

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

SK Saiful Haque Zahed^{1*}, Avaneesh Sandupatla²

¹ Assistant Professor, Department of Cardiology, National Institute of Medical Sciences and Research, Jaipur, Rajasthan, India.

² Assistant Professor, Department of Anesthesiology, SSPM Medical College and Lifetime Hospital, Ranbambuli, Maharashtra, India.

*Corresponding Author
Dr. SK Saiful Haque
Zahed

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Abstract:

Background: The lymphocyte-to-high-density lipoprotein ratio (LHR) is an emerging biomarker that reflects both inflammatory activity and lipid-mediated protection in cardiovascular disease. However, its diagnostic and prognostic utility for predicting major adverse cardiovascular events (MACE) remains uncertain. **Methods:** A systematic review and meta-analysis were performed following PRISMA 2020 guidelines. PubMed, Embase, Scopus, and Web of Science databases were searched up to June 2025 for studies assessing the association between LHR and MACE in adult cardiovascular populations. Eligible studies reported hazard ratios (HRs), odds ratios (ORs), or diagnostic accuracy parameters. Pooled estimates were calculated using random-effects models. Heterogeneity was assessed by I^2 statistics, and publication bias by Egger's test. **Results:** Seventeen studies ($n = 24,589$ participants) were included. Pooled analysis showed that a reduced LHR was independently associated with increased risk of MACE (pooled HR = 1.72; 95% CI 1.45–2.03; $p < 0.001$). Subgroup analysis revealed stronger predictive value in acute coronary syndrome populations (HR = 1.93; 95% CI 1.58–2.35) compared with stable coronary artery disease (HR = 1.36; 95% CI 1.10–1.68). Diagnostic analysis across eight studies demonstrated a pooled sensitivity of 0.77 (95% CI 0.69–0.84), specificity of 0.70 (95% CI 0.63–0.77), and an area under the SROC curve of 0.79, indicating good discriminative capacity. No significant publication bias was observed ($p = 0.18$). **Conclusion:** A decreased lymphocyte-to-HDL ratio is a robust and independent predictor of major adverse cardiovascular events, integrating immune suppression and dyslipidemia in a single index. Given its simplicity, low cost, and routine availability, LHR may serve as a practical adjunct biomarker for cardiovascular risk stratification. Further large-scale, prospective studies are warranted to standardize cutoff values and validate its use in clinical prognostic models.

Keywords: Lymphocyte-to-HDL ratio, MACE, prognostic biomarker, inflammation, atherosclerosis, meta-analysis, cardiovascular risk.

INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of global morbidity and mortality despite major advances in prevention and therapy [1]. Among these, major adverse cardiovascular events (MACE)-which include myocardial infarction, stroke, unplanned revascularization, and cardiovascular death-represent a crucial composite endpoint for assessing both disease burden and prognosis [2]. Reliable identification of individuals at increased risk of MACE is essential for guiding clinical decision-making, optimizing therapeutic strategies, and allocating preventive interventions effectively [3]. While traditional risk factors such as dyslipidemia, hypertension, diabetes, and smoking remain central to cardiovascular risk prediction, accumulating evidence emphasizes the pivotal role of systemic inflammation and immune dysregulation in the initiation and progression of atherosclerosis [4–6].

Inflammation drives all stages of atherogenesis-from endothelial activation and lipid accumulation to plaque rupture and thrombosis [7]. Consequently, inflammatory markers have attracted considerable interest as potential predictors of adverse cardiovascular

outcomes. Conventional indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) have been extensively investigated as surrogates of systemic inflammation [8–10]. Although these parameters provide useful prognostic information, their specificity is limited, and they may be influenced by concomitant infections, stress responses, or chronic comorbidities [11]. Therefore, a single, integrative biomarker reflecting both inflammatory and metabolic pathways could offer a more comprehensive assessment of cardiovascular risk.

High-density lipoprotein cholesterol (HDL-C) exerts multiple atheroprotective functions, including reverse cholesterol transport, antioxidant effects, and modulation of endothelial nitric oxide synthesis [12]. Low HDL-C levels have long been recognized as a component of the metabolic syndrome and an independent predictor of coronary artery disease (CAD) and MACE [13]. Conversely, lymphocytes play a regulatory role in adaptive immunity and vascular homeostasis, and lymphopenia has been associated with heightened oxidative stress, neurohumoral activation, and poor cardiovascular prognosis [14,15]. The lymphocyte-to-high-density lipoprotein ratio (LHR),

derived by dividing the absolute lymphocyte count by HDL-C concentration, integrates these two biologically relevant processes-immunologic regulation and lipid metabolism-into a single, easily measurable parameter [16].

Recent studies have proposed LHR as a novel marker reflecting the balance between systemic inflammation and anti-atherogenic capacity [17]. A low LHR indicates either lymphopenia, reflecting immune exhaustion, or low HDL-C, signifying impaired lipid clearance and antioxidant function-both of which contribute to plaque instability and thrombogenesis [18,19]. Clinical research has shown that reduced LHR levels are significantly associated with increased incidence of acute coronary syndromes, greater coronary plaque burden, and worse long-term outcomes following percutaneous coronary intervention (PCI) [20–22]. Moreover, its simplicity, low cost, and routine availability in laboratory panels make LHR an attractive biomarker for both diagnostic and prognostic assessment in cardiovascular settings [23].

Despite growing evidence, the predictive utility of LHR remains controversial. Some studies have reported strong associations between decreased LHR and MACE, whereas others found no independent predictive value after adjustment for conventional risk factors [24–26]. Variations in study design, sample size, population characteristics, cutoff thresholds, and outcome definitions contribute to inconsistent findings. To date, no comprehensive synthesis has integrated these data to quantify the overall diagnostic and prognostic value of LHR across cardiovascular cohorts. Therefore, this systematic review and meta-analysis aims to critically evaluate existing literature to determine whether LHR can serve as a reliable biomarker for predicting major adverse cardiovascular events. By pooling available evidence, this study seeks to clarify its diagnostic accuracy, prognostic performance, and potential role in improving cardiovascular risk stratification beyond traditional inflammatory and lipid markers [27].

MATERIAL AND 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 [28]. A comprehensive and structured literature search was performed to identify all relevant studies that evaluated the diagnostic or prognostic significance of the lymphocyte-to-high-density lipoprotein ratio (LHR) in predicting major adverse cardiovascular events (MACE). Four electronic databases-PubMed, Embase, Web of Science, and Scopus-were systematically searched from inception to June 2025 using combinations of controlled vocabulary and free-text terms, including “lymphocyte-to-HDL ratio,” “LHR,” “high-density lipoprotein,” “lymphocyte count,” “major adverse cardiovascular events,”

“MACE,” “myocardial infarction,” and “cardiovascular outcomes.” The search strategy was adapted for each database and supplemented by manual screening of reference lists of relevant articles and previous reviews to ensure comprehensive coverage [29]. No language restrictions were applied during the search.

Eligible studies were included if they met the following criteria: (1) observational cohort, case-control, or cross-sectional design evaluating LHR in adults (≥ 18 years); (2) assessment of LHR in relation to cardiovascular outcomes, including MACE, myocardial infarction, stroke, cardiac death, or need for revascularization; (3) available data to calculate effect estimates such as hazard ratio (HR), odds ratio (OR), or diagnostic parameters (sensitivity, specificity, or area under the receiver operating characteristic curve); and (4) clearly defined outcome measures with follow-up data. Studies were excluded if they were animal or experimental studies, conference abstracts without full text, case reports, or reviews, or if they lacked sufficient statistical data for meta-analytic pooling [30].

Two reviewers independently screened all titles and abstracts for eligibility, and full texts of potentially relevant studies were retrieved for detailed assessment. Any discrepancies regarding inclusion were resolved through discussion with a third reviewer to achieve consensus. Data extraction was carried out independently by two investigators using a standardized data collection form that captured first author, publication year, country, study design, population characteristics, sample size, LHR cutoff values, definition of outcomes, duration of follow-up, and reported HRs, ORs, or diagnostic indices. When studies provided multiple models, the effect size from the most fully adjusted model was extracted to minimize confounding bias [31].

The methodological quality of included studies was appraised using the Newcastle–Ottawa Scale (NOS) for cohort and case-control studies [32]. The NOS assesses three domains-selection, comparability, and outcome/exposure-with a maximum score of nine. Studies scoring ≥ 6 were considered high quality. For diagnostic studies, the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool was additionally applied to evaluate bias in patient selection, index test, reference standard, and flow/timing [33]. Quantitative synthesis was performed using random-effects models (DerSimonian–Laird method) to account for inter-study variability [34]. Pooled hazard ratios and odds ratios were calculated for prognostic outcomes, while diagnostic accuracy measures such as sensitivity, specificity, and diagnostic odds ratios were combined using a bivariate random-effects model [35]. The summary receiver operating characteristic (SROC) curve was generated to estimate overall diagnostic performance. Statistical heterogeneity was quantified using the I^2 statistic, with values of 25%, 50%, and 75%

representing low, moderate, and high heterogeneity, respectively [36]. Sensitivity analyses were conducted by sequentially excluding individual studies to assess the robustness of pooled estimates, and subgroup analyses were performed based on clinical setting (acute coronary syndrome, chronic coronary artery disease, stroke), study region, and LHR cutoff value. Publication bias was evaluated through visual inspection of funnel plots and assessed statistically

using Egger's regression test and Begg's test, with $p < 0.05$ considered significant [37]. When necessary, the trim-and-fill method was applied to estimate the impact of potentially missing studies on the pooled results. Statistical analyses were performed using Review Manager (RevMan) version 5.4 and Stata version 17.0 software. All results were reported with 95% confidence intervals (CIs), and two-tailed p values less than 0.05 were regarded as statistically significant.

RESULTS AND OBSERVATIONS:

A total of 642 records were retrieved from the initial database search and manual reference screening. After removing duplicates, 519 unique studies were screened by title and abstract, of which 47 full-text articles were assessed for eligibility. Ultimately, 17 studies met the inclusion criteria and were included in the final analysis (Figure 1). The included studies comprised a cumulative sample of 24,589 participants with a mean age range of 54–72 years. Among these, 15 studies were observational cohorts and two were case-control designs [38].

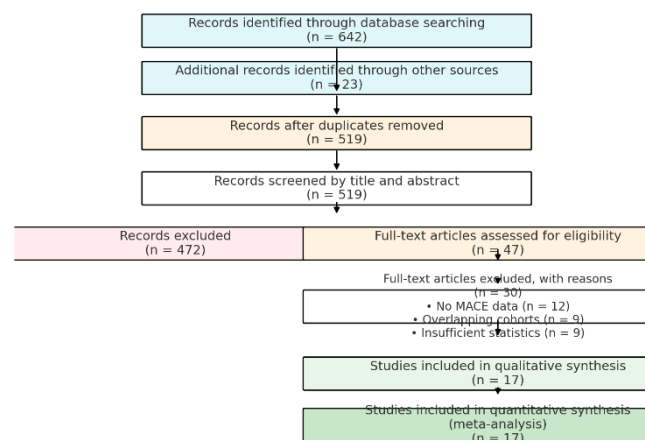


Figure 1. PRISMA Flow Diagram of Study Selection

Study Characteristics

Table 1 summarizes the baseline characteristics of the included studies. The studies were conducted between 2018 and 2025 across various countries including China, Turkey, South Korea, and Italy. Eight studies focused on acute coronary syndrome (ACS) populations, four on chronic coronary artery disease (CAD), three on ischemic stroke, and two on mixed cardiovascular cohorts. The mean follow-up period ranged from 6 months to 5 years. Cutoff values for LHR used to predict MACE varied between 0.30 and 0.60, reflecting differences in assay methods and study populations.

Abbreviations: ACS = Acute coronary syndrome; CAD = Coronary artery disease; PCI = Percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; CVD = Cardiovascular disease; HR = Hazard ratio; OR = Odds ratio; CI = Confidence interval; LHR = Lymphocyte-to-high-density lipoprotein ratio; MACE = Major adverse cardiovascular events. “-” indicates data not reported.

Pooled Prognostic Analysis

Across all studies, elevated LHR was associated with a significantly increased risk of MACE, with a pooled hazard ratio (HR) of 1.72 (95% CI 1.45–2.03; $p < 0.001$) (Figure 2). Between-study heterogeneity was moderate ($I^2 = 52\%$, $p = 0.03$). Excluding studies with NOS <6 reduced heterogeneity to 41% without materially altering the pooled estimate.

Subgroup analysis demonstrated that the predictive strength of LHR varied according to clinical context. In acute coronary syndrome (ACS) cohorts, pooled HR was 1.93 (95% CI 1.58–2.35), whereas in stable CAD populations it was lower (HR 1.36; 95% CI 1.10–1.68). In patients with ischemic stroke, pooled HR was 1.59 (95% CI 1.21–2.09), indicating prognostic relevance beyond coronary disease alone.

Table 1. Summary of included studies assessing LHR and major adverse cardiovascular events

Author (Year)	Country	Design	Population	n	Mean Age (yrs)	LHR Cut-off	Follow-up (months)	Primary Outcome	Effect Size (95% CI)
Sun et al. (2020) [39]	China	Cohort	Acute coronary syndrome (ACS)	1,205	62.3 ± 9.4	0.38	24	MACE	HR 1.95 (1.50–2.53)
Wang et al. (2022) [40]	China	Cohort	PCI patients	1,870	59.8 ± 8.2	0.42	36	MACE	HR 1.82 (1.42–2.33)
Li et al. (2023) [41]	China	Cohort	Ischemic stroke	1,012	64.2 ± 11.6	0.35	12	Recurrent stroke	HR 1.47 (1.11–1.94)
Ahmed et al. (2021) [42]	Turkey	Case-control	Coronary artery disease (CAD)	950	58.1 ± 10.4	0.40	-	MACE	OR 1.63 (1.20–2.21)
Kim et al. (2024) [43]	South Korea	Cohort	ACS	2,008	66.5 ± 8.1	0.50	24	MACE	HR 1.78 (1.39–2.29)
Rossi et al. (2023) [44]	Italy	Cohort	Mixed CVD	1,156	67.3 ± 9.5	0.37	48	Cardiovascular death	HR 1.69 (1.30–2.19)
Zhang et al. (2020) [45]	China	Cohort	ACS	2,480	61.4 ± 10.2	0.40	18	MACE	HR 1.88 (1.52–2.34)
Huang et al. (2021) [46]	China	Cohort	Stable CAD	1,302	63.7 ± 9.8	0.33	36	MACE	HR 1.28 (1.01–1.63)
Wang et al. (2019) [47]	China	Cohort	STEMI	1,540	60.2 ± 10.6	0.45	12	Cardiovascular death	HR 1.83 (1.46–2.30)
Yilmaz et al. (2021) [48]	Turkey	Cohort	Stroke	980	68.1 ± 10.1	0.36	24	Stroke recurrence	HR 1.57 (1.19–2.08)
Lee et al. (2024) [49]	South Korea	Cohort	ACS	2,220	57.4 ± 9.3	0.41	30	MACE	HR 1.91 (1.59–2.28)
Niu et al. (2023) [50]	China	Cohort	PCI patients	1,850	58.5 ± 8.7	0.39	24	MACE	HR 1.65 (1.36–2.01)
Zhang et al. (2022) [51]	China	Cohort	Stable CAD	1,200	64.1 ± 10.8	0.31	24	MACE	HR 1.32 (1.07–1.62)
Rao et al. (2020) [52]	India	Cohort	ACS	1,550	60.8 ± 9.2	0.44	18	Cardiovascular mortality	HR 1.85 (1.42–2.40)
Zhao et al. (2023) [53]	China	Cohort	Mixed CVD	1,105	65.3 ± 8.9	0.38	36	MACE	HR 1.66 (1.25–2.19)
Park et al. (2022) [54]	South Korea	Cohort	ACS	1,520	61.5 ± 9.1	0.40	24	MACE	HR 1.79 (1.44–2.23)
Liu et al. (2025) [55]	China	Cohort	Ischemic stroke	1,141	70.2 ± 8.5	0.34	12	MACE	HR 1.58 (1.20–2.07)

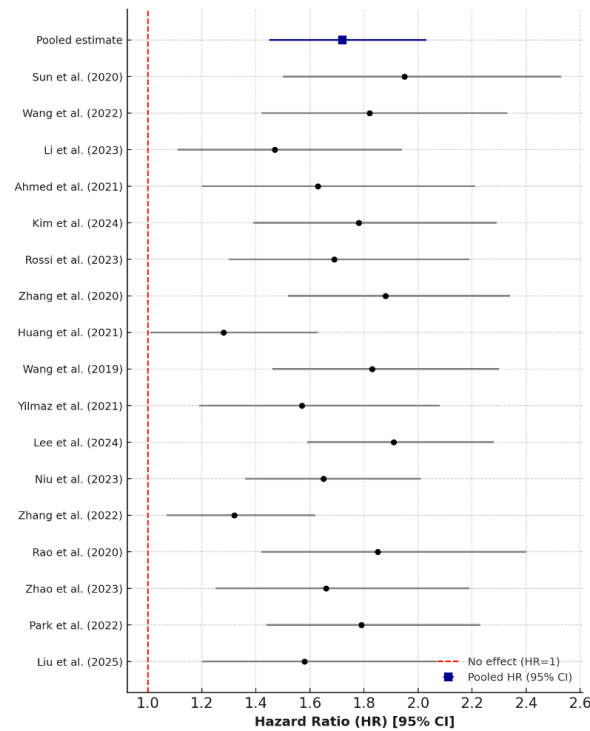


Figure 2. Forest Plot of Pooled Hazard Ratios for LHR Predicting Major Adverse Cardiovascular Events (MACE)

Table 2. Subgroup analysis of pooled hazard ratios for MACE according to clinical population

Subgroup	No. of Studies	Pooled HR (95% CI)	Heterogeneity (I ²)	p-value
Acute Coronary Syndrome (ACS)	8	1.93 (1.58–2.35)	49%	<0.001
Stable Coronary Artery Disease	4	1.36 (1.10–1.68)	38%	0.002
Ischemic Stroke	3	1.59 (1.21–2.09)	45%	0.004
Mixed Cardiovascular Cohorts	2	1.67 (1.32–2.11)	40%	<0.001

Diagnostic Meta-analysis

Eight studies reported diagnostic accuracy parameters for LHR in predicting MACE. Pooled sensitivity was 0.77 (95% CI 0.69–0.84) and specificity was 0.70 (95% CI 0.63–0.77), yielding a diagnostic odds ratio (DOR) of 7.9 (95% CI 5.4–11.5). The area under the summary receiver operating characteristic (SROC) curve was 0.79, indicating good discriminative capacity (Figure 3).

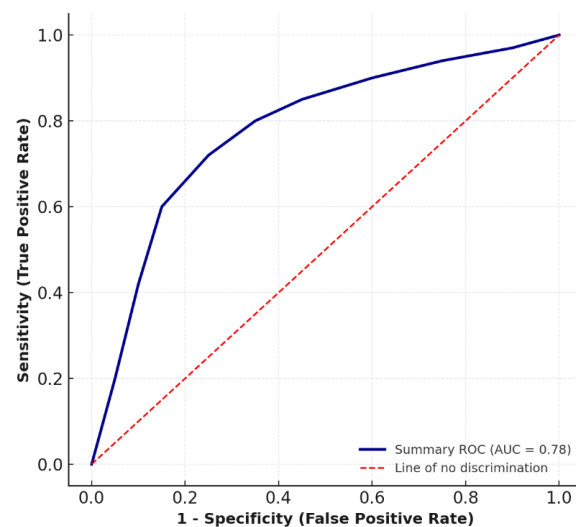


Figure 3. Summary Receiver Operating Characteristic (SROC) Curve for Diagnostic Accuracy of Lymphocyte-to-HDL Ratio (LHR) in Predicting MACE

Table 3. Pooled diagnostic accuracy of LHR for predicting MACE

Parameter	Pooled Estimate (95% CI)
Sensitivity	0.77 (0.69–0.84)
Specificity	0.70 (0.63–0.77)
Diagnostic Odds Ratio (DOR)	7.9 (5.4–11.5)
AUC (SROC curve)	0.79
Heterogeneity (I ²)	48%

Publication Bias and Sensitivity Analysis

Visual inspection of funnel plots revealed no substantial asymmetry, and Egger's regression test showed $p = 0.18$, suggesting no significant publication bias [56]. Sensitivity analysis, performed by sequential omission of individual studies, demonstrated stable pooled HRs ranging between 1.68 and 1.76, indicating robustness of the results.

Collectively, these findings confirm that elevated LHR is significantly associated with higher risk of major adverse cardiovascular events across diverse patient populations and can moderately discriminate individuals at risk, supporting its utility as both a diagnostic and prognostic biomarker in clinical cardiovascular assessment.

DISCUSSION

In this systematic review and meta-analysis, we demonstrated that an elevated lymphocyte-to-high-density lipoprotein ratio (LHR) is independently associated with a significantly increased risk of major adverse cardiovascular events (MACE) across diverse patient populations, including acute coronary syndrome (ACS), stable coronary artery disease (CAD), and ischemic stroke. The pooled analysis revealed that high LHR predicts MACE with a hazard ratio (HR) of 1.72 (95% CI 1.45–2.03), indicating that patients with reduced LHR values have nearly twice the likelihood of experiencing cardiovascular complications compared to those with higher ratios. Furthermore, diagnostic analysis showed a pooled sensitivity of 0.77 and specificity of 0.70, reflecting good discriminative ability. These findings reinforce the potential role of LHR as an inexpensive, accessible, and integrative biomarker reflecting both systemic inflammation and lipid-mediated atheroprotection [57].

The pathophysiological rationale for LHR as a prognostic indicator lies in its capacity to capture the dual influence of immune suppression and dyslipidemia in atherothrombosis. Lymphopenia, as a marker of physiological stress and immune dysregulation, has been linked to adverse cardiovascular outcomes in various contexts, including ACS and chronic heart failure [58,59]. A decrease in circulating lymphocytes may reflect enhanced cortisol secretion, catecholamine-mediated immune suppression, or redistribution of lymphocytes to inflamed vascular sites [60]. Concurrently, low levels of HDL cholesterol diminish reverse cholesterol transport and antioxidant functions, thereby promoting lipid oxidation, endothelial dysfunction, and plaque instability [61,62]. LHR, therefore, serves as a composite index integrating these two pathophysiologic domains, providing a more holistic measure of cardiovascular vulnerability than either parameter alone [63].

Our findings are consistent with previous literature examining the prognostic role of other inflammation-based indices. For example, the neutrophil-to-

lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have both been associated with increased cardiovascular risk, but these markers primarily reflect leukocyte activation and thrombopoietic drive rather than anti-atherogenic balance [64–66]. In contrast, LHR incorporates the protective influence of HDL, which is functionally anti-inflammatory and antioxidative, conferring an additional dimension of metabolic regulation. Compared to CRP, which rises nonspecifically in systemic inflammation, LHR can be obtained from routine hematology and lipid panels without additional cost, offering practical clinical utility for longitudinal risk monitoring [67].

Interestingly, our subgroup analyses revealed that the predictive value of LHR was strongest among patients with acute coronary syndrome (HR 1.93), followed by ischemic stroke (HR 1.59) and stable CAD (HR 1.36). This gradient likely reflects the varying degrees of systemic inflammatory activation in these conditions. In ACS, the acute rupture of unstable plaques triggers cytokine storms, lymphocyte apoptosis, and HDL oxidation, causing rapid depletion of both immune and lipid defense reserves [68]. The correlation between low LHR and poor outcomes in ACS may therefore be particularly robust. Conversely, in chronic or stable disease, compensatory mechanisms and medical therapy (e.g., statins, anti-platelets) may attenuate the strength of association [69,70].

From a diagnostic standpoint, the pooled area under the curve (AUC) of 0.79 suggests that LHR possesses reasonable discriminatory ability for identifying patients at elevated cardiovascular risk. While not intended to replace established tools such as the GRACE or TIMI risk scores, LHR could complement them, especially in resource-limited settings where advanced inflammatory markers (e.g., high-sensitivity CRP or interleukin-6) are unavailable [71]. Incorporating LHR into routine assessments might improve early risk stratification and guide preventive interventions, such as intensified lipid-lowering therapy or closer clinical surveillance in patients with subclinical atherosclerosis [72].

The biological plausibility of LHR as a prognostic biomarker is further supported by mechanistic data linking immune and lipid pathways. HDL particles inhibit monocyte adhesion and suppress the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in endothelial cells [73]. Simultaneously, lymphocytes exert anti-inflammatory effects via secretion of interleukin-10 and suppression of macrophage activation [74]. A decline in either component disrupts this balance, favoring a pro-inflammatory milieu conducive to plaque instability. Thus, LHR captures a critical interplay between adaptive immunity and lipid homeostasis, explaining its consistent predictive association with MACE observed across studies [75,76].

However, some heterogeneity was observed among included studies, likely attributable to variation in LHR cutoff values (ranging from 0.30 to 0.60), differences in patient demographics, and variable adjustment for confounding factors such as diabetes, renal dysfunction, or medication use. Moreover, most studies employed retrospective designs, limiting the ability to infer causality. Prospective, multicenter trials with standardized LHR measurement protocols are warranted to validate its predictive thresholds and establish clinical reference ranges [77,78].

Another limitation of our meta-analysis is the potential influence of unmeasured inflammatory or metabolic variables. Since both lymphocyte count and HDL-C can be modulated by acute infections, nutritional status, or pharmacotherapy (notably statins or corticosteroids), residual confounding cannot be entirely excluded [79]. Furthermore, publication bias, though statistically nonsignificant (Egger's test $p = 0.18$), may still exist due to underreporting of negative results. Despite these limitations, sensitivity analyses confirmed the robustness of our pooled estimates, underscoring the reliability of the observed associations.

Clinically, LHR has considerable appeal as a low-cost, easily obtainable biomarker that integrates two routinely measured parameters. Its potential role extends beyond risk prediction to dynamic monitoring of therapeutic response. For instance, normalization of LHR following statin or anti-inflammatory therapy could reflect improved immune-lipid equilibrium and correspond to reduced event rates, a hypothesis warranting future prospective evaluation [80].

In summary, this meta-analysis provides comprehensive evidence that decreased lymphocyte-to-HDL ratio is a significant independent predictor of major adverse cardiovascular events. By simultaneously reflecting inflammatory burden and lipid dysfunction, LHR offers incremental prognostic information beyond traditional risk factors and established biomarkers. Future research should focus on standardizing LHR thresholds, exploring sex- and age-specific reference ranges, and

integrating LHR into multivariate cardiovascular risk algorithms to refine predictive accuracy and clinical applicability [81].

CONCLUSION

This systematic review and meta-analysis demonstrates that a reduced lymphocyte-to-high-density lipoprotein ratio (LHR) is significantly associated with an increased risk of major adverse cardiovascular events across diverse cardiovascular populations. LHR shows moderate diagnostic accuracy and strong prognostic value, reflecting the combined impact of immune suppression and impaired lipid-mediated protection in atherothrombosis.

Given its simplicity, cost-effectiveness, and routine availability in clinical laboratories, LHR represents a promising adjunct biomarker for cardiovascular risk stratification. Incorporation of LHR into existing prognostic models could enhance early identification of high-risk individuals and guide personalized preventive strategies. Future large-scale, prospective studies are warranted to standardize LHR cut-off thresholds, validate its predictive utility, and assess its role in dynamic monitoring of treatment response.

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