



Elevated Plasma Fibrinogen and the Risk of Stroke: A Hospital Based Prospective Case-Control Study in Uyo, Nigeria

**Timothy A. Ekwere^{1*}, Olufisayo G. Ayoade², Bertha C. Ekeh³
and Franklin O. Dike³**

¹Department of Haematology, University of Uyo/University of Uyo Teaching Hospital, Uyo, Nigeria.

²Department of Chemical Pathology, University of Uyo/University of Uyo Teaching Hospital, Uyo, Nigeria.

³Department of Internal Medicine, Neurology Unit, University of Uyo/University of Uyo Teaching Hospital,
Uyo, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i2031104

Editor(s):

(1) Dr. Muhammad Torequl Islam, Bangabandhu Sheikh MujiburRahman Science and Technology University, Bangladesh and Ton DucThang University, Viet Nam.

Reviewers:

(1) S. Vijayalakshmi, The Tamil Nadu Dr. M.G.R. Medical University, India.

(2) Faehaa Azher Al-Mashhadane, University of Mosul, Iraq.

Complete Peer review History: <https://www.sdiarticle4.com/review-history/74478>

Original Research Article

**Received 14 July 2021
Accepted 24 September 2021
Published 30 September 2021**

ABSTRACT

Background: Stroke is one of the leading causes of morbidity and mortality globally. In recent time, there is increasing evidence that suggest that increased plasma fibrinogen is associated with increased risk of stroke with unfavourable clinical outcome.

Objectives: To determine the plasma fibrinogen levels in stroke patients and compare with healthy controls.

Study Design: The study design was Prospective case- control study.

Place and Duration of Study: The study was conducted in the department of Internal Medicine (Neurology Unit) and the department of Haematology between March to August, 2019.

Methodology: A case- control study consisting of 41 patients (21M: 19F) diagnosed with stroke in line with WHO definition and confirmed by CT-Scan of the brain were recruited consecutively into the study. 20 (10M: 10F) healthy age and gender matched consenting adults were used as controls. Plasma fibrinogen was determined for both the patients and controls using ELISA method. Also, socio-demographic and clinical data were collected using questionnaire designed for the study. The level of significance was set at P=.05.

Results: The mean plasma fibrinogen level of 458.0 ± 89.1 was significantly higher in the stroke patients compared to the controls 307.8 ± 61.5 ($P < 0.001$). An increasing level of plasma fibrinogen was observed with increasing age in both the patients and controls. However, this increase was not statistically significant ($P = 0.98$). Also, the plasma fibrinogen level was significantly higher in the female patients (501.21 ± 83.96) than the males 420.59 ± 77.02 ($P = 0.003$).

Conclusion: Plasma fibrinogen was significantly higher in the stroke patients compared to the controls with female patients having a significantly higher levels than males. Also, the plasma fibrinogen levels appear to increase proportionally with increasing age.

Keywords: Fibrinogen; stroke; hypertension; cardiovascular disease; ischemia; thrombosis.

1. INTRODUCTION

Stroke otherwise referred to as cerebrovascular accident (CVA) is one of the leading causes of morbidity and mortality worldwide [1]. The global burden of the disease is on the increase and it is likely to worsen particularly in many low- and middle-income countries over the next few decades based on projections by WHO [1]. In India it accounts for about 1% of all hospital mortality and responsible for about 20% of central nervous system (CNS) related disorders [2]. In Nigerian, Wahab et.al, [3] reported a prevalence of 1.14 per 1000 with a 30-days fatality rate of 40% in south-western region while Enewereji et.al, [4] reported a prevalence of 1.63 per 1000 in a rural community in the south-eastern region.

Pathologically, stroke may either be haemorrhagic or ischaemic (thrombotic). The later results from the atherosclerotic obstruction of large cervical and cerebral arteries with ischaemia in all or part of the territory of the occluded artery while the former results from spontaneous intracerebral haemorrhage (as oppose to traumatic ones) are mainly due to arteriolar hypertensive disease, and rarely to coagulopathy, vascular malformation within the brain and diet [1].

Studies among the Caucasian population shows that about 80-85% of all stroke cases are ischaemic, while 10-15% are haemorrhagic. [1,5] However, studies from Asian countries reported a relatively higher proportion of haemorrhagic stroke of 20-30% compared to the Caucasian [1,6]. In West African sub-region, a study among adults less than 50 years reported ischaemic and haemorrhagic stroke in the proportion of 47.5% and 52.5% respectively [7].

In recent time, fibrinogen has emerged as an important predictor of cardiovascular disease. Findings from epidemiological studies have

shown that high plasma fibrinogen levels correlate strongly with the frequency of thrombotic complications of stroke, atherosclerosis and myocardial infarction [6,8]. Thrombogenesis is central to the pathogenesis of stroke and myocardial infarction, and fibrinogen a procoagulant protein is involved in the series of reactions that results in thrombus formation via its interaction with thrombin an enzyme in the coagulation cascade [9]. Increased levels of fibrinogen have been reported in patients with stroke and a much higher levels have been reported in patients with ischaemic stroke compared with haemorrhagic stroke. In addition, evidence have shown that it is an independent risk factor for further recurrence of stroke [2,10].

With the increasing incidence of stroke in our environment and the dearth of literature that examine the plasma fibrinogen levels in these patients, this study has the potential of providing valuable information on the predictive role of this procoagulant protein in the occurrence of this disease. Therefore, this study aims to determine the plasma fibrinogen levels in stroke patients receiving care in a tertiary health facility in Uyo, Nigeria.

2. METHODOLOGY

2.1 Study Site

This study was conducted in the Neurology Unit of department of Internal Medicine and department of Haematology University of Uyo Teaching Hospital a tertiary care hospital in the South-South, region of Nigeria. Neurology clinic is one of the many specialized clinics in the hospital that offers care to patients with neurodegenerative diseases including stroke patients.

2.2 Study Design

This was a prospective case-control study designed to achieve the set objective of the study.

2.3 Study Population

Patients diagnosed with stroke in line with the WHO clinical definition of stroke and confirmed by computer tomography scan (CT-scan) of the brain were recruited consecutively into the study over a 6 months period (March-August 2019). Age and sex matched healthy individuals were used as controls for the study. A total of 61 participants consisting of 41 stroke patients (cases) and 20 healthy persons (controls) were consecutively recruited into the study.

2.4 Sample Collection/ Analytical Procedure

4.5 millilitres of blood was drawn from the ante-cubital vein under aseptic condition using a sterile disposable syringe from each of the participants (patients and controls). This was dispensed into 0.5mls of trisodium citrate anticoagulant bottle (ratio 9:1), mixed thoroughly and then centrifuged at 3000g for 5minutes. The plasma was extracted into a cryo-tube and labelled with the unique identification number assigned to that patient. Same procedure was done for the control samples. The processed samples were stored at -20°C until they were needed for fibrinogen assay. Fibrinogen assay was done using Enzyme linked immunosorbent assay (ELISA) technique.

2.5 Inclusion Criteria

Newly diagnosed adult patients with stroke in line with WHO definition/criteria which include; rapidly developing clinical signs of focal (or global) disturbances of cerebral function, with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of vascular origin.

Adult patients who had CT-scan of the brain to confirm above WHO definition/criteria for strike and who gave oral and signed informed consent were recruited into the study during the study period (March –August 2019).

2.6 Exclusion Criteria

Patients less than 18 years of age, patients whose Clinical diagnosis were not confirmed by CT- scan of the brain and those with incomplete clinical data.

2.7 Data Collection

Data was collected using questionnaire designed for the study. This includes; age, sex, blood pressure, plasma fibrinogen level.

2.8 Data Analysis

Data was analysed using SPSS for windows version 17. The results were presented in simple tables. Descriptive and inferential statistics such as t-test were used as appropriate. The level of significance was set at $P = .05$.

3. RESULTS

A total of sixty-one (61) participants were recruited for this study within the study duration. Forty-one (41) were cases while 20 were the controls. The male to female ratio in both arm of the study was 1:1. The median age range of both the cases and controls were 60(85-40) years and 62 (78-45) years respectively Table 1.

Majority (90%) of the controls subjects have their mean fibrinogen levels within the reference range. On the other hand, majority (73.2%) of the stroke patients have elevated plasma fibrinogen compared to the controls. The difference was statistically significant ($p=0.0001$). Table 2.

The plasma fibrinogen levels increase progressively with increasing age above 50 years with the highest levels seen among participants age 70 years and above. However, this increase was not statistically significant Table 3.

The mean fibrinogen level among the female patients was significantly higher than the male patients. This difference was statistically significant ($p=0.032$). Table 4.

4. DISCUSSION

From epidemiological studies, it has been shown that elevated fibrinogen level is strongly and independently correlated with the risk of coronary arterial disease (CAD), stroke and peripheral arterial disease. [2,8,11] Elevated levels of fibrinogen have been linked to stroke severity with corresponding increased mortality a year after the onset of an acute event with poor functional outcome [12]. Furthermore, stroke patients with an initial lower plasma fibrinogen level have been found to have a better functional outcome than those with higher level [13].

In this study, the plasma level of fibrinogen was significantly higher in patients with stroke than in the non-stroke or control group ($P < .001$). Our finding is consistent with the studies from other authors. [12,13]. Abdelgwad et.al, [14] found that a high plasma fibrinogen level was associated

with poor outcome three months after acute ischaemic stroke. Similarly, Swarowska et al, [12] reported that sustained elevation of fibrinogen during stroke is linked with a reduced chance of favourable outcome independent of the baseline fibrinogen level. However, few studies have reported no significant difference in the plasma fibrinogen levels between stroke and non-stroke patients despite an observed gradual increment during serial measurement. [13,15] Fibrinogen is an acute phase protein and its plasma level like other inflammatory makers are elevated during the onset of stroke [14]. High levels are related to stroke severity and increased mortality.

The age demographic trend in this study shows an increasing plasma fibrinogen level with advancing age with the highest levels found among patients aged 70years and above. However, this increase was not statistically significant ($P=0.98$). Various epidemiological studies have reported an increasing plasma

fibrinogen level with age and this has been linked with increased risk for thrombotic disease. [8,16] Data from the Northwick Park Heart Study II among healthy middle age men, reported an increasing fibrinogen level with increasing age among other risk factors for coronary heart disease. [16] Hager et.al [17] also reported an age dependent rise in fibrinogen levels among healthy individuals with a peak concentration in those older than 65 years. Age dependent increase in plasma fibrinogen has been attributed to a reduction in the fibrinolytic activity that occurs with aging. Gleerup et.al, [18] confirm this assertion in their study on the effect of aging on platelet function and fibrinolytic activity. They found that fibrinolytic activity decreases significantly with age as evident by prolongation of the euglobin clot lysis time and plasminogen activator inhibitor-1 (PAI-1). This report has been corroborated by other authors [16,17] and perhaps responsible for the increasing fibrinogen levels with increasing age observed in this study.

Table 1. Age and sex distribution of the participants

Variables	Study groups n (%)		Total (n=61)	Statistical indices
	Stroke (n=41)	Control (n=20)		
Sex				
Male	22 (53.7)	10 (50.0)	32 (52.5)	Df=1
Female	19 (46.3)	10 (50.0)	29 (47.5)	$X^2 = 0.0721$ $P = .788$
Age (years)				
40-49	6 (14.6)	4 (20.0)	10 (16.4)	Df=3
50-59	12 (29.3)	4 (20.0)	16 (26.2)	
60-69	15 (36.6)	11 (55.0)	26 (42.6)	$P = .310$
70 and above	8 (19.5)	1 (5.0)	9 (14.8)	
Median (range)	60 (85-40)	62 (78-45)	61 (85-40)	

+fischer. exact test

Table 2. Mean plasma fibrinogen levels of male and female subjects and controls

Variables	Study groups		Total (n=61)	Statistical indices
	Stroke (n=41)	Control (n=20)		
Fibrinogen (mg/l)				Df=1
200-400	11 (26.8)	18 (90.0)	29 (47.5)	$P < .0001$
Above 400	30 (73.2)	2 (10.00)	32 (52.5)	t-test=-6.7778
Mean (SD)	458.0 (89.1)	307.8 (61.5)	408.7 (107.4)	$P < .001$

Table 3. The plasma fibrinogen levels in the different age groups

Age (Years)	n	Mean Fibrinogen ± SD	Statistical indices
40-49	10	407.40 ± 106.622	
50-59	16	400.06 ± 101.129	F= .56
60-69	26	411.73 ± 120.325	$P = .98$
70 and above	9	416.78 ± 95.965	

Table 4. The mean plasma fibrinogen levels in male and female subjects

Variables	Stroke Patients		Statistical indices
	Male (n=22)	Female (n=19)	
Fibrinogen (mg/l)	420.59±77.02	501.21±83.96	t-test =3.185 P= .003

Furthermore, the mean plasma fibrinogen level in this study was significantly higher among female stroke patients compared to their male counterparts ($P=.003$). Our finding is in keeping with the studies by Mistry et.al [2] and Li et.al. [16] Both studies reported a significantly higher level of plasma fibrinogen in female stroke patients than males. However, it contrasts with the studies by Harithia et.al [15] and Samir et.al,[17] who found no significant gender differences in the plasma fibrinogen levels of stroke patients. The effect of hormonal differences and influence of oral contraceptive use and menopause in addition to some other risk factors are perhaps responsible the higher levels of fibrinogen seen in female stroke patients.

A major limitation of this study was the fact that serial measurement of fibrinogen could not be done. Hence, may not fully reflect some of the observed causal relationship.

We therefore, suggest a long-term prospective cohort study of patients with acute stroke with serial plasma fibrinogen assessment to validate the findings from this study. Furthermore, the use of fibrinogen lowering agents need to be further evaluated in the management of stroke patients.

5. CONCLUSION

The plasma fibrinogen level was significantly higher in the stroke patients compared with the controls, and showed increasing level with age with women have a significantly higher levels than men.

CONSENT

All participants in this study signed a written informed consent before being recruited in the study.

ETHICAL APPROVAL

Ethical approval was obtained from the Institutional Health Research Ethics Committee (IHREC) of the Hospital before the commencement of this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M Bennett DA, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014;383:245–255.
2. Mistry P, Chawla KP, Rai HP, Jaiswal P. Plasma fibrinogen levels in stroke. *J Postgrad Med.* 1990;36:1-4.
3. Wahab KW. The burden of stroke in Nigeria. *Int J Stroke.* 2008;3(4):290-292.
4. Enwereji K, Nwosu M, Ogunniyi A, Nwani P, Asomugha AL, Enwereji E. Epidemiology of stroke in a rural community in south-eastern Nigeria. *Journal of Vascular Health and Risk Management* 2014;10:375-388.
5. Sudlow CLM and Warlow CP. Comparable studies of the incidence of stroke and its pathological types. Results from an international collaboration. *Stroke.* 1997;28:491-499.
6. Asian Acute Stroke Advisory Panel. Stroke epidemiological data of nine Asian countries. *J Med Assoc Thai.* 2000;83:1-7.
7. Sarfo SF, Ovbiagele B, Gebregziabher M, Wahab K, Akinyemi R, Akpalu A, et.al. Stroke among young West Africans. Evidence from the SIREN (Stroke Investigative Research and Educational Network) Large Multisite Case–Control Study. *Stroke.* 2018;49:1116-1122.
8. Tanne D, Benderly M, Gouldbourt U, Boyko V, Brunner D, Graff E, et.al. A prospective study of plasma fibrinogen levels and the risk of stroke among participants in the bezafibrate infarction prevention study. *Am J Med.* 2001;111(6):457- 463.
9. Di Minno G, Mancini M. Measuring plasma fibrinogen to predict stroke and myocardial infarction. *Arteriosclerosis.* 1990;10:1-7.

10. Shao-Yuan Chuang, Chyi-Huey Bai, Wei-Hung Chen, Li-Ming Lien, Wen-Harn Pan. Fibrinogen independently predicts the development of Ischemic Stroke in a Taiwanese population CVDFACTS study. *Journal of the American Heart Association* 2009;108:1524
11. Danesh J, Lewington S, Thompson SG, Lowe GD, Collins R, Kostis JB, et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA*. 2005; 294(14):1799–809.
12. Swarowska M, Janowska A, Polczak A, Mrowiec AK, 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(4):1142–1147
13. Del Zoppo GJ, Levy DE, Wasiewski WW, Pancioli AM, Demchuk AM, Trammel J, et.al. Hyper fibrinogenemia and functional outcome from acute ischemic stroke. *Stroke* 2009; 40(5): 1687-1691.
14. Abdelgawad DM, Elbassiouny AA, Youssef RA, Eldin NS, Elrakawy M. Elevated plasma fibrinogen levels predict poor clinical outcome after acute ischemic stroke. *Egypt J Neurol Psychiatry Neurosurg* 2014;51(1):61–67.
15. Haritha B, Sangeetha B, Sreevaani M. Fibrinogen level in ischaemic stroke. *IORS journal of pharmacy and biological sciences* 2015;10(3): 91-98
16. Li T, Wang F, Peng R, Pei S, Hou Z, Lu Bin et.al. Sex related differences in the association between plasma fibrinogen and non-calcified or mixed coronary atherosclerotic plaques. *Biology of Sex Differences*. 2018;9:51.
17. Samir GM, Khalil OA, Fawzy MS, Sade K, Ayam MEM. Study of fibrinogen level in acute ischaemic stroke patients in medical intensive care unit. *Egyptian Journal of Critical Care Medicine*. 2020;7(2):51-56.
18. Romero JR, Morris J, Pikula A. Stroke prevention: Modifying risk factors. *Therapeutic Advances in Cardiovascular Disease*. 2008;2(4):287-303.

© 2021 Ekwere et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<https://www.sdiarticle4.com/review-history/74478>