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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

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SYSTEMATIC REVIEWS

Prognostic value of neutrophil-to-lymphocyte ratio in gastric cancer patients undergoing neoadjuvant chemotherapy: A systematic review and meta-analysis

Zhen-Hua Wei, Min Tuo, Chen Ye, Xiao-Fan Wu, Hong-Hao Wang, Wen-Zhen Ren, Gao Liu, Tian Xiang

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Abstract

BACKGROUND

In recent studies, accumulating evidence has revealed a strong association between the inflammatory response and the prognosis of many tumors. There is a certain correlation of neutrophil-to-lymphocyte ratio (NLR) with the prognosis in gastric cancer (GC) patients undergoing neoadjuvant chemotherapy (NAC). However, the existing research results have remained controversial.

AIM

To explore the relationship between NLR ratio and prognosis of GC patients receiving NAC.

METHODS
A thorough systematic search was performed in databases such as PubMed, Embase, Web of Science, and Cochrane Library, the search is available until February 29, 2024, and studies exploring the interaction of NLR with clinical outcomes were collected. Relevant studies meeting pre-defined inclusion and exclusion criteria were carefully chosen. The outcomes included progression-free survival (PFS), relapse-free survival, disease-free survival (DFS), and overall survival (OS). The hazard ratio (HR) and its corresponding 95% confidence interval (CI) were utilized for estimation.

RESULTS
Our analysis encompassed 852 patients and incorporated data from 12 cohort studies. The comprehensive analysis revealed a significant association of high NLR with reduced OS (HR = 1.76; 95%CI: 1.22-2.54, P = 0.003), relapse-free survival (HR = 3.73; 95%CI: 1.74-7.96, P = 0.0007), and PFS (HR = 2.32; 95%CI: 1.42-3.81, P = 0.0008) in patients. However, this correlation in disease-free survival was not significant. NLR demonstrated its crucial role in effectively predicting the OS of GC patients undergoing NAC at different detection times, ages, regions, and NLR thresholds.

CONCLUSION
In GC patients receiving NAC, an elevated NLR is strongly associated with reduced OS and PFS. NLR has become an effective biomarker for patient prognosis evaluation, providing valuable insights for the treatment strategies of NAC in GC patients.

Key Words: Neutrophil-to-lymphocyte ratio; Gastric cancer; Neoadjuvant chemotherapy; Prognostic factors; Meta-analysis

Core Tip: This study systematically evaluated the relationship between neutrophil to lymphocyte ratio (NLR) and prognosis in patients with gastric cancer (GC) receiving neoadjuvant chemotherapy (NAC). This is the first meta-analysis to evaluate the association between NLR and prognosis in patients with NAC for GC. In summary, NLR levels are highly correlated with the prognosis of GC patients receiving NAC, and NLR can be used as an effective biomarker for prognosis assessment of GC patients.

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INTRODUCTION

Gastric cancer (GC) is a malignancy affecting the digestive tract and poses a significant health risk to individuals. Based on the latest global cancer statistics from the International Agency for Research on Cancer of the World Health Organization (GLOBOCAN2022), GC ranks fifth among all malignancies in terms of both incidence and mortality, involving 980000 new cases and 650000 deaths[1]. The emergence and progression of GC can be intricately linked to factors such as our dietary habits, lifestyle, and genetic factors. Surgery is an important approach for the treatment of GC, and there is a comprehensive treatment plan including chemoradiotherapy, immunology, and targeted therapy. In recent years, diagnostic techniques, surgical techniques, and the concept of accelerated recovery during perioperative period have been continuously developed, and there has been a notable enhancement in the 5-year survival among patients with GC. However, a considerable proportion of GC patients at progressive or advanced stage are unable to undergo surgery after diagnosis or relapse after radical gastrectomy, and the treatment effect is not satisfactory. Therefore, the application of neoadjuvant chemotherapy (NAC) will be beneficial for patients with progressive or advanced GC. NAC is a recommended therapeutic strategy for managing locally advanced GC. It serves multiple purposes, including reducing tumor stage and volume, enhancing the R0 resection rate, addressing micrometastasis, and evaluating the sensitivity and tolerance of chemotherapy drugs. Importantly, NAC does not contribute to an increase in the incidence or mortality of the disease[2]. Although there are many NAC regimens for GC, the most frequently employed combinations include S-1 + oxaliplatin and oxaliplatin + capecitabine[3-5]. To identify individuals who can potentially derive benefits from NAC, it becomes imperative to discover precise predictors that can effectively determine NAC outcomes, which is of great significance for improving patients' survival outcomes and providing better treatment measures.

Recently, extensive investigations have been conducted to explore the correlation of systemic inflammatory response with the occurrence and development of tumors, revealing a significant correlation between systemic inflammatory

response and prognosis[6-8]. They exert a pivotal influence at every stage of tumor development. The proliferation, migration, and invasive potential of malignant cells, the failure and metastasis of an anti-tumor immune response, and other characteristics will change with changes in inflammatory cells[7]. Studies have demonstrated that certain peripheral blood parameters, including white blood cell, neutrophil, lymphocyte, monocyte, and platelet count, as well as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), can serve as potential indicators of the inflammatory status associated with tumors[9,10]. It has been reported that NLR has been proven to be a valuable prognostic indicator for predicting patient outcomes in the context of GC treatment[11,12], which indicates the correlation of neutrophil count with lymphocyte count. In addition, this indicator can effectively reflect the inflammation and immune status of the body when exposed to external pathogens or internal physiological changes. The study by Gong *et al*[13] on 91 patients with locally advanced GC undergoing NAC and D2 gastrectomy showed that NLR holds promise as a dependable prognostic marker for predicting survival outcomes in locally advanced GC patients prior to NAC. NLR and PLR were significantly decreased, patient overall survival (OS) was prolonged, and NLR levels were negatively correlated with the survival prognosis after NAC[13]. It can be concluded that exploring the changes of NLR in GC patients receiving NAC is expected to provide novel insight and methodology for improving patient survival.

Although most researchers have emphasized the prognostic value of NLR for GC patients undergoing radical gastrectomy, only a few researchers have focused on the importance of NLR for GC patients receiving NAC. To date, limited research has been conducted to investigate the prognostic relevance of the NLR specifically in patients undergoing NAC. Therefore, this meta-analysis aims to evaluate the impact of NLR on the prognosis of GC patients receiving NAC.

MATERIALS AND METHODS

Literature search

The study methodology was duly registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42024505051), adhering to the recommended guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA2009)[14]. The formulation of search strategies was carried out collaboratively by three investigators, namely Wei ZH, Tuo M, and Ye C. Subject words and keywords were selected to search multiple databases such as PubMed, Embase, Cochrane Library, and Web of Science. The search encompassed the entire database inception period up until February 29, 2024. A wide range of phrases were used in the search, such as "gastric cancer", "neutrophil", "neutrophil-to-lymphocyte ratio (NLR)", "neoadjuvant chemoradiotherapy". Literature retrieval strategies are presented in Supplementary Table 1.

Study selection

The studies included in the analysis should comply with PICOS principles: (1) P: GC patients undergoing NAC (which refers to systemic chemotherapy performed before local treatment. The purpose of this therapy is to reduce the tumor size and kill invisible metastatic cells early, thus facilitating subsequent surgery, radiotherapy, and other treatments for GC patients); (2) I: Relatively high NLR value; (3) C: Relatively low NLR value; (4) O: Patient's prognosis [OS, relapse-free survival (RFS), disease-free survival (DFS), and progression-free survival (PFS)]; and (5) S: Observational study. The following criteria were used for study exclusion: (1) Reviews, comments, conference abstracts, case reports, and letters; (2) Studies that lacked adequate information to calculate the hazard ratio (HR) and its corresponding 95% confidence interval (CI); (3) Studies that did not provide survival data; (4) Studies using duplicate data or overlapping databases. Three researchers (Wei ZH, Tuo M, and Ye C) conducted a thorough review of the titles and abstracts of the studies obtained from the database, followed by the retrieval and evaluation of full-text articles to identify eligible studies for inclusion. During the process of study selection, any disagreements were resolved through consensus during the study selection process.

Data extraction

Data extraction was carried out independently by two investigators (Wei ZH and Tuo M). Any disagreements were resolved through consensus of co-authors. The extracted information included first author's name, study period, country (study site), study type, NLR detection time, study population, NAC regimen, total sample size, sample size for different genders, patient age, tumor-node-metastasis staging of GC, NLR threshold, as well as HRs (95%CI) for OS, RFS, DFS, and PFS. Importantly, the collected data were stratified into high NLR/low NLR group. In cases where the research data reported as low NLR/high NLR group[15,16], the reciprocals of the corresponding HR values and their CIs were collected, and the upper and lower confidence limits were interchanged accordingly. This ensured that the low NLR/high NLR group was appropriately converted to the high NLR/low NLR group for subsequent statistical analysis.

Quality assessment

The assessment of studies included in the meta-analysis was conducted using the Newcastle Ottawa Scale, which evaluated three aspects: Selection, comparability, and outcomes. Each study could obtain a maximum score of 9 on the scale[16]. Studies with scores ranging from 7 to 9 were categorized as high-quality[17].

Statistical analysis

To assess the prognostic significance of the NLR in GC patients undergoing NAC, pooled HRs and their corresponding 95%CIs were calculated. Heterogeneity was measured through Cochran's *Q* test and higgins I^2 statistic[18]. A random-effects model was adopted for data merging. In addition, subgroup analysis and sensitivity analysis were conducted to validate the robustness of results pertaining to OS and PFS and to explore potential factors contributing to the observed heterogeneity. To evaluate the potential presence of publication bias, funnel plots and the Egger's test were adopted. Statistical significance was considered when the *P* value was less than 0.05. All statistical analyses were conducted through STATA 15.0 and Review Manager (Version 5.4).

RESULTS

Study characteristics

After the initial search of the databases, a total of 203 articles were identified. Following a thorough examination, 34 articles were excluded due to duplicate publications. Upon assessing the titles and abstracts of the residual studies, 156 studies were ruled out. Subsequently, a comprehensive assessment was conducted on the full texts of 13 articles. 4 studies were ruled out primarily because they lacked the necessary data required for conducting survival analysis. In the final analysis, altogether 9 studies, comprising 852 patients, were enrolled in the meta-analysis[13,15-17,19-23] (Figure 1).

Among the 9 eligible studies, geographic diversity was observed, with 1 study performed in Japan, 1 in Egypt, 1 in Rome, 1 study in Poland, and the remaining 5 in China. It was worth noting that each article included 2 cohort studies in the 3 eligible articles[17,20,22], with a total of 12 cohort studies. One study was prospective[21], with the remaining 11 being retrospective[13,15-17,19,20,22,23]. Between 2020 and 2023, a total of 9 cohort studies were published in English. Additionally, 3 were published in English in 2013, 2014, and 2017, respectively. Of the 12 cohort studies, the oldest was published in 2013 by Jin *et al*[17]. All studies adopted NAC and were grouped into high NLR/low NLR group for analysis. Regarding the measurement of NLR, 2 studies measured NLR before treatment[16,19], and 10 studies examined NLR before treatment and after NAC[13,15,17,20-23]. In terms of NLR evaluation, 10 studies explored the prognostic significance of NLR for OS[13,15,16,19-23], 4 studies explored its prognostic significance for PFS[17,19,23], 2 studies explored its prognostic significance for RFS[20], and 2 studies explored its prognostic significance for DFS[15,16]. Characteristics of the included studies are listed in Table 1.

Study quality

The Newcastle Ottawa Scale scores of all 12 studies were between 7-8, indicating the high quality of the studies (Supplementary Table 2).

Meta-analysis results

NLR and OS: Our investigation focused on exploring the correlation of NLR with OS in a total of 959 patients across 10 cohort studies. In these studies, 2 only provided NLR values before the treatment, while 8 provided NLR values both before treatment and after NAC. Given the significant heterogeneity observed among the studies (I^2 = 58%, *P* = 0.01), a random-effects model was employed (Figure 2A). The analysis revealed a significant association of high NLR with shorter OS in GC patients undergoing NAC (HR = 1.76, 95%CI: 1.22-2.54; *P* = 0.003, Figure 2A).

To test potential heterogeneity, subgroup analysis was performed based on the detection time, age, region, and NLR threshold. The findings of these analyses are presented in Table 2. Firstly, significant associations were found between elevated NLR and shorter OS in both pre-treatment (HR = 1.76; 95%CI: 1.22-2.54; *P* = 0.003) and post-treatment (HR = 1.83; 95%CI: 1.22-2.75; *P* = 0.004) studies. Secondly, age-based subgroup analysis revealed that the predictive value of NLR for OS was limited to patients aged 60 years and above (HR = 2.13, 95%CI: 1.24-3.67; *P* = 0.006), while for patients under 60 years, the predictive significance of NLR for OS was not marked (HR = 1.40, 95%CI: 0.79-2.48; *P* = 0.250). Thirdly, region-based subgroup analysis revealed that NLR had no significant predictive significance for OS in the Asian population (HR = 1.36; 95%CI: 0.94-1.97; *P* = 0.100). However, NLR showed marked predictive significance for OS in populations in Africa (HR = 3.26; 95%CI: 1.14-9.28; *P* = 0.03) and Europe (HR = 2.36; 95%CI: 1.02-5.44; *P* = 0.04). In addition, subgroup analyses of both high NLR threshold (≥ 2.0) (HR = 1.99; 95%CI: 1.01-3.94; *P* = 0.049) and low NLR threshold (< 2.0) (HR = 1.65; 95%CI: 1.11-2.46; *P* = 0.01) indicated that NLR could predict OS in GC patients receiving NAC.

NLR and RFS: Two studies provided data on NLR and RFS, involving 94 patients, and both studies provided NLR values before and after treatment. Consistent with our OS analysis results, high NLR was significantly correlated with shorter RFS (HR = 3.73, 95%CI: 1.74-7.96; *P* = 0.0007, Figure 2B). There was no significant evidence of heterogeneity among the included studies (I^2 = 0%, *P* = 0.52).

NLR and DFS: The correlation of NLR with DFS was investigated, with data from two studies involving 202 patients. Among them, one study only provided NLR values before treatment, while the other study provided NLR values before and after treatment. The studies did not demonstrate a marked predictive value of NLR for DFS (HR = 1.08, 95%CI: 0.46-2.56; *P* = 0.86, Figure 2C), which required further exploration.

NLR and PFS: Finally, four studies involved data on the correlation between NLR and PFS, involving 227 patients. Among them, one study only provided NLR values before treatment, while the remaining three studies provided NLR

Table 1 Baseline characteristics of the included literature

Ref.	Study period	Country	Study design	Time of test	Population	Neoadjuvant chemotherapy	Patients (*n*)	Gender		Age	NLR threshold
								Male	Female		
Gong *et al* [13]	2007-2015	China	Retrospective	Before and after NAC	II-III	DOF, DF, FOLFOX	91	69	22	55	1.05
Jin *et al*[17]	2004-2009	China	Retrospective	Before and after NAC	III-IV	FOLFOX	46	36	10	60	2.50
el Aziz[19]	2010-2014	Egypt	Retrospective	Before NAC	III-IV	FOLFOX	70	47	23	53	3.00
Liu *et al* [15]	2016-2019	China	Retrospective	Before and after NAC	II-III	SOX, XELOX	111	83	28	58	1.75
Kasahara *et al*[20]	2011-2016	Japan	Retrospective	Before and after NAC	II	S-1	47	30	17	66	2.41
Chen *et al* [16]	2008-2015	China	Retrospective	Before NAC	II-III	SOX, XELOX	91	70	21	57	2.17
Zurlo *et al* [23]	2012-2017	Rome	Retrospective	Before and after NAC	III B-III C	XELOX, DOF	65	41	24	63	2.50
Pikuła *et al* [22]	2012-2020	Poland	Retrospective	Before and after NAC	II-III	EOX, FLOT-4	106	65	41	61	1.94
Li *et al*[21]	2014-2018	China	Prospective	Before and after NAC	II-IV A	DOF	225	172	53	60	2.57

NAC: Neoadjuvant chemotherapy; NLR: Neutrophil to lymphocyte ratio; DOF: Doxorubicin + oxaliplatin + fluorouracil; DF: Doxorubicin + fluorouracil; FOLFOX: Fluorouracil + oxaliplatin + calcium folinate; SOX: S-1 + oxaliplatin; XELOX: Oxaliplatin + capecitabine; S-1: Tegafur; EOX: Epirubicin + oxaliplatin + capecitabine; FLOT-4: Fluorouracil + oseltamivir + folinate + tegafur.

values before and after treatment. The research findings all indicated that NLR could predict the PFS of GC patients receiving NAC, and NLR was markedly correlated to PFS (HR = 2.32, 95%CI: 1.42-3.81; P = 0.0008, Figure 2D).

Sensitivity analysis

We conducted a sensitivity analysis to assess the robustness of our analysis findings and determine the clinical relevance of NLR. Given the limited availability of studies investigating RFS and DFS, we only conducted sensitivity analysis on OS and PFS. The results showed that after sequentially deleting each study, the effect size consistently fell within the original range. These findings suggested that no individual study had a disproportionate influence on the results of OS (Figure 3A) and PFS (Figure 3B), which validated the reliability of the analysis outcomes.

Publication bias

Publication bias was evaluated through the utilization of funnel plots and Egger's test. The symmetric funnel plot provided evidence of the absence of publication bias in the analysis of PFS (Egger: P = 0.224) (Figure 4A). Conversely, the results obtained from the Egger's test indicated the presence of publication bias in the analysis of OS (Egger: P = 0.026) (Figure 4B). However, the limited number of studies (lee than 3 studies) for the remaining analysis precluded us from conducting a comprehensive assessment of publication bias.

DISCUSSION

The majority of GC patients are diagnosed an advanced stage of the disease, and many patients have missed the optimal time for surgical treatment. Multimodal systemic comprehensive therapies, such as perioperative chemotherapy, radiation therapy, and targeted immunotherapy[24], for advanced GC have markedly contributed to improving the survival rates of patients[25]. We currently have a range of treatment options for GC, but predicting the prognosis of patients remains a huge challenge. In recent years, an increasing number of studies have highlighted the strong association of systemic inflammatory response with patient prognosis in numerous malignant tumors. GPS, PLR, NLR, and MLR are relatively reliable indicators for predicting the prognosis of GC patients[26,27]. A recent research by Lin *et al*

Table 2 Subgroup analysis of overall survival in patients with neoadjuvant chemotherapy for gastric cancer

Subgroup	OS			
	Study	HR (95%CI)	*P* value	I^2
Total	10	1.76 (1.22-2.54)	0.003	58%
Time of test				
Pre-NAC	10	1.76 (1.22-2.54)	0.003	58%
Post-NAC	8	1.83 (1.22-2.75)	0.004	59%
Age				
≥ 60 years	6	2.13 (1.24-3.67)	0.006	70%
< 60 years	4	1.40 (0.79-2.48)	0.25	37%
Region				
Asia	6	1.36 (0.94-1.97)	0.1	37%
Africa	1	3.26 (1.14-9.28)	0.03	NA
Europe	3	2.36 (1.02-5.44)	0.04	65%
NLR cut-off				
≥ 2	5	1.99 (1.01-3.94)	0.049	73%
< 2	5	1.65 (1.11-2.46)	0.01	12%

NAC: Neoadjuvant chemotherapy; NLR: Neutrophil to lymphocyte ratio; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

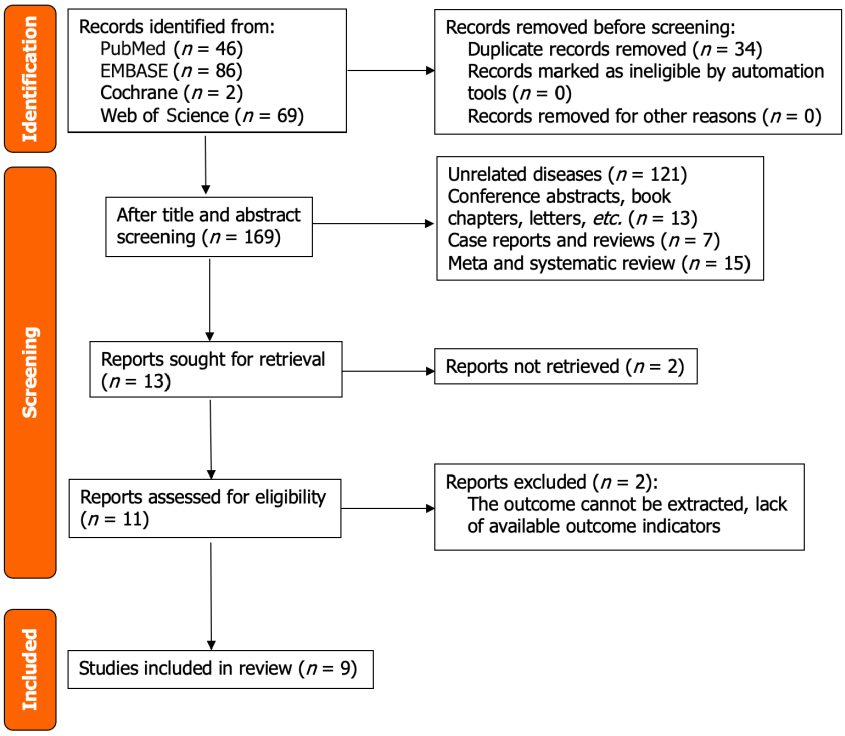

Figure 1 Flow chart of literature screening.

[28] suggested that patients with advanced GC who received a 2-week combined chemotherapy regimen of Docetaxel and S-1 achieved better chemotherapy outcomes in the low Glasgow Prognostic Score group, indicating a significant correlation between Glasgow Prognostic Score and patient prognosis. The study by Nguyen *et al*[29] showed that inflammatory markers such as NLR, MLR, and PLR could predict the prognosis of GC patients, and the combined detection by NLR, MLR, PLR, and tumor markers (carcinoembryonic antigen) improved the diagnosis rate of GC. It had high sensitivity and specificity in the diagnosis of GC, which was helpful for early diagnosis, detection, and treatment of GC

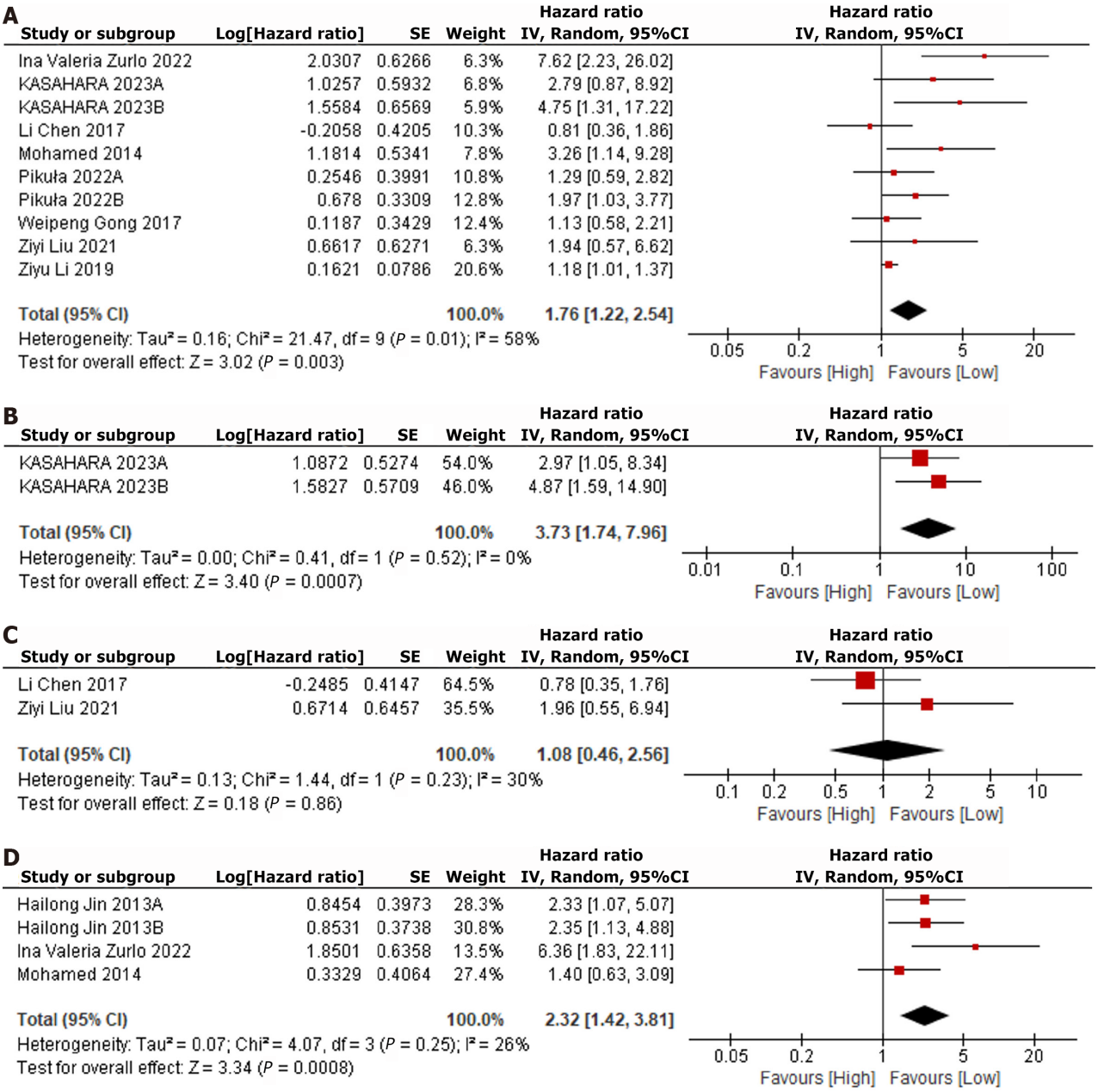

Figure 2 Forest plots for the association between neutrophil to lymphocyte ratio and overall survival, relapse-free survival, disease-free survival, progression-free survival. A: Forest plots for the association between neutrophil to lymphocyte ratio (NLR) and overall survival; B: Forest plots for the association between NLR and relapse-free survival; C: Forest plots for the association between NLR and disease-free survival; D: Forest plots for the association between NLR and progression-free survival. CI: Confidence interval.

patients. Compared with other prognostic indicators, NLR can comprehensively reflect the inflammatory status of the body[30] (involving not only the intensity of the inflammatory response, but also the overall function of the immune system). Therefore, NLR has high accuracy and reliability in predicting the prognosis of locally advanced or late stage GC patients. The study by Liu *et al*[15] has shown that an increase in NLR values is closely related to poor prognosis in GC patients. A high NLR value may indicate an exacerbation of inflammation in the patient's body, which may directly affect the growth and spread of tumors, or indirectly exacerbate the condition by affecting the body's immune response. A study by el Aziz *et al*[19] has revealed a correlation of elevated levels of NLR with poorer prognosis, shorter survival, and a relatively higher risk of recurrence. Therefore, as a reliable indicator for predicting the prognosis of GC, NLR holds marked potential for developing personalized treatment regimens, optimizing treatment strategies, and reducing recurrence and mortality rates. To date, limited research has been conducted to investigate the prognostic significance of NLR in GC patients undergoing NAC. Subsequently, an analysis was conducted to examine the association of NLR scores with the prognosis and survival in GC patients undergoing NAC.

In this meta-analysis, a comprehensive cohort of 852 patients was included to assess the prognostic significance of NLR in GC patients undergoing NAC. In the included original studies, patients were divided into a relatively high NLR group and a relatively low NLR group based on different thresholds, and the findings demonstrated a marked negative correlation of NLR with OS, RFS, and PFS, that is, the higher level of NLR indicted the worse prognosis. Kishi *et al*[31]

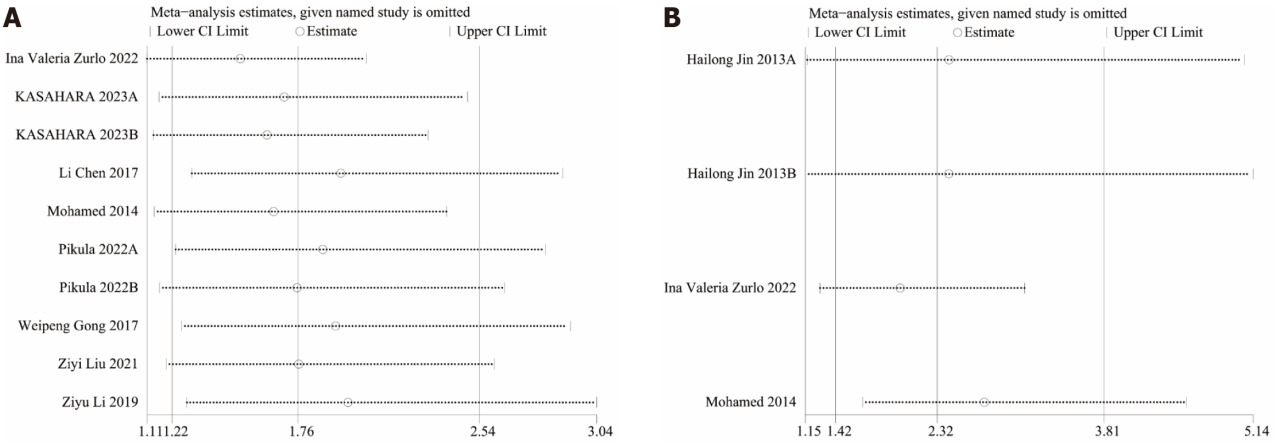

Figure 3 Sensitivity analysis of overall survival and progression-free survival. A: Sensitivity analysis of overall survival; B: Sensitivity analysis of progression-free survival. CI: Confidence interval.

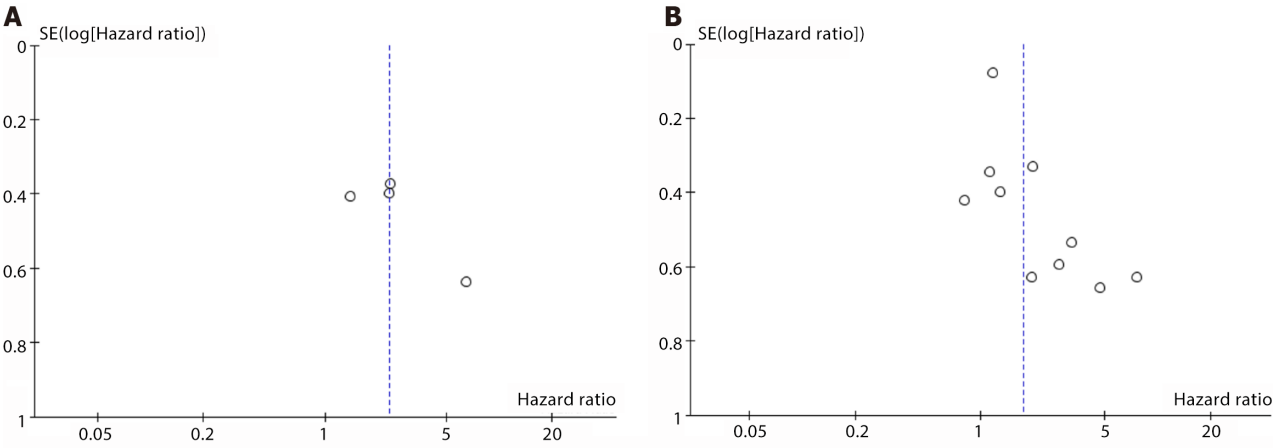

Figure 4 Funnel plot for the evaluation of publication bias for progression-free survival and overall survival. A: Funnel plot for the evaluation of publication bias for progression-free survival; B: Funnel plot for the evaluation of publication bias for overall survival.

reported on 38 patients with GC undergoing radical gastrectomy and postoperative chemotherapy showed that postoperative chemotherapy could normalize preoperative high levels of NLR, thereby improving patient survival. Therefore, NLR is a reliable factor in predicting the prognosis of GC patients undergoing chemotherapy. Another study showed that ovarian cancer patients undergoing NAC had better OS and PFS with lower NLR levels (HR = 1.72, 95%CI: 1.18-2.51)[32]. The results from above studies were consistent with our conclusion. It showed that after NAC, the lower level of NLR in GC patients indicated better OS and PFS. It could be concluded that the prognosis of patients could be evaluated by detecting the level of NLR. In contrast, our study focused on evaluating the prognosis of GC patients who lost the timing for surgery and only received NAC. After undergoing NAC in different malignant tumor, patient prognosis has also been significantly improved, indicating that NAC is particularly important in the treatment of malignant tumors. In this study, the relationship between NLR and DFS was not significant. This difference might be due to the fact that a very small number of GC patients could achieve DFS after receiving NAC, but there was a lack of studies on NLR data for these patients. It might also be related to differences in NLR detection time. We found that many studies conducted blood sampling within 2 to 6 weeks after the initial administration of chemotherapy drugs. Research evidence has suggested that activated white blood cells usually take at least 4 weeks to fully exert their effects after entering the bloodstream[33]. Thus, the reliability of the data obtained from blood sampling within 4 weeks after chemotherapy remains to be explored. Future research can verify whether changes in NLR detection time indeed affect clinical outcomes, and whether differences in detection time can affect patient prognosis.

To provide a more detailed analysis, subgroup analysis was conducted to further explore the relationship between NLR and OS. According to the study findings, NLR demonstrated predictive value for all indicators, except for those under 60 years old and Asian patients. For individuals under 60 years old, the predictive significance of NLR for OS was not marked (HR = 1.40, 95%CI: 0.79-2.48; P = 0.250), which might be correlated to the patient's immune system function and prognosis. Compared with older patients (≥ 60 years old), younger patients (< 60 years old) had a stronger immune system function, stronger anti-tumor ability, and better prognosis. Given the restricted number of included articles, a definitive conclusion regarding the predictive significance of NLR for OS in patients under 60 years old is currently lacking. Therefore, further studies are warranted to confirm whether NLR can predict the prognosis of patients under 60

years old. In addition, our research has shown that the predictive value of NLR for OS is significantly better in Europe and Africa than in Asia, which may be due to differences in the epidemiology, histopathological characteristics, and immune response of GC patients from different countries and races. First, there are significant differences in the incidence rate and OS rate of GC among Asia, Europe and other countries. The incidence rate and mortality rate of GC in Asia are generally high, while the incidence rate in Europe is relatively low[1]. This geographical difference may be related to specific genetic risk factors and different infectious agents (*Helicobacter pylori* infection is one of the leading pathogenic factors of GC in Asia) in the population. Secondly, there are differences in clinical characteristics among GC patients in different regions. According to the study by Janjigian *et al*[34], there are differences in the initial site, histological classification, and surgical approach of GC patients in Eastern and Western countries. These differences reflect the specificality of different populations in the occurrence and progression of GC, thereby affecting the application value of NLR in predicting GC in different regions.

The interplay between the systemic inflammatory response and tumor development is evident. The progression of tumors depends on the degree of systemic inflammatory response, which is an important component of the tumor microenvironment. Systemic inflammatory response can to some extent reflect the prognosis of patients. Some studies explored the mechanism of action of inflammatory factors in various malignant tumors, and found that a multifaceted interplay exists between tumor host immune and systemic inflammatory response[35-37]. When tumors damaged body tissues, it could trigger the local or systemic release of inflammatory factors from the immune system to fight against tumor invasion. In addition, various immune cells are polarized again in inhibiting the recruitment of cytotoxic immune cells, which disrupts the dynamic balance in tumor-host immune and promotes the occurrence and development of tumors. Various inflammatory indicators such as white blood cell, neutrophil, lymphocyte, monocyte, NLR, and PLR, are closely related to different types of tumors[38-42]. NLR has previously been identified as a reliable indicator for predicting the prognosis of GC patients. Saito *et al*[43] first proposed the correlation of NLR with survival in GC patients, and it was found that patients with high levels of NLR had poorer prognosis. Sahinli and Türker[44] have showed that the higher preoperative NLR level indicates the worse postoperative DFS and OS in GC patients. We need to explore why NLR can be an important indicator for predicting patient prognosis. When our tissues are infiltrated by tumor cells, our immune system will activate the systemic inflammatory response and release inflammatory cells to fight against the tumor microenvironment. As the main immune cells in the body, neutrophils and lymphocytes exert distinct effects during the anti-tumor immune response. Neutrophils inhibit our immune system and promote tumor progression, while lymphocytes inhibit the proliferation and migration of tumor cells through cytotoxic cell death. In particular, neutrophils exert promoting effects on tumor progression through various mechanisms. They contribute to the stimulation of tumor suppressor gene mutations, facilitate angiogenesis, secrete enzymes and cytokines that enhance tumor cell proliferation and metastasis, and actively reshape the extracellular matrix[45,46]. Lymphocytes play an important role in the anti-tumor process. When the systemic inflammatory effect of the body is triggered, a large amount of inflammatory factors are released, which further expose the suppression of innate cellular immune responses, resulting in a decrease in T8 lymphocytes and an increase in T4 helper lymphocytes, thus enhancing the anti-tumor effect[47]. Therefore, NLR shows the dynamic process of the body's inflammatory and immune response regulation. In addition, as an inflammatory indicator, NLR also reflects the transformation of this balance. When the body's inflammatory response and immune system are imbalanced, there is a chance to promote tumor growth. It can be concluded that high levels of NLR can promote tumor growth, weaken anti-tumor effects, and ultimately lead to poor prognosis in patients.

Although our meta-analysis provided reliable information, there were also some limitations. Firstly, the majority of the included studies in our analysis were performed in Asia, especially in China and Japan. One study was conducted in Africa, and three studies were conducted in Europe. Hence, it is essential to interpret our conclusions within the specific geographical contexts of the included studies. Caution is warranted when extrapolating our findings to patients residing in different regions, particularly the Americas and other geographical areas. Secondly, the majority of studies included employed a retrospective design rather than a prospective design. The retrospective design might introduce confounders that would affect the reliability of our results. Another limitation of the included studies was the variability in the cutoff values of NLR used. These thresholds ranged from 1.05 to 3. Due to inconsistency of data, inherent heterogeneity might be introduced in our meta-analysis. A subgroup analysis was conducted based on the NLR threshold, and it was found that the heterogeneity of the low NLR threshold (< 2.0) group (HR = 1.99; 95%CI: 1.01-3.94; P = 0.049; I^2 = 12%) was lower than that of the high NLR threshold (≥ 2.0) group (HR = 1.65; 95%CI: 1.11-2.46; P = 0.01; I^2 = 73%). Therefore, it can be concluded that the heterogeneity of OS may be related to different NLR thresholds. In the future clinical research process, we may consider the balance among multiple factors such as patient age, region, and NLR threshold, include patients of different age groups, determine multiple NLR thresholds, apply different analysis methods to determine the optimal NLR threshold, and conduct multi-center studies to avoid heterogeneity differences. In addition, there was publication bias in certain indicators in our study, indicating that the credibility of the evidence for these indicators needed further investigation. In order to improve reliability and comparability in future research, researchers must set up a standardized threshold for NLR.

CONCLUSION

To summarize, our meta-analysis findings indicate that in GC patients receiving NAC, high NLR is significantly correlated with shorter OS and PFS. However, the studies we included in the analysis still have issues such as a large number of retrospective studies, small sample sizes, high heterogeneity, and limited study areas. Consequently, there is a crucial need for a substantial number of prospective studies to confirm the efficacy and predictive value of NLR in GC

patients undergoing NAC.

FOOTNOTES

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