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Prognostic significance of the pretreatment pan-immune-inflammation value in cancer patients: an updated meta-analysis of 30 studies

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Background: The pan-immune-inflammation value (PIV) has been reported as a promising prognostic biomarker in multiple cancers but still remains inconclusive. The objective of this study is to systematically investigate the association of the pretreatment PIV with survival outcomes in cancer patients, based on available literature.

Methods: Online databases including PubMed, Embase and the Web of Science were thoroughly searched for studies evaluating the prognostic role of the pretreatment PIV in cancers from the inception to June 2023. Hazard ratios (HRs) with 95% confidence intervals (CIs) were always assessed using a random-effects model. Statistical analyses were performed using Stata 12.0.

Results: Thirty studies were finally included after comprehensively study searching. In total, 8,799 cancer patients were enrolled in this meta-analysis. The pooled results demonstrated that patients in the high PIV group had a significantly poorer overall survival (HR = 2.07; 95%CI: 1.77–2.41; $I^2 = 73.0\%$) and progression-free survival (HR = 1.83; 95%CI: 1.37–2.45; $I^2 = 98.2\%$) than patients in the low PIV group. The prognostic significance of the PIV score on overall survival and progression-free survival was observed across various geographical regions, tumor stages and treatment strategies. Sensitivity analyses supported the stability of the above combined results.

Conclusion: This meta-analysis demonstrated that the pretreatment PIV could be a non-invasive and efficacious prognostic biomarker for cancer patients.

KEYWORDS

cancer, pan-immune-inflammation value, overall survival, progression-free survival, meta-analysis

1. Introduction

With the global population and the proportion of elderly people growing, cancer has become one of the leading causes of death worldwide (1). Although the development of surgery and medical treatment has made great progress in cancer patients, the prognosis for these patients remains not yet satisfactory (2). Therefore, based on the estimated survival time of cancer patients, it is essential to develop individualized and effective treatment strategies to improve their chances of survival. Currently, anti-tumor therapy relies primarily on a

conventional staging system. Nevertheless, in clinical practice, the staging system alone is not able to support treatment decision-making as well as prognosis assessment well (3, 4). It is therefore urgent to construct novel prognostic markers to guide more precise treatment for cancer patients.

The accumulating evidence suggests that host inflammation and immune status play an important role in the progression, treatment response and survival outcomes of cancer patients (5, 6). Based on this insight, several inflammation/immune-related biomarkers have been developed to predict the clinical outcomes of cancer patients, such as neutrophil to lymphocyte ratio (NLR) (7), platelet to lymphocyte ratio (PLR) (8) and monocyte to lymphocyte ratio (MLR) (9). Recently, a newly developed prognostic biomarker—the pan-immune-inflammation value (PIV), has garnered significant interest of clinicians (10). PIV integrates neutrophils, platelets, monocytes and lymphocyte together, and has been reported to be a better prognostic predictor than these simple biomarkers, including NLR, PLR and MLR (11, 12). To be specific, PIV is calculated using serum neutrophil, platelet, monocyte and lymphocyte (neutrophil \times platelet \times monocyte/lymphocyte), which was first introduced by Fuca et al. (13) in 2020 as a prognostic index for metastatic colorectal cancer receiving chemotherapy combined with target therapy. After that, the prognostic role of the PIV has been explored in various cancers (14–16). A recent meta-analysis of 15 studies demonstrated that a high PIV was associated with a poor prognosis in cancer patients (17). Nonetheless, it is important to note that some common tumor types, such as pancreatic cancer and hepatic cancer, were not available in this meta-analysis. Besides, abstract without sufficient data was also included for analysis. These factors undoubtedly have a certain impact on the universality and reliability of the results.

As growing body of additional research has been addressed to further explore the prognostic value of PIV in cancer patients. We therefore performed an updated pooled analysis to systematically explore the relationship between the pretreatment PIV and survival outcomes in cancer patients.

2. Methods

2.1. Search strategy

This meta-analysis was conducted as per the PRISMA guidelines (18) (see PRISMA checklist in the Supplementary Information) to identify literature evaluating the association of pretreatment PIV with survival outcomes in cancer patients. Related studies from the Web of Science, PubMed, and Embase were thoroughly examined from the inception to June 30, 2023. The key word “pan-immune-inflammation value” was applied to search potential studies. During the search process, studies published in any language were included. In addition, references to enrolled studies and related reviews were prudently scanned for additional reporting. The search was performed by two investigators (Y-HJ and RS) independently.

2.2. Study selection

The inclusion criteria were as follows: (1) patients were pathologically diagnosed as cancer; (2) patients were divided into two

groups according to the pretreatment PIV cut-off value; (3) studies investigated the relationship between the pretreatment PIV and survival outcomes of cancer patients. The exclusion criteria were: (1) letters, case reports, abstracts or reviews; (2) duplicated studies.

2.3. Data extraction and quality assessment

Data extraction and subsequent cross-checks were performed by two independent reviewers (YH-J and RS). Information extracted from included studies was as follows: first author, year of publication, country, study interval, sample size, cancer type, selection method, cut-off value, period of blood collection, information on exclusion of diseases affecting blood parameters, age, sex, tumor stage, treatment strategy, survival data and follow-up time. The quality assessment of included literature was evaluated via the method by Lin et al. (19). After careful evaluation from 9 domains, a study could get a total score ranging from 0 to 9. Quality assessment was not used as exclusion criterion for included studies.

2.4. Outcome assessment

In this study, the primary endpoint was to explore the relationship between the pretreatment PIV and survival outcomes in cancer patients. Long-term survival outcomes included overall survival (OS), progression-free survival (PFS), disease-free survival (DFS) and recurrence-free survival (RFS). Since DFS, RFS and PFS share the similar endpoints, they were analyzed together as one outcome, PFS, as previously suggested (20, 21).

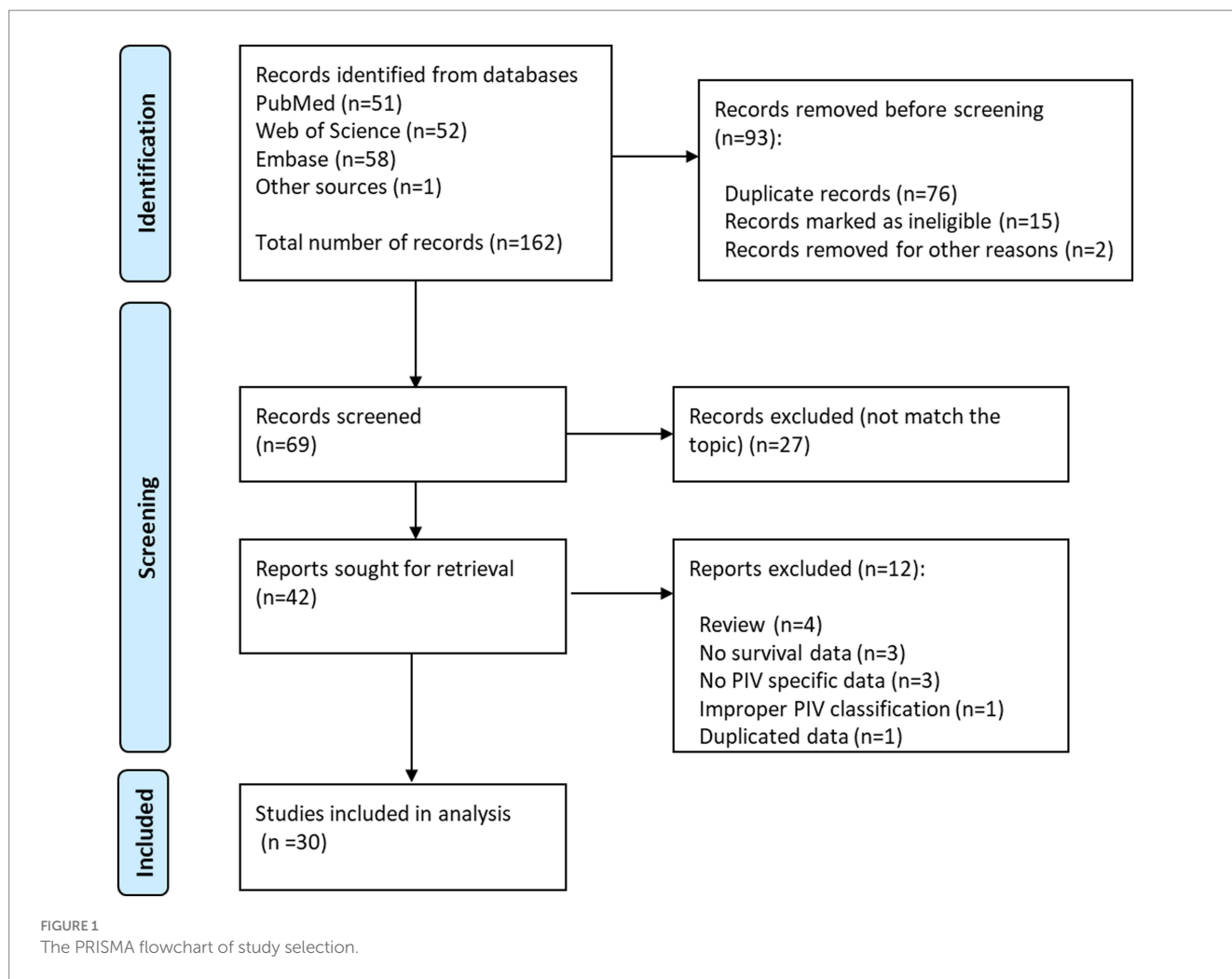
2.5. Statistical analysis

Stata 12.0 statistical software was used to perform all the statistical analyses. Hazard ratios (HRs) with 95% confidence intervals (CIs) reported from multivariate analyses were preferentially used to incorporate survival outcomes. Otherwise, univariate assessments were the sources of effect sizes. In addition, for studies whose survival data were not directly available, corresponding HRs with 95% CIs were extracted from the survival curves through the methods reported by Tierney et al. (22). In the present study, I^2 statistics were utilized to evaluate inter-study heterogeneity, and a random-effects model was always performed, which accounts for variance across included studies (23, 24). Subgroup analyses and meta-regression analyses were applied to explore the sources of heterogeneity. Leave-one-out sensitivity analyses were utilized to assess the reliability of pooled results. Possible publication bias was evaluated using Begg's test. If there was a significant publication bias, a trim and fill analysis was employed to assess the impact of it on the pooled result. p values <0.05 were considered statistically significant.

3. Results

3.1. Study characteristics

The initial search of online databases yielded a total of 162 records. By removing duplicated studies, and reviewing titles, abstracts and



full-text studies, 30 studies (11–16, 25–48) with 32 cohorts were ultimately incorporated in our meta-analysis (Figure 1). The main characteristics of these studies were shown in Tables 1, 2. In total, 8,799 participants from China, Germany, Italy, Japan, Slovenia, Spain and Turkey were enrolled in the present study. These studies were published from 2020 to 2023, with a sample size ranging from 49 to 1,312. The most common cancer type was gastrointestinal cancer, followed by breast cancer and lung cancer. As regards blood parameters, the period of blood collection before treatment ranged from 1 day to 1 month, and most of the included studies did not mention the exclusion of diseases affecting hematological parameters. The cut-off value of PIV ranged from 164.6 to 600.0. In terms of main primary treatments, surgery was performed in 8 cohorts, chemo/radiotherapy was performed in 8 cohorts and immunotherapy contained treatment was performed in 7 cohorts. The median follow-up time ranged from 9.5 to 78.4 months. The literature quality of these studies was good with a median score of 8 (range: 7–9, Supplementary Table S1).

3.2. Relationship between the PIV and OS

A total of 8,462 patients from 27 cohorts were included in the pooled analysis of OS. The pooled result revealed that higher PIV

predicted poorer OS (HR=2.07; 95%CI:1.77–2.41; $I^2 = 73.0\%$; Figure 2). Furthermore, subgroup analyses based on country, study center, sample size, cancer type, selection method, cut-off value, treatment strategy, tumor stage, analysis method and follow-up time were performed. As shown in Table 3 and Supplementary Figure S1, the pooled outcomes from all subgroup analyses consistently revealed that patients in the high PIV group had a significantly worse OS compared to those in the low PIV group. In addition, a meta-regression analysis based on these variables was performed to investigate the source of heterogeneity. As shown in Supplementary Table S2, none of these covariates had a significant effect on the hazard ratios of OS (all p values>0.05).

3.3. Relationship between the PIV and PFS

In total, 25 cohorts involving 5,391 patients reported on PFS. The pooled HR was 1.83 (95%CI: 1.37–2.45; $I^2 = 98.2\%$), suggesting that higher PIV was associated with a significantly worse PFS (Figure 3). Similarly, subgroup analyses based on above variables were performed due to the significant heterogeneity existed. We found that in almost all subgroups analyses, patients in the high PIV group has an inferior PFS, except for the pooled results from melanoma (HR= 1.13; 95% CI: 0.86–1.47) and univariate analysis (HR= 1.53;

TABLE 1 Basic information of included studies.

References	Country	Study design	Study interval	Cancer type	Sample size	Age, years (Median/ Mean)	Sex (Male/ Female)	Selection method	Cut-off value	The period of blood collection	Exclusion of diseases affecting blood parameters
Baba et al. (14) (training)	Japan	S;R	2005–2020	Esophageal cancer	433	66.5 ± 8.5	376/57	ROC	164.6	Within 1 week before treatment	NA
Baba et al. (14) (validation)	Japan	S; R	2005–2020	Esophageal cancer	433	66.3 ± 8.9	384/49	ROC	164.6	Within 1 week before treatment	NA
Chen et al. (15)	China	S; R	2014–2019	Lung cancer	94	48 (Range, 18–76)	55/39	Median	364	Within 3 weeks before treatment	Yes
Corti et al. (16)	Italy	M; R	2014–2020	Colorectal cancer	163	NA	90/73	MSR	492	Within 1 week before treatment	NA
Demir et al. (25)	Turkey	S; R	2006–2020	Breast cancer	243	36 (Range, 21–40)	0/243	Median	301	Before treatment	Yes
Efil et al. (26)	Turkey	S; R	2008–2016	Colorectal cancer	304	62 (Range, 19–91)	182/122	Median	491	Within 2 weeks before treatment	NA
Fucà et al. (13)	Italy	M; R	2008–2018	Colorectal cancer	438	62 (IQR, 53–68)	275/163	MSR	380	Before treatment	NA
Fucà et al. (27)	Italy	S; R	2010–2020	Melanoma	228	NA	142/86	MSR	600	Before treatment	NA
Gambichler et al. (28)	Germany	S; R	NA	Merkel cell carcinoma	49	77 (Range, 51–95)	25/24	ROC	372	Within 1 week at diagnosis	NA
Güven et al. (29)	Turkey	S; R	2016–2020	Multiple cancers	120	61 (IQR, 54–67)	86/34	Median	513.4	Before treatment	NA
Güven et al. (30)	Turkey	S; R	2005–2020	Head and neck cell carcinoma	199	59 (IQR, 53–67)	180/19	ROC	404	Within 1 week before treatment	NA
Karadağ et al. (11)	Turkey	S; R	2013–2021	Hepatocellular carcinoma	120	64 (IQR, 55–72)	101/19	Median	286.15	Before treatment	Yes
Kucuk et al. (31)	Turkey	M; R	2010–2021	Lung cancer	89	61 (Range, 37–79)	75/14	ROC	417	Within 1 week before treatment	Yes
Liang et al. (32)	China	S; R	2013–2016	Colorectal cancer	753	NA	473/280	ROC	231	Within 1 week before treatment	NA
Ligorio et al. (33)	Italy	S; R	2014–2020	Breast cancer	57	53 (Range, 26–78)	0/57	Median	285	Before treatment	Yes
Lin et al. (19)	China	S; R	2010–2012	Breast cancer	1,312	48 (IQR, 41–57)	0/1312	MSR	310.2	Within 1 week before treatment	Yes
Mesti et al. (34)	Slovenia	S; R	2018–2020	Melanoma	129	66.2 (Range, 30.1–84.5)	84/53	Median	390	Before treatment	Yes
Pérez-Martelo et al. (35)	Spain	S; R	2015–2018	Colorectal cancer	130	68.8 (Range, 26–88)	96/34	MSR	380	Within 1 month before treatment	NA
Provenzano et al. (36)	Italy	S; R	2008–2020	Breast cancer	78	NA	0/78	Median	228	Within 1 week before treatment	NA

(Continued)

TABLE 1 (Continued)

References	Country	Study design	Study interval	Cancer type	Sample size	Age, years (Median/ Mean)	Sex (Male/ Female)	Selection method	Cut-off value	The period of blood collection	Exclusion of diseases affecting blood parameters
Qi et al. (37)	China	S;P	2019–2022	Esophageal Cancer	51	62 (Range, 39–75)	44/7	ROC	232.8	Before treatment	NA
Sahin et al. (38)	Turkey	S; R	2008–2019	Breast cancer	743	48.0 (Range, 22.0–83.5)	0/743	ROC	306.4	Within 2 weeks before treatment	Yes
Sato et al. (39)	Japan	S; R	2013–2020	Colorectal cancer	86	70 (Range, 37–93)	50/36	ROC	209	Before treatment	Yes
Sato et al. (40)	Japan	S; R	2000–2019	Colorectal cancer	758	NA	466/292	ROC	376	Before treatment	Yes
Susok et al. (41)	Germany	S; R	NA	Melanoma	62	67 (Range, 18–85)	40/22	ROC	455	Before treatment	NA
Topkan et al. (42)	Turkey	S; R	2007–2020	Glioblastoma Multiform	204	58 (Range, 21–80)	135/69	ROC	385	The first day of treatment	Yes
Topkan et al. (43)	Turkey	S; R	2007–2020	Pancreatic adenocarcinoma	178	57 (Range, 26–79)	137/41	ROC	464	The first day of treatment	Yes
Wang et al. (44)	China	S; R	2010–2018	Gastric cancer	89	59 (Range, 32–78)	69/20	ROC	218.7	Before treatment	NA
Yazgan et al. (45)	Turkey	S; R	2010–2021	Prostate cancer	114	64 (IQR, 60–70)	114/0	Median	366	Within 1 month before treatment	NA
Yeh et al. (46)	China	S; R	2005–2017	Oral cavity cell carcinoma	853	53.5	780/73	ROC	268	Before treatment	NA
Yekedüz et al. (47)	Turkey	M; R	NA	Renal cell carcinoma	152	60 (IQR, 54–67)	117/35	MSR	372	Within 1 week before treatment	NA
Zeng et al. (48) (training)	China	M; R	2018–2020	Lung cancer	53	NA	34/19	Median	581.95	Before treatment	NA
Zeng et al. (48) (validation)	China	M; R	2015–2021	Lung cancer	84	NA	75/9	Median	581.95	Before treatment	NA

Retro, retrospective study; Pro, prospective study; M, multiple center; S, single center; ROC, receiver operator characteristic curve; MSR, maximally selected rank; IQR, interquartile range; NA, not available.

TABLE 2 Survival information of included studies.

References	Sample	Treatment strategy	Tumor stage	Survival outcomes	Multivariate analysis	Median follow-up time, months
Baba et al. (14) (training)	433 (225:208)	Surgery	Mixed	OS	No	NA
Baba et al. (14) (validation)	433 (210:223)	Surgery	Mixed	OS	Yes	58.8
Chen et al. (15)	94 (47:47)	First-line ALK inhibitor	Mixed	OS;PFS	Yes; Yes	47.0 (IQR, 38.5–55.5)
Corti et al. (16)	163 (63:100)	Immunotherapy	Metastatic	OS;PFS	Yes; Yes	31
Demir et al. (25)	243 (122:121)	Surgery	Mixed	OS	No	NA
Efil et al. (26)	304 (152:152)	Surgery	Non-metastatic	OS; DFS	Yes; Yes	NA
Fucà et al. (13)	438 (230:208)	Chemotherapy combined with target therapy	Metastatic	OS; PFS	Yes; Yes	38.4 (IQR, 27.4–50.9)
Fucà et al. (27)	228 (51:177)	Immunotherapy combined with target therapy	Metastatic	OS; PFS	Yes; Yes	35.3
Gambichler et al. (28)	49 (31:18)	Mixed therapy	Non-metastatic	RFS	No	NA
Güven et al. (29)	120 (60:60)	Immunotherapy	Metastatic	OS; PFS	Yes; Yes	9.62
Güven et al. (30)	199 (101:98)	Chemoradiotherapy	Non-metastatic	OS;DFS	Yes; Yes	71.59
Karadağ et al. (11)	120 (60:60)	Mixed therapy	Mixed	OS	Yes	9.5 (IQR:3–23)
Kucuk et al. (31)	89 (57:36)	Chemoradiotherapy	Non-metastatic	OS; PFS	Yes; Yes	19.7 (Range, 4.0–88.1)
Liang et al. (32)	753 (347:379)	Surgery	Mixed	OS	Yes	NA
Ligorio et al. (33)	57 (29:28)	Taxane/trastuzumab/pertuzumab	Metastatic	OS; PFS	Yes; Yes	36.6
Lin et al. (19)	1,312 (152:1160)	Surgery	Non-metastatic	OS	Yes	78.4 (IQR, 53.1–88)
Mesti et al. (34)	129 (65:64)	Immunotherapy	Metastatic	OS; PFS	No; Yes	22.5
Pérez-Martelo et al. (35)	130 (70:60)	Chemotherapy	metastatic	OS; PFS	Yes; Yes	NA
Provenzano et al. (36)	78 (39:39)	Chemotherapy	metastatic	OS; PFS	Yes; Yes	47.4
Qi et al. (37)	51 (NA:NA)	Neoadjuvant chemoradiotherapy and pembrolizumab	Mixed	PFS	No	20
Sahin et al. (38)	743 (246:351)	Neoadjuvant chemotherapy	Non-metastatic	OS;DFS	No; No	67.5 (Range, 10.5–194.4)
Sato et al. (39)	86 (63:23)	Surgery	Non-metastatic	RFS	Yes	35 (Range, 1–104)
Sato et al. (40)	758 (190:568)	Surgery	Non-metastatic	OS; RFS	Yes; Yes	63.5
Susok et al. (41)	62 (NA:NA)	Immunotherapy	Mixed	PFS	No	NA
Topkan et al. (42)	204 (129:75)	Radiotherapy and temozolomide	Metastatic	OS; PFS	No; No	17.6 (Range, 2.4–108.3)
Topkan et al. (43)	178 (109:69)	Concurrent chemoradiotherapy	Non-metastatic	OS; PFS	Yes; Yes	17.9 (Range, 3.2–104.0)
Wang et al. (44)	89 (34:55)	Surgery	Non-metastatic	DFS	No	29.1 (Range, 4.1–115.8)
Yazgan et al. (45)	114 (57:57)	Androgen receptor-signaling inhibitors	Mixed	OS	Yes	34.6
Yeh et al. (46)	853 (366:487)	Surgery	Mixed	OS;DFS	Yes; Yes	NA
Yekedüz et al. (47)	152 (75:77)	Immunotherapy	Metastatic	OS; PFS	Yes; Yes	29.1
Zeng et al. (48) (training)	53 (27:26)	Immunotherapy and chemotherapy	Mixed	OS; PFS	Yes; Yes	NA
Zeng et al. (48) (validation)	84 (28:56)	Immunotherapy and chemotherapy	Mixed	OS; PFS	Yes; Yes	14

OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival; IQR, interquartile range; NA, not available.

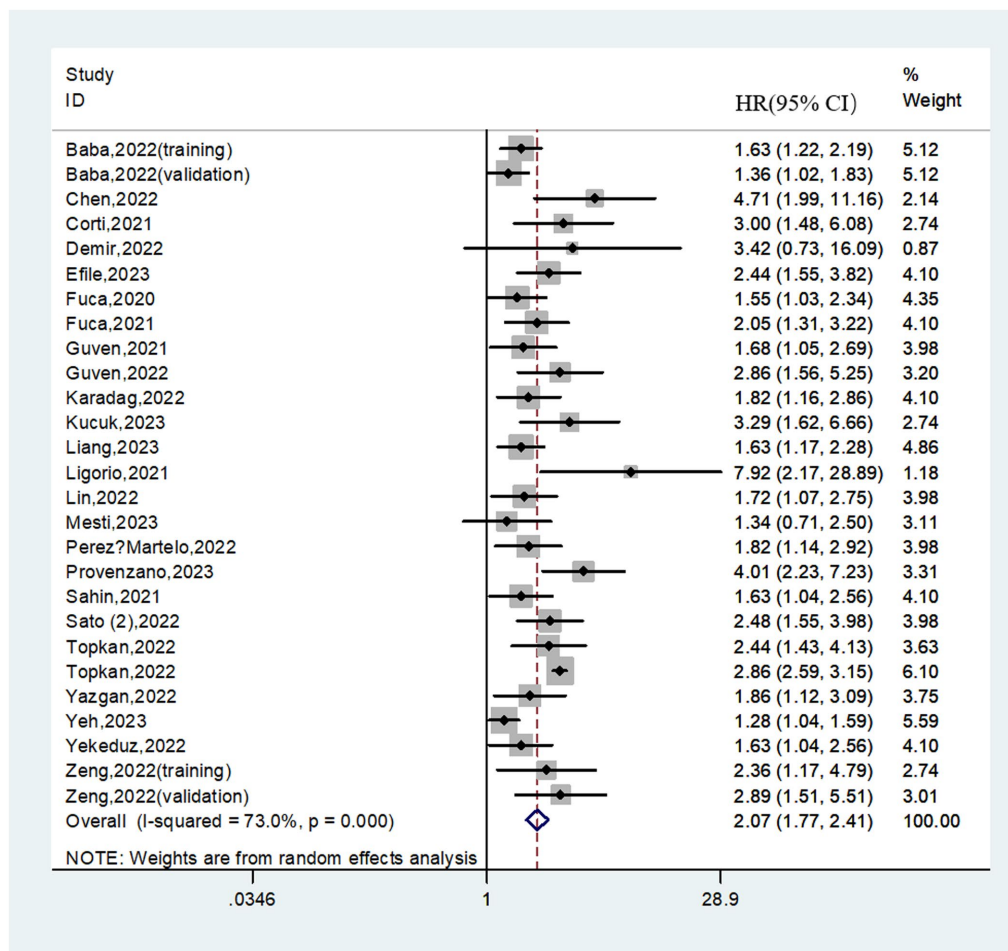


FIGURE 2 Forest plot assessing the relationship between the PIV and OS.

95% CI: 0.99–2.35) (Table 4 and Supplementary Figure S2). Additionally, meta-regression analysis revealed that none of these factors was the source of heterogeneity (all *p* values>0.05; Supplementary Table S2).

3.4. Sensitivity analyses and publication bias

Sensitivity analyses were conducted to assess the robustness of the pooled OS and PFS. After omitting any individual study, pooled HRs with 95% CIs for both OS and DFS were not significantly altered (Supplementary Figure S3).

The Begg’s funnel plots were applied to evaluate the potential publication bias. As shown in Supplementary Figure S4, the funnel plot for PFS was bilaterally symmetric with a Begg’s *p* value of 0.691, indicating that there was no significant publication bias for PFS. While for OS, the Begg’s funnel plot was asymmetric with the *p* value <0.0001, which suggested a high risk of publication bias for this outcome. Trim-and-fill analysis was therefore applied, supplementing a total of 8 unpublished cohorts to balance the funnel plot. Finally, PIV was still associated with inferior OS

(HR = 1.82; 95%CI: 1.56–2.13), indicating the robustness of the pooled result.

4. Discussion

Cancer-related inflammation is prevalent in patients with malignant diseases, which has been confirmed to promote cancer progression and advancement (6). Traditionally, host inflammation status can be detected through several blood biomarkers, such as neutrophil count, platelet count, and lymphocyte count. Additionally, evidence from numerous studies has demonstrated that their ratios can be applied to predict patient’s short-term and long-term outcomes, especially in cancer patients (7, 8). Importantly, these markers have the natural advantage of being non-invasive, objective, and cost-effective, which provides great potential for their wide clinical applications.

In recent years, a new biomarker, the pan-immune-inflammation value, which consists of serum neutrophil, platelet, monocyte and lymphocyte, has attracted the attention of clinicians due to its promising prognostic significance in several malignancies (12, 30, 39). A recent meta-analysis by Guven et al. (17) has initially demonstrated that high PIV was associated with decreased survival outcomes in

TABLE 3 Subgroup analyses for OS of PIV-high patients vs. PIV-low patients.

Subgroup	Cohorts	Patients	Pooled analysis		I square (%)
			HR	95%CI	
All patients	27	8,462	2.07	1.77–2.41	73.0
Country					
Asian	20	7,239	2.03	1.69–2.43	76.8
Non-Asian	7	1,043	2.23	1.60–3.12	57.5
Study center					
Single center	21	7,483	2.04	1.70–2.44	77.6
Multicenter	6	1,159	2.14	1.63–2.82	26.6
Sample size					
<150	11	1,068	2.34	1.83–3.00	44.8
>150	16	7,574	1.93	1.58–2.36	80.8
Cancer type					
Gastrointestinal	10	3,710	1.96	1.55–2.48	80.3
Breast	5	2,433	2.61	1.56–4.38	63.2
Lung	4	320	3.09	2.15–4.42	0.0
Melanoma	2	357	1.76	1.17–2.63	16.0
Others	6	1,642	1.76	1.37–2.28	51.2
Selection method					
ROC curve	10	4,643	1.97	1.50–2.59	87.5
Median	11	1,396	2.37	1.85–3.03	40.0
MSR	6	2,423	1.81	1.49–2.20	0.0
Cut-off value					
<350	10	5,025	1.75	1.42–2.15	58.6
>350	17	3,437	2.25	1.93–2.62	44.8
Treatment strategy					
Surgery	8	5,089	1.66	1.39–1.98	45.1
Chemo/radiotherapy	8	2,059	2.37	1.87–3.01	61.0
Immunotherapy contained	7	929	1.95	1.58–2.39	0.0
Others	4	385	2.71	1.56–4.73	61.7
Tumor stage					
Non-metastatic	7	3,583	2.43	1.99–2.96	41.5
Mixed	10	3,180	1.73	1.43–2.09	47.3
Metastatic	10	1,699	2.06	1.64–2.59	43.9
Analysis method					
Univariate	5	1,752	1.72	1.40–2.12	0.0
Multivariate	22	6,710	2.14	1.79–2.55	75.9
Follow-up					
<30 months	8	1,076	2.16	1.69–2.76	61.2
>30 months	12	4,617	2.20	1.74–2.77	57.9
NA	7	2,769	1.69	1.39–2.41	38.4

cancer patients. Nevertheless, this meta-analysis included only 15 studies (including an abstract) and several common cancer types (such as pancreatic cancer, hepatic cancer and prostate cancer) were not available, which made the prognostic value of PIV in cancer patients still inconclusive. To clarify this issue accurately, an updated

meta-analysis including 30 studies with 8,799 cancer patients was performed. Through our quantitatively analyses, we convinced that an elevated PIV markedly predicted poorer OS (HR = 2.07; 95%CI: 1.77–2.41) and PFS (HR = 1.83; 95%CI: 1.37–2.45) in cancer patients. Additionally, benefiting from the inclusion of sufficient studies,

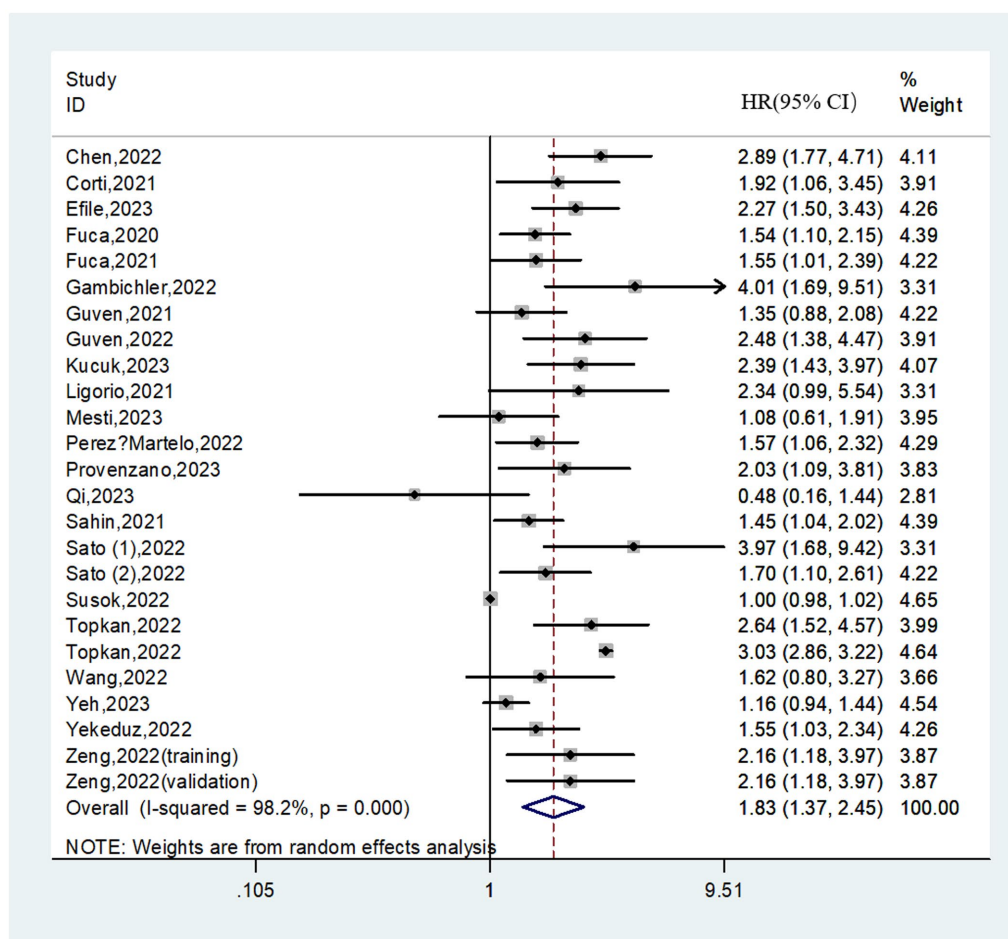


FIGURE 3 Forest plot accessing the relationship between the PIV and PFS.

we were able to perform detailed subgroup analyses, as well as sensitivity and publication bias analyses. It can be seen that the PIV achieved reliable performance in predicting prognosis. Therefore, the PIV may be a valuable and effective inflammatory index to evaluate the oncological outcomes of patients with malignancies.

Dysregulation of inflammatory and immune cells in the tumor microenvironment has been identified as being involved in the tumor progression (49–51). Simultaneously, a higher PIV may result from higher neutrophils, monocytes, and platelets and/or lower lymphocytes. Although the detailed mechanisms of the PIV’s prognostic value in malignancies are unclear, they can be explained as follows: First, neutrophils, as the most common innate immune cells, have been reported to promote tumor invasion and metastasis by secreting VEGFA, MMPs, and other chemokines such as IL-6 and TGF-β (52, 53). At the same time, elevated neutrophils can also cause T cell activation disorders by largely releasing nitric oxide, arginase, and reactive oxygen species, ultimately inhibiting the body’s killing effect on cancer cells (54). Second, monocytes, especially those differentiated into tumor-associated macrophages (TAMs), can induce apoptosis of T cells with antitumor functions (55). In addition, TAM density has been shown to affect tumor tissue angiogenesis by stimulating the production and secretion of pro-angiogenic factors (56, 57). Third, platelets, are reported to induce

epithelial–mesenchymal transition and angiogenesis by secreting TGF-β, VEGF and FGF. Moreover, platelets are also able to recruit neutrophils and monocytes, thereby promoting the distant metastasis of tumor cells. Finally, lymphocytes, especially cytotoxic T lymphocytes, play an essential role in cancer immune surveillance and defense (58). It has been reported that high lymphocyte levels in the tumor microenvironment are beneficial for inducing lysis and apoptosis of cancer cells, thereby inhibiting cancer cell proliferation and metastasis (59). On the contrary, lymphopenia has been shown to be associated with a poor prognosis in cancer patients (60).

Notably, the pooled outcomes from subgroup analyses demonstrated that the prognostic value of the PIV for both OS and PFS was consistent in treatment strategies, such as surgery (HR = 1.66 and 1.80), chemo/radiotherapy (HR = 2.37 and 2.06), immunotherapy (HR = 1.95 and 1.40). Given that patients with malignancies would receive one or more anti-tumor treatment strategies, these results showed that PIV could provide prognosis prediction for malignant patients receiving different treatments, especially for those receiving chemo/radiotherapy. In addition, PIV has been shown to have considerable prognostic value across different tumor species, particularly in lung cancer (HR = 3.09 and 2.43). Moreover, the prognostic value of PIV was not affected by the country of publication,

TABLE 4 Subgroup analyses for PFS of PIV-high patients vs. PIV-low patients.

Subgroup	Cohorts	Patients	Pooled analysis		I square (%)
			HR	95% CI	
All patients	25	5,391	1.83	1.37–2.45	98.2
Country					
Asian	16	4,057	1.93	1.49–2.50	87.8
Non-Asian	9	1,334	1.59	1.20–2.12	79.2
Study center					
Single center	19	4,412	1.81	1.28–2.55	98.6
Multicenter	6	979	1.80	1.48–2.18	0.0
Sample size					
<150	14	1,171	1.80	1.33–2.43	83.7
>150	11	4,220	1.85	1.36–2.50	91.5
Cancer type					
Gastrointestinal	9	2,197	1.89	1.37–2.60	83.3
Breast	3	878	1.63	1.23–2.15	0.0
Lung	4	320	2.43	1.85–3.19	0.0
Melanoma	5	419	1.13	0.86–1.47	50.8
Others	6	1,577	1.81	1.28–2.55	71.3
Selection method					
ROC curve	12	3,361	1.86	1.19–2.91	99.1
Median	8	919	1.93	1.53–2.44	31.9
MSR	5	1,111	1.58	1.32–1.90	0.0
Cut-off value					
<350	7	1,957	1.56	1.12–2.16	59.7
>350	18	3,434	1.92	1.35–2.74	98.7
Treatment strategy					
Surgery	5	2,090	1.80	1.22–2.64	72.4
Chemo/radiotherapy	8	2,059	2.06	1.53–2.78	84.2
Immunotherapy contained	9	1,042	1.40	1.07–1.82	72.3
Others	3	200	2.96	2.02–4.33	0.0
Tumor stage					
Non-metastatic	9	2,495	2.29	1.76–3.00	74.0
Mixed	6	1,197	1.46	1.04–2.04	85.2
Metastatic	10	1,699	1.61	1.39–1.87	0.0
Analysis method					
Univariate	6	1,198	1.53	0.99–2.35	83.4
Multivariate	19	4,193	1.91	1.52–2.39	86.5
Follow-up					
<30 months	9	1,096	1.75	1.24–2.49	83.7
>30 months	10	2,844	1.86	1.56–2.22	21.9
NA	6	1,451	1.59	1.16–2.20	86.8

cut-off value, and tumor stage, further confirming the clinical universality and efficacy of PIV in cancer patients.

This meta-analysis had several limitations must be acknowledged. First, all of the included studies except one by Qi et al. (37) were designed to be retrospective, which may increase the risk of selection bias. Second, the heterogeneities of pooled outcomes for both OS and

PFS were remarkable, even though the subgroup analyses and sensitivity analyses showed consistent results, we failed to find the sources of heterogeneity. Third, significant inconsistencies in the measurement of blood parameters in the included studies, including but not limited to factors such as measurement time, may have contributed to the large variability in the cut-off values of PIV, and

may also have had some impact on the confidence of our pooled results. Finally, the cut-off values of PIV varied widely due to various factors such as disease type, population differences, sample size, and detection method, which somewhat limits the clinical use of PIV.

5. Conclusion

In conclusion, the present meta-analysis demonstrates an association between elevated pre-treatment PIV and poor survival outcomes in cancer patients. PIV has the potential to be a noninvasive and effective prognostic biomarker for cancer 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.

Author contributions

YH-J: Funding acquisition, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. RS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review & editing, Visualization. XJ-Q: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

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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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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2023.1259929/full#supplementary-material>

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