

Post-Stroke Depression and Serum High Sensitivity C-Reactive Protein among the Acute Stroke Population of a Teaching Hospital in Ilorin, Nigeria

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Abstract Background: The association between post-stroke depression (PSD) and inflammatory markers has been investigated, but the results were conflicting. We aim to explore the relationship between post-stroke depression (PSD) and high sensitivity C-Reactive Protein (hs-CRP) in a stroke population at the University of Ilorin Teaching Hospital (UITH), Ilorin, Nigeria. **Subjects and Method:** Ninety patients admitted within 72 hours of their first-ever acute stroke were consecutively recruited and followed up for 3 months. They were age- and gender-matched with 90 stroke-free controls. Serum levels of hs-CRP were measured at admission and the first interview in the study and control groups. In both groups, depression and its severity were assessed using the Mini International Neuropsychiatric Interview (MINI) Plus and Hamilton Depression (HAM-D) scales. The National Institutes of Health Stroke-Scale (NIHSS) and Modified Rankin Scale (mRS) were used to assess stroke severity and functional disability. **Results:** The median ages of stroke patients and controls were 59 (IQR, 51–70) and 60 (IQR, 52–65) years, respectively. PSD was present in 22.2% of cases compared to 10.0% in controls ($p=0.026$). There was no significant difference between serum hs-CRP levels in patients with PSD and those without depression (19.35 [IQR, 12.98–23.38] mg/L vs. 18.50 [IQR, 14.3–20.93] mg/L, $P=0.694$). Factors associated with PSD included stroke severity at admission ($\chi^2=11.480$; $p=0.001$) and perceived poor social support ($\chi^2=8.889$; $p=0.003$). However, stroke severity was the only independent predictor of PSD with an adjusted OR of 7.568 (95%CI, 1.874–30.566; $p=0.004$). **Conclusion:** Our patients have a high frequency of PSD, independently associated with stroke severity. Focused rehabilitation of those at risk of PSD is encouraged to reduce its burden.

Keywords: acute stroke, high sensitivity C-reactive protein, Nigeria, post-stroke depression, UITH

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1. Introduction

Stroke is a leading cause of death and neurological disability that imposes heavy burden on families [1]. It produces a wide range of mental/emotional disorders, which include: post-stroke depression (PSD), mania, bipolar disorder, anxiety disorder, apathy without depression, psychotic disorder, pathological affect, and catastrophic reaction [2].

Post-stroke depression is estimated to affect approximately one-third of patients with stroke, with the risk being about two-fold higher at 18 months compared to stroke-free individuals [3,4]. In the USA, Desmond *et al* [5] reported a depression prevalence of 11.2% at 3-month post-stroke versus 5.2% in stroke-free controls. House *et al* [6] in the UK reported a prevalence of PSD at 1 month (12%), 6

months (13%), and 12 months (5%) post-stroke and 7.5% in their controls. Andersen *et al* [7] in Denmark found a prevalence of 17%, 12.1%, and 5.2% at one, three and six months post-stroke, respectively, compared to 7.4% in stroke-free controls. In Nigeria, Oni *et al* [8] reported a PSD prevalence of 22.9%, while none of their controls had depression. Ajiboye *et al* [9] and Oladiji *et al* [10] found depression prevalence of 19.2% and 25.5% among stroke patients attending out-patient neurology clinics, respectively. Post-stroke depression is strongly associated with increased length of hospital stay, increased degree of neurological impairments, higher risk of dependency, and worse rehabilitation outcomes [11].

Several aetiological mechanisms for PSD have been proposed, which comprise biological, social, and psychological theories [12]. Biological theories have four main hypotheses: lesion location, biogenic amines,

inflammatory cytokines, and gene polymorphism [12]. Spalletta *et al* [13] proposed the inflammatory cytokines hypothesis for PSD based on a strong association of proinflammatory cytokines, such as Tumor Necrosis Factor- α (TNF- α), Interleukin-1 β (IL-1 β), IL-6, IL-8, and IL-18, with ischaemic brain injury, thereby resulting in specific subtypes of depression. For example, some cytokines such as IFN-alpha affect serotonin metabolism and the hypothalamus–pituitary–adrenal (HPA) axis, with consequent depression [14,15].

C-Reactive Protein (CRP) is a glycoprotein produced by the liver and plays a significant role in developing atherosclerotic disease in cardiac and cerebral circulation [16,17]. The high sensitivity C-reactive protein (hs-CRP) measures CRP in the low range, from 0.5 to 10 mg/L, and is more precise, with long half-life than standard CRP when measuring baseline concentrations [18]. Kowalska *et al* [19] reported that serum hs-CRP >4.3mg/L was associated with depressive symptoms 3 months post-stroke. Similarly, previous studies found that admission serum levels of hs-CRP were an independent predictor of PSD 6 months post-stroke [20,21]. However, Belmaker and Agam [22] found no association between serum hs-CRP and PSD.

In Sub-Saharan Africa (SSA), including Nigeria, the relationship between serum hs-CRP and the presence of PSD has yet to be investigated. Thus, we examined the frequency and predictors of PSD among hospitalized stroke cohorts, evaluated the relationship between admission serum hs-CRP and the risk of developing PSD three months post-stroke, and compared findings with stroke-free controls' findings.

2. Subjects and Method

The study was conducted in the Stroke Unit of the University of Ilorin Teaching Hospital (UIH), Ilorin, a 600-bed tertiary hospital in north-central Nigeria.

The study participants were consecutively consenting adult patients with acute stroke who were hospitalized between October 2019 and July 2021 and met the inclusion criteria. Patients admitted to the Stroke Unit within 72 hours of symptom onset and had cranial computed tomographic (CT) scan or magnetic resonance imaging (MRI) confirmation of the pathologic type were recruited and followed up for 3 months. We excluded patients with a previous history of psychiatric illness, pre-stroke diagnosis of dementia or significant cognitive impairment, severe aphasia or dysarthria, significant acute neurological illness other than stroke, history (within preceding three months) of myocardial infarction, surgery, and malignancies, underlying known chronic inflammatory conditions (connective tissue and bowel diseases), and those with history of liver insufficiency. Age- and sex- matched stroke-free controls were recruited from the same institution's Department of Family Medicine clinic using systematic random sampling until the estimated sample size was reached.

The validated Questionnaire for Verifying Stroke-Free Status (QVSFS) was used to screen out undiagnosed stroke to recruit appropriate controls [24]. The same exclusion criteria were applied for the controls as for the

study group. Informed consent was taken from each eligible patient or control before entry into the study. Approval for the study was obtained from the Ethics and Research Committee (ERC) of the hospital (ERC PAN/2019/01/1861).

2.1. Data Collection

2.1.1. Socio-demographic and Clinical Variables

The Proforma Questionnaire designed for the study captured variables such as age, sex, body mass index (BMI), social support, level of education, family history of psychiatric disorders, and history of conventional vascular risk factors was obtained by interview with the assistance of two trained research assistants who were resident doctors in the hospital. Each participant was allotted a numerical code written on the questionnaires. The stroke-free group also completed the proforma questionnaire at first contact.

In the cases, stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) [25] at admission, 1 month and 3 months. The NIHSS is a 15-item impairment scale that quantitatively measure vital components of standard neurological examination [25]. Admission NIHSS score was used to classify stroke severity as mild <8, moderate 8-16, and severe ≥ 17 [26]. The instrument has been previously validated and used in stroke studies in Nigeria [27].

The functional outcome in the study group was assessed at 1 month and 3 months after stroke using the modified Rankin Scale (mRS). The mRS is an observer-rated global measure of handicap which is rated zero (no symptoms) to five (severely disabled or bedridden) [23,28]. Patients with an mRS score of 0–2 were categorized as having a good outcome, and those with a score of > 2 as unfavourable [23,29]. The mRS has been used in previous studies to measure functional outcomes in stroke patients [27,29].

2.1.2. Screening for Depression

The primary endpoint was a psychological evaluation for the study group three months post-stroke and first contact for the controls. One of us (MOS) used the depression diagnostic module of MINI plus [30] to conduct interviews for all participants (study and control groups). The diagnoses were made according to the International Classification of Diseases, tenth revision (ICD-10) criteria. The severity of depressive symptoms was assessed using a 17-item Hamilton Depression (HAM-D) scale for the participants (study and control) who had a positive screening for depression when the MINI plus tool was used. The HAM-D Scale, an observer-rated instrument, consists of 17 items assessing depression symptoms [31]. Patients who scored >7 on the HAM-D scale were considered to have PSD. The score is further graded as mild (8-13), moderate (14-18), severe (19-22), and very severe (≥ 23) [32]. The HAM-D scale has been used in previous studies of stroke populations in Nigeria [33].

2.1.3. Blood Collection and Laboratory Testing

At baseline, 2mls of blood was collected using standard aseptic techniques via venipuncture into plain bottles at 8:00 am after the admission for patients in the study group

and at the first interview for the control participants. The freshly collected blood was taken to the laboratory, where it was allowed to clot by placing the tubes in a vertical position at room temperature for 60 minutes. The clotted blood was centrifuged at 12000g after retraction for 10 minutes, and serum was transferred into new plain tubes and stored at -20°C until the time of assay. In vitro quantitative determination of the hs-CRP was carried out by a Chemical Pathologist in the Department of Chemical Pathology, UITH, Ilorin, using the human hs-CRP ELISA kit manufactured by Monobind, Germany. The ELISA protocol and other standard laboratory procedures were strictly followed.

2.2. Data Analysis

All analyses were performed using IBM SPSS Statistics version 20. Results were expressed as percentages for categorical variables and as means (standard deviation, SD) or medians (quartiles) for the continuous variables, depending on the normal or nonnormal distribution of data. Proportions were compared using the Chi-square (χ^2) test, Fisher exact test, and Student's t-test was employed for the normally distributed variables. In contrast, the Mann-Whitney U test was employed for the asymmetrically

distributed variables. The association between clinical depression, hs-CRP, and other variables was determined by logistic regression analysis using odds ratios and their respective 95% confidence intervals.

3. Results

One hundred eight first-ever acute stroke patients were admitted during the study period. However, 12 (11.1%) of them died within one month of their stroke, 6 (5.6%) were lost to follow-up, while the remaining 90 (83.3%) participants (study group) completed the 3-month follow-up study. The controls comprised 90 age- and sex-matched stroke-free volunteers.

3.1. Socio-demographic and Clinical Parameters of the Participants

The median ages of stroke patients and controls were 59.50 (IQR, 51–70) and 60.00 (IQR, 52–65) years, respectively. There was a higher frequency of alcohol use and Cigarette smoking among stroke patients compared to controls (alcohol: 15.6% vs. 3.3%, $p=0.004$ and (cigarette smoking: 12.2% vs. 3.3%, $p=0.022$) (Table 1).

Table 1. Comparison of socio-demographic characteristics of the study group and control participants

Variables	Stroke N=90 n (%)	Control N=90 n (%)	t / χ^2	p value
Age group (years)				
20–30	1 (1.1)	1 (1.1)	$\chi^2 = 7.839$	0.250
31–40	5 (5.6)	5 (5.6)		
41–50	14 (15.5)	12 (13.3)		
51–60	32 (35.6)	30 (33.3)		
61–70	16 (17.8)	30 (33.3)		
71–80	14 (15.5)	9 (10.0)		
81–90	8 (8.9)	3 (3.4)		
Median (IQR) (years)	59.50 (51–70)	60.00 (52–65)		
Sex				
Male	49 (54.4)	42 (46.7)	$\chi^2 = 1.089$	0.297
Female	41 (45.6)	48 (53.3)		
Educational Qualification				
No formal education	16 (17.8)	16 (17.8)	$\chi^2 = 4.082$	0.253
Primary	15 (16.7)	26 (28.9)		
Secondary	21 (23.3)	17 (18.9)		
Tertiary	38 (42.2)	31 (34.4)		
Occupation				
Employed	59 (65.6)	67 (74.4)	$\chi^2 = 1.875$	0.392
Unemployed	13 (14.4)	11 (12.2)		
Retired	18 (20.0)	12 (13.3)		
Marital Status				
Single	1 (1.1)	6 (6.7)	$\chi^2 = 7.561$	0.057 ^F
Married	72 (80.0)	76 (84.4)		
Divorced	1 (1.1)	1 (1.1)		
Widowed	16 (17.8)	7 (7.8)		
Vascular risk factors				
Hypertension	39 (43.3)	34 (37.8)	6.568	0.087
Diabetes Mellitus	6 (6.7)	4 (4.4)		
HTN-DM	16 (17.8)	8 (8.9)		
None	29 (32.2)	44 (48.9)		
Cigarette				
Yes	11 (12.2)	3 (3.3)	5.246	0.022
No	79 (87.8)	87 (96.7)		
Alcohol				
Yes	14 (15.6)	3 (3.3)	8.466	0.004
No	76 (84.4)	87 (96.7)		

$p < 0.050$ (significant); χ^2 = chi square test; t = student's t-test; ^F = Fisher's Exact Test, IQR=interquartile range, HTN: Hypertension; DM: Diabetes.

Table 2. Stroke severity and functional outcome in the stroke patients

Variables	At admission	At 1 month	At 3 months
NIHSS n(%)			
Mean	8.42±3.97	6.63±2.94	5.06±2.70
Median (IQR)	6 (6.0–9.0)	6 (4.0–6.0)	4 (4.0–4.3)
Mild <8	47(52.2)	70(77.8)	77(85.6)
Moderate 8–16	39(43.3)	19(21.1)	12(13.3)
Severe ≥17	4 (4.4)	1(1.1)	1 (1.1)
mRS n(%)			
≤2		3(4.3)	13(14.4)
>2		87(96.7)	77(85.6)

NIHSS: National Institutes of Health Stroke Scale score: Mild <8; moderate 8–16; and severe ≥17; **IQR:** interquartile range; **mRS:** Modified Rankin scale score ≤2 = Good outcome; **mRS** >2 = Unfavourable outcome.

Among the study participants, 49 (54.4%) were male, 61 (67.8%) had an ischemic stroke, and 46 (51.1%) had a right hemispheric stroke.

At admission, the median NIHSS score was 6.0 (IQR, 6–9). Overall, an unfavorable outcome at 3-month was observed in 77 patients (85.6%), defined by a Rankin scale, > 2, whereas a total of 13 (14.4%) patients had a good functional outcome defined by an mRS 0–2 (Table 2).

3.2. Comparison of the Prevalence of PSD among Study Participants and Depression in the Control Group

The prevalence of depression in stroke patients (PSD) was 20 (22.2%), while 9 (10.0%) in the control group were diagnosed with depression ($\chi^2=4.974$; $p=0.026$). Among the study group with PSD, 13 (65%) had severe to very severe depressive illness, while 1 (5%) and 6 (30%) had mild and moderate depressive episodes, respectively, using the HAM-D score.

3.3. Comparison of the Serum hs-CRP in the Study Group and Control Participants

The stroke survivors' (study group) showed significantly higher levels of serum hs-CRP than stroke-free volunteers (controls) (18.10 [IQR, 12.40–20.93] mg/L versus 2.20 [IQR, 0.90–3.93] mg/L; $p<0.001$) (Table 3).

Among the stroke survivors, 3 (3.3%) cases had low to normal serum value of hs-CRP (≤3.0mg/L), while a

majority of patients, 87 (96.7%), had high risk (>3.0mg/L) for future cardiovascular events. This is statistically significant when compared to controls, where only 32 (35.6%) respondents had high risk, while 58 (64.4%) were in the category of low/normal ($\chi^2=75.010$; $p<0.001$).

However, among stroke survivors, there was no significant difference between study participants with PSD and those without depression (19.35 [IQR, 12.98–23.38] mg/L vs. 18.50 [IQR, 14.3–20.93] mg/L, $P=0.694$; Table 3). A similar trend of non-significant difference was found between controls with depression and those without depression (3.30 [IQR, 2.50–6.60] mg/L vs. 1.90 [IQR, 0.90–3.75] mg/L, $P=0.102$).

3.4. Predictors of Post-Stroke Depression (PSD)

Table 4 showed that perceived poor social support ($\chi^2= 8.889$; $p=0.003$) and stroke severity at admission ($\chi^2= 11.480$; $p=0.001$) were significantly associated with PSD following chi-square analysis. Although the median score of admission serum hs-CRP among respondents with PSD was slightly higher than those without PSD (19.35 [IQR, 12.98–23.38] mg/L vs. 18.50 [IQR, 14.3–20.93] mg/L), this did not attain the level of significance ($p = 0.694$). Other variables did not show an association.

Following regression analysis after adjusting for possible covariates, stroke severity at admission ($OR=7.568$, 95% CI [1.874–30.566], $p=0.004$) was the only significant predictor of PSD (Table 5).

Table 3. Comparison of serum hs-CRP in the study group and control participants

Serum hs-CRP (mg/L)	Stroke N=90 n(%)	Control N=90 n(%)	t/ χ^2	P
Low/Normal (≤ 3.0)	3 (3.3)	58 (64.4)	$\chi^2 = 75.010$	<0.001
High risk (> 3.0)	87 (96.7)	32 (35.6)		
Mean score	16.69±6.29	3.31±3.23	t=17.952	<0.001
Median (IQR) (mg/L)	18.10(12.40–20.93)	2.20(0.90–3.93)		<0.001 ^{xx}
	Stroke with PSD N=20 n(%)	Stroke without depression N=70 n(%)		
Low/Normal(≤ 3.0)	0 (0.0)	2 (2.9)	0.584	1.000 ^F
High risk (>3.0)	20 (100.0)	68 (97.1)		
Mean score	18.12±6.78	16.91±6.08	t=0.765	0.446
Median (IQR) (mg/L)	19.35(12.98–23.38)	18.50 (14.3–20.93)		0.694 ^{xx}

$p < 0.050$ (significant); χ^2 = chi square test; t = student's t-test; ^F = Fisher's Exact Test; IQR = interquartile range; ^{xx}p value was assessed using Mann-Whitney U test.

Table 4. Factors associated with depression (PSD) among stroke participants

Variables	Depression (PSD)		t / χ^2	P
	Present N=20 n (%)	Absent N=70 n (%)		
Mean age (years)	55.95±13.79	61.74±13.35	-1.699	0.093
Mean BMI (kg/m ²)	26.30±5.64	25.63±3.58	0.640	0.524
Gender				
Male	11 (55.0)	38 (54.3)	0.003	0.955
Female	9 (45.0)	32 (45.7)		
Occupational status				
Employed	14 (70.0)	45 (64.3)	1.915	0.367 ^F
Unemployed	4 (20.0)	9 (12.9)		
Retired	2 (10.0)	16 (22.8)		
Marital status				
Single	1 (5.0)	0	6.334	0.175 ^F
Married	15(75.0)	58 (82.9)		
Separated	1(5.0)	0 (0.0)		
Divorced	0 (0.0)	1(1.4)		
Widow	3(15.0)	11(15.7)		
Cigarette smoking				
Yes	3 (15.0)	8 (11.4)	0.185	0.667
No	17 (85.0)	62 (88.6)		
Alcohol use				
Yes	3 (15.0)	10 (14.3)	0.006	0.936
No	17 (85.0)	60 (85.7)		
Social Support				
Good	7 (35.0)	50 (71.4)	8.889	0.003
Poor	13 (65.0)	20 (28.6)		
Stroke type				
Ischaemic	11 (55.0)	50 (71.4)	1.922	0.166
Haemorrhagic	9 (45.0)	20 (28.6)		
Stroke lateralization				
Right hemisphere	8 (40)	38 (54.3)	1.270	0.260
Left hemisphere	12 (60)	32 (45.7)		
NIHSS at admission				
Mild	4(20.0)	44 (62.9)	11.480	0.001 ^F
Moderate/Severe	16 (80.0)	26 (37.1)		
NIHSS at 1 month				
Mild	15 (75.0)	58(82.9)	0.627	0.518 ^F
Moderate/Severe	5 (25.0)	12(17.1)		
mRs at 1month				
Good outcome	0 (0.0)	3 (4.3)	0.887	1.000 ^F
Unfavourable outcome	20 (100.0)	67 (95.7)		
mRs at 3 months				
Good outcome	1 (5.0)	12 (17.1)	1.856	0.283 ^F
Unfavourable outcome	19 (95.0)	58 (82.9)		
Serum hs-CRP				
High risk	20 (100.0)	68 (97.1)	0.584	1.000 ^F
Low/Normal	0 (0.0)	2 (2.9)		
Median score(mg/L)	19.35	18.50		0.694 ^{xx}

p < 0.050 (significant); χ^2 = chi square test; t = student's t-test; ^F: Fisher's exact Test; ^{xx}p was assessed using Mann-Whitney U test.

Table 5. Univariate and multivariate logistic regression analysis for PSD

Predictors	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	P
Age	0.967	0.930–1.006	0.097	0.972	0.929–1.018	0.229
Gender	0.972	0.358–2.637	0.955	0.960	0.252–3.664	0.953
BMI	1.038	0.926–1.164	0.521	1.064	0.915–1.237	0.419
Stroke type	2.045	0.736–5.685	0.170	1.262	0.331–4.807	0.734
Stroke laterality	1.781	0.648–4.894	0.263	1.562	0.476–5.121	0.462
Social support	1.667	0.593–4.687	0.333	1.755	0.449–6.860	0.419
hs-CRP	1.034	0.950–1.125	0.442	1.041	0.944–1.148	0.418
NIHSS at admission	6.769	2.043–22.433	0.002	7.568	1.874–30.566	0.004
NIHSS at 1 month	1.611	0.491–5.284	0.431	0.488	0.108–2.204	0.351
mRs at 3 month	3.931	0.479–32.255	0.202	1.946	0.196–19.355	0.570

OR: odds ratio; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; hs-CRP: High-sensitivity C-reactive protein; mRs: Modified Rankin Scale.

4. Discussion

This study investigated the relationship between PSD and serum hs-CRP among the first-ever acute stroke patients in comparison to stroke-free controls.

4.1. Comparison of Prevalence of Depression in the Study Group and Controls

This study found a depression prevalence of 22.2% among the stroke cohorts at 3-month post-stroke versus 10% in the controls using MINI plus. This compares well with the prevalence of 22.9% (PSD) reported by Oni *et al* [8] in Nigeria; however, none of their controls (stable hypertension) was clinically depressed based on the Schedule of Clinical Assessment in Neuropsychiatry (SCAN) tool. The differences in the control prevalence rate could be due to the patient's characteristics and the assessment scales used. Herrmann and colleagues [34] in Canada reported a PSD prevalence of 22% at 3-month post-stroke. Similarly, Townend *et al* [35] in Australia and Wang *et al* [36] in China found PSD prevalence of 21% and 26.8% at 3-month post-stroke, respectively. The results in these studies are consistent with the findings in the present study, even though no control groups were used in their studies. However, Andersen and colleagues [7] reported a varying prevalence of depression among the first-ever stroke cases at 1 month (17%), 3 months (12.1%), and 6 months (5.2%) post stroke and 7.4% in their controls based on the HAM-D scores of >13. Desmond and colleagues [5] reported a prevalence of 11.2% at 3-month post stroke versus 5.2% in stroke-free controls using the HAM-D scale; lower than the results in the present study. Desmond's study recruited only ischemic stroke cohorts compared to all stroke cases in the present study. However, Hayee and colleagues [37] reported a prevalence rate of 41% among the first-ever stroke patients at 3 months following stroke versus 18% in the controls. These differences were maintained at 12-month post-stroke (42% vs. 19%) based on Beck's depression inventory (BDI score >10). A possible reason for this might be due to differences in the patient's

characteristics, diagnostic tools used, timing of assessment, and sample size, among others.

4.2. Comparison of the Serum hs-CRP in the Study Group and Controls

The present study found a significantly high level of admission serum hs-CRP among the stroke cohorts compared to stroke-free controls (18.10 [IQR, 12.40–20.93] mg/L versus 2.20 [IQR, 0.90–3.93] mg/L). The results agree with the findings (17.7 ± 14.4 mg/L vs. 1.1 ± 1.7 mg/L) by Abubakar *et al* [38] in Lagos, Nigeria, even though the latter study measured mean serum CRP. Difusa and colleagues [39] in India reported the mean serum hs-CRP values of 7.91 ± 3.0 mg/L and 2.19 ± 0.3 mg/L in stroke cases and controls, respectively. Tu *et al* [23] in China found higher median serum hs-CRP levels in acute ischaemic stroke patients as compared to normal controls (4.4 [IQR, 2.1–15.0] mg/L vs. 2.8 [IQR, 1.7–4.0] mg/L). These differences may be due to genetics, stroke type, timing of sample collection, and assay. This was supported by the study of Ben-Assayag *et al* [40], where genetics was reported to influence CRP production. Also, Di Napoli *et al* [41] in Italy reported that plasma CRP increases markedly over 72 hours (with 4-point samples) before it stabilizes with median CRP scores ranging from 7.9 mg/L, 46 mg/L, 70 mg/L, and 83.3 mg/L at admission, 24 hours, 48 hours, and 72 hours respectively following spontaneous intracerebral hemorrhage. In a separate study, Di Napoli and colleagues [42] opined that elevated serum hs-CRP could occur in the presence of overt inflammatory disease or infection. They recommended that data interpretation be cautiously and possibly CRP titration repeated after the underlying acute insult has resolved for long-term stratification purposes.

Furthermore, we found a significantly high median serum level of admission hs-CRP among stroke cohorts with PSD at 3-month after stroke, as compared with those with depression in stroke-free controls (19.35 [IQR, 12.98–23.38] mg/L vs. 3.30 [IQR, 2.50–6.60] mg/L). The inflammatory cascade of events has been well described in both stroke and depression [43], highlighting the significance of pro-inflammatory cytokines acting as

biochemical mediators. There are a few available studies on the relationship between serum hs-CRP and PSD with varying results. One study found that a higher serum level of CRP ($>9.2\text{mg/L}$) was related to more significant depressive symptoms at 8-day post-stroke, while CRP $>4.3\text{mg/L}$ was associated with depressive symptoms 3 months post stroke [19]. Also, some authors reported an increased risk of PSD at 6-month post stroke with admission serum hs-CRP values of $\geq 8.5\text{mg/L}$ [20,21]. Other researchers found no association [22].

Also, the present study found a serum hs-CRP median value of 3.30mg/L in depressed stroke-free controls. A previous study conducted among a healthy population in Northern Finland found that men with serum hs-CRP values of $>3\text{mg/L}$ had a four-fold increased risk of recurrent depression [44]. Similarly, a mean serum concentration level of hs-CRP of 5.64mg/L and 5.40mg/L was reported in non-stroke patients with major depressive disorder in males and females, respectively [45]. However, Valkanova and colleagues found that raised CRP was related to a small but significant risk of subsequent depression [46].

4.3. Predictors of Post-Stroke Depression (PSD)

Our study observed that the admission serum hs-CRP value measured within 72 hours of stroke onset is not significantly related to the risk of PSD at 3 months after stroke. This is consistent with findings by Jimenez *et al* [47] in Spain which showed no significant association between the serum CRP level and the risk of PSD at 1-month post stroke. However, studies by Yang *et al* [20] and Tang *et al* [21] found a significant relationship between admission serum hs-CRP value and PSD at 6 months post stroke. Also, Cheng and colleagues [48] found that a higher CRP level measured within 24 hours after stroke onset predicts an increased risk of depression one-year post-stroke. Possible reasons for these differences may include differences in sample size, diagnostic tools, assessment timing, and assay method in the different studies [20,47,48]. Therefore, multi-centre collaborative (longitudinal) studies are required to clarify further the relationship between serum hs-CRP and the risk of PSD.

Furthermore, the current study found a significant association between perceived poor social support and PSD, which agrees with previous studies [35,49]. Social support helps alleviate psychological problems associated with impairment in chronic illnesses, including stroke and provides the motivation that may enhance the quality of life of stroke patients [50]. This might explain why respondents with perceived good social support had less risk of depression when compared to those with poor social support.

Previous studies have shown a significant association between stroke severity and the risk of developing PSD at 6-month post stroke using NIHSS score [20,21,51]. The present study showed that respondents with moderate to severe stroke at admission were significantly more likely to develop PSD at 3-month post-stroke. This is in keeping with the results of previous studies [52,53]. However, Li *et al* [54] did not find such an association in China.

Previous studies on the relationship between functional outcomes and PSD needed to be more consistent due to

wide discrepancies in the instruments used. Townend *et al* [35] and Astrom *et al* [49] reported that functional disability measured at 3-month after stroke was a significant predictor of PSD. One study revealed that functional impairments do not determine the onset of depression but interact with depression, resulting in a poorer long-term functional recovery [49]. In contrast, other studies [20,21,54] found no association, which is in keeping with the findings in the present study.

Following multivariate regression analysis, stroke severity was the only independent predictor found in this study, with approximately 7.6-fold odds of developing PSD at 3-month after stroke, consistent with findings previously reported in other studies, though at 6-month post stroke [20,21]. However, admission serum hs-CRP and levels of social support were not predictive in our study, contrary to findings from some other previous studies [20,21,35,53].

Similar to findings from previous publications [8,9], the present study showed that age, gender, BMI, occupational status, and stroke type, including laterality, were not significantly associated with PSD. Some studies have, however, reported a significant relationship between age [21], female gender [10,55], and right hemispheric stroke [10] with PSD.

4.4. Limitations of the Study

This study was performed at a tertiary care center, and all recruited stroke patients were admitted to a dedicated Stroke Unit and treated by Neurologists specializing in stroke. This might have contributed to improved neurologic outcomes and decreased PSD prevalence. Serum hs-CRP was measured only once at admission among study participants. The study therefore provided no data on the pattern of change of serum hs-CRP at 3-month follow-up. The assessment of depression was made only at a single point. Repeated measurement at different points for one year would have given more insight into the trend of depression, but due to limited resources, this could not be achieved. Some patients who died and those who lost to follow-up before completing the 3-month follow-up study were excluded. This group of people might have suffered a more severe stroke, predisposing them to depression which might have been missed.

4.5. Strength of the Study

This is the first study to examine the relationship between serum hs-CRP and the development of PSD among first-ever stroke patients in Nigeria, as no documented previous studies were found. All subjects (stroke survivors) recruited had neuro-imaging (CT/MRI) to confirm stroke diagnosis. Internationally standardized and validated instruments were used in this study. This makes the study comparable to other standard international studies on the topic.

5. Conclusion

Depression is a common post-stroke complication, with a prevalence of 22.2% versus 10% in controls. Stroke

severity was the only independent predictor of PSD in this study. Furthermore, there was no significant difference in admission serum hs-CRP levels between stroke survivors with PSD and those without depression. More longitudinal studies, especially in Nigeria and other low- and middle-income countries (LMICs) are needed to determine the role of serum hs-CRP in developing PSD. There is also a need for clinicians and other health professionals involved in stroke care to have a high index of suspicion for PSD to initiate appropriate care to ensure better clinical outcome.

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Declarations of Conflicting Interests

The author(s) declare that there are no conflicts of interest.

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