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Original Research Article

In-Hospital Recovery in Acute Ischemic Stroke with Extracranial and Intracranial Arterial Stenosis

Harish Chandika[1], Saravanan S[2], Sankaranarayanan P[3]

[1]Senior Resident, Department of Neurology, Tirunelveli Medical College, Tirunelveli, Tamilnadu
[2]Professor and Head of the Department, Department of Neurology, Tirunelveli Medical College, Tirunelveli, Tamilnadu
[3]Assistant Professor, Department of Neurology, Tirunelveli Medical College, Tirunelveli, Tamilnadu

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Corresponding Author: Dr. Harish Chandika
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Abstract:

Background: Stroke is a leading cause of mortality and disability globally, with extracranial atherosclerotic stenosis (ECAS) and intracranial atherosclerotic stenosis (ICAS) being critical determinants of stroke outcomes. This study examines how ECAS and ICAS affect recovery in acute ischemic stroke patients.

Methods: This cross-sectional observational study included 390 patients with acute ischemic stroke admitted to Tirunelveli Medical College Hospital from August 2022 to November 2023. Patients were categorized into four groups based on stenosis type: non-stenosis, ICAS-only, ECAS-only, and combined ICAS+ECAS. Baseline characteristics, risk factors, and functional outcomes (measured by the modified Rankin Scale, mRS) were analyzed. Hazard ratios and multiple linear regression analyses were used to identify predictors of recovery.

Results: Among the 390 patients, 73% were male, with the mean age highest in the combined ICAS+ECAS group (63.0 years). Smoking was significantly associated with the ICAS group, while coronary artery disease (CAD) was more common in patients with both ICAS and ECAS. Regression analysis identified smoking, dyslipidemia, CAD, ICAS, and combined ICAS+ECAS as significant predictors of poorer outcomes, while age, gender, hypertension, and diabetes were not predictive.

Conclusion: Patients with ICAS and concurrent ICAS+ECAS exhibited poorer recovery outcomes. Targeted interventions focusing on lifestyle modification and early risk factor management are recommended to improve recovery outcomes in acute ischemic stroke patients.

Keywords: Intracranial atherosclerotic stenosis, extracranial atherosclerotic stenosis and Recovery in stroke, Risk factors of stroke.

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Introduction

Stroke is a leading cause of death worldwide and a prominent neurological condition among adults.[1] Stroke is characterized by a focal deficit in brain function, most commonly hemiplegia, with or without signs of focal higher cerebral dysfunction (such as aphasia), hemisensory loss, visual field defect, or brain-stem deficit. Stroke damages the brain parenchyma through ischemia (from vessel occlusion) or hemorrhage (from vessel rupture). Ischemic stroke can be caused by atherosclerosis, thrombosis, embolism, vasoconstriction, or due to venous pathology. Atherosclerotic disease in the arteries supplying the brain can often be the cause of cerebral ischemic stroke. The distribution of atherosclerotic disease in the cerebral vasculature can be divided into two types, namely extracranial (EC) location involving large vessels in the neck region and intracranial (IC) location involving medium-sized vessels in Intradural segments of the cerebrovascular tree.[2] The etiology of stroke affects both the prognosis and outcome. Large artery atherosclerosis is one of the imaging markers that predict the prognosis of stroke.[3] The Chinese Intracranial Atherosclerosis (CICAS) study investigated the prevalence and risk factors for recurrent stroke in patients with large artery occlusive disease in China. The CICAS study found a higher prevalence of intracranial artery atherosclerosis than extracranial artery atherosclerosis (46% vs 14%).[4] The coexistence of intracranial artery stenosis and the extracranial lipid-rich necrotic core was associated with a higher risk of subsequent vascular events.[5] Identification of higher-risk patients is crucial for customized monitoring and treatment.[6] This study focuses on concurrent or individual involvement of extracranial or intracranial arteries in patients with acute ischemic stroke and their impact on in-hospital recovery.

Materials and Methods

Data derivation and study population

Study design: Cross-sectional observational study

All patients aged more than 18 years admitted with acute ischemic stroke in the neurology ward, Tirunelveli Medical College Hospital, Tirunelveli, from August 2022 to November 2023 were enrolled for the study after applying inclusion and exclusion criteria,

Inclusion Criteria: Patients with acute ischemic stroke aged more than 18 years

Exclusion Criteria:

- Stroke in young patients aged less than18 years
- Patients who are not willing to participate in the study
- Patients with a modified Rankin scale score (mRS) of more than 2 before admission
- Written informed consent was obtained from all the patients enrolled in the study.
- Data were collected using a structured proforma.

Definitions and assessment

Stroke diagnosis is based on clinical symptoms and MRI findings. MRI was used to identify acute infarctions. Intracranial arterial occlusion is assessed by contrast-enhanced magnetic resonance angiography. Extracranial vascular occlusion, which includes extracranial internal carotid, common carotid, and vertebral artery is assessed by B-mode ultrasonography and Doppler studies.

According to the Warfarin-Aspirin Symptomatic Intracranial Disease Study criteria,[7] two experts ascertained the degree of intracranial atherosclerotic stenosis (ICAS).

The following arterial segments of the intracranial arteries were included for assessment: bilateral intracranial internal carotid artery (locations of stenosis distal to the ophthalmic artery), anterior cerebral artery A1/A2, middle cerebral artery M1/M2, posterior cerebral artery P1/P2 and basilar artery.[8] The extracranial part of the internal carotid artery and vertebral artery, bilateral external carotid artery, and bilateral proximal part of the arteria subclavia were assessed using the North American Symptomatic Carotid Endarterectomy Trial criteria.[9]

In this study, the severity of ICAS was categorized into two groups: no stenosis or <50% stenosis, ≥50% stenosis or occlusion (including 50%–69% stenosis, 70%–99% stenosis, and occlusion). The degree of extracranial atherosclerotic stenosis (ECAS) was dichotomized into <50% or no stenosis and ≥50% stenosis or occlusion.

The modified Rankin scale (mRS) score was noted at the time of admission and at the time of discharge. In this study, patients with an mRS score of less than two were considered as early recovery, while those with a score greater than two were considered as late recovery.

Statistical analysis

The study population was divided into four subgroups: (1) non-stenosis group, which was defined as <50% or no ICAS without ≥50% ECAS; (2) ICAS-only group, defined as ≥50% ICAS or intracranial artery occlusion without ≥50% ECAS; (3) ECAS-only group, defined as <50% or no ICAS with ≥50% ECAS; and (4) ICAS+ECAS group, defined as ≥50% ICAS or intracranial artery occlusion with ≥50% ECAS.

Baseline characteristics and outcomes were assessed among patients of defined groups (ICAS, ECAS, ICAS+ECAS, and non-stenosis). The frequency of iintracranial and extracranial arterial occlusion in patients with acute ischemic stroke was assessed. The relationship between the distribution (intracranial or extracranial) of large artery atherosclerosis and mRS score was evaluated by multiple linear regression analysis. The association of each type of stenosis with recovery was assessed with hazard ratio analysis or risk ratio estimation.

Results

Demographic and Risk factors: A total of 390 patients with acute ischemic stroke were included in the study.

Age: Mean ages were similar across groups, with the highest mean age observed in the ICAS+ECAS group (63.0 years) and the lowest in the ECAS group (53.6 years). The difference in age among groups was not statistically significant (p-values ranged from 0.05 to 0.5).

Gender: Among 390 patients, 73% (286 patients) were male, and 27% (104 patients) were female. The proportion of males was consistently higher across all groups. Notably, the ICAS+ECAS group had a lower male-to-female ratio, with a statistically significant difference observed ($p = 0.04$).

Smoking: A higher prevalence of smoking was observed in the ICAS group and the non-stenosis group. A significant association with smoking was observed in the intracranial atherosclerotic stenosis group ($p = 0.004$) and the non-stenosis group ($p = 0.0009$).

Alcohol Consumption: Alcohol consumption prevalence showed no significant differences across groups (p-values > 0.05).

Hypertension (HTN): Although HTN was common across all groups, no significant

differences were observed in the distribution (p-values ranged from 0.08 to 0.754).

Dyslipidemia: Dyslipidemia was prevalent across all groups, with a significant difference observed in the ICAS+ECAS group (p = 0.001).

Diabetes Mellitus (DM): No significant differences in DM prevalence were observed among groups (p-values > 0.05).

Coronary Artery Disease (CAD): A significant association was noted in the ICAS and ICAS+ECAS groups (p-values ranged from 0.01 to 0.0008), with a notably lower occurrence in the ECAS-only group.

Modified Rankin Scale (mRS): A higher proportion of patients with a mRS score >2 was observed in the ICAS and ICAS+ECAS groups, suggesting worse functional outcomes. The differences in mRS scores among groups were significant (p = 0.000002 for ICAS, 0.04 for ECAS, and 0.0002 for ICAS+ECAS).

Table 1: Comparison between the subgroups of stenosis – Demographic and clinical characteristics

		ICAS		**ECAS**		**ICAS+ECAS**		**mRS Score**		**Non-stenosis**	
		0%-49% (n=332)	**50% - 99% (n=58)**	**0%-49% (n=368)**	**50% - 99% (n=22)**	**Yes (n=7)**	**No (n=383)**	**≤2 (n=225)**	**>2 (n=165)**	**Yes (n=303)**	**No (n=87)**
Age	Mean	56.892	55.707	56.902	53.591	63.000	56.601	55.689	58.115	56.990	55.759
	SD	12.390	12.556	12.287	14.191	13.478	12.375	12.725	11.852	12.205	13.108
	p-value	0.5		0.22		0.176		0.05		0.41	
Gender	Male	248	38	272	14	5	281	174	112	229	57
	Female	84	20	96	8	2	102	51	53	74	30
	p-value	0.15		0.32		1		0.04		0.07	
Smoking	Yes	147	38	173	12	5	180	117	68	130	55
	No	185	20	195	10	2	203	108	97	173	32
	p-value	0.004		0.51		0.2		0.04		0.0009	
Alcohol	Yes	124	28	146	6	1	151	88	64	117	35
	No	208	30	222	16	6	232	137	101	186	52
	p-value	0.14		0.27		0.25		1		0.8	
HTN	Yes	128	30	151	7	4	154	93	65	117	41
	No	204	28	217	15	3	229	132	100	186	46
	p-value	0.08		0.5		0.44		0.754		0.17	
Dyslipidemia	Yes	96	12	103	5	1	107	48	60	90	18
	No	236	46	265	17	6	276	177	105	213	69
	p-value	0.265		0.8		0.67		0.001		0.104	
DM	Yes	119	25	139	5	2	142	90	54	112	32
	No	213	33	229	17	5	241	135	111	191	55
	p-value	0.304		0.178		1		0.167		1	
CAD	Yes	39	0	38	1	0	39	15	24	38	1
	No	293	58	330	21	7	344	210	141	265	86
	p-value	0.001		0.71		1		0.01		0.0008	
mRS at discharge	≤2	208	17	208	17	1	224			190	35
	>2	124	41	160	5	6	159			113	52
	p-value	0.000002		0.07		0.04				0.0002	

Distribution of stenosis among subgroups: There were 303 patients (77.6%) in the non-stenosis group, 58 patients (14.8%) in the ICAS-only group, 22 patients (5.6%) in the ECAS-only group, and 7 patients (1.7%) in the combined ICAS and ECAS group. In the ICAS-only group, 38 patients (66%) were male and 20 patients (34%) were female, among 22 patients in the ECAS group 14 patients were (64%) male and 8 patients (36%) were female, and out of 7 patients in the concurrent ICAS and ECAS group 5 patients (71%) were male ad 2 patients (29%) were female.

Table 2: Comparison of mRS score between stenosis groups

mRS Score	ICAS (n=58)	ECAS (n=22)	ICAS+ECAS (n=7)
≤2	17	17	1
>2	41	5	6
p=0.00016			

Recovery outcomes measured by the mRS scores differed significantly across stenosis groups (ICAS, ECAS, ICAS+ECAS), with a significant p-value of 0.00016, indicating variability in recovery based on stenosis type.

Multiple Linear Regression Analysis:

Table 3: Multiple linear regression analysis on the factors influencing the mRS score

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%
Age	0.002841	0.001862	1.526078	0.127827	-0.00082	0.006501
Sex	0.054741	0.066541	0.822667	0.411216	-0.0761	0.185579
Smoking	0.303615	0.078142	3.885428	0.000121	0.149968	0.457262
Alcohol	-0.25138	0.072608	-3.4622	0.000597	-0.39415	-0.10862
HTN	0.091885	0.051991	1.767339	0.077978	-0.01034	0.194113
Dyslipidemia	-0.21024	0.05301	-3.96613	0.000156	-0.31448	-0.10601
DM	0.074304	0.052757	1.408431	0.159825	-0.02943	0.178038
CAD	-0.20673	0.081018	-2.55159	0.011116	-0.36603	-0.04742
ICAS	-0.43795	0.067894	-6.4505	0.000056	-0.57145	-0.30445
ECAS	0.064317	0.101694	0.63246	0.527469	-0.13564	0.264275
ICAS+ECAS	-0.68175	0.176837	-3.85525	0.000136	-1.02946	-0.33404

Significant Predictors:

Smoking: Positively associated with higher mRS scores ($p < 0.001$), indicating worse functional outcomes in smokers.

Alcohol: Negative association with mRS scores ($p = 0.001$), suggesting better outcomes for non-drinkers.

Dyslipidemia: Negative association ($p < 0.001$), indicating a protective effect or potentially less severe outcomes among patients without dyslipidemia.

Coronary Artery Disease (CAD): Negative association ($p = 0.011$), pointing to worse functional outcomes among CAD patients.

ICAS and ICAS+ECAS: Both ICAS ($p < 0.001$) and ICAS+ECAS ($p < 0.001$) showed a significant negative association with mRS scores, indicating poorer outcomes in patients with intracranial or combined stenosis.

Non-significant Predictors: Age, gender, hypertension (HTN), and diabetes mellitus (DM) were not associated with higher mRS scores in this study, suggesting these variables may not independently influence functional outcomes.

Hazard Ratio Analysis for Stenosis Types

Table 4: Association of stenosis type with recovery

	(95% CI)	p-value
ICAS	0.904 (0.68291-1.126)	<0.001
ECAS	0.95 (0.8024-1.097)	<0.001
ICAS+ECAS	1.0601 (0.9756-1.14459)	<0.001
mRS	0.401 (0.093-0.709)	0.0108
Non-Stenosis	0.9149 (0.662-1.167)	<0.001

ICAS: The hazard ratio for ICAS was 0.904 with a 95% confidence interval (0.68291-1.126) and a P-value < 0.001, indicating a statistically significant association between ICAS and delayed recovery (higher mRS scores).

ECAS: The hazard ratio for ECAS was 0.95 (CI: 0.8024-1.097), with a P-value < 0.001, showing that extracranial stenosis alone is significantly associated with functional outcomes but with a neutral to weak effect size.

ICAS+ECAS Combination: The combined effect of ICAS and ECAS presented a hazard ratio of 1.0601 (CI: 0.9756-1.14459) with a P-value < 0.001. This combination had a slight association with worse recovery outcomes.

mRS: A distinct finding was observed with mRS, which had a hazard ratio of 0.401 (CI: 0.093-0.709, P = 0.0108), reflecting a reduced functional recovery rate among patients with significant ICAS or ECAS.

Discussion

Atherosclerotic disease is a systemic disease that affects different arterial territories with shared pathophysiological pathways and risk factors.[10] A higher prevalence of ICAS was reported in Asian patients with ischaemic cerebrovascular disease.[11] Our study was conducted in South India, among 390 patients studied, 5.6% had ECAS, 14.8% had ICAS and 1.7% had both ICAS plus ECAS. A study by Das P J et al[12] found that the prevalence of significant extracranial carotid artery stenosis (8.9%) is low in northeast Indian patients with ischemic stroke. Vajpeyee A et al[13] study showed a higher incidence of intracranial stenosis based on angiography. Similarly, the study by Johnsen L-H et al[14] concluded that the prevalence of ICAS in a general population of Caucasians was relatively high and similar to that of extracranial internal carotid artery stenosis in previous population-based studies. Our study findings reinforce existing literature that highlights the prevalence and impact of ICAS and combined stenosis on stroke outcomes. ICAS and combined stenosis are shown to be major contributors to stroke-related morbidity, aligning with findings in studies of Asian populations, which report higher intracranial atherosclerosis rates compared to Western populations.

Age variations and a predominance of males across groups suggest a higher prevalence of both ICAS and ECAS among middle-aged to older men. However, the ICAS+ECAS group had older patients, indicating a potential age-related vulnerability for concurrent stenosis. Smoking was notably prevalent in the ICAS group, aligning with the established risk of intracranial stenosis among smokers and found to be a significant predictor of worse outcomes, aligning with literature on the detrimental effects of smoking on vascular health. The higher occurrence of CAD in ICAS plus ECAS patients underscores the potential link between extensive arterial disease and systemic cardiovascular risk.

The negative associations observed with dyslipidemia and CAD may reflect complex interactions with other risk factors and the overall cardiovascular health status of patients. The negative association between alcohol and mRS scores suggests potentially better outcomes among non-drinkers, though this association warrants further exploration to control for other lifestyle factors. Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack by the American Heart Association/American Stroke Association also emphasized the management of vascular risk factors (Diabetes, hypertension, and smoking).[3] Despite guideline-recommended therapy, patients with ischaemic cerebrovascular disease with ICAS had a higher risk of subsequent stroke, composite vascular events, or death.[15,16] ECAS is also a predictor of recurrent stroke and vascular events in patients with ischaemic cerebrovascular disease.[17,18] Although ICAS and ECAS were different phenotypes of systemic atherosclerosis, coexistence with ECAS was common in patients with ICAS.[19,20] Based on a study of 7-Tesla MRI and autopsy, the burden of ICAS was associated with extracranial artery atherosclerotic lesions.[21,22]

The ICAS and combined ICAS+ECAS groups demonstrated significantly worse functional outcomes, highlighting the compounded risk of intracranial and concurrent stenoses on stroke recovery. These findings suggest a need for enhanced monitoring and management of patients with multiple stenotic sites, as they may face elevated risks of ischemic events and poorer recovery trajectories. The study by Suo Y et al[23] showed that concurrent ICAS and ECAS is associated with a higher possibility of 1-year recurrent stroke or composite vascular events. Similarly, Li J et al found that the co-existing cerebrovascular atherosclerotic diseases, particularly co-existing carotid lipid-rich necrotic core and intracranial stenosis, are independent predictors for subsequent vascular events. Zhang W et al[24] study showed that intracranial and extracranial atherosclerotic stenosis is associated with white matter hyperintensities. This association is significant in ECAS but attenuated in ICAS.

The hazard ratio analysis underscores the differential impact of ICAS and ECAS on patient recovery. Although both types of stenosis show significant associations with poorer functional outcomes, the effect sizes were generally weak to neutral (near 1), suggesting that ICAS and ECAS alone may not drastically alter recovery. However, the combined ICAS+ECAS association slightly exceeds 1, indicating potential additive effects on functional impairment.

Clinical implications: The high prevalence of ICAS, especially in conjunction with risk factors such as smoking and CAD, indicates a need for targeted intervention strategies focusing on lifestyle modification and managing cardiovascular risk. For instance, smoking cessation and CAD management could significantly mitigate risks associated with ICAS and improve outcomes.

Our study results highlight that ICAS and combined stenosis should be considered high-priority conditions in stroke management. Given the poor outcomes associated with these conditions, early detection and treatment are essential.

Limitations: We used ultrasonography to detect extracranial artery atherosclerotic stenosis, which is operator-dependent. Recent studies emphasized the predictive value of imaging markers other than

luminal stenosis of extracranial arteries, including high-risk non-stenotic carotid plaque, [25] calcification, [26] or inflammation. [17] Second limitation of the study, is that the sample size of the subgroup analysis was small.

Conclusion

Intracranial atherosclerotic stenosis and concurrent intracranial and extracranial atherosclerotic stenosis were associated with delayed recovery in acute ischemic stroke, thereby affecting quality of life and causing increased morbidity.

Early and rapid evaluation of intracranial and extracranial atherosclerotic stenosis is essential for timely intervention and accelerated recovery in acute ischemic stroke.

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