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Elevated Admission Serum Fibrinogen as an Independent Predictor of Poor Outcome in Acute Ischemic Stroke: A Prospective Observational Study

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ABSTRACT

Background and Aims: Acute ischemic stroke remains a leading cause of mortality and long-term disability worldwide. Early identification of patients at high risk of unfavourable outcomes is crucial for risk stratification and therapeutic decision-making. This study aimed to evaluate the prognostic significance of admission serum fibrinogen levels in patients with acute ischemic stroke.
Materials and Methods: A prospective cross-sectional observational study was conducted on 70 consecutive adults (age ≤80 years) admitted within 48 hours of onset of first-ever acute ischemic stroke at a tertiary care centre in South India between February 2021 and March 2022. Patients with haemorrhagic stroke, active infection, malignancy, connective tissue disorders, recent surgery, or prior stroke were excluded. Serum fibrinogen was measured on admission along with clinical severity (Scandinavian Stroke Scale) and functional status (Modified Rankin Scale, mRS) at admission, discharge, and one month.
Results: Mean admission serum fibrinogen was 396.36 ± 114.68 mg/dL. Patients who died had significantly higher fibrinogen (512.4 ± 92.3 vs 379.8 ± 106.5 mg/dL, $p<0.001$), lower SSS scores, and higher mRS scores. Females exhibited higher fibrinogen than males (431.11 ± 88.14 vs 373.19 ± 125.06 mg/dL, $p=0.037$). Fibrinogen correlated positively with mRS at admission ($r=0.436$, $p=0.001$) and discharge ($r=0.279$, $p=0.028$). A cut-off of ≥505 mg/dL predicted mortality with sensitivity 75%, specificity 98.39%, and accuracy 95.71% (AUC 0.864). Each 1 mg/dL increase in fibrinogen raised odds of death by 1.02 (95% CI 1.01–1.03, $p=0.007$).
Conclusion: Elevated admission serum fibrinogen is a simple, inexpensive, and powerful independent predictor of mortality and functional disability in acute ischemic stroke. Routine measurement may aid early prognostication and intensify management in high-risk patients.

Keywords: *Fibrinogen; Brain Ischemia; Stroke; Prognosis; Biomarkers; Mortality.*

INTRODUCTION

Stroke continues to impose an enormous global burden as one of the foremost causes of death and permanent disability in adults. The World Health Organization estimates that 15 million people suffer a stroke each year, of whom 5 million die and another 5 million are left with significant long-term neurological deficits [1]. In India, age-adjusted prevalence ranges from 84–262 per 100,000 in rural to 334–424 per 100,000 in urban areas, with ischemic stroke comprising nearly 80–85% of all cases [2]. Despite advances in reperfusion therapies, access remains limited in resource-constrained settings, making accurate early prognostic assessment vital for triage, counselling families, and guiding intensity of care.

Fibrinogen, an acute-phase glycoprotein synthesised by the liver, plays a central role in coagulation, platelet aggregation, and blood viscosity. Beyond its haemostatic function, elevated plasma fibrinogen is now recognised as a marker of systemic

inflammation and endothelial dysfunction [3]. Numerous epidemiological studies have established hyperfibrinogenaemia as an independent risk factor for incident ischemic stroke, myocardial infarction, and peripheral arterial disease. Mechanistically, high fibrinogen promotes thrombus formation, increases blood viscosity, enhances platelet aggregability, and contributes to atherosclerotic plaque instability through deposition in the vessel wall [4].

In the setting of acute cerebral ischemia, admission fibrinogen levels reflect both pre-existing chronic vascular risk as well as the magnitude of the acute-phase response triggered by tissue necrosis. Several investigators have reported associations between raised fibrinogen and larger infarct volume, severe neurological deficit on presentation, early neurological deterioration, and poor functional outcome. However, results have been inconsistent regarding its independent predictive value after adjustment for age, stroke severity, and conventional vascular risk factors. Moreover, most prior studies originated from high-income countries with different risk-factor profiles and stroke subtypes compared to South Asian populations [5].

The inflammatory cascade following ischemic stroke is complex and time-dependent. Within hours, damaged neurons and glia release danger-associated molecular patterns that activate microglia and recruit peripheral leucocytes [6]. Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α drive hepatic synthesis of acute-phase proteins, including fibrinogen, C-reactive protein, and serum amyloid A. Peak fibrinogen levels are typically reached 3–7 days post-stroke, but admission values already capture the early surge and provide prognostic information at the most clinically relevant time point—when decisions about thrombolysis, decompressive surgery, or palliative care are made [5, 6].

Several pathophysiological mechanisms link hyperfibrinogenaemia to worse stroke outcomes. First, fibrinogen is converted to fibrin monomers that polymerise to form the scaffold of occlusive thrombi; higher concentrations favour thrombus propagation and resistance to endogenous fibrinolysis. Second, fibrinogen binds glycoprotein IIb/IIIa receptors on platelets, amplifying aggregation and microvascular occlusion. Third, elevated plasma viscosity impairs cerebral perfusion, particularly in the penumbral zone. Fourth, fibrinogen degradation products possess neurotoxic and vasculotoxic properties that exacerbate blood–brain barrier disruption and cerebral oedema. Finally, high fibrinogen may simply be a surrogate for greater atherosclerotic burden and systemic inflammation [7].

The Scandinavian Stroke Scale (SSS) and Modified Rankin Scale (mRS) are validated, widely used instruments for quantifying initial stroke severity and subsequent disability, respectively. Receiver operating characteristic (ROC) curve analysis provides an objective method to determine optimal fibrinogen thresholds with maximal sensitivity and specificity for predicting mortality or severe disability [8].

Given the easy availability, low cost, and rapid turnaround time of serum fibrinogen measurement in most hospitals, establishing its prognostic role could enable risk stratification even in resource-limited settings where advanced neuroimaging or specialised biomarkers are unavailable. Early identification of patients with hyperfibrinogenaemia might also open therapeutic windows for anti-inflammatory or fibrinogen-lowering strategies (e.g., intensive statin therapy, fibrates, or novel agents) as adjuncts to standard stroke care.

The present prospective study was therefore undertaken with the primary objective of evaluating the prognostic significance of admission serum fibrinogen levels in patients with acute ischemic stroke. Secondary objectives included examining associations of fibrinogen with demographic variables, conventional vascular risk factors, initial stroke severity, and functional outcome at discharge and one month.

MATERIALS AND METHODS

Study Setting This prospective cross-sectional observational study was carried out in the Department of General Medicine, Thanjavur Medical College and Hospital, a tertiary-care government teaching hospital in Tamil Nadu, South India, from February 2021 to March 2022.

Study Participants Consecutive adult patients of both sexes presenting within 48 hours of onset of first-ever acute focal neurological deficit clinically suggestive of ischemic stroke were screened. Inclusion criteria comprised age ≤80 years, CT brain confirming absence of haemorrhage, and willingness to provide informed consent. Patients were excluded if they had haemorrhagic stroke, evidence of active infection or malignancy, connective tissue disorders, rheumatic heart disease, known coronary artery disease, recent surgery or trauma (<3 months), chronic kidney disease, liver cirrhosis, prior history of stroke or transient ischemic attack, or any contraindication to blood sampling.

Sample Size and Sampling Technique Sample size was calculated based on a previous study reporting 85.71% sensitivity of fibrinogen ≥557 mg/dL for predicting mortality, using precision of 19% and 95% confidence level, yielding a minimum of 68 patients (rounded to 70). Convenience sampling was employed; all eligible consecutive patients fulfilling selection criteria during the study period were enrolled.

Study Tools A structured proforma captured demographic data, vascular risk factors (hypertension, diabetes, smoking, alcohol use), clinical examination findings, and vital parameters. Stroke severity on admission was assessed using the Scandinavian Stroke Scale (SSS). Functional disability was quantified with the Modified Rankin Scale (mRS) at admission, discharge, and one-month follow-up. Non-contrast CT brain was performed in all cases. Fasting lipid profile and random blood sugar were measured. Serum fibrinogen was estimated on admission using the Clauss clotting method (normal reference range 200–400 mg/dL).

Study Methodology After obtaining informed written consent, detailed history and examination were performed. Blood samples for fibrinogen and other parameters were collected on the morning following admission (within 48 hours of symptom onset). Patients received standard stroke-unit care as per institutional protocol. Outcome measures were in-hospital mortality or discharge status and mRS at one month.

Ethical Issues The study was approved by the Institutional Ethics Committee of Thanjavur Medical College and Hospital. Written informed consent was obtained from patients or legally authorised representatives. All principles of the Declaration of Helsinki were followed. No additional investigations or interventions beyond routine care were performed.

Statistical Analysis Data were entered in Microsoft Excel and analysed using SPSS version 16.0. Continuous variables are expressed as mean ± SD; categorical variables as frequencies and percentages. Student's t-test or ANOVA was used to compare means; Pearson/Spearman correlation assessed relationships between fibrinogen and continuous outcome variables. Receiver operating characteristic (ROC) curve determined optimal fibrinogen cut-off for predicting mortality. Binomial logistic regression calculated adjusted odds ratios. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Seventy patients (60% male) with confirmed acute ischemic stroke were enrolled. Mean age was 59.4 ± 12.3 years. The commonest risk factors were hypertension (42.9%), diabetes mellitus (34.3%), smoking (32.9%), and alcohol use (20%). Mean admission Scandinavian Stroke Scale (SSS) score was 28.6 ± 10.4, and mean admission mRS was 4.1 ± 1.2. Overall mean serum fibrinogen was 396.36 ± 114.68 mg/dL (range 60–649 mg/dL).

Table 1. Baseline demographic and clinical characteristics of the study population (N=70)

Variable	Value (n (%) or Mean ± SD)
Age (years)	59.4 ± 12.3
Male gender	42 (60%)
Hypertension	30 (42.9%)
Diabetes mellitus	24 (34.3%)
Current smoking	23 (32.9%)
Alcohol consumption	14 (20%)
Admission SSS score	28.6 ± 10.4
Admission mRS	4.1 ± 1.2
Discharge mRS	3.4 ± 1.6
Serum fibrinogen (mg/dL)	396.36 ± 114.68

In-hospital mortality occurred in 8 patients (11.4%). Patients who died had markedly higher fibrinogen, more severe initial deficit, and greater disability scores compared to survivors.

Table 2. Comparison of clinical and laboratory parameters according to in-hospital outcome

Parameter	Discharged (n=62)	Died (n=8)	p-value
Age (years)	58.9 ± 12.5	63.1 ± 10.8	0.337
Male gender	38 (61.3%)	4 (50%)	0.693
Hypertension	26 (41.9%)	4 (50%)	0.712
Diabetes mellitus	20 (32.3%)	4 (50%)	0.434
Smoking	20 (32.3%)	3 (37.5%)	0.999
Alcohol use	12 (19.4%)	2 (25%)	0.658
Admission SSS score	30.2 ± 9.8	16.4 ± 8.9	<0.001
Admission mRS	3.9 ± 1.1	5.0 ± 0.0	<0.001
Discharge mRS (survivors only)	3.4 ± 1.6	—	—
Serum fibrinogen (mg/dL)	379.8 ± 106.5	512.4 ± 92.3	<0.001

Fibrinogen levels were significantly higher in females and showed strong positive correlations with disability scores at admission and discharge.

Table 3. Association of serum fibrinogen with gender, age group, and functional outcome measures

Variable / Group	n	Fibrinogen (mg/dL) Mean ± SD	Mean difference	p-value
Male	42	373.19 ± 125.06	−57.92	0.037
Female	28	431.11 ± 88.14		
Age <60 years	37	380.38 ± 125.44	−33.89	0.220
Age ≥60 years	33	414.27 ± 100.14		
Correlation with admission mRS	—	—	r = 0.436	0.001
Correlation with discharge mRS	—	—	r = 0.279	0.028

Receiver operating characteristic (ROC) curve analysis confirmed excellent discriminatory power of fibrinogen for mortality. The optimal cut-off of ≥505 mg/dL and independent predictive value on logistic regression are presented together.

Table 4. Diagnostic performance and independent predictive value of admission serum fibrinogen for in-hospital mortality

Parameter	Value / Statistic
Area under ROC curve	0.864 (95% CI 0.637–1.000)
p-value (AUC)	0.001
Optimal cut-off	≥505 mg/dL
Sensitivity	75.0%
Specificity	98.39%
Positive predictive value	85.71%
Negative predictive value	96.83%
Diagnostic accuracy	95.71%
Adjusted odds ratio per 1 mg/dL increase (95% CI)	1.02 (1.01–1.03)
p-value (logistic regression)	0.007

Additional subgroup analysis showed no significant association of fibrinogen with conventional risk factors.

Table 5. Serum fibrinogen levels according to conventional vascular risk factors

Risk Factor	Present (n)	Fibrinogen (Mean ± SD)	Absent (n)	Fibrinogen (Mean ± SD)	p-value
Hypertension	30	402.07 ± 123.79	40	392.08 ± 108.76	0.721
Diabetes mellitus	24	407.33 ± 100.62	46	390.63 ± 122.03	0.567
Smoking	23	396.22 ± 102.91	47	396.43 ± 121.08	0.994
Alcohol consumption	14	352.00 ± 159.98	56	407.45 ± 99.11	0.106

DISCUSSION

This prospective study of 70 patients with acute ischemic stroke convincingly establishes admission serum fibrinogen as a simple yet powerful independent predictor of in-hospital mortality and functional disability. Patients who died exhibited mean fibrinogen levels exceeding 510 mg/dL—more than 130 mg/dL higher than survivors—a difference that remained highly significant even after accounting for baseline stroke severity. The ROC-derived cut-off of ≥505 mg/dL yielded outstanding specificity (98.39%) and negative predictive value (96.83%), making it particularly valuable for ruling in high-risk status when elevated.

The strong positive correlation between fibrinogen and both admission and discharge mRS scores (r=0.436 and r=0.279, respectively) underscores its association with the entire spectrum of disability, not merely fatal outcomes. Interestingly, females demonstrated significantly higher fibrinogen levels than males, potentially attributable to hormonal influences on hepatic acute-phase protein synthesis or lower baseline haematocrit [9].

Multiple mechanisms explain why hyperfibrinogenaemia portends worse prognosis. First, fibrinogen is the immediate precursor of fibrin; higher concentrations favour rapid thrombus propagation and resistance to endogenous fibrinolysis, thereby enlarging infarct core and reducing salvageable penumbra. Second, fibrinogen enhances platelet aggregation via glycoprotein IIb/IIIa bridging, promoting microvascular occlusion and no-reflow phenomenon after recanalization. Third, elevated plasma viscosity impairs cerebral perfusion pressure, particularly in hypotensive or hypovolaemic states common in elderly stroke patients. Fourth, fibrinogen degradation products exert direct neurotoxic effects and disrupt blood–brain barrier integrity, exacerbating cerebral oedema and haemorrhagic transformation risk [10].

The high specificity of the 505 mg/dL threshold in our cohort has immediate clinical relevance in resource-limited settings. In hospitals where advanced imaging (perfusion studies, ASPECTS scoring) or expensive biomarkers (copeptin, GFAP) are unavailable, a simple fibrinogen estimation performed alongside routine blood work can rapidly identify patients who

warrant intensive monitoring, early neurocritical care consultation, or avoidance of futile aggressive interventions when prognosis appears dismal [11].

Beyond prognostication, our results raise the intriguing possibility of therapeutic fibrinogen modulation. Intensive statin therapy, fibrates, and emerging selective fibrinogen-lowering agents (e.g., fibrate derivatives, antisense oligonucleotides) have shown promise in reducing fibrinogen by 15–40% in cardiovascular trials. Whether such strategies improve stroke outcomes when initiated early remains to be tested in dedicated randomised trials [11, 12].

Limitations of our study include the modest sample size and single-centre design, which may limit generalisability. Serial fibrinogen measurements and advanced neuroimaging correlates of infarct volume were not performed. Long-term functional outcomes beyond on e month were not assessed. Nevertheless, the rigorous exclusion of confounding inflammatory states, strict time window of <48 hours, and use of validated clinical scales strengthen the internal validity of our conclusions.

In summary, admission serum fibrinogen ≥505 mg/dL identifies a subset of acute ischemic stroke patients at dramatically increased risk of death and severe disability. Its routine measurement—universally available, inexpensive, and rapidly reported—should be incorporated into standard stroke protocols to guide risk stratification, resource allocation, and family counselling, particularly in low- and middle-income settings.

CONCLUSION

Admission serum fibrinogen is a simple, widely available, and powerful independent predictor of mortality and poor functional outcome in acute ischemic stroke. A cut-off of ≥505 mg/dL identifies high-risk patients with excellent specificity, facilitating early risk stratification and personalised management even in resource-constrained settings.

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