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Original Article

Platelet to lymphocyte ratio might be a prognostic factor of colorectal cancer (CRC): a meta-analysis

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Abstract: Colorectal cancer (CRC) is the third most prevalent cancer in the world. Recent reports have demonstrated that there is a relationship between Platelet-lymphocyte ratio (PLR) and survival of CRC. However, the results were inconsistent. We carried out a PubMed (Medline), EMBASE database search covering all published articles. The strength of association between PLR and overall survival (OS) of CRC was estimated by pooled ORs with corresponding 95% CIs. Thirteen independent studies were included in this meta-analysis, which were involved 3896 CRC patients. PLR was associated with a significantly shorter OS of CRC (OR=1.54; 95% CI, 1.37-1.73; I^2=23%). In the race subgroup analysis, both Asians (OR=1.70; 95% CI, 1.43-2.01; I^2=11%) and Caucasians (OR=1.42; 95% CI, 1.21-1.67; I^2=26%) with higher PLR had shorter OS. In the subgroup analysis according to site of CRC, PLR was associated with shorter OS of colon cancer (OR=1.84; 95% CI, 1.30-2.61; I^2=0%). In conclusion, this meta-analysis suggested that PLR might be a potential novel biomarker for prognosis of CRC.

Keywords: Colorectal cancer, PLR, meta-analysis, overall survival

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer in the world [1]. Previous studies have suggested that the mechanisms of CRC development is complex, involving multiple processes, such as inflammation, alterations in DNA synthesis and damage repair, cell survival and apoptosis, etc. [2]. Inflammation has been shown to enable various cancer characteristics, thus affecting prognosis. Recent evidence has indicated that relative differences in neutrophil, platelet and lymphocyte counts, and platelet-lymphocyte ratio (PLR) are systemic indicators of prognosis [3]. Recent reports have demonstrated that there is a relationship between PLR and survival of CRC [4-17]. However, the results were inconsistent. This meta-analysis quantitatively assesses the results from published studies to provide a more precise estimate of the association between PLR and overall survival (OS) of CRC.

Methods

Search strategy

We carried out a PubMed (Medline), EMBASE database search covering all published articles with a combination of the following key words: "platelet-lymphocyte ratio or platelet to lymphocyte ratio" and "Colorectal cancer or CRC". In addition, we searched for potentially relevant studies by checking the titles and abstracts to retrieve any other eligible studies.

Selection criteria

Eligible studies included in this meta-analysis were in accordance with the following criteria: a) they were studies which explored the association between PLR and OS of CRC; b) they provided information about odds ratios (ORs) with 95% confidence intervals (95% CIs) or other available data for estimating them. The main exclusion reasons were insufficient formation for data extraction, case only studies, repeated or overlapped publications.

Data extraction

The following information was extracted from all eligible studies independently by two investigators: first author's name, year of publication, ethnicity, age, site, sample size, follow-up duration, and adjustment. As regard to disagreements, the two investigators negotiated with each other to reach a consensus finally.

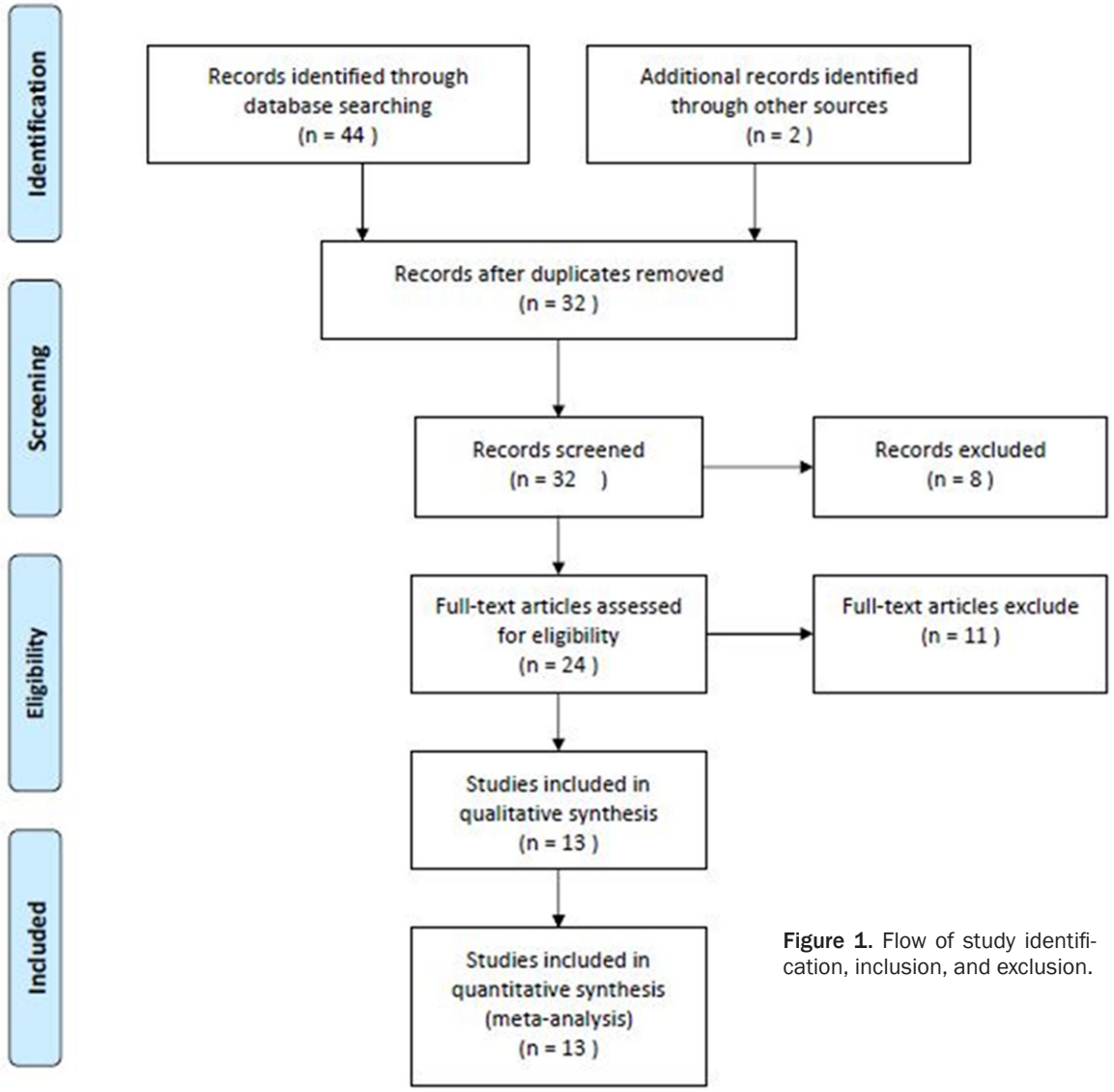

Figure 1. Flow of study identification, inclusion, and exclusion.

Statistical analysis

The strength of association between PLR and OS of CRC was estimated by pooled ORs with corresponding 95% CIs. Heterogeneity assumption was assessed via the χ^2-based Q-test. The significance level suggested a statistically significant heterogeneity among the studies when P<0.05 for the Q-test. Pooled ORs were evaluated by the fixed effects model when P>0.05 in Q test; otherwise, the random-effects model was adopted. Funnel plots and Begg' test were used to evaluate potential publication bias (P<0.05 was considered as representative of statistical significance). Sensitivity analysis was carried out to examine the stability of the result by removing each study in turn. All statistical analyses involved in this meta-analysis were performed with the STATA software version 12.0 (Stata Corporation, College Station, TX, USA). P<0.05 was regarded statistically significant.

Results

Study characteristics

Based on the search criteria, 44 studies were obtained initially through literature search from the PubMed and EMBASE web databases and 14 were excluded after reviewing abstracts. In the rest 32 studies, 19 were removed. Therefore, as displayed in **Figure 1**, 13 independent studies concerned with association between

Table 1. Characteristics of the included studies

First author	Year	Ethnicity	Mean Age	Site	Follow-up Month	Sample Size	Adjusted for
Kwon	2012	Asian	64	Colorectal	33.6	200	Sex, Positive lymph node ratio, Differentiation, NLR, Stage, CEA
Carruthers	2012	Caucasian	63.8	Rectal	37.1	160	NA
He	2013	Asian	56	Colorectal	21.9	243	CEA, NLR
Son	2013	Asian	60	Colon	42	624	Stage, CEA, Grade, Age, NLR
Szkandera	2013	Caucasian	64	Colon	68	372	Age, lymphovascular invasion, clinical stage
Neofytou	2014	Caucasian	65	Colorectal	33	140	Age, adjuvant chemotherapy, NLR
Ying	2014	Asian	60	Colorectal	NA	205	Sex, Age, Location, TNM, Grade, Chemotherapy, NLR
Azab	2015	Caucasian	68	Colorectal	41	580	Age, Stage, Lymph nodes, Surgery
Choi	2015	Asian	68.7	Colorectal	48	549	NA
Li	2015	Asian	62.9	Colon	NA	110	Age, NLR, CA199, Differentiation, Lymph nodes, Chemotherapy
Neal	2015	Caucasian	64.8	Colorectal	29.7	302	NA
Ozawa	2015	Asian	65	Colorectal	64	234	NA
Song	2015	Asian	52	Colorectal	3.1	177	NA

NLR, Neutrophil to lymphocyte ratio; NA, not available.

Table 2. Results of this meta-analysis

	OR (95% CI)	*P* Value	I^2 (%)	*P* Value
Overall	1.54 (1.37-1.73)	<0.00001	23	0.22
Ethnicity				
Asian	1.70 (1.43-2.01)	<0.00001	11	0.35
Caucasian	1.42 (1.21-1.67)	<0.0001	26	0.25
Site				
Colon	1.84 (1.30-2.61)	0.0006	0	0.57
Follow-up				
<40 months	1.46 (1.26-1.69)	<0.00001	23	0.26
>40 months	1.88 (1.46-2.42)	<0.00001	0	0.73
Sample size				
<300	1.69 (1.43-2.01)	<0.00001	16	0.30
>300	1.42 (1.21-1.67)	<0.0001	20	0.29
Adjust				
Yes	1.65 (1.39-1.95)	<0.00001	0	0.49
No	1.45 (1.24-1.71)	<0.00001	38	0.15

PLR and OS of CRC were finally included in this meta-analysis, which were involved 3896 CRC patients. The major characteristics of the 8 studies were summarized in **Table 1**.

Results of meta-analysis

The results of the association between PLR and OS of CRC are summarized in **Table 2**. PLR was associated with a significantly shorter OS of CRC (OR=1.54; 95% CI, 1.37-1.73; I^2=23%; **Figure 2**). In the race subgroup analysis, both Asians (OR=1.70; 95% CI, 1.43-2.01; I^2=11%) and Caucasians (OR=1.42; 95% CI, 1.21-1.67; I^2=26%) with higher PLR had shorter OS. In the subgroup analysis according to site of CRC, PLR was associated with shorter OS of colon cancer (OR=1.84; 95% CI, 1.30-2.61; I^2=0%). In the subgroup analysis by follow-up duration, both long duration and short duration were associated with poorer prognosis (OR=1.46; 95% CI, 1.26-1.69; I^2=23% and OR=1.88; 95% CI, 1.46-2.42; I^2=0%, respectively). In the subgroup analysis by sample size, both large studies and small studies showed similar results (OR=1.69; 95% CI, 1.43-2.01; I^2=16% and OR=1.42; 95% CI, 1.21-1.67; I^2=20%, respectively). In the subgroup analysis by adjustment, the results were also statistical significantly (**Table 2**). Sensitivity analysis was performed to test the effect of single study on the combined results. By sequentially omitting each study one by one, the significance of pooled ORs were not influenced excessively (**Figure 3**), implying the results of this meta-analysis were relatively stable and credible. **Figure 4** showed the publication bias plot in the meta-analysis. The plots shape, as well as the *P* value from Egger's regression (P=0.01), showed evidence of publication bias.

Discussion

In this meta-analysis, we investigated the association between PLR and OS of CRC including 3896 CRC patients. We found that CRC patients with elevated PLR showed short OS. In the stratified analysis by ethnicity, the significant

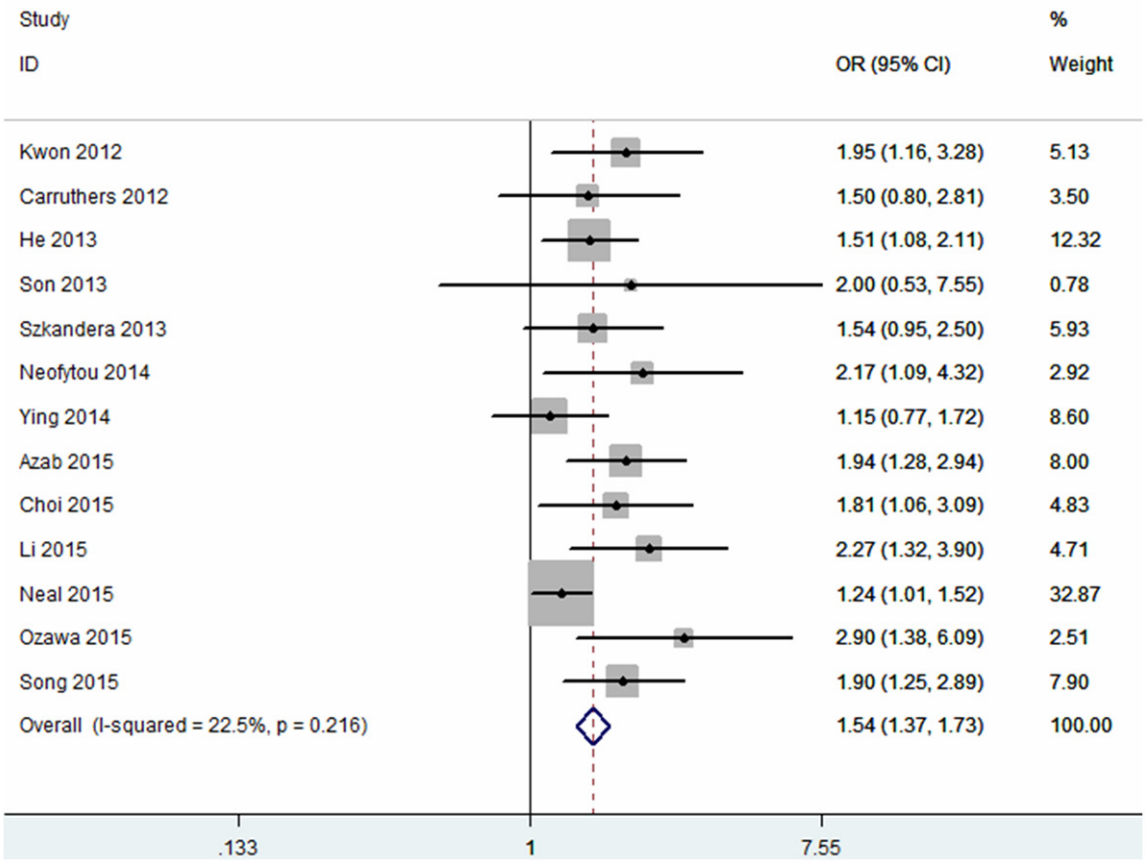

Figure 2. Meta-analysis for the association between PLR and OS of CRC.

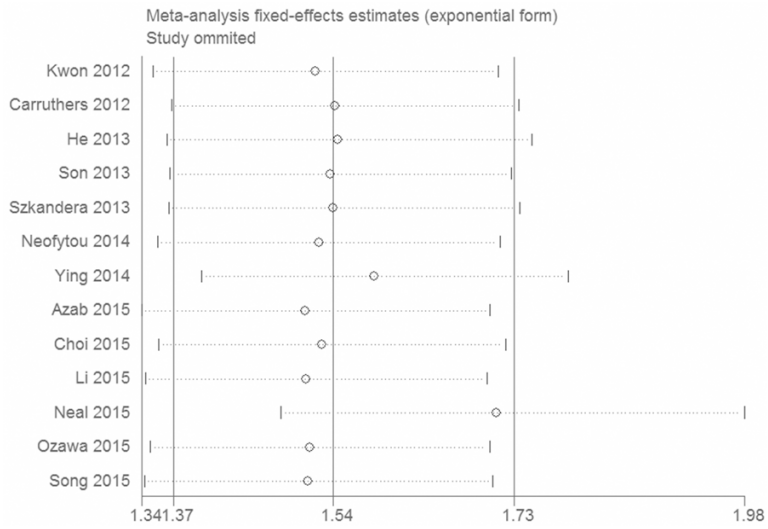

Figure 3. Sensitivity analysis for the association between PLR and OS of CRC.

association was observed in Asians and Caucasians. In the stratified analysis by site of CRC, PLR significantly associated with short OS of colon cancer risk. We also performed sensitivity analysis by excluding studies to verify the stability of results.

Many cancers arise from sites of infection, chronic irritation and inflammation [18]. Inflammatory responses play decisive roles at different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis [19]. Inflammation also affects immune surveillance and responses to therapy. Nakamura et al. found that PLR is an important predictor of prognosis in patients with recurrent cervical cancer following concurrent chemoradiation therapy (CCRT) [20]. Lian et al. suggested that PLR and NLR measurements can provide important diagnostic and prognostic results in patients with resectable

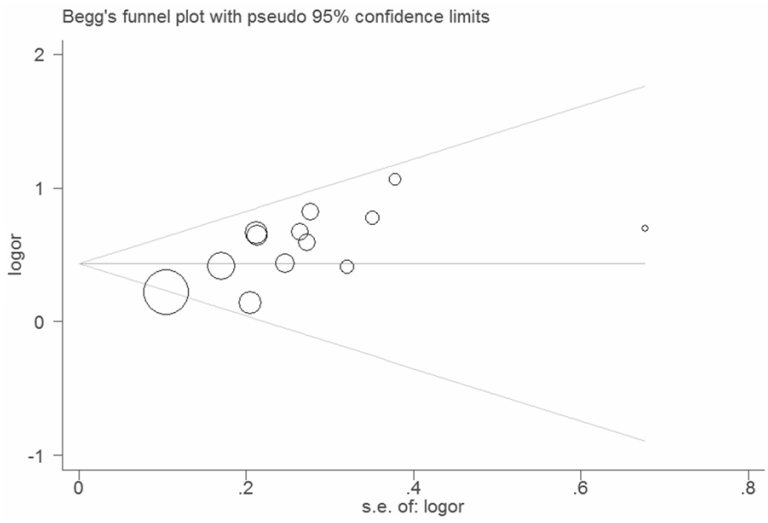

Figure 4. Funnel plot for the association between PLR and OS of CRC.

gastric cancer [21]. Que and colleagues indicated that Elevated preoperative PLR as an independent prognostic factor is superior to NLR in predicting clinical outcome in patients with soft tissue sarcoma [22]. Additionally, Demir et al. found that PLR changes indicate systemic inflammation that occurs after RAI therapy because of thyroid remnant tissue ablation [23]. Akdag et al. found that increased PLR correlates with the severity of calcific aortic stenosis [24]. Durmus et al. found that PLR were higher in heart failure patients than in age-sex matched controls [25]. Ahbap et al. reported that ESRD patients on maintenance HD revealed higher values for NLR and PLR in patients with higher levels of inflammation along with a significant positive correlation of both NLR and PLR with hs-CRP levels [26].

Although we have presented a comprehensive study of the association between PLR and OS of CRC, several limitations should be noted. Firstly, the limited number of the publications enrolled in our study and the sample size of each report were relatively small. Secondly, most of the enrolled publications were Asians, and none of these enrolled publications are African. Thirdly, some studies were based on single-factor estimates, which may result in a serious confounding bias, for the reason of lack of original data, without adjustment for age, sex and other factors.

In conclusion, this meta-analysis suggested that PLR might be a potential novel biomarker for prognosis of CRC.

Disclosure of conflict of interest

None.

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