Original Article

Access this article online
Quick Response Code:

Website: http://www.braincirculation.org
DOI: 10.4103/bc.bc_52_24

# Association of baseline plasma fibrinogen levels with cognitive and affective status at 30 and 90 days in individuals with ischemic stroke: A prospective study from Nigeria

**Adekola B. Ademoyegun[1,2], Taofeek O. Awotidebe[2], Marufat O. Odetunde[2], Samuel O. Inaolaji[1], Serifat O. Bakare[3], Funmilola W. Azeez[3], Olanrewaju Olayemi[4,5]**

*Departments of [1]Physiotherapy and [4]Internal Medicine, Osun State University Teaching Hospital, [3]Department of Family Medicine, Accident and Emergency Unit, Osun State University Teaching Hospital, [5]Department of Medicine, Osun State University, Osogbo, [2]Department of Medical Rehabilitation, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria*

**Address for correspondence:**
Dr. Adekola B. Ademoyegun, Department of Physiotherapy, Osun State University Teaching Hospital, PMB 5000, Osogbo, Nigeria.
E-mail: aademoyegun@gmail.com

Submission: 20-05-2024
Revised: 15-09-2024
Accepted: 18-09-2024
Published: 28-12-2024

**Abstract:**

**BACKGROUND:** The influence of fibrinogen as a risk factor in developing poststroke neuropsychological and cognitive problems is underreported. This study aimed to evaluate the relationship between baseline fibrinogen levels and depression, anxiety, and cognition 30- and 90-day after stroke.

**METHODS:** This prospective study involved 48 patients with first-ever mild-to-moderate ischemic stroke, whose plasma fibrinogen levels were assessed within 24 h of stroke onset. Clinical depression, anxiety, and cognitive impairment were evaluated by the Hospital Anxiety and Depression Scale and Montreal Cognitive Assessment at 30- and 90-day after stroke.

**RESULTS:** After adjusting for important covariates, the multiple linear regression models showed that baseline plasma fibrinogen was associated with the symptoms of depression, anxiety, and cognitive decline at both 30- and 90-day follow-up ($P < 0.05$). The receiver operating characteristic curve showed that baseline fibrinogen threshold > 409.0 mg/dl (82.4% sensitivity and 71.0% specificity), >405.0 mg/dl (80.0% sensitivity and 71.4% specificity), and > 400.0 mg/dl (80.6% sensitivity and 76.5% specificity) could respectively predict the presence of depression, anxiety, and cognitive impairment 90 days after stroke.

**CONCLUSIONS:** High levels of baseline plasma fibrinogen are associated with the onset and severity of symptoms of depression, anxiety, and cognitive decline at 30 and 90 days after stroke. This study shows that fibrinogen may be a viable target for monitoring and intervention in the management of poststroke neuropsychological and cognitive disorders. Future clinical trials are needed to clarify whether defibrinogenation will prevent or reduce the rate and severity of symptoms of depression, anxiety, and cognitive decline among patients with ischemic stroke.

**TRIAL REGISTRATION:** Pan African Clinical Trial Registry (registration number: PACTR202406755848901).

**Keywords:**

Anxiety, cognitive decline, depression, fibrinogen, stroke

## Introduction

Ischemic stroke involves the occlusion of cerebral vessels, leading to brain ischemia affecting neurons and neuronal activities.[1,2] The pathogenesis, progression, and resolution of ischemic stroke center on many inflammatory cells, including fibrinogen.[1-3] Fibrinogen is a major

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** WKHLRPMedknow_reprints@wolterskluwer.com

**How to cite this article:** Ademoyegun AB, Awotidebe TO, Odetunde MO, Inaolaji SO, Bakare SO, Azeez FW, *et al*. Association of baseline plasma fibrinogen levels with cognitive and affective status at 30 and 90 days in individuals with ischemic stroke: A prospective study from Nigeria. Brain Circ 2024;10:308-15.


© 2024 Brain Circulation | Published by Wolters Kluwer Health – Medknow

acute-phase protein recruited in the event of brain ischemia.[4,5] Fibrinogen is essential in the inflammation cascade following ischemic stroke, especially as related to hemostasis.[6] As a hemostasis-related function in acute ischemic stroke, fibrinogen is involved in platelet aggregation, mediation of endothelia-leukocyte interactions, and blood viscosity.[4]

Studies have shown the importance of plasma fibrinogen level at the acute stage to clinical outcomes or prognosis. Even after adjusting for other important confounders, including age, smoking, and hypertension, evidence shows a sustained relationship between fibrinogen and clinical outcomes in patients with ischemic stroke.[5,7] Recently, a review involving 21,473 stroke patients from 52 studies by Bao *et al*.[8] showed that stroke patients with high concentrations of fibrinogen were 1.65 times more likely to have a poor clinical outcome (modified Ranking Scale score >2), 1.31 times more likely to die from stroke, 1.23 times more likely to have repeat stroke, 2.38 times more likely to have an early worse neurological decline, or 1.43 times more likely to have a poststroke cardiac arrest. However, data on the predictive value of fibrinogen on neuropsychological and cognitive variables post-stroke are sparse. Post-stroke emotional problems and cognitive impairments are highly prevalent and impair rehabilitation outcomes, stroke prognosis, and psychosocial life of the patients.[9-11] Thus, the study aimed to investigate the association of plasma fibrinogen level at admission with depression, anxiety, and cognition at 30- and 90-day follow-up in individuals with mild-to-moderate ischemic stroke.

## Methods

### Study design

This was a prospective cohort study.

### Participants

One hundred and one patients with ischemic stroke were assessed for eligibility at our hospital between May and December 2023. Out of which 50 patients participated in the study and ultimately 48 participants were able to complete the 3-month follow-up. The inclusion criteria were having mild-to-moderate ischemic stroke (National Institute of Health Stroke Scale [NIHSS] scores ≤15), having acute ischemic stroke confirmed by a radiological technique such as computed tomography scan and being admitted within 24 h of onset, and being 18 years and older. Patients with recurrent stroke, who underwent any surgical procedure including endovascular therapy, on treatment with recombinant tissue plasminogen activator (rt-PA), fibrinogen concentrate, and defibrinogenating agents, with other neurological problems, for example, Parkinson's disease, with major communication problem, with prior cognitive impairment, for example, dementia and that declined consent were excluded [Figure 1]. According to G*Power 3.1.9.4 software, multiple linear regression with 0.05 probability error, 0.35 effect size, 80% power, and 4 predictors needed a minimum of 40 samples.[12] The Ethical Committee of the hospital approved the study (UTH/REC/2023/05/766). Each participant signed informed consent.

### Variables

The sociodemographics of the participants, including age and sex were assessed. Baseline clinical characteristics such as body mass index, number of comorbidities (diabetes mellitus, high blood pressure, hyperlipidemia, coronary heart disease, alcoholism, cigarette smoking, respiratory, and urinary tract infection), and stroke severity, which was assessed with NIHSS. Within 24 h of stroke onset, venous blood samples were obtained inside tubes containing 3.2% sodium citrate. The blood was then centrifuged at 300 g× for 10 min. The concentration of plasma fibrinogen was assessed with the Clauss method using HemosIL® Q.F.A. Thrombin (Bovine) kit. The medical laboratory scientist who performed the fibrinogen analysis was blind to the neuropsychological and cognitive assessments.

At 30- and 90-day follow-up, the level of depression, anxiety, and cognition of the participants was evaluated by one of the authors (SOI), who was blinded to laboratory measures. The level of depression and anxiety was evaluated by the Hospital Anxiety and Depression Scale (HADS), whereas the Montreal Cognitive Assessment (MoCA) was employed to evaluate the level of cognition. The HADS, developed by Zigmond and Snaith,[13] has been validated in the assessment of depression and anxiety among stroke survivors.[14] The instrument has a total of 14 items, 7 items for each subscale (depression-subscale and anxiety-subscale), and is rated on a 4-point Likert scale (0–3). The maximum

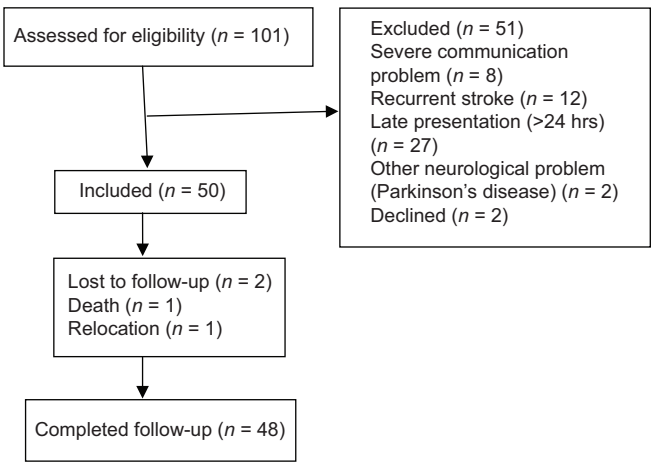



**Figure 1:** Study recruitment chart

score for each scale is 21 with a higher score indicating higher risks of symptoms of depression or anxiety. HADS scores of ≥7 were considered having depression or anxiety symptoms.[15] The Cronbach's alpha of the culturally adapted HADS to the study setting employed in this study was 0.821.

The MoCA was introduced by Nasreddine *et al*.[16] for the evaluation of cognitive functions in individuals with mild cognitive problems. MoCA is a 30-point test administration that evaluates many areas of cognitive function, with a higher score indicating better cognition.[15,17,18] MoCA has been translated into many languages and has good psychometric properties among stroke survivors.[15,17,18] The MoCA was administered to the participants, filled, and rated and stroke patients with MoCA scores of ≤19 out of possible 30 scores were considered having cognitive decline.[19] The Cronbach's alpha of the translated version of MoCA to the study setting employed in the present study was 0.827.

## Data analysis

Data were summarized using mean, standard deviation, frequency, and percentage. Independent *t*-test was used to assess the difference in baseline fibrinogen concentration between patients with or without any neuropsychological problem. Pearson's correlation coefficients were applied to assess correlations among clinical, demographics, and baseline fibrinogen. Furthermore, baseline fibrinogen tertiles were calculated and its correlation with 30- and 90-day depression, anxiety, and cognitive parameters was undertaken with Spearman rho correlation coefficients. Separate models of multiple linear regressions were performed to investigate the associations of the 30- and 90-day depression, anxiety, and cognitive assessments with baseline plasma fibrinogen. Each model was adjusted for age, number of comorbidities, and NIHSS scores. The receiver operating characteristic (ROC) curve and Youden's index were employed to determine the baseline fibrinogen optimum values in predicting depression, anxiety, and cognitive impairment at both follow-up times. The alpha level was set at $P < 0.05$. All statistical analyses were performed using the SPSS (IBM Corp., Armonk, N.Y., USA) version 21.

# Results

The mean age of the participants was 64.2 ± 9.36 years. Out of 48 patients included, 27 (56.3%) were male. The rate of depression improves from 62.5% at 30 days to 35.4% at 90 days of follow-up. The mean baseline fibrinogen was 417.3 ± 76.3 mg/dl. There was no significant difference in the baseline fibrinogen between the included patients and those lost to follow-up ($P > 0.05$). Table 1 shows the general and clinical features of the participants. The differences in baseline fibrinogen about 30- and 90-day neuropsychological and cognitive parameters of the participants are presented in Table 2. At 30-day follow-up, the depressed, anxious, and cognitively declined group had significantly higher baseline plasma fibrinogen (438.2 ± 69.4 mg/dl vs. 382.5 ± 76.4 mg/dl, $P = 0.013$, Cohen's $d = 0.76$; 431.9 ± 71.8 mg/dl vs. 385.3 ± 78.6 mg/dl, $P = 0.049$, Cohen's $d = 0.61$; 440.8 ± 67.9 mg/dl vs. 365.7 ± 69.7 mg/dl, $P < 0.01$, Cohen's $d = 1.09$). Similarly, participants with depression, anxiety, and cognitive decline at 90-day follow-up had significantly higher baseline plasma fibrinogen (464.7 ± 62.7 mg/dl vs. 391.4 ± 71.2 mg/dl, $P < 0.01$, Cohen's $d = 1.09$; 455.6 ± 70.9 mg/dl vs. 389.9 ± 68.8 mg/dl, $P < 0.01$, Cohen's $d = 0.94$; and 440.1 ± 69.4 mg/dl vs. 375.8 ± 72.2 mg/dl, $P < 0.01$, Cohen's $d = 0.91$).

The correlation coefficients showed a positive correlation between baseline fibrinogen and depression and anxiety and a negative correlation with cognition at both time points ($P < 0.05$) [Table 3]. The baseline fibrinogen tertiles are shown in Table 4. Fibrinogen levels in the lowest, middle, and highest tertiles were < 381.6 mg/dl, 381.6–458.1 mg/dl, and >458.1 mg/dl, respectively. The baseline fibrinogen tertiles were similarly positively correlated with depression and anxiety and negatively correlated with cognition at both time points ($P < 0.05$). Findings from linear regression models show a significant positive association of baseline plasma fibrinogen with both 30- and 90-day depressive (30-day: β =0.426, $P = 0.006$; 90-day: β =0.500, $P = 0.001$) and anxiety (30-day: β =0.421, $P = 0.007$; 90-day: β =0.510,

**Table 1: General and clinical characteristics of the participants (*n*=48)**

| Variable | Mean±SD/*n* (%) |
|---|---|
| Age (years) | 64.2±9.36 |
| Sex, male | 27 (56.3) |
| Number of comorbidities | 1.94±0.60 |
| BMI (kg/m$^2$) | 25.9±2.66 |
| Baseline NIHSS | 7.13±2.90 |
| Baseline fibrinogen (mg/dl) | 417.3±76.3 |
| 30-day HADS-D score | 7.77±3.59 |
| 30-day HADS-D score ≥7 | 30 (62.5) |
| 90-day HADS-D score | 5.50±3.47 |
| 90-day HADS-D score ≥7 | 17 (35.4) |
| 30-day HADS-A score | 7.95±3.05 |
| 30-day HADS-A score ≥7 | 33 (68.8) |
| 90-day HADS-A score | 5.88±3.15 |
| 90-day HADS-A score ≥7 | 20 (41.7) |
| 30-day MoCA score | 16.6±6.02 |
| 30-day MoCA score ≤19 | 33 (68.8) |
| 90-day MoCA score | 18.1±6.08 |
| 90-day MoCA score ≤19 | 31 (64.6) |

SD: Standard deviation, NIHSS: National Institute of Health Stroke Scale, HADS-D: Hospital Anxiety and Depression Scale-Depression Sub-Scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety Subscale, MoCA: Montreal Cognitive Assessment, BMI: Body mass index

**Table 2: Comparison of baseline plasma fibrinogen about 30- and 90-day neuropsychological and cognitive functions in patients with ischemic stroke**

| Variable | *n* | Mean±SD (mg/dl) | *t* | Df | *P* | Mean difference (mg/dl) | SE difference | 95% CI of difference - LLCI–ULCI | Cohen's d |
|---|---|---|---|---|---|---|---|---|---|
| 30-day HADS-D | | | | | | | | | |
| ≥7 score | 30 | 438.2±69.4 | 2.594 | 46 | 0.013* | 55.7 | 21.5 | 12.5–98.9 | 0.76 |
| <7 score | 18 | 382.5±76.4 | | | | | | | |
| 90-day HADS-D | | | | | | | | | |
| ≥7 score | 17 | 464.7±62.7 | 3.557 | 46 | 0.001* | 73.4 | 20.6 | 31.8–114.9 | 1.09 |
| <7 score | 31 | 391.4±71.2 | | | | | | | |
| 30-day HADS-A | | | | | | | | | |
| ≥7 score | 33 | 431.9±71.8 | 2.026 | 46 | 0.049* | 46.6 | 23.0 | 0.30–92.9 | 0.61 |
| <7 score | 15 | 385.3±78.6 | | | | | | | |
| 90-day HADS-A | | | | | | | | | |
| ≥7 score | 20 | 455.6±70.9 | 3.219 | 46 | 0.002* | 65.7 | 20.4 | 24.6–106.8 | 0.94 |
| <7 score | 28 | 389.9±68.8 | | | | | | | |
| 30-day MoCA | | | | | | | | | |
| ≤19 score | 33 | 440.8±67.9 | 3.525 | 46 | 0.001* | 75.2 | 21.3 | 32.2–118.1 | 1.09 |
| ≥20 score | 15 | 365.7±69.7 | | | | | | | |
| 90-day MoCA | | | | | | | | | |
| ≤19 score | 31 | 440.1±69.4 | 3.027 | 46 | 0.004* | 64.4 | 21.3 | 21.6–107.2 | 0.91 |
| ≥20 score | 17 | 375.8±72.2 | | | | | | | |

*Significant difference at *P*<0.05. CI: Confidence interval, SD: Standard deviation, HADS-D: Hospital Anxiety and Depression Scale-Depression Sub-Scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety Subscale, MoCA: Montreal Cognitive Assessment, LLCI/ULCI: Lower/upper limit CI, SE: Standard error

**Table 3: Correlation matrix among baseline plasma fibrinogen, 30- and 90-day depression, anxiety, cognition, and other factors in patients with ischemic stroke**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Baseline fibrinogen | 1 | | | | | | | | | |
| HADS-D‡ | 0.424* | 1 | | | | | | | | |
| HADS-D§ | 0.494* | 0.907* | 1 | | | | | | | |
| HADS-A‡ | 0.396* | 0.651* | 0.789* | 1 | | | | | | |
| HADS-A§ | 0.464* | 0.726* | 0.852* | 0.930* | 1 | | | | | |
| MoCA‡ | −0.475* | −0.357† | −0.411* | −0.340† | −0.366† | 1 | | | | |
| MoCA§ | −0.458* | −0.379* | −0.447* | −0.415* | −0.379* | 0.975* | 1 | | | |
| Baseline NIHSS | 0.262 | 0.209 | 0.279 | 0.198 | 0.162 | −0.619* | −0.634* | 1 | | |
| Number of comorbidity | 0.350† | 0.053 | 0.026 | −0.025 | −0.016 | −0.244 | −0.273 | 0.176 | 1 | |
| Age | 0.215 | 0.156 | 0.187 | 0.167 | 0.152 | −0.190 | −0.174 | 0.153 | 0.325† | 1 |

*Correlation at *P*<0.001, †Correlation at *P*<0.05, §90-day assessment, ‡30-day assessment. HADS-D: Hospital Anxiety and Depression Scale-Depression Subscale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety Sub-Scale, MoCA: Montreal Cognitive Assessment, NIHSS: National Institute of Health Stroke Scale

*P* = 0.001) symptoms. Furthermore, baseline plasma fibrinogen was negatively associated with cognition at 30 days (β = −0.321, *P* = 0.010) and 90 days (β = −0.288, *P* = 0.019) of follow-up [Table 5].

The results of ROC analysis providing the baseline fibrinogen cutoff points for the presence of symptoms of depression, anxiety, and cognitive impairment at 30- and 90-day follow-up are presented in Table 6. A significant area under the curve (AUC) was observed for baseline fibrinogen in predicting symptoms of depression, anxiety, and cognitive impairment at both follow-up times, except in predicting the presence of anxiety symptoms at 30-day follow-up (AUC = 0.671; *P* = 0.060). Meanwhile, Youden Index showed that baseline fibrinogen values >409.0 mg/dl (82.4% sensitivity and 71.0% specificity), >405.0 mg/dl (80.0% sensitivity; 71.4% specificity), and > 400.0 mg/dl (80.6% sensitivity and 76.5% specificity) were associated with 90-day symptoms of depression, anxiety, and cognitive impairment, respectively. The ROC curves between baseline fibrinogen and the presence of depression, anxiety, and cognitive impairment are illustrated in Supplementary Figure 1.

## Discussion

This study assessed the association of baseline plasma fibrinogen with depression, anxiety, and cognition at 30- and 90-day follow-up. In the present study, the neuropsychological and cognitive functioning improves from 30- to 90-day follow-up. From the 30- to 90-day assessment, the prevalence of depression, anxiety, and cognitive decline improved from 62.5%, 68.8%, and 68.8%,

**Table 4: Correlation of baseline fibrinogen tertiles with 30- and 90-day depression, anxiety, and cognition in patients with ischaemic stroke**

| Variable | Fibrinogen lowest tertile (*n*=18) | Fibrinogen middle tertile (*n*=14) | Fibrinogen highest tertile (*n*=16) | $r_s$ | *P* |
|---|---|---|---|---|---|
| Fibrinogen (mg/dl) | <381.6 | 381.6–458.1 | >458.1 | - | - |
| 30-day HADS-D score, $\bar{x}$±SD | 5.89±2.14 | 8.64±3.25 | 9.13±4.38 | 0.361 | 0.012* |
| 90-day HADS-D score, $\bar{x}$±SD | 3.39±1.97 | 6.07±3.02 | 7.38±3.40 | 0.459 | 0.001* |
| 30-day HADS-A score, $\bar{x}$±SD | 6.33±2.97 | 8.57±2.34 | 9.25±3.00 | 0.420 | 0.003* |
| 90-day HADS-A score, $\bar{x}$±SD | 4.00±2.61 | 6.50±2.13 | 7.44±3.50 | 0.451 | 0.001* |
| 30-day MoCA score, $\bar{x}$±SD | 20.3±5.54 | 15.0±4.77 | 13.8±5.65 | −0.458 | 0.001* |
| 90-day MoCA score, $\bar{x}$±SD | 21.9±5.94 | 16.3±4.84 | 15.5±5.27 | −0.435 | 0.002* |

*Significant correlation. $r_s$: Spearman rho correlation coefficients. HADS-D: Hospital Anxiety and Depression Scale-Depression Subscale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety Subscale, MoCA: Montreal Cognitive Assessment, SD: Standard deviation

**Table 5: Association of baseline plasma fibrinogen with 30- and 90-day depression, anxiety, and cognition in stroke patients**

| Variable† | HADS-D scores at 30-day follow-up | | | | | HADS-D scores at 90-day follow-up | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *B* (95% CI) | SE | Beta | *t* | *P* | *B* (95% CI) | SE | Beta | *t* | *P* |
| Baseline fibrinogen | 0.020 (0.006–0.034) | 0.007 | 0.426 | 2.861 | 0.006* | 0.023 (0.010–0.035) | 0.006 | 0.500 | 3.597 | 0.001* |
| | $F$=2.862; $R$=0.459; $R^2$=0.210 | | | | | $F$=4.868; $R$=0.558; $R^2$=0.312 | | | | |
| **Variable†** | **HADS-A scores at 30-day follow-up** | | | | | **HADS-A scores at 90-day follow-up** | | | | |
| | *B* (95% CI) | SE | Beta | *t* | *P* | *B* (95% CI) | SE | Beta | *t* | *P* |
| Baseline fibrinogen | 0.017 (0.005–0.029) | 0.006 | 0.421 | 2.837 | 0.007* | 0.021 (0.009–0.033) | 0.006 | 0.510 | 3.554 | 0.001* |
| | $F$=2.972; $R$=0.465; $R^2$=0.217 | | | | | $F$=3.901; $R$=0.516; $R^2$=0.266 | | | | |
| **Variable†** | **MoCA scores at 30-day follow-up** | | | | | **MoCA scores at 90-day follow-up** | | | | |
| | *B* (95% CI) | SE | Beta | *t* | *P* | *B* (95% CI) | SE | Beta | *t* | *P* |
| Baseline fibrinogen | −0.025 (−0.044–−0.006) | 0.009 | −0.321 | −2.684 | 0.010* | −0.023 (−0.042–−0.004) | 0.009 | −0.288 | −2.430 | 0.019* |
| | $F$=10.344; $R$=0.700; $R^2$=0.490 | | | | | $F$=10.706; $R$=0.706; $R^2$=0.499 | | | | |

*Significant association, †Each model is adjusted for age, baseline stroke severity, and number of comorbidity. HADS-D: Hospital Anxiety and Depression Scale-Depression Subscale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety Subscale, MoCA: Montreal Cognitive Assessment, SE: Standard error, CI: Confidence interval

**Table 6: The receiver operating characteristics of baseline fibrinogen levels with 30- and 90-day symptoms of depression, anxiety, and cognitive impairment in patients with ischemic stroke**

| Variable | Baseline fibrinogen cut-off value (mg/dl) | Sensitivity (%) | Specificity (%) | AUC (95% CI) | *P* |
|---|---|---|---|---|---|
| Presence of depressive symptoms at 30-day follow-up | 365.5 | 83.3 | 56.0 | 0.739 (0.590–0.888) | 0.006* |
| Presence of depressive symptoms at 90-day follow-up | 409.0 | 82.4 | 71.0 | 0.794 (0.660–0.928) | 0.001* |
| Presence of anxiety symptoms at 30-day follow-up | 370.0 | 78.8 | 60.0 | 0.671 (0.492–849) | 0.060 |
| Presence of anxiety symptoms at 90-day follow-up | 405.0 | 80.0 | 71.4 | 0.759 (0.615–0.903) | 0.002* |
| Presence of cognitive impairment at 30-day follow-up | 370.5 | 84.8 | 73.3 | 0.794 (0.639–0.949) | 0.001* |
| Presence of cognitive impairment at 90-day follow-up | 400.0 | 80.6 | 76.5 | 0.750 (0.594–0.907) | 0.004* |

*AUC at $P$<0.05. CI: Confidence interval, AUC: Area under curve

respectively, to 35.4%, 41.67%, and 64.6%. The gradual improvement of neuropsychological and cognitive functioning (depression, anxiety, and cognition) from stroke onset to 3 months has been mentioned previously in the literature.[11,20,21] This is more so as the recruited patients in this study were with mild-to-moderate ischaemic stroke. Although the rates of depression, anxiety, and cognitive decline vary based on many factors, including time and scale or method of assessment and sociodemographics,[10,11] the rates obtained in this study are in line with what is reported for stroke patients in the first 90 days of stroke incidence.[9-11,20]

The results of this study showed that elevated baseline plasma fibrinogen predicts worse symptoms of depression, anxiety, and cognitive decline at both 30 and 90-day after an ischemic stroke event. There is a dearth of data investigating the longitudinal association of fibrinogen with depression, anxiety, and cognition.[8] To our knowledge, only two studies have attempted to relate baseline fibrinogen levels with long-term neuropsychological and cognitive variables among stroke survivors.[22,23] Liu *et al*.[22] reported a negative relationship between baseline plasma fibrinogen and cognitive decline, measured by Mental State Examination, 3 months after stroke. Furthermore, Luan *et al*.[23] showed that stroke patients with higher baseline fibrinogen (≥3.64 g/L) are about twice more likely to present with poststroke emotional incontinence 1 month poststroke.

The link between fibrinogen concentration and cognitive decline has been attributed to blood–brain barrier (BBB) dysfunction.[8] Similar to the observation in patients with Alzheimer's disease, the disruption of BBB after stroke enables the fibrinogen (in fibrin form) to penetrate and infiltrate the brain parenchyma and the eventual cognitive decline.[8,24] This mechanism has been noted to be mediated by the binding of fibrin to Aβ42, activation of microglia and astrocytes, and the resultant neurodegeneration.[22] Thus, it is not unreasonable to infer that higher baseline fibrinogen levels after ischaemic stroke will cause higher fibrin deposits in brain tissues and more long-term cognitive decline. The mechanism by which fibrinogen induces cognitive decline can also be adduced for symptoms of depression and anxiety. Depression, anxiety, and cognitive decline share similar neuropsychological pathways.[25,26] In this study, there are bidirectional correlations among depression, anxiety, and cognitive decline. Further, stroke patients with higher baseline inflammatory factors such as interleukin-6 present with higher clinical depression, anxiety, and impaired cognition;[22,23] thus, it is not surprising that fibrinogen, as a main inflammatory marker in acute ischemic stroke, could serve as an independent predictor of depression, anxiety, and cognitive decline.

Since fibrinogen levels at admission can be objectively monitored and reproduced, the findings of this study revealed that stroke patients with higher baseline fibrinogen levels should be closely monitored for psychological problems and cognitive decline from the time of admission. A cutoff point for baseline fibrinogen levels that could predict neuropsychological and cognitive problems is also desirable. In the present study, baseline fibrinogen levels > 365.5 mg/dl, >370.0 mg/dl, and > 370.5 mg/dl, respectively, predict the presence of symptoms of depression, anxiety, and cognitive impairment 30-day post ischemic stroke. A similar finding has shown that stroke patients with baseline fibrinogen levels ≥ 364.0 mg/dl showed symptoms of poststroke emotional incontinence 1 month after stroke.[23] Previous research has shown that baseline fibrinogen levels above 350 mg/dl could serve as a prognostic value for stroke severity, prognosis, and outcome.[27,28] Conversely, the presence of affective disorders and cognitive decline 90 days after stroke was predicted in this study by higher levels of baseline fibrinogen levels. Specifically, baseline fibrinogen levels >409 mg/dl, >405 mg/dl, and >400 mg/dl were obtained in this study as criterion values for the presence of 90-day post-stroke depression, anxiety, and cognitive impairment, respectively. This suggests that patients with baseline fibrinogen values ≥400 mg/dl may have persistent symptoms of depression, anxiety, and cognitive decline up to 3 months after stroke. Studies have previously reported worse long-term clinical outcomes for stroke patients with baseline fibrinogen values upward of 400 mg/dl.[2,7,29] Our results corroborated these findings by showing that this category of patients may not only present with worse neurological problems but also with persistent emotional and cognitive dysfunctions.

Furthermore, the capability of baseline fibrinogen concentrations to predict symptoms of depression, anxiety, and cognitive decline in this study indicated that efforts should be made to modify higher fibrinogen concentrations early after a stroke incident. Evidence has shown that fibrinogen could be targeted for intervention in stroke management. A previous study showed an inconclusive finding on the effect of administering a defibrinogenating agent 6 h after an ischemic event on clinical outcomes.[30] Further interventional studies and clinical trials on the direct and indirect mechanisms between fibrinogen concentration and stroke outcomes have been advocated.[6] Meanwhile, the results of this study show that fibrinogen values early after stroke can serve as prognostic factors for depression, anxiety, and cognitive decline in ischemic stroke. Identifying higher baseline fibrinogen concentration as a risk factor for developing depression, anxiety, and cognitive decline poststroke could help to reduce their prevalence, severity, and associated burden.

## Limitations

The findings of this study have some limitations. First, we recruited only mild-to-moderate ischemic stroke patients, thus limiting the generalizability of our findings. Future studies should include hemorrhagic and more severe stroke survivors. Second, the small sample of patients recruited out of those assessed for eligibility may have introduced selection bias. Third, we employed self-report in the assessment of depression, anxiety, and cognitive function, which may have introduced report and recall bias. Fourth, although patients on rt-PA, fibrinogen concentrate, or defibrinogenating agents were not included in this study, the possible effects of other acute and subacute interventions and other personal and environmental factors (e.g., level of social support) on the patient's outcome variables were not considered. Fifth, the fibrinogen levels were only assessed once within 24 h of stroke onset, but not at 1$^{st}$ and 3$^{rd}$ month of the ischemic event, thus, the possible changes in fibrinogen concentration after the initial baseline assessment might also affect the neuropsychological and cognitive functions. These factors should be considered in future studies. Furthermore, future studies should consider the use of more objective and real-world neuropsychological assessments. For instance, the use of mobile cognitive assessment may provide data on real-world cognitive function.[31] Finally, as a result of the small sample size, we could not control for all co-founding variables, thus, more patients should be employed in future studies.

## Conclusions

The baseline plasma fibrinogen levels independently predict 30- and 90-day symptoms of depression, anxiety, and cognitive decline in individuals with mild-to-moderate ischemic stroke. This result showed that fibrinogen is a viable target for monitoring and intervention in managing depression, anxiety, and cognitive function after a stroke episode.

### Author contributions

(I) Concept and design: AB Ademoyegun, TO Awotidebe; (II) Administrative support: SO Bakare, FW Azeez, O Olayemi; (III) Provision of study materials or patients: AB Ademoyegun, SO Bakare, FW Azeez, O Olayemi; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

### Ethical policy and institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all patients. The study was approved by the Research Ethics Committee of the Osun State University Teaching Hospital, Osogbo, Nigeria [UTH/REC/2023/05/766, dated on May 25th, 2023].

### Data availability statement

The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Financial support and sponsorship

Nil.

### Conflicts of interest

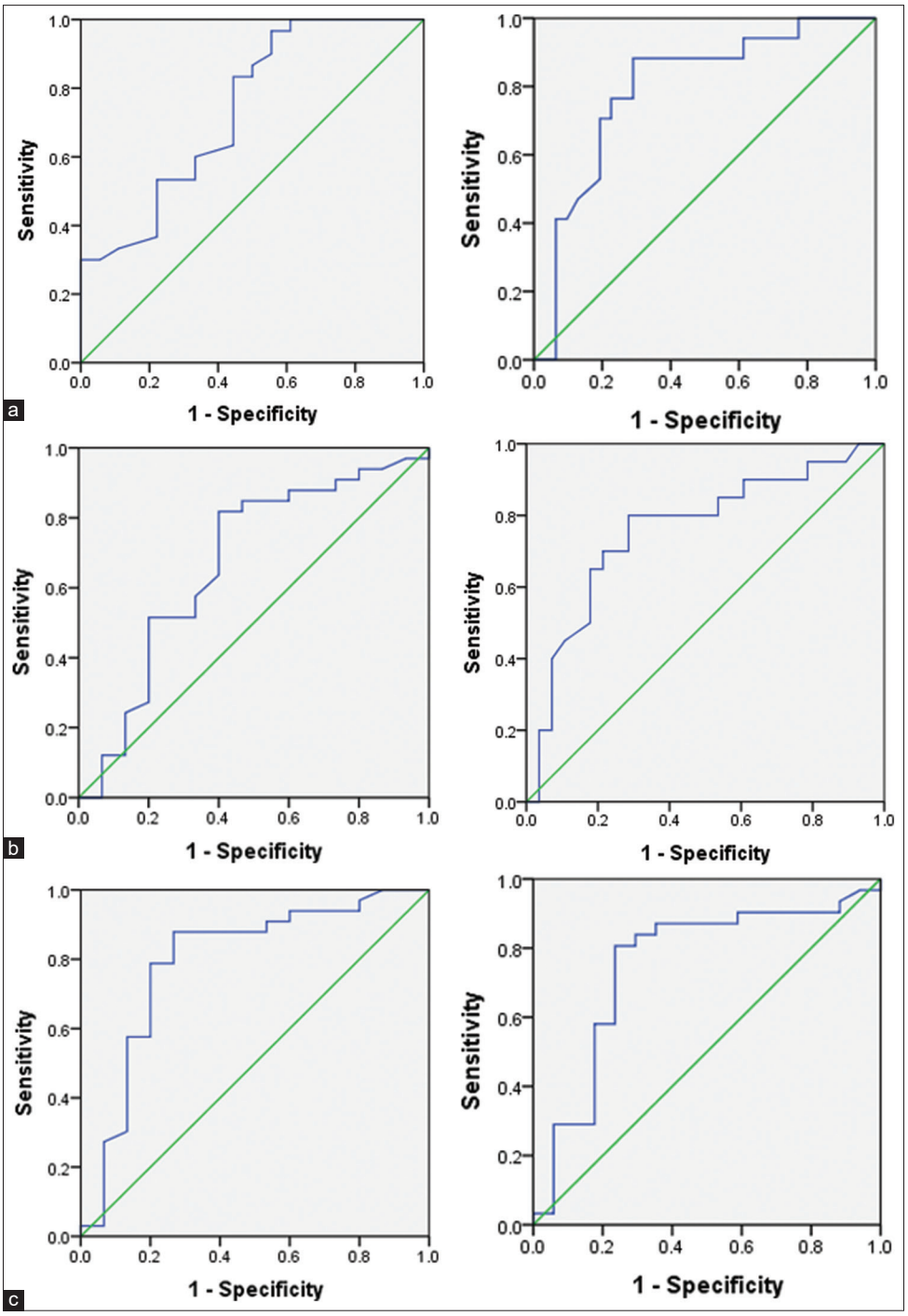
There are no conflicts of interest.

## References

1. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. Circ Res 2017;120:472-95.
2. Peycheva M, Deneva T, Zahariev Z. The role of fibrinogen in acute ischaemic stroke. Neurol Neurochir Pol 2021;55:74-80.
3. Anrather J, Iadecola C. Inflammation and stroke: An overview. Neurotherapeutics 2016;13:661-70.
4. Prasad MK, Marandi S, Mishra B, Guria RT, Kumar A, Birua H, *et al.* Association of fibrinogen with ischemic stroke: A systematic review and meta-analysis. Cureus 2023;15:e34335.
5. Pikija S, Trkulja V, Mutzenbach JS, McCoy MR, Ganger P, Sellner J. Fibrinogen consumption is related to intracranial clot burden in acute ischemic stroke: A retrospective hyperdense artery study. J Transl Med 2016;14:250.
6. Swarowska M, Janowska A, Polczak A, Klimkowicz-Mrowiec A, Pera J, Slowik A, *et al.* The sustained increase of plasma fibrinogen during ischemic stroke predicts worse outcome independently of baseline fibrinogen level. Inflammation 2014;37:1142-7.
7. Samir GM, Khalil OA, Fawzy MS, Sadek AM. Study of fibrinogen level in acute ischemic stroke patients in medical intensive care unit. Egypt J Crit Care Med 2020;7:2.
8. Bao Q, Zhang J, Wu X, Zhao K, Guo Y, Yang M, *et al.* Clinical significance of plasma D-dimer and fibrinogen in outcomes after stroke: A systematic review and meta-analysis. Cerebrovasc Dis 2023;52:318-43.
9. Khazaal W, Taliani M, Boutros C, Abou-Abbas L, Hosseini H, Salameh P, *et al.* Psychological complications at 3 months following stroke: Prevalence and correlates among stroke survivors in Lebanon. Front Psychol 2021;12:663267.
10. Baraka A, Meda J, Nyundo A. Predictors of post-stroke cognitive impairment at three-month following first episode of stroke among patients attended at tertiary hospitals in Dodoma, central Tanzania: A protocol of a prospective longitudinal observational study metadata. PLoS One 2023;18:e0273200.
11. Liu L, Xu M, Marshall IJ, Wolfe CD, Wang Y, O'Connell MD. Prevalence and natural history of depression after stroke: A systematic review and meta-analysis of observational studies. PLoS Med 2023;20:e1004200.
12. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods 2009;41:1149-60.
13. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
14. Pedroso V, Vieira EL, Brunoni AR, Lauterbach EC, Teieira A. Psychopathological evaluation and use of the hopital anxiety and depression scale in a sample of Brazillian patient with post-stroke depression. Arch Clin Psychiatry 2016;43:147-50.
15. Lee EH, Kim JW, Kang HJ, Kim SW, Kim JT, Park MS, *et al.* Association between anxiety and functional outcomes in patients with stroke: A 1-year longitudinal study. Psychiatry Investig 2019;16:919-25.
16. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, *et al.* The Montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-9.
17. Smith T, Gildeh N, Holmes C. The Montreal cognitive assessment: Validity and utility in a memory clinic setting. Can J Psychiatry 2007;52:329-32.
18. Toglia J, Fitzgerald KA, O'Dell MW, Mastrogiovanni AR, Lin CD. The mini-mental state examination and Montreal cognitive assessment in persons with mild subacute stroke: Relationship to functional outcome. Arch Phys Med Rehabil 2011;92:792-8.
19. Wei X, Ma Y, Wu T, Yang Y, Yuan Y, Qin J, *et al.* Which cutoff value of the Montreal cognitive assessment should be used for post-stroke cognitive impairment? A systematic review and meta-analysis on diagnostic test accuracy. Int J Stroke 2023;18:908-16.
20. Shin CN, Sin MK, Lee E, Lee J, An K, Sim J. Depression and anxiety one month after stroke. Asian Pac I Nurs J 2016;1:82-90.
21. Chun HY, Ford A, Kutlubaev MA, Almeida OP, Mead GE. Depression, anxiety, and suicide after stroke: A narrative review of the best available evidence. Stroke 2022;53:1402-10.
22. Liu Y, Chen H, Zhao K, He W, Lin S, He J. High levels of plasma fibrinogen are related to post-stroke cognitive impairment. Brain Behav 2019;9:e01391.
23. Luan X, Cheng H, Chen Y, Cheng L, Zhou S, Song J, *et al.* High levels of plasma fibrinogen and prothrombin time are related to post-stroke emotional impairment. Brain Res 2020;1748:147017.
24. Cortes-Canteli M, Mattei L, Richards AT, Norris EH, Strickland S. Fibrin deposited in the Alzheimer's disease brain promotes neuronal degeneration. Neurobiol Aging 2015;36:608-17.
25. Zhang SH, Wang YL, Zhang CX, Zhang CP, Xiao P, Li QF, *et al.* Effect of interactive dynamic scalp acupuncture on post-stroke

cognitive function, depression, and anxiety: A multicenter, randomized, controlled trial. Chin J Integr Med 2022;28:106-15.

26. Lu W, Pai M, Scholes S, Xue B. Do depressive symptoms link chronic diseases to cognition among older adults? Evidence from the health and retirement study in the United States. J Affect Disord 2021;294:357-65.
27. Turaj W, Słowik A, Dziedzic T, Pułyk R, Adamski M, Strojny J, *et al.* Increased plasma fibrinogen predicts one-year mortality in patients with acute ischemic stroke. J Neurol Sci 2006;246:13-9.
28. Di Napoli M, Papa F, Bocola V. Prognostic influence of increased C-reactive protein and fibrinogen levels in ischemic stroke. Stroke 2001;32:133-8.
29. Lee SJ, Hong JM, Lee SE, Kang DR, Ovbiagele B, Demchuk AM, *et al.* Association of fibrinogen level with early neurological deterioration among acute ischemic stroke patients with diabetes. BMC Neurol 2017;17:101.
30. Levy DE, del Zoppo GJ, Demaerschalk BM, Demchuk AM, Diener HC, Howard G, *et al.* Ancrod in acute ischemic stroke: Results of 500 subjects beginning treatment within 6 hours of stroke onset in the ancrod stroke program. Stroke 2009;40:3796-803.
31. Moore RC, Swendsen J, Depp CA. Applications for self-administered mobile cognitive assessments in clinical research: A systematic review. Int J Methods Psychiatr Res 2017;26:e1562.




**Supplementary Figure 1:** (a) Receiver operating characteristic curve between baseline fibrinogen and presence of depressive symptoms among patients with ischaemic stroke at 30-day (left) and 90-day (right) follow-up. (b) Receiver operating characteristic curve between baseline fibrinogen and presence of anxiety symptoms among patients with ischemic stroke at 30-day (left) and 90-day (right) follow-up. (c) Receiver operating characteristic curve between baseline fibrinogen and presence of cognitive impairment among patients with ischaemic stroke at 30-day (left) and 90-day (right) follow-up