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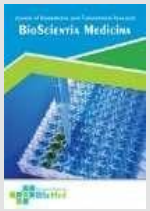

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Stratifying Neurological Severity in Acute Ischemic Stroke: The Independent and Combined Prognostic Value of Admission D-Dimer and High-Sensitivity C-Reactive Protein

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A B S T R A C T

Background: Early risk stratification in acute ischemic stroke (AIS) is critical for optimizing patient management. The roles of inflammation and thrombosis in stroke pathophysiology suggest that high-sensitivity C-reactive protein (hs-CRP) and D-Dimer may serve as valuable prognostic biomarkers. This study aimed to evaluate the independent and combined value of admission D-Dimer and hs-CRP levels for predicting neurological severity in AIS patients. **Methods:** We conducted a prospective, cross-sectional study at Haji Adam Malik General Hospital, Medan, Indonesia, involving 60 consecutive AIS patients. Neurological severity was assessed upon admission using the National Institutes of Health Stroke Scale (NIHSS), with patients categorized into moderate (NIHSS 5-18) and severe (NIHSS >18) groups. Plasma D-Dimer and serum hs-CRP levels were quantified. Statistical analyses included the Mann-Whitney U test, Spearman's correlation, Receiver Operating Characteristic (ROC) curve analysis, and multivariate logistic regression to determine the independent predictive value of the biomarkers. **Results:** Of the 60 patients, 31 (51.7%) were classified as having severe stroke. Both D-Dimer and hs-CRP levels were significantly higher in the severe group compared to the moderate group (D-Dimer: median 3220 ng/mL vs. 670 ng/mL, P<0.001; hs-CRP: median 5.6 mg/dL vs. 0.9 mg/dL, P<0.001). ROC analysis demonstrated strong predictive performance for severe stroke, with an Area Under the Curve (AUC) of 0.89 (95% CI: 0.81-0.97) for D-Dimer and 0.83 (95% CI: 0.72-0.94) for hs-CRP. A combined model incorporating both biomarkers yielded a superior AUC of 0.92 (95% CI: 0.85-0.99). In multivariate logistic regression, both elevated D-Dimer (Odds Ratio [OR]: 6.8, 95% CI: 2.1-22.5, P=0.001) and hs-CRP (OR: 4.5, 95% CI: 1.5-13.8, P=0.008) remained independent predictors of severe stroke after adjusting for age and gender. **Conclusion:** Admission levels of D-Dimer and hs-CRP are powerful, independent prognostic markers for neurological severity in patients with acute ischemic stroke. Their use, particularly in combination, could enhance early risk stratification and guide clinical decision-making.

1. Introduction

Acute ischemic stroke (AIS) stands as a monumental global health challenge, representing a primary cause of long-term disability and mortality worldwide.[1] The condition, precipitated by the sudden occlusion of a cerebral artery, triggers a cascade of events including energy failure, ion pump dysfunction, and ultimately, irreversible neuronal death.[2] The global burden of stroke is immense, with projections indicating a continuous rise in incidence, particularly

in developing nations within South, East, and Southeast Asia, including Indonesia.[3] The clinical trajectory of AIS patients is highly variable and depends critically on the extent of the initial ischemic insult. Therefore, the early identification of patients at high risk for severe neurological deficits is paramount for triaging, optimizing therapeutic strategies, and managing patient and family expectations.[4]

The clinical assessment of stroke severity is standardized by the National Institutes of Health Stroke Scale (NIHSS), a reliable tool for quantifying neurological deficits. While the NIHSS is the cornerstone of initial evaluation, it is a clinical measure that reflects the consequence of the ischemic event.[5] There is a pressing need for objective, accessible, and affordable biological markers (biomarkers) that can complement clinical scales by providing insight into the underlying pathophysiological processes driving stroke severity. Such biomarkers could offer prognostic information from the moment of admission, potentially even before the full extent of the neurological deficit is clinically apparent.[6]

The pathophysiology of AIS is intrinsically linked to two interconnected processes: thrombosis and inflammation. The formation of a thrombus or the arrival of an embolus is the proximate cause of vessel occlusion.[7] The subsequent breakdown of this fibrin-rich clot by the endogenous fibrinolytic system releases specific fibrin degradation products into the circulation, most notably D-Dimer. Elevated plasma D-Dimer levels are thus a direct indicator of active thrombosis and fibrinolysis.[8] Several studies have proposed that the magnitude of D-Dimer elevation reflects the size of the initial thrombus burden and, consequently, correlates with the volume of the resulting cerebral infarct and the severity of the stroke.

Concurrently, ischemia and subsequent reperfusion injury incite a potent local and systemic inflammatory response. High-sensitivity C-reactive protein (hs-CRP), an acute-phase reactant synthesized by the liver in response to inflammatory cytokines, is one of the most well-established markers of systemic inflammation. Elevated hs-CRP levels have been associated with an increased risk of incident cardiovascular events, including stroke, likely by promoting atherosclerosis and plaque instability.[9] In the acute setting of stroke, hs-CRP levels rise in response to the tissue injury, and the degree of this elevation may reflect the magnitude of the inflammatory cascade, which itself contributes to secondary brain injury and worsens outcomes.

While previous studies have independently linked D-Dimer and hs-CRP to stroke outcomes, there is a scarcity of research that rigorously evaluates their combined prognostic utility and establishes their independence from other clinical factors in specific populations, such as those in Southeast Asia. Investigating these markers in an Indonesian cohort is particularly valuable for validating their utility in a different genetic and environmental context.[10] Therefore, the aim of this study was to determine the independent and combined prognostic value of admission D-Dimer and hs-CRP levels for stratifying neurological severity, as measured by the NIHSS, in patients with acute ischemic stroke. The novelty of our research lies in the comprehensive assessment of these biomarkers, including the generation of specific predictive cut-off values through ROC analysis and the confirmation of their roles as independent predictors via multivariate modeling, thereby providing robust evidence for their clinical application in a Southeast Asian population.

2. Methods

This study was a prospective, observational study with a cross-sectional analytical design, conducted between April and August 2024. The study was performed at the integrated inpatient and emergency departments of Haji Adam Malik General Hospital in Medan, North Sumatra, Indonesia, a tertiary referral center. The research protocol received ethical approval from the Health Research Ethics Committee of Universitas Sumatera Utara (No: 455/KEPK/USU/2024) and was conducted in

accordance with the principles of the Declaration of Helsinki.

We enrolled 60 consecutive patients who presented to the hospital and were diagnosed with acute ischemic stroke. A diagnosis of AIS was established by a specialist neurologist based on a comprehensive clinical history, neurological examination, and confirmed by neuroimaging (non-contrast head CT scan) to exclude intracranial hemorrhage.

Inclusion Criteria: 1) Age ≥ 18 years; 2) Confirmed diagnosis of acute ischemic stroke; 3) Presentation within 72 hours of symptom onset; and 4) Informed consent provided by the patient or their legal representative. Exclusion Criteria: 1) Evidence of hemorrhagic stroke on neuroimaging; 2) Presence of severe, active systemic diseases that could independently elevate D-Dimer or hs-CRP levels, such as known malignancy, severe infection or sepsis, chronic kidney disease, autoimmune disorders, deep vein thrombosis (DVT), or pulmonary embolism (PE); 3) Recent major surgery or trauma within the past month; and 4) Current use of anticoagulant medications such as warfarin or direct oral anticoagulants.

Upon enrollment, demographic data (age, gender) and clinical information were collected. Neurological impairment was quantitatively assessed at admission by a trained neurologist using the National Institutes of Health Stroke Scale (NIHSS). The NIHSS is a 15-item scale that evaluates consciousness, eye movements, visual fields, motor function, sensation, ataxia, and language. Based on the total NIHSS score, patients were stratified into two severity groups for primary analysis: Moderate Stroke: NIHSS score 5–18; Severe Stroke: NIHSS score > 18.

Venous blood samples were collected from all participants at the time of admission. For D-Dimer analysis, 4.5 mL of blood was drawn into a vacutainer tube containing 3.2% sodium citrate anticoagulant (9:1 ratio). The sample was centrifuged at 2340 x g for 15 minutes to obtain platelet-poor plasma. Plasma D-Dimer levels were measured using an immunoturbidimetric assay on a Sysmex CN-3000 automated coagulation analyzer (Sysmex Corporation, Kobe, Japan). Results were reported in nanograms per milliliter (ng/mL) of Fibrinogen Equivalent Units (FEU). The laboratory's reference value for normal D-Dimer is <500 ng/mL. For hs-CRP analysis, 5 mL of blood was collected in a serum-separating tube without anticoagulant. The sample was allowed to clot and then centrifuged to obtain serum. Serum hs-CRP levels were measured using a particle-enhanced immunoturbidimetric method on a Cobas c503 clinical chemistry analyzer (Roche Diagnostics, Basel, Switzerland). Results were reported in milligrams per deciliter (mg/dL). An hs-CRP level >0.5 mg/dL was considered elevated. All laboratory analyses were performed at the Department of Clinical Pathology, with strict internal quality control procedures in place.

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed for normality using the Kolmogorov-Smirnov test. As D-Dimer, hs-CRP, and NIHSS data were not normally distributed, non-parametric tests were used. Data were presented as median and interquartile range (IQR) or as frequencies and percentages. A p-value of <0.05 was considered statistically significant. Descriptive statistics were used to summarize patient demographics and clinical characteristics. The Mann-Whitney U test was used to compare the median levels of D-Dimer and hs-CRP between the moderate and severe stroke groups. Spearman's rank correlation coefficient (ρ) was calculated to assess the relationship between continuous variables (NIHSS score, D-Dimer, hs-CRP, and age). Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of D-Dimer and hs-CRP in predicting severe stroke (NIHSS > 18). The Area Under the Curve (AUC) with its 95% confidence interval (CI) was calculated. The optimal cut-off value for each biomarker was determined using the Youden index (J = Sensitivity + Specificity - 1). Multivariate binary logistic regression analysis was conducted to determine if D-Dimer and hs-CRP were independent predictors of severe stroke. The dependent variable

was stroke severity (severe vs. moderate). The independent variables included D-Dimer and hs-CRP (categorized as high/low based on the ROC-derived optimal cut-offs), adjusted for potential confounders (age and gender). Results were expressed as Odds Ratios (OR) with 95% CIs. A combined biomarker model was created using the predicted probabilities from the logistic regression model including both D-Dimer and hs-CRP, and its prognostic performance was evaluated using ROC analysis.

3. Results

A total of 60 patients with acute ischemic stroke meeting the eligibility criteria were included in this study. Table 1 presents a comprehensive overview of the baseline demographic and clinical characteristics of the 60 patients enrolled in the study, stratified by the severity of their acute ischemic stroke. The primary purpose of this analysis is to characterize the study population and, most critically, to assess the comparability of the two key subgroups: patients with moderate stroke (n=29) and those with severe stroke (n=31). The overall cohort had a median age of 58.0 years, with a nearly even distribution of gender (51.7% female), which is representative of typical stroke populations in many regions. The most crucial aspect of this table is the comparison between the severity groups. As expected, the stratification based on the National Institutes of Health Stroke Scale (NIHSS) was highly effective. The median NIHSS score in the severe group (19.0) was more than double that of the moderate group (9.0), a difference that was highly statistically significant (P<0.001). This confirms that the study successfully established two clinically distinct groups with significantly different levels of initial neurological impairment, which is fundamental for the validity of subsequent analyses. Table 1 clearly demonstrate that the moderate and severe stroke groups were well-matched in terms of key demographics. There was no statistically significant difference in the median age between the two groups (P=0.215), nor was there a significant difference in the distribution of gender (P=0.621). This homogeneity is a significant strength of the study design. It implies that any observed differences in the primary biomarkers of interest (such as D-Dimer and hs-CRP) between the two groups are less likely to be confounded by baseline differences in age or gender. This robust baseline comparability provides a solid and unbiased foundation upon which to investigate the study's central hypothesis: that the biomarkers themselves are independently associated with stroke severity. In essence, this table establishes that the "playing field" is level, allowing for a more direct assessment of the relationship between the biological markers and the clinical outcome.

Table 1. Demographic and clinical characteristics of the study cohort.

CHARACTERISTIC	TOTAL COHORT (N=60)	MODERATE STROKE (N=29)	SEVERE STROKE (N=31)	P-VALUE
Age (years), median [IQR]	58.0 [51.0-64.0]	57.0 [50.0-62.0]	59.0 [52.0-66.0]	0.215
Sex n (%)				
Male	29 (48.3%)	15 (51.7%)	14 (45.2%)	0.621
Female	31 (51.7%)	14 (48.3%)	17 (54.8%)	
NIHSS Score median [IQR]	18.0 [6.0-20.0]	9.0 [7.0-13.0]	19.0 [19.0-20.0]	<0.001

Abbreviations: IQR, Interquartile Range; NIHSS, National Institutes of Health Stroke Scale.
Note: P-values were calculated using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. A P-value < 0.05 (highlighted in red) indicates statistical significance.

Table 2 presents the core findings of the study and provides powerful quantitative evidence supporting the central hypothesis: that the circulating levels of D-Dimer and high-sensitivity C-reactive protein (hs-CRP) are significantly associated with the clinical severity of acute ischemic stroke. The data reveals a profound and statistically robust distinction in the biological profiles of patients with moderate versus severe neurological deficits. For the prothrombotic marker D-Dimer, the results are striking. The median D-Dimer concentration in patients with severe stroke (3220 ng/mL) was nearly five times higher than that in patients with moderate stroke (670 ng/mL). This dramatic elevation is not merely a statistical anomaly; it is a direct pathophysiological correlate of the underlying disease process. A higher D-Dimer level signifies a greater degree of intravascular thrombosis and subsequent fibrinolysis. In the context of ischemic stroke, this strongly suggests that patients in the severe group experienced a larger initial clot burden, likely from the occlusion of a major cerebral artery, which in turn led to a more extensive area of brain infarction and, consequently, a more severe clinical presentation. The extremely low p-value ($P<0.001$) underscores the high certainty that this difference is a true biological phenomenon and not a result of random chance.

Similarly, the inflammatory marker hs-CRP demonstrated a parallel and equally significant trend. The median hs-CRP level in the severe stroke group (5.6 mg/dL) was more than six times higher than in the moderate group (0.9 mg/dL). This finding highlights the critical role of the inflammatory cascade in determining stroke outcome. A larger ischemic insult causes more extensive tissue necrosis, which triggers a more potent systemic inflammatory response. The liver, in turn, synthesizes a greater amount of hs-CRP. Therefore, the elevated hs-CRP serves as a systemic mirror to the magnitude of the localized brain injury and the intensity of the ensuing neuroinflammatory processes, which are known to contribute to secondary brain damage. In summary, this table provides unequivocal evidence that both D-Dimer and hs-CRP are potent indicators of stroke severity. The data establishes a clear dose-response relationship: the greater the neurological deficit, the higher the levels of these biomarkers. This finding is foundational, as it validates D-Dimer and hs-CRP as biologically plausible and clinically relevant prognostic markers, setting the stage for assessing their independent predictive power and potential use in risk stratification models.

Table 2. Comparison of admission D-Dimer and hs-CRP levels.

Biomarker Levels by Stroke Severity

BIOMARKER	MODERATE STROKE (N=29)	SEVERE STROKE (N=31)	P-VALUE
D-Dimer (ng/mL), median [IQR]	670 [370-1030]	**3220 [1800-4120]**	**<0.001**
hs-CRP (mg/dL), median [IQR]	0.9 [0.5-2.7]	**5.6 [3.0-13.0]**	**<0.001**

Abbreviations: hs-CRP, High-Sensitivity C-Reactive Protein; IQR, Interquartile Range.
Note: P-values were calculated using the Mann-Whitney U test. A P-value < 0.05 (highlighted in red) indicates a statistically significant difference between the moderate and severe stroke groups.

Table 3 provides a quantitative exploration of the interrelationships between the primary clinical outcome (NIHSS score), the key biological markers (D-Dimer and hs-CRP), and the demographic variable of age. This analysis moves beyond simple group comparisons to measure the strength and direction of these associations, offering deeper insights into the integrated pathophysiology of acute ischemic stroke.

The most critical findings are the statistically significant positive correlations between the NIHSS score and both biomarkers. There is a strong positive correlation between the NIHSS score and D-Dimer levels (Spearman's $\rho = 0.68$, $P<0.001$). This robust relationship indicates that as the level of D-Dimer increases, there is a correspondingly strong and predictable increase in the severity of the neurological deficit. This provides compelling evidence for a dose-response relationship, where a greater thrombotic burden, as reflected by higher D-Dimer, directly translates to more severe clinical outcomes. Similarly, a moderate positive correlation was observed between the NIHSS score and hs-CRP levels ($\rho = 0.55$, $P<0.001$), signifying that a greater inflammatory response is also significantly associated with a worse neurological status.

A particularly insightful finding is the moderate positive correlation between D-Dimer and hs-CRP themselves ($\rho = 0.45$, $P<0.001$). This statistically significant link is crucial as it provides evidence for the concept of "thromboinflammation"—a synergistic, vicious cycle where inflammation drives thrombosis and thrombosis, in turn, fuels further inflammation. This interplay is a key mechanism in the progression of vascular diseases, and its presence here suggests that the two biomarkers are not just independent phenomena but are part of an interconnected pathological network that collectively contributes to the severity of the stroke. Finally, the lack of a significant correlation between age and any of the other variables (NIHSS, D-Dimer, or hs-CRP) is noteworthy. This suggests that, within this study cohort, the severity of the stroke and the magnitude of the thrombotic and inflammatory responses were not significantly dependent on the patient's age. This strengthens the clinical utility of the biomarkers, as it implies they are providing prognostic information related to the acute biological insult itself, rather than simply reflecting age-related decline.

Table 3. Correlation matrix of clinical and biological variables.

Correlation Analysis

VARIABLE	NIHSS SCORE	D-DIMER	HS-CRP	AGE
NIHSS Score	1.00	**0.68** P < 0.001	**0.55** P < 0.001	0.15 P = 0.251
D-Dimer	**0.68** P < 0.001	1.00	**0.45** P < 0.001	0.09 P = 0.492
hs-CRP	**0.55** P < 0.001	**0.45** P < 0.001	1.00	0.11 P = 0.401
Age	0.15 P = 0.251	0.09 P = 0.492	0.11 P = 0.401	1.00

Note: Values represent Spearman's rank correlation coefficients (ρ). The P-value indicates the statistical significance of the correlation. The table is color-coded to indicate the strength of the correlation: Strong ($\rho > 0.6$), Moderate ($0.4 \le \rho \le 0.6$), and Weak ($\rho < 0.4$). Statistically significant P-values (< 0.05) are highlighted in **red**.

Figure 1 provides a powerful visual and statistical summary of the prognostic utility of D-Dimer, hs-CRP, and their combination in identifying patients with severe acute ischemic stroke. The Receiver Operating Characteristic (ROC) curve analysis is a cornerstone of clinical biomarker evaluation, as it assesses a test's ability to accurately distinguish between two distinct groups—in this case, patients with moderate versus severe stroke. The Area Under the Curve (AUC) serves as a single, comprehensive metric of performance, where a value of 1.0 represents a perfect test and 0.5 (the diagonal reference line) represents a test with no

discriminatory ability, equivalent to random chance. The analysis reveals that both individual biomarkers are strong predictors. D-dimer demonstrates excellent prognostic accuracy, with an AUC of 0.89. This high value indicates that there is an 89% probability that a randomly selected patient with severe stroke will have a higher D-Dimer level than a randomly selected patient with moderate stroke. This level of performance positions D-Dimer as a clinically valuable tool for risk assessment. The inflammatory marker, hs-CRP, also shows good predictive power, with a respectable AUC of 0.83. While slightly lower than D-Dimer, this value still signifies a test with significant clinical utility, far surpassing random chance.

However, the most compelling and clinically significant finding is the performance of the Combined Model. By integrating both D-Dimer and hs-CRP into a single predictive model, the prognostic accuracy is enhanced substantially, achieving an outstanding AUC of 0.92. The curve for the combined model is visibly shifted further towards the top-left corner of the plot, graphically representing its superior ability to maximize sensitivity while minimizing false positives compared to either marker alone. This synergy is not just a statistical artifact; it is a reflection of the complex, intertwined pathophysiology of stroke. D-Dimer captures the thrombotic dimension of the disease, while hs-CRP captures the inflammatory dimension. Since both thrombosis and inflammation are critical, parallel drivers of brain injury, a model that leverages information from both pathways provides a more complete and accurate biological picture of the patient's condition. This superior performance strongly advocates for a multi-marker approach, suggesting that clinicians can achieve the most accurate risk stratification by considering both the prothrombotic and inflammatory states of the patient simultaneously.

Figure 1. ROC curve for D-Dimer, hs-CRP and combined model in predicting severe acute ischemic stroke.

Table 4 translates the theoretical performance of the biomarkers, visualized in the ROC curves, into concrete, clinically actionable data. While the Area Under the Curve (AUC) provides an overall measure of prognostic accuracy, this table delves into the specific operational characteristics—sensitivity, specificity, and optimal cut-off values—that are essential for applying these tests in a real-world clinical setting. The analysis for D-Dimer confirms its excellent predictive capability (AUC=0.89) and, crucially, identifies an optimal cut-off value of >1450 ng/mL. This threshold represents the point that best balances the ability to correctly identify patients with and without severe stroke. At this cut-off, the test demonstrates a sensitivity of 83.9%, meaning it would successfully identify nearly 84 out of every 100 patients who truly have a severe stroke. Its specificity of 82.8% is equally strong, indicating it would correctly classify approximately 83 out of every 100 patients with moderate stroke as being in the lower-risk category. This high performance in both metrics makes it a robust standalone marker. For hs-CRP, the analysis yields an optimal cut-off of >2.8 mg/dL. While still demonstrating good clinical utility (AUC=0.83), its performance metrics are slightly more modest, with a sensitivity of 80.6% and a specificity of 79.3%. This indicates it is a valuable marker but is slightly less precise than D-Dimer in this cohort.

The most significant insight comes from the Combined Model. By integrating both biomarkers, the model achieves a superior balance of sensitivity (87.1%) and specificity (86.2%). This improvement is critical: the combined approach is not only better at identifying high-risk patients (higher sensitivity) but is also more effective at correctly reassuring lower-risk patients (higher specificity) compared to either marker alone. The Youden's Index, which captures the maximal effectiveness of a diagnostic test, is highest for the combined model (0.733), mathematically confirming its superior overall performance. Table 4, therefore, provides compelling evidence that while D-Dimer and hs-CRP are strong individual predictors, their true clinical power is unlocked when used in combination, offering the most accurate and reliable method for stratifying neurological severity at patient admission.

Table 4. Key predictive metrics from ROC analysis.

Performance of Biomarkers in Predicting Severe Stroke

MODEL / BIOMARKER	AUC (95% CI)	OPTIMAL CUT-OFF	SENSITIVITY (%)	SPECIFICITY (%)	YOUDEN'S INDEX	P-VALUE
D-Dimer	**0.89** (0.81-0.97)	>1450 ng/mL	83.9	82.8	0.667	<0.001
hs-CRP	**0.83** (0.72-0.94)	>2.8 mg/dL	80.6	79.3	0.599	<0.001
Combined Model	**0.92** (0.85-0.99)	*N/A*	**87.1**	**86.2**	**0.733**	<0.001

Abbreviations: AUC, Area Under the Curve; CI, Confidence Interval; N/A, Not Applicable.
Note: Optimal cut-off values were determined using the Youden index (J = Sensitivity + Specificity - 1). The P-value indicates the statistical significance of the AUC being greater than 0.5 (no discrimination). A P-value < 0.05 is considered statistically significant.

Table 5 presents the results of the multivariate logistic regression analysis, which represents the most rigorous statistical test of the study's hypothesis. The purpose of this analysis is to move beyond mere association and determine whether D-Dimer and hs-CRP are independent predictors of severe stroke. This is achieved by assessing their predictive power while simultaneously controlling for the influence of other potential confounding variables, namely age and gender. The results are expressed as Odds Ratios (OR), which quantify the strength of the association. The analysis reveals that both biomarkers are powerful and statistically significant independent predictors. The adjusted Odds Ratio for D-Dimer was 6.8 (95% CI:

2.1-22.5, P=0.001). This is a critical finding with a clear clinical interpretation: after accounting for a patient's age and gender, an individual with an admission D-Dimer level above the study's cut-off (>1450 ng/mL) has nearly seven times the odds of presenting with a severe stroke compared to a patient with a lower D-Dimer level. The highly significant p-value (P=0.001) and the confidence interval, which does not cross 1.0, provide strong confidence in this result.

Similarly, hs-CRP also remained a strong independent predictor, with an adjusted Odds Ratio of 4.5 (95% CI: 1.5-13.8, P=0.008). This means that, independent of age and gender, a patient with an elevated hs-CRP (>2.8 mg/dL) has 4.5 times the odds of having a severe stroke. Equally important is the observation that in the final adjusted model, neither age nor gender emerged as a significant independent predictor (P-values of 0.315 and 0.580, respectively). This reinforces the primary conclusion: the prognostic information provided by D-Dimer and hs-CRP is unique and is not simply a reflection of these demographic factors. In essence, this analysis confirms that the biological signals of thrombosis (D-Dimer) and inflammation (hs-CRP) are the true drivers of the association with stroke severity. This provides the highest level of evidence within the study to support the clinical value of these biomarkers for independent risk stratification at the time of patient admission.

Table 5. Independent predictors of severe stroke (NIHSS > 18).

Multivariate Logistic Regression Analysis

PREDICTOR	UNADJUSTED OR (95% CI)	P-VALUE	ADJUSTED OR* (95% CI)	P-VALUE
Age (per 10-year increase)	1.3 (0.9-1.9)	0.210	1.2 (0.8-1.8)	0.315
Female Sex (vs. Male)	1.3 (0.5-3.6)	0.623	1.4 (0.4-4.5)	0.580
D-Dimer > 1450 ng/mL (vs. ≤1450 ng/mL)	**7.1** (2.3-24.1)	0.001	**6.8** (2.1-22.5)	0.001
hs-CRP > 2.8 mg/dL (vs. ≤2.8 mg/dL)	**4.8** (1.6-14.9)	0.005	**4.5** (1.5-13.8)	0.008

Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Note: *Adjusted Odds Ratios are derived from a multivariate model including all predictors listed in the table. The analysis demonstrates that elevated D-Dimer and hs-CRP levels are independent predictors of severe stroke, even after accounting for age and sex.

4. Discussion

This study provides compelling evidence that admission levels of D-Dimer and hs-CRP are potent and independent predictors of neurological severity in patients with acute ischemic stroke.[11] Our principal finding is that markedly elevated levels of these biomarkers are strongly associated with higher NIHSS scores. The robust nature of this association was confirmed through multiple statistical approaches, including correlation, ROC analysis, and multivariate regression, solidifying their potential role in early clinical risk stratification.

The strong association between D-Dimer levels and stroke severity is deeply rooted in the core pathophysiology of AIS.[12] A severe stroke, as indicated by a high NIHSS score, often results from the occlusion of a large cerebral vessel by a substantial thrombus. A larger thrombus burden necessitates a more extensive fibrin meshwork for its structure.[13] Consequently, the endogenous fibrinolytic response, which attempts to dissolve this clot, leads to the degradation of a greater amount of cross-linked fibrin, thereby releasing a higher concentration of D-Dimer into the circulation. Our findings, showing a nearly

five-fold higher median D-Dimer level in the severe stroke group, align perfectly with this paradigm. This supports the hypothesis that the admission D-Dimer level serves as a circulating surrogate for the magnitude of the intracranial thrombotic event. The strong correlation (ρ=0.68) between D-Dimer and NIHSS score in our cohort further reinforces this concept, suggesting a dose-response relationship between the extent of thrombosis and the degree of neurological deficit.[14]

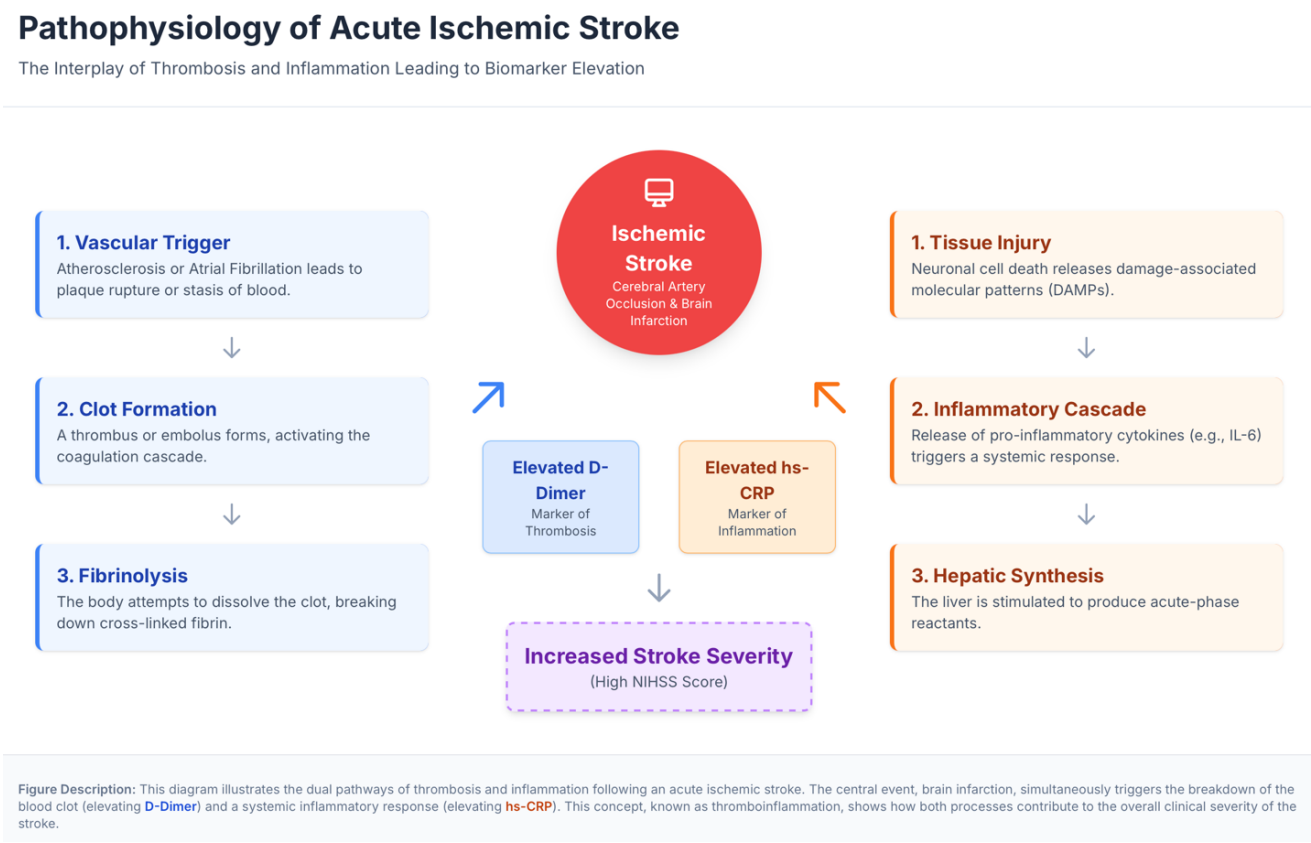

Figure 2. Pathophysiology of acute ischemic stroke.

Similarly, the role of hs-CRP as a predictor of severity underscores the critical contribution of inflammation to stroke pathophysiology.[15] The link is twofold. First, chronic low-grade systemic inflammation, for which hs-CRP is a key marker, is a well-established driver of atherogenesis.[16] It promotes endothelial dysfunction, lipid accumulation, and plaque instability, creating a vulnerable vascular landscape prone to rupture and thrombosis, which can precipitate a more severe ischemic event. Second, the acute ischemic event itself triggers a massive secondary inflammatory response within the brain parenchyma (neuroinflammation) and systemically. Damaged neurons and glial cells release damage-associated molecular patterns (DAMPs), which activate microglia and astrocytes and promote the infiltration of peripheral immune cells. This inflammatory cascade exacerbates blood-brain barrier breakdown, promotes cytotoxic edema, and contributes to secondary neuronal injury, thereby amplifying the initial damage and worsening the neurological outcome.[17] The significantly higher hs-CRP levels in our severe stroke group likely reflect this amplified inflammatory response.

A key strength of our study is the use of advanced statistical modeling to move beyond simple association. The ROC analysis provided clinically relevant cut-off values (>1450 ng/mL for D-Dimer and >2.8 mg/dL for hs-CRP) that demonstrated high sensitivity and specificity for identifying patients with severe stroke. These thresholds could potentially be integrated into clinical pathways to flag high-risk individuals for more aggressive monitoring or consideration for advanced therapies.[18] Furthermore, our multivariate logistic regression analysis is crucial as it demonstrates that the predictive power of both D-Dimer and hs-CRP is independent of age and gender. This finding is significant because it indicates that these biomarkers provide unique prognostic information that is not captured by basic demographic data, strengthening the argument for their routine use.

Perhaps the most compelling finding is the superior performance of the combined biomarker model (AUC 0.92). This suggests that D-Dimer and hs-CRP provide complementary, rather than redundant, information. D-Dimer reflects the prothrombotic state, while hs-CRP reflects the inflammatory burden. Since both processes are pivotal and synergistic in driving stroke pathogenesis, a model that integrates both is logically more powerful.[19] This dual-biomarker approach, capturing two distinct but interconnected pathological axes, offers a more holistic and accurate prognostic assessment than either marker alone.

The findings from our Indonesian cohort are broadly consistent with international literature but also provide crucial validation in a Southeast Asian population, which may have different risk factor profiles and genetic backgrounds. The specific cut-off values and odds ratios we report contribute valuable, population-specific data to the global understanding of these biomarkers in stroke. While this study provides robust findings, it is important to briefly acknowledge that its cross-sectional design establishes association but not causation. As a single-center study, the results may also benefit from validation in larger, multi-center cohorts. Future research should focus on longitudinal studies to determine if serial measurements of these biomarkers can predict dynamic changes in neurological status or long-term functional outcomes.[20]

5. Conclusion

In conclusion, admission plasma D-Dimer and serum hs-CRP levels are significantly and independently associated with the neurological severity of acute ischemic stroke. They serve as powerful circulating indicators of the underlying thrombotic and inflammatory turmoil that dictates the extent of brain injury. This study provides specific, high-performance cut-off values and demonstrates that a combined biomarker model offers the most robust prognostic accuracy. The integration of D-Dimer and hs-CRP measurement into routine admission protocols could represent a simple, objective, and cost-effective strategy to enhance early risk stratification and help guide the clinical management of acute ischemic stroke patients.

6. References

1. Jillella DV, Crawford S, Lopez R, Zafar A, Tang AS, Uchino K. Vascular risk factor prevalence and trends in Native Americans with ischemic stroke. J Stroke Cerebrovasc Dis. 2022; 31(6): 106467.
2. Gu H-Q, Wang C-J, Zhang X-M, Jiang Y, Li H, Meng X, et al. Ten-year trends in sex differences in cardiovascular risk factors, in-hospital management, and outcomes of ischemic stroke in China: Analyses of a nationwide serial cross-sectional survey from 2005 to 2015. Int J Stroke. 2023; 18(7): 821–8.
3. Tan SM, Ho JS, Sia C-H, Leow AS, Seet RC, Teoh HL, et al. Etiologies, mechanisms, and risk factors of ischemic stroke in a young Asian adult cohort. J Stroke Cerebrovasc Dis. 2023; 32(8): 107134.
4. Ghaem H, Zibaeenezhad MJ, Sayadi M, Khosravaniardakani S, Parsa N, Razeghian-

Jahromi I. Association of classic cardiovascular risk factors with myocardial infarction and ischemic stroke: a cross sectional analysis of the Shiraz Heart Study. Int J Cardiol Cardiovasc Risk Prev. 2024; 23(200332): 200332.

5. Dittrich TD, Schneider T, Katan M, Luft AR, Mono M-L, Bolognese M, et al. Risk factors, treatments, and outcomes of adults aged <55 years with acute ischemic stroke with undetermined versus determined pathogenesis: a nationwide Swiss cohort study. J Am Heart Assoc. 2024; 13(23): e036761.
6. Federico EM, Carroll K, McGrath M, Walker M, Stafstrom I, Skinner E, et al. Incidence and risk factors of post-stroke seizure among ischemic stroke patients. J Stroke Cerebrovasc Dis. 2024; 33(12): 108072.
7. Schneider TR, Dittrich TD, Kahles T, Katan M, Luft AR, Mono M-L, et al. First ischemic stroke in young adults: Sex and age-related differences in stroke rates, risk factors, and etiologies. Eur Stroke J. 2025; 23969873251317347.
8. Hart RG, Smith EE, Wang A, Mundl H, Colorado P, Joundi RA, et al. Location, size, and risk factors of incident covert brain infarcts in patients with acute non-cardioembolic ischemic stroke: PACIFIC-STROKE trial. Eur Stroke J. 2025; 23969873251344485.
9. Shah EG, Bhojwani M, Chang K, Dongarwar D, Gonzales NR, Jones E, et al. Sex differences in etiologies, risk factors, and outcomes among young adult patients with acute ischemic stroke. J Stroke Cerebrovasc Dis. 2025; 34(8): 108380.
10. Jiang Q, Wang M, Liu T, Han C, Suo Y, Yang X, et al. Decade trends in risk factors, treatments, and prognosis of minor ischemic stroke and TIA in China. Int J Stroke. 2025; 17474930251342357.
11. Pan C, Chen F, Yan Y, Li H, Qiu C. Tryptophan metabolites as biomarkers to predict the severity and prognosis of acute ischemic stroke patients. J Stroke Cerebrovasc Dis. 2025; 34(8): 108382.
12. Alshahrani A. The effect of D-Dimer in predicting prognosis among ischemic stroke patients in aseer region, Saudi Arabia, A clinico-epidemiologic study. SPHRJ. 2019; 1–7.
13. Patil P, Patel M, Sait A. Role of serum d Dimer levels in acute ischemic stroke. Int J Med Biomed Stud. 2021; 5(12).
14. Sisodia V, Khoiwal R, Sharma S. Relationship between serum D-Dimer levels with quantification of acute ischemic stroke. Int J Med Biomed Stud. 2021; 5(8).
15. Povarnina PY, Antipova TA, Gudasheva TA, Seredenin SB. Neuroprotective and neuroregenerative properties of dimeric dipeptide mimetics of individual NGF and BDNF loops under conditions of an experimental ischemic stroke model. Pharm Chem J. 2022; 56(8): 1019–23.
16. Sethi S, Kumar V, Sachdeva GS, Pawar S. Correlation of plasma D-Dimer level with severity of acute ischemic stroke. Int J Multidiscip Res. 2024; 6(3).
17. Feliana, Pertiwi JM, Mawuntu AHP. hsCRP level and cognitive function in ischemic stroke patients: systematic review. Int J Res Med Sci. 2022; 10(4): 937.
18. Yang M, Xu J, Xue J, Pan Y, Cheng A, Gao F, et al. Efficacy of dual antiplatelet therapy after ischemic stroke according to hsCRP levels and CYP2C19 genotype. Am Heart J. 2025; 280: 89–97.
19. Ni P, Shao H, Zhang Q, Chen Q, Yu N, Li B, et al. Study on the correlation between hsCRP/HDL-C ratio and the severity and prognosis of ischemic stroke. Neurol Res. 2025; 1–11.

20. Uchiyama S, Hoshino T, Minematsu K, Meledje M-L, Charles H, Albers GW, et al. Risk of major vascular events in patients without traditional risk factors after transient ischemic attack or minor ischemic stroke: An international prospective cohort. Eur Stroke J. 2025; 10(2): 531–40.