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ORIGINAL RESEARCH

Prognostic significance of platelet-to-lymphocyte ratio in non-small-cell lung cancer: a meta-analysis

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Background: The platelet-to-lymphocyte ratio (PLR) is a useful predictive factor in several cancers. However, the prognostic value of PLR in patients with non-small-cell lung cancer (NSCLC) is still indistinct. Therefore, it was necessary for us to perform a meta-analysis to assess the prognostic value of PLR in patients with NSCLC.

Methods: A systematic literature search was performed by using PubMed, EMBASE, and Web of Science databases for relevant studies until May 2015. Published studies investigating the association between PLR and overall survival (OS) and disease-free survival (DFS) were selected. Data from each eligible study were extracted. A meta-analysis was performed to analyze the prognostic value of PLR by using the hazard ratio (HR) and 95% confidence intervals (95% CI).

Results: A total of seven studies involving 1,554 patients were included in our meta-analysis. Our pooled results demonstrated that high PLR was associated with poor OS (HR: 1.60, 95% CI: 1.34–1.90, I^2=22.3%, $P_{heterogeneity}$ =0.259) and DFS (HR: 1.38, 95% CI: 1.11–1.73, I^2=0%, $P_{heterogeneity}$ =0.482). Subgroup analysis between PLR and OS was performed in a further investigation. When the patients were segregated according to ethnicity, sample size, cutoff value, stage, and treatment modality, high PLR was also significantly correlated with OS. There was no significant heterogeneity among included studies.

Conclusion: High PLR is associated with poor prognosis in patients with NSCLC. PLR may be a significant predictive biomarker in patients with NSCLC.

Keywords: non-small cell lung cancer, platelet-to-lymphocyte ratio, prognosis, meta-analysis, overall survival, disease-free survival

Introduction

Lung cancer is the most common cause of cancer-related deaths with a 5-year survival rate of about 16%.[1] Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer diagnoses. Although there is a significant improvement in the multidisciplinary treatment of patients with NSCLC, the prognosis still remains poor. A promising breakthrough to improve the long-term survival is the application of accurate predictive markers that can guide therapeutic strategies and monitor disease progress. Therefore, it is crucial for us to identify better predictors for prognosis in patients with NSCLC.

In an attempt to better estimate the prognosis, many prognostic parameters have been investigated, such as tumor–node–metastasis (TNM) stage, performance status, weight loss, and other miscellaneous factors. Recently, it is widely recognized that systemic inflammatory response plays an important role in the initiation and progression of cancer.[2] Molecular factors and biological pathways including upregulation of cytokines, chemokines and inflammatory mediators, promotion of angiogenesis, local immunosuppression, inhibition of apoptosis, and DNA damage are involved

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in this response and are associated with an increased risk of metastasis.[3] There is increasing evidence that measures of the systemic inflammatory response, such as neutrophil, lymphocyte, C-reactive protein (CRP), and the Glasgow Prognostic Score (GPS), have prognostic value in a variety of cancers.[4]

The platelet–lymphocyte ratio (PLR), defined as the absolute platelet count divided by the absolute lymphocyte count, has gained a lot of interest in recent years. Published data suggested that elevated PLR was an important prognostic factor in esophageal cancer,[5] gastric cancer,[6] renal cell cancer,[7] and malignant pleural mesothelioma.[8] However, due to the inconsistent results, the prognostic value of PLR in NSCLC remains unclear.[9–15] In this study, therefore, we performed a systematic review and meta-analysis including the most recent studies, aimed at achieving a relatively comprehensive and accurate conclusion concerning the prognostic significance of PLR in patients with NSCLC.

Materials and methods

Literature search

This meta-analysis was executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] A systematic literature search was conducted by using PubMed, EMBASE, and Web of Science databases to assess the prognostic value of PLR in patients with NSCLC. The search strategy was based on combinations of the following search terms: ("platelet-to-lymphocyte ratio" or "platelet–lymphocyte ratio" or "platelet lymphocyte ratio" or "PLR") and ("lung cancer" or "lung carcinoma" or "non-small cell lung cancer" or "non small cell lung cancer" or "NSCLC"). The last search was updated on May 20, 2015. Only human research was included in our meta-analysis. Moreover, the references in the identified articles were also retrieved for further relevant studies.

Inclusion/exclusion criteria

Studies were eligible for inclusion in this meta-analysis if they met the following criteria: 1) patients with NSCLC confirmed by pathology; 2) the PLR was measured before treatment; 3) investigated the relationship between PLR and prognosis (overall survival [OS], and disease-free survival [DFS]); 4) reported a hazard ratio (HR) and 95% confidence intervals (CIs) or the data sufficient to estimate the HR and 95% CIs; 5) to be published as full texts without language limits. The exclusion criteria were 1) abstracts, case reports, reviews, letters, editorials, and conference presentations; 2) insufficient data to extract or estimate the HRs and the 95% CIs.

Data extraction

The two primary investigators (Qiang and Guo) independently evaluated and extracted data from each study. All studies were double-checked and disagreements were resolved by discussion and consensus. Information extracted included the following: 1) publication details, including author, publication year, country, and study period; 2) characteristics of the studied population, including sample size, stage of disease, and PLR cutoff value; 3) HRs and 95% CIs for the association between PLR and prognosis (OS and DFS). If several estimates were presented in the same article, we selected the most powerful one (multivariate analysis was superior to univariate analysis).

Statistical analysis

Pooled HRs and their 95% CIs from each study were used to evaluate the relationship between PLR and prognosis. The heterogeneity of pooled results was analyzed by using Cochran's Q-test and Higgins' I^2 statistics. A significant heterogeneity was defined as Q-test P-value <0.10 or $I^2>50\%$.[17] When no significant heterogeneity existed among studies, the fixed-effects (Mantel–Haenszel method) model was used to generate the pooled HRs and 95% CIs. Otherwise, the random-effects (DerSimonian–Laird method) model was applied. A combined HR >1 indicated a worse survival, and it was considered statistically significant if the 95% CI did not overlap with the null value of one. Sensitivity analyses were performed to evaluate the stability of the results. Publication bias of literatures was assessed using funnel plot. All statistical tests were two sided, and the significance level was set at 5%. All analyses were carried out with the statistical software Stata, version 12.0 (Stata corporation, College Station, TX, USA).

Results

The flow diagram of literature retrieval procedure is shown in Figure 1. The initial search strategies retrieved a total of 214 studies. After excluding duplicate studies and screening the titles or abstracts, ten full-text articles concerning PLR and the prognosis of NSCLC were further evaluated. Three of them were eliminated because they did not provide specific data for survival. Therefore, according to the search strategies, a total of seven eligible studies were included in our meta-analysis finally. Three studies were performed in the People's Republic of China, two were performed in Turkey,

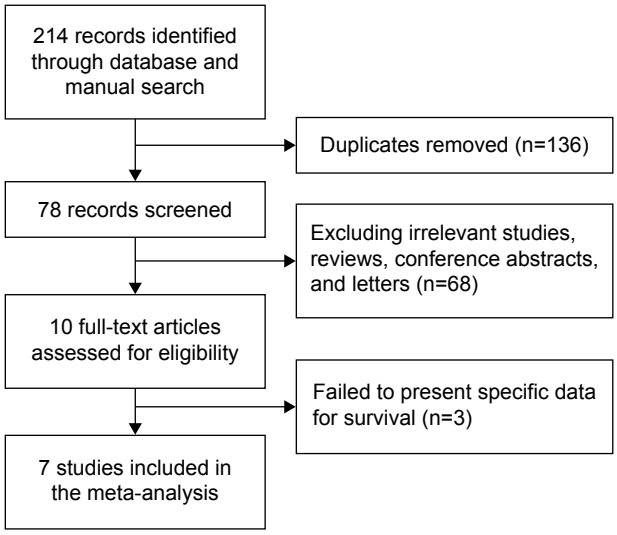

Figure 1 Flow diagram of study selection for the meta-analysis.

one in the UK, and one in Mexico, respectively. Two studies (Pinato et al[12]; Zhang et al[13]) included operable early stage cases (stage I–II or I–IIIA), four studies (Sánchez-Lara et al[9]; Liu et al[10]; Unal et al[11]; Wu et al[15]) only included inoperable late-stage cases (stage III–IV), and one study (Kos et al[14]) included all stage cases (stage I–IV). A total of 1,554 patients (1,040 males, 514 females) with NSCLC were included in this meta-analysis. The number of patients in each study ranged from 94 to 400. The cutoff value of PLR used in each study was not consistent, ranging from 119.5 to 300.0, with a median of 171. The main characteristics of included studies are summarized in Table 1.

All these seven studies presented data on PLR and OS, but only three studies reported data on PLR and DFS. Our pooled results demonstrated that high PLR was significantly associated with poor OS (HR: 1.60, 95% CI: 1.34–1.90, I^2=22.3%, $P_{\text{heterogeneity}}$=0.259) (Figure 2) and DFS (HR: 1.38, 95% CI: 1.11–1.73, I^2=0%, $P_{\text{heterogeneity}}$=0.482) (Figure 3). There was no significant heterogeneity between these studies.

In a further investigation, subgroup analyses were performed with confounders such as ethnicity, sample size, and cutoff value (Figure 4). Subgroup analyses by ethnicity indicated that high PLR predicted poor prognosis for patients both in Caucasian populations (HR =1.56, 95% CI: 1.19–2.04, P=0.001) and in Asian cases (HR =1.62, 95% CI: 1.29–2.04, P<0.001) (Figure 4A). When studies were stratified by sample size, we found the combined HRs were 1.56, 95% CI: 1.18–2.06 for studies with less than 200 cases and HR 1.62, 95% CI: 1.30–2.03 for studies with more than 200 cases (Figure 4B). This result demonstrated that high PLR remained to be an unfavorable prognostic

Table 1 Characteristics of all included studies

Study	Country	Ethnicity	Study period	Study design	Number of patients (M/F)	Stage	Treatment	Cutoff value	Survival analysis	Model	Number of events (%)	HR	95% CI
Sánchez-Lara et al[9]	Mexico	Caucasian	2009–2011	Prospective	119 (55/64)	IIIB–IV	C	150	OS	Adjusted	NA	1.16	0.52–2.50
Liu et al[10]	People's Republic of China	Asian	2001–2012	Retrospective	210 (139/71)	III–IV	C	152.6	OS	Adjusted	NA	2.025	1.405–2.919
Unal et al[11]	Turkey	Caucasian	NA	NA	94 (88/6)	II–III	C + R	194	OS	Adjusted	Death: 81 (86.2)	1.87	1.20–2.91
									DFS	Unadjusted	Complete remission: 13 (13.8); regression: 44 (46.8); stable disease: 14 (14.9); disease progression: 23 (24.5)	1.6	1.03–2.49
Pinato et al[12]	UK	Caucasian	2004–2011	Prospective	220 (110/110)	I–IIIA	S + C/R	300	OS	Unadjusted	Death: 61 (28)	1.6	0.6–5.6
Zhang et al[13]	People's Republic of China	Asian	2006–2009	Retrospective	400 (272/128)	I–II	S	171	OS	Unadjusted	Death: 86 (21.5)	1.985	1.269–3.104
									DFS	Unadjusted	Recurrence: 117 (29.3)	1.534	1.022–2.304
Kos et al[14]	Turkey	Caucasian	2005–2011	Retrospective	145 (130/15)	I–IV	S/C/R	198.2	OS	Adjusted	Death: 89 (61.4)	1.45	1.04–2.32
Wu et al[15]	People's Republic of China	Asian	2007–2012	Retrospective	366 (246/120)	III–IV	C	119.5	OS	Adjusted	NA	1.189	0.852–1.658
									DFS	Adjusted	NA	1.079	0.729–1.596

Abbreviations: M/F, male/female; NA, not available; OS, overall survival; DFS, disease-free survival; C, chemotherapy; R, radiotherapy; S, surgery; HR, hazard ratio; CI, confidence interval.

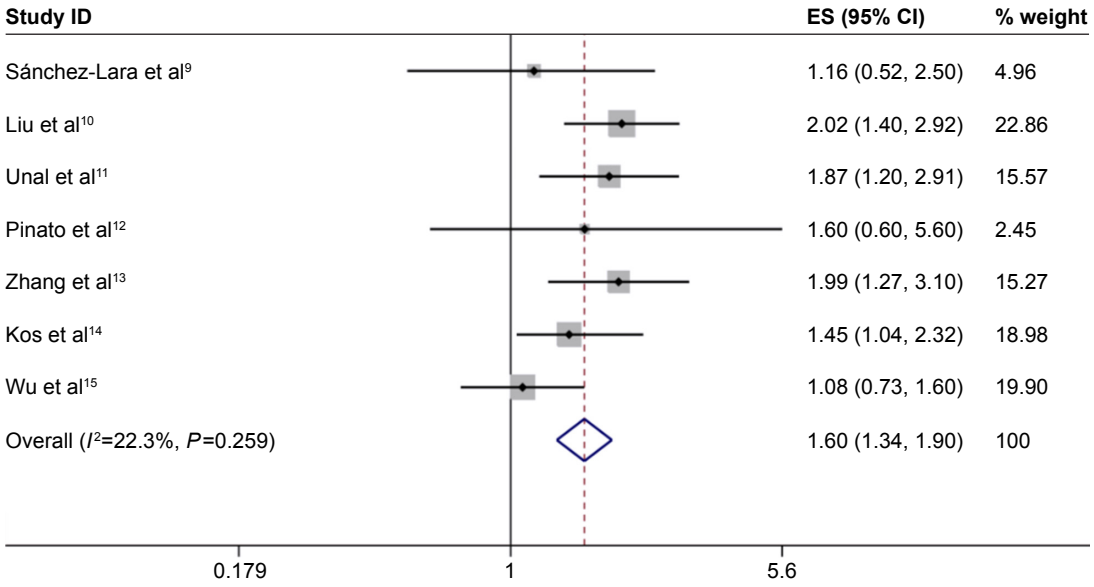

Figure 2 Forest plot of the association between PLR and OS in NSCLC.
Abbreviations: ES, effect size; CI, confidence interval; PLR, platelet-to-lymphocyte ratio; OS, overall survival; NSCLC, non-small cell lung cancer.

factor regardless of sample size. With stratification by cutoff value ≤171 and cutoff value >171, the data showed that the pooled HR was 1.58 (95% CI: 1.27–1.97) and 1.62 (95% CI: 1.22–2.17), respectively (Figure 4C). When studies were stratified by stage and treatment modality, we found the combined HRs were 1.56, 95% CI: (1.25–1.94) for studies with inoperable late-stage cases and 1.93, 95% CI: (1.27–2.92) for studies with operable early stage cases (Figure 4D). This result demonstrated that high PLR remained to be an unfavorable prognostic factor regardless of disease stage and treatment modality.

We conducted leave-one-out sensitivity analysis to check if any individual study affected the results. We found that removing any single study in turn did not significantly affect the pooled HRs in the present meta-analysis (Figure 5). This result indicates that the present meta-analysis was proven to have good reliability.

The Begg's funnel plot was performed to evaluate publication bias of the included studies. As shown in Figure 6, the funnel plot was symmetric. There was no significant publication bias in our study.

Discussion

To the best of our knowledge, this is the first meta-analysis to investigate the prognostic value of PLR in patients with NSCLC. In our meta-analysis, the pooled results demonstrated

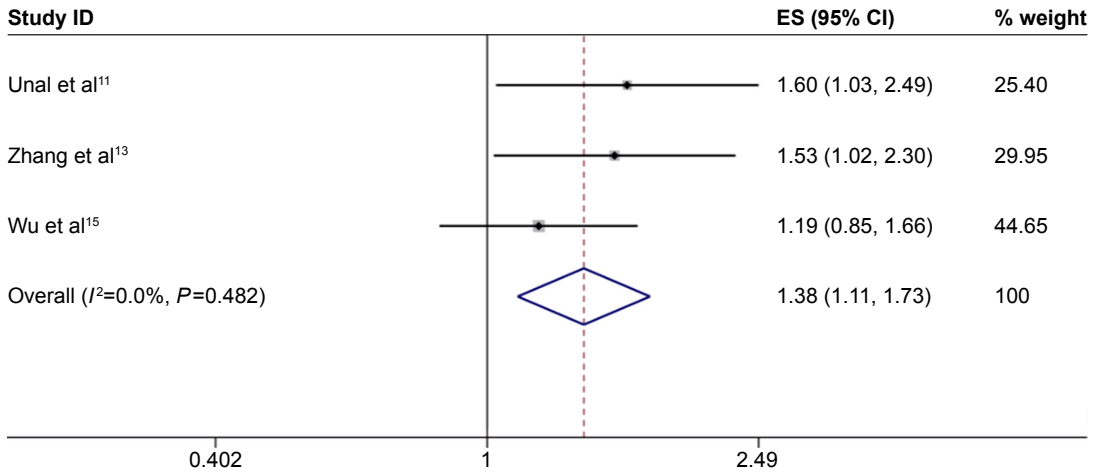

Figure 3 Forest plot of the association between PLR and DFS in NSCLC.
Abbreviations: ES, effect size; CI, confidence interval; PLR, platelet-to-lymphocyte ratio; DFS, disease-free survival; NSCLC, non-small cell lung cancer.

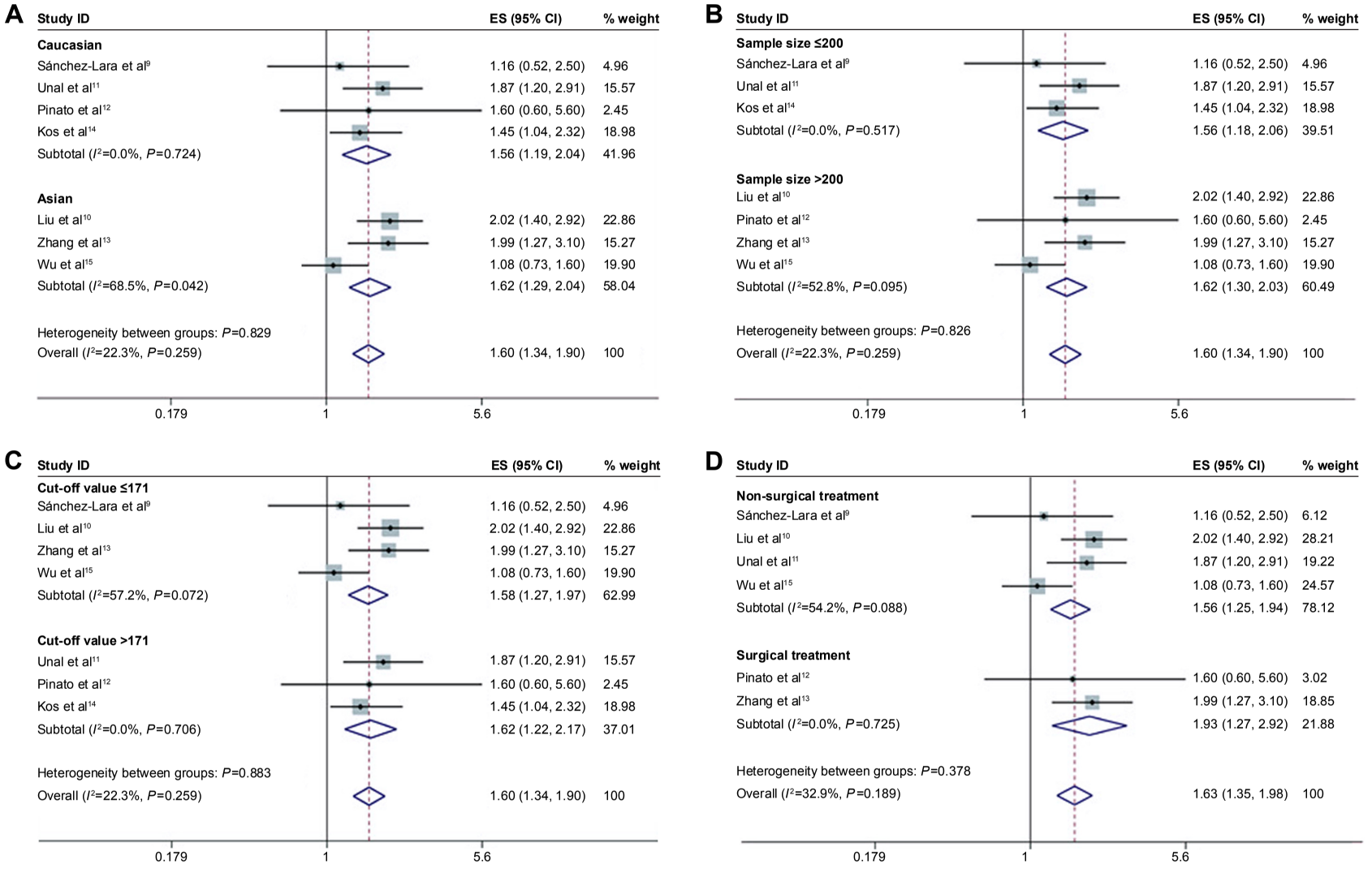

Figure 4 Forest plot of the association between PLR and OS in NSCLC by subgroup analyses.
Notes: Subgroup analysis by population (**A**), sample size (**B**), cutoff value (**C**), stage, and treatment modality (**D**).
Abbreviations: ES, effect size; HR, hazard ratio; CI, confidence interval; PLR, platelet-to-lymphocyte ratio; OS, overall survival; NSCLC, non-small cell lung cancer.

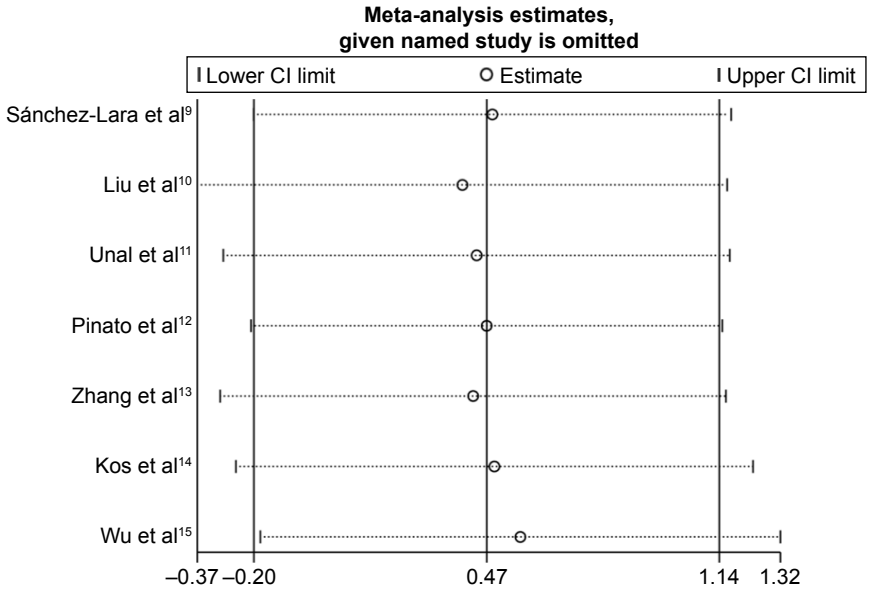

Figure 5 Sensitivity analysis on the relationship between PLR and OS in NSCLC.
Abbreviations: CI, confidence interval; PLR, platelet-to-lymphocyte ratio; OS, overall survival; NSCLC, non-small cell lung cancer.

that high PLR was associated with poor OS (HR: 1.60, 95% CI: 1.34–1.90, I^2=22.3%, $P_{heterogeneity}$=0.259) and DFS (HR: 1.38, 95% CI: 1.11–1.73, I^2=0%, $P_{heterogeneity}$=0.482) in patients with NSCLC. We performed further subgroup analyses to evaluate the association between PLR and OS in the included studies. When the patients were segregated according to ethnicity and sample size, high PLR was also significantly correlated with OS. These results, on the other hand, indicated that the high levels of PLR could significantly predict the poor OS in patients with NSCLC regardless of ethnicity and sample size. In addition, when stratified by cutoff value, the results were also significant no matter what cutoff value was used.

Over the past few decades, a number of prognostic factors for NSCLC have been identified, including TNM stage, genetic factors, and performance status. Recently, there is increasing evidence that a systemic inflammatory response is of prognostic value in various types of cancers. Several inflammatory biomarkers such as PLR, NLR, CRP, and the modified Glasgow Prognostic Score (mGPS) are associated with prognosis of cancer patients.[18] Pretreatment PLR is inversely related to prognosis in numerous cancers. However, its role in NSCLC is still unclear. The results of our study support the view that a high pretreatment PLR is a poor prognostic factor in NSCLC. Furthermore, the sensitivity analysis found that no single study could affect the pooled HRs in our meta-analysis. There was no publication bias in our study. These findings indicated that our meta-analysis was stable and reliable.

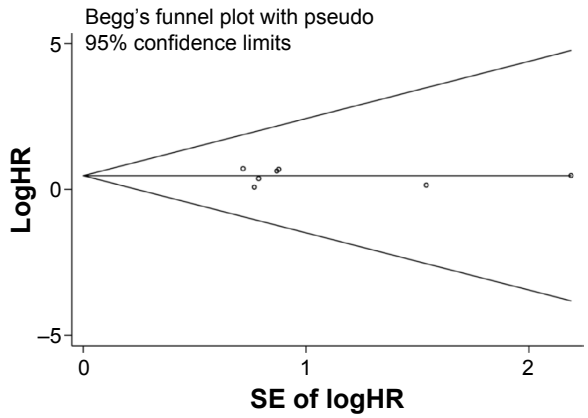

Figure 6 Funnel plot for detecting publication bias.
Abbreviations: HR, hazard ratio; SE, standard error.

However, the mechanism underlying the association of PLR with prognosis of NSCLC is still incompletely understood. Platelets play an important role in cancer progression. Previously published studies have proposed that thrombocytosis is an independent unfavorable prognostic factor in patients with NSCLC.[19] Platelet (PLT) aggregation promotes the adhesion and encapsulation of circulating tumor cells. This enhances the ability of tumor cells to escape from antitumor immunity.[20] Furthermore, activated PLT release vascular endothelial growth factor and numerous cytokines, which stimulate tumor growth by increasing angiogenesis.[21–23] In addition, increased PLT aggregation supposed to be involved in the development of hematogenous metastases by promoting microcirculatory adhesion and colonization

of tumor cells.[24] On the other hand, lymphocytes are major compartments of the immune system, which play a key role in defending against cancers. Zhang et al[25] reported elevated peripheral lymphocytes to be a favorable prognostic factor. Similarly Kobayashi et al[26] reported that a low lymphocyte count was an independent unfavorable prognostic factor in patients with resected node negative NSCLC. Thus, lymphocytopenia reflects impaired lymphocyte-mediated antitumor reaction. As a combination of circulating platelet and lymphocyte counts, an elevated PLR represent both thrombocytosis and lymphocytopenia, thereby contributing to aggressive cancer progression and poor survival. However, further investigation is needed to explain the exact mechanism.

There were some limitations in our study. First, the number of included studies was limited. Second, due to lack of relevant prospective studies, most of the included studies were retrospective and single institution case series. Third, because of the lack of appropriate data, the correlation between PLR and other clinicopathological parameters was not analyzed.

In conclusion, the current meta-analysis revealed that high level of PLR was significantly associated with poor OS and DFS in patients with NSCLC. As PLR is readily available and cost-effective, we propose that PLR should be used as a prognostic biomarker to improve selection of treatment modalities for individual NSCLC patients. However, the clinical utility of the PLR needs to be validated by more well-designed and large-scale investigations in the future.

Disclosure

The authors report no conflicts of interest in this work.

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