

Clinicopathological and prognostic value of preoperative lymphocyte to monocyte ratio for hepatocellular carcinoma following curative resection

A meta-analysis including 4,092 patients

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Abstract

Background: Previous studies have reported that lymphocyte-to-monocyte ratio (LMR) had novel prognostic value in hepatocellular carcinoma (HCC). The purpose of this meta-analysis was to synthetically evaluate the prognostic role of preoperative LMR in HCC patients following curative resection.

Methods: Eligible studies were acquired through searching Pubmed, Web of Science, Cochrane Library and EMBASE update to September 2019. Merged hazard ratios (HRs) and 95% confidence intervals (CIs) were applied as effect sizes.

Results: A total of ten studies containing 4,092 patients following liver resection were enrolled in this meta-analysis. The pooled results demonstrated that preoperative elevated LMR indicated superior survival outcome (HR: 0.58, 95% CI: 0.34–0.96, $P = .035$) and recurrence-free survival (RFS)/disease-free survival/time to recurrence (HR = 0.76, 95% CI: 0.58–0.98, $P = .034$). The significant prognostic role of preoperative LMR was detected in the subgroup of all publication year, country of origin, sample sizes <300, TNM stage of I–IV and LMR cut-off value ≤ 4 . Furthermore, high LMR was significantly associated with male, high AFP, large tumor size, incomplete tumor capsule, advanced TNM stage and BCLC stage, and presence of PVTT.

Conclusion: Elevated preoperative LMR indicated superior survival outcome in HCC patients following curative resection, and might serve as a novel prognostic biomarker.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, HCC = hepatocellular carcinoma, OS = overall survival, TTR = time to recurrence, LMR = lymphocyte to monocyte ratio.

Keywords: hepatocellular carcinoma, curative resection, lymphocyte to monocyte ratio, meta-analysis, prognosis

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and is the fourth leading cause of cancer-related death worldwide.^[1] At present, surgical resection is still the most effective treatment for HCC.^[2] However, the 5-year overall survival of HCC patients after radical resection remains poor due

to the high recurrence rate in spite of recent therapeutic improvement,^[3–6] such as technological advances in surgery, preoperative diagnosis and perioperative treatment.^[7,8] Therefore, it is necessary to develop sensitive and specific biomarkers to predict overall survival (OS) and recurrence after operation in HCC patients.

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Previous studies have proved systemic inflammation can promote cancer growth, invasion and metastasis in malignant tumor patients.^[9–11] Several reports showed that preoperative systemic inflammatory status was related to tumor recurrence and overall survival in HCC patients.^[12–14] Serum inflammatory indices, such as lymphocyte-to-monocyte ratio (LMR),^[15] platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR),^[13,16,17] have been found to have better prognostic value in HCC patients. LMR, the ratio of lymphocytes to monocytes, as a fungible biomarker of TILs and TAMs, has been declared to be a prognostic indicator of surgical outcome after curative resection in HCC patients.^[15,18,19] As a routinely available and low-cost inflammatory biomarker, LMR can be conveniently applied in clinical work. Several evidences demonstrated that elevated LMR, defined as lymphocyte counts divided by monocyte counts, was significantly related to favorable prognosis in HCC patients.^[20,21]

Previous meta-analysis showed that increased pretreatment LMR indicated better prognosis in HCC patients. However, in addition to inclusion of abstract, this study included the patients all from China, that may result in publication bias.^[22] Therefore, it was an urgent need for us to conduct a comprehensive meta-analysis to further evaluate the prognostic role of preoperative LMR in HCC patients who underwent hepatectomy. In addition, the association between preoperative LMR and clinicopathological characteristics was also explored.

2. Materials and methods

2.1. Search strategy

This meta-analysis was performed in the light of the PRISMA statement.^[23] We searched the relevant literature through Pubmed, EMBASE, Web of Science and Cochrane databases update to September 2019. The main search terms were used as following: “HCC” or “hepatocellular carcinoma” or “liver cancer” or “liver tumor” or “liver neoplasms” or “liver cell carcinoma,” “LMR” or “lymphocyte monocyte ratio” or “lymphocyte to monocyte ratio” or “lymphocyte-to-monocyte ratio” or “lymphocyte-monocyte ratio,” “survival” or “prognostic” or “prognosis” or “recurrence” or “clinical outcome”. Relevant references were manually scanned and retrieved for eligible articles.

2.2. Inclusion criteria

The inclusion criteria were showed as following:

- (1) HCC patients were diagnosed by histopathology;
- (2) HCC patients underwent curative resection;
- (3) studies explored the relationship between preoperative LMR and OS and/or recurrence-free survival (RFS) and/or disease-free survival (DFS) and/or time to recurrence (TTR);
- (4) the cut-off value of LMR could be extracted from studies; and
- (5) enough information was provided for calculating hazard ratio (HR) with 95% confidence interval (CI).

2.3. Exclusion criteria

The exclusion criteria were as described below:

- (1) reviews, abstracts, letters, case reports, nonclinical studies and comments;
- (2) non English writing articles;

- (3) duplicate data or repeat reports.

2.4. Data extraction and quality assessment

Qualitative evaluation and data extraction were performed by 2 independent reviewers (Shuwen Lin and Ye Lin). Articles that could not be judged through title and abstract were further reviewed by full-text. In case of disagreement, a consensus would be reached after discussion with the third reviewer (Yinghua Fang). The following parameters of each study were recorded: first author, publishing year, study region, type of publication, total number of patients, time of follow-up, treatment, age, cut-off value, tumor stage, survival analysis method (univariate, multivariate), prognostic outcome (OS, DFS, RFS and TTR) and HRs with their 95% CIs.

The quality evaluation of each selected study was implemented by 2 independent reviewers (Shuwen Lin and Ye Lin) by reference to the Newcastle-Ottawa Scale (NOS).^[24] The main contents of NOS were as follows: case selection (0–4 points), groups comparability (0–2 points), and clinical outcome (0–3 points). The studies with NOS scores ≥ 6 were identified as high-quality studies.

2.5. Statistical analysis

The meta-analysis was performed using STATA statistical software version 15.1 (STATA, College Station, TX). The heterogeneity among the studies was evaluated using Cochran *Q* test and I-squared test.^[25] A fixed-effects model was adopted without significant heterogeneity ($P > .10$ for the *Q*-test and $I^2 < 50\%$). If not, a random-effects model was employed. The extracted HRs and 95% CIs were aggregated to assess the prognostic outcome. Odds ratios (ORs) and their 95% CIs were used to appraise the connection between LMR and clinicopathological characteristics. Subgroup analyses were performed to clarify the heterogeneity of different studies based on publication year, country, sample size, cut-off value of LMR, TNM stage. Sensitivity analyses were also carried out to further assess the stability of our final results. Egger linear regression tests and Begg funnel plots were applied to investigate publication bias. A 2-sided *P*-values of $< .05$ was considered as statistical significance.

2.6. Ethical approval

Ethical committee approval was not required. Because we did not conduct any clinical research in this manuscript, we just extracted the data from existing publications.

3. Results

3.1. Search results

A total of 175 articles were finally obtained according to initial retrieval strategy. After excluding 40 duplicates, 135 records were extracted for further reviewing. Of these, 122 records were excluded of obvious unrelated through screening titles and abstracts. After full-text articles reviewed for eligibility, 3 records were excluded because of conference abstract, non-survival analysis and insufficient data. Ultimately, 10 articles, including 4092 patients, were included in quantitative synthesis.^[19,20,26–33] The PRISMA flow diagram of the selection process was presented in Fig. 1.

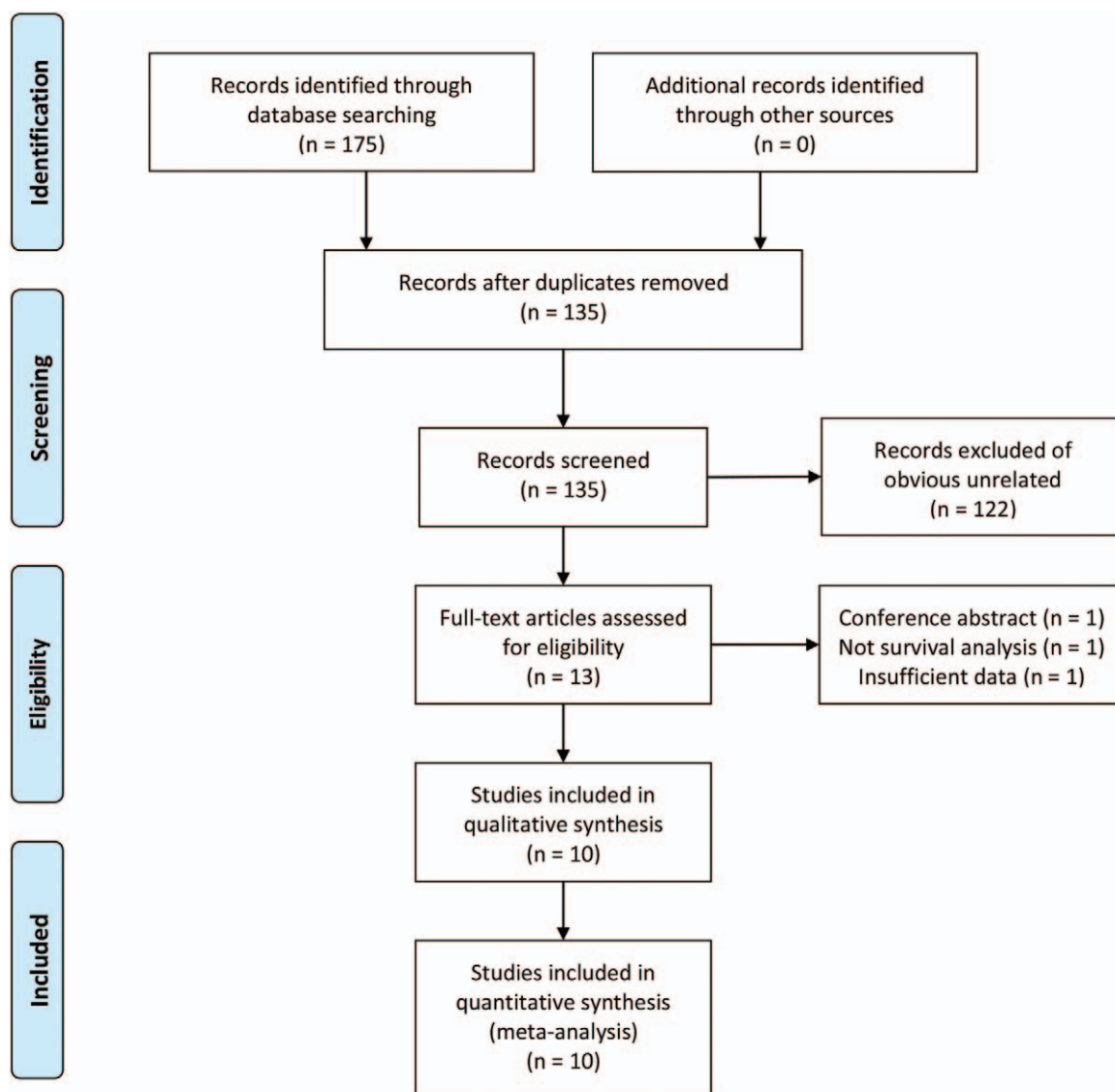


Figure 1. Flow chart of the included studies.

3.2. Characteristics of the included studies

All 10 studies were published in full-text between 2015 and 2019. A total of 4,092 patients underwent surgical resection. Among these studies, 7 were from China, 2 from Japan and the last 1 from USA. The sample sizes ranged from 210 to 1020. Nine studies showed the prognostic outcome of preoperative LMR on OS, 7 studies on RFS, 2 studies on DFS and 1 on TTR. The cut-off values of LMR ranged from 3 to 4.5. HRs and their 95% CIs were given directly from the 10 studies with univariable and/or multivariable analyses. The range of NOS scores was from 5 to 7. The detailed characteristics of all studies were presented in Table 1.

3.3. Meta-analysis

3.3.1. LMR and OS in HCC. Nine studies including 3,072 participants reported the relation between preoperative LMR and OS. Due to significant heterogeneity ($I^2=94.0\%$, $P<.001$), a random-effects model was employed. The final results showed that elevated preoperative LMR was connected with satisfactory OS (HR: 0.58, 95% CI: 0.34–0.96, $P=.035$; Fig. 2).

To explore the reason of heterogeneity, we performed subgroup analyses with regard to publication year, country, sample size, cut-off value of LMR and TNM stage (Table 2). Subgroup analyses showed that elevated preoperative LMR revealed prolonged OS in HCC patients, regardless of publication year (≤ 2017 and > 2017) and country of origin (China, Japan and USA). Subgroup analyses on sample size revealed that increased LMR indicated better OS in studies of sample sizes < 300 (HR=0.36, 95% CI: 0.14–0.94, $P=.037$, random-effects model, $I^2=93.2\%$), but not sample sizes ≥ 300 (HR=0.96, 95% CI: 0.53–1.71, $P=.889$, random-effects model, $I^2=94.0\%$). When stratified by cut-off value of LMR, the result demonstrated that high LMR was related to favorable OS in the subgroup of cut-off value ≤ 4 (HR=0.24, 95% CI: 0.13–0.42, $P<.001$, random-effects model, $I^2=76.9\%$), rather than cut-off value > 4 (HR=1.13, 95% CI: 0.73–1.74, $P=.590$, random-effects model, $I^2=88.8\%$). Subgroup analyses by TNM stage, the data predicted that LMR was of better prognostic value in HCC patients with TNM stage of I–IV (HR=0.24, 95% CI: 0.10–0.59,

Table 1
Characteristics of the studies included in the meta-analysis.

Study cohort	Year	Study region	Type of publication	No. of patients	Follow-up (mo) (median and range)	Treatment	Age (years)	Cut-off	Outcome	Stage (TNM /BCLC)	HR	NOS score
Lin ZX	2015	China	Full-text	210	34.8 (1.7-106.6)	Hepatectomy	NR	3.23	OS/RFS	NR	M/U	7
Wu SJ	2016	China	Full-text	450	45.5 (2-93)	Hepatectomy	49.63 (17-81)	3.77	OS/RFS	I-IV	M/U	7
Liao R	2016	China	Full-text	256	44 (1.5-84)	Hepatectomy	53	3.33	OS/RFS	I-II	M/U	5
Zheng J	2017	US	Full-text	370	56	Hepatectomy	65 ± 12	4.3	OS/RFS	NR	U	5
Shi S	2017	China	Full-text	271	26 (5-101)	Hepatectomy	60 (27-81)	4.5	OS/TTR	I-III	M/U	7
Li GJ	2017	China	Full-text	253	33 (6-85)	Hepatectomy	60 ± 1.8	3	OS/RFS	I-IV	M/U	7
Yang TB	2017	China	Full-text	1020	60	Hepatectomy	NR	3.23	DFS	I-III	M/U	7
Yang YT	2018	China	Full-text	652	NR	Hepatectomy	48.01 ± 11.5	4.01	OS/DFS	0-C	M/U	7
Itoh S	2019	Japan	Full-text	281	68.4 (1.2-189.6)	Hepatectomy	68 (28-87)	4.28	OS/RFS	A-C	M/U	7
Shimizu T	2019	Japan	Full-text	329	46 (0.08-133.5)	Hepatectomy	NR	4.35	OS/RFS	I-III	M/U	7

OS: overall survival; RFS: recurrence-free survival; DFS: disease-free survival; TTR: time to recurrence, HR: hazard ratio, obtained by reporting in text (R). "M" means the HR come from multivariate analysis, "U" means the HR comes from univariate analysis; TNM: tumor-node-metastasis; BCLC: Barcelona Clinic Liver Cancer, NR: not reported; NOS: Newcastle–Ottawa Quality Assessment Scale.

$P = .002$, random-effects model, $I^2 = 86.8\%$), but not in patients with TNM stage of I-III (HR = 0.51, 95% CI: 0.11–2.28, $P = .375$, random-effects model, $I^2 = 95.2\%$).

3.3.2. LMR and RFS/DFS/TTR in HCC. Ten studies comprising 4092 patients explored the relation between preoperative LMR and RFS/DFS/TTR. A random-effects model was applied for analysis due to significant heterogeneity ($P < .001$, $I^2 = 89.7\%$). The final result revealed that low preoperative LMR indicated poor RFS/DFS/TTR (HR = 0.76, 95% CI: 0.58–0.98, $P = .034$; Fig. 3)

3.3.3. LMR and clinicopathological characteristics. To clarify the relationship between preoperative LMR and clinicopathological features of HCC patients, we analyzed 16 clinical

parameters (Table 3). The pooled analysis stated that high LMR was significantly related to gender (male vs female; HR = 0.79, 95% CI: 0.65–0.96, $P = .020$), AFP (>400 ng/mL vs <400 ng/mL; HR = 0.56, 95% CI: 0.33–0.95, $P = .030$), tumor size (≥ 5 cm vs <5 cm; HR = 0.56, 95% CI: 0.43–0.73, $P < .001$), TNM stage (I vs II-III; HR = 1.52, 95% CI: 1.22–1.90, $P < .001$), BCLC stage (A vs B/C; HR = 1.46, 95% CI: 1.13–1.89, $P = .004$), tumor capsule (complete vs incomplete; HR = 1.23, 95% CI: 1.02–1.48, $P = .029$) and PVTT (yes vs. no; HR = 0.69, 95% CI: 0.51–0.93, $P = .016$). Nevertheless, LMR was not corrected with other clinicopathological indicators such as age, liver cirrhosis, tumor differentiation, tumor number, HBsAg, HCV-Ab, diabetes mellitus, child-pugh classification and MVI.

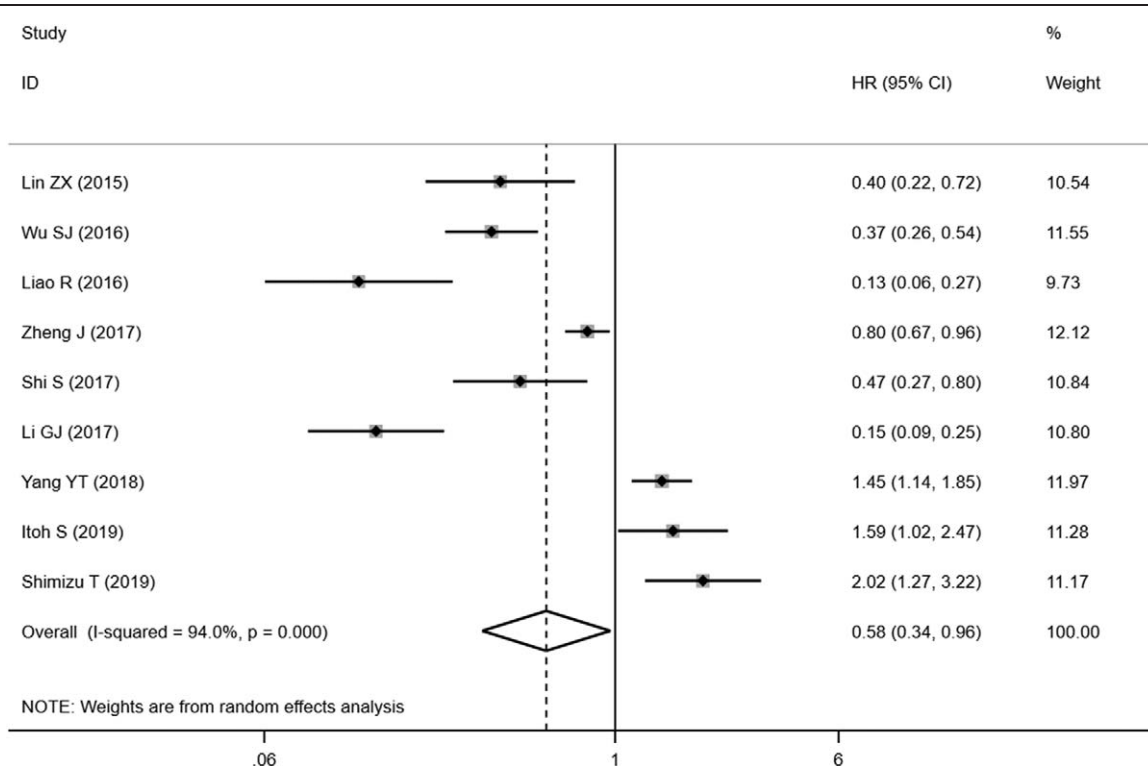


Figure 2. Meta-analysis of the association between LMR and overall survival (OS) of hepatocellular carcinoma (HCC). Results are presented as individual and pooled hazard ratios (HRs), and 95% confidence intervals (CIs).

Table 2
Pooled hazard ratios (HRs) for OS according to subgroup analyses.

Subgroup	No. of studies	No. of patients	Effects model	HR (95%CI)	P value	Heterogeneity	
						I ² (%)	Ph
Overall	9	3072	Random	0.58 (0.34-0.96)	.035	94	<.001
Publication year:							
≤2017	6	1810	Random	0.33 (0.18-0.60)	<.001	91.6	<.001
>2017	3	1262	Fixed	1.57 (1.29-1.90)	<.001	0	.466
Country:							
China	6	2092	Random	0.36 (0.16-0.83)	.016	95.1	<.001
Japan	2	610	Fixed	1.78 (1.29-2.45)	<.001	0	.462
US	1	370		0.80 (0.67-0.96)	.014		
Sample size:							
<300	5	1271	Random	0.36 (0.14-0.94)	.037	93.2	<.001
≥300	4	1801	Random	0.96 (0.53-1.71)	.889	94	<.001
Cut-off value:							
≤4	4	1169	Random	0.24 (0.13-0.42)	<.001	76.9	.005
>4	5	1903	Random	1.13 (0.73-1.74)	.59	88.8	<.001
TNM stage							
I-III	3	856	Random	0.51 (0.11-2.28)	.375	95.2	<.001
I-IV	2	703	Random	0.24 (0.10-0.59)	.002	86.8	.006

HR: hazard ratio; 95% CI: 95% confidence interval; Ph: p values of Q test for heterogeneity test; TNM: tumor-node-metastasis.

3.4. Sensitivity analysis and publication bias

In order to test the stability of the results, we conducted sensitivity analyses (Fig. 4). Each single study was taken away to assess the influence of individual data sets on the combined HR for OS. The results displayed that no single study influenced the pooled

HR, which revealed that our final results were reasonably credible and stable.

Publication bias was assessed by the Begg funnel plot and Egger linear regression test. The results demonstrated that no significant publication bias was found in this meta-analysis ($P > |z| = 0.118$ for Begg test and $P > |t| = 0.206$ for Egger test).

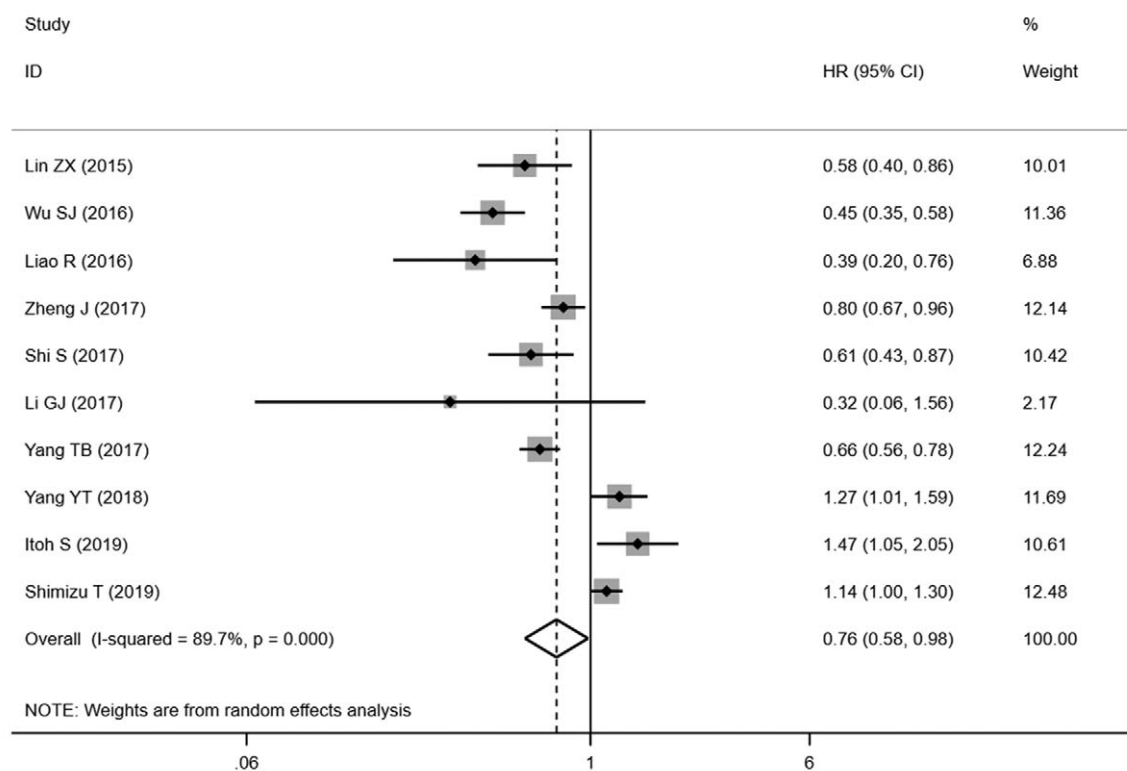


Figure 3. Meta-analysis of the association between LMR and DFS/RFS/TTR of hepatocellular carcinoma (HCC). Results are presented as individual and pooled hazard ratios (HRs), and 95% confidence intervals (CIs).

Table 3
Meta-analysis of the association between LMR and clinicopathological features of HCC.

Parameter	No. of studies	No. of patients	OR (95% CI)	P	Heterogeneity	
					I ² (%)	Ph
Gender (male vs female)	8	3466	0.79 (0.65-0.96)	.02	0	.581
Age (≥ 60 vs <60)	3	1483	0.87 (0.66-1.14)	.315	0	.715
AFP (> 400 ng/mL vs <400 ng/mL)	4	2332	0.56 (0.33-0.95)	.03	87.3	<.001
Liver cirrhosis (yes vs no)	8	3451	0.86 (0.62-1.19)	.354	67.5	.003
Differentiation (poor vs moderate/high)	7	3137	0.90 (0.76-1.06)	.21	0.9	.417
Tumor number (multiple vs single)	6	3003	0.95 (0.73-1.23)	.682	51.8	.066
Tumor size (≥ 5 cm vs <5 cm)	5	2204	0.56 (0.43-0.73)	<.001	38.1	.167
TNM stage (I vs II-III)	3	1620	1.52 (1.22-1.90)	<.001	60.9	.077
BCLC stage (A vs B/C)	3	1355	1.46 (1.13-1.89)	.004	15.2	.307
HBsAg (pos vs neg)	5	2552	1.037 (0.825-1.303)	.756	0	.855
HCV-Ab (pos vs neg)	3	1629	0.82 (0.59-1.14)	.236	0	.945
DM (yes vs no)	2	1301	0.96 (0.62-1.47)	.84	0	.457
Child-pugh (A vs B)	5	2535	1.28 (0.93-1.77)	.132	0	.622
MVI (yes vs no)	3	1511	0.69 (0.40-1.17)	.169	64.9	.058
Tumor capsule (complete vs incomplete)	4	2153	1.23 (1.02-1.48)	.029	0	.8
PVTT (yes vs no)	3	1546	0.69 (0.51-0.93)	.016	0	.444

HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein; TNM: tumor-node-metastasis; BCLC: Barcelona Clinic Liver Cancer; DM: diabetes mellitus; MVI: microvascular invasion; PVTT: portal vein tumor thrombus.

4. Discussion

Surgical resection such as anatomic hepatectomy is the primary therapeutic method for hepatocellular carcinoma (HCC) patients.^[34,35] However, the recurrence rate after surgical resection is still high.^[36] Previous studies have demonstrated that several tumor-related indicators such as inflammation-related markers and tumor properties histological features, can serve as predictive factors for recurrence.^[10,37,38] Preoperative LMR, as a systemic inflammatory biomarker, has been shown to be associated with prognosis in HCC patients.^[26-29]

Our analysis results pooled 10 studies comprising 4,092 HCC patients undergoing hepatectomy, and showed that increased preoperative LMR predicted favorable OS and RFS/DFS/TTR. Because of significant heterogeneity, we performed subgroup analyses. The results of subgroup analyses demonstrated that

preoperative LMR was of prognostic value in OS regardless of publication year and country of origin. However, in the subgroup of sample sizes <300 and TNM stage of I-IV, our results revealed that high LMR indicated better OS in HCC patients. Furthermore, the LMR cut-off value for OS in HCC patients was quite different in previous studies, and the stratified analysis illustrated that cut-off value of LMR ≤4 might have better prognostic value for OS. Moreover, we further investigated the connection between preoperative LMR and clinicopathological features of HCC patients following curative resection. The pooled results demonstrated that high LMR was significantly associated with male, high AFP, large tumor size, incomplete tumor capsule, advanced TNM stage and BCLC stage, and presence of PVTT. Consequently, preoperative LMR may be considered as a novel prognostic factor for HCC patients following curative resection.

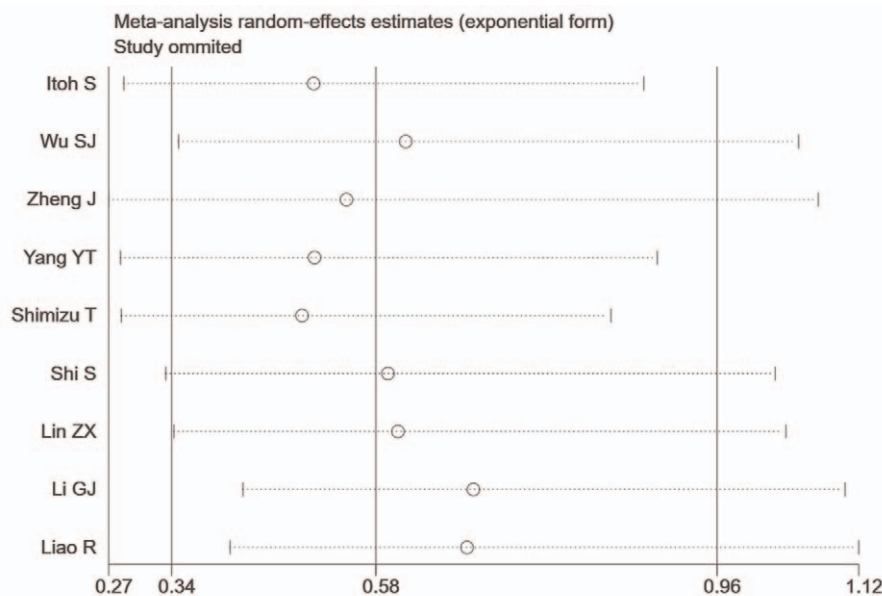


Figure 4. Chart of sensitivity analysis.

The definite mechanisms of the link between preoperative LMR and survival outcome in HCC patients following curative resection is still not understood. Increasing studies have shown that the infiltrating inflammatory microenvironment may significantly affect the survival outcome of HCC. Inflammatory immune cells, such as tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs), their imbalance often results in progression of HCC.^[39–41] Lymphocyte, as a considerable component of human immune system, can inhibit tumorigenesis and relapse and regulate the immune function by producing cytokines and inducing cytotoxic death.^[42] Besides directly killing tumor cells, lymphocytes can change tumor microenvironment and prevent tumorigenesis and tumor relapse by migrating and infiltrating into the tumor microenvironment.^[42–44] As a result, low lymphocyte count might lead to weak antitumor activity and poor clinical prognosis.^[45] Another important ingredient of human immune system is called monocyte. Monocytes are a type of white blood cells that can further differentiate into tumor associated macrophages (TAMs). TAMs can influence tumor microenvironment and promote tumorigenesis, recurrence and metastasis by secreting multiple inflammatory mediators and cytokines.^[40,46,47] Previous studies have reported that TAMs, originated from circulating monocytes, could infiltrate into HCC matrix, thereby accelerating angiogenesis, proliferation, immunosuppression and metastasis of tumor.^[48–50] Peripheral blood monocytes may be related to the count of TAMs and are considered as a prognostic biomarker of HCC.^[51] In summary, LMR may reflect human immune function and anti-tumor ability. A low LMR indicates defective inflammatory microenvironment and antitumor immune activity.

However, several limitations were left in this present study. Firstly, the included studies were all retrospective, that may cause some bias. Large-scale multicenter prospective cohorts are required to clarify the prognostic value of preoperative LMR in HCC following curative resection. Secondly, significant heterogeneity arose among the eligible studies. The emergence of heterogeneity may originate from several potential factors, such as gender, age, country of origin, LMR cut-of value, tumor stage and so on. Thirdly, the included studies were all published in English, that may result in publication bias. Finally, the cut-off value of LMR was varied among studies. We speculate that it may be due to the inconsistent number of patients in groups hence changing the cut-off value, and resulting in different HR. In future studies, the optimal cut-off value of LMR should be validated for advanced research needs and clinical applications.

In conclusion, our study showed that elevated preoperative LMR indicated superior survival outcome in HCC patients following curative resection, and could serve as a surprising prognostic biomarker. Due to the limitations of this meta-analysis, further large-scale, multicentered, well-designed, prospective, randomized, and controlled analysis are essential to validate the prognostic role of preoperative LMR in HCC patients following curative resection.

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Author contributions

Shuwen Lin and Zhixiang Jian conceived of the study, participated in its design and helped to draft the manuscript.

Shuwen Lin, Ye Lin and Yinghua Fang were responsible to searching the paper. Ye Lin, Yinghua Fang, Zhikang Mo and Xiaocheng Hong collected the data. Zhixiang Jian and Shuwen Lin participated in the design of the study and performed the statistical analysis. Chenggang Ji revised the manuscript. All authors read and approved the final manuscript.

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Writing – original draft: Shuwen Lin, Ye Lin, Yinghua Fang.

Writing – review & editing: Shuwen Lin, Ye Lin, Yinghua Fang, Zhixiang Jian.

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