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Prognostic role of the lymphocyte-to-monocyte ratio in colorectal cancer

An up-to-date meta-analysis

Qingbin Wu, MD[a,b], Tao Hu, MD[a,b], Erliang Zheng, MD[a,b], Xiangbing Deng, MD[a], Ziqiang Wang, MD, PhD[a,*]

Abstract

Background: Although previous meta-analyses have proved that lymphocyte-to-monocyte ratio (LMR) is a prognostic factor in solid cancers, its prognostic role in colorectal cancer (CRC) remains controversial. We, therefore, conducted this up-to-date meta-analysis to evaluate the prognostic role of the LMR in CRC.

Methods: A systematic search was performed in PubMed and Embase for relevant studies in November 2016. Article assessing the prognostic role of LMR in CRC was enrolled in this meta-analysis. Data and characteristics of each study were extracted. A meta-analysis was performed to generate pooled hazard ratio (HR) and 95% confidence intervals (95% CIs) for overall survival (OS) and disease-free survival. Begg funnel plot was used to evaluate publication bias.

Results: Eleven studies published between 2014 and 2016 with a total of 9045 patients were enrolled in this meta-analysis. Our findings indicated that a low LMR predicted a worse OS (HR 1.57, 95% CI 1.30–1.90, $P < .001$) and disease-free survival. (HR 1.25, 95% CI 1.13–1.39, $P < .001$) for patients with CRC. Subgroup analyses according to stage (I–III and IV) and LMR cut-off value (<3.00 and ≥3.00) showed a significant prognostic value of LMR on OS. Begg funnel plot showed that publication bias existed in this meta-analysis.

Conclusions: This up-to-date meta-analysis shows that a low LMR is associated with poor survival in patients with CRC, although the publication bias is existed. Large-sample multicenter prospective cohort is needed to assess the role of the LMR in CRC patients.

Abbreviations: CI = confidence interval, CRC = colorectal cancer, DFS = disease-free survival, HR = hazard ratio, LMR = lymphocyte-to-monocyte ratio, OS = overall survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, TILs = tumor-infiltrating lymphocytes.

Keywords: colorectal cancer, lymphocyte-to-monocyte ratio, prognosis

1. Introduction

Colorectal cancer (CRC) is 1 of the most common cancers and 1 of the leading causes of cancer death worldwide.[1] About 1.36 million were diagnosed with CRC and 0.7 million died of it in 2012.[1] Although the therapeutic strategies have been developed in recent decades, the 5-year overall survival (OS) of CRC is unsatisfactory because of local recurrence or metastasis. Many factors can predict the prognosis of CRC, for instance tumor stage, cell differentiation grade, vascular invasion, and neural invasion. However, some patients with good prognostic factors still have poor prognosis. Thus, there is an urgent need to find other new biomarker to predict the prognosis of CRC and help choose the optimal therapeutic strategies.

Since the first report by Virchow[2] in 1881 described the association between inflammation and tumorigenesis, strong evidence has suggested that inflammation plays a critical role in cancer onset, development, and therapeutic response.[3–6] Published studies have demonstrated that several systemic inflammatory factors can be used to predict the prognosis for CRC patients, such as platelet-to-lymphocyte ratio[7] and neutrophil-to-lymphocyte ratio.[8,9] As a new factor of systemic inflammatory, lymphocyte-to-monocyte ratio (LMR) has been drawing increasing attention lately.

The LMR is the ratio calculated by dividing the absolute lymphocyte counts by the absolute monocyte counts from the blood test. Lymphocytes participate in cytotoxic cell death and inhibition of tumor cell proliferation and migration.[10,11] Lymphopenia usually indicates disease severity and can make cancer cells escape from the immune of tumor-infiltrating lymphocytes (TILs).[12] TILs are formed by lymphocytes migrating into the tumor microenvironment.[13] It has been proved that decreased levels of TILs predict a worse survival in patients with CRC.[14–16] Conversely, monocytes can promote tumor progression and metastasis.[6,17] Several proinflammatory

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[a] Department of Gastrointestinal Surgery, West China Hospital, [b] West China School of Medicine, Sichuan University, Chengdu, China.

[*] Correspondence: Ziqiang Wang, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Guo Xue Xiang No. 37, Chengdu 610041, China (e-mail: wangzqzyh@163.com).

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cytokines, secreted from monocytes, are associated with poor prognosis in cancer patients, such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1.[18] Besides, tumor-associated macrophages, derived from circulating monocytes, have a role in suppressing adaptive immunity and promoting angiogenesis, invasion, and migration.[19] From the above, a decreased LMR could generate a favorable immune microenvironment that promotes cancer development. In other words, a decreased LMR could be associated with poor prognosis in cancer patients.

Previous literatures have proved that an elevated pretreatment LMR is associated with survival benefit in hematologic malignancies.[20–22] In addition, 2 meta-analyses also have revealed that elevated pretreatment LMR can predict a good prognosis in patients with solid cancers.[23,24] One meta-analysis[23] included 3 studies focusing on CRC and did not analyze the association between LMR and CRC; the other[24] did analyze the association between LMR and CRC, but it only enrolled four studies. Since there have been published several other studies assessing the prognostic role of LMR in CRC in the past 2 years,[25–28] and the results of those studies remains controversial, we conducted an up-to-date meta-analysis to investigate the association between the LMR and the survival in CRC.

2. Materials and methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplemental 1 PRISMA Checklist, http://links.lww.com/MD/B711). The ethical approval was not necessary because this study was a meta-analysis.

2.1. Search strategy

A systematic literature search with no limits was performed in PubMed (Medline) and Embase. Our search strategy included terms "LMR, lymphocyte-to-monocyte ratio, lymphocyte to monocyte ratio, or lymphocyte monocyte ratio," and "rectal cancer, rectal carcinoma, colon cancer, colon carcinoma, CRC, or colorectal carcinoma" (Supplemental 2 Search Strategy, http://links.lww.com/MD/B711). The last search was performed on November 10, 2016. Besides, a manual search of references of articles and reviews was also performed for additional potentially eligible studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria for selecting studies for this meta-analysis were as follows: all patients were pathologically diagnosed and did not have any tumors besides CRC; the lymphocyte and monocyte were measured before treatment; cohort studies reporting the association between LMR and OS or disease-free survival (DFS) was reported; hazard ratio (HR) and 95% confidence intervals (CIs) of OS or DFS was reported.

The exclusion criteria studies were as follows: studies that did not report HR or 95% CI; abstracts, letters, editorials, reviews, expert opinions, or case reports; studies with a sample size less than 20.

2.3. Data extraction

Two independent reviewers (Q.W. and T.H.) reviewed all candidate articles. Discrepancies were resolved by discussion. If agreement could not be reached, a third reviewer (Z.W.) would be required. The following items were collected from each study: first author's name, year of publication, country of the study population, cancer location, stage, main treatment, sampling time, cut-off value for LMR, number of patients, and the HRs with 95% CI, and median survival time of OS and DFS.

2.4. Quality assessment

We used the Newcastle–Ottawa Scale (NOS) to assess the quality of enrolled studies.[29] The total scores were 9, and study with scores ≥7 was considered as high quality study.

2.5. Statistical analysis

The primary objective of this meta-analysis was to evaluate the association of pretreatment LMR and OS in patients with CRC. The DFS was the secondary outcome. A pooled HR with 95% CI was calculated according to HR and 95% CI from each study. Multivariate analysis was selected when both univariate and multivariate analyses were existed. Higgins I^2 statistic and Cochran Q test were used for heterogeneity test. A fixed-effects model was applied if $I^2 \leq 50\%$ and $P \geq .10$. Correspondingly, the random-effects model was applied if $I^2 \geq 50\%$ and $P \leq .10$. If high heterogeneity existed, the sensitivity analysis was conducted by removing 1 study each time to decrease heterogeneity. Begg funnel plot was used to evaluate publication bias. All statistical analyses were carried out using the comprehensive meta-analysis program (Version 2, Biostat, Englewood, NJ).

3. Results

3.1. Description of included studies

A flow chart of the literature search was shown in Fig. 1. The initial search algorithm retrieved a total of 82 studies. Besides, 1

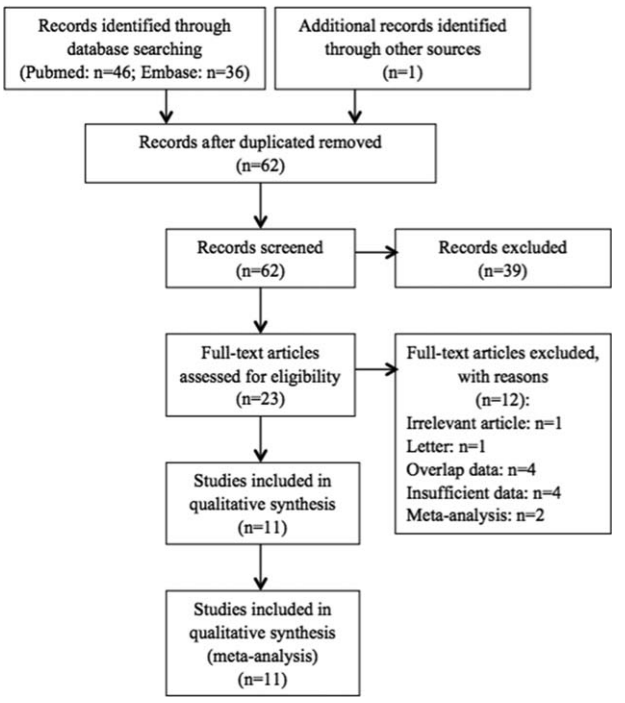

Figure 1. PRISMA diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1

Characteristics of all identified studies.

First author	Year	Country	Cancer location	Stage	Main treatment	Sampling time	LMR cut-off	No. of patients		Score
								Total	Low LMR	
Song[30]	2015	Korea	Colon and rectum	IV	PT	Pretherapy	3.40 ROC	177	113	7
Lin[25]	2016	China	Colon and rectum	IV	PC	3 d before chemotherapy	3.11 ROC	488	216	7
Kozak[31]	2015	USA	Colon and rectum	I–III	Surgical ± AC	30 d before surgery	2.60 Median	129	65	8
Shibutani[32]	2015	Japan	Colon and rectum	IV	PC	7 d before chemotherapy	3.38 ROC	104	38	8
Neal[33]	2015	UK	Colon and rectum	IV	Surgical ± NAC ± AC	Presurgery	2.35 ROC	302	83	7
Neofytou[34]	2015	UK	Colon and rectum	IV	NAC + surgical ± AC	10 d before surgery	3.00 ROC	140	75	8
Ozawa[35]	2015	Japan	Colon and rectum	IV	NAC + surgical ± AC	14 d before surgery	3.00 ROC	117	38	8
Stotz[36]	2014	Austria	Colon	II–III	Surgical ± AC	3 d before surgery	2.14 ROC	349	133	8
Xiao[26]	2015	China	Rectum	II	Surgical ± AC	Presurgery	3.78 Median	280	140	7
Li[27]	2016	China	Colon and rectum	I–III	Surgical ± AC	Presurgery	2.83 X-tile program	5336	1348	8
Chan[28]	2016	Australia	Colon and rectum	I–III	Surgical ± NAC ± AC	30 d before surgery	2.83 MaxStat analysis	1623	826	7

First author	Overall survival					Disease-free survival				
	HR (95% CI)	*P*	Multivariate analysis	Median survival (mos)		HR (95% CI)	*P*	Multivariate analysis	Median survival (mos)	
				Low LMR	High LMR				Low LMR	High LMR
Song[30]	1.66 (1.09–2.52)	0.018	Yes	5.9	12.4	—	—	—	—	—
Lin[25]	1.51 (1.14–2.00)	0.004	Yes	16.6	19.4	—	—	—	—	—
Kozak[31]	3.70 (1.47–9.43)	0.006	Yes	53.4	101.7	3.03 (1.08–8.85)	0.036	Yes	—	—
Shibutani[32]	0.58 (0.31–1.06)	0.077	Yes	—	—	—	—	—	—	—
Neal[33]	1.57 (1.16–2.11)	0.003	No	—	—	—	—	—	—	—
Neofytou[34]	2.43 (1.32–4.48)	0.004	Yes	55.0	85.0	1.21 (0.81–1.82)	0.338	No	—	—
Ozawa[35]	—	—	—	—	—	0.79 (0.51–1.24)	0.300	No	—	—
Stotz[36]	1.96 (1.21–3.23)	0.007	Yes	124.0	139.0	—	—	—	—	—
Xiao[26]	—	—	—	—	—	1.24 (1.04–1.48)	0.015	Yes	—	—
Li[27]	1.31 (1.07–1.61)	0.008	Yes	—	—	1.30 (1.14–1.50)	<0.001	Yes	—	—
Chan[28]	1.76 (1.48–2.09)	<0.001	Yes	—	—	—	—	—	—	—

—=Not reported, AC=adjuvant chemotherapy, CI=confidence interval, HR=hazard ratio, LMR=lymphocyte-to-monocyte ratio, NAC=neoadjuvant chemotherapy, PC=palliative chemotherapy, PT=palliative therapy (including palliative surgery, chemotherapy, or radiotherapy), ROC=receiver operating characteristic.

additional record was identified through other sources. There existed 62 studies after duplicated removed. After the initial review, only 23 relevant studies were further evaluated. Of these studies, 12 reports were excluded due to following reasons: 1 was irrelevant article; 1 was letter; 4 included overlap patients; 4 did not provide sufficient data for estimating the HR and 95% CI; and 2 were meta-analysis. Thus, 11 studies[25–28,30–36] published between 2014 and 2016 were included in our meta-analysis. The characteristics of the included studies were summarized in Table 1. A total of 9045 patients were enrolled. The studies came from the USA (n=1), UK (n=2), Austria (n=1), Japan (n=2), South Korea (n=1), Australia (n=1), and China (n=3). Seven studies reported that blood test was done within 30 days before treatment, whereas other 4 studies only reported blood test was done before treatment without time. LMR was calculated using the white blood cell counts. All enrolled studies had high quality (NOS scores ≥7).

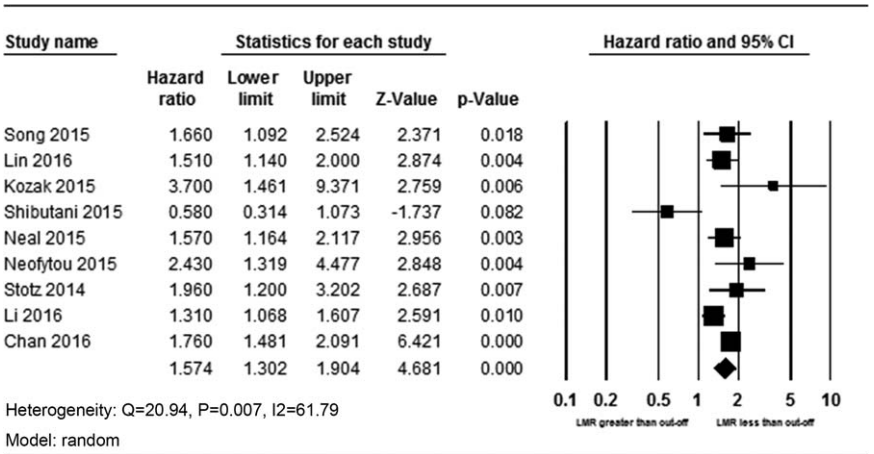

Figure 2. Forest plot of HR and 95% CI for overall survival. CI=confidence interval, HR=hazard ratio.

Table 2

Subgroup analyses according to stage and LMR cut-off value.

	Model	No. of studies	HR	95% CI	*P*
Overall	Random	9	1.57	1.30–1.90	<.001
Stage					
I–III	Random	4	1.70	1.30–2.23	<.001
IV	Random	5	1.45	1.06–1.99	.021
LMR cut-off					
<3.00	Random	5	1.60	1.43–1.80	<.001
≥3.00	Random	4	1.47	1.19–1.80	<.001

CI = confidence interval, HR = hazard ratio, LMR = lymphocyte-to-monocyte ratio.

3.2. Primary outcome: OS

Nine studies enrolling 8648 patients presented the data on LMR and OS. The random-effects model was used for the analysis due to the significant heterogeneity ($Q = 20.94$, $P = .007$, $I^2 = 61.79$). A pooled HR of 1.57 (95% CI 1.30–1.90, $P < .001$) showed that patients with low LMR have worse OS after treatment (Fig. 2). We conducted sensitivity analysis by removing 1 study each time, and the outcomes remained unchanged. Exploratory subgroup analyses according to stage and LMR cut-off values were performed (Table 2). In the subgroup analysis by stage, a prognostic role of LMR was observed for stage I to III and IV CRC (HR 1.70, 95% CI 1.30–2.23, $P < .001$; and HR 1.45, 95% CI 1.06–1.99, $P = .021$, respectively). The cut-off values used in included studies ranged from 2.14 to 3.78. Thus, we divided enrolled studies into 2 groups according to cut-off values: <3.00 and ≥3.00. Subgroup analysis showed a low LMR was associated with worse OS in <3.00 group (HR 1.60, 95% CI 1.43–1.80), and also in ≥3.00 group (HR 1.47, 95% CI 1.19–1.80, $P < .001$).

A total of 5 studies enrolling 6002 patients presented the data on LMR and DFS. Because a minor heterogeneity ($Q = 7.17$, $P = .127$, $I^2 = 44.19$) was observed, a fixed-effects model was used. A pooled HR of 1.25 (95% CI 1.13–1.39, $P < .001$) showed that patients with a low LMR have shorter DFS after treatment (Fig. 3).

3.3. Publication bias

A Begg funnel plot was used for the assessment of potential publication bias according to primary outcome (Fig. 4). According to the result, we observed evidence of publication bias ($P < .05$).

4. Discussion

The systemic inflammation is a key component of cancer progression since it can not only destroy cancer cells but also establish the tumor microenvironment to aids cancer cells proliferation and metastasis.[6,37,38] Literatures have demonstrated that several systemic inflammatory factors can be used to predict the prognosis of CRC patients, such as platelet-to-lymphocyte ratio[7] and neutrophil-to-lymphocyte ratio.[8,9] As a new factor of systemic inflammatory, LMR has been proved to be a predictor for haematologic malignancies,[39] and also for solid cancers.[23,24] Nishijima et al[24] showed that LMR was a prognostic factor for CRC patients in subgroup analysis, which included 4 studies. However, several other studies published later, and the results of those studies remain controversial.[25–28] Therefore, we conducted this up-to-date meta-analysis to investigate the prognostic role of LMR in CRC patients.

In our meta-analysis, we enrolled 11 articles comprising 9045 patients. According to the results, CRC patients with a low LMR had significantly worse OS, and also DFS. Additionally, to investigate the impact of different stage and cut-off values on the prognostic effect of LMR, we conducted subgroup analyses by stage and cut-off values. In the subgroup analysis, we found that the results remained unchanged that low LMR was an unfavorable predictor regardless of the different cut-off values and metastasis or not.

Although there have been 2 meta-analyses focusing on the prognostic role of LMR in solid cancer patients, both of them have limitations when it comes to the association of LMR and CRC patients. Teng et al[23] only included 3 reports focusing on CRC and did not analyze the association between LMR and CRC. The other study[24] did analyze the association between LMR and CRC, the results of which are in line with our results, but it only enrolled 4 studies. Besides, it did not do subgroup analysis for CRC patients. Our meta-analysis has following merits to cover these shortages. First, we included 11 studies with 9045 CRC patients, which is far more than previous meta-analysis. Second, we did subgroup analyses by stage and cut-off value, and the results remained unchanged.

Though this meta-analysis proved that LMR could be a prognostic factor for patients with CRC, it had some limitations that called for cautious interpretation of the results. First, there existed significant heterogeneity when analyzing the relationship between LMR and OS. Thus, the sensitivity analysis was conducted by removing 1 study each time. The outcomes remained unchanged compared with primary outcome. Therefore, we speculated that the heterogeneity might be caused by

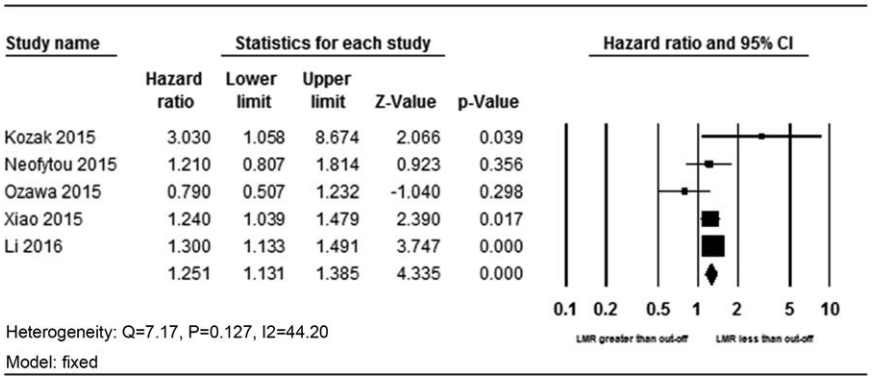

Figure 3. Forest plot of HR and 95% CI for disease-free survival. CI = confidence interval, HR = hazard ratio.

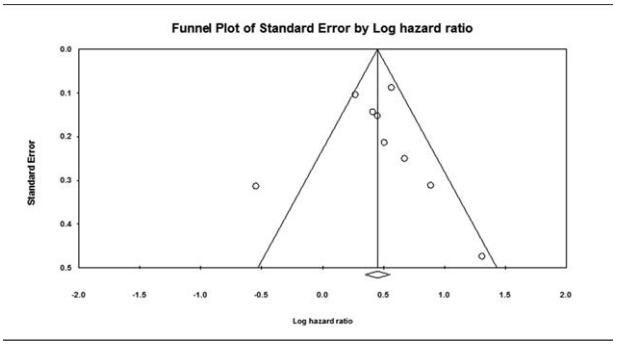

Figure 4. Begg funnel plot for the assessment of potential publication bias according to the primary outcome.

factors such as age, sex, stage, and cut-off value. Second, besides articles with OS or DFS as an endpoint, we also searched for articles with cancer-specific survival, postrecurrence survival, time to recurrence, or progression-free survival as an endpoint. However, we found only 3 articles for cancer-specific survival[33–35]—1 for postrecurrence survival,[34] 1 for time to recurrence,[36] and 1 for progression-free survival.[25] Given the small number, we did not analyze these endpoints in the meta-analysis. Third, all enrolled studies were retrospective study, which might induce patient selection bias. Fourth, there existed publication bias. The possible reason might be that the studies with negative results were difficult to publish. Despite these limitations, we believe that our results provide valuable support for the prognostic role of LMR in CRC patients.

In conclusion, this meta-analysis shows that a low LMR is associated with poor survival in patients with CRC, although the publication bias is existed. Large-sample multicenter prospective cohort is needed to assess the role of the LMR in CRC patients.

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