Prevalence, Trajectory, and Predictors of Poststroke Fatigue among Ghanaians

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Background and Purpose: Poststroke fatigue (PSF) is rife among stroke survivors and it exerts a detrimental toll on recovery from functional deficits. The burden of PSF is unknown in sub-Saharan Africa. We have assessed the prevalence, trajectory, and predictors of PSF among 60 recent Ghanaian stroke patients. *Methods:* Study participants in this prospective cohort (recruited between January 2017 and June 2017) were stroke survivors, aged greater than 18 years, with CT scan confirmed stroke of less than 1-month onset. PSF was assessed using the Fatigue Severity Scale (FSS) at enrollment, months 3, 6, and 9. Those with a score of greater than or equal to 4 points on FSS were categorized as "fatigued." A multivariate logistic regression analysis was performed to identify independent predictors of PSF at enrollment and at month 9. *Results:* Sixty-five percent (65%) of our sample were males with a mean age of 55.1 ± 12.7 years. In addition to all participants having hypertension, 85% had dyslipidemia and 25% had diabetes mellitus. Ischemic strokes comprised 76.6% of the study population. The prevalence of PSF was 58.9% at baseline and declined to 23.6% at month 9, $P = .0002$. Diabetes mellitus was significantly associated with PSF at baseline with an adjusted odds ratio of 15.12 (95% CI: 1.70-134.30), $P = .01$. However, at month 9, age greater than or equal to 65 years, adjusted odds ratio (aOR) of 7.02 (95% CI: 1.16-42.52); female sex, aOR of 8.52 (1.23-59.16), and depression, aOR of 8.86 (1.19-65.88) were independently associated with PSF. *Conclusions:* Approximately 6 out of 10 Ghanaian stroke survivors experience PSF within the first month of stroke onset. PSF persists in approximately 1 out of 4 stroke survivors at 10 months after the index stroke. Further studies to elucidate the underlying mechanisms for PSF are required and adequately powered interventional multicenter trials are eagerly awaited to provide solid evidence base for the clinical management of PSF.

Key Words: Poststroke fatigue—Ghana—risk factors—depression

Introduction

Poststroke fatigue (PSF) is a major enduring and disabling complaint after stroke with detrimental impacts on quality of life, rehabilitation, work capacity, suicide risk, and all-cause mortality.[1-7] PSF is variously described as a sense of early exhaustion with weariness, lack of energy, and an aversion to effort[8] involving physical, emotional, and cognitive experiences[9] and is usually not relieved by rest.[10] The prevalence of PSF has varied between 23% and 75% from various reports.[11] Factors associated with PSF include female sex, older age, presence of neurological deficits, sleep disturbances, use of medications, depression, cognitive dysfunction, prestroke fatigue, family dysfunction, and location of strokes.[11-15] A meta-analysis of

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randomized controlled trials of interventions for PSF found insufficient evidence for 5 pharmacological interventions: fluoxetine, enerion, (-)-OSU6162, citicoline, and a combination of Chinese herbs, and 2 nonpharmacological interventions namely a fatigue education program and a mindfulness-based stress reduction program to prevent or treat PSF.[16,17]

The burden of PSF is unknown on the African continent. However, similar to other Low- and Middle-Income countries on the globe, the burden of stroke in sub-Saharan Africa (SSA) is rising[18-23] although recent estimates suggest higher lifetime risk of stroke and stroke related mortality in East and central Asia.[24,25] Stroke in SSA characteristically affects a younger age group and is associated with significant poststroke mortality and morbidity including depression, cognitive impairment, and social stigma.[26-36] Poststroke rehabilitation in the region is severely challenged due to limited availability of physiotherapists and the high cost of rehabilitation services.[37-40] In view of the aforementioned features of stroke in SSA, we postulated that PSF may be prevalent in the region. We therefore sought to assess and describe the frequency, the trajectory, and the factors associated with PSF among a prospective cohort of stroke survivors.

Methods

Study Design and Setting

This study is a secondary analysis of a cohort of 60 recent Ghanaian stroke survivors involved a pilot randomized trial assessing the feasibility of using a mobile health intervention under nurse guidance to improve blood pressure (BP) control.[41] Our study was approved by the Committee on Human Research Publication and Ethics of the School of Medical Sciences, Kwame Nkrumah University of Science and Technology, in Kumasi, Ghana, as well as the Institutional Review Board at the Medical University of South Carolina. The study was conducted at the Neurology Clinic of the Komfo Anokye Teaching Hospital, a tertiary medical center in Kumasi, Ghana. Kumasi is the second largest city in Ghana with an estimated population of 4 million inhabitants. The Neurology clinic was instituted in 2011 and currently runs once a week providing care for adults greater than 16 years with neurologic disorders from 6 out of the 10 administrative regions of Ghana and serves an estimated population of 10 million.[42] The protocol and baseline characteristics of study participants have been previously published elsewhere.[41,43,44] Prospective assessments for PSF were conducted at baseline, months 3, 6, and 9.

Evaluation of Study Participants

We collected demographic information including age, gender, educational, and occupational status as well as location of residence. Vascular risk factor profile was assessed among stroke survivors based on self-report, use of relevant medications, and review of medical records for evidence of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, or other cardiac disorders, and history of cigarette smoking and alcohol use. The following criteria were used to assess vascular risk factor status and PSF.

- PSF was assessed using the Fatigue Severity Scale (FSS), one of the most widely used instruments in stroke studies[45,46] with good validity and reliability.[47,48] FSS evaluates the influence of fatigue on daily life and contains 9 items, each with a score ranging from 1 (completely disagree) to 7 (completely agree) on a Likert scale. The average score of the 9 item responses was calculated for each participant. Participants with a score of greater than or equal to 4 points were categorized as "fatigued" with higher scores indicating more severe fatigue.
- Participant weight was measured in kilograms using a scale with patient standing at the anatomical position on a scale, and height measured in centimeters using a stadiometer with patient standing at the anatomical position in front of the stadiometer. The weight and height measurements were used to calculate the body mass index at enrollment.
- BP was measured thrice on the upper left arm using a validated automatic sphygmomanometer, after at least 5 min of rest and the second and third readings were averaged for analysis. Hypertension was diagnosed if the patient was on antihypertensive medications over the last 15 consecutive days or if the patient had a systolic and/or diastolic BP of greater than or equal to 140/90 mmHg.
- Participants were considered to have diabetes mellitus if they were on hypoglycemic medications or if their fasting blood glucose levels were greater than 126 mg/dl and/or HbA1C greater than 6.5%.
- Dyslipidemia was defined as a high total cholesterol greater than 200 mg/dl or LDL-cholesterol greater than 130 mg/dl, triglyceride greater than 150 mg/dl or HDL-cholesterol less than 40 mg/dl for women and less than 50 mg/dl for men or previous use of statin for dyslipidemia.
- Current smoking status and alcohol intake status were ascertained from either the patient self-report or report from a reliable relative. A high alcohol intake was defined as greater than or

equal to 14 units per week for women, and greater than or equal to 21 units per week for men.

Stroke type was defined radiologically into ischemic and hemorrhagic based on cranial CT scan done at onset of stroke symptoms for all study participants. Stroke severity was assessed using National Institute of Health Stroke Scale,[49] and functional status was assessed using the Barthels' Activities of Daily Living.[50] The Hamilton Depression Rating Scale[51] was used to assess risk of depression. Data were obtained by 2 trained Research Assistants by reviewing medical charts, and interviewing stroke survivors and/or their proxies where applicable.

Statistical Analysis

Means and medians were compared using the Student's *t* test or Mann-Whitney's *U* test for paired comparisons. Proportions were compared using the chi-squared test with Yates correction for proportions with subgroupings less than 5. Pearson's correlation coefficient was calculated for 2 continuous variables. A multivariate logistic regression analysis was performed to identify independent predictors of PSF at enrollment and at month 9. The putative factors included in the multivariable logistic regression were carefully selected on the basis of literature review and empiric evidence from our data (significant associations observed in bivariate analyses). In all analysis, 2-tailed *P* values <.05 were considered statistically significant with no adjustments for multiple comparisons. Descriptive statistics were used for trajectory of PSF. Statistical analysis was performed using SPSS version 19 and GraphPad Prism version 7.

Results

Demographic and Clinical Characteristics of Study Participants

We recruited 60 recent stroke survivors with hypertension within 1 month of onset of stroke with a mean age of 55.1 ± 12.7 years, of which 65% were males. Ischemic strokes constituted 76.6% of primary stroke types. In addition

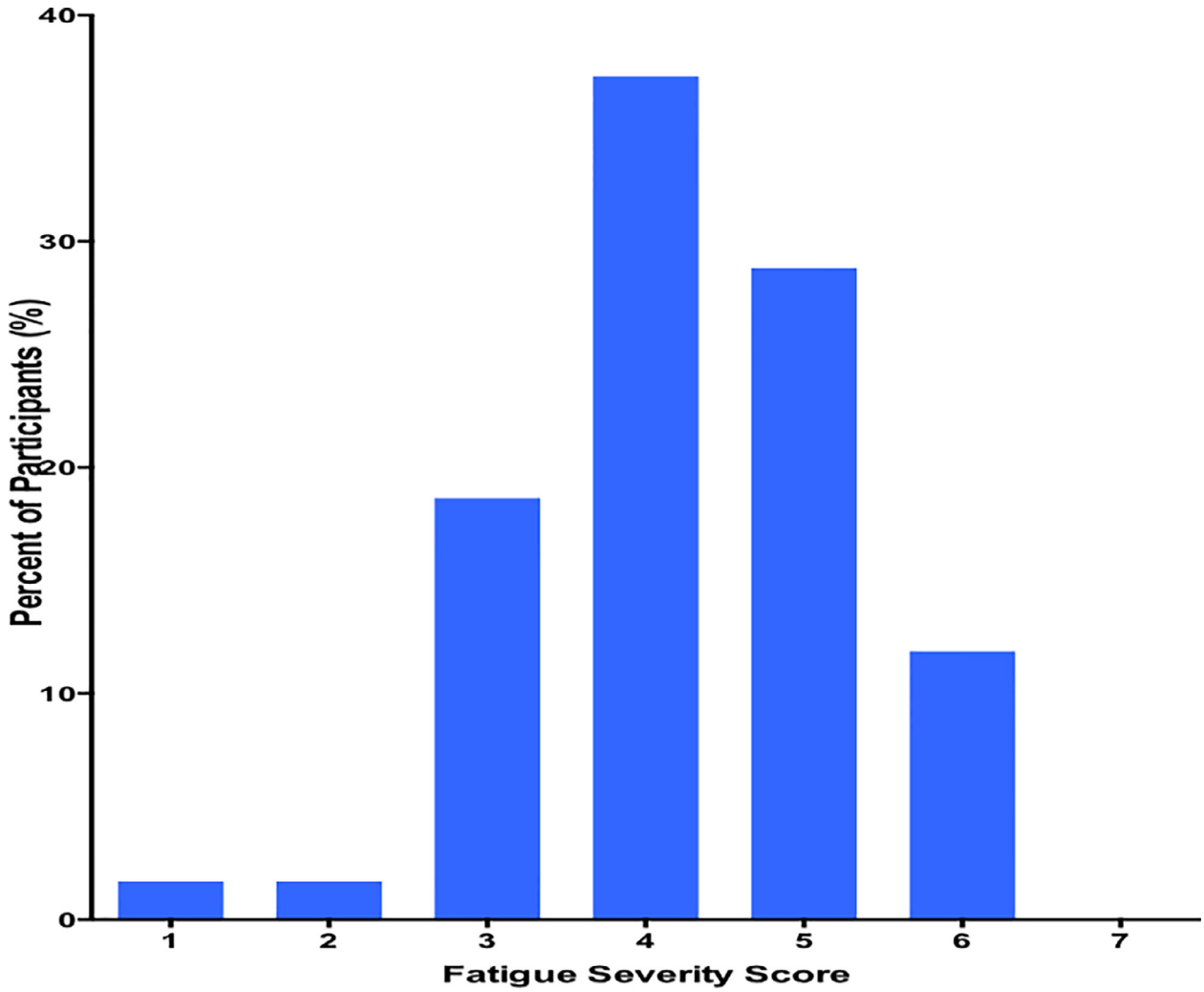

Figure 1. *Distribution of fatigue severity scores among Ghanaian stroke patients.*

to all participants having hypertension, 85% had dyslipidemia and 25% had diabetes mellitus (see STROBE statement).

Prevalence of PSF at Baseline

The mean averaged score on the FSS at baseline was 4.2 ± 1.1. The distribution of FSS scores as depicted in Figure 1 shows a rightward shift towards more severe fatigue symptoms for the prospective cohort recruited within 1 month after stroke (Fig 1). The prevalence of PSF was 58.9% (95% CI: 45.9%-70.8%). Table 1 shows a comparison of demographic and clinical characteristics of the study population according to PSF status. Demographic and clinical characteristics were comparable between the 2 groups with the following notable exceptions. First, there was a preponderance of diabetes mellitus among those with PSF at baseline of 38.9% compared with 4.2% among those without PSF, $P = .002$. Second, the mean systolic BP among participants with PSF of 137.3 ± 27.8 mmHg was significantly lower than 153.7 ± 21.8 mmHg among those without PSF, $P = .02$. Third, statin therapy was more likely to have been initiated poststroke among those without PSF, 87.5% versus 61.1% among those with PSF at baseline, $P = .03$ (Table 1).

Trajectory of PSF

Mean scores of FSS declined from 37.4 ± 9.3 at baseline, to 33.0 ± 8.0 at month 3, 33.8 ± 7.5 at month 6 and to 30.5 ± 9.8 at month 9, $P = .0005$. Scores on the Hamilton's Depression Rating Scale (HDRS) declined significantly at the same time points (Fig 2A). The slope of decline in FSS scores over time among those with low risk score for depression, HDRS (0-7) at baseline compared with those with HDRS scores greater than 7 at baseline was not significantly different (P value = .97, for comparison of 2 slopes by linear regression). However, at month 9, there was a significantly lower mean FSS score of 24.2 ± 5.4 among those with no depression risk at baseline compared with 32.4 ± 10.2, $P = .01$ among those at high risk of depression at baseline (Fig 2B). The trajectory of FSS scores among those on fluoxetine was not significantly divergent from those not on fluoxetine (Fig 2C). The slopes of FSS scores over time among participants with

Table 1. *Demographic and clinical characteristics of study participants according to Fatigue Severity Score*

Characteristic	Fatigue Severity Score <4 n = 24	Fatigue Severity Score ≥4 n = 36	Total n = 60	*P* value
Age, mean ± SD	56.3 ± 13.5	54.3 ± 12.3	55.1 ± 12.7	.56
Females, n (%)	8 (33.3)	13 (36.1)	21 (35.0)	.83
Location of residence, n (%)				.29
Urban	16 (66.7)	19 (52.8)	35 (58.3)	
Semi-urban/rural	8 (33.3)	17 (47.2)	25 (41.7)	
Educational status, n (%)				.07
None	0 (0.0)	3 (8.3)	3 (5.0)	
Primary	8 (33.4)	20 (55.6)	28 (46.7)	
Secondary	11 (45.8)	7 (19.4)	18 (30.0)	
Tertiary	5 (20.8)	6 (16.7)	11 (18.3)	
Stroke type				.80
Ischemic	18 (75.0)	28 (77.8)	46 (76.7)	
Hemorrhagic	6 (25.0)	8 (22.2)	14 (23.3)	
Diabetes mellitus, n (%)	1 (4.2)	14 (38.9)	15 (25.0)	.002**
Systolic BP, mean ± SD	153.7 ± 21.8	137.3 ± 27.8	143.8 ± 26.6	.02
Diastolic BP, mean ± SD	94.8 ± 13.4	87.7 ± 16.4	90.5 ± 15.5	.08
Waist circumference, mean ± SD	93.3 ± 12.4	91.0 ± 11.6	91.9 ± 11.9	.48
Body mass index, mean ± SD	27.7 ± 5.2	26.2 ± 5.6	26.8 ± 5.5	.33
Barthels index, mean ± SD	75.4 ± 22.6	78.3 ± 24.1	77.2 ± 23.4	.64
NIHSS score, mean ± SD	4.7 ± 2.8	4.6 ± 3.5	4.7 ± 3.2	.94
HDRS score, mean ± SD	10.7 ± 5.8	10.9 ± 5.7	10.9 ± 5.7	.90
# Antihypertensive medications, mean ± SD	2.9 ± 1.0	2.4 ± 0.9	2.6 ± 1.0	.09
Methyldopa, n (%)	4 (16.7)	11 (30.6)	15 (25.0)	.22
Angiotensin receptor blocker, n (%)	14 (58.3)	19 (52.8)	33 (55.0)	.67
Fluoxetine, n (%)	9 (37.5)	16 (44.4)	25 (41.7)	.59
Statins, n (%)	21 (87.5)	22 (61.1)	43 (71.7)	.03*
Antiplatelets, n (%)	15 (62.5)	16 (44.4)	31 (51.7)	.17
Multivitamins, n (%)	3 (12.5)	8 (22.2)	11 (18.3)	.34

Abbreviations: BP, blood pressure; SD, standard deviation.
*P value<0.05.
**P value<0.005.

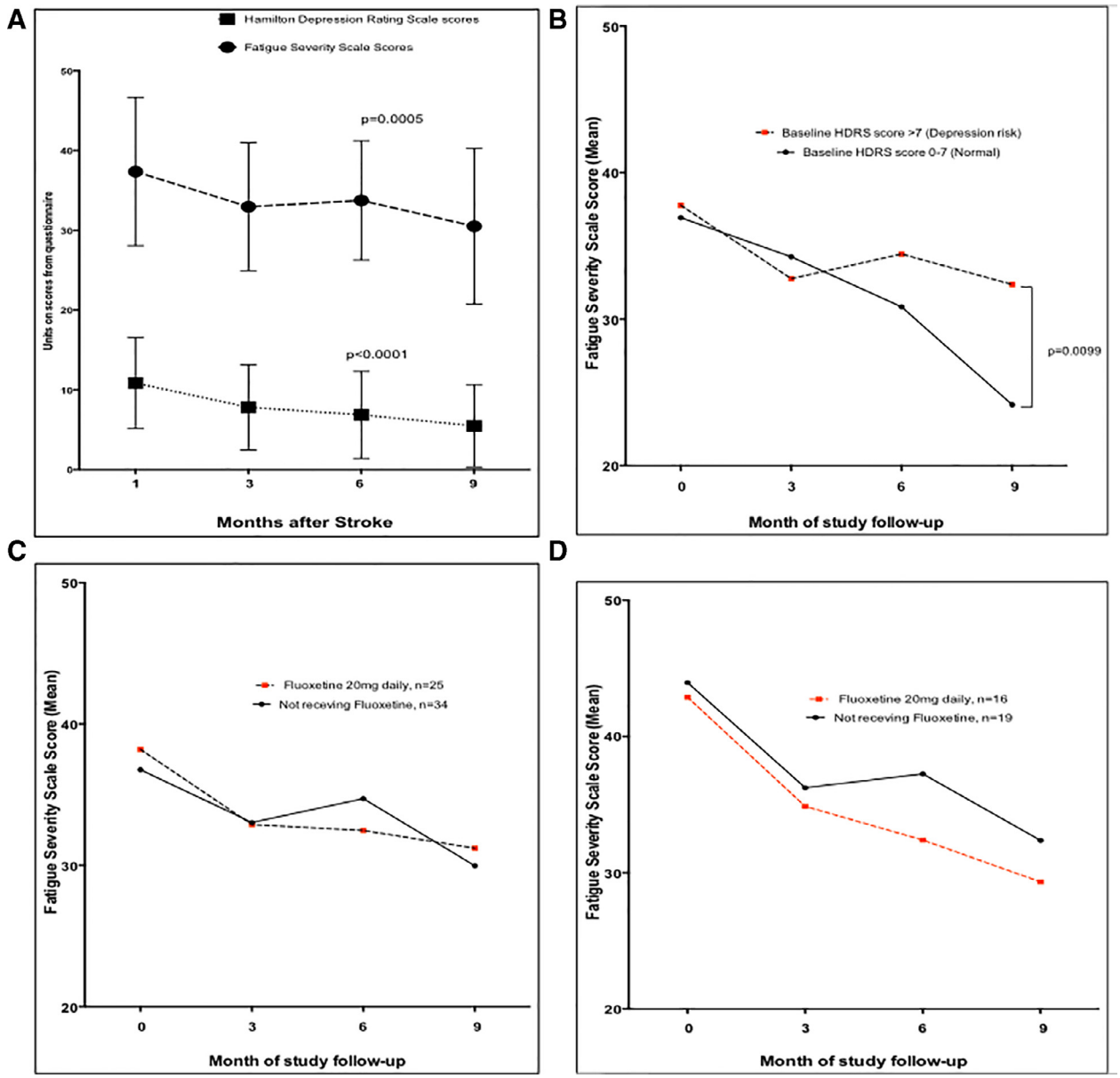

Figure 2. *Trajectory of poststroke fatigue among Ghanaians. (A) Trajectory of poststroke fatigue scores in relation to depression scores assessed using the Hamilton Depression Rating Scale over time. (B) Trajectory of fatigue severity scores over time according to baseline depression risk assessed using the Hamilton Depression Rating Scale cut-off of 0-7 (normal) versus >7 (risk of depression). (C) Comparison of trajectories of fatigue scores among those prescribed fluoxetine and those not on fluoxetine at baseline. (D) Comparison of trajectory of fatigue severity scores among a subset of patients with poststroke fatigue prescribed fluoxetine versus those not on fluoxetine over time. Dots are means and bar represent standard deviations.*

PSF at baseline on fluoxetine compared with those not on fluoxetine were not significantly different, P value = .92, for comparison of 2 slopes by linear regression (Fig 2D). Overall, the proportion of stroke survivors at baseline with PSF was 33 of 56 (58.9%) with a significant decline to 13 of 55 (23.6%) at month 9, P = .0002 (Fig 3).

Factors Associated with PSF at Baseline

In unadjusted analyses, having no or primary level education, having diabetes mellitus, systolic BP at enrollment and use of statin were associated with risk of PSF. Upon adjustment in a multivariate analysis, only diabetes mellitus maintained a significant association with PSF with adjusted odds ratio of 15.12 (95% CI: 1.70-134.30), P = .01, explaining 28% of the variance of the outcome variable. Having no/primary education had aOR of 3.35 (95% CI: .94-11.97), P = .06 compared with secondary and tertiary educational attainment and use of statin, aOR of .25 (.05-1.13), P = .07 were not significantly associated with PSF upon adjustment for confounders (Table 2).

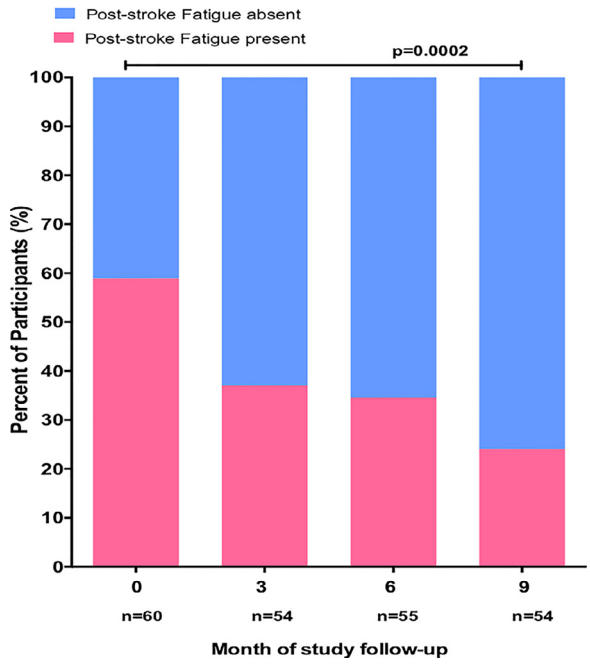

Figure 3. *Proportion of study participants with poststroke fatigue at enrollment and during follow-up.*

Factors Associated with PSF at Month 9 of Follow-Up

Four factors were associated with persisting PSF at month 9 in unadjusted analysis, namely age greater than or equal to 65 years, female gender, Hamilton depression rating score greater than 7 at month 9, and stroke severity at month 9 measured using National Institute of Health Stroke Scale. In adjusted analysis, factors which remained significantly associated with PSF at month 9 were, age greater than or equal to 65 years, aOR of 7.02 (95% CI: 1.16-42.52); female gender, aOR of 8.52 (1.23-59.16), and depression, aOR of 8.86 (1.19-65.88) (Table 3).

Discussion

We have evaluated the burden, trajectory, and factors associated with PSF among a sample of 60 stroke survivors in Ghana. At enrollment into the study, we found that approximately 60% of Ghanaian stroke survivors had PSF within 1 month of incident stroke onset. Among studies that have estimated the prevalence of PSF within 2-4 weeks after stroke, the prevalence of PSF in our cohort concurs with 57% from Norway,[52] 56% from Japan,[53] 52% from the Netherlands[54] but is higher than 40% recorded in a Chinese cohort[16] with acute ischemic stroke. Early onset PSF in our cohort was adversely associated with diabetes mellitus while having no or primary educational attainment and use of statins therapy after stroke were moderated into nonsignificance in adjusted analyses. Diabetes mellitus as a risk factor for PSF among stroke survivors has also been observed among Norwegians who had survived a stroke for at least 6 months.[7]

There were significant reductions in both the severity and frequency of PSF over the course of follow-up. This notwithstanding, almost a quarter of stroke survivors in the cohort still had PSF approximately 10 months after their incident strokes. Interestingly, the resolution of PSF over time occurred in tandem with regression of poststroke depression emphasizing the well-established association between poststroke depression and PSF.[1,7,16,52] The downward trajectory of fatigue severity scores over the course of time was steeper among participants with low risk for depression and diverged from those with higher scores on the Hamilton depression rating scale at baseline (Fig 2A) with a significant difference at month 9 between the 2 groups. Consequently, depression at month 9 was significantly and independently associated with persisting PSF with an adjusted odds ratio of 8.86. It is noteworthy that although no specific interventions were specifically tested to treat PSF among stroke survivors in

Table 2. *Factors associated with poststroke fatigue at baseline*

Predictor	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age ≥65 years	.69 (.21-2.25)	.54	-	-
Female gender	1.13 (.38-3.35)	.83	-	-
No/primary education	3.54 (1.19-10.50)	.03	3.35 (.94-11.97)	.06
Secondary education or higher	1.00			
Urban residence	.59 (.19-1.63)	.29	-	-
Rural/semi-urban residence	1.00			
Diabetes mellitus	14.64 (1.77-120.88)	.01	15.12 (1.70-134.30)	.01
Body mass index, each unit higher	.95 (.87-1.05)	.33	-	-
Systolic blood pressure, each 10 mmHg higher	.77 (.61-.97)	.02	.97 (.77-1.22)	.77
Diastolic blood pressure, each 10 mmHg higher	.74 (.52-1.05)	.09	-	-
NIHSS score >4	1.18 (.42-3.33)	.75	-	-
Ischemic stroke	.95 (.30-3.00)	.93	-	-
Statin use after stroke	.22 (.06-0.89)	.03	.25 (.05-1.13)	.07

Abbreviations: NIHSS, National Institute of Health Stroke Scale.

Table 3. *Factors associated with poststroke fatigue at month 9*

Predictor	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age ≥65 years	5.83 (1.50-22.71)	.01	7.02 (1.16-42.52)	.03
Female gender	4.00 (1.09-14.71)	.04	8.52 (1.23-59.16)	.03
HDRS score at month 9 of >7	15.17 (3.05-75.31)	.0009	8.86 (1.19-65.88)	.03
NIHSS score at month 9 of >4	12.50 (2.05-76.15)	.006	5.44 (.49-60.67)	.17
Ischemic stroke	6.00 (.70-51.30)	.10	-	-
Hemorrhagic stroke (referent)	1.00			
Diabetes mellitus	3.14 (.84-11.72)	.09	-	-
Body mass index, each unit higher	1.06 (.95-1.17)	.31		
Number of antihypertensive medications	.66 (.33-1.30)	.23	-	-
Fluoxetine use			-	-
Continuously for 9 months	1.78 (.32-9.85)	.51		
Started and stopped	1.58 (.29-8.62)	.60		
Started later	2.85 (.48-17.10)	.25		
Never used	1.00			
Interaction between fluoxetine use at month 9 and HDRS >7	8.67 (1.37-54.88)	.02		

Abbreviations: HDRS, Hamilton's Depression Rating Scale.

this study, study physicians prescribed fluoxetine, a selective serotonin reuptake inhibitor, for up to 40% of participants. However, the slopes of decline in FSS scores over time among those with PSF at baseline did not significantly differ by fluoxetine use. Activation of the kynurenine pathway in the acute phase of stroke has been linked with serotonin synthesis which has been shown to play key pathological roles in poststroke depression and fatigue.[55] Hence it has been postulated that treatment for depression with psychostimulants might be useful in the management of PSF. However, no beneficial effects for anti-depressants or psycho-stimulants have been demonstrated on PSF in randomized controlled trial (RCTs) performed to date largely due to insufficient power to detect significant differences in these studies.[56,57] Perhaps the complex nature of PSF with its admixture of interacting biological, physical, psychological, and behavioral factors may lend it potentially amenable to a combination of interventions including cognitive behavioral and physical training therapies.

A limitation of our study is the relatively small sample size which resulted in wide confidence intervals for adjusted odds ratios. This was a secondary analysis of a pilot clinical trial data with no formal power calculations performed a priori to assess the predictors of PSF. Other key variables known to be associated with PSF such as prestroke fatigue, myocardial infarction, and family dysfunction were not assessed in the current study with potential for residual confounding due to these and other unmeasured covariates. We also cannot draw causal associations between PSF and the factors identified in the present study. In spite of these limitations, our study findings contribute to the weight of evidence accruing in support of the salience and burden of PSF globally and within the context of a resource-limited setting such as ours.

In conclusion, 6 in 10 Ghanaian stroke survivors experience PSF within a month of stroke onset with persistence of fatigue in about 1 in 4 at 10 months after incident stroke. Larger scale observational studies are required to elucidate the underlying mechanisms and potential overlaps between PSF and poststroke depression with the need for adequately powered interventional multicenter trials eagerly awaited to provide solid evidence base for the clinical management of PSF.

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Declarations of Interests

None to declare.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.02.002.

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