Original Article

Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as biomarkers to prognosticate survival in advanced gastric cancer patients in the era of immunotherapy: a systematic review and meta-analysis

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Background: Gastric cancer (GC) remains an important global health concern with limited treatment options for advanced cases. Immunotherapy has shown promising results, but identifying predictive biomarkers for treatment efficacy is challenging. Novel inflammatory markers, such as the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), derived from complete blood count measurements, have gained attention as potential prognostic indicators. This systematic review and meta-analysis investigates the roles of the PLR and NLR as predictors of overall survival (OS) and progression-free survival (PFS) in advanced GC and gastroesophageal junction cancer (GEJC) patients treated with immunotherapy.

Methods: A comprehensive search of the literature was conducted through PubMed, Embase, and Cochrane Library to identify relevant studies. A total of 16 studies involving NLR and 8 studies involving PLR were included. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to assess the association between high biomarker values and poor OS and PFS. Subgroup analyses were performed to explore potential sources of heterogeneity. Poor OS, PFS were defined by each study as statistically significant shorter survival.

Results: A high NLR was significantly associated with worse OS (HR: 2.11; 95% CI: 1.70–2.62) and PFS (HR: 1.76; 95% CI: 1.43–2.17). High PLR was also significantly associated with poorer OS (HR: 1.77; 95% CI: 1.44–2.17) and PFS (HR: 1.61; 95% CI: 1.33–1.96). Subgroup analyses and sensitivity analyses supported the robustness of these findings. Publication bias was noted in NLR analysis for OS but not for PFS. PLR analysis showed low publication bias.

Conclusions: Elevated NLR and PLR are associated with unfavorable OS and PFS outcomes in advanced GC/GEJC patients on immunotherapy. These findings imply the utility of these easily accessible biomarkers in prognostic assessment. However, standardized cutoff values and further research on interactions with the tumor microenvironment and comorbidities are needed. Additional prospective studies are warranted to validate these findings for both biomarkers.

Keywords: Advanced gastric cancer (advanced GC); immunotherapy; platelet-to-lymphocyte ratio (PLR); neutrophil-to-lymphocyte ratio (NLR); meta-analysis

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Introduction

Gastric cancer (GC) remains the fourth most commonly diagnosed malignancy and the fourth leading cause of cancer-related death, with approximately 990 thousand diagnoses and 800 thousand deaths per year according to worldwide estimates (1,2). Approximately two-thirds of newly diagnosed cases are locally advanced, metastatic, or unresectable, and the 5-year overall survival (OS) for these patients is short (3).

Chemotherapy is the long-standing standard first-line treatment for advanced GC; however, treatment options for these patients have evolved in recent years. The CheckMate 649 trial found that nivolumab added to chemotherapy was associated with increased OS in human epidermal growth factor receptor 2 (HER2)-negative disease compared to chemotherapy alone (4). Additionally, the KEYNOTE-811 phase 3 study demonstrated that pembrolizumab added to chemotherapy and trastuzumab was associated with improvement in the objective response rate in the first-line setting for HER2-positive advanced GC (5). As a result, nivolumab and pembrolizumab were listed as first-line treatment options for HER2-negative and HER2-positive advanced GC, respectively, in the 2022 National Comprehensive Cancer Network (NCCN) guidelines (6).

Treatment options for advanced GC in later lines diverge according to guidelines. The ATTRACTION-2 trial demonstrated that nivolumab was associated with improved OS in advanced GC patients who were chemo-refractory to first- and second-line treatments (7). This prompted the incorporation of nivolumab as a third-line treatment option in the Asian setting for patients who underwent no previous treatment with immune checkpoint inhibitors (ICIs) (8-10). Currently, both NCCN and European Society for Medical Oncology (ESMO) guidelines for advanced GC do not recommend ICI use as third-line treatment (6,11).

Despite the increasing use of immunotherapy in advanced GC, relevant questions remain concerning the limited efficacy of drugs in a subset of patients, drug-related toxicity, and cost-associated considerations. While the combined predictive score has been widely adopted to define eligibility for ICI therapy, some studies suggest that the treatment efficacy of immunotherapy agents may be irrespective of the patient's programmed cell death protein ligand 1 (PD-L1) status (12,13). Moreover, some data reported poor survival outcomes in subsets of advanced GC patients who were eligible for ICI treatment (14). Taken together, these factors prompt a thorough search for biomarkers that can predict ICI efficacy.

Epstein-Barr virus status, tumor mutation burden, and microsatellite instability have been described as biomarkers of ICI effectiveness (15-17). Nevertheless, the diversity of epidemiologic prevalence, substantial associated costs, and invasiveness of certain tests hinder the universal implementation of these biomarkers for GC patients (18-21). New, easily available, and cost-effective biomarkers are needed to predict outcomes in immune checkpoint blockade in advanced GC.

In recent years, novel inflammatory markers derived from complete blood count measurements have gained considerable attention for their potential as indicators of disease severity and prognosis. The platelet-to-lymphocyte ratio (PLR) is an emerging inflammatory marker derived from complete blood count measures. It has been studied as a prognostic, diagnostic, and disease severity marker in diverse conditions, such as chronic obstructive pulmonary

Highlight box

Key findings

- There is potential for the use of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic biomarkers for advanced gastric cancer (GC) patients receiving immunotherapy, with elevated levels associated with poorer survival outcomes.

What is known and what is new?

- Immunotherapy is increasingly used for advanced GC, but predicting treatment outcomes remains challenging.
- This study presents evidence supporting the use of novel inflammatory markers, NLR and PLR, as potential prognostic indicators for advanced GC patients undergoing immunotherapy, shedding light on their predictive value.

What is the implication, and what should change now?

- Incorporating NLR and PLR assessments into routine clinical practice for advanced GC patients receiving immunotherapy could enhance prognostic accuracy and guide treatment decisions.

disease (COPD), coronavirus disease (COVID), and ankylosing spondylitis (22-24). In oncology, the hypothesis of higher PLR values correlating with worse survival outcomes was investigated in several malignancies with conflicting results (25-28).

Similarly, the neutrophil-to-lymphocyte ratio (NLR) is another novel inflammatory measure that is also obtainable from complete blood count measurements. Several studies have demonstrated its use as a reliable predictor of severity for diverse conditions, including sepsis, COVID 2019 (COVID-19), and acute pancreatitis (24,29,30). In oncology, the NLR has been studied in numerous malignancies as a diagnostic and prognostic tool (31-33). In recent years, several studies have explored the potential of NLR as a prognostic biomarker for advanced GC treated with immunotherapy, and the results vary. Two meta-analyses have been published on the matter, with partly divergent findings. Since their inception, new studies have emerged. Our primary aim in this study is to conduct a systematic review and meta-analysis to comprehensively assess the predictive roles of novel inflammatory markers—PLR and NLR—as indicators of OS and progression-free survival (PFS) in patients with advanced GC and gastroesophageal junction cancer (GEJC) undergoing immunotherapy. Despite evolving treatment options and the increasing utilization of immunotherapy in these patients, our study intends to address the persistent need for reliable biomarkers to predict treatment efficacy and outcomes in this specific therapeutic landscape. For NLR, this will be an updated study, while for PLR, this study will mark the inaugural meta-analysis in this population. We present this article in accordance with the PRISMA reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-808/rc).

Methods

We conducted a systematic search of eligible articles published up to 3 April 2023 in the following databases: Cochrane Library, Embase, and PubMed. The designed search strategy consisted of words, characters, and Boolean operators as follows: ("plr" OR "nlr" OR "platelet" OR "neutrophil") AND ("gastric" OR "gastrointestinal") AND ("immunotherapy" OR "PD" OR "checkpoint" OR "nivolumab" OR "pembrolizumab" OR "ipilimumab OR "atezolizumab" OR "avelumab" OR "durvalumab"). Additional filters were applied to Embase to narrow down the results to gastric neoplasms. A list of articles was generated from each database and imported into Rayyan software, where duplicates were removed manually (34). The "Blind Mode" was activated, and two independent investigators screened studies for inclusion. Conflicting decisions were resolved by a third reviewer.

PICOS strategy used for this study is as follows: (I) population: patients with advanced GC/GEJC treated with immunotherapy; (II) intervention: patients with biomarker value equal or higher to cut-off; (III) control: patients with biomarker value less than cut-off; (IV) outcome: OS and PFS; and (V) study design: prospective and retrospective studies comparing low biomarker group *vs.* high biomarker. This meta-analysis was registered in the PROSPERO network with the following ID: CRD42023460928.

Selection criteria

Inclusion criteria were as follows: (I) the population encompassed advanced GC/GEJC patients who received immunotherapy as their treatment regimen, irrespective of treatment line; (II) examined the prognostic significance of baseline NLR or PLR in relation to OS or PFS; (III) presented hazard ratio (HR) along with its corresponding 95% confidence interval (CI); (IV) study from any country, written in English language; and (V) full text articles or conference abstracts. Exclusion criteria were as follows: (I) studies not providing data on the targeted population; (II) comprehensive studies encompassing other cancer types and not providing distinct datasets for advanced GC/GEJC subgroups; (III) studies featuring intersecting populations and data regarding the same biomarker were subject to analysis, with the article containing the smaller patient cohort being excluded; and (IV) expert opinions, reviews, nonhuman studies or case reports.

Data extraction

Two independent reviewers carefully extracted data as follows: first author surname, year of publication, country of origin, NLR cutoff value, PLR cutoff value, methods of determining cutoff value, number of patients enrolled, center design, median follow-up, median age of patients and ICI type. Subsequently, the data were imported into Microsoft Excel (2019 version). Inconsistencies were subsequently resolved by a third reviewer. The evaluation of quality was conducted employing the Newcastle-Ottawa scale (NOS), wherein specific ratings were assigned to each study included. Studies attaining scores of 7 or greater were

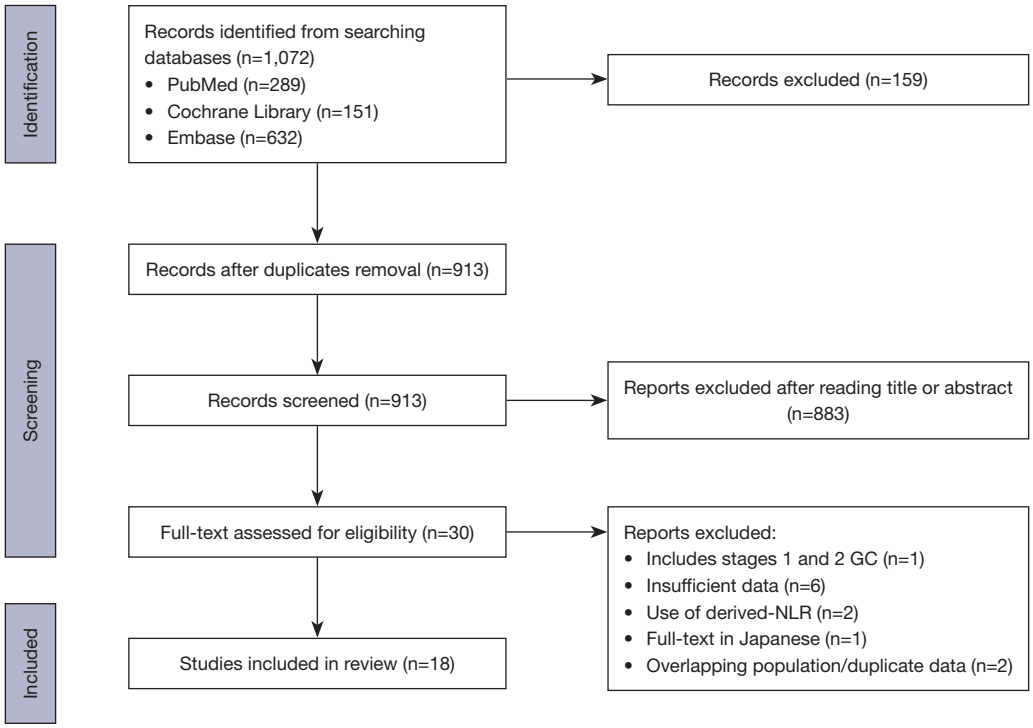

Figure 1 PRISMA flow chart detailing the selection process. GC, gastric cancer; NLR, neutrophil-to-lymphocyte ratio.

categorized as exhibiting high quality.

Statistical analysis

HRs and their corresponding 95% CIs were pooled employing the generic inverse variance and random-effects model. Heterogeneity was assessed using the Higgins I^2 model, wherein values of I^2 exceeding 50% represented substantial heterogeneity. Subgroup analyses were also conducted in this manner. Publication bias was assessed using visual inspection of funnel plots and their triangular region. All statistical tests were two-sided and were considered significant if $P<0.05$. All analyses were undertaken utilizing Review Manager version 5.4.

Results

Selection process

A total of 1,072 articles were obtained from the three databases. Following the elimination of duplicate entries, 913 articles underwent initial screening based on their titles and abstracts, of which 883 were found to be unrelated to the subject matter under review. Subsequently, a detailed examination of the full texts of the remaining 30 studies was carried out, leading to the exclusion of 12 studies in accordance with our predefined exclusion criteria. Ultimately, this systematic review included 18 studies (12,35-51). Our selection process is summarized in *Figure 1*.

Study characteristics

Predominantly conducted within Asia, the studies were distributed as follows: 9 studies in China, 7 in Japan, and 1 in Korea. The sole non-Asian study was conducted by Formica *et al.* (35) This collection of studies spans the years between 2018 and 2023. Sixteen studies investigated the prognostic value of NLR, while 8 investigated PLR. Among the articles regarding NLR, 14 included NLR prognostic values for OS and 11 for PFS. Among the studies investigating PLR, 7 included reporting of the prognostic values for OS and 6 for PFS. A diverse range of cutoff values was adopted by the included articles, varying from 2.5 to 5.0 for NLR and from 139.41 to 267.00 for PLR. Detailed methods for establishing cutoffs, as well as general information, are outlined in *Table 1*. Notably, Qu *et al.* (50) performed distinct analyses for patients receiving immunotherapy as a first-line treatment and those treated

Table 1 Included study characteristics

Study	Year	Study period	Country	Type of study	Median follow-up	No. of patients	Biomarker	Cutoff value	Cutoff method	Survival analysis	Outcomes	ICI	Median age (years)	Center design
Tanaka *et al.*	2022	Oct 2017–Oct 2019	Japan	Prospective	1 year	70	NLR	5.00 (NLR)	Unclear	Multivariate	OS	Nivolumab	69	Multicentric
Ruan *et al.*	2021	Dec 2016–Sep 2017	China	Prospective	4.5 months	58	NLR, PLR	2.70 (NLR), 267.00 (PLR)	ROC curve	Multivariate	OS, PFS	Toripalimab	60	Multicentric
Kim *et al.*	2022	Nov 2014–Feb 2016	Korea	Prospective	28.3 months	45	NLR	2.90 (NLR)	Median	Univariate (OS), multivariate (PFS)	OS, PFS	Nivolumab	60	Single-center
Xiang *et al.*	2022	Dec 2020–Apr 2021	China	Retrospective	14.2 months	103	NLR	2.38 (NLR)	ROC curve	Multivariate	PFS	Camrelizumab	62	Single-center
Wan *et al.*	2022	Dec 2017–Dec 2020	China	Retrospective	27.3 months	45	NLR, PLR	3.85 (NLR), 214.08 (PLR)	ROC curve	Multivariate	OS, PFS	Camrelizumab, sintilimab, tislelizumab, toripalimab, envafolimab, CS1001, HX008	64	Single-center
Gou (I) *et al.*	2021	Jan 2016–Jan 2020	China	Retrospective	Unclear	137	NLR	3.23 (NLR)	ROC curve	Multivariate	OS, PFS	Nivolumab, pembrolizumab, sintilimab, toripalimab	59	Single-center
Gou (II) *et al.*	2022	Oct 2016–Aug 2021	China	Retrospective	Unclear	237	PLR	139.41 (PLR)	ROC curve	Multivariate	OS, PFS	Nivolumab, pembrolizumab, sintilimab, toripalimab	59	Single-center
Yamada *et al.*	2020	Dec 2014–Feb 2019	Japan	Retrospective	175 days	89	NLR	2.50 (NLR)	ROC curve	Multivariate	OS, PFS	Nivolumab	Unclear	Single-center
Ota *et al.*	2020	Dec 2014–Sep 2018	Japan	Retrospective	4.9 months	98	NLR	3.00 (NLR)	ROC curve	Multivariate (OS), univariate (PFS)	OS, PFS	Nivolumab	66	Single-center
Ogata *et al.*	2018	Jun 2017–Dec 2017	Japan	Retrospective	171 days	26	NLR	5.00 (NLR)	Literature	Univariate	OS, PFS	Nivolumab	64	Multicentric
Hayano *et al.*	2023	Oct 2018–Dec 2021	Japan	Retrospective	Unclear	70	NLR, PLR	2.42 (NLR), 152.50 (PLR)	Unclear	Univariate	PFS	Nivolumab, pembrolizumab	71	Single-center
Li *et al.*	2023	May 2015–May 2021	China	Retrospective	9.4 months	54	NLR, PLR	Unclear	Median	Multivariate	OS	Nivolumab, pembrolizumab	58	Single-center

Table 1 (*continued*)

Table 1 (*continued*)

Study	Year	Study period	Country	Type of study	Median follow-up	No. of patients	Biomarker	Cutoff value	Cutoff method	Survival analysis	Outcomes	ICI	Median age (years)	Center design
Sakai *et al.*	2022	Sep 2017–Mar 2020	Japan	Retrospective	150 days	117	NLR	2.54 (NLR)	Median	Multivariate	OS	Nivolumab	71	Multicentric
Qu (I) *et al.*	2022	Jul 2019–Mar 2020	China	Retrospective	17.5 months	53	NLR, PLR	3.11 (NLR), 243.33 (PLR)	ROC curve	Multivariate	OS, PFS	Camrelizumab, sintilimab, toripalimab, pembrolizumab, nivolumab	Unclear	Single-center
Qu (II) *et al.*	2022	Jul 2019–Mar 2020	China	Retrospective	15.9 months	53	NLR, PLR	3.11 (NLR), 243.33 (PLR)	ROC curve	Multivariate	OS, PFS	Camrelizumab, sintilimab, toripalimab, pembrolizumab, nivolumab	Unclear	Single-center
Suzuki *et al.*	2021	Oct 2017–Feb 2019	Japan	Retrospective	4.8 months	72	NLR	5.00 (NLR)	Unclear	Multivariate	OS	Nivolumab	70	Multicentric
Namikawa *et al.*	2020	Oct 2017–Dec 2019	Japan	Retrospective	32 months	29	NLR	2.50 (NLR)	Median	Univariate	OS, PFS	Nivolumab	71	Single-center
Formica *et al.*	2020	Jun 2014–Dec 2018	England	Retrospective	27 months	57	NLR, PLR	Continuous (NLR), 200.00 (PLR)	Unclear	Multivariate	OS	Nivolumab, pembrolizumab, avelumab	63	Multicentric
Chen *et al.*	2022	Aug 2015–Apr 2019	China	Retrospective	23.8 months	139	PLR	173.70 (PLR)	ROC curve	Multivariate	OS, PFS	Undisclosed	60	Single-center

ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; PFS, progression-free survival.

in later lines. This prompted us to treat that investigation as two separate studies, each subjected to its own independent analysis. Therefore, we named the two groups "Qu (I)" for the first line and "Qu (II)" for the second and later lines. Gou *et al.* (44) conducted two studies with overlapping populations, one of which included reporting of results for the NLR role as a prognostic tool, while the other did the same for the PLR (42,44). We decided to include both studies since each one would pertain to separate analyses, one for NLR [named "Gou (I)"] and the other for PLR [named "Gou (II)"].

Analysis

In this meta-analysis, we investigated the predictive significance of differentiating between low and high biomarker values (NLR and PLR) concerning OS and PFS. Our OS analysis involved pooling HRs and their corresponding 95% CIs by comparing low biomarker values with high biomarker values across the included studies. Whenever feasible, we prioritized multivariate HR and 95% CI data but also incorporated univariate data if it was the only available information. A similar process was employed in the analysis of PFS.

Analysis for OS

In relation to NLR, 10 out of the 15 studies included reporting of a significant HR for OS, indicating a statistically significant association between a high NLR and worse OS prognosis. Our pooled analysis resulted in an HR of 2.11 with 95% CI (1.70–2.62) and a heterogeneity of 45%.

Regarding PLR, only 3 out of the 8 studies presented a significant HR and 95% CI, indicating a significant association between high PLR and unfavorable OS prognosis. Our pooled analysis yielded an HR of 1.77 with 95% CI (1.44–2.17) and a heterogeneity of 0%. The results are shown in *Figure 2*.

Analysis of PFS

In relation to NLR, only 5 out of the 12 studies included reporting of a significant HR for PFS. Although not significant, the results of Namikawa *et al.* (47) tended to suggest that high NLR values were associated with better PFS outcomes in contrast to other studies. Our pooled analysis resulted in an HR of 1.76 with 95% CI (1.43–2.17) and a heterogeneity of 25%.

Regarding PLR, only 3 out of the 8 studies presented a significant HR and 95% CI for the PFS analysis, indicating a significant association between high PLR and unfavorable PFS prognosis. Our pooled analysis yielded an HR of 1.61 with 95% CI (1.33–1.96) and no heterogeneity (0%). The results are shown in *Figure 3*.

Subgroup analysis

The wide range of cutoff values across studies, different countries of origin, different study designs, and variation in follow-up periods rendered a subgroup analysis suitable for our systematic review. Both OS and PFS data underwent subgroup analysis. The data were categorized based on NLR cutoff values (≥3 or <3) or PLR cutoff values (>200 or ≤200), the country of origin, follow-up period (<12 or ≥12 months), sample size (>80 or ≤80), survival analysis approach, study design, and the number of centers involved (1 or >1). The outcomes of NLR subgroup analyses are presented in *Tables 2,3*. The outcomes of PLR subgroup analyses are presented in *Tables 4,5*.

Risk of bias

We evaluated potential bias employing the Newcastle-Ottawa approach, scrutinizing three key domains: selection (0–4 points), comparability (0–2 points), and outcome (0–3 points). Each included article was appraised by two independent reviewers. Any disparities in the assigned scores were addressed through the involvement of a third reviewer to ensure consensus. The outcomes are presented in *Table 6*. In the selection domain, all studies achieved the highest score. This was because in each study, both arms were sourced from an identical cohort, and the clinical data were acquired from secure medical records. The majority of studies obtained the highest score within the Comparability domain, as they applied multivariate analysis for the evaluated outcomes. Some studies lost points in the outcome domain due to short or undisclosed follow-up periods. In summary, all the studies were deemed to be of high quality, with the lowest assigned score being 7.

Publication bias

Figures 4,5 display the NLR and PLR funnel plots for OS and PFS, respectively. Considering NLR funnel plots, visual inspection revealed a high possibility of publication bias for OS analysis, with the plot showing asymmetry and the Formica *et al.* (35) study falling outside the funnel. A low possibility of publication bias for PFS analysis can be concluded based on the minor asymmetry depicted in the funnel plot, with the study falling within the triangular region.

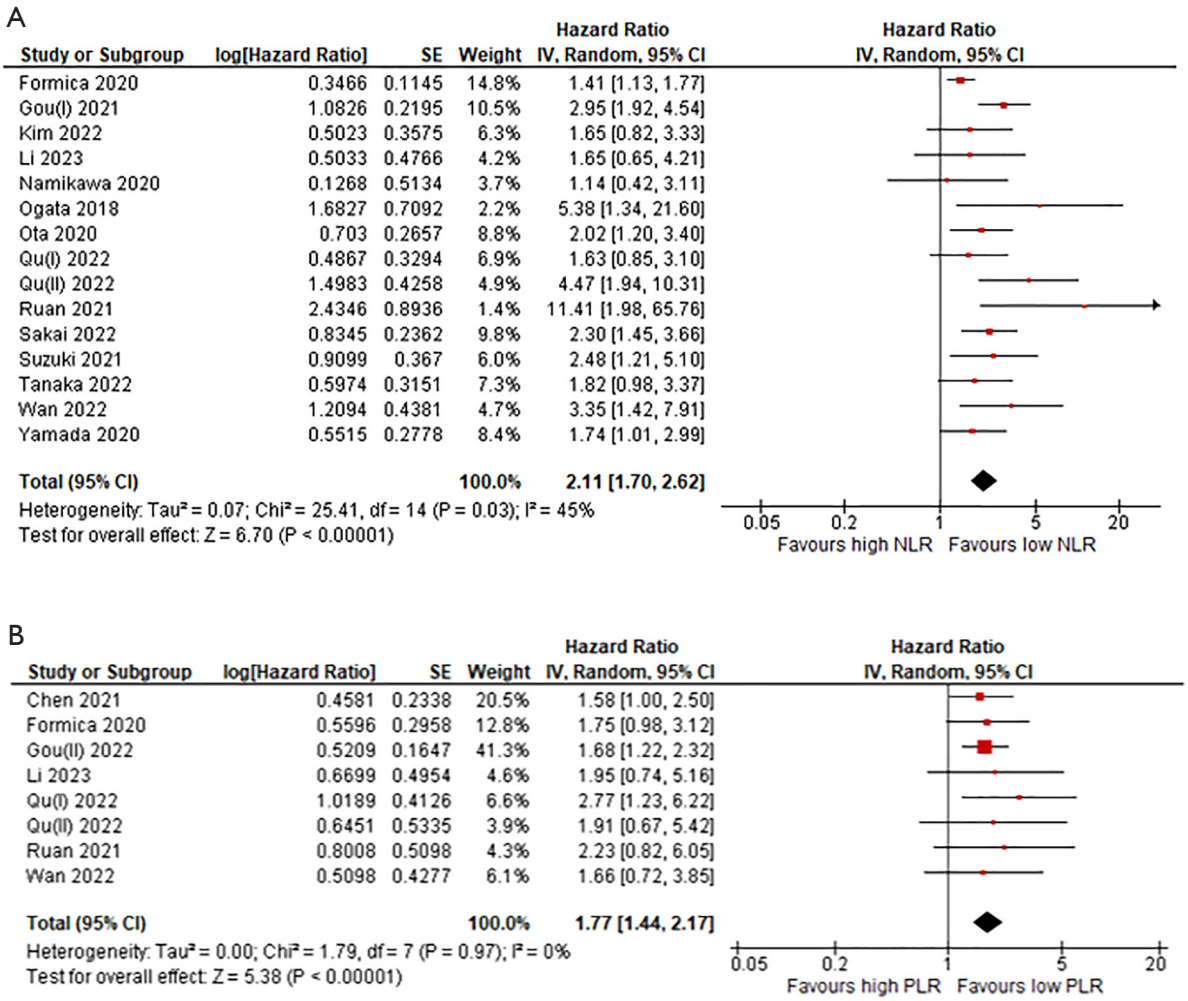

Figure 2 Forest plots for OS assessment according to biomarker. (A) NLR forest plot; (B) PLR forest plot. SE, standard error; IV, inverse variance; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; OS, overall survival.

In relation to PLR funnel plots, visual inspection revealed a low possibility of publication bias for both OS and PFS. In both analyses, minor asymmetry was found, and all included studies fell within the triangular region.

Discussion

This meta-analysis aimed to investigate PLR and NLR roles in predicting the prognosis of advanced GC patients treated with immunotherapy. Conflicting data across studies prompted a thorough investigation into this matter. Our investigation evaluated the prognostic value of baseline NLR in 16 studies comprising 1,176 patients. Our study found correlations between high NLR values and shorter OS and between high NLR values and shorter PFS, with HRs and P values indicating significant correlations. Our meta-analysis assessed the prognostic value of the PLR in advanced GC/GEJC patients treated with immunotherapy across eight studies encompassing 766 patients. To the best of our knowledge, this is the first systematic review to investigate the role of PLR in this population. The pooled results unveiled a significant association between high PLR and poor OS and between high PLR and poor PFS. Remarkably, heterogeneity was null for both PLR analyses, highlighting the low risk of bias related to our findings. Our findings are in line with many of the included studies conclusions regarding association between high biomarker value and worsened survival.

Our study comes in light of two previous meta-analyses that investigated the prognostic role of NLR in our target

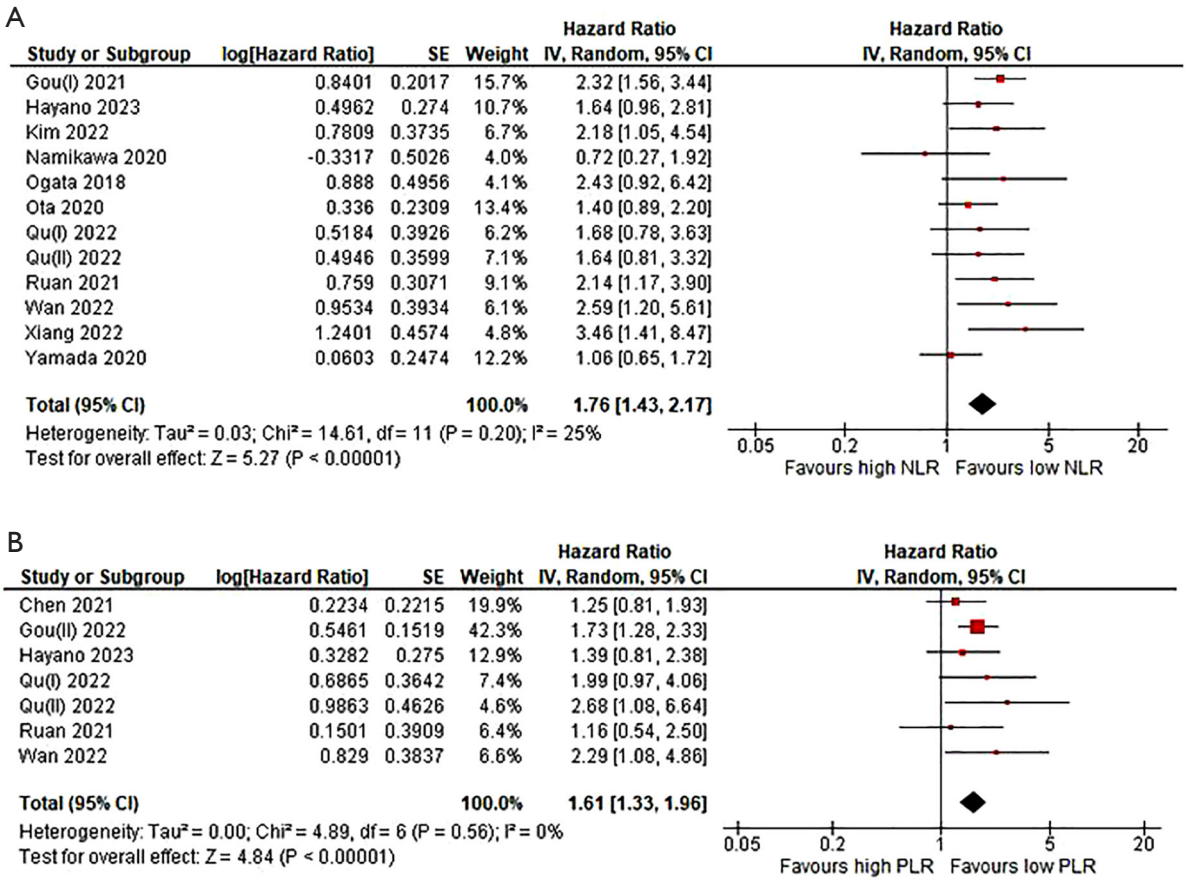

Figure 3 Forest plots for PFS assessment according to biomarker. (A) NLR forest plot; (B) PLR forest plot. SE, standard error; IV, inverse variance; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PFS, progression-free survival.

population. In their meta-analysis of nine studies, Zhang *et al.* (52) found a significantly poorer OS for patients with high NLR but failed to find a significant relationship between high NLR and poor PFS. Within a short period of time after this study was published, Li *et al.* (53) published another meta-analysis investigating the same group of patients in 10 studies. In this systematic review, significant associations were found between poor OS prognosis and high NLR values and between poor PFS prognosis and high NLR values. The discrepant results regarding PFS prompted us to consider the need for further investigation. Moreover, additional studies have been published since their search deadlines. Our results are consistent with those of Li *et al.* (53), with shorter P values and stricter 95% CIs for PFS analysis.

For the sake of clarity, it is worth briefly discussing the possible mechanisms that may explain how inflammation and the novel inflammatory markers PLR and NLR influence cancerization and disease progression.

Inflammation is a pivotal process that contributes to the establishment of the cancer microenvironment and persistent tumor cell proliferation (54). Inflammatory pathways have been recognized as factors that can influence responses to drug treatments in cancer (55). Therefore, it is imperative to study inflammatory biomarkers in oncology, as these could potentially play a crucial role in diagnosing and prognosticating malignancies.

The NLR is an emerging biomarker, and the reasons underlying its prognostic utility as an inflammatory marker are incompletely understood. Emerging evidence links tumor-infiltrating neutrophils as key cells in promoting an immunosuppressive state by upregulating PD-L1 on cancer cells (56,57). Wang *et al.* (58) demonstrated a significant positive correlation between the expression of CD54, a neutrophil activating protein, and PD-L1 neutrophils from GC patients, highlighting the possible interplay between

Table 2 NLR subgroup analysis for OS

Subgroups	Number of studies	Effects model	HR (95% CI)	P	Heterogeneity	
					I^2 (%)	P
Cutoff						
≥3	8	Random	2.48 (1.96–3.15)	<0.001	6	0.39
<3	5	Random	1.96 (1.32–2.89)	<0.001	32	0.21
Continuous	1		1.41 (1.13–1.77)	0.002		
Undisclosed	1		1.65 (0.65–4.21)	0.29		
Country						
Japan	7	Random	2.04 (1.61–2.58)	<0.001	0	0.65
China	6	Random	2.74 (1.88–4.14)	<0.001	36	0.17
Korea	1		1.67 (0.82–3.33)	0.16		
England	1		1.41 (1.13–1.77)	0.002		
Survival analysis						
Multivariate	11	Random	2.23 (1.73–2.88)	<0.001	54	0.02
Univariate	4	Random	1.72 (1.11–2.66)	0.01	9	0.35
Sample size						
≥80	4	Random	2.29 (1.80–2.92)	<0.001	0	0.46
<80	11	Random	2.08 (1.54–2.82)	<0.001	48	0.04
Center						
Multicenter	6	Random	2.19 (1.46–3.27)	<0.001	60	0.03
Single center	9	Random	2.15 (1.79–2.65)	<0.001	19	0.28
Study design						
Retrospective	12	Random	2.12 (1.67–2.69)	<0.001	48	0.03
Prospective	3	Random	2.25 (1.09–4.65)	0.03	52	0.12
Follow-up						
<12 months	6	Random	2.23 (1.56–3.19)	<0.001	20	0.28
≥12 months	8	Random	1.90 (1.44–2.50)	<0.001	44	0.09
Unclear	1		2.94 (1.92–4.54)	<0.001		

NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; HR, hazard ratio; CI, confidence interval.

neutrophils and cancer-induced immunosuppression. Although some differences in gene and protein expression have been described between intratumoral and peripheral neutrophils, the scholars also reported an association between higher levels of peripheral neutrophils in comparison to healthy subjects, suggesting a link between the two cell populations (58). Indeed, in a 2021 study, Ruan *et al.* (51) identified a strong association between higher levels of enriched intratumoral neutrophils in GC patients with a high baseline NLR compared to those with a low NLR. Moreover, higher expression of biomarkers related to neutrophil recruitment and plasticity was reported in patients with a high NLR (51). CD4 and CD8 lymphocytes have been described in tumor cell destruction through immunosurveillance, a process of identifying and eliminating immunogenic cancer cell clones (59). A higher NLR translates in a degree of immunosurveillance loss and there is a tendency to interpret this biomarker as a surrogate for

Table 3 NLR subgroup analysis for PFS

Subgroups	Number of studies	Effects model	HR (95% CI)	P	Heterogeneity	
					I^2 (%)	P
Cutoff						
≥3	6	Random	1.80 (1.37–1.38)	<0.001	0	0.64
<3	6	Random	1.64 (1.12–2.39)	0.01	48	0.08
Country						
Japan	5	Random	1.33 (1.01–1.77)	0.04	10	0.35
China	6	Random	2.21 (1.71–2.84)	<0.001	0	0.80
Korea	1		2.17 (1.05–4.54)	0.037		
Survival analysis						
Multivariate	7	Random	1.96 (1.47–2.62)	<0.001	35	0.16
Univariate	5	Random	1.49 (1.12–1.99)	0.006	0	0.50
Sample size						
≥80	4	Random	1.74 (1.11–2.72)	0.02	67	0.03
<80	8	Random	1.82 (1.41–2.35)	<0.001	0	0.62
Center						
Multicenter	2	Random	2.21 (1.33–3.69)	0.002	0	0.82
Single center	10	Random	1.70 (1.34–2.17)	<0.001	34	0.13
Study design						
Retrospective	10	Random	1.70 (1.33–2.17)	<0.001	34	0.13
Prospective	2	Random	2.16 (1.35–3.43)	0.001	0	0.96
Follow-up						
<12 months	4	Random	1.51 (1.07–2.12)	0.02	30	0.23
≥12 months	6	Random	1.89 (1.31–2.75)	<0.001	23	0.26
Unclear	2	Random	2.05 (1.49–2.83)	<0.001	2	0.31

NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

such a decline. The possible implications are not only the use of NLR as a baseline marker to assess prognostic, but as a dynamic tool to monitor immune status during treatment.

PLR is another novel inflammatory marker, and its role as a prognostic tool for several types of cancer remains controversial. Notably, there are several mechanisms explaining the interaction between tumor cells and platelets during metastization. One of the primary mechanisms involves the activation of platelets by tumor cells through the release of substances such as ADP, TXA2, and chemokines (60). In addition to these interactions, platelets are implicated in shielding circulating tumor cells from recognition by the immune system and in facilitating invasion of healthy tissues (61). In contrast to these factors, $CD8^+$ T lymphocytes are recognized as the main players in the immune response against malignancies, developing complex crosstalk with surrounding immune cells in the tumor microenvironment and influencing inflammatory responses (62). The reasons surrounding the role of the PLR in tumor prognosis are incompletely understood, but these factors may help elucidate its role since both components, platelets, and lymphocytes, are implicated in cancer dynamics.

It is challenging to draw final conclusions for both

Table 4 PLR subgroup analysis for OS

Subgroups	Number of studies	Effects model	HR (95% CI)	P	Heterogeneity	
					I^2 (%)	P
Cutoff						
>200	4	Random	2.13 (1.35–3.35)	0.001	0	0.85
≤200	3	Random	1.67 (1.31–2.12)	<0.0001	0	0.96
Undisclosed	1		1.96 (0.74–5.16)			
Country						
China	7	Random	1.77 (1.42–2.21)	<0.001	0	0.94
England	1		1.75 (0.98–3.12)	0.06		
Survival analysis						
Multivariate	6	Random	1.85 (1.47–2.33)	<0.001	0	0.58
Univariate	2	Random	1.72 (1.07–2.77)	0.03	0	0.92
Sample size						
≥80	2	Random	1.65 (1.27–2.15)	<0.001	0	0.83
<80	6	Random	1.97 (1.41–2.76)	<0.001	0	0.96
Center						
Multicenter	2	Random	1.86 (1.13–3.07)	0.02	0	0.68
Single center	6	Random	1.75 (1.39–2.19)	<0.001	0	0.90
Study design						
Retrospective	7	Random	1.75 (1.41–2.16)	<0.001	0	0.95
Prospective	1		2.22 (0.82–6.05)	0.12		
Follow-up						
<12 months	2	Random	2.08 (1.04–4.18)	0.04	0	0.85
≥12 months	5	Random	1.89 (1.42–2.53)	<0.001	0	0.55
Unclear	1		1.69 (1.22–2.32)	0.001		

PLR, platelet-to-lymphocyte ratio; OS, overall survival; HR, hazard ratio; CI, confidence interval.

NLR and PLR solely based on our findings. Ideally, the results from a systematic review in addition to individual patient data could provide a better understanding of the real prognostic role of NLR and PLR. Here, we seek to assess whether their significance is relevant in the era of immunotherapy. A number of studies have explored the role of NLR in advanced GC patients treated with chemotherapy, the traditional regimen for advanced disease. Many of these have resulted in findings that suggest a possible role in prognosticating survival outcomes (63-65). When considered collectively, our findings indicate the continued utility of NLR continuity in the context of immunotherapy. Data for the predictive role of PLR in chemotherapy are scarce and conflicting, with some studies indicating a potential use and others presenting inconclusive findings (66,67). Similarly, our meta-analysis assessment of PLR consisted of studies that had small sample sizes and were retrospective in nature.

One concern that arose in the aftermath of our statistical data completion was the limited follow-up of some of the included studies and the effect this could have on our conclusions from NLR analyses for OS and PFS. Therefore, we chose to conduct a subgroup analysis of follow-up ≥12 and <12 months. In both groups, a significant association

Table 5 PLR subgroup analysis for PFS

Subgroups	Number of studies	Effects model	HR (95% CI)	P	Heterogeneity	
					I^2 (%)	P
Cutoff						
>200	4	Random	1.90 (1.29–2.80)	0.001	0	0.50
≤200	3	Random	1.53 (1.22–1.91)	<0.0001	0	0.45
Country						
China	6	Random	1.65 (1.34–2.03)	<0.001	0	0.47
Japan	1		1.39 (0.81–2.38)	0.2		
Survival analysis						
Multivariate	4	Random	1.68 (1.29–2.18)	<0.001	14	0.32
Univariate	3	Random	1.47 (1.01–2.14)	0.04	0	0.58
Sample size						
≥80	2	Random	1.53 (1.13–2.08)	0.007	31	0.23
<80	5	Random	1.71 (1.25–2.34)	<0.001	0	0.52
Center						
Multicenter	1		1.16 (0.54–2.50)	0.71		
Single center	6	Random	1.65 (1.35–2.01)	<0.001	0	0.53
Study design						
Retrospective	6	Random	1.65 (1.35–2.01)	<0.001	0	0.53
Prospective	1		1.16 (0.54–2.50)	0.71		
Follow-up						
<12 months	1		1.16 (0.54–2.50)	0.709		
≥12 months	4	Random	1.73 (1.21–2.48)	0.003	18	0.30
Unclear	2	Random	1.64 (1.26–2.13)	<0.001	0	0.49

PLR, platelet-to-lymphocyte ratio; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

was found between high NLR and worse OS and PFS prognosis. We attempted to conduct a similar analysis of follow-up ≥180 and <180 days; however, the results were similarly significant for both groups, and we did not include this analysis in our data. These findings highlighted that our findings are consistent and that studies with short follow-up may not have interfered with our results. We also chose to perform subgroup analyses of multivariate studies for OS and PFS. Every multivariate analysis displayed results consistent with our main findings that high NLR and PLR are associated with shorter OS and PFS. The results can be seen in *Tables 2-5*.

These consistent results favor an implementation of both biomarkers as possible tools to assess prognosis in advanced GC patients treated with immune-checkpoint blockade. However, we don't believe that NLR and PLR are yet to be relied as a decision-making tool to indicate Immunotherapy based on their baseline values. We expect that new, larger studies will possibly validate this role in the future.

Previous studies have also investigated NLR role in prognosticating survival in early stage and locally advanced GC. A 2021 Italian study with a cohort of locally advanced patients treated with neoadjuvant chemotherapy demonstrated that baseline high NLR is significantly correlated with worse OS and PFS (3). A 2022 study also investigated patients with locally advanced disease receiving preoperative chemotherapy, finding a significant association between higher values of NLR and decreased OS (68).

These results are in concordance with our findings and suggest the utility of novel biomarkers to prognosticate survival across the landscape of GC scenarios.

The present study is not the first systematic review to investigate the prognostic use of novel inflammatory markers in cancer. In 2018, a Chinese meta-analysis explored the significance of NLR in predicting OS and PFS prognosis among advanced cancer patients with various malignancies, such as renal cell, hepatocellular, and colorectal cancers, who underwent immunotherapy. It was concluded that NLR was a prognostic factor for both types of survival, although with high levels of heterogeneity (67). Similarly, two meta-analyses investigating PLR use to prognosticate survival in lung cancer patients treated with immune checkpoint blockade revealed significant associations between high PLR and worse survival outcomes. Taken together, these findings highlight the potential role of emerging biomarkers in cancer management in the era of immunotherapy. Complete blood counts and their derived novel inflammatory markers have been ruled cost-effective tools in several instances (69,70). Their straightforward application and affordability support their adoption, particularly when their ability to predict treatment prognosis has been validated. This is especially valid when prices for medications can exceed tens of thousands of US$ per year as is the case for immunotherapy (71-73).

Some issues, however, raise questions regarding the implementation of NLR and PLR in clinical practice. The first issue relates to the potential influence of other comorbidities on NLR and PLR levels, which could interfere with their ability to be used in prognosticating cancer. The influence of other concomitant diseases on biomarker levels has not been studied, and an investigation into this topic is timely and appropriate. Another question that arises is the current scarce understanding regarding dynamics between neutrophils, platelets, lymphocytes, and the tumor microenvironment, as their interaction is

Table 6 Bias assessment

Authors	Selection	Comparability	Outcome	Total score
Tanaka *et al.*	****	**	***	9
Ruan *et al.*	****	**	**	8
Kim *et al.*	****	*	***	8
Xiang *et al.*	****	**	**	8
Wan *et al.*	****	**	***	9
Gou (I) *et al.*	****	**	**	8
Gou (II) *et al.*	****	**	**	8
Yamada *et al.*	****	**	**	8
Ota *et al.*	****	**	**	8
Ogata *et al.*	****	*	**	7
Hayano *et al.*	****	*	**	7
Li *et al.*	****	**	**	8
Sakai *et al.*	****	**	***	9
Qu *et al.*	****	**	***	9
Suzuki *et al.*	****	**	**	8
Namikawa *et al.*	****	*	**	8
Formica *et al.*	****	**	***	9
Chen *et al.*	****	**	***	9

Each asterisk (*) represents 1 point in NOS score. NOS, Newcastle-Ottawa scale.

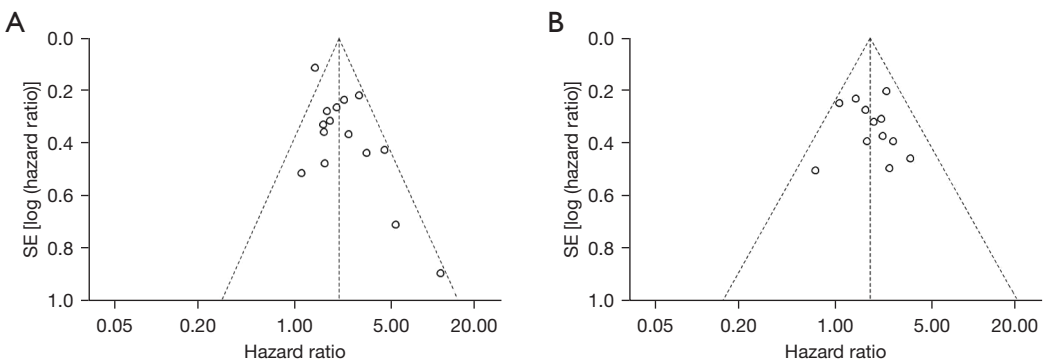

Figure 4 NLR funnel plots of publication bias according to survival type (A) for OS; (B) for PFS. SE, standard error; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

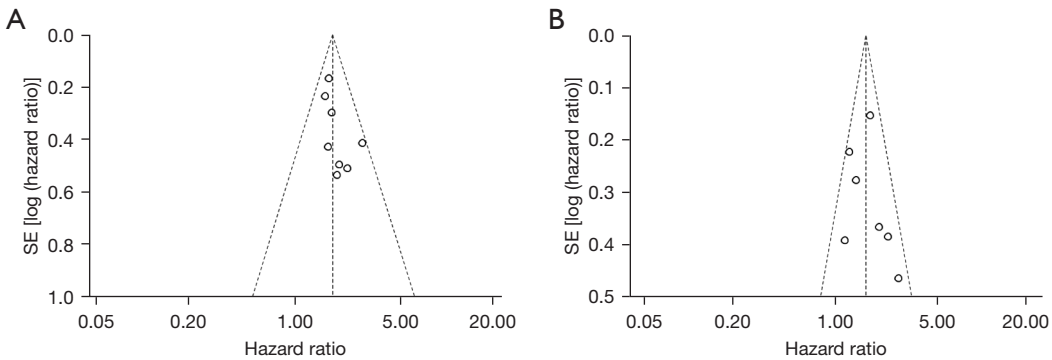

Figure 5 PLR funnel plots of publication bias according to survival type (A) for OS; (B) for PFS. SE, standard error; PLR, platelet-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

complex and intricate. This lack of knowledge contributes to the unknown variation in NLR and PLR levels. Currently, there is a lack of studies dedicated to thoroughly investigating the dynamics of novel inflammatory markers, and research efforts in this direction are needed.

The wide range of cutoff values across studies is another point of contention when considering NLR and PLR as biomarkers for prognosis in oncology. This divergence is, in part, a consequence of the diverse methods employed by studies with respect to cutoff points. Currently, there is no standardized value that can be used across studies. We conducted subgroup analysis investigating cutoffs ≥3 and <3 for NLR and >200 and ≤200 for PLR, with all analyses resulting in a significant association between high PLR and poor OS and PFS. The exact cutoff values for NLR and PLR remain unknown. A multicenter and international task to determine standardized cutoffs for each biomarker is needed to align conclusions of different studies around one common cutoff value.

Our meta-analysis possesses some limitations. First, our study encompassed a mixture of studies, with a combination of prospective and retrospective designs, thereby introducing a risk of bias, especially for the PLR analysis. Second, as previously highlighted, there is a diversity of cutoff values across studies, and definitive cutoff values could not be determined. Furthermore, we had a high risk of publication bias in our NLR analysis for OS. Additionally, we pooled data from multivariate and univariate models.

Despite these considerations, we believe that our meta-analysis boasts several positive aspects. The present systematic review exclusively included high-quality studies. Moreover, we had a remarkable heterogeneity of 0% in most of the PLR assessments, which reduced the risk of bias. Furthermore, although most studies related to our topic were conducted in Asia, we included one conducted in Europe, diversifying the population.

Conclusions

In conclusion, an elevated NLR has been demonstrated to have significant correlations with unfavorable OS and PFS outcomes among patients with advanced GC/GEJC undergoing immunotherapy. These findings underscore its potential utility as an accessible biomarker for prognostic assessment in the era of immunotherapy. Elevated PLR has also been shown to have significant associations with shortened OS and PFS. However, careful consideration should be given to this finding, as the data for PLR primarily consist of retrospective studies with small sample sizes. Additional prospective studies, as well as research delving into the interactions between neutrophils, platelets, lymphocytes, and the microenvironment, are further needed to validate our findings regarding both biomarkers.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-808/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-808/coif). P.N.A. Jr received lecture honoraria from Aché, Amgen, AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, Gilead, GSK, Merck Co, Sanofi, Servier, and United Medical; received Advisory Board Fee from Adium, Gilead, and Daiichi Sankyo; and received support for attending a meeting from AstraZeneca. None of them are related to this manuscript. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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