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Date submitted: 18/11/2018

Date accepted: 28/12/2018

To access Nepal Journal of Neuroscience,
Archives scan QR code:

**How to Cite**

Karn, R., & Subedi, K. (2018). Study of the Outcome Differences among the Ischemic Stroke Subtypes based on TOAST Classification at Tribhuvan University Teaching Hospital, Nepal. Nepal Journal of Neuroscience, 15(3), 39-48.

<https://doi.org/10.3126/njn.v15i3.23280>

Study of the Outcome Differences among the Ischemic Stroke Subtypes based on TOAST Classification at Tribhuvan University Teaching Hospital, Nepal.

The objective of this study was to explore the outcome differences among ischemic stroke subtypes based on “Trial of ORG 10172 in Acute Stroke Treatment (TOAST)” system in a tertiary referral hospital.

A hospital based prospective longitudinal study was conducted involving 182 patients. Modified Rankin Scale (MRS) was used to assess functional outcome, Kaplan-Meier product-limit method and Cox proportional hazards regression analysis were used to evaluate rates and identify predictors of survival and recurrent stroke.

MRS were statistically different across stroke subtypes at 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 different at 30 days ($p < 0.0001$) and at 6 months ($p = 0.009$). Before adjusting for age, 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 6 months ($p = 0.024$), however 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 was an 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 recurrence rates were highest among large artery atherosclerotic stroke. Lacunar stroke has better post 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, stroke prognosis, chances of recurrence, and long-term survival among different ischemic stroke subtypes.² The TOAST investigators devised a series of definitions to classify patients with ischemic stroke into 5 core etiologic groupings: (1) Large artery 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 attributable to 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 deep ischemic 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

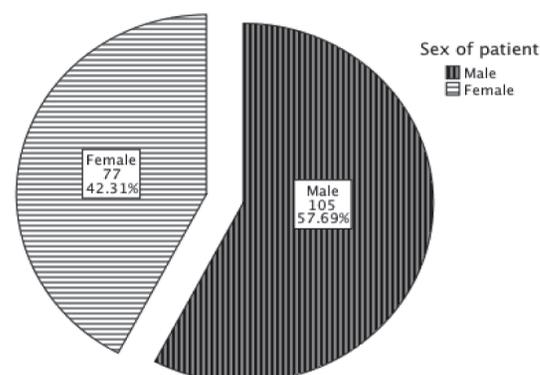


Figure 1. Sex distribution of the patients

edema, mass effect, brain shift syndrome, or hemorrhagic transformation of the incident cerebral infarction.

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 \pm SD and results on categorical variables were expressed in Number (%). The Chi square (χ^2) test was used to compare Rankin scores 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 Stroke of other determined etiology. 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).

TOAST classification

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

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

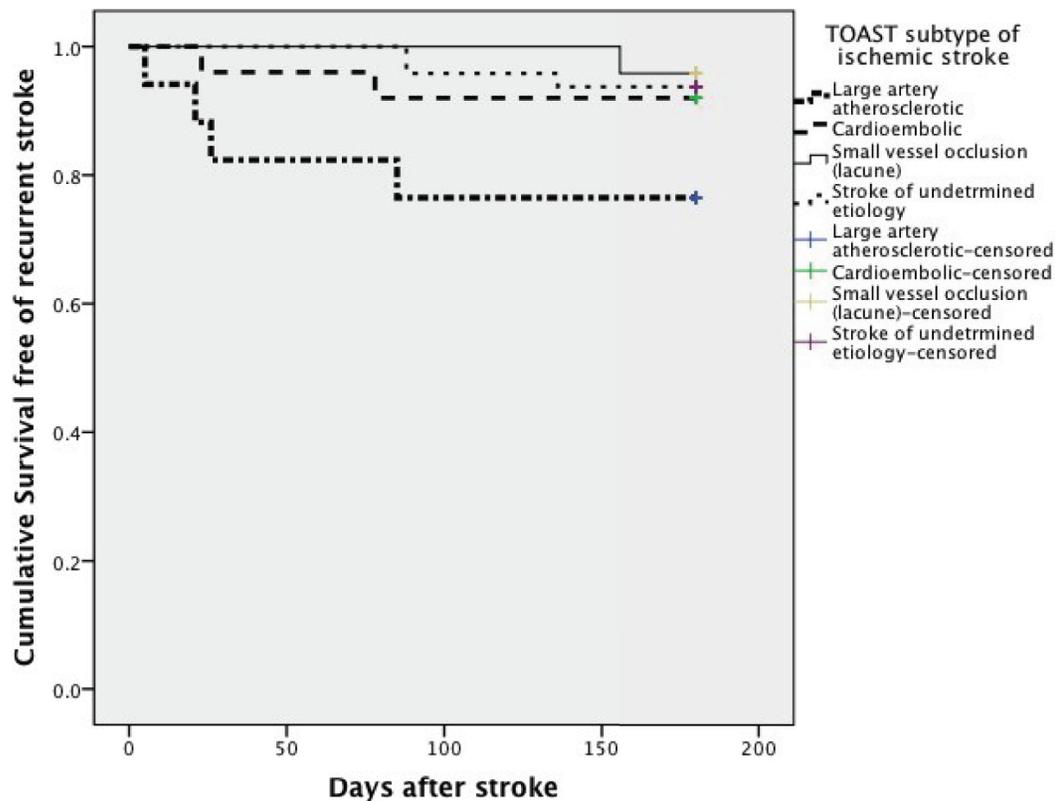


Figure 2. TOAST subtypes of ischemic stroke

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) |

TOAST classification

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

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 (log rank) | P 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 subtypes before 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 2.00 respectively; 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).

TOAST classification

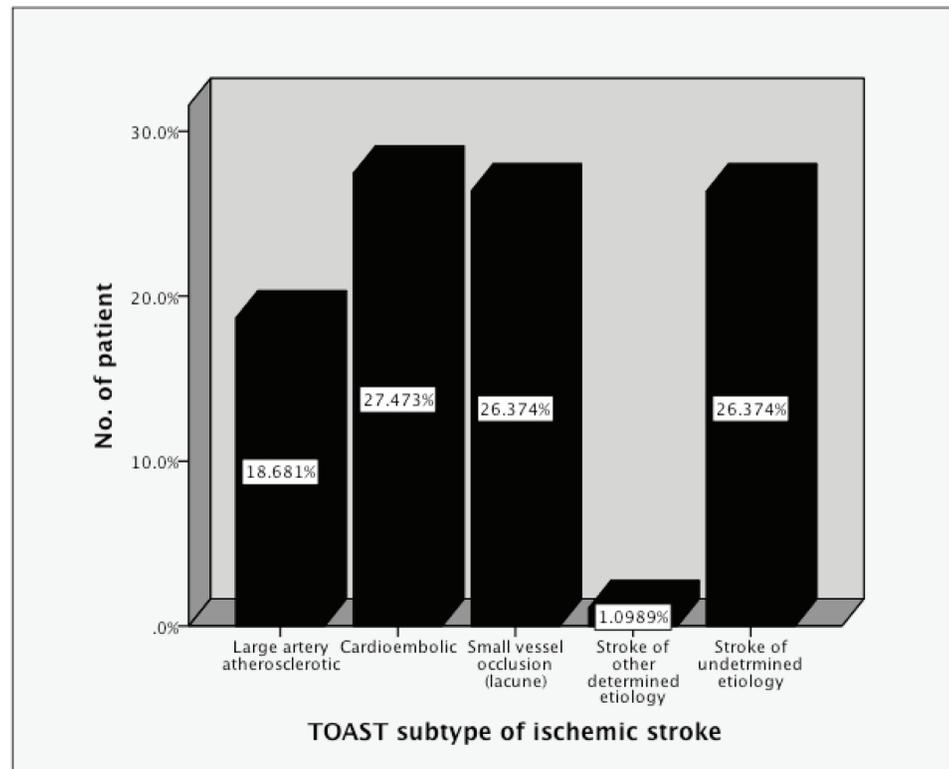


Figure 3. Observed percentage surviving (Kaplan-Meiere estimates) free of recurrent stroke after incident is chemic stroke

| Variable | 30-d Risk Ratio | | 6 month Risk Ratio | |
|-------------------------------|-------------------|--------|--------------------|--------|
| | (95% CI) | pValue | (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)

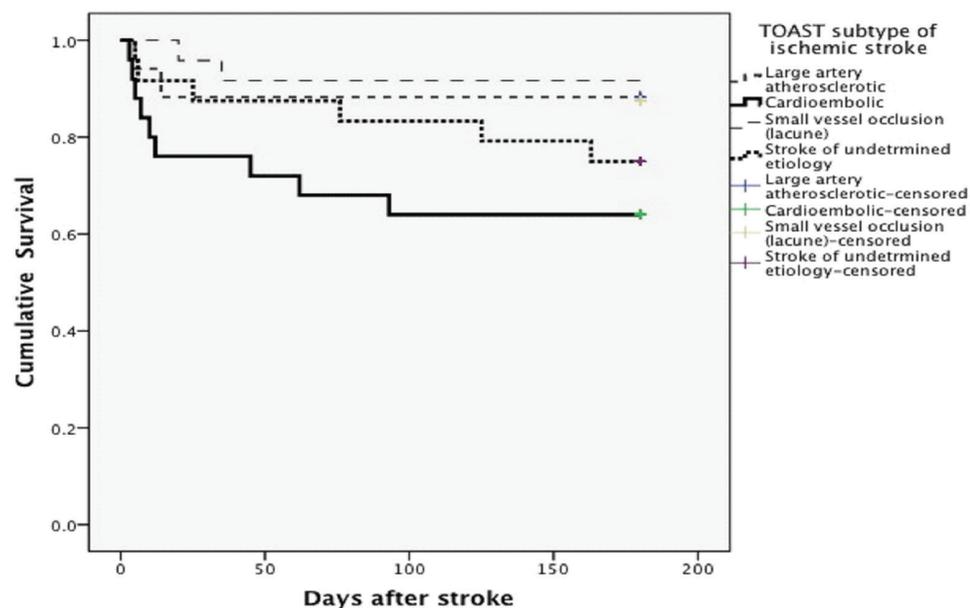


Figure 4. Observed percentage surviving (Kaplan-Meier estimates) after incident ischemic stroke.

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, <0.0001 and <0.0001 respectively) as well as at 6 months with hazard ratios 2.92, 3.87, 15.24 and 62.01 respectively (p values 0.003, <0.0001, <0.0001 and <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, and first or recurrent stroke. We also studied the risk of early recurrence in different stroke subtypes. More than 17.6% of patients

TOAST classification

| Variable | 30-d Risk Ratio | | 6 month Risk Ratio | |
|-----------------------------------|--------------------|---------|---------------------|---------|
| | (95% CI) | p Value | (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% as reported in previous studies.^{8,9,13,15} These variations in recurrence 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 impairment 6 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, which found 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 than cardioembolic 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.

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