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Prognostic value of platelet to lymphocyte ratio in patients with cervical cancer: an updated systematic review and meta-analysis

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Abstract

Background The identification of biomarkers that reliably forecast cervical cancer (CC) outcomes is a key area of research. Several studies have explored the link between the platelet-to-lymphocyte ratio (PLR) and cervical cancer prognosis, though the results are not entirely conclusive.

Methods PubMed, Embase, Web of Science, and the Cochrane Library were used to search, with studies published up to May 30, 2024. The selection of studies followed predetermined inclusion and exclusion criteria. Overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS) were primary outcomes. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated. Sensitivity and subgroup analyses were performed to evaluate the stability and investigate potential heterogeneity. Review Manager version 5.4.1 and STATA version 15.0 were conducted to analyze.

Results Thirty cohort studies, involving 8,597 patients, were included. The pooled data showed that a higher PLR was associated with worse OS significantly (HR = 1.77, 95% CI: 1.43–2.19; $p < 0.0001$), PFS (HR = 1.69, 95% CI: 1.26–2.27; $p = 0.0004$), and DFS (HR = 1.57, 95% CI: 1.12–2.18; $p = 0.008$). Subgroup analysis indicated that the prognostic relevance of PLR was most prominent in patients who underwent both surgery and radiotherapy, as well as those from Asia and the America. Furthermore, a PLR threshold above 150 was associated with improved predictive accuracy.

Conclusion Increased PLR among cervical cancer patients was significantly correlated with reduced OS, PFS, and DFS, pointing to its potential role as an independent prognostic marker. Nonetheless, additional prospective research is required to verify this finding.

Keywords Platelet-to-lymphocyte ratio, Cervical cancer, Prognostic value of survival, Meta-analysis

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Introduction

As the most prevalent malignant tumors among females, cervical cancer's incidence and mortality rates rank among the highest in gynecological cancers and are increasing, affecting younger women. A study shows that in 2020, over 58% of global cervical cancer cases occurred in Asia, followed by Africa (20%), Europe (10%), and Latin America (10%). It is estimated that over half of the deaths occurred in Asia (58%), followed by Africa (22%) and Latin America (9%), while Europe only accounted for 7.6% [1]. Although the incidence of cervical cancer has decreased due to widespread vaccination and screening efforts, it remains a major cause of cancer-related deaths in women, particularly in developing countries, posing a significant threat to women's health and lives.The identification of biomarkers is essential for predicting outcomes and guiding treatment strategies in cervical cancer patients. Recent research underscores the important role that the systemic inflammatory response (SIR) plays in tumor progression. This systemic response is initiated by the release of pro-inflammatory cytokines, while ongoing inflammation encourages cellular mutations and proliferation, creating a tumor-promoting environment. Inflammation caused by cancer, along with immunosuppressive factors, impacts immune and inflammatory cells in the peripheral blood-such as neutrophils, lymphocytes, platelets, and monocytes-resulting in alterations to hematologic parameters, which are a common systemic feature of cancer [2]. These alterations are associated with tumor progression, including invasion and metastasis [3]. Several combinations of biomarkers, such as the Neutrophil-to-Lymphocyte Ratio (NLR), PLR, and Lymphocyte-to-Monocyte ratio (LMR), have been investigated. Among these, PLR is regarded as a possible indicator of ongoing pro-inflammatory and pro-coagulant activity in cancer cases [4]. It is widely reproducible, simple to detect in clinical environments, and has been applied to forecast prognosis and recurrence in multiple types of cancer.

The prognostic significance of PLR in cervical cancer is still a topic of debate. Fullerton et al. discovered that higher PLR levels were linked to worse OS and PFS in patients with cervical cancer [5]. Conversely, some other studies have found no substantial prognostic relevance of PLR in these individuals [6]. Initially, a meta-analysis conducted by Ma et al. on the prognostic significance of systemic blood immune markers in cervical cancer emphasized the predictive value of PLR. This analysis incorporated 12 studies focused on PLR, involving a total of 3668 patients, and concluded that higher PLR levels were significantly correlated with poor OS and DFS/PFS in cervical cancer patients [7]. Recent research has continued to investigate the prognostic role of PLR in these patients. The objective of this study is to present an updated meta-analysis by systematically reviewing scientific databases to assess the relationship between PLR and OS, PFS, and DFS in cervical cancer patients. Subgroup analyses will be conducted to determine the most appropriate patient populations and conditions where PLR serves as an effective prognostic marker.

Materials and methods

Literature search

This study adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42024583779, https://www.crd.york.ac.uk/prospero/#recordDetails). Study members ZTY and CZY independently developed the search strategy, selecting subject terms and keywords. Searches were conducted across various databases, including PubMed, Web of Science, and the Cochrane Library, Embase, covering publications up to May 30, 2024. Broad search terms such as "Uterine Cervical Neoplasms," "Blood Platelets," and "Lymphocytes" were used. A detailed description of the search strategy is available in Supplementary Table 1.

Study selection

The selected studies satisfied the following criteria: (1) patients had a confirmed pathological diagnosis of cervical cancer; (2) studies evaluated the prognostic influence of PLR on OS, PFS, or DFS; (3) studies presented HR with 95% CI, either directly reported or calculable from available data; (4) patients were divided into high-PLR and low-PLR groups according to predetermined cut-off values; and (5) fully published research findings. The exclusion criteria included: (1) reviews, commentaries, conference abstracts, case reports, and letters; (2) studies with insufficient data to calculate HR and 95% CI; (3) studies lacking survival information; and (4) studies with overlapping or duplicated data.

Two researchers, ZTY and CZY, independently reviewed the titles and abstracts of the studies retrieved from the databases, then accessed and assessed the full-text articles for eligibility. Any disagreements that occurred during the selection process were resolved by reaching a consensus.

Data extraction

Data extraction was independently performed by two researchers, ZTY and CZY, with any discrepancies settled by consensus among all co-authors. The extracted data included the first author's name, year of publication, country of study, study design, sample size, study duration, patient age, BMI, treatment methods, tumor stage, timing of PLR measurement, PLR cut-off values,

follow-up period, and HRs with 95% CIs for OS, PFS, and DFS.

Quality assessment

The quality of the studies included was evaluated using the Newcastle-Ottawa Quality Assessment Scale (NOS), which assesses three main criteria: selection, comparability, and outcome, with a maximum score of 9. Studies scoring between 7 and 9 were classified as high-quality research [8].

Statistical analysis

To evaluate the prognostic importance of the PLR in individuals with CC, HRs were calculated for OS, DFS, and PFS, with 95% CIs. Heterogeneity was assessed by applying Cochran's Q test and Higgins' I^2 statistic, where a P-value below 0.1 in the Q test or an I^2 value exceeding 50% suggested significant heterogeneity. A random-effects approach was utilized for analyzing the data. To confirm the reliability of the OS and PFS results and to detect potential sources of variability, subgroup analyses and sensitivity checks were conducted. Funnel plots and Egger's test were applied to assess potential publication bias, with statistical significance defined as a P-value less than 0.05. The statistical analyses were performed using the software STATA version 15.1 and Review Manager version 5.4.

Results

Study characteristics

350 studies were initially identified through database searches, 157 being excluded due to duplication. After screening the titles and abstracts of the remaining studies, 147 were removed. The full text of 53 studies was then reviewed, and 25 were excluded because they lacked sufficient data for survival analysis. Ultimately, 28 studies involving 8,597 patients were included [5, 6, 9–34] (see Fig. 1).

Among the 28 eligible studies, 22 were conducted in Asian countries, 4 in European nations, and 2 in the

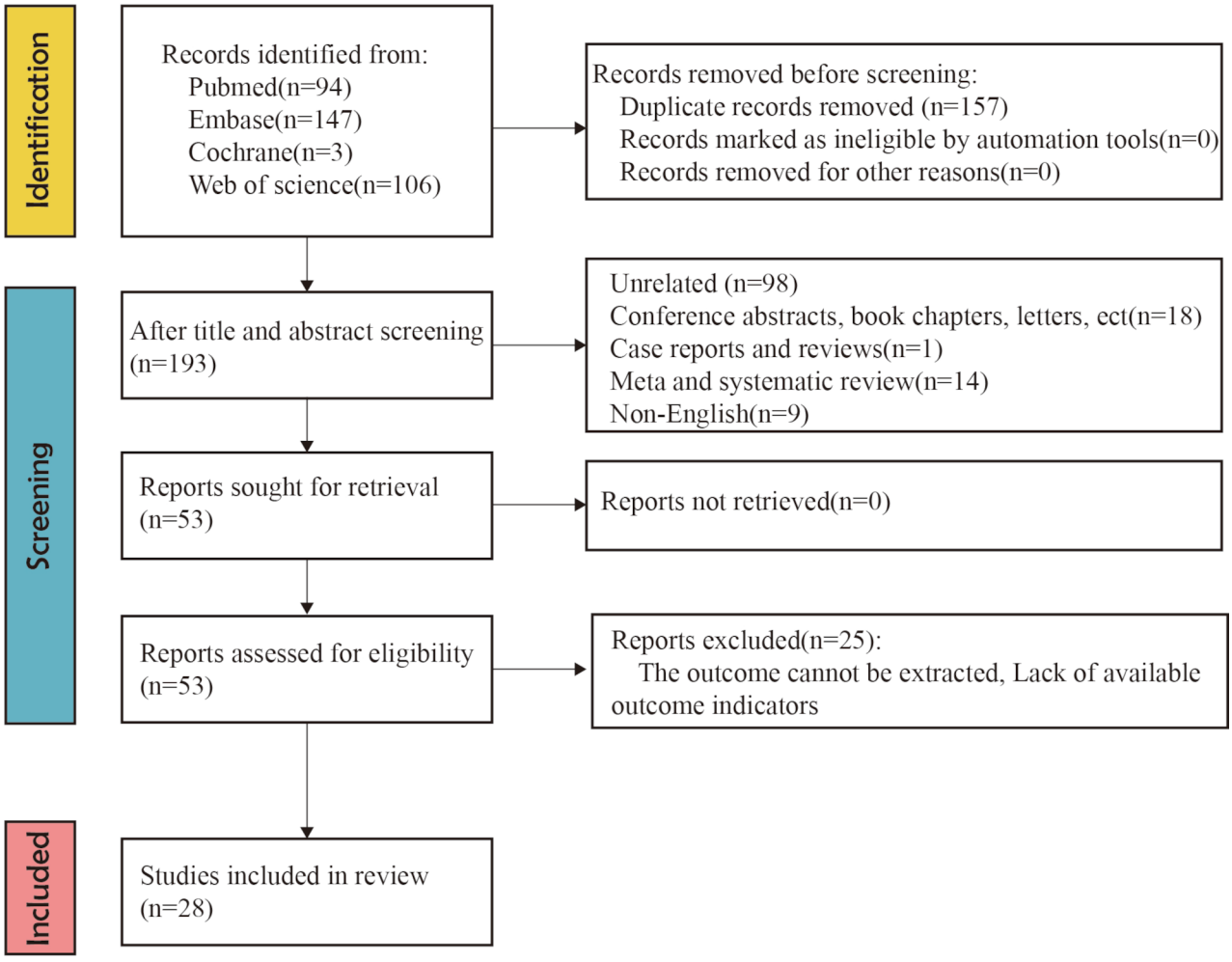

Fig. 1 Flow chart of literature screening

Americas. All studies were retrospective in nature and published in English between 2013 and 2023. Two studies in this analysis included two separate cohort studies each [11, 24]. Every study focused on cervical cancer patients, categorizing them into high and low PLR groups, with PLR levels measured at baseline before treatment. Regarding prognostic outcomes, all 28 cohort studies assessed the prognostic relevance of PLR on OS, 5 studies investigated its impact on DFS, and 13 explored its relationship with PFS. The characteristics of the included studies are outlined in Table 1.

Study quality

All 28 studies had NOS scores between 7 and 8, indicating high quality (Supplementary Table 2).

Meta-analysis results

PLR and OS

In total, 30 cohort studies, comprising 8,597 participants, explored the relationship between the PLR and OS. Pre-treatment PLR data were reported in 28 of these studies. Given the considerable heterogeneity observed across the studies (I^2 = 87%, $p < 0.0001$), the analysis was performed using a random-effects model. The results indicated that cervical cancer patients in the high-PLR group experienced significantly worse OS compared to those in the low-PLR group (HR = 1.77, 95% CI: 1.43–2.19; $p < 0.0001$, refer to Fig. 2A).

Subgroup analyses were performed to investigate potential sources of heterogeneity, considering factors such as patient age, geographic region, treatment approaches, and PLR cut-off values. Elevated PLR remained significantly correlated with shorter OS in studies conducted in Asia and America (HR = 1.71, 95% CI: 1.43–2.06, $p < 0.00001$; HR = 1.95, 95% CI: 1.69–2.25, $p < 0.00001$). However, no significant relationship between PLR and OS was observed in studies from Europe (HR = 1.80, 95% CI: 0.92–3.53, $p = 0.08$). Further subgroup analyses based on treatment types, average patient age, and PLR thresholds also indicated that higher PLR levels were consistently linked to shorter OS ($p < 0.05$). The results suggest that the heterogeneity of OS may be related to patients' age, region and PLR cutoff value. The detailed findings of these subgroup analyses are provided in Table 2.

PLR and PFS

Thirteen cohort studies, including a total of 3,405 patients, investigated the relationship between PLR and PFS. Pre-treatment PLR data were available in 12 of the studies. The results showed that higher PLR levels were significantly associated with reduced PFS in patients with CC (HR = 1.69, 95% CI: 1.26–2.27; $p = 0.0004$, refer to Fig. 2B). Given the substantial heterogeneity among the studies (I^2 = 77%, $p < 0.0001$), a random-effects model was employed for the analysis.

In the subgroup analysis, a higher PLR cut-off value (> 150) showed a significant association with reduced PFS ($p = 0.001$), while no significant relationship was found when the PLR cut-off was below 150 ($p = 0.39$). Additionally, elevated PLR was significantly linked to shorter PFS across various regions, age groups, and treatment methods ($p < 0.05$).

PLR and DFS

Five studies, comprising 1,716 patients, investigated the association between PLR and DFS. All studies reported pre-treatment PLR values. Similar to the findings from the OS and PFS analyses, an elevated PLR was significantly linked to shorter DFS in CC patients (HR = 1.57, 95% CI: 1.12–2.18; $p = 0.008$, see Fig. 2C). There was no notable heterogeneity (I^2 = 37%, $p = 0.17$), confirming that higher pre-treatment PLR is associated with reduced DFS in CC patients.

Subgroup analysis showed no significant correlation between PLR and DFS in patients who received surgery alone or chemoradiotherapy alone (HR = 1.34, 95% CI: 0.59–3.07, $p = 0.49$; HR = 1.87, 95% CI: 1.00–3.50, $p = 0.05$). However, one study found a significant link between higher PLR and shorter DFS in patients who underwent surgery combined with chemoradiotherapy (HR = 1.59, 95% CI: 1.06–2.39, $p = 0.03$). Furthermore, elevated PLR was associated with shorter DFS in studies conducted in Asia (HR = 1.62, 95% CI: 1.07–2.46, $p = 0.02$), while no significant relationship was observed in European studies ($p = 0.36$). Regardless of age group or PLR cut-off values, higher PLR was consistently connected to shorter DFS ($p < 0.05$). These findings suggest that the heterogeneity of PFS may be related to treatment methods and patient years.

Sensitivity analysis

A sensitivity analysis was conducted to evaluate the stability of the results concerning the clinical relevance of pre-treatment PLR values. The analysis revealed that, even after the sequential exclusion of individual studies, the effect sizes remained within the original range. This suggests that no single study had a significant impact on the overall results for OS (Fig. 3A), PFS (Fig. 3B), or DFS (Fig. 3C), thereby affirming the robustness of the analysis.

Publication bias

Funnel plots and Egger's test were used to evaluate potential publication bias. The asymmetry observed in the funnel plots suggested the existence of some bias in the analyses for OS and PFS, whereas no significant bias was identified for DFS. Egger's test provided additional confirmation of the lack of significant publication

Table 1 Basic characteristics of the included literature

Author	Year	Study period	Region	Study design	Therapy	Time of test	Sample size	Age	TNM stage	PLR cut-off	Outcome	Quality score
Ayhan et al.	2022	2008–2018	Turkey	Retrospective cohort	Surgery	Pretreatment	163	49	IA2-IIIC2	145	OS, PFS	7
Chen et al.	2016	2006–2009	China	Retrospective cohort	Surgery	Pretreatment	407	44	IB1-IIA	143.47	OS	7
Chen et al.	2023	2016–2021	China	Retrospective cohort	Radiochemotherapy	Pretreatment	138	60.1	IB-IVA	236	OS	7
Ferioli et al.	2023	2007–2021	Italy	Retrospective cohort	Radiochemotherapy	Pretreatment	173	56	IB-IVA	210	OS, DFS	7
Fullerton et al.	2023	1999–2015	Canada	Retrospective cohort	Radiochemotherapy	Pretreatment	196	NA	I-IV	250	OS, PFS	7
Gao et al.	2023	2017–2020	China	Retrospective cohort	Radiotherapy	Baseline	110	NA	I-IV	186.88	OS, PFS	7
Guo et al.	2023	2014–2017	China	Retrospective cohort	Surgery	NA	109	53.95	IA-IIA	111.96	OS	7
Haraga et al.[]	2016	2007–2013	Japan	Retrospective cohort	Radiochemotherapy	Pretreatment	95	61.5	IB1-IVA	171	OS, PFS	7
Haraga et al.[]	2016	2007–2013	Japan	Retrospective cohort	Radiotherapy	Pretreatment	36	61.5	IB1-IVA	171	OS	7
He et al.	2018	2007–2009	China	Retrospective cohort	Surgery or radiotherapy plus chemotherapy	Pretreatment	229	44	I-IV	149.27	OS	7
Holub et al.	2019	2009–2016	Spain	Retrospective cohort	Surgery or radiotherapy plus chemotherapy	Pretreatment	151	52.8	I-IV	210	OS	8
Ida et al.	2018	2004–2015	Japan	Retrospective cohort	Surgery or radiotherapy plus chemotherapy	Pretreatment	79	52.4	recurrent advanced	260	OS	7
Jiang et al.[]	2021	2009–2017	China	Retrospective cohort	Surgery or radiotherapy plus chemotherapy	Pretreatment	501	48.88	IB-IIA	163.41	OS, PFS	8
Jiang et al.[]	2021	2009–2017	China	Retrospective cohort	Surgery or radiotherapy plus chemotherapy	Pretreatment	82	48.88	IB-IIA	163.41	OS	8
Jonska-Gmyrek et al.	2018	2003–2008	Poland	Retrospective cohort	Surgery or radiotherapy plus chemotherapy	Pretreatment	94	53	I-IV	158	OS	7
Lee et al.	2017	2011–2014	Korea	Retrospective cohort	Surgery or radiotherapy plus chemotherapy	Pretreatment	145	52	I-IV	170	PFS	7
Lee et al.	2020	2005–2016	Korea	Retrospective cohort	Radiochemotherapy	Before and after treatment	125	53.67	IIB-IIIB	NA	OS, PFS	7
Li et al.	2021	2011–2016	China	Retrospective cohort	Radiochemotherapy	Pretreatment	260	51	IIB	154.17	OS, PFS	7
Li et al.	2023	2009–2014	China	Retrospective cohort	Radiochemotherapy	Baseline	795	51	IIB-IVA	164.29	OS	7
Medici et al.	2023	2007–2021	Italy	Retrospective cohort	Radiochemotherapy	Pretreatment	173	56	IB-IVA	210	OS, DFS	7
Nakamura et al.	2015	2005–2014	Japan	Retrospective cohort	Radiochemotherapy	Pretreatment	32	52.6	recurrent advanced	322	OS	7
Nakamura et al.	2018	1997–2013	Japan	Retrospective cohort	Radiochemotherapy	Pretreatment	98	65	I-IV	212	OS	8
Nuchpramool et al.	2018	2001–2016	Tailand	Retrospective cohort	Surgery or radiotherapy plus chemotherapy	Pretreatment	460	47	IA2-IB1	119	OS, DFS	8
Onal et al.	2016	2006–2014	Turkey	Retrospective cohort	Radiochemotherapy	Pretreatment	235	57	IB2-IVA	133.02	OS, PFS	7
Thuler et al.	2021	2006–2009	Brazil	Retrospective cohort	Surgery or radiotherapy plus chemotherapy	Pretreatment	1266	49.8	I-IV	146.7	OS	7
Wang et al.	2023	2013–2015	China	Retrospective cohort	Radiotherapy	Pretreatment	178	53.85	IIB-III	186.67	OS	7
Zhang et al.	2018	2005–2009	China	Retrospective cohort	Surgery	Pretreatment	235	46	IB-IIA	176.5	OS, PFS	7
Zhang et al.	2023	2007–2015	China	Retrospective cohort	Radiochemotherapy	NA	965	53.4	IIB-IIIB	174.8	OS, PFS	7
Zheng et al.	2016	2005–2012	China	Retrospective cohort	Surgery + Radiochemotherapy	Pretreatment	795	49.5	IA-IIA	128.3	OS, DFS	7
Zhu et al.	2018	2012–2014	China	Retrospective cohort	Surgery	Pretreatment	339	45	IA-IIB	143.79	OS, PFS	7

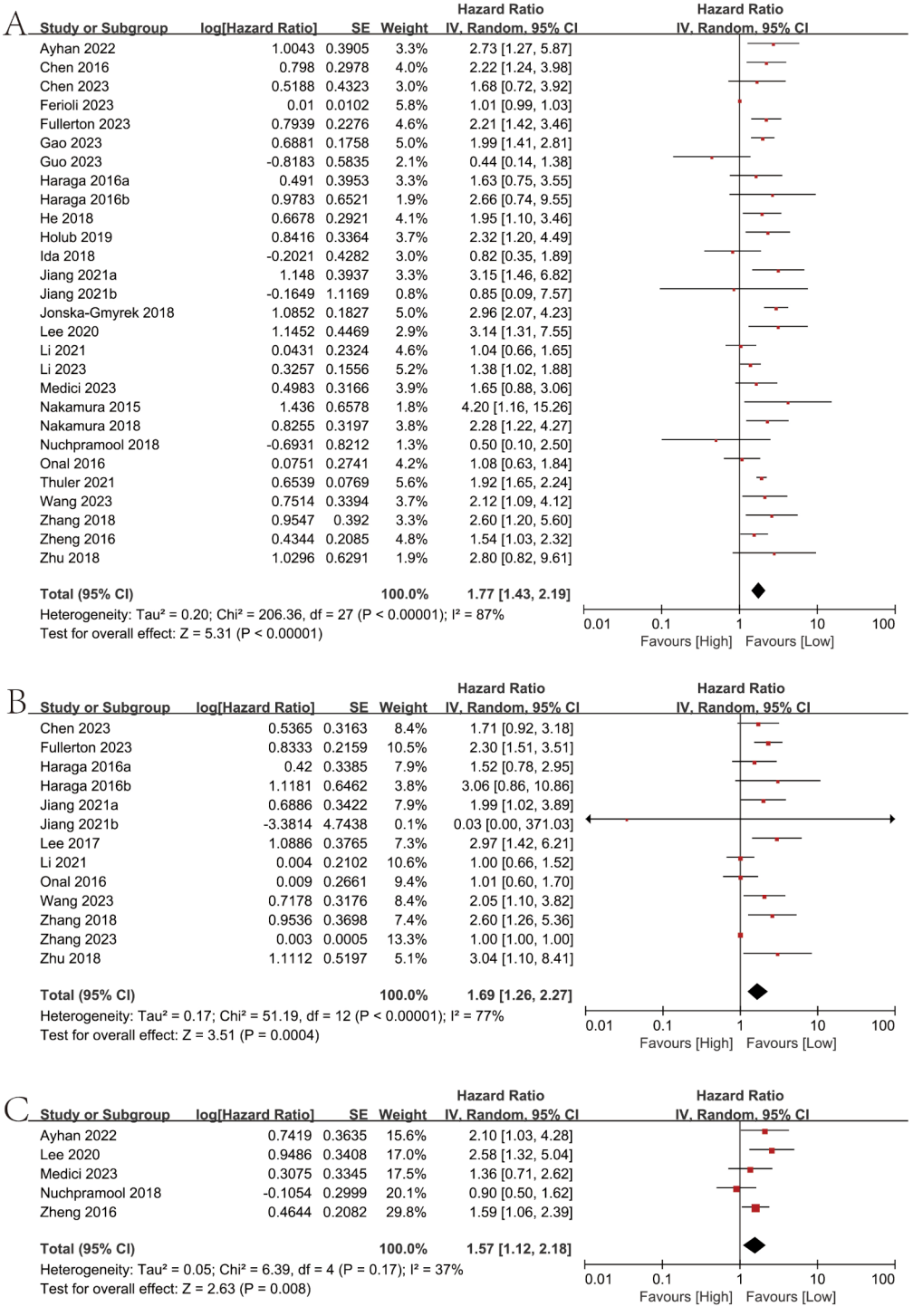

Fig. 2 (**A**) Forest plots for the association between PLR and OS; (**B**) Forest plots for the association between PLR and PFS; (**C**) Forest plots for the association between PLR and DFS

Table 2 Pooled HRs for OS, DFS and PFS in subgroup analyses

Subgroup	OS(Baseline)				DFS(Baseline)				PFS(Baseline)			
	Study	HR [95%CI]	*P* value	I^2	Study	HR [95%CI]	*P* value	I^2	Study	HR [95%CI]	*P* value	I^2
Total	28	1.77 [1.43, 2.19]	<0.00001	87%	5	1.57 [1.12–2.18]	0.008	37%	13	1.69 [1.26, 2.27]	0.0004	77%
Treatment												
Surgery	5	1.97 [1.14, 3.38]	0.01	51%	2	1.34 [0.59, 3.07]	0.49	69%	2	2.74 [1.52, 4.94]	0.0008	0
Radiochemotherapy	14	1.66 [1.29, 2.14]	<0.0001	78%	2	1.87 [1.00, 3.50]	0.05	45%	8	1.43 [1.06, 1.93]	0.02	74%
Surgery + Radiochemotherapy	1	1.54 [1.03, 2.32]	0.04	NA	1	1.59 [1.06, 2.39]	0.03	NA	NA	NA	NA	NA
Mean/median age												
≥ 50y	16	1.60 [1.22, 2.09]	0.0006	80%	2	1.87 [1.00, 3.50]	0.05	45%	7	1.55 [1.12, 2.16]	0.008	47%
< 50y	9	1.99 [1.58, 2.52]	<0.00001	0	3	1.43 [0.92, 2.22]	0.11	47%	4	2.36 [1.51, 3.67]	0.0001	0
Region												
Asia	22	1.71 [1.43, 2.06]	<0.00001	36%	4	1.62 [1.07, 2.46]	0.02	52%	12	1.61 [1.21, 2.15]	0.001	70%
America	2	1.95 [1.69, 2.25]	<0.00001	0	NA	NA	NA	NA	1	2.30 [1.51, 3.51]	0.0001	NA
Europe	4	1.80 [0.92, 3.53]	0.08	93%	1	1.36 [0.71, 2.62]	0.36	NA	NA	NA	NA	NA
PLR cut-off												
≥ 150	9	1.66 [1.28, 2.15]	0.0001	47%	1	1.36 [0.71, 2.62]	0.36	NA	11	1.74 [1.25, 2.42]	0.001	79%
< 150	18	1.82 [1.39, 2.38]	<0.0001	84%	3	1.43 [0.92, 2.22]	0.11	47%	2	1.60 [0.55, 4.64]	0.39	72%

bias for DFS (Egger: $p = 0.76$). However, substantial bias was detected for OS and PFS (Egger: $p = 0.000$, $p = 0.001$) (refer to Fig. 4).

Discussion

Systemic inflammatory responses play a key role in the development and progression of tumors. Research has shown that the interaction between tumor cells and inflammatory cells promotes processes such as angiogenesis, extracellular matrix remodeling, and the establishment of metastatic sites. The migration of inflammatory cells or overproduction of inflammatory cytokines further supports tumor growth. Non-steroidal anti-inflammatory drugs (NSAIDs) have been demonstrated to reduce the risk of certain cancers, including colorectal and breast cancer, as well as decrease cancer-related mortality [35]. Changes in blood parameters primarily reflect systemic inflammatory responses, making inflammation-based markers, such as the PLR, valuable prognostic indicators for cancer patients. PLR testing is inexpensive, straightforward, and easily available in clinical practice. Numerous studies have linked elevated PLR to a poor prognosis in various solid tumors, including colorectal cancer [36], small cell lung cancer [37], and gastric cancer [38]. However, the prognostic significance of PLR in cervical cancer remains debated, and the mechanisms behind it are not fully understood.

This meta-analysis incorporated 28 studies involving 8,597 cervical cancer patients to evaluate the prognostic significance of PLR in terms of OS, PFS, and DFS. Elevated PLR was found to be significantly linked with worse OS, PFS, and DFS in patients with cervical cancer. Sensitivity analysis confirmed the stability of these findings. These results are consistent with previous meta-analyses [7, 39–42]. Compared with them, our study, which incorporates additional studies and a larger patient population, offers a more up-to-date and comprehensive analysis that further supports the prognostic importance of PLR in cervical cancer. The characteristics of the previous meta-analyses are outlined in Table 3.

We observed significant heterogeneity in OS ($I^2 = 87\%$) and PFS ($I^2 = 77\%$), but not in DFS. In order to provide a more detailed analysis, we performed a subgroup analysis from four aspects: treatment mode, age, region and PLR cut-off. Subgroup analysis showed that the heterogeneity of OS may be related to the patient's age, region and PLR cutoff value; The heterogeneity of PFS may be related to treatment methods and patient years. The results for OS were consistent in Asian and American populations, while European studies showed no significant association between PLR and either OS or DFS, possibly due to the ethnic differences in the prognosis of cervical cancer patients.Persistent racial differences in the incidence and mortality of cervical cancer have been reported in

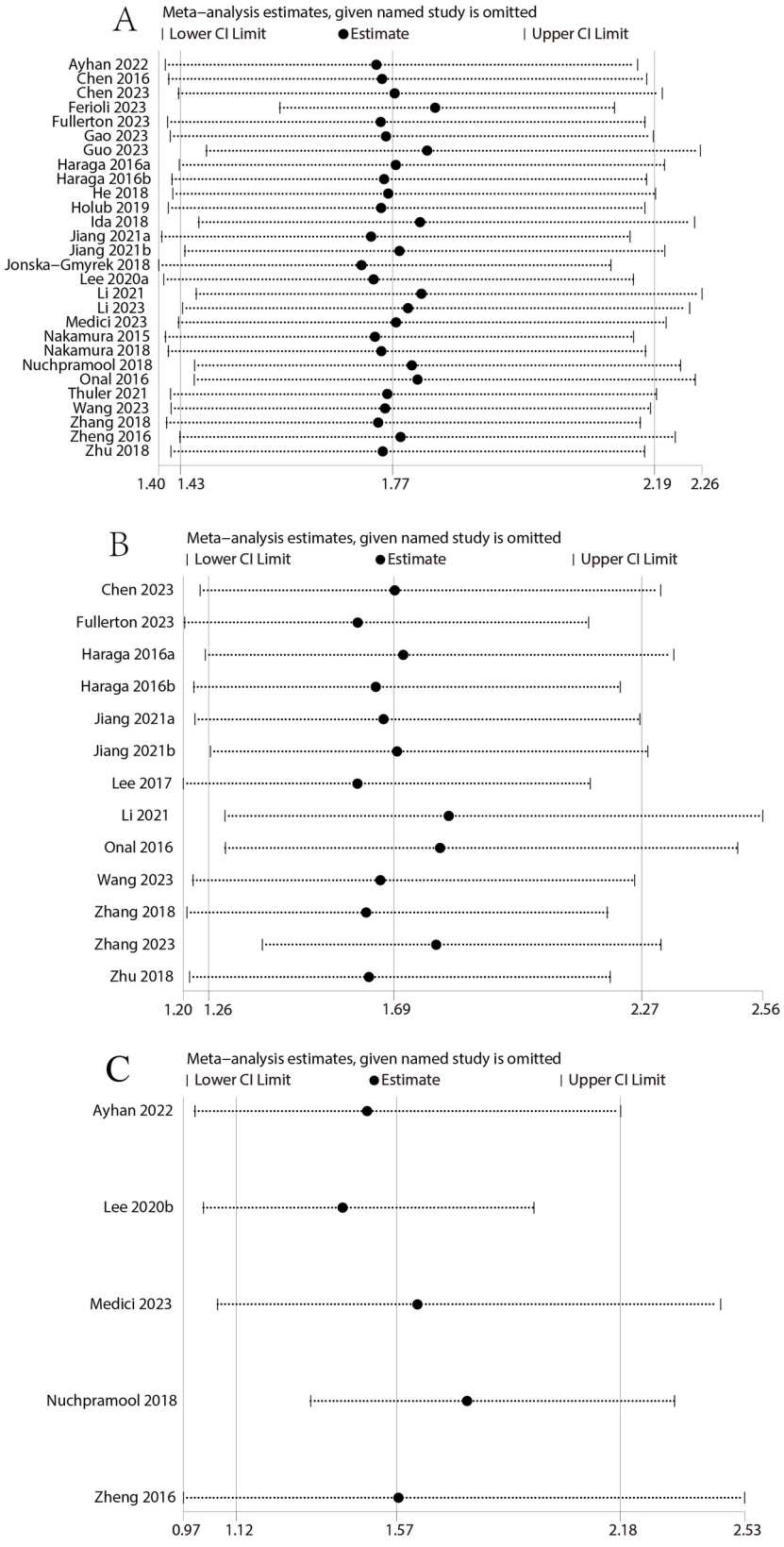

Fig. 3 Sensitivity analysis of (**A**) OS, (**B**) DFS, (**C**) DFS

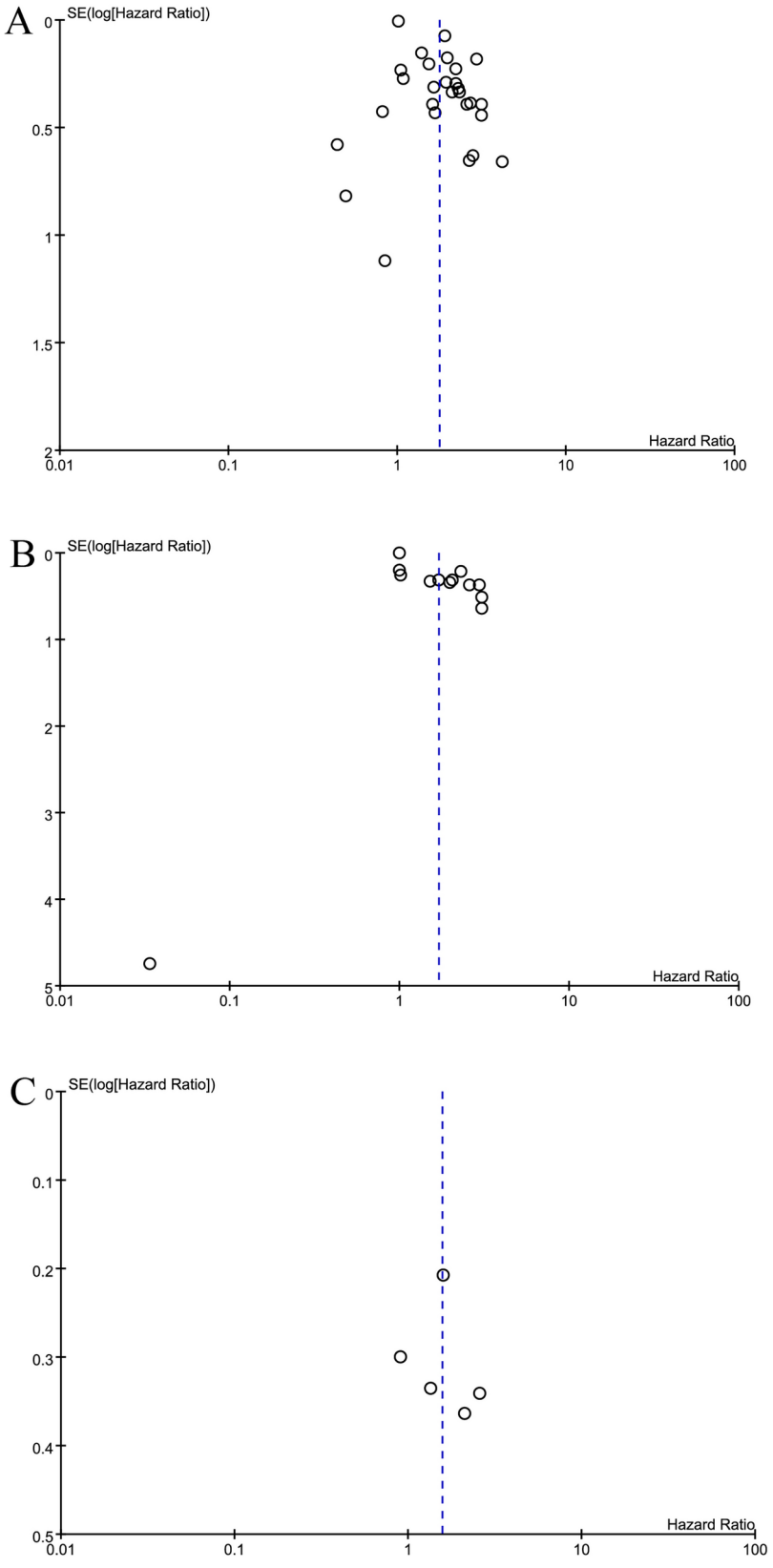

Fig. 4 Funnel plot for the evaluation of publication bias for (**A**) OS, (**B**) PFS and (**C**) DFS

Table 3 The characteristics of previous meta-analyses

Author	Year	Number of studies	Number of cases	Outcome	Conclusion
Ma et al.	2018	12	3668	PLR, DFS/PFS	The pre-treatment PLR could serve as a predicative biomarker of poor prognosis for patients with cervical cancer.
Jiang et al.	2019	11	3172	OS, PFS	Higher PLR is correlated with negative OS and PFS in patients with cervical malignancies.
Yang et al.	2019	8	2616	OS, PFS	Elevated pre-treatment PLR may be an adverse prognostic factor for OS and PFS in patients with cervical cancer.
Han et al.	2021	17	5094	OS	Higher PLR was significantly associated with shorter OS in patients with cervical cancer.
Kang et al.	2022	7	1749	OS, EFS	High PLR is an unfavorable clinical pathological factor affecting OS and EFS in cancer patients.

the United States, with one of the largest mortality gaps between Black and White populations across all cancers [43]. However, most of the knowledge about cervical cancer, including the best treatment, is derived from the study of cervical squamous cell carcinoma (SCC) patients, who are mainly white [44]. A study found that although black women have the lowest incidence of cervical adenocarcinoma (ADC), their mortality rate of ADC is the highest compared with all other groups. While Black women also experience the highest incidence and mortality rates of SCC, the survival disparity in the ADC subtype is more pronounced, suggesting that this subtype-specific difference may be linked to systemic inequalities affecting the quality of care [45].In European countries, where the majority of patients are White, those with cervical cancer may experience better prognoses. The prognostic significance of PLR across different treatment methods was also evaluated. Elevated PLR predicted shorter DFS in patients undergoing surgery combined with chemoradiotherapy but had no significant prognostic value for those treated with surgery or chemoradiotherapy alone. A potential reason, beyond the limited number of studies for better phrasing, could be the differences in disease severity among patients in the surgery, chemoradiotherapy, and combined treatment groups, which may have influenced the results. Subgroup analysis assessing the effect of varying PLR cut-off values on prognosis showed that, regardless of the threshold used, patients with higher PLR had lower OS and DFS compared to those with lower PLR. However, for PFS, no significant impact was observed when the threshold was below 150, suggesting that a PLR cut-off of 150 or greater may provide better predictive accuracy. Subgroup analyses based on sample size demonstrated consistent effects, further supporting PLR as a reliable prognostic marker in cervical cancer. In conclusion, our findings suggest that cervical cancer patients with higher pre-treatment PLR may face a greater risk of post-treatment cancer progression or recurrence, underscoring the importance of close monitoring.

PLR, calculated from platelet and lymphocyte counts, is an indicator of both systemic inflammation and immune status [46]. Research suggests that approximately 20% of cancer patients develop thromboembolic events, such as pulmonary embolism (PE) and deep vein thrombosis (DVT) [47]. Tumor cells release interleukin-6 (IL-6), which stimulates the liver to produce thrombopoietin (TP), thereby increasing megakaryocyte and platelet production, leading to thrombocytosis and a hypercoagulable state in cancer patients [48]. Activated platelets then release inflammatory cytokines and chemokines, which contribute to tumor growth. Once tumor cells enter the bloodstream, platelets shield circulating tumor cells (CTCs) from natural killer (NK) cells and apoptosis induced by TNF-α [49, 50]. Activation of the TGF-β/Smad and NF-κB signaling pathways triggers epithelial-mesenchymal transition (EMT) in cancer cells, facilitating their proliferation and metastasis [51]. Reduced lymphocyte levels impair the immune system's ability to combat cancer cells, particularly affecting tumor-infiltrating lymphocytes (TILs), allowing tumors to evade immune detection through TIL exhaustion and apoptosis [52]. CD8 T cells, along with other activated T lymphocytes, induce apoptosis and exhibit cytotoxic effects on cancer cells, helping to prevent metastasis [53]. Elevated PLR reflects the activation of transcription factors involved in inflammation, such as NF-κB, STAT3, and HIF1α [54, 55], which drive the production of pro-tumor cytokines like TNF-α, IL-1β, and IL-6 [56, 57]. Therefore, PLR is viewed as an indicator of immune function and a possible prognostic marker in cancer.

While our meta-analysis provides valuable insights, it is not without limitations. The majority of the studies included were conducted in Asia, especially in countries like China and Japan, so the results should be interpreted within this regional context. Caution should be taken when attempting to apply these findings to patients from Europe, Africa, the Americas, and other regions. Additional studies are necessary to verify the prognostic role of PLR in cervical cancer patients outside of Asia. Moreover, most studies included in our analysis were retrospective in nature, which could have introduced confounding factors that might affect the reliability of the results. We also observed publication bias in the

analysis of OS and PFS. We identified potential sources of heterogeneity to be patient age, treatment modality, geographical location, and PLR cutoff values. However, since the majority of the selected studies measured PLR at baseline before treatment (with two studies failing to specify the measurement timing), and considerable variations existed in patient staging, subgroup analysis based on measurement timing and other factors was not feasible. This underscores the importance of grouping cervical cancer patients according to treatment method, age, stage, and PLR measurement timing in future clinical original research, followed by statistical analysis. Additionally, a multicenter research design should be adopted to incorporate patients from diverse regions to the fullest extent possible, thereby facilitating larger sample size analysis and addressing the issue of heterogeneity. The PLR cut-off values across the studies ranged from 111.96 to 322, contributing to variability and potentially adding heterogeneity to the meta-analysis. To enhance reliability and comparability in future research, standardized methods, such as ROC curve analysis and randomized controlled trials (RCTs), are essential to establish an optimal threshold for PLR, so as to improve the correlation with clinical practice.

Conclusion

Our meta-analysis indicates that elevated PLR is significantly correlated with a poor prognosis, including reduced OS, PFS, and DFS in cervical cancer patients. This suggests that PLR could serve as an independent and valuable prognostic marker, supporting treatment decisions, especially in the context of immunotherapy. Subgroup analyses revealed that the prognostic significance of PLR is more prominent in patients receiving both surgery and chemoradiotherapy, as well as in those from Asia and the Americas. Additionally, using a PLR threshold above 150 may improve its predictive accuracy. Nevertheless, due to the limitations present in the studies included in our analysis, further prospective trials are necessary to validate these findings across different regions and treatment strategies.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions
All authors contributed to the study conception and design. Tianyu Zhu: Conceptualization, Methodology, Software, Writing- Original draft, Data curation, Visualization were performed; Zhaoying Chen and Beichen Zhang: Investigation, Writing - Original Draft, Writing - Reviewing and Editing were performed; Xianqing Wu: Conceptualization, Supervision, Project administration were performed. All authors read and approved the final manuscript.

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Data availability
The data used to support the findings of this study are included within the article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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