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ORIGINAL RESEARCH

Systemic Inflammation Mediates the Association Between Atrial Fibrillation and Functional Outcomes After Ischemic Stroke

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Background: Atrial fibrillation (AF) is a major risk factor for ischemic stroke and is associated with worse neurological outcomes. The mechanisms underlying this relationship, particularly the role of systemic inflammation as a mediator linking AF to post-stroke functional outcomes, remain insufficiently understood.

Methods: We conducted a retrospective cohort study of 463 patients with acute ischemic stroke (median age 67.0 years [IQR 56.0–74.0]; 27.0% female), including 96 with AF. Candidate mediators were identified using least absolute shrinkage and selection operator (LASSO) regression and single-mediator causal mediation models were applied adjusting for established confounders. Robustness was evaluated using E-values.

Results: Patients with AF had more severe neurological deficits and had poorer 90-day functional outcomes. The multivariable model incorporating LASSO-selected variables demonstrated better predictive performance (AUC 0.829) compared to a confounder-only model (AUC 0.757). Mediation analysis demonstrated that neutrophil-to-lymphocyte ratio (NLR) and systemic inflammation response index (SIRI) significantly mediated 22.3% and 17.0% of the association between AF and poor functional outcome, suggesting that systemic inflammation contributes meaningfully to AF-related post-stroke disability.

Conclusion: NLR and SIRI partially mediate the association between AF and poor functional outcomes after ischemic stroke, suggesting that systemic inflammation may serve as a potential prognostic marker and that these indices could aid early risk stratification.

Keywords: atrial fibrillation, ischemic stroke, systemic inflammation, neutrophil-to-lymphocyte ratio, mediation analysis

Introduction

Atrial fibrillation (AF) is one of the most prevalent cardiac arrhythmias worldwide and a well-established risk factor for ischemic stroke.[1,2] Patients with AF tend to experience more severe neurological deficits, larger infarct volumes, and higher risks of mortality and long-term disability compared with those without AF.[3] However, the mechanisms underlying the association between AF and adverse functional outcomes after stroke remain incompletely understood.[4]

Systemic inflammation is increasingly recognized as a potential mechanistic bridge between AF pathogenesis and post-stroke injury.[5] Experimental and clinical studies show that inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-2 (IL-2), interleukin-8 (IL-8), and C-reactive protein (CRP) contribute to atrial structural remodeling, endothelial dysfunction, and thrombogenesis.[6–9] Recent multi-omic evidence further highlights immune-cell infiltration and fibroblast activation in AF-related atrial tissue.[10] These inflammatory processes extend into the cerebrovascular system, where dysregulated innate and adaptive immunity—particularly neutrophil activation, lymphocyte depletion, oxidative stress, and blood–brain barrier breakdown—worsen cerebral injury and impair recovery after ischemic stroke.[11–13]

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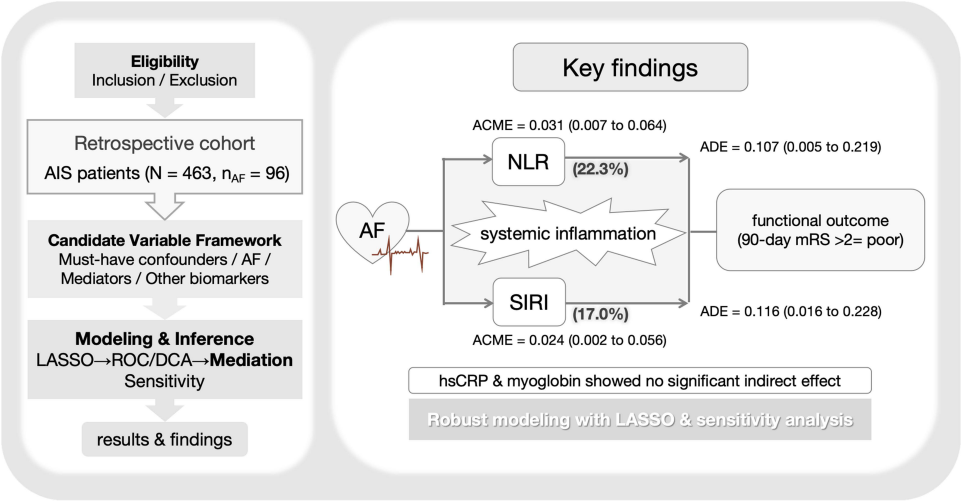
Graphical Abstract



Composite inflammation-based indices, such as neutrophil-to-lymphocyte ratio (NLR), the systemic inflammation response index (SIRI) and the systemic immune-inflammation index (SII) capture multiple dimensions of immunity and have shown strong associations with cardiovascular and cerebrovascular outcomes.[11,14–16] These markers reflect the balance between neutrophil-driven innate immunity and lymphocyte-mediated regulation, both of which play critical roles in stroke-related secondary injury.[17–19] Emerging inflammation–lipid composite indices, such as the neutrophil-to-total cholesterol ratio (NTR) and the high-density lipoprotein-to-lymphocyte ratio (HLR) have also shown early potential, although their roles are less established.[20,21]

Despite growing evidence linking AF, inflammation, and stroke prognosis, it remains unclear whether systemic inflammation mediates the relationship between AF and post-stroke functional outcomes. Prior studies have primarily examined inflammatory biomarkers as predictors rather than mechanistic intermediates, and few studies have formally quantified indirect pathways using mediation analysis.[22] Causal mediation analysis, combined with modern variable-selection approaches such as the least absolute shrinkage and selection operator (LASSO), offers a robust framework to identify candidate mediators and quantify indirect effects in multivariable contexts.[23] Sensitivity tools such as E-values further enable the assessment of robustness to potential unmeasured confounding.[24]

Therefore, this study aimed to evaluate whether systemic inflammatory markers mediate the association between AF and 90-day functional outcomes after acute ischemic stroke (AIS). We focused on established inflammatory indices such as NLR and SIRI, while also exploring emerging inflammation–lipid markers. By applying LASSO-guided mediator selection and formal causal mediation analysis, this study seeks to quantify the contribution of systemic inflammation to AF-related functional impairment and identify clinically informative biomarkers in AF-associated ischemic stroke.

Methods

Study Design and Participants

This retrospective cohort study included consecutive adult patients admitted with AIS to the Stroke Center of the First Affiliated Hospital of Soochow University between September 2023 and April 2025. All patients received standard-of-care acute stroke management, including reperfusion therapies (intravenous thrombolysis or mechanical thrombectomy) when clinically indicated, according to national stroke guidelines. The distribution of reperfusion therapies was similar between AF and non-AF groups, and for patients who underwent thrombolysis or thrombectomy, blood samples were obtained before the procedure. Blood samples for inflammatory markers were collected under fasting conditions in the early morning of the second hospital day and analyzed in a single certified hospital laboratory.

AF, including both previously diagnosed AF and AF newly detected during hospitalization, was confirmed by 12-lead electrocardiography or ≥24-hour continuous cardiac monitoring. Functional outcomes were assessed at 90 days using the modified Rankin Scale (mRS), with poor outcome defined as mRS >2.[25] Among the screened patients, those with pre-stroke disability (mRS >2), incomplete clinical records, active malignancy, autoimmune disorders, or documented acute infection at admission were excluded. Among 500 screened patients, 37 met the exclusion criteria (23 with incomplete data, 9 with acute systemic inflammation, and 5 with malignancy or other systemic diseases), resulting in 463 patients included in the final analysis. Clinical and laboratory data were extracted from electronic medical records.

Inflammatory Marker Assessment

The inflammatory indices were calculated using standard hematologic and biochemical parameters as follows:

$$\text{NLR} = \text{neutrophil count} / \text{lymphocyte count};$$

$$\text{SIRI} = (\text{neutrophil count} \times \text{monocyte count}) / \text{lymphocyte count};$$

$$\text{NTR} = \text{neutrophil count} / \text{total cholesterol level};$$

$$\text{HLR} = \text{HDL} - \text{cholesterol concentration} / \text{lymphocyte count}.$$

Additional inflammatory indices were calculated using conventional formulas and are summarized in Supplementary Table S8.

Statistical Analysis

Continuous variables were examined for distributional properties, and skewed variables were log-transformed and Z-standardized before analysis. Missing data were handled using multiple imputation with chained equations. Candidate variables for further analysis were selected based on two criteria: (1) differences between AF and non-AF groups ($p < 0.1$), and (2) significant association with poor 90-day functional outcome in univariable logistic regression ($p < 0.05$). Variables meeting these thresholds were categorized a priori into four groups: must-have confounders, the core variable of interest (AF), candidate mediators, and other associated variables.

To identify appropriate mediators while minimizing multicollinearity and overfitting, a two-layer LASSO regression procedure was implemented. In the first layer, only candidate mediators were penalized while confounders were forced into the model. In the second layer, other associated variables were introduced to obtain a more comprehensive model structure. Cross-validated λ was chosen to minimize prediction error and variables with non-zero coefficients were retained for further modeling. Predictive performance of the confounder-only model and full model (must-have confounders + AF + LASSO-selected variables) was compared using receiver operating characteristic (ROC) curves, area under the receiver operating characteristic (AUC) curve, calibration metrics, and decision curve analysis.

Single-mediator causal mediation analyses were performed using a traditional, frequency-based framework. For each mediator, a linear regression model was fitted with AF and confounders as predictors. The outcome model was specified for the mediator (continuous), and a logistic regression model was used for the outcome (poor 90-day mRS). Mediation effects, including the average causal mediation effect (ACME), average direct effect (ADE), total effect, and proportion mediated, were estimated using 5000 bootstrap simulations. Significance was defined as a 95% confidence interval not crossing zero.

To evaluate robustness to potential confounding by baseline stroke severity, a sensitivity analysis excluding the NIHSS score from both mediator and outcome models was conducted. The E-values were calculated to assess the strength of confounding required to explain away the observed effects. Model assumptions, including linearity, normality, and homoscedasticity, were examined using residual diagnostics and Q-Q plots. In the mediation models, the mediator was modeled using linear regression and the outcome using logistic regression with a logit link function, each adjusted for AF and the prespecified confounders. These model structures were consistent across all single-mediator analyses. No correction for multiple testing was applied because the mediators were defined a priori based on biological plausibility.

Software and Packages

All statistical analyses were conducted in R (version 4.3.2). Causal mediation analyses were conducted using the mediation package, and data manipulation and visualization were performed with dplyr, openxlsx, and ggplot2, along with other relevant packages.

Results

A total of 463 patients with AIS were included, of whom 96 (20.7%) had AF. Compared with patients without AF, those with AF were older, more often female, and presented with more severe neurological deficits, as reflected by higher baseline NIHSS scores (Table 1 and Supplementary Table S1). Univariable logistic regression identified several variables

Table 1 Baseline Characteristics of Patients with and without Atrial Fibrillation

Characteristics	Total (n = 463)	Non-AF (n = 367)	AF (n = 96)	P-value
Basic Demographics				
Age (years)	67.0 (56.0, 74.0)	63.0 (54.0, 72.0)	76.5 (70.0, 81.3)	<0.001
Sex (female), n (%)	125 (27.0)	85 (23.2)	40 (41.7)	<0.001
BMI	24.4 (22.2, 26.8)	24.5 (22.5, 26.9)	24.2 (21.3, 26.3)	0.166
Clinical Scores				
NIHSS	3.0 (1.0, 5.0)	3.0 (1.0, 4.0)	4.5 (2.0, 10.0)	<0.001
90d-mRS	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0 (1.0, 4.0)	<0.001
Cardiovascular Diseases				
HTN history, n (%)	332 (71.7)	259 (70.6)	73 (76.0)	0.351
DM history, n (%)	137 (29.6)	110 (30.0)	27 (28.1)	0.82
Heart Failure, n (%)	6 (1.3)	0 (0.0)	6 (6.3)	<0.001
AF history, n (%)	52 (11.2)	1 (0.3)	51 (53.1)	<0.001
Acute Treatment & Intervention				
Thrombolysis, n (%)	110 (23.8)	74 (20.2)	36 (37.5)	<0.001
Thrombectomy, n (%)	7 (1.5)	4 (1.1)	3 (3.1)	0.159
Inflammation & Immune Markers				
hsCRP	3.5 (1.3, 9.7)	3.0 (1.2, 8.5)	5.8 (2.4, 14.7)	<0.001
NLR	2.6 (1.8, 4.1)	2.6 (1.8, 3.8)	3.5 (2.2, 6.3)	<0.001
LMR	3.0 (2.1, 4.1)	3.2 (2.3, 4.2)	2.5 (1.6, 3.5)	<0.001
SII	525.0 (364.3, 862.4)	512.7 (366.2, 805.5)	615.5 (362.2, 1060.8)	0.043
SIRI	1.5 (0.9, 2.6)	1.4 (0.9, 2.5)	1.8 (1.1, 3.8)	0.002
NTR	3.1 (2.1, 4.8)	2.9 (2.0, 4.4)	4.0 (2.6, 6.0)	<0.001
HLR	0.6 (0.5, 0.9)	0.6 (0.4, 0.8)	0.8 (0.6, 1.1)	<0.001
Cardiac Biomarkers				
hsTnT	10.1 (7.0, 15.6)	9.4 (6.7, 14.5)	13.1 (9.6, 17.6)	<0.001
NT-proBNP	80.3 (40.0, 299.2)	60.7 (32.8, 128.4)	991.5 (520.7, 1805.3)	<0.001

Notes: Data are presented as median (Q_1, Q_3) for continuous variables and number (%) for categorical variables. Continuous variables are presented as median with interquartile range (Q_1, Q_3), and categorical variables as counts with percentages. Group differences between patients with and without AF were evaluated using the Mann–Whitney *U*-test for non-normally distributed continuous variables (reported as Z statistic), and using the Chi-square test for categorical variables; Fisher's exact test was applied when expected frequencies were <5. All statistical tests were two-tailed.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; 90d-mRS, 90-day modified Rankin Scale; HTN, hypertension; DM, diabetes mellitus; hsCRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; NTR, neutrophil-to-total cholesterol ratio; HLR, high-density lipoprotein-to-lymphocyte ratio; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

associated with poor 90-day outcome (Supplementary Table S2), which were subsequently grouped into six must-have confounders, one core variable (AF), sixteen candidate mediators, and forty-seven other associated variables (Supplementary Table S3).

The two-layer LASSO regression procedure was applied to identified candidate mediators and additional predictors (Supplementary Tables S4, S5 and Figure 1). In the first layer, high-sensitivity C-reactive protein (hsCRP), NLR, SIRI, and myoglobin were retained, while NTR, HLR, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were not selected. In the second layer, additional variables—including direct bilirubin (DBIL), fasting blood glucose (FBG), and high-density lipoprotein cholesterol (HDL-C) were additionally selected, and AF remained selected across models. The final multivariable model (AF + six must-have confounders + LASSO-selected variables) outperformed the confounder-only model (AUC 0.829 vs 0.757), with acceptable calibration and superior net benefit on decision curve analysis (Figure 2a–c and Supplementary Table S6).

We next assessed whether the selected inflammatory markers mediated the relationship between AF and poor 90-day functional outcome (Table 2 and Figure 3). In single-mediator causal mediation analyses with 5000 bootstrap simulations, NLR and SIRI demonstrated statistically significant indirect effects, indicating a partial but meaningful inflammatory contribution:

NLR: ACME = 0.031 (95% CI 0.007–0.064), proportion mediated 22.3%

SIRI: ACME = 0.024 (95% CI 0.002–0.056), proportion mediated 17.0%

In contrast, hsCRP and myoglobin did not show statistically significant indirect effects. ADE E-values indicated that direct effects were relatively robust to potential unmeasured confounding (hsCRP 1.520; NLR 1.466; SIRI 1.499; myoglobin 1.538).

A sensitivity analysis excluding baseline NIHSS yielded results consistent with the primary mediation analysis (Supplementary Table S7). NLR and SIRI continued to show significant indirect effects, whereas hsCRP and myoglobin showed smaller and statistically non-significant effects. ADE E-values indicated that the direct effects remained robust to potential unmeasured confounding.

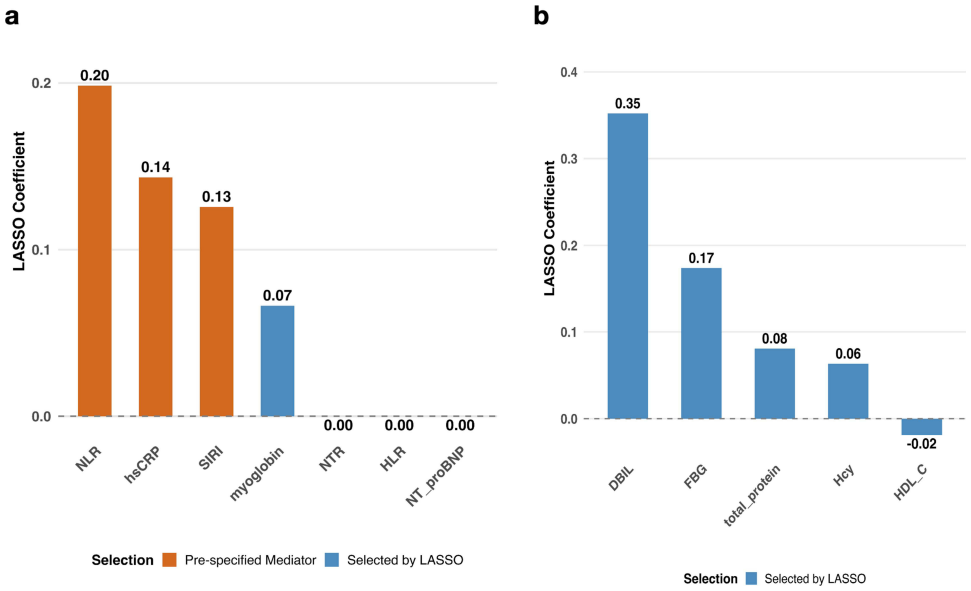


Figure 1 LASSO regression–selected variables in candidate mediators and other associated variables. (**a** and **b**) show variables with non-zero coefficients identified by cross-validated LASSO regression. (**a**) Candidate mediators (layer 1) with predicting 90-day poor functional outcome (mRS > 2) while forcing must-have confounders (age, sex, BMI, hypertension, diabetes, NIHSS) into the model. Pre-specified mediators are highlighted in Orange, and additional selected mediators are shown in blue. (**b**) Other associated variables (layer 2) selected for model supplementation using the same procedure as layer 1, with attention to avoiding multicollinearity and overfitting. Coefficient values are shown above bars.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; hsCRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; NTR, neutrophil-to-total cholesterol ratio; HLR, high-density lipoprotein-to-lymphocyte ratio; SIRI, systemic inflammation response index; NT-proBNP, N-terminal pro–B-type natriuretic peptide; hsTnT, high-sensitivity troponin T; DBIL, direct bilirubin; FBG, fasting blood glucose; Hcy, homocysteine.

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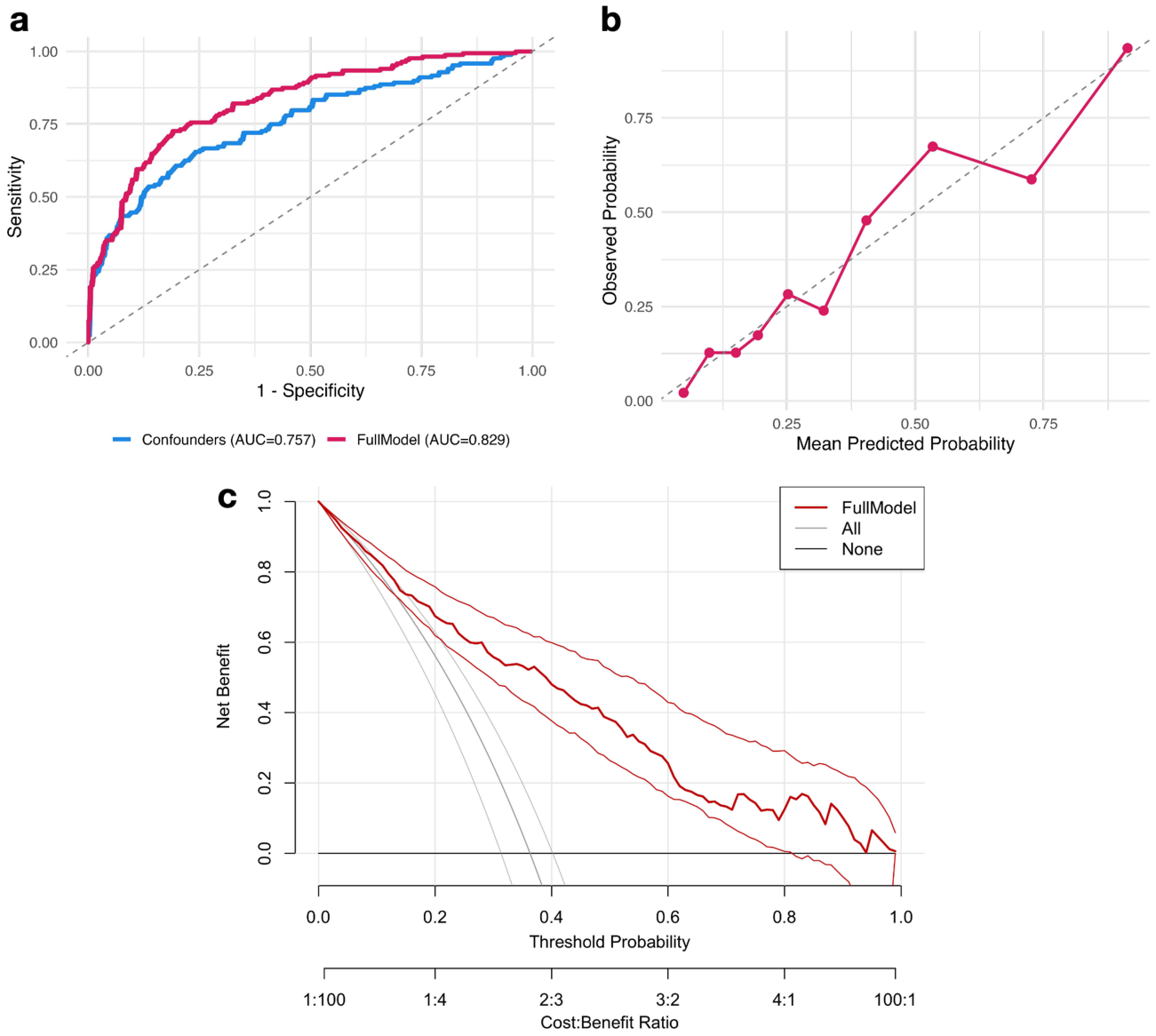

Figure 2 Predictive performance of the full model with selected variables versus the confounder-only model for 90-day poor functional outcome. Comparison of model performance between the full selected-variable model and confounder-only model in the entire cohort and atrial fibrillation (AF) subgroup. (**a**) Receiver operating characteristic (ROC) curves: Discrimination performance measured by area under the curve (AUC). The full model includes confounders (age, sex, BMI, hypertension history, diabetes history, NIHSS) plus selected inflammatory biomarkers (hsCRP, NLR, SIRI, myoglobin, DBIL, FBG, HDL-C, Hcy, total protein). The confounder-only model contains only baseline clinical variables (age, sex, BMI, hypertension history, diabetes history, NIHSS). (**b**) Calibration plots: Agreement between predicted probabilities and observed outcomes across risk deciles. The diagonal dashed line represents ideal calibration. Points display the mean predicted probability versus observed event rate within each decile, with deviations indicating miscalibration. (**c**) Decision curve analysis (DCA): Clinical utility assessed by net benefit across threshold probabilities. Comparisons include the full model, confounder-only model, treat-all strategy, and treat-none strategy.

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic; DCA, decision curve analysis; AF, atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; hsCRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; SIRI, systemic inflammation response index; DBIL, direct bilirubin; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine.

Model diagnostics supported the assumptions of the causal mediation framework. The residuals-versus-fitted values plot showed no systematic deviations, and Q–Q plots indicated approximate normality of residuals, supporting the validity of the linear mediator models (Supplementary Figure S1).

Discussion

In this exploratory analysis, we examined whether systemic inflammation mediates the association between AF and poor functional outcomes in AIS. Our findings indicate that both NLR and SIRI partially mediate this relationship, accounting

Table 2 Mediation Analysis Results with E-Values for Each Inflammatory Mediator Adjusted for Full Confounders

Mediator	ACME (95% CI)	ADE (95% CI)	Total (95% CI)	Prop Mediated	ADE E-value
hsCRP	0.013 (−0.003 to 0.035)	0.125 (0.016 to 0.237)	0.139 (0.030 to 0.252)	9.50%	1.52
NLR	0.031 (0.007 to 0.064)	0.107 (0.005 to 0.219)	0.141 (0.035 to 0.257)	22.30%	1.466
SIRI	0.024 (0.002 to 0.056)	0.116 (0.016 to 0.228)	0.142 (0.035 to 0.257)	17.00%	1.499
myoglobin	0.008 (−0.004 to 0.031)	0.129 (0.025 to 0.242)	0.138 (0.032 to 0.253)	5.60%	1.538

Notes: This table summarizes the results of the mediation analysis for each mediator using the full confounder model. For each mediator, the Average Causal Mediation Effect (ACME), Average Direct Effect (ADE), and Total Effect are presented with their 95% confidence intervals (CI). The Proportion Mediated indicates the fraction of the total effect that is mediated through each respective mediator. The analysis adjusted for the following confounders: age, sex, BMI, history of hypertension, history of diabetes, and baseline stroke severity (NIHSS score). The E-value quantifies the robustness of the observed effect to potential unmeasured confounding.

Abbreviations: ACME, Average Causal Mediation Effect; ADE, Average Direct Effect; Total, Total Effect; Prop_Mediated, Proportion of the Effect Mediated; CI, Confidence Interval; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index.

for 22.3% and 17.0% of the total effect, respectively. These findings underscore the contribution of inflammatory activation to AF-related post-stroke disability.[7,14,26,27] The validity of these mediation effects was supported by diagnostic evaluations confirming that the assumptions of the linear mediation models were adequately met.

The biological mechanisms underlying these associations are increasingly understood. AF can amplify systemic inflammatory responses, contributing to endothelial dysfunction, hypercoagulability, and immune dysregulation, all of which may worsen ischemic injury.[28,29] NLR reflects the balance between neutrophil-driven pro-inflammatory activity and lymphocyte-mediated regulatory processes. Elevated neutrophils exacerbate ischemic injury by releasing reactive

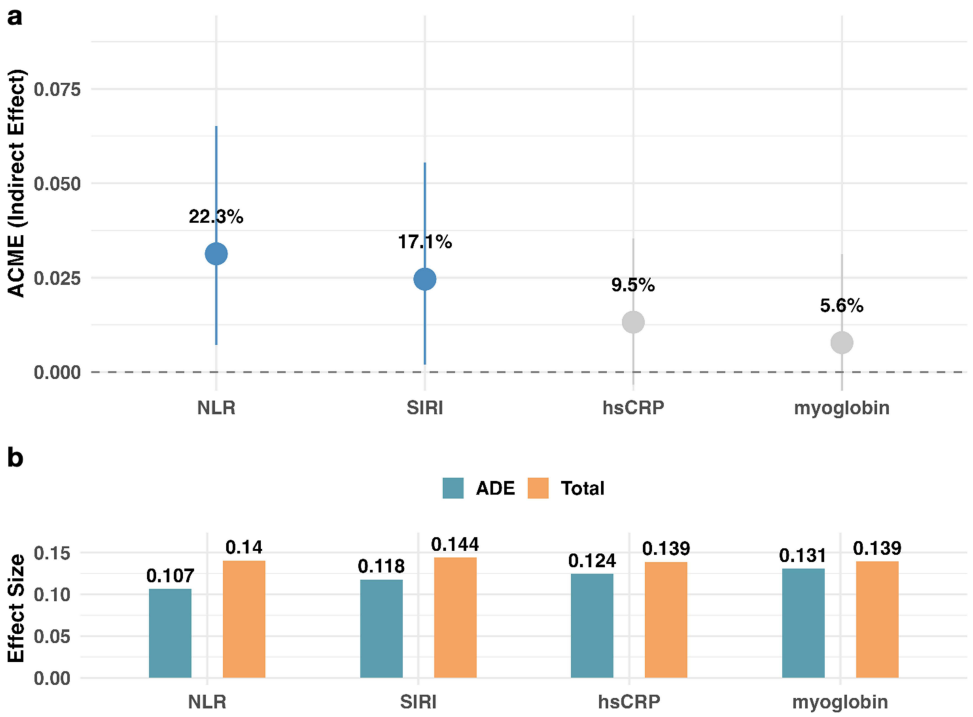

Figure 3 Mediation analysis of AF and 90-day poor functional outcome. This figure illustrates the mediation effects of selected inflammatory biomarkers on the association between atrial fibrillation (AF) and 90-day poor functional outcome. (**a**) Each point represents the Average Causal Mediation Effect (ACME) of a specific mediator (NLR, SIRI, hsCRP, myoglobin). Vertical lines indicate 95% confidence intervals (CIs). Blue points denote statistically significant mediation, and gray points denote non-significant mediation. Numbers above each point show the proportion of the total effect mediated (Prop_Mediated), expressed as a percentage. The horizontal dashed line at zero indicates no indirect effect. (**b**) Bar plots show the Average Direct Effect (ADE) and the Total Effect (ACME + ADE) for each mediator. Bars are color-coded (ADE: blue, Total: Orange). Numerical values above bars represent the effect sizes. This panel highlights how much of the total effect is directly attributable to AF versus mediated through inflammatory markers. The figure is based on the combined cohort analysis with confounders (age, sex, BMI, hypertension, diabetes, baseline NIHSS) included in the full model. ACME and ADE were estimated using bootstrapping with 5000 simulations.

Abbreviations: ACME, Average Causal Mediation Effect; ADE, Average Direct Effect; Total, sum of ACME and ADE; CI, confidence interval; Prop_Mediated, proportion of total effect mediated by the mediator; AF, atrial fibrillation; NLR, neutrophil-to-lymphocyte ratio; SIRI, systemic inflammation response index; hsCRP, high-sensitivity C-reactive protein.

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oxygen species, proteases, and neutrophil extracellular traps, leading to blood-brain barrier disruption and microvascular damage.[11,30] Reduced lymphocyte counts further diminish anti-inflammatory and reparative responses, increasing vulnerability to secondary brain injury.[29,31] SIRI extends this concept by integrating neutrophil, lymphocyte, and monocyte counts, capturing a broader systemic inflammatory burden that appears to influence stroke recovery in patients with AF.[14] These findings provide a plausible mechanistic explanation for our observed mediation effects.

While previous studies have reported associations between elevated NLR or SIRI and adverse outcomes in AIS, they did not quantify the extent to which inflammatory dysregulation contributes to the excess risk attributable to AF. Our mediation analysis extends the existing evidence by demonstrating that more than one-fifth of the detrimental impact of AF on 90-day functional outcome is mediated through NLR, highlighting a potentially modifiable inflammatory pathway linking AF and stroke severity.

Interestingly, other inflammatory markers, including hsCRP and myoglobin, did not show significant mediation effects, despite their known associations with stroke and inflammation.[32,33] This may reflect differences in specificity and timing. hsCRP often rises later than NLR or SIRI and is influenced by diverse systemic inflammatory sources, whereas myoglobin lacks central nervous system specificity.[34–36] Consequently, these markers may be less sensitive for capturing the acute inflammatory processes that mediate AF-related ischemic injury.

Our results align with previous work demonstrating that inflammation contributes to adverse outcomes after stroke,[37,38] but extend these findings by quantifying the mediating role of specific markers in AF-related stroke. Prior studies have shown that elevated NLR or SIRI is associated with early neurological deterioration or mortality in AIS,[7,26] yet the mediating pathway linking AF, inflammation, and functional outcomes had not been directly assessed. By demonstrating that NLR and SIRI capture inflammation-related risk, our study suggests that these markers could aid early prognostic assessment and guide individualized management strategies. In this context, NLR and SIRI could also be incorporated into existing stroke prognostic models and potentially serve as early triggers for anti-inflammatory therapeutic strategies in patients with AF-related ischemic stroke. For example, patients with elevated NLR or SIRI might benefit from more intensive monitoring, early rehabilitation, or potentially targeted anti-inflammatory interventions, though such strategies require validation in prospective trials.[39–41]

While our study focused on NLR and SIRI due to their clinical availability, reproducibility, and established associations with outcomes, emerging markers such as NTR and HLR may offer additional prognostic information in AIS. Future studies should evaluate whether incorporating these novel markers can further refine risk stratification.

Several limitations should be acknowledged. First, the retrospective single-center design limits causal inference and generalizability, and reliance on electronic medical records may introduce selection bias. Second, although a cross-validated penalty was applied during LASSO selection to reduce overfitting, the modest sample size relative to the number of candidate mediators may still result in residual overfitting, potentially affecting the accuracy of estimated mediation effects. This concern is consistent with reports that LASSO can yield overly sparse solutions or retain noise predictors when applied to high-dimensional data with limited sample sizes.[42] Third, the selection of biomarkers for analysis was based on predefined indices, but residual bias cannot be excluded, and other unmeasured inflammatory markers may contribute to the association between AF and outcomes. Fourth, missing data were handled using multiple imputation, which assumes that data are missing at random; deviations from this assumption could bias results. Fifth, the absence of external validation limits the generalizability of our findings. Nonetheless, sensitivity analyses—including E-value assessment and alternative model specifications—support the robustness of the observed mediation effects. Given these limitations, prospective multicenter studies with standardized inflammatory profiling and temporally precise mediator measurements are essential to confirm the causal pathways suggested by our mediation analysis.[43,44]

Looking forward, future research could combine detailed inflammatory profiling—including cytokines such as IL-6 and TNF-α—with neuroimaging and functional assessments to clarify the pathways linking AF, systemic inflammation, and stroke recovery. Randomized trials testing interventions that modulate NLR or SIRI may provide insight into whether reducing systemic inflammation can improve outcomes in high-risk ischemic stroke patients with AF.[45,46]

In summary, our study suggests that systemic inflammation, reflected by NLR and SIRI, partially mediates the association between AF and poor functional outcomes after ischemic stroke. These widely available inflammatory markers may help identify high-risk patients and inform strategies to improve stroke recovery.

Conclusion

In conclusion, this exploratory study suggests that NLR and SIRI may partially mediate the association between AF and poor functional outcomes after ischemic stroke. Systemic inflammation may therefore represent a partial pathway linking AF and poor prognosis rather than a definitive causal mechanism. These readily accessible inflammatory markers may assist in identifying high-risk patients and informing individualized management strategies. Nevertheless, the findings should be interpreted with caution, and prospective, multicenter studies are needed to validate these mediation effects and determine whether targeting systemic inflammation can improve outcomes in AF-related ischemic stroke.

Data Sharing Statement

Data are available in anonymous form upon reasonable request after ethics clearance and approval from the corresponding author. De-identified data supporting the findings of this study are available from the corresponding author upon reasonable request and after obtaining ethics clearance.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the First Affiliated Hospital of Soochow University (Approval No. 2025838). The requirement for informed consent was waived because the study used de-identified retrospective data.

Author Contributions

Xinyi He: Data curation, Formal analysis, Visualization, Writing – original draft. Haixing Xiao: Formal analysis, Writing – original draft. Qi Fang: Methodology, Validation, Writing – review & editing, Supervision, Funding acquisition. Xiang Tang: Methodology, Funding acquisition, Writing – review & editing. All authors 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.

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Disclosure

The authors report no conflicts of interest in this work.

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