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The pretreatment platelet-to-lymphocyte ratio predicts clinical outcomes in patients with cervical cancer

A meta-analysis

Jian-ying Ma, MD, Li-chi Ke, MD, Qin Liu, MD*

Abstract

Introduction: The platelet-to-lymphocyte ratio (PLR) has been reported to possess significant prognostic value in multiple types of cancer. However, its prognostic value in patients with cervical remains controversial. We conducted a meta-analysis to evaluate the prognostic value of pretreatment PLR in cervical cancer.

Methods: We searched the MEDLINE, EMBASE, and Cochrane databases to identify studies evaluating the prognostic significance of the pretreatment PLR in patients with cervical cancer. The end points were overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and clinicopathological parameters. All statistical analyses were conducted with Stata 13.0.

Results: A total of 12 studies comprising 3668 patients with cervical cancer were included. Elevated PLR was significantly correlated with poor OS [hazard ratio (HR): 1.56, 95% confidence interval (CI): 1.32–1.85, $P < .001$] and DFS/PFS (HR = 1.56; 95% CI = 1.26–1.94; $P < .001$). In addition, elevated PLR was highly correlated with lymphovascular space invasion (+), lymph node metastasis (+), tumor size (>4 cm), grade (G3).

Conclusion: The pretreatment PLR could serve as a predicative biomarker of poor prognosis for patients with cervical cancer.

Abbreviations: CI = confidence interval, DFS = disease -free survival, HR = hazard ratio, NOS = Newcastle-Ottawa Scale, OS = overall survival, PFS = progression-free survival, PLR = platelet-to-lymphocyte ratio.

Keywords: cervical cancer, meta-analysis, platelet-to-lymphocyte ratio, prognosis

1. Introduction

Cervical cancer is the third most commonly diagnosed cancer and the second leading cause of cancer death in women, with an estimated 500,000 new-diagnosed cases and approximately 250,000 deaths.[1,2] Nearly one-third of patients with cervical cancer die due to disease recurrence or progression. For patients with early stage cervical cancer, radical resection followed by chemotherapy or chemoradiation is an effective treatment option. Presently, many tumor-specific parameters are identified as prognostic factors for cervical cancer, and most of these factors are based on postoperative pathological findings such as tumor size, lymph node status, depth of invasion, and histologic grade are identified as prognostic factors for cervical cancer.[3–5] Although clinical staging is a powerful preoperative predictor, the clinical staging is often inaccurate, especially in some patients with advanced disease.[6,7] Therefore, a reliable and readily accessible preoperative prognostic biomarker is required to identify risk classification and even guide the treatment.

Inflammation can largely influence several stages of tumorigenesis, from tumor initiation to promotion and metastatic progression.[8] Increasing evidence shows that inflammatory cells in the tumor microenvironment play a key role in tumor development through inducing proliferation and survival of cancer cells, promoting angiogenesis and metastasis. Accordingly, inflammation-based prognostic indicators, such as the plasma fibrinogen, Glasgow prognostic score, C-reactive protein, and platelet-to-lymphocyte ratio (PLR) have been investigated in various cancers.[9,10] The pretreatment PLR has been demonstrated as significant predictors in patients with cervical cancer.[4,11,12] However, several studies failed to find its prognostic value.[13–15] We therefore conducted a meta-analysis to assess the prognostic role of PLR and analyze the relationship between PLR and clinicopathological parameters in patients with cervical cancer.

2. Materials and methods

2.1. Search strategies

A range of online databases was systematically searched for eligible studies with the deadline of May, 2018. Search terms included: "cervix" or "cervical" and "tumor" or "cancer" or "neoplasm" or "carcinoma" or "malignancy," and "platelet

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J-yM and L-cK contributed equally to this work.

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Department of Breast surgery, Thyroid Surgery, Pancreatic Surgery, Huangshi Central Hospital of Edong Healthcare Group, Hubei Polytechnic University, Huangshi, Hubei, China.

* Correspondence: Qin Liu, Department of Breast Surgery, Thyroid Surgery, Pancreatic Surgery, Huangshi Central Hospital of Edong Healthcare Group, Hubei Polytechnic University, No. 141, Tianjin Road, Huangshi, Hubei, China (e-mail: liuq2017@yeah.net).

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lymphocyte ratio" or "PLR." The whole process of search was conducted by 2 reviewers, independently.

2.2. Selection criteria

The inclusion criteria for this study were as follows: all selected literatures investigated PLR and survival in cervical cancer; the diagnosis of cervical cancer was pathologically confirmed; sufficient data were provided to calculate the hazard ratio (HR) and 95% confidence interval (CI); and (reported a cut-off value for PLR. Articles were excluded from the analyses if they were case reports, letters, or conference abstracts; unable to extract relevant metrics data; and duplicate publication.

2.3. Data extraction and quality assessment

All eligible studies were reviewed and extracted independently by 2 reviewers. Data were extracted as follows: surname of first author, publication year, area, number of patients, follow-up period, treatment, tumor size, histological subtype, depth of stromal infiltration, tumor grade, International Federation of Obstetricians and Gynecologists (FIGO) stage, lymphovascular space invasion, lymph node metastasis, cut-off values, survival analysis methods, and HR as well as corresponding 95% CI.

The Quality Assessment of Newcastle-Ottawa Scale (NOS) was adopted to evaluate the methodological quality of included studies.[16] This scale consists of 4 primary domains—Selection, Comparability, and Outcome, which were scored separately. For quality assessment, scores ranged from 0 (lowest) to 9 (highest), and studies with scores of 6 or more were rated as high quality. Validity of included studies was assessed by 2 independent reviewers.

2.4. Statistical analysis

HRs and their 95% CI were combined to evaluate the effective value of PLR on prognosis. Odds ratio and 95% CIs were used for the evaluation of associations between PLR and clinicopathologic variables. All analyses were conducted with Stata 13.0 statistical software (StataCorp, College Station, TX). A P value $<.05$ was considered to be statistically significant. If the statistical variables were described in the study, we extracted them directly. Otherwise, they were calculated with Kaplan-Meier survival curves which were read by Engauge Digitizer version 4.1 according to the methods described by Tierney et al and Parmar et al.[17,18] The between-study heterogeneity was evaluated with chi-squared test and I^2 statistics. A chi-squared test of $P<.10$ or I^2 >50% showed the existence of heterogeneity. Subgroup analysis was further performed to explore the source of existing heterogeneity. To validate the credibility of the result, sensitivity analyses were performed by removing each study. Publication bias was estimated by Begg and Egger test.

3. Results

3.1. Study selection and study characteristics

The selection process is shown in Figure 1. The search strategy identified 60 potentially relevant records. Forty-seven articles remained after exclusion of duplicated data. Finally, 12 studies with a combined 3668 patients met the criteria and were enrolled into the meta-analysis.[4,11–15,19–24]

The major characteristics of the 12 eligible studies are listed in Table 1. Of the 12 studies, 7 studies were from China, 4 were from Japan, and 1 was from Turkey. All articles reported the outcomes of overall survival (OS), and 8 studies presented disease-free survival (DFS)/progression-free survival (PFS) as primary outcome. HRs were reported directly in 11 studies. Most of the included studies used multivariate analysis method. The primary treatments were various among the 12 included studies, including surgery, chemoradiotherapy, and mixed treatments.

3.2. Quality assessment

The quality of all eligible studies varied from 6 to 9, with average 7.5 according to NOS. Therefore, all studies included subsequent analysis.

3.3. Meta-analysis

3.3.1. Impact of PLR on OS. All studies with 3668 patients reported adjusted HRs for OS. The pooled result showed that elevated PLR was associated with poor OS (HR: 1.56, 95% CI: 1.32–1.85, $P<.001$), with no heterogeneity ($I^2=3.1\%$, $P=.415$; Fig. 2). The correlation between PLR and OS was further assessed by subgroup analysis based on the main features, including area, tumor stage, cut-off for PLR, treatment, and analysis method (Table 2). The results showed that elevated PLR predicted poor prognosis in Asian patients (HR = 1.57; 95% CI = 1.31–1.87; $P<.001$). In the exploratory subgroup analyses stratified by treatment methods, elevated PLR significantly predicted shorter OS in patients that received surgery (HR = 1.61; 95% CI = 1.09–2.38; $P=.02$) and mixed treatments (HR = 1.52; 95% CI = 1.24–1.87; $P<.001$). Pooled HRs for DFS/recurrence-free survival were stratified by disease stage, the negative effect of elevated PLR on OS was observed in patients with stages I–II (HR = 1.61; 95% CI = 1.21–2.15; $P=.001$) and stages I–IV subgroups (HR = 1.47; 95% CI = 1.19–1.81; $P<.001$). Moreover, subgroup analyses demonstrated that elevated PLR predicted worse OS in patient with cervical cancer, regardless of the analysis method (univariate and multivariate), and the cut-off value for neutrophil–lymphocyte ratio (NLR) (≥150 and <150).

3.3.2. Impact of PLR on DFS/PFS. Eight studies reported HRs for DFS/PFS. The combined data showed that elevated PLR was significantly correlated with worse DFS/PFS, with the pooled HR of 1.56 (Fig. 3). There is no significant heterogeneity between included studies ($I^2=32.5\%$; $P=.169$).

3.3.3. Correlation of PLR with clinicopathological features. The association between PLR and several clinicopathological parameters are illustrated in Table 3. The elevated PLR was highly correlated with lymphovascular space invasion (yes vs no; HR = 1.55, 95% CI: 1.17–2.05, $P=.002$), lymph node metastasis (yes vs no; HR = 2.39, 95% CI: 1.19–4.79, $P=.01$), tumor size (>4 vs <4 cm; HR = 1.89, 95% CI: 1.19–3.01, $P=.007$), grade (G3 vs G2/G1; HR = 1.42, 95% CI: 1.15–1.76, $P=.001$). However, elevated PLR was not related to age (≥45 vs <45; HR = 0.83, 95% CI: 0.63–1.10, $P=.19$), histological subtype (squamous vs nonsquamous; HR = 1.52, 95% CI: 0.55–4.21, $P=.42$), depth of stromal infiltration (≥1/2 vs <1/2; HR = 1.14, 95% CI: 0.91–1.42, $P=.27$), and FIGO stage (II vs I; HR = 1.18, 95% CI: 0.97–1.44, $P=.10$).

3.3.4. Sensitivity analysis and publication bias. We found that the result was not obviously impacted by any single study,

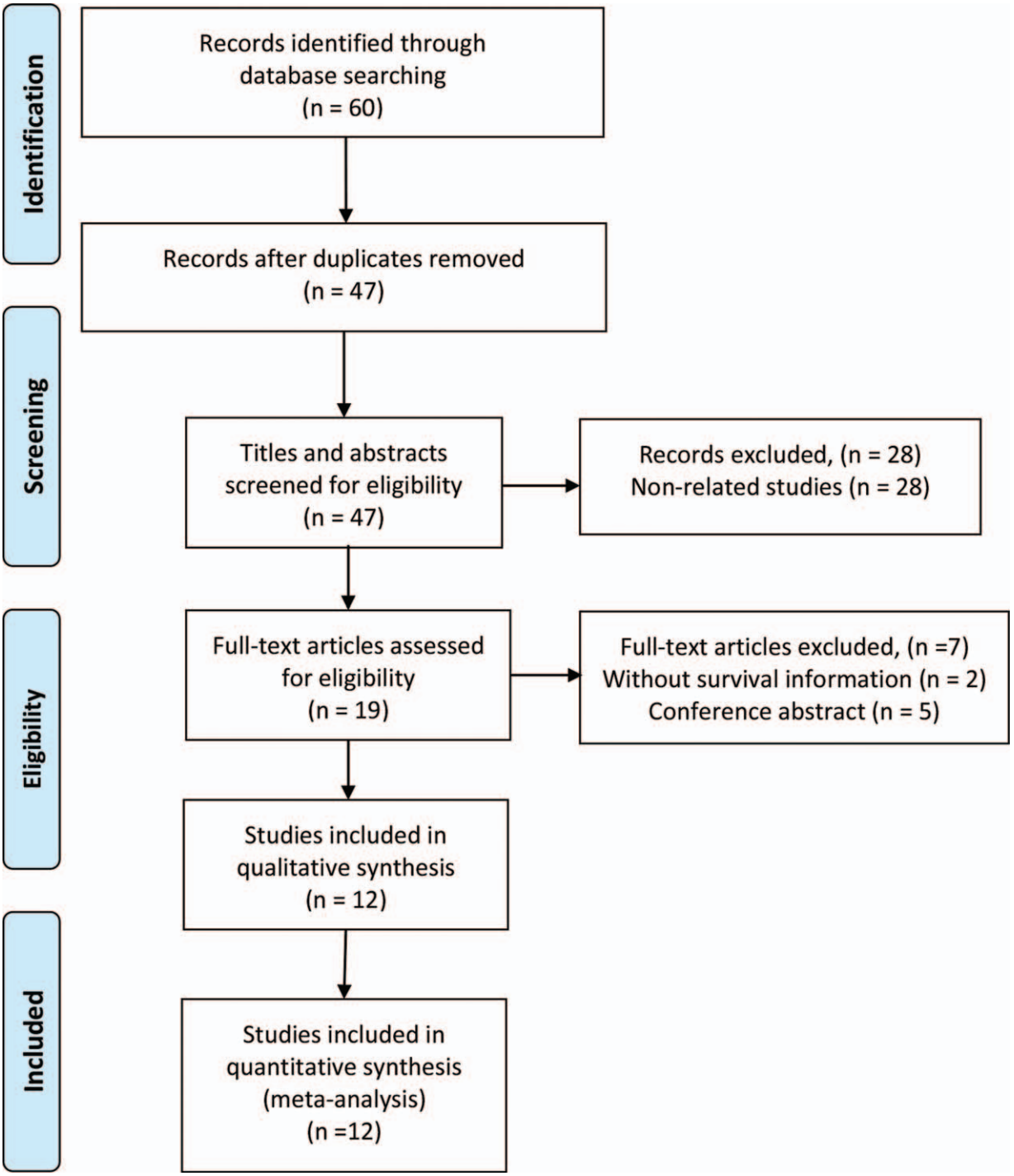

Figure 1. Flow diagram of the study selection process.

therefore indicating that our results were statistically robust (Fig. 4). There was no significant publication bias in OS ($P = .075$ for Begg test and $P = .070$ for Egger test, Fig. 5).

4. Discussion

In the current study, we thoroughly searched multiple databases and retrieved 12 studies with regard to the prognostic value of pretreatment PLR for cervical cancer. As far as we know, the present study is the first meta-analysis to investigate the clinical relevance and prognostic value of pretreatment PLR in patients with cervical cancer. The combined results showed that elevated PLR is significantly associated with poor OS and DFS/PFS. We also performed subgroup analyses, the results indicated that elevated PLR was significantly associated with shorter OS in patients that received surgery and mixed treatments. Elevated PLR also predicted worse OS, regardless of the analysis method, and the cut-off value for NLR. In addition, elevated PLR was

Table 1

Characteristics of the studies included in the meta-analysis.

Author	Year	Area	Follow-up, mo	Treatment	No. patients	Stage	Cut-off value	Survival analysis	Analysis	NOS score
Chen	2016	China	NA	Mixed	407	IB–IIA	138.35	OS/RFS	MV	6
Haraga	2016	Japan	49.70	Chemoradiotherapy	131	I–IV	171.00	OS/PFS	UV	7
He	2018	China	NA	Mixed	229	I–IV	149.27	OS	UV	7
Ida	2018	Japan	15 (2–93)	Mixed	79	I–IV	260	OS	MV	6
Kozasa	2017	Japan	NA	Mixed	597	IA–IVA	131.44	OS/PFS	MV	8
Nakamura	2015	Japan	NA	Chemoradiotherapy	32	I–IV	322.0	OS	MV	7
Onal	2016	Turkey	31.7 (3.7–114.2)	Chemoradiotherapy	235	IB–IVA	133.02	OS/PFS	MV	9
Wang	2017	China	64 (6–142)	Surgery	129	I–IV	148.9	OS	UV	9
Zhang	2014	China	69 (6–100))	Mixed	460	I–II	150	OS/PFS	UV	9
Zhang	2018	China	77 (32–96)	Mixed	235	IB–IIA	176.5	OS/PFS	UV	7
Zheng	2016	China	62.3 ± 26.7	Mixed	795	IA–IIA	128.3	OS/DFS	MV	8
Zhu	2018	China	44 (6–61)	Surgery	339	IA–IIB	139.2	OS/PFS	MV	8

DFS = disease-free survival, MV = multivariate, NA = not available, NOS = Newcastle-Ottawa Scale, OS = overall survival, PFS = progress-free survival, RFS = recurrence-free survival, UV = univariate.

highly correlated with lymphovascular space invasion (+), lymph node metastasis (+), tumor size (>4 cm), and grade (G3). Taken together, the pretreatment PLR may be as a convenient and reliable biomarker in the prognosis of cervical cancer.

The mechanism between elevated PLR and poor outcome of cervical cancer remains unclear. Emerging evidence has indicated that the strong linkage between systemic inflammatory response and tumor development.[8,25,26] Platelets, as critical sources of cytokines, bind vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor-β (TGF-β) family proteins, which enables platelets to act as reservoirs for

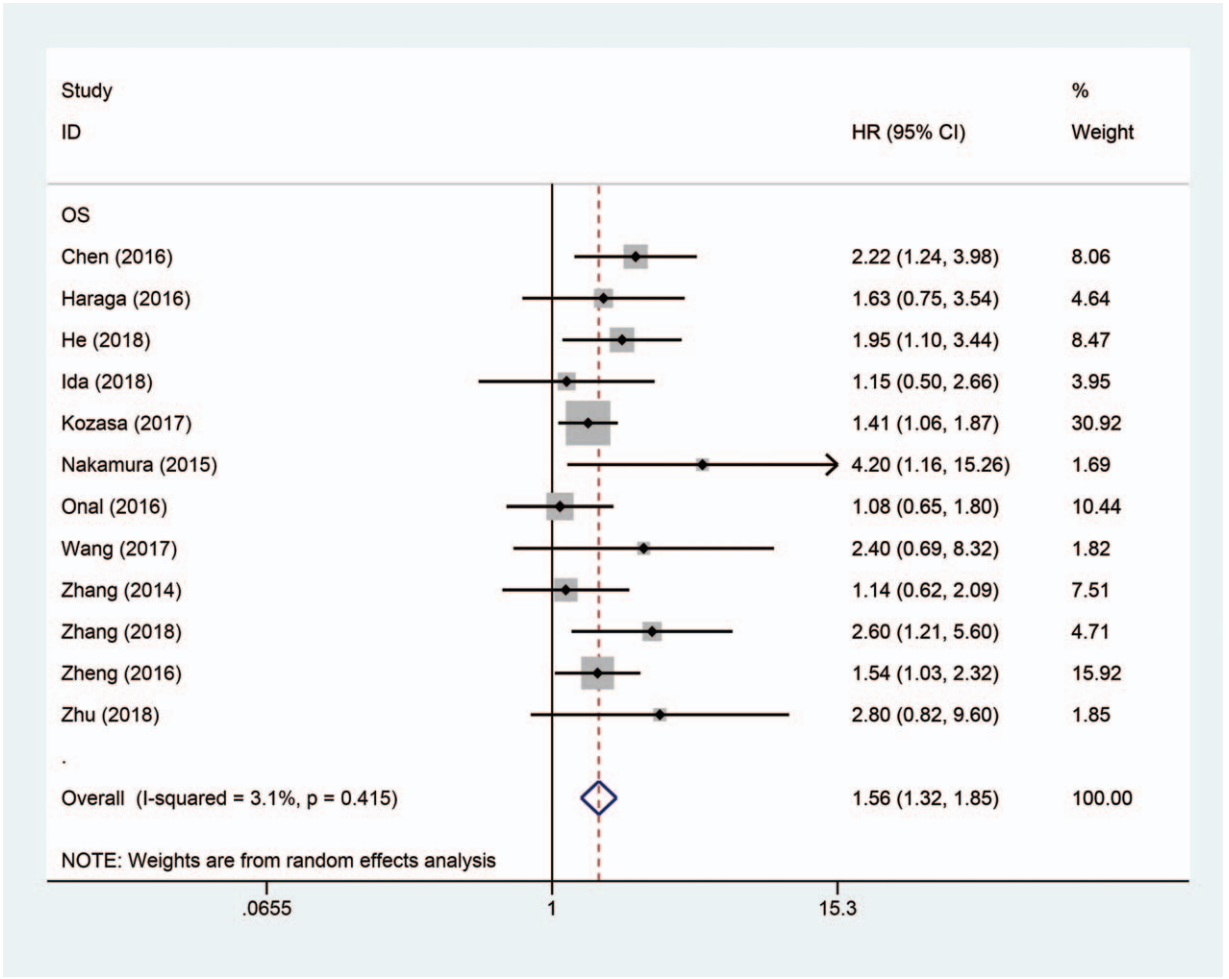

Figure 2. Forest plots for the association between platelet-to-lymphocyte ratio (PLR) and OS. CI = confidence interval, HR = hazard ratio, OS = overall survival.

Table 2

Pooled hazard ratios for overall survival according to subgroup analyses.

Subgroup	No. studies	No. patients	HR (95% CI)	*P*	Heterogeneity I^2 (%)	Heterogeneity P_h
Overall	12	3668	1.56 (1.32–1.85)	<.001	3.1	.415
Area						
Asian	11	3433	1.57 (1.31–1.87)	<.001	0	.63
Non-Asian	1	235	1.08 (0.63–1.84)	.78	–	–
Treatment						
Surgery	2	468	1.61 (1.09–2.38)	.02	0	.51
Chemoradiotherapy	3	398	1.40 (0.92–2.13)	.11	48	.15
Mixed	7	2802	1.52 (1.24–1.87)	<.001	0	.60
Stage						
I–II	5	2236	1.61 (1.21–2.15)	.001	0	.57
I–IV	7	1432	1.47 (1.19–1.81)	<.001	0	.43
Cut-off						
≥150	5	937	1.68 (1.03–2.74)	<.001	2	.38
<150	7	2731	1.54 (1.27–1.85)	<.001	0	.56
Analysis method						
Univariate	5	1184	1.62 (1.15–2.30)	.006	0	.68
Multivariate	7	2484	1.49 (1.23–1.80)	<.001	9	.36

CI = confidence interval, HR = hazard ratio.

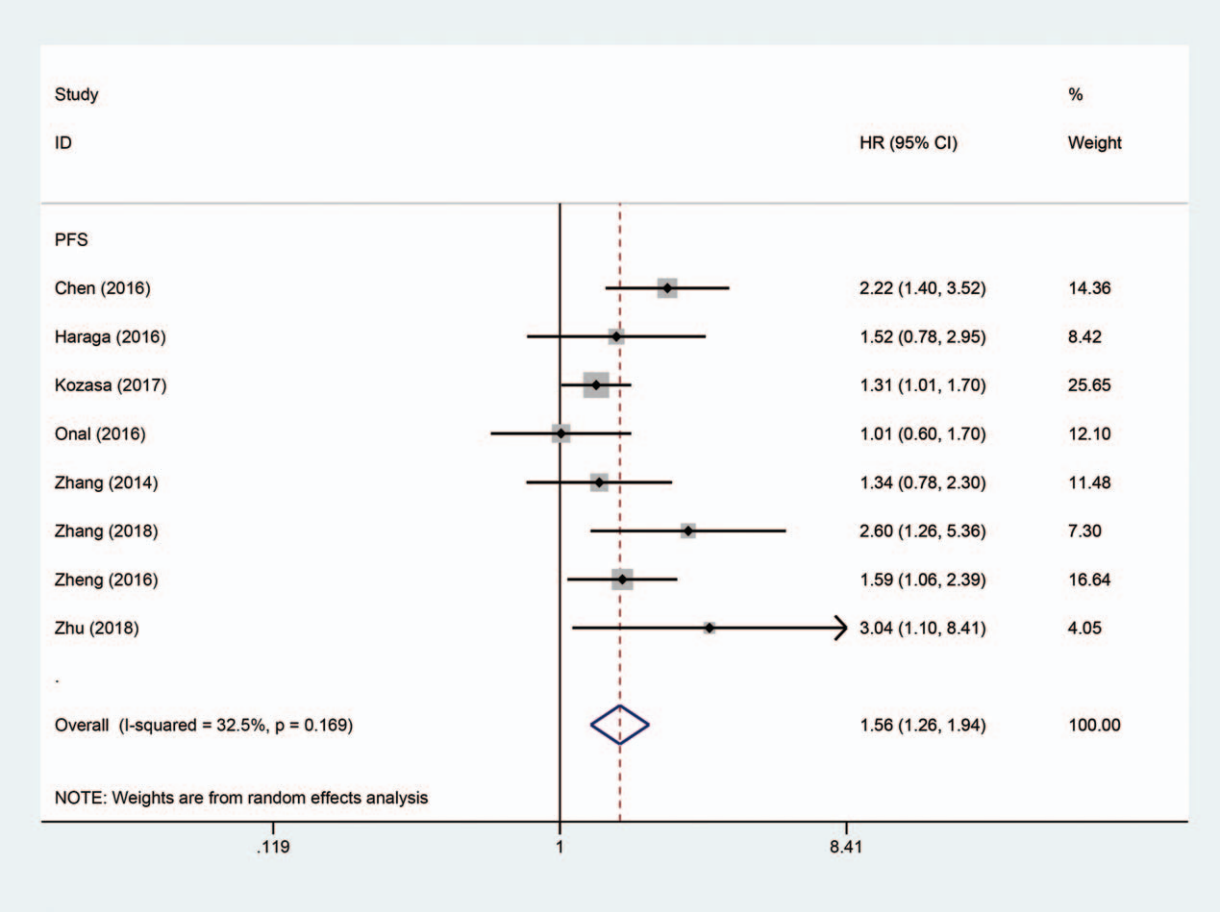

Figure 3. Forest plots for the association between platelet-to-lymphocyte ratio (PLR) and disease-free survival (DFS)/PFS. CI = confidence interval, HR = hazard ratio, PFS = progression-free survival.

Table 3

Meta-analysis of the association between platelet-to-lymphocyte ratio and clinicopathological features of cervical cancer.

Characteristics	No. studies	No. patients	OR (95% CI)	*P*	Heterogeneity	
					I^2 (%)	P_h
Age (≥45 vs <45)	2	825	0.83 (0.63–1.10)	.19	0	.93
Histological subtype (squamous vs nonsquamous)	2	1030	1.52 (0.55–4.21)	.42	87	.006
Depth of stromal infiltration (≥1/2 vs <1/2)	3	1340	1.14 (0.91–1.42)	.27	0	.93
Lymphovascular space invasion (yes vs no)	2	1100	1.55 (1.17–2.05)	.002	0	.37
Lymph node metastasis (yes vs no)	4	1575	2.39 (1.19–4.79)	.01	87	<.001
Tumor size (>4 vs <4 cm)	3	1210	1.89 (1.19–3.01)	.007	61	.07
Grade (G3 vs G2/G1)	4	2135	1.42 (1.15–1.76)	.001	0	.40
FIGO stage (II vs I)	3	1620	1.18 (0.97–1.44)	.10	0	.69

CI = confidence interval, OR = odds ratio.

secreted growth factors that regulate tumor angiogenesis, cell proliferation, migration, and metastasis.[27–29] Lymphocytes play critical roles in the host immune response. They can inhibit the proliferative and metastatic ability of cancer cells via inducing cytotoxic cell death and cytokine production.[30] Tumor-infiltrating lymphocytes are involved in several stages of tumor progression.[31,32] Tumor-infiltrating CD8+ and CD4+ T lymphocytes has been suggested to be a poor prognostic factor in multiple malignancies.[33–35] Conversely, low lymphocyte counts may lead to inadequate immune responses, resulting in poor survival of many cancers.[36,37] Thus, PLR may represent a balance between the tumor promotion reaction and antitumor immune function.

Despite our efforts to perform an accurate and comprehensive analysis, this meta-analysis still has several limitations. First, due to the lack of a unified standard, different cut-off values applied in various studies, which may affect the outcomes of the value that PLR plays as a biomarker in cervical cancer prognosis. Second, all of the included studies were retrospective and published in English. Third, a large proportion of the included studies were from Asia. It remains unclear whether these findings might be applied to other populations. Therefore, more large-scale studies are warranted to assess the prognostic value of pretreatment PLR for patients with cervical cancer.

5. Conclusions

In summary, our results indicated that the pretreatment PLR is associated with unfavorable outcomes in conjunction with advanced clinicopathological features in patients with cervical

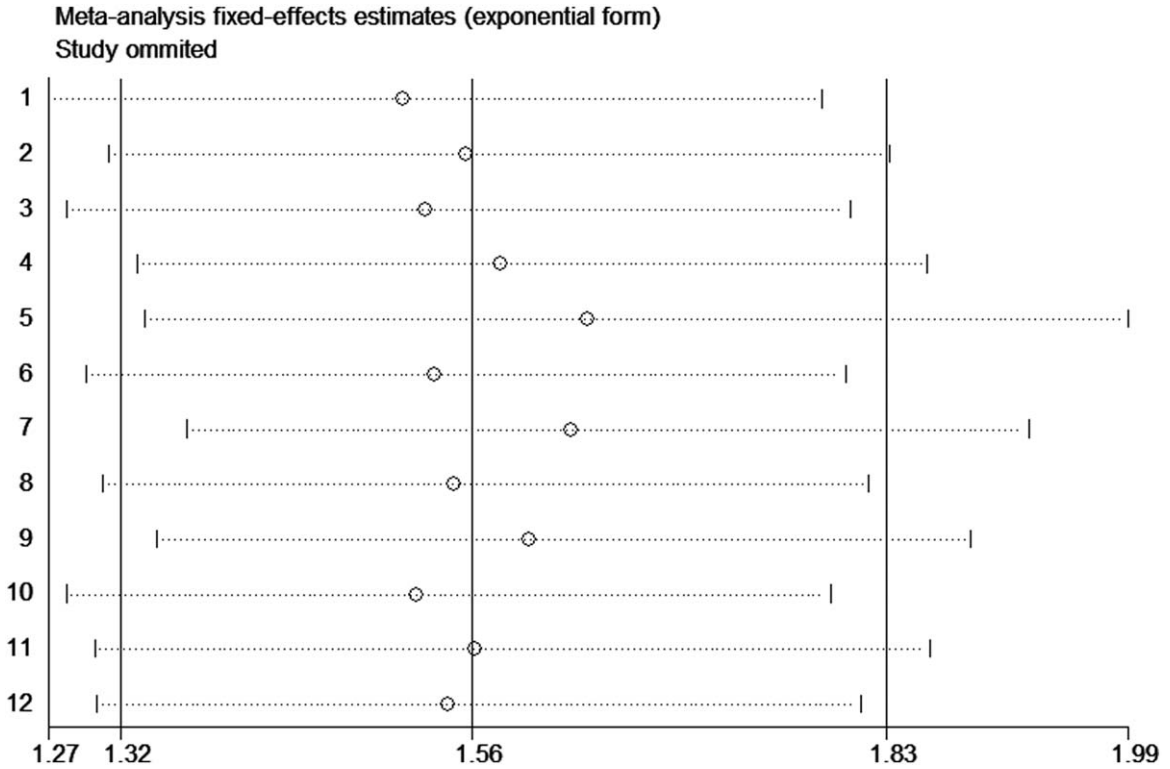

Figure 4. Sensitivity analysis of platelet-to-lymphocyte ratio (PLR) on overall survival (OS) in cervical cancer patients.

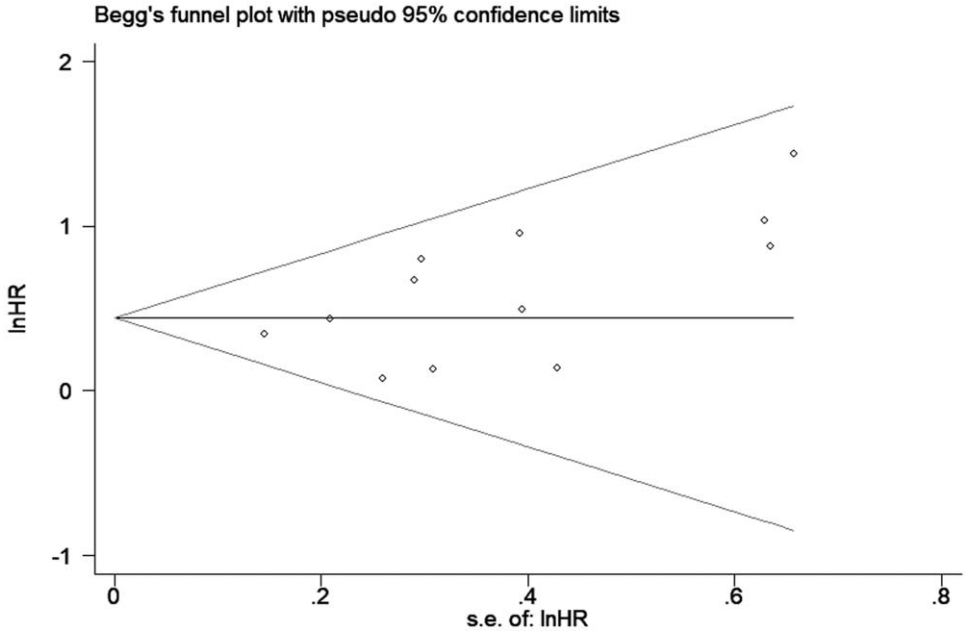

Figure 5. Begg's funnel plot of publication bias test for overall survival (OS) in cervical cancer. HR = hazard ratio.

cancer, suggesting that PLR could be a significant independent prognostic factor in patients with cervical cancer.

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Author contributions

Conceived and designed the experiments: JYM, LCK, and QL. Performed the experiments: JYM, LCK, QL. Analyzed the data: JYM, LCK, QL. Contributed reagents/materials/analysis tools: JYM, LCK, QL. Wrote the paper: all authors.
Conceptualization: Jian-ying Ma, Li-chi Ke, Qin Liu.
Data curation: Jian-ying Ma, Li-chi Ke, Qin Liu.
Formal analysis: Jian-ying Ma, Li-chi Ke, Qin Liu.
Funding acquisition: Jian-ying Ma, Li-chi Ke, Qin Liu.
Investigation: Jian-ying Ma, Li-chi Ke, Qin Liu.
Methodology: Jian-ying Ma, Li-chi Ke, Qin Liu.
Project administration: Jian-ying Ma, Li-chi Ke, Qin Liu.
Resources: Jian-ying Ma, Li-chi Ke, Qin Liu.
Software: Jian-ying Ma, Li-chi Ke, Qin Liu.
Supervision: Jian-ying Ma, Li-chi Ke, Qin Liu.
Validation: Jian-ying Ma, Li-chi Ke, Qin Liu.
Visualization: Jian-ying Ma, Li-chi Ke, Qin Liu.
Writing – original draft: Jian-ying Ma, Li-chi Ke, Qin Liu.
Writing – review and editing: Jian-ying Ma, Li-chi Ke, Qin Liu.

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