

## Research Article

### Prognostic Value of Platelet-To-Lymphocyte Ratio in Oncologic Outcomes of Gastric Cancers: What Should We Expect from a Meta-Analysis?

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#### Abstract

**Background:** Platelet to lymphocyte ratio (PLR) was observed to be a marker of poor prognosis in patients with Gastric Neoplasm. However, the PLR prognostic role in Gastric Neoplasm is still inconsonant. The goal of this analysis was to understand the relation between PLR and outcomes in patients with Gastric Neoplasm by meta-analysis.

**Methods:** Interrelated literatures were retrieved from EMBASE, web of science, PubMed, Ovid and Cochrane library databases. Risk ratio

(HR) and 95% confidence interval (CIs) were used as performance indicators for meta-analysis. Altogether 14,052 patients in 29 articles contained in the meta-analysis last. Outcomes were analyzed using random effect methodology, regression analysis, and sensitivity analyses.

**Results:** The summary outcomes displayed that the increase of PLR was significantly related to the decrease of OS (HR: 1.526, 95% CI: 1.268-1.836,  $p=0.001$ ) in patients with Gastric Neoplasm and OS (HR: 1.01, 95% CI: 1.00-1.02,  $p=0.000$ ) in patients with Gastric Neoplasm. Subgroup analysis showed that a higher PLR values significantly indicated worse OS in Asian human populations, patients at early stage, sample size>200 and patients receiving chemotherapy. Sensitivity analysis reveal the stabilization of our consequence. The results of regression analysis of sample size display that the sample size was related to heterogeneity. The adjusted random effects pooled HRs which method of the trim-and-fill showed a statistically significant relation of OS and PLR level.

**Conclusion:** This meta-analysis findings revealed that elevated PLR probably indicates poor prognosis for the patients of Gastric Neoplasm.

**Keywords:** Gastric Neoplasm; Meta-analysis; PLR; Prognosis

#### Abbreviations

CI: Confidence Interval

GN: Gastric Neoplasm

HR: Risk Ratio

LVI: Lymphatic Vessels Invasion

NLR: Neutrophil to Lymphocyte Ratio

NOS: Newcastle-Ottawa Scale

OS: Overall Survival

PLR: Platelet to Lymphocyte Ratio

VPI: Visceral Pleural Invasion

#### Background

As the fourth most pervasive malignant illness and the second reason of cancer-related mortalities worldwide, Gastric Neoplasm (GN) have an overall poor survival [1,2]. Surgery is the only possible way to achieve results in radical gastrectomy. According to the pathological type and clinical stage of Gastric Neoplasm in advanced patients, a biologic target therapy method combining perioperative chemotherapy, radiotherapy and comprehensive treatment should be developed. Since excess treatment can extend survival time of 10-20% of cancer patients with partial or holistic progression, it is urgent to distinguish high-stake patients with worse prognosis so that new stronger programs can be initiated as early as possible to improve survival [3].

Previous studies have determined that the stage, large tumor size, presence of lymphatic vessels (LVI) or Visceral Pleural Invasion (VPI)

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and other clinicopathological features are the characteristics of worse prognosis in early GN [4-6]. However, the current staging system for GN is insufficient for indicating the outcome of treatment and reflecting the underlying biological heterogeneity of the results. Except for TNM staging, other factors can only be assessed after surgery [7]. Therefore, it is of major implications to study non-invasive and readily available preconditioning variables to assess survival outcomes for Gastric Neoplasm. A growing body of evidence shows that the inflammatory response may contain a momentous part in the progress of tumors [8-11]. Inflammation factors, such as C-Reactive Protein Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), and Glasgow Prognostic Score have assessed in multitudinous types of tumors [12-16]. PLR as an indicate of systemic inflammation was linked to worse prognostic for multifarious caners including ovarian cancer, carcinoma of the lungs, and Lower gastrointestinal carcinoma and so on [17-20].

Recent researches have shown that PLR has potential prognostic effects in sick people with GN. However, In the light of their findings, there are still inconsistencies regarding the role of PLR in the prognosis of GN. Meta-analysis can surmount the limitations of disparate sample sizes in unit research to produce optimal estimates. So, it is especially important to explore the prognostic function of PLR comprehensively and systematically in Gastric Neoplasm by meta-analysis. In this research, our objective is to predictive the possible prognostic function of pretreatment PLR in GN by write a meta-analysis of all qualified published articles.

## Methods

### Search strategy

We conducted an integrated search of the literature without date limitation as show below: Web of Science, PubMed, The Cochrane Library, Embase, Scopus, and Ovid databases. All the literatures were updated to May 31, 2020. The main search terms used to generate the search strategy included: “Stomach Neoplasms” (e.g., “Gastric Neoplasm”, “Cancer of Stomach”, “Gastric Neoplasm,” “Stomach Cancers” and “Gastric Neoplasm”) and “PLR” (e.g., “Platelet ratio of lymphocyte” and “platelet-lymphocyte ratio”). The reference of all enrolled articles was examined for correlation articles.

### Inclusion and exclusion criteria

In this meta-analysis, articles were choose based on the major inclusion criteria as show below:

1. The diagnosis of Gastric Neoplasm was definite by preoperative biopsy or postoperative pathological examination.
2. Serum based methods was used to quantify PLR.
3. The PLR and overall survival (OS) were correlation.

The general exclusion criteria for our study were as show below:

1. Case reports, letters, abstracts, review articles, or nonclinical research.
2. Articles were limited to those written in English;
3. Articles was simply not enough data for 95% confidence interval (CI) and estimating hazard ratio (HR);
4. Articles with duplicate analysis or repeat data reported in other studies.

### Data extraction and quality assessment

All candidate articles were carefully screened independently by two authors. The articles, which may not be categorized based on titles and abstracts were evaluated full-text search. When occurred the controversy, agreement was attained in discussion with a third author. For each article, Evaluation items were as follows: the first author's name, total number of cases, publication year, region, gender, cut-off value, follow ups, tumor type, treatment strategy, HRs with 95% Cis and study design. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included articles independently by two reviewers. Studies with NOS scores  $\geq 6$  was assigned for high-grade articles.

### Statistical analysis

The HR and 95%CI directly obtained from each article. If  $HR^1$ , it represents that GN patients with elevator PLR expression have a poor prognosis. Higgins I-squared and Cochran's Q test statistic were used to evaluate the heterogeneity among the enrolled trials. Sensitivity analysis was used for assessing risk of bias of individual studies. Pooled HRs, 95% CIs, and p-values were generated employing both fixed-effects (Mantel-Haenszel method) and random effects (DerSimonian-Laird method) models. A random-effects model was used for significant heterogeneity and a fixed-effects model for insignificant heterogeneity. Sources of heterogeneity were explored and explained by subgroup analysis, sensitivity analysis and meta-regression among the outcomes of different articles. Potential Publication bias was evaluated by Egger's tests and Begg funnel plot, with  $p^0.05$  indicating significant asymmetry. All Statistical Hypothesis Testing were two-sided and values of  $p^0.05$  were identified as statistically significant. All the statistical calculations and analyses were done with STATA statistical software version 12.0 (Texas State University, USA).

## Results

### Study characteristics

Altogether 519 studies were obtained from the originally search strategies. 29 articles published between 2009 and 2020 with in all 14, 052 patients were ultimately drawn in our meta-analysis [21-49]. We have summarized the study selection process in a flow diagram (Figure 1). The majority of participants were Asian (69%) and others (31%) were Caucasian. Eleven articles were from China, four articles were from Japan, three articles were done in Korea and USA, respectively, two in UK, one in Singapore, Jordan and Turkey, respectively. All HRs and 95% CIs were founded directly in original articles. Nine of these articles enrolled  $\wedge 200$  patients and about 20 articles had more than 200 patients. And the cut-off values of PLR were not consistent across included articles which varied from 80 to 200. This meta-analysis included patients at all stages of disease. Sufficient information of OS and PLR in patients with GN was offered in all of the 29 articles. Studies characteristics are summarized in Table 1, Figure 1 shows a flow chart of the search results and the number of studies contained in this meta-analysis.

### PLR and OS in gastric neoplasm

Summarize the data from all the articles revealed that the increased PLR was conspicuous contact with worse OS (HR: 1.01, 95% CI: 1.00–1.02,  $P=0.000$ ) and a significant heterogeneity was discovered

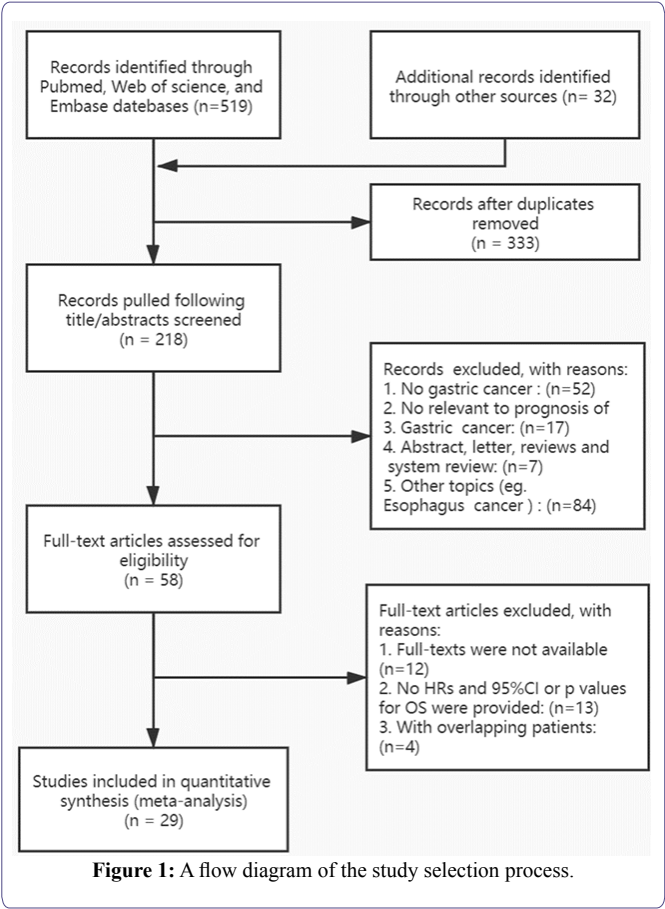
( $I^2=88.8\%$ ,  $PH=0.001$ , Table 2, Figure 2). To find the possible source of heterogeneity, subgroup analyses enrolled by ethnicity, tumor stage, sample size, variable analysis, treatment methods and PLR cut-off were done, the results revealed that the rise of PLR had more conspicuous prognostic function for OS in Asian populations (HR: 1.0, 95% CI: 1.0–1.01,  $p=0.00$ ;  $I^2=76.4\%$ ,  $PH=0.248$ ). In addition, when classification by the processing method, increased PLR conspicuous indicated worse OS in patients take in chemotherapy (HR: 1.17, 95% CI: 0.82–1.68,  $P<0.001$ ) has significant heterogeneity

( $I^2 = 92.3\%$ ,  $PH=0.143$ ), But having a mixing process of patients with no prognosis efficiency: (HR 1.41, 95% CI: 1.21–1.64,  $p^0.00$ ;  $I^2=81\%$ ,  $PH=0.068$ ). It is worth noting that PLR with a cutoff value greater than 160 still suggest a worse OS for GN (HR: 1.01, 95% CI: 1.00–1.02,  $p^0.001$ ;  $I^2=87$ . When  $PLR \leq 160$ , the prognostic efficiency disappeared (HR: 1.41, 95% CI: 1.11–1.81,  $P=0.00$ ;  $I^2=91.5\%$ ,  $PH=0.005$ ). Interestingly, increased PLR display worse OS in patients with early cancer (Table 2).

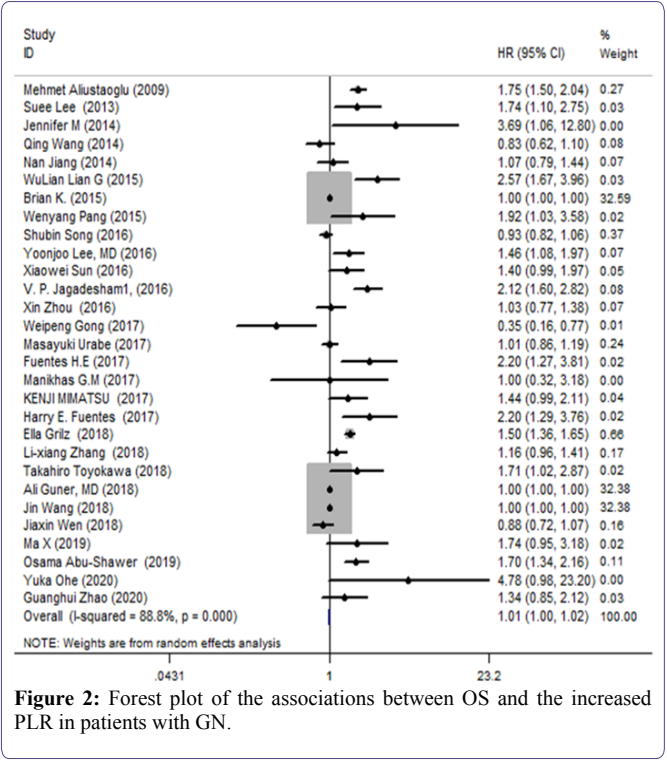
Author	Year	Study region	Ethnicity	Sample size	Follow up (months)	Treatment	Median age	Cut off	Outcome	Stage	HR	NOS score
Weipeng Gong	2017	China	Asian	111	22	chemotherapy	60.00	161	OS	Whole	R(M)	6
WuLian Lian G	2015	China	Asian	162	60	Surgery	56.30	208	OS	Whole	R(U)	7
Ella Grilz	2018	Vienna	Caucasian	1,469	24	Combined	61.00	264	OS	Whole	R(M)	7
Brian K.	2015	Singapore	Asian	312	43.5	Surgery	62.50	275	OS	Early	P(U)	7
Li-xiang Zhang	2018	China	Asian	904	60	Combined	60.00	160	OS	Whole	R(M)	7
Ma X	2019	China	Asian	119	75	Combined	61.00	160	OS	Whole	R(M)	8
Wenyang Pang	2015	China	Asian	492	60	Combined	63.00	155.67	OS	Whole	R(U)	6
Masayuki Urabe	2017	Japan	Asian	2054	63.3	Surgery	64.00	150.6	OS	Whole	R(M)	8
Takahiro Toyokawa	2018	Japan	Asian	240	100.5	Combined	64.50	188	OS	Advanced	R(M)	6
Shubin Song	2016	China	Asian	1,990	37	Surgery	62.00	139.12	OS	Whole	R(M)	8
Osama Abu-Shawer	2019	Jordan	Asian	502	150	Combined	54.00	150	OS	Whole	R(M)	7
Fuentes H. E	2017	United States	Caucasian	112	21.3	chemotherapy	58.00	150	OS	Whole	R(M)	6
Yoonjoo Lee, MD	2016	Korea	Asian	312	1.5	Combined	65.00	200	OS	Early	R(M)	5
Ali Guner, MD	2018	Korea	Asian	1032	12	Surgery	60.00	124.71	OS	Whole	P(U)	6
Yuka Ohe	2020	Japan	Asian	41	60	Combined	65.00	180	OS	Advanced	R(M)	7
Jennifer M	2014	Canada	Caucasian	93	39.1	Surgery	61.25	245.2	OS	Whole	P(U)	6
Xiaowei Sun	2016	China	Asian	305	24	Combined	57.00	120	OS	Whole	R(U)	8
Jin Wang	2018	China	Asian	273	6	chemotherapy	57.00	150	OS	Advanced	R(U)	6
Suee Lee	2013	Korea	Asian	174	14.9	chemotherapy	60.00	160	OS	Whole	R(M)	6
Guanghai Zhao	2020	China	Asian	110	11.6	chemotherapy	65.00	143.39	OS	Advanced	R(M)	6
Qing Wang	2014	China	Asian	439	40	Surgery	50.00	160	OS	Advanced	R(M)	7
V. P. Jagade-sham	2016	UK	Caucasian	199	48	Combined	63.00	125.3	OS	Advanced	R(M)	6
Mehmet Aliustaoglu	2009	Turkey	Caucasian	168	45	chemotherapy	60.10	160	OS	Advanced	R(U)	6
Xin Zhou	2016	China	Asian	451	37.7	Combined	60.00	142.5	OS	Whole	R(U)	6
Manikhas G.M	2017	United States	Caucasian	32		chemotherapy	60.00	245.9	OS	Whole	R(M)	6
Nan Jiang	2014	China	Asian	850	42	Combined	64.00	184	OS	Whole	P(M)	6
Jiaxin Wen	2018	UK	Caucasian	723	10	Combined	66.00		OS	Advanced	P(U)	6
KENJI MI-MATSU	2017	Japan	Asian	271		Combined	68.00	150	OS	Advanced	R(U)	6
Harry E. Fuentes	2017	USA	Caucasian	112	21.3	Combined	58.00	260	OS	Advanced	R(M)	7

**Table 1:** Key characteristics of all articles in the meta-analysis.

OS: Overall Survival; HR: Hazard Ratio; 95% CI, 95% confidence interval; pH value, P values of Q test for heterogeneity test; U: Univariate; M: Multivariate. NOS: Newcastle Ottawa Quality Assessment Scale. Combined, treatment contain chemotherapy, surgery and radiotherapy.



data of the combined ORs, each individual research was omitted every time. Detail on sensitivity analysis are shown in Figure 3. With sequential omitted of each single article, the overall results were essentially unchanged, this further supports the stabilization of our outcomes.



Sensitivity analysis

A sensitivity analysis was done to identify potential sources of heterogeneity. For the sake of explore the effect of the individual

Analysis	N	References	Random-effects model		Fixed-effects model		Heterogeneity	
			HR (95%CI)	p	HR (95%CI)	p	I <sup>2</sup>	pH
OS	29	1-29	1.01(1.00, 1.02)	0	1.00(1.00, 1.00)	0	88.80%	0.0001
Subgroup 1: Surgery	6	23, 28, 32, 34-35, 40	1.00(1.00, 1.01)	0	1.00(1.00, 1.00)	0	79.30%	0
Chemotherapy	6	21, 37-39, 42, 44	1.17(0.82, 1.68)	0	1.00(1.00, 1.00)	0	92.30%	0.1432
Combined	17	22, 24-26, 28-31, 33, 36, 41, 43, 45-49	1.41(1.21, 1.64)	0	1.29(1.22, 1.37)	0	81.00%	0.0687
Subgroup 2: Asian	21	21, 23-29, 31-33, 35-40, 42-43, 45, 47, 49	1.00(1.00, 1.01)	0	1.00(1.00, 1.00)	0	76.40%	0.248
Caucasian	8	22, 30, 34, 41, 42, 44, 46, 48	1.63(1.27, 2.08)	0	1.5(1.4, 1.61)	0	84.00%	0
Subgroup 3: cutoff value>160	18	24-27, 28-30, 32, 36-43, 46-47	1.01(1.00, 1.02)	0	1.00(1.00, 1.00)		87.20%	0.135
cutoff value≤160	11	21-23, 31, 33-35, 44-45, 48-49	1.41(1.11, 1.81)	0	1.00(1.00, 1.00)		91.50%	0.005
Subgroup 4: Early stage	2	23, 31	1.17(0.81, 1.69)	0.014	1.00(1.00, 1.00)	0.014	83.40%	0.392
Advanced stage	10	33, 37, 39-42, 46-49	1.38(1.09, 1.76)	0	1.00(1.00, 1.00)	0	91.20%	0.008
Whole stage	17	21-22, 24-27, 28-30, 32, 34-36, 38, 43-45	1.29(1.12, 1.49)	0	1.00(1.00, 1.00)	0	88.80%	0.001
Subgroup 5: sample size≤200	12	21, 25, 30, 33-34, 35, 38-39, 41-42, 44, 48	1.77(1.41, 2.21)	0.004	1.8(1.62, 2.01)	0.004	59.60%	0
sample size>200	17	22-24, 26-29, 31-32, 36-37, 40, 43, 45-47	1.00(1.00, 1.01)	0	1.00(1.00, 1.00)	0	85.90%	0.173
Subgroup 6: Univariate analysis	10	23, 26, 32, 34-36, 42-43, 46-47	1.00(1.00, 1.01)	0	1.00(1.00, 1.00)	0	89.60%	0
Multivariate analysis	19	21, 22, 24-25, 27-31, 33, 37-41, 44-45, 48	1.30(1.13, 1.50)	0	1.00(1.00, 1.00)	0	89.10%	0.309

Table 2: Summary of the meta-analysis results.

N: Number of Studies; HR: Hazard Ratio; 95% CI: 95% Confidence Interval; PH: P values of Q test for Heterogeneity Test; OS: Overall Survival.

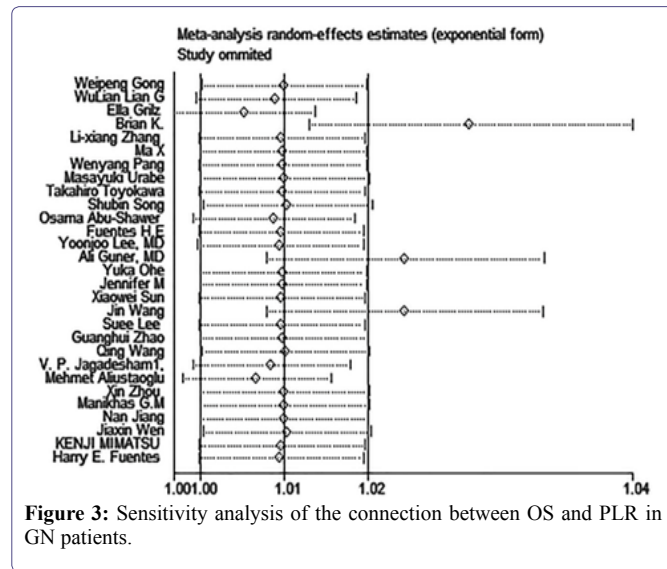


Figure 3: Sensitivity analysis of the connection between OS and PLR in GN patients.

## Meta regression analysis

The regression analysis of sample size showed that Sample size was related to heterogeneity, which could explain 55% of the heterogeneity. Cut off value, Stage, variable, therapy, design, follow up Months, age, had no obvious correlation with heterogeneity (Figure 4).

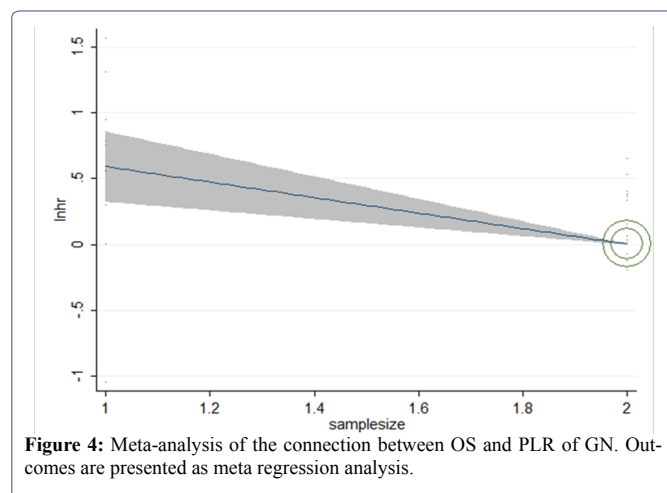


Figure 4: Meta-analysis of the connection between OS and PLR of GN. Outcomes are presented as meta regression analysis.

## Publication bias

The publication bias was tested by the Berg Funnel Diagram and the Egger line regression. Publication bias was not detected by the funnel plot, but OS publication bias may test by Egger's line regression test ( $P^{|t|}=0.000$  for Egger's test and  $Pr^{|z|}=0.378$  for Begg's test (Figures 5 and 6). The dissymmetry of contour funnel plot was obvious suggested there could be publication bias (Figure 6). The hollow circles explain a number of missing articles that locate in the non-signification region of the plot, indicated that the asymmetry was partly attributed to publication bias, which was further ascertained with the Egger's test ( $p^{|t|}=0.001$ ). The adjusted random affects amalgamative HRs of 1.007 (95% CI, 0.998 to 1.017) achieved using the trim-and-fill method, which was concurrent with our primary analysis (Figure 7).

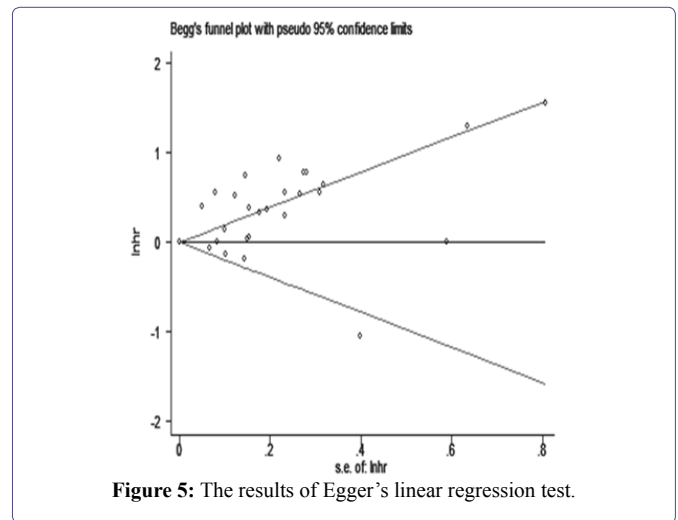


Figure 5: The results of Egger's linear regression test.

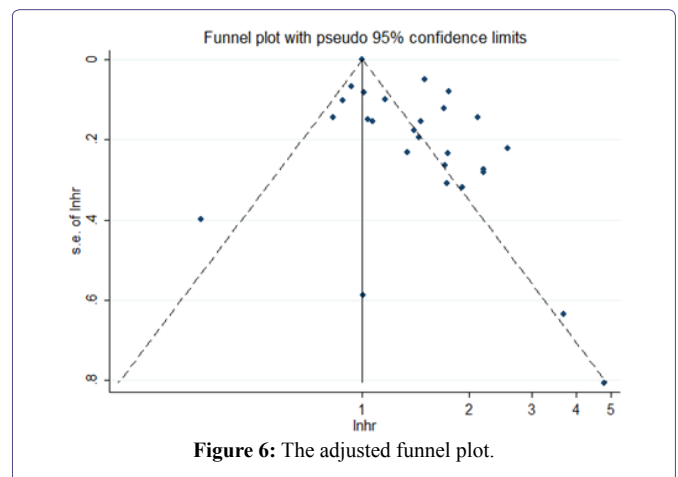


Figure 6: The adjusted funnel plot.

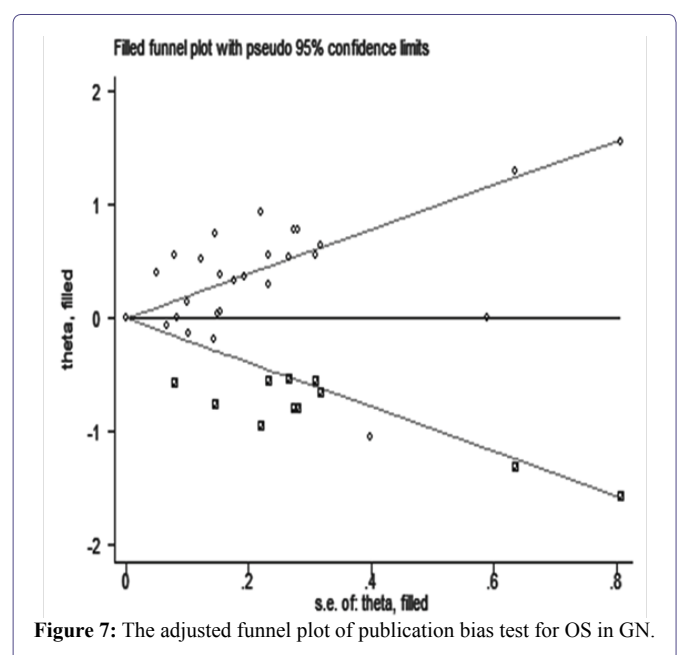


Figure 7: The adjusted funnel plot of publication bias test for OS in GN.

## Discussion

A good deal of articles was reported the prognostic function of PLR standard in Gastric Neoplasm patients, but the role of it was inconclusive and inconsistent. So, we write meta-analysis to acquire a clearer estimation of the prognostic function of PLR in GN by evaluate the published articles. Our meta-analysis assembly the results of 14, 052 GN patients from 29 single articles, predicating that increased PLR significantly indicted worse OS (HR: 1.01,95%CI: 1.00–1.02,  $P < 0.001$  Figure 2) of GN patients. Subgroup analyses stratified by ethnicity, tumor stage, sample size, variable analysis, treatment methods and PLR cut-off were done, the outcomes revealed that the increased PLR had higher conspicuous prognostic role for OS in Asian populations. In addition, when categorized via treatment methods, the increased PLR significantly indicated lower OS in patients accepting chemotherapy with obvious heterogeneity. It is worth noting that PLR with cutoff value greater than 160 still indicates worse OS of GN.

Sensitivity analysis showed the coincident pooled HRs did non-significant change when every single research was moved out. The Sensitivity analysis results clips verified the stabilization of our work. The regression analysis of sample size revealed that the sample size was related to heterogeneity (Figure 3). The regression analysis of sample size displayed that Sample size could explain 55% of the heterogeneity. (Figure 4). Publication bias is done via Begg's funnel plot and Egger's line regression test route. Publication bias was not discovered by the funnel plot, but OS publication bias may detect by Egger's line regression test (Figure 5). The asymmetry of contour funnel plot was obvious, indicating that there may be exist publication bias (Figure 6). The adjusted random effects pooled HRs of 1.007(95% CI, 0.998 to 1.017) gained via the trim-and-fill method, which was coincident with our primary analysis (Figure 7). Taking all these results into account, PLR is an important marker in the prognosis of GN.

Cancer- interrelated inflammation responses play a significant role at disparate stages of cancer progression including initiation, promotion, and metastasis [50-52]. The exact mechanisms underlying the processes between tumor and inflammation in these cancer patients are remain elusive at present [53]. There has been a growing appreciation that the inflammation plays a crucial part of the progression of malignancies [54]. Platelets can enhance the tumor growth and metastasis by platelet-derived thrombospondin, platelet factor and growth factor [55]. It has been suggested that tumor-infiltrating T cells accelerate cancer growth and proliferate through the suppression by anti-tumor immune responses [56]. Therefore, PLR can mirror an improved host inflammatory reactivity to more aggressive tumor biology and higher cancer burden [57].

PLR, which can beneficial to the clinical decision-making process with respect to GN treatment and results, is a promising prognostic inflammation biomarker. There were a few limitations of this analysis need to be elaboratively take into account. First, there was significant heterogeneity in the study time including sample size (12=55%,  $P=0.002^{*}0.05$ ). The origin of heterogeneity cannot be fully traced, although the use of sensitivity analysis and meta regression analysis, Second, the study was excluding the articles published not in English language, so the possibility of publication bias cannot be excluded. Furthermore, Heterogeneity may influence the explain of the outcomes of our meta-analyses. Heterogeneity could be due to a variety of factors, such as age distribution, Gender, PLR Cut-Off Value and so on.

## Conclusion

In conclusion, this meta-analysis suggests that the increased PLR might be an inexpensive and effective prognostic factor of patients with GN. In future, more articles are necessary to explore these findings in the future.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and materials

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

### Competing interests

The authors declare that they have no competing interests.

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### Author contributions

WeiHong Kuang designed the study and had full access to all data in the study and take responsibility for the integrity of data and the accuracy of the data analysis. Jie Liu had roles in the data analysis, literature searches, and was a major contributor in writing the manuscript. Lin yang had roles inpatient management, data analysis, and data interpretation. Yichun Ji contributed to data collection. Dongfeng Chen and Meiling Zhu responsibility for the experiments designed of the study and data collection. All authors contributed to approved and reviewed the final version of the manuscript. Jie Liu and Jianjiang Hua share the first authorship; the order in which they are listed was determined by workload.

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