Systematic Review and Meta-Analysis

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Prognostic role of platelet–lymphocyte ratio in colorectal cancer

A systematic review and meta-analysis

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Abstract

Many studies have been reported that platelet–lymphocyte ratio (PLR) may be associated with the prognosis of colorectal cancer (CRC), but the results are inconsistent. Current opinion on the prognostic role of the PLR in CRC is inconsistent and inconclusive. Therefore, we conduct a meta-analysis that combines these studies and to identify the prognostic value of PLR in patients with CRC. Data were retrieved from PubMed, EMBASE, Cochrane Library, and Web of Science databases that came from inception through January 2016. We extracted data from the characteristics of each study and analyzed the relationship between PLR and overall survival (OS), disease-free survival (DFS), or other prognosis in patients with CRC by using the hazard ratio (HR) and 95% confidence intervals (95% CIs). Of the 256 identified studies, 15 studies were included and a total of 3991 patients were included. In a meta-analysis, patients with an elevated PLR had a significantly lower OS (pooled HR, 1.53; 95% CI, 1.24–1.89; $P \leq 0.001$), DFS (pooled HR, 1.68; 95% CI, 1.07–2.62; $P = 0.023$). Even after sensitivity analyses and trim and fill method, high PLR remains significantly predictive poorer OS, but not DFS. In addition, our meta-analysis indicated that increased PLR is also significantly associated with the poor tumor differentiation [odds ratio (OR) 2.12; 95% CI, 1.45–3.08, $P < 0.001$)], the propensity toward depth of infiltration (OR 1.69; 95% CI, 1.20–2.39, $P = 0.003$), and recurrence in patients with CRC (HR, 2.71; 95% CI, 1.31–5.60, $P = 0.005$). This meta-analysis suggested that a high peripheral blood PLR can be used as a predictor of OS connected with clinicopathological parameters in patients with CRC, not DFS. These ratios may thus contribute to inform more personalized treatment decisions and predict treatment outcomes.

Abbreviations: PLR = platelet–lymphocyte ratio, CI = confidence interval, CRC= colorectal cancer, OS = overall survival, DFS = disease-free survival, HR= hazard ratio, TNM=tumor–node–metastasis, CRP = C reactive protein, NLR = neutrophil to lymphocyte ratio, OR= odds ratio.

Keywords: colorectal cancer, meta-analysis, platelet–lymphocyte ratio, prognosis

1. Introduction

Colorectal cancer (CRC) is one of the most common cancers of the digestive track and the third leading cause of cancer-related death in the world.[1] Although there have been rapid developments in diagnostic and treatment technologies, 5-year survival rates are not promising for postsurgery of CRC as result of tumor local recurrence or distal metastasis.[2,3]

Currently, the classical TNM staging system has been commonly considered the suitable methods to estimate the outcomes in patients with CRC, which focuses on tumor, nodes, distal metastasis. As "gold standard" for guiding therapy,[4] these systems are also limited for predicting the prognosis precisely and guiding the clinical practice appropriately, because many patients with the same stage turned out to be significantly heterogeneous prognosis.[5,6] Therefore, it is vital to seek appropriate prognostic factors for these patients in order to choose patients for systematic treatment.

Recently, the systemic inflammation status is revealed to be associated with the prognosis of solid tumors.[7,8] Some sensitive biomarkers can be obtained before pretreatment, which could be novel and convenient for these patients to design the appropriate therapeutic strategy and assess prognosis. Studies have demonstrated that biomarkers may provide insight into resectability of carcinoma than conventional pathological staging classifications.[9,10] Inflammatory markers contain typical C-reactive protein (CRP) in several cancers, frequently reported neutrophil to lymphocyte ratio (NLR) in various types of cancer, and platelet–lymphocyte ratio (PLR) and so on.[11–13] The high CRP was regarded as the relationship with poor prognostic factor of cancer,[14] and a promising predictor of recurrence and prognosis in patients with rectal cancer treated by chemoradiotherapy.[15] An elevated NLR has been found to be an indicator of poor prognosis in patients with CRC.[16] As for PLR, owing to the variance in the study design or relatively limited sample sizes,

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some research showed a decreased survival in patients with elevated PLR,[17–24] whereas others did not demonstrate the relationship between prognosis and PLR.[15,25–30] Until now, there was no meta-analysis accessing the prognostic utility of PLR in patients with CRC.

Thus, we perform this meta-analysis to clarify the prognostic value of PLR for predicting CRC. To the best of our knowledge, it is the first meta-analysis investigated the association between elevated pretreatment PLR and clinical outcomes and clinicopathological parameters in CRC.

2. Methods

2.1. Data sources and searches

A systematic literature search was performed in January 2016. Our search strategy included terms for "PLR" [e.g., "(platelet to lymphocyte ratio," "platelet–lymphocyte ratio," "platelet-to-lymphocyte ratio"], and "CRC" [e.g., "colorectal cancer," "colon cancer," "rectal cancer"]. Using the above search term, PubMed, Embase, Cochrane Library, and Web of Science databases were queried. No language and publication type was restricted.

The institutional review board of the Shengjing Hospital Affiliated with China Medical University approved the study. All procedures were performed in accordance with the Declaration of Helsinki.

2.2. Study selection and data extraction

Studies meeting the following criteria were included: the diagnosis of CRC was diagnosed from pathological examination; the PLR was measured with a peripheral blood test before treatment and (or) the present clinical guidelines; association of pretreatment PLR with overall survival (OS), disease-free survival (DFS), or others relevant prognosis was informed; if studies' hazard ratios (HRs) were not directly reported, estimation of the HR could be reconstructed by other data[31]; if multiple articles were on the same study population partially overlapping patients, only the most complete and typical study was included. We excluded editorials, comments, abstracts, meetings, or case reports. The selection of studies scanned independently by 2 of the authors (DT and YF), and a third person (QS) was consulted to resolve any disagreements. The relevant information was collected, which contained the following: study information: the first author's last name, year of publication, study location, research time, and sample size; patient information: age, stage of disease, treatment method, and follow-up time; cutoff value of NLR, and HR, 95% CI or *P* value of PLR for OS and DFS.

2.3. Assessment of paper quality

The Newcastle–Ottawa Scale (NOS), which was designed for retrospective and prospective studies, was adopted to assess studies quality included in this research.[32] A high-quality study was defined as the study with ≥6 points on NOS.

2.4. Statistical analysis

We calculated pooled HRs from each study of HRs and their 95% CIs to estimate prognostic role of PLR in CRC patients. If there was significant heterogeneity ($I^2 \geq 50\%$ and $P < 0.1$), random effects (DerSimonian–Laird method) models were conducted to generate the pooled HRs/ORs. Otherwise, fixed-effects (Mantel–Haenszel method) were performed. Subgroup analysis was applied to explore the possible source of heterogeneity according to the origins of participants (East or West), the therapy of treatment (surgery or nonsurgery), cut-offs (single or multiple), sample size (large or small), and result of study (positive vs negative). ORs were used to estimate the association between PLR and clinicopathological characteristics. Egger linear regression test and Begg funnel plot test were used to evaluate publication bias.[33,34] A trim and fill method was applied to estimate asymmetry in the funnel plot.[35] All statistical analyses including graphical presentations were performed with STATA version 12.0 (StataCorp, CollegeStation, TX, USA). $P < 0.05$ was considered statistically significant.

3. Results

As shown in Fig. 1, we found that the initial search algorithm retrieved a total of 256 studies. After excluding 233 irrelevant or duplicate articles by screening the title and title and abstract, the left 23 full-text articles were reviewed. Of them, another 8 studies had to be excluded, as they were conference abstracts (n = 3), reports without associating PLR with survival parameters, such as OS or DFS (n = 2), or articles without sufficient data (n = 3). Finally, our meta-analysis included 15 studies with a total number of 3991 patients to assess the value of PLR as prognostic biomarkers in CRC. The basic characteristics of the 15 studies are summarized in Table 1. There were 14 studies that reported the association between the PLR and OS. Six studies evaluated the NLR for outcomes of patients. Of the 15 eligible articles, 4 studies were from China, 2 cohorts from the UK, 1 cohort from the Austria, 3 from the Korea, 3 from the Japan, 1 from Hungary, and 1 from Canada. Six groups in the original multivariate analysis directly provided HR, and there were 4 HRs coming from univariate analysis and 5 HRs deduced from survival curves. For the risk of OS, PLR was related with poor survival in 7 studies,[17–24] and the rest of studies did not show the relationship between the PLA and decreased survival.[15,25–30]

4. Meta-analysis

4.1. PLR and OS

There was significant heterogeneity between studies for categorized PLR ($I^2 = 55.80\%$; $P = 0.006$) in the 14 studies evaluating OS, so the random-effect model was performed to calculate the pooled HR, and its 95% CI. The pooled HR of 1.53 (95% CI, 1.24–1.89) indicated that patients with elevated PLR have shorter OS (Fig. 2A).

4.2. PLR and DFS

We observed a significant subtle positive association between PLR and the DFS of patients (synthesized HR, 1.68; 95% CI, 1.07–2.62; $P = 0.023$) after pooling the data with heterogeneity ($I^2 = 69.80\%$, $P = 0.005$), indicating that higher PLR values were likely to predict poor DFS (Fig. 2B).

4.3. Subgroup analysis and meta-regression

It is the heterogeneity that was significantly apparent in both pooled HR of OS ($I^2 = 55.8\%$, $P = 0.006$) and DFS ($I^2 = 69.8\%$, $P = 0.005$), so we tried to identify the source of heterogeneity in the present study. The subgroup analysis was stratified to evaluate HR of OS and by region (eastern vs western), major

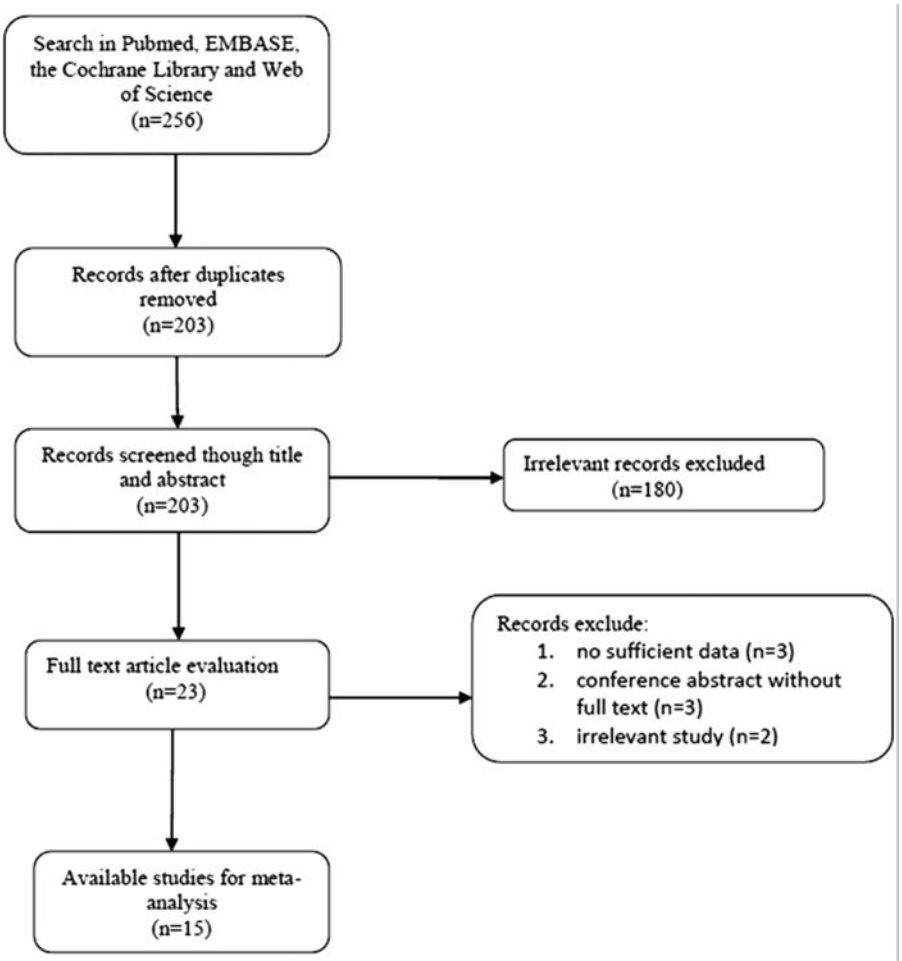

Figure 1. Flow chat of literature search and selection.

therapy (surgery vs non-surgery), respective cut-off value (single vs multiple), sample size (large vs small), and the result of HR (positive vs negative). In multivariate analysis, meta-regression was used to explain the source of the heterogeneity, and the rest subgroup of results showed that region of publication ($P=0.687$), therapeutic schedule ($P=0.853$), respective cut-off value ($P=0.117$), and sample size ($P=0.702$) did not obviously contribute to the source of heterogeneity (Table 2). But the result of studies (positive vs negative) might partly explain the source of heterogeneity ($P=0.009$). The results are the same with univariate analysis. Given the small number of studies for DFS, the meta-regression analysis was not conducted.

4.4. Sensitivity analyses

We removed 1 study each time to check the influence of the individual data set to the pooled HRs of OS. The combined HR and its 95% CIs were not obviously affected. The result confirmed the robustness of the outcome of this study (Fig. 3A). However, the combined HR of DFS did not show robustness of the outcome of this study after deleting 1 study each time (Fig. 3B).

4.5. Publication bias

There was publication bias in OS ($P=0.013$) and DFS ($P=0.025$) among these included studies as inferred through the visual inspection of the Begg funnel plot or Egger plot. Therefore, we needed to use a trim and fill method to estimate the asymmetry in the funnel plot. With filled unpublished studies, the recalculated pooled HRs of OS did not significantly alter by filling 5 unpublished studies (HR, 1.39; 95% CI, 1.14–1.69; $P=0.008$; Fig. 4A). However, the pooled HRs did not show the correlation between PLR and DFS (HR, 1.40; 95% CI, 0.95–2.01; $P<0.001$; Fig. 4B).

4.6. PLR and tumor clinicopathologic parameters

A total of 7 studies reported that the correlation between the PLR and tumor differentiation, and the combined data showed that high PLR was related with poor tumor differentiation (OR, 2.12; 95% CI, 1.45–3.08; $P<0.001$, Fig. 5A) with no heterogeneity. There were 6 retrieved cohorts about information on PLR and clinical stage, but the pooled estimates did not display that elevated pretreatment PLR tended to be linked with advancing clinical stage (OR, 1.29; 95% CI, 0.86–1.96; $P=0.220$; Fig. 5B). The combined estimates (OR, 1.69; 95% CI, 1.20–2.39; $P=0.003$; Fig. 5C) indicated that patients with higher PLR showed propensity toward depth of infiltration with no obvious heterogeneity. The synthesized data from 2 research showed that elevated PLR was associated with recurrence of CRC (HR, 2.71; 95% CI, 1.31–5.60; $P=0.005$; Fig. 5D).

Table 1

Main characteristics of all the studies included in the meta-analysis.

Study	Year	Country	Age, yrs (median and range)	Sample (male/female)	Survival analysis	HR (95% CI)	Treatment (predominant)	Cut-off	No. of different level PLR
Song et al[24]	2015	Korea	Mean: 52 (range 25–81)	83/94	OS	R (U)	Chemotherapy	150/150–300/300	73/78/26
Ozawa et al[23]	2015	Japan	≥65: N=156; <65: N=78	142/92	OS and DFS	R (E)	Resection	25.4*	181/53
Neal et al[21]	2015	UK	Mean: 64.8; (range 26–85)	192/110	OS	R (E)	Resection	150/150–300/300	133/129/40
Mori et al[20]	2015	Japan	Mean: 66.9 (range 35–89)	87/65	DFS	R (U)	Resection	150	84/68
Choi et al[17]	2015	Canada	Mean: 68.7 (range 28.3–92.6)	296/253	OS and DFS	R (U)	Resection	295	498/51
Ying et al[30]	2014	China	≥60: N=135; <60: N=70	144/61	OS and DFS	R (M)	Resection	176	126/79
Szkandera et al[29]	2014	Austria	Mean: 64 (range 27–95)	217/155	OS	R (M)	Resection	225	192/164/16†
Sun et al[28]	2014	China	Mean: 59 (range 46–72)	135/120	OS and DFS	R (M)	Resection	150/150–300/300	134/105/15
Neofytou et al[22]	2014	UK	>70: N=31; ≤70: N=109	88/52	OS and DFS	R (M)	Resection	150	82/58
Baranyai et al[25]	2014	Hungary	Mean: 67 (range: 56–78)	180/156	OS	R (E)	Resection	300	113/5
Liu et al[19]	2013	China	≥65: N=26; <65: N=114	46/94	OS	R (M)	Resection	250	115/25
Toiyama et al[15]	2013	Japan	≥65: N=42; <65: N=42	62/22	OS and DFS	R (E)	Chemotherapy; Radiation	150	52/32
Son et al[27]	2013	Korea	≥60: N=329; <60: N=295	368/256	OS and DFS	R (M)	Resection	300	604/16
He et al[26]	2013	China	>50: N=94; ≤50 ys: N=149	155/88	OS	R (E)	Chemotherapy	150/150–300/300	113/108/22
Kwon et al[18]	2012	Korea	≥60: N=107; <60: N=71	109/69	OS	R (M)	Resection	150/150–300/300	117/69/14

Study	Primary site (colon/rectum/ synchronous)	Tumor differentiation (well or moderate/ poor)	CEA	Follow-up (months) (Median and range)	Sample of distant metastasis	Stage	Summary results	NOS score
Song et al[24]	125/52	NR	>5 ng/mL N=140 ≤5 ng/mL N=31	8.3 (0.8–70)	NR	III–IV	Positive (OS)	4
Ozawa et al[23]	139/42	139/82/13	NR	64 (1–173)	0	II	Positive (OS) Positive (DFS)	7
Neal et al[21]	153/149	NR	≥200 ng/mL N=16; <200 ng/mL N=286	29.7 (4–96)	302	IV	Positive (OS)	7
Mori et al[20]	NR	NR	≥5 ng/mL N=72 <5 ng/mL N=85	NR	NR	I–III	Positive (DFS)	6
Choi et al[17]	470/77	101/418/30	NR	48 (0–124.8)	0	I–III	Positive (OS)	8
Ying et al[30]	140/65	NR	NR	NR	NR	I–III	Negative (OS)	6
Szkandera et al[29]	372	NR	NR	68 (1–190)	0	II–III	Negative (OS)	7
Sun et al[28]	255	203/52	≥5 ng/mL N=94 <5 ng/mL N=161	60	0	I–III	Negative (OS); Negative (DFS)	8
Neofytou et al[22]	NR	NR	NR	33 (1–103)	140	IV	Positive (OS); Positive (DFS)	8
Baranyai et al[25]	218/118	50/221/65	NR	NR	118	I–IV	Negative (OS)	4
Liu et al[19]	70/	7/91/42	NR	60	NR	I–IV	Positive (OS)	6
Toiyama et al[15]	84	73/11	>5 ng/mL N=38; ≤5 ng/mL N=46	56 (2–147)	0	I–III	Negative (OS); Negative (DFS)	6
Son et al[27]	624	NR	≥5 ng/mL N=172 <5 ng/ml N=450	42 (1–66)	0	I–III	Negative (OS) Positive (DFS)	6
He et al[26]	175/68	NR	NR	20.54 (2.53–86.97)	NR	IV	Negative (OS)	6
Kwon et al[18]	114/96	103/81/16	≥5 ng/mL N=44 <5 ng/mL N=156	33.3 (NR)	8	I–IV	Positive (OS)	6

"M" means the HR comes from multivariate analysis, "U" means the HR comes from univariate analysis.

DFS = disease-free survival, HR = hazard ratio; obtained by reporting in text (R) or estimating (E), NOS = Newcastle–Ottawa Quality Assessment Scale, NR = not reported, OS = overall survival, PLR = platelet to lymphocyte ratio.

* The cut-off values were determined by using a receiver-operating characteristic (ROC) curve analysis in the study.

† The cut-off values were unknown.

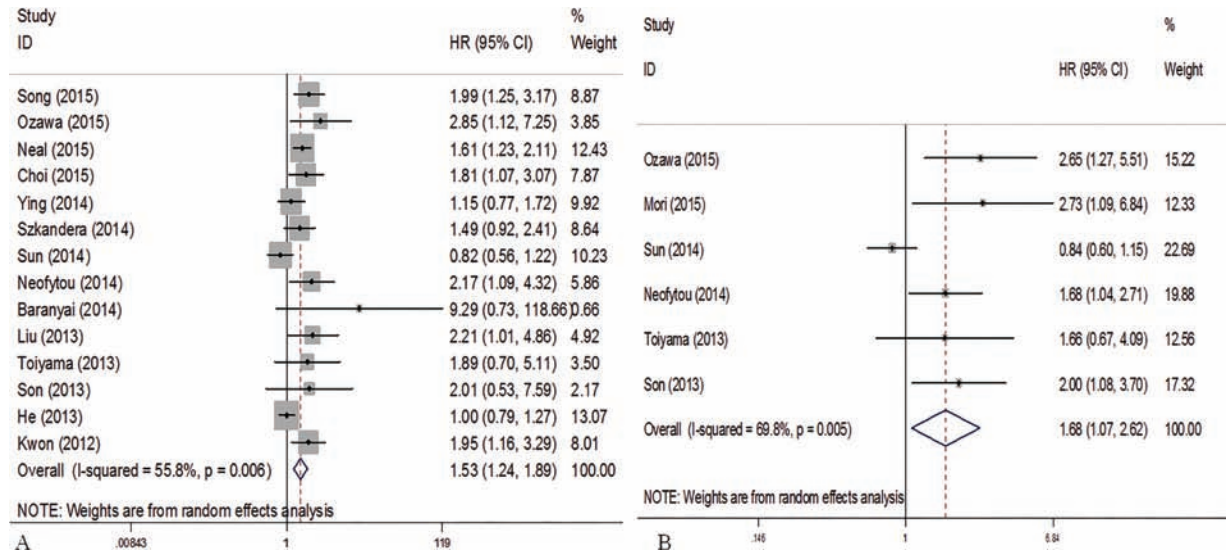

Figure 2. (A) Meta-analysis of the association between elevated PLR and OS in patients with CRC, and (B) Forest plot of studies evaluating the association between PLR and DFS in CRC.

5. Discussion

Our meta-analysis, including 15 individual studies of 4001 patients, demonstrated that elevated PLR was associated with poor OS through a random-effects model, but not DFS, in patients with CRC. In addition, subgroup analyses suggested that a high PLR was an effective prognostic factor for poor survival patients who underwent resection, but we did not find the correlation between the elevated PLR and prognosis of patients who received nonsurgery. We also found that elevated PLR was related with poor tumor differentiation, T grade development, and recurrence. This finding suggested a potential role for PLR as a predictor of survival, particularly in terms of postresection follow-up.

The systemic inflammatory response plays an important role in the progression of numerous cancers through genetic mutations, genomic instability, and epigenetic modifications, tumor metastasis, and cancer cell proliferation during different stages of tumor development.[8,36] Recent research have shown platelet secreting several angiogenic and tumor growth factors, such as vascular endothelial growth factor and platelet-derived growth factor, which might influence tumor progression, and also release microparticles that help tumor cells escape from the elimination of natural killer.[37,38] On the contrary, lymphocytes are basic components of the adaptive and innate immune system and the cellular basis of immunosurveillance and immunoediting, and $CD8^+$ and $CD4^+$ T-lymphocyte interaction among each other could be proven to induce tumor cell apoptosis in antitumor

Table 2

Summary of the subgroup analysis and the meta-regression results.

		Random-effects model		Heterogeneity	Meta-regression
Analysis	**NO.**	**HR (95% CI)**	***P*1 value**	***P*2 value**	***P*3 value**
Overall survival	14	1.53 (1.24 to 1.89)	<0.001	0.006	
Subgroup 1: Area					0.687
Eastern	9	1.45 (1.09–1.93)	0.012	0.008	
Western	5	1.68 (1.37–2.06)	<0.001	0.614	0.853
Subgroup 2: treatment					
Surgery	11	1.57 (1,25–1.98)	<0.001	0.047	
Nonsurgery	3	1.45 (0.83–2.51)	0.189	0.022	
Subgroup 2: cut-off					0.117
Single cut-off	9	1.64 (1.31–2.00)	<0.001	0.461	
Multiple cut-offs	5	1.35 (0.97–1.88)	0.076	0.001	
Supgroup 3: sample size					0.702
<200	4	2.06 (1.48–2.85)	<0.001	0.991	
≥200	10	1.40 (1.10–1.78)	0.006	0.008	
Supgroup 4: result of study					0.009
Positive	7	1.83 (1.83–1.58)	<0.001	0.882	
Negative	7	1.13 (0.89–1.44)	0.303	0.180	
Disease-free survival	6	1.68 (1.07–2.62)	0.023	0.005	

For OS, subgroup analyses were performed with random-effect model by treatment (surgical vs nonsurgical), study location (Eastern vs Western regions), cut-off value for NLR (single cut-off vs multiple cut-offs), sample size (<200 vs ≥200), and result of study (positive vs negative). Meta-regression analysis was applied.95% CI = 95% confidence interval, HR = hazard ratio, NO = number of studies (cohorts), OR = odds ratio.

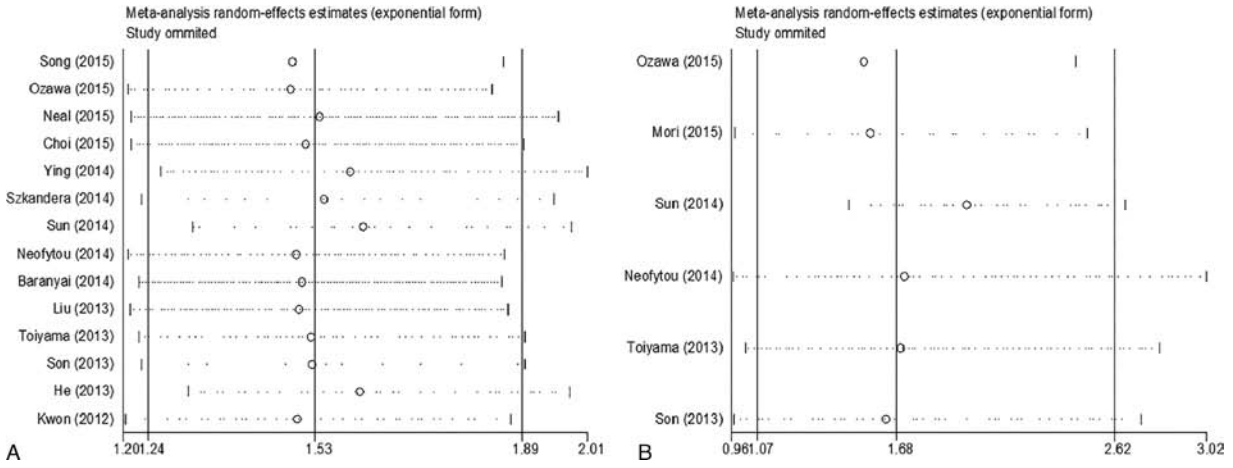

Figure 3. (A) Sensitivity analyses for confirming robustness of OS by removing 1 study each time, while (B) the corresponding pooled HRs of DFS were materially changed by deleting each time.

reaction of the immune system, which has been demonstrated to increase the survival of patients for the efficacy of chemotherapy in CRC patients.[39–41] Taken together, the relative ratio of elevated platelets and decreased lymphocytes predicts the prognosis of patients with CRC. Current opinion on the prognostic role of the PLR in CRC is inconsistent and inconclusive.

Our results of meta-analysis indicated that pretreatment PLR was predictive of OS. As routinely available and less expensive in many hospitals, PLR tests may be widely applied in prognosis of patients with CRC, especially for curative resection. However, we did not find that elevated PLR was related with the combined DFS after adjusting for heterogeneity and publication bias. This result of study may come from limiting studies.

There are still some limitations in our meta-analysis. First, the majority of the enrolled studies in our meta-analysis were retrospective, which led to be more prone to some biases. Second, heterogeneity was observed among the included studies for OS and DFS. The results of our meta-regression suggested that the result of HR is a vital source of heterogeneity among the included studies. In addition, many other possible factors could cause the heterogeneity, such as histology type, TNM stage differences, study region, treatment method, PLR cutting value, and estimate method of HR. After sensitivity analyses, prognostic value was not weakened. Third, there were 5 HRs of studies that recalculated the HR on the basis of the method reported by Parmar et al,[31] which also contributed to the heterogeneity of pooled HR. Moreover, there is another inevitable problem that is publication bias. Studies are easier to be published with positive results. Through trim and fill analysis, the outcome of this study with OS upholds the prognostic role of PLR in CRC patients. However, the conjoined HR of DFS was undermined after sensitivity analyses and "trim and fill" analysis. Additional large cohorts of prospective studies are needed to correct for heterogeneity and publication bias.

In conclusion, the pretreatment PLR is a useful factor to predict the OS in CRC and connected with clinicopathological parameters, not for DFS. These ratios may thus contribute to inform more personalized treatment decisions and predict treatment outcomes.

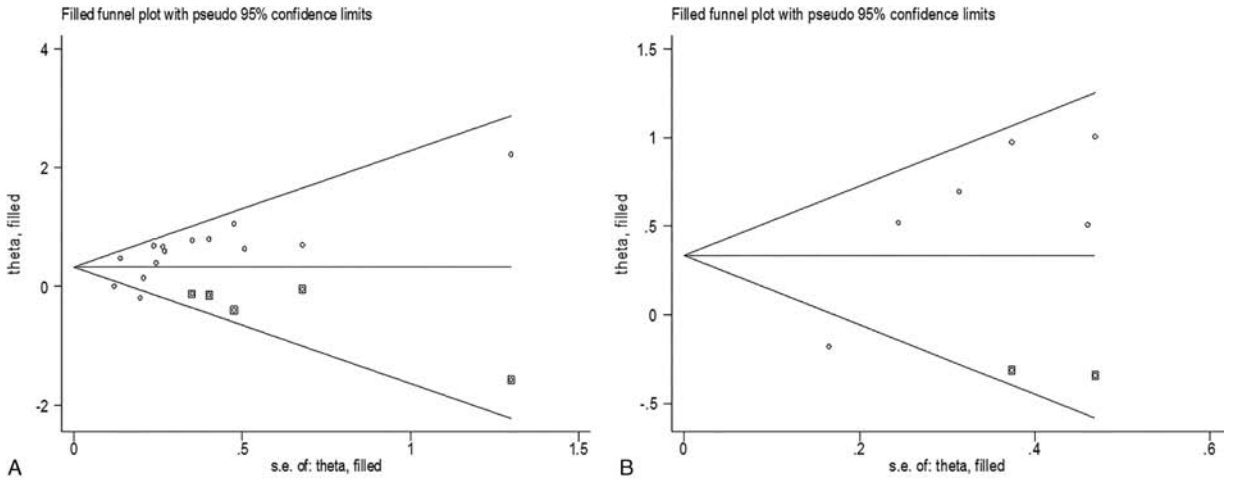

Figure 4. Funnel plot adjusted using a trim and fill method for (A) OS, and (B) for DFS. Diamonds: Included studies; diamonds in squares: Presumed missing studies.

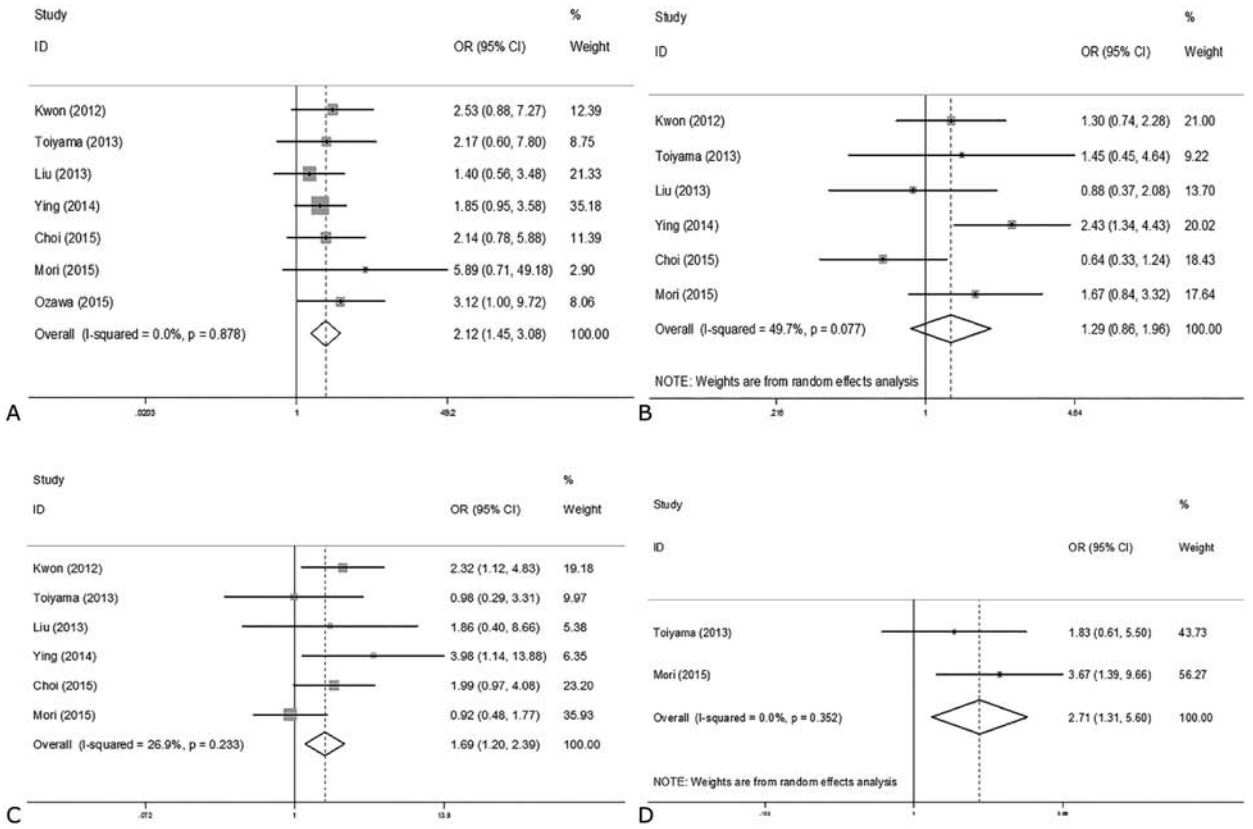

Figure 5. Forest plots showing the odds ratio (OR) and the corresponding 95% confidence intervals (CIs), describing the association between elevated PLR and clinicopathological parameters. (A) Degree of tumor differentiation (poor vs well or moderate); (B) clinical stage (I+II vs III+IV); (C) depth of infiltration (T1+T2 vs T3 +T4); (D) tumor of recurrence (yes vs no).

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