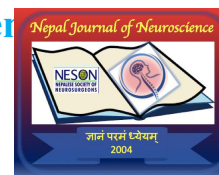


Prevalence And Risk Factors for Early Delirium in First-Ever Ischemic Stroke: An Observational Study

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Abstract

Introduction: Post-stroke delirium worsens the cognitive and physical disabilities after ischemic stroke. Early detection and treatment can improve outcomes. The study aims to determine the prevalence and risk factors for early post-stroke delirium in patients with acute ischemic stroke.

Materials and Methods: Demographic and clinical data were collected from adult patients with first-ever ischemic stroke presenting within 24 hours of symptom onset. The Confusion Assessment Method for Intensive Care Unit (CAM-ICU) was used to screen for delirium. Early delirium was defined as delirium occurring within 48 hours of admission. Univariate and multivariate analyses were done to identify risk factors associated with early delirium.

Results: The study included 146 patients, of whom 44(30%) developed early post-stroke delirium. On univariate analysis, risk factors identified were older age, severe stroke, aphasia, hemi-neglect, hemianopia, dysphagia, cortical location of infarcts, stroke due to large artery atherosclerosis, total anterior circulation stroke, large vessel occlusion, cerebral edema, early aspiration, post-stroke seizures, and early neurological deterioration. Older age (OR 1.14 per year [CI 1.08-1.21], $p < .001$), presence of large vessel occlusion (OR 5.19 [CI 1.41-19.39], $p = 0.01$), and aphasia (OR 1.89 [CI .95-3.76], $p = 0.04$) emerged as independent risk factors in multivariate logistic regression analysis.

Conclusion: Early delirium occurred in one-third of patients with acute ischemic stroke. Intrinsic stroke-related factors, rather than infections or metabolic causes, are major predisposing factors. Aspiration pneumonia secondary to dysphagia is a modifiable risk factor. Screening for delirium should begin early after hospitalisation for acute ischemic stroke.

Key words: Early delirium, Ischemic stroke, Risk factors, Screening

Introduction

Delirium is an acute confusional state characterised by fluctuations in attention and awareness. A variety of systemic insults, such as infections and critical illnesses, can precipitate delirium. It is a common neuro-psychiatric complication of acute ischemic stroke, where an interplay of

systemic factors and neurological damage combine to produce an acute encephalopathy.¹ A recent meta-analysis has estimated the incidence of post-stroke delirium to range from 7-66% with an average of 25%.² Post-stroke delirium is associated with adverse physical and cognitive outcomes both in the acute setting and long-term.

Delirium occurs more commonly in patients with stroke compared to those with other medical or surgical conditions, where the incidence rates range from 10 to 25%.³ It is important to institute delirium screening early, as it has been shown that effective management results in improved patient outcomes.⁴ Previous research has shown that delirium develops early after hospitalisation following ischemic stroke.^{5,6} Studies have demonstrated that post-stroke delirium has an onset within seventy-two hours of admission in a majority of patients.⁷ Focal neurological defects due to the stroke, such as aphasia and hemi-neglect, are predisposing factors for delirium; however, there are conflicting reports regarding the location of infarcts and the side of involvement.^{8,9} Moreover, there are only a few studies on the risk factors associated with delirium in the early post-stroke period, during which stroke-related deficits are at their maximum.

Hence, we aimed to detect the prevalence and risk factors for early post-stroke delirium in patients with first-ever ischemic stroke.

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Study Design and Setting

This is an analytical cross-sectional study conducted in the stroke unit of Government Medical College Thriuvananthapuram, a large tertiary care hospital located in the southern part of India, which admits more than six hundred patients with acute ischemic and haemorrhagic stroke in a year. The study was conducted over a period of 5 months from January to May 2025. Ethical approval was obtained from the Human Ethics Committee before study initiation.

Study Population and Sampling

All patients admitted with acute ischemic stroke were assessed, and patients ≥ 18 years of age with symptom onset within 24 hours were included in the study, after obtaining written informed consent. Patients with previous ischemic or haemorrhagic stroke and those who remained comatose, with Glasgow Coma Scale (GCS) < 8 , throughout the first two days of hospitalisation were excluded. Patients with pre-existing cognitive impairment were also excluded. The sample size is estimated using $n = p_1(1-p_1) + p_2(1-p_2) * (Z_{\alpha/2} + Z_{\beta})^2 / (p_1 - p_2)^2$ where p_1 and p_2 = proportion of risk factors in patients with and without delirium. Using $p_1 = .35$ and $p_2 = .15$ as per previous studies, sample size was calculated to be 73 in each group, total 146 patients.

Data Collection Tools and Instruments

Baseline demographic data and co-morbidities such as age, gender, vascular risk factors, clinical characteristics, stroke causes, stroke subtypes, and complications were recorded on a standard data collection form. Imaging (Computerised Tomography [CT]/Magnetic resonance Imaging [MRI] brain) was reviewed to assess Alberta Stroke Program Early CT score (ASPECTS) score, location (cortical, subcortical, or brainstem/cerebellar) of infarcts, and presence of cerebral edema, secondary hemorrhage, or atrophy. Large vessel occlusion was defined as occlusion of the M1 or M2 segment of the middle cerebral artery or the basilar artery on CT angiography. Stroke etiology was classified as large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology based on Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. Stroke subtyping was done using the Oxfordshire Community Stroke Project (OCSP) classification, based on neuroimaging and clinical features, as Total Anterior Circulation Stroke (TACS), Partial Anterior Circulation Stroke (PACS), Posterior Circulation Stroke (POCS) and Lacunar stroke (LACS).

Delirium assessment was done within 48 hours of admission by neurology residents, using the validated screening tool, the Confusion Assessment Method for Intensive care Unit (CAM-ICU), and was confirmed using the Diagnostic and Statistical Manual-5 (DSM-5) criteria. The residents were trained in the use of CAM-ICU and DSM-5. The CAM-ICU is an adaptation of the Confusion Assessment Method for use in critically ill non-verbal/intubated patients.¹⁰ It is the most commonly used delirium screening tool in neuro-intensive settings and has been validated in ischemic stroke.¹¹ A positive test requires the presence of both inattention and a change in baseline level of consciousness, along with either disorganised thinking or an altered level of consciousness at the time of examination. The CAM-ICU was translated into the local language, Malayalam, by two independent translators and was

back-translated to English. The translated questionnaire was then critically reviewed and validated.

The primary outcome was the occurrence of early delirium which was defined as delirium occurring within 48 hours of admission. Neurological deficits and stroke severity were assessed using the National Institutes of Health Stroke Scale (NIHSS). Functional ability was assessed with the use of the modified Rankin Scale (mRS) and poor mRS was defined as $mRS \geq 3$. Early neurological deterioration was defined as increase in NIHSS by ≥ 4 within 48 hours.

Statistical Analysis

Standard descriptive statistics are used to report demographic and clinical characteristics. Mean and standard deviation (SD) are used for normally distributed continuous variables, and median and interquartile range (IQR) for non-normal data. Student's *t* test and Mann Whitney U tests are used to compare continuous variables. Categorical variables are expressed as numbers and percentages and compared using the chi-square test. Significant factors in univariate analysis were entered in a multivariate logistic regression analysis to determine independent risk factors. Statistical significance was set at a two-tailed *p*-value < 0.05 . SPSS version 23 was used for statistical analysis.

Results

One hundred forty-six patients were included in the study. Early delirium occurred in 44 (30%) of patients. The demographic characteristics of patients with and without delirium are shown in Table 1. Delirium was significantly associated with older age and stroke due to large artery atherosclerosis.

Table 1: Demographic variables of patients with and without delirium.

	With Delirium (n= 44)	W i t h o u t delirium(n=102)	p value
Age	71.66 $\pm$ 11.62	60.64 $\pm$ 11.82	<.001*
Male gender	24(55)	70(69)	0.1
Poor socioeconomic status	37(84)	91(89)	0.39
Lower educational status	36(82)	90(88)	0.3
Rural residence	25(57)	45(44)	0.16
Diabetes	24(55)	50(49)	0.54
Hypertension	27(61)	61(60)	0.86
Cardiac disease	13(30)	27(26)	0.7
Atrial Fibrillation	2(5)	5(5)	0.92
Smoking	16(36)	37(36)	0.99
Alcoholism	17(39)	33(32)	0.46
Stroke Cause			
Large artery atherosclerosis	31(71)	40(39)	<.001*
Cardio-embolic	4(9)	13(13)	0.52
Small vessel disease	3(7)	37(36)	0.002*
Other determined causes	3(7)	3(3)	0.27
Undetermined	3(7)	9(9)	0.69

Numbers in brackets are percentages.

*Statistically significant at $p < 0.05$

Table 2 displays the clinical and radiological variables associated with delirium. On univariate analysis, delirium was significantly associated with a higher NIHSS score and lower GCS scores at admission. Stroke-related focal neurological deficits of aphasia, hemianopia, hemi-neglect, and dysphagia were significantly associated with delirium. On imaging, lower ASPECTS score, presence of large vessel occlusion on CT angiogram, cortical location of infarcts, and presence of cerebral edema were associated with delirium. Secondary hemorrhage was not associated with delirium. Total anterior circulation strokes were associated with delirium, whereas patients with lacunar stroke were less likely to develop delirium. Delirium was associated with complications of post-stroke seizures, early neurological deterioration, poorer mRS scores, and aspiration pneumonia.

Table 2: Clinical and radiological features of patients with and without delirium

	With Delirium (n=44)	Without Delirium (n=102)	p value
Clinical features			
Right hemiplegia	27(61)	32(31)	0.001*
Left hemiplegia	12(27)	39(38)	0.2
Hemianopia	16(36)	20(20)	0.03*
Aphasia	20(45)	13(13)	<.001*
Hemi-neglect	22(50)	24(24)	0.002*
Dysphagia	21(47)	16(16)	<.001*
NIHSS Score (median, IQR)	16(12,19)	7(3,11)	<.001*
Low GCS at admission (<13)	12(27)	9(9)	0.004*
Treated with thrombolysis	30(64)	66(65)	0.68
RBS at admission	155±62	160±64	0.62
Post-stroke seizures	3(7)	0(0)	0.008*
mRS poor (≥3)	34(77)	51(50)	0.002*
Aspiration Pneumonia	4(9)	2(2)	0.04*
Early neurological deterioration	7(16)	5(5)	0.03*
Imaging features			
Rt hemispheric infarcts	20(45)	42(41)	0.63
Left hemispheric infarcts	19(43)	39(38)	0.57
Large vessel occlusion	26(59)	27(26)	<.001*
Cerebral Edema	10(23)	9(9)	0.02*
Hemorrhagic transformation	12(27)	19(19)	0.24
Atrophy	5(11)	11(11)	0.91
Stroke Subtype			
Total Anterior circulation stroke	16(36)	14(14)	0.002*
Partial Anterior circulation stroke	19(43)	36(35)	0.37
Posterior circulation stroke	5(11)	8(8)	0.49
Lacunar stroke	4(9)	43(42)	<.001*

Numbers in brackets are percentages except where specified

*Statistically significant at $p < 0.05$

Odds ratios (OR) and 95% Confidence intervals (CI) for significant variables on univariate analysis are shown in table 3. On multivariate analysis, older age (OR 1.14 per year [CI 1.08-1.21], $p < .001$), presence of large vessel occlusion on CT angiography (OR 5.19 [CI 1.41-19.39], $p = 0.01$) and aphasia (OR 1.89 [CI .95-3.76], $p = 0.04$) emerged as independent risk factors.

Table 3: Odds ratio for significant variables associated with delirium on univariate analysis.

Variable	Odds Ratio (CI)
Right hemiplegia	3.47(1.66-7.26)
Hemianopia	2.43(1.07-5.14)
Aphasia	5.71(2.48-13.09)
Hemi-neglect	3.25(1.54-6.86)
Dysphagia	4.91(2.21-10.88)
Low GCS at admission (<13)	3.88(1.49-10.05)
Early Neurological deterioration	3.67(1.10-12.29)
Low ASPECTS (<7)	3.46(1.26-9.48)
Cortical Infarcts	3.8(1.73-8.34)
Large vessel occlusion	4.01(1.90-8.45)
Cerebral Edema	3.04(1.14-8.12)
Large artery atherosclerosis	3.69(1.73-7.90)
Total Anterior Circulation Stroke	3.59(1.56-8.27)
Post-stroke seizures	7.39(.75-73.13)
mRS score poor(≥3)	3(1.37-6.58)
Aspiration pneumonia	5(.88-28.39)

CI- 95% confidence intervals

Discussion

Early post-stroke delirium (PSD) occurred in one in three patients with first-ever acute ischemic stroke. This finding aligns with previous studies, which have estimated the incidence of early PSD to range from 15% to 39%.⁵⁻⁸

Older age was one of the major risk factors and was an independent risk factor for developing delirium. Structural brain damage, reduced perfusion to unaffected areas, and cholinergic deficit have been proposed as mechanisms of delirium pathophysiology.¹² Aging could affect the complex interplay between these factors, contributing to the increased incidence in elderly patients. Reduced cognitive reserve of the aging brain has also been implicated in the pathogenesis.¹² Several stroke-related risk factors for early PSD were identified. These included cognitive deficits such as aphasia and hemineglect, as well as physical deficits such as visual loss due to hemianopia and dysphagia.

Aphasia was an independent risk factor for developing early post-stroke delirium, which is in accordance with previous studies.^{13,14} Language function can be affected by post-stroke damage as well as by delirium itself. Aphasia in the post-stroke setting is doubly dangerous as it not only causes delirium but also complicates the assessment, as language comprehension is required for completing most of the tests. Aphasia interferes

with the assessment of attention and disorganized thinking, and careful examination is necessary to identify delirium in the presence of aphasia. Hemi-neglect, which causes impairment in attention, a core symptom of delirium, was expectedly associated with higher rates of delirium.⁷

Visual disturbance is a well-recognized predisposing factor for post-stroke delirium and we found hemianopia to be associated with higher risk for early PSD. It can sometimes be difficult to distinguish between hemi-neglect and hemianopia, especially in confused patients. Other studies have also found that pre-existing visual defects increased the risk of developing delirium.¹³ Thus, deprivation of visual input appears to be the primary mechanism by which hemianopia influences the occurrence of delirium.

We found that the cortical location of infarcts was associated with the development of delirium, whereas lacunar infarcts had a lower risk of delirium. This finding is in keeping with previous studies in post-stroke delirium.¹⁴ Cortical involvement causes greater disturbance of cognitive functions such as aphasia and neglect, which may be responsible for higher incidence of delirium. Previous research has given conflicting results regarding the lateralisation of infarcts related to delirium. Right hemispherical strokes were found to be predictive of delirium in many studies, whereas others have found left cortical stroke related to delirium.⁵⁻⁸ However, our study did not show either right or left-sided infarcts to be associated with delirium, a finding that has also been reported in a recent meta-analysis.¹⁵ Rather, large vessel occlusion and total anterior circulation strokes were associated with delirium. This suggests that cortical location and area of brain affected, rather than the side of involvement, might be the key factor in the development of early PSD.

Large vessel occlusion and total anterior circulation strokes tend to cause larger infarcts, with greater cortical involvement and impaired cognitive functions, resulting in a higher incidence of delirium. In line with this, we found that severe stroke, patients with right-sided weakness and those with higher functional disability at admission were associated with delirium. This has also been supported by previous studies, which have concluded that total anterior circulation strokes and severe strokes with higher NIHSS and mRS scores at admission predispose to delirium.¹³⁻¹⁵ Right-sided weakness was found to be a risk factor but it was not related to the location of infarcts in cortical, subcortical or brainstem regions. This suggests that higher functional disability due to the involvement of the right upper limb may be the cause for this observation. Severe strokes may cause greater neuroinflammation and disturbances of neurotransmission, leading to an acute encephalopathy.

We did not find treatment with thrombolysis or the presence of secondary hemorrhage on follow-up imaging to be related to delirium. However, imaging evidence of cerebral edema was associated with delirium. Cerebral edema usually co-occurs with large strokes in the middle cerebral artery territory, which have previously been reported to cause delirium. Post-stroke seizures were more common in patients with early PSD. Cortical infarcts, which were found to predispose to delirium, could also trigger seizures. Further research is needed on whether delirium itself is a precipitating factor for post-stroke seizures.

Dysphagia and aspiration pneumonia were significantly associated with the development of early PSD. Early swallow

assessment and oral feed restriction in patients with impairment may mitigate its development. In contrast to delirious patients with general medical conditions and those assessed later in the post-stroke period, infections and metabolic derangements were less commonly seen in early PSD. Early neurological deterioration was more common in patients with early PSD; the relationship may be bidirectional, as delirium causes impairment in alertness and attention, contributing to the worsened NIHSS. The strength of our study is that we concentrated on identifying the stroke-related risk factors in a homogenous population of patients with first-ever ischemic stroke without pre-existing cognitive deficits. The use of the DSM-5 criteria, which is widely regarded as the gold standard, to confirm the presence of delirium provides an accurate assessment of delirium incidence in patients with stroke-related neurological defects. However, our study had several limitations. The single-center nature of our study and the exclusion of patients with previous stroke and cognitive deficits may limit the generalisability of our study. Screening for delirium was done only once within the first 48 hours, and daily screening may have increased detection rates. We did not collect data regarding the use of psychotropic medications, which may have been a risk factor for early PSD.

Conclusion

Delirium is a common clinical problem after acute ischemic stroke and results in higher morbidity. Stroke-related factors contribute to early PSD. Dysphagia and aspiration are potentially modifiable risk factors. Early screening for delirium should be made routine in stroke units.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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