Systematic Review and Meta-Analysis

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Platelet-to-lymphocyte ratio as a potential prognostic factor in nasopharyngeal carcinoma

A meta-analysis

Rui-Xiang Cen, MD[a], Yu-Gang Li, MD[b,*]

Abstract

Background: The aim of this study was to investigate the use of pretreatment platelet-to-lymphocyte ratio (PLR) as a prognostic marker in patients with nasopharyngeal carcinoma (NPC).

Methods: A literature search was conducted using online databases such as MEDLINE, EMBASE, Cochrane Library, and WangFang. Overall survival (OS), progression-free survival (PFS), and clinicopathological features were generated and compared.

Results: Ten studies that included 3388 patients were analyzed in this meta-analysis. Among them, 8 studies with 3033 patients with NPC investigated the prognostic role of PLR for OS and showed that elevated PLR was associated with poor OS (HR: 1.77, 95% CI: 1.46–2.15, $P < .001$). Five studies that included 1156 patients investigated the role of PLR in predicting PFS, and showed that high PLR was associated with poor PFS (HR: 1.65, 95% CI: 1.26–2.17, $P < .001$). Moreover, high PLR correlated with the N stage (N2-3 vs N0-1; OR: 1.55, 95% CI: 1.02–2.34, $P = .04$).

Conclusion: Our study suggested that high PLR is associated with worse prognosis in patients with NPC. Pretreatment PLR could serve as a simple, promising indicator for prognostic evaluation in patients with NPC.

Abbreviations: CAR = C-reactive protein to albumin ratio, CI = confidence interval, HR = hazard ratio, IMRT = intensity modulated radiotherapy, NLR = neutrophil to lymphocyte ratio, NOS = Newcastle-Ottawa Scale, NPC = nasopharyngeal carcinoma, OR = Odds ratio, OS = overall survival, PFS = progression-free survival, PLR = Platelet-to-lymphocyte ratio, TILs = Tumor-infiltrating lymphocytes.

Keywords: meta-analysis, nasopharyngeal carcinoma, platelet-to-lymphocyte ratio, prognosis

1. Introduction

Nasopharyngeal carcinoma (NPC), a malignant tumor derived from nasopharyngeal epithelium, is one of the most common head and neck cancers in south China and southeast Asia.[1] Due to its anatomical location and radiosensitivity, radiotherapy with or without chemotherapy remains the standard treatment.[2] With the wide application and progress of intensity modulated radiotherapy (IMRT) technology, the nasopharyngeal lesion control rate increased significantly.[3] Due to the onset of deep location, early diagnosis is difficult, and 5% to 6% patients have had distant metastasis at the time of presentation.[4] Although the combination of chemotherapy, targeted drug therapy, and surgical treatment has improved the prognosis of patients to some extent, the overall effect remains unsatisfactory.[5,6] Therefore, a better understanding of the carcinogenic mechanisms and the use of ideal cancer biomarkers is required to improve the diagnosis and prognosis of patients with NPC.

Cancer-associated inflammation has been reported to increase the risk of tumor development and angiogenesis.[7] The tumor-associated inflammatory response consists of inflammatory cells and a range of inflammatory mediators.[8] Recently, inflammation-based models such as the neutrophil-to-lymphocyte-ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein-to-albumin ratio (CAR) have been developed to predict oncological outcomes in various solid cancers.[9–11] As a new inflammation-based scoring index, a combination of lymphocyte and platelet count has been recently reported. PLR has been widely investigated for its value in predicting the prognosis of patients with NPC[12,13]; however, it has not been fully elucidated. Thus, we conducted this meta-analysis to assess the relationship of PLR with the prognosis and clinicopathology of patients with NPC.

2. Materials and methods

2.1. Search strategies

Relevant studies were selected using the online databases MEDLINE, EMBASE, Cochrane Library, and WanFang. Search terms were confined to the following main words and Medical Subject Headings (MeSH) terms: "PLR" or "platelet-to-lymphocyte ratio"

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or "platelet to lymphocyte ratio" or "platelet lymphocyte ratio", and "nasopharyngeal cancer" or "nasopharyngeal carcinoma" or "nasopharyngeal tumor" or "nasopharyngeal neoplasms." The literature search was conducted from inception of this study to February 10, 2019. All analyses were based on previous published studies. Thus, this study did not require ethic approval or informed consent.

2.2. Inclusion and exclusion criteria

The criteria for inclusion were as follows:

1. Studies reporting the association between pretreatment PLR, prognosis, or clinicopathological features in NPC;
2. Studies where PLR was assessed by cut-off value or median into different risk strata; and
3. studies that provided sufficient information for extraction or calculation of the individual hazard ratio (HR) or odds ratio (OR) and associated 95% confidence intervals (CI).

The criteria for exclusion of studies were as follows:

1. lack of appropriate data that could be extracted or calculated,
2. duplicate publications, and
3. reviews, meta-analysis, letters, and conference abstracts.

2.3. Data extraction

Two reviewers independently reviewed articles for inclusion/exclusion criteria. The following information was extracted: the first author name, publication year, country, age, number of patients, sex, tumor stage (non-metastatic and metastatic), TNM stage, treatment type (chemotherapy and combination of radiotherapy and chemotherapy), cut-off value, follow-up duration, and survival outcome.

2.4. Quality assessment

In this meta-analysis, the quality assessment for non-randomized studies was evaluated by two reviewers independently based on the Newcastle-Ottawa quality assessment scale (NOS).[14] Based on this scale, studies are awarded a maximum score of 9 points; studies with NOS values greater than 6 are considered high quality studies.

2.5. Statistical analysis

HRs with corresponding 95% CIs were used to estimate the association of PLR with NPC survival rates. In this meta-analysis, the HRs and 95% CIs were directly extracted if a study reported the survival analysis; otherwise, they were computed from the Kaplan–Meier graph using Engauge Digitizer software (version 4.1).[15,16] Statistical heterogeneity was quantified by I^2 statistic. A random effects model was used[17] with prominent heterogeneity ($I^2 > 50\%$ or P for heterogeneity < 0.10) and contrast ($I^2 < 50\%$ and P for heterogeneity $> .10$), and a fixed effects model was also adopted Stata 13.0 (StataCorp, College station, TX). We performed a sensitivity analysis in order to validate the robustness of the pooled results by removing each study. The risk of publication bias was assessed by visual inspection of Begg funnel plot and Egger's linear regression test.[18,19] P values $< .05$ were considered statistically significant.

3. Results

3.1. Study selection

The literature search identified 42 records: 10, 22, 2, and 8 from MEDLINE, EMBASE, Cochrane Library, Wan Fang, respectively. As shown in the flow diagram (Fig. 1), 28 records were retained after excluding duplicate studies. The titles and abstracts were then screened and 13 articles were removed as irrelevant. Fifteen full-text articles remained for further assessment, 5 of which were excluded after not meeting the inclusion criteria. In total, 10 studies were eligible for quantitative synthesis.[20–29]

3.2. Study characteristics

All included studies were conducted in China and published between 2015 and 2018. There were 9 studies that reported non-metastatic disease, and 1 study that reported metastatic disease. Most patients were treated with radiotherapy and chemo-radiotherapy. Of the 10 studies, four reported HRs both for overall survival (OS) and progression-free survival (PFS), 4 reported the HR for OS, and 1 reported the HR for PFS. In addition, prognostic data on OS or PFS were directly retrieved from 8 studies. PLR cut-off values ranged from 108.33–174, and studies with NOS scores ranging from 6 to 9 stars were regarded as high-quality studies. The detailed characteristics of the eligible articles are presented in Table 1.

4. Meta-analysis

4.1. PLR and overall survival

As shown in Table 2, 8 studies with 3033 patients were used to investigate the role of PLR in predicting OS of patients with NPC. The pooled results showed that elevated PLR was associated worse prognosis (HR: 1.77, 95% CI: 1.46–2.15, $P < .001$, Fig. 2). Furthermore, a subgroup analysis was performed to further explore the prognostic value of PLR in NPC (Table 2). The results demonstrated that elevated PLR predicted worse OS in patients with non-metastatic disease (HR: 1.79, 95% CI: 1.46–2.19; $P < .001$). However, no prognostic value was observed in patients with metastatic disease (HR: 1.62, 95% CI: 0.87–3.00, $P = .128$). Similarly, a significant relationship was detected between high PLR and shorter OS in patients who received a combination treatment (HR: 2.04, 95% CI: 1.26–3.31; $P < .001$). Moreover, the sample size, cut-off for PLR, and analysis method did not affect the significant predictive value of PLR in patients with NPC.

4.2. PLR and progression-free survival

The association between high PLR and progression-free survival (PFS) has been reported in Figure 3. The analysis showed a HR of 1.65, with 95% CI: 1.26–2.17, which indicated a significantly negative association between PLR and PFS (Fig. 3).

4.3. PLR and clinicopathological characteristics

Our results demonstrated that high PLR was related to N stage (N2–3 vs N0–1; OR: 1.55, 95% CI: 1.02–2.34, $P = .04$). However, no obvious association was found between the PLR and sex (male vs female; OR: 0.96, 95% CI: 0.63–1.48, $P = .86$),

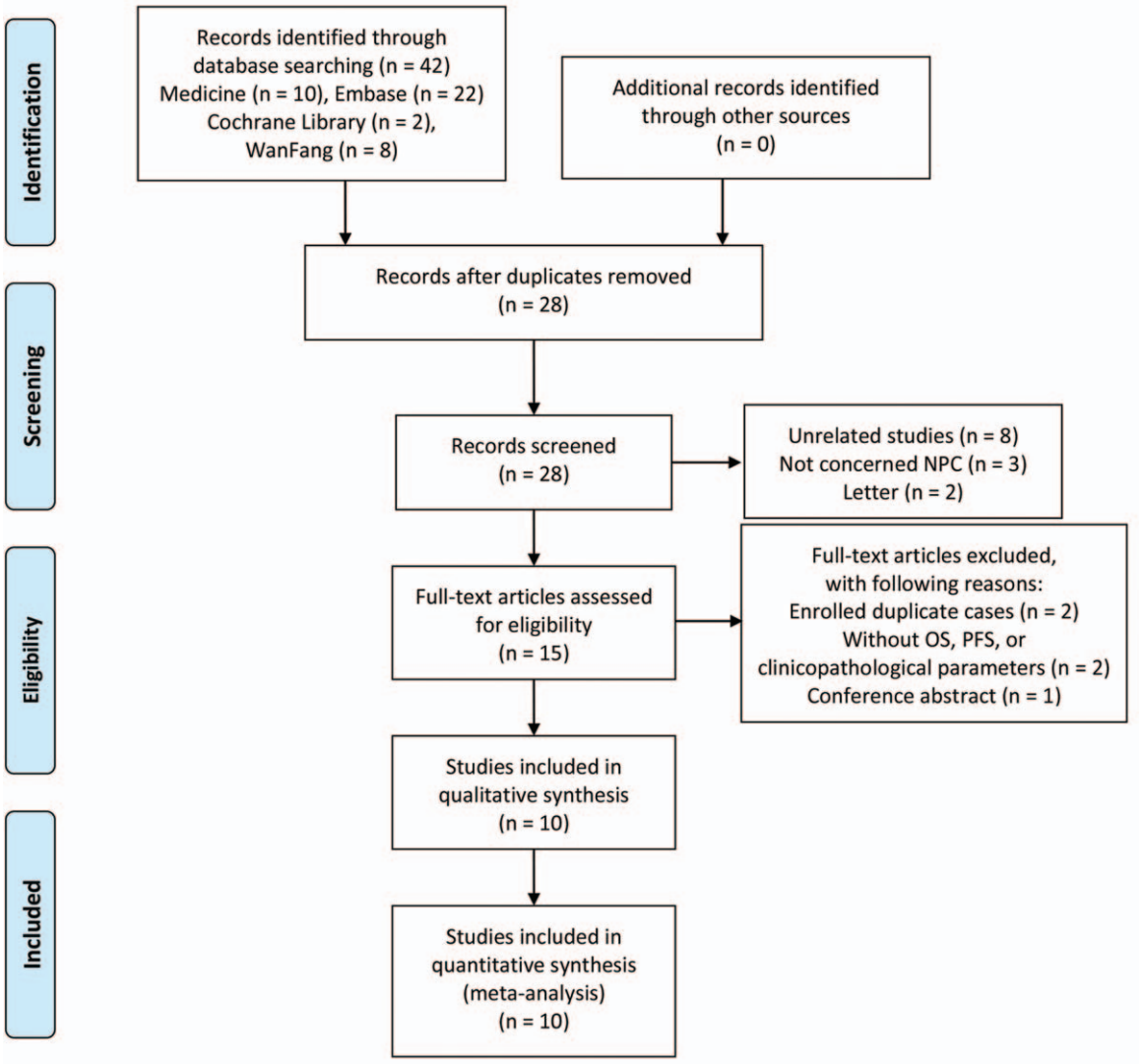

Figure 1. Flow diagram showing the study retrieval and selection process.

age (> median vs < median; OR: 1.19, 95% CI: 0.79–1.77, $P = .40$), TNM stage (III-IV vs I-II; OR: 1.03, 95% CI: 0.51–2.05, $P = .94$), and T stage (T3-4 vs T1-2; OR: 2.14, 95% CI: 0.75–6.13, $P = .16$).

4.4. Sensitivity analysis and publication bias

To test the stability of the meta-analysis of LMR, OS, and PFS, a sensitivity analysis was performed. The results showed that our meta-analysis was steady, since pooled HRs did not alter

Table 1

Characteristics of the studies included in the meta-analysis.

Author	Year	Country	Study type	Follow-up (months)	Treatment	Age (yr)	No. of patients	Stage	Cut-off value	Survival analysis	Analysis	NOS score
Jin	2017	China	R	44 (6–87)	Mixed	53 (12–72)	91	Non-metastatic	143.3	OS/PFS	MV	7
Jiang	2015	China	R	NA	Mixed	46 (39–55)	1261	Non-metastatic	153.64	OS/CSS	MV	6
Li	2017	China	P	NA	Mixed	NA	388	Non-metastatic	166	OS	MV	7
Sun	2016	China	R	50 (5–84)	Mixed	46 (15–76)	251	Non-metastatic	167.2	OS/PFS	MV	7
Sun	2017	China	R	15.3 (1–66)	Chemotherapy	45 (24–72)	148	Metastatic	152	OS	MV	7
Lu	2017	China	R	68 (5–77)	Mixed	47 (10–76)	140	Non-metastatic	174	OS/PFS	UV	9
Jiang	2018	China	R	53 (3–64)	Mixed	46 (18–86)	247	Non-metastatic	108.33	PFS	MV	6
Ye	2018	China	R	67.5 (4.8–85.5)	Mixed	48 (17–82)	427	Non-metastatic	123.0	OS/PFS	MV	7
Tang	2018	China	P	NA	Mixed	45 (18–68)	108	Non-metastatic	159.6			6
Jiang	2017	China	R	38.3 (2–164.6)	Mixed	50 (20–80)	327	Non-metastatic	112.0	OS	MV	8

CSS = cancer-specific survival, MV = multivariate, NA = not available, OS = overall survival, P = Prospective, PFS = progression-free survival, R = Retrospective.

Table 2

Pooled hazard ratios (HRs) for OS according to subgroup analyses.

Subgroup	No. of studies	No. of patients	HR (95% CI)	*P* value	Heterogeneity	
					I^2 (%)	P_h
Overall	8	3033	1.77 (1.46–2.15)	<.001	0	.708
Sample size						
≥300	4	2295	1.64 (1.31–2.05)	<.001	0	.693
<300	4	738	2.19 (1.52–3.15)	<.001	0	704
Disease stage						
Non-metastatic	7	2885	1.79 (1.46–2.19)	<.001	0	.750
Metastatic	1	148	1.62 (0.87–3.00)	.128		
Treatment						
Mixed	7	2885	1.79 (1.46–2.19)	<.001	0	.750
Chemotherapy	1	148	1.62 (0.87–3.00)	.128		
Cut-off for PLR						
≥150	5	2188	1.80 (1.41–2.30)	<.001	0	.482
<150	3	845	1.74 (1.28–2.37)	<.001	0	.575
Analysis method						
Univariate	1	140	2.56 (1.14–5.79)	.010		
Multivariate	7	2893	1.74 (1.43–2.12)	<.001	0	.707

Mixed: radiotherapy and chemoradiotherapy.

significantly after eliminating the included studies in sequence (Figs. 4 and 5). As shown in Figures 6 and 7, there was no significant publication bias in both OS ($P = .216$ for Begg test) and PFS ($P = 1.000$ for Begg test).

5. Discussion

Inflammation has previously been recognized as an important factor in the development of tumors in humans.[7,30,31] PLR has been considered as an accurate, readily obtained, and low-cost

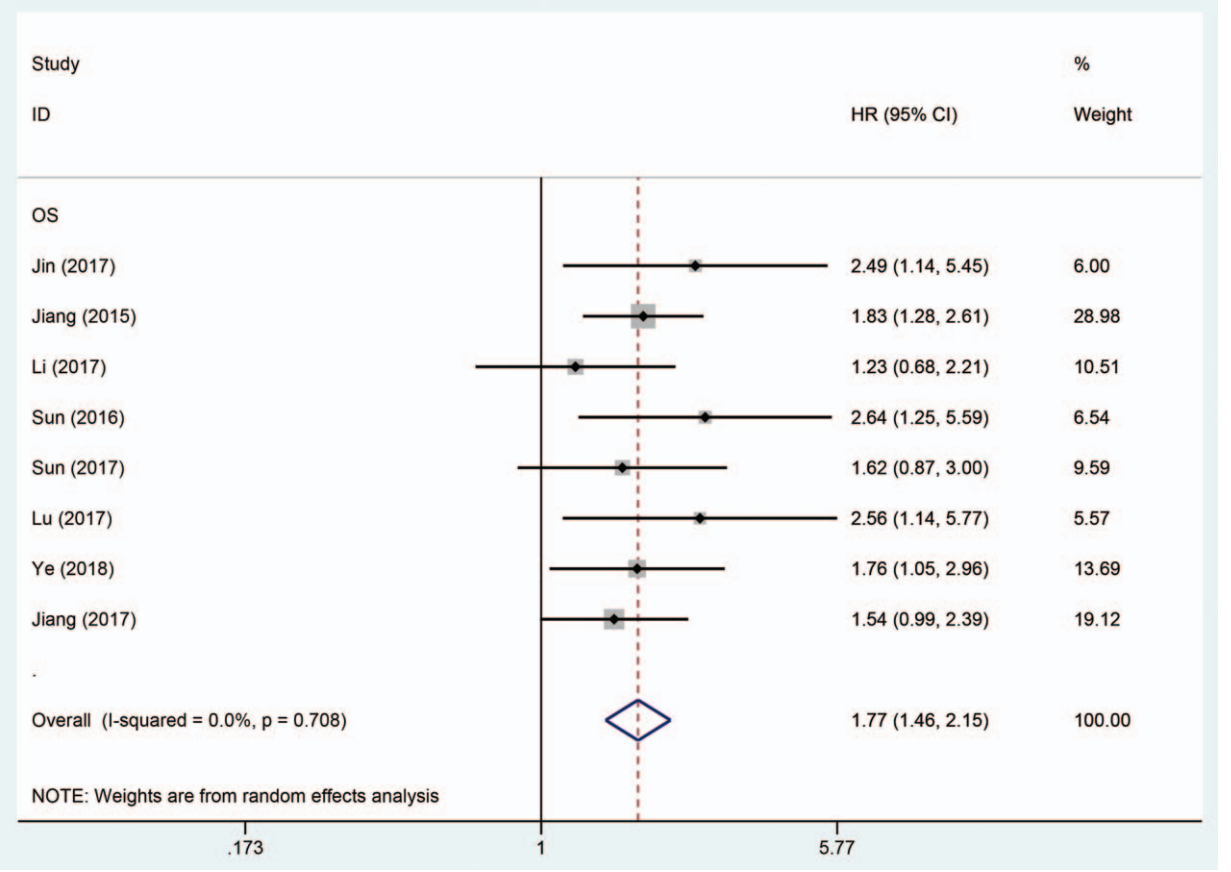

Figure 2. Pooled HR of PLR for OS in patients with NPC. HR = hazard ratio, NPC = nasopharyngeal carcinoma, OS = overall survival, PLR = Platelet-to-lymphocyte ratio.

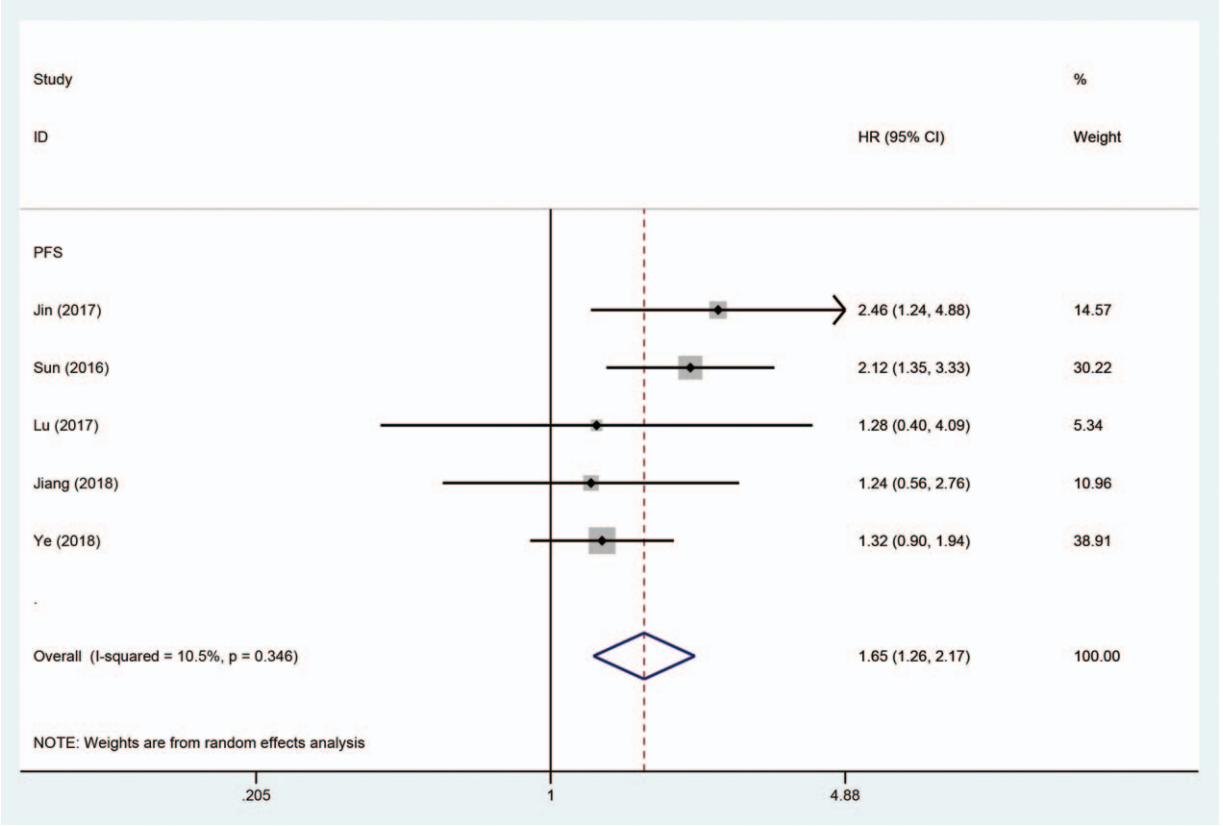

Figure 3. Pooled HR of PLR for PFS in patients with NPC. HR = hazard ratio, NPC = nasopharyngeal carcinoma, PFS = progression-free survival, PLR = Platelet-to-lymphocyte ratio.

indicator for evaluating patient status and prognosis that allows patients and physicians make accurate treatment decisions prior to clinical intervention. Here, we performed a meta-analysis, including 10 studies that included 3388 patients with NPC to evaluate the prognostic value of PLR on OS and PFS. According to the pooled results, there was a significant correlation of high PLR with poor survival of patients with NPC. The subgroup analyses maintained the significant prognostic effect of PLR on

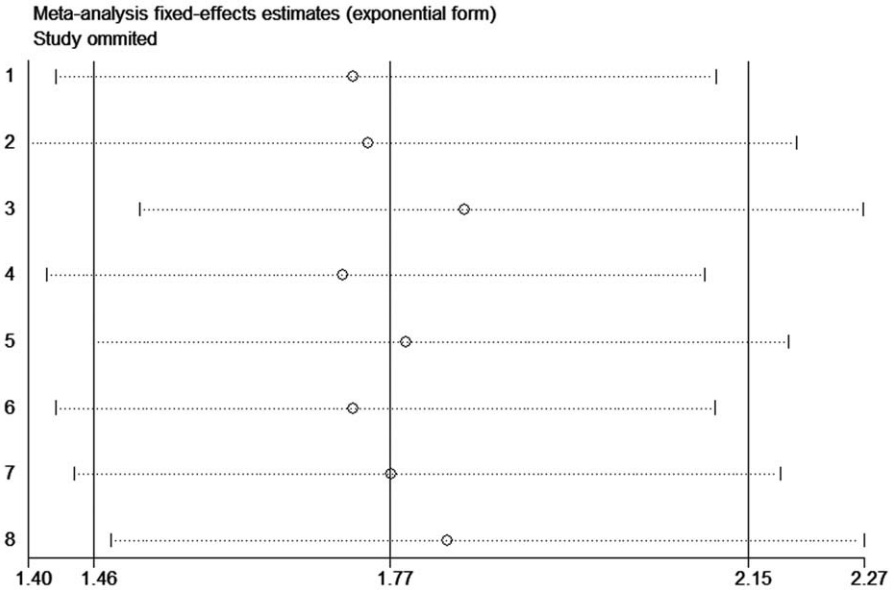

Figure 4. Sensitivity analysis of PLR on OS in patients with NPC. NPC = nasopharyngeal carcinoma, OS = overall survival, PLR = Platelet-to-lymphocyte ratio.

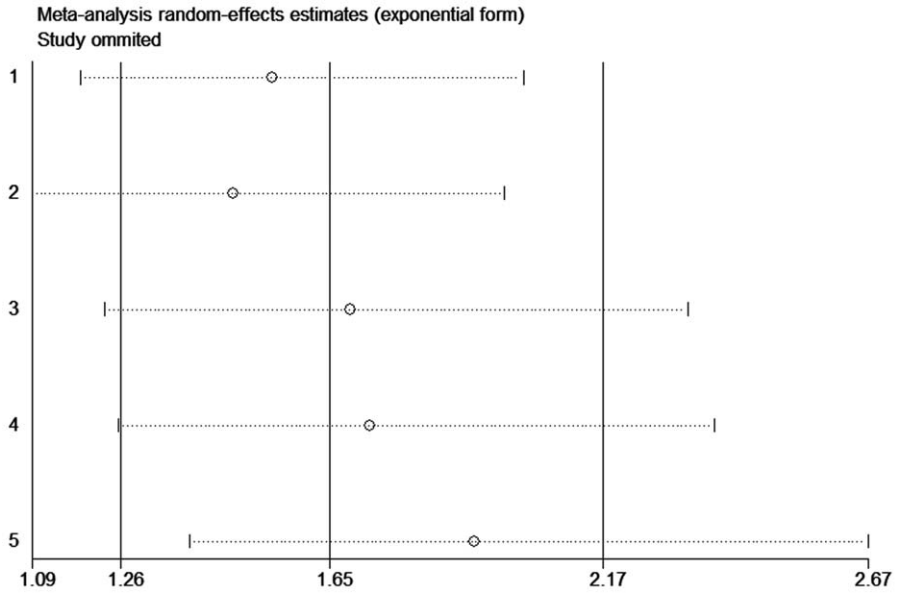

Figure 5. Sensitivity analysis of PLR on PFS in patients with NPC. NPC = nasopharyngeal carcinoma, PFS = progression-free survival, PLR = Platelet-to-lymphocyte ratio.

OS and PFS for NPC. Moreover, high PLR was associated advanced N stage. We believe that our study makes a significant contribution to the literature because prognostic biomarkers are highly needed to guide the proper management of patients with NPC and improve their outcomes. PLR provides a potential new prognostic biomarker for cancer control that will help counteract the burden of this disease.

Although the potential mechanisms regarding the prognostic ability of PLR are multifaceted and have not been clarified, research has demonstrated that platelets can produce inflammatory cytokines and chemokines which can lead to tumor progression.[32] Platelets promote tumor angiogenesis and stroma formation by secreting vascular endothelial growth factor and facilitating inflammatory cell migration.[33–35] IL-6 can stimulate the differentiation of megakaryocytes to platelets and participate in neutrophil recruitment.[36] Several studies have shown that IL-6 can stimulate thrombopoietin production and lead to increase in platelet counts in patients with cancer.[37] Lymphocytes play important roles in cell-mediated anti-tumor immune responses and tumor immunological surveillance.[38] Tumor infiltrating lymphocytes are important components of the anti-tumor immune microenvironment and participate in several stages of tumor progression.[39,40] Thus, the prognostic impact of PLR may represent a balance between the tumor promotion functions and anti-tumor immune reactions.

Several limitations of this study should be considered. First, all included studies were carried out in China and more cohort studies from other regions are necessary to identify the common features in our findings. Hence, it is possible that our findings may not extend to other populations across the world. Additionally, this meta-analysis included a predominance of retrospective studies and lacked random control test studies; retrospective

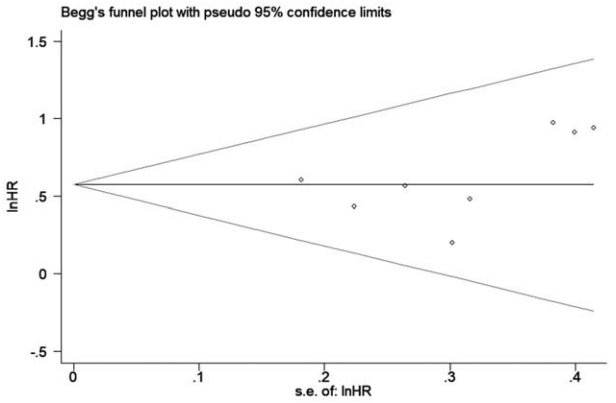

Figure 6. Begg funnel plot of publication bias test for OS in patients with NPC. NPC = nasopharyngeal carcinoma, OS = overall survival.

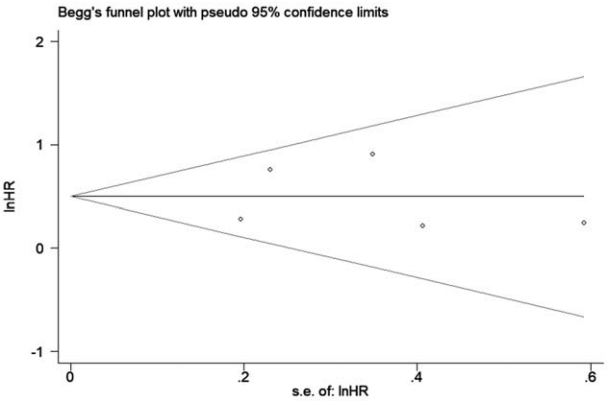

Figure 7. Begg funnel plot of publication bias test for PFS in patients with NPC. NPC = nasopharyngeal carcinoma, PFS = progression-free survival.

studies may provide confounding variables. Although our study has several limitations, it is the first and most comprehensive meta-analysis to systematically assess the prognostic value of PLR in patients with NPC. We believe that our study makes a significant contribution to the literature because prognostic biomarkers are required for the proper management of patients with NPC to improve their outcomes. The meta-analysis provides a statistical inspection of scientific studies, and its evidence level is superior to the individual studies themselves. Our findings provide a potential new reliable tool for cancer control and will help mitigate the burden of this disease.

6. Conclusions

The results of the present study suggest that high pretreatment PLR is associated with poor OS and PFS in patients with NPC. As an easily accessible parameter, PLR provides a promising indicator for the prognostic evaluation of patients with NPC.

Author contributions

Conceptualization: Rui-Xiang Cen, Yu-gang Li.
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Formal analysis: Rui-Xiang Cen, Yu-gang Li.
Investigation: Rui-Xiang Cen, Yu-gang Li.
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Visualization: Rui-Xiang Cen, Yu-gang Li.
Writing – original draft: Rui-Xiang Cen, Yu-gang Li.
Writing – review & editing: Rui-Xiang Cen, Yu-gang Li.

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