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The Role of Serum Fibrinogen as a Prognostic Biomarker in Patients of Acute Cerebrovascular Accident

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ABSTRACT

In India, stroke incidence is rising due to modifiable risk factors, making it a leading cause of premature death and disability. Fibrinogen is a crucial inflammatory marker involved in the pathophysiology of various cardiovascular events, including stroke. Its levels tend to increase following an acute stroke, serving as an independent risk factor for recurrence and predicting adverse cardiovascular outcomes. To evaluate the relationship between serum fibrinogen levels and stroke severity. This prospective, observational study involved 100 patients with clinically diagnosed stroke admitted to a tertiary care hospital, Gujarat. Exclusion criteria included malignancy, trauma, transient ischemic attacks (TIA) and chronic hepatic or renal diseases. Data collection involved demographic information, clinical examination and relevant investigations, including serum fibrinogen levels. For all patients, the National Institutes of Health Stroke Scale (NIHSS), Intra cerebral Hemorrhage (ICH) score and Modified Rankin Scale (MRS) were calculated. The mean age of participants was 62.23±12.16 years, with a predominance of males (70%) and ischemic strokes (75%). Common risk factors included hypertension (56%) and diabetes (43%). The mean plasma fibrinogen level among stroke patients was 531.1±200.65 mg/dL. Patients with hypertension, diabetes, obesity and smoking habits had significantly elevated fibrinogen levels compared to their counterparts. Elevated fibrinogen levels correlated strongly with increased stroke severity [NIHSS: $r=0.75$, $p<0.001$; MRS: $r=0.82$, $p<0.001$]. The findings highlight the significant association between elevated fibrinogen levels and stroke severity, particularly in older patients and those with comorbid conditions. This strong correlation supports the potential role of fibrinogen as a valuable biomarker for assessing clinical outcomes in stroke patients, emphasizing the need for routine monitoring in clinical practice.

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Key Words
Fibrinogen, prognostic biomarker, risk factors, severity, stroke

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INTRODUCTION

Stroke is a major global health concern, contributing to high mortality, adult disability and substantial socioeconomic burdens worldwide[1,2]. It is characterized by impaired blood flow leading to brain damage, with approximately 80% of strokes being ischemic and 20% hemorrhagic[3]. Globally, stroke is the second leading cause of mortality and the third leading cause of disability[4]. In India, stroke prevalence varies between 44.29-559 per 100,000 persons, with an annual incidence of 105-152 per lakh. The increasing prevalence of modifiable risk factors has made stroke a significant cause of premature death and disability in the country[5]. Atherosclerosis plays a crucial role in the pathogenesis of stroke and cardiovascular events, with hypertension being the most significant risk factor. Individuals with hypertension have a three to four times higher risk of stroke[6]. Non-modifiable risk factors include age, sex and race/ethnicity, while modifiable factors such as hypertension, smoking, poor diet, physical inactivity and elevated fibrinogen levels contribute to stroke risk[4]. Stroke outcomes are affected by age, sex, stroke severity and comorbidities, but predicting outcomes remains complex[7,8]. There are many inflammatory markers whose levels tend to increase after an acute attack of stroke[9]. Fibrinogen, a key inflammatory marker, rises after ischemic stroke and myocardial infarction. It is an independent risk factor for stroke recurrence and predicts future stroke events and adverse cardiovascular outcomes. Therefore, early fibrinogen measurement and management are essential in stroke patients[10,11]. Fibrinogen promotes inflammation, atherogenesis and thrombogenesis by infiltrating vessel walls, increasing blood viscosity and enhancing platelet aggregation and thrombus formation. It binds to ICAM-1 on endothelial cells, mediating platelet adhesion and contributing to endothelial damage. These effects are compounded by decreased fibrinolytic activity and plasminogen levels in cardiovascular disease[12,13]. Fibrinogen also facilitates platelet crosslinking via the glycoprotein IIb-IIIa receptor, a key target of receptor inhibitors. Measuring fibrinogen levels may offer greater specificity for vascular disease than other acute-phase reactants like C-reactive protein[14]. Despite numerous studies establishing the association between elevated fibrinogen levels and poor stroke outcomes, the diagnostic reliability of fibrinogen assessment remains debated. This study aims to evaluate the prognostic significance of serum fibrinogen in relation to stroke severity.

MATERIALS AND METHODS

Study Design: A prospective, observational study.

Study Population: A total of 100 patients, clinically diagnosed with stroke and admitted to the Department of Medicine at a tertiary care hospital, Gujarat, were included based on the inclusion and exclusion criteria.

Inclusion Criteria:

- Patients willing to provide informed consent.
- Patients with a confirmed diagnosis of stroke.
- Age >18 years.

Exclusion Criteria:

- Patients with a diagnosis of malignancy, trauma, or subdural/epidural hemorrhages.
- Patients whose symptoms resolved within 24 hours of admission (i.e., TIA).
- Patients with pre-existing chronic hepatic or renal diseases.

Methodology: Ethical approval was obtained from the Institutional Review Board (IRB) and written informed consent was obtained from all patients. Demographic data such as name, age, sex, OPD/IPD number, address, medical history and clinical examination findings were documented using a pre-designed proforma. The patient history focused on stroke-related symptoms and associated risk factors. A detailed clinical examination was performed to identify neurological deficits and the National Institutes of Health Stroke Scale (NIHSS) and Intracerebral Hemorrhage (ICH) score were calculated for all patients. Modified Rankin Scale (MRS) was used at the time of admission to assess the degree of disability in stroke patients. The relevant investigations included hemoglobin levels, total white blood cell count, routine urine analysis, blood glucose, blood urea, serum creatinine, serum lipid profile and serum fibrinogen. Electrocardiography (ECG), chest X-ray and brain imaging (CT scan/MRI) were performed for all patients, while echocardiography was done as needed.

Statistical Analysis: Data were collected using a pre-designed proforma and entered into Microsoft Excel 2016, with analysis conducted in Epi Info version 7.1.4.0. Descriptive statistics (mean±SD) summarized continuous variables, while categorical variables were expressed as frequencies and percentages. Comparisons of fibrinogen levels between two groups were made using an independent t-test, and those among three groups were analyzed with ANOVA. Correlation analysis assessed the relationship between fibrinogen levels and stroke severity scores (NIHSS, ICH, and MRS). A p-value of<0.05 was deemed statistically significant.

RESULTS AND DISCUSSIONS

Stroke was most common in the 61-70 age group (34%), followed by those over 70 (25%), with a mean age of 62.23±12.16 years. Most patients were male

(70%) and ischemic stroke (75%) was more prevalent than hemorrhagic stroke (25%). Hypertension was the leading risk factor (56%), followed by diabetes (43%), smoking (34%) and alcohol use (30%). Elevated cholesterol (>200mg/dL) was found in 54% of patients, high triglycerides in 52% and low HDL (<40mg/dL) in 60%. HbA1c was elevated (>6.5%) in 57%. Hemiparesis was the most common symptom (52%), with stroke severity moderate to severe in 23% of patients. NIHSS scores indicated 29% had mild strokes, 24% moderate, 23% moderate to severe and 24% severe. GCS scores showed 58% had mild impairment, 25% moderate and 17% severe. Most patients (95%) were discharged, while 5% died (Table 1).

Table 1: Characteristic of Patients with Acute Cerebrovascular Accident (CVA)

Age (Mean±SD, yeras)	**62.23±12.16**	
Gender		
Male	70	70.0
Female	30	30.0
Type of stroke		
Ischemic	75	75.0
Haemorrhagic	25	25.0
Risk factors		
Hypertension	56	56.0
DM	43	43.0
IHD	12	12.0
Obesity	40	40.0
Smoking	34	34.0
Alcohol	30	30.0
None	9	9.0
Clinical features		
Hemiparesis	52	52.0
Vertigo ,vomiting	18	18.0
Slurring of speech	16	16.0
Altered sensorium	14	14.0
Convulsion	8	8.0
Loss of consciousness	5	5.0
More than one symptoms 1	13	13.0
Lipid profile		
Cholesterol (mg/dL)		
≥200	54	54.0
<200	46	46.0
TG (mg/dL)		
≥150	52	52.0
<150		
HDL (mg/dL)		
≥40	40	40.0
<40	60	60.0
HbA1c (%)		
≥6.5	57	57.0
<6.5	43	43.0
MRS score		
1	15	15.0
2	17	17.0
3	20	20.0
4	23	23.0
5	20	20.0
6	5	5.0
NIHSS		
Mild (1-4)	29	29.0
Moderate (5-15)	24	24.0
Moderate to severe (16-20)	23	23.0
Severe (21-42)	24	24.0
GCS score		
13-15	58	58.0
8-12	25	25.0
3-8	17	17.0
ICH score		
<3	20	20.0
≥3	5	5.0
Outcome		
Discharge	95	95.0
Death	5	5.0

Mean plasma fibrinogen in stroke patients was 531.1±200.65. Plasma fibrinogen levels varied significantly across age groups, increasing from 351.58±115.02mg/dL in patients under 50-672.05±174.31mg/dL in those aged 61-70, then decreasing in patients over 70 (428.20±152.61mg/dL) (p=0.01). No significant gender differences were observed. Fibrinogen levels were higher in hemorrhagic stroke patients (612.6±150.45mg/dL) compared to ischemic stroke patients (503.93±208.63mg/dL) (p=0.01). Hypertensive, diabetic, obese, and smoking patients had significantly elevated fibrinogen levels compared to their counterparts (p<0.001). Higher levels were also associated with cholesterol >200mg/dL, triglycerides ≥150mg/dL and lower HDL (p<0.001). Fibrinogen levels increased progressively with worsening modified Rankin Scale (MRS) and National Institutes of Health Stroke Scale (NIHSS) scores. Patients with an MRS score of 6 had the highest fibrinogen level (910.80±99.09mg/dL), while those with an NIHSS score of 21-42 had a mean level of 772.50±144.85mg/dL. Similarly, patients with lower Glasgow Coma Scale (GCS) scores (3-8) had elevated fibrinogen levels (788.41±156.70mg/dL) (p=0.001). Mean fibrinogen level was significantly high in non survived patients (783.6±155.9) compared to survived patients (517.8±194.4, p-0.001) (Table 2).

There was a strong positive correlation between fibrinogen levels and NIHSS score (r=0.75, p<0.001) as well as MRS score (r=0.82, p<0.001). A significant negative correlation was found between fibrinogen levels and GCS (r=-0.76, p<0.001). Additionally, a moderate positive correlation was observed between fibrinogen levels and cholesterol (r=0.37, p<0.001) and triglycerides (r=0.51, p<0.001), while a weak negative correlation was noted with HDL levels (r=-0.32, p<0.001) (Table 3).

Age and Gender: In our study, stroke was most prevalent among individuals aged 61-70 years, with a mean age of 62.23±12.16 years. Plasma fibrinogen levels significantly increased with age, reaching 672.05±174.31mg/dL in the 61-70 age group (p=0.01). This trend aligns with findings from Keerthi[15], who reported a mean age of 61.56 years and Dube[16], with a mean age of 58.63 years, both noting higher fibrinogen levels in older populations. Estrogen is thought to protect females against atherosclerosis and stroke, resulting in a 1.25 times higher stroke incidence in males[15]. In our study, 70% of stroke cases were male, yet fibrinogen levels did not differ significantly between gender (561.2±206.38mg/dL in females vs. 518.2±198.24mg/dL in males). Conversely, Keerthi[15] reported higher fibrinogen levels in males (393.3

Table 2: Association of Fibrinogen Levels with Characteristics in Stroke Patients

Characteristics	Number of patients	Mean fibrinogen level	p-value
Age			
<50	17	351.58±115.02	0.01
51-60	24	565.75±173.87	
61-70	34	672.05±174.31	
>70	25	428.20±152.61	
Gender			
Male	70	518.2±198.24	0.32
Female	30	561.2±206.38	
Type of stroke			
Ischemic	75	503.93±208.63	0.01
Haemorrhagic	25	612.6±150.45	
Blood pressure			
Hypertension	56	625.96±157.82	< 0.001
Normotensive	44	410.36±184.92	
DM			
Present	43	655.67±166.52	< 0.001
Absent	57	437.12±171.67	
IHD			
Present	12	474.18±164.01	< 0.001
Absent	88	643.42±154.52	
Body weight			
Obese (BMI > 30)	40	627.32±183.89	< 0.001
Non obese (BMI < 30)	60	466.95±186.38	
Smoking			
Present	34	714.52±165.49	0.001
Absent	66	436.60±144.04	
Alcohol use			
Present	30	432.63±184.16	< 0.001
Absent	70	573.30±193.61	
Lipid profile			
Cholesterol (mg/dL)			
≥200	54	634.55±178.16	< 0.001
<200	46	409.65±152.52	
TG (mg/dL)			
≥150	52	641.65±185.42	< 0.001
< 150	48	411.33±139.00	
HDL (mg/dL)			
≥40	40	449.25±167.95	< 0.001
< 40	60	585.66±203.31	
HbA1c (%)			
> 6.5	57	437.12±171.61	< 0.001
< 6.5	43	655.67±166.52	
MRS score			
1	15	301.00±136.01	0.001
2	17	388.88±53.25	
3	20	470.55±88.83	
4	23	593.04±139.99	
5	20	718.95±132.73	
6	5	910.80±99.09	
NIHSS			
Mild (1-4)	29	380.41±121.81	0.001
Moderate (5-15)	24	431.79±139.54	
Moderate to severe (16-20)	23	572.82±117.92	
Severe (21-42)	24	772.50±144.85	
GCS score			
13-15	58	411.60±122.33	0.001
8-12	25	633.36±147.83	
3-8	17	788.41±156.70	
ICH score			
< 3	20	588.0±133.64	0.001
≥3	5	711.0±189.35	
Outcome			
Non survived		783.6±155.9	0.001
Survived		517.8±194.4	

Table 3: Correlation Between Fibrinogen Level and Other Variables

Variables	Pearson Correlation (r)	p-value
NIHSS	0.75	< 0.001
MRS	0.82	< 0.001
GCS	-0.76	< 0.001
Cholesterol (mg/dl)	0.37	< 0.001
TG (mg/dl)	0.51	< 0.001
HDL (mg/dl)	-0.32	< 0.001

mg/dL) compared to females (323.18mg/dL), a finding supported by Dube[16] and A.R. Kumar[17].

Type of Stroke: In our study, ischemic stroke was more prevalent, accounting for 75% of cases, while hemorrhagic stroke constituted 25%. This is consistent with findings by Anderson[18], who reported 89.9% ischemic and 10.1% haemorrhagic strokes . Similarly, Keerthi[15] observed ischemic stroke in 68% of patients and hemorrhagic stroke in 32%.

Clinical Presentation: Clinically, hemiparesis was the most common presentation in 52% of stroke patients, followed by slurring of speech (22%). These findings are consistent with Vaidya[19], who reported hemiparesis in 48% and slurred speech in 25% of cases, confirming that hemiparesis remains the most common stroke symptom.

Risk Factor: Tobacco smoke increases the risk of stroke and heart disease through various mechanisms, including carboxyhemoglobinemia, increased platelet aggregation, elevated fibrinogen levels, reduced HDL cholesterol and the direct toxic effects of compounds like 1,3-butadiene, which accelerates atherosclerosis. Alcohol consumption is also an independent risk factor for both ischemic and hemorrhagic strokes. Stroke incidence increases significantly with rising blood pressure, with approximately 40% of strokes attributed to systolic blood pressure exceeding 140 mm Hg. Additionally, dyslipidemia, particularly elevated total and LDL cholesterol, plays a significant role in stroke development[15]. In our study, hypertension emerged as the most common risk factor (52%), followed by diabetes (43%), smoking (34%) and alcohol consumption (30%). Similarly, Appuraj[20] reported that 44% of patients were hypertensive, 30% had diabetes, 46% were smokers, 28% consumed alcohol, 50% were obese and 60% had hypercholesterolemia. In contrast, Keerthi[15] identified smoking as the most prevalent risk factor (64%), followed by hypertension (62%) and alcoholism (54%), with cardiovascular disease being the least common (10%). In our study, patients with hypertension, diabetes, obesity and smoking habits had significantly elevated fibrinogen levels compared to their counterparts ($p<0.001$). Higher fibrinogen levels were also observed in patients with cholesterol >200mg/dL, triglycerides ≥150mg/dL and lower HDL ($p<0.001$). These findings are in line with Appuraj[20], who also demonstrated a significant association between elevated fibrinogen levels and the presence of hypertension, diabetes, smoking and hypercholesterolemia. Keerthi[15] also found that fibrinogen levels were elevated among smokers, alcoholics, hypertensive and diabetic patients.

Furthermore, Dube[16] identified a positive correlation between fibrinogen and total cholesterol, LDL-cholesterol and triglycerides, though not with HDL levels.

Severity of Stroke: In the present study, fibrinogen levels demonstrated a progressive increase with worsening NIHSS and MRS scores. Patients with an MRS score of 6 exhibited the highest fibrinogen level (910.80±99.09mg/dL), while those with NIHSS scores between 21-42 had a mean fibrinogen level of 772.50±144.85mg/dL. Similarly, patients with lower GCS scores (3-8) showed elevated fibrinogen levels (788.41±156.70 mg/dL), with statistical significance (p=0.001). Strong positive correlations were identified between fibrinogen levels and both NIHSS (r=0.75, p<0.001) and MRS scores (r=0.82, p<0.001), alongside a significant negative correlation with GCS (r=-0.76, p<0.001). These findings are consistent with those of Appuraj[20], who reported that fibrinogen levels increased with higher NIHSS scores, ranging from 312mg/dL in patients with mild impairment (NIHSS score <5) to 771.18mg/dL in those with very severe impairment (NIHSS score ≥13). Additionally, Appuraj[20] found that patients with an MRS score of 1 had a mean fibrinogen level of 441.43mg/dL, while those with higher disability levels (MRS scores of 3, 4, and 5) exhibited progressively higher fibrinogen levels (683.64mg/dL, 734.44mg/dL and 764.44mg/dL, respectively). Dube[16] further corroborated these findings, noting significant increases in plasma fibrinogen levels across varying NIHSS scores (316.6 mg/dL for scores 0-6, 340.5 mg/dL for scores 7-12 and 358.8mg/dL for scores ≥13), with a positive correlation noted on day 1 (r=0.43). Overall, these studies reinforce the potential of fibrinogen as a marker for assessing stroke severity and associated outcomes.

Mortality Rate: In the present study, mortality rate was 5%. Non-survivors exhibited significantly higher mean fibrinogen levels (783.6±155.9mg/dL) compared to survivors (517.8±194.4mg/dL, p<0.001). This aligns with findings from Patel[21], who reported mean fibrinogen levels of 584.34±8.21mg/dL in non survivors deceased patients versus 510.23±9.32mg/dL in survivors (p=0.04). Additionally, Keerthi[15] noted 14% mortality rate and higher fibrinogen level among non survivors. These results highlight the significant association between elevated fibrinogen levels and increased mortality in stroke patients.

CONCLUSION

The majority of stroke patients were male, with ischemic stroke identified as the predominant type. Key predisposing factors included hypertension, diabetes mellitus and dyslipidemia. A significant proportion of patients presented with moderate to severe stroke severity. Fibrinogen levels were notably elevated in older age groups, those with hemorrhagic stroke and individuals with risk factors such as hypertension, uncontrolled diabetes, obesity, smoking and dyslipidemia. The strong association of fibrinogen with stroke severity and mortality underscores its potential as a valuable biomarker for assessing clinical outcomes, highlighting the importance of monitoring fibrinogen levels in stroke patients.

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