

Prognostic value of peripheral blood lymphocyte-to-monocyte ratio in patients with solid tumors: a meta-analysis

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Background: Although accumulating evidence suggests peripheral blood lymphocyte-to-monocyte ratio (LMR) could act as a prognosis predictor in various tumors, the prognostic value of LMR still remains controversial. We carried out this meta-analysis to evaluate the association of pre-treatment LMR with survival outcomes in patients with solid tumors.

Methods: Eligible studies were collected and extracted by searching PubMed and Embase databases up to June 3, 2015. The pooled hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed to assess the prognostic value of LMR quantitatively.

Results: Eighteen studies with a total of 8,377 participants were enrolled in this meta-analysis. Our findings indicated that elevated pre-treatment LMR predicted a significantly favorable overall survival (HR=0.59, 95% CI: 0.53–0.67) and disease-free survival (HR=0.74, 95% CI: 0.68–0.80) in solid tumor patients. Subgroup analyses revealed that enhanced LMR was significantly associated with favorable overall survival in patients with digestive system cancers (HR=0.63, 95% CI: 0.49–0.81), urinary tract tumors (HR=0.66, 95% CI: 0.52–0.84), lung cancer (HR=0.62, 95% CI: 0.54–0.72), and nasopharyngeal carcinoma (HR=0.50, 95% CI: 0.43–0.57).

Conclusion: This meta-analysis showed that enhanced LMR may indicate a favorable prognosis in patients with solid tumors.

Keywords: LMR, solid tumors, prognosis, meta-analysis

Introduction

Cancer has been an enormous burden in our society and it is one of the leading causes of death in both developing and developed countries. There were approximately 14.1 million new cancer cases and 8.2 million cancer-related deaths in 2012 worldwide.¹ Although the diagnostic and therapeutic approaches have improved in the past decades, cancer patients still have an unsatisfying prognosis mainly due to local recurrence and distal metastasis.² Therefore, it is of great significance for us to identify a practical biomarker to determine the optimal therapeutic strategies and predict the prognosis of cancers.

It is widely accepted that systemic inflammatory response plays a crucial role in the pathogenesis and progression of cancers.^{3,4} Several systemic inflammatory indicators, such as platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and neutrophil-to-lymphocyte ratio (NLR), have been explored to predict the prognosis in a wide variety of tumors.^{5–8} Among these predictors, lymphocytes are considered to play the crucial roles in the antitumor immunological reaction. An elevated pre-treatment lymphocyte count has been reported to be connected with the good prognosis of patients with Hodgkin lymphoma and non-small cell lung cancer.^{9,10} Monocytes can secrete a variety of proinflammatory cytokines, such as

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tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which are associated with poor prognosis in cancer patients.¹¹ Therefore, LMR, calculated as a simple ratio between lymphocyte and monocyte, may be a better prognostic factor for hematologic malignancies and solid tumors.^{9,10,12–17} However, the prognostic value of LMR for solid tumors patients remains controversial. Some studies revealed that the elevated pre-treatment LMR level was associated significantly with favorable prognosis for patients with solid tumors, such as gastric cancer,^{6,16} pancreatic cancer,⁸ lung cancer,^{10,12} nasopharyngeal carcinoma,^{14,15} and so on.^{13,18} Other studies had different views on this conclusion.^{5,6,19,20} Hutterer et al's¹⁹ research showed that LMR was not an independent prognostic factor for renal cell carcinoma patients' overall survival (OS) in multivariate analysis. A similar result was found for patients with gastric cancer in Deng et al's⁶ study. Therefore, we embarked on this meta-analysis to shed light on the association between LMR and the survival of patients with solid tumors.

Materials and methods

Search strategy and eligible criteria

A systematic literature search was carefully performed by using PubMed and Embase databases (updated on June 3, 2015). The search keywords were shown as follows: “lymphocyte monocyte ratio”, “lymphocyte to monocyte ratio”, “lymphocyte-monocyte ratio”, “lymphocyte-to-monocyte ratio”, “LMR” and “cancer”, “carcinoma”, “neoplasm”, and “tumor”. Searches were supplemented by scanning the references of selected articles. If there were overlapping and duplicate datasets detected on the same patient cohort, only the most informative or most recent report was involved in the analysis.

Studies selected in this meta-analysis need to satisfy the following criteria: (1) it researched on the patients with solid tumors; (2) it investigated the association between LMR and OS or disease-free survival (DFS); (3) LMR was calculated from peripheral blood cell count before any treatment was administered. Studies were excluded if they had any of the following items: (1) letters, case reports, conference abstracts, laboratory studies, or reviews; (2) study without sufficient data to extract the HR and its 95% CI; (3) LMR measured after anticancer treatment; and (4) duplicate publications.

Data extraction and qualitative assessment

The following information was independently extracted from each eligible study by two investigators (JJT and TYZ):

first authors' surname, publication year, sample size, country of origin, median age, types of diseases, disease stage, tumor grade, treatment strategy, follow-up, cut-off values, HR, and 95% CI of LMR for survival outcomes. The authors discussed to reach a consensus when there was disagreement. If the results were reported by both univariate and multivariate analysis, we choose the latter because it was more precise due to consideration of the confounding factors.

The quality of selected studies was independently evaluated by two reviewers (JJT and TYZ) according to the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses.²¹ Each study was judged from three broad perspectives, namely selection, comparability, and outcome. The score was obtained by using a “star system”, and studies with scores of 6 or more were considered as high quality.

Data analysis

The aggregated HRs and 95% CIs were used to evaluate the impact of LMR on OS or DFS. The statistical variables were directly extracted from the study, or calculated from available numerical data based on the method suggested by Tierney et al.²² An observed HR less than 1.0 implied a better prognosis in patients with high LMR. We performed the chi-square-based *Q*-statistic test and calculated the *I*-squared (*I*²) statistic to assess the interstudy heterogeneity. A fixed-effects model was selected if the heterogeneity among the enrolled studies was not significant ($P > 0.05$ for the *Q*-test and $I^2 < 50\%$). Otherwise, a random-effects model was applied. Publishing bias of literatures was assessed by using the Begg's funnel plot and Egger's linear regression test. All *P*-values were two-tailed, and $P < 0.05$ was considered to be statistically significant. Statistical analyses were conducted using Stata package version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Study selection and quality

According to the literature search methods as described earlier, a total of 1,283 studies were initially selected. After removing the duplicates, 743 studies were identified. However, 702 irrelevant studies were excluded by screening the title and abstract. Because this approach was not informative, 41 full-text articles were reviewed for further evaluation. In this process, we selected 18 studies and excluded 23 studies. Among these excluded studies, 15 were excluded because they reported the prognostic value of other inflammation index but not LMR-specific data; three were excluded, because the data of HR and 95% CI

were not available; two were excluded, because the survival outcomes did not focus on OS or DFS. Three other studies were also ineligible, because the LMR involved was measured after treatment. Finally, 18 studies^{6–8,10,12–16,18–20,23–28} were enrolled in our meta-analysis. The flowchart of the studies selection process is shown in Figure 1. The quality score evaluated by the NOS ranged from 6 to 8 with a mean value of 6.7.

Characteristics of the included studies

The main characteristics of the 18 enrolled studies are shown in Table 1. All studies were retrospective. Sixteen studies reported OS, and eight studies investigated DFS. This meta-analysis enrolled a total of 8,377 participants, who were diagnosed with a variety of solid tumors, including pancreatic carcinoma,⁸ esophageal squamous cell carcinoma,⁷ gastric cancer,^{6,16} lung cancer,^{10,12,23} colorectal cancer,^{18,24} nasopharyngeal carcinoma,^{14,15,25} and others.^{26–28} Among the 18 enrolled studies, 13 studies evaluated Asian populations, and five evaluated Caucasian patients. The LMR cutoff values ranged from 2.14 to 5.22 and were identified with different methods among studies: 13 studies using receiver operating characteristic (ROC) curve analysis, four using the

median LMR of the patient group, and one using log-rank test. Nine studies enrolled more than 300 patients, and nine studies enrolled less than 300 patients. All studies used the white blood cell counts based on pre-treatment laboratory data to calculate LMR. For all patients who underwent surgical treatment, LMR was measured preoperative. The effect of pre-treatment LMR on survival outcomes in all studies was assessed by multivariate analysis.

Meta-analysis results

Relationship between LMR and OS

For 16 studies evaluating the correlation between LMR and OS, there appeared to have an overall moderate but not statistically significant level of heterogeneity ($I^2=44.7\%$, $P=0.024$). Hence, a random-effects model was applied to pool the HR and its 95% CI (Figure 2). We found that an elevated pre-treatment LMR predicted a significantly favorable OS with combined HR of 0.59 (95% CI: 0.53–0.67, $P<0.001$) (Table 2).

To minimize the influence of heterogeneity, we further conducted seven subgroup analyses based on ethnicity, LMR cut-off value, sample size, median age, type of cancers, and tumor stage/grade (Table 2). In the subgroup of ethnicity, a pooled analysis of nine studies in Asians demonstrated that increased LMR was significantly associated with enhanced OS (HR=0.61, 95% CI: 0.53–0.69, random-effects model, $I^2=55.5\%$). Enhanced OS in Caucasians with elevated pre-treatment LMR was also found by merging five studies with pooled HR of 0.56 (95% CI: 0.45–0.71, fixed effect model; $I^2=19.4\%$). When stratified by cancer type, the result indicated that LMR was a favorable prognostic marker in patients with digestive system carcinomas (HR=0.63, 95% CI: 0.49–0.81, random-effects model; $I^2=61.4\%$), urinary tract tumors (HR=0.66, 95% CI: 0.52–0.84, fixed-effects model; $I^2=0.0\%$), lung cancer (HR=0.62, 95% CI: 0.54–0.72, fixed-effects model; $I^2=5.1\%$), and nasopharyngeal carcinoma (HR=0.50, 95% CI: 0.43–0.57, fixed-effects model; $I^2=0.0\%$) (Figure 3). In the subgroup of the LMR cut-off value, merging eight studies of cut-off value >3 indicated that increased LMR was significantly associated with enhanced OS (HR=0.63, 95% CI: 0.54–0.73, random-effects model; $I^2=55.0\%$). The same outcome was also shown in meta-analysis of studies of cut-off value ≤ 3 (HR=0.53, 95% CI: 0.46–0.61, fixed-effects model; $I^2=0.0\%$). In the subgroup of sample size, we found that no matter the sample size >300 or <300 , high LMR level was still a favorable predictor for OS (HR=0.63, 95% CI: 0.54–0.73, HR=0.55, 95% CI: 0.48–0.64, respectively). When stratified by tumor stage, we found that

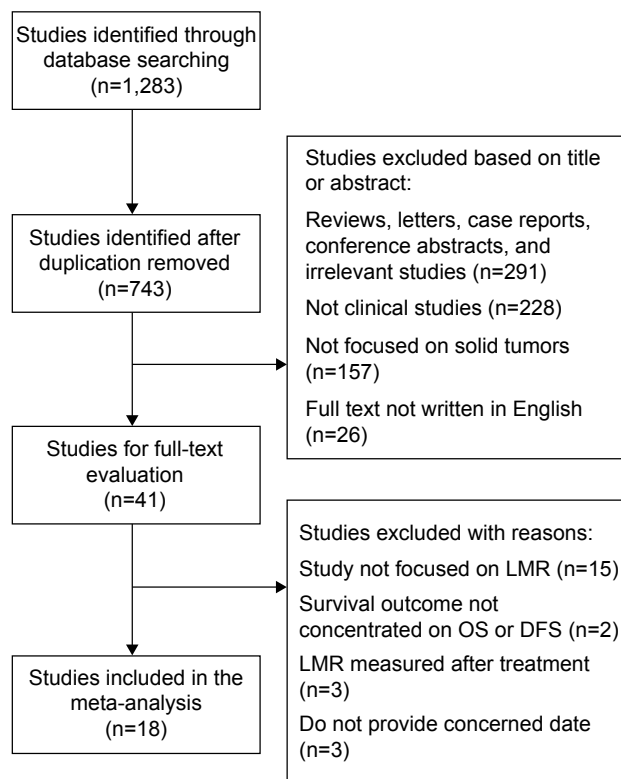


Figure 1 Flow diagram of the study search and selection process.

Abbreviations: DFS, disease-free survival; LMR, Lymphocyte-to-monocyte ratio; OS, overall survival.

Table 1 Main characteristics of the eligible studies

First author publication year	Country of origin	Ethnicity	Number	Age (years) (median and range)	Grade	Cancer type	Stage	Treatment received	Cut-off value	Follow-up (months)	Survival outcome ratios	Hazard ratios	NOS
Qi et al, 2015 ⁸	People's Republic of China	Asian	211	<60 (101) >60 (110)	-	PC	Mixed*	Chemotherapy	3.30 median	NR	OS	Reported	6
Han et al, 2015 ⁷	People's Republic of China	Asian	218	60.5 (32-84)	G1-3	ESCC	Non-metastatic	Surgery ± chemotherapy/ radiotherapy	2.57 ROC	38.6 (3.0-71.0)	OS/DFS	DE	6
Deng et al, 2015 ⁶	People's Republic of China	Asian	389	65 (29-92)	G1-4	GC	Mixed*	Surgery	4.95 ROC	24.0 (3.0-60.0)	OS/DFS	Reported	7
Stotz et al, 2014 ¹⁸	Austria	Caucasian	372	64 (27-95)	G1-3	CC	Non-metastatic	Surgery ± chemotherapy	2.14 ROC	68.0 (1.0-190.0)	OS	Reported	7
Zhou et al, 2014 ¹⁶	People's Republic of China	Asian	426	>60	G1-3	GC	Non-metastatic	Surgery ± chemotherapy	4.32 ROC	39.6 (2.6-85.6)	OS	Reported	7
Kozak et al, 2015 ²⁴	USA	Caucasian	129	67 (30-95)	G1-3	CRC	Non-metastatic	Surgery ± chemotherapy	2.60 median	24.7 (4.2-101.7)	OS/DFS	Reported	8
Li et al, 2013 ¹⁴	People's Republic of China	Asian	1,547	51 (6-87)	-	NPC	Non-metastatic	Radiotherapy ± chemotherapy	5.22 ROC	67.1 (1.4-99.0)	OS/DFS	Reported	8
Lin et al, 2014 ¹⁵	People's Republic of China	Asian	256	53.6 (35-69)	-	NPC	Metastatic	Chemotherapy	5.07 ROC	22.6 (5.1-42.3)	OS	Reported	8
Lin et al, 2014 ¹⁰	People's Republic of China	Asian	370	63.6 (36-72)	-	NSCLC	Metastatic	Chemotherapy	4.56 ROC	NR	OS	Reported	6
Hutterer et al, 2014 ¹⁹	Austria	Caucasian	678	65 (20-88)	G1-4	ccRCC	Non-metastatic	Surgery	3.00 ROC	44.0 (0.0-130.0)	OS	DE	7
Hutterer et al, 2015 ¹³	Austria	Caucasian	182	70	G1-4	UTUC	Non-metastatic	Surgery	2.00 ROC	NR	OS	Reported	6
Szkandera et al, 2014 ²⁰ (a)	Austria	Caucasian	170(T)	64	G1-3	STS	Non-metastatic	Surgery + adjuvant treatments	2.85 LRT	Over120	OS/DFS	Reported	6
Szkandera et al, 2014 ²⁰ (b)	Austria	Caucasian	170(V)	61	G1-3	STS	Non-metastatic	Surgery + adjuvant treatments	2.85 LRT	Over120	OS/DFS	Reported	6
Hu et al, 2014 ¹²	People's Republic of China	Asian	1,453	59 (20-84)	G1-4	LC	Non-metastatic	Surgery	3.68 ROC	NR	OS/DFS	DE	6
Go et al, 2014 ²³	Korea	Asian	188	>60 (43-82)	-	SCLC	Mixed*	Chemotherapy ± radiotherapy	4.19 ROC	41.9 (2.1-92.5)	OS	DE	7
Zhang et al, 2015 ²⁶	People's Republic of China	Asian	124	65 (30-78) <65 (61)	G1-G3	BCa	Mixed*	Surgery ± chemotherapy/ radiotherapy	2.80 ROC	NR	OS	Reported	6
Jiang et al, 2015 ²⁵	People's Republic of China	Asian	672	>65 (63) 46 (13-79)	-	NPC	Metastatic	Chemotherapy/ radiotherapy	2.14 ROC	NR	OS	Reported	6
Ni et al, 2014 ²⁸	People's Republic of China	Asian	542	49	G1-3	BC	Non-metastatic	Surgery + NCT	4.25 ROC	45.9 mean	DFS	Reported	7
Xiao et al, 2015 ²⁷	People's Republic of China	Asian	280	<61 (133) >61 (147)	G1-3	RC	Non-metastatic	Surgery ± chemotherapy	3.78 median	52.0 (0.5-106.4)	DFS	Reported	7

Note: *Represents a mixed group including both no-metastatic and metastatic diseases.

Abbreviations: BCa, bladder cancer; BC, breast cancer; CC, colon cancer; ccRCC, clear cell renal cell carcinoma; CRC, colorectal cancer; DE, data-extrapolated; DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; LC, lung cancer; LRT, log-rank test; NOS, Newcastle-Ottawa Scale; NPC, nasopharyngeal carcinoma; NR, not reference; NSCLC, non-small cell lung cancer; NCT, neoadjuvant chemotherapy; OS, overall survival; PC, pancreatic cancer; RC, rectal cancer; ROC, receiver operating characteristic; SCLC, small cell lung cancer; STS, soft tissue sarcoma; T, training set; UTUC, upper urinary tract urothelial carcinoma; V, validation set.

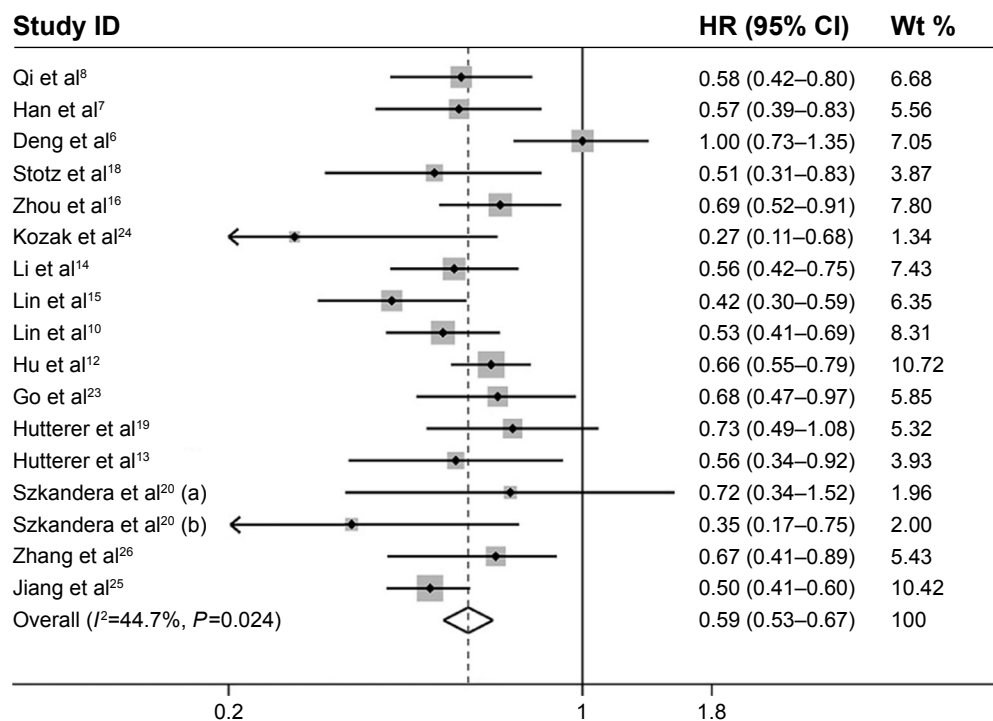


Figure 2 Forest plots of studies evaluating the association between LMR and OS in solid tumor patients.

Note: Weights are from random-effects analysis.

Abbreviations: CI, confidence interval; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; OS, overall survival; wt, weight.

high levels of LMR predict a better OS for non-metastatic diseases (HR=0.62, 95% CI: 0.55–0.69), metastatic diseases (HR=0.49, 95% CI: 0.43–0.57), and mixed group (HR=0.72, 95% CI: 0.56–0.93). Similarly, subgroup analyses stratified by median age and tumor grade did not alter the prognostic role of LMR in OS (Table 2).

Relationship between LMR and DFS

For eight studies evaluating DFS, a fixed-effects model was used in that there was no significant heterogeneity among them ($I^2=44.2$, $P=0.073$). The pooled HR was 0.74 (95% CI: 0.68–0.80) (Figure 4), which indicated that high LMR level was significantly connected with favorable DFS. Similar to OS analyses, subgroup analyses stratified by ethnicity, LMR cutoff value, sample size, median age, type of cancers, and tumor stage/grade were also conducted. As shown in Table 2, the pooled outcomes indicated that high LMR was also significantly associated with favorable DFS in all subgroup analyses.

Heterogeneity analysis

To explore the most possible sources of heterogeneity in the OS meta-analysis, a sensitivity analysis was performed by removing one study each time and evaluating the pooled HRs again. We found that Deng et al's⁶ study distinctively influenced the overall results (Figure 5A). When we removed

this study from the analysis, the heterogeneity became insignificant ($P=0.298$, $I^2=13.6%$), whereas the pooled outcome still indicated that LMR was a favorable predictor for OS (HR=0.58, 95% CI: 0.53–0.62). Consequently, we considered that Deng et al's study was responsible for the heterogeneity. We also performed a meta-regression to explore the potential factors that lead to heterogeneity in the OS meta-analysis. As a result, factors including published year ($P=0.72$), ethnicity ($P=0.52$), tumor type ($P=0.92$), median age ($P=0.23$), tumor stage ($P=0.52$), tumor grade ($P=0.55$), and sample size ($P=0.28$) did not significantly contribute to the heterogeneity, whereas LMR cutoff value ($P=0.07$) was perhaps the source of heterogeneity. In the DFS studies,^{6,7,12,14,20,24,27,28} we also conducted a sensitivity analysis. The result showed that no individual study significantly affected the pooled outcome (Figure 5B).

Publication bias

We assessed a publication bias of the enrolled studies by using the Begg's funnel plot and Egger's test. In the analyses of OS, the funnel plots seemed symmetrical (Figure 6A). The P -value of Begg's and Egger's tests was 0.34 and 0.54, respectively. Hence, no proof of significant publication bias was detected for OS. However, the asymmetric funnel plots (Figure 6B) and the result of Egger's test ($P=0.03$) indicate a potential publication bias for DFS.

Table 2 Overall and subgroup analyses results of OS or DFS stratified by ethnicity, sample size, cut-off value, median age, cancer type, and tumor stage/grade

Subgroup	OS						DFS					
	Study number	Patients number	HR (95% CI)	P-value	Model	I^2 (%)	Study number	Patients number	HR (95% CI)	P-value	Model	I^2 (%)
Total	16	7,556	0.59 (0.53–0.67)	<0.001	Random	0.024	8	4,898	0.74 (0.68–0.80)	<0.001	Fixed	0.073
Ethnicity												
Asian	11	5,854	0.61 (0.53–0.69)	<0.001	Random	0.013	6	4,429	0.75 (0.69–0.82)	<0.001	Fixed	0.276
Caucasian	5	1,702	0.56 (0.45–0.71)	<0.001	Fixed	0.287	2	469	0.36 (0.21–0.60)	<0.001	Fixed	0.950
Sample size												
>300	8	5,907	0.63 (0.54–0.73)	<0.001	Random	0.011	4	3,931	0.75 (0.67–0.83)	<0.001	Fixed	0.201
<300	8	1,649	0.55 (0.48–0.64)	<0.001	Fixed	0.332	4	967	0.56 (0.39–0.80)	<0.001	Random	0.048
Median age												
>60	12	3,628	0.67 (0.41–0.89)	<0.001	Fixed	0.094	5	1,374	0.66 (0.49–0.87)	<0.001	Random	0.023
<60	4	3,928	0.54 (0.45–0.65)	<0.001	Random	0.063	3	3,524	0.72 (0.64–0.80)	<0.001	Fixed	0.653
Tumor stage												
Non-metastatic	9	2,598	0.62 (0.55–0.69)	<0.001	Fixed	0.476	0	–	–	–	–	–
Metastatic	3	837	0.49 (0.43–0.57)	<0.001	Fixed	0.554	1	389	–	–	–	–
Mixed*	4	912	0.72 (0.56–0.93)	0.011	Random	0.094	7	4,509	0.72 (0.66–0.79)	<0.001	Fixed	0.164
Tumor grade												
GI–3	5	3,082	0.58 (0.48–0.70)	<0.001	Fixed	0.268	5	1,842	0.71 (0.62–0.81)	<0.001	Fixed	0.084
GI–4	4	2,703	0.73 (0.58–0.92)	0.008	Random	0.099	2	1,491	0.79 (0.69–0.90)	<0.001	Fixed	0.112
Cut-off value												
>3	9	4,964	0.63 (0.54–0.73)	<0.001	Random	0.023	5	4,211	0.76 (0.70–0.83)	<0.001	Fixed	0.283
≤3	7	2,592	0.53 (0.46–0.61)	<0.001	Fixed	0.431	3	687	0.51 (0.37–0.68)	<0.001	Fixed	0.417
Cancer type												
Digestive system cancer	6	1,745	0.63 (0.49–0.81)	<0.001	Random	0.024	4	1,016	0.76 (0.58–0.98)	0.037	Random	0.073
Urinary tract tumor	3	985	0.66 (0.52–0.84)	0.001	Fixed	0.716	0	–	–	–	–	–
NPC	3	2,475	0.50 (0.43–0.57)	<0.001	Fixed	0.459	1	1,547	0.67 (0.53–0.84)	<0.001	–	–
Lung cancer	3	2,011	0.62 (0.54–0.72)	<0.001	Fixed	0.349	1	1,453	0.75 (0.65–0.87)	<0.001	–	–
Others	1	340	0.60 (0.30–0.85)	0.01	Fixed	0.180	2	882	0.60 (0.46–0.78)	<0.001	Fixed	0.203

Note: *Represents a mixed group including both no-metastatic and metastatic diseases.

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NPC, nasopharyngeal carcinoma; OS, overall survival.

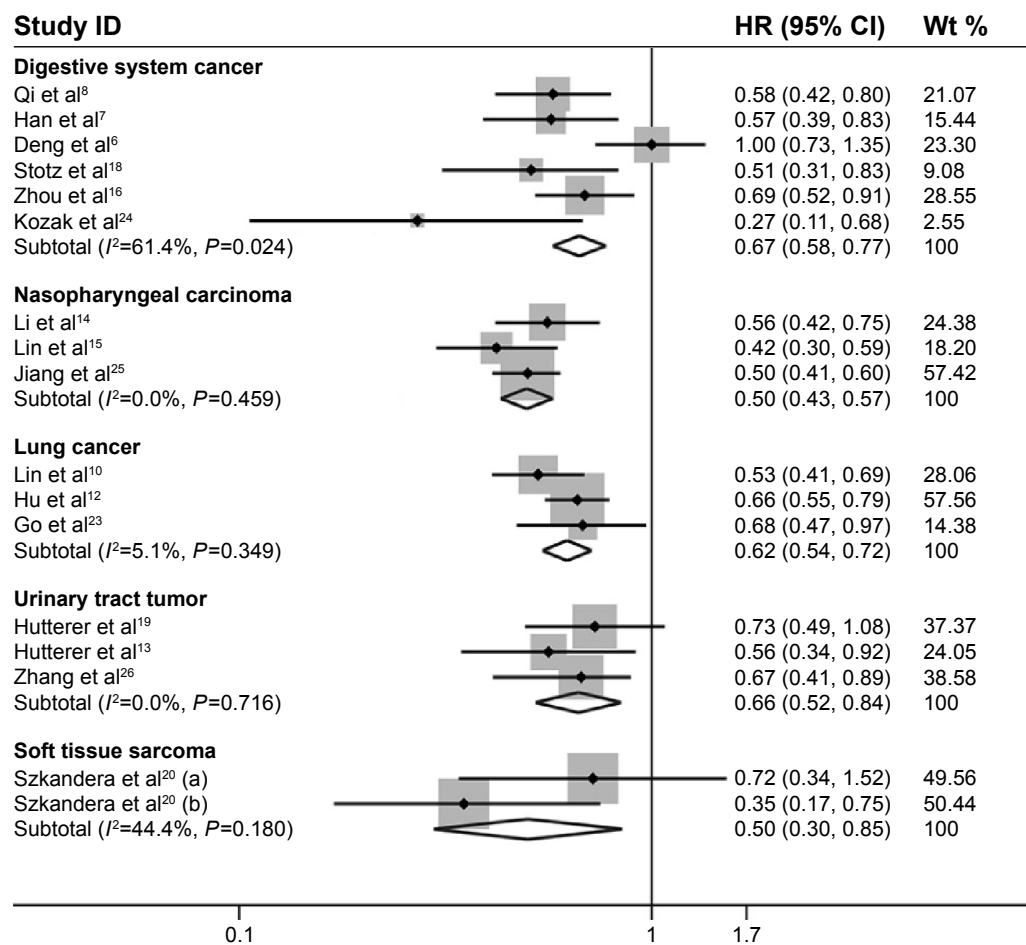


Figure 3 Forest plots for the subgroup analysis of OS in different malignant diseases. **Abbreviations:** CI, confidence interval; HR, hazard ratio; OS, overall survival; wt, weight.

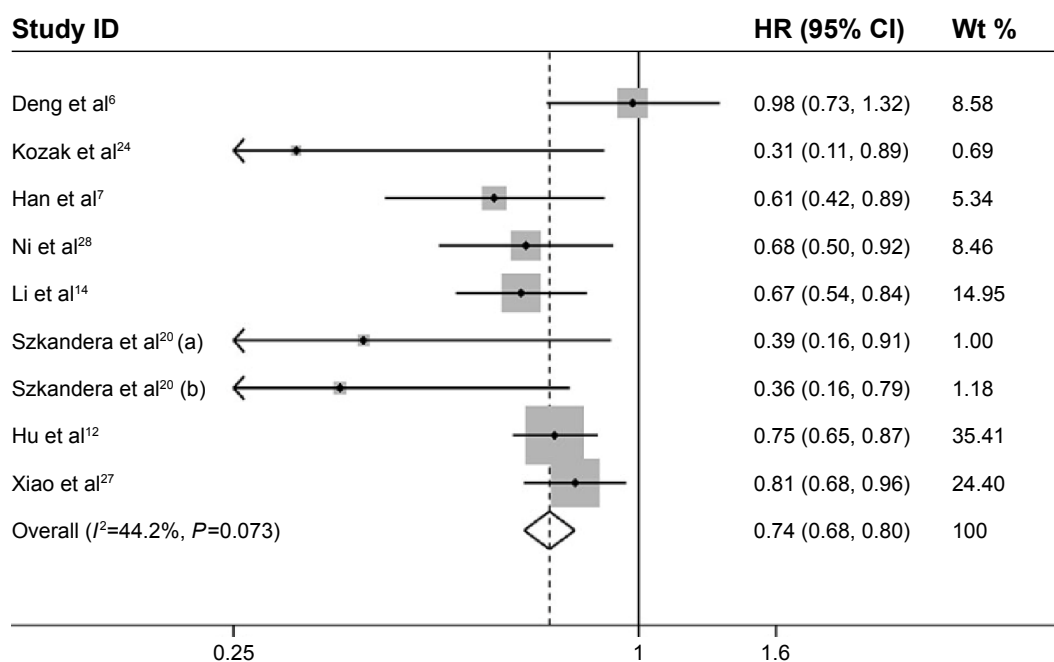


Figure 4 Forest plots of studies evaluating the association between LMR and DFS in solid tumor patients. **Abbreviations:** CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; wt, weight.

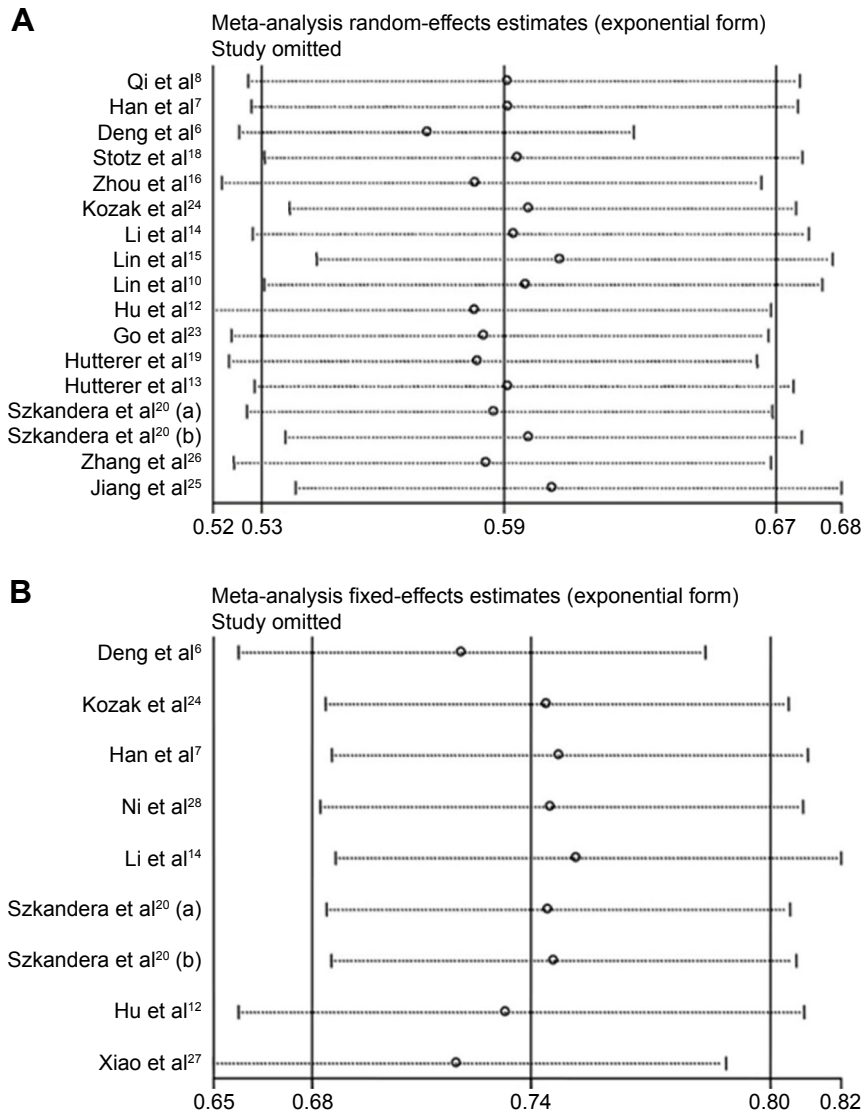


Figure 5 Sensitivity analysis for meta-analysis of LMR. **Notes:** (A) Effect of single study on the pooled HR for LMR and OS of patients. (B) Effect of single study on the pooled HR for LMR and DFS of patients. **Abbreviations:** DFS, disease-free survival; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; OS, overall survival.

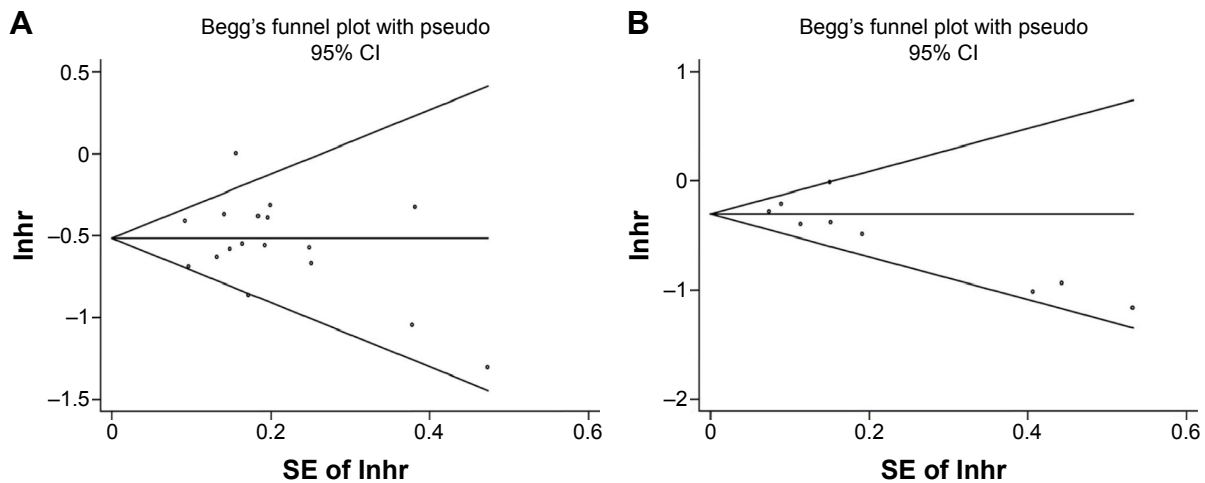


Figure 6 Publication bias in this meta-analysis. **Notes:** (A) Begg's funnel plots of publication bias for merged analysis of OS. (B) Begg's funnel plots of publication bias for merged analysis of DFS. **Abbreviations:** CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; SE, standard error.

Discussion

During the past few years, many kinds of predictors have been found and applied for predicting solid tumors outcomes, including inflammatory factors. Many tumors may rise from the sites of chronic irritation, infection, and inflammation.²⁹ Inflammation is a key component of cancer progression. Cancer-related inflammation also aids malignant cells proliferation and promotes tumor-correlated angiogenesis and metastasis.⁴ As important inflammatory markers, lymphocytes and monocytes have been independently connected with the prognosis of various malignant neoplasms.^{30,31} The pre-treatment LMR potentially balances the effects of lymphocytes, and monocytes makes it a useful prognostic factor. Moreover, because pre-treatment hematological tests are routinely measured in the clinic, LMR seems to be an easily obtained, inexpensive, and a robust predictor.

To the best of our knowledge, our meta-analysis is the first systematic study to determine the prognostic value of LMR in patients with solid tumors. Our combined results showed that elevated LMR was associated with favorable OS and DFS. Furthermore, subgroup analyses were performed based on types of cancers, ethnicity, cut-off value, median age, sample size, and tumor stage/grade. We found that elevated LMR was a favorable predictor for both Asians and Caucasians, but the association in Caucasians was stronger than that in Asians. We also showed that high LMR was connected with favorable OS and DFS in patients diagnosed with digestive system cancers, as well as nasopharyngeal carcinoma and lung cancer. Similar results were also shown in other six subgroup analyses. Therefore, LMR is a promising prognostic biomarker that can be used to estimate survival outcomes of solid tumor patients. To find the potential sources of heterogeneity in studies for OS, sensitivity analysis and meta-regression were conducted. Result of the sensitivity analysis indicated that the study of Deng et al⁶ was responsible for the heterogeneity. Deng et al's study assessed the prognostic value of NLR, derived (dNLR), PLR, and LMR in patients with gastric cancer. It found that elevated LMR was significantly associated with enhanced OS in univariate analysis but insignificantly in multivariate analysis. The insignificant prognostic effect of elevated LMR in this study perhaps induced a negative result in our meta-analysis. The result of meta-regression showed that LMR cut-off value may be the potential sources of heterogeneity. Studies included using different methods to explore the LMR cut-off value. However, subgroup analyses demonstrated that LMR was an effective prognostic factor, regardless of the cut-off value >3 or ≤ 3 .

At present, the exact mechanism of the prognostic value of LMR in solid tumor patients is poorly understood. Several

underlying mechanisms for this association are listed as follows. First, lymphocytes as crucial components of host immunity play important role in the antitumor immunological reaction by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration.^{4,29} Previous studies have reported that tumor-infiltrating lymphocytes are associated with favorable prognosis in patients with various carcinomas.^{31,32} Infiltrated CD4⁺ and CD8⁺ T cells are essential to the antitumor immunological reaction and can induce tumor cell apoptosis via interaction among each other.^{33,34} However, systemic inflammation response from malignant cells could cause immunosuppression, for which tumor cells can escape host immune surveillance.³⁵ A low lymphocyte count has been found in many human neoplasms, and it is often associated with worse clinical outcomes, which may be due to the depressed lymphocyte-mediated immune response to the tumor.³⁶ On the other hand, macrophages derived from circulating monocytes show specific phenotypic characteristics. Increasing evidence demonstrated the high density of tumor-associated macrophages in a wide spectrum of tumors is associated with increased tumor-correlated angiogenesis, invasiveness, and poor outcomes.³⁷ Macrophages may enhance tumor development and angiogenesis by releasing TNF- α , vascular endothelial growth factor, and epidermal growth factor.^{38,39} As mentioned earlier, LMR combined with the effects of lymphocyte and monocyte may be a stronger predictor of prognosis for cancer patients.

Although the present meta-analysis showed that high LMR level was associated with favorable outcomes, the results should be interpreted cautiously for several limitations identified in our study. First, there was some heterogeneity among included studies. Heterogeneity might be caused by the differences in age, sex, ethnicity, sample sizes, types of the tumors, disease stage, treatment received, cut-off values of LMR, durations of follow-up, and other factors. Despite a random-effects model was applied, the factor and study found responsible for heterogeneity should be paid attention to while considering the related conclusions. Second, several HRs and 95% CI were calculated from available numerical data in the studies, which may bring minor deviations. Third, the cut-off value of LMR applied in the enrolled studies was not unified. Fourth, the eligible studies were all retrospective analysis. Finally, although no evidence of significant publication bias was noted in OS meta-analysis, there was significant publication bias in DFS meta-analysis. Several reasons may lead to the publication bias. On the one hand, our study included only published articles and meanwhile they were all written in English. On the other hand, studies with positive results were more

easily to be published than those with negative results. Even though published, they were usually unassessable due to the concise reports of results.

Conclusion

In summary, our study demonstrated that increased pre-treatment LMR is correlated with significantly favorable outcomes in patients with solid tumors. We consider that LMR, a widely available, inexpensive, and robust inflammatory biomarker, could be widely used to evaluate the prognosis of solid tumors. However, because all studies included in our meta-analysis were retrospective, larger prospective, and multicenter studies should be performed to confirm the predictive value of LMR. Future studies based on large sample to explore a definitive LMR cut-off value are also recommended. Additionally, specific therapies or interventions to modify a low pre-treatment LMR level may be proven to be beneficial in improving the prognosis of patients with solid tumors. Targeting systemic inflammation may be an effective treatment for tumor patients with low LMR. All of these possibilities are necessary to be addressed in the near-future studies.

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Disclosure

The authors report no conflicts of interest in this work.

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