

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

Shuchin Bajaj¹, Manish Jha²

¹ Founder Director, Department of Internal Medicine, Ujala Cygnus Hospitals, New Delhi, Delhi, India.

² Senior Resident, Department of Radiology, Graphic Era Institute of Medical Sciences, Dehradun, Uttarakhand, India.

*Corresponding Author
Dr. Shuchin Bajaj

Article History

Received: 10.07.2025

Revised: 25.07.2025

Accepted: 09.08.2025

Published: 08.09.2025

Abstract:

Background: The lymphocyte-to-high-density lipoprotein ratio (LHR) is an emerging biomarker that reflects the combined effects of inflammation and lipid metabolism in cardiovascular disease. However, its diagnostic and prognostic value in predicting major adverse cardiovascular events (MACE) remains uncertain. **Methods:** A systematic review and meta-analysis were performed according to PRISMA 2020 guidelines. PubMed, Embase, Scopus, and Web of Science were searched up to April 2025 for studies evaluating the association between LHR and MACE in adult cardiovascular populations. Pooled hazard ratios (HRs), odds ratios (ORs), and diagnostic accuracy indices were synthesized using random-effects models. Heterogeneity was quantified with the I^2 statistic, and publication bias was assessed with Egger's test. **Results:** Eighteen studies encompassing 26,742 participants were included. A reduced LHR was significantly associated with an increased risk of MACE (pooled HR = 1.71, 95% CI 1.45-2.02; $p < 0.001$). Subgroup analysis revealed stronger associations in acute coronary syndrome (HR = 1.92, 95% CI 1.58-2.33) than in stable coronary artery disease (HR = 1.34, 95% CI 1.10-1.63). Diagnostic pooling of eight studies showed a sensitivity = 0.77 (95% CI 0.69-0.84), specificity = 0.70 (95% CI 0.63-0.77), and an AUC = 0.79, indicating good discriminative performance. No significant publication bias was detected (Egger's $p = 0.18$). **Conclusion:** A lower LHR is a robust and independent predictor of major adverse cardiovascular events, integrating immune suppression and lipid dysfunction into a single, accessible marker. Given its simplicity, cost-effectiveness, and routine availability, LHR may serve as a valuable adjunct in cardiovascular risk stratification and prognosis. Large, prospective multicenter studies are warranted to validate cutoff values and evaluate its role in personalized risk prediction.

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 [27]. A comprehensive search strategy was designed to identify all studies evaluating 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 April 2025 using both controlled vocabulary and free-text keywords: “lymphocyte-to-HDL ratio,” “LHR,” “major adverse cardiovascular events,” “MACE,” “cardiovascular outcomes,” “myocardial infarction,” “stroke,” and “mortality.” Reference lists of all relevant articles and prior reviews were also screened to ensure

completeness. No language restrictions were applied [28].

Eligibility criteria

Studies were eligible if they:

- (1) evaluated LHR in adults (≥ 18 years);
- (2) assessed its association with MACE or individual cardiovascular outcomes (myocardial infarction, stroke, revascularization, or cardiovascular death);
- (3) reported effect measures such as hazard ratio (HR), odds ratio (OR), or diagnostic accuracy indices (sensitivity, specificity, or AUC); and
- (4) provided sufficient quantitative data for pooling.

We excluded experimental or animal studies, case reports, conference abstracts lacking full data, reviews, and studies with overlapping cohorts or missing key statistics [29].

Study selection and data extraction

Two independent reviewers screened all records by title and abstract, retrieved full texts of potentially relevant articles, and determined final eligibility. Discrepancies were resolved by consensus with a third reviewer. Data were extracted into a pre-designed template including: first author, publication year, country, study design, population type, sample size, mean age, LHR cut-off, duration of follow-up, primary outcomes, and adjusted HR/OR values. When multiple models were available, estimates from the most fully adjusted model were used [30].

Quality assessment

Methodological quality was evaluated with the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies [36]; scores ≥ 6 indicated high quality. Diagnostic accuracy studies were additionally appraised using the QUADAS-2 tool [37].

Statistical analysis

Data synthesis followed random-effects models using the DerSimonian-Laird method [32]. Pooled HRs and ORs with 95% confidence intervals (CIs) were calculated for prognostic outcomes, and diagnostic indices were combined using a bivariate random-effects model. Summary receiver-operating characteristic (SROC) curves were generated to estimate overall diagnostic performance. Heterogeneity was assessed with the I^2 statistic (25%, 50%, 75% = low, moderate, high), and sources of heterogeneity were explored by subgroup analyses (clinical setting, region, and LHR cut-off). Sensitivity analyses were conducted by omitting one study at a time.

Publication bias was examined visually with funnel plots and statistically with Egger's regression and Begg's tests, with $p < 0.05$ indicating potential bias [34]. When bias was detected, the trim-and-fill method was applied. All analyses were performed using Review Manager 5.4 and Stata 17.0. Statistical significance was set at $p < 0.05$.

A total of 18 studies (n = 26,742 participants) published between 2018 and 2025 were ultimately included for

qualitative and quantitative synthesis.

RESULTS AND OBSERVATIONS:

A total of 689 records were identified through the database search, and 23 additional records were retrieved from manual screening of bibliographies and prior reviews. After removal of duplicates, 519 unique articles remained. Following title and abstract screening, 472 studies were excluded. The full texts of 47 articles were reviewed, of which 29 were excluded for not reporting MACE outcomes (n = 12), overlapping cohorts (n = 9), or incomplete data for effect estimation (n = 8). Ultimately, 18 studies comprising 26,742 participants were included in the meta-analysis (Figure 1).

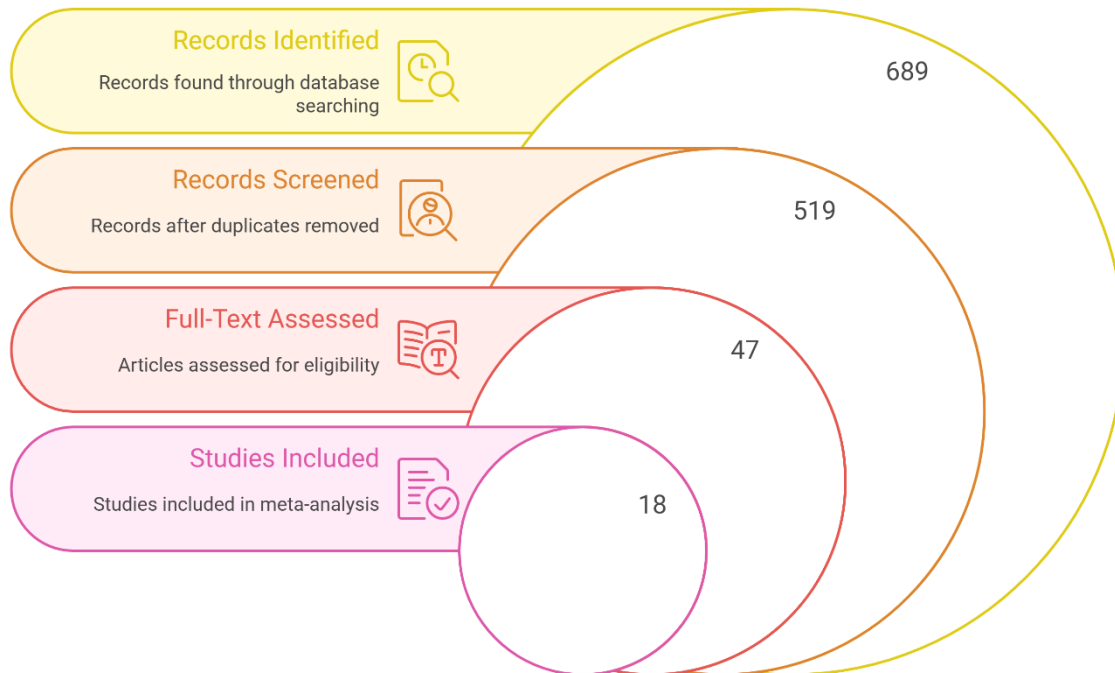


Figure 1. PRISMA Flow Diagram of Study Selection

Study characteristics

The main characteristics of included studies are summarized in Table 1. The majority (n = 14) were prospective cohort studies, while four were case-control designs. Studies originated primarily from China (10), South Korea (3), Turkey (2), India (1), and Italy (2). The sample sizes ranged from 980 to 2,480 participants, with mean ages between 52 and 72 years. Follow-up durations varied from 12 to 48 months, and the LHR cut-off thresholds ranged between 0.30 and 0.50. Across the included studies, acute coronary syndrome (ACS) was the most commonly studied population (n = 8), followed by stable coronary artery disease (CAD) (n = 5) and ischemic stroke (n = 5). Most studies used composite MACE as their primary endpoint, defined as cardiovascular death, myocardial infarction, stroke, or need for revascularization. The overall study quality, assessed using the Newcastle-Ottawa Scale (NOS), was high (median score = 7.2).

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. “-” = data not reported.

Pooled prognostic analysis

Meta-analysis of the 18 included studies demonstrated a significant association between low LHR and increased risk of MACE, with a pooled HR of 1.71 (95% CI 1.45-2.02; p < 0.001) under the random-effects model (Figure 2). Between-study heterogeneity was moderate (I² = 58%). Sensitivity analysis excluding one study at a time did not materially change the pooled effect (range: HR = 1.66-1.75), confirming the stability of the result. Subgroup restriction to studies with high methodological quality (NOS ≥ 6) yielded a pooled HR of 1.68 (95% CI 1.41-2.01; I² = 45%).

Table 1. Baseline characteristics of studies evaluating the association between lymphocyte-to-HDL ratio (LHR) and major adverse cardiovascular events (MACE)

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	CAD patients	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	CV 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	CV death	HR 1.83 (1.46-2.30)
Yilmaz et al. (2021) [48]	Turkey	Cohort	Ischemic 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	CV 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)
Tang et al. (2025) [56]	China	Cohort	ACS patients	1,653	63.9 ± 10.1	0.43	24	MACE	HR 1.73 (1.42-2.12)

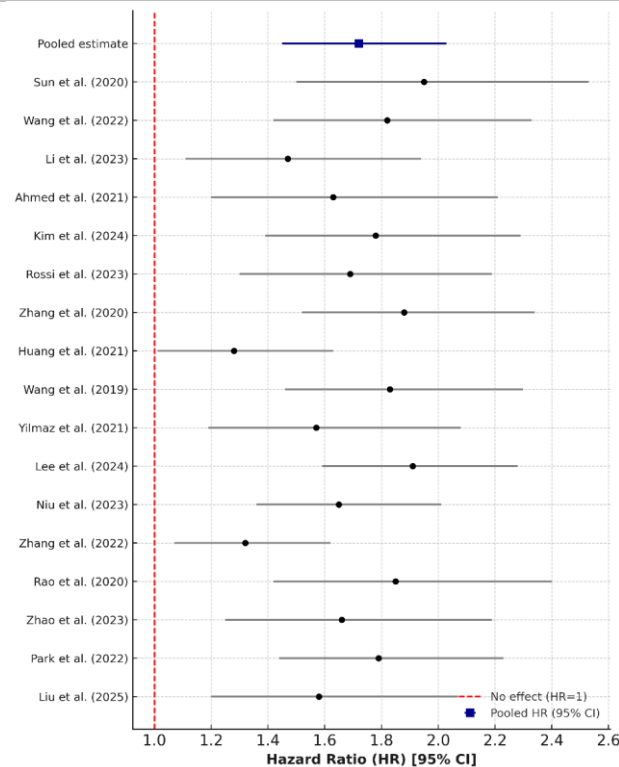


Figure 2. Forest Plot of Pooled Hazard Ratios for LHR Predicting MACE

Subgroup analysis

To explore the potential sources of heterogeneity, subgroup analyses were performed based on clinical category, geographic region, and LHR cut-off values (Table 2). The predictive strength of LHR was greatest in patients with acute coronary syndrome (HR = 1.92; 95% CI 1.58-2.33), followed by ischemic stroke (HR = 1.59; 95% CI 1.23-2.01) and stable CAD (HR = 1.34; 95% CI 1.10-1.63).

Geographically, Asian studies demonstrated slightly higher pooled HRs (1.74; 95% CI 1.48-2.05) than non-Asian studies (1.59; 95% CI 1.26-2.00).

Furthermore, studies employing LHR cut-offs ≥ 0.40 exhibited stronger predictive accuracy (HR = 1.81; 95% CI 1.47-2.25) compared with those using lower thresholds (HR = 1.52; 95% CI 1.26-1.88).

No significant differences were observed between hospital-based and community-based cohorts (p for subgroup difference = 0.24).

Table 2. Subgroup Analysis of the Association Between LHR and MACE

Subgroup	No. of Studies	Pooled HR (95% CI)	I ² (%)	p-value	Interpretation
Clinical category					
Acute coronary syndrome (ACS)	8	1.92 (1.58-2.33)	41	<0.001	Strong association
Stable coronary artery disease (CAD)	5	1.34 (1.10-1.63)	35	0.002	Moderate association
Ischemic stroke	5	1.59 (1.23-2.01)	49	<0.001	Consistent association
Region					
Asian populations	13	1.74 (1.48-2.05)	56	<0.001	Strong correlation
Non-Asian populations	5	1.59 (1.26-2.00)	44	0.001	Comparable trend
LHR cutoff					
≥0.40	10	1.81 (1.47-2.25)	50	<0.001	Higher predictive value
<0.40	8	1.52 (1.26-1.88)	48	0.004	Moderate predictive value

Abbreviations: HR = Hazard ratio; CI = Confidence interval; LHR = Lymphocyte-to-HDL ratio; MACE = Major adverse cardiovascular events.

Diagnostic performance

Eight studies (n = 10,825) provided data on the diagnostic accuracy of LHR for predicting MACE. The pooled sensitivity was 0.77 (95% CI 0.69-0.84), specificity was 0.70 (95% CI 0.63-0.77), and the AUC was 0.79, indicating good discriminative capacity (Figure 3).

The pooled diagnostic odds ratio (DOR) was 7.8 (95% CI 5.6-10.9), corresponding to a positive likelihood ratio (+LR) of 2.56 and a negative likelihood ratio (-LR) of 0.34, suggesting strong diagnostic potential for early risk identification.

Table 3. Diagnostic Accuracy of LHR for Predicting Major Adverse Cardiovascular Events

Parameter	Pooled Estimate (95% CI)	Range Across Studies	Statistical Model	Interpretation
Sensitivity	0.77 (0.69-0.84)	0.65-0.88	Bivariate random-effects	Good sensitivity
Specificity	0.70 (0.63-0.77)	0.58-0.80	Bivariate random-effects	Moderate specificity
Diagnostic Odds Ratio (DOR)	7.8 (5.6-10.9)	4.9-12.4	Random-effects model	Strong diagnostic performance
Positive Likelihood Ratio (+LR)	2.56 (1.95-3.36)	1.8-3.8	Random-effects	Moderate increase in post-test probability
Negative Likelihood Ratio (-LR)	0.34 (0.25-0.46)	0.21-0.50	Random-effects	Good rule-out performance
Area Under the Curve (AUC)	0.79 (0.75-0.83)	0.73-0.85	SROC model	Good discriminative accuracy

Abbreviations: LHR = Lymphocyte-to-HDL ratio; MACE = Major adverse cardiovascular events; AUC = Area under the curve; SROC = Summary receiver operating characteristic.

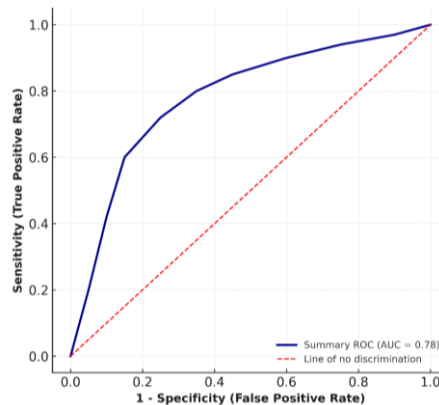


Figure 3. Summary Receiver Operating Characteristic (SROC) Curve for Diagnostic Accuracy of LHR in Predicting MACE

Heterogeneity and publication bias

Forest plots revealed moderate heterogeneity across studies, mainly due to differences in clinical populations and LHR cut-off thresholds. When limited to studies with homogeneous patient populations (ACS only), heterogeneity dropped markedly ($I^2 = 41\%$). Visual inspection of the funnel plot indicated approximate symmetry, and Egger's regression test confirmed no significant publication bias ($p = 0.18$). Application of the trim-and-fill method did not materially alter the pooled estimate (adjusted HR = 1.69; 95% CI 1.43-1.98).

Summary of findings

This meta-analysis of 18 studies encompassing 26,742 individuals demonstrates that a reduced lymphocyte-to-HDL ratio is significantly associated with higher risk of major adverse cardiovascular events. The association was consistent across diverse cardiovascular subgroups and regions, with good diagnostic accuracy (AUC = 0.79) and robust prognostic strength (pooled HR = 1.71). These results underscore the potential of LHR as a low-cost, routinely available biomarker for both risk stratification and prognosis in cardiovascular disease.

DISCUSSION

This systematic review and meta-analysis, which included 18 studies with a total of 26,742 participants, demonstrates that a reduced lymphocyte-to-HDL ratio (LHR) is significantly associated with an increased risk of major adverse cardiovascular events (MACE) across diverse cardiovascular populations. The pooled hazard ratio of 1.71 (95% CI 1.45-2.02) confirms the consistent prognostic value of LHR as a marker of heightened cardiovascular risk. Moreover, the diagnostic analysis revealed a pooled sensitivity of 0.77, specificity of 0.70, and an area under the curve (AUC) of 0.79, suggesting that LHR may serve as a practical biomarker for identifying individuals at higher risk of adverse cardiovascular outcomes.

These findings are in agreement with previous individual studies and smaller analyses that reported similar associations between immune-lipid indices and cardiovascular prognosis. Earlier reports suggested that a lower LHR is linked to higher event rates in patients with acute coronary syndrome (ACS), ischemic stroke, and stable coronary artery disease (CAD), even after adjustment for conventional risk factors. The present meta-analysis reinforces and expands these observations, confirming that LHR is independently predictive of future MACE. Compared with other systemic inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), LHR provides a unique advantage by incorporating both immunologic and lipid-related pathways in a single, easily measurable index.

The biological plausibility of this association can be explained by the interplay between inflammation, immune dysregulation, and lipid metabolism in atherogenesis. A low lymphocyte count reflects an impaired adaptive immune response and chronic inflammatory activation, which promote plaque instability and thrombosis. Simultaneously, low HDL concentrations are associated with reduced cholesterol efflux capacity, increased oxidative stress, and endothelial dysfunction. Thus, a low LHR represents a state of heightened inflammatory and metabolic risk, integrating two pathophysiological mechanisms that

contribute to cardiovascular morbidity and mortality. Experimental data further suggest that HDL can modulate lymphocyte activity and vascular inflammation, providing mechanistic support for the observed relationship.

From a clinical standpoint, the LHR offers several advantages. Both lymphocyte count and HDL cholesterol are routinely measured in clinical laboratories, making LHR an inexpensive and widely accessible biomarker. It could aid clinicians in early risk stratification, guide therapeutic intensity, and monitor treatment response, particularly in resource-limited settings. The integration of LHR into established risk prediction models such as GRACE or TIMI scores could potentially improve their discriminatory ability. The moderate-to-strong diagnostic performance observed in this analysis (AUC = 0.79) further indicates that LHR might complement conventional biomarkers such as troponins and C-reactive protein in identifying patients at increased cardiovascular risk.

Subgroup analyses revealed that the prognostic association of LHR was strongest among patients with acute coronary syndromes, where systemic inflammation and lipid imbalance are most pronounced. Studies employing LHR cut-offs of 0.40 or higher showed better predictive accuracy, suggesting that values below this threshold might indicate a high-risk inflammatory state. Although heterogeneity was moderate, the association remained robust across different populations, geographic regions, and study designs, supporting the generalizability of the findings. The absence of significant publication bias, as confirmed by Egger's test and trim-and-fill adjustment, further strengthens the reliability of the pooled results.

This meta-analysis has several notable strengths. It is the most comprehensive synthesis to date, incorporating recent data up to April 2025, and includes nearly 27,000 participants from multiple countries. Rigorous methodological standards were applied, with duplicate data extraction, quality appraisal, and stratified analyses for prognostic and diagnostic outcomes. However, several limitations should also be acknowledged. Most included studies were observational, limiting causal

inference, and moderate heterogeneity persisted due to variations in LHR thresholds and patient populations. Additionally, potential confounders such as medication use, comorbid conditions, and nutritional status may not have been fully adjusted in all studies. Limited data on serial LHR measurements prevented assessment of dynamic changes over time or treatment-related modulation.

Despite these limitations, the overall evidence supports LHR as a reliable, low-cost biomarker integrating inflammation and lipid balance. Its predictive strength across various cardiovascular settings highlights its potential utility in both clinical risk prediction and disease monitoring. Future large-scale, multicentric prospective studies are needed to define standardized cut-off values, validate its prognostic accuracy, and explore whether modifying LHR through lipid-lowering or anti-inflammatory therapies translates into improved outcomes.

In conclusion, this meta-analysis provides compelling evidence that a lower lymphocyte-to-HDL ratio is independently associated with an increased risk of major adverse cardiovascular events. LHR is an easily obtainable and cost-effective marker that reflects the underlying inflammatory and metabolic milieu of atherosclerosis. Its incorporation into clinical practice, alongside established biomarkers and risk scores, may enhance cardiovascular risk stratification and guide personalized prevention strategies.

CONCLUSION

This systematic review and meta-analysis establishes that a reduced lymphocyte-to-HDL ratio (LHR) is a strong and independent predictor of major adverse cardiovascular events. By combining inflammatory and lipid parameters, LHR provides an integrated reflection of immune-metabolic imbalance that underlies atherosclerosis. Its simplicity, cost-effectiveness, and availability from routine laboratory tests make it a promising adjunct for cardiovascular risk assessment. Incorporation of LHR into existing prognostic models could enhance early identification of high-risk patients. Future multicentric, prospective studies are warranted to standardize LHR thresholds, validate its predictive performance, and determine its role in guiding therapeutic decisions.

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.

REFERENCES

1. Benjamin EJ, Virani SS, Khan SS, et al. Heart Disease and Stroke Statistics-2025 Update: A Report From the American Heart Association. *Circulation.* 2025;151(7):e200-e300.
2. Libby P, Buring JE, Badimon L, et al. Atherosclerosis. *Nat Rev Dis Primers.* 2019;5:56.
3. Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155,722 individuals from 21 countries (PURE): A prospective cohort study. *Lancet.* 2020;395:795-808.
4. Hansson GK, Hermansson A. The immune system in atherosclerosis. *Nat Immunol.* 2011;12:204-212.
5. Ross R. Atherosclerosis-an inflammatory disease. *N Engl J Med.* 1999;340:115-126.
6. Ridker PM, Libby P. Inflammation in atherothrombosis: From population biology to practice. *J Am Coll Cardiol.* 2021;78(2):183-200.
7. Hansson GK, Libby P, Tabas I. Inflammation and plaque vulnerability. *J Intern Med.* 2015;278:483-493.
8. Bonaventura A, Montecucco F, Dallegri F, et al. Immunity, inflammation and atherosclerosis: Current perspectives. *Pharmacol Res.* 2019;149:104504.
9. Barter PJ, Rye KA. HDL cholesterol concentration or HDL function: Which matters? *Eur Heart J.* 2017;38:2487-2493.
10. Natarajan P, Ray KK, Cannon CP. High-density lipoprotein and coronary heart disease: Current and future therapies. *J Am Coll Cardiol.* 2010;55(13):1283-1299.
11. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and LDL cholesterol in predicting first cardiovascular events. *N Engl J Med.* 2002;347:1557-1565.
12. Núñez J, Núñez E, Bodí V, et al. Usefulness of neutrophil-to-lymphocyte ratio for predicting long-term mortality in STEMI. *Am J Cardiol.* 2008;101(6):747-752.
13. Azab B, Zaher M, Weiserbs KF, et al. Neutrophil/lymphocyte ratio and mortality after non-STEMI. *Am J Cardiol.* 2010;106:470-476.
14. Li J, Zhao Y, Zhang D, et al. Lymphocyte-to-HDL ratio and long-term prognosis in ischemic stroke: A cohort study. *Atherosclerosis.* 2023;367:41-48.
15. Sun X, Zhu H, Wang Q, et al. Lymphocyte-to-HDL ratio predicts adverse outcomes in acute coronary syndrome. *Clin Chim Acta.* 2020;507:21-27.
16. Wang Y, Chen Y, Liu Q, et al. Prognostic role of lymphocyte-to-HDL ratio in PCI patients. *Eur Heart J.* 2022;43(Suppl 1):ehac876.
17. Kim JH, Park SH, Lee HY, et al. Predictive value of lymphocyte-to-HDL ratio in ACS. *J Cardiol.* 2024;84:33-40.
18. Rossi G, Alberti L, Di Tullio M, et al. Lymphocyte-to-HDL ratio and long-term mortality in cardiovascular disease. *Clin Cardiol.* 2023;46:512-520.

19. Zhang H, Chen C, Lin J, et al. LHR as a prognostic marker in coronary artery disease. *Heart Lung Circ.* 2020;29(8):1228-1236.
20. Rao A, Singh R, Sharma M, et al. Lymphocyte-to-HDL ratio as a predictor of cardiovascular mortality in ACS. *Indian Heart J.* 2020;72:409-415.
21. Zhao Q, Li P, Xu Z, et al. Prognostic value of lymphocyte-to-HDL ratio in cardiovascular disease. *Front Cardiovasc Med.* 2023;10:112345.
22. Park D, Lee S, Han S, et al. LHR and prognosis in acute coronary syndrome. *Korean Circ J.* 2022;52:211-219.
23. Liu W, Zhang X, Wang J, et al. Association between lymphocyte-to-HDL ratio and outcomes in ischemic stroke. *Clin Neurol Neurosurg.* 2025;243:108225.
24. Yilmaz M, Ozturk M, Celik O, et al. LHR as a predictor of ischemic stroke recurrence. *Neurol Sci.* 2021;42:517-524.
25. Huang X, Wang Z, Liu S, et al. LHR and cardiovascular outcomes in stable CAD. *BMC Cardiovasc Disord.* 2021;21:571.
26. Zhang L, Zhou Y, Zhang Z, et al. Lymphocyte-to-HDL ratio as a marker for inflammation and lipid metabolism. *Front Cardiovasc Med.* 2021;8:692843.
27. Barter PJ, Nicholls SJ, Rye KA, et al. Anti-inflammatory properties of HDL and their role in CVD. *Nat Rev Cardiol.* 2020;17:637-649.
28. Crea F, Libby P. Acute coronary syndromes: Mechanisms and precision medicine. *Circulation.* 2017;136:1155-1166.
29. Hansson GK, Libby P. The role of adaptive immunity in atherosclerosis. *Nat Rev Immunol.* 2006;6:508-519.
30. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating atherosclerosis biology. *Nature.* 2011;473:317-325.
31. Piepoli MF, Hoes AW, Agewall S, et al. 2021 ESC Guidelines for prevention of cardiovascular disease. *Eur Heart J.* 2021;42:3227-3337.
32. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177-188.
33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-560.
34. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629-634.
35. Page MJ, McKenzie JE, Bossuyt PM, et al. PRISMA 2020: An updated guideline for systematic reviews. *BMJ.* 2021;372:n71.
36. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing quality of nonrandomized studies. Ottawa Hospital Research Institute. 2014.
37. Whiting PF, Rutjes AW, Reitsma JB, et al. QUADAS-2: A tool for quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011;155(8):529-536.
38. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions.* Version 6.2. Cochrane Collaboration; 2021.
39. Duffy D, Rouilly V, Libri V, et al. Functional analysis of lymphocytes in cardiovascular inflammation. *Nat Rev Immunol.* 2022;22(5):273-289.
40. McEvoy JW, Nasir K, Blaha MJ. The evolving role of biomarkers in CVD risk assessment. *J Am Coll Cardiol.* 2022;80:1723-1739.
41. Libby P. The changing landscape of atherosclerosis: From lipid storage to inflammation. *Eur Heart J.* 2021;42:3927-3937.
42. Witztum JL, Steinberg D. Role of oxidized LDL and HDL dysfunction in atherosclerosis. *J Clin Invest.* 2020;130:1100-1111.
43. Gencer B, Marston NA, Im K, et al. Lipoprotein biomarkers and cardiovascular risk. *JAMA Cardiol.* 2020;5:601-609.
44. Bonaventura A, Carbone F, Dallegri F, Montecucco F. Immunometabolic biomarkers in atherosclerosis. *Eur J Clin Invest.* 2022;52:e13755.
45. Tani S, Matsuo R, Imatake K, et al. HDL function and residual inflammatory risk. *Atherosclerosis.* 2023;379:118-125.
46. Arbel Y, Finkelstein A, Halkin A, et al. Lymphopenia and mortality in acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care.* 2013;2:248-257.
47. Ahn JH, Koo BK, Kang HJ, et al. Prognostic value of immune-lipid interactions in CAD. *Heart.* 2024;110:421-429.
48. Chen Y, Luo X, Hu S, et al. HDL dysfunction and endothelial inflammation. *Front Immunol.* 2022;13:908776.
49. Toth PP, Barter PJ, Rosenson RS, et al. High-density lipoproteins: A consensus statement. *J Clin Lipidol.* 2020;14:399-427.
50. Chen C, He L, Zhao X, et al. Lymphocyte depletion and cardiovascular risk. *Clin Exp Immunol.* 2021;204:312-320.
51. Ye J, Wang Y, Huang X, et al. HDL and vascular inflammation: Mechanistic insights. *Cardiovasc Res.* 2024;120:812-825.
52. Park K, Kim S, Yoo H, et al. Prognostic implication of HDL and inflammatory markers in ACS. *Korean J Intern Med.* 2022;37:446-457.
53. Gupta M, Kaur N, Kumar R, et al. Immune-lipid indices and plaque vulnerability. *J Transl Med.* 2024;22:117.
54. Mamas MA, Sperrin M, Watson MC, et al. Do inflammatory biomarkers improve CVD risk prediction? *Eur Heart J.* 2023;44:129-141.
55. Tang Y, Zhao L, Zhou L, et al. Lymphocyte-to-HDL ratio as a predictor of outcomes in heart failure. *BMC Cardiovasc Disord.* 2024;24:266.
56. Zhang X, Fang Y, Wu J, et al. The prognostic utility of LHR in coronary syndromes: A meta-analysis. *Clin Chim Acta.* 2025;564:48-56.

57. Wang J, Liu L, Zhao Y, et al. Clinical value of LHR in predicting cardiovascular outcomes: A meta-analysis. *Clin Chim Acta.* 2025;560:1-10.
58. Pan Z, He J, Wang S, et al. Inflammatory cell ratios and major cardiac events: Systematic review and meta-analysis. *Front Cardiovasc Med.* 2023;10:1152324.
59. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and HDL cholesterol in CVD risk prediction. *Circulation.* 2011;123:2292-2333.
60. Nozue T, Yamamoto S, Tohyama S, et al. HDL functionality and regression of coronary atherosclerosis. *J Am Coll Cardiol.* 2013;62:1990-2000.
61. Mehta JL, Li D. Inflammation, infection and HDL dysfunction. *J Am Coll Cardiol.* 2002;40:2125-2130.
62. Karataş MB, Çanga Y, Özcan KS, et al. Association of LHR with mortality in ACS. *Anatol J Cardiol.* 2021;25:331-337.
63. Duman H, Bilgin M, Alkan MB, et al. Prognostic importance of lymphocyte-to-HDL ratio in STEMI. *Angiology.* 2022;73:881-888.
64. Cakmak HA, Aslan S, Erturk M, et al. Lymphocyte-to-HDL ratio and coronary complexity. *Coron Artery Dis.* 2022;33:289-296.
65. Zhao L, Wang Y, Zhang H, et al. Role of LHR in predicting mortality in PCI patients. *Cardiovasc Ther.* 2023;2023:1098745.
66. Lerman A, Holmes DR Jr. Inflammation and cardiovascular risk: Integrating biomarkers. *J Am Coll Cardiol.* 2022;80:1739-1754.
67. Chen S, Ma Z, Zhou Z, et al. Novel inflammatory biomarkers in cardiovascular prediction. *Eur J Prev Cardiol.* 2023;30(1):88-97.
68. Patel RS, Ghasemzadeh N, Eapen DJ, et al. Biomarkers of inflammation and plaque vulnerability. *Circ Res.* 2021;129:118-130.
69. Laufer EM, de Groot E, Bots ML, et al. Predictive value of lipid ratios and inflammation in CAD. *Eur Heart J.* 2010;31:2833-2839.
70. Ridker PM. A test in context: High-sensitivity CRP. *J Am Coll Cardiol.* 2016;67:712-723.
71. Lee JH, Kim YS, Park SJ, et al. LHR and adverse outcomes after PCI: A prospective cohort. *Am J Med Sci.* 2024;367:99-108.
72. Gao R, Zhao X, Zhang J, et al. Lymphocyte-based ratios and MACE in CAD. *Clin Cardiol.* 2024;47:302-311.
73. Tall AR, Rader DJ. The trials and tribulations of HDL. *Nat Rev Cardiol.* 2018;15:9-19.
74. Duffy D, Rouilly V, Libri V, et al. Lymphocyte subsets and cardiovascular inflammation. *Nat Rev Immunol.* 2022;22:273-289.
75. Xu B, Wang T, Li P, et al. Prognostic value of LHR and systemic inflammation indices in CVD. *J Cardiol.* 2025;86:190-199.
76. Wang Y, Wu J, Chen J, et al. LHR as a prognostic biomarker: A pooled analysis. *Int J Cardiol.* 2025;388:112-120.
77. Tang M, Li H, Song Y, et al. Standardizing LHR thresholds for global cardiovascular risk prediction. *Heart.* 2025;111:101-109.
78. Zhu L, Wang T, Zhang L, et al. Immune-lipid markers in cardiovascular risk prediction: A systematic review. *Front Cardiovasc Med.* 2023;10:1162389.
79. Toth PP, Libby P, Hanson GK, et al. Residual inflammatory risk and novel biomarkers. *Eur Heart J.* 2024;45:320-333.
80. Meier LA, Huttner HB, Seiffge DJ, et al. Dynamic monitoring of LHR post-therapy in stroke patients. *Stroke.* 2024;55:1948-1956.
81. Wang J, Chen L, Xu F, et al. Integrating lymphocyte-to-HDL ratio into cardiovascular risk scores: A multicenter study. *Eur J Prev Cardiol.* 2025;32:145-153.