Clinicopathological and Prognostic Significance of Platelet-Lymphocyte Ratio (PLR) in Gastric Cancer: A 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 38 studies (39 cohorts) with 23,317 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: 1.25-1.51, p < 0.001; I2= 82.10%, Ph < 0.001) and disease-free survival (DFS) (HR 1.52, 95%CI 1.22–1.90, P< 0.001, I2= 88.6%, Ph< 0.001) of GC patients. Furthermore, patients with elevated PLR had a higher risk of lymph node metastasis (OR = 1.33, 95% CI: 1.03–1.70, p=0.027), serosal invasion (T3 +T4) (OR = 1.58, 95% CI: 1.09–1.31, p=0.017) and increased advanced stage (III+IV) (OR = 1.37, 95% CI: 1.00–1.89, p=0.050). 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.

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 October 13, 2019. 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 Figure 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 $\geq$ 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 et al. [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 I2 > 50% indicated significant heterogeneity among studies, and the random-effects model (DerSimonian-Laird method) was performed to calculate the pooled HRs [14]. 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 38 studies (39 cohorts) [7, 11-13, 17-50] with 23,317 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 Feng1 and Fan Feng2. The selection process of the included studies according to the PRISMA guidelines was shown in Figure 1. We summarized the characteristics of the included studies in Table 1. Among them, 6 studies were from Europe and the United States, 32 studies were from Asia. The patients from 25 studies had surgery treatment, while 3 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.

PLR and prognosis of GC

There were 33 cohorts with 21,581 GC patients evaluating PLR for OS[7, 11-13, 17, 19-27, 29-34, 37, 38, 41-50]. 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: 1.25-1.51, p < 0.001), and significant heterogeneity was observed (I^2= 82.10%, P_h < 0.001, Table 2, Figure 2).

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: 1.37, 95% CI: 1.24-1.51, p < 0.001; I^2= 81.40%, 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: 1.25-1.54, p < 0.001; I^2= 80.70%, 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: 1.46, 95% CI: 1.23-

1.75, p < 0.001; I^2= 81.40%, P_h < 0.001) and <=150 (HR: 1.35, 95% CI: 1.17-1.55, p < 0.001; I^2= 78.30%, 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 and >500 groups (HR: 1.43, 95% CI: 1.22-1.68, p < 0.001; I^2= 79.10%, P_h < 0.001) and <=150 (HR: 1.33, 95% CI: 1.17-1.52, p < 0.001; I^2= 85.50%, 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, I^2= 88.6%, P_h< 0.001) (Table 2, Figure 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 =14, OR = 1.33, 95% CI: 1.03–1.70, p=0.027), serosal invasion (T3 +T4) (n =12, OR = 1.58, 95% CI: 1.09–1.31, p=0.017) and increased advanced stage (III+IV) (n =14, OR = 1.37, 95% CI: 1.00–1.89, p=0.050). Whereas elevated PLR value was not shown to be associated with tumor size, tumor differentiation and tumor location.

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 Figure 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 did not show any evidence of obvious asymmetry (Figure 5). Egger's tests (P=0.087) indicated that no publication bias was found in this meta-analysis either.

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 [51]. 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 [52-54]. The inflammation results are involved in lymphocytopenia, neutrophilia, thrombocytosis and leukocytosis [55, 56]. 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 [53]. Recently, emerging evidence indicates that inflammatory reaction is an important factor for the initiation, progression and prognosis of numerous cancers, such as GC [57, 58]. Helicobacter pylori infection in GC is characterized by an inflammatory infiltrate, consisting mainly of neutrophils and T cells [59]. Moreover, circulating lymphocytes were reported that could reflect patient's inflammatory status [60]. 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, 61-64].

The PLR, which combines platelet and lymphocyte counts, is a representative index of systemic inflammation and immune status [65, 66]. Accumulating evidence indicates the correlation of PLR with different stages of tumor development, chemotherapeutic response and prognostic survival outcomes of GC patients [38, 42, 66]. 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, 67]. Lymphocytes have an important role in cancer immune surveillance and prevent development of malignancy [68]. A pro-inflammatory status leads to compromised cell-mediated immunity and an impaired T-lymphocytic response via cytokines [69]. The decrease in CD4+ T-helper lymphocytes may result in a suboptimal lymphocyte mediated immune response to tumor cells [70]. The T-lymphocytic cell-mediated malnutrition is a major cause of delayed wound healing [71, 72]. 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, 65, 73]. Otherwise, Aggregated platelets can promote tumor growth via releasing pro-angiogenic mediators within the micro-vasculature of tumors [74]. 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 [75]. Therefore, lymphocytopenia and thrombocytosis are considered as negative prognostic markers in various cancers [76-79]. 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 [80, 81]. 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 38 studies (39 cohorts) with 23,317 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 [82-86]. Previous meta-analysis did not find significantly association between PLR and OS or DFS in GC, maybe because of the limited studies included [80, 81]. 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; P_h: 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. Funding The work was supported by Youth Research Fund Project of the Health and Family Planning Commission of Nantong (WQ2015052), the Project for Medical Key Youth Talent of Nantong (Youth 005) 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. Acknowledgements Not applicable.

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Tables

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 Aliustaoglu	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
Dawei Yuan	2014	China	Asian	Surgery	NA	150	2009-2012	280	OS/DFS	7
Nan Jiang	2014	China	Asian	Surgery	42(1-103)	184	2005-2007	377	OS	8
Lian Lian	2015	China	Asian	Surgery	60	208	2007-2010	162	OS/DFS	8
Fen Wang	2015	China	Asian	Chemotherapy	40	235	2010-2011	120	NA	6
KaiYu Sun	2015	China	Asian	Surgery	55.75(0.8-186)	140	1998-2008	632	OS	8
Xuechao Liu	2015	China	Asian	Surgery	NA	180	2015-2010	455	OS	7
Meral Gunaldi	2015	Turkey	Caucasian	Mixed	11.5	160	NA	245	OS	6
M. Messager	2015	UK	Caucasian	Surgery	31.8(4-131)	192	2001-2014	153	OS/DFS	8
Qiwen Deng	2015	China	Asian	Surgery	24(3-60)	132	2007-2009	389	OS/DFS	8
Jun-Te Hsu	2015	China	Asian	Surgery	30	132	2005-2011	1030	OS	8
Eun Young Kim	2015	Korea	Asian	Surgery	NA	126	2000-2009	1986	OS/DFS	7
Wenyang Pang	2016	China	Asian	Surgery	NA	155.67	2009-2011	492	NA	6
Xin Zhou	2016	China	Asian	Surgery	NA	167	2006-2008	451	OS	7
Neng Lou	2017	China	Asian	Surgery	NA	106	2006-2014	312	NA	6
Weipeng Gong	2017	China	Asian	Surgery	22(8-67)	161	2007-2015	91	OS	8
Kenichi Inaoka	2017	Japan	Asian	Surgery	NA	71	1999-2016	312	NA	6
Masayuki Urabe	2017	Japan	Asian	Surgery	63.3	NA	1999-2014	1363	OS/DFS	8
Shubin Song	2017	China	Asian	Surgery	37(3-108	139.12	2007-2011	1990	OS	8
Fan Feng(1)	2017	China	Asian	Surgery	24.9(1-75)	130.675	2008-2015	1621	OS	8
Fan Feng(2)	2017	China	Asian	Surgery	24.9(1-75)	130.675	2008-2015	1622	OS	8
Kenji Mima Tsu	2017	Japan	Asian	Surgery	NA	200	2006-2016	33	OS	7
Kang Wang	2017	China	Asian	Surgery	45(1-185)	120	1994-2005	444	OS	8
Harry E. Fuentes	2017	USA	Caucasian	Mixed	21.3(9.5-42.6)	260	2010-2015	112	OS	7
Mikito Mori	2018	Japan	Asian	Surgery	37(5-108)	149.4	2006-	100	NA	7

							2017			
Hongtai Shi	2018	China	Asian	Surgery	36(1-75)	135	2012-2014	688	OS	8
YuChen Pan	2018	China	Asian	Surgery	59.9	115	2008-2012	870	OS	8
Guangsheng Zhu	2018	China	Asian	Surgery	NA	117.78	2010-2016	248	OS	7
Hai-Jeon Yoon	2018	Japan	Asian	Surgery	34.5（6.5-74.8）	10.1	2011-2016	134	OS/DFS	8
Yan Zhang	2018	China	Asian	Mixed	NA	172	2011-2014	182	OS/DFS	7
Ji lin	2018	China	Asian	Surgery	NA	116.85	2015-2016	670	OS	7
A. Ramos-Esquivel	2018	Costa Rica	Caucasian	Mixed	13.21(0-84)	350	2009-2012	381	OS/DFS	7
Jiaxin Wen	2018	UK	Caucasian	Surgery	NA	150	2003-2015	668	OS	7
Osama Abu-Shawer	2019	Jordan	Asian	Mixed	NA	150	NA	447	OS	7
Xinran Zhang	2019	China	Asian	Surgery	44.9(1-188.9)	168.5	2000-2010	2752	OS	8
Cuixia Liu	2019	China	Asian	Surgery	NA	152.2	2009-2012	400	NA	6

Abbreviations: NA: not available; OS: overall survival; DFS: disease-free survival; NOS: Newcastle-Ottawa Scale.

Table 2. Main results of the meta-analysis

	Factors	No. of studies	No. of patients	Effects model	HR (95% CI)	*p*	Heterogeneity I2	Heterogeneity P_H
OS	**Overall**	33	21581	Random	1.37(1.25-1.51)	<0.001	82.10%	<0.001
	Ethnicity							
	Caucasian	6	1727	Random	1.42(0.94-2.15)	0.097	87.20%	<0.001
	Asian	27	19854	Random	1.37(1.24-1.52)	<0.001	81.40%	<0.001
	Treatment							
	Chemotherapy	2	342	Random	1.22(0.64-2.32)	0.553	84.20%	0.012
	Surgery	25	19433	Random	1.39(1.25-1.54)	<0.001	80.70%	<0.001
	Mixed	6	1806	Random	1.38(0.98-1.93)	0.062	88.20%	<0.001
	Cut-off							
	<=150	17	14043	Random	1.35(1.17-1.55)	<0.001	78.30%	<0.001
	>150	15	6175	Random	1.46(1.23-1.75)	<0.001	81.40%	<0.001
	Sample size							
	<=500	21	5689	Random	1.43(1.22-1.68)	<0.001	79.10%	<0.001
	>500	12	15892	Random	1.33(1.17-1.52)	<0.001	85.50%	<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.

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

Variables	No. of studies	No. of patients	Effects model	OR (95% CI)	p	Heterogeneity I^2	Heterogeneity P_H
Tumor differentiation (Moderate/High vs. Poor)	15	6098	Fixed	1.09(0.97-1.22)	0.144	7%	0.375
Tumor location (Cardia vs. Non-cardia)	8	2503	Fixed	1.04(0.85-1.27)	0.710	0%	0.897
Tumor size (<=5 vs. >5cm)	7	1692	Random	1.03(0.64-1.65)	0.902	78%	<0.001
Lymph node metastasis (No vs. Yes)	14	6460	Random	1.33(1.03-1.70)	0.027	73.40%	<0.001
Depth of invasion (T1–T2 vs. T3–T4)	12	5958	Random	1.58(1.09-2.31)	0.017	86.90%	<0.001
TNM (Tis-II vs. III-IV)	14	5638	Random	1.37(1.00-1.89)	0.05	80.00%	<0.001

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

Figures

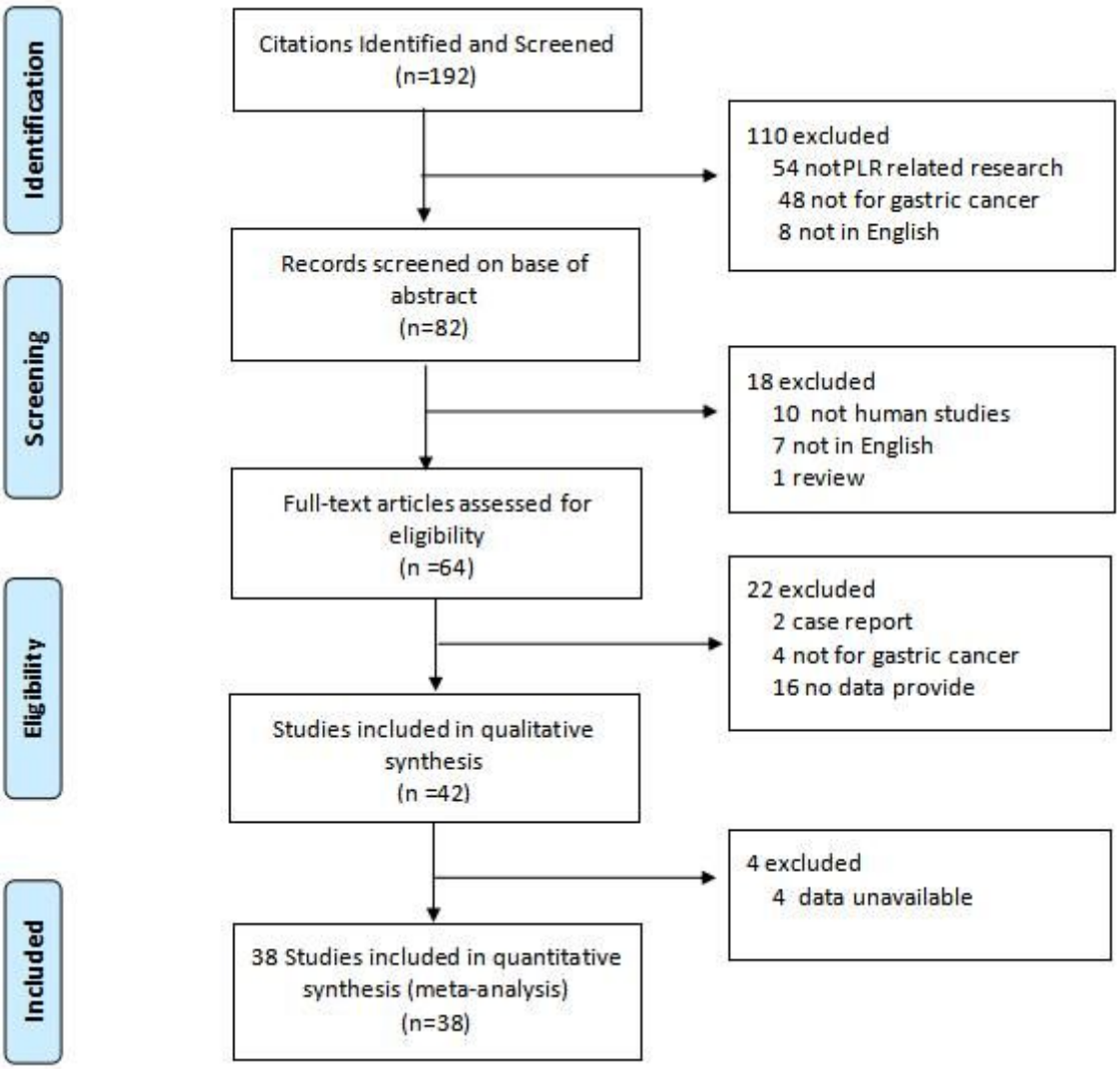

Figure 1

The flow diagram of publications selection.

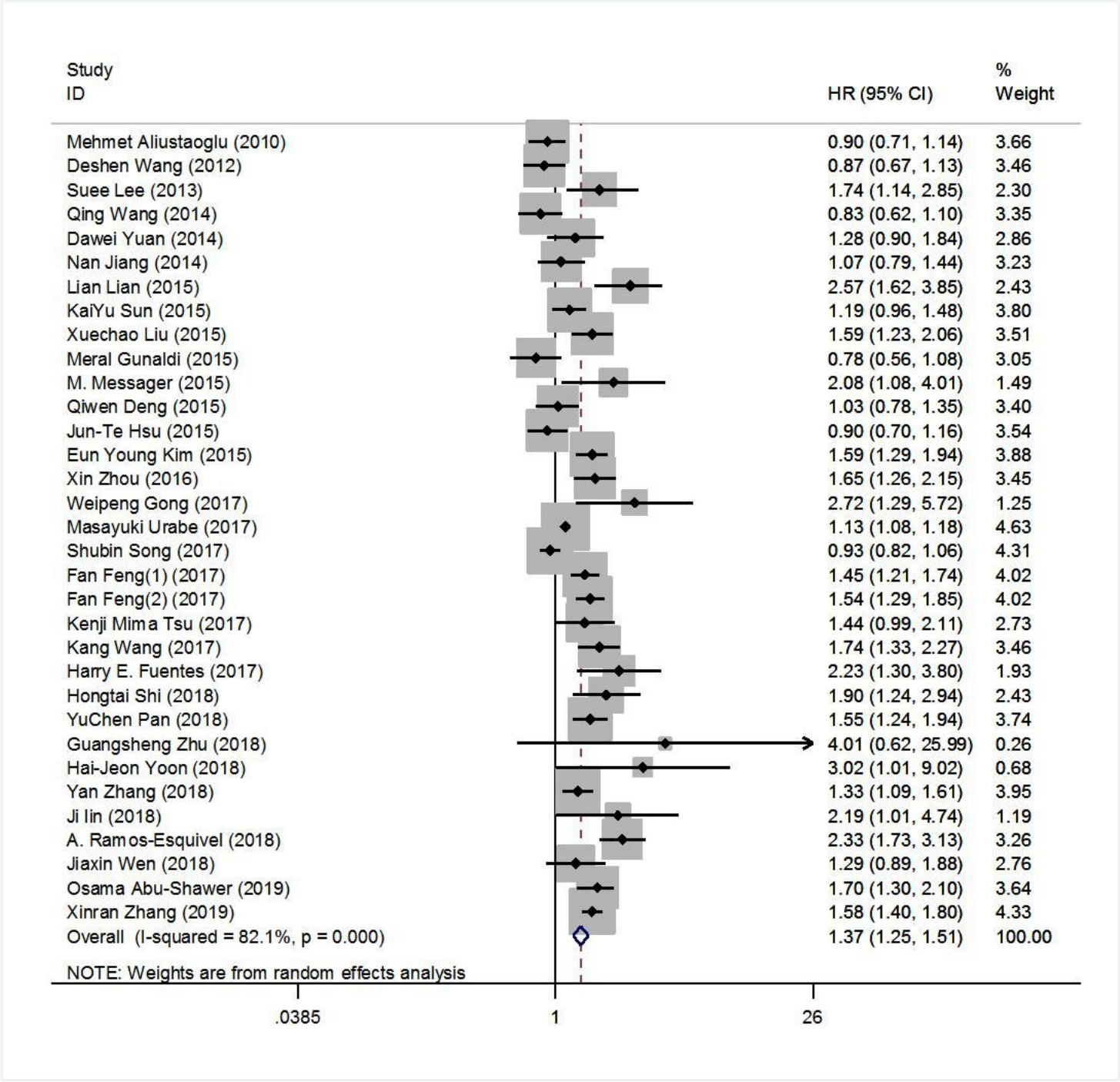

Figure 2

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

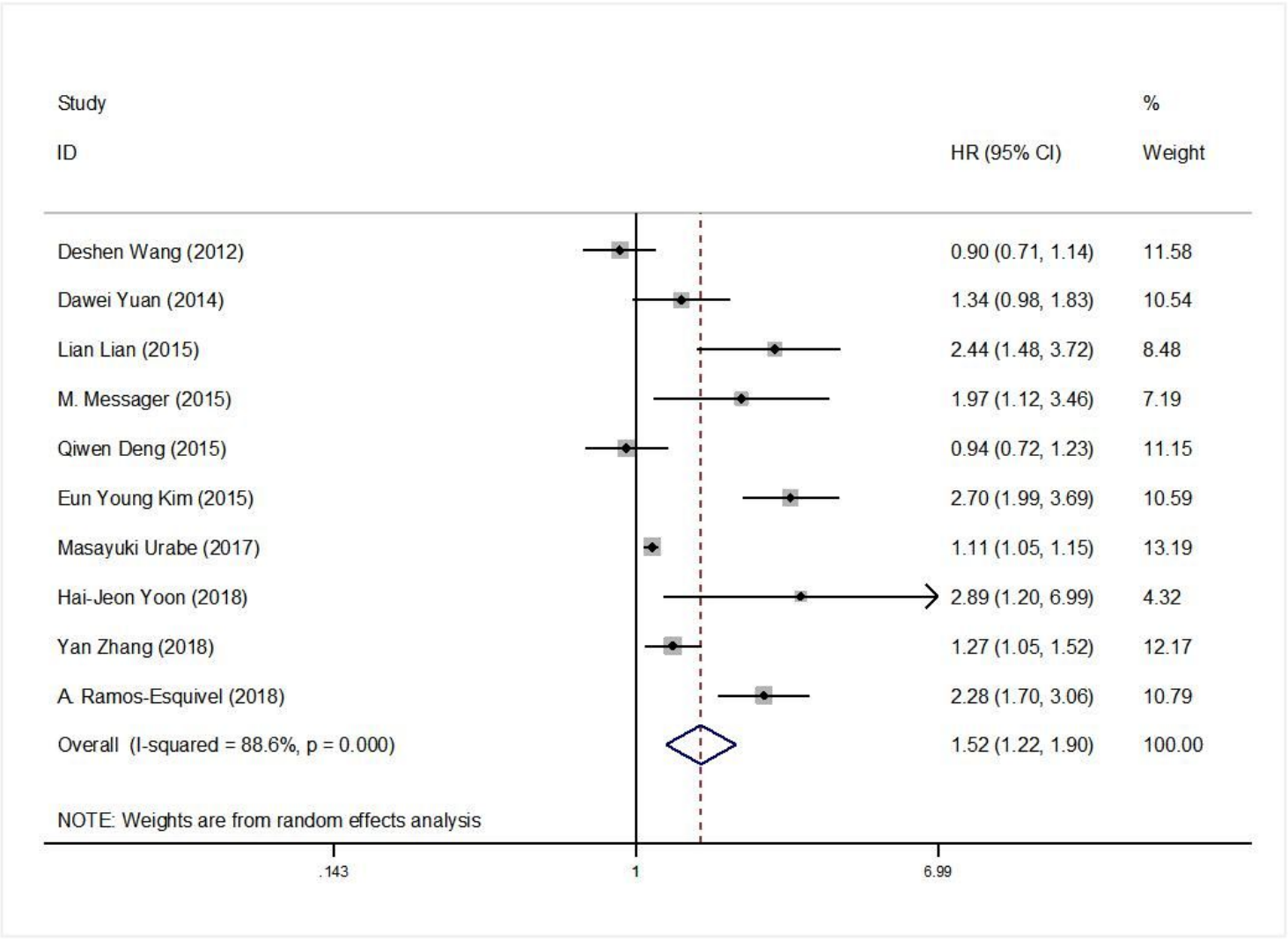

Figure 3

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

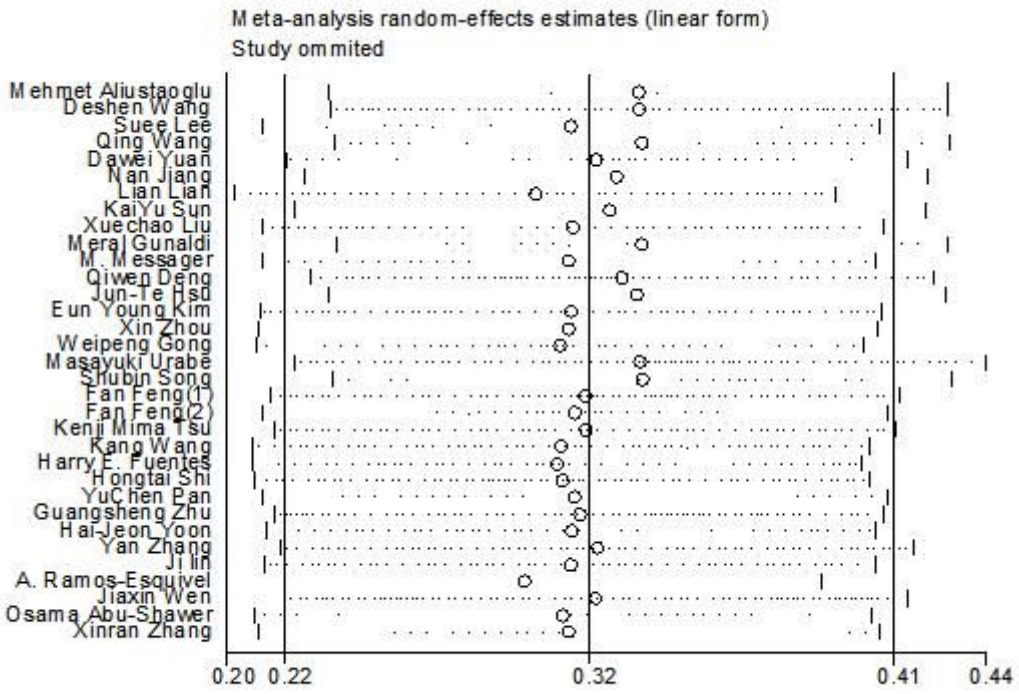

Figure 4

Sensitivity analysis of PLR for OS in GC patients.

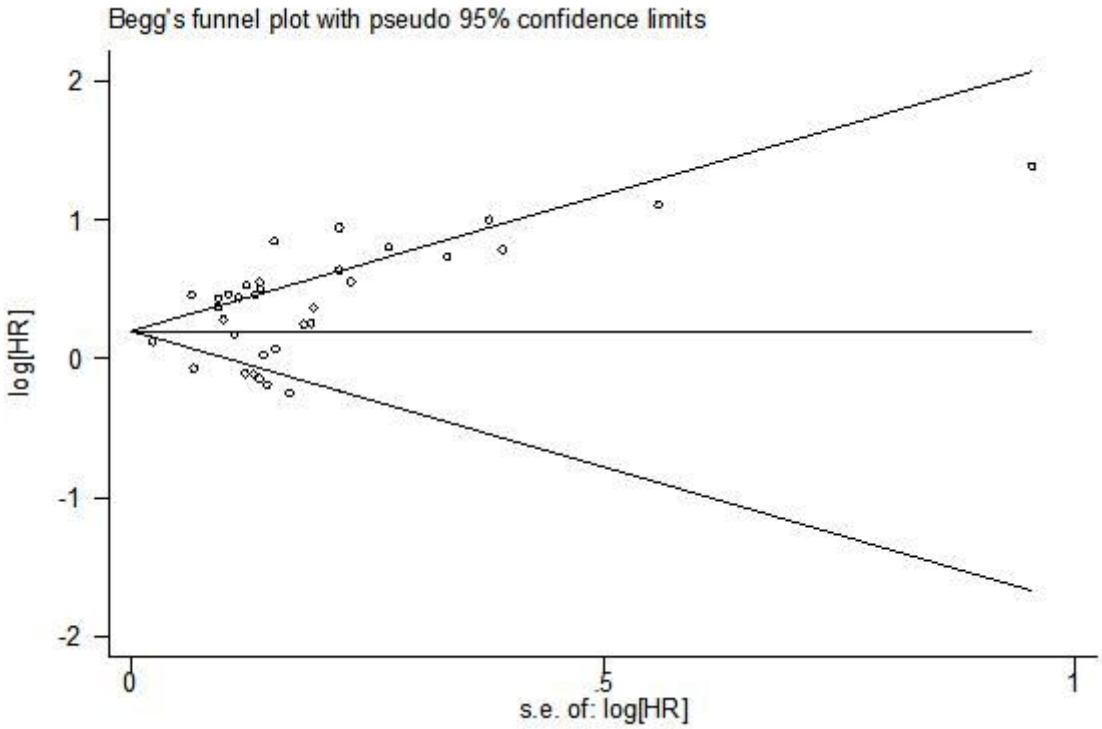

Figure 5

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