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Post-Stroke Seizures: Frequency, Predictors and Health Impact (Clinical And Epidemiological Study)

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ABSTRACT

Background: Post-stroke seizures (PSS), a common complication of cerebrovascular stroke (CVS), are classified into early post-stroke seizures (EPSS) and late post-stroke seizures (LPSS). Identifying the frequency, predictors, and health impact of PSS is crucial for optimal post-stroke management.

Objective: To determine the risk factors, frequency, and PSS predictors, particularly LPSS, and to assess their impact on clinical and functional outcomes in stroke patients.

Patients and methods: This nested case-control study included 422 stroke patients from two Egyptian university hospitals, with 115 developing PSS (20 EPSS, 95 LPSS) and 307 serving as controls. Patients were assessed for clinical and neuroimaging factors, metabolic profiles, and stroke severity using Barthel Index (BI).

Results: Among 1,530 stroke patients, 11.6% developed seizures (5.4% EPSS and 6.2% LPSS). Predictors for LPSS included diabetes mellitus (95% CI = 1.06–4.46, P = 0.044), ischemic stroke (95% CI = 1.05–2.12, P = 0.044), psychotic manifestations (95% CI = 1.27–3.87, P = 0.037), and cortical lesions (95% CI = 1.08–4.90, P = 0.046). Interestingly, hypercholesterolemia (P = 0.041) and hypertriglyceridemia (P = 0.039) were protective against LPSS. LPSS patients had poorer functional outcomes, with 68.4% showing poor/very poor BI scores.

Conclusion: LPSS occurs in 6.2% of stroke patients, with diabetes, psychosis, ischemic stroke, and cortical lesions identified as significant predictors. Elevated cholesterol and triglycerides may have a protective role. LPSS is associated with worse clinical and functional outcomes.

Keywords: Post-stroke seizures, predictors, cerebrovascular stroke, late seizures, functional outcome.

INTRODUCTION

Seizures are a recognized complication following cerebrovascular stroke (CVS). Post-stroke seizures (PSS) are classified into early (EPSS) and late (LPSS) based on specific temporal criteria [1].

EPSS occurs within the first seven days after stroke, while LPSS develops beyond this period. According to the most recent International League Against Epilepsy (ILAE) classification, LPSS is now regarded as a form of vascular epilepsy that does not necessitate a recurrent stroke episode for diagnosis [2].

The incidence of PSS is reported to be 6.1% at one year, 9.5% at five years, and 11.5% at ten years post-stroke. PSS exhibits a bimodal distribution, with an initial peak occurring within the first 24 hours and a second peak emerging between six to twelve months after the stroke [3]. Distinguishing between EPSS and LPSS is crucial, as the latter is linked to a higher risk of seizure recurrence and informs decisions regarding long-term antiepileptic therapy. The prevalence of EPSS ranges from 2.2% to 33%, while LPSS is observed in 3% to 67% of cases. Previous studies have shown that approximately 50% of individuals with LPSS and 30% of those with EPSS experience recurrent seizures [4].

Although the exact pathophysiology of PSS remains unclear, current evidence suggests that EPSS may be triggered by acute neuronal injury, resulting in blood-brain barrier disruption, ion channel dysfunction, and excitotoxicity mediated by glutamatergic pathways. In contrast, LPSS is thought to be driven by alterations in neuronal membrane properties related to gliosis, inflammation, neurodegeneration, and impaired neuroplasticity, leading to neuronal hyper-excitability and hyper-synchronization [5].

Several risk factors for PSS have been identified, including cortical involvement, cerebral hemorrhage or hemorrhagic transformation, stroke severity, cardioembolic stroke, recurrent strokes, younger age, family history of seizures, and genetic predisposition. Additionally, the 'watershed' areas of the brain are considered independent predictors of PSS [6].

The occurrence of PSS has a significant adverse effect on stroke survivors, contributing to increased mortality and morbidity. Given the wide variability in reported outcomes and the limited number of established predictors for PSS, our study seeked to explore the prevalence, risk factors, and predictors of PSS in post-stroke populations.

PATIENTS AND METHODS

This investigation was conducted as a nested case-control (NCC) study, where cases of the disease were identified within a predefined cohort, and for each case, a set number of matched controls was selected from cohort members who had not developed the disease at the time the case occurred. Between June 2017 and May 2021, a cohort of 1,530 patients presenting with acute cerebrovascular stroke (within one week of onset) was recruited from the stroke unit and neurology ward. These patients were subsequently

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followed up in the outpatient clinics of Aswan and Assiut University Hospitals. A total of 115 patients who developed PSS and met the inclusion and exclusion criteria were included in the study—20 with recurrent EPSS and 95 with LPSS. Additionally, 307 individuals who did not develop PSS were selected as controls.

Exclusion criteria: Patients with transient ischemic attacks, non-stroke brain lesions such as tumors, those who declined to participate, individuals with known metabolic disorders, patients with a prior epilepsy diagnosis, those unable to communicate due to sensory aphasia or delirium, and patients receiving epileptogenic medications such as clozapine or tramadol hydrochloride.

All participants underwent brain imaging via CT or MRI to confirm stroke diagnosis. Based on clinical presentation and neuroimaging findings, patients were categorized as having either ischemic or hemorrhagic stroke, including cerebral and subarachnoid hemorrhage, with detailed localization of cerebral abnormalities.

Study tools: Data regarding stroke risk factors, either self-reported or provided by family members, were collected, covering socio-demographic details, hypertension, diabetes mellitus, cardiovascular diseases, smoking habits, family history, and stroke recurrence. Upon admission, all patients underwent a thorough neurological and general examination, including an assessment of BMI, with obesity defined as a BMI of $\geq$ 30 kg/m². Fasting lipograms were performed after at least 14 hours of fasting, with hypercholesterolemia and hypertriglyceridemia defined as cholesterol levels exceeding 239 mg/dl and triglyceride levels above 200 mg/dl, respectively. Additionally, serum uric acid levels were measured, with hyperuricemia defined as levels higher than 6 mg/dl in females and 7 mg/dl in males [7]. Electrocardiograms (ECG) and/or echocardiograms were conducted to detect any arrhythmia or ischemia (CON-TEC, model: ECG100G, China).

Stroke severity was assessed using the Barthel Index (BI) [8], which classifies patients into three categories: Severe dependency (BI score < 60), moderate dependency (BI score 60-<95), and independence or minimal disability (BI score ≥95). Additionally, the Arabic version of the Hamilton Depression Rating Scale (HDRS) [9] and the Mini-Mental State Examination (MMSE) [10] were administered by a psychologist to evaluate depression and cognitive function, respectively. Dementia was diagnosed in patients with MMSE scores of 23 or lower, while depression was identified in those scoring above 7 on the HDRS. Diagnoses of dementia and depression were made in accordance with DSM-V criteria [11]. Electroencephalography (EEG) was performed on patients experiencing seizures. Within eighteen months, PSS onset, type, and recurrence were evaluated through a 20-30 minute EEG session. The clinical outcomes for all stroke patients were assessed both clinically and using the BI at the conclusion of the follow-up period.

Sample size calculation: The sample size calculation was performed using G*Power 3 software [29]. A minimum of 422 stroke patients, divided into two groups (115 with PSS and 307 without PSS), was necessary to detect an effect size of 0.1 in the mean BMI, HDRS, MMSE, and BI scores, with a significance level of 0.05 and a statistical power of 90% for a two-tailed test.

Ethical considerations: This study was conducted after approval by The Research Ethics Committee of Aswan University (IRB: 501/1/21). All patients provided written informed consents prior to their enrollment, which included their agreement to participate in the study and for the publication of the resulting data. The consent process ensured the protection of patient confidentiality and privacy. This research adhered to the principles outlined in the Declaration of Helsinki and The Code of Ethics of the World Medical Association for studies involving human subjects.

Statistical analysis

The researchers utilized SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA) for data analysis. Descriptive statistics, such as means, standard deviations, and percentages, were computed. The Chi-square test or Fisher's exact test was applied to assess differences in frequency distributions between groups. For comparison of binary data means, an independent t-test was conducted. Key variables from the univariate analysis were incorporated into a multivariable logistic regression model to identify independent predictors of seizures in stroke patients, with results presented as odds ratios (OR), 95% confidence intervals (CI), and p-values. A p-value of 0.05 or less was considered statistically significant.

RESULTS

Figure (1) illustrated the flow of participants through a study selection process, starting from an initial group of 1,764 assessed for eligibility criteria. Out of these, 234 participants were excluded, resulting in 1,530 potential cases and controls. Among these, 62 were lost to follow-up for non-recurrent Early-Onset Seizures (EPSS). This left a final sample of 422 participants who were enrolled and consented from a remaining 1,468.

The participants were further divided into three groups:

1. **Late-Onset Seizures (n=95)** – classified as LPSS cases.
2. **Recurrent Early-Onset Seizures (n=20)** – classified as EPSS cases.
3. **No Seizures (n=307)** – serving as the control group.

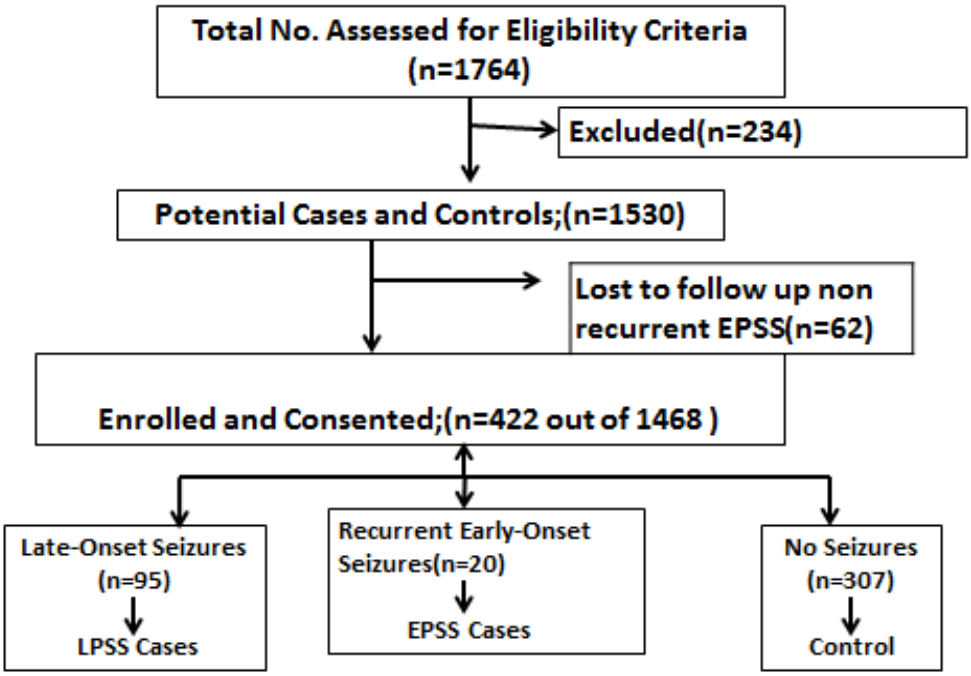

Fig. 1: Flow Chart of PSS Cases.

The mean patients' age of LPSS and those without seizures were 54.3 ± 12.8 and 62.3 ± 14.2 years, respectively **(P=0.008)**. LPSS was detected in 27% and 20.7% of female and male patients, respectively (P=0.139). Some vascular risk factors such as hypertension, cardiac diseases, smoking, hyperuricemia, obesity, family history of epilepsy and of stroke had insignificant effect on LPSS. On the other hand, diabetes mellitus was reported among 46.3% of LPSS patients versus 29.6% of those without seizures **(P=0.024)**. On the contrary, hypercholesterolemia and hypertriglyceridemia were recorded more significantly in patients without PSS (P<0.05) [Table 1].

Table (1): Baseline characteristics of the studied stroke cases

	No Seizures (n=307)	Late-Onset Seizures (n=95)	P-value
Age/years	62.28 ± 14.2	54.25 ± 12.8	**= 0.008***
Sex (Male/Female)	172/135	45/50	= 0.139**
Smoking	96 (31.3%)	25 (26.3%)	= 0.602**
Obesity	50 (16.6%)	15 (15.8%)	= 0.849**
Hypertension	124 (40.4%)	35 (36.8%)	= 0.310**
Diabetes Mellitus	91 (29.6%)	44 (46.3%)	**= 0.024****
Heart Disease	94 (30.6%)	28 (29.5%)	= 0.754**
Hypercholesterolemia	167 (54.4%)	35 (36.8%)	**= 0.002****
Hypertriglyceridemia	115 (37.5%)	25 (26.3%)	**= 0.029****
Hyperuricemia	117 (38.1%)	30 (31.6%)	= 0.248**
FH of Epilepsy	12 (3.9%)	5 (5.3%)	= 0.373**
FH of Stroke	19 (6.2%)	5 (5.3%)	= 0.739**

*Independent t-test was used to compare the means among groups, **Chi-square analysis was used to compare the frequency among groups, FH; family history.

Table (2) showed the common presenting neurological symptoms of patients with LPSS, where LPSS developed more significantly in patients presented with severe initial stroke, of ischemic type, psychotic manifestations, with multiple lesions or middle cerebral artery affection. Moreover, LPSS developed in patients presented with initial disturbed conscious level, speech disorder, dementia, depression and cortical lesion but the differences were non-significant.

Table (2): Clinical related factors among the studied stroke cases

	No Seizures (n=307)	Late-Onset Seizures (n=95)	P-value*
Disturbed Consciousness	88 (28.7%)	32 (33.7%)	= 0.464*
Motor Deficit (Severe)	45 (14.7%)	27 (28.4%)	**= 0.019***
Speech Disorder	56 (18.2%)	18 (18.9%)	= 0.744*
Dementia	26 (8.4%)	11 (11.6%)	= 0.127*
Depression	62 (20.2%)	23 (24.2%)	= 0.241*
Psychosis	19 (6.2%)	14 (14.7%)	**= 0.041***
Stroke Subtype:			
• **Infarction**	260 (84.7%)	80 (84.2%)	**= 0.005***
• **Hemorrhage**	47 (15.3%)	15 (15.8%)	
Side of Lesion:			
• **Right**	142 (46.2%)	50 (52.7%)	= 0.341*
• **Left**	139 (45.3%)	35 (36.8%)	
• **Bilateral**	26 (8.5%)	10 (10.5%)	
Neuroimaging:			
• **Cortical Lesion**	118 (38.4%)	40 (42.1%)	= 0.301*
• **Middle Cerebral Artery**	12 (3.9%)	10 (10.5%)	**= 0.017***
• **Multiple Lesions**	62 (20.2%)	35 (36.8%)	**= 0.001***
Barthel Index I:			
• **Mean SD**	61.56±10.1	49.14± 9.4	**< 0.001****
• **Median (IQR)**	64 (6)	48 (7)	
• **Poor/Very Poor**	88 (28.7%)	59 (62.1%)	**< 0.001***
• **Excellent**	219 (71.3%)	36 (37.9%)	

*Chi-square analysis was used to compare the frequency among group, **Independent t-test was used to compare the means among groups, IQR.

Table (3) illustrated the differences of the most significant data of patients with recurrent EPSS and LPSP. Where, recurrent EPSS developed significantly more in patients of younger ages (50.3 ± 16.4 years), presented with psychoses, generalized seizures, cerebral hemorrhage, with middle cerebral artery or multiple lesions. On the contrary, cortical lesion and focal with/without generalized seizures were detected in LPSS patients more significantly than recurrent EPSS. Moreover, recurrent EPSS were developed more in male patients but with statistically insignificant difference.

Table (3): Recurrent EPSS and LPSS comparison

	Recurrent EPSS (n=20/1530) 1.3%	**LPSS** (n=95/1530) 6.2%	P-value
Age/years	50.29 ± 16.4	54.25 ± 12.8	= 0.217*
Sex (Male/Female)	12/8	45/50	= 0.208**
Diabetes Mellitus	5 (25%)	44 (46.3%)	**= 0.038****
Hypercholesterolemia	4 (20%)	35 (36.8%)	**= 0.041****
Hypertriglyceridemia	6 (30%)	25 (26.3%)	= 0.194**
Motor Deficit (Severe)	6 (30%)	41 (43.2%)	**= 0.039****
Psychosis	11 (45%)	24 (25.3%)	**= 0.027***
FH of Epilepsy	2 (10%)	5 (5.3%)	= 0.373**
FH of Stroke	1 (5%)	5 (5.3%)	= 0.739**
Stroke Subtype:			
• **Infarction**	8 (40%)	80 (84.2%)	**= 0.029****
• **Hemorrhage**	12 (60%)	15 (15.8%)	
Seizure Subtype:			
• **Generalized**	14 (70%)	51 (53.7%)	**= 0.042****
• **Focal ± generalization**	6 (30%)	44 (46.3%)	
Neuroimaging:			
• **Cortical Lesion**	4 (20%)	40 (42.1%)	**= 0.037****
• **MCA**	9 (45%)	10 (10.5%)	**= 0.018****
• **Multiple lesions**	13 (70%)	35 (36.8%)	**= 0.038****

*Independent t-test was used to compare the means among groups, **Chi-square analysis was used to compare the frequency among groups, FH: family history, MCA: middle cerebral artery.

After adjusting for age and sex, the final multivariate model contained seven independent predictors, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, ischemic stroke, psychotic manifestations, cortical lesions and multiple lesions. In other words, patients with diabetes mellitus, psychotic manifestations and multiple lesions had double the risk of LPSP [AOR=1.82, 1.75 and 1.66, respectively]. Moreover, patients presented with ischemic stroke and cortical lesion were 1.5 and 3.7 times, respectively, more liable to have LPSS [AOR= 1.46 and 3.69 respectively]. Finally, there were 51% and 40% probability of LPSS with each point descent of serum cholesterol and triglycerides, respectively [AOR = 0.49 and 0.596, **P = 0.041** and **0.039,** respectively] (Table 4).

Table (4): Predictors of LPSS among stroke Patients: Logistic regression model

Variable	Univariate		Multivariate	
	OR (95% CI)	P-value	HR (95% CI)	P-value
Age/years	0.956 (0.942–0.970)	< **0.001**	0.854 (0.790–0.995)	= **0.033**
Sex (Female)	1.416 (0.892–2.246)	= 0.140	1.241 (0.845–2.656)	= 0.215
Diabetes Mellitus	1.824 (1.024–3.125)	= **0.040**	2.556 (1.061–4.464)	= **0.044**
Hypercholesterolemia	0.489 (0.305–0.785)	= **0.003**	0.625 (0.446–0.884)	= **0.041**
Hypertriglyceridemia	0.596 (0.357–0.995)	= **0.048**	0.775 (0.457–0.901)	= **0.039**
Infarction Stroke	1.458 (1.083–2.574)	= **0.033**	1.688 (1.045–2.122)	= **0.044**
Severe Motor Deficit	1.624 (0.972–3.021)	= 0.246		
CT (Cortical Lesion)	3.689 (1.102–6.195)	= **0.038**	3.045 (1.081–4.901)	= **0.046**
CT (MCA)	2.058 (1.043–4.949)	= **0.011**		
CT (Multiple Lesions)	1.656 (1.023–3.334)	= **0.028**	2.024 (1.112–4.177)	= **0.035**
Psychosis	1.751 (1.143–3.115)	= **0.022**	2.155 (1.270–3.867)	= **0.037**

HR: Hazard Ratio, CI: Confidence Interval, LPSS: late post-stroke seizure, CT: computed tomography, MCA: middle cerebral artery.

Figures (2 and 3) showed outcome of our patients, according to BI more than two-thirds of patients with LPSS (68.4%) had poor/very poor outcome compared to less than half of those without seizures (49.5%, **P=0.014).** Clinically, also there was a significant deterioration in LPSS patients as compared to those without seizures **(P<0.001).**

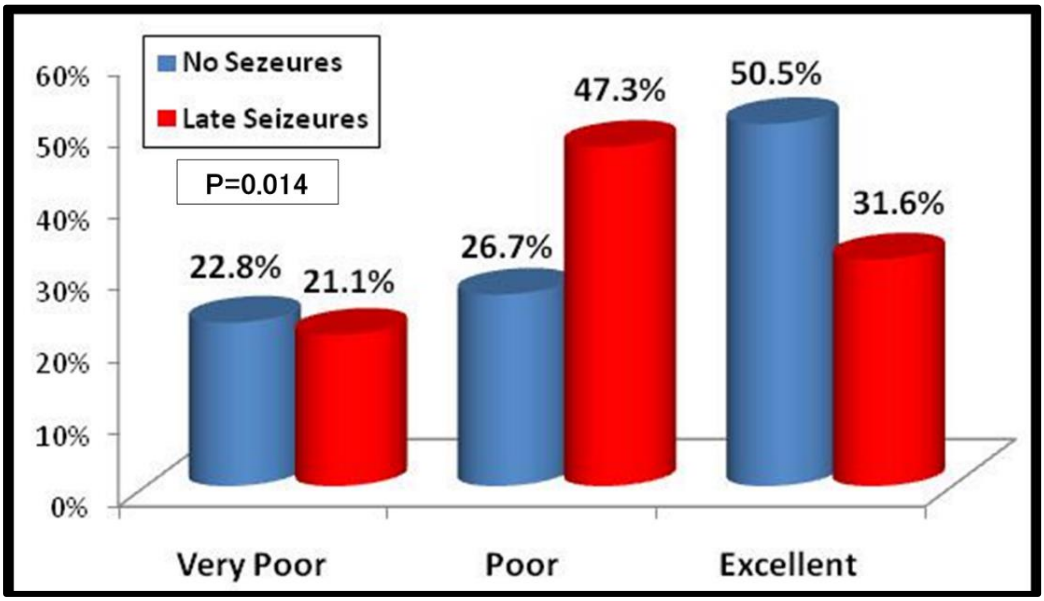

Figure (2): Rates of Improvements according to BI 2 among groups.

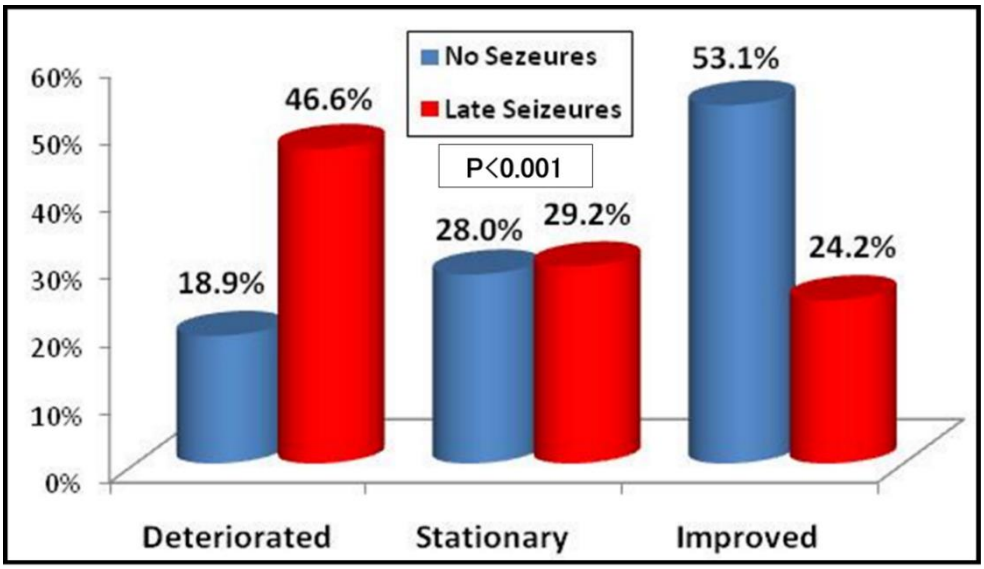

Figure (3): Rates of clinical Improvements among groups.

DISCUSSION

The considerable variability in seizure occurrence following a stroke is largely attributed to the diverse temporal thresholds used to define different categories of PSS. Our study found the overall prevalence of PSS to be 11.6%, with EPSS at 5.4% and LPSS at 6.2%, which is aligning closely with the findings of **Roivainen *et al.*** [12]. Approximately 25% of the EPSS patients experienced seizure recurrence. In line with the most recent ILAE definition [3], the cumulative incidence of PSE in our cohort was 7.5%, which is consistent with the 7% reported by **Zou *et al.*** [13].

Age was identified as a predictor for the onset of PSS, with younger individuals at greater risk [14]. In our cohort, the mean age is comparable to that reported by **Goswami *et al.*** [14]. Youth may act as a risk factor for PSS, as younger patients tend to develop more extensive cerebral infarcts, while older adults are more prone to small vessel disease [15].

Regarding sex differences and PSS onset, we observed a higher incidence of LPSS in females compared to males, whereas recurrent EPSS was more frequent in males, though these differences did not reach statistical significance, which is consistent with **Sarfo *et al.*** [16].

The relationship between vascular risk factors and PSS remains contentious. Our data, are supported by another study [17] that revealed no significant association between metabolic factors such as obesity, hyperuricemia, smoking, hypertension, and cardiac diseases with PSS onset. However, another study [12] reported these factors to be more prevalent among PSS patients. Additionally, hyperglycemia post-cerebral ischemia, as shown in animal studies, may contribute to epileptogenesis by impairing cellular metabolism [18]. Our findings confirmed that diabetes mellitus is a significant predictor of PSS development. Interestingly, similar to the observations of **Devuyst *et al.*** [19], we found elevated cholesterol and triglyceride levels may offer a protective effect against PSS development.

Although numerous studies suggest that hemorrhagic stroke is a stronger predictor of PSS [20, 21], our findings, along with a Chinese study [22], identified ischemic stroke as a significant predictor for PSS development. Acute ischemia triggers an increase in extracellular glutamate levels, a neurotransmitter linked to subsequent neuronal injury [4]. Glutamate excitotoxicity, a well-established mechanism in experimental stroke models, leads to extensive neuronal depolarization, causing simultaneous release of glutamate and GABA, which contributes to cellular death [20].

Conrad *et al.* [23] also noted that the severity of early neurological deficits is associated with PSS. Our results demonstrated a significant association between lower BI scores and PSS, implying that severe strokes, characterized by widespread cortical lesions, are more likely to result in seizures. Furthermore, both our study and **Pitkänen *et al.*** [24] found a higher prevalence of PSS in patients with depression and dementia, although the differences were not statistically significant. This may be due to disruptions in glutamate and dopamine pathways [25].

We also observed a correlation between strokes with psychotic symptoms and an increased likelihood of PSS. This could be due to intracerebral circuit disruptions or functional cortical disconnection, compounded by the impact of inflammatory mediators from vascular injury or systemic responses. Studies suggest that lesions associated with seizures may elevate the risk of post-stroke psychosis [26]. **Khan *et al.*** [27] similarly reported a higher incidence of post-stroke psychosis in patients with PSS. Consequently, we concluded that post-stroke psychosis serves as a predictor for PSS, with a bidirectional relationship between psychosis and seizures.

Previous research has highlighted cortical lesions [28], middle cerebral artery involvement, and

multifocal infarcts as key risk factors for PSS. In our study, PSS was more prevalent among patients with cortical or multiple lesions and those with greater middle cerebral artery involvement. Acute ischemia and hypoxia in stroke patients can lead to significant neuronal damage, particularly in cortical regions supplied by cerebral arteries [24]. The high concentration of neurons and axons in the cortex, which are susceptible to epileptic discharges, explains why cortical lesions are frequently identified as strong predictors of PSS in multiple studies.

In line with previous studies [29-31], our results demonstrated that PSS are associated with poorer functional recovery and outcomes following a stroke. Among elderly patients, seizures significantly impact quality of life by imposing restrictions on activities such as driving, increasing the risk of falls and fractures, and enhancing susceptibility to side effects from antiepileptic drugs [32, 33]. Additionally, animal studies suggest that recurrent seizures during acute ischemic stroke can enlarge the infarct size and impair functional recovery. This is attributed to the increased metabolic and oxygen demands placed on ischemic tissue near the infarcted area due to seizures [34].

Secondary epilepsy after a stroke arises from various etiological factors. Cerebrovascular diseases often lead to secondary epilepsy, and epileptic seizures, in turn, may worsen these conditions, perpetuating a detrimental cycle [35].

The limitations of this NCC study included potential selection bias due to the matching process and the reliance on retrospective data, which may introduce recall bias. Additionally, the relatively small sample size of patients with recurrent EPSS and LPSS limited the statistical power and generalizability of the findings. The study did not fully account for potential confounding factors such as variations in stroke treatment and medication adherence. Future prospective studies with larger and more diverse populations are recommended to validate these findings.

CONCLUSION

In conclusion, PSS occurred in 11.6% of stroke patients, with LPSS being slightly more frequent than EPSS. Key predictors of LPSS included diabetes mellitus, ischemic stroke, psychotic manifestations, and cortical or multiple lesions. Interestingly, hypercholesterolemia and hypertriglyceridemia were found to have a protective effect against the development of LPSS. LPSS patients exhibited poorer clinical and functional outcomes compared to those without seizures. These findings underscored the importance of early identification and management of high-risk stroke patients to improve post-stroke outcomes. Further research is warranted to explore the protective role of lipid levels in PSS development.

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