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ORIGINAL RESEARCH

Risk Factors for Post-Stroke Seizures in a Tertiary Care Center: A Case–Control Study

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Purpose: Stroke is the second leading cause of global deaths. Post-stroke seizures (PSS) can lead to lasting complications, such as prolonged hospitalizations, increased disability rates, and higher mortality. Our study investigates the associated factors that contribute to post-stroke seizures in patients at a local tertiary hospital.

Patients and Methods: We designed a case–control study where patients admitted with PSS were recruited with consent. Controls admitted for stroke without seizure were then included. Suitability based on exclusion criteria was ensured before recording their sociodemographic and clinical data. An EEG was performed and read by two certified neurologists before the data was analyzed.

Results: We recruited 180 participants, 90 cases and 90 matched controls. Gender (p=0.013), race (p=0.015), dyslipidemia (p<0.001), prior stroke (p<0.031), large artery atherosclerosis (p<0.001), small vessel occlusions (p<0.001), blood pressure on presentation (p<0.028) and thrombolysis administration (p<0.029) were significantly associated with the occurrence of PSS. An increase in odds of PSS was observed in the male gender (1.974), dyslipidemia (3.480), small vessel occlusions (4.578), and in participants with epileptiform changes on EEG (3.630). Conversely, lower odds of PSS were seen in participants with high blood pressure on presentation (0.505), large artery atherosclerosis (0.266), and those who underwent thrombolysis (0.319).

Conclusion: This study emphasized that identifying post-stroke seizures may be aided by EEGs and recognizing at-risk groups, which include males of Chinese descent in Asia, dyslipidemia, small vessel occlusions, those with low to normal blood pressure on presentation, and epileptiform changes in EEGs.

Plain Language Summary: The research aims to establish the risk factors associated with post-stroke seizures in an Asian population and their similarity to the Western literature. Our findings highlight the critical risk factors to identify in at-risk patients, which may prompt changes in guidelines in future to enhance patient outcomes and improve the quality of care.

Keywords: seizures, stroke, post-stroke epilepsy, epilepsy, electroencephalogram

Introduction

Globally, stroke accounted for 11.6% of all deaths in 2019, making it the second leading cause of death.[1] Despite significant advancement in stroke management over the last decade, survivors continue to experience disabilities and lasting complications. The burden of post-stroke psychological issues is a significant concern and places unnecessary strain on healthcare resources. Post-stroke seizure is defined as single or multiple convulsive episodes after stroke and thought to be related to reversible or irreversible cerebral damage due to stroke regardless of the time of onset following the stroke.[2] Post-stroke epilepsy refers to recurrent seizures following stroke with a confirmed diagnosis of epilepsy.[2] Early seizures (acute symptomatic seizures) occur within seven days following an infarct, whereas late seizures (remote

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symptomatic seizures) occur beyond a week.[3] One previous study conducted in the US reported that ischemic and haemorrhagic stroke accounted for 11% of epilepsy cases.[4]

The prevalence of PSS varies from 4% to 43%, with the highest rates following cortical and large haemorrhagic infarcts.[5] The incidence increases from 1.5% at three months to 9% at five years post-stroke.[6] PSS undoubtedly negatively impact a patient's prognosis, with prolonged hospitalisations, rising disability rates, poorer quality of life, and increased hospital expenses, leading to significantly higher mortality and severe disability in stroke patients.[7,8] The type of seizure observed may vary from focal to bilateral convulsive seizures,[9] generalized seizures[10] and status epilepticus.[11]

Significant variations exist in stroke frequency, fatality, and incidence across populations.[12] In Asia, a higher prevalence of lacunar stroke and intracerebral haemorrhage in men is observed, with South Asians facing a 1.5 to 2-fold higher risk compared to Europeans.[13,14] Apart from stroke subtype, size, location, severity of the vascular lesion, and early seizures, the reported findings on seizure predictors may be variable.[15] Other independent predictors identified for PSS were young age, larger lesions, and haemorrhagic lesions[6] The risk of post-stroke epilepsy was higher in patients with hemorrhagic stroke compared to those with ischemic stroke in a Taiwanese study.[16]

Despite existing studies, limited research addresses PSS risk factors locally. This study aims to fill this gap by analyzing sociodemographic, clinical and stroke-related variables in patients at a local tertiary hospital.

Methodology

Study Design

This prospective case–control study was conducted between March 2023 and October 2023 in Hospital Canselor Tuanku Muhriz, the National University of Malaysia, with the local Ethics and Research Board approval (FF-2023-098). A case–control study was conducted to investigate the risk factors associated with post-stroke seizures, which are relatively unknown among the Malaysian population. As a result, targeted risk factors are currently unaddressed and need to be mitigated. Funding was obtained from the National University of Malaysia. All patients admitted with the diagnosis of stroke with seizures were recruited via purposive sampling. The control group consists of patients who had been diagnosed with stroke but without seizures. The participants in the case and control groups were closely matched to minimize bias.

The patients are diagnosed with acute ischemic stroke on presentation based on their clinical history, examination and radiographic evidence of cerebral infarct in imaging. Those presenting with debilitating neurological diseases, stroke mimics (underlying seizures, epilepsy, hyperglycemia, metabolic causes, infection, and cerebral venous sinus thrombosis), prior history of seizure, traumatic brain injury, previous neurosurgery, and cerebral tumours were excluded from this study.

The following clinical information was gathered using a data collection sheet during patient recruitment: socio-demographic details, relevant clinical data, including the National Institute of Health Stroke Scale (NIHSS) score at presentation, classification of stroke based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) (large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology), modified Rankin Scale (mRS) score at discharge, the timing of seizure after stroke onset, type of seizure, and frequency of seizure.

An EEG was performed for all participants inpatient within 72 hours of admission, and recorded on the Nicolet One Extension (V32 Amplifier) using 24 reusable gold electrodes affixed to the scalp according to the international 10–20 system. The abbreviations on the EEG are as follows: Fp – frontopolar, C – central, F – frontal, T – temporal, P – parietal, and O – occipital. Bipolar longitudinal and average referential montages were utilized for evaluation. Each recording was approximately half an hour with the filter configuration as follows: 50 Hz filter; low-frequency filter: 0.5 Hz; high-frequency filter: 70 Hz.

Two trained neurologists blinded to the clinical and radiological findings evaluated the EEG. Each gave an individual report of the EEG based on the findings. Upon comparison of individual reports, any discrepancies are discussed, with the EEG recording re-examined before producing a final joint report for classification. An abnormal EEG was defined as generalized slowing (GS), focal slowing (FS), or the presence of epileptiform patterns (spikes, sharp waves, rhythmic and

periodic patterns). Spikes were defined as sharp-pointed peaks lasting 20–70ms and amplitude more than 50 microV. Sharp waves were sharp-pointed peaks lasting 70–200 ms and amplitude of 100–200 microV. Periodicity refers to a series of spike or sharp wave complexes occurring at regular intervals. Generalized slowing was defined when the dominant rhythm is within the theta (4–8 Hz) or delta (< 4 Hz) frequency bands, occurring over all regions of the head. Focal slowing (FS) was defined as slow activity (theta or delta) occurring at a limited region of the head.

Statistical Analysis

We used the IBM SPSS Version 26 statistical program for data entry and analysis. Ninety-five percent confidence intervals were reported where applicable, and the significance threshold was pre-set at p-value <0.05. Normality testing for continuous variables was performed using the ratio of skewness, standard error and kurtosis as the sample size was more than 100. Categorical variables [eg gender, race, comorbidities, blood pressure classification, causes of stroke, classification of stroke and seizure, location of stroke, type of stroke treatment, NIHSS and mRS] and not normally distributed continuous variables were reported as frequencies and percentages. Data transformation was not performed as comparison of risk factors were of categorical variables. Thus, the mean and standard deviation (SD) were used to define normally distributed continuous variables [eg age, systolic and diastolic blood pressure measurements]. A non-parametric comparative test was used as the variables were categorical with a dichotomous outcome. Thus, the non-parametric Mann–Whitney *U*-test was applied to compare the qualitative variables. Lastly, the Odds Ratio was used to analyze the risk of post-stroke seizure across variables.

Results

Sociodemographic Characteristics

A total of 292 patients admitted with ischaemic stroke were screened for this study. Eventually, 180 patients were recruited based on the inclusion and exclusion criteria stated and divided equally between cases and controls, as shown in Table 1. The participants were between 33 and 91 years of age, with a mean age of 64.42 years (SD ±13.4) for the control group and 66.96 years (SD ±1.31) for the cases. As part of our analysis, we performed normality testing on all continuous variables, including age, systolic and diastolic blood pressure, NIHSS score, and mRS on discharge. The skewness ratio, standard error and kurtosis were used for normality testing as the sample size was more than fifty. Therefore, medium-sized samples' absolute z-scores for either skewness or kurtosis that were larger than 3.29 indicated a non-normal distribution. The median NIHSS score within our cohort was 6, with an interquartile range of 10. From our investigation, age and blood pressure readings demonstrated a normal distribution pattern amongst stroke with and without seizure cohorts. The present study identified a significantly higher prevalence of concomitant dyslipidemia and small vessel occlusion among case participants as compared to their respective controls. The other parameters were almost identical between the control and experimental groups.

One hundred and seven participants demonstrated EEG abnormalities, with 63 participants in the cases group and 44 in the control group, as shown in Table 2. Abnormal EEGs were seen in higher proportion among case groups in those with dyslipidemia, small vessel occlusion and lacunar type stroke. The majority of abnormalities detected were focal changes, with a higher proportion of participants with epileptiform changes in the cases group.

Associations Between Post-Stroke Seizure and its Risk Factors

A non-parametric test was utilized to investigate the relationship between sociodemographic factors, underlying comorbidities, stroke and seizure characteristics, treatment, potential complications, and PSS among study participants. The Mann–Whitney *U*-test was used to analyze the above-mentioned risk factors, with the outcome being post-stroke seizure in the case group. The Mann–Whitney *U*-test results revealed that several factors including gender (U = 3375, z = −2.241, p =0.013), race (U = 3451, z = −1.877, p=0.015), dyslipidemia (U = 2835, z = −4.026, p <0.001), previous history of stroke (U =3510, z = −1.863, p <0.031), large artery atherosclerosis (U = 2835, z = −4.128, p <0.001), and small vessel occlusion (U = 2610, z = −4.800, p <0.001), were significantly associated with the occurrence of seizure following a stroke as shown in Table 3. Additionally, blood pressure on presentation (U = 3555, z = −1.917, p <0.028)

Table 1 Sociodemographic Characteristics of Study Participants

Variable	Case, N (%)	Control, N (%)
Gender:		
Female	33 (36.7)	48 (53.3)
Male	57 (63.3)	42 (46.7)
Race:		
Malay	32 (35.6)	44 (48.9)
Chinese	44 (48.9)	37 (41.1)
Indian	13 (14.4)	8 (8.9)
Others	1(1.1)	1 (1.1)
Comorbidities:		
Hypertension		
No	17 (18.9)	26 (28.9)
Yes	73 (81.1)	64 (71.1)
Diabetes mellitus		
No	38 (42.2)	49 (54.4)
Yes	52 (57.8)	41 (45.6)
Dyslipidemia		
No	35 (38.9)	62 (68.9)
Yes	55 (61.1)	28 (31.1)
Atrial fibrillation		
No	76 (84.4)	76 (84.4)
Yes	14 (15.6)	14 (15.6)
Ischemic heart disease		
No	73 (81.1)	79 (87.8)
Yes	17 (18.9)	11 (12.2)
Previous stroke		
No	52 (57.8)	64 (71.1)
Yes	38 (42.2)	26 (28.9)
Previous intracranial haemorrhage		
No	89 (98.9)	87 (96.7)
Yes	1 (1.1)	3 (3.3)
Smoking		
No	73 (81.1)	69 (76.7)
Yes	17 (18.9)	21 (23.3)
Blood Pressure classification		
Optimal	7 (7.8)	8 (8.9)
Normal	8 (8.9)	2 (2.2)
At Risk	12 (13.3)	6 (6.7)
Mild	6 (6.7)	7 (7.8)
Moderate	14 (15.6)	15 (16.7)
Severe	9 (10.0)	25 (27.8)
Isolated Systolic Hypertension	34 (37.8)	27 (30.0)
Hypertension on presentation		
No	27 (30.0)	16 (17.8)
Yes	63 (70.0)	74 (82.2)
Large artery atherosclerosis		
No	69 (76.7)	42 (46.7)
Yes	21 (23.3)	48 (53.3)
Cardioembolic		
No	80 (88.9)	74 (82.2)
Yes	10 (11.1)	16 (17.8)

(*Continued*)

Table 1 (Continued).

Variable	Case, N (%)	Control, N (%)
Small vessel occlusion		
No	35 (38.9)	67 (74.4)
Yes	55 (61.1)	23 (25.6)
Stroke of other determined aetiology		
No	87 (96.7)	88 (97.8)
Yes	3 (3.3)	2 (2.2)
Stroke of undetermined aetiology		
No	88 (97.8)	89 (98.9)
Yes	2 (2.2)	1 (1.1)
Type of seizure		
Generalized	59 (65.6)	0 (0.0)
Focal	31 (34.4)	0 (0.0)
Side of stroke		
Bilateral	3 (3.3)	3 (3.3)
Left	36 (40.0)	44 (48.9)
Right	51 (56.7)	43 (47.8)
Location of stroke		
Subcortical	42 (46.7)	42 (46.7)
Cortical	48 (53.3)	48 (53.3)
Vascular territories		
Lacunar	37 (41.1)	29 (32.2)
Middle Cerebral Artery (MCA)	32 (35.6)	35 (38.9)
Anterior Cerebral Artery (ACA)	10 (11.1)	7 (7.8)
Posterior Cerebral Artery (PCA)	6 (6.7)	7 (7.8)
Brainstem	3 (3.3)	8 (8.9)
Infratentorial	2 (2.2)	4 (4.4)
Thrombolysis		
No	85 (94.4)	76 (84.4)
Yes	5 (5.6)	14 (15.6)
Thrombectomy		
No	87 (96.7)	84 (93.3)
Yes	3 (3.3)	6 (6.7)
EEG finding		
Normal	27 (30.0)	46 (51.1)
Abnormal	63 (70.0)	44 (48.9)
Hemorrhagic transformation		
No	87 (96.7)	86 (95.6)
Yes	3 (3.3)	4 (4.4)
	Mean, SD (95% CI)	
Age	66.96 ± 1.31 (64.35–69.56)	64.42 ± 13.40 (61.62–67.23)
Systolic Blood Pressure	151.24 ± 30.50 (144.86–157.63)	159.51 ± 32.80(152.64–166.38)
Diastolic Blood Pressure	83.62 ± 15.71 (80.33–86.91)	89.21 ± 20.62 (84.89–93.53)
	Median (IQR)	
NIHSS	6 (10)	6 (11)
mRS on Discharge	3 (3)	3 (2)

Abbreviations: EEG, Electroencephalogram; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; SD, Standard deviation; CI, Confidence Interval; IQR, Interquartile range.

Table 2 Sociodemographic Characteristics of Study Participants with Abnormal EEG

Variables	Case, N (%)	Control, N (%)
Study participants with abnormal EEG	63 (58.9)	44 (41.1)
Sex:		
Female	23 (21.5)	26 (24.3)
Male	40 (37.4)	18 (16.8)
Race:		
Malay	19 (17.8)	20 (18.7)
Chinese	33 (30.8)	18 (16.8)
Indian	10 (66.7)	5 (33.3)
Others	1 (50.0)	1 (50.0)
Comorbidities:		
Hypertension		
No	11 (10.3)	9 (8.4)
Yes	52 (48.6)	35 (32.7)
Diabetes mellitus		
No	26 (24.3)	19 (17.76)
Yes	37 (34.6)	25 (23.4)
Dyslipidemia		
No	26 (24.3)	31 (29.0)
Yes	37 (34.6)	13 (12.1)
Atrial fibrillation		
No	54 (50.5)	36 (33.6)
Yes	9 (8.4)	8 (7.5)
Ischemic heart disease		
No	52 (48.6)	39 (36.4)
Yes	11 (10.3)	5 (4.7)
Previous stroke		
No	37 (34.6)	30 (28.0)
Yes	26 (24.3)	14 (13.1)
Previous intracranial haemorrhage		
No	62 (57.9)	42 (39.3)
Yes	1 (0.9)	2 (1.9)
Smoking history		
No	51 (47.7)	35 (32.7)
Yes	12 (11.2)	9 (8.4)
BP classification		
Optimal	6 (5.6)	6 (5.6)
Normal	4 (3.7)	1 (0.9)
At Risk	9 (8.4)	3 (2.8)
Mild	4 (3.7)	2 (1.9)
Moderate	12 (11.2)	6 (5.6)
Severe	6 (5.6)	11 (10.3)
Isolated Systolic Hypertension	22 (20.6)	15 (14.0)
Hypertension on presentation		
No	19 (17.8)	10 (9.3)
Yes	44 (41.1)	34 (31.8)
Large artery atherosclerosis		
No	45 (42.1)	17 (15.9)
Yes	18 (16.8)	27 (25.2)

(*Continued*)

Table 2 (Continued).

Variables	Case, N (%)	Control, N (%)
Cardioembolic		
No	55 (51.4)	35(32.7)
Yes	8 (7.5)	9 (8.4)
Small vessel occlusion		
No	27 (25.2)	38 (35.5)
Yes	36 (33.6)	6 (5.6)
Stroke of other determined etiology		
No	62 (57.9)	42 (39.3)
Yes	1 (0.9)	2 (1.9)
Stroke of undetermined etiology		
No	62 (57.9)	44 (41.1)
Yes	1 (0.9)	0 (0.0)
Seizure characteristics		
Type of seizure		
Generalized	38 (35.5)	0 (0.0)
Focal	25 (23.4)	0 (0.0)
Side of stroke		
Bilateral	1 (0.9)	2 (1.9)
Left	28 (26.2)	18 (16.8)
Right	34 (31.8)	24 (22.4)
Stroke location		
Subcortical	24 (22.4)	13 (12.1)
Cortical	39 (36.4)	31 (29.0)
Vascular territories		
Lacunar	22 (20.6)	8 (7.5)
Middle Cerebral Artery (MCA)	28 (26.2)	25 (23.4)
Anterior Cerebral Artery (ACA)	5 (4.7)	3 (2.8)
Posterior Cerebral Artery (PCA)	6 (5.6)	3 (2.8)
Brainstem	2 (1.9)	4 (3.7)
Infratentorial	0 (0.0)	1 (0.9)
Treatment		
Thrombolysis		
No	59 (55.1)	35 (32.7)
Yes	4 (3.7)	9 (8.4)
Thrombectomy		
No	61 (57.0)	39 (36.4)
Yes	2 (1.9)	5 (4.7)
Type of EEG changes		
Focal changes		
Non-focal	31 (29.0)	16 (15)
Focal	32 (29.9)	28 (26.2)
Diffuse (Generalized) changes:		
Non Diffuse	45 (42.1)	32 (29.9)
Epileptiform changes		
Non epileptiform	50 (46.7)	40 (37.4)
Epileptiform	13 (12.1)	4 (3.7)
Hemorrhagic transformation		
No	60 (56.1)	41 (38.3)
Yes	3 (2.8)	3 (2.8)

Abbreviations: EEG, Electroencephalogram; BP, Blood Pressure.

Table 3 Associations Between Risk Factors and Post-Stroke Seizures

Variables	Group	Mean Rank	U	Z	p-value
Sex	Case	98	3375	−2.241	0.013*
	Control	83			
Race	Case	97.15	3451.5	−1.877	0.015*
	Control	83.85			
Hypertension	Case	95	3645	−1.569	0.117
	Control	86			
Diabetes mellitus	Case	96	3555	−1.636	0.102
	Control	85			
Dyslipidemia	Case	104	2835	−4.026	<0.001*
	Control	77			
Atrial fibrillation	Case	90.5	4050	0	1
	Control	90.5			
Ischemic heart disease	Case	93.5	3780	−1.23	0.219
	Control	87.5			
Previous stroke	Case	96.5	3510	−1.863	0.031*
	Control	84.5			
Previous intracranial haemorrhage	Case	89.5	3960	−1.008	0.313
	Control	91.5			
Smoking	Case	88.5	3870	−0.729	0.466
	Control	92.5			
Blood Pressure classification	Case	88.34	3855.5	−0.571	0.568
	Control	92.66			
Hypertension on presentation	Case	85	3555	−1.917	0.028*
	Control	96			
Large artery atherosclerosis	Case	77	2835	−4.128	<0.001*
	Control	104			
Cardioembolic	Case	87.5	1	−1.269	0.205
	Control	93.5			
Small vessel occlusion	Case	106.5	2610	−4.8	<0.001*
	Control	74.5			
Stroke of other determined aetiology	Case	91	4005	−0.452	0.651
	Control	90			
Stroke of undetermined aetiology	Case	91	4005	−0.581	0.562
	Control	90			
Side of stroke	Case	94.37	3702	−1.135	0.256
	Control	86.63			
Location of stroke	Case	90.5	4050	0	1
	Control	90.5			
Vascular territories	Case	85.15	3568.5	−1.454	0.146
	Control	95.85			
Thrombolysis	Case	86	3645	−2.177	0.029*
	Control	95			
Thrombectomy	Case	89	3915	−1.023	0.306
	Control	92			
EEG Focal vs Non-Focal	Case	92.5	3870	−0.631	0.528
	Control	88.5			
EEG Diffuse vs Non- Diffuse	Case	93.5	3780	−1.197	0.231
	Control	87.5			
EEG Epileptiform vs Non-Epileptiform	Case	95	3645	−2.287	0.011*
	Control	86			
Hemorrhagic Transformation	Case	90	4005	−0.384	0.701
	Control	91			

Notes: *p-value, significant at <0.05; U, Mann–Whitney test; Z, Z value.

and thrombolysis treatment for stroke (U = 3645, z = −2.177, p <0.029) were also significantly associated with the occurrence of post-stroke seizure.

Risk of Post-Stroke Seizures

The risk of developing a seizure following a stroke event was examined using Odds Ratio (OR). The contingency table was examined and the odds ratio was calculated. Adjustments for potential confounders were not made as factors associated with increased post-stroke seizure are relatively unknown. In this study, the male gender had a statistically significant increased odds of post-stroke seizure at 1.974 (CI 1.088–3.583), as depicted in Table 4. Besides that, concurrent comorbid conditions, including hypertension, diabetes mellitus, atrial fibrillation, ischemic heart disease, and past stroke, had been shown to have elevated odds of post-stroke seizure but were not statistically significant. Dyslipidemia had a significantly elevated risk of post-stroke seizure outcome at OR 3.480 (CI 1.880–6.439) and is statistically significant. Small vessel occlusions were also associated with an elevated risk at OR 4.578 (CI 2.424–8.643). Conversely, the study found that participants with high blood pressure on presentation, large artery atherosclerosis and those that underwent thrombolysis showed decreased odds of post-stroke seizure. Notably, the results indicated a statistically significant increase in the risk of post-stroke seizure in individuals with epileptiform changes on their EEG, with an odds ratio of 3.630 (CI 1.136–11.603).

Table 4 Odds for Post-Stroke Seizure Based on Each Risk Factor

Variables	OR	95% CI
Sex (Male / Female)	1.974*	1.088–3.583
Race (Chinese, Non-Chinese)	1.370	0.760–2.470
Hypertension	1.744	0.869–3.504
Diabetes Mellitus	1.635	0.907–2.948
Dyslipidemia	3.480**	1.880–6.439
Atrial fibrillation	1.000	0.447–2.239
Ischemic heart disease	1.672	0.735–3.807
Previous intracranial haemorrhage	0.326	0.033–3.193
Smoking	0.765	0.373–1.571
Hypertension on presentation	0.505*	0.250–1.020
Large artery atherosclerosis	0.266**	0.140–0.505
Cardioembolic	0.578	0.247–1.354
Small vessel occlusion	4.578**	2.424–8.643
Stroke of other determined aetiology	1.517	0.247–9.304
Stroke of undetermined aetiology	2.023	0.180–22.713
Location of stroke	1.000	0.557–1.796
Thrombolysis	0.319*	0.110–0.928
Thrombectomy	0.483	0.117–1.993
EEG abnormalities	2.439	1.323–4.497
EEG focal changes	1.222	0.657–2.273
EEG diffuse changes	1.625	0.732–3.608
EEG Epileptiform changes	3.630*	1.136–11.603
Haemorrhagic transformation	0.741	0.161–3.411

Notes: * p value <0.05, ** p value <0.001.
Abbreviations: EEG, Electroencephalogram; OR, Odds ratio; CI, Confidence Interval.

Discussion

Our findings demonstrated an association between gender, race, dyslipidemia, history of stroke, large artery atherosclerosis, small vessel occlusions, blood pressure on presentation, and thrombolysis administration with PSS. The odds of PSS were elevated among males, those with dyslipidemia, small vessel occlusions, and in participants with epileptiform changes on EEG. Lower odds of PSS were seen in those with high blood pressure on presentation, large artery atherosclerosis, and those given thrombolysis treatment.

Sociodemographic Factors

The present study involved a cohort comprising 180 participants, with an equal distribution of individuals between the control and case groups. Notably, the elderly population was more prevalent in the study, as evidenced by a mean age range of 64.42 to 66.96. This is not unusual, as the prevalence of stroke in the elderly is significantly higher as published in the World Stroke Organization 2022 global fact sheet, where over two-thirds of cases occur beyond 50 years old.[17] The number of comorbidities observed increases with age, particularly beyond 65 years old and may contribute to the risk of stroke.[18]

Post-stroke seizure events are significantly associated with sociodemographic factors, especially gender and race, with a p-value of less than 0.05. Our study found that the male gender is 1.974 times more likely to develop PSS, which is comparable to other similar studies reporting a predominance of PSS among males.[19–22] However, other studies demonstrated conflicting results, with higher incidence of early PSS among women in studies from Saudi Arabia and Canada.[23,24] Besides that, a meta-analysis by Ma et al suggested there was no association between gender and epileptic seizures.[25] Conflicting results in these studies may be due to coagulation status, sex hormones, genetic backgrounds, social interactions, and lifestyle choices.[26]

From our analysis, males of Chinese descent were at particular risk for PSS. In Singapore, the highest incidence of stroke was observed among Chinese men, although a lower than expected response rate confounded the study.[27] There are existing studies pointing to the high prevalence of atherosclerosis and carotid plaques among Chinese men of advancing age.[28] This is possibly linked to an elevated presence of dyslipidemia with high triglyceride and low-density lipoprotein among the Chinese population.[29,30] All these factors may contribute to an increased rate of post-stroke seizure among the population, given its links to dyslipidemia. It is important to note that our participants' mean age is above 65 years old. Therefore, this may not reflect the exponential rise in the rate of obesity and metabolic disorders among younger populations in this region due to the shift in food consumption trends over the past three decades.[31] Studies focusing on stroke among young adults in the near future would reveal more data that would support the hypothesis that gender and race may be less significant than comorbidities in years to come.

Clinical Factors

In both our cohorts, most comorbidities observed were nearly equivalent, except for dyslipidemia. As mentioned earlier, dyslipidemia is a prominent risk factor and is significantly associated with PSS, with 3.48 times higher odds of developing PSS in our study. Existing studies also suggest an increased risk of PSS in stroke patients with underlying hypertension, dyslipidemia, or diabetes.[32] Cleary et al reported that total serum cholesterol and other vascular risk factors, such as myocardial infarction, peripheral vascular disease, hypertension, and left ventricular hypertrophy, are related to late-onset epilepsy.[33] The use of statins reduced the risk of progression to PSS in several studies, supporting the role of lower serum cholesterol in reducing PSS risk.[34,35] This is especially important in this region where rates of dyslipidemia are relatively high.[36]

Blood pressure on presentation was another significant factor for PSS. Our study suggests that the case group had lower or normal median blood pressure on presentation than the control group. Hundozi et al have reported similar findings and this may be attributed to the protective effect of arterial hypertension against early epileptic seizures after ischemic stroke stems from improvement in brain perfusion and the reduction in the size of the ischemic area.[37] Some studies did suggest that hypertension is not an independent risk factor for PSS, and another reported a higher incidence of PSS with hypertension.[25,32] Therefore, we may not fully understand the mechanism of how blood pressure relates to PSS,

and it might be detrimental to maintain higher blood pressure levels that may increase the risk of haemorrhagic transformation in ischemic strokes which invariably predisposes to early epileptic seizures.[38]

Stroke due to small vessel occlusion was significantly associated with PSS with an increase in risk by 4.57 folds. Small vessel diseases are known to cause deep infarcts, albeit small, as seen in imaging as leukoaraiosis, although its role in PSS is unclear.[39] Coupled with hypertension, it is identified as an independent risk factor for seizures in advancing age in a few studies.[40,41] This may be attributed to the upregulation of the receptor angiotensin II type I in the hippocampus of patients with mesial temporal sclerosis, suggesting an independent role of the renin–angiotensin system in temporal lobe epilepsy.[42,43] On the other hand, Ferreira-Atuesta et al reported that small vessel occlusion only carries a lower risk of acute symptomatic seizures post-stroke, approximately 6%.[44]

In our cohort, participants who had thrombolytic therapy had a reduced risk of post-stroke seizure with an odds ratio of 0.31. Several studies have reported that patients who had thrombolysis for ischaemic stroke did not show an associated risk for post-stroke seizure or epilepsy.[44–47] Reperfusion therapies may aid in reducing the subsequent size of the infarct by rescuing the tissue within the ischaemic penumbra, which is potentially pro-epileptogenic.[46] On the contrary, reperfusion has been associated with seizures in some studies, especially when complicated by the presence of microbleeds or secondary haemorrhages. However, these studies have several confounders, including the severity of the patients requiring reperfusion treatment who generally have a higher NIHSS score and larger lesion area on presentation.[44,46] The overall benefit seen is likely achieved by carefully selecting patients for thrombolysis.

Interestingly, atrial fibrillation, a known risk factor for cardioembolic stroke, was not associated with PSS in our study. Studies have identified it as a risk factor for late-onset and early-onset PSS due to its association with cortical damage.[19,48–50] Our findings were supported by studies from Taiwan and Lithuania, demonstrating that atrial fibrillation was not associated with an increased risk for PSS.[34,51] Beghi et al also reported that there was no significant association between cardioembolic stroke and acute symptomatic seizures.[15] It is imperative to thoroughly examine the various factors influencing atrial fibrillation in PSS that will contribute to its management.

The prevalence of abnormal EEG in this study is relatively high, with 107 participants with documented abnormal EEG from both cases and controls. Dyslipidemia was the most prevalent comorbidity with regard to EEG abnormalities. While large artery atherosclerosis has been identified as a common observation in patients with PSS, the same was not demonstrated in the present study. However, the small sample size limits the generalizability of this finding. In addition, the stroke localization was similar between both cohorts except for stroke involving the lacunar territories, which was more common among the case group. These findings add to the growing body of literature on the comorbidity and pathophysiology of seizures and stroke.

The electroencephalogram (EEG) aids in detection and prognostication in acute stroke by detecting seizures and specific stroke patterns, such as lateralized periodic discharges, which are associated with early seizures.[52–55] We observe a relatively higher proportion of patients with PSS demonstrating EEG abnormalities. As expected, those with the presence of epileptiform discharges were more likely to develop seizures, 3.63 times higher. Our data was concordant with a prospective study that epileptiform discharge in early post-stroke EEG is an independent predictor of epilepsy one year after stroke.[56] Specific EEG patterns such as periodic lateralized epileptic discharges are found to be closely related to early seizures.[55] Interictal epileptiform discharges have been documented as a predictive biomarker for seizure recurrence in post-stroke epilepsy.[57] EEG background asymmetry and focal epileptiform discharges have a greater seizure recurrence risk in post-stroke patients.[58] The cerebral hemodynamic changes from PSS result from electrophysiological instability, neurotransmitter imbalance, disruption of neuronal network, and post-stroke glial proliferation and activation.[7]

Based on our study, the at-risk population should be screened and risk stratified at an earlier age to initiate treatment early as necessary. Additionally, performing imaging techniques such as CT angiography of the brain to identify large and small vessel occlusions would be beneficial for prognostication. Expanding thrombolysis services to more hospitals is likely to improve overall stroke management outcomes and reduce the risk of post-stroke seizures (PSS). Future studies should investigate the risk of PSS in patients with different stroke subtypes, such as hemorrhagic stroke.

Limitations

Due to limited resources, we did not perform continuous EEG monitoring for our participants. Doing so would increase the detection rate of abnormalities in the EEG during hospitalization. In addition, as a single-centred study, these findings may not represent the overall population. Therefore, large-scale prospective studies need to be conducted to enhance our understanding of post-stroke seizure risks and their impact on individuals and society. Besides that, seizures occurring following discharge from the hospital may not be picked up, particularly, those who present with focal seizures as it is a prospective case–control study. Purposive sampling was utilized due to its flexibility to facilitate recruitment of case and controls. However, we are aware that this may be prone to potential bias.

Conclusion

Post-stroke seizures (PSS) can lead to poorer functional outcomes and extended hospitalization. This study highlights the importance of using EEGs to identify PSS and recognizing at-risk groups, which include males of Chinese descent in Asia, individuals with dyslipidemia, those with small vessel occlusions, and patients presenting with low to normal blood pressure. Recognizing these factors is crucial for developing comprehensive and effective management plans. Our findings contribute to the understanding of PSS risk factors and underscore the need for targeted interventions. Future research should focus on longitudinal studies to further elucidate the pathogenesis of PSS and explore the effectiveness of tailored management strategies in improving patient outcomes.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical Publication Statements

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The study complies with the Declaration of Helsinki. The ethics committee approval was obtained for this study.

Patient Consent Statement

Patients were informed regarding the purpose of the study and consent was obtained.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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