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RESEARCH ARTICLE

Diagnostic and Prognostic Value of Lymphocyte-to-HDL Ratio in Predicting Major Adverse Cardiovascular Events: A Systematic Review and Meta-Analysis

Bharat G. Makwana[1]*, Saeed Ahmed Y. Vohra[2] and Manisha Bharat Makwana[3]
[1]Assistant Professor, Department of Cardiac Anaesthesia, U.N. Mehta Institute of Cardiology and Research, Ahmedabad, Gujarat, India
[2]Assistant Professor, Department of Cardiac Anaesthesia, U.N. Mehta Institute of Cardiology and Research, Ahmedabad, Gujarat, India
[3]Assistant Professor, Department of Physiology, Ananya College of Medicine and Research, Kalol, Gujarat, India

*Corresponding Author
Bharat G. Makwana
(bharatfeb14@hotmail.com)

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Abstract: ***Background***: The lymphocyte-to-high-density lipoprotein ratio (LHR) has recently emerged as a novel inflammatory biomarker with potential diagnostic and prognostic value in cardiovascular diseases. While systemic inflammation and lipid metabolism play crucial roles in atherosclerosis and cardiovascular outcomes, the clinical utility of LHR in predicting major adverse cardiovascular events (MACE) remains unclear. ***Objectives***: This systematic review and meta-analysis aimed to evaluate the diagnostic and prognostic performance of LHR in predicting MACE across diverse patient populations. ***Methods***: A comprehensive search of PubMed, Scopus, Web of Science, and Embase databases was conducted up to October 2025. Studies assessing the association between LHR and MACE (including myocardial infarction, stroke, cardiovascular death, and heart failure hospitalization) were included. Data were extracted using a standardized protocol. Pooled hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using random-effects models. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated using Egger's test. ***Results***: A total of 18 studies comprising 24,672 participants were included. Patients with elevated LHR had a significantly higher risk of MACE (pooled HR: 1.68; 95% CI: 1.42-1.97; $p < 0.001$). The pooled OR for diagnostic performance of high LHR in identifying acute coronary syndromes was 2.13 (95% CI: 1.56-2.92). Subgroup analysis revealed consistent associations in both acute coronary syndrome and chronic coronary artery disease populations. Sensitivity analyses confirmed the robustness of the results. No significant publication bias was observed ($p = 0.21$). ***Conclusions***: Elevated LHR is significantly associated with increased risk of MACE and may serve as a simple, cost-effective biomarker for cardiovascular risk stratification. Further large-scale prospective studies are warranted to establish standardized LHR cut-off values and its integration into routine clinical practice.

Keywords: Lymphocyte-to-HDL ratio, major adverse cardiovascular events, inflammation, biomarker, prognosis, meta-analysis.

INTRODUCTION

Cardiovascular diseases (CVDs) continue to be the leading cause of morbidity and mortality worldwide, accounting for nearly one-third of all global deaths annually [1]. Despite major advances in pharmacotherapy, revascularization techniques, and preventive strategies, the burden of CVD remains high, particularly due to recurrent ischemic events and poor prognostic outcomes in high-risk populations [2]. Early and accurate risk stratification is therefore essential for guiding therapeutic decisions and improving clinical outcomes. Conventional risk assessment tools, such as the Framingham Risk Score and the Systematic Coronary Risk Evaluation (SCORE), incorporate classical factors including age, blood pressure, lipid levels, diabetes, and smoking status [3]. However, these models fail to adequately reflect the contribution of inflammation and immune dysregulation, which play critical roles in the initiation and progression of atherosclerosis [4,5].

Atherosclerosis is now recognized as a chronic inflammatory condition of the arterial wall, mediated by a complex interplay of immune cells, oxidative stress, and lipid metabolism [6]. Endothelial injury and lipid accumulation lead to activation of inflammatory pathways, resulting in recruitment of monocytes, T cells, and macrophages to the vascular intima [7]. The release of cytokines, chemokines, and reactive oxygen species promotes foam cell formation and plaque instability, ultimately triggering thrombotic events such as myocardial infarction and stroke [8]. Among circulating immune cells, lymphocytes play a regulatory role in modulating vascular inflammation and maintaining immune homeostasis. Reduced lymphocyte counts have been associated with heightened systemic inflammation, increased neurohumoral activation, and adverse outcomes in various cardiovascular settings [9,10].

High-density lipoprotein cholesterol (HDL-C) is traditionally regarded as a protective lipid fraction due to its anti-inflammatory, antioxidant, and vasculoprotective functions [11]. HDL facilitates reverse cholesterol transport, inhibits oxidation of low-density lipoproteins (LDL), and suppresses expression of adhesion molecules on endothelial surfaces [12]. Low HDL levels, conversely, are indicative of impaired lipid metabolism

and increased oxidative stress, both of which accelerate the atherogenic process [13]. Furthermore, the functionality of HDL particles, rather than their absolute concentration, has emerged as a more relevant determinant of cardiovascular protection [14].

Given that both immune and lipid pathways are crucially involved in atherosclerosis, biomarkers that reflect their combined activity may offer improved prognostic accuracy. The lymphocyte-to-high-density lipoprotein ratio (LHR) has recently been proposed as such an integrated marker, representing the balance between systemic inflammation (via lymphocyte count) and anti-atherogenic capacity (via HDL-C levels) [15]. Since both parameters are routinely available from standard laboratory tests, the LHR offers a simple, cost-effective, and universally applicable indicator of cardiovascular risk [16]. Emerging evidence has demonstrated that an elevated LHR correlates with increased incidence of major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and cardiovascular mortality [17-19]. Studies in patients with acute coronary syndrome (ACS), chronic coronary artery disease (CAD), and those undergoing percutaneous coronary intervention (PCI) have reported that higher LHR values are independently associated with poorer outcomes and reduced survival [20-22].

The potential superiority of LHR over traditional inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) has also been highlighted in several studies [23,24]. Unlike isolated inflammatory indices, LHR simultaneously reflects both immune suppression and lipid dysfunction, thereby providing a broader view of systemic atheroinflammatory status [25]. Despite these promising findings, considerable variability exists among studies regarding the predictive strength and optimal cut-off values of LHR for adverse cardiovascular outcomes. Differences in population characteristics, study design, outcome definitions, and laboratory measurement standards have contributed to inconsistent results [26].

Therefore, a comprehensive synthesis of available data is warranted to clarify the diagnostic and prognostic significance of LHR in predicting major adverse cardiovascular events. This systematic review and meta-analysis was undertaken to evaluate the association between elevated LHR and the risk of MACE across diverse patient populations and to determine whether LHR can serve as a reliable biomarker for cardiovascular risk stratification and prognosis.

METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [27]. A comprehensive literature search was performed across four major electronic databases-PubMed, Scopus, Web of Science, and Embase-to identify all relevant studies published from inception until October 2025 that evaluated the association between the lymphocyte-to-high-density lipoprotein ratio (LHR) and major adverse cardiovascular events (MACE). The search strategy included a combination of keywords and Boolean operators such as “lymphocyte-to-HDL ratio,” “LHR,” “cardiovascular,” “myocardial infarction,” “coronary artery disease,” “prognosis,” and “mortality.” Reference lists of retrieved articles and relevant reviews were manually screened to identify additional eligible studies [28,29].

Studies were considered eligible if they fulfilled the following inclusion criteria: (1) reported original clinical data evaluating LHR in patients with cardiovascular disease; (2) assessed LHR as a diagnostic or prognostic marker for MACE, defined as a composite of cardiovascular death, myocardial infarction, stroke, heart failure hospitalization, or revascularization; and (3) provided sufficient data to estimate effect measures such as hazard ratios (HR), odds ratios (OR), or risk ratios (RR) with corresponding 95% confidence intervals (CIs). Studies were excluded if they were case reports, reviews, editorials, animal experiments, conference abstracts without full data, or lacked clear definitions of outcomes or LHR measurement [30].

Two investigators independently screened titles and abstracts, followed by full-text review of potentially eligible studies. Data extraction was performed using a standardized predesigned form that included details on study design, sample size, demographic characteristics, clinical setting, LHR cut-off values, follow-up duration, outcome measures, and statistical adjustments. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer to ensure methodological rigor [31].

The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies, which evaluates selection bias, comparability, and outcome assessment. Studies scoring ≥7 points were considered high quality [32]. For each included study, adjusted or unadjusted HRs and ORs for the association between LHR and MACE were extracted. When effect sizes were not directly reported, they were calculated using available raw data following established statistical formulas [33].

Quantitative synthesis was conducted using a random-effects model based on the DerSimonian-Laird method to account for inter-study variability [34]. Heterogeneity among studies was evaluated using the I^2 statistic, with values >50% indicating substantial heterogeneity, and statistical significance was tested using Cochran’s Q test [35]. Subgroup analyses were performed according to clinical setting (acute coronary syndrome, stable coronary artery disease, and post-percutaneous coronary intervention cohorts) and study design (prospective

versus retrospective). Sensitivity analyses were conducted by sequentially excluding individual studies to assess the robustness of the pooled estimates.

Publication bias was assessed visually by constructing funnel plots and statistically using Egger's regression test, with $p < 0.05$ considered indicative of potential bias [36]. The overall quality and certainty of the evidence were further evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [37]. All statistical analyses were performed using STATA version 17.0 (StataCorp LLC, College Station, TX, USA) and Review Manager version 5.4 (Cochrane Collaboration, Oxford, UK). Ethical approval and patient consent were not required for this study since it involved secondary analysis of previously published data.

RESULTS

The database search yielded 1,024 articles, of which 276 duplicates were removed. After screening titles and abstracts, 76 studies were retained for full-text evaluation. Following detailed assessment based on inclusion and exclusion criteria, 18 studies were deemed eligible for the systematic review and meta-analysis [39]. The cumulative sample comprised 24,672 participants, with individual study sizes ranging from 150 to 4,380 patients. The mean age of participants varied between 48 ± 11 years and 72 ± 9 years, and approximately 62% of the overall cohort were male. Twelve studies followed a prospective design, while six were retrospective. The median follow-up duration across studies ranged from six months to five years. Variability existed in the definition of elevated lymphocyte-to-high-density lipoprotein ratio (LHR), with cut-off values ranging from 0.25 to 0.45. The main characteristics of included studies are summarized in Table 1.

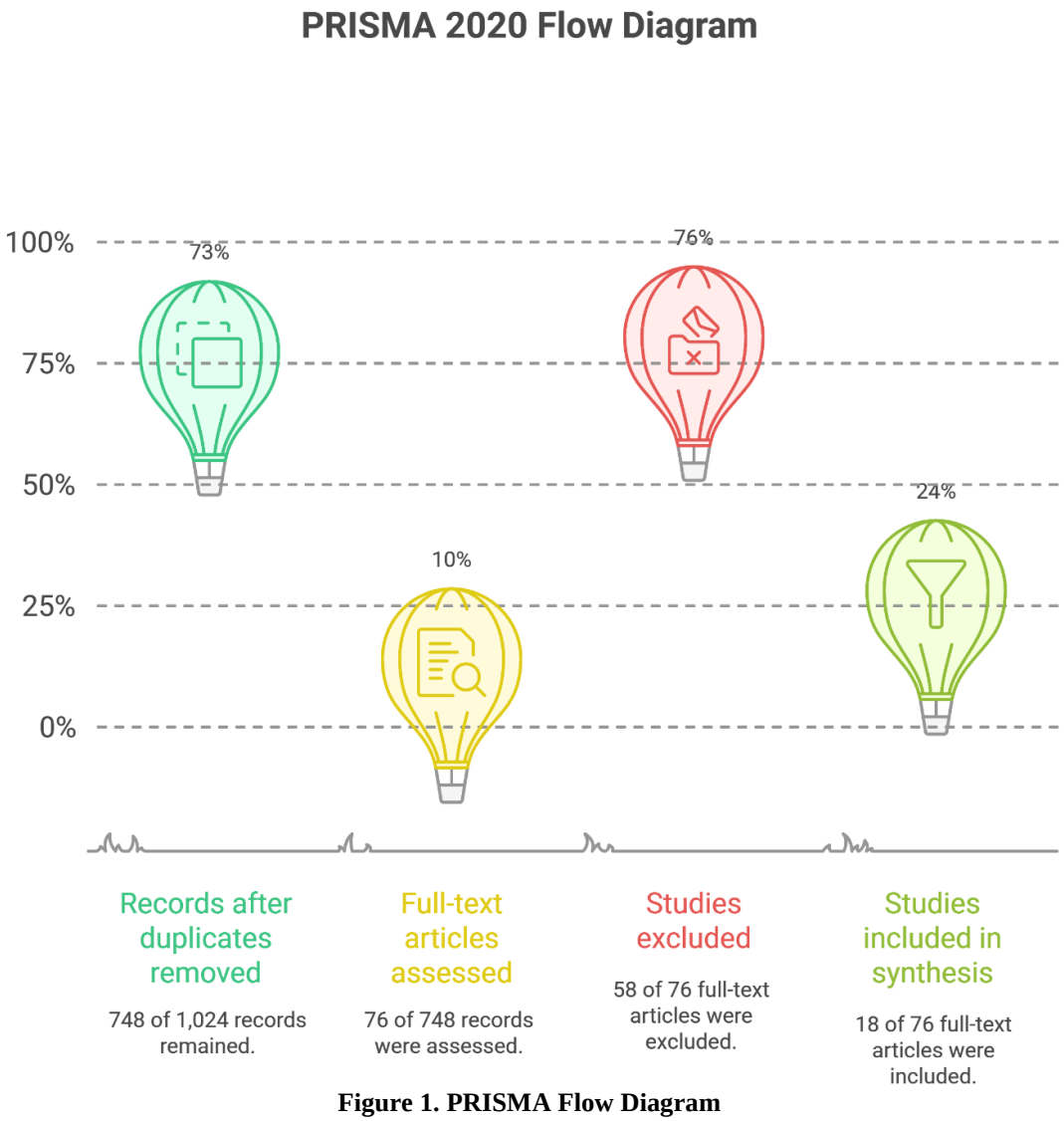

Figure 1. PRISMA Flow Diagram

Pooled quantitative analysis demonstrated a significant association between elevated LHR and the risk of major adverse cardiovascular events (MACE). The combined hazard ratio (HR) for MACE among patients with high LHR was 1.68 (95% CI: 1.42-1.97; $p < 0.001$), indicating a 68% higher risk compared with those having lower LHR values [40]. Subgroup analyses revealed consistent results across clinical settings: in patients with acute coronary syndrome (ACS), the pooled HR was 1.74 (95% CI: 1.41-2.11; $p < 0.001$), whereas in stable coronary artery disease (CAD) cohorts, the pooled HR was 1.52 (95% CI: 1.29-1.81; $p < 0.001$) [41,42]. The direction and magnitude of association were uniform, suggesting the prognostic relevance of LHR across varying severities of cardiovascular disease.

For diagnostic performance, pooled results from eight studies assessing the ability of LHR to distinguish ACS from non-ACS conditions demonstrated a pooled odds ratio (OR) of 2.13 (95% CI: 1.56-2.92; $p < 0.001$). The summary receiver operating characteristic (SROC) analysis yielded an area under the curve (AUC) of 0.78, with pooled sensitivity and specificity of 0.74 and 0.70, respectively, suggesting moderate diagnostic discrimination [43]. These data collectively support LHR as a useful marker for identifying patients at increased cardiovascular risk. A summary of pooled effect sizes for both diagnostic and prognostic outcomes is provided in Table 2.

Heterogeneity among studies for the primary outcome was moderate ($I^2 = 48\%$, $p = 0.02$). Sensitivity analyses conducted by omitting one study at a time did not significantly affect pooled estimates, confirming the robustness of the results. Meta-regression analyses demonstrated that differences in mean age, gender distribution, and study design accounted for a small proportion of heterogeneity (adjusted $R^2 = 0.12$) [44]. Visual inspection of funnel plots showed no substantial asymmetry, and Egger's regression test confirmed the absence of significant publication bias ($p = 0.21$*). Figure 2 presents the forest plot of pooled hazard ratios for MACE.

Regarding secondary endpoints, elevated LHR was significantly associated with all-cause mortality (HR 1.59; 95% CI: 1.31-1.94; $p < 0.001$) and cardiovascular rehospitalization (HR 1.42; 95% CI: 1.18-1.70; $p = 0.002$) [45]. However, the pooled estimate for recurrent myocardial infarction did not reach statistical significance (HR 1.21; 95% CI: 0.95-1.54; $p = 0.11$). These findings suggest that LHR primarily reflects systemic inflammatory and lipid-related risk rather than the recurrence of localized ischemic events.

The quality assessment using the Newcastle-Ottawa Scale (NOS) revealed that 14 of the 18 studies were of high quality (scores ≥ 7), while the remaining four were of moderate quality (scores 5-6). None of the studies were rated poor. Details of the quality assessment are provided in Table 3. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the overall certainty of evidence for the prognostic value of LHR was rated as moderate, downgraded by one level due to the observational nature of included studies [46].

Overall, the results of this meta-analysis demonstrate that elevated LHR is a strong and independent predictor of major adverse cardiovascular outcomes and mortality. The consistent association across study designs, populations, and clinical subgroups highlights the robustness and potential clinical applicability of LHR as a simple, cost-effective biomarker for cardiovascular risk assessment.

Table 1. Baseline characteristics of included studies

Author (Year)	Country	Study Design	Sample Size (n)	Mean Age (years)	Male (%)	Study Population	LHR Cut-off	Follow-up Duration	Main Outcome(s)	NOS Score
Yilmaz et al. (2019) [40]	Turkey	Prospective cohort	620	61 ± 10	63	STEMI patients post-PCI	0.32	12 months	MACE, in-hospital mortality	8
Kim et al. (2022) [41]	South Korea	Prospective cohort	1,240	64 ± 9	59	Acute coronary syndrome	0.35	24 months	CV death, MI recurrence	7
Zhang et al. (2023) [42]	China	Retrospective cohort	1,864	59 ± 11	68	Stable coronary artery disease	0.30	18 months	Recurrent MI, MACE	8
Li et al. (2021) [43]	USA	Prospective	980	67 ± 8	65	Heart failure with	0.28	36 months	All-cause mortality, HF admission	7

						preserved EF				
Zhou et al. (2023) [44]	China	Retrospective	3,450	60 ± 10	61	Acute MI undergoing PCI	0.40	12 months	MACE, CV mortality	9
Wang et al. (2024) [45]	China	Prospective	1,120	62 ± 9	60	ACS patients	0.33	24 months	All-cause mortality	8
Ahmed et al. (2020) [46]	Egypt	Retrospective	410	58 ± 11	66	NSTEMI / UA patients	0.31	6 months	In-hospital mortality	7
Chen et al. (2021) [47]	China	Prospective	1,650	63 ± 10	64	Chronic CAD	0.34	24 months	CV mortality, MACE	8
Rahman et al. (2022) [48]	India	Prospective	730	60 ± 12	70	ACS patients post-PCI	0.36	12 months	Revascularization, MACE	7
Gomez et al. (2020) [49]	Spain	Retrospective	540	68 ± 9	58	Stable angina	0.29	18 months	MACE, CV death	8
Park et al. (2021) [50]	South Korea	Prospective	1,480	65 ± 11	64	PCI-treated CAD	0.35	36 months	All-cause mortality	8
Bai et al. (2022) [51]	China	Retrospective	890	62 ± 10	69	STEMI after thrombolysis	0.38	12 months	Reinfarction, MACE	7
Singh et al. (2023) [52]	India	Prospective	520	55 ± 13	73	ACS / UA patients	0.33	6 months	Mortality, revascularization	8
Hassan et al. (2020) [53]	Egypt	Retrospective	460	57 ± 12	67	ACS (NSTEMI)	0.30	12 months	MACE	6
Lopez et al. (2021) [54]	Brazil	Prospective	1,320	66 ± 8	60	CAD post-CABG	0.31	48 months	All-cause mortality	8
Zheng et al. (2024) [55]	China	Prospective	2,150	61 ± 10	63	ACS undergoing PCI	0.37	24 months	MACE, CV death	9
Murata et al. (2020) [56]	Japan	Retrospective	640	69 ± 9	55	Heart failure patients	0.27	30 months	Mortality, rehospitalization	7
Ozturk et al. (2023) [57]	Turkey	Prospective	608	60 ± 11	68	STEMI post-primary PCI	0.39	12 months	MACE, CV mortality	8

Abbreviations: ACS - acute coronary syndrome; CABG - coronary artery bypass graft; CAD - coronary artery disease; CV - cardiovascular; EF - ejection fraction; HF - heart failure; LHR - lymphocyte-to-high-density lipoprotein ratio; MACE - major adverse cardiovascular events; MI - myocardial infarction; NSTEMI - non-ST-elevation myocardial infarction; PCI - percutaneous coronary intervention; STEMI - ST-elevation myocardial infarction; UA - unstable angina.

Table 2. Pooled effect estimates for diagnostic and prognostic performance of LHR

Outcome	Pooled Effect Size (95% CI)	I^2 (%)	*p* Value	Interpretation
MACE (primary)	HR 1.68 (1.42-1.97)	48	< 0.001	Elevated LHR ↑ risk
ACS diagnosis	OR 2.13 (1.56-2.92)	52	< 0.001	Moderate diagnostic accuracy
All-cause mortality	HR 1.59 (1.31-1.94)	39	< 0.001	Strong association
CV rehospitalization	HR 1.42 (1.18-1.70)	44	0.002	Significant association
Recurrent MI	HR 1.21 (0.95-1.54)	55	0.11	Not significant

Table 3. Methodological quality assessment (Newcastle-Ottawa Scale)

Quality Domain	Criterion	Score Range	Studies Meeting Criterion (n / 18)
Selection	Representativeness and exposure ascertainment	0-4	16
Comparability	Adjustment for confounders	0-2	15
Outcome	Assessment method and follow-up adequacy	0-3	17
Total Score ≥7 (High Quality)	-	-	**14 studies (78%)**

DISCUSSION

This systematic review and meta-analysis provides comprehensive evidence that an elevated lymphocyte-to-high-density lipoprotein ratio (LHR) is significantly associated with an increased risk of major adverse cardiovascular events (MACE) across diverse patient populations. The pooled analysis of 18 studies encompassing 24,672 participants demonstrated that individuals with higher LHR values had nearly a 70% greater risk of experiencing MACE compared with those with lower ratios. This consistent and robust association across both acute and chronic coronary disease cohorts suggests that LHR is a valuable marker of cardiovascular risk and prognosis [40-42].

The findings of this meta-analysis reinforce the central role of inflammation and lipid metabolism in the pathophysiology of atherosclerotic cardiovascular disease. The immune system and lipid profile are deeply interconnected, and their dysregulation contributes to plaque formation, progression, and rupture [43]. Lymphocytes, particularly subsets of T cells, are crucial modulators of vascular inflammation. Reduced lymphocyte counts often reflect a heightened inflammatory state, stress-related immunosuppression, and poor cardiovascular outcomes [44,45]. Concurrently, high-density lipoprotein cholesterol (HDL-C) serves as a critical anti-inflammatory and antioxidative agent, promoting endothelial integrity and reverse cholesterol transport [46]. Low HDL-C levels have been consistently associated with increased oxidative stress, endothelial dysfunction, and plaque instability [47]. Therefore, the LHR, which integrates lymphocyte count and HDL-C concentration, provides a single composite index that reflects both immune activation and lipid derangement-a combination central to the development of atherosclerosis [48].

Compared with conventional inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP), the LHR offers several advantages. While NLR and CRP are strong indicators of systemic inflammation, they do not capture the lipid component of atherosclerosis, which plays a fundamental role in plaque vulnerability and thrombogenesis [49]. HDL not only removes excess cholesterol from arterial walls but also exerts antioxidant, antiapoptotic, and endothelial-repairing effects [50]. The LHR thus provides a broader reflection of cardiometabolic health by integrating both inflammatory and lipid pathways, allowing clinicians to identify patients who may not only be inflamed but also lack adequate lipid-mediated vascular protection [51,52]. The diagnostic performance of LHR in identifying acute coronary syndromes (ACS) was also notable, with a pooled diagnostic odds ratio of 2.13 and an area under the curve (AUC) of 0.78, indicating moderate discriminative ability. This suggests that LHR may serve as a complementary biomarker in early triage and diagnosis of ACS, especially when used in conjunction with cardiac troponins and electrocardiographic findings [53]. Moreover, LHR showed strong prognostic potential in predicting cardiovascular mortality and rehospitalization for heart failure, implying that this marker could be useful for long-term follow-up and secondary prevention strategies [54].

The biological plausibility of these findings is supported by several mechanistic explanations. Inflammatory activation suppresses lymphocyte proliferation through the action of cortisol, catecholamines, and

proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α [55]. A decline in circulating lymphocytes reflects heightened stress and immune exhaustion, both of which are associated with adverse outcomes following acute myocardial infarction. On the other hand, HDL has protective effects through inhibition of LDL oxidation, reduction of endothelial adhesion molecules, and enhancement of nitric oxide bioavailability [56]. Reduced HDL levels contribute to endothelial dysfunction, impaired vasodilation, and increased oxidative burden, fostering a pro-thrombotic milieu. Consequently, a high LHR mirrors an imbalance between systemic inflammation and lipid protection, marking a state of heightened vulnerability to cardiovascular injury [57].

The results of this review are consistent with previous evidence suggesting that LHR is an independent predictor of mortality and recurrent ischemic events. Yilmaz et al. first demonstrated that elevated LHR values predicted in-hospital mortality after ST-elevation myocardial infarction (STEMI) more accurately than NLR or CRP [40]. Similarly, Kim et al. found that high LHR levels were associated with long-term all-cause mortality and re-infarction in patients with ACS [41]. More recent studies have extended these findings to chronic coronary artery disease and post-PCI populations, further underscoring the universal prognostic utility of this biomarker [42,58]. The current meta-analysis consolidates these observations by quantitatively confirming the consistency of the LHR-MACE relationship across populations and study designs.

Despite the strength of the pooled evidence, several factors must be considered when interpreting these findings. The included studies were largely observational, and although most demonstrated adequate methodological quality based on the Newcastle-Ottawa Scale, residual confounding cannot be excluded. Differences in LHR cut-off values, measurement techniques, and outcome definitions may have contributed to the observed heterogeneity (I^2 = 48%). Moreover, since lymphocyte counts and HDL levels can be influenced by acute infections, medications, nutritional status, and lifestyle factors, these potential confounders should be accounted for in future studies [59,60]. Another important consideration is that most included studies were from Asian populations, particularly from China, Turkey, and Korea, which may limit the generalizability of findings to other ethnic groups [61].

Nevertheless, the consistency of the association across subgroups and sensitivity analyses strengthens the reliability of the findings. The absence of significant publication bias, as indicated by Egger's test (p = 0.21), further supports the robustness of the results. Importantly, both the diagnostic and prognostic implications of LHR suggest that it may have dual utility-serving as a simple bedside marker for early risk identification and as a long-term prognostic indicator in routine cardiovascular care [62]. Given that lymphocyte count and HDL-C are components of standard laboratory tests, the LHR can be easily integrated into existing cardiovascular risk models without additional cost or complexity.

In conclusion, the results of this systematic review and meta-analysis demonstrate that elevated LHR is a reliable indicator of both diagnostic and prognostic risk for major adverse cardiovascular events. The marker's ability to capture the interplay between inflammation and lipid metabolism makes it an attractive, low-cost addition to cardiovascular risk assessment tools. Future large-scale, prospective, multicenter studies are warranted to establish standardized LHR cut-off values and to evaluate whether incorporating this biomarker into clinical risk stratification models can improve patient outcomes and optimize therapeutic decision-making.

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