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ORIGINAL RESEARCH

Threshold Effect of the Lymphocyte to HDL-C Ratio on the Risk of Stroke-Associated Pneumonia After Acute Ischemic Stroke: A Retrospective Cohort Study

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Background: Stroke-associated pneumonia (SAP) is a severe complication of acute ischemic stroke (AIS). While post-stroke immunosuppression and metabolic dysregulation are implicated in its pathogenesis, biomarkers integrating these pathways are needed for early risk stratification. We evaluated the lymphocyte-to-HDL-cholesterol ratio (LHR), a marker of immune-metabolic status, as a predictor for SAP.

Methods: We retrospectively analyzed 978 consecutive AIS patients from a single-center cohort. The primary outcome, SAP, was diagnosed based on modified Centers for Disease Control and Prevention criteria within the first 7 days of hospitalization. The relationship between the LHR, calculated from baseline measurements on admission, and SAP was assessed using smooth curve fitting and multivariable logistic regression, adjusting for potential confounders (eg, age, sex, key comorbidities, and thrombolysis treatment). The association's robustness was tested via subgroup and sensitivity analyses.

Results: SAP occurred in 9.2% (90/978) of patients. A distinct nonlinear, L-shaped association was found: SAP risk increased sharply as LHR fell below an empirically identified threshold of approximately 1.0, while remaining consistently low at higher LHR values. In the fully adjusted model, a low LHR (<1.0) was independently associated with a nearly twofold increased risk of SAP (adjusted OR 1.98; 95% CI, 1.20–3.24; $p < 0.05$). The association was robust across major subgroups (eg, by age), though a trend toward a stronger effect was observed in male patients (p for interaction = 0.06).

Conclusion: A low admission LHR (<1.0) serves as a novel, independent predictor of SAP in AIS patients, exhibiting a clinically relevant data-driven threshold effect. As a cost-effective and readily available biomarker reflecting the interplay between immunity and metabolism, LHR holds significant potential for early risk stratification using this empirically derived cut-off, particularly in resource-limited settings.

Keywords: lymphocyte-to-HDL-C ratio, acute ischemic stroke, Stroke, associated pneumonia, neuroinflammation

Introduction

Stroke-associated pneumonia (SAP) represents a major complication with high clinical impact following acute ischemic stroke (AIS).[1] Its incidence varies substantially, with prevalence rates reported between 4% and 23% across populations and studies; nonetheless, it remains the most common post-stroke infection.[2,3] The clinical repercussions of developing SAP are severe; it is independently associated with a more than two-fold increase in in-hospital mortality, prolonged hospitalization, and substantially poorer functional outcomes.[4,5] Therefore, the early identification of high-risk patients is a cornerstone of modern stroke care. It allows for the implementation of targeted prophylactic strategies designed to

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reduce SAP incidence, shorten hospital stays, and alleviate the profound economic burden associated with this complication.[6–9]

The pathophysiology underlying SAP is intricate, stemming largely from a cascade of systemic responses triggered by the initial cerebral injury. A key mechanism is the development of stroke-induced immunodepression syndrome (SIDS). This state is characterized by lymphocytopenia and suppressed cell-mediated immunity—the severity of which is often proportional to the initial stroke severity—which renders patients vulnerable to opportunistic infections.[10–12] Beyond immune suppression, metabolic dysregulation also contributes to infection susceptibility, as stroke is frequently accompanied by systemic inflammation and metabolic perturbations.[13,14] Notably, dysregulated lipid profiles are also implicated. Specifically, reduced high-density lipoprotein cholesterol (HDL-C) may amplify a pro-inflammatory milieu that facilitates SAP.[15,16] The lymphocyte-to-HDL-C ratio (LHR), calculated as the peripheral lymphocyte count divided by the serum HDL-C concentration, has emerged as an integrated biomarker reflecting both immune status and lipid metabolism.[17,18] Lower LHR has been associated with adverse outcomes in cardiovascular and infectious diseases, and preliminary evidence suggests its potential prognostic value in stroke.[19] To our knowledge, no studies have examined whether LHR predicts SAP risk in AIS patients, nor has a clinically meaningful cutoff been identified.

However, many existing prediction models for SAP are limited by their reliance on complex, expensive assays or fail to adequately integrate the critical crosstalk between post-stroke immunosuppression and metabolic dysfunction. Therefore, there is a clear need for a simple, accessible biomarker that can guide bedside decision-making. Identifying a distinct risk threshold for such a marker would be particularly valuable, as it could trigger early preventive strategies for high-risk patients. With this clinical goal in mind, we aimed to evaluate the LHR—a simple, integrative biomarker reflecting this immune-metabolic axis. We hypothesized that the relationship between LHR and SAP risk is not linear, but rather exhibits a distinct threshold below which risk escalates sharply. Accordingly, this study was designed with a multi-step objective: first, to establish the independent predictive power of LHR for SAP in a large cohort of AIS patients; second, to elucidate the precise shape of the dose-response curve using advanced statistical modeling; and finally, to define a specific LHR cutoff that could be translated into a practical, bedside tool for early risk stratification.

Materials and Methods

Study Design and Ethical Approval

This single-center, retrospective cohort study was conducted at the Xiaolan People' s Hospital of ZhongShan. The study protocol was approved by the Ethics Committee of Xiaolan People's Hospital of Zhongshan (Approval No. [2025–014]). Given the retrospective nature of the investigation and the use of anonymized data, the requirement for individual informed consent was waived by the committee. All patient data were fully anonymized prior to analysis to ensure confidentiality. This report was prepared in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and its extension for studies using routinely collected health data, the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.[20,21]

Patient Selection

We retrospectively enrolled a cohort of consecutive patients admitted to the hospital between October 2019 and November 2022. The diagnosis of AIS was established based on clinical presentation and confirmed by evidence of acute infarction on brain computed tomography (CT) or magnetic resonance imaging (MRI). To be eligible for inclusion, patients had to be aged ≥18 years, hospitalized within 72 hours of symptom onset, and have a confirmed AIS diagnosis according to the American Heart Association/American Stroke Association (AHA/ASA) guidelines.[22] We excluded individuals with pre-existing or active infection on admission, defined as a body temperature >38.0°C, or documented evidence of an infectious process. Further exclusion criteria included a history of significant immunosuppressive conditions (eg, HIV infection, organ transplantation), ongoing treatment with immunosuppressants, presence of malignancy, severe renal or hepatic disease. Finally, patients with incomplete or missing baseline data for lymphocyte counts and HDL-C levels, which are essential for calculating the LHR, were also excluded from the analysis. The final study population included 978 consecutive patients with acute ischemic stroke from our institution. This cohort was established

after a data-cleaning step where 36 statistical outliers in admission LHR measurements were removed. These outliers were quantitatively defined as values lying more than 1.5 times the interquartile range (IQR) beyond the first and third quartiles, as is standard for the boxplot technique.[23,24] Upon review, these values were considered statistically extreme rather than biologically implausible and were excluded to prevent their disproportionate influence on the regression analyses. A complete overview of participant enrollment is presented in Figure 1.

Data Collection and Covariates

Baseline data were retrieved from the electronic medical record system. We recorded demographic variables (age, sex), vascular risk factors and comorbidities (hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation), and a key acute treatment variable, the receipt of intravenous thrombolysis. To construct our composite immune-metabolic biomarker, we utilized two distinct blood samples reflecting different physiological states. The first, a non-fasting sample drawn immediately upon admission, was analyzed to assess the acute inflammatory and systemic stress response. This included the complete blood count (providing absolute lymphocyte, neutrophil, and total leukocyte counts) and key biochemical markers indicative of systemic stress (plasma glucose, uric acid). The second, a fasting sample (≥8 hours) collected the following morning, was used to establish the patient's baseline metabolic profile, which comprised the full lipid panel: total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and glycated hemoglobin [HbA1c]. Our primary variable of interest, the lymphocyte-to-HDL-C ratio (LHR), was subsequently calculated by dividing the absolute lymphocyte count from the admission sample by the HDL-C concentration from the fasting sample, thereby integrating an acute immune-stress marker with a baseline metabolic marker.[25]

Outcome Definition

The primary outcome of interest was the development of SAP within the first 7 days of hospitalization. The diagnosis of SAP was made according to the modified Centers for Disease Control and Prevention criteria.[26] This required the presence of new or progressive radiographic infiltrates on a chest X-ray, in conjunction with at least two of the following

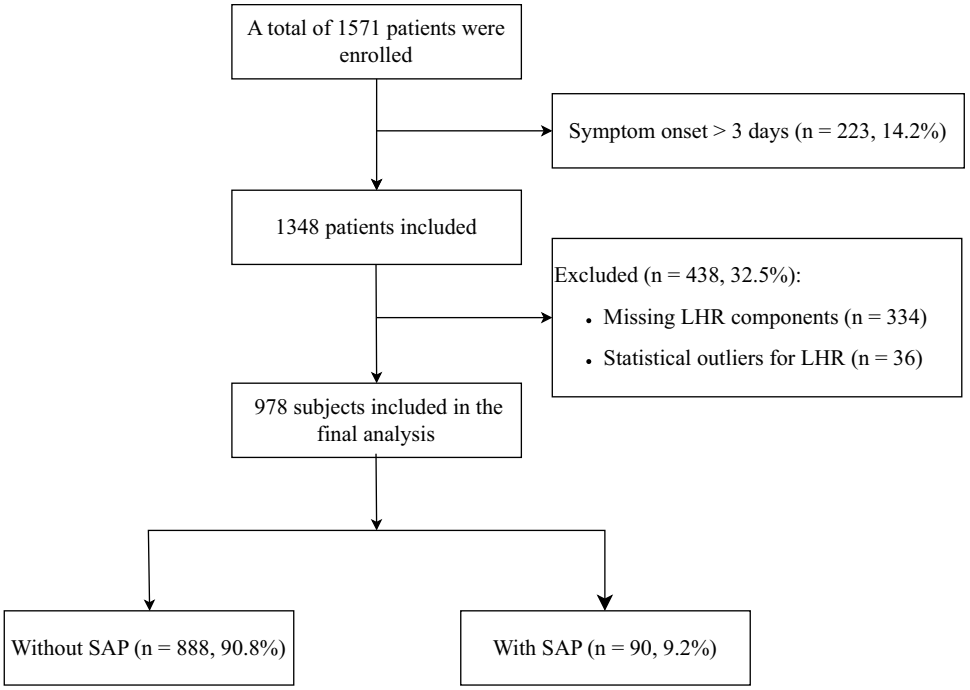

Figure 1 Flow chart visualizing the patient selection process.
Abbreviations: SAP, stroke-associated pneumonia; LHR, lymphocyte-to-HDL-C ratio; HDL-C, high-density lipoprotein cholesterol.

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clinical signs developing after the stroke onset: 1) fever (body temperature >38.0°C); 2) productive cough with purulent sputum; or 3) abnormal respiratory examination findings consistent with pneumonia.

Statistical Analysis

Continuous variables were presented as mean ± SD or median (IQR) based on their distribution, which was assessed by the Shapiro–Wilk test. Categorical variables were expressed as n (%).

Between-group comparisons were performed using the Student's *t*-test or Mann–Whitney *U*-test for continuous variables and the chi-square test for categorical variables, as appropriate.

To investigate the functional form of the relationship between LHR and the incidence of SAP, curve fitting analysis (Generalized Additive Model) was performed, allowing for exploration of both linear and non-linear patterns. A subsequent two-piecewise linear regression analysis was performed to identify the optimal LHR threshold based on the maximum likelihood method. This threshold was used to dichotomize the LHR for risk stratification.

To evaluate the association between LHR levels and the risk of SAP, we utilized multivariate logistic regression models. Three hierarchical models were developed: a crude model, a partially adjusted model (Model 1: adjusted for age and sex), and a fully adjusted model (Model 2). The fully adjusted model controlled for a range of potential confounders, which were selected based on their established association with SAP in prior literature and their clinical relevance. These included sex, age, clinical history (diabetes, hypertension, atrial fibrillation, coronary heart disease), length of stay, laboratory values (white blood cells, uric acid, glucose), and receipt of intravenous thrombolysis. Prior to the final analysis, multicollinearity among these covariates was assessed using the variance inflation factor (VIF), and no significant collinearity was detected (all VIF < 5). Patients were categorized into low and high LHR groups according to the fitted threshold (inflection point) identified from the smoothing curve, and odds ratios (ORs) with 95% confidence intervals were reported for each group.

The final analytical cohort of 978 patients was established by including only individuals with complete data for the primary outcome (SAP) and the main exposure variables (lymphocyte count and HDL-C). For the covariates included in the multivariable models, we first assessed the extent of missing data. Variables with more than 20% missing values were designated to be excluded from the analysis; however, all covariates included in the final models had less than 20% missing data. We employed multiple imputation using the multivariate imputation by chained equations algorithm to handle the missing data in covariates, under the assumption that the data were missing at random. We generated five imputed datasets. The estimates from the logistic regression models performed on each of these five datasets were then pooled into a single estimate using Rubin's rules to obtain the final odds ratios, 95% confidence intervals, and p-values.

Furthermore, to ensure the robustness of our findings, we conducted two prespecified sensitivity analyses. First, we performed subgroup analyses and formally tested for interactions by including multiplicative interaction terms between the LHR category and each stratification variable (eg, sex, age) in the fully adjusted model. Second, we repeated the primary regression analysis on the complete dataset to assess the influence of extreme LHR values. A two-sided *p*-value < 0.05 was established as the threshold for statistical significance. All analyses were performed using R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics and SAP Incidence

A total of 978 patients with acute ischemic stroke were included in the study, with baseline characteristics summarized in Table 1. Overall, 90 patients (9.2%) developed SAP. A comparative analysis revealed significant differences between the with SAP and without SAP groups. Patients who developed SAP were significantly older (68.28 ± 14.43 vs 62.08 ± 12.63 years; $p < 0.001$) and had a higher prevalence of atrial fibrillation (16.7% vs 5.3%; $p < 0.001$) and coronary heart disease (15.6% vs 7.6%; $p = 0.015$). From a laboratory perspective, the SAP group presented with a state of heightened inflammation and immunodepression upon admission, characterized by significantly higher white blood cell [median 9.10 vs 7.60, p <0.001] and neutrophil counts[median 6.92 vs 5.28, p <0.001] and, critically, a marked reduction in lymphocyte counts [1.27 ± 0.59 vs 1.58 ± 0.56, p <0.001]. As a direct consequence, the Lymphocyte-to-HDL-C ratio

Table 1 Baseline Characteristics of Patients with and without SAP

Variable Names	Level	Overall	Without SAP	With SAP	*p*
n		978	888	90	
Demographic Characteristics					
Age, years		62.65±12.92	62.08±12.63	68.28±14.43	<0.001
Gender (%)	Male	655 (67.0)	595 (67.0)	60 (66.7)	1.000
	Female	323 (33.0)	293 (33.0)	30 (33.3)	
Comorbidities, n (%)					
Diabetes (%)	No	631 (64.5)	571 (64.3)	60 (66.7)	0.74
	Yes	347 (35.5)	317 (35.7)	30 (33.3)	
Coronary Heart Disease (%)	No	897 (91.7)	821 (92.5)	76 (84.4)	0.015
	Yes	81 (8.3)	67 (7.6)	14 (15.6)	
Atrial Fibrillation (%)	No	916 (93.7)	841 (94.7)	75 (83.3)	<0.001
	Yes	62 (6.3)	47 (5.3)	15 (16.7)	
Hypertension (%)	No	149 (15.2)	137 (15.4)	12 (13.3)	0.71
	Yes	829 (84.8)	751 (84.6)	78 (86.7)	
Laboratory Parameters					
White Blood Cells WBC		7.80 (6.40–9.70)	7.6 (6.3–9.5)	9.1 (7.4–10.9)	<0.001
Neutrophils		5.40 (4.14–7.48)	5.28 (4.09–7.21)	6.92 (5.53–9.48)	<0.001
Lymphocytes		1.55±0.57	1.58±0.56	1.27±0.59	<0.001
Blood Glucose (mmol/l)		6.78 (5.57–9.19)	6.76 (5.57–9.32)	7.2 (5.64–8.17)	0.63
Uric Acid		347 (282–426.75)	348.5 (283.75–427)	332 (260–418.75)	0.34
HbA1c		5.90 (5.50–7)	5.9 (5.5–7.1)	5.9 (5.5–6.7)	0.60
TC (mmol/l)		4.58 (3.96–5.30)	4.6 (3.98–5.27)	4.46 (3.64–5.39)	0.59
TG (mmol/l)		1.42 (1.00–1.97)	1.44 (1.02–1.98)	1.18 (0.84–1.84)	0.11
HDL (mmol/l)		1.06 (0.90–1.27)	1.06 (0.9–1.26)	1.11 (0.87–1.44)	0.09
LDL (mmol/l)		3.08±0.98	3.09±0.96	3.03±1.21	0.58
Primary Biomarker					
LHR group, n (%)	≥1	730 (74.6)	679 (76.5)	51 (56.7)	<0.001
	<1	248 (25.4)	209 (23.5)	39 (43.3)	

Notes: Data are presented as mean ± standard deviation for normally distributed variables, as median (interquartile range) for skewed variables, or as n (%) for categorical variables. P-values were calculated using the Student's *t*-test, Mann–Whitney *U*-test, or Chi-square test as appropriate.

Abbreviations: SAP, stroke-associated pneumonia; HbA1c, Glycated Hemoglobin; TC, Total Cholesterol; TG, Triglycerides; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; LHR, lymphocyte-to-HDL-C ratio.

(LHR), our novel biomarker integrating both immune and metabolic status, was significantly lower in patients who developed SAP compared to their counterparts (43.3% vs 23.5%; $p < 0.001$).

Non-Linear Association and Threshold Effect of LHR on SAP Risk

To investigate the dose-response relationship between LHR and SAP, we first modeled LHR as a continuous variable using a Generalized Additive Model (GAM), adjusted for clinical confounders. The resulting smooth curve analysis demonstrated a significant non-linear association with SAP risk (Figure 2). The curve illustrates a steep, inverse relationship in the lower range of LHR values, where increasing LHR confers a strong protective effect. However, this protective effect appears to diminish as the curve begins to flatten. This visual evidence strongly suggested a threshold effect, which prompted formal statistical analysis to precisely define and quantify this relationship. It should be noted that the confidence intervals widened for LHR values greater than 2.0, suggesting greater uncertainty of the risk estimate in this range due to a smaller number of subjects.

To statistically test this observation, we performed a two-piecewise linear regression analysis with the results detailed in Table 2. The analysis identified an optimal inflection point at LHR = 1.0 using the maximum likelihood method. Below this threshold (LHR < 1.0), there was a potent and statistically significant protective association: each unit increase in LHR was associated with a 90% reduction in the odds of SAP (OR = 0.10, 95% CI: 0.03–0.34, $p < 0.05$). In

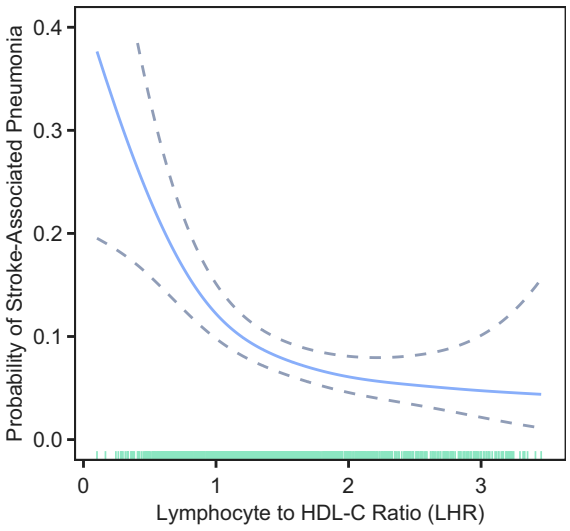

Figure 2 Non-linear association between LHR and SAP risk (curve smoothing).
Abbreviations: SAP, stroke-associated pneumonia; LHR, lymphocyte-to-HDL-C ratio; HDL-C, high-density lipoprotein cholesterol.

stark contrast, for LHR values at or above this 1.0 threshold, the association was nullified and no longer statistically significant (OR = 0.90, 95% CI: 0.56–1.45, $p = 0.66$). Furthermore, the log-likelihood ratio test confirmed that the two-piecewise model provided a significantly better fit to the data than a standard linear model ($p < 0.05$). These results provide robust statistical validation for a non-linear relationship and establish LHR = 1.0 as a data-driven cutoff for risk stratification.

Independent Association Between Low LHR and SAP Risk

To formally evaluate the independent association between LHR levels and the risk of SAP, we utilized the data-driven threshold of 1.0 to categorize patients into low (<1.0) and high (≥1.0) LHR groups. The results of the hierarchical multivariate logistic regression analyses are detailed in Table 3. In the unadjusted crude model, patients in the low LHR group exhibited a significantly higher risk of developing SAP compared to the high LHR group (OR = 2.48, 95% CI: 1.59–3.87, $p < 0.001$). This association remained robust after adjusting for age and sex in Model 1 (OR = 2.19, 95% CI: 1.39–3.45, $p < 0.001$). Crucially, even after comprehensive adjustment for baseline demographics, clinical comorbidities, laboratory values, and treatment variables in the fully adjusted Model 2, a low LHR level was confirmed as an independent and significant predictor of SAP (OR = 1.98, 95% CI: 1.20–3.24, $p < 0.007$), indicating that these patients had approximately double the odds of developing SAP. To translate this finding into its practical clinical significance, we examined the raw incidence rates. SAP occurred in 15.7% of patients in the low LHR group, compared to 7% in the high

Table 2 Two-Piecewise Linear Regression Analysis for the Association Between LHR and SAP Risk

Variable	No. of Patients	(OR[1], 95% CI)	*p*-value
LHR (as a continuous variable)[a]	978	0.55(0.38–0.80)	0.002
Piecewise analysis with threshold at 1.0			
<1	248	0.10(0.03–0.34)	<0.001
≥1	730	0.90(0.56–1.45)	0.66
p for log likelihood ratio test			0.005

Notes: [a]The OR for "LHR (as a continuous variable)" was derived from a standard logistic regression model. For the piecewise analysis, the OR represents the change in risk for each one-unit increase of LHR within the specified stratum. The *p* for the log-likelihood ratio test assesses whether the two-piecewise model provides a significantly better fit than the standard single-line model.
Abbreviations: LHR, lymphocyte-to-HDL-C ratio; SAP, stroke-associated pneumonia; OR, odds ratio; CI, confidence interval.

Table 3 Multivariable Logistic Regression Analysis of the Association Between LHR Category and Risk of SAP

Variable	Crude Model (OR, 95% CI)	*p*-value	Model 1 (OR, 95% CI)	*p*-value	Model 2 (OR, 95% CI)	*p*-value
LHR(≥1)	Ref		Ref		Ref	
LHR(<1)	2.48(1.59–3.87)	<0.001	2.19(1.39–3.45)	<0.001	1.98(1.20–3.24)	<0.007

Notes: Crude model: No variables are adjusted. Model 1: Adjusted for sex and age. Model 2: Adjust for sex, age, clinical history (diabetes, hypertension, atrial fibrillation, coronary heart disease), length of stay, laboratory values (white blood cells, uric acid, glucose), and recipient of intravenous thrombolysis.

LHR group. This yields a clinically meaningful absolute risk difference (ARD) of 8.7%. Furthermore, this translates to a Number Needed to Screen (NNS) of 12, indicating that for every 12 AIS patients screened with this LHR threshold, one additional patient at high risk for SAP could be identified.

Subgroup Analysis and Sensitivity Analyses

To further assess the robustness and generalizability of the association between LHR and SAP, we conducted a subgroup analysis across various pre-specified clinical subgroups (Figure 3). Overall, the predictive value of a low LHR for an increased SAP risk remained consistent across nearly all subgroup, with no statistically significant interactions detected (all p for interaction > 0.05). For instance, the association was stable regardless of age (>60 vs ≤60 years, p for interaction = 0.84), history of hypertension (p for interaction = 0.94), or receipt of venous thrombolysis (p for interaction = 0.69). Notably, while not reaching the conventional threshold for statistical significance, a potential trend was observed in the gender subgroup (p for interaction = 0.06), where the effect of low LHR appeared more pronounced in male patients (OR 3.43, 95% CI 1.98–5.91) than in females (OR 1.35, 95% CI 0.60–2.91). Therefore, while these findings support the general robustness of LHR as a predictor, the observed trend in the gender subgroup suggests its prognostic strength may be more pronounced in men and warrants further investigation. Finally, it should be noted that the confidence intervals were considerably wide in some smaller subgroups (eg, those with diabetes), reflecting the limited statistical power to assess effect modification in these strata.

We also conducted a prespecified sensitivity analysis by repeating the primary regression analysis on the complete dataset without excluding extreme LHR values. The results, presented in Supplementary Table S1, demonstrated that the association between a low LHR and SAP risk remained highly stable For this analysis, the LHR was dichotomized at a cutoff of 1.0, a threshold selected based on the inflection point identified in our primary non-linear dose-response analysis (Figure 2). After adjusting for all potential confounders in Model 2, a low LHR (<1.0) was still independently and significantly associated with an elevated risk of SAP (OR = 2.08, 95% CI: 1.24–3.45, $p < 0.005$). This finding was consistent across the crude (OR = 2.56, 95% CI: 1.64–3.98) and partially adjusted (Model 1: OR = 2.24, 95% CI: 1.41–3.51) models. The persistence of this significant association confirms that our primary results were not unduly influenced by the exclusion of outliers, thereby reinforcing the validity of LHR as a robust predictor for SAP.

Discussion

The principal finding of this study is the identification of a significant, nonlinear association between the admission LHR and the risk of SAP in patients with acute ischemic stroke. Utilizing flexible modeling techniques, we identified a distinct inflection point at an LHR threshold of approximately 1.0. Below this threshold, the risk of SAP increased sharply, whereas above it, the risk plateaued. After adjusting for key demographic, clinical, and laboratory confounders, a low LHR (<1.0) emerged as a robust independent predictor, conferring approximately double the odds of developing SAP. This association was remarkably consistent across all prespecified subgroups and remained stable in sensitivity analyses. Taken together, these findings strongly suggest that a disruption of immune-metabolic homeostasis, specifically when LHR falls below the 1.0 threshold, critically increases susceptibility to post-stroke infection. This positions LHR not merely as a linear risk correlate, but as a promising and readily available biomarker for identifying high-risk patients at the bedside.

Our findings extend prior observations that post-stroke immune dysregulation is a key factor in stroke-associated infections beyond classical clinical risk factors such as dysphagia and reduced consciousness.[27,28] The rationale for

Variable	Group	Count	Percent	OR(95%CI)	P_for_Interaction
Gender					**0.055**
Female					
	High	224	69.350	ref	
	Low	99	30.650	1.349(0.598,2.91)	
Male					
	High	506	77.252	ref	
	Low	149	22.748	3.428(1.979,5.913)	
Age					**0.841**
<=60					
	High	352	79.819	ref	
	Low	89	20.181	2.494(1.064,5.573)	
>60					
	High	378	70.391	ref	
	Low	159	29.609	2.257(1.316,3.852)	
Diabetes					**0.11**
No					
	High	448	70.998	ref	
	Low	183	29.002	3.179(1.853,5.484)	
Yes					
	High	282	81.268	ref	
	Low	65	18.732	1.359(0.519,3.173)	
Coronary_Heart_Disease					**0.5**
No					
	High	666	74.247	ref	
	Low	231	25.753	2.415(1.485,3.898)	
Yes					
	High	64	79.012	ref	
	Low	17	20.988	3.818(1.075,13.333)	
Atrial_Fibrillation					**0.123**
No					
	High	693	75.655	ref	
	Low	223	24.345	2.692(1.651,4.359)	
Yes					
	High	37	59.677	ref	
	Low	25	40.323	0.982(0.288,3.188)	
Hypertension					**0.936**
No					
	High	121	81.208	ref	
	Low	28	18.792	2.354(0.59,8.136)	
Yes					
	High	609	73.462	ref	
	Low	220	26.538	2.49(1.54,4.004)	
Venous_Thrombolysis					**0.693**
No					
	High	631	74.675	ref	
	Low	214	25.325	2.669(1.58,4.481)	
Yes					
	High	99	74.436	ref	
	Low	34	25.564	2.161(0.85,5.345)	

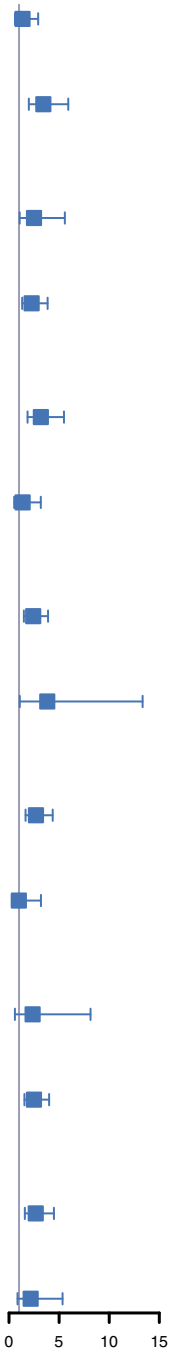

Figure 3 Subgroup analyses of LHR and SAP risk. Bold values indicate the P-values for interaction.
Abbreviations: SAP, stroke-associated pneumonia; LHR, lymphocyte-to-HDL-C ratio; HDL-C, high-density lipoprotein cholesterol.

evaluating LHR stems from its integration of two intertwined post-stroke pathophysiological pathways. On one hand, lymphopenia serves as a hallmark of stroke-induced immunodepression (SIDS), driven by sympathetic and HPA-axis activation and accelerated lymphocyte apoptosis.[12] On the other hand, HDL-C exerts crucial anti-inflammatory and anti-infective actions, meaning lower levels may critically diminish host defense.[29–31] Crucially, these two pathways are mechanistically linked by the systemic inflammatory surge, characterized by elevated

markers like IL-6 and CRP, which is known to exacerbate both lymphopenia and HDL dysfunction after stroke.[32–35] While prior biomarker studies have evaluated single indices (eg, lymphocyte count) or other inflammatory composites,[15,36–38] our approach, by integrating an adaptive-immunity marker (lymphocyte count) with a lipid-mediated anti-inflammatory marker (HDL-C), provides a more holistic signal of the underlying immune–metabolic imbalance.[18,25] In line with our previous work showing associations of fibrinogen and lymphocyte-to-monocyte ratio with SAP risk,[36,39] the present study extends this research line by introducing LHR as an integrated immune–metabolic biomarker.

A key finding of our study is the nonlinear relationship between LHR and SAP risk, with a distinct inflection point 1.0. This suggests a "tipping-point" phenomenon: once adaptive immunity (represented by lymphocytes) drops below a critical threshold relative to HDL-mediated regulation, susceptibility to infection rises disproportionately. Conversely, LHR values above this cut-point do not appear to confer further protection, potentially indicating a saturation of HDL-related pathways or ceiling effects in lymphocyte-dependent defense.[40] This nonlinear pattern offers a more nuanced understanding than a simple linear association and provides a clinically actionable threshold for risk stratification. A particularly intriguing secondary finding was the potential modification of this effect by gender, with the association between LHR and SAP appearing stronger and reaching statistical significance only in males. This observation, while exploratory, may be rooted in fundamental sex-related biological differences. For instance, the known immunoprotective effects of estrogen and its role in maintaining higher HDL-C levels in females could provide a buffer against the post-stroke immune-metabolic collapse.[41] While the interaction test did not reach the conventional threshold for statistical significance ($p = 0.06$) and this finding must be interpreted with caution, this strong trend highlights a crucial area for future investigation. Larger prospective studies are warranted to confirm this potential sex-specific effect and elucidate the underlying mechanisms.

The translational potential of our findings is significant. Given that its components are part of routine blood panels, LHR represents a readily implementable, universally accessible, and cost-neutral biomarker for SAP risk stratification. Its key advantage lies in the ability to flag high-risk patients (LHR < 1.0) upon admission, creating a crucial window to initiate an individualized, proactive infection prevention care path. For instance, clinicians could implement a "SAP prevention bundle" for this cohort, which might include intensified dysphagia screening, stricter oral hygiene protocols, prioritized consultation with respiratory therapists, and enhanced surveillance for subtle signs of infection. This approach is particularly valuable in resource-constrained healthcare systems. From a public health perspective, the biomarker's cost-effectiveness extends beyond its zero-cost calculation; it lies in enabling a shift from universal precautions to a targeted, risk-based model. This allows for the strategic allocation of limited resources—such as specialized nursing time or prophylactic therapies—to patients who will benefit most, thereby preventing high-cost complications, reducing hospital stays, and ultimately promoting both clinical efficacy and equity in stroke care delivery.

Our study has several limitations. First, the single-center design and the inclusion of an exclusively Chinese cohort limit the external validity of our findings. The generalizability of the specific LHR threshold of 1.0, in particular, requires confirmation in large, multi-center, and multi-ethnic prospective studies before it can be widely applied. Second, despite extensive adjustments, residual confounding from unmeasured factors cannot be entirely excluded, most notably the absence of data on standardized dysphagia screening and baseline stroke severity (eg, NIHSS score). Third, our study may be subject to selection bias due to the exclusion of patients with missing LHR data or those identified as statistical outliers. While we cannot rule out systematic differences in the group with missing data, the concern regarding outliers was mitigated by a dedicated sensitivity analysis. This analysis, which included the outliers, confirmed that our primary findings remained robust, suggesting this exclusion did not substantially bias our results. Lastly, we used lymphocyte and HDL-C values from two different time points. While we hypothesize this reflects an interaction between acute stress and baseline metabolic state, future prospective studies should validate LHR using single-timepoint measurements to confirm its prognostic utility. Looking ahead, future large-scale prospective studies are crucial not only to confirm our findings across diverse populations but also to assess the incremental predictive value of integrating LHR into established clinical scoring systems, such as the A2DS2 score.[42]

Conclusion

A low LHR, particularly below a threshold of 1.0, serves as an independent and nonlinear predictor of SAP in patients with AIS. This study identifies LHR as a promising, cost-effective, and readily available biomarker that integrates both immune and metabolic dysregulation. Its implementation holds potential to improve early risk stratification and guide targeted interventions to mitigate SAP; however, these findings warrant validation in future large-scale prospective cohorts.

Abbreviations

AIS, acute ischemic stroke; SAP, stroke-associated pneumonia; SII, systemic immune-inflammation index; LHR, Lymphocyte to HDL-C Ratio; SIDS, stroke-induced immunosuppression syndrome.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to patient privacy and ethical restrictions. However, data supporting the findings of this study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Xiaolan People's Hospital of Zhongshan (The Fifth People's Hospital of ZhongShan), approval number [2025-014]. The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study. All procedures performed in this study were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Specific individual contributions are as follows: Xiaoqiang Li (Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Supervision); Hui Du (Data curation, Investigation, Writing – Review & Editing); Guifeng Zhang (Resources, Data curation, Validation, Writing – Review & Editing); Zhibin Song (Methodology, Software, Visualization, Writing – Review & Editing); Mei Qi (Data curation, Project administration, Writing – Review & Editing); and Hui Wang (Supervision, Writing – Review & Editing).

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Disclosure

The authors declare that there is no conflict of interest.

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