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

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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

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.[7–10] 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.[11]

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;[12] 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[13–30] (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.[11] Whenever available, HRs

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Table 1

Baseline characteristics of included studies.

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
Asano et al	2016	Breast cancer	II–III	Japan	177	Neoadjuvant chemotherapy	150	DFS/OS/pCR	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	2018	Breast cancer	II–III	Colombia	288	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/pCR	6	M	On the basis of previous studies
Gong et al	2017	Gastric cancer	I–III	China	91	Neoadjuvant chemotherapy	161	OS	6	M	ROC
Graziano et al	2018	Breast cancer	NA	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	I–III	China	41	Neoadjuvant chemotherapy	130	PFS/OS	7	U	Software analysis
Kubo et al	2019	Pancreatic ductal adenocarcinoma	I–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	Preoperative Chemoradiotherapy	235	pCR	6	—	NA
Messager et al	2015	Oesophageal and junctional adenocarcinoma	I~–III	The United Kingdom	153	Neoadjuvant chemotherapy	192	DFS/OS	7	M	ROC
Neofytou et al	2014	Colorectal cancer	NA	The United Kingdom	140	Neoadjuvant chemotherapy	150	DFS/OS	6	U	ROC
Solak Mekic et al	2018	Colorectal cancer	III–IV	The United States	71	Neoadjuvant chemoradiotherapy	150	DFS/OS	5	U	Software analysis
Tang et al	2018	Gastric cancer	III	China	104	Neoadjuvant chemotherapy	130.7	OS	6	M	ROC
Toiyama et al	2015	Rectal cancer	I–III	Japan	89	Neoadjuvant chemoradiotherapy	150	DFS/OS	6	M	On the basis of previous studies
Wu et al	2019	Esophageal cancer	I–III	China (Taiwan)	105	Concurrent chemoradiotherapy	146.05	OS	6	M	Software analysis
Yang et al	2018	Colorectal cancer	NA	China	98	Neoadjuvant chemotherapy	114.15	PFS/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 Cochran Q test (P value for heterogeneity) and I^2 statistics. $I^2 > 50\%$ 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.[13–16,18,20,22–26,28–30] 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 ($P < .012$, $I^2 = 51.9\%$, 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 ($P = .001$, $I^2 = 71.5\%$, 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 ($P < .05$, $I^2 = 0\%$, 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 univariate 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, $P = .216$).

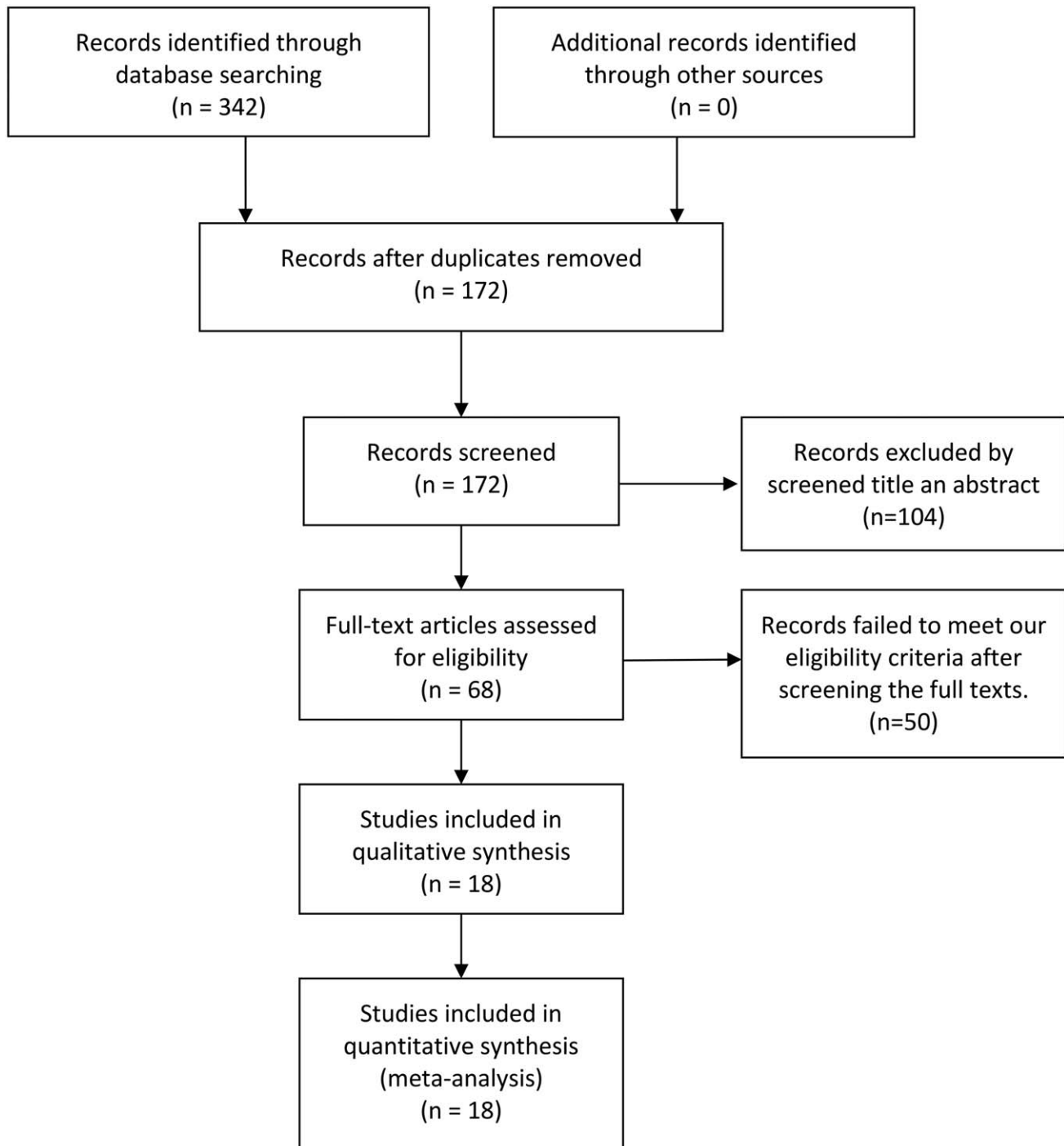Subgroup analysis according to methods for determining cutoff values indicated that PLR had prognostic effects on OS

Figure 1. Flow chart of this study.

(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;[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)	*	*	*	—	**	*	*	—	7
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
Messager 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.
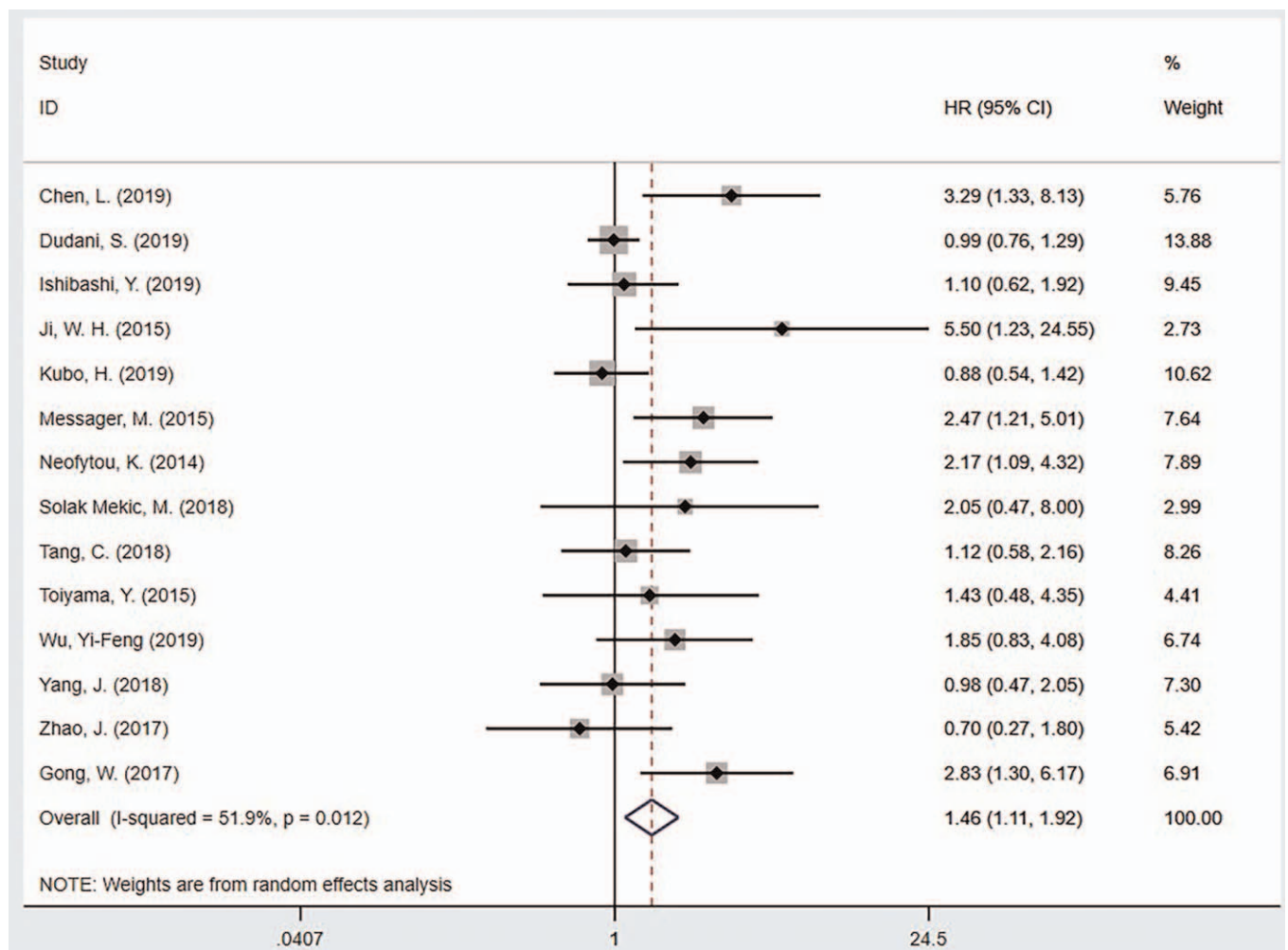
Figure 2. Forest plots for associations between platelet-to-lymphocyte ratio and overall survival, a low platelet-to-lymphocyte ratio served as a prognostic indicator of favorable overall survival.
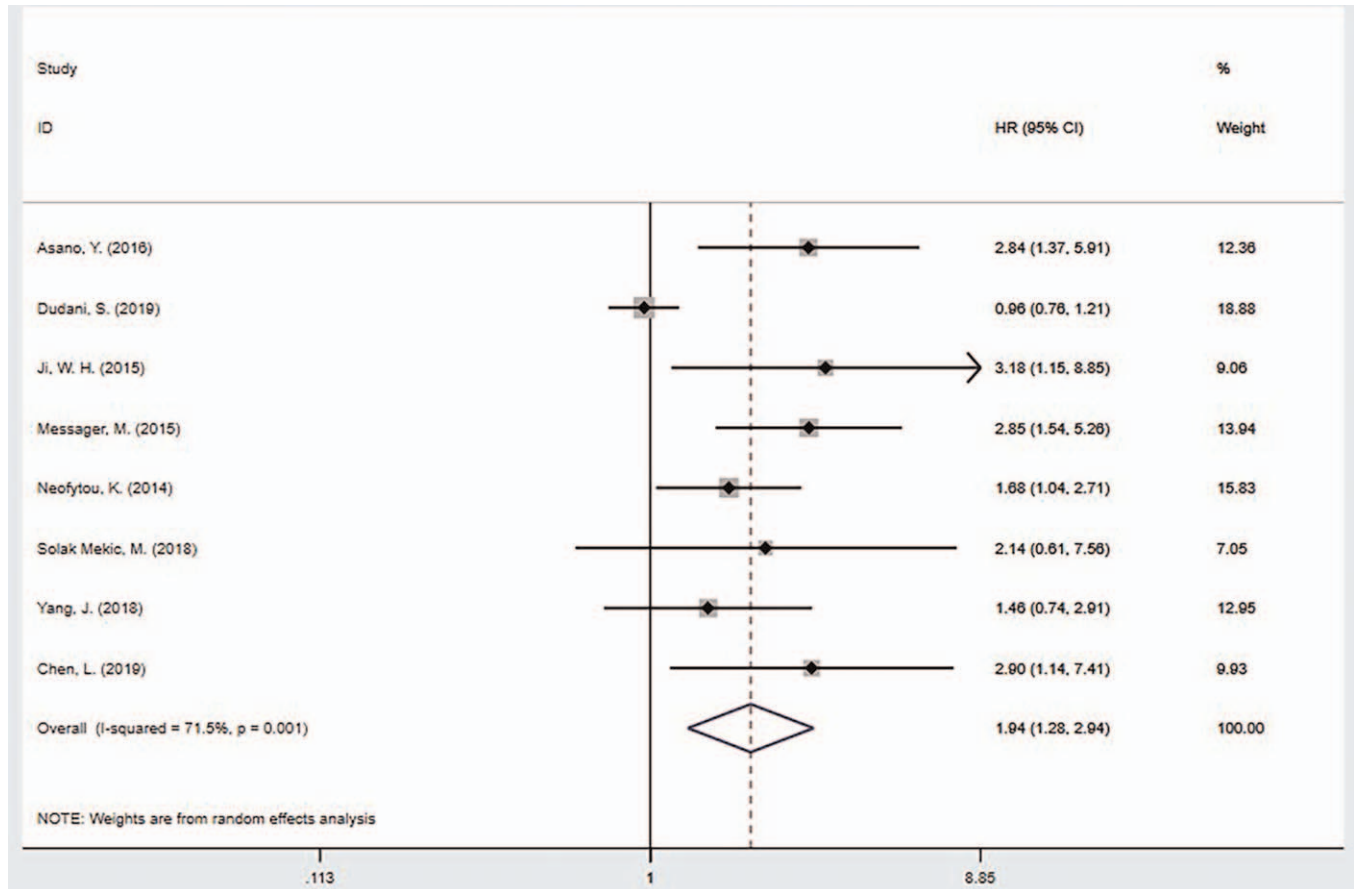
Figure 3. Forest plots for associations between platelet-to-lymphocyte ratio and disease-free survival, a higher platelet-to-lymphocyte ratio was associated with lower disease-free survival.

$(P=.603)$ 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
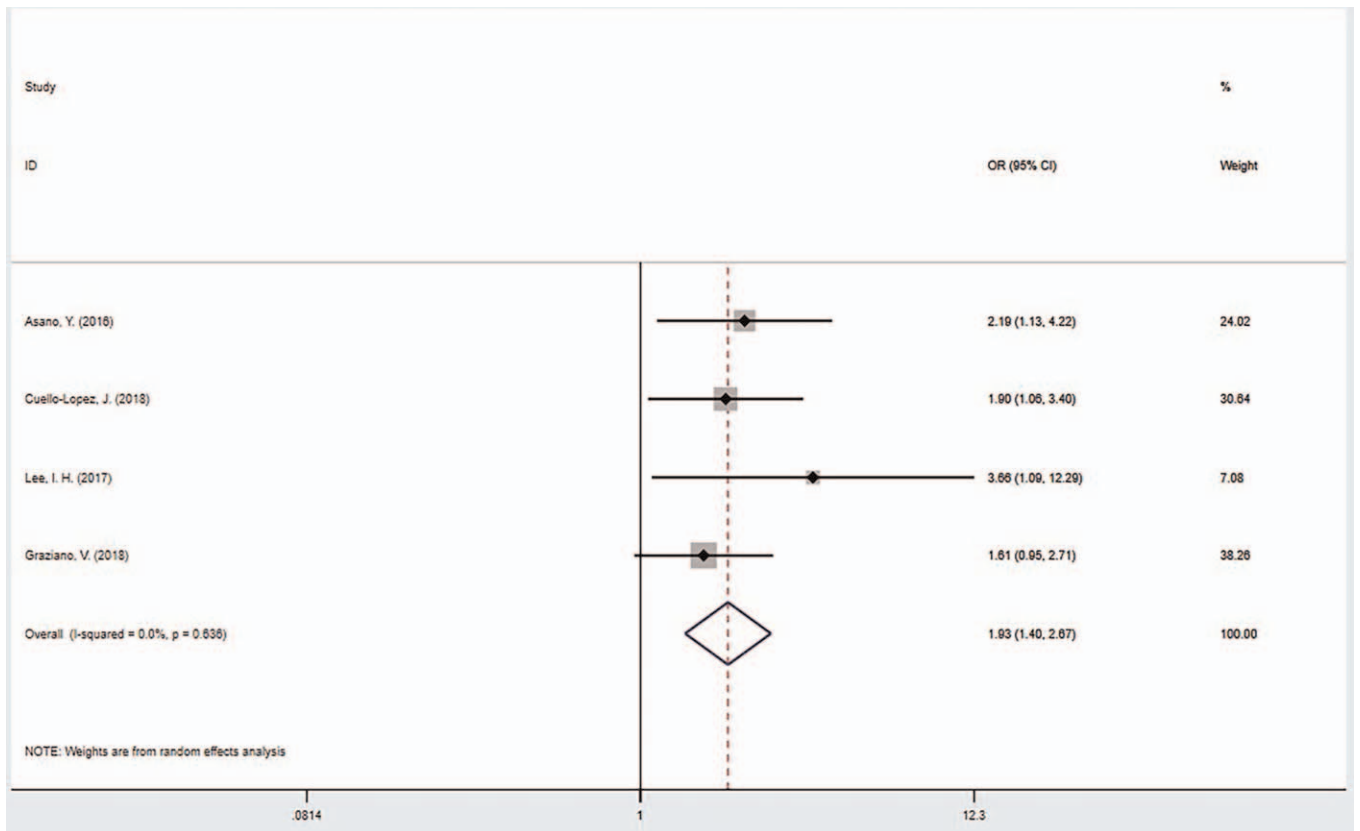
Figure 4. Forest plots for associations between platelet-to-lymphocyte ratio and pathological complete response, a lower platelet-to-lymphocyte ratio was associated with a higher pathological complete response rate.

Table 3

Subgroup analyses for OS and DFS.

(a) Subgroup analyses for OS

	N	HR (95%CI)	P value	I^2
Overall				
Region	14	1.46 (1.11–1.92)	.012	51.9%
Asia	10	1.41 (1.00–1.99)	.042	48.5%
				68.0%
Non-Asia	4	1.66 (0.93–2.96)	.025	
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 (1.39–2.79)	.162	32.0%
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	I^2
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)

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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.
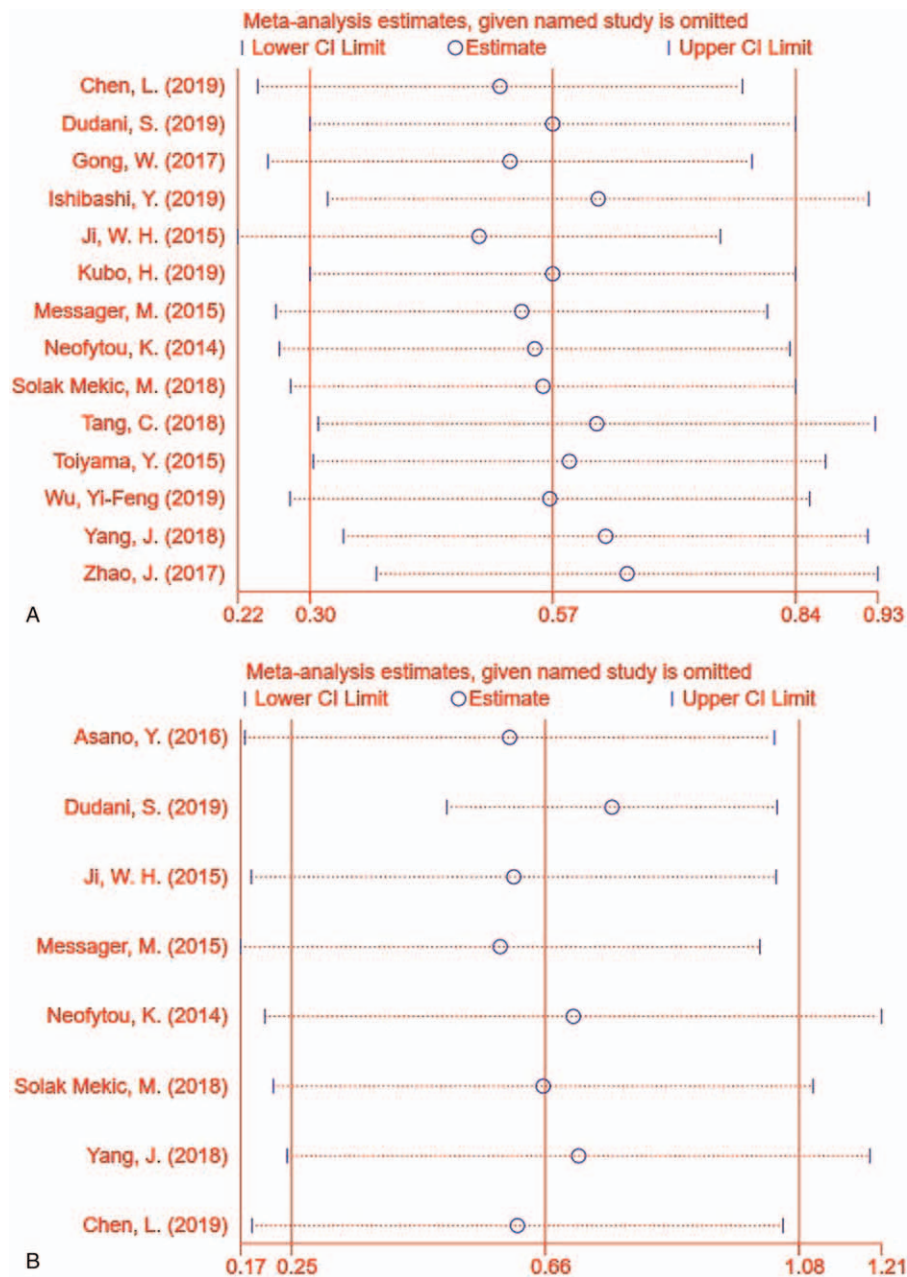
Figure 5. (A) Sensitivity analysis for overall survival, The effect of platelet-to-lymphocyte ratio on overall survival was robust and (B) sensitivity analysis for disease-free survival, 1 study introduced heterogeneity.
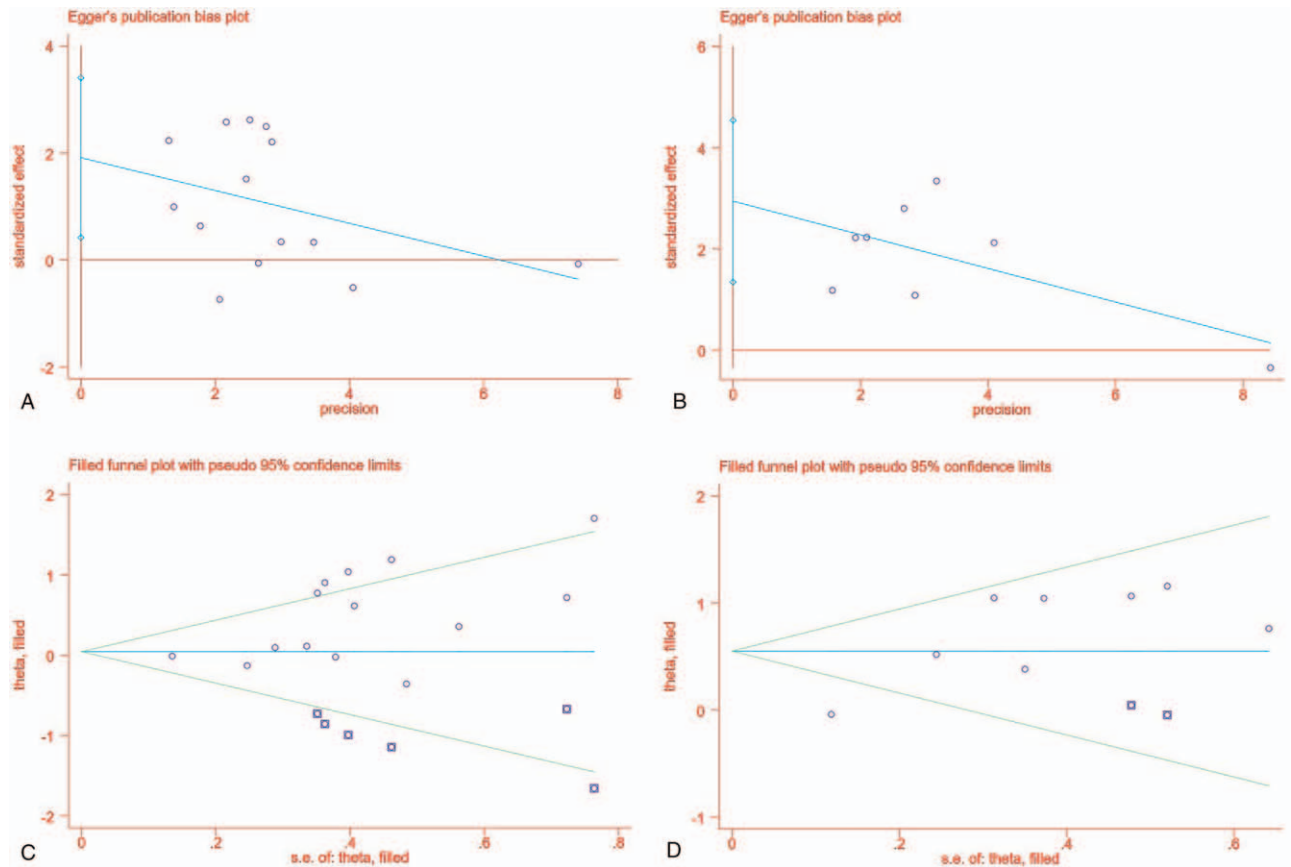
Figure 6. (A) Egger linear regression test for overall survival; (B) Egger linear regression test for disease-free survival; (C) Funnel plot used trim-and-fill methods for overall survival, a publication bias appears to overestimate OS; and (D) Funnel plot used trim-and-fill methods for disease-free survival. The results are roughly consistent with the primary results.

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[46] and induce platelet activation by secreting platelet agonists.[47] 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.[48,49] 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.

Acknowledgments

Author contributions

References

[1] Ludmir EB, Palta M, Willett CG, Czito BG. Total neoadjuvant therapy for rectal cancer: an emerging option. Cancer 2017;123:1497–506.

[2] Pathak M, Dwivedi SN, Deo SVS, Thakur B, Sreenivas V, Rath GK. Neoadjuvant chemotherapy regimens in treatment of breast cancer: a systematic review and network meta-analysis protocol. Syst Rev 2018;7:89.

[3] Abarbanel DN, Seki SM, Davies Y, et al. Immunomodulatory effect of vancomycin on Treg in pediatric inflammatory bowel disease and primary sclerosing cholangitis. J Clin Immunol 2013;33:397–406.

[4] Moore MM, Chua W, Charles KA, Clarke SJ. Inflammation and cancer: causes and consequences. Clin Pharmacol Ther 2010;87:504–8.

[5] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.

[6] Marusawa H, Jenkins BJ. Inflammation and gastrointestinal cancer: an overview. Cancer Lett 2014;345:153–6.

[7] Cannon NA, Iyengar P, Ahn C, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors following stereotactic radiation therapy for early-stage non-small cell lung cancer. J Thorac Oncol 2014;90:1.

[8] Ferroni P, Riondino S, Formica V, et al. Venous thromboembolism risk prediction in ambulatory cancer patients: clinical significance of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio. Int J Cancer 2015;136:1234–40.

[9] Lai Q, Castro Santa E, Rico Juri JM, Pinheiro RS, Lerut J. Neutrophil and platelet-to-lymphocyte ratio as new predictors of dropout and recurrence after liver transplantation for hepatocellular cancer. Transpl Int 2014; 27:32–41.

[10] Zhang G-M, Zhu Y, Luo L, et al. Preoperative lymphocyte-monocyte and platelet-lymphocyte ratios as predictors of overall survival in patients with bladder cancer undergoing radical cystectomy. Tumor Biol 2015;36:8537–43.

[11] Li X, Dai D, Chen B, Tang H, Xie X, Wei W. The value of neutrophil-to-lymphocyte ratio for response and prognostic effect of neoadjuvant chemotherapy in solid tumors: a systematic review and meta-analysis. J Cancer 2018;9:861–71.

[12] Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:1204–12.

[13] Neofytou K, Smyth EC, Giakoustidis A, Khan AZ, Cunningham D, Mudan S. Elevated platelet to lymphocyte ratio predicts poor prognosis after hepatectomy for liver-only colorectal metastases, and it is superior to neutrophil to lymphocyte ratio as an adverse prognostic factor. Med Oncol 2014;31:239.

[14] Ji WH, Jiang YH, Ji YL, Li B, Mao WM. Prechemotherapy neutrophil: lymphocyte ratio is superior to the platelet: lymphocyte ratio as a prognostic indicator for locally advanced esophageal squamous cell cancer treated with neoadjuvant chemotherapy. Dis Esophagus 2015;29:403–11.

[15] Messager M, Neofytou K, Chaudry MA, Allum WH. Prognostic impact of preoperative platelets to lymphocytes ratio (PLR) on survival for oesophageal and junctional carcinoma treated with neoadjuvant chemotherapy: a retrospective monocentric study on 153 patients. Eur J Surg Oncol 2015;41:1316–23.

[16] Toiyama Y, Inoue Y, Kawamura M, et al. Elevated platelet count as predictor of recurrence in rectal cancer patients undergoing preoperative chemoradiotherapy followed by surgery. Int Surg 2015;100:199–207.

[17] Asano Y, Kashiwagi S, Onoda N, et al. Platelet-lymphocyte ratio as a useful predictor of the therapeutic effect of neoadjuvant chemotherapy in breast cancer. PLoS One 2016;11:e0153459.

[18] Gong W, Zhao L, Dong Z, et al. After neoadjuvant chemotherapy platelet/lymphocyte ratios negatively correlate with prognosis in gastric cancer patients. J Clin Lab Anal 2017;32:e22364.

[19] Lee IH, Hwang S, Lee SJ, et al. Systemic inflammatory response after preoperative chemoradiotherapy can affect oncologic outcomes in locally advanced rectal cancer. Anticancer Res 2017;37:1459–65.

[20] Zhao J, Xu J, Zhang R. Clinical and prognostic significance of pathological and inflammatory markers in mucinous rectal cancer patients receiving neoadjuvant chemoradiotherapy and curative surgery. Med Sci Monit 2017;23:4826–33.

[21] Cuello-Lopez J, Fidalgo-Zapata A, Lopez-Agudelo L, Vasquez-Trespalacios E. Platelet-to-lymphocyte ratio as a predictive factor of complete pathologic response to neoadjuvant chemotherapy in breast cancer. PLoS One 2018;13:e0207224.

[22] Solak Mekic M, Pedisic I, Sobat H, et al. The role of complete blood count parameters in patients with colorectal cancer. Acta Clin Croat 2018;57:624–9.

[23] Tang C, Cheng X, Yu S, et al. Platelet-to-lymphocyte ratio and lymphocyte-to-white blood cell ratio predict the efficacy of neoadjuvant chemotherapy and the prognosis of locally advanced gastric cancer patients treated with the oxaliplatin and capecitabine regimen. Onco Targets Ther 2018;11:7061–75.

[24] Yang J, Xu H, Guo X, et al. Pretreatment inflammatory indexes as prognostic predictors for survival in colorectal cancer patients receiving neoadjuvant chemoradiotherapy. Sci Rep 2018;8:3044.

[25] Chen L, Hao Y, Cong X, et al. Peripheral venous blood platelet-to-lymphocyte ratio (PLR) for predicting the survival of patients with gastric cancer treated with SOX or XELOX regimen neoadjuvant chemotherapy. Technol Cancer Res Treat 2019;18:1533033819829485.

[26] Dudani S, Marginean H, Tang PA, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictive and prognostic markers in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation. BMC Cancer 2019;19:664.

[27] Graziano V, Grassadonia A, Iezzi L, et al. Combination of peripheral neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio is predictive of pathological complete response after neoadjuvant chemotherapy in breast cancer patients. Breast 2019;44:33–8.

[28] Ishibashi Y, Tsujimoto H, Hiraki S, et al. Predictive value of immuno-inflammatory and nutritional measures modulated by neoadjuvant chemotherapy on the response of neoadjuvant chemotherapy and long-term outcomes in patients with esophageal cancer. Oncol Lett 2019; 19:487–97.

[29] Kubo H, Murakami T, Matsuyama R, et al. Prognostic impact of the neutrophil-to-lymphocyte ratio in borderline resectable pancreatic ductal adenocarcinoma treated with neoadjuvant chemoradiotherapy followed by surgical resection. World J Surg 2019;43:3153–60.

[30] Wu YF, Chu SC, Chang BS, Cheng YT, Wang TF. Hematologic markers as prognostic factors in nonmetastatic esophageal cancer patients under concurrent chemoradiotherapy. Biomed Res Int 2019;2019:1263050.

[31] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

[32] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test 1997;315:629–34.

[33] Song W, Tian C, Wang K, Zhang RJ, Zou SB. Preoperative platelet lymphocyte ratio as independent predictors of prognosis in pancreatic cancer: a systematic review and meta-analysis. PLoS One 2017;12: e0178762.

[34] Asher V, Lee J, Innamaa A, Bali A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol 2011;13:499–503.

[35] Azab B, Shah N, Radbel J, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol 2013;30:432.

[36] Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg 2010;200:197–203.

[37] Gu X, Gao XS, Qin S, et al. Elevated platelet to lymphocyte ratio is associated with poor survival outcomes in patients with colorectal cancer. PLoS One 2016;11:e0163523.

[38] Koukourakis G. Which is the best neoadjuvant (pre-surgery) chemoradiation regimen for locally advanced rectal carcinoma? Short or long course of radiation therapy? Do we have new data? J BUON 2020;25:51–61.

[39] Liu X, Wang J, Hu K, et al. Neoadjuvant chemoradiotherapy or radiotherapy in patients aged 75 years or older with locally advanced rectal cancer. J Cancer 2020;11:3536–42.

[40] Sha YJ, Wu HT, Wen XY, Wang CB. [Clinical factors of pathological complete response after neoadjuvant chemoradiotherapy in rectal cancer]. Zhonghua Yi Xue Za Zhi 2020;100: 859–63.

[41] Thanikachalam K, Damarla V, Seixas T, et al. Neoadjuvant phase II trial of chemoradiotherapy in patients with resectable and borderline resectable pancreatic cancer. Am J Clin Oncol 2020.

[42] Wang J, Fan J, Li C, et al. The impact of chemotherapy completion on the efficacy of irinotecan in the preoperative chemoradiotherapy of locally advanced rectal cancer: an expanded analysis of the CinClare Phase III Trial. Clin Colorectal Cancer 2020.

[43] Zvirych VV, Michailovich YI, Gorbach OI, Khranovska NM. Immunohistochemical and genetic prognostic factors of neoadjuvant chemoradiotherapy efficacy in personalized treatment of local advanced rectal cancer. Wiad Lek 2020;73:589–96.

[44] Zhong W, Xue X, Dai L, Li R, Nie K, Zhou S. Neoadjuvant treatments for resectable rectal cancer: a network meta-analysis. Exp Ther Med 2020;19:2604–14.

[45] Kumar T, Pai E, Singh R, Francis NJ, Pandey M. Neoadjuvant strategies in resectable carcinoma esophagus: a meta-analysis of randomized trials. World J Surg Oncol 2020;18:59.

[46] Troxler M, Dickinson K, Homer-Vanniasinkam S. Platelet function and antiplatelet therapy. Br J Surg 2007;94:674–82.

[47] Plantureux L, Crescence L, Dignat-George F, Panicot-Dubois L, Dubois C. Effects of platelets on cancer progression. Thromb Res 2018;164 (Suppl 1):S40–7.

[48] Contursi A, Sacco A, Grande R, Dovizio M, Patrignani P. Platelets as crucial partners for tumor metastasis: from mechanistic aspects to pharmacological targeting. Cell Mol Life Sci 2017;74:3491–507.

[49] Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 2011;20:576–90.