



Evaluation of the prognostic role of platelet-lymphocyte ratio in cancer patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis



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ABSTRACT

Objective: Whether platelet-lymphocyte ratio (PLR) is a prognostic factor for cancer patients treated with immunotherapy is under debate. In this study, we aimed to evaluate the relationship between PLR and survival of cancer patients treated with immune checkpoint inhibitors (ICIs).

Methods: A systematic search was performed in databases including PubMed, Embase, and the Cochrane library to retrieve potential eligible clinical studies assessing the prognosis of cancer patients with high versus low PLR after immunotherapy, from the establishment of the database to June 2019. Quality evaluation of included studies was performed, and meta-analyses with regards to overall survival (OS) and progression-free survival (PFS) were conducted using RevMan 5.3 and STATA 11.

Results: A total of 12 eligible studies with 1340 cancer patients were included. Combined results showed that elevated PLR was a negative factor affecting the efficacy of ICIs in cancer patients. Patients with high PLR had a significantly shorter OS compared to those with low PLR (hazard ratio (HR) = 2.02, 95% confidence interval (CI): 1.46 to 2.80, $P < 0.0001$), as well as PFS (HR = 1.74, 95%CI: 1.27 to 2.38, $P = 0.0006$). Similar results were observed in sensitivity analyses. Subgroup analyses revealed that the prognostic role of PLR on OS and PFS was dependent on cancer type, region, and cutoff value. For NSCLC patients, the disease stage, ICIs agent, and line of treatment may not influence the prognostic role of PLR.

Conclusion: PLR could be a routinely potential prognostic factor for ICIs. Low PLR may be associated with better survival for cancer patients when treated with immunotherapy.

1. Introduction

In recent years, the treatment landscape of multiple solid cancers has changed dramatically. One of the most promising treatment strategies is immunotherapy [1]. The prognosis of these patients has improved by immunotherapy, especially the immune checkpoint inhibitors [1,2]. However, not all of these patients could benefit from immune checkpoint inhibitors [2]. Therefore, it is necessary to identify biomarkers that can predict treatment outcomes universally.

Systemic inflammatory response plays an important role in the development of tumor [3]. As an effective indicator reflecting the severity of systemic inflammatory response, attentions have focused on the predictive role of platelet-lymphocyte ratio (PLR) in recent years [4]. PLR is defined as the ratio of platelets to lymphocytes. Studies show that platelets and lymphocytes play multiple roles in the inflammatory response [5–7]. Platelet elevation accelerates tumor progression by

promoting the formation of new blood vessels and the production of adhesion molecule [8,9]. In contrast, lymphocytes are an important component of anti-tumor immunity, releasing a range of cytokines that activate anti-tumor immunity [10]. Recently, the prognosis of multiple solid tumors is related to a series of inflammatory factors such as PLR have been confirmed [11,12]. In addition, elevated PLR is closely related to poor prognosis in a variety of cancer patients [11]. However, the role of PLR in the prognosis of cancer patients treated with immunotherapy remains unclear.

Recent studies have evaluated the significance of PLR in patients with non-small cell lung cancer (NSCLC), melanoma, and other cancers [13–18]. The study by Zer et al. [19] reported that there was no significant relation between baseline PLR and efficacy of immunotherapy when using a cutoff value of 200. Other studies suggested a strong association between clinical outcomes and PLR [13–18]. More recently, a meta-analysis also evaluated the prognostic significance of baseline PLR

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in immune checkpoint inhibitor treated cancer patients [20]. They found no significant relevance between PLR and survival of these cancer patients. These studies suggest that using PLR to predict the prognosis of cancer patients treated with immunotherapy remains controversial. To clarify this issue, we conducted a meta-analysis to assess the predictive role of PLR in relation to the survival of cancer patients treated with immunotherapy.

2. Materials and methods

This study was performed according to the criteria of the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This study was not registered.

2.1. Search strategy

The systematic search was performed in databases including PubMed, the Cochrane library, and EMBASE without language limitation. The search time was from the establishment of the database to June 2019. Two reviewers conducted literature search and preliminary screening of the literature, independently. The mesh terms and free terms were used in different combination, and these terms were “Platelet to lymphocyte ratio”, “PLR”, “immune checkpoint inhibitor”, “immunotherapy”, “nivolumab”, “ipilimumab”, “pembrolizumab”, “atezolizumab”, and “programmed death 1 receptor antibody”. The search was further expanded by manually checking related references. The corresponding author was contacted if there was not enough data. When there was an inconsistency, it was resolved through discussion or determined by a third reviewer to ensure the stability of the results.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as following: (1) the diagnosis of cancer was confirmed by histopathology or other essential evidences; (2) adequate and accurate definition of PLR and its pre- and/or post-treatment cutoff values; (3) assessing the relationship between pre- and/or post-treatment PLR levels and survival outcomes. Exclusion criteria: (1) reviews, comments, letters, expert opinions, summary of meetings or reports; (2) insufficient data about the PLR and survival.

2.3. Study screening and data extraction

Titles and abstracts were read by two reviewers independently, and excluded non-related studies. For the rest of the studies, the full-texts were screened to identify references that met the inclusion criteria. If there was any disagreement, the third reviewer would help solving it. Data needed to extracted were general information, including title, author, region, study time, publication time; subjects, sample size, tumor type, and treatment. The primary endpoint was HR of high versus low PLR for overall survival, and the secondary was HR of PFS.

2.4. Study quality evaluation

The NOS scale was applied to assess the overall quality of the included studies [21]. According to the NOS scale, there are three main aspects to be evaluated, and they are study population selection (0–4 points: representativeness of cases, selection of controls, exposure ascertainment, and no death when investigation begin), comparability (0–2 points: comparable on confounders), and results evaluation (0–3 points: outcome assessment, adequate follow-up, and loss to follow-up rate.) with maximum 9 points. A high quality study is defined as its NOS score ≥ 6 . Low quality literature was excluded after evaluation.

2.5. Statistical analysis

The extracted data were statistically analyzed using Review

Manager 5.3 and Stata 11.0 software. The statistical effect indicators used were HR and its related 95% CI. Before the meta-analysis, the χ^2 test was used for heterogeneity testing. If $P > 0.1$ and $I^2 < 50\%$, it indicated that there was no significant heterogeneity and a fixed effect model was used. If $P \leq 0.1$ and $I^2 > 50\%$, it indicated that there was significant heterogeneity among the included studies, and the random effect model was applied [22]. When there was significant heterogeneity between the eligible studies, a sensitivity analysis was performed to explore the potential source of heterogeneity. To further examine the source of heterogeneity, we also performed subgroup analysis with regards to region, PLR thresholds, and cancer type if possible. With regard to cutoff value of PLR, we used 170 as the threshold for grouping studies. The funnel plot was used to detect the publication bias of clinical outcomes. For combined analysis, a $P < 0.05$ was considered as there was a significant difference between the compared two groups.

3. Results

3.1. Literature screening result

According to the above search strategy, 96 articles were retrieved. After reading the titles and abstracts, 81 of them were discarded. Based on the mentioned inclusion and exclusion criteria and the quality assessment result, 3 of them were further excluded and a total of 12 articles [13–18,23–28] were finally included in the analysis (Fig. 1). All of them were retrospective studies, involving 1340 cases. All studies reported the relationship between PLR and survival. The baseline information of the included studies is shown in Table 1. The quality assessment result suggested that all the included were considered as high quality (Table 2).

3.2. Results of meta-analysis

3.2.1. The relationship between PLR and OS and PFS

Twelve studies [13–18,23–28] reported the relationship between PLR levels and OS in cancer patients treated with immune checkpoint inhibitors. The study of Laura [25] showed PLR was significantly associated with OS without reporting HR. The heterogeneity test showed significant heterogeneity ($P < 0.1$, $I^2 = 91\%$) between the included studies, so a random effect model was used. The combined HR was 2.02 (95% CI: 1.46 to 2.80, $P < 0.0001$), indicating that an increase in PLR was associated with shorter OS in cancer patients treated with immune checkpoint inhibitors (Fig. 2A).

Ten studies [13–18,23,24,27,28] reported the relationship between PLR levels and PFS in cancer patients with immunotherapy treatment. The heterogeneity test showed significant heterogeneity between the include studies ($P < 0.1$, $I^2 = 86\%$), so the random effect model was used. The study of Svaton [18] was excluded due to significant heterogeneity. The combined HR was 1.74 (95% CI: 1.27 to 2.38, $P = 0.0006$), suggesting a significant correlation between PLR and PFS (Fig. 2B).

3.3. Subgroup analysis in various cancer types

We also performed subgroup analysis to further explore the relation between PLR, OS and PFS. The main cancer types (non-small cell lung cancer and other cancers), region (Asia, America, and Europe), and PLR threshold (< 170 and ≥ 170) were used as the factors of subgroup analysis. As shown in Fig. 3, the prognostic roles of PLR for OS (Fig. 3A) and PFS (Fig. 3B) were dependent on cancer type. For patients with NSCLC, the OS (HR = 1.91; 95%CI: 1.40 to 2.61; $P < 0.0001$) and PFS (HR = 1.52; 95%CI: 1.27 to 1.82; $P < 0.00001$) of low PLR group were significantly better than those with high PLR. The association between PLR and survival of other cancer patients also exhibited a similar pattern, but not statistically significant for PFS (OS, HR = 2.48,

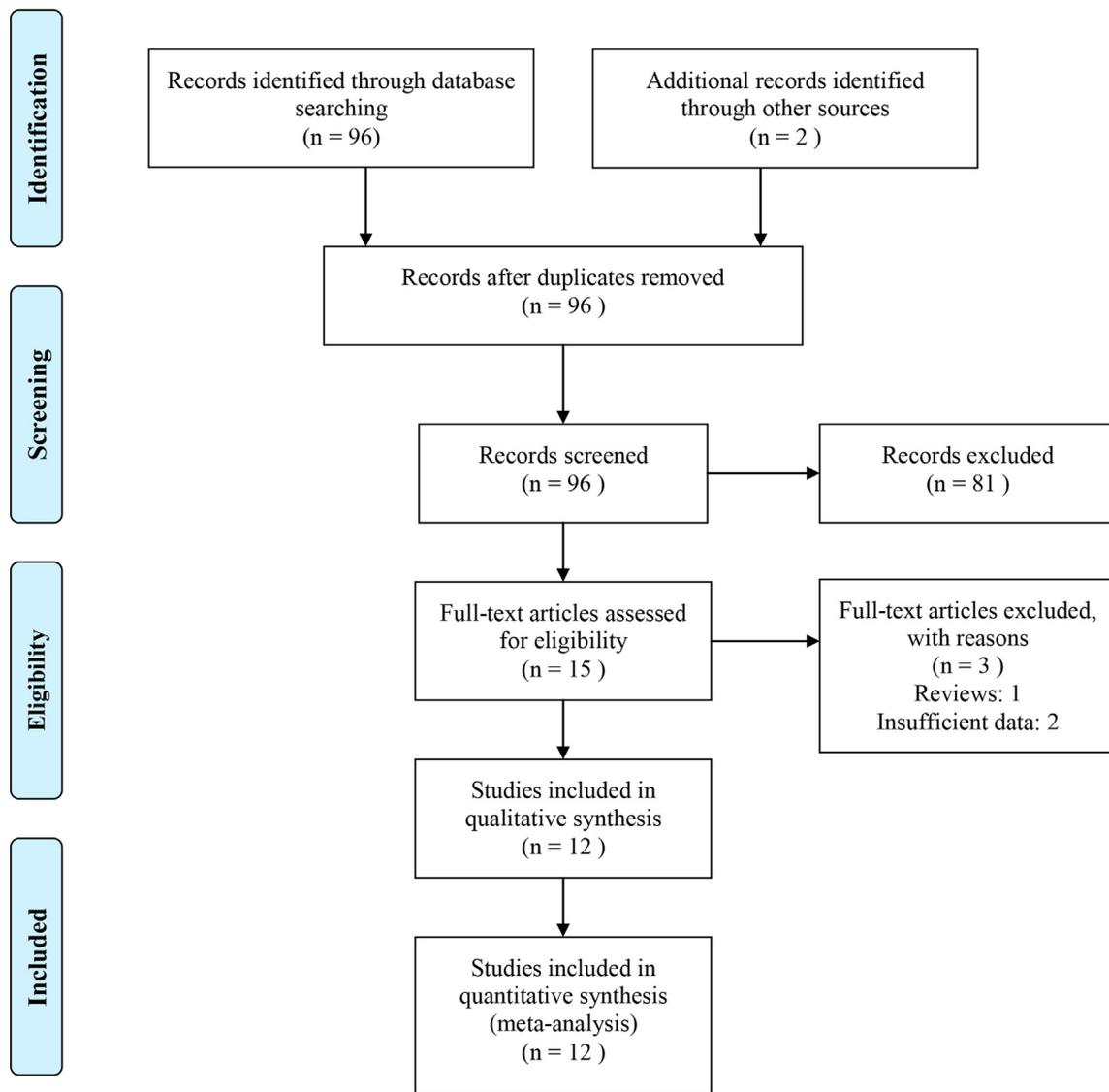


Fig. 1. Flow chart of selecting and including eligible studies. After carefully review, a total of 12 retrospective studies are included. Three studies are excluded due to one of them is a review and the other two studies fail to provide sufficient data on the association between PLR and survival.

$P < 0.00001$; PFS, HR = 1.84, $P = 0.12$).

With regard to cutoff value of PLR, we selected 170 as the threshold (Fig. 4). The combined HR from studies using a smaller cutoff value of PLR (<170) suggested that significantly increased risks of mortality and

progression were found in patients with high PLR when compared to those with low PLR (OS, HR = 2.10, 95%CI: 1.64 to 2.69, $P < 0.00001$, Fig. 4A; PFS, HR = 2.06, 95%CI: 1.54 to 2.74, $P < 0.00001$, Fig. 4B). The HRs combined from the studies using cutoff

Table 1
Baseline characteristics of included studies.

Authors	Year	N	Age	Sex (M/F)	cutoff value	Region	Cancer type	Treatment	Outcomes
Bilen	2019	90	NR	53/37	45	America	Multiple	Immunotherapy	OS, PFS
Diem	2017	52	66 (46–88)	29/23	262	Europe	NSCLC	Nivo	OS, PFS
Khoja	2016	183	58 (24–89)	115/68	215	America	Melanoma	Ipi	OS, PFS
Russo	2018	28	68 (45–82)	25/3	160	Europe	NSCLC	Nivo	OS, PFS
Suh	2018	54	68 (43–80)	42/12	169	Asia	NSCLC	Nivo, Pemb	OS, PFS
Svaton	2018	120	65	71/49	169.1	Europe	NSCLC	Nivo	OS, PFS
Laura	2017	65	65 (30–86)	40/25	NR	Europe	NSCLC	Nivo, Pembro or Atezo	OS
Oh	2018	274	NR	NR	400	America	NSCLC	Immunotherapy	OS, PFS
Amaral	2019	32	61 (40–82)	20/12	Mean	Europe	NSCLC	Nivo, Pemb	OS, PFS
Giorgi	2019	313	65(40–84)	235/78	232	Europe	RCC	Nivo	OS, PFS
Liu	2019	44	60 (43–74)	33/11	144	Asia	NSCLC	Nivo	OS, PFS
Qi	2019	85	NR	42/43	164	Asia	Multiple	Immunotherapy	OS, PFS

Abbreviation: N, number; M, male; F, female; NR, not reported; OS, overall survival; PFS, progression-free survival; NSCLC, non-small cell lung cancer; RCC, renal cell cancer; Nivo, Nivolumab; Ipi, Ipilimumab; Pemb, Pembrolizumab; Atezo, Atezolizumab.

Table 2
Quality assessment using NOS scale.

Authors	Year	Selection				Comparability		Outcome		Score
		A	B	C	D	E	F	G	H	
Bilen	2019	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Diem	2017	☆	☆	☆		☆☆	☆	☆		7
Khoja	2016	☆	☆	☆		☆☆	☆	☆	☆	8
Russo	2018	☆	☆	☆	☆	☆☆	☆	☆		8
Suh	2018	☆	☆	☆	☆	☆☆	☆	☆		8
Svaton	2018	☆	☆	☆	☆	☆☆	☆	☆		8
Laura	2017	☆	☆	☆		☆☆	☆	☆		7
Oh	2018	☆	☆	☆		☆☆	☆	☆		7
Amaral	2019	☆	☆	☆		☆☆	☆	☆		7
Giorgi	2019	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Liu	2019	☆	☆	☆	☆	☆☆	☆	☆		8
Qi	2019	☆	☆	☆	☆	☆☆	☆	☆	☆	9

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability, according to the instruction of NOS.

value ≥ 170 also exhibited similar trend. There was significant difference in OS (HR = 2.02, $P = 0.02$) but not PFS (HR = 1.18, $P = 0.24$) between low versus high PLR groups (Fig. 4).

The population of the included studies were from Asia (n = 3), America (n = 3) and Europe (n = 5). For patients from different region (Fig. 5), the combined estimates of OS (HR = 2.11, 95%CI: 1.70 to 2.62; $P < 0.00001$, Fig. 5A) and PFS (HR = 1.55, 95%CI: 1.11 to 2.17; $P = 0.01$, Fig. 5B) were both significant for European. For patients from Asia, the combined estimates of OS (HR = 2.83, 95%CI: 1.44 to 5.57; $P = 0.003$, Fig. 5A) and PFS (HR = 2.31, 95%CI: 1.61 to 3.32; $P < 0.00001$, Fig. 5B) were also significantly in favor of low PLR. For American, high PLR were in favor of increased risk of mortality, but

there were no significant differences ($P > 0.05$ for all).

3.4. Subgroup analysis in NSCLC patients

We further assessed the impact of disease stage, immune checkpoint inhibitor type, and line of treatment on OS and PFS (Supplementary Fig. 1). As NSCLC is the most common cancer in these studies, the impact of PLR on OS and PFS in this population is focused. The subgroup analyses showed that advanced stage NSCLC patients with low PLR had a significantly better OS when compared to those with high PLR ($I^2 = 29\%$, HR = 2.09; 95%CI: 1.58–2.76, $P < 0.01$, Supplemental Fig. 1A). For NSCLC patients treated with Nivolumab, the OS was still significantly in favor of low PLR ($I^2 = 38\%$, HR = 2.24; 95%CI: 1.61–3.11, $P < 0.01$, Supplementary Fig. 1B). In NSCLC patients receiving immune checkpoint inhibitor after second or higher line of treatment, those with low PLR had a significantly prolonged OS compared to patients with high PLR ($I^2 = 34\%$, HR = 2.07; 95%CI: 1.51–2.83, $P < 0.01$, Supplementary Fig. 1C). Low risk of heterogeneity ($I^2 < 40\%$, $P > 0.1$) was observed in these subgroup analyses.

In term of PFS, similar results were observed without significant heterogeneity (all $P > 0.1$). For NSCLC patients with high versus low PLR, the PFS were significantly improved in subgroup analyses of disease stage (advanced stage, $I^2 = 3\%$, HR = 1.63; 95%CI: 1.27–2.07, $P < 0.01$, Supplementary Fig. 1D), immune checkpoint inhibitor agent (nivolumab, $I^2 = 25\%$, HR = 1.67; 95%CI: 1.20–2.32, $P < 0.01$, Supplementary Fig. 1E), and line of treatment (first or higher line, $I^2 = 0\%$, HR = 1.43; 95%CI: 1.13–1.81, $P < 0.01$, second or higher line, $I^2 = 45\%$, HR = 2.01; 95%CI: 1.16–3.47, $P = 0.01$, Supplementary Fig. 1F).

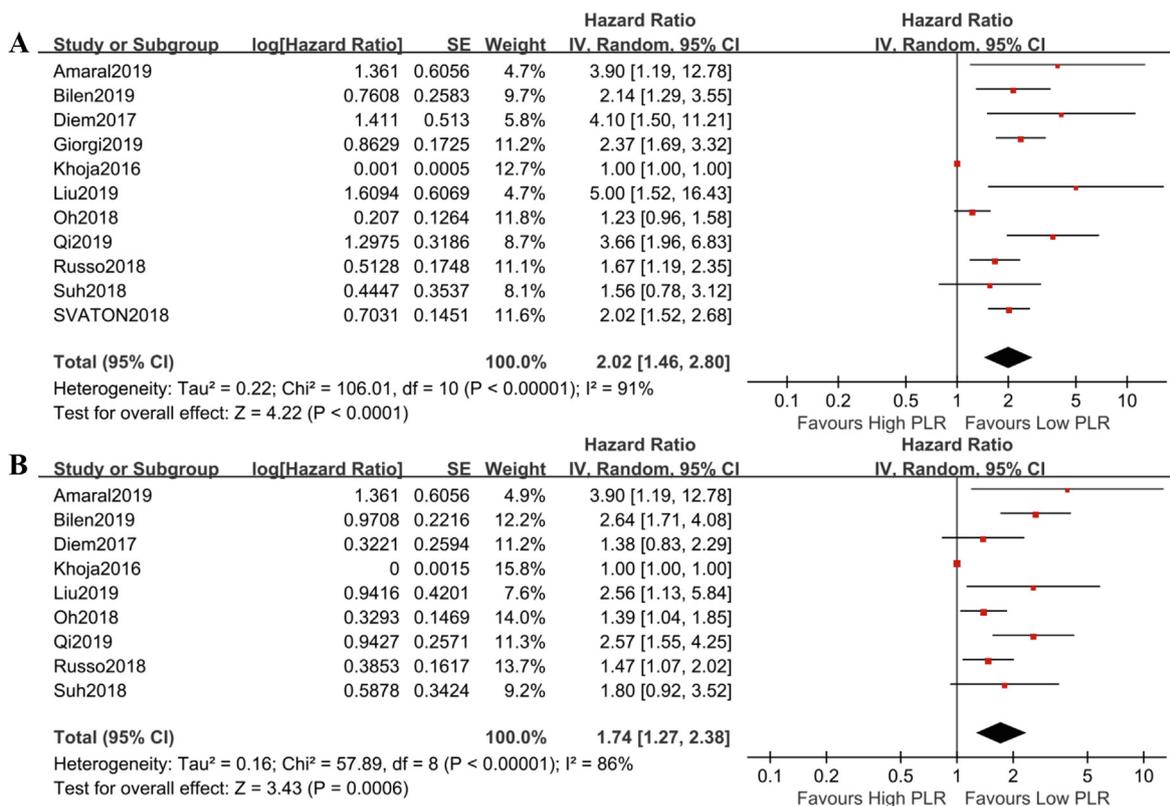


Fig. 2. Forest plots of comparison between high versus low PLR in cancer patients treated with immune checkpoint inhibitors. In this illustration of statistical results, squares represent hazard ratios. The overall impact of PLR on OS and PFS is evaluated using random effect model in various cancer patients. The study of Khoja 2016 is the main source of heterogeneity. A, The combined result suggests the risk of death in patients with high PLR increased by 2.02 times than those with low PLR; B, For PFS, the risk of disease progression in cancer patients with high PLR is 1.74 times than those with low PLR.

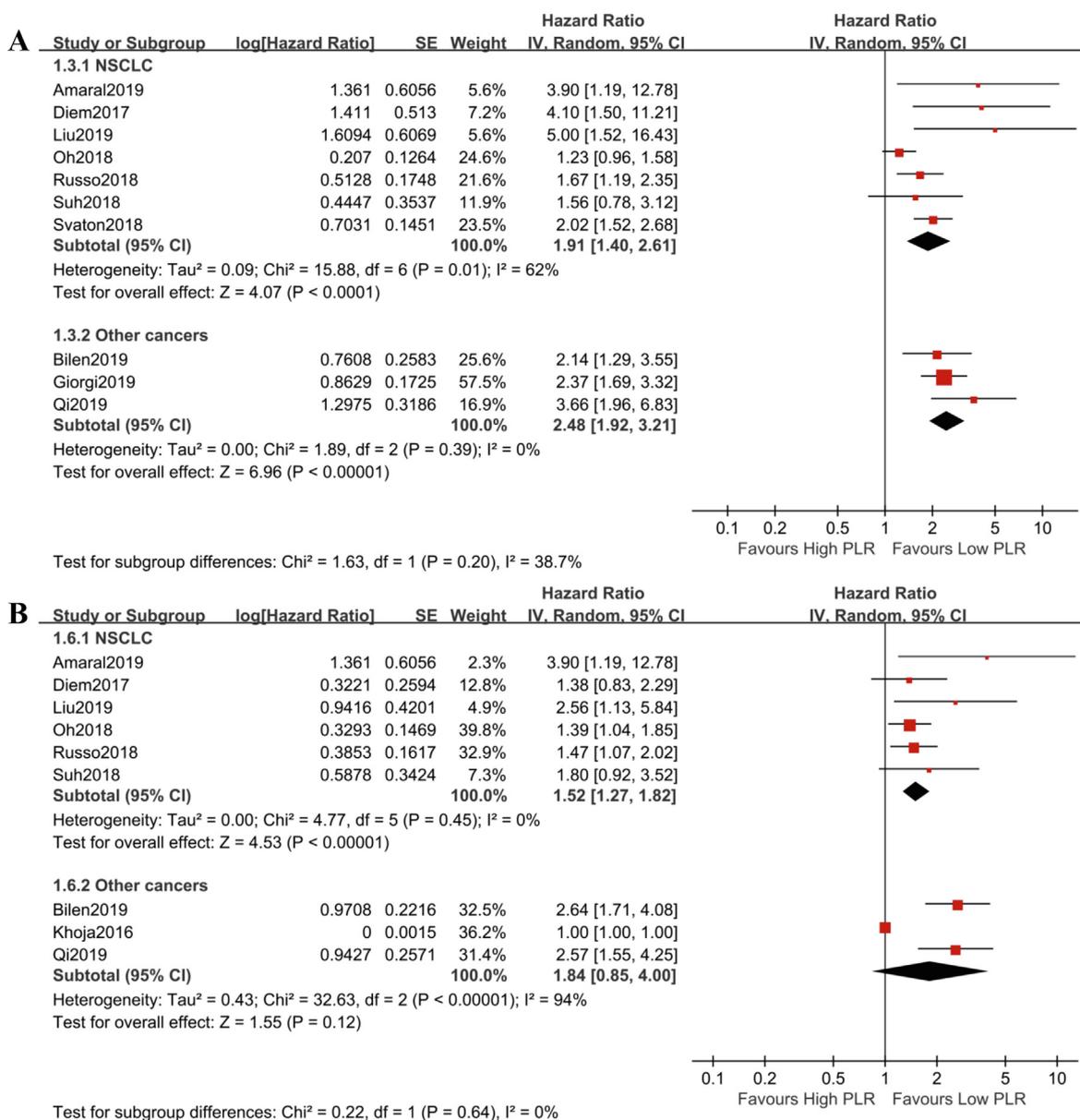


Fig. 3. Subgroup analyses with regard to cancer type. Due to significant heterogeneity observed in the overall analyses, subgroup analyses of OS and PFS are performed in term of cancer type. A, the combined results show that high PLR is associated with poor OS, regardless of cancer types; B, subgroup analysis of PFS in term of different cancer type. Improved PFS is observed in NSCLC patients with low PLR.

3.5. Publishing bias assessment

For OS and PFS, the HRs and their related 95% CIs were combined and analyzed by funnel plot to assess the publication bias. The results are shown in Fig. 6A and B. The funnel plots of OS and PFS were not basically symmetrical, suggests high risk of potential publication bias in this study. The results of Egger’s test for OS and PFS also indicated that the risks of publication bias were high (For OS, $P = 0.001$; for PFS, $P = 0.003$).

3.6. Sensitivity analysis

In order to explore the potential heterogeneity within the included studies of OS analysis, the sensitivity analysis was used (Fig. 6C) and found the results were stable after excluding each one of the included studies. Due to the significant heterogeneity, we tried to find the sources of differences. After excluding the studies of Khoja [15] and Oh [23], the heterogeneity test suggested that there was no significant

heterogeneity ($P = 0.22$, $I^2 = 25%$), and the fixed effect model was used. The pooled HR for OS in cancer patients with high versus low PLR was 2.23 (95% CI: 1.83 to 2.72, $P < 0.00001$), showing a constant prognostic role of PLR.

Next, we performed sensitivity analysis to find the main source of heterogeneity in PFS analysis (Fig. 6D), and the results were similar after excluding each one of the included studies. Due to the significant heterogeneity, we tried to find the sources of differences. After excluding three studies [15,18,23], the heterogeneity test showed the P value was 0.14 ($I^2 = 37%$), and the fixed effect model was used. The combined HR was 1.99 (95% CI: 1.53 to 2.58, $P < 0.00001$), indicating that elevation of PLR was significantly associated with poor PFS in cancer patients treated with immune checkpoint inhibitors. Further exclusion of Bilen’s study [13] and Amaral’s study [24], the heterogeneity test showed that there was no significant heterogeneity ($P > 0.1$, $I^2 = 20%$), and the pooled HR was 1.75 (95% CI: 1.36 to 2.26, $P < 0.0001$), still in accordance with the above results.

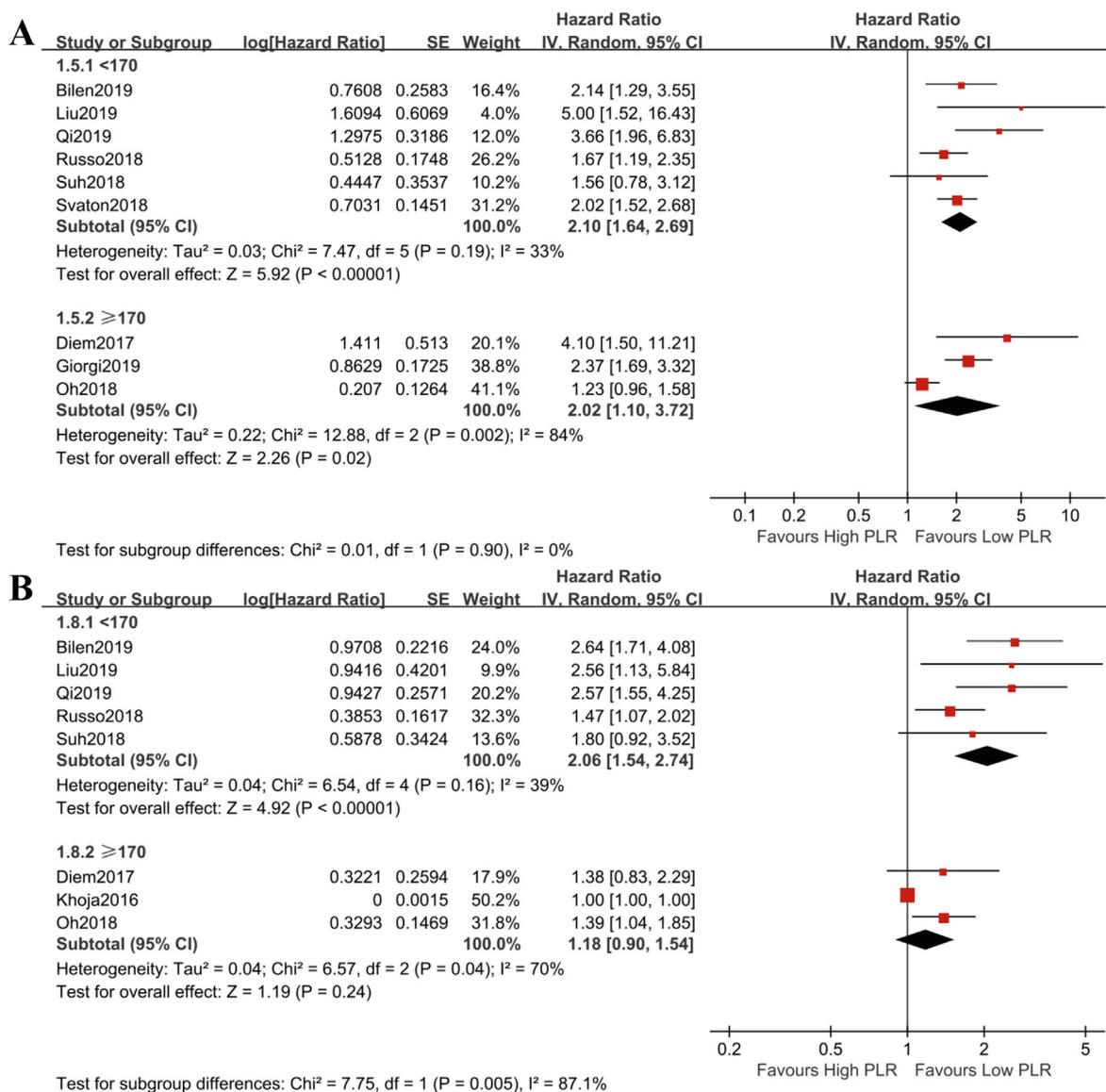


Fig. 4. Subgroup analyses with regard to PLR cutoff value. Due to significant heterogeneity observed in the overall analyses, subgroup analyses of OS and PFS are performed in term of PLR cutoff value. For studies using cutoff value less than 170, low risks of heterogeneity are observed ($P > 0.1$); A, subgroup analysis of OS in term of different cutoff value. When using < 170 as the cutoff value of PLR, the risk of mortality in patients with high PLR is 2.10 times higher than those with low PLR. B, subgroup analysis of PFS in term of different cutoff value. When using < 170 as the cutoff value of PLR, the risk of progression in high PLR patients is 2.06 times than those with low PLR.

4. Discussion

There are convincing evidences suggesting that PLR is related with traditional clinical treatment outcomes in cancer patients [11]. However, the role of PLR in predicting efficacy of immunotherapy in various cancer patients is still controversial. In this study, we investigated the value of PLR in predicting survival outcomes in various cancer patients treated with immune checkpoint inhibitors. The results of our study indicated that cancer patients with high PLR was associated with shorter OS and PFS after immunotherapy, suggesting elevated PLR could be a routinely potential prognostic factor for various cancer patients when receiving immune checkpoint inhibitors, especially for NSCLC patients.

In this study, a meta-analysis of data from 12 related studies involving a total of 1340 patients was performed to obtain a more accurate assessment of the prognostic significance of PLR for cancer patients. This study found that patients with high PLR levels had increased risk of death (HR: 2.02) and disease progression (HR: 1.74). In addition,

the included studies [15,16] indicated that patients with low immunotherapy response had a higher PLR ratio, suggesting that PLR may be used to predict the immunotherapy sensitivity of cancer patients.

Although several kinds of markers, such as tumor mutation burden, immune-related adverse events, PD-L1 expression, sex, and NLR, have been suggested to be significantly associated with immune checkpoint inhibitor efficacy, potential biomarkers to predict the outcome of immunotherapy are still needed. PLR can also serve as a predictor of immune checkpoint inhibitor efficacy. A review by Prelaj [29] exhibited the evidence of PLR was related with poor overall survival in cancer patients after immunotherapy. A recent meta-analysis [20] included four studies to evaluate the association between PLR level and survival of cancer patients after treating with immune checkpoint inhibitors. After combing the extracted data, they found there was no significant relevance between PLR and clinical endpoints in patients treated with immune checkpoint inhibitors (HR = 1.14, $P > 0.05$ for PFS; HR = 1.35, $P > 0.05$ for OS). Their results were calculated based on significant heterogeneity ($I^2 = 61.7\%$ for PFS; $I^2 = 80.2\%$ for OS).

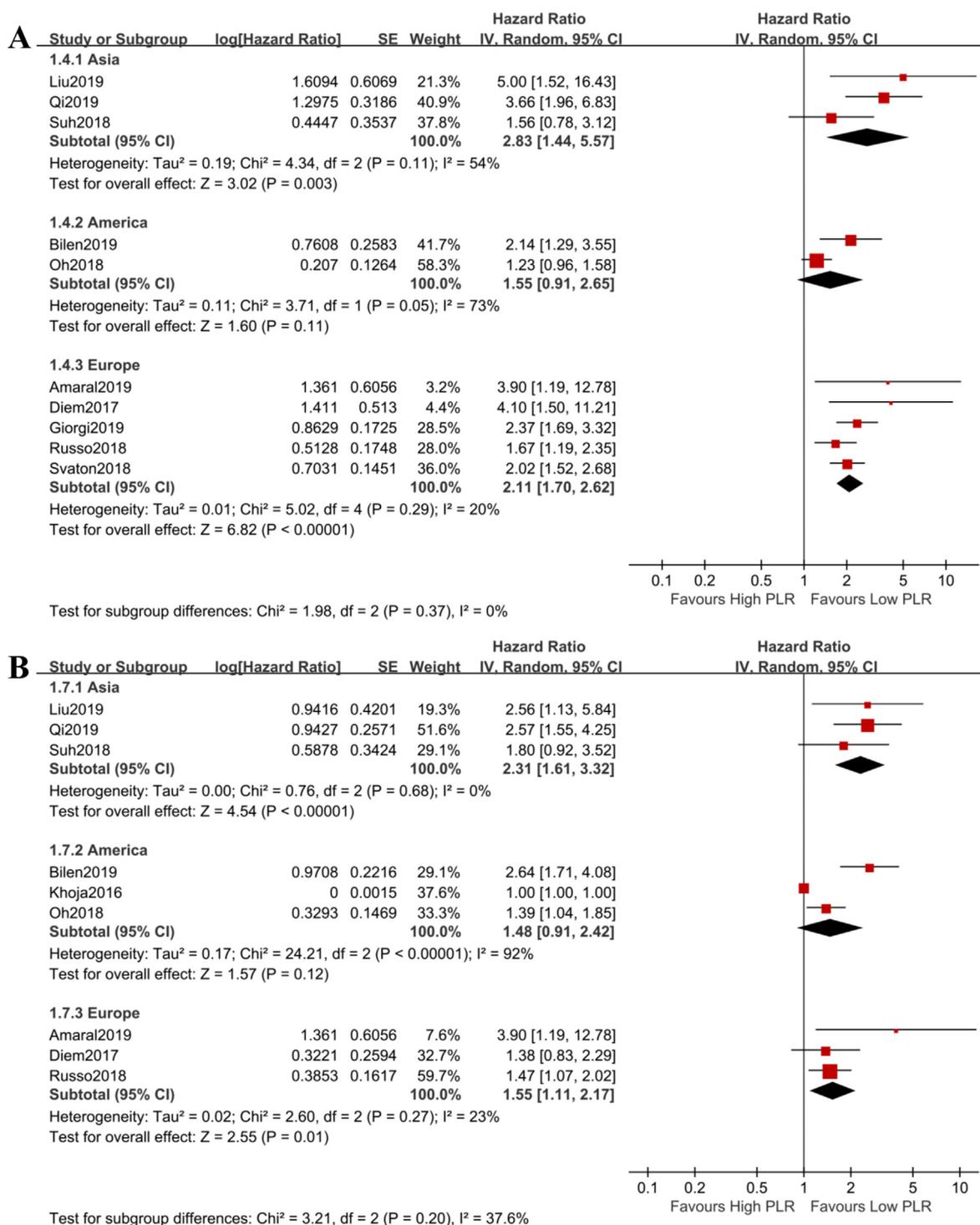


Fig. 5. Subgroup analyses in term of study region. The studies are grouped into three regions as following: Asia, America, and Europe. Low PLR is associated with low risk of death and progression regardless of region, though not all the subgroup analyses results are statistically significant. A, OS subgroup analysis in term of different study regions; B, PFS subgroup analysis in term of different study regions.

However, we found a significant association between PLR and survival of cancer patients when treated with immune checkpoint inhibitors with significantly low risk of heterogeneity.

As a simple and routine blood test, it is easy to measure and calculate the value of PLR. Although we found positive connection between PLR and efficacy of immune checkpoint inhibitors, there are still several major concerns that should be addressed before applying it in clinical practice. First issue is about the definition of baseline PLR. All the studies reported that the PLR was calculated based on baseline

blood test, but there were variations in the definition of baseline, such as timing of blood test and treatment history. These differences could increase the risk of heterogeneity. Second issue is about the cutoff value of PLR. How to identify the optimal value for grouping patients into high versus low PLR is one of the most challenging questions. The cutoff values of defining high versus low PLR ranged from 45 to 400 among the included studies, associated with different risks of death. Our results suggest that the increase of the cutoff value of PLR is associated with reduced prognostic effect. It is even not significant for PFS when the

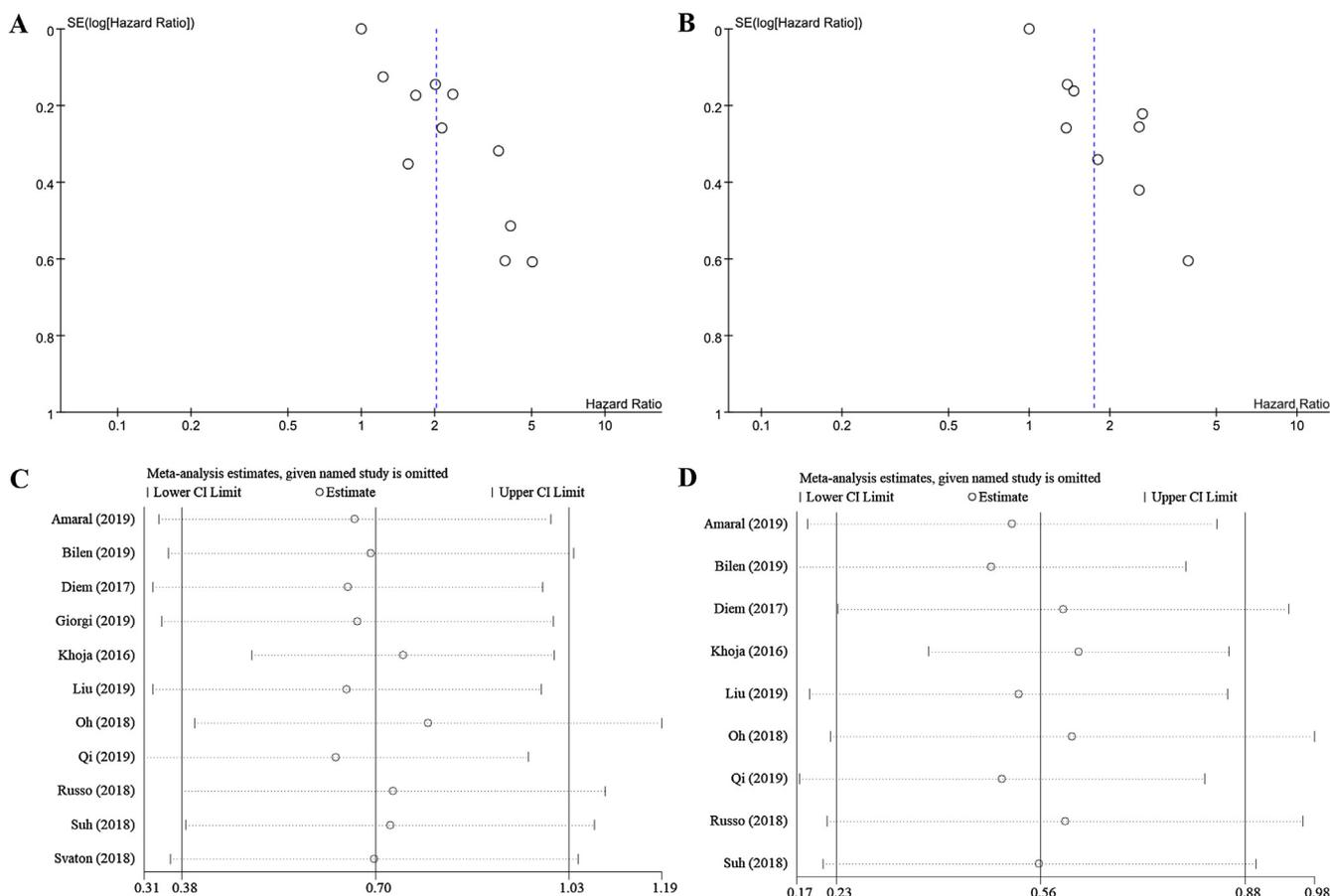


Fig. 6. Sensitivity analyses for OS and PFS, and Funnel plots for detecting publication bias in terms of survival data. A, sensitivity analysis with regard to studies included for OS; B, sensitivity analysis with regard to studies included for PFS; C, funnel plot using data of OS to detect publication bias; D, funnel plot using data of PFS to detect publication bias.

PLR cutoff value is ≥ 170 , indicating its prognostic role is not reliable. Third, systemic inflammation has been known as an enabling mechanism behind cancer and it is always changing. What is the mechanism of using baseline PLR to predict efficacy of immunotherapy in the setting of a changing system. For these reasons, it should be caution to apply PLR in clinical practice.

There were some limitations in this study: (1) the present meta-analysis only included retrospective studies, resulting in a lower strength of the demonstration than that of the clinical randomized controlled trials. We also searched unpublished studies or even those with negative results, trying to minimize the reporting/publication bias that likely affected the study results; (2) the heterogeneity of this study may be related to regions, cancer types, and PLR cut-off values. Due to the small number of samples in the study, heterogeneity in selection bias was unavoidable. In addition, the PLR threshold in different studies varied widely. To explore the source of heterogeneity, we performed a subgroup analysis, and it showed that the predictive role of PLR for cancer patients was not affected by the above confounding factors; (3) the baseline characteristics of included studies were different, such as race, treatment, sample size, PLR cutoff, and disease type and stage, leading to high risk of selection bias. Therefore, the significance of PLR in predicting survival of cancer patients treated with immunotherapy still requires further investigation.

5. Conclusions

The results of this study indicate that cancer patients with elevated PLR have a poor prognosis in the setting of immune checkpoint inhibitors. As it is a cheap and convenient clinical indicator, more

attention should be paid to PLR in clinical significance. The influence of PLR on the prognosis of cancer patient treated with immunotherapy needs to be comprehensively evaluated by multi-center RCT.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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None.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Authors' contributions

Huilin Xu worked as the supervisor and participated in processes of study design, study selection, data extraction and analysis, writing, and

quality evaluation.

Aihua Liu performed the study selection, data extraction, and writing.

Wenxian Dong participant in the process of quality evaluation, data extraction.

Anbing He performed the data extraction, statistically analysis.

Dehong Cao performed quality evaluation, data extraction, and analysis.

Acknowledgments

Not applicable.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.intimp.2019.105957>.

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