Prognostic value of platelet-to-lymphocyte ratio in neoadjuvant chemotherapy for solid tumors
A PRISMA-compliant meta-analysis

Yuming Long, BSc, Yingtian Zhang, BSc, Liwei Ni, BSc, Xuya Yuan, BSc, Yuanliang Liu, BSc, Jialong Tao, BSc, Yusong Zhang, PhD∗

Abstract
Introduction: Previous research indicates that the platelet-to-lymphocyte ratio (PLR) may be an indicator of poor prognosis in many tumor types. However, the PLR is rarely described in patients undergoing neoadjuvant chemotherapy (NAC) for solid tumors. Thus, we performed a meta-analysis to investigate the prognostic value of this ratio for patients with solid tumors treated by NAC.

Methods: A comprehensive search of the literature was conducted using the PubMed, EMBASE, Cochrane Library, and Web of Science databases, followed by a manual search of references from the retrieved articles. Pooled hazard ratios (HRs) with 95% confidence interval (CIs) were used to evaluate the association between PLR and 3 outcomes, namely, overall survival, disease-free survival, and pathological complete response rate after NAC.

Results: Eighteen studies published no earlier than 2014 were included in our study. A lower PLR was associated with better overall survival (HR = 1.46, 95% CI, 1.11–1.92) and favorable disease-free survival (HR = 1.81, 95% CI, 1.27–2.59). A PLR that was higher than a certain cutoff was associated with a lower pathological complete response rate in patients with cancer who received NAC (Odds ratio = 1.93, 95% CI, 1.40–2.87).

Conclusion: Elevated PLR is associated with poor prognosis in various solid tumors. PLR may be a useful biomarker in delineating those patients with poorer prognoses who may benefit from neoadjuvant therapies.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, NOS = Newcastle–Ottawa Scale, OR = odds ratio, OS = overall survival, PFS = progression-free survival, PLR = platelet-to-lymphocyte ratio, NAC = neoadjuvant chemotherapy, nCRT = neoadjuvant chemoradiotherapy, pCR = pathological complete response, ROC = receiver operating characteristic curve.

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

1. Introduction
Neoadjuvant chemotherapy (NAC) or neoadjuvant chemoradiotherapy (nCRT) plays a crucial role in the treatment of locally advanced cancer.1–3 The prognostic predictors of cancer patients receiving NAC have been a topic of discussion and research for many years. Numerous studies have demonstrated that cancer-associated inflammation affects different stages of cancer development and progression.4,5 Chronic inflammation secondary to infection has been linked to approximately 25% of all cancer mortalities.4,6 Inflammation first affects blood parameters, and abnormalities in blood cells, such as neutrophilia, thrombocytosis, and lymphopenia, have been found in patients with tumors. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are 2 readily available

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Department of Oncology, The Second Affiliated Hospital of Soochow University, 1055, Sanxiang Road, Suzhou, Jiangsu, PR China.

∗Correspondence: Yusong Zhang, Department of Oncology, The Second Affiliated Hospital of Soochow University, 1055, Sanxiang Road, Suzhou 215004, Jiangsu, PR China (e-mail: zhangyusong1991@163.com).

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serologic biomarkers that are widely believed to represent the degree of systemic inflammation, and accumulating clinical observations indicate that elevated PLR associates with poor outcomes in different types of tumors; thus, these parameters have been studied as prognostic markers in a range of malignancies. Blood tests are routinely performed before any kind of oncologic treatment, so the biomarkers have raised most interest. Several of these parameters have been converted into ratios or prognostic scores, such as NLR, PLR, and lymphocyte-to-monocyte ratio, reflecting poor cancer outcomes in solid tumors. 

A prior meta-analysis concluded that a high PLR is an independent factor associated with poorer overall survival (OS) in many solid tumors and comparable with other established hematologic markers of inflammation; however, research on the value of PLR to patients receiving NAC is scarce. In this context, we sought to review the existing evidence available systematically and assess the prognostic value of PLR on OS and disease-free survival (DFS) in patients receiving NAC.

2. Methods

2.1. Ethics statement

All analyses were based on previously published studies, this article does not contain any studies with human participants or animals performed by any of the authors, thus ethical approval and patient consent are not applicable.

2.2. Literature search

This meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. A systematic literature search was performed using PubMed, EMBASE, Cochrane Library, and Web of Science databases to evaluate the prognostic value of PLR in patients who underwent NAC. The search was updated in February 2020. Our searches were conducted with the following keywords and MeSH search terms: ((PLR or platelet to lymphocyte ratio or platelet-lymphocyte ratio) AND (cancer or tumor or neoplasm)) AND (AND neoadjuvant chemotherapy OR preoperative chemotherapy OR primary chemotherapy). Citation lists of retrieved articles were screened manually to ensure the sensitivity of the search strategy. We comprehensively examined the selected studies and reviews and finally found 18 references that fulfilled the inclusion criteria and provided the data necessary for the meta-analysis (Table 1).

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) patients were diagnosed with solid tumor(s) by pathology and received NAC or nCRT; 2) PLR was measured prior to treatment as a categorical variable; 3) PLR was measured via serum-based methods; 4) the relationship between PLR and OS and DFS was evaluated; and 5) the full text of the study was available. No language limits were set in this work. The exclusion criteria were as follows: 1) the obtained article was a review, letter, case report, or nonhuman research; 2) insufficient data to extract hazard ratios (HRs) and 95% confidence intervals (CIs) were not available, and 3) they reported on non-human research.

2.4. Data extraction and quality assessment

OS and DFS were the primary outcomes of interest; if information about DFS was not available, the definitions of DFS and progression-free survival were considered similar and could be combined in an analysis. When available, HRs

Table 1

| Study | Publish year | Tumor type | Disease stage | Country | Sample size | Neoadjuvant treatment regimens | PLR cutoff | Survival analysis | NOS score | Variable type | Methods for determining cutoff |
|-------|--------------|------------|---------------|---------|-------------|-------------------------------|------------|-------------------|-----------|---------------|------------------------------|
| Asans et al 2016 | Breast cancer | II–III | Japan | 177 | Neoadjuvant chemotherapy | 150 DFS/OS | 5 M | On the basis of previous studies |
| Chen et al 2019 | Gastric cancer | II–III | China | 91 | Neoadjuvant chemotherapy | 162 DFS/OS | 6 M | ROC |
| Cuello-Lopez et al 2019 | Breast cancer | II–III | Colombia | 296 | Neoadjuvant chemotherapy | NA pCR | 7 M | On the basis of previous studies |
| Dudani et al 2019 | Rectal cancer | II–III | Canada | 1237 | Neoadjuvant chemotherapy | 150 DFS/OS | 6 M | On the basis of previous studies |
| Dong et al 2017 | Gastric cancer | II–III | China | 91 | Neoadjuvant chemotherapy | 161 OS | 6 M | ROC |
| Gaziano et al 2019 | Breast cancer | II–III | Italy | 373 | Neoadjuvant chemotherapy | 104.47 pCR | 6 — | ROC |
| Ishibashi et al 2019 | Esophageal cancer | II–III | Japan | 85 | Neoadjuvant chemotherapy | 107.3 OS | 6 U | NA |
| Ji et al 2015 | Esophageal squamous cell cancer | II–III | China | 41 | Neoadjuvant chemotherapy | 130 DFS/OS | 7 U | Software analysis |
| Kubo et al 2019 | Pancreatic ductal adenocarcinoma | II–IV | Japan | 119 | Neoadjuvant Chemoradiotherapy | 150 OS | 6 U | On the basis of previous studies |
| Lee et al 2017 | Rectal cancer | II–IV | Korea | 291 | Neoadjuvant Chemoradiotherapy | 235 pCR | 6 — | NA |
| Messager et al 2015 | Oesophageal and junctional adenocarcinoma | I–II | The United Kingdom | 153 | Neoadjuvant chemotherapy | 192 DFS/OS | 7 M | ROC |
| Nedyofu et al 2014 | Colorectal cancer | NA | The United Kingdom | 140 | Neoadjuvant chemotherapy | 150 DFS/OS | 6 U | ROC |
| Solak Mleku et al 2018 | Colorectal cancer | II–IV | The United States | 71 | Neoadjuvant Chemoradiotherapy | 150 DFS/OS | 5 U | Software analysis |
| Tang et al 2018 | Gastric cancer | II | China | 104 | Neoadjuvant chemotherapy | 130.7 OS | 6 M | ROC |
| Tolyama et al 2015 | Rectal cancer | I–II | Japan | 89 | Neoadjuvant Chemoradiotherapy | 150 DFS/OS | 6 M | On the basis of previous studies |
| Wu et al 2019 | Esophageal cancer | II–III | China (Taiwan) | 105 | Concurrent chemoradiotherapy | 146.05 OS | 6 M | Software analysis |
| Yang et al 2018 | Colorectal cancer | NA | China | 98 | Neoadjuvant Chemoradiotherapy | 114.15 DFS/OS | 5 M | NA |
| Zhao et al 2017 | Rectal cancer | II–III | China | 100 | Neoadjuvant Chemoradiotherapy | 150 OS | 5 M | ROC |

DFS = disease-free survival, M = multivariable analyses, NA = not available, NOS = Newcastle–Ottawa Scale, OS = overall survival, PFS = progression-free survival, PLR = platelet-to-lymphocyte, ROC = receiver operating characteristic curve, U = univariate analyses.
for survival associated with pathological complete response (pCR) were also collected. OS was defined as the time from the date of surgery to death, DFS was defined as the time from the date of surgery to the date of tumor relapse (local recurrence and/or distant metastases) or death, and pCR was defined as the complete absence of cancer tissue in all postoperative materials. Two reviewers (YL and YZ) independently extracted the useful data from the eligible studies. The following information was gathered: first author’s name, publication year, publication type, tumor type, country of study, total sample size, cutoff PLR value, neoadjuvant treatment method, and survival outcome type. HRs were extracted from multivariable analyses whenever available and extracted or estimated from univariable analyses using Kaplan–Meier survival curves as described by Tierney et al.[31] Quality assessment of the included studies was independently conducted by 2 reviewers using the Newcastle–Ottawa Quality Assessment Scale (NOS, scores of 0–9 stars). Any discrepancies were discussed and resolved by consensus.

2.5. Statistical analysis

Pooled HRs and 95% CIs were used to analyze the relationship between PLR and prognosis (OS and DFS). Heterogeneity was assessed using the Cochrane Q test (P value for heterogeneity) and I² statistics. If I² > 50% or P < .05 was considered to indicate significant heterogeneity. If significant heterogeneity was found, a random-effect model was used; otherwise, a fixed-effect model was used. The HR was representative of the high blood PLR over the low blood PLR. A combined HR > 1 indicates a poorer prognosis, and it was considered statistically significant if the 95% CI for the HR did not overlap. The pCR rates and total numbers of patients in the low- and high-PLR groups were extracted to calculate odds ratios (ORs) and 95% CIs; the results were then pooled with other ORs to obtain the final results. A pooled OR > 1 frequently indicates that a low PLR is related to a relatively better pCR rate. Publication bias was assessed using Egger linear regression test, and P < .05 was considered to indicate significant publication bias.[32] All statistical analyses were conducted with Stata/SE version 15.1 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Study selection and characteristics

The flowchart of the study selection process is shown in Figure 1, and the basic features of the 18 studies are summarized in Table 1. All studies were published in 2014 or later and highlighted recent interest in investigating the prognostic value of PLR. A total of 3653 patients were included in our meta-analysis, and the sample size of the included studies ranged from 41 to 1237. In detail, 4 studies on rectal cancer,[16,19,20,26] 3 studies on breast cancer,[17,21,27] 3 studies on colorectal cancer,[13,22,24] 3 studies on gastric cancer,[18,23,25] 3 studies on esophageal cancer,[14,28,30] 1 study on esophageal and junctional adenocarcinoma,[15] and 1 study on pancreatic ductal adenocarcinoma[29] were included in this work. The countries in which the studies were published included the People’s Republic of China (n = 7), Japan (n = 4), the United Kingdom (n = 2), Canada (n = 1), Colombia (n = 1), Italy (n = 1), Korea (n = 1), and the United States (n = 1). During the quality assessment, the scores of the included trials ranged from 5 to 8; here, an NOS score of ≥6 indicates a high-quality study (Table 2).

3.2. PLR and OS in solid tumors

A total of 14 trials comprising 2524 patients reported HRs for OS.[13–16,18,20,22–26,30] A pooled HR of 1.46 (95% CI: 1.11–1.92, Fig. 2) revealed that a high PLR is related to an unfavorable OS. The results of heterogeneity testing indicated significant heterogeneity (P < .012, I² = 51.9%, Fig. 2).

3.3. PLR and DFS in solid tumors

A total of 8 trials including 2008 patients reported HRs for DFS.[13–15,17,22,24–26] Overall, a low PLR was associated with a high DFS (HR = 1.94, 95% CI: 1.28–2.94, Fig. 3). A high level of heterogeneity was also found (P = .001, I² = 71.5%, Fig. 3).

3.4. PLR and pCR in solid tumors

A total of 4 trials including 2075 patients reported HRs for pCR rate.[15,17,21,27] A low PLR was associated with a high pCR rate (OR = 1.93, 95% CI: 1.40–2.67, Fig. 4). Significant heterogeneity was not observed (P > .05, I² = 0%, Fig. 4).

3.5. Subgroup analysis

Exploratory subgroup analyses were conducted according to geographic region (Asia and non-Asia), sample size (large and small), variable type (multivariable and univariate), cutoff value (≥150 and <150), and methods for determining cutoff (receiver operating characteristic curve/software analysis and reference to a previous study).

Exploratory subgroup analysis according to geographic region showed that a high PLR could predict poor OS (HR: 1.41, 95% CI: 1.00–1.99, P = .042) and DFS (HR: 2.30, 95% CI: 1.54–3.46, P = .457) in Asian studies. By comparison, the data for OS (OR = 1.66, 95% CI: 0.93–2.96) and DFS (HR: 1.64, 95% CI: 0.93–2.89, P = .003) for studies conducted outside of Asia did not show a statistical association.

Subgroup analysis by sample size showed that a high PLR could predict poor OS in the <100 groups (HR: 1.82, 95% CI: 1.15–2.87, P = .101) but was not significantly related to OS in the ≥100 groups (HR: 1.26, 95% CI: 0.92–1.74, P = .051). Moreover, a high PLR was a consistent predictor of poor DFS regardless of the group analyzed.

Pooled HRs for OS were stratified by variable type, and elevated PLRs predicted decreased OS in patients surveyed via multivariable analyses (HR: 1.48, 95% CI: 1.04–2.09, P = .021) but not in those surveyed via univariable analyses (HR: 1.49, 95% CI: 0.89–2.51, P = .063). Subgroup analysis by variable type showed that high PLRs result in poor DFS.

The cutoff values ranged from 104 to 235. We stratified cutoff values into 2 subgroups, namely, <150 and ≥150. Stratification by cutoff value revealed that patients with PLR ≥150 have a significantly poorer OS (HR: 1.49, 95% CI: 1.10–2.03, P = .012); however, the prognostic effect of this parameter disappeared in patients with PLR <150 (HR: 1.41, 95% CI: 0.67–2.98, P = .117). The pooled results of PLRs for DFS among the cutoff subgroups showed a statistical association with DFS in the ≥150 groups (HR: 1.94, 95% CI: 1.18–3.20, P = .001) but not in the <150 groups (HR: 1.96, 95% CI: 0.94–4.10, P = .16).

Subgroup analysis according to methods for determining cutoff values indicated that PLR had prognostic effects on OS.
(HR: 1.97, 95% CI: 1.39–2.79, P = .162) and DFS (HR: 2.24, 95% CI: 1.62–3.08, P = .604) when studies were analyzed using receiver operating characteristic curve/software; however, when the method of determination was a reference to the previous study, the prognostic efficiency of this parameter disappeared in the pooled results.

Overall, the results of subgroup analysis for these variables did not alter the prognostic role of PLR on OS and DFS. Details of the subgroup analyses are summarized in Table 3(a) and (b).

3.6. Sensitivity analysis
Sensitivity analysis was performed by assessing the potential impact of individual studies on the pooled data. The results of sensitivity analyses demonstrated that no individual study had an excessive influence on the stability of the pooled effect of comparisons for OS and DFS (Fig. 5(A) and (B)). The effect of PLR on OS was robust. During analysis of the relation between PLR and DFS, heterogeneity was introduced by 1 outlier study with HR=0.96;\(^\text{[26]}\) exclusion of this study reduced \(I^2\) to 0%.
### Table 2
Quality assessment of eligible studies with Newcastle–Ottawa Scale.

| Author                  | Representativeness of exposed cohort | Selection of unexposed cohort | Ascertainment of exposure | Outcomes of interest not present at the start of study | Comparability based on the design or analysis | Ascertainment of outcome | Follow-up long enough for outcomes to occur | Adequacy of followup | Total quality score |
|-------------------------|-------------------------------------|------------------------------|---------------------------|--------------------------------------------------------|-----------------------------------------------|-------------------------|------------------------------------------------|-----------------------|---------------------|
| Asano et al (2016)      | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 8                   |
| Chen et al (2019)       | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Cuello-Lopez et al (2018)| •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 7                   |
| Dudani et al (2019)     | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Gong et al (2017)       | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Graziano et al (2018)   | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Ishibashi et al (2019)  | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 5                   |
| Ji et al (2015)         | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Kubo et al (2019)       | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Lee et al (2017)        | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Messenger et al (2015)  | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Neofytou et al (2014)   | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 5                   |
| Solak Mekic et al (2018)| •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 5                   |
| Tang et al (2018)       | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Toiyama et al (2015)    | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Wu et al (2019)         | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Yang et al (2018)       | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |
| Zhao et al (2017)       | •                                   | •                           | •                         | •                                                      | •                                             | •                       | •                                                | •                     | 6                   |

Asterisk represents a point.

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**Figure 2.** Forest plots for associations between platelet-to-lymphocyte ratio and overall survival, a low platelet-to-lymphocyte ratio served as a prognostic indicator of favorable overall survival.
and changed the pooled estimate to 2.16 (95% CI, 1.65–2.83; \( P = .00 \)).

Further, meta-regression showed that tumor type is 1 of the sources of inter-study heterogeneity for OS. The variance component decreased from 0.1203 to 0.06668, thereby indicating that it can explain 52% of the heterogeneity observed.

3.7. Publication bias

Egger linear regression test was conducted to evaluate the effect of publication bias of the included cohorts on OS and DFS. The \( P \) values for Egger test in the HRs for OS and DFS were 0.016 (Fig. 6(A)) and 0.004 (Fig. 6(B)), respectively. After trim fill analysis, the pooled HR for OS based on the random-effect model was 1.046 (95% CI, 0.774–1.413; Fig. 6(C)), thus suggesting that a publication bias appears to overestimate OS. By comparison, the pooled HR for DFS was 1.734 (95% CI, 1.214–2.478; Fig. 6(D)). The results are roughly consistent with the primary results and indicate that publication bias is not evident in the present meta-analysis.

4. Discussion

PLR is commonly used as a systematic marker of inflammation and has gained the interest of physicians in recent years. Some studies have demonstrated that pretreatment PLR is associated with poor prognosis in several malignancies.\(^{[12,33–37]}\) However, Dudani et al reported that elevated baseline PLRs are neither prognostic for DFS and OS nor predictive of pCR.\(^{[26]}\) Because the exact relationship between PLR and the OS and DFS of patients receiving NAC is yet unknown, we conducted a meta-analysis to determine the relevant relationships. In some cases, the addition of NAC resulted in greater tumor downsizing and increasing the rate of complete resection, improved the pCR rate, and demonstrated local control, but the relative effects are controversial.\(^{[38–45]}\) To the best of our knowledge, meta-analyses are a more comprehensive update that systematically and quantitatively evaluates this topic. In the present meta-analysis of 18 studies including 3653 cases, we evaluated the prognostic role of PLR in solid tumors following NAC or nCRT. The results of this study suggest that pretreatment PLR could be used as a prognostic factor for patients with solid tumors after neoadjuvant therapy. Specifically, a low PLR was associated with good OS and DFS and a high pCR rate. By our meta-analysis, we study the level of pretreatment PLR and its relationship to the pathologic complete response to NAC in patients with solid tumors, and we evaluate the prognostic value of PLR with respect to the survival outcome in cancer patients after NAC.

The underlying mechanisms by which PLR influences the survival of patients with solid tumors remain largely unknown. Host immune system and tumor interactions are significantly associated with patients’ prognosis, and measurement of simple systemic immune reaction markers, such as neutrophils, lymphocytes, and PLR, can generally represent the host-tumor
Figure 4. Forest plots for associations between platelet-to-lymphocyte ratio and pathological complete response, a lower platelet-to-lymphocyte ratio was associated with a higher pathological complete response rate.

### Table 3

**Subgroup analyses for OS and DFS.**

#### (a) Subgroup analyses for OS

|                | N  | HR (95%CI)       | P value | I²       |
|----------------|----|-----------------|---------|----------|
| Overall        |    |                 |         |          |
| Region         | 14 | 1.46 (1.11–1.92) | .012    | 51.9%    |
| Asia           | 10 | 1.41 (1.00–1.99) | .042    | 48.5%    |
| Non-Asia       | 4  | 1.86 (0.93–2.96) | .025    | 66.0%    |
| Sample size    |    |                 |         |          |
| Large (≥100)   | 7  | 1.26 (0.92–1.74) | .051    | 52.2%    |
| Small (<100)   | 7  | 1.82 (1.15–2.87) | .101    | 43.4%    |
| Variable type  |    |                 |         |          |
| Multivariable  | 9  | 1.48 (1.04–2.09) | .021    | 58.8%    |
| Univariate     | 5  | 1.49 (0.89–2.51) | .063    | 55.1%    |
| Cutoff         |    |                 |         |          |
| ≥150           | 11 | 1.49 (1.10–2.03) | .012    | 56.0%    |
| <150           | 3  | 1.41 (0.67–2.98) | .117    | 53.4%    |
| Methods for determining cutoff | | | | |
| ROC/software analysis | 9 | 1.97 (1.39–2.70) | .162 | 30.0% |
| Referring to the previous study | 3 | 0.98 (0.78–1.23) | .723 | 0 |
| NA             | 2  | 1.05 (0.67–1.65) | .805    | 0        |

#### (b) Subgroup analyses for DFS

|                | N  | HR (95%CI)       | P value | I²       |
|----------------|----|-----------------|---------|----------|
| Overall        |    |                 |         |          |
| Region         | 8  | 1.94 (1.28–2.94) | .001    | 71.5%    |
| Asia           | 4  | 2.30 (1.54–3.46) | .457    | 0        |
| Non-Asia       | 4  | 1.64 (0.93–2.89) | .003    | 78.4%    |
| Sample size    |    |                 |         |          |
| Large (≥100)   | 4  | 1.80 (1.00–3.23) | .000    | 83.5%    |
| Small (<100)   | 4  | 2.11 (1.34–3.32) | .541    | 0        |
| Variable type  |    |                 |         |          |
| Multivariable  | 6  | 1.92 (1.13–3.26) | .001    | 75.8%    |

(continued)
Table 3
(continued).

(b) Subgroup analyses for DFS

|                  | N  | HR (95% CI)   | P value | I² |
|------------------|----|---------------|---------|----|
| Univariate       | 2  | 1.96 (1.15–3.34) | .267    | 18.8% |
| Cutoff           |    |               |         |     |
| ≥150             | 6  | 1.94 (1.18–3.20) | .001    | 77.0% |
| <150             | 2  | 1.96 (0.94–4.10) | .216    | 34.6% |
| Methods for determining cutoff |     |               |         |     |
| ROC/software analysis | 5  | 2.24 (1.62–3.08) | .604    | 0   |
| Referring to the previous study | 2  | 1.56 (0.54–4.49) | .006    | 87.0% |
| NA               | 1  | 1.46 (0.74–2.91) |         |     |

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, NA = not available, OS = overall survival, ROC = receiver operating characteristic curve.

Figure 5. (A) Sensitivity analysis for overall survival, The effect of platelet-to-lymphocyte ratio on overall survival was robust and (B) sensitivity analysis for disease-free survival, 1 study introduced heterogeneity.
interaction conditions. Over 20% of all human cancer cases are estimated to be associated with chronic inflammation. As reported in several studies, cancer cells can secrete vascular endothelial growth factors to stimulate megakaryocyte differentiation and induce platelet activation by secreting platelet agonists. Platelets can come into direct contact with tumor cells and secrete a series of cytokines, including platelet-derived growth factor, TGF-β, and prostaglandin E2, thereby enhancing the epithelial–mesenchymal transition of tumor cells. Lymphocytopenia is a key component of a high PLR. Lymphocytes represent the cellular basis of cancer immunosurveillance. Compelling evidence indicates that lymphocytes induce cytotoxic cell death and inhibit tumor cell proliferation and migration, thereby dictating the host’s immune response to cancer.

Several potential limitations of this study should be acknowledged. First, because NAC is not given to patients with certain tumor types, only 6 cancer types were eligible for analysis in our study. A major disadvantage of this study is the discordance of variable tumors, which could lead to inter-study heterogeneity. Second, some studies (35%) provided only HRs from univariable analysis, which could introduce a bias by overestimating the prognostic role of PLR. HRs in multivariable analyses may be rendered nonsignificant due to the inclusion of other markers of systemic inflammation, such as NLR, lymphocyte-to-monocyte ratio, and hemoglobin, into the multivariable model. Third, considering that all included studies had a retrospective design, the potential for unmeasured biases cannot be discounted. In addition, conditions that may affect systemic inflammatory responses other than cancers, such as metabolic syndrome, inflammatory disease, cardiovascular or cerebrovascular disease, and any medication related to inflammatory conditions, were not evaluated due to the retrospective nature of this study.

5. Conclusion

Our meta-analysis pooled 18 studies to assess the prognostic effect of PLR on OS, DFS, and pCR rate in patients who received NAC. In summary, a low PLR served as a prognostic indicator of favorable OS and DFS in patients with various types of solid tumors after NAC. Furthermore, a lower PLR was associated with a higher pCR rate. Thus, PLR, as a cost-effective and readily available biomarker, may be useful in the clinical setting. However, these results must be interpreted with caution because of the limitations listed above. Further prospective studies with larger sample sizes and suitable patients are necessary to confirm our findings and elucidate the underlying biology.

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