The predictive value of lymphocyte-to-monocyte ratio in the prognosis of acute coronary syndrome patients: A systematic review and meta-analysis

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Abstract

The association between the lymphocyte-to-monocyte ratio (LMR) and prognosis of patients with acute coronary syndrome (ACS) is not fully understood. We performed this systematic review and meta-analysis to evaluate the correlation between LMR and mortality or major adverse cardiac events (MACE) in patients with ACS.Methods A systematic search was performed in PubMed, MEDLINE, EMBASE, the Cochrane Library, Scopus and Web of science. The association between LMR and mortality or MACE was analyzed in patients with ACS. The search was updated to August 1, 2019.Results A total of 5 studies comprising 3122 patients were included in this meta-analysis. The results showed that lower LMR predicted short-term mortality/MACE (odds ratio [OR] = 2.61, 95% confidence interval [CI]: 1.15–5.94, P = 0.022) and higher long-term mortality/MACE (OR = 2.10, 95% CI: 1.06–4.19, P = 0.035). According to our subgroup analysis, there still has a statistical significance for LMR predict short-term mortality/MACE in lager sample size researches (≥600, OR = 3.50, 95% CI: 1.84–6.67, p < 0.001),Turkey researches (OR = 4.16, 95% CI: 2.32–7.46, p < 0.001), younger patients researches (< 62, OR = 3.76, 95% CI: 2.29–6.18, p < 0.001).Conclusions This study suggested that lower LMR value might be associated with higher short-term mortality/MACE and long-term mortality/MACE in patients with ACS.

Background

Coronary heart disease (CHD) is one of the largest causes of death and disease burden worldwide [1]. Acute coronary syndrome (ACS) is a severe category of CHD. ACS includes unstable angina (UA), ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). Some studies indicate that nearly half of all deaths from coronary heart disease occur after ACS [2, 3]. Therefore, the prognosis of ACS patients has aroused extensive research. CHD has a strong relationship with atherosclerotic plaques [4-6]. The atherosclerotic plaques are accompanied by the infiltration of inflammatory cells (neutrophils, monocytes and lymphocytes) [7-9]. Recent many studies researched the relationship between inflammatory markers and the prognosis of ACS.

The neutrophil-to-lymphocyte ratio (NLR) has been established a valuable independent predictor of the prognosis of ACS, the severity of CHD, cardiovascular mortality [10-12]. Compared with neutrophils, monocytes play a more important role in the development and progression of atherosclerotic disease [13]. Monocytes are not only participants in atherosclerosis, but also passive responders of disease [14]. In addition, many studies showed that monocytes are associated with myocardial infarction (MI) and left ventricular remodeling [15, 16].

Previous studies have shown the relationship between lymphocyte-monocyte ratio (LMR) and the prognosis of ACS. However, the relationship between LMR and prognosis of ACS remains to be further discussion. We performed this meta-analysis to comprehensively summarize the relationship between LMR and mortality/major adverse cardiac events (MACE) in patients with ACS.

Methods

Search strategy

This meta-analysis was performed followed the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic literature search was conducted in PubMed, MEDLINE, EMBASE, the Cochrane Library, Scopus and Web of science. The following terms were used to search literatures: “STEMI”,“UA”, “NSTEMI”, “lymphocyte to monocyte ratio”, “lymphocyte-to-monocyte ratio”, “lymphocyte/monocyte ratio”, “monocyte/lymphocyte ratio”, “mortality”, “MACE” and “major adverse cardiac events”. The latest update was performed in August 1, 2019. In order to identify other potentially relevant literatures, the reference lists of all retrieved articles were also screened. If necessary information was missing, we emailed the authors to obtain additional information.

Inclusion and exclusion criteria

Studies were included if they met all the following criteria: (1) articles were published as full-text in English; (2) patients with ACS (STEMI, UA, NSTEMI); (3) LMR (odds ratio [OR], 95% confidence interval [CI]) was available; (4) the outcomes were associated with mortality or MACE. Studies were excluded if they met any of the following characteristics: (1) nonhuman studies; (2) duplicate studies; (3) absence of LMR or mortality/MACE. Two investigators (Run-Chang Wang and Qing Zhang) read the literature independently of each other. Disagreements were solved by discussion with other investigators.

Data extraction and quality assessment

The following data were extracted: the first author, country of patients, duration, mean age, sample size of patients, LMR cut-off value, diseases of patients, ORs and 95% CIs and outcomes. The outcomes of the studies included mortality (including in-hospital, 30-day, 36-month and long-term mortality) and MACE (including stroke/transient ischemic attack, target vessel revascularization, non-fatal MI, and cardiac death). The methodological quality of each study was evaluated with Newcastle-Ottawa Scale (NOS) system [17]. The maximum score is 9 and the study with a NOS score ≥ 6 was considered as a high-quality study.

Statistical analysis

All statistical analyses were in the present study were conducted with STATA statistical software (version 13.1). We only synthesized the OR and corresponding 95% CI to analysis of the relationship between LMR and mortality/MACCE. Between-study heterogeneity was assessed using Cochrane's Q and I^2 texts. A fixed-effects model was applied in the absence of significant heterogeneity ($I^2 \leq 50\%$), or the random effect model was applied ($I^2 > 50\%$). A two-sided p value of less than 0.05 was considered statistically significant.

Results

The literature search and include studies

A flowchart of the literature search was shown in Figure 1. Initially, in the primary search from the major databases, a total of 674 studies were included. After removing duplicates and screening title and abstracts, a total of 132 papers were remained, but 118 of them did not meet our purpose. The remaining 14 articles were assessed for eligibility based on full-text review, 9 were deemed ineligible. After qualitative and quantitative analysis, according to the inclusion criteria, only 5 studies published from 2015 to 2019 were selected for our meta-analysis [18-22].

The main characteristics of the included studies were listed in Table 1. A total of 3122 patients were included. These studies were all observation researchers and two conducted in Turkey [18, 19], three conducted in China [20-22]. The mean age of the patients ranges from 58.9 years old to 63.5 years old. One studies explicitly stated that there were no statistically significant differences of age between LMR groups [20], but four studies showed statistically significant differences of age [18, 19, 21, 22]. Three studies enrolled STEMI patients and all the patients underwent percutaneous coronary intervention (PCI) [18-20]. Two studies enrolled NSTEMI patients [21, 22]. One of the studies explicitly stated that the enrolled NSTEMI patient underwent PCI [21], while the other did not specify if enrolled patient underwent PCI [22]. Three studies reported the mortality [18, 19, 21], and two studies reported MACE [20, 22]. According to the Newcastle-Ottawa scale (NOS) [17], all cohort studies were of high quality and had scores of seven or more.

LMR and Mortality/MACE

The short-term was included in-hospital and 30-day. Others were defined as long-term. The combined analysis of 4 studies covering 2444 patients described the relationship between LMR and short-term mortality/MACE [18-20, 22], the result showed that LMR predicted short-term mortality/MACE (OR = 2.61, 95% CI: 1.15–5.94, P = 0.022, Figure 2A), with high heterogeneity among studies (I^2 = 85.1%, p < 0.001). The combined analysis of 3 studies covering 1302 patients described the relationship between LMR and long-term mortality/MACE. The pooled outcome for low LMR value compared with high LMR value group was found to be 2.10 (95% CI: 1.06– 4.19, P = 0.035, Figure 2B), also with high heterogeneity among studies (I^2 = 93.0%, p < 0.001).

Subgroup analysis

We conducted subgroup analysis to further analyze the association between LMR and mortality/MACE according to country of patients (Turkey and China), diseases of patients (STEMI and NSTEMI), sample size (≥600 and <600) and mean age (≥62 and <62). For 4 studies that researched LMR and short-term mortality/MACE [18-20, 22]. According to the results of subgroup analysis (Table 2), Low LMR predicted short-term mortality/MACE showed a statistical significance in Turkey researches (OR = 4.16, 95% CI: 2.32–7.46, p < 0.001), large sample size researches (≥600, OR = 3.50, 95% CI: 1.84–6.67, p < 0.001), younger patients researches (< 62, OR = 3.76, 95% CI: 2.29–6.18, p < 0.001). But there didn't show a statistical significance in China ACS patients, STEMI patients and small sample size researches. According to the change of I^2, the sources of heterogeneity among studies might be country, sample size

and mean age of patients. For 3 studies that researched LMR and long-term mortality/MACE [19-21]. According to the results of subgroup analysis (Table 3), Low LMR predicted long-term mortality/MACE didn't show a statistical significance in any subgroup. According to the change of I^2, the sources of heterogeneity among studies might be country and mean age of patients.

Discussion

ACS has a high morbidity and remains one of the major causes of mortality in the world [2, 3]. Previous studies pointed that LMR might be associated with the prognosis of ACS patients [18-22]. Here we performed this meta-analysis to comprehensive analyze the relationship between LMR and prognosis of patients with ACS. The aggregated results showed that a lower LMR might predict a higher mortality/MACE in patients with ACS.

In this meta-analysis, we enrolled 5 studies comprising 3122 patients to evaluate the relationship between LMR and mortality/MACE in patients with ACS [18-22]. LMR might be a predictor for short-term mortality/MACE. However, in the subgroup analysis, we found that lower LMR was a poor predictor to predict short-term mortality/MACE in China ACS patients, STEMI patients and small sample size researches. This was different from previous research results [20, 21] and suggested that the predictive value of LMR for ACS patients might be influenced by regional factors and the type disease of the patients.

Our results also showed that LMR might have the predictive value for long-term mortality/MACE. We conducted subgroup analysis to further analyze the results. However, the results didn't show statistical significance in any subgroup, which showed that we need to be cautious about the value of LMR in predicting long-term mortality/MACE.

ACS is related to atherosclerosis, which is accompanied with the infiltration of inflammatory cells [7-9]. Lymphocytes and monocytes are pivotal immune cells and have an important role in the inflammatory response and the formation of atherosclerosis plaque [23, 24]. Previous studies showed that lymphocytes and monocytes impacted the healing of MI [25-27]. Lymphocytes might be driven by recognition of cardiac auto antigens, became activated after MI, and facilitated the healing of the myocardium [25]. MI could activate adrenergic signaling and trigger the production of monocytes. Excessive mononuclear growth might impair myocardial healing and exacerbate cardiovascular complications [26, 27]. The above results indicated that lymphocyte and monocyte might be related to the prognosis of the MI patients.

Our studies had some limitations. Firstly, we did subgroup analysis and identified possible sources of heterogeneity. We could not accurately locate heterogeneity because of the subgroup analysis was observational. The heterogeneity might also arise from other sources. Secondly, we should be cautious about our results because of the huge heterogeneity. Thirdly, only five studies were included in the meta-analysis and two studies included relatively small sample size, it influenced the accuracy of the study

and presence of publication bias could not be evaluated. Fourthly, all the enrolled studies were observational researchers, which also relatively influence the accuracy of the study.

To the best of our knowledge, this is the first meta-analysis addressing the relationship between LMR and the mortality/MACE in patients with ACS. This meta-analysis showed that LMR could be a value predictor in predicting short-term mortality/MACE and long-term mortality/MACE in patients with ACS. What's more, in many primary hospitals, routine blood is the most rapid and basic detection methods which can immediately determine the patient's condition. The LMR might be used as an inexpensive and useful marker with prognostic significance in patients with ACS.

Conclusions

In summary, this meta-analysis showed that LMR might be used as a useful marker with prognostic significance in patients with ACS. A low LMR value might be effective in predicting the risk of short-term mortality/MACE and long-term mortality/ MACE in patients with ACS. But additional research was required to verify its effectiveness.

Abbreviations

LMR: lymphocyte-to-monocyte ratio; CHD: coronary heart disease; ACS: acute coronary syndrome; MACE: major adverse cardiac events; OR: odds ratio; CI: confidence interval; STEMI: ST-elevated myocardial infarction; UA: unstable angina; NSTEMI: non-ST-segment elevation myocardial infarction; NLR: neutrophil-to-lymphocyte ratio; MI: myocardial infarction; PRISMA: Preferred Reporting Items of Systematic Reviews and Meta-Analyses, NOS: Newcastle-Ottawa Scale; PCI: percutaneous coronary intervention.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The manuscript is approved by all authors for publication.

Availability of data and materials

Because this is a meta-analysis, all of data included in this study could be found in the included references.

Competing interests

The authors declare that they have no competing interests.

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No funding was received.

Authors' contributions

RCW and QZ contributed to the study conceive, the data acquisition, analysis, interpretation, the drafting, revision of the manuscript and agreed to be accountable for all aspects of the work. CTZ contributed to the study conceive, the supervision, data interpretation and performed revision of the manuscript. LS and XQQ contributed to the study conceive, design, data analysis, interpretation and revised the manuscript. All authors read and approved the final manuscript.

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References

1. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Probl Cardiol. 2010;35(2):72-115.
2. Makki N, Brennan TM, Girotra S. Acute coronary syndrome. J Intensive Care Med. 2015;30(4):186-200.
3. Li SJ, Barywani S, Fu M. Relationship between Physical Inactivity and Long-term Outcome in Patients Aged >= 80 Years with Acute Coronary Syndrome. Curr Med Sci. 2018;38(1):64-69.
4. Dalen JE, Alpert JS, Goldberg RJ, Weinstein RS. The epidemic of the 20(th) century: coronary heart disease. Am J Med. 2014;127(9):807-812.
5. Laskey W, Siddiqi S, Wells C, Lueker R: Improvement in arterial stiffness following cardiac rehabilitation. Int J Cardiol. 2013;167(6):2734-2738.

6. Tang W, Pankow JS, Carr JJ, Tracy RP, Bielinski SJ, North KE, et al. Association of sICAM-1 and MCP-1 with coronary artery calcification in families enriched for coronary heart disease or hypertension: the NHLBI Family Heart Study. BMC Cardiovasc Disord. 2007;7:30.
7. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012;32(9):2045-2051.
8. Libby P, Ridker PM, Hansson GK, Leducq Transatlantic Network on A. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009;54(23):2129-2138.
9. Pant S, Deshmukh A, Gurumurthy GS, Pothineni NV, Watts TE, Romeo F, et al. Inflammation and atherosclerosis--revisited. J Cardiovasc Pharmacol Ther. 2014;19(2):170-178.
10. Chen J, Chen MH, Li S, Guo YL, Zhu CG, Xu RX, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting the severity of coronary artery disease: a Gensini score assessment. J Atheroscler Thromb. 2014;21(12):1271-1282.
11. Kaya MG, Akpek M, Lam YY, Yarlioglues M, Celik T, Gunebakmaz O, et al. Prognostic value of neutrophil/lymphocyte ratio in patients with ST-elevated myocardial infarction undergoing primary coronary intervention: a prospective, multicenter study. Int J Cardiol. 2013;168(2):1154-1159.
12. Guo TM, Cheng B, Ke L, Guan SM, Qi BL, Li WZ, et al. Prognostic Value of Neutrophil to Lymphocyte Ratio for In-hospital Mortality in Elderly Patients with Acute Myocardial Infarction. Curr Med Sci. 2018;38(2):354-359.
13. Woollard KJ, Geissmann F. Monocytes in atherosclerosis: subsets and functions. Nat Rev Cardiol. 2010;7(2):77-86.
14. Santos-Gallego CG, Picatoste B, Badimon JJ. Pathophysiology of acute coronary syndrome. Curr Atheroscler Rep. 2014;16(4):401.
15. Eskandarian R, Ghorbani R, Asgary Z. Relationship between leucocytosis and left ventricular ejection fraction in patients with acute myocardial infarction. Singapore Med J. 2013;54(1):40-43.
16. Maekawa Y, Anzai T, Yoshikawa T, Asakura Y, Takahashi T, Ishikawa S, et al. Prognostic significance of peripheral monocytosis after reperfused acute myocardial infarction:a possible role for left ventricular remodeling. J Am Coll Cardiol. 2002;39(2):241-246.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-605.
18. Kurtul A, Yarlioglues M, Celik IE, Duran M, Elcik D, Kilic A, et al. Association of lymphocyte-to-monocyte ratio with the no-reflow phenomenon in patients who underwent a primary percutaneous coronary intervention for ST-elevation myocardial infarction. Coron Artery Dis. 2015;26(8):706-712.
19. Kiris T, Celik A, Varis E, Akan E, Akyildiz ZI, Karaca M, et al. Association of Lymphocyte-to-Monocyte Ratio With the Mortality in Patients With ST-Elevation Myocardial Infarction Who Underwent Primary Percutaneous Coronary Intervention. Angiology. 2017;68(8):707-715.
20. Wang Q, Ma J, Jiang Z, Wu F, Ping J, Ming L. Association of lymphocyte-to-monocyte ratio with in-hospital and long-term major adverse cardiac and cerebrovascular events in patients with ST-elevated myocardial infarction. Medicine. 2017;96(34):e7897.

21. Fan Z, Li Y, Ji H, Jian X. Prognostic utility of the combination of monocyte-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with NSTEMI after primary percutaneous coronary intervention: a retrospective cohort study. BMJ open. 2018;8(10):e023459.
22. Chen H, Li M, Liu L, Dang XW, Zhu DJ, Tian G. Monocyte/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients with non-ST-elevation myocardial infarction. Medicine. 2019;98(26).
23. Camici PG, Rimoldi OE, Gaemperli O, Libby P. Non-invasive anatomic and functional imaging of vascular inflammation and unstable plaque. Eur Heart J. 2012;33(11):1309-U1329.
24. Hofmann U, Frantz S. Role of Lymphocytes in Myocardial Injury, Healing, and Remodeling After Myocardial Infarction. Circ Res. 2015;116(2):354-367.
25. Hofmann U, Beyersdorf N, Weirather J, Podolskaya A, Bauersachs J, Ertl G, et al. Activation of CD4+ T lymphocytes improves wound healing and survival after experimental myocardial infarction in mice. Circulation. 2012; 125(13):1652-1663.
26. Ruparelia N, Godec J, Lee R, Chai JT, Dall'Armellina E, McAndrew D, et al. Acute myocardial infarction activates distinct inflammation and proliferation pathways in circulating monocytes, prior to recruitment, and identified through conserved transcriptional responses in mice and humans. Eur Heart J. 2015;36(29):1923-1934.
27. Dutta P, Nahrendorf M. Monocytes in myocardial infarction. Arterioscler Thromb Vasc Biol. 2015;35(5):1066-1070.

Tables

Table 1 The main characteristics of the included studies

Study (year)	Country	Duration	Mean Age (years)	LMR cut-off value	Patient's diseases	Sample	Outcomes	Quality(NOS)
Kurtul et al. (2015) [18]	Turkey	2012-2015	58.9	2.292	STEMI	857	In-hospital mortality	7
Kiris et al. (2017) [19]	Turkey	2010-2013	61.5	1.67	STEMI	318	30-day mortality 36-month mortality/ MACE	7
Wang et al. (2017) [20]	China	2013-2016	63.5	2.62	STEMI	306	In-hospital MACE Long-term MACE	7
Fan et al. (2018) [21]	China	2010-2015	62.34	2.78	NSTEMI	678	Long-term mortality/ MACE	7
Cheng et al. (2019) [22]	China	2013-2017	60.77	2.33	NSTEMI	963	In-hospital MACE	8

Abbreviations: *LMR* lymphocyte-to-monocyte ratio, *STEMI* ST-elevated myocardial infarction, *NSTEMI* non-ST-elevated myocardial infarction, *MACE* major adverse cardiac events.

Table 2 The association between LMR and short-term mortality/MACE according to different subgroups

Subgroup		Studies(No.)	I^2 (%)	P(I^2)	OR(95% CI)	P(OR)
Country	Turkey	2	0.0	0.988	4.16(2.32,7.46)	<0.001
	China	2	70.1	0.067	1.63(0.71,3.74)	0.248
Disease	STEMI	3	88.3	0.000	2.57(0.94,7.05)	0.067
	NSTEMI	1	-	-	2.89(1.12,7.43)	0.027
Sample	≥600	2	0.0	0.585	3.50(1.84,6.67)	<0.001
	<600	2	89.8	0.002	2.10(0.62,7.13)	0.235
Mean Age	≥62	1	-	-	1.19(1.07,1.32)	0.001
	<62	3	0	0.812	3.76(2.29,6.18)	<0.001

Abbreviations: *OR* odds ratio, *CI* confidence interval.

Table 3 The association between LMR and long-term mortality/MACE according to different subgroups

Subgroup		Study(No.)	I^2 (%)	OR	P(OR)
Country	Turkey	1	-	2.54(1.55,4.15)	<0.001
	China	2	95.4	1.94(0.78,4.87)	0.157
Disease	STEMI	2	81.3	1.70(0.85,3.41)	0.136
	NSTEMI	1	-	3.17(2.16,4.65)	<0.001
Sample	≥600	1	-	3.17(2.16,4.65)	<0.001
	<600	2	87.3	1.70 (0.85,3.41)	0.136
Mean Age	≥62	2	95.4	1.94(0.78,4.87)	0.157
	<62	1	-	2.54(1.55,4.15)	<0.001

Abbreviations: *OR* odds ratio, *CI* confidence interval.

Figures

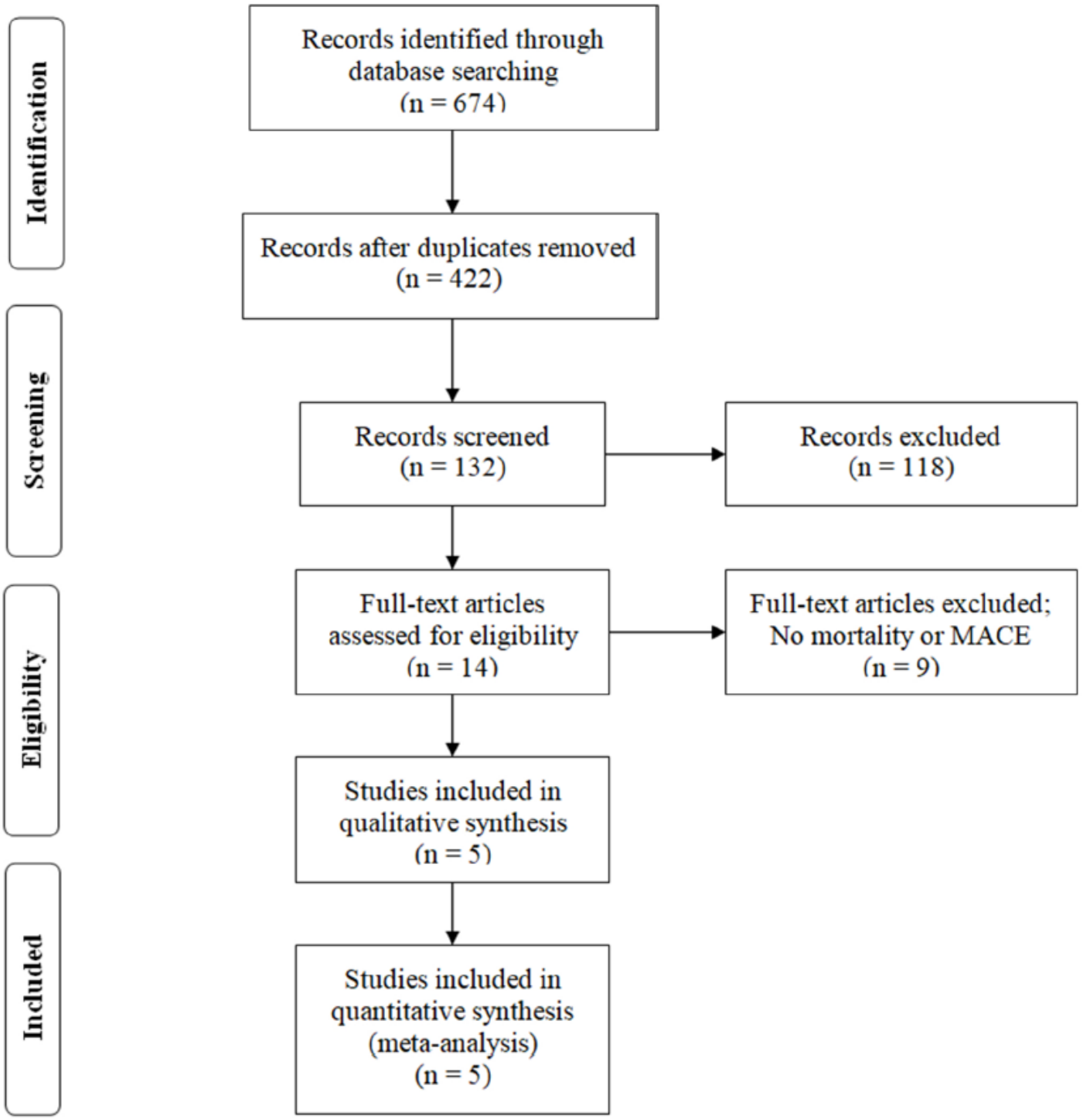

Figure 1

PRISMA flowchart describing literature search and article selection.

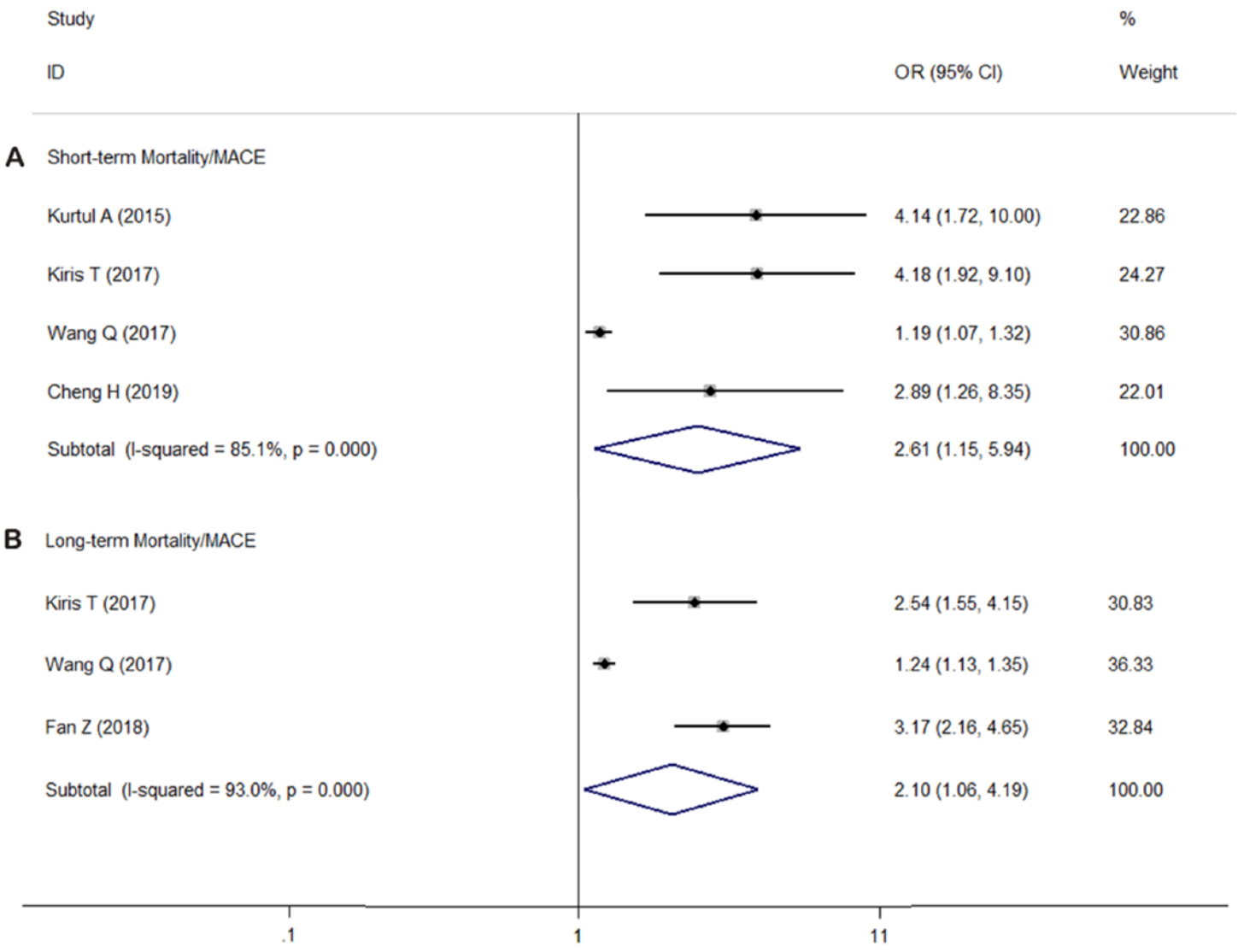

Figure 2

Forest plot of the association between lymphocyte-to-monocyte ratio and outcomes. A Low LMR predicted short-term mortality/MACE, B Low LMR predicted long-term mortality/ MACE. LMR lymphocyte-to-monocyte ratio, MACE major adverse cardiac events, OR odds ratio, CI confidence interval.