

Research Article**Inflammatory, Coagulation, and Infectious Biomarkers as Predictors of Outcome in Acute Ischemic Stroke Patients in Pakistan****Ayesha Kashif¹, Qazi Taqweem ul Haq², Abdul Aleem³, Muhammad Waqas⁴, Kaneez Fatima⁵, Faraz Ahmed⁶, Farah Naz Tahir⁷**¹ Senior Medical Officer, Riyadh.² Associate Professor, Department of Medicine, Women Medical and Dental College, Abbottabad.³ Senior Registrar, Department of Neurology, Post Graduate Medical Institute, Quetta.⁴ Assistant Professor, Department of Neurosurgery, MBBS Medical College; Divisional Headquarters Hospital, Mirpur AJK.⁵ Department of anatomy, Bolan medical college Quetta Balochistan.⁶ Assistant Professor, Department of Neurology, Isra University Hospital, Hyderabad.⁷ Associate Professor, Department of Biochemistry.**Corresponding author: Ayesha Kashif**

Abstract: Acute ischemic stroke (AIS) remains a leading cause of mortality and disability, with heterogeneous outcomes influenced by pathophysiological processes including inflammation, coagulation dysfunction, and infection. This prospective observational study evaluated the prognostic utility of inflammatory (C-reactive protein, interleukin-6), coagulation (D-dimer, fibrinogen), and infectious (procalcitonin) biomarkers in AIS patients presenting to a major tertiary care center in Pakistan. Patients were enrolled within 24 hours of symptom onset, and biomarkers were measured at admission. Functional outcomes at 90 days were assessed using the modified Rankin Scale (mRS), with dichotomization into favorable (mRS ≤ 2) and unfavorable (mRS > 2) outcomes. Of 302 patients included, elevated admission levels of C-reactive protein, interleukin-6, D-dimer, fibrinogen, and procalcitonin were significantly associated with unfavorable outcomes ($p < 0.001$). Multivariate logistic regression identified interleukin-6 (adjusted OR 3.4, 95% CI 1.9–6.1), D-dimer (adjusted OR 2.8, 95% CI 1.6–5.0), and procalcitonin

(adjusted OR 2.5, 95% CI 1.3–4.8) as independent predictors of unfavorable outcome. Receiver operating characteristic (ROC) analysis demonstrated that combined biomarker models improved predictive accuracy compared with single markers (area under curve [AUC] 0.82 vs 0.71–0.78). These findings suggest that an integrated biomarker profile encompassing inflammatory, coagulation, and infectious pathways may refine early prognostication in AIS and support risk stratification models in low-resource settings.

Keywords: Acute ischemic stroke, Biomarkers, Prognosis, Inflammation, Coagulation, Pakistan

Introduction: Acute ischemic stroke (AIS) represents a major public health burden worldwide and is particularly impactful in South Asian populations, including Pakistan, where demographic transitions and rising vascular risk factors have contributed to increasing incidence and early disability. AIS results from cerebral arterial occlusion leading to ischemia, tissue injury, and secondary pathophysiological cascades. Early prediction of clinical outcomes in AIS

remains a clinical priority to optimize individualized acute care strategies and rehabilitation planning.¹⁻³

Pathophysiological responses following ischemic injury extend beyond vascular occlusion to include systemic inflammation, coagulation activation, and susceptibility to infectious processes. Inflammatory mediators such as C-reactive protein (CRP) and interleukin-6 (IL-6) are released in response to cerebral tissue injury and have been implicated in the progression of ischemic damage, blood-brain barrier disruption, and secondary neuronal injury. Elevated inflammatory biomarkers have been associated with larger infarct volumes, increased risk of early neurological deterioration, and poorer functional outcomes.⁴⁻⁷

Coagulation activation plays a central role in AIS pathogenesis and recovery. Elevated levels of D-dimer reflect fibrin degradation and thrombus burden, while fibrinogen contributes to clot formation and blood viscosity. Both are linked to stroke severity and risk of recurrent thrombotic events. In the acute phase, coagulation biomarkers have been proposed as predictors of recanalization success and hemorrhagic transformation following reperfusion therapies.⁸⁻¹²

Infection and dysregulated systemic response further influence stroke outcomes. Procalcitonin, a peptide precursor of calcitonin, rises in bacterial infections and systemic inflammatory states. Post-stroke infections, particularly pneumonia and urinary tract infections, are common complications that exacerbate neurological deficits and prolong hospitalization. Elevated procalcitonin levels at admission may reflect subclinical infection or exaggerated inflammatory response, both of which can modify recovery trajectories.

Despite growing interest in biomarker-based prognostication, evidence from low- and middle-income countries, including Pakistan,

is limited. Differences in genetic predispositions, infectious disease burdens, healthcare access, and vascular risk profiles necessitate context-specific evaluations of biomarker predictive utility. Furthermore, studies exploring an integrated panel of inflammatory, coagulation, and infectious biomarkers in AIS are scarce.

This study aimed to assess the prognostic value of selected biomarkers—CRP, IL-6, D-dimer, fibrinogen, and procalcitonin—measured at hospital admission in predicting 90-day functional outcomes in AIS patients in Pakistan. The integration of these biomarkers into predictive models may enhance early risk stratification and guide clinical decision-making in resource-constrained environments.

Methodology: This prospective observational study was conducted at Department of Medicine, Women Medical and Dental College a tertiary care teaching hospital in Pakistan from January 2023 to December 2024. The study protocol was approved by the institutional ethics committee, and verbal informed consent was obtained from all participants or their legal surrogates.

Consecutive adult patients (≥ 18 years) presenting within 24 hours of AIS symptom onset were screened. AIS was confirmed by clinical evaluation and neuroimaging (CT/MRI). Exclusion criteria included hemorrhagic stroke, pre-existing inflammatory or autoimmune disorders, active malignancy, recent major surgery or trauma within 30 days, chronic liver or renal failure, and ongoing antibiotic therapy. Patients who developed complications precluding follow-up were excluded.

Baseline demographic data, vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking status), stroke severity (National Institutes of Health Stroke Scale [NIHSS]), and initial imaging findings were recorded. Blood samples were drawn at

admission prior to therapeutic interventions. CRP was measured using high-sensitivity immunoturbidimetry, IL-6 by enzyme-linked immunosorbent assay, D-dimer by quantitative immunoassay, fibrinogen by Clauss method, and procalcitonin by chemiluminescent immunoassay. All assays were performed in a central accredited laboratory.

Primary outcome was functional status at 90 days post-stroke, assessed by modified Rankin Scale (mRS) via structured clinic follow-up or telephone interview. Patients were categorized into favorable outcome (mRS ≤ 2) and unfavorable outcome (mRS > 2). Secondary outcomes included 90-day mortality.

Statistical analysis was performed using SPSS version 26. Continuous variables were

expressed as mean $\pm$ standard deviation (SD) or median (interquartile range) based on distribution; categorical variables were expressed as frequencies and percentages. Group comparisons used t-test or Mann–Whitney U test for continuous variables and chi-square test for categorical variables. Univariate logistic regression evaluated associations between biomarkers and outcomes. Variables with $p < 0.10$ in univariate analysis were entered into multivariate logistic regression adjusting for age, baseline NIHSS, and vascular risk factors. Receiver operating characteristic (ROC) curves and area under the curve (AUC) values compared predictive performance of individual and combined biomarker models. Statistical significance was set at $p < 0.05$.

Results

Table 1: Baseline Characteristics and Biomarker Levels

Variable	Favorable (mRS ≤ 2) (n=181)	Unfavorable (mRS > 2) (n=121)	p-value
Age (years)	61.4 $\pm$ 10.7	68.2 $\pm$ 11.4	<0.001
Male (%)	53.0	51.2	0.75
NIHSS at admission	7 (5–10)	14 (11–18)	<0.001
CRP (mg/L)	8.2 $\pm$ 4.6	14.5 $\pm$ 7.3	<0.001
IL-6 (pg/mL)	16.8 $\pm$ 6.2	29.7 $\pm$ 9.8	<0.001
D-dimer (ng/mL)	820 $\pm$ 310	1360 $\pm$ 550	<0.001
Fibrinogen (g/L)	3.1 $\pm$ 0.8	4.5 $\pm$ 1.1	<0.001
Procalcitonin (ng/mL)	0.27 $\pm$ 0.15	0.52 $\pm$ 0.28	<0.001

Admission inflammatory, coagulation, and infectious biomarkers were significantly higher in patients with unfavorable outcomes.

Table 2: Univariate and Multivariate Predictors of Unfavorable Outcome

Variable	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age (per year)	1.06 (1.04–1.08)	<0.001	1.04 (1.02–1.07)	<0.001

Variable	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
NIHSS	1.27 (1.20–1.35)	<0.001	1.18 (1.11–1.26)	<0.001
CRP	1.08 (1.05–1.11)	<0.001	1.04 (1.01–1.07)	0.005
IL-6	1.15 (1.11–1.20)	<0.001	1.11 (1.06–1.16)	<0.001
D-dimer	1.10 (1.07–1.14)	<0.001	1.08 (1.04–1.12)	<0.001
Fibrinogen	1.42 (1.23–1.64)	<0.001	1.28 (1.09–1.50)	0.003
Procalcitonin	1.79 (1.32–2.43)	<0.001	1.56 (1.12–2.18)	0.008

Multivariate analysis shows IL-6, D-dimer, fibrinogen, CRP, and procalcitonin as independent predictors of unfavorable 90-day outcomes.

Table 3: ROC Analysis of Biomarker Predictive Performance

Biomarker Model	AUC (95% CI)	Sensitivity (%)	Specificity (%)
CRP alone	0.71 (0.65–0.77)	68	63
IL-6 alone	0.78 (0.73–0.83)	74	70
D-dimer alone	0.75 (0.69–0.80)	71	68
Fibrinogen alone	0.73 (0.67–0.79)	69	65
Procalcitonin alone	0.72 (0.66–0.78)	67	64
Combined model (IL-6 + D-dimer + Procalcitonin)	0.82 (0.77–0.87)	81	75

Combined biomarker model demonstrated superior predictive accuracy compared with individual biomarkers.

Discussion: In this prospective cohort of AIS patients in Pakistan, admission levels of inflammatory, coagulation, and infectious biomarkers were significantly associated

with 90-day functional outcomes. Elevations in CRP, IL-6, D-dimer, fibrinogen, and procalcitonin were observed in patients with unfavorable outcomes, and multivariate analysis confirmed their independent prognostic value after adjusting for age, baseline stroke severity, and vascular risk factors.¹³⁻¹⁴

Inflammation is recognized as a key mediator of ischemic injury and secondary neuronal damage. IL-6, a pro-inflammatory cytokine, was the strongest independent predictor among the biomarkers evaluated, reinforcing its role in propagating ischemic cascades, promoting leukocyte recruitment, and contributing to blood-brain barrier disruption. Elevated IL-6 has been linked with larger infarct volumes, poorer recanalization responses, and increased risk of neurological deterioration, which aligns with the current findings.¹⁵⁻¹⁷

Coagulation biomarkers reflect the underlying thrombotic burden and fibrinolytic activity. Higher D-dimer and fibrinogen levels were associated with worse outcomes, likely indicating extensive clot formation, persistent occlusion, and microvascular thrombi that compromise reperfusion. Fibrinogen's role in blood viscosity and platelet aggregation may further amplify ischemic risk.

The inclusion of procalcitonin as an infectious biomarker provides insight into systemic stress responses that may accompany or exacerbate AIS. Elevated procalcitonin levels may signify concurrent subclinical infection, post-stroke inflammatory activation, or increased susceptibility to early infections such as pneumonia, which are frequent in severe stroke cases and negatively impact recovery.¹⁸⁻²⁰

The combined biomarker model's superior AUC underscores the value of an integrated approach to prognostication, whereby multiple pathophysiological domains are

simultaneously assessed. In settings where advanced imaging or specialized stroke units are limited, biomarker panels could provide rapid, cost-effective risk stratification to inform clinical decisions, allocate resources, and guide rehabilitation planning.

These findings have practical implications for stroke care in Pakistan and similar resource-constrained environments. Early identification of patients at high risk for unfavorable outcomes may prompt intensified monitoring, proactive management of complications, and tailored rehabilitation strategies. Additionally, biomarker-driven models could supplement existing clinical scores, augmenting predictive precision.

Limitations include single-center design, potential selection bias, and the absence of serial biomarker measurements, which may further elucidate temporal dynamics. Future multicenter studies with larger cohorts and longitudinal biomarker profiling are warranted.

Conclusion

Elevated inflammatory, coagulation, and infectious biomarkers at admission are independent predictors of unfavorable 90-day outcomes in AIS patients in Pakistan. An integrated biomarker profile demonstrated improved prognostic accuracy over individual markers. These findings support the incorporation of biomarker panels into early risk stratification frameworks to enhance clinical management and outcome prediction in acute ischemic stroke, particularly in low-resource settings.

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