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Study of the Outcome Differences among the Ischemic Stroke Subtypes basedon TOAST Classificationat TribhuvanUniversity Teaching Hospital, Nepal.

The objective of this study was to explore the outcome differen cesamong is chemic stroke sub types based on "Trial of ORG 10172 in Acute Stroke Treatment (TOAST)" system in a tertiary referral hospital.

A hospital based prospectiv elongitudinal study was conducted involving 182 patients. Modified Rank in Scale (MRS) was used to assess functional out come, Kaplan-Meierproduct- limit method and Coxproportional hazards regression analys is were used to evaluate rates and identify predictors of survival and recurrent stroke.

MRS were statistically different across stroke subtypesat 30 days and 6 months ($p<0.0001$ and ($p<0.0001$) respectively). Lacunar stroke was associated with milder deficits. Estimated rates of recurrent stroke were significantly differentat 30 days ($p<0.0001$)and at 6 months ($p=0.009$). Before adjusting forage, sex, stroke severity, and diabetes mellitus, infarct subtype was not an independent determinant of recurrent stroke within 30 days ($p=0.057$);but was at 6months ($p=0.024$), how ever after same adjustment it was independent determinant both at 30 days ($p=0.030$) and at 6 months ($p=0.025$). Estimated death rates were significantly different both at 30 days ($p=0.026$) and at 6 months ($p=0.009$).Ischemic stroke subtype wasan independent determinant of 6-month survival both before ($p=0.016$) and after ($p=0.027$) adjustment for different parameters; however, was not of 30-day survival both before ($p=0.054$) and after ($p=0.993$) same adjustment.

Early recurrencerates were highest among largeartery atherosclerotic stroke. Lacunar strokehas betterpost stroke functional status. Survival is poorest among cardioembolic stroke.

Keywords: TOAST, Ischemic stroke, survival

Ischemic stroke has different causes and mechanisms. The use of subtype classification system helps to understand the differences in frequency of various stroke risk factors, incidence, strokeprognosis, chancesof recurrence, and long-termsurvival among different is chemic stroke subtypes.[2] The TOAS Tinvestigatorsdevised aseries of definitions to classify patients with is chemic stroke into 5 coreetiologic groupings:(1) Largeartery atherosclerosis, (2) Small artery occlusion(lacune), (3) Cardioembolism, (4) Stroke of other determined etiology,(5) Stroke of undetermined etiology, based on clinical impression and diagnostic findings.[1]

Studies of survival and recurrence after stroke have been reported throughout the world,[4,5,11,15,16]but there is limited data from Nepal on outcomes for individual subtypes of ischemic stroke. Comparison of functional outcome, survival and recurrence rates for specific ischemic stroke mechanisms helps identify patients at higher risk for stroke recurrence and death, plan future strategy for prevention,and permit health care policy makers to evaluate the burden attributableto individual pathophysiological mechanisms of ischemic stroke. This study attempts to assess functional outcome, and to estimate and compare rates and identify determinants of recurrence and death for patients with common ischemic stroke subtypes at Tribhuvan University Teaching Hospital (TUTH), one of the largest tertiary care centers of Nepal.

Material and Methods

A prospective observational hospital based study was conducted after approval from Institutional Review Board, Institute of Medicine, Tribhuvan University. All patients aged 18 years and over admitted with diagnosis of ischemic stroke were followed up for six months from the date of admission. Diagnosis of ischemic stroke was based on clinical, biochemical, and radioimaging (CT or MRI of brain) findings. Classification of the ischemic stroke into subtypes was based on TOAST classification criteria. Data were recorded at admission, 1 month, 3 months and 6 months regarding recurrence, mortality and motor outcome. Motor outcome was assessed by modified Rankin scale.

Brain CT or MRI among patients with lacunar stroke demonstrated either no lesion to explain the syndrome or a deepischemic stroke in a location consistent with the clinical syndrome ≤15 mm in size.[7,10] Recurrent stroke was defined as a new neurological deficit fitting the definitions for ischemic or hemorrhagic stroke, occurring after a period of unequivocal neurological stability or improvement lasting ≥24 hours and not attributable to edema, mass effect, brain shift syndrome, or hemorrhagic transformation of the incident cerebral infarction.

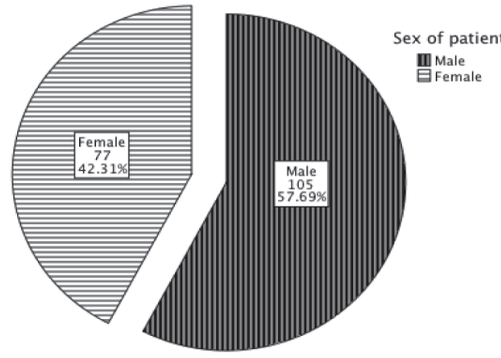

Figure 1. Sex distribution of thepatients

The Modified Rankin Scale (MRS) was used to measure functional status before the stroke, the functional outcome after cerebral infarction at 1 month and 6 months after the stroke. The scale runs from 0-6, running from perfect health without symptoms to death.[12]

Statistical Analysis

Patients with rare causes of stroke were excluded from the analysis because of the small number of subjects. Statistical analysis was done using IBM SPSS Statistics for Windows, Version 20. Continuous variables were expressed as mean ± SD and results on categorical variables wereexpressed in Number (%). The Chi square (X2) test was used to compare Rankinscores among the subtypes. The Kaplan-Meier product-limit method was used to estimate rates of survival and recurrent stroke after cerebral infarction for the 4 common ischemic stroke subtypes except Strokeof other determinedetiology. The log-rank test was used to compare rate estimates and the Cox proportional hazards model was used to estimate the impact in terms of risk ratios of possible determinants of survival and recurrent stroke after cerebral infarction. Results were considered statistically significant if p-value was less than 0.05.

Results

One hundred and eighty-two (182) patients with ischemic stroke were included in the study. Mean age (in years) was 65.01 ± 13.689 among which 57.7 % were male **(Figure 1)** and the majority (82.4%) were from the hilly region of Nepal. Diabetes was found in 16.5% while hypertension was noted in 46.7%. Ischemic heart disease was found in 17.6% while congestive heart failure was in 12.1% of study population. Cerebral cortical impairment was noticed in 36.3%, the majority had aphasia (Table 1 and 2).

Variables	Minimum	Maximum	Mean ± Std. Deviation
Age (in years)	25	87	65.01 ± 13.689
Modified Rankin Scale			
before present stroke	0	4	0.87 ± 1.380
Modified Rankin Scale			
at 1 month of stroke	0	6	2.66 ± 1.803
Modified Rankin Scale			
at 6 month of stroke	0	6	2.71 ± 2.013
NIHSS of patient at presentation	0	32	13.64 ± 8.75

Table 1. Mean of continuous variables (n=180)

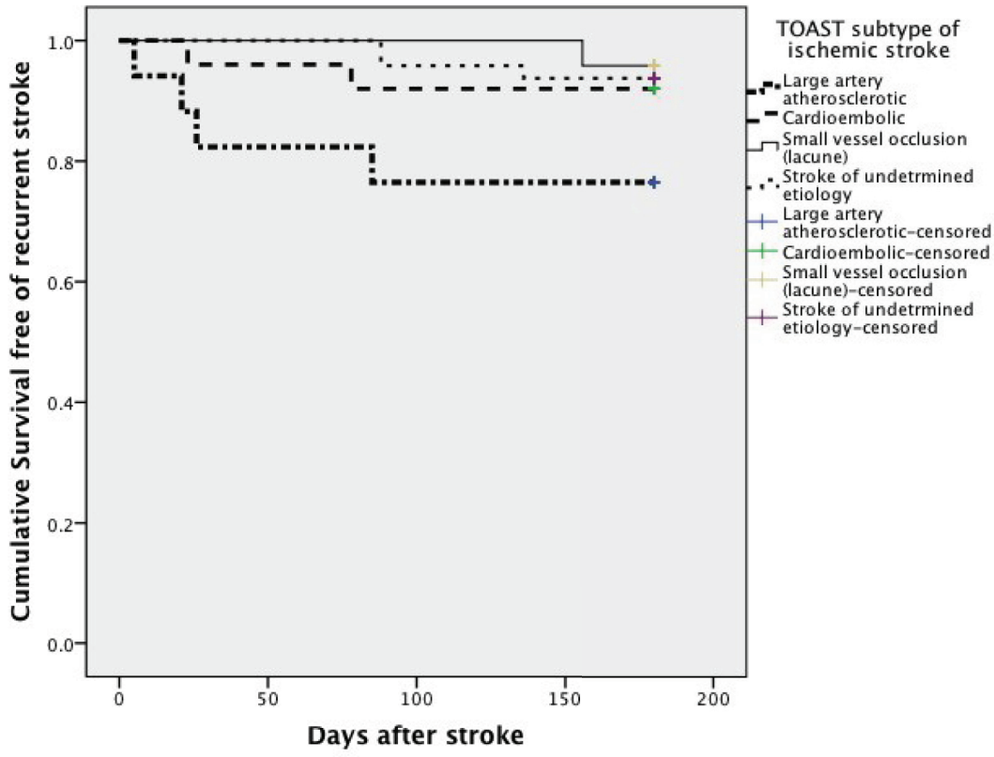

Figure 2. TOAST subtypes of ischemicstroke

Previous ischemic events were documented in 18.7%. First neuroimaging was found normal in 52.7%. Among abnormal imaging findings, cortical lesions (53.3%) were the most common followed by subcortical lesions (41.2%). Atrial fibrillation (18.7%) was the commonest cause of cardioembolic stroke; nonatherosclerotic vasculopathy was found in only 2 (1.1%) and hypercoagulable state or hematological disorder were not noted in any patient. Posterior circulation infarctions were documented in only 10 (5.5%). Cardioembolic stroke (27.5%) was the commonest type ischemic stroke followed by the stroke of undetermined etiology (26.4%) and small vessel occlusion (lacune) (26.4%). Large artery atherosclerotic strokes contributed to only 18.7% of total and stroke of

Variables	Number of patient (%)
Sex	
Male	105(57.7)
Female	77(42.3)
Address	
Himal	8(4.4)
Pahad	150(82.4)
Tarai	24(13.2)
Ischemic heart disease	32(17.6)
Congestive heart failure	22(12.1)
Diabetes	30(16.5)
Hypertension	85(46.7)
Cerebral cortical impairment	66(36.3)
Intermittent claudication in patient	8(4.4)
Previous ischemic event	34(18.7)
Previous transient ischemic attack	8(4.4)
In same vascular territory	6(3.3)
In more than one vascular territory	2(1.1)
Previous stroke	28(15.4)
In same vascular territory	12(6.6)
In more than one vascular territory	16(8.8)
Carotid bruit	6(3.3)
Diminished pulse	12(6.6)
First Imaging(CT OR MRI)-	
Normal	96(52.7)
Abnormal	86(47.3)
Imaging(CT OR MRI) abnormality	
Cortical	97(53.3)
Subcortical hemispheric	75(41.2)
Cerebellar	4(2.2)
Brain Stem	6(3.3)
Causes of cardioembolic stroke	
RHD	10(5.5)

AF	30(16.5)
RHD with AF	4(2.2)
DCM	4(2.2)
ASD	2(1.1)
Atrial fibrillation	34(18.7)
Nonatherosclerotic Vasculopathy	2(1.1)
Hypercoagulable State	0(0)
Hematologic disorder	0(0)
Type of stroke	
Anterior circulation	172(94.5)
Posterior Circulation	10(5.5)
TOAST subtype of ischemic stroke	
Large artery atherosclerotic	34(18.7)
Cardioembolic	50(27.5)
Small vessel occlusion(lacune)	48(26.4)
Stroke of other determined etiology	2(1.1)
Stroke of undetrmined etiology	48(26.4)
Mortality within 6 month	42(23.1)
Recurrence of stroke within 6 month	17(9.3)

Table 2. Frequency of different categorical variables (n=180)

Time	Rankin Score	Atherosclerosis With Stenosis n= 34 (%)	Ischemic Stroke of Cardioembolic n= 50 (%)	Lacunar n= 48(%)	Uncertain Cause n=48(%)	P (χ^2)
Before stroke	0-3	32(94)	44(88)	48(100)	40(83.3)	
	4-6	2(5.9)	6(22)	0(0)	8(16.7)	0.005
At 30 days	0-3	26(76.5)	22(44)	46(95.8)	32(66.7)	
	4-6	8(23.5)	28(56)	2(4.2)	16(33.3)	0.0001
At 6 month	0-3	24(70.6)	24(48)	48(100)	32(66.7)	
	4-6	10(29.4)	26(52)	0(0)	16(33.3)	0.0001

Table 3. Functional Status Among Patients With Common Ischemic Stroke Subtypes

Number of patients (%)With Recurrent Stroke Among Each Ischemic Stroke Subtype.

Time After With Stenosis	Atherosclerosis	Cardioembolic	Lacunar	Ischemic Stroke of. Uncertain Cause	P (log rank)	First Stroke
7 days	2(5.9)	0(0)	0(0)	0(0)		
30 days	6(17.6)	2(4)	0(0)	0(0)	<0.0001	
90 days	8(23.5)	4(8)	0(0)	2(4.2)		
6 month	8(23.5)	4(8)	2(4.2)	3(6.3)	0.009	

Table 4. Kaplan-Meier Estimates of Probabilities of Recurrent Stroke After First Ischemic Stroke for Common Ischemic Stroke Subtypes

other determined etiology were recorded in only 2(1.1%) **(Figure 2)**. Mean NIHSS was 13.64 ± 8.755 (Table 1 and 2). Patients with uncommon causes of stroke (n=2,1.1%) were excluded from the analysis because of the small number of subjects and hence only 180 patients were subjected to further analysis.

Functional Outcome

The Rankin scores among the 180 patients with common ischemic stroke subtypesbefore the stroke, at 30 days and at 6 months of stroke is presented in Table 3. Patients with lacunar ischemic stroke had milder maximal neurological deficits and better post stroke Rankin scores compared with patients with other subtypes. Patients with cardioembolic stroke had poorer prestroke functional status (22%), more severe neurological deficits at 30 days (56%) and at 6 months (52%), and poorer functional outcome compared with other subtypes(p values, 0.005, 0.0001 and 0.0001 respectively).

Recurrence

During the 6 months follow-up, 17 patients among the 4 common subtypes had recurrent stroke. Table 4 and Figure 3 present the Kaplan-Meier estimates of recurrent stroke for the different subtypes. 8 patients had recurrent stroke within 30 days, 6 of them had large-vessel atherosclerosis with stenosis as the first stroke subtype. All 30- day recurrent strokes were ischemic. Ischemic stroke subtypes had significant difference in 30-day and 6-month recurrence rate with p values <0.0001 and 0.009 respectively (Table 4). Ischemic stroke subtype (Atherosclerosis with stenosis) was a not significant independent determinant of 30 days recurrence (P=0.057) compared with Cardioembolic stroke. Ischemic stroke subtype (Atherosclerosis with stenosis) was a significant independent determinant of 6-month recurrence (P=0.029) compared with Ischemic stroke of unknown cause.

In Cox proportional hazards model, previous ischemic events and NIHSS at admission were the statistically significant predictors of recurrence at 30 days with hazard ratios 4.45 and 6.57 respectively; and p values 0.035 and 0.021 respectively. These predictors were not significant at 6 months with hazard ratio 2.75 and 2.00respectively; and p values 0.074 and 0.153 respectively (Table 5).

Ischemic stroke subtype was a not significant independent determinant of 30-day recurrence before (p=0.057) but was significant after (p=0.030) adjusting for age, stroke severity, and diabetes mellitus. At 6 month this was an independent predictor of recurrence both before (0.024) and after (0.025) adjusting for age, stroke severity, and diabetes mellitus with the proportional hazards model (Table 5).

Survival

42 patients died during follow-up. Table 6 and Figure 4 present the Kaplan-Meier estimates of rates of death for the different stroke subtypes. Cardioembolic subtype had maximum 30 days and 6 months mortality, which was statistically significant (log rank, P=0.026 and 0.009 respectively).

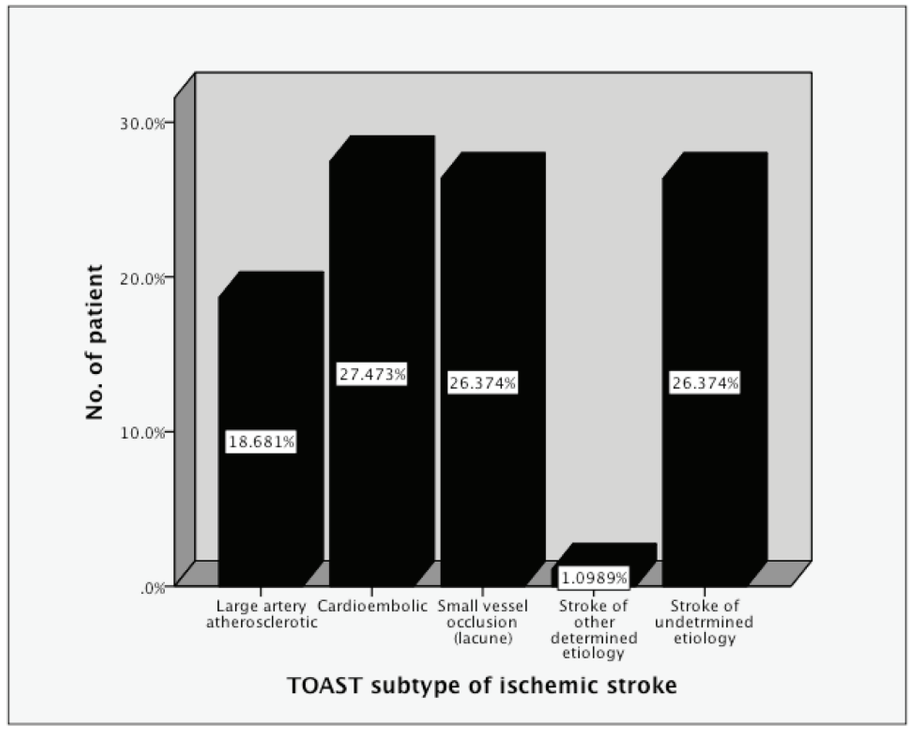

Figure 3.Observed percentage surviving (Kaplan-Meiere stimates) free of recurrent stroke after incident is chemic stroke

Variable	30-d Risk Ratio (95% CI)	pValue	6 month Risk Ratio (95% CI)	pValue
Age	2.65(0.53-13.13)	0.233	1.27(0.48-3.34)	0.625
Male Sex	2.18 (0.44-10.82)	0.340	1.03(0.39-2.72)	0.946
Diabetes	1.67(0.34-8.23)	0.531	0.67(0.15-2.92)	0.592
HTN	1.13(0.28-4.53)	0.860	0.60(0.22-1.63)	0.317
Previous ischemic events	4.45(1.11-17.81)	0.035	2.75(0.91-6.69)	0.074
Rankin 4-6	2.44 (0.61-9.75)	0.208	1.42(0.53-3.84)	0.490
NIHSS	6.57 (1.33-32.56)	0.021	2.00(0.77-5.19)	0.153
Stroke subtype				
Atherosclerosis with stenosis	4.72(0.95-23.40)	0.057	4.38(1.16-16.52)	0.029
Cardioembolic			1.32(0.30-5.92)	0.713
Lacunar			0.66(0.11-3.95)	0.649

Table 5. Cox Proportional Hazards Models Examining Influence of Ischemic Stroke Subtype and other variables on Survival Free of Subsequent Stroke (Recurrence)

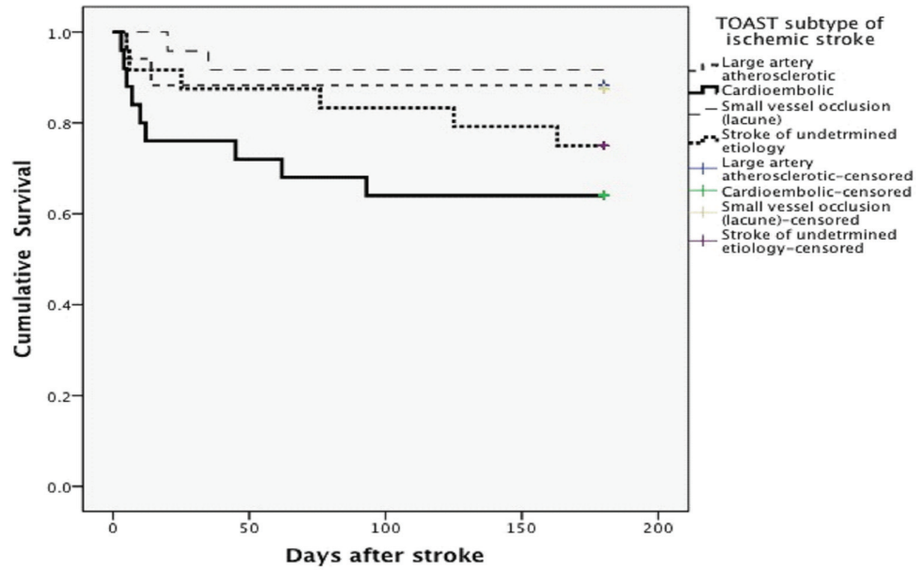

Figure 4. Observed percentage surviving (Kaplan-Meier estimates) afterincident ischemicstroke.

Number of patients (%) Dead Among Each Ischemic Stroke Subtype

Time After First Stroke	Atherosclerosis With Stenosis	Cardioembolic	Lacunar	Ischemic Stroke of Uncertain Cause	P (log rank)
7 days	2(5.9)	8(16)	0(0)	4(8.3)	
30 days	4(11.8)	12(24)	2(4.2)	6(12.5)	<0.026
90 days	4(11.8)	16(32)	4(8.3)	8(16.7)	
6 month	4(11.8)	18(36)	6(12.5)	12(25)	<0.009

Table 6. Kaplan-Meier Estimates of Probabilities of Death After First Ischemic Stroke for Common Ischemic Stroke Subtypes

In Cox proportional hazards model, age, AF, worst functional outcome (mRS=4-6) and NIHSS at admission were the statistically significant predictors of mortality at 30 days with hazard ratios 4.70, 5.25, 8.25 and 28.89 respectively (p values 0.005,<0.0001, <0.0001and <0.0001 respectively) as well as at 6 months with hazard ratios2.92, 3.87, 15.24 and 62.01 respectively (p values 0.003, <0.0001, <0.0001and<0.0001 respectively) (Table 7). Ischemic heart disease was not statistically significant predictors of mortality at 30 days with hazard ratio 2.54 (p value 0.076) but statistically significant predictors of mortality at 6 months with hazard ratio 3.93 (p value 0.005).

Ischemic stroke subtype was a not significant independent determinant of 30-day survival before (p=0.054) as well as after (p=0.993) adjusting for age, diabetes mellitus, ischemic heart disease, congestive heart failure, AF, NIHSS and functional outcome. At 6 months, this was an independent predictor of survival both before (0.016) and after (0.027) adjusting for age, diabetes mellitus, ischemic heart disease, congestive heart failure, AF, NIHSS and functional outcome with the proportional hazards model (Table 7).

Discussion

This study is first of its kind in Nepal reporting the outcomes for the 4 common subtypes of ischemic stroke. All patients were included in the study regardless of risk factors, race, age, gender, prognosis, andfirst or recurrent stroke. We also studied the risk of early recurrence in different stroke subtypes. More than 17.6% of patients

Variable	30-d Risk Ratio (95% CI)	p Value	6 month Risk Ratio (95% CI)	pValue
Age	4.70(1.61-13.67)	0.005	2.92(1.42-5.97)	0.003
Male Sex	0.71(0.32-1.59)	0.410	0.69(0.37-1.29)	0.244
Persistent atrial fibrillation	5.25(2.35-11.72)	<0.0001	3.87(2.05-7.30)	<0.0001
Diabetes	1.75(0.69-4.40)	0.237	1.80(0.88-3.67)	0.109
HTN	1.09(0.49-2.42)	0.838	0.91(0.48-1.69)	0.754
Congestive heart failure	1.59 (0.93–2.70)	0.245	1.67 (1.21–2.30)	0.134
Ischemic heart disease	2.54(0.98-3.84)	0.076	3.93(1.96-12.78)	0.005
Rankin 4-6	8.25(0.3.27-20.80)	<0.0001	15.24(6.70-33.22)	<0.0001
NIHSS	28.89(6.78-123.02)	<0.0001	62.01(14.92-257.75)	<0.0001
Stroke subtype				
Atherosclerosis with stenosis	0.94(0.26-3.33)	0.924	0.46(0.15-1.43)	0.179
Cardioembolic	2.12(0.79-5.66)	0.132	1.65(0.80-3.43)	0.178
Lacunar	0.32(0.64-1.58)	0.161	0.47(0.18-1.25)	0.129

Table 7. Cox Proportional Hazards Models Examining the Influence of Ischemic Stroke Subtype on Survival

with ischemic stroke due to large vessel atherosclerosis with stenosis had a recurrent stroke within 30 days of the first stroke, which is same as 18 % in one study and higher than 8% -14% asreported in previous studies.[8,9,13,15] These variations inrecurrence rates may be due to differences in age, sex, race, risk factors and methodological differences. We identified ischemic stroke subtype as a determinant of recurrent stroke (Table 5), similar to Stroke Data Bank study of Hier et al.[6, 14]

We found significant differences among ischemic stroke subtypes, for maximal neurological deficits at the time of stroke and functional outcome at 3 months and 6 months;and also for prestroke functional status (Table 3). Prestroke functional status was best among lacunar stroke or ischemic stroke due to large- vessel atherosclerosis with stenosis and worst among cardioembolic stroke. These could be probably due to a higher prevalence of heart disease and cardiac related prestroke. Patients with lacunar and large-vessel atherosclerosis stroke had similar prestroke Rankin score, but maximal deficits at 30 days were worse among large- vessel stenosis patients compared with lacunar infarction. Patients with lacunar infarcts had the best functional outcomes, with 80% having minimal or no impairment6 months after the stroke.

Similar to earlier studies, we found that patients with cardioembolic stroke had worse 30-day and long-term survival than the patients with noncardioembolic stroke **(Table 6, Figure 4)**.[3] Mortality of cardioembolic stroke patients was about 2.5 times more at 30 days compared to patients with stroke due to large-vessel atherosclerosis with stenosis and 3.5 times more at 6 months. This is in contrast to the Northern Manhattan Stroke Study, whichfound similar 30-day and 6-month survival rates.[15] We found that ischemic stroke due to atherosclerosis

with stenosis is associated with better 6-month survival thancardioembolic stroke, even after adjustment for age, diabetes mellitus, ischemic heart disease, congestive heart failure, AF, NIHSS and functional outcome (Table 7). This finding could be due to unrecognized risk factors, which may be relatively underrepresented or overrepresented among patients with cardioembolic stroke or patients with large-vessel atherosclerosis with stenosis, as described by Petty et al.[9]

Conclusion

Ischemic stroke due to large-vessel atherosclerosis with stenosis has the highest rate of early recurrence. Functional status are worse among patients with cardioembolic stroke and best among those with lacunar stroke, both before and after stroke. Survival is also worst among those cardioembolic stroke patients.

References:

1. Arsava EM, Helenius J, Avery R, Sorgun MH, Kim GM, Pontes-Neto OM, et al. Assessment of the Predictive Validity of Etiologic Stroke Classification. **JAMA Neurology 74 (4):** 419-26, 2017
2. Ay H, Arsava EM, Andsberg G, Benner T, Brown RD, Chapman SN, et al. Pathogenic ischemic stroke phenotypes in the NINDS-stroke genetics network. **Stroke 45 (12):** 3589-96, 2014
3. Broderick JP, Phillips SJ, O'Fallon WM, Frye RL, Whisnant JP. Relationship of cardiac disease to stroke occurrence, recurrence, and mortality. **Stroke 23 (9):** 1250-6, 1992
4. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. **Stroke 25 (2):** 333-7, 1994
5. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Long-term risk of first recurrent stroke in the Perth Community Stroke Study. **Stroke 29 (12):** 2491-500, 1998
6. Hier DB, Foulkes MA, Swiontoniowski M, Sacco RL, Gorelick PB, Mohr JP, et al. Stroke recurrence within 2 years after ischemic infarction. **Stroke 22 (2):**155-61, 1991
7. Ince B, Petty GW, Brown RD, Chu CP, Sicks JD, Whisnant JP. Dolichoectasia of the intracranial arteries in patients with first ischemic stroke: a population-based study. **Neurology 50 (6):** 1694-8, 1998
8. Moroney JT, Bagiella E, Paik MC, Sacco RL, Desmond DW. Risk factors for early recurrence after ischemic stroke: the role of stroke syndrome and subtype. **Stroke 29 (10):** 2118-24, 1998
9. Petty GW, Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes : a population-based study of functional outcome, survival, and recurrence. **Stroke 31 (5):1062-8**, 2000
10. Petty GW, Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. **Stroke 30 (12):** 2513-6,1999
11. Petty GW, Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975 through 1989. **Neurology 50 (1):** 208-16, 1998
12. Rankin J. Cerebral vascular accidents in patients over the age of 60. I. General considerations. **Scottish Medical Journal 2 (4):** 127-36, 1957
13. Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR. Determinants of early recurrence of cerebral infarction. The Stroke Data Bank. **Stroke 20 (8):** 983-9,1989
14. Sacco RL, Hauser WA, Mohr JP, Foulkes MA. One-year outcome after cerebral infarction in whites, blacks, and Hispanics. **Stroke 22 (3):** 305-11, 1991
15. Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. **Neurology 44 (4):** 626-34,1994
16. Sacco RL, Wolf PA, Kannel WB, McNamara PM. Survival and recurrence following stroke. The Framingham study. **Stroke 13 (3):** 290-5, 1982