

Differential Associations of Inflammatory Biomarkers and Clinical Risk Factors with Acute Coronary Syndrome versus Ischemic Stroke: A Comparative Hospital-Based Study in Northwest Iran

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Abstract

Background

Systemic inflammation plays a differential role in acute coronary syndrome (ACS) and acute ischemic stroke (AIS), yet direct head-to-head comparisons of inflammatory biomarkers and clinical risk factors between these conditions remain limited, particularly in non-Western populations. This study compared clinical risk factor profiles and admission inflammatory biomarkers between patients with ACS and AIS in Northwest Iran.

Methods

This prospective, hospital-based comparative study enrolled 285 consecutive patients (150 ACS, 135 AIS) admitted to two tertiary referral centers in Urmia, Iran, between April 2025 and May 2026.

Demographic, clinical, and admission laboratory data, including high-sensitivity C-reactive protein (hs-CRP) and white blood cell (WBC) count, were collected. Given substantial missingness in lipid and inflammatory markers that differed significantly by disease group ($p < 0.001$), multivariable logistic regression was performed on multiply imputed data (20 imputations) as the primary analysis, with complete-case analysis ($n = 190$) as a sensitivity check. Sex-by-biomarker interaction terms were prespecified and tested but not retained unless statistically supported.

Results

Patients with AIS were significantly older (65.76 ± 16.91 vs. 61.48 ± 11.42 years, $p = 0.012$), predominantly female (54.8% vs. 26.7%, $p < 0.001$), and exhibited higher systolic blood pressure (138.24 ± 25.96 vs. 127.17 ± 22.03 mmHg, $p < 0.001$) and elevated admission hs-CRP (26.84 ± 33.78 vs. 3.37 ± 9.58 mg/L, $p < 0.001$). Conversely, ACS patients demonstrated higher smoking rates (54.0% vs. 29.6%, $p < 0.001$) and higher LDL cholesterol (105.68 ± 42.94 vs. 88.93 ± 34.49 mg/dL, $p = 0.002$). Prespecified interaction terms between sex and both hs-CRP and WBC count were not statistically significant (all $p > 0.28$) and were not retained in the final model. In the parsimonious multivariable model, male sex (aOR 0.285, 95% CI 0.145–0.561, $p < 0.001$), higher hs-CRP (aOR 1.081, 95% CI 1.034–1.130, $p = 0.001$), higher WBC count (aOR 0.9999, 95% CI 0.9998–0.9999, $p < 0.001$), higher SBP (aOR 1.025, 95% CI 1.009–1.041, $p = 0.002$), higher LDL cholesterol (aOR 0.985, 95% CI 0.973–0.998, $p = 0.020$), prior personal history of ischemic stroke (aOR 17.61, 95% CI 3.48–89.0, $p = 0.001$), and family history of stroke (aOR 0.236, 95% CI 0.089–0.628, $p = 0.004$) were each independently associated with clinical presentation. The final model demonstrated strong discriminative performance (AUC = 0.908, 95% CI 0.864–0.952), significantly exceeding a biomarker-only model (AUC = 0.809; DeLong's $p = 0.0018$).

Conclusions

This study provides one of the first direct, prospective comparisons of admission inflammatory biomarkers and clinical risk profiles between AIS and ACS in a Middle Eastern population. Admission hs-CRP, WBC count, LDL cholesterol, and personal/family vascular history each independently distinguished the two conditions, with no evidence that these associations were modified by sex. Given the confounding of recruitment site with disease group inherent to this two-center design, these findings should be regarded as hypothesis-generating and warrant confirmation in future multi-center studies.

Introduction

Cardiovascular and cerebrovascular diseases (CVDs) remain the leading causes of global mortality and long-term disability, placing an immense clinical and economic strain on healthcare systems worldwide, particularly in developing nations undergoing rapid epidemiological transitions(1,2). Although ACS and AIS share a common pathophysiological foundation rooted in atherosclerosis and subsequent thromboembolism, growing clinical evidence suggests that the relative impact and predictive value of individual risk factors diverge significantly between these two macrovascular distinct conditions(3,4). For instance, while hypertension acts as a primary driver for cerebral events, dyslipidemia and smoking exhibit a more pronounced propensity for coronary vascular beds(5,6).

Beyond traditional metabolic risk factors, systemic inflammatory pathways are increasingly recognized as critical, yet differential, mediators in the acute phases of both ischemia-reperfusion injuries and plaque ruptures(7,8). Systemic biomarkers, such as high-sensitivity C-reactive protein (hs-CRP) and total white blood cell (WBC) count, often demonstrate heterogeneous profiles depending on the specific vascular territory affected(9). Some evidence further suggests that biological sex may modulate these inflammatory responses, though findings remain inconsistent and are drawn predominantly from Western populations with distinct genetic backgrounds, lifestyles, and dietary patterns(10,11).

In the Middle East, and specifically in Iran, the burden of macrovascular diseases has nearly doubled over recent decades, driven by rapid urbanization, population aging, and a surging metabolic risk profile, now accounting for over one-third of all-cause national mortalities(12,13). Despite this high burden, prior regional literature has heavily relied on composite cardiovascular endpoints or general population surveys, leaving a notable gap in direct, head-to-head comparisons between consecutive ACS and AIS patients in acute tertiary care settings(14,15). More importantly, direct comparisons of admission inflammatory biomarkers between ACS and AIS patients in Middle Eastern settings remain scarce(16,17).

The present study was designed to address this gap. Rather than relying on composite cardiovascular endpoints or single-disease studies, the dominant approach in regional literature to date, we directly compared consecutive patients admitted with ACS and AIS within the same clinical and geographic context, allowing inflammatory and clinical risk profiles to be contrasted head-to-head rather than inferred indirectly. By conducting this comparative analysis at two tertiary academic hospitals in Northwest Iran, we aimed to characterize how demographic factors, traditional risk profiles, and

admission inflammatory biomarkers diverge between these two acute vascular presentations. As a secondary aim, given known sex differences in cardiovascular disease presentation, we examined whether sex modified these biomarker associations. In a region where macrovascular disease burden is rising rapidly but head-to-head, prospectively collected data remain scarce, this study offers a rare direct test of whether and how ACS and AIS truly diverge at the point of clinical presentation.

Methods

Study Design and Setting

This prospective, hospital-based comparative study was conducted across two tertiary referral academic centers in Urmia, West Azerbaijan Province, Northwest Iran, between April 2025 and May 2026. Reflecting real-world referral patterns for specialized acute care, patients with AIS were recruited exclusively from Imam Khomeini Hospital (a tertiary neurology/stroke center), while patients with ACS were enrolled exclusively at Seyyed al-Shohada Hospital, a specialized tertiary cardiology center. As a direct consequence of this site-based recruitment strategy, disease group is structurally confounded with recruitment center; this design constraint is addressed further in the Limitations section.

The study was initially conceptualized with a retrospective design. However, due to significant data attrition and incomplete routine medical charting regarding prior clinical history, risk factors, and acute laboratory profiles, the protocol was pragmatically adapted into a prospective design. Data capture was achieved through standardized, structured face-to-face interviews with patients or their immediate next of kin (in cases of cognitive or neurological impairment) during the index admission, which was subsequently cross-verified with official electronic hospital medical records.

Participants and Eligibility Criteria

A total of 285 consecutive adult patients (≥ 18 years old) were enrolled using a consecutive sampling approach, comprising 150 patients with confirmed ACS (including myocardial infarction and unstable angina) and 135 patients with confirmed AIS.

This case–case comparative design, without a disease-free control group or population-at-risk denominator, was chosen to evaluate the relative distribution of clinical and biomarker profiles between two acute vascular presentations, rather than to estimate absolute incidence or population-level risk for either condition.

Inclusion criteria for the AIS group required a definitive clinical diagnosis by a staff neurologist, structurally corroborated by computed tomography (CT) and/or magnetic resonance imaging (MRI). For the ACS group, inclusion required confirmation by a staff cardiologist based on acute clinical presentation, ischemic electrocardiographic alterations, and serial cardiac biomarker elevations.

Exclusion criteria across both groups included: hemorrhagic stroke, transient ischemic attack (TIA) without radiographic evidence of acute infarction, and an inability or refusal of the patient or legal

guardian to provide informed consent.

Data Collection and Covariates

A standardized clinical questionnaire was administered within the first 48 hours of hospital admission to gather comprehensive baseline data:

- Demographics: Age, sex, and educational level (stratified into illiterate, up to high school diploma, and university or higher education).
- Anthropometrics: Height, weight, body mass index (BMI), and abdominal circumference.
- Traditional Risk Factors: Documented history of hypertension, diabetes mellitus, smoking status, alcohol consumption, and family history of cardiovascular disease, diabetes, or stroke.
- Clinical Parameters: Admission systolic and diastolic blood pressure, number of active antihypertensive medications, prior personal history of ischemic stroke, and family history of cerebrovascular accident (stroke).
- Systemic Inflammatory and Laboratory Biomarkers: High-sensitivity hs-CRP, lipid profiles (including total cholesterol, triglycerides, high-density lipoprotein (HDL), and LDL cholesterol), and complete blood count parameters (including total WBC count, absolute neutrophils, lymphocytes, and mixed cells).

Owing to institutional pragmatic limits and routine clinical care paths, laboratory tests were limited to those ordered by the primary treating physicians. Consequently, lipid profiles exhibited higher completeness within the ACS group compared to the AIS group.

Statistical Analysis

Statistical analyses were performed using Stata statistical software (version 19, StataCorp LLC, College Station, TX, USA).

Categorical variables are reported as frequencies and percentages, with group differences evaluated using Pearson's chi-square tests or Fisher's exact tests, where appropriate. Continuous variables are expressed as mean $\pm$ standard deviation (SD) and compared across groups using linear regression model-based testing.

To evaluate factors associated with AIS presentation (coded as 1) relative to ACS (coded as 0), multivariable binary logistic regression was conducted. Covariates demonstrating a univariate association at $p < 0.20$ were considered for model entry, followed by backward elimination to derive a parsimonious final model. Given prior literature suggesting sex-specific inflammatory responses in cardiovascular disease, interaction terms between sex and hs-CRP, and between sex and WBC count, were prespecified and tested(18,19); terms not reaching statistical significance were not retained in the final model (see Results).

The discriminative capacity of the final model was evaluated using receiver operating characteristic (ROC) curve analysis, with formal comparisons between nested models performed using DeLong's non-parametric test(20).

All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Given evidence of non-random missingness (detailed below), multiply imputed data constituted the primary analytical sample ($n=285$); a complete-case analysis ($n=190$) was performed as a sensitivity analysis, and also served as the basis for ROC curve analyses.

Missing Data Handling

Lipid profiles and hs-CRP were missing in 60–62 of 285 patients (21–22%), attributable to differences in routine laboratory ordering practices between the two centers. Formal testing showed that missingness in LDL cholesterol was significantly associated with disease group ($\chi^2=26.17$, $p<0.001$), and this association persisted after adjustment for age and sex (logistic regression, $p<0.001$), indicating a Missing at Random (MAR) rather than Missing Completely at Random mechanism(21,22). Because complete-case analysis under MAR conditions can introduce selection bias, multiple imputation by chained equations (predictive mean matching, 20 imputations) was performed for systolic blood pressure, LDL, hs-CRP, and WBC count, using disease group, sex, prior cardiovascular/cerebrovascular history, and age as auxiliary predictors(21,23). The multiply imputed dataset ($n=285$) served as the primary analytical sample; results were compared against a complete-case sensitivity analysis ($n=190$) to assess robustness of the findings.

Ethical Considerations

The study protocol received formal approval from the Institutional Ethics Committee of IR.UMSU.REC.1404.418. Prior to enrollment and data collection, written informed consent was obtained from all participants or their legally authorized representatives. The study strictly adhered to the ethical principles outlined in the Declaration of Helsinki.

Results

Between April 2025 and May 2026, a total of 285 consecutive adult patients were prospectively enrolled in this hospital-based comparative study, comprising 150 patients with ACS and 135 patients with AIS.

Baseline Characteristics

Baseline characteristics are presented in Table 1. Patients with AIS were significantly older (65.76 ± 16.91 vs. 61.48 ± 11.42 years, $p=0.012$) and more frequently female (54.8% vs. 26.7%, $p<0.001$) than those with ACS. Educational attainment was lower in the AIS group, with a higher proportion of illiterate patients (53.3% vs. 34.0%, $p=0.002$). Admission systolic blood pressure (SBP) was significantly higher in the AIS group (138.2 ± 26.0 vs. 127.2 ± 22.0 mmHg, $p<0.001$), while current smoking was significantly more prevalent among ACS patients (54.0% vs. 29.6%, $p<0.001$). Patients with AIS had markedly elevated

admission hs-CRP (26.84 ± 33.78 vs. 3.37 ± 9.58 mg/L, $p < 0.001$), whereas ACS patients demonstrated higher LDL cholesterol (105.68 ± 42.94 vs. 88.93 ± 34.49 mg/dL, $p = 0.002$) and higher WBC count ($8,408 \pm 6,031$ vs. $6,173 \pm 5,476$ / μ L, $p = 0.002$). A prior personal history of ischemic stroke was significantly more common in the AIS group (27.4% vs. 1.3%, $p < 0.001$), while family history of stroke was more common in the ACS group (22.7% vs. 11.1%, $p = 0.015$).

[Table 1]

Missing Data Assessment

Lipid profiles and hs-CRP were missing in 60–62 of 285 patients (21–22%), reflecting differences in routine laboratory ordering practices between the two participating centers. Formal testing indicated that missingness in LDL cholesterol was significantly associated with disease group ($\chi^2 = 26.17$, $p < 0.001$), an association that persisted after adjustment for age and sex ($p < 0.001$). This pattern is consistent with a Missing at Random (MAR) rather than a Missing Completely at Random mechanism, indicating that a standard complete-case approach could introduce selection bias. Multiple imputation by chained equations (predictive mean matching, 20 imputations) was therefore performed as the primary analytical strategy, with complete-case analysis retained as a sensitivity check.

Sex-by-Biomarker Interaction Testing

Prespecified interaction terms between sex and hs-CRP, and between sex and WBC count, were tested in the multivariable model. Neither interaction reached statistical significance in the primary multiply imputed analysis (sex $\times$ hs-CRP: $p = 0.976$; sex $\times$ WBC count: $p = 0.284$) or in the complete-case sensitivity analysis (sex $\times$ hs-CRP: $p = 0.884$; sex $\times$ WBC count: $p = 0.074$). Accordingly, these interaction terms were not retained in the final model.

Multivariable Analysis

In the parsimonious multivariable model (multiply imputed data, $n = 285$), male sex was independently associated with lower odds of AIS relative to ACS presentation (aOR 0.285, 95% CI 0.145–0.561, $p < 0.001$). Higher admission hs-CRP was independently associated with higher odds of AIS (aOR 1.081 per unit, 95% CI 1.034–1.130, $p = 0.001$; Figure 1C), while higher WBC count was independently associated with lower odds of AIS (aOR 0.9999, 95% CI 0.9998–0.9999, $p < 0.001$; Figure 1B) – both associations independent of sex. Higher SBP (aOR 1.025 per mmHg, 95% CI 1.009–1.041, $p = 0.002$) and a prior personal history of ischemic stroke (aOR 17.61, 95% CI 3.48–89.0, $p = 0.001$) were associated with higher odds of AIS, while higher LDL cholesterol (aOR 0.985 per mg/dL, 95% CI 0.973–0.998, $p = 0.020$; Figure 1A) and family history of stroke (aOR 0.236, 95% CI 0.089–0.628, $p = 0.004$) were associated with lower odds of AIS. The overall model was statistically significant ($F(7, 5801.6) = 7.44$, $p < 0.001$). The wide confidence interval observed for prior personal history of stroke reflects the marked imbalance in this variable's distribution between groups (1.3% in ACS vs. 27.4% in AIS) rather than model instability;

variance inflation factors for all covariates were low (mean VIF=1.10, range 1.03–1.19), indicating no meaningful multicollinearity.

[Table 2]

Discriminative Performance and ROC Curve Analysis

To evaluate the discriminative capacity of the final multivariable model in distinguishing AIS from ACS, receiver operating characteristic (ROC) analysis was performed on the complete-case sample (n=190), consistent with the sensitivity analysis described above. A biomarker-only model (hs-CRP and WBC count) yielded an area under the curve (AUC) of 0.809 (95% CI: 0.746–0.872). Incorporating clinical covariates (sex, SBP, LDL, prior personal history of stroke, family history of stroke) significantly improved discriminative performance to an AUC of 0.908 (95% CI: 0.864–0.952; DeLong's test, $\chi^2(1)=9.78$, $p=0.0018$), indicating meaningful incremental value of clinical variables beyond inflammatory biomarkers alone.

To assess whether this performance was disproportionately driven by the markedly imbalanced personal-history-of-stroke variable, the model was re-evaluated after its exclusion. Discriminative performance remained excellent (AUC=0.883, 95% CI: 0.835–0.931), though formally lower than the full model (DeLong's test, $\chi^2(1)=5.44$, $p=0.020$). This indicates that while personal history of stroke contributes meaningfully to model discrimination, the model retains strong discriminative capacity even in its absence.

In an exploratory analysis, we examined whether substituting total WBC count with the neutrophil-to-lymphocyte ratio (NLR) altered model performance, in the subsample with complete NLR data (n=188). NLR was not independently associated with disease group in the adjusted model (OR=0.94, 95% CI: 0.84–1.05, $p=0.282$), and discriminative performance of the NLR-substituted model (AUC=0.906, 95% CI: 0.861–0.951) did not differ significantly from the primary WBC-based model (DeLong's test, $\chi^2(1)=0.00$, $p=0.952$). Total WBC count was therefore retained as the primary cellular inflammatory marker.

[Figure 2]

Sensitivity Analyses

Findings were consistent in the complete-case analysis (n=190; e.g., sex: aOR 0.288, 95% CI 0.122–0.680, $p=0.005$; hs-CRP: aOR 1.069, 95% CI 1.030–1.110, $p<0.001$; WBC count: aOR 0.9999, 95% CI 0.9998–1.000, $p=0.040$) and after additional adjustment for age and educational attainment, supporting the robustness of the primary model (Supplementary Table S1).

[Figure]

Discussion

Direct, head-to-head comparisons of ACS and AIS remain surprisingly rare, despite both conditions sharing a common atherosclerotic and thromboembolic origin. Most regional data rely on composite cardiovascular endpoints or single-disease study populations, leaving open the question of how risk factors and inflammatory biomarkers actually diverge between these two territories when measured side-by-side in the same clinical setting. In this prospective, hospital-based study of 285 consecutive patients from Northwest Iran, we found that admission hs-CRP, WBC count, LDL cholesterol, SBP, sex, and personal/family vascular history each independently distinguished AIS from ACS presentation – associations that proved robust across multiple sensitivity analyses, including formal handling of substantial non-random missingness through multiple imputation.

These findings are broadly consistent with prior literature indicating that the relative contribution of individual risk factors differs between cerebrovascular and coronary vascular beds, with hypertension more strongly linked to cerebral events and dyslipidemia more closely tied to coronary events(15,24). Our results extend this pattern to a non-Western, Middle Eastern population, where such territory-specific comparisons remain scarce.

We had prespecified interaction terms between sex and both hs-CRP and WBC count, based on prior literature suggesting sex-related variation in inflammatory responses to vascular injury(18,19). Neither interaction reached statistical significance, in either the primary multiply imputed analysis or the complete-case sensitivity analysis, and both hs-CRP and WBC count were independently, rather than sex-dependently, associated with clinical presentation. This null result should be interpreted with appropriate caution rather than as definitive evidence against sex-related effect modification: our sample, while adequate for detecting main effects, had limited power to detect interaction effects, which typically require substantially larger samples than main-effects analyses. Existing evidence on sex differences in inflammatory biomarkers in cardiovascular disease remains itself inconsistent across studies and populations(25,26). Our findings suggest that, at minimum, any such effect modification is not large enough to be detected in a sample of this size, and future adequately powered, multi-center studies will be needed to clarify whether true sex-specific inflammatory patterns exist in this population.

The inverse association observed between LDL cholesterol and AIS presentation is consistent with the previously described "lipid paradox" in stroke populations and may reflect differences in underlying vascular pathology – lipid-rich atheromatous plaques being more characteristic of coronary disease, whereas ischemic stroke in this study population, which included a substantial proportion of older women, may more often relate to hypertensive small-vessel disease or cardioembolic mechanisms not well captured by serum lipid levels(27–29). We note, however, that this study's case–case design, which lacks a disease-free comparison group, precludes any inference about whether LDL is a risk factor for either condition in the general population; it can only speak to relative differences between patients already presenting with one of the two conditions.

A prior personal history of ischemic stroke was strongly associated with AIS presentation in this sample, which is clinically intuitive: patients with an established cerebrovascular history carry an elevated risk of

recurrent stroke and are more likely to present again with AIS than with a first coronary event(24,30). In contrast, family history of stroke was associated with relatively lower odds of AIS — a less immediately intuitive finding. One possible explanation is that patients with a known family history of stroke, and their treating physicians, may pursue earlier and more intensive cerebrovascular risk-factor modification (antihypertensive and antiplatelet therapy), potentially shifting the clinical expression of shared atherosclerotic risk toward the coronary rather than cerebral vascular bed(31,32). This interpretation remains speculative, as treatment intensity was not systematically captured, and should be treated as hypothesis-generating rather than established mechanism. We also note that the odds ratio for personal history of stroke was accompanied by a wide confidence interval (3.48–89.0), reflecting the marked imbalance in this variable's distribution between groups (1.3% in ACS vs. 27.4% in AIS) rather than model instability; variance inflation factors across all covariates were low (mean 1.10), arguing against problematic collinearity(33).

Beyond individual associations, the final model demonstrated strong discriminative performance in distinguishing AIS from ACS presentation (AUC=0.908), meaningfully exceeding that of inflammatory biomarkers alone (AUC=0.809; $p=0.0018$). This gap is itself informative: it suggests that while systemic inflammation captures a substantial part of what separates these two presentations, clinical and hemodynamic context — blood pressure, lipid profile, and vascular history — adds real, non-redundant information rather than merely echoing the biomarker signal. Notably, model performance remained high (AUC=0.883) even after excluding personal history of stroke, indicating that this discriminative ability was not solely an artifact of a single strongly imbalanced covariate, although this variable did contribute a statistically detectable increment ($p=0.020$). In a further exploratory step, replacing total WBC count with the neutrophil-to-lymphocyte ratio — a marker increasingly favored in the inflammation literature for its presumed specificity — neither improved discrimination nor reached independent significance, suggesting that in this sample, the simpler and more widely available total WBC count performs at least as well as a more complex composite index(34,35).

This study has several strengths, including prospective, consecutive enrollment across two tertiary academic centers with specialist-confirmed diagnoses, and a rigorous approach to missing data. Because approximately one-fifth of lipid and hs-CRP values were missing, and this missingness was significantly associated with disease group rather than occurring completely at random, we conducted our primary analysis using multiple imputation rather than complete-case analysis alone, with the complete-case approach retained as a sensitivity analysis(36–38). Findings were consistent across both approaches and after additional adjustment for age and educational attainment, supporting the robustness of the observed associations.

Several important limitations must be acknowledged. First, and most critically, patients with ACS and AIS were recruited from two separate, disease-specific tertiary centers, meaning that recruitment site is completely confounded with disease group. Consequently, we cannot exclude the possibility that some of the observed differences reflect variation in referral patterns, patient case-mix, or laboratory procedures between the two centers rather than true pathophysiological differences between the two

conditions; this confounding cannot be resolved through statistical adjustment and should be addressed in future multi-center studies with harmonized recruitment across both conditions at each site. Second, this is a case–case comparison without a disease-free control group or population-at-risk denominator; it can characterize relative differences between two patient groups but cannot establish absolute risk, incidence, or causal risk-factor status for either condition. Third, because inflammatory biomarkers were measured at the time of acute presentation rather than before disease onset, they should be interpreted as concurrent correlates of clinical presentation rather than predictors of future events. Fourth, despite the use of multiple imputation to address non-random missingness, residual bias from unmeasured determinants of missingness cannot be entirely excluded. Fifth, the sample size, while adequate for the primary comparisons, limited statistical power for interaction and subgroup analyses. Finally, this study was conducted at two centers in a single region of Iran, and findings may not generalize to other populations or healthcare settings.

Within these constraints, our findings support the value of evaluating ACS and AIS separately rather than relying solely on composite cardiovascular endpoints, and suggest that admission hs-CRP and WBC count are associated with clinical presentation independent of sex in this population. These associations should be regarded as hypothesis-generating rather than as a basis for sex-stratified clinical decision-making at this stage, given the null interaction findings reported here.

Conclusions

This study offers one of the first direct, prospective comparisons of admission inflammatory biomarkers and clinical risk profiles between ACS and AIS in a Middle Eastern population — a region where such head-to-head data remain scarce despite a rapidly rising macrovascular disease burden. Admission hs-CRP, WBC count, LDL cholesterol, and personal/family history of stroke each independently distinguished the two conditions, independent of sex, and the final model demonstrated strong discriminative performance. Given the confounding of recruitment site with disease group inherent to this two-center design, these findings should be regarded as hypothesis-generating, and set a methodological benchmark — rigorous handling of missing data and formal interaction testing — for future multi-center studies designed to disentangle site-level confounding and test these associations at scale.

Abbreviations

ACS: Acute Coronary Syndrome

AIS: Acute Ischemic Stroke

aOR: Adjusted Odds Ratio

AUC: Area Under the Curve

BMI: Body Mass Index

CI: Confidence Interval

CT: Computed Tomography

CVD: Cardiovascular Disease

DBP: Diastolic Blood Pressure

HDL: High-Density Lipoprotein

hs-CRP: High-Sensitivity C-Reactive Protein

LDL: Low-Density Lipoprotein

MAR: Missing at Random

MCAR: Missing Completely at Random

MI: Multiple Imputation

MRI: Magnetic Resonance Imaging

NLR: Neutrophil-to-Lymphocyte Ratio

OR: Odds Ratio

ROC: Receiver Operating Characteristic

SBP: Systolic Blood Pressure

SD: Standard Deviation

TIA: Transient Ischemic Attack

VIF: Variance Inflation Factor

WBC: White Blood Cell

Declarations

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Author Contributions

Conceptualization and Proposal Writing: Porkawosh S, Jalali A. Data Collection: Hoseini M, Salehzadeh A, Dalili M, Khademvatani S, Ghasemiazar A. Data Management: Hoseini M. Statistical Analysis: Heidari M, Hoseini M. Writing Original Draft: Hoseini M. Supervision and Clinical Validation (Cardiology): Khademvatani K. Supervision and Clinical Validation (Neurology): Mosarrezaii A.

All authors read and approved the final manuscript.

Declaration of AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used Claude Sonnet 5 pro (Anthropic) to improve language clarity, grammar, and readability of the author-written text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the final version of the publication.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare no competing interests.

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Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images, or videos).

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Characteristics	ACS (n=150)	AIS (n=135)	Total (n=285)	p-value
Age (years), mean $\pm$ SD	61.48 $\pm$ 11.42	65.76 $\pm$ 16.91	63.51 $\pm$ 14.42	0.012
Biological Sex				<0.001
Female	40 (26.7%)	74 (54.8%)	114 (40.0%)	
Male	110 (73.3%)	61 (45.2%)	171 (60.0%)	
Educational Attainment				0.002
Illiterate	51 (34.0%)	72 (53.3%)	123 (43.2%)	
Up to High School Diploma	91 (60.7%)	61 (45.2%)	152 (53.3%)	
Academic/University	8 (5.3%)	2 (1.5%)	10 (3.5%)	
BMI, mean $\pm$ SD	27.17 $\pm$ 4.63	27.30 $\pm$ 4.73	27.23 $\pm$ 4.67	0.816
Abdominal Circumference (cm), mean $\pm$ SD	101.53 $\pm$ 12.51	99.16 $\pm$ 14.71	100.38 $\pm$ 13.64	0.168
Systolic Blood Pressure (mmHg), mean $\pm$ SD	127.17 $\pm$ 22.03	138.24 $\pm$ 25.96	132.44 $\pm$ 24.57	<0.001
Diastolic Blood Pressure (mmHg), mean $\pm$ SD	87.79 $\pm$ 65.00	82.97 $\pm$ 15.26	85.49 $\pm$ 48.18	0.407
Current Smoking, %	54.0	29.6	42.5	<0.001
History of Diabetes, %	32.0	30.0	31.0	0.768
Family History of Diabetes, %	30.0	25.9	28.1	0.445
History of Hypertension, %	53.3	62.2	57.5	0.130
Family History of Hypertension, %	51.3	59.3	55.1	0.179
Number of Antihypertensive Meds, mean $\pm$ SD	0.81 $\pm$ 1.03	0.70 $\pm$ 0.88	0.76 $\pm$ 0.96	0.337
Prior Personal History of Ischemic Stroke, %	1.3	27.4	13.7	<0.001
Family History of Stroke, %	22.7	11.1	17.2	0.015
hs-CRP (mg/L), mean $\pm$ SD	3.37 $\pm$ 9.58	26.84 $\pm$ 33.78	13.85 $\pm$ 26.34	<0.001
LDL Cholesterol (mg/dL), mean $\pm$ SD	105.68 $\pm$ 42.94	88.93 $\pm$ 34.49	99.05 $\pm$ 40.57	0.002
WBC Count (/ μ L), mean $\pm$ SD	8,407.6 $\pm$ 6,031.2	6,173.4 $\pm$ 5,475.6	7,363.3 $\pm$ 5,874.9	0.002

Note: Data are expressed as frequency (percentage) for categorical variables, and as mean $\pm$ standard deviation (SD) for continuous variables. Abbreviations: ACS, acute coronary syndrome; AIS, acute ischemic stroke; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SD, standard deviation; WBC, white blood cell. *P*-values were derived from Pearson's chi-square test or Fisher's exact test for categorical variables, and linear regression model-based testing for continuous variables. A *p*-value < 0.05 is considered statistically significant.

Table 2. Final Multivariable Logistic Regression Model for AIS versus ACS Presentation (Multiply Imputed Data, n=285)

Variable	aOR	95% CI	<i>p</i> -value
Sex (Male vs. Female)	0.285	0.145–0.561	<0.001
hs-CRP (per unit)	1.081	1.034–1.130	0.001
WBC count (per unit)	0.9999	0.9998–0.9999	<0.001
SBP (per mmHg)	1.025	1.009–1.041	0.002
LDL cholesterol (per mg/dL)	0.985	0.973–0.998	0.020
Prior personal history of ischemic stroke	17.61	3.48–89.0	0.001
Family history of stroke	0.236	0.089–0.628	0.004

aOR, adjusted odds ratio; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; WBC, white blood cell. Model $F(7, 5801.6)=7.44$, $p<0.001$. Sex $\times$ hs-CRP and Sex $\times$ WBC count interaction terms were tested and not retained (see Results).

Figures

Figure 1.

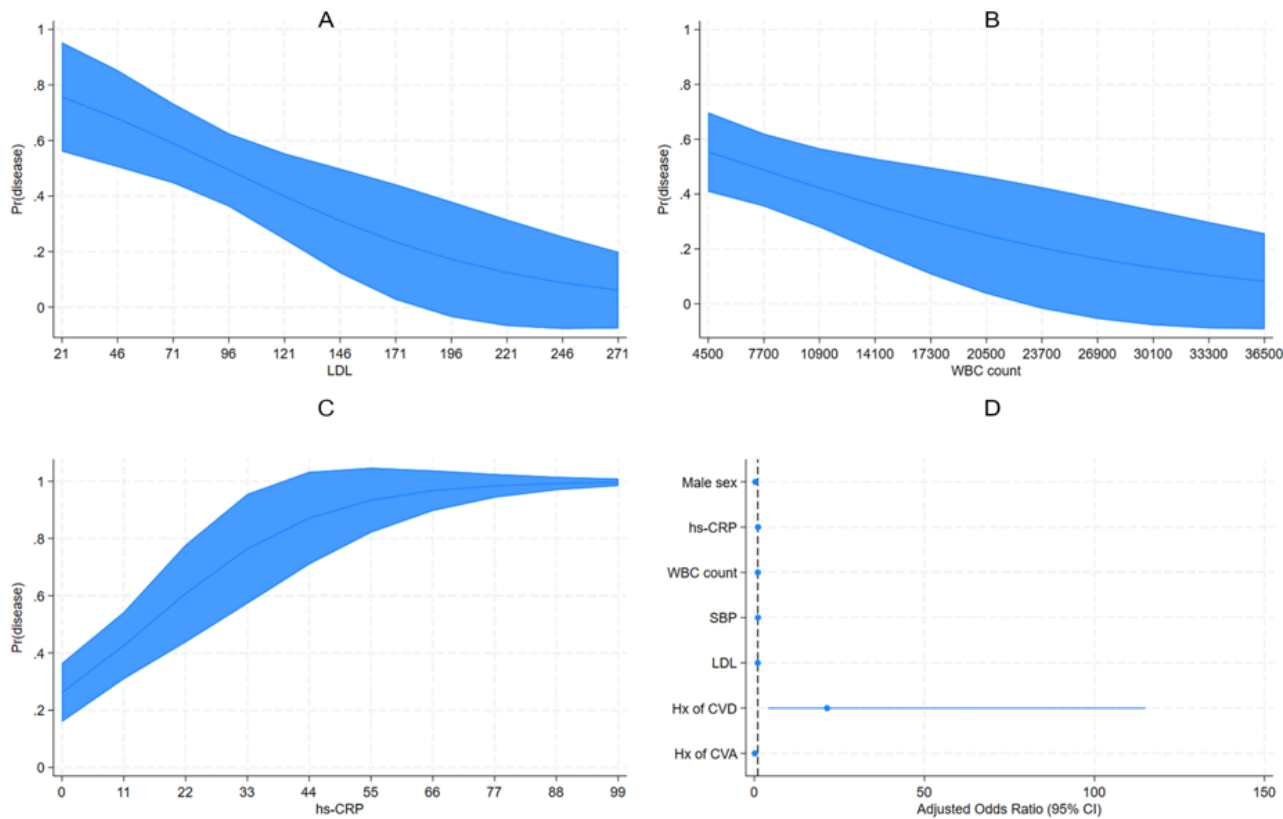


Figure 1

Multivariable-adjusted predicted probability of ischemic stroke (AIS) versus acute coronary syndrome (ACS) presentation across key biomarkers, and summary forest plot of the final model. (A) Adjusted predicted probability of AIS presentation across LDL cholesterol levels, holding other covariates at their means. (B) Adjusted predicted probability of AIS presentation across white blood cell (WBC) count. (C) Adjusted predicted probability of AIS presentation across admission high-sensitivity C-reactive protein (hs-CRP) levels. (D) Forest plot of adjusted odds ratios (95% CI) for all covariates in the final multivariable model. Sex-by-biomarker interaction terms (sex×hs-CRP, sex×WBC count) were tested and not statistically significant (see Results) and are therefore not depicted. Shaded areas (A–C) and horizontal lines (D) represent 95% confidence intervals.

Figure 2.

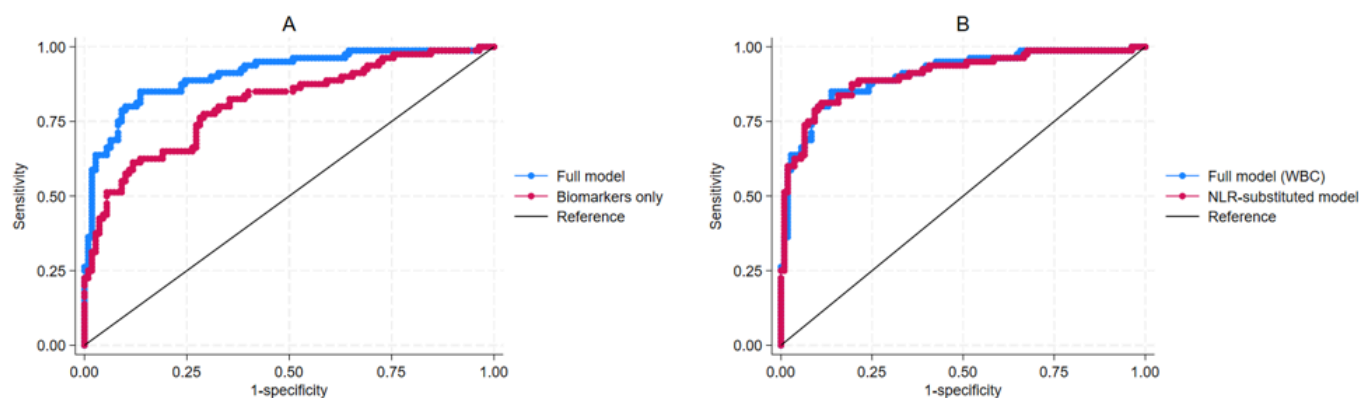


Figure 2

Receiver operating characteristic (ROC) curves for discriminative performance of the final multivariable model. (A) Comparison of the biomarker-only model (hs-CRP and WBC count; AUC=0.809) versus the full multivariable model (AUC=0.908; DeLong's $p=0.0018$). (B) Comparison of the full model using total WBC count (AUC=0.906) versus a model substituting WBC count with the neutrophil-to-lymphocyte ratio (NLR; AUC=0.906; DeLong's $p=0.952$), performed in the subsample with complete NLR data ($n=188$).

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