Fibrinogen as a Predictor of Early Neurological Deterioration in Acute Ischemic Stroke – Evidence From the Indian Population

Vishal Mehta[1] ⓘ, Akhya Sharma[2], Divya Jyoti[1], Rathod Prabhakar[1], Ritesh Kumar[1], Rishi T. Guria[1] and Chandra B. Sharma[1]

[1]Department of Medicine, Rajendra Institute of Medical Sciences, Ranchi, India. [2]Department of Internal Medicine, Loyola Medicine-MacNeal Hospital, Berwyn, IL, USA.

ABSTRACT

BACKGROUND: Early neurological deterioration (END) is a common occurrence in ischemic stroke and contributes significantly to poor outcomes. Although multiple factors that predict END have already been identified, the role of fibrinogen – a key component of the coagulation pathway, is controversial.

OBJECTIVE: To assess the role of fibrinogen in predicting END and poor hospital outcome in patients with acute ischemic stroke.

DESIGN: Single-centre prospective observational study.

METHODS: 141 patients with acute ischemic stroke were analyzed in this prospective observational study from a single tertiary-care hospital in East India. END was defined as a worsening of ≥2 points on the National Institutes of Health Stroke Scale (NIHSS) within 7 days of admission. A score of 3-5 on the Modified Rankin Scale (mRS), a stroke recurrence event or death during hospital stay was considered poor hospital outcome. We performed univariate analysis using age, sex, body-mass index (BMI), hypertension, diabetes, NIHSS scores, stroke etiology, blood glucose and lipid parameters and plasma fibrinogen to develop a logistic regression model to establish the independent predictors of END and poor outcome.

RESULTS: Age (Odds Ratio (OR) 1.034 [95% CI 1.001-1.069], $P = .046$), NIHSS score at admission (OR 1.152 [95% CI 1.070-1.240], $P < .001$) and fibrinogen (OR 1.011 [95%CI 1.006-1.015], $P < .001$) were independent predictors of END in patients with acute ischemic stroke. Factors independently associated with poor outcome were NIHSS score at admission (OR 1.257 [95% CI 1.150-1.357], $P < .001$), fasting plasma glucose (OR 1.007 [95% CI 1.001-1.013], $P = .020$), and fibrinogen [OR 1.004 [95% CI 1.000-1.007], $P = .038$).

CONCLUSION: The significant role of fibrinogen in determining neurological worsening and subsequent poor outcomes in patients with acute ischemic stroke may help in early prognostication and guided therapeutic interventions.

KEYWORDS: early neurological deterioration, acute ischemic stroke, fibrinogen, outcome, national institutes of health stroke scale

Introduction

Stroke is defined as an abrupt onset of a neurological deficit that is attributable to a focal vascular cause. It is the second leading cause of death worldwide. Worldwide, approximately 80% of strokes are attributable to ischemic cerebral infarction and 20% are attributable to the hemorrhagic variety. According to the Global Burden of Disease Study 2019,[1] stroke incidence has increased by 70% from 1990 to 2019, while stroke prevalence has increased by 85.0% and stroke deaths by 43%. Despite a fall in stroke incidence and mortality in developed countries, developing countries continue to demonstrate an increasing trend. The consequences of stroke related disability and death are significant for both society and individuals. Therefore, all measures capable of decreasing disability are extremely important.

Ischemic stroke is caused by interruption of blood flow to a part of the brain and is the most common variety of stroke worldwide. The Trial of Org 10 172 in Acute Stroke Treatment (TOAST) classifies ischemic stroke into five subtypes: 1) large-artery atherosclerosis, 2) cardio-embolism, 3) small-vessel

occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology.[2] Early Neurological Deterioration (END) is a common occurrence in ischemic stroke and is associated with an increased risk of functional disability and mortality.[3,4] Although various factors have been identified to predict the occurrence of END in ischemic stroke such as age, sex, diabetes, initial stroke severity, stroke subtype and radiological parameters, similar data for the Indian population is lacking.

Patients with ischemic stroke have a significantly increased mean fibrinogen level as compared to patients with only risk factors for stroke.[5] Fibrinogen despite having been found to be associated with increased ischemic stroke risk,[6,7] minor stroke recurrence,[8] and poor outcome in patients with ischemic stroke,[9,10] has not yet been shown to be associated with END, except in diabetics.[11] Despite evidence from a large number of studies establishing the association between fibrinogen and poor outcome in ischemic stroke, the diagnostic role and reliability of fibrinogen assessment remains a matter of debate. Because fibrinogen is also associated with other known prognostic factors in stroke, the role of fibrinogen may be attenuated by adjusting for these confounding factors. There is also no evidence to prove that fibrinogen lowering therapy necessarily improves prognosis. This study aimed to determine predictors of END and poor outcome in an Indian cohort with acute ischemic stroke, focusing on the role of fibrinogen.

Material and Methods

Target Sample Size

Sample size was calculated according to parameters reported by Lee et al[11] using IBM Sample Power 3.0. In this study mean fibrinogen was 357 ± 130 mg/dL and odds ratio for END group was 1.2 at 450 mg/dL. Using 5% alpha error and 80% power, for a cohort study using logistic regression, the estimated sample size was 316.

Study Design and Population

In this prospective observational study, 177 patients diagnosed with acute ischemic stroke, meeting our inclusion criteria were consecutively enrolled from a single tertiary-care hospital in East India between 1st January 2020 and 30th June 2021. 36 patients had to be excluded due to loss to follow-up and incomplete clinical data. The inclusion and exclusion criteria for participants are listed below:

Inclusion criteria:

1. Patients aged 18 years and above.

2. Patients with radiological evidence of ischemic stroke either on CT or MR imaging of the brain.

3. Patients with first ever ischemic stroke admitted within 7 days of onset of symptoms.

Exclusion criteria:

1. History of other neurological disease such as transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhage, or brain tumors.

2. History of other concurrent medical illness such as renal or hepatic failure, malignant disease, or coronary artery disease.

3. Incomplete clinical data.

The flowchart of the study is shown in Figure 1.

Data Acquisition

Baseline data including age, gender, and body mass index were obtained for all patients. The presence of risk factors such as hypertension and diabetes mellitus were taken into consideration in the analysis. We defined the presence of hypertension as either a history of previously diagnosed hypertension or newly diagnosed hypertension (Systolic BP ≥140 mmHg or Diastolic BP ≥90 mmHg after repeated examinations) as per 2018 European Society of Cardiology/European Society of Hypertension guidelines.[12] Diabetes was defined as a history of previously diagnosed diabetes or newly diagnosed diabetes (Fasting Plasma Glucose ≥126 mg/dL or glycosylated hemoglobin (HbA1c) ≥ 6.5%) according to the 2019 American Diabetes Association guidelines.[13]

At admission a detailed clinical examination was performed and a baseline NIHSS score was calculated. An imaging study (CT or MR brain) was performed to establish the diagnosis. NIHSS scores were monitored daily to check for END, which was defined as an increase in the NIHSS score by ≥ 2 points within 7 days of admission. Lab data including fasting plasma glucose, HbA1c, plasma fibrinogen, serum total cholesterol, triglycerides, LDL and HDL-C were obtained at admission. Fibrinogen concentration in plasma was measured using the Clauss fibrinogen assay. The TOAST classification was used to categorize different stroke subtypes and outcome at discharge was determined using the mRS. We defined poor outcome as an mRS score of 3 - 5 at discharge, the presence a recurrent stroke event during hospitalization or death. Each participant was allotted a progressive identification number to maintain anonymity. Participant selection was performed by individuals blinded to type of ischemic stroke and pre-existing patient conditions that could have confounded data acquisition.

Statistical Analysis

Statistical analysis was performed using the SPSS software, version 26.0 (SPSS Inc., Chicago, IL). Continuous variables were reported as mean ± standard deviation and categorical variables as counts and percentages. A univariate analysis was performed for both END and poor outcome, using the
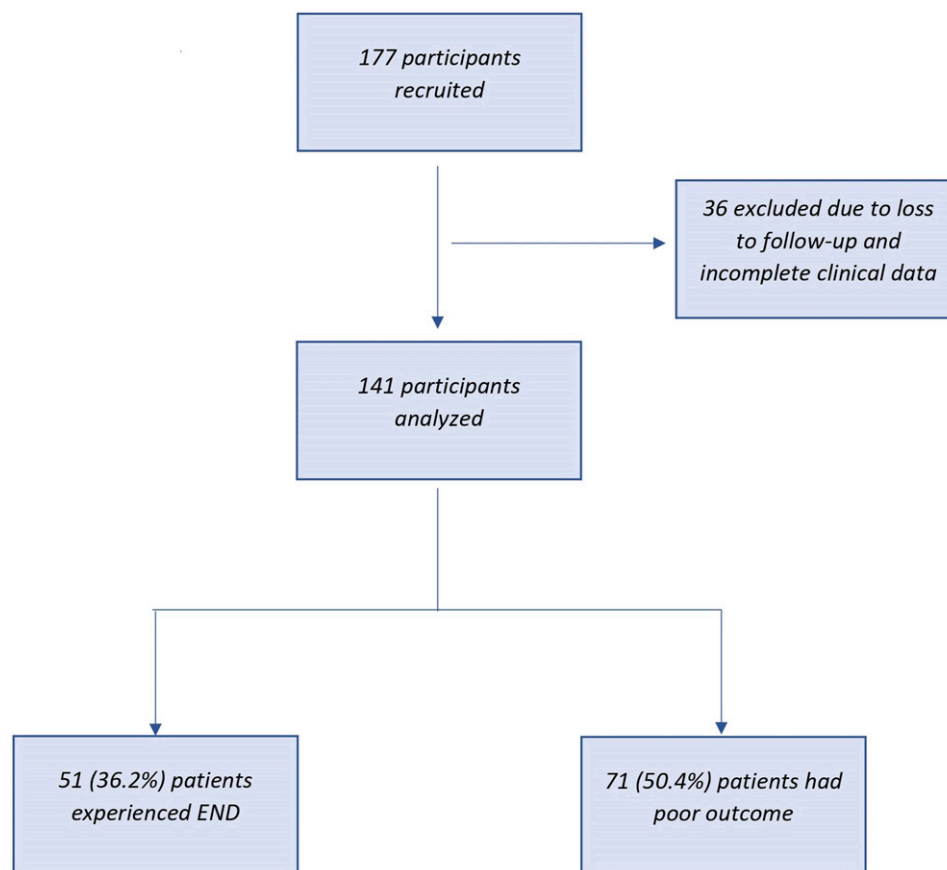
Figure 1. Flowchart of the study.

independent samples T test, Mann-Whitney U test and Kruskal-Wallis test for continuous variables, and chi-square test and fisher's exact test for categorical variables as appropriate. Then, logistic regression models were developed to determine independent predictors of END and poor outcome. Variables with a *P* value ≤.05 by univariate analysis were considered for inclusion in logistic regression analysis. Finally, adjusted odds ratio (ORs) and 95% confidence intervals (CIs) were calculated to estimate risk factors for END and poor outcome. A *P* value ≤.05 was considered significant.

Results

Patient Characteristics

Out of the 141 patients analyzed, 51 (36.2%) experienced END and 71 (50.4%) had a poor outcome. The mean age of the population was 59.9 ± 14.9 years. Patients in the END group were significantly older (63.9 ± 14.2, *P* = .017). Older patients were also more likely to have a poorer outcome, however this difference was statistically not significant (*P* = .079). Out of the 141 research participants, 84 (59.6%) were and male and 57 (40.4%) were female. 30/84 (35.7%) males experienced END, while 21/57 (36.8%) females experienced END. The poor outcome group included 44 males (52.3% of all males) and 26 females (50.9% of all females). Patients with END were more

likely to be diabetic than patients without END (24/51 and 27/90 respectively, P = .047).

We used the TOAST classification to categorize ischemic stroke into different subtypes. Large-vessel atherosclerosis was the most common stroke subtype accounting for 48.2% (69/141) of all ischemic strokes. This was followed by small vessel occlusion (17.7%, 25/141), cardio-embolic stroke (14.2%, 20/141), stroke of undetermined etiology (14.2%, 20/141) and stroke of other determined etiology (5.7%, 8/141). There was no significant correlation between stroke subtype and development of END (*P* = .285), however it was associated with poor outcome (*P* = .019).

Analysis of END

A univariate analysis was performed in which age, diabetes, NIHSS score at admission, fasting plasma glucose (FPG), HbA1c, and fibrinogen were found to be factors associated with END (Table 1).

For multivariate analysis, we developed a logistic regression model, in which variables found to be significantly associated with END by univariate analysis (*P* < .05) were considered. The logistic regression model demonstrated that age (OR 1.034 [95% CI 1.001-1.069], *P* = .046), NIHSS score at admission (OR 1.152 [95% CI 1.070-1.240], *P* < .001) and fibrinogen (OR 1.011 [95% CI 1.006-1.015], *P* < .001) were independent predictors of END in patients with acute ischemic stroke (Table 2).

Table 1. Comparison Between END and Non-END Groups.

	END (N = 51)	NON-END (N = 90)	P VALUE
Age (years)	63.9 ± 14.2	57.7 ± 14.9	.017
Male sex	30 (58.8%)	54 (60%)	.892
BMI (kg/m^2)	21.1 ± 3.9	20.4 ± 3.2	.310
Hypertension	40 (78.4%)	60 (66.7%)	.177
Diabetes	24 (47.1%)	27 (30%)	.047
Initial NIHSS	13.4 ± 6.2	7.8 ± 6.2	<.001
Discharge NIHSS	17.8 ± 6.4	7.3 ± 6.0	<.001
TOAST			.285
Large-artery atherosclerosis	25	43	
Cardioembolic	6	14	
Small vessel disease	6	19	
Stroke of other determined etiology	3	5	
Stroke of undetermined etiology	11	9	
Fasting plasma glucose (mg/dL)	159 ± 86.4	117.5 ± 65.0	.002
HbA1c (%)	7.4 ± 2.9	6.0 ± 2.2	.002
Fibrinogen (mg/dL)	464.6 ± 121.1	315.1 ± 113.5	<.001
Lipid profile			
Total cholesterol (mg/dL)	166.5 ± 46.1	153.8 ± 42.8	.104
LDL (mg/dL)	95.8 ± 38.3	86.6 ± 35.3	.154
HDL (mg/dL)	41.3 ± 10.9	41.5 ± 10.8	.934
TG (mg/dL)	135.1 ± 79.4	122.3 ± 57.1	.270
CRP (mg/L)	7.06 ± 2.02	6.27 ± 2.74	.076

Table 2. A Logistic Regression Model Including Potential Factors Associated with END.

	ODDS RATIO [95% CI]	P VALUE
Age (years)	1.034 [1.001-1.069]	.046
Diabetes	1.878 [.393-2.975]	.430
Initial NIHSS	1.152 [1.070-1.240]	<.001
Fasting plasma glucose (mg/dL)	1.013 [.997-1.029]	.104
HbA1c (%)	.785 [.521-1.183]	.247
Fibrinogen (mg/dL)	1.011 [1.006-1.015]	<.001

Analysis of Outcome

Out of the 141 patients, 71 (50.4%) had a poor outcome, and 70 (49.6%) had a good outcome. The mean mRS score of patients with a poor outcome was 3.9 ± 1.2, and that of the good outcome group 1.7 ± .6. Stroke recurrence was observed in 7/141 (5%) patients. On univariate analysis (Table 3), factors associated with poor outcome included the presence of diabetes (P = .045), the NIHSS score at admission (P < .001), stroke subtype according to TOAST classification (P = .019), presence of END (P < .001), fasting

plasma glucose (P = .001), HbA1c (P < .001), and plasma fibrinogen (P < .001).

A logistic regression model, developed to determine independent predictors of END using the variables diabetes, NIHSS score at admission, TOAST classification, END, fasting plasma glucose, HbA1c, and fibrinogen, demonstrated that NIHSS score at admission (OR 1.257 [95% CI 1.150-1.357], P < .001), fasting plasma glucose (OR 1.007 [95%CI 1.001-1.013], P = .020), and fibrinogen [OR 1.004 [95% CI 1.000-1.007], P = .038) to be independent predictors of poor outcome (Table 4).

Discussion

In this study on 141 patients with acute ischemic stroke, 51 (36.2%) patients had END and 71 (50.4%) had a poor outcome. Among the different stroke subtypes large artery atherosclerosis was the most common type comprising 48.2% of total ischemic strokes, followed by small vessel occlusion (17.7%) and cardio-embolism (14.2%). While the incidence of atherosclerotic and cardio-embolic stroke is similar to those published previously, the incidence of small vessel disease was marginally lower in our cohort (17.7% vs 20 − 42%).[14] Patients

Table 3. Comparison Between Poor Outcome and Good Outcome Groups.

	POOR OUTCOME (N = 71)	GOOD OUTCOME	P VALUE (N = 70)
Age (years)	62.1 ± 14.8	57.7 ± 14.7	.790
Male sex	40 (56.3%)	44 (62.8%)	.494
BMI (kg/m^2)	20.9 ± 3.9	20.4 ± 3.2	.415
Hypertension	55 (77.5%)	45 (64.3%)	.062
Diabetes	31 (43.7%)	20 (28.5%)	.045
Initial NIHSS	13.3 ± 6.9	6.2 ± 4.3	<.001
Discharge NIHSS	16.3 ± 7.4	5.9 ± 4.2	<.001
TOAST			.019
Large-artery atherosclerosis	41	27	
Cardioembolic	7	13	
Small vessel disease	7	18	
Stroke of other determined etiology	3	5	
Stroke of undetermined etiology	13	7	
END	49 (69%)	2 (2.9%)	<.001
Fasting plasma glucose (mg/dL)	153 ± 86.9	1171.6 ± 55.9	.001
HbA1c (%)	7.3 ± 3.1	5.8 ± 1.6	<.001
Fibrinogen (mg/dL)	410.8 ± 144.2	314.1 ± 127.8	<.001
Lipid profile			
Total cholesterol (mg/dL)	161.1 ± 46.1	155.8 ± 42.6	.469
LDL (mg/dL)	91.8 ± 37.5	88.1 ± 35.7	.550
HDL (mg/dL)	41.0 ± 10.9	41.8 ± 10.7	.653
TG (mg/dL)	131.5 ± 69.7	122.3 ± 62.3	.413
CRP (mg/L)	6.86 ± 2.32	6.24 ± 2.69	.142

Table 4. A Logistic Regression Model Including Potential Factors Associated With Poor Outcome.

	ODDS RATIO [95% CI]	P VALUE
Diabetes	1.19 [.770-1.53]	.120
Initial NIHSS	1.257 [1.150-1.357]	<.001
TOAST		
Large-artery atherosclerosis (reference)		
Cardioembolic	.382 [.095-1.532]	.738
Small vessel disease	.256 [.068-.966]	.129
Stroke of other determined etiology	.178 [.026-1.207]	.198
Stroke of undetermined etiology	.637 [.139-2.918]	.710
Fasting plasma glucose (mg/dL)	1.007 [1.001-1.013]	.020
HbA1c (%)	.989 [.614-1.590]	.962
Fibrinogen (mg/dL)	1.004 [1.000-1.007]	.038

with cardioembolic stroke were significantly younger than patients with atherosclerosis (46.1 ± 17.8 and 63.4 ± 11.9 respectively, P < .001). This is likely due to the high prevalence of Rheumatic Heart Disease and Atrial Fibrillation amongst young patients in our population subset. Unusually, the NIHSS scores for cardioembolic stroke (7.7 ± 5.7) were lower than that for atherosclerotic stroke (10.0 ± 7.1). This may be due to an admission bias at our hospital. A limitation of

resources and hospital beds enforces selective admission of more severe and younger patients.

The number of patients who developed END are higher than those published in recent studies.[11,15,16] This is likely due to the fact that none of the patients presented to our emergency department within the window for intravenous thrombolysis, the unavailability of mechanical thrombectomy at our centre, and also because our definition of END encompasses a longer time period after symptom onset (7 days vs 2-3 days in other studies).[15,16] An Indian study,[16] found the incidence of END to be 22%, however the number of patients treated with intravenous thrombolysis or mechanical thrombectomy has not been mentioned. Therefore, timely access to affordable healthcare would be the first and most crucial step in reducing the incidence of END in developing countries.

Factors independently associated with development of END (Table 2) included age (OR 1.034 [95% CI 1.001-1.069], P = .046), NIHSS score at admission (OR 1.152 [95% CI 1.070-1.240], P < .001) and fibrinogen (OR 1.011 [95%CI 1.006-1.015], P < .001).

Age has been previously identified as a predictor for END by Park et al[17] and Gong et al.[18] Older patients have different risk factor profiles and mechanism of ischemic injury compared to younger individuals.[19] Hypertension and hyperlipidemia and atrial fibrillation are more common in older patients, and these are significant risk factors for ischemic stroke. In females, the neuroprotective effect as well as antiatherogenic effects of estrogens decline as the age. They are also more likely to receive less effective treatment.[19] Contraindications to endovascular procedures may also play a role in neurological worsening in such patients.

Patients with a higher NIHSS score at admission are also at an increased risk for END. This is consistent with findings of previous studies.[16,20,21] DeGraba et al,[22] reported that 65.9% patients with an NIHSS >7 had neurological worsening, compared with only 14.8% patients with an NIHSS ≤7. They also found 45.5% patients with an initial NIHSS score <7, to be normal at 48 hours (NIHSS score 0 or 1). In patients with non-lacunar strokes, 67.5% with an NIHSS >7 had significant infarct progression on CT or MR imaging. Other studies report a threshold NIHSS score of 12 above which there is an increased risk of END.[16,23] Our study emphasizes the value of initial NIHSS scores, in predicting patients at a higher risk of neurological worsening in the acute phase of ischemic stroke. Initial NIHSS score may also help to identify those patients who may benefit from more intensive inpatient treatment, because even though they are more likely to develop END, it has been reported that "major neurological improvement" occurs in 22-28% stroke patients within the first 48 hours.[24]

The association of fibrinogen with END in acute ischemic stroke has been reported previously, but only in patients with concurrent diabetes mellitus.[11] In our study patients with END had significantly higher fibrinogen levels (464.6 ± 121.1), compared to patients without END (315.1 ± 113.5, P < .001). Fibrinogen leads to formation of fibrin clots which is a part of the final common pathway of the coagulation cascade. It is also responsible for platelet aggregation by binding to glycoprotein IIb/IIIa receptors. Hyperfibrinogenemia is common in patients with diabetes, a strong risk factor for ischemic stroke. Prolonged glycation of fibrinogen, insulin resistance, and metabolic syndrome may contribute to this phenomenon. While, it has been established that fibrinogen plays a key role in atherogenesis and is involved in the pathogenesis of coronary artery disease, stroke, and peripheral arterial disease, its association with neurological worsening in patients with acute ischemic stroke has not been clearly established. Identification of patients with high fibrinogen levels may help us identify a group of patients who may require stronger antiplatelet therapy, or even fibrin-depleting agents. Reduced fibrin may reduce blood viscosity and help in clot dissolution restoring cerebral blood flow. Data from 8 trials, involving 5701 patients, fibrin-depleting agents such as ancrod and defibrase reduced mortality and disability rates, and also the number of stroke recurrences. However, one must keep in mind the fact that fibrin-depleting agents increase the risk of symptomatic intracranial hemorrhage by two-folds.[25]

NIHSS score at admission (OR 1.257 [95% CI 1.150 – 1.357], P < .001), fibrinogen [OR 1.004 [95% CI 1.000-1.007], P = .038), fasting plasma glucose (OR 1.007 [95%CI 1.001-1.013], P = .020), and were independent predictors of poor outcome in our study (Table 4). It has been established that stroke severity is the most important predictor of functional outcome in ischemic stroke,[26-28] and we wish to re-emphasize this fact. The mean NIHSS score in the poor outcome group was 13.3 ± 6.9, and that in the good outcome group was 6.2 ± 4.3. It is important to look for signs of END in these patients, especially as this would also prevent subsequent poor outcome in them. Fasting plasma glucose was also an independent risk factor for poor functional outcomes, similar to previous studies. Xue et al,[29] found fasting plasma glucose to be indicative of a poor functional outcome at 3-months following ischemic stroke, in patients without a prior history of diabetes. A study from China also reported unfavorable outcomes and increased mortality in ischemic stroke patients with high fasting plasma glucose.[30] The role of high fasting glucose levels in determining stroke outcome is incompletely understood. It is hypothesized that high glucose may offset the balance between coagulation and fibrinolytic pathways, leading to impaired recanalization.

Further, impaired nitric oxide mediated vasodilation may reduce cerebral blood flow, and increased oxidative stress disrupts the blood-brain barrier, promoting inflammatory reactions and eventual reperfusion injury.

Hyperfibrinogenemia has been associated with increased stroke severity.[31] Because stroke severity is strongly associated with poor outcome and mortality, it is conceivable that fibrinogen levels too would correlate with poor functional outcomes. Even after adjusting for stroke severity, fibrinogen has been found to be an independent predictor of poor functional outcome and mortality in ischemic stroke.[32] Our findings are consistent with these. As fibrinogen has been found to be strong predictor for END as well as consequent poor stroke outcomes, it is possible that routine assays for this easily detectable and readily available biomarker would help clinicians in stratifying patients into a high-risk group mandating a more intensive therapeutic approach in them.

Our study had several limitations. The study was performed on a relatively small sample size of 141 patients. COVID – 19 pandemic restrictions leading to limited hospital admissions and time constraints were the reasons that a larger sample size could not be achieved. It may be necessary to reproduce these findings in a larger cohort to estimate the degree of association between different parameters with END and outcome. We have used a long temporal definition for END (<7 days), to include multiple heterogenous mechanisms. This definition may be different from that used in previous studies. This could have caused an overestimation of the incidence of END. Other parameters that could influence END and outcome such as the role of infection, duration of hospital stay and time between stroke onset and hospitalization, radiological parameters and different treatment modalities could not be taken into consideration for this study due to limited resource availability.

Conclusion
Fibrinogen independently predicts END and outcome in patients with acute ischemic stroke. Routine plasma fibrinogen assays may help clinicians in stratifying patients into a high-risk group, who may require more potent antiplatelet therapy or use of fibrin-depleting agents.

Acknowledgements

ORCID iD
Vishal Mehta https://orcid.org/0000-0003-0617-9753

REFERENCES

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795-820.
2. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1): 35-41.
3. Huang ZX, Wang QZ, Dai YY, et al. Early neurological deterioration in acute ischemic stroke: A propensity score analysis. *J Chin Med Assoc*. 2018;81(10): 865-870.
4. Dávalos A, Cendra E, Teruel J, et al. Deteriorating ischemic stroke: risk factors and prognosis. *Neurology*. 1990;40(12):1865-1869.
5. Peycheva M, Deneva T, Zahariev Z. The role of fibrinogen in acute ischaemic stroke. *Neurol Neurochir Pol*. 2021;55(1):74-80.
6. Chuang SY, Bai CH, Chen WH, Lien LM, Pan WH. Fibrinogen independently predicts the development of ischemic stroke in a Taiwanese population: CVDFACTS study. *Stroke*. 2009;40(5):1578-1584.
7. Spada RS, Toscano G, Chiarenza S, Mauro SD, et al. Ischemic stroke and fibrinogen in the elderly. *Arch Gerontol Geriatr Suppl*. 2004;38(9):403-406.
8. Rothwell PM, Howard SC, Power DA, Gutnikov SA, et al. Fibrinogen concentration and risk of ischemic stroke and acute coronary events in 5113 patients with transient ischemic attack and minor ischemic stroke. *Stroke*. 2004;35(10): 2300-2305.
9. Di Napoli M, Papa F, Bocola V. Prognostic influence of increased C-reactive protein and fibrinogen levels in ischemic stroke. *Stroke*. 2001;32(1):133-138.
10. Turaj W, Słowik A, Dziedzic T, Pulyk R, et al. Increased plasma fibrinogen predicts one-year mortality in patients with acute ischemic stroke. *J Neurol Sci*. 2006;246(1-2):13-19.
11. Lee SJ, Hong JM, Lee SE, et al. Association of fibrinogen level with early neurological deterioration among acute ischemic stroke patients with diabetes. *BMC Neurol*. 2017;17(1):101.
12. Williams B, Manica G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *Eur Heart J*. 2018;39(33):3021-3104.
13. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2019*. *Diabetes Care*. 2019;42(suppl 1): S13-S28.
14. Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. *Neurology*. 2013;81(3):264-272.
15. Karepov VG, Gur AY, Bova I, Aronovich BD, Bornstein NM. Stroke-in-evolution: infarct-inherent mechanisms versus systemic causes. *Cerebrovasc Dis*. 2006;21(1-2): 42-46.
16. Bhatia K, Mohanty S, Tripathi BK, Gupta B, Mittal MK. Predictors of early neurological deterioration in patients with acute ischaemic stroke with special reference to blood urea nitrogen (BUN)/creatinine ratio & urine specific gravity. *Indian J Med Res*. 2015;141(3):299-307.
17. Park TH, Lee JK, Park MS, et al. Neurologic deterioration in patients with acute ischemic stroke or transient ischemic attack. *Neurology*. 2020;95(16):e2178-e2191.
18. Gong P, Zhang X, Gong Y, et al. A novel nomogram to predict early neurological deterioration in patients with acute ischaemic stroke. *Eur J Neurol*. 2020;27(10): 1996-2005.
19. Chen RL, Balami JS, Esiri MM, Chen LK, Buchan AM. Ischemic stroke in the elderly: an overview of evidence. *Nat Rev Neurol*. 2010;6(5):256-265.
20. Hou L, Zhang Y, Zheng D, et al. Increasing trimethylamine N-oxide levels as a predictor of early neurological deterioration in patients with acute ischemic stroke. *Neurol Res*. 2020;42(2):153-158.
21. Duan Z, Guo W, Tang T, Tao L, Gong K, Zhang X. Relationship between high-sensitivity C-reactive protein and early neurological deterioration in stroke patients with and without atrial fibrillation. *Heart Lung*. 2020;49(2):193-197.
22. DeGraba TJ, Hallenbeck JM, Pettigrew KD, et al. Progression in acute stroke: value of the initial NIH stroke scale score on patient stratification in future trials. *Stroke*. 1999;30:1208-1212.
23. Lin LC, Yang JT, Weng HH, Hsiao CT, Lai SL, Fann WC. Predictors of early clinical deterioration after acute ischemic stroke. *Am J Emerg Med*. 2011;29(6):577-581.
24. Toni D, Fiorelli M, Zanette EM, et al. Early spontaneous improvement and deterioration of ischemic stroke patients. A serial study with transcranial Doppler ultrasonography. *Stroke*. 1998;29(6):1144-1148.

25. Hao Z, Liu M, Wardlaw JM, Lin S, et al. Fibrinogen depleting agents for acute ischemic stroke. *Cochrane Database Syst Rev*. 2012;3. Art.No.: CD000091.
26. Adams HP Jr, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999;53(1):126-131.
27. Koennecke HC, Belz W, Berfelde D, et al. Factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit. *Neurology*. 2011; 77(10):965-972.
28. Weimar C, König IR, Kraywinkel K, Ziegler A, Diener HC. German stroke study collaboration. age and national institutes of health stroke scale score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia:

development and external validation of prognostic models. *Stroke*. 2004;35(1): 158-162.
29. Xue WY, Xu YC, Wu YW, Yang M. Observation of elevated fasting blood glucose and functional outcome after ischemic stroke in patients with and without diabetes. *Oncotarget*. 2017;8(40):67980-67989.
30. Yao M, Ni J, Zhou L, et al. Elevated fasting blood glucose is predictive of poor outcome in non-diabetic stroke patients: A sub-group analysis of SMART. *PLoS One*. 2016;11(8):e0160674.
31. Di Napoli M, Papa F. Should neurologists measure fibrinogen concentrations? *J Neurol Sci*. 2006;246(1-2):5-9.
32. Di Napoli M, Singh P. Is plasma fibrinogen useful in evaluating ischemic stroke patients?: why, how, and when. *Stroke*. 2009;40(5):1549-1552.