Original Article

Prognostic prediction of the platelet-to-lymphocyte ratio in hepatocellular carcinoma: a systematic review and meta-analysis

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Background: Platelet-to-lymphocyte ratio (PLR) has been used to predict the prognosis of patients with hepatocellular carcinoma (HCC) with inconsistent results. This meta-analysis aimed to clarify the prognostic value of PLR in patients with HCC.

Methods: We systematically retrieved relevant literature published in the PubMed, Embase, Web of Science, and Cochrane databases up to November 20, 2021. The primary outcomes were the hazard ratios (HRs) and their 95% confidence intervals (CIs) for overall survival (OS), and secondary study outcomes were recurrence-free survival (RFS), disease-free survival (DFS), progression-free survival (PFS). All statistical analyses were conducted by Review Manager 5.4.1 and STATA 16.0 software.

Results: A total of 21 studies comprising 8,779 patients were included in this meta-analysis. Pooled results suggested that a high PLR was significantly associated with poor OS (HR: 1.34, 95% CI: 1.18–1.52, $P<0.00001$; $I^2=59\%$, $P=0.0005$), RFS or DFS (HR: 1.35, 95% CI: 1.13–1.63, $P=0.001$; $I^2=69\%$, $P=0.002$), and PFS (HR: 1.55, 95% CI: 1.09–2.22, $P=0.02$; $I^2=73\%$, $P=0.02$). The subgroup analysis for OS showed, when the PLR cutoff value was greater than 150, the heterogeneity decreased to 0 (HR: 1.48, 95% CI: 1.33–1.68, $P<0.00001$; $I^2=0\%$, $P=0.56$); when the HBsAg positive population was increased to 100%, the heterogeneity decreased to 0 (HR: 1.46, 95% CI: 1.22–1.73, $P<0.0001$; $I^2=0\%$, $P=0.45$); compared with other regions in the world, it was more significant in China (HR: 1.43, 95% CI: 1.26–1.62, $P<0.00001$; $I^2=52\%$, $P=0.01$). In addition, scatter plot showed that the HR was negatively correlated with the proportion of patients with liver cirrhosis.

Conclusions: This meta-analysis suggests that PLR is a negative correlation prognostic biomarker for HCC, high PLR values indicate poor OS, RFS, DFS and PFS, especially in hepatitis B virus (HBV) related patients.

Keywords: Platelet-to-lymphocyte ratio (PLR); hepatocellular carcinoma (HCC); survival; meta-analysis; systematic review

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide (1). The occurrence of HCC is closely related to the occurrence of hepatitis B virus/hepatitis C virus (HBV/HCV) infected hepatitis and cirrhosis. A large amount of evidence shows that chronic inflammation and immune response play an important role in tumor progression and prognosis (2). Routine clinical indexes such as platelets, lymphocytes, neutrophils and/or monocytes often do not change significantly in non-acute infected patients such as cancer patients, which cannot be used as the clinical biomarkers to predict the progress or improvement of the disease. However, many studies have found that the ratios of these conventional indicators, such as platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR), have good predictive value for the prognosis of cancer patients, these ratios are widely studied as predictive biomarkers in order to provide early warning for clinical treatment results in those patients with cancers (3-5). With the further elucidation of the role of platelets in tumors, PLR seems to be more effective in predicting the prognosis of tumors.

In many pathological conditions, the platelet-derived factors affect not only hemostasis but also immune response and tumor development. The increased number of platelets can suppress the antitumor immune responses derived from natural killer (NK) cells and activated T cells. The platelets can affect cancer development and metastatic progression by releasing vascular endothelial growth factor (VEGF) and other angiogenic cytokines (6,7).

A healthy immune system is necessary to control malignant diseases (8). Lymphocytes are the key immune cells in the antitumor immune response and can limit the proliferation and metastasis of tumor cells (9). Generally, cancer prognosis depends on the host immune response and tumor aggressiveness. A low lymphocyte count is usually associated with immunosuppression, indicating an inadequate immune response on the part of the host (10). Lymphopenia is commonly observed in patients with advanced cancers and correlates with poor prognosis in terms of overall survival (OS) and progression-free survival (PFS) in patients with various types of cancer (11) including small cell lung cancer (12), colorectal cancer (13), and sarcoma (14).

The PLR as a biomarker was investigated to predict the prognosis of HCC in many independent studies. However, the prognostic value of PLR in HCC patients remains to be clarified. In this study, the association between PLR and the prognoses of patients with HCC was investigated by meta-analysis. We present the following article in accordance with the MOOSE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1197/rc) (15).

Methods

Search strategy

We carried out a comprehensive literature search in the PubMed, Embase, Web of Science, and Cochrane databases up to November 20, 2021, with the following keywords: "PLR" or "platelet lymphocyte ratio" or "platelet to lymphocyte ratio" or "platelet-to-lymphocyte ratio" or "platelet-lymphocyte ratio" and "carcinoma, hepatocellular" or "carcinomas, hepatocellular" or "hepatocellular carcinomas" or "liver cell carcinoma, adult" or "liver cancer, adult" or "adult liver cancer" or "adult liver cancers" or "cancer, adult liver" or "cancers, adult liver" and "prognostic" or "prognosis" or "prognoses". Detailed search strategies were presented in Table S1. This systematic review and meta-analysis was registered on PROSPERO with registration CRD42021281803.

Inclusion and exclusion criteria

We conducted the study using the following inclusion criteria: (I) available full-text publication; (II) English language; (III) focus on patients diagnosed with HCC; (IV) OS and/or recurrence-free survival (RFS), disease-free survival (DFS), PFS, and identified a cutoff value to stratify low and high PLR. Articles that met any of the following criteria were excluded: (I) duplicate publications; (II) literature published as letters, reviews, conference abstracts, case reports, or expert consensus; (III) unable to directly obtain hazard ratio (HR) and 95% confidence interval (CI) data; (IV) studies with overlapping patients.

Paper screening and data extraction

Data extraction was performed independently by two researchers (DZL and XJH), disagreements were resolved by another researcher (JG), and those studies not meeting the inclusion criteria were excluded. The data extraction procedure followed the rules of MOOSE guidelines (15).

Quality assessment

The quality of each study was evaluated using the Newcastle-Ottawa Scale (NOS) score. The maximum score was 9, and studies with a NOS score ≥7 were considered high-quality studies (Table S2).

Statistical analysis

We used Review Manager 5.4.1 and STATA 16.0 software for data analysis. HR with corresponding 95% CI was used to evaluate the association between the PLR and clinical outcomes of patients with HCC. The I^2 and Q tests were applied to quantify the heterogeneity between eligible studies. When there was no statistically significant heterogeneity, we used the fixed-effects model for pooling the results; otherwise, the random-effects model was applied ($I^2>50\%$ and $P<0.05$ indicate significant heterogeneity). We also performed subgroup analyses to identify the sources of heterogeneity and analyze the factors related to clinical significance. Publication bias was evaluated by funnel plots, the Begg's test and the Egger's test. It was considered to have no publication bias when $P>0.05$. If a significant publication bias existed, a trim-and-fill analysis was performed. Sensitivity analyses were carried out to evaluate the stability of the results by excluding each study.

Results

Literature search

In total, 783 articles were identified from the 4 online databases (PubMed =154, Web of Science =398, Embase =220, and Cochrane =11), and 303 were removed due to duplication. After scanning the titles and abstracts, 443 articles were excluded, of these, 382 were unrelated, 5 were review papers, 1 was case report, 12 were conference abstracts, 8 were not English language, Then, 64 articles were retrieved for full-text evaluation. Among them, 20 studies involved liver transplantation, and 7 studies involved radiotherapy. We excluded these two groups in consideration of immunosuppressant therapy that patients received after liver transplantation and the effect of radiotherapy on platelets. We ruled out a study which focused on early recurrent HCC patients. Considering that ruptured hemorrhage may affect prognosis, we excluded a study of spontaneous ruptured HCC. There were overlapping samples in two or four studies. We excluded small sample studies among them and retained higher sample studies [included: Yang *et al.* (6), Yang *et al.* (16), Tian *et al.* (17), Shen *et al.* (18)]. As for PLR, we excluded a study due to PLR not at baseline and two studies due to PLR not as categorical variables (19,20). He *et al.* (21), Kabir *et al.* (22), and Dharmapuri *et al.* (23) reported the predictive value of the NLR-PLR score (combining the NLR score with the PLR score) in patients with HCC. Huang *et al.* (24) stratified PLR into three levels to assess the prognostic impact on HCC patients. These above articles were all excluded. Finally, 21 studies (6,16-18,25-41) were included in this systematic review and meta-analysis. A flow diagram of the study selection process is presented in *Figure 1*.

Characteristics of the included studies

These studies were published from 2015 to 2021. The 21 studies included a total of 8,779 patients. Seventeen reports were carried out in China, three in Japan, one in Turkey. The cutoff values of PLR in the included studies ranged from 75.3 to 167.7. Nineteen studies provided data on OS (all studies directly reported HRs by multivariate analysis). Six studies reported data on RFS. Two studies reported data on DFS. Three studies reported data on PFS. Because most patients were in the intermediate or advanced stages in studies focused on PFS, this part will be analyzed separately.

Eight studies included patients who underwent surgical resection. Three studies included patients who had undergone radiofrequency ablation (RFA). Three studies included patients who received a molecularly targeted agent (MTA). Three study included patients who received transarterial chemoembolization (TACE). One study included patients who were treated with the combination therapy of TACE and sorafenib. One study included patients who were treated with the combination therapy of TACE and RFA. Two studies included patients who received various treatment methods. Nineteen were retrospective cohort studies. Two were prospective cohort studies.

The reported mean/median age of patients ranged between 47.5 and 72.1 years, excluding five studies without exact age. A total of 19 studies reported the proportion of HBV patients (range, 13.4% to 100%). A total of 11 studies reported the proportion of liver cirrhosis patients (range, 15.8% to 91.0%). A total of 12 studies performed Barcelona Clinic Liver Cancer (BCLC) stage for patients, five studies which the proportion of patients with early-stage accounted for more than 50%, seven studies which patients with intermediate or advanced stage accounted for more than 50%.

Of all the included studies, the scores of quality assessment were ≥7 according to the NOS score (14 studies scored 7 and seven studies scored 8), which indicated

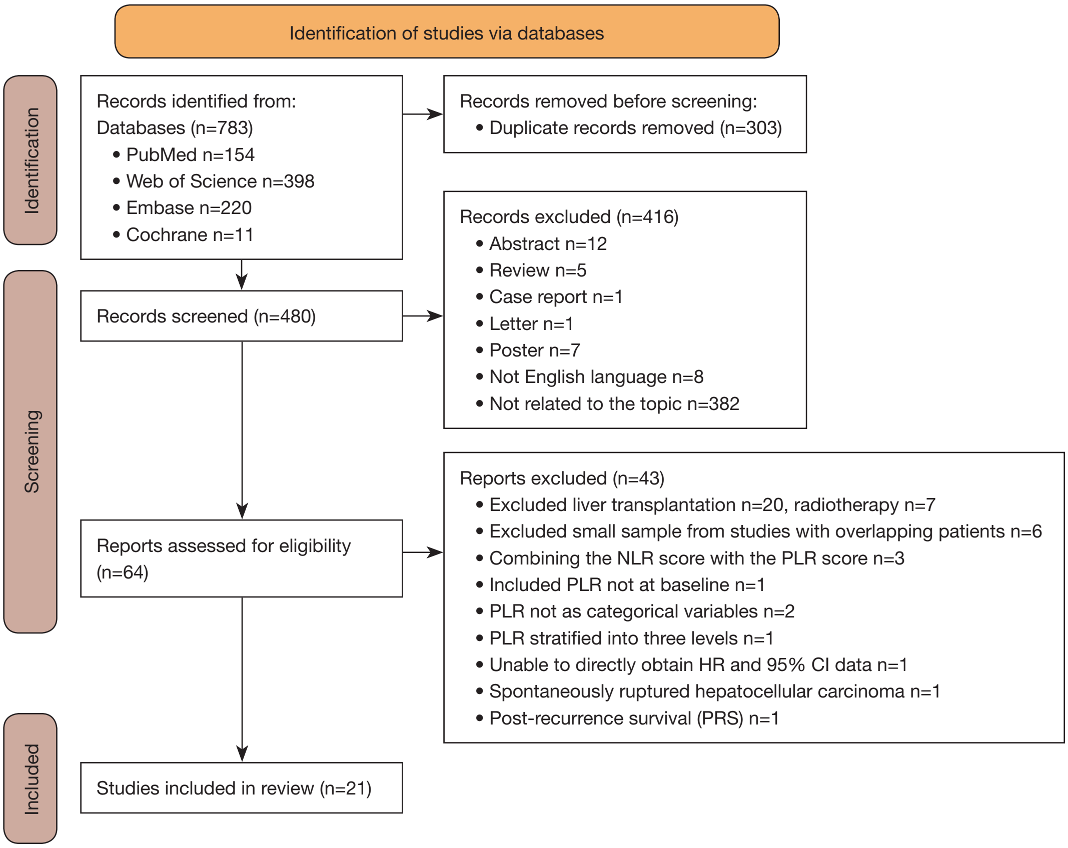

Figure 1 Selection of studies included in the analysis. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

that all enrolled articles were of high quality. The basic characteristics of the included studies were shown in *Table 1*.

Correlation between the PLR and OS

There were nineteen studies comprising 8,269 patients with HCC provided data for evaluating the relationship between the PLR and OS. We found that an elevated PLR had a close relationship with shorter OS in HCC, with a pooled HR of 1.34 (95% CI: 1.18–1.52, P<0.00001). Because the significant heterogeneity among the included studies (I^2=59%, P=0.0005), the pooled HR and 95% CI were calculated by a random-effects model (*Figure 2*).

Correlation between the PLR and RFS/DFS

Eight studies consisting of 4,387 patients with HCC reported an association between the PLR and RFS/DFS. The pooled data showed that a high PLR was a predictor of poorer RFS/DFS (HR: 1.35, 95% CI: 1.13–1.63, P=0.001), which was similar to the results of the PLR and OS. We used a random-effects model to calculate because there was a significant heterogeneity among these studies (I^2=69%, P=0.002) (*Figure 3*).

Correlation between the PLR and PFS

There were three studies that reported on the relationship between the PLR and PFS. The pooled HR indicated a significantly shorter PFS in patients with a high PLR (HR: 1.55, 95% CI: 1.09–2.22, P=0.02). According to the heterogeneity (I^2=73%, P=0.02), a random-effects model was used to analyze these data (*Figure 4*).

Subgroup analyses

There were 19 studies investigating the association between preoperative PLR and OS of HCC patients,

Table 1 The characteristics of the included studies for meta-analysis

Author	Year	Country	Study design	Age (years)	Male (n% of total)	Treatment	Cutoff value	N (high)/N (total)	NOS score	Outcome	HBsAg positive (n% of total)	Liver cirrhosis (n% of total)	BCLC stage (n% of total)
Shen *et al.* (18)	2019	China	RCS	NR	85.0	Hepatectomy	167.7	181/480	7	OS, RFS	87.8	65.4	A 51.7; B 48.3
Yang *et al.* (6)	2020	China	RCS	50.0 (median)	88.2	Hepatectomy	150.0	236/1,174	8	OS, RFS	100.0	60.7	0/A 59.2; B 40.8
Qin *et al.* (25)	2020	China	RCS	50.5 (mean)	83.8	Hepatectomy	150.0	NR/925	7	OS, RFS	NR	NR	0/A 42.5; B/C 57.5
Chen *et al.* (26)	2021	China	RCS	NR	81.7	RFA	75.3	212/382	7	DFS	80.1	NR	NR
Xin *et al.* (27)	2021	China	RCS	NR	19.1	RFA	125.3	158/256	7	OS, RFS	80.9	91.0	NR
Li *et al.* (28)	2020	China	RCS	50.0 (median)	88.8	Surgery 89.0%; surgery + ablation 2.0%; surgery + TACE 9.0%	132.4	135/545	7	OS	93.4	NR	NR
Yang *et al.* (16)	2018	China	RCS	47.5 (mean)	86.8	Hepatectomy	99.5	295/652	7	OS, DFS	95.6	83.3	0/A 54.1; B/C 45.9
Nakano *et al.* (29)	2021	Japan	PCS	72.1 (median)	80.0	Sorafenib or lenvatinib	122.8	NR/728	7	OS, PFS	17.0	NR	B 38.0; C 62.0
Itoh *et al.* (30)	2019	Japan	RCS	68.0 (median)	79.7	Hepatectomy	129.5	NR/281	7	OS	19.2	21.4	NR
Wu *et al.* (31)	2021	China	RCS	NR	83.6	Hepatectomy	117.1	NR/347	7	OS	86.5	64.0	0/A 50.4; B 4.9; C 44.7
Yılmaz *et al.* (32)	2021	Turkey	RCS	63.0 (median)	71.3	Sorafenib	112.0	103/150	7	OS	44.7	NR	A 30.7; B 69.3
Zhang *et al.* (33)	2021	China	RCS	55.0 (median)	86.0	TACE + sorafenib	100.0	157/314	8	OS, PFS	85.7	69.4	B 54.1; C 45.9
Tada *et al.* (34)	2021	Japan	RCS	72.0 (median)	77.0	Lenvatinib	150.0	89/283	8	OS	13.4	NR	0/A 11.7; B/C 87.3; D 1.0
Chen *et al.* (35)	2018	China	RCS	56.1 (mean)	74.9	RFA	131.8	NR/287	7	OS	61.3	75.2	NR
Tian *et al.* (17)	2016	China	RCS	56.0 (median)	87.7	TACE	96.1	61/122	8	OS	100.0	NR	NR
Ji *et al.* (36)	2016	China	RCS	51.0 (mean)	88.8	Hepatectomy	115.0	139/321	7	OS	87.5	78.8	NR
Wu *et al.* (37)	2020	China	RCS	NR	66.9	Hepatectomy	150.0	216/595	7	OS	NR	NR	NR
Pang *et al.* (38)	2018	China	RCS	52.2 (mean)	78.9	Hepatectomy 66.2%; RFA 33.8%	95.3	205/470	8	OS, RFS	100.0	NR	A 54.9; B 32.1; C + D 13.0
Long *et al.* (39)	2020	China	PCS	57.0 (mean)	66.6	TACE + RFA	100.0	27/48	7	OS, RFS	100.0	60.0	B 100.0
Xue *et al.* (40)	2015	China	RCS	53.0 (mean)	88.7	TACE	150.0	115/291	8	OS	78.4	15.8	B 62.5; C 37.5
Liu *et al.* (41)	2021	China	RCS	57.0 (median)	87.5	TACE	92.0	67/128	8	PFS	14.1	NR	NR

RCS, retrospective cohort study; PCS, prospective cohort study; NR, not report; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; N (total), total number of eligible patients; N (high), number of patients with high PLR; NOS, Newcastle-Ottawa Scale; OS, overall survival; RFS, recurrence-free survival; DFS, disease-free survival; PFS, progression-free survival; HBsAg, hepatitis B surface antigen; BCLC, Barcelona Clinic Liver Cancer.

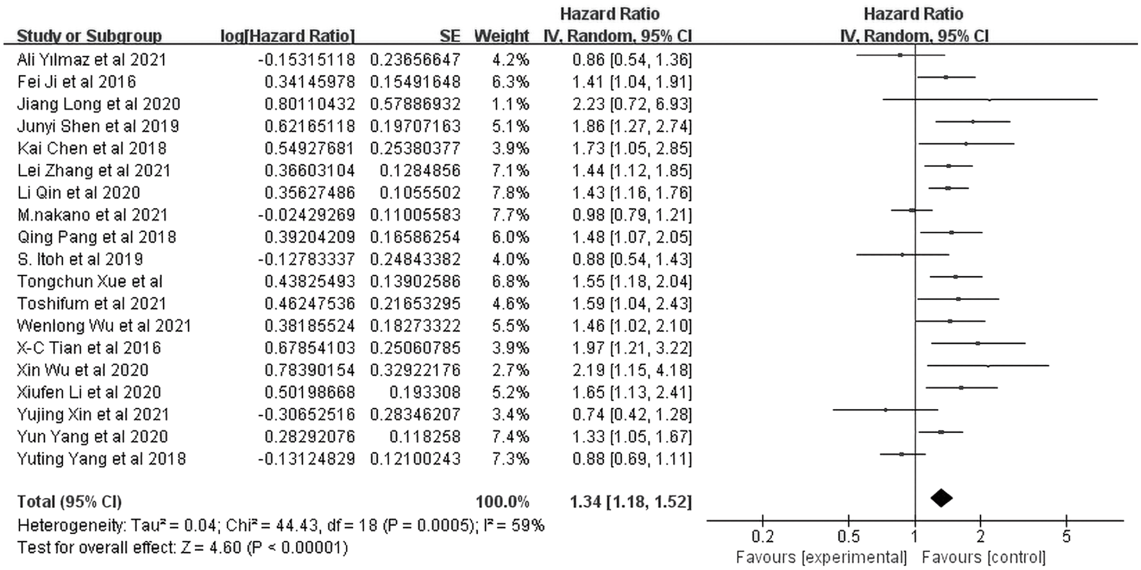

Figure 2 Forest plot of the association between PLR and OS in patients with HCC. SE, standard error; IV, interval variable; CI, confidence interval; PLR, platelet-to-lymphocyte ratio; OS, overall survival; HCC, hepatocellular carcinoma.

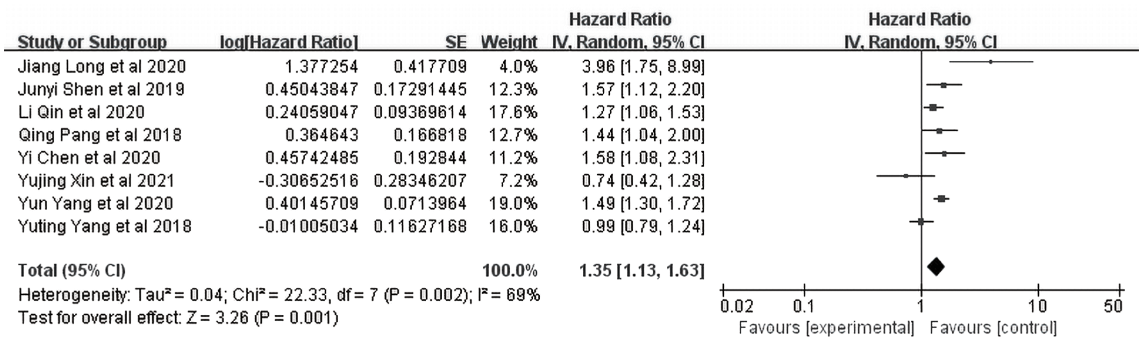

Figure 3 Forest plot of the association between the PLR and RFS/DFS in patients with HCC. SE, standard error; IV, interval variable; CI, confidence interval; PLR, platelet-to-lymphocyte ratio; RFS, recurrence-free survival; DFS, disease-free survival; HCC, hepatocellular carcinoma.

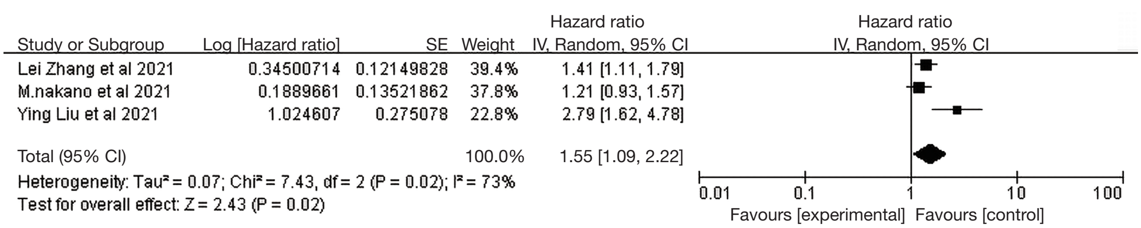

Figure 4 Forest plot of the association between the PLR and PFS in patients with HCC. SE, standard error; IV, interval variable; CI, confidence interval; PLR, platelet-to-lymphocyte ratio; PFS, progression-free survival; HCC, hepatocellular carcinoma.

high PLR was significantly associated with poor OS, but there was significant heterogeneity among these studies. We performed subgroup analyses to identify the potential sources of heterogeneity. In the subgroup, according to the treatment, we classified patients treated with TACE or MTA as unresectable group and those who received hepatectomy or RFA as resectable group. A higher correlation between the PLR and OS was found in all subgroups (HR: 1.32, 95% CI: 1.05–1.68, P=0.02; HR: 1.31, 95% CI: 1.11–1.55, P=0.002; HR: 1.70, 95% CI: 1.19–2.44, P=0.004). Although, the heterogeneity reduced to 0 in the mixed subgroup (I^2=0%, P=0.62), this subgroup was made up of two studies comprising 593 patients, the number of patients decreased significantly compared with the other two subgroups, it was not rigorous to say that the source of heterogeneity came from this.

In the subgroup analysis of cutoff values, an increased PLR was associated with worse OS in the studies with cutoff values ≥150 (HR: 1.49, 95% CI: 1.33–1.68, P<0.00001). Of note, in this subgroup, the heterogeneity reduced to 0. However, marginally statistical significance was found in the group with PLR cutoff value ≤100 (HR: 1.38, 95% CI: 1.00–1.90, P=0.05) and 100< PLR <150 (HR: 1.18, 95% CI: 0.96–1.45, P=0.13). This indicated that PLR cutoff value may play a prominent role in the source of heterogeneity and the cutoff value of PLR as a promising prognostic biomarker may be suitable for ≥150. The results were showed in *Table 2*. To further confirm this point, we verified it in groups with different treatment as described below.

In the resectable group which consisted of 11 studies, we divide them into two subgroups according to the cutoff value. In cutoff value ≥150 group, the pooled HR was 1.47 (95% CI: 1.28–1.69, P<0.00001), and there was no significant heterogeneity (I^2=20%, P=0.29). In cutoff value <150 group, the pooled HR was 1.16 (95% CI: 1.02–1.32, P=0.03), and there was significant heterogeneity (I^2=66%, P=0.007) (*Figure 5A*).

In the unresectable group which consisted of 6 studies, we divide them into two groups in the same way. In cutoff value ≥150 group, the pooled HR was 1.56 (95% CI: 1.24–1.96, P=0.0001), and there was no significant heterogeneity (I^2=0%, P=0.93). In cutoff value <150 group, the pooled HR was 1.17 (95% CI: 1.01–1.36, P=0.03), and there was significant heterogeneity (I^2=74%, P=0.010) (*Figure 5B*). These results suggested that the optimal cutoff of PLR was ≥150.

The subgroup analysis based on region revealed that a higher PLR was associated with shorter OS in the Chinese group (HR: 1.43, 95% CI: 1.26–1.62, P<0.00001). However, no association between the PLR and OS was observed in other countries (HR: 1.04, 95% CI: 0.81–1.33, P=0.77). Regarding PLR and OS, there were 17 studies reported the proportion of HBV patients of total. We divided them into three groups according to the proportion of HBV patients. A significant outcome prediction relationship between the PLR and OS was seen in all HBV patient group (100%) (HR: 1.46, 95% CI: 1.22–1.73, P<0.0001) and high proportion group (80–100%) (HR: 1.31, 95% CI: 1.03–1.65, P=0.02), but not in low proportion group (≤80%) (HR: 1.21, 95% CI: 0.94–1.56, P=0.14). Of note, in the all HBV patient group, the heterogeneity reduced to 0. This indicated that the proportion of HBV patients may play a role in the source of heterogeneity. The results of subgroup analysis by sample size (≥320.0 or <320.0), age (≥55.0 or <55.0), treatment and BCLC stage showed that elevated PLR was still significantly associated with poor OS in patients with HCC, which indicated that our pooled HR result for OS was stable and reliable. The results were summarized in *Table 2*.

A total of 11 studies reported the proportion of liver cirrhosis patients. Because HCC appears frequently in patients with cirrhosis (42) and thrombocytopenia is a common hematological complication of liver cirrhosis (43). Does a background of cirrhosis affect the prognostic value of PLR? Due to the proportion of liver cirrhosis patients in most of studies were more than 50%, and we could not completely distinguish the cirrhotic and non-cirrhotic groups, but we could preliminarily explore the prognostic significance of PLR in group with different proportions of patients with cirrhosis. As shown in Figure S1, it was worth noting that the predictive effect of PLR for OS was more weaken as the proportion increased.

Publication bias

As shown in *Figure 5*, publication bias was analyzed by funnel plots. For the OS group, the funnel plot was asymmetric (*Figure 6A*). The results of the Begg's test (P=0.08) and the Egger's test (P=0.01) were different. So we further applied the trim and fill method, the pooled results indicated that there might be five unpublished or missing studies existing in the meta-analysis of OS (represented by little triangles). However, the association between PLR and OS was still statistically significant even if the five studies were published (HR: 1.22, 95% CI: 1.06–1.38), indicating that publication bias could not impact on the results for OS (*Figure 6B*). For the RFS/DFS groups, the funnel plots were

Table 2 Subgroup analyses reflecting the association between the PLR and OS in patients with HCC

Subgroup	Number of studies	Number of patients	Statistical model	Pooled results			Heterogeneity	
				HR	95% CI	P value	I^2 (%)	P value
Treatment								
Resectable	11	5,788	Random	1.31	1.11–1.55	0.002	63	0.002
Unresectable	6	1,888	Random	1.32	1.05–1.68	0.02	68	0.008
Mixed	2	593	Fixed	1.70	1.19–2.44	0.004	0	0.62
Cutoff value								
≤100	5	1,606	Random	1.38	1.00–1.90	0.05	74	0.004
100–150	8	2,915	Random	1.18	0.96–1.45	0.13	59	0.02
≥150.0	6	3,748	Fixed	1.49	1.33–1.68	<0.00001	0	0.56
Age (years)								
≥55.0	8	2,213	Random	1.29	1.02–1.63	0.03	61	0.01
<55.0	7	4,378	Random	1.34	1.14–1.58	0.0004	61	0.02
NR	4	1,678	Random	1.45	0.97–2.17	0.07	66	0.03
Sample size								
≥320.0	10	6,237	Random	1.35	1.15–1.59	0.0003	66	0.002
<320.0	9	2,032	Random	1.33	1.08–1.64	0.008	53	0.03
Region								
China	15	6,827	Random	1.43	1.26–1.62	<0.00001	52	0.01
Others	4	1,442	Random	1.04	0.81–1.33	0.77	43	0.16
HBsAg positive (n% of total)								
100	4	1,814	Fixed	1.46	1.22–1.73	<0.0001	0	0.45
80–100	7	2,915	Random	1.31	1.03–1.65	0.02	71	0.002
≤80	6	2,020	Random	1.21	0.94–1.56	0.14	65	0.01
NR	2	1,520	Fixed	1.49	1.22–1.81	<0.0001	35	0.22
BCLC stage (n% of total)								
0 + A >50	5	3,123	Random	1.33	1.03–1.72	0.03	73	0.005
B + C + D >50	7	2,739	Random	1.29	1.16–1.44	<0.00001	59	0.02
NR	7	2,407	Random	1.41	1.09–1.84	0.01	56	0.03

PLR, platelet-to-lymphocyte ratio; OS, overall survival; HCC, hepatocellular carcinoma; NR, not report; HBsAg, hepatitis B surface antigen; BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratios; CI, confidence interval.

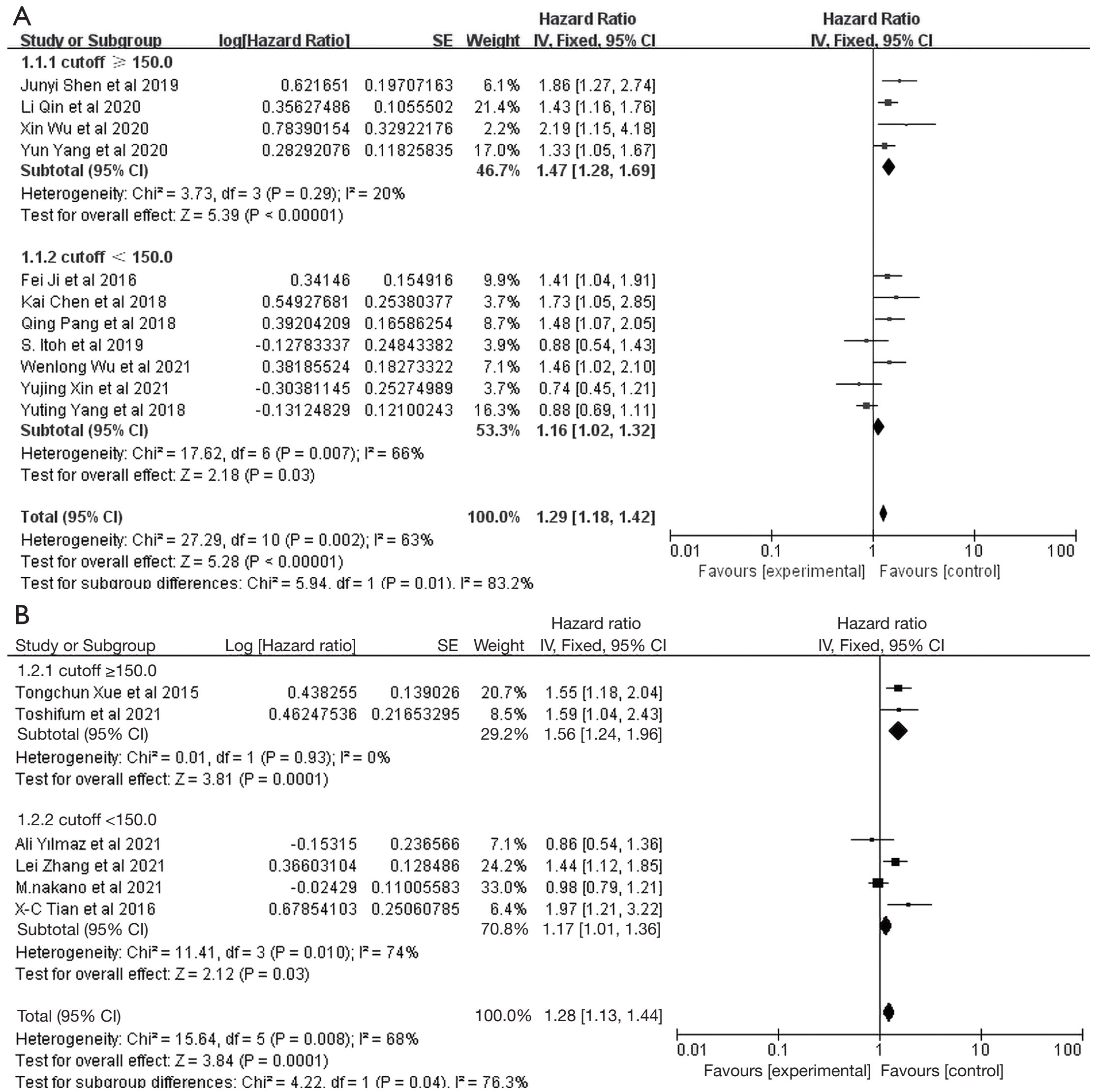

Figure 5 Cutoff value of PLR in the resectable group (A) and in the unresectable group (B). SE, standard error; IV, interval variable; CI, confidence interval; PLR, platelet-to-lymphocyte ratio.

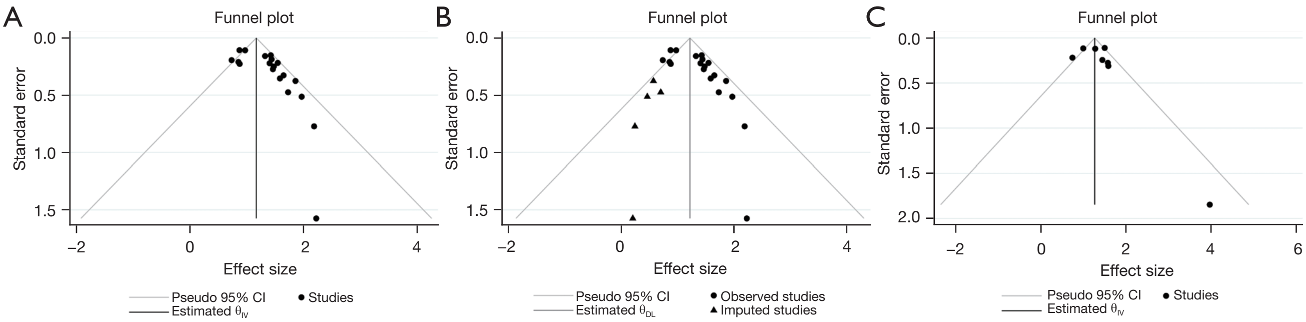

Figure 6 Funnel plots assessing publication bias for OS (A), trim and filled method for OS (B), funnel plot for RFS and DFS (C). CI, confidence interval; IV, interval variable; DL, damping-like; OS, overall survival; RFS, recurrence-free survival; DFS, disease-free survival.

Table 3 Sensitivity analysis results for the association between the PLR and OS

Omitting studies	Pooled results of remaining studies			Heterogeneity	
	HR	95% CI	P value	I^2 (%)	P value
Ylmaz *et al.*, 2021, (32)	1.37	1.21–1.55	<0.00001	59	0.0009
Ji *et al.*, 2016, (36)	1.34	1.17–1.53	<0.0001	62	0.0003
Long *et al.*, 2020, (39)	1.34	1.18–1.52	<0.00001	61	0.0004
Shen *et al.*, 2019, (18)	1.32	1.16–1.50	<0.0001	59	0.0009
Chen *et al.*, 2018, (35)	1.33	1.17–1.51	<0.0001	61	0.0005
Zhang *et al.*, 2021, (33)	1.34	1.17–1.53	<0.0001	61	0.0004
Qin *et al.*, 2020, (25)	1.34	1.17–1.53	<0.0001	61	0.0004
Nakano *et al.*, 2021, (29)	1.38	1.22–1.56	<0.00001	53	0.004
Pang *et al.*, 2018, (38)	1.34	1.17–1.52	<0.0001	61	0.0004
Itoh *et al.*, 2019, (30)	1.37	1.20–1.55	<0.00001	59	0.0007
Xue *et al.*, 2015, (40)	1.33	1.16–1.52	<0.0001	60	0.0005
Tada *et al.*, 2021, (34)	1.33	1.17–1.52	<0.0001	61	0.0004
Wu *et al.*, 2021, (31)	1.34	1.17–1.52	<0.0001	61	0.0003
Tian *et al.*, 2016, (17)	1.32	1.16–1.50	<0.0001	59	0.0007
Wu *et al.*, 2020, (37)	1.32	1.17–1.50	<0.0001	59	0.0007
Li *et al.*, 2020, (28)	1.33	1.17–1.51	<0.0001	60	0.0005
Xin *et al.*, 2021, (27)	1.37	1.21–1.55	<0.0001	58	0.001
Yang *et al.*, 2020, (6)	1.35	1.17–1.54	<0.0001	62	0.0003
Yang *et al.*, 2018, (16)	1.38	1.23–1.56	<0.00001	48	0.01

PLR, platelet-to-lymphocyte ratio; OS, overall survival; HR, hazard ratio; CI, confidence interval.

more symmetric. The Begg's test (P=0.26) and the Egger's test (P=0.12) provided evidence of no significant publication bias (*Figure 6C*).

Sensitivity analysis

We also performed a sensitivity analysis to assess the impact of the PLR by omitting each study one by one. The pooled OS and RFS/DFS results were not significantly affected by removing any of the studies, indicating the robustness of our findings. The details were shown in *Tables 3,4*.

Discussion

The present meta-analysis of 21 studies, including 8,779 patients with HCC, showed that higher PLR was associated with worse OS, RFS/DFS and PFS in patients with HCC.

In this study, we divided 19 studies into three groups based on different cutoff values (range, 75.3 to 167.7). We found that increased PLR was associated with poor OS in the studies with cutoff values ≥150 (HR: 1.48, 95% CI: 1.33–1.68, P<0.00001) and the heterogeneity reduced to 0. We held the opinion that high PLR had a poor prognostic value in the survival of patients with HCC when cutoff values ≥150. To further confirm this point, small subgroup analysis was also performed based on different cutoff value in both unresectable group and resectable group, and studies were divided into those with cutoff value of less than 150 and more than 150. The results showed that elevated PLR were still significantly associated with poor OS in all subgroups, but the heterogeneity reduced to 0% and 20% in cutoff ≥150 subgroups. It was suggested that the optimal cutoff value of PLR for HCC patients was ≥150. This indicted that patients can choose appropriate treatment

Table 4 Sensitivity analysis results for the association between the PLR and RFS/DFS

Omitting studies	Pooled results of remaining studies			Heterogeneity	
	HR	95% CI	P value	I^2 (%)	P value
Long *et al.*, 2020, (39)	1.33	1.22–1.46	<0.00001	62	0.02
Shen *et al.*, 2019, (18)	1.34	1.22–1.46	<0.00001	72	0.001
Qin *et al.*, 2020, (25)	1.38	1.24–1.52	<0.00001	72	0.001
Pang *et al.*, 2018, (38)	1.34	1.23–1.47	<0.00001	73	0.001
Chen *et al.*, 2021, (26)	1.34	1.22–1.47	<0.00001	72	0.001
Xin *et al.*, 2021, (27)	1.37	1.26–1.50	<0.00001	66	0.007
Yang *et al.*, 2020, (6)	1.27	1.13–1.42	<0.0001	69	0.004
Yang *et al.*, 2018, (16)	1.43	1.30–1.57	<0.00001	57	0.03

PLR, platelet-to-lymphocyte ratio; RFS, recurrence-free survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

according to different disease status such as high surgical risk (44,45).

Chronic HBV (CHB) infection is one of the high-risk factors for human HCC, responsible for 50~80% of HCC cases worldwide (46). Subgroup analysis based on the proportion of HBV patients confirmed that a high PLR was significantly associated with poor OS in all HBV patients group (100%) (HR: 1.46, 95% CI: 1.22–1.73, P<0.0001) and high proportion group (80–100%) (HR: 1.31, 95% CI: 1.03–1.65, P=0.02), but not relevant in low proportion group (≤80%) (HR: 1.21, 95% CI: 0.94–1.56, P=0.14). This suggested that PLR was suitable for colony with a high proportion of HBV patients. Of note, the heterogeneity reduced to 0 in all HBV-related HCC patients group, it could be a source of heterogeneity. Notably, the subgroup analysis based on region revealed that high PLR values were associated with worse OS in Chinese group (HR: 1.43, 95% CI: 1.26–1.62, P<0.00001) but not in other countries (HR: 1.04, 95% CI: 0.81–1.33, P=0.77). The reason may be that CHB infection is the major pathogenic factor for HCC in China (47).

Therefore, the association between PLR and OS were found to be more significant in studies with HBV-related HCC patients, and the cutoff value of PLR as a promising prognostic biomarker was suitable for ≥150. Further researches were preferred to investigate the associations of PLR in these group types.

In this study, we defined patients who were treated with TACE or MTA as unresectable group and patients who received hepatic resection or RFA as resectable group. Subgroup analysis showed that a higher PLR seemed to have shorter OS in both group (HR: 1.32, 95% CI: 1.05–1.68, P=0.02; HR: 1.31, 95% CI: 1.11–1.55, P=0.002). Generally speaking, patients in unresectable group are in advanced stage and associated with metastasis. But this conclusion contradicted Song's research (48) which showed that a high PLR had no prognostic efficiency for OS in HCC patients with metastatic disease. Probably because Song only included two studies in the metastatic disease group.

Platelets play an important role in the process of tumor angiogenesis. The effects of platelets and the cytokines they secrete on tumor progression are not fully understood, but elevated platelet counts are associated with poorer outcomes in many different types of solid cancers (49,50). Activated platelets significantly increased the adhesion between tumor cells and endothelial cells, thereby promoting tumor metastasis (51). Furthermore, platelets are a rich source of proangiogenic factors. They can secrete large amounts of angiogenic cytokines, such as VEGF (52) and platelet-derived growth factor (PDGF) (53). Interleukin-6 (IL-6) is considered to be a focal factor for VEGF expression in patients with malignant tumors (50). Therefore, cancer cells can indirectly affect platelets by synthesizing IL-6 and then stimulating tumor angiogenesis and growth. Increased number of platelets can suppress the antitumor immune responses of NK cells (7). Therefore, platelets, as a biological index affecting cancer progression, directly affect the judgment of PLR on cancer prognosis.

However, the formation of primary HCC is often accompanied by liver cirrhosis. Liver cirrhosis will lead to hypersplenism and then lead to a significant decrease of platelets. At this time, the decrease of platelets is not due to the progress of cancer, but due to hypersplenism caused by liver cirrhosis. Therefore, PLR will be affected by liver cirrhosis as a prognostic biomarker in cirrhosis related HCC. Our data showed that the proportion of patients with liver cirrhosis, from the scatter plot we knew that HR for OS decreased as the proportion of HBV patients went up. Therefore, PLR as prognostic biomarker may be more suitable for non-cirrhosis HCC patients.

There are several limitations of this meta-analysis. First, the subgroup analysis in this study was rough, such as different treatments, which was due to insufficient subgroup data. The results may not be particularly accurate when studying subgroup effects. Particularly, treatment including tyrosine kinase inhibitors (TKIs) as well as TACE may affect platelet values, therefore it would be very interesting to study subgroup analyses based on treatment modality. Second, funnel plots showed slight asymmetry in the PLR and OS analysis, indicating the possibility of publication bias. The potential cause may be that unpublished studies reported negative results. In addition, the prognosis of HCC is not only determined by PLR but also influenced by multiple factors such as surgical complications (54). It is better to consider all the prognostic factors together in clinic.

Conclusions

In summary, this meta-analysis shows that PLR is a useful prognostic biomarker for HCC and high PLR may indicate a poor prognosis in HBV related HCC. Further well-designed prospective studies are required to verify its clinical application.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1197/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1197/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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