Clinicopathological and Prognostic Significance of Platelet-Lymphocyte Ratio (PLR) in Gastric Cancer: An Updated Meta-Analysis

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Abstract

Background
Systemic inflammatory parameters, such as the elevator PLR (platelet-lymphocyte ratio), have been found to be associated with the prognosis in gastric cancer (GC); however, the results remain controversial. So we aimed to evaluate the prognostic role of the PLR in gastric cancer by conducting this meta-analysis.

Methods
We performed a systematic literature search in PubMed, Embase and the Cochrane Library. The hazard ratio (HR) /Odds Ratio (OR) and its 95% confidence (CI) of survival outcomes and clinicopathological parameters were calculated.

Results
A total of 49 studies (51 cohorts) with 28,929 GC patients were included in the final meta-analysis. The pooled results showed that elevated PLR was significantly associated with poor overall survival (OS) (HR: 1.37, 95% CI: 1.26-1.49, p < 0.001; I² = 79.90%, Pₜ < 0.001) and disease-free survival (DFS) (HR 1.52, 95% CI 1.22-1.90, P < 0.001, I² = 88.6%, Pₜ < 0.001) of GC patients. Furthermore, patients with elevated PLR had a higher risk of lymph node metastasis (OR = 1.17, 95% CI: 1.02–1.33, p = 0.023), serosal invasion (T3 + T4) (OR = 1.34, 95% CI: 1.10–1.64, p = 0.003) and increased advanced stage (III + IV) (OR = 1.20, 95% CI: 1.06–1.37, p = 0.004).

Conclusions
This meta-analysis demonstrated that elevated PLR was a prognostic factor for poor OS and DFS, and associated with clinicopathological parameters in patients with GC.

Background
Gastric cancer (GC) is a kind of common malignant tumor and one of the main causes of cancer-related mortality and morbidity worldwide [1]. For patients with early-stage gastric cancer often have no symptoms, majority of patients are already diagnosed at an advanced stage. Complete or partial resection is the only potential curative treatment. However, most gastric cancer patients will suffer recurrence and metastasis after resection, which lead to the poor level of 5-year survival rate [2]. Because individual patients with different disease status and physical conditions should receive
individualized therapeutic regimens, it is essential to identification of more potential prognostic biomarkers and different risk groups. Therefore, strong prognostic markers are critical for the diagnosis and survival of gastric cancer patients to select tailor treatment.

The systemic inflammatory response (SIR), which is associated with the outcome of a variety of malignancies and tumor-related inflammation, is considered an important components of tumor progression [3]. Immune and inflammatory cells in peripheral blood, such as neutrophils, lymphocytes, platelets, monocytes, play important roles in the tumor microenvironment and lead to invasion and metastasis of tumor cells [4]. Some indexes of the SIR-related cells, such as the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR), have be used to predict survival and recurrence of various cancers, including gastric cancer [5–8]. Investigations have demonstrated that PLR, an important marker of SIR, is highly repeatable, cost-effective and widely available [9]. PLR is considered to be a marker of endogenous residual anticancer pre-inflammatory and pre-coagulative response that arises in malignancies [10]. Accumulated studies have reported the function of PLR in the diagnosis and prognosis of gastric cancer. For example, Kim et al. found that elevated PLR predicted poor overall survival (OS) and disease-free survival (DFS) in GC patients after surgery [11]. However, some other studies did not detect the significant prognostic value of PLR for GC patients [12, 13]. According to the results, the prognostic role of PLR in GC patients remains inconsistent. So we conducted this meta-analysis to evaluate the prognostic significance of PLR for OS and DFS, and the associations between PLR and clinicopathological features in GC patients.

Materials And Methods

Literature search

We performed a systematic literature search in PubMed, Embase and the Cochrane Library. The search strategy terms are as follows: (PLR or “platelet lymphocyte ratio” or “platelet-to-lymphocyte ratio” or “platelet-lymphocyte ratio”) and (“gastric cancer” or “gastric adenocarcinoma” or “gastric carcinoma” or “GC” or “gastric neoplasm” or “stomach tumor” or “stomach neoplasm”). The last search was updated to April 8, 2020. Only studies in English were included. This study was conducted
according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the selection process of the meta-analysis is shown in Fig. 1. No ethical approval and patient consent are required in this study.

**Inclusion and exclusion criteria**

Studies included in the meta-analysis need to meet the following criteria: (1) the diagnosis of gastric cancer must be confirmed by pathological examination; (2) there was available data to be investigated which was provided by the original article, such as HR and 95%CI for the OS and (or) DFS, the number of patients with various clinicopathological features; (3) the blood samples was obtained before treatment, PLR was calculated as the ratio of the platelets to lymphocytes; Studies were excluded based on the following criteria: (1) letters, conference abstracts, posters or review articles; (2) insufficient data to estimate from the article; (3) not human research or not published in English.

**Data extraction and quality assessment**

All studies were assessed independently by two authors according to the designed eligibility criteria. Any questions or disagreements were resolved by consulting another co-author. The extracted data from each study included: first author, publication year, country, study design (retrospective or prospective), study period, treatment regimens, follow-up time, cut-off value of PLR, the number of patients with various clinicopathological features, such as tumor location, differentiation, size, depths of tumor invasion, lymph node metastasis, TNM stage, HRs with 95% CIs of OS and DFS. The quality of each study was assessed according to the Newcastle-Ottawa Scale (NOS) by two authors [14]. Studies with an NOS score ≥ 6 were considered as high-quality researches.

**Statistical analysis**

HRs and 95% CIs for OS and DFS were obtained directly from each study if available or were calculated from the necessary data according to the methods published by Tierney [15]. Cochran’s Q test and Higgins I-squared statistic were used to evaluate the heterogeneity of pooled results. A p-value < 0.1 for the Q-test or $I^2 > 50\%$ indicated significant heterogeneity among studies, and the random-effects model (DerSimonian-Laird method) was performed to calculate the pooled HRs. Otherwise, the fixed-effects model (Mantel-Haenszel method) was applied [16]. Odds ratios (OR) and
95% CI were used to analysis the relationship between PLR and clinicopathological factors. Publication bias of the literature was evaluated by Begg’s funnel plot and Egger’s linear regression tests, and p > 0.05 indicated that there was no significant publication bias. Sensitivity analysis was performed by removing each single study in turn to validate the stability of the pooled results. All statistical analysis was performed with STATA software version 14.0 (STATA Corporation, College Station, TX, USA). Results with p < 0.05 were considered statistically significant, and all the results were two sided.

Results

Study characteristics

A total of 49 studies (51 cohorts) [7, 11–13, 17–61] with 28,929 GC patients were included in the final meta-analysis. As in Fan Feng’s study [37], the GC patients were included in a training set and a validation set independently, therefore, the two cohorts were extracted separately and named as Fan Feng(1) and Fan Feng(2). As same in Aldemir’s study, GC patients were divided into surgery group and chemotherapy group. So we named the two groups as Aldemir (1) and Aldemir (2) [60]. The selection process of the included studies according to the PRISMA guidelines was shown in Fig. 1. We summarized the characteristics of the included studies in Table 1. Among them, 10 studies were from Europe and the United States, 41 studies were from Asia. The patients from 27 studies had surgery treatment, while 8 studies of advanced-stage patients had chemotherapy strategy, and 6 studies of patients had mixed treatment (including chemotherapy, surgery, radiotherapy, targeted therapy and supportive care). The cut-off values of PLR used by the included studies varied from 10.1 to 350. Therefore, we selected PLR = 150 to divide the included studies in subgroup analysis. All studies with NOS scores ≥ 6 were regarded as high quality studies.

Table 1: Characteristics of included studies in meta-analysis.

| Author          | Year | Country | Ethnicity | Treatment | Follow-up (month) | Cut-off | Study period | Patients(n) | Survival analysis | NOS score |
|-----------------|------|---------|-----------|-----------|-------------------|---------|--------------|-------------|-------------------|-----------|
| Mehmet Aliustao glu | 2010 | Turkey  | Caucasian | Chemotherapy | NA                | 160     | 2004–2008    | 168         | OS                | 7         |
| Deshen Wang     | 2012 | China   | Asian     | Surgery   | 39.9(23.77–57.43) | 150/300 | 2006–2009    | 324         | OS/DFS            | 8         |
| Suee Lee        | 2013 | Korea   | Asian     | Chemotherapy | 14.9(1.47.9)   | 160     | 2007–2010    | 174         | OS                | 7         |
| Qing Wang       | 2014 | China   | Asian     | Mixed     | NA                | 160     | 2006–2014    | 439         | OS                | 7         |
| Author          | Year | Country | Ethnicity | Method       | Median OS | Median OS/DFS | OS/DFS 2007-2009 | OS/DFS 2017-2018 | Median OS/DFS 2013-2015 | Median OS/DFS 2016-2018 |
|-----------------|------|---------|-----------|--------------|-----------|---------------|--------------------|---------------------|------------------------|------------------------|
| Yoon Hai-Jeon   | 2014 | China   | Asian     | Surgery     | 214       | 280           | 8                  | 7                   | 8                      | 8                      |
| Nanjiang        | 2015 | China   | Asian     | Surgery     | 208       | 201           | 9                  | 2                   | 7                      | 7                      |
| Fan Wang        | 2015 | China   | Asian     | Surgery     | 235       | 201           | 7                  | 7                   | 7                      | 7                      |
| Kaiyu Sun       | 2015 | China   | Asian     | Surgery     | 140       | 45            | 7                  | 7                   | 7                      | 7                      |
| Xuechao Liu     | 2015 | China   | Asian     | Surgery     | 180       | 453           | 7                  | 7                   | 7                      | 7                      |
| Meral Gunaldi   | 2015 | Turkey  | Caucasian | Mixed       | 160       | 245           | 6                  | 6                   | 6                      | 6                      |
| M. Message      | 2015 | UK      | Caucasian | Surgery     | 192       | 153           | 8                  | 8                   | 8                      | 8                      |
| Qiwen Deng      | 2015 | China   | Asian     | Surgery     | 132       | 389           | 8                  | 8                   | 8                      | 8                      |
| Jun-Teh Hsu     | 2015 | China   | Asian     | Surgery     | 132       | 1030          | 8                  | 8                   | 8                      | 8                      |
| Eun Young Kim   | 2015 | Korea   | Asian     | Surgery     | 126       | 1986          | 7                  | 7                   | 7                      | 7                      |
| Aldemir(1)      | 2015 | Turkey  | Caucasian | Surgery     | NA        | 53            | 7                  | 7                   | 7                      | 7                      |
| Aldemir(2)      | 2015 | Turkey  | Caucasian | Chemotherapy| NA        | 50            | 7                  | 7                   | 7                      | 7                      |
| Wenyang Pang    | 2015 | China   | Asian     | Surgery     | 155.67    | 492           | 6                  | 6                   | 6                      | 6                      |
| Xin Zhou        | 2015 | China   | Asian     | Surgery     | 167       | 451           | 7                  | 7                   | 7                      | 7                      |
| Jin Wang        | 2015 | China   | Asian     | Chemotherapy| NA        | 273           | 7                  | 7                   | 7                      | 7                      |
| Neng Lou        | 2015 | China   | Asian     | Surgery     | 106       | 312           | 6                  | 6                   | 6                      | 6                      |
| Weipeng Gong    | 2015 | China   | Asian     | Surgery     | 161       | 91            | 8                  | 8                   | 8                      | 8                      |
| Kenichi Inaoka  | 2015 | Japan   | Asian     | Surgery     | 71        | 312           | 6                  | 6                   | 6                      | 6                      |
| Masayuki Urabe  | 2015 | Japan   | Asian     | Surgery     | 63.3      | 1363          | 8                  | 8                   | 8                      | 8                      |
| Shubin Song     | 2015 | China   | Asian     | Surgery     | 139.12    | 1990          | 8                  | 8                   | 8                      | 8                      |
| Fan Feng(1)     | 2015 | China   | Asian     | Surgery     | 130.675   | 1621          | 8                  | 8                   | 8                      | 8                      |
| Fan Feng(2)     | 2015 | China   | Asian     | Surgery     | 130.675   | 1622          | 8                  | 8                   | 8                      | 8                      |
| Kenji Mima Tsu  | 2015 | Japan   | Asian     | Surgery     | 200       | 33            | 7                  | 7                   | 7                      | 7                      |
| Kang Wang       | 2015 | China   | Asian     | Surgery     | 120       | 444           | 8                  | 8                   | 8                      | 8                      |
| Harry E. Fuentes| 2015 | USA     | Caucasian | Mixed       | 260       | 112           | 7                  | 7                   | 7                      | 7                      |
| Mikito Mori     | 2015 | Japan   | Asian     | Surgery     | 149.4     | 100           | 7                  | 7                   | 7                      | 7                      |
| Hongtai Shi     | 2015 | China   | Asian     | Surgery     | 135       | 688           | 8                  | 8                   | 8                      | 8                      |
| Yuchen Pan      | 2015 | China   | Asian     | Surgery     | 115       | 870           | 8                  | 8                   | 8                      | 8                      |
| Guangsheng Zhu  | 2015 | China   | Asian     | Surgery     | 117.78    | 248           | 7                  | 7                   | 7                      | 7                      |
| Hai-Jeon Yoon   | 2015 | Japan   | Asian     | Surgery     | 10.1      | 134           | 8                  | 8                   | 8                      | 8                      |
| Yan Zhang       | 2015 | China   | Asian     | Mixed       | 172       | 182           | 7                  | 7                   | 7                      | 7                      |
| Ji Lin          | 2015 | China   | Asian     | Surgery     | 116.85    | 670           | 7                  | 7                   | 7                      | 7                      |
| A. Ramos-esquibel| 2015 | Costa Rica | Caucasian | Mixed       | 350       | 381           | 7                  | 7                   | 7                      | 7                      |
| Jiaxin          | 2015 | UK      | Caucasian | Surgery     | 150       | 668           | 7                  | 7                   | 7                      | 7                      |
PLR and prognosis of GC

There were 44 cohorts with 26,901 GC patients evaluating PLR for OS [7, 11–13, 17, 19–27, 29–34, 37, 38, 41–51, 53–61]. The main results of this meta-analysis are listed in Table 2. We found that elevated PLR was significantly associated with a worse outcome for OS (HR: 1.37, 95% CI: 1.26–1.49, p < 0.001), and significant heterogeneity was observed ($I^2 = 79.90\%, P_h < 0.001$, Table 2, Fig. 2).
Table 2
Main results of the meta-analysis

| Factors          | No. of studies | No. of patients | Effects model | HR (95% CI)   | p   | Heterogeneity |
|------------------|----------------|-----------------|---------------|---------------|-----|---------------|
|                  |                |                 |               | p             |     |               |
| OS               | Overall        | 44              | 26901         | Random        | 1.37(1.26–1.49) | < 0.001 | 79.90% | < 0.001 |
| Ethnicity        | Caucasian      | 9               | 1981          | Random        | 1.31(0.96–1.79) | 0.092 | 84.10% | < 0.001 |
| Treatment        | Chemotherapy   | 7               | 967           | Random        | 1.34(0.96–1.88) | 0.084 | 76.10% | < 0.001 |
|                  | Surgery        | 31              | 24128         | Random        | 1.39(1.26–1.52) | < 0.001 | 79.10% | < 0.001 |
|                  | Mixed          | 6               | 1806          | Random        | 1.38(0.98–1.93) | 0.062 | 88.20% | < 0.001 |
| Cut-off          | <=150          | 20              | 15181         | Random        | 1.36(1.20–1.54) | < 0.001 | 75.00% | < 0.001 |
|                  | > 150          | 23              | 10357         | Random        | 1.42(1.24–1.63) | < 0.001 | 78.50% | < 0.001 |
| Sample size      | <=500          | 29              | 6924          | Random        | 1.42(1.24–1.64) | < 0.001 | 75.70% | < 0.001 |
|                  | > 500          | 15              | 19977         | Random        | 1.34(1.20–1.50) | < 0.001 | 85.00% | < 0.001 |
| DFS              | Overall        | 10              | 5354          | Random        | 1.52(1.22–1.90) | < 0.001 | 88.60% | < 0.001 |
| Abbreviations: HR: hazard ratio; 95% CI: 95% confidence interval; $P_h$: p values of Q test for heterogeneity test; OS: overall survival; DFS: disease-free survival.

Subgroup analysis was performed stratified by ethnicity, treatment, cut-off value of PLR and sample size. The results showed that elevated PLR had more significantly prognostic value for OS in Asian populations (HR: 1.39, 95% CI: 1.28–1.52, p < 0.001; $I^2 = 79.20\%$, $P_h < 0.001$), but not in Caucasian populations. Furthermore, when different treatment methods were considered, elevated PLR significantly predicted shorter OS in patients receiving surgery treatment (HR: 1.39, 95% CI: 1.26–1.52, p < 0.001; $I^2 = 79.10\%$, $P_h < 0.001$), but did not have prognostic efficiency for patients receiving chemotherapy or mixed treatment. Considering different cut-off values, both PLR with cut-off value > 150 (HR: 1.42, 95% CI: 1.24–1.63, p < 0.001; $I^2 = 78.50\%$, $P_h < 0.001$) and <= 150 (HR: 1.36, 95% CI: 1.20–1.54, p < 0.001; $I^2 = 75.00\%$, $P_h < 0.001$) predicted poor OS for GC. Of note, we found that PLR, as a negative prognostic marker, was significantly associated with the OS in GC patients both in sample size <= 500 groups (HR: 1.42, 95% CI: 1.24–1.64, p < 0.001; $I^2 = 75.70\%$, $P_h < 0.001$) and > 500 groups (HR: 1.34, 95% CI: 1.20–1.50, p < 0.001; $I^2 = 85.00\%$, $P_h < 0.001$; Table 2).
Ten studies with 5354 subjects explored the influence of PLR on DFS of GC patients [7, 11, 12, 20–22, 24, 26, 42, 44, 47]. The pooled data of our meta-analysis indicated that the PLR was associated with DFS (HR 1.52, 95%CI 1.22–1.90, P < 0.001, I² = 88.6%, P_h < 0.001) (Table 2, Fig. 3).

PLR and clinicopathological parameters of GC
To further explore the impact of PLR on the clinicopathological parameters in GC, we extracted the patient amounts from parts of included studies in PLR high and PLR low groups according to the TNM stage, tumor differentiation, depth of invasion, tumor size, tumor location, lymph node metastasis. As shown in Table 3, in comparison to low PLR groups, the high PLR groups had a higher risk of lymph node metastasis (n = 15, OR = 1.17, 95% CI: 1.02–1.33, p = 0.023), serosal invasion (T3 + T4) (n = 13, OR = 1.34, 95% CI: 1.10–1.64, p = 0.003) and increased advanced stage (III + IV) (n = 16, OR = 1.20, 95% CI: 1.06–1.37, p = 0.004). Whereas elevated PLR value was not shown to be associated with tumor size, tumor differentiation and tumor location.

Table 3
Meta-analysis of the association between PLR and clinicopathological parameters of GC.

| Variable                              | No. of studies | No. of patients | Effects  | OR (95% CI) p | Heterogeneity |
|---------------------------------------|----------------|-----------------|----------|---------------|--------------|
| Tumor differentiation (Moderate/High vs. Poor) | 18             | 6721            | Fixed    | 1.04(0.98–1.11) | 0.173        | 7.30%   | 0.367   |
| Tumor location (Cardia vs. Non-cardia) | 10             | 2905            | Fixed    | 0.99(0.87–1.12) | 0.837        | 6.00%   | 0.386   |
| Tumor size (< = 5 vs. >5 cm)          | 8              | 2596            | Random   | 1.04(0.88–1.23) | 0.634        | 74.20%  | <0.001  |
| Lymph node metastasis (No vs. Yes)    | 15             | 6752            | Random   | 1.17(1.02–1.33) | 0.023        | 71.90%  | <0.001  |
| Depth of invasion (T1–T2 vs. T3–T4)   | 13             | 6250            | Random   | 1.34(1.10–1.64) | 0.003        | 86.20%  | <0.001  |
| TNM (Tis-II vs. III-IV)               | 16             | 6834            | Random   | 1.20(1.06–1.37) | 0.004        | 77.30%  | <0.001  |

Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval; P_h: p values of Q test for heterogeneity test.

Sensitivity analysis
We performed sensitivity analysis for the OS by removing every single study at a time to check if individual study influenced the results. The results of the sensitivity analysis were shown in Fig. 4. The corresponding pooled HRs did not substantially change, which indicated that the results of our meta-analysis were stable and robust.
Publication bias
Begg’s funnel plot and the Egger’s linear regression test were performed to assess publication bias. The figure of the Begg’s funnel plot showed obvious asymmetry (Fig. 5) and Egger’s tests ($P = 0.004$) indicated significant publication bias. However, our finding that elevated PLR is associated with lower OS did not change after the adjustment for publication bias using the trim and fill method [62].

Discussion
The current meta-analysis was designed to investigate the prognostic value of elevated PLR for DFS and OS in GC patients. Pooled results demonstrated that elevated PLR was associated with poor OS and DFS. Moreover, elevated PLR was correlated with lymph node metastasis, serosal invasion and advanced TNM stage with GC.

Despite the development of new surgical techniques and the use of chemotherapy and radiotherapy, gastric cancer still remains one of the main causes of cancer-related mortality and morbidity worldwide [63]. Because individual GC patients present with different conditions, including different degrees of invasion, differentiation and TNM stages, the survival outcomes may vary. Therefore, identification of more prognostic factors and different risk groups would contribute to the optimization of individualize treatment. It is important to identify a reliable biomarker, which is simple, low-cost, and effective, to predict the prognosis of patients with gastric cancer.

In recent years, the studies about the relationship between the inflammation and tumor have been developed. Inflammatory cells are critical factors in the tumor cell micro-environment and important for repair of tissue damage [64-66]. The inflammation results are involved in lymphocytopenia, neutrophilia, thrombocytosis and leukocytosis [67, 68]. The tumor-generated inflammatory reaction may contribute to tumor growth, progression and metastasis through several mechanisms, including the up-regulation of inflammatory mediators and cytokine, aberrant activation of immune regulatory cytokines, suppression of apoptosis, and DNA damage [65]. Recently, emerging evidence indicates that inflammatory reaction is an important factor for the initiation, progression and prognosis of numerous cancers, such as GC [69, 70]. Helicobacter pylori infection in GC is characterized by an inflammatory infiltrate, consisting mainly of neutrophils and T cells [71]. Moreover, circulating
lymphocytes were reported that could reflect patient’s inflammatory status [72]. Thus, some inflammation-based parameters, such as lymphocyte count, systemic immune-inflammation index (SII), platelet-lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR), have been used to predict survival and recurrence in cancer patients [44, 73–76].

The PLR, which combines platelet and lymphocyte counts, is a representative index of systemic inflammation and immune status [77, 78]. Accumulating evidence indicates the correlation of PLR with different stages of tumor development, chemotherapeutic response and prognostic survival outcomes of GC patients [38, 42, 78]. The specific mechanisms involved are complex and remains unclear. One potential explanation is that a decreased PLR may reflect four disadvantages including an inflammatory status, immune disorders, malnutrition and a tendency for micro-vessel thrombosis [39, 79]. Lymphocytes have an important role in cancer immune surveillance and prevent development of malignancy [80]. A pro-inflammatory status leads to compromised cell-mediated immunity and an impaired T-lymphocytic response via cytokines [81]. The decrease in CD4 + T-helper lymphocytes may result in a suboptimal lymphocyte mediated immune response to tumor cells [82]. The T-lymphocytic cell-mediated malnutrition is a major cause of delayed wound healing [83, 84].

Platelet count is an additional index of a systemic inflammatory response and potential micro-vessel thrombosis, which could inhibits wound healing via the deterioration of blood circulation in tissues [11, 77, 85]. Otherwise, Aggregated platelets can promote tumor growth via releasing pro-angiogenic mediators within the micro-vasculature of tumors [86]. Platelets also inhibit tumor cell extravasation by potentiating tumor-cell-induced endothelial cell retraction, and enhance tumor cell adhesion and spreading across the extracellular matrix, which contribute to the promotion of tumor cell proliferation and metastasis [87]. Therefore, lymphocytopenia and thrombocytosis are considered as negative prognostic markers in various cancers [88–91]. However, a decreased lymphocyte count or an increased platelet count alone may not reflect the host systemic inflammatory response and tumorigenesis process. Thus, the PLR, which combines platelet and lymphocyte counts, may reflect the bonding prognostic information of these two processes, which could be a stronger predictor of outcome in GC than platelet or lymphocyte count alone. In addition, the value of PLR could be
acquired from the routine laboratory tests, which provides clinical implications at a low cost. Accumulated studies have assessed the association between PLR and the diagnosis and prognosis of gastric cancer. Some studies showed that elevated PLR predicted poor OS and DFS in GC patients after surgery [22, 24]. However, some other studies did not detect the significant prognostic value of PLR for GC patients [7, 47]. Lian et al. reported that low PLR levels correlated with better clinicopathological features, including decreased depth of invasion, less lymph node metastasis and early tumor stage [44]. Recently, a meta-analysis containing 8 studies comprising 4,513 patients was conducted and showed that PLR was not a reliable predictor for OS in patients with GC, while another meta-analysis including 13 studies with 6,280 patients indicated that elevated PLR could be a significant prognostic biomarker for poor OS [92, 93]. Thus, the prognostic value of the PLR remains inconclusive in gastric cancer. So we conducted this update meta-analysis to evaluate the prognostic role of the PLR in gastric cancer.

The current study, including 49 studies (51 cohorts) with 28,929 GC patients, not only investigated the prognostic value of PLR for OS and DFS, but also explored the associations between PLR and clinicopathological characteristics of GC. This analysis demonstrated that elevated PLR lead to a higher risk of lymph node metastasis, increased serosal invasion (T3 + T4) risk and advanced stage (III + IV) in patients with gastric cancer. Although the specific mechanism is still incompletely understood, our results are in accordance with other studies about various cancers, such as pancreatic ductal adenocarcinoma, hepatocellular carcinoma and colorectal cancer [94–98]. Previous meta-analysis did not find significantly association between PLR and OS or DFS in GC, maybe because of the limited studies included [92, 93]. Our meta-analysis including much more studies suggested that elevated PLR might have powerful prognostic efficiency for poor OS in GC and could predict shorter DFS in GC. What’s more, subgroup analyses for OS revealed the similar result in Asian populations, but not in Caucasian populations. Moreover, we also eliminated the effect of different treatment methods on the prognostic value of the PLR. Our results showed that elevated PLR significantly predicted shorter OS in patients receiving surgery treatment, but did not have prognostic efficiency for patients receiving chemotherapy or mixed treatment. Except for the reason of too few
studies included, another possible major reason is that the patients in the chemotherapy or mixed groups have huge differences in medical conditions and disease status, resulting in inability to obtain significant results. To evaluate the effect of different cut-off values on the prognostic value of PLR in GC patients, subgroup analyses showed that patients with elevated PLR suffered worse OS than those with low PLR, regardless of the different cut-off values. The same effects were indicated in the subgroup analyses by different sample size of patients. These results might strengthen the possibility that PLR could act as a reliable prognostic biomarker in GC.

There were some limitations need to be addressed in this meta-analysis. Firstly, the inclusion criteria of this meta-analysis were constrained to studies published in English language only. So publication bias cannot be excluded. Secondly, almost all the included studies were retrospective, which could contribute to more susceptible to some biases. Fortunately, the asymmetry in the funnel plots showed no significantly publication bias, thus maintaining the substantial consistency of the results. Thirdly, different cut-off values of PLR were used in each study which could contribute to the heterogeneity. Subgroup analysis was conducted based on the different PLR cut-off values, while the results were not substantially change. Therefore, further well-designed studies, especially randomized controlled trials (RCTs) are needed to determine the most appropriate cut-off value of PLR to predict the complication risks and survival outcomes in patients with GC.

Conclusions
In conclusion, we found that elevated PLR was a prognostic factor for poor OS and DFS in GC patients. Furthermore, elevated PLR was correlated with a higher risk of serosal invasion, lymph node metastasis and advanced TNM stage (III + IV) in gastric cancer. The present study suggests that the PLR could provide reliable information before treatment for patients with gastric cancer.

Abbreviations
HR: hazard ratio; OR: odds ratio; 95% CI: 95% confidence interval; Ph: p values of Q test for heterogeneity test; OS: overall survival; DFS: disease-free survival. PLR: platelet-lymphocyte ratio; GC: gastric cancer; SIR: systemic inflammatory response; NLR: neutrophil to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; NOS: Newcastle-Ottawa Scale;

Declarations
Ethics approval and consent to participate

All the data supporting our findings in this paper were freely downloaded from the PubMed, EMBASE, the Cochrane Library. No ethical approval or written informed consent for participation was required.

Consent for publication

Not applicable.

Availability of data and materials

All data for this study are publicly available and are ready for the public to download at no cost from the official websites of the PubMed, EMBASE, the Cochrane Library. There is no need to have the formal permission to use data for this study. The sources and data robustness have been described in the section of “Methods”.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

XZ, WZ and YY were involved in drafting the manuscript. XQ and LS made contributions to the concepts, acquisition and analysis of the data. CZ was involved in acquisition of data and preparing the Figs. LY and GL designed and revised the manuscript. All authors have read and approved the final manuscript.

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Figures

Figure 1

The flow diagram of publications selection.
Figure 2

The forest plot between elevated PLR and OS in GC patients.
Figure 3

The forest plot between elevated PLR and DFS in GC patients.
Figure 4

Sensitivity analysis of PLR for OS in GC patients.
Begg’s funnel plot of publication bias test for OS in GC patients.