imaging but also muscle strength and physical performance (9).This means that the correct diagnosis of preoperative sarcopenia requires more time and medical resources.

In recent years, as a new method of diagnosis and prediction, radiomic features have been increasingly used for the individualized treatment of tumors (12, 13). Young proposed a new diagnosis method for sarcopenia based on convolutional neural network and radiomics, which proved the feasibility of radiomics in the diagnosis of sarcopenia. However, he did not include muscle strength or physical performance in the sarcopenic auto-diagnosis model, which left their model of sarcopenia somewhat limited (14). In this study, we propose the concept of "radiomic sarcopenia" using sarcopenia features extracted from three-dimensional imaging. Our study aimed to determine whether this new method could be used to diagnose sarcopenia more quickly and objectively before surgery, and whether it could be used to predict postoperative survival and complication prognosis of patients with GC more accurately than the conventional method.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

We retrospectively recruited patients who were diagnosed with gastric adenocarcinoma by preoperative gastroscopy in two affiliated hospitals of Wenzhou Medical University from December 2014 to June 2019 and who were able to undergo radical surgery (614 patients). The exclusion criteria included patients who refused surgery or were switched to palliative surgery during the operation (20 patients), patients who did not undergo preoperative imaging examination or for whom imaging data were unavailable (35 patients), patients with other tumors or serious organic diseases (6 patients), and patients who were lost to follow-up or for whom the total follow-up time was less than 1 year (3 patients). A total of 550 patients were finally collected and analyzed. All patients underwent radical gastrectomy, and all operations were performed by senior surgeons who independently performed radical gastrectomy for more than 200 cases. The management of GC treatment during the perioperative period was based on the 2010 edition of the Japanese Gastric Cancer Treatment Guidelines (15). This study was approved by the Ethics Committee of the two affiliated hospitals of Wenzhou Medical University and conformed to the tenets of the Declaration of Helsinki.

Data Collection

The following variables were collected for each patient: (1) clinical characteristics, including age, gender, body mass index (BMI), nutritional risk screening (NRS-2002) score, and the tumor–node–metastasis (TNM) stage of the tumor; (2) operative information, including gastrectomy

range, method of reconstruction, laparoscopic surgery and organ combined resection. Postoperative complications were defined as grade II and above surgical outcomes in accordance with the Clavien–Dindo classification (16). Patients were followed up telephonically or with hospital recalls, and survival status and tumor recurrence were recorded. The follow-up frequency was once every 3 months for the first year, once every 6 months for the second to fifth year, and then once a year. The last follow-up date was in February 2021.

Research Groups

In a chronological order, a time-dependent grouping method was adopted to divide the patients with gastric malignant tumors into either a training cohort (261 cases from 2014 to 2016) and validation cohort (289 cases from 2017 to 2019). Patients in the training group were included in the selection of sarcopenia-related radiomic features. Patients in the validation group did not participate in the screening of features or the establishment of a prognostic model of sarcopenia, they were involved solely in accuracy verification of the model.

Diagnosis of Original Sarcopenia

The range of skeletal muscles can distinguish from other tissue between −29 and +150 Hounsfield units scale in CT scan (17). Muscle area was calculated using a dedicated processing system (INFINITT PACS software, version 3.0.11.3, BN17 32 bit; INFINITT Healthcare Co., Ltd., Seoul, South Korea). At the cross-section of the third lumbar vertebra (L3), the areas of all skeletal muscles of the patient (the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis) were measured preoperatively, and the sum of these areas was calculated as described previously (17). Low muscle mass was defined as L3 skeletal muscle index (SMI) $\leq$ 40.8 cm^2/m^2 for men and 34.9 cm^2/m^2 for women (18). To minimize bias, two professionally radiologists completed the muscle area measurement independently and were blinded to patients' clinicopathological data.

Muscle strength and physical function were determined by measuring preoperative grip strength and 6-m usual gait speed, respectively. Each patient was required to squeeze an electronic hand dynamometer (EH101; Camry, Guangdong Province, China) to obtain the preoperative grip strength. Low muscle strength was defined as a hand grip strength <26 kg for men and <18 kg for women (11). Patients were asked to walk 6 m at their normal speed, and the duration was recorded to calculate the 6-m usual gait speed. Low muscle performance was defined as a 6-m usual gait speed <0.8 m/s (11).

Based on the EWGSOP and AWGS (11), patients with low skeletal muscle mass plus low muscle strength and/or low physical performance were defined as original sarcopenia.

Extraction of Radiomic Features

All patients underwent enhanced abdominal computed tomography (CT). A 64-slice spiral CT scanner (Siemens; Erlangen, Germany) was used with a slice thickness of 0.75–1.25 mm and covering the entire abdomen (250–400 slices). The portal phase CT image was uploaded to ITK-SNAP (19) (version 3.8.0[1]) for semi-automatic drawing of the psoas major muscle region and 3D reconstruction (**Figure 1A**). The muscle area was drawn by two experienced researchers and examined by another radiologist. The outline image of the patient's region of interest (ROI) is shown in **Figure 1A**. The original CT image and ROI were preserved as medical digital imaging files in NRRD formats, and PyRadiomics 18 was used for automatic feature extraction in the Python environment (version 3.7.2[2]). The detailed list of radiomic muscle feature extraction parameters adjustment and Z-score standardized processing is shown below.

Parameter Adjustment and Z-Score Standardization

The radiomic feature extraction parameters were adjusted as follows: normalize: false; padDistance: 10; resampledPixelSpacing: [1, 1, 1], Original: []; Wavelet: []. All other parameters used default settings. The PyRadiomics package with extraction parameters mentioned above process the original CT image and ROI image and to produce radiomic features for each patients. Eighteen first-order features, 14 shape-related features (shape-3D), 22 gray level co-occurrence matrix features, 22 gray level run length matrix features, 16 gray level size zone matrix features, 5 neighboring gray tone difference matrix features, and 14 gray level dependence matrix features were extracted, with a total of 833 features after wavelet transformation (20). All features of all patients were standardized by Z-score (with the mean and standard deviation of the training group). The method used is as follows. For the sequence$X = [x_1, x_2, ..., x_n]$, the formula for Z-score transformation was as follows: $y_i = \frac{x_i - \overline{x}}{\sigma(X)}$, of which $\overline{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$, and $\sigma(x) = \sqrt{\frac{n}{(n-1)}\sum_{i=1}^{n}(x_i - \overline{x})^2}$. Finally, the standard sequence was given by $Y = [y_1, y_2, ..., y_n]$.

Screening of Valuable Characteristics and Establishment of Diagnostic Model for Radiomic Sarcopenia

In the screening of sarcopenia-related radiomic characteristics and establishment of a diagnostic model, 550 patients were divided into training and validation cohorts chronologically. Eight hundred and thirty-three characteristics in the training group were screened preliminary using Spearman's test ($p < 0.05$) (21). The remaining features were analyzed by using least absolute shrinkage and selection operator (LASSO) regression analysis. Radiomic scores were calculated using the LASSO regression built by the training cohort. The patients in the validation group were considered for accuracy verification of the radiomic diagnostic model. Based on the extracted radiological features of sarcopenia, the diagnostic criteria for radiomic sarcopenia in both groups were established.

[1]http://www.itksnap.org/

[2]https://python.org/

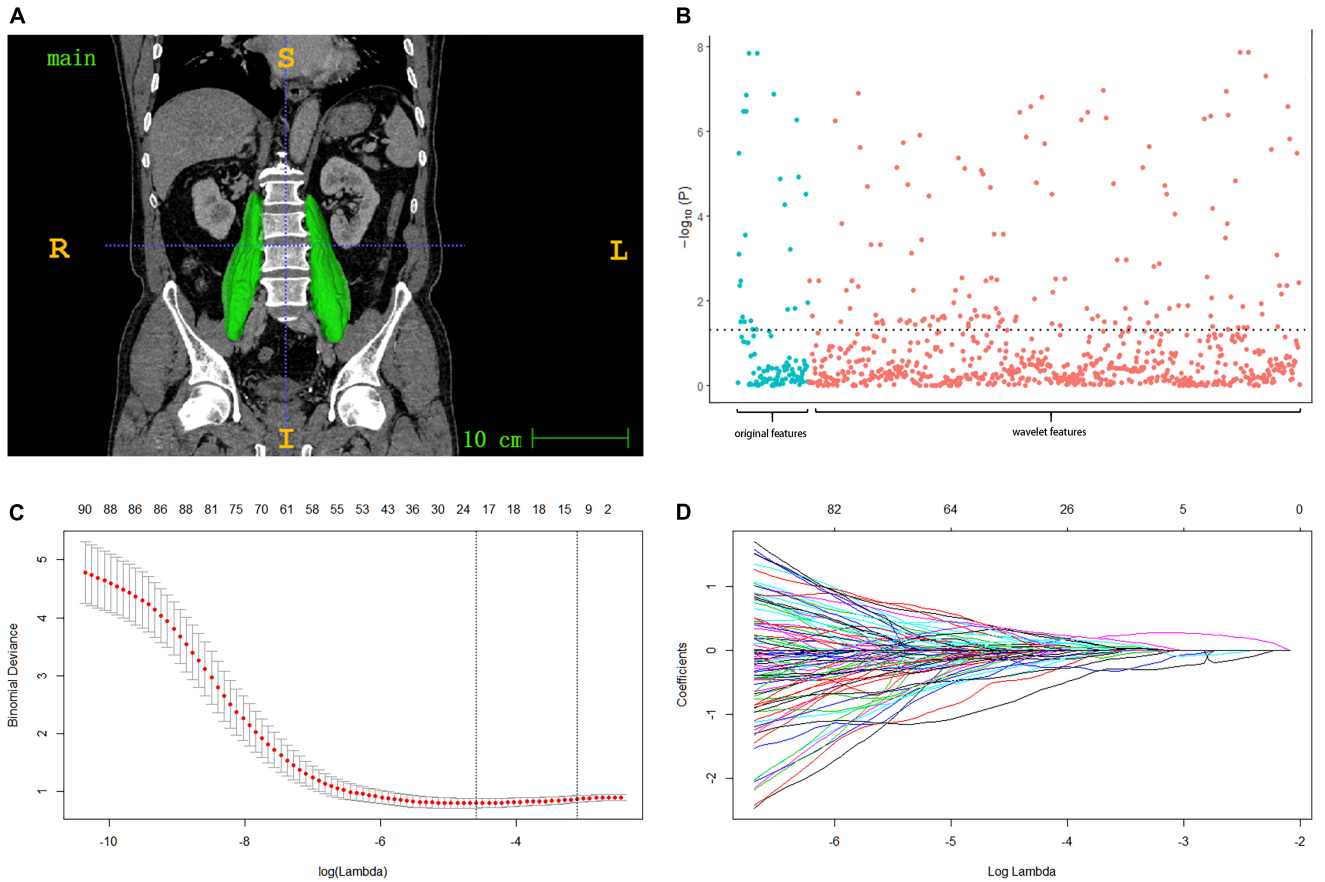

FIGURE 1 | (A) Muscle ROI: after the muscle region is labeled in ITK-SNAP software, semi-automatic drawing is adopted to check the psoas major muscle region and 3d reconstruction. **(B)** Manhattan plot presenting the strength of association –log10 (*p*-value) of spearman's rho between the psoas radiomic features and the original sarcopenia (diagnosed by SMI, grip strength and walking speed). **(C,D)** Model with smallest lambda was selected lambda 0.0451, ln (lambda) –3.098, and 14 features selected from the lasso were included in the subsequent radiomic score model.

Statistical Analysis

The Kolmogorov–Smirnov test was carried out to evaluate the distributions of continuous data. Normally distributed data were expressed as means ± standard deviations (SDs). The valuable radiomic features selected by Spearman's test were used for LASSO regression with the R package "glmnet" (22). The t-test was used to compare continuous data (age and BMI) between the training and validation cohorts, while the chi-squared test or Fisher's exact test were used to compare categorical data. Multivariate logistic adjusted regression analysis based on the findings of the univariate analysis was performed to validate the independent correlation between radiomic sarcopenia and postoperative complications. Receiver operator characteristic (ROC) curve analysis (23) was used to compare different diagnostic models, and the Kaplan–Meier method (24) was used to estimate the survival curve. Significance was determined by a threshold of $p < 0.05$. Spearman's test and LASSO regression were performed using R software (version 3.6.0[3]). Logistic analysis, ROC curve analysis, and Kaplan–Meier method were processed through SPSS version 22.0 (IBM Corp, Armonk, NY, United States).

[3]http://www.R-project.org

RESULTS

Clinical Characteristics of Patients

In this study (**Table 1**), the training cohort had 261 patients (201 males, 60 females) while the validation cohort had 289 patients (202 males, 87 females). There was no significant difference in sex between the cohorts ($p = 0.06$). The mean age of the training cohort was 64.6 ± 10.2 years and 64.9 ± 10.7 years in the validation cohort. No significant difference in age was found between the two cohorts ($p = 0.698$). There was no significant difference in preoperative nutritional indicators between the two cohorts, such as BMI ($p = 0.522$) or NRS-2002 score ($p = 0.117$). Preoperative assessments of sarcopenia, such as SMI ($p = 0.561$), low grip strength ($p = 0.208$), and low walking speed ($p = 0.177$), were not significantly different between the groups. The number of patients who chose laparoscopic surgery in the validation cohort was higher than that in the training

TABLE 1 | Clinical characteristics of patients.

Factors	Training group	Validation group	*P-value*
Age, years	64.6 ± 10.2	64.9 ± 10.7	0.698
BMI, kg/m^2	22.6 ± 3.1	22.8 ± 3.0	0.522
Gender			0.060
Female	60 (23.0%)	87 (30.1%)	
Male	201 (77.0%)	202 (69.9%)	
NRS-2002 score			0.117
1–2	164 (62.8%)	204 (70.6%)	
3–4	78 (29.9%)	72 (24.9%)	
5	19 (7.3%)	13 (4.5%)	
Low SMI			0.561
No	183 (70.1%)	196 (67.8%)	
Yes	78 (29.9%)	93 (32.2%)	
Low grip strength			0.208
No	195 (74.7%)	202 (69.9%)	
Yes	66 (25.3%)	87 (30.1%)	
Low walking speed			0.177
No	222 (85.1%)	257 (88.9%)	
Yes	39 (14.9%)	32 (11.1%)	
Laparoscopic surgery			0.009
No	189 (72.4%)	179 (61.9%)	
Yes	72 (27.6%)	110 (38.1%)	
Total gastric resection			0.662
No	156 (59.8%)	178 (61.6%)	
Yes	105 (40.2%)	111 (38.4%)	
Combined resection			0.263
No	233 (89.3%)	266 (92.0%)	
Yes	28 (10.7%)	23 (8.0%)	
Anastomotic type			0.251
Roux-en-Y	127 (48.7%)	130 (45.0%)	
Billroth I	98 (37.5%)	104 (36.0%)	
Billroth II	36 (13.8%)	55 (19.0%)	
TNM stage			0.172
I	82 (31.4%)	112 (38.8%)	
II	52 (19.9%)	56 (19.4%)	
III	127 (48.7%)	121 (41.9%)	
Postoperative complications			0.399
No	199 (76.2%)	228 (79.2%)	
Yes	62 (23.8%)	61 (20.8%)	

Data shown in the table: Mean ± SD/N (%).
BMI, body mass index; NRS-2002, nutritional risk screening; SMI, skeletal muscle index; TNM, tumor–node–metastasis.

cohort (38.1 vs. 27.6%, p = 0.009). There were no significant differences in tumor characteristics or prognosis between the two cohorts, including total gastric resection (p = 0.662), anastomotic type (p = 0.251), TNM stage (p = 0.172), and postoperative complications (p = 0.399). The consistency of the basic clinical characteristics between the two groups can make our results in the verification group more reliable.

Feature Screening and Establishment of a Radiomic Diagnostic Model of Sarcopenia

Initially, 115 of 833 radiomic features associated with original sarcopenia were screened by Spearman's rho (p < 0.05) (**Figures 1A,B**). LASSO regression was used to further reduce the number of features. At a lambda of 0.0451 (lambda with the minimal binomial deviance plus one standard error), 14 features were included in the final LASSO model (**Figures 1C,D**). Radiomic scores for each group were calculated by the model built with the training cohort. The cut-off value of the radiomic score was selected by the maximum Youden's index (sensitivity + specificity - 1) (25) for predicting postoperative complications in the training cohort, which was set to −1.59.

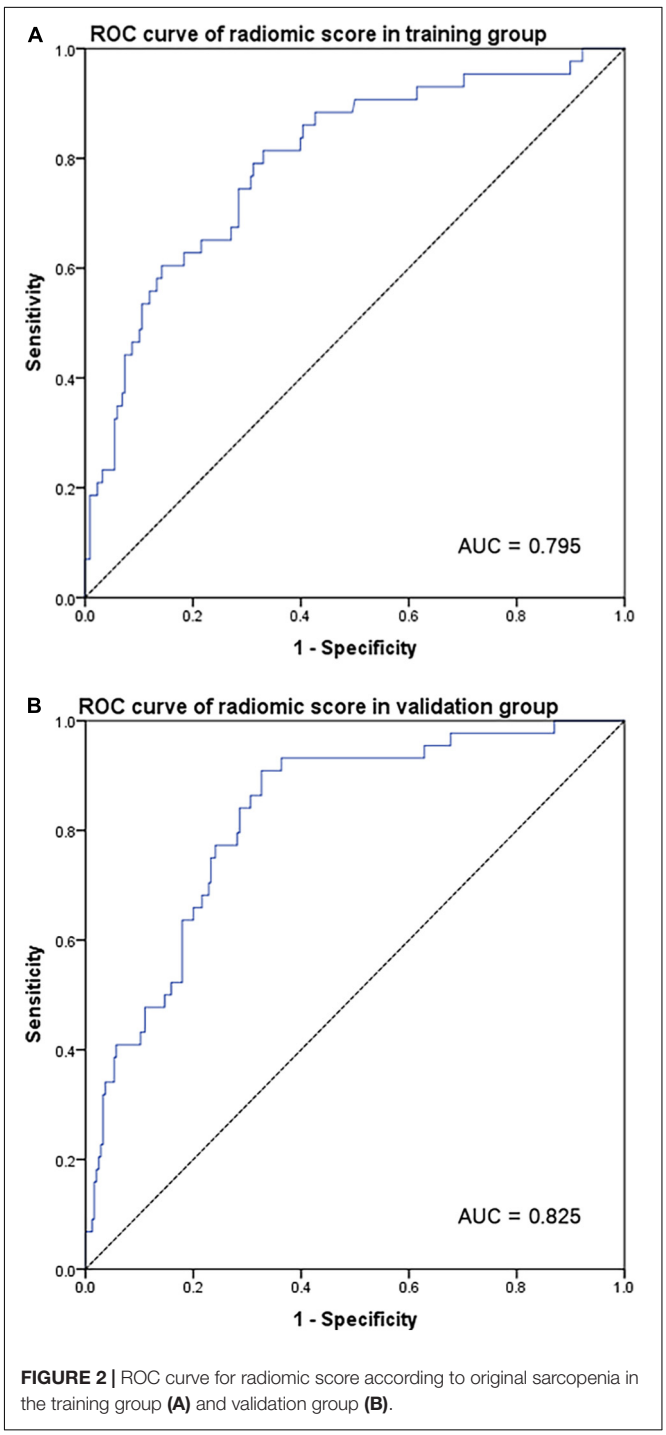

FIGURE 2 | ROC curve for radiomic score according to original sarcopenia in the training group **(A)** and validation group **(B)**.

Correlation Between Radiomic Sarcopenia and Original Sarcopenia

In the training group (**Figure 2A**), using original sarcopenia as a reference value, the area under the ROC curve (AUC) for the radiomic score was 0.795 (95% CI = 0.720–0.870, $p < 0.001$). The validation cohort (**Figure 2B**) also had a high AUC of 0.825 (95% CI = 0.763–0.887, $p < 0.001$). Radiomic scores were both correlated with original sarcopenia in both the training and validation cohorts. **Supplementary Figures 2A–C** show the correlations between radiomic scores and low grip strength, low walking speed, and low SMI in the validation cohort, respectively. **Supplementary Figures 2D–F** show similar correlations in the training cohort.

Univariate and Multivariate Analysis of Short-Term Complications

As shown in **Table 2**, in the training cohort, univariate analysis showed that radiomic sarcopenia [odds ratio (OR), 3.3; 95% CI 1.8–6.0; $p < 0.001$], age (OR, 2.3; 95% CI, 1.3–4.1; $p = 0.006$), endoscopic surgery (OR, 0.8; 95% CI, 0.4–1.4; $p = 0.018$), combined resection (OR, 2.7; 95% CI, 1.2–6.2; $p = 0.015$), and Billroth I (OR, 0.5; 95% CI, 0.2–0.9; $p = 0.025$) were significantly correlated with grade II and above complications. There was no significant correlation between the occurrence of postoperative complications and sex, BMI, NRS-2002, total gastric resection, or TNM stage. In the multivariate analysis after adjustment for potential related factors, endoscopic surgery ($p = 0.032$) and radiomic sarcopenia ($p = 0.003$) remained independent predictors of major postoperative complications.

In the validation cohort, univariate analysis showed that radiomic sarcopenia (OR, 3.6; 95% CI, 2.0–6.5; $p < 0.001$), age (OR, 1.9; 95% CI, 1.0–3.4; $p = 0.037$), BMI (OR, 2.7; 95% CI, 1.1–6.6; $p = 0.028$), NRS-2002 (OR, 2.6; 95% CI, 1.4–4.9; $p = 0.028$), total gastric resection (OR, 1.8; 95% CI, 1.0–3.2; $p = 0.04$), combined resection (OR, 6.1; 95% CI, 2.5–14.6; $p < 0.001$), anastomotic type ($p = 0.013$), and TNM stage ($p = 0.007$) were associated with short-term prognosis. The multivariate analysis showed that radiomic sarcopenia ($p < 0.001$), NRS-2002 ($p = 0.013$), combined resection ($p < 0.001$), anastomotic type ($p = 0.028$), and TNM stage ($p = 0.050$) were independent predictive risk factors for major complications after surgery.

Differences in Predicting Tumor Prognosis Between the Two Sarcopenia Evaluation Methods

In the training group, based on Kaplan–Meier curve analysis, patients with original sarcopenia had a worse overall survival (OS) than normal patients [hazard ratio (HR), 1.741; 95% CI, 1.044–2.903; $p = 0.031$) (**Figure 3A**). Meanwhile, radiomic sarcopenia had a better prognostic value: the OS time of those

TABLE 2 | Univariate and multivariate analysis of postoperative complications.

Factors	Training group			Validation group		
	Univariate analysis		Multi- analysis *c* value	Univariate analysis		Multi- analysis *P-value*
	OR (95%CI)	*P-value*		OR (95%CI)	*P-value*	
Radiomic sarcopenia	3.3 (1.8, 6.0)	<0.001	0.003*	3.6 (2.0, 6.5)	<0.001	<0.001*
Gender		0.197			0.767	
Female	Ref			Ref		
Male	0.7 (0.3, 1.2)	0.197		0.9 (0.5, 1.7)	0.767	
Age > 65 years	2.3 (1.3, 4.1)	0.006	0.142	1.9 (1.0, 3.4)	0.037	0.135
BMI < 18.5 kg/m^2	1.8 (0.7, 4.5)	0.198		2.7 (1.1, 6.6)	0.028	0.622
NRS-2002 score		0.106			<0.001	0.013*
1–2	Ref			Ref		
3–4	1.3 (0.7, 2.5)	0.39		2.6 (1.4, 4.9)	0.026	0.005
5	2.8 (1.0, 7.5)	0.04		4.8 (1.5, 15.2)	0.079	0.112
Laparoscopic surgery	0.8 (0.4, 1.4)	0.018	0.032*	0.8 (0.4, 1.4)	0.397	
Total gastric resection	1.6 (0.9, 2.8)	0.135		1.8 (1.0, 3.2)	0.040	0.762
Combined resection	2.7 (1.2, 6.2)	0.015	0.124	6.1 (2.5, 14.6)	< 0.001	<0.001*
Anastomotic type		0.007	0.177		0.013	0.028*
Roux-en-Y	Ref			Ref		
Billroth I	0.5 (0.2, 0.9)	0.025	0.154	0.6 (0.3, 1.1)	0.093	0.316
Billroth II	1.7 (0.8, 3.8)	0.162	0.450	0.3 (0.1, 0.7)	0.008	0.010
TNM stage		0.173			0.007	0.050*
I	Ref			Ref		
II	1.5 (0.6, 3.5)	0.393		3.3 (1.5, 7.5)	0.004	0.015
III	1.9 (1.0, 3.8)	0.065		2.5 (1.2, 5.1)	0.011	0.182

BMI, body mass index; NRS-2002, nutritional risk screening; TNM, tumor–node–metastasis; OR, odds ratio; CI, confidence interval; ref, reference.
**Statistically significant in multivariate analysis.*

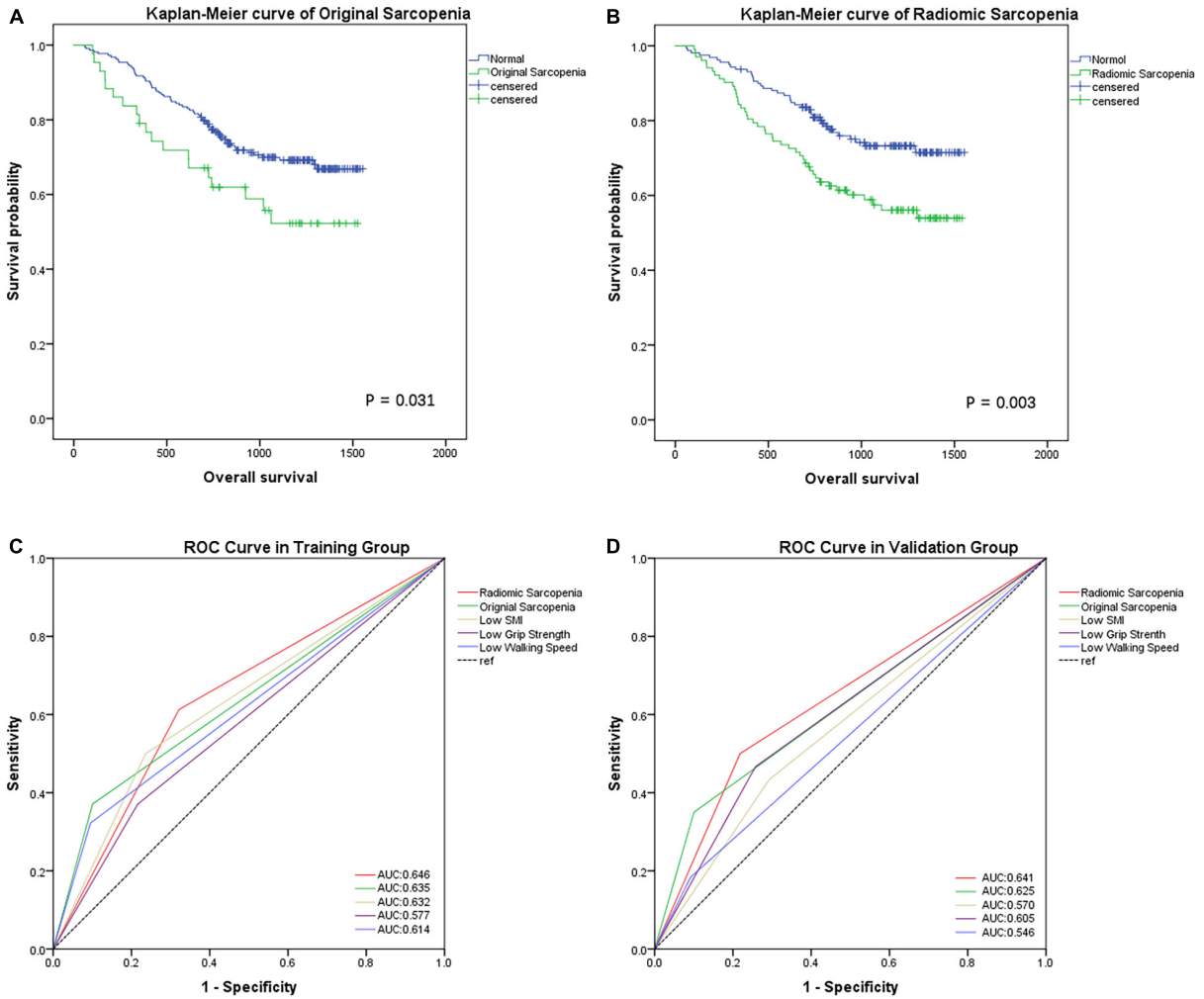

FIGURE 3 | Kaplan–Meier analysis for overall survival (days) of GC patients in the training group according to original sarcopenia **(A)** and radiomic sarcopenia **(B)**. ROC curves for the preoperative characteristics of different sarcopenia models according to short-term complications after gastrectomy in training group **(C)** and validation group **(D)**.

with radiomic sarcopenia was significantly shorter than normal patients (HR, 1.880; 95% CI, 1.225–2.885; $p = 0.003$) (**Figure 3B**).

SMI, grip strength, and walking speed were correlated with postoperative complications in both cohorts (AUCs: 0.632, 0.577, and 0.614, respectively in the training cohort; 0.570, 0.605, 0.546, respectively, in the validation cohort). Moreover, original sarcopenia was more accurate than other indicators (**Figures 3C,D**). However, radiomic sarcopenia had a higher AUC in predicting short-term complications than original sarcopenia in both cohorts (AUCs: 0.646 vs. 0.635 in the training cohort; 0.641 vs. 0.625 in validation cohort) (**Figures 3C,D**).

DISCUSSION

The incidence of sarcopenia is 5–13% in people aged 60–70 years and may reach 50% in people aged >80 years (26). In China, the prevalence among men aged ≥70 years is approximately 12.3%, while the prevalence among women is approximately 7.6% (27). In our previous study, we observed a poor clinical prognosis in patients with sarcopenia, and sarcopenia was an independent predictor of postoperative complications and poor long-term survival (28, 29).

However, original sarcopenia definition does not only needs to consider muscle mass but also muscle strength and physical performance. Pre-diagnosis of sarcopenia requires image reading and specialized personnel, which involves time and energy in analyzing grip strength and walking pace. CT is a useful muscle mass analysis tool for diagnosing traditional sarcopenia; however, the muscle status on CT has not been well analyzed. In this study, we proposed the concept of radiomic sarcopenia through features of sarcopenia extracted from CT. This new type of sarcopenia index can be extracted using a three-dimensional imaging method, which objectively examines muscle mass, muscle strength, and physical performance. Compared with original sarcopenia, radiomic sarcopenia is based on the

extraction of image histology features with objectivity and rigor, which can reduce the diagnostic deviation caused by subjective evaluation of grip strength and walking pace. Simultaneously, it has a higher sensitivity and specificity in predicting postoperative complications and is also an independent predictor of major postoperative complications and poor long-term survival.

Radiomic technology captures tissue heterogeneity in a non-invasive manner and uses automated high-throughput data feature extraction algorithms to convert image data into high-resolution, minable image feature data (30, 31). In sarcopenia assessment, after measuring the muscle mass from CT, we also need to evaluate muscle strength and physical performance, which require more time and energy. Meanwhile, radiomic sarcopenia assessment requires a shorter time, given that the assessment results can be obtained instantaneously after CT measurements. Radiomic sarcopenia does not require clinicians to measure a patient's grip strength or usual gait speed, thereby reducing manpower and medical resources. Clinically, the use of radiomics in diagnosing sarcopenia can help clinicians identify the presence of sarcopenia more quickly and conveniently. Clinicians can implement nutritional and clinical interventions based on this new diagnostic method to establish a better perioperative diagnosis and treatment system for GC patients.

In this study, both in the training group and the validation group, radiomic sarcopenia had a high AUC for predicting complications. Although there was no obvious improvement in sensitivity and specificity compared with original sarcopenia, radiomic sarcopenia had a similar accuracy and were faster to obtain and more convenient to use. In **Table 1**, although the number of patients in the cohorts was different, there was no obvious difference in basic characteristics, which can indicate that our results in the validation group are credible. In terms of long-term survival, owing to the lack of survival follow-up time for GC patients from 2017 to 2019 (the validation cohort), the survival analysis was only performed for the training cohort and not the validation cohort.

To the best of our knowledge, this study is the first to propose the use of radiomic sarcopenia in predicting the short-term and survival prognosis of GC patients after surgery. However, this study had some limitations. Owing to limited resources, we included only 550 patients, this sample size may not be sufficiently representative. Therefore, in future research, we need to include more patients and more centers for comprehensive and systematic verification. We look forward to the establishment of an index-like radiomic diagnosis of sarcopenia through image feature extraction, instead of a subjective scale, to objectively evaluate the nutritional status of the body, this will help in reducing the diagnosis cost and ensure quicker and more accurate diagnosis.

CONCLUSION

Extracted sarcopenia features based on CT can predict the long-term survival and short-term complications of GC patients after surgery. The accuracy of our model was verified using training and verification cohorts. Compared with original sarcopenia, radiomic sarcopenia can not only effectively improve the accuracy of survival and complication prediction, but also shorten the time and steps of traditional screening, reducing the subjectivity of sarcopenia assessment.

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 two affiliated hospitals of Wenzhou Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XS and W-JC contributed to conception and design of the study. L-BX, Z-XH, and H-HZ contributed to the acquisition of the data. X-DC, W-TZ, M-MS, and Y-QC contributed to the analysis and interpretation of the data. X-DC, W-TZ, and L-BX drafted the manuscript. Z-SL revised the manuscript. All authors critically revised the manuscript and gave final approval of the version to be submitted.

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We certify that we comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2019 (32).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.850929/full#supplementary-material

Supplementary Figure 1 | The flowchart of participant.

Supplementary Figure 2 | ROC curve for radiomic score according to low grip strength, low walking speed, and low SMI in the training group **(A–C)** and validation group **(D–F)**.

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ORIGINAL RESEARCH
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Association of Underweight and Weight Loss With Poor Prognosis and Poor Therapy Effectiveness in Brain Metastases: A Retrospective Study

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Background: The prognostic role of body mass index (BMI) in patients with brain metastases is controversial. We aim to investigate the impact of BMI on prognosis and anti-cancer therapy effectiveness in brain metastases.

Methods: Patients diagnosed with brain metastases between Oct 2010 and July 2019 were followed for mortality through April 2021. The prognostic role of BMI on overall survival was assessed by a restricted cubic spline (RCS) using a flexible model to visualize the relationship between the BMI values and hazard ratios of all-cause mortality, followed by a cox regression model. The disparity of survival outcomes in patients receiving anti-cancer therapies or those did not was evaluated according to the classification of BMI.

Results: A total of 2,466 patients were included in the analysis, including 241 in the underweight (BMI < 18.5 kg/m^2) group, 1,503 in the normal weight group (BMI 18.5–23.9 kg/m^2), and 722 in the overweight (BMI ≥ 24 kg/m^2) group. Relative to the normal weight group, underweight patients were associated with poor prognosis (adjusted HR 1.25, 95% CI 1.07–1.46, $p = 0.005$). However, those in the overweight group showed similar overall survival when compared to the normal-weight group. Patients with weight loss were associated with a higher risk of mortality compared with patients without significant weight loss. In underweight patients, there was an insignificant difference in survival outcomes whether they received anti-cancer therapies or not.

Conclusion: Underweight and significant weight loss were associated with poor prognosis in brain metastases. Meanwhile, anti-cancer therapies did not significantly improve overall survival in patients with underweight. These findings suggest that improving nutrition to maintain body weight is critical for patients with brain metastases.

Keywords: brain metastases, body mass index–BMI, overall survival (OS), underweight, anti-cancer therapy

INTRODUCTION

Brain metastases are detected in approximately 10–40% of patients with cancer (1, 2). Over the decades, the incidence of brain metastases is increasing due to improved imaging techniques and effective systemic treatment of primary cancers (3). Although aggressive therapy has been used, the prognosis is generally poor (4, 5). Several factors were investigated to predict prognosis in these patients, such as age, Karnofsky Performance status, type of primary tumor, and location and number of brain metastases (6). However, the impact of BMI on prognosis in brain metastases was unclear.

The major influence of BMI on cancer prognosis can be rationalized by the effect of fat tissue on hormones and metabolism (7). It was reported that a higher BMI might be advantageous for cancer prognosis because more energy reserves could be drawn on through aggressive treatment (7). Meanwhile, genome expression analysis found that cancer-promoting genes of metabolism and fatty acid presented lower expression in patients with higher BMI (8). However, higher BMI may be associated with worse cancer prognosis *via* increasing serum insulin concentrations and the bioavailability of insulin-like growth factor-I (9). Lean muscle mass is also lost during cancer progression, a phenomenon known as cancer cachexia, with occurrence of other metabolic derangements (10). The complex relationship between BMI and cancer, including brain metastases, remains poorly understood.

In brain metastases, a retrospective analysis including 624 patients with brain metastases reported that the median overall survival of underweight patients was 3 months, which was significantly shorter than healthy or patients who are overweight/obese (7–8 months, $p < 0.001$) (11). Lareida et al. evaluated the correlation of BMI with survival outcomes in brain metastasis, and demonstrated that overweight was associated with better outcomes, while underweight associated with worse outcomes (12). However, another study identified that BMI $\geq$ 25 kg/m^2 had a negative impact on overall survival compared with BMI $<$ 25 kg/m^2 (median overall survival: 13.7 vs. 30.6 months, $p < 0.001$) (13). Whether BMI is a significant predictor of prognosis in brain metastases remains controversial.

Here, we examined whether BMI is a prognostic factor in patients with brain metastases. We performed a retrospective analysis based on 2,466 patients with brain metastases to identify the impact of BMI and weight change on prognosis and to evaluate the disparity of survival outcomes in patients receiving anti-cancer therapies or those who did not according to the classification of BMI.

MATERIALS AND METHODS

Patients and Data Collection

We retrospectively collected data from West China hospital between Oct 2010 and July 2019. The last follow-up time was April 2021. The survival status of patients was also used in the household registration system in China. Patient consent was waived by the Institutional Review Board because no intervention was given, and no patients' privacy was leaked. To be included in this study, patients had to be pathologically confirmed to have cancer and had radiologic findings of brain metastases. Patients were excluded if they had neoplastic meningitis or were age $<$ 18 years old.

Body mass index was calculated as weight (kg) divided by height squared (m^2). The first BMI record was assessed when brain metastases were diagnosed. Subsequently, BMI was assessed every 8 weeks to collect weight change data. Patients were divided into three different BMI categories according to the guidelines for prevention and control of overweight and obesity in Chinese adults: underweight group ($<$18.5 kg/m^2), normal-weight group (18.5–23.9 kg/m^2), and overweight or obese group ($\geq$24 kg/m^2) (14). After brain metastases diagnosis, patients with BMI decreasing by $\geq$ 1 kg/m^2 were regarded as having significant weight loss. If BMI decreased $<$ 1 kg/m^2, it was not regarded as a meaningful change in BMI. Overall survival (OS) was defined as the interval from diagnosis of brain metastases to death.

Statistical Analyses

Differences between baseline characteristics among the BMI categories were assessed using the chi-square test for categorical variables. A restricted cubic spline (RCS) was used to visualize the relationship between the BMI values and hazard ratios of all-cause mortality, followed by a cox regression model. The

TABLE 1 | Characteristics of patients.

Variable	BMI<18.5 (*n* = 241)	BMI 18.5–23.9 (*n* = 1,503)	BMI ≥ 24 (*n* = 722)	*P*-value
Sex				0.003
Female	115 (48%)	663 (44%)	270 (37%)	
Male	126 (52%)	840 (56%)	452 (63%)	
Age				0.05
<57 years	106 (44%)	769 (51%)	383 (53%)	
≥57 years	135 (56%)	734 (49%)	339 (47%)	
KPS				0.46
>70	189 (78%)	1,244 (83%)	606 (84%)	
≤70	52 (22%)	259 (17%)	116 (16%)	
Accept chemotherapy				0.11
Yes	151 (63%)	1,012 (67%)	504 (70%)	
No	90 (37%)	491 (33%)	218 (30%)	
Accept radiotherapy				0.62
Yes	103 (43%)	650 (43%)	327 (45%)	
No	138 (57%)	853 (57%)	395 (55%)	
Accept target therapy				0.85
Yes	59 (24%)	382 (25%)	176 (24%)	
No	182 (76%)	1,121 (75%)	546 (76%)	
Metastasis from lung cancer				0.65
Yes	129 (54%)	812 (54%)	375 (52%)	
No	112 (46%)	691 (46%)	347 (48%)	
The number of brain metastases				0.32
Single	55 (23%)	366 (24%)	194 (27%)	
Multiple	186 (77%)	1,137 (76%)	528 (73%)	

BMI, body mass index (recorded when brain metastases was diagnosed); KPS, Karnofsky performance status.

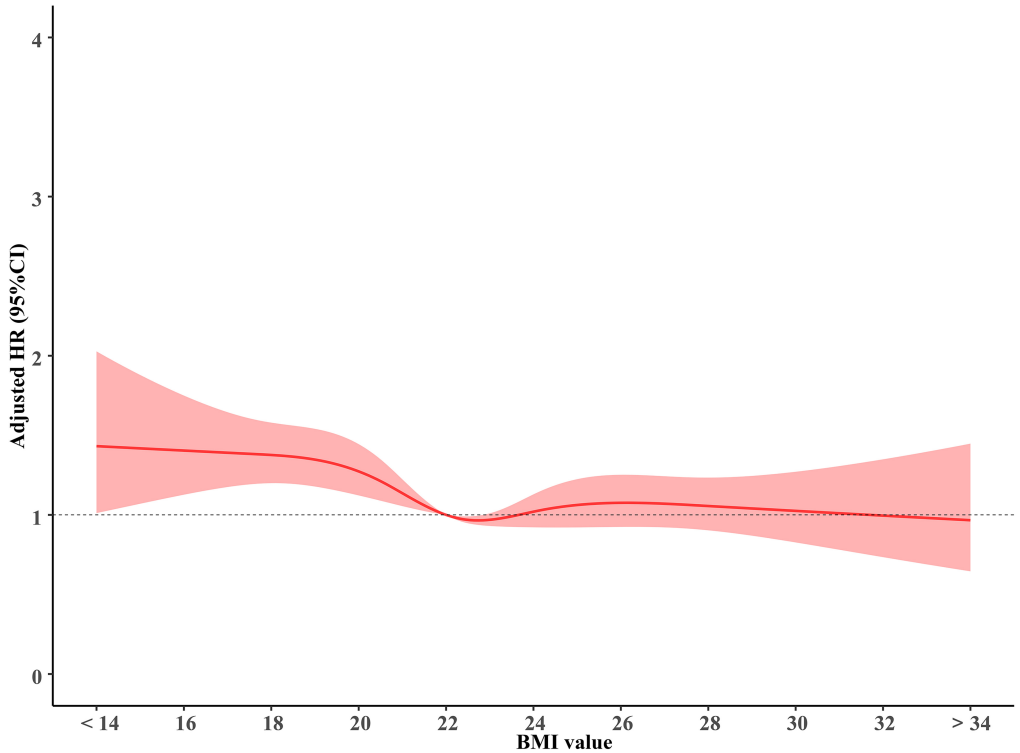

FIGURE 1 | The association of BMI with overall survival. BMI, body mass index (recorded when brain metastases was diagnosed).

Kaplan–Meier curves were applied to compare the difference among the BMI categories. We estimated the adjusted-hazard ratio (adjusted-HR) and 95% confidence interval (95%CI) by the Cox regression model, and the adjusted HR considered factors including sex, age, Karnofsky performance status score, primary cancer site, the radiotherapy, target therapy, chemotherapy, and the location and number of brain metastases. The cutoff value of age was determined by the median value. These factors were reported as prognostic variables (15). We added BMI to the variables of Graded Prognostic Assessment for brain metastases (GPA: number of brain metastases, Karnofsky performance status, age, and extracranial metastases) (16) to establish a novel prediction model. The receiver operating characteristic curve (AUC) and integrated discrimination improvement (IDI) were used to assess the increased certainty provided by BMI (17). The interactions between BMI and the subgroups were assessed to identify the potential influence factors. *P*-values, were reported as two-sided and < 0.05 were considered statistical difference. All analysis was performed by R software (version 4.0.3, Vienna, Austria).

RESULTS

Characteristics of Patients

A total of 2,466 patients were included in the analysis, with a median BMI of 22.39 kg/m^2 (IQR 20.31–24.33 kg/m^2). There were 241 in the underweight group, 1,503 in normal-weight group, and 722 in the overweight or obese group, with a median BMI of 17.53 kg/m^2 (IQR 16.73–18.03 kg/m^2), 21.62 kg/m^2 (IQR 20.31–22.84 kg/m^2), and 25.63 kg/m^2 (IQR 24.61–27.01 kg/m^2), respectively. The median age was 57 years (IQR 49–65 years). Among these patients, 57.5% (1,418/2,466) were men and 42.5% (1,048/2,466) were women. Compared to the underweight group, a higher proportion of male patients was found in the overweight or obese group (63% vs. 52%). In the other baseline characteristics, there was no statistical significance among the three groups (**Table 1**).

Body Mass Index as a Prognostic Factor for Overall Survival

As shown in **Figure 1**, BMI was a prognostic factor for OS in brain metastases. The hazard ratios were increased for patients with a lower BMI, indicating that underweight individuals had a poorer prognosis. Notably, the BMI effect on OS was significantly non-linear on the relative hazard scale; from the BMI of approximately 22 kg/m^2 to the highest BMI in the cohort, the hazard ratios presented insignificant differences for patients with increased BMI.

The Impact of Body Mass Index and Weight Loss on Overall Survival

Relative to patients with normal weight, patients who are underweight were associated with poor prognosis (adjusted HR 1.25, 95%CI 1.07–1.46, $p = 0.005$). However, the overweight

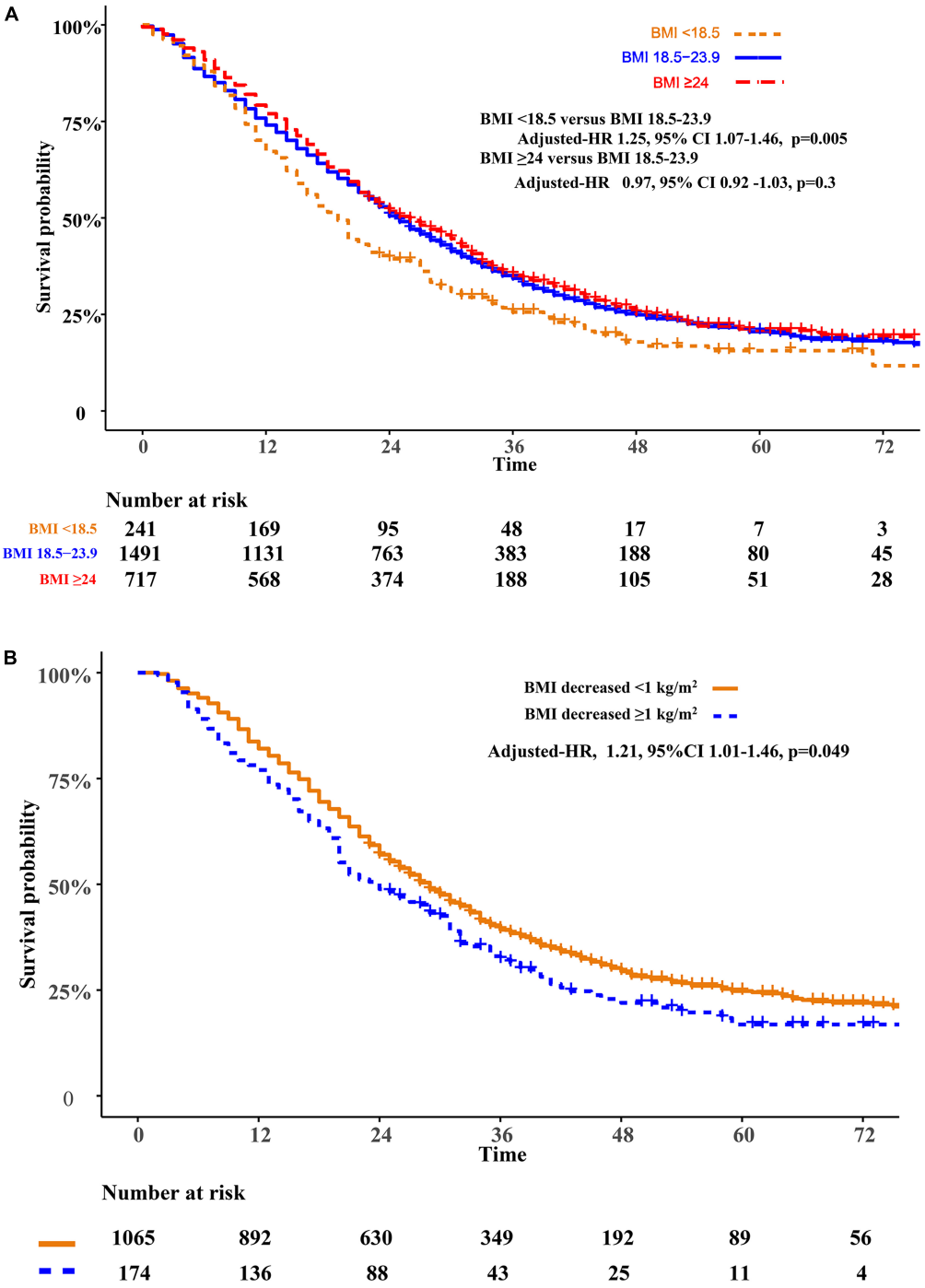

FIGURE 2 | Overall survival comparisons of BMI **(A)** and weight change **(B)**. BMI, body mass index (recorded when brain metastases was diagnosed).

or obese group showed similar overall survival (adjusted HR 0.97, 95%CI 0.92–1.03, $p = 0.3$) when compared to the normal-weight group. Patients with weight loss were associated with a higher risk of mortality (adjusted HR 1.21, 95%CI 1.01–1.46, $p = 0.049$)compared with patients without significant weight loss (**Figure 2**). We modified the GPA model for brain metastasis prognosis by adding BMI information. Adding BMI to the GPA significantly improved the performance (IDI 5.2%, $p < 0.001$; AUC, $p < 0.001$) for predicting overall survival than GPA alone (**Supplementary Figures 1, 2**).

Subgroup Analysis and Interaction Tests

In subgroup analysis, we found that analysis of P for interaction across each of these subgroups was insignificant not only

TABLE 2 | Subgroup analysis.

Subgroup	Events	Total	BMI < 18.5 vs. BMI ≥ 18.5		Test for interaction
			Adjusted-HR (95%CI)	*P*-value	
Sex					0.93
Female	705	1,048	1.29 (1.02–1.62)	0.03	
Male	1,055	1,418	1.28 (1.05–1.57)	0.03	
Age					0.86
<57 years	854	1,258	1.25 (0.99–1.59)	0.06	
≥57 years	906	1,208	1.30 (1.06–1.59)	0.01	
KPS					0.91
>70	1,434	2,039	1.29 (1.09–1.53)	0.004	
≤70	326	427	1.24 (0.89–1.73)	0.2	
Accept chemotherapy					0.45
Yes	1,188	1,667	1.21 (1.01–1.47)	0.049	
No	572	799	1.33 (1.03–1.70)	0.03	
Accept radiotherapy					0.63
Yes	777	1,080	1.31 (1.04–1.65)	0.02	
No	983	1,386	1.20 (0.98–1.47)	0.08	
Accept target therapy					0.3
Yes	414	617	1.29 (0.94–1.78)	0.11	
No	1,346	1,849	1.24 (1.05–1.48)	0.01	
Accept therapy for primary cancer					0.29
Yes	1,445	2,058	1.32 (1.11–1.57)	0.001	
No	315	408	1.06 (0.76–1.49)	0.72	
Metastasis from lung cancer					0.14
Yes	960	1,316	1.16 (0.94–1.44)	0.16	
No	800	1,150	1.42 (1.14–1.78)	0.001	
The number of brain metastases					0.28
Single	386	615	1.65 (1.17–2.32)	0.004	
Multiple	1,374	1,851	1.22 (1.03–1.45)	0.02	

BMI, body mass index (recorded when brain metastases was diagnosed); KPS, Karnofsky performance status.

in BMI < 18.5 kg/m^2 vs. ≥ 18.5 kg/m^2 (**Table 2**), but also in the underweight vs. the normal weight group and the overweight vs. normal weight (**Supplementary Table 1**). Meanwhile, subgroup analysis of patients' metastasis from breast cancer or prostate cancer found that there were no significant differences between the overweight and the normal weight group (adjusted HR 0.91, 95%CI 0.71–1.15, $p = 0.43$; p for interaction was 0.39).

The Correlation of Body Mass Index With Therapy Effectiveness

Compared with patients who declined therapy, patients receiving therapy obtained a better OS in the normal weight group (adjusted-HR 0.72, 95%CI 0.62–0.85, $p < 0.01$) and the overweight or obesity group (adjusted-HR 0.64, 95%CI 0.50–0.81, $p < 0.01$). However, in patients who are underweight, there was no significant difference in OS whether they received cancer treatment or not (adjusted HR 0.87, 95%CI 0.60–1.25, $p = 0.44$). We further asked if patients who are underweight obtained a survival benefit from chemotherapy, radiotherapy, and target therapy. Compared to patients who declined therapy, there were no overall survival benefit in patients receiving radiotherapy (adjusted-HR 1.14, 95%CI 0.82–1.54, $p = 0.47$), chemotherapy (adjusted-HR 0.82, 95%CI 0.59–1.14, $p = 0.24$), or targeted therapy (adjusted-HR 0.98, 95%CI 0.68–1.42, $p = 0.93$) (**Figure 3**).

DISCUSSION

Our study showed that patients who are underweight and patients with significant weight loss both experienced an increased risk of mortality. In addition, we found that anti-cancer therapies do not significantly improve overall survival in patients who are underweight. These findings highlight the possibility of prolonging survival in patients with brain metastasis by maintaining or increasing body weight.

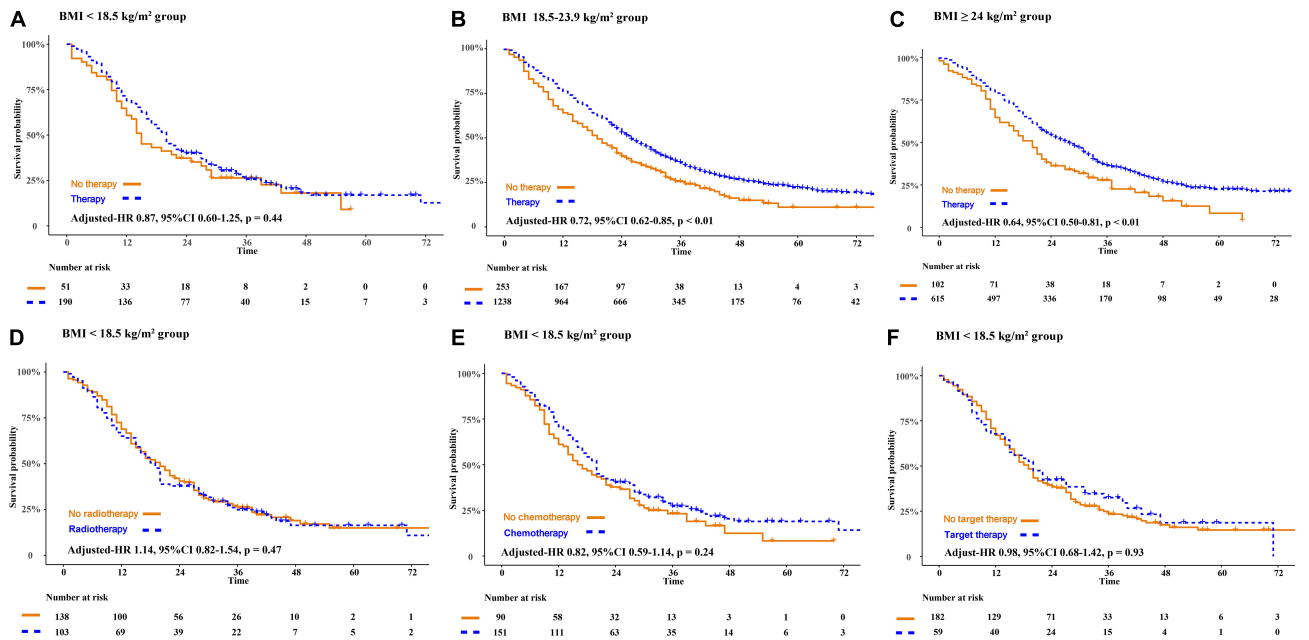

FIGURE 3 | The disparity of survival outcome in patients receiving anti-cancer therapies or not according to the classification of BMI. BMI, body mass index (recorded when brain metastases was diagnosed).

Alternatively, since weight loss is quite common in cancer, weight may be an indicator of the disease process and may not be actionable.

A previous study indicated that BMI was strongly associated with prognosis in patients with brain metastases (11). A Swiss study based on 703 patients with brain metastases reported that high BMI was correlated with better overall survival (p = 0.03), and underweight with worse outcomes (p = 0.047) (12). It showed that the worse outcome in patients who are underweight was driven by those with primary lung cancer (p = 0.005), and that there was no difference between the patients who are underweight and the patients with normal weight in other types of cancer (p = 0.87) (12). However, that study included only 50 cases in the underweight group, and a biased estimate may have occurred due to the small dataset.

Some of the conflicting results from previous reports may be due to the different cancer types studied. For example, underweight patients (BMI < 18.50 kg/m^2) had higher mortality (HR 1.61, 95% CI 1.53–1.70, $p < 0.0001$) compared with patients with normal weight (BMI 18.50–24.99 kg/m^2) in colorectal cancer (18, 19). However, Troeschel et al. suggested that obesity at diagnosis (HR 1.23, 95% CI 1.11–1.35) and weight gain (HR 1.27, 95% CI 1.12–1.45) after a prostate cancer diagnosis may be associated with higher all-cause mortality (20). In breast cancer, overweight or obesity has a negative impact on the effectiveness of neoadjuvant chemotherapy (21). In our study population, we found no differences in overall survival between patients who are overweight and normal weight, with brain metastasis from different cancers, including lung cancer (test for interaction: p = 0.31), breast cancer, or prostate cancer (test for interaction: p = 0.39). It should be noted that there are differences in baseline BMI between our study population and those from other studies; the proportion of obese individuals in this cohort is lower.

Among patients who are underweight, we found no significant differences in OS for patients receiving chemotherapy, radiotherapy, or targeted therapy compared to those who declined therapy. A tangentially relevant study was a meta-analysis involving 3,768 individual patients with cancer treated with immune checkpoint inhibitors, where the median OS was significantly higher in overweight or in patients with obesity than in patients who are not overweight (20.7 vs. 11.3 months, $p < 0.001$) (22). It remains unclear whether an optimal combination of cancer therapy and nutrition may provide benefits for underweight patients.

Some limitations in this study should be acknowledged. The retrospective nature of our study from a single institution may potentially affect results. Firstly, we could not collect the information about the disease course of primary cancer and the treatment for primary cancer before brain metastases were diagnosed. It is unknown whether low BMI itself puts patients at risk of disease progression or is an indicator of disease progression, or whether the treatment process of primary cancer resulted in low BMI and heightened the risk for mortality. Second, the limited number of patients (n = 241) in the underweight group place limits on the statistical power. Additionally, in the subgroup analysis of breast cancer or prostate cancer, we could not compare the underweight with the normal-weight group, because only six patients with brain metastases from breast cancer or prostate cancer were underweight. Finally, we were unable to adjust for some underlying diseases in our analysis due to missing data, which could affect our results. For example, overweight individuals have a disposition for diabetes,

but diabetes was associated with an increased risk of cancer-related mortality (23, 24).

CONCLUSION

Underweight and significant weight loss is associated with poor prognosis in brain metastases. Meanwhile, anti-cancer therapies do not significantly improve overall survival of patients who are underweight. This suggests the importance of maintaining body weight and nutrition in patients with brain metastases.

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 West China Hospital of Sichuan University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YH, YZ, and FF: study concept and design. YH, YZ, YP, RZ, ZL, and JY: acquisition and interpretation of the data. YH and YZ: drafting of the manuscript and statistical analysis. WC, FF, and XP: critical revision of the manuscript. FF and XP: administrative and technical support. All authors final approval of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.851629/full#supplementary-material

Supplementary Figure 1 | Area under receiver operating characteristic curve (AUC) to assess the increased certainty provided by BMI. GPA, Graded Prognostic Assessment for brain metastases; BMI, body mass index (recorded when brain metastases was diagnosed).

Supplementary Figure 2 | The modified-GPA model for brain metastasis prognosis by adding BMI information. BMI, body mass index (recorded when brain metastases was diagnosed); KPS, Karnofsky performance status.

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Prognostic Value of Preoperative Nutritional Assessment and Neutrophil-to-Lymphocyte Ratio in Patients With Thymic Epithelial Tumors

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Introduction: Systemic nutrition and immune inflammation are the key factors in cancer development and metastasis. This study aimed to compare and assess four nutritional status and immune indicators: prognostic nutritional index (PNI), nutritional risk index (NRI), neutrophil-to-lymphocyte ratio (NLR), and the systemic immune-inflammatory index (SII) as prognostic indicators for patients with thymic epithelial tumors.

Materials: We retrospectively reviewed 154 patients who underwent thymic epithelial tumor resection at our hospital between 2004 and 2015. The optimal cutoff value for each nutritional and immune index was obtained using the X-tile software. Kaplan-Meier curves and Cox proportional hazards models were used for survival analysis.

Results: Univariate analysis showed that PNI, NRI, NLR, SII, albumin (ALB), the albumin/globulin ratio (A/G), WHO stage, T stage, and drinking history were associated with the overall survival (OS) of patients ($P < 0.05$). The NRI, NLR, A/G, ALB, T stage, and WHO stage were significant independent prognostic factors of OS in multivariate analysis ($P < 0.05$). Finally, we constructed a coNRI-NLR model to predict OS and recurrence-free survival (RFS).

Conclusions: This study suggests that the preoperative NRI, NLR, and coNRI-NLR model may be important prognostic factors for patients with thymic epithelial tumors who undergo surgical resection.

Keywords: thymic epithelial tumor, prognostic factor, nutritional risk index, neutrophil-to-lymphocyte ratio, overall survival, recurrence free survival

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INTRODUCTION

Thymic epithelial tumors are rare malignancies which frequently occur in the anterior mediastinum of adults, and include thymomas and thymic carcinomas (1, 2). Although surgery is an effective treatment, since thymic epithelial tumors only account for around 0.2–1.5% of all malignancies, there is currently no standard, comprehensive treatment protocol (3, 4). A recent meta-analysis showed that postoperative radiotherapy can improve the overall survival rate of Masaoka-Koga stage II and III thymoma, but no prospective studies have confirmed these results (5).

Additionally, a study of postoperative chemotherapy has not yet reached a definite conclusion, because thymomas are an indolent tumor with a low incidence and relatively long survival time. Therefore, it is difficult to predict tumor prognosis and recurrence and to formulate individualized treatment plans.

Preoperative nutritional status is associated with postoperative complications and overall survival (OS) in patients with cancer (6), and many indicators containing nutritional variables have been found to play a role in predicting the prognosis of patients with various cancer, such as esophageal cancer (7), non-small cell lung cancer (8), colorectal cancer (9), and oral cancer (10). However, the relationship between the nutritional risk index (NRI) or prognostic nutritional index (PNI) and clinical outcomes in patients with thymic epithelial tumors remains unclear and has not been validated.

Additionally, inflammation plays an important role in the development and progression of cancer (11–13). Inflammation-related indicators such as the systemic immune-inflammatory index (SII) and neutrophil-to-lymphocyte ratio (NLR) play a role in predicting prognosis in breast cancer (14), kidney cancer (15), lung cancer (16), esophageal cancer (17, 18), and other tumors. Considering the close relationship between inflammation and tumor development, this study also assessed inflammation-related factors.

As research predicting tumor prognosis and recurrence is of great significance when determining individualized treatment and postoperative adjuvant therapy for patients with thymic epithelial tumors, we studied the ability of the four most commonly reported nutritional and immune-inflammation-related indicators (PNI, NRI, SII, and NLR) to predict the prognosis of thymic epithelial tumors. In addition, we explored new indicators that have an impact on prognosis, in order to more accurately and conveniently predict the prognosis and recurrence of thymic epithelial tumors.

MATERIALS AND METHODS

This study was approved by the Medical Ethics Committee of Sun Yat-sen University Cancer Center (B2020-353-01), and included patient data collected at Sun Yat-sen University Cancer Center (record number: RDDA2021002090). The study complied with the Declaration of Helsinki.

This study retrospectively analyzed 154 patients who underwent thymic epithelial tumor resection at our center between May 2004 and August 2015. The inclusion criteria were as follows: (1) age > 18 years; (2) complete surgical resection (R0, no residual disease); (3) presence of histopathologically confirmed thymic epithelial tumors, including thymoma and thymic carcinoma (TC); and (4) complete relevant laboratory tests (such as routine blood tests, and routine biochemical tests)

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; HGB, hemoglobin; ALB, albumin; A/G, albumin/globulin; BMI, body mass index; SII, systemic immune-inflammation Index; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index; NRI, nutritional risk index; pT stage, Pathological T stage OS, overall survival; RFS, recurrence-free survival; TC, thymic carcinoma; HR, hazard ratio; CI, confidence interval; ROC, receiver operating characteristic curve; AUC, area under the curve; TET, thymic epithelial tumor.

TABLE 1 | Patient and tumor-related characteristics of thymic tumor (n =154).

Characteristic	N	%
Gender		
Male	80	51.9
Female	74	48.1
Age (years)		
≤60	121	78.6
>60	33	21.4
Smoking history		
Never	119	77.3
Ever	35	22.7
Drinking history		
No	135	87.7
Yes	19	12.3
Family history of tumor		
No	131	85.1
Yes	23	14.9
Tumor size(cm)		
≤6	85	55.2
>6	69	44.8
pT stage		
T1	122	79.2
T2-3	32	20.8
WHO stage		
A-AB	62	40.3
B1-B3	77	50
C	15	9.7
Myasthenia gravis		
No	143	92.9
Yes	11	7.1
ALB		
≤42.6	57	37
>42.6	97	63
A/G		
≤2.0	135	87.7
>2.0	19	12.3
BMI		
≤18.8	16	10.4
>18.8	138	89.6
HGB		
≤124.0	36	23.4
>124.0	118	76.6
NRI		
≤99.6	15	9.7
>99.6	139	90.3
NLR		
≤2.7	129	83.8
>2.7	25	16.2
PLR		
≤147.9	125	81.2
>147.9	29	18.8
SII		
≤688.5	129	83.8
>688.5	25	16.2
PNI		
≤50.9	35	22.7
>50.9	119	77.3

NLR, neutrophil-to-lymphocyte ratio; HGB, hemoglobin; ALB, albumin; A/G, albumin/globulin; BMI, body mass index; SII, systemic immune-inflammation Index; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index; NRI, nutritional risk index; pT stage, Pathological T stage.

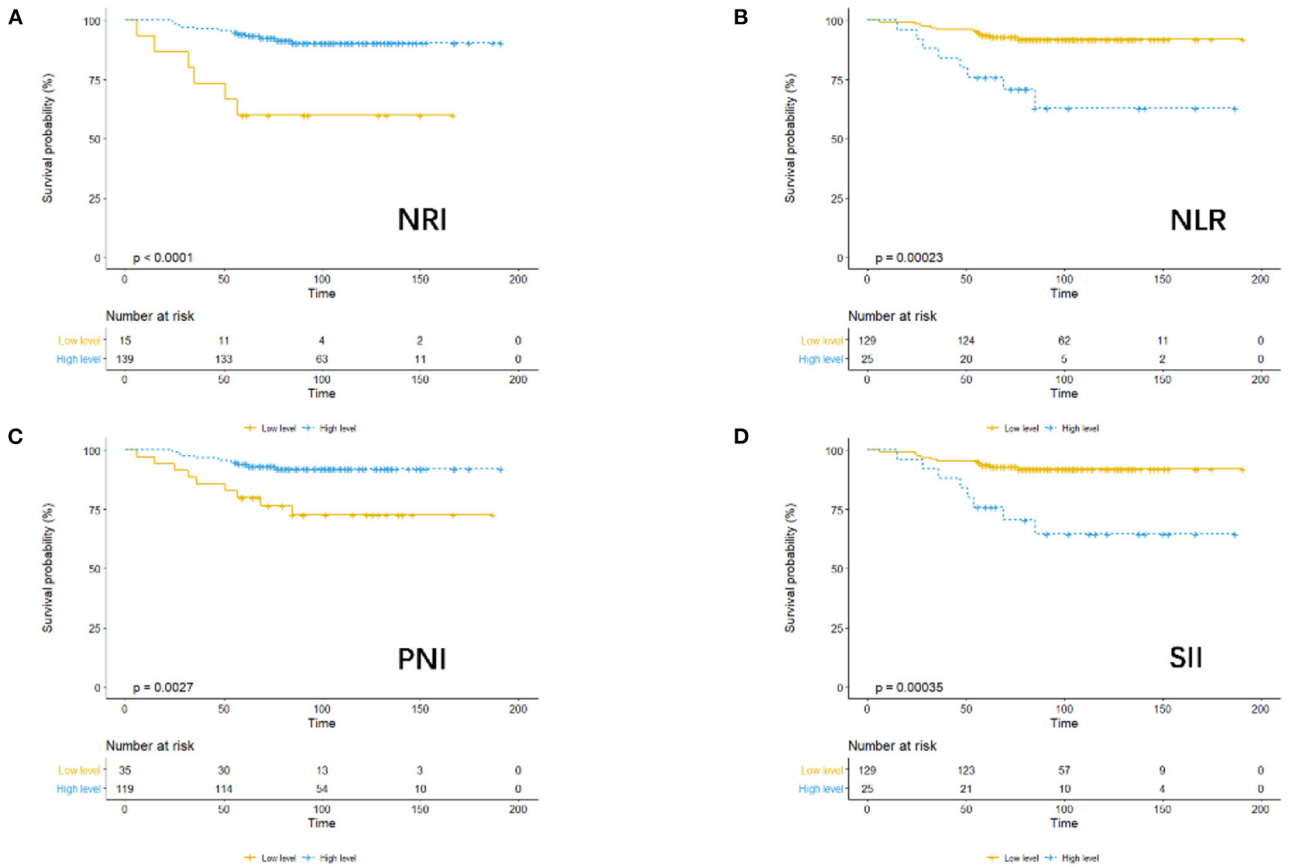

FIGURE 1 | KM analysis of NRI **(A)**, NLR **(B)**, PNI **(C)**, and SII **(D)** based on overall survival.

within 7 days before surgery. The exclusion criteria were as follows: (1) Patients who received radiotherapy or chemotherapy prior to surgery, before and after surgery, or an unknown sequence of treatment with surgery. (2) Patients with more than one malignancy or history of other malignancies. (3) Postoperative survival time less than 3 months. (4) Follow-up time less than 5 years. (5) Cryoablation as the surgical method. (6) If the patient only underwent thymoma biopsy. (7) Incomplete follow-up information.

Data Collection

Data were collected for the following clinical variables: hematological indicators (obtained within 1 week before surgery), lymphocyte count, neutrophil count, albumin level (ALB), platelet count, globulin level, patient's age, sex, smoking history, drinking history (drinking alcohol every day, although the specific amount of drinking was not limited or described), family history of tumors, tumor size, myasthenia gravis symptoms, histological subtype, and body mass index (BMI). In this study, T staging was obtained by combining imaging data with intraoperative records and postoperative pathological information, and we staged all patients according to the 8th edition of the TNM staging system.

Follow Up

Patients were followed-up every 6–12 months for the first 2 years, every 12 months for the third to fifth years, and annually thereafter. The follow-up investigations included chest CT scan and hematological examination (including routine blood tests, routine biochemical tests, and investigation of tumor markers), and the final follow-up timepoint was August 2020. The primary endpoints were overall survival (OS) and recurrence free survival (RFS).

Variable Definition

All hematological indicators were collected within 7 days before surgery. The formula for calculating nutritional indicators is as follows: BMI = weight/height^2 (kg/m^2); NLR = neutrophil count/lymphocyte count; SII = platelet count × neutrophil count/lymphocyte count; PLR = platelet count/lymphocyte count; PNI = albumin (g/l) + 0.005 × lymphocyte count (μl), as derived from Onodera et al. (19). NRI was calculated according to the formula: NRI = (1.519 × albumin, g/1) (41.7 × current/ideal body weight), as defined by Buzby et al. (20). The ideal body weight was calculated according to the Lorenz equation; for males: Height – 100 – [(Height – 150)/4], and for females: Height – 100 – [(Height – 150)/2.5].

TABLE 2 | Univariate and multivariate analysis results in thymic epithelial tumor ($n = 154$).

	Univariate analysis		Multivariate analysis	
	P	HR	95%CI	*P*
Gender	0.079			
Male vs. Female				
Age (years)	0.939			
≤60 vs. >60				
Smoking history	0.275			
Never vs. Ever				
Drinking history	0.046			
No vs. Yes				
Family history of tumor	0.255			
No vs. Yes				
Tumor size	0.06			
≤6 vs. >6				
pT stage	0	Reference		
T1 vs. T2-3		3.542	1.118-11.228	0.032
WHO stage	0	Reference		
A-AB vs. B1-B3		0.815	0.210-3.169	
A-AB vs. C		6.699	0.1.813-24.749	0.003
Myasthenia gravis	0.418			
No vs. Yes				
ALB	0.002	Reference		
≤42.6 vs. >42.6		0.235	0.069-0.802	0.021
A/G	0.039	Reference		
≤2.0 vs. >2.0		12.182	3.178-46.693	0
BMI	0.01			
≤18.8 vs. >18.8				
HGB	0.097			
≤124.0 vs. >124.0				
NRI	0	Reference		
≤99.6 vs. >99.6		0.19	0.052-0.692	0.012
NLR	0.001	Reference		
≤2.7 vs. >2.7		3.471	1.212-9.941	0.02
PLR	0.079			
≤147.9 vs. >147.9				
SII	0.001			
≤688.5 vs. >688.5				
PNI	0.005			
≤50.9 vs. >50.9				

NLR, neutrophil-to-lymphocyte ratio; HGB, hemoglobin; ALB, albumin; A/G, albumin/globulin; BMI, body mass index; SII, systemic immune-inflammation Index; PLR, platelet-lymphocyte ratio; PNI, prognostic nutritional index; NRI, nutritional risk index; pT stage, Pathological T stage.

Data Analysis

Statistical analyses were performed using SPSS 25.0 (IBM, Chicago, Illinois, USA), and R software (version 4.0.3; https://www.r-project.org/). X-Tile software was used to obtain the optimal cutoff values for nutritional and inflammatory predictors (http://www.tissuearray.org/rimmlab). Survival analysis was performed using the Kaplan-Meier log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazard regression models. Relative risks were assessed using hazard ratios (HRs) and 95% confidence intervals (CI). Receiver operating characteristic (ROC) curve analysis was used to compare area under the curve (AUC) values between different models. All tests were two-way, and the significance level was set at $p < 0.05$.

RESULTS

Patient Characteristics

A total of 154 patients with thymic epithelial tumors were included in this study, including 80 men and 74 women, with an average age of 50.66 ± 12.45 years and an average tumor size of 6.71 ± 3.11 cm (**Table 1**). **Table 1** also shows patient's WHO staging, T staging, smoking history, drinking history, myasthenia gravis (MG) status and other relevant clinical information.

Optimal Cutoff Values for Preoperative PNI, NRI, NLR, and SII

Considering OS as the endpoint, the optimal cut-off values of preoperative PNI, NRI, NLR, and SII were determined using X-tile software. The cutoff values were as follows: PNI: 50.9 ($p = 0.05$), NRI: 99.6 ($p = 0.000$), NLR: 2.7 ($p = 0.001$), and SII: 688.5 ($p = 0.001$). For further analysis, patients were divided into low or high groups for PNI, NRI, NLR, and SII based on the relevant cut-off values.

Association of PNI, NRI, NLR, and SII With Survival Outcomes

Using OS as the endpoint, we compared the outcomes in terms of OS among patients assigned to the low- and high-level PNI, NRI, NLR, and SII groups, as demonstrated by the KM survival curves (**Figure 1**).

Univariate and Multivariate Survival Analysis

According to the results of the univariate Cox regression analysis, 10 variables were significantly associated with OS: WHO stage, T stage, drinking history, BMI, ALB, PNI, NRI, NLR, SII, and A/G (**Table 2**). In multivariate Cox regression analysis, six parameters were defined as independent prognostic factors for OS: T stage (T1 vs. T2-3), WHO stage (A-AB vs. B1-B3, and A-AB vs. C), ALB, A/G, NRI, and NLR (**Table 2**).

coNRI-NLR Model Construction

According to the coNRI-NLR model score, those with high NRI and low NLR were given 2 points; those with high NRI and high NLR and those with low NRI and low NLR were given 1 point; and those with low NRI and high NLR were given 0 points. Patients were divided into low-risk (Score 2), middle-risk (Score 1) and high-risk (Score 0) groups and the KM curve related to OS and RFS were assessed (**Figure 2**; $p < 0.001$). Additionally, ROC analysis was used to compare the coNRI-NLR model with NRI and NLR. The AUC of the coNRI-NLR model value was 0.792, which was higher than that of either NRI (0.684) or NLR (0.650) alone (**Figure 3**).

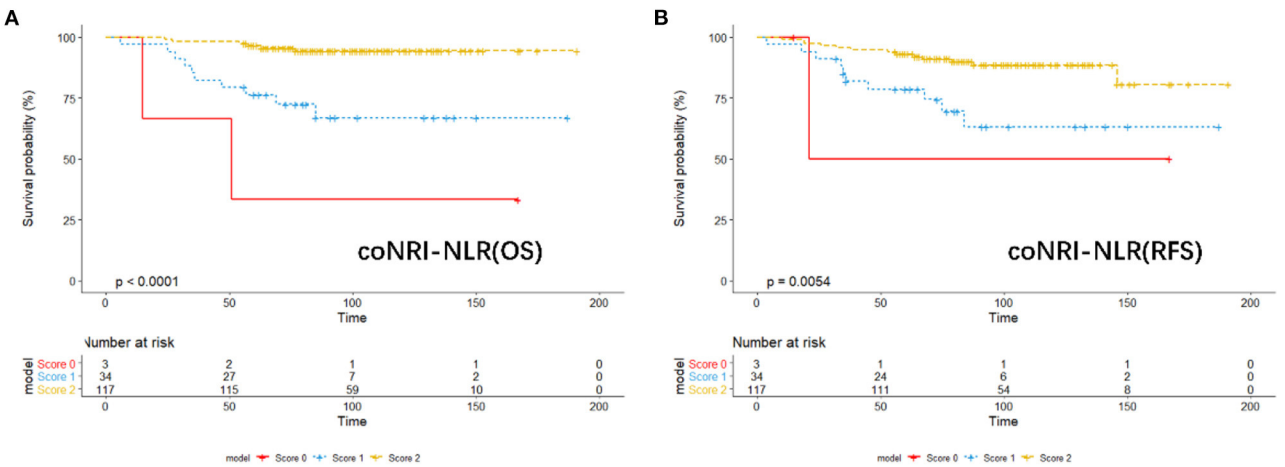

FIGURE 2 | KM analysis of the model of coNRI-NLR based on overall survival **(A)** and relapse-free survival **(B)**.

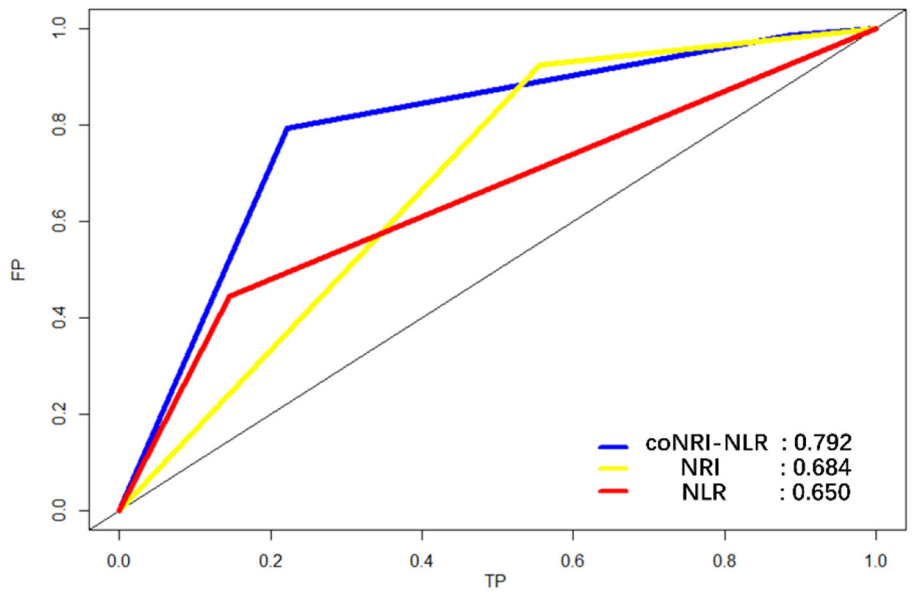

FIGURE 3 | Receiver operating characteristic curve (ROC) analysis for the sensitivity and specificity of the model coNRI-NLR, NRI, and NLR.

DISCUSSION

By comprehensively considering multiple clinical factors and four nutritional status and immune-inflammatory indicators of patients, we conducted univariate and multivariate analyses and concluded that NRI and NLR had significant effects on OS. Additionally, the coNRI-NLR prognostic model constructed from these two factors also has the ability to predict postoperative prognosis in patients with thymic epithelial tumors.

At present, several published studies have assessed prognostic factors for patients with thymic epithelial tumors. Initially, the research of Fang et al. established a predictive model for thymic tumor recurrence through multi-center analysis combined with T staging and WHO staging (21). And a study by Luo et al. constructed a similar model by integrating lactate dehydrogenase and clinical data (22). Additionally, Wang et al. analyzed data from the Surveillance, Epidemiology, and End Results (SEER) database to establish a clinically relevant OS prognostic model (23). However, few studies have comprehensively evaluated the PNI, NRI, NLR, and SII in patients with thymic epithelial tumors.

The NLR is a hematological marker of systemic inflammation. In this study, univariate and multivariate analyses revealed that the NLR could effectively predict the OS of patients with thymic epithelial tumors. Nakajima et al. also found that elevated preoperative NLR was associated with poor prognosis after thymoma resection (24). Negri et al. also concluded that a high preoperative NLR is associated with shorter Disease Free Survival in patients undergoing thymectomy (25). In this study,

the prognostic value of the NLR was better than that of the PLR, which is consistent with He's research conclusion (26). However, the current research assessing the NLR is still limited, and more patient samples and prospective studies remain to be fully evaluated.

Combining ALB and BMI, the NRI reflects the nutritional status of the body and may predict the prognosis of cancer patients. Our findings agree with a study of gastric cancer reported in 2018 (27). Subsequently, a large-scale prospective study of 1,395 patients by He et al. (10) found that the prognostic performance of the NRI was better than that of the PNI in oral cancer, which is also consistent with our findings. Furthermore, in an analysis of the preoperative immune nutritional status of 244 patients with thymoma who underwent thymectomy, Cui et al. (28) found that preoperative immune nutritional support can effectively reduce postoperative complications for thymoma patients with MG. Additionally, their intervention was found to reduce postoperative infection and the risk of complications and hospitalization.

A growing body of research has recently identified novel prognostic factors for cancer. However, most studies of this type have focused on biomarkers, which require complicated molecular and genetic testing (29, 30). The spending and complexity of these tests limit their practical application. By contrast, our study used laboratory test results as prognostic factors as part of routine clinical surveillance. In addition, blood tests routinely used in clinical medicine are more reliable than most tests performed in biological laboratories and do not require specialized equipment or expertise. As a final step in our analysis, we constructed the coNRI-NLR model which combined two independent predictors of prognosis. By comparing the area under the AUC curve, the model was found to be superior to the NRI or NLR alone in terms of its prognostic ability.

Our study proposes an efficient coNRI-NLR model that can classify patients into three subgroups with significant differences in recurrence-free survival and overall survival. It can predict the prognosis of patients with thymic epithelial tumors. The model is used as follows: if the patient has a higher NRI ($>$99.6) and a lower NLR ($\leq$2.7) before surgery, it means that the patient may have a better prognosis, If the patient has a lower NRI ($\leq$99.6) and a higher NLR ($>$2.7) before surgery, it is considered that the patient may have a high risk of recurrence. It is recommended that clinicians should fully evaluate the value of postoperative adjuvant therapy to implement the best possible Individualized treatment strategies.

This study has several limitations. First of all, it was a single-center study with a relatively small sample size. Secondly, our study did not analyze other important inflammatory biomarkers such as interleukin and C-reactive protein. Finally, this study did not consider postoperative dynamic changes in the related nutritional and immune-inflammatory indices.

CONCLUSIONS

Preoperative PNI, NRI, NLR, and SII in patients with thymic epithelial tumors have prognostic value, especially NRI and NLR. Compared with other noninvasive or invasive examination methods, the values required to calculate the NRI and NLR can be obtained relatively easily and at low-cost. In addition, the coNRI-NLR model had better predictive performance than the individual indicators assessed in this study.

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 Medical Ethics Committee of Sun Yat-sen University Cancer Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

G-WM and Y-YH: conception and design of the work and interpretation of data. G-WM: provision of study materials or patients. Y-YH and XL: acquisition of data. S-HL, Y-YH, and YH: analysis of data. Y-YH and S-HL: drafted the manuscript. G-WM, YH, and Y-YH: substantially revised the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.868336/full#supplementary-material

Supplementary Figure 1 | KM analysis of T stage **(A)**, WHO **(B)**, BMI **(C)**, and ALB **(D)** based on overall survival.

Supplementary Figure 2 | KM analysis of A/G **(A)** and Drinking history **(B)** based on overall survival.

Supplementary Figure 3 | KM analysis of T stage, WHO, BMI and ALB based on overall survival.

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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.

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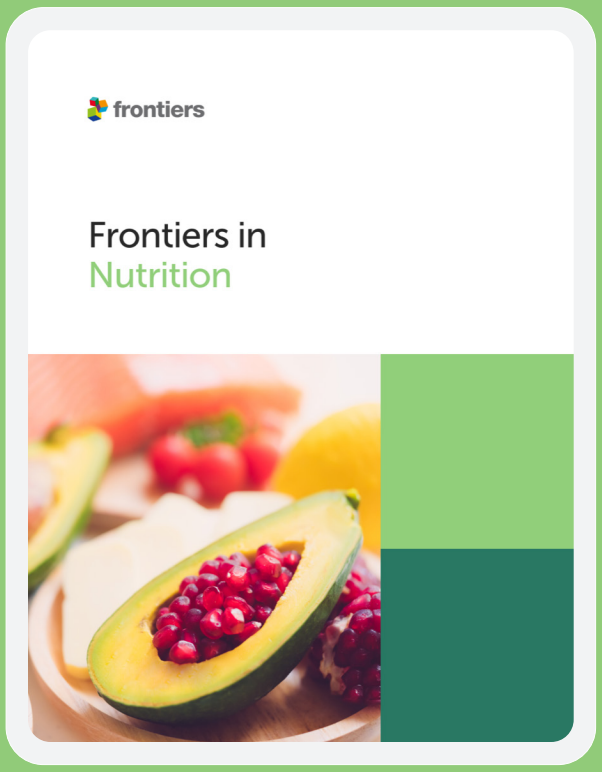

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