# A Study of Seven Day Mortality in Acute Ischemic Stroke in a Teaching Hospital in Chitwan

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## ABSTRACT

**Background:** Stroke mortality rate indicates a measure in hospital quality care. Most of the available data are from developed countries and are for late mortality. Only few studies on 7-day fatality, a recently implemented indicator of early stoke mortality, are reported. We attempted to identify the predictors of clinical outcome by 7th day in acute ischemic stroke.

**Methods:** This descriptive study included 100 consecutive cases of acute ischemic stroke admitted to Neurology center of a teaching hospital in Chitwan, Nepal. Common risk factors were identified. The cases were classified as per TOAST classification and severity at admission assessed using National Institutes of Health Stroke Scale. Univariate and multivariate analysis was used to analyze the data.

**Results:** Thirteen percent patients expired by 7th day. On univariate analysis severity of stroke, fever, atrial fibrillation, hypertension at admission and early neurological deterioration were related to early 7-day mortality where as age, gender, smoking, diabetes mellitus, coronary artery disease, early onset seizures, dyslipidemaia, and hematocrit were unrelated to early mortality. Multivariate analysis showed that only NIHS score was significantly correlated with early mortality.

**Conclusions:** A mortality rate of 13 percent was noted by 7th day. A positive association was noted with stroke severity, early neurological deterioration, arterial fibrillation, hypertension and fever at onset.

**Keywords:** Early mortality; Early onset seizure; Early neurological deterioration; Ischemic stroke

## INTRODUCTION

Stroke is medical emergency encountered in clinical practice causing permanent neurological damage, disability and resulting in death. Complications of stroke occur in first 7 days and that too in first 4 days,[1] hence first 7 days are vital period for diagnosis and management of stroke which may alter prognosis and outcome if treated timely.[2] In addition stroke case fatality provides an indirect measure of quality care.[3,4] Only few studies are available regarding the early 7-day mortality.[5-8] Seven day case fatality is recently implemented as an indicator to measure early stroke mortality.[7] It is with this background, this study was done prospectively to determine factors predicting early mortality in newly established neurology unit.

## METHODS

A descriptive study was conducted in Neurology center of College of Medical Sciences (COMS), Bharatpur Chitwan, Nepal after clearance from Ethical Review Committee. One hundred consecutive cases of ischemic stroke, admitted to intensive care unit during the period from November 2007 to April 2009, were included in the present study after obtaining written consent from

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their relatives which was especially designed for the research. Only new (not recurrent) definite stroke cases were included after a detail history. Plain CT scan of head as well as contrast enhanced where required was done to diagnose acute ischemic stroke and to exclude hemorrhagic stroke, subarachnoid hemorrhage, TIAs, brain tumor, and malignancy. TOAST classification[9] and modified National Institute of Health Stroke Scale (NIHSS)[10] was applied for categorizing and assessing the severity of stroke at admission. An increase in NIHSS score by 2 or more points or (or stroke related death) between admission day and day 5 was taken as criteria of early neurological deterioration (END).[11] Early onset seizure (EOS) was defined as seizure occurring during acute stage of ischemic disease (2 days prior to onset to 2 weeks after it).[12] The risk factors were identified in each case. JNC-7 criteria,[13] American Diabetes Association (ADA) criteria[14] and National Cholesterol Education Program (NCEP III) guidelines[15] were applied for diagnosis and assessing hypertension, diabetes mellitus and dyslipidemia respectively.

All the cases were treated according to the American stroke Association's guidelines (ASA)[16] which included treatment in ICU with airway and ventilator support for the patients having altered sensorium. Hypoxic patients with stroke received supplemental oxygen. Aspirin (initially 325 mg followed by 75 mg daily) was given to all the patients on admission. Antihypertensive agents were withheld unless the systolic blood pressure was >220 mm Hg or the diastolic blood pressure was >120 mm Hg or when target organ dysfunction recognized. When indicated blood pressure was only lowered by 15% during the first 24 hours after onset of stroke. Patients with seizures received anticonvulsants. In febrile patients, temperature was controlled with hydrotherapy and acetaminophen or ibuprofen. Source of infection was investigated and if detected proper treatment was given. No neuroprotective drugs or vasodilators were used. All patients were put on deep vein thrombosis prophylaxis. The patients were examined at periodic interval to detect early deterioration and to institute remedial measures. Early 7-day fatality, irrespective of cause of death, was chosen as the primary outcome event.

Univariate followed by multivariate analysis was done to asses relationships between various risk factors, NIHS score and early mortality. The data was analyzed using SPSS ver 16 and p value was determined using Chi square test.

## RESULTS

During the study period hundred patients with acute ischemic stroke were admitted and investigated. The mean age was 67.15 $\pm$ 12.58 years and 66% were males. Risk factors detected were hypertension in 72%, smoking in 66%, dyslipidemia in 53%, alcohol in 43%, atrial fibrillation in 25%, diabetes mellitus in 19% and coronary artery disease in 15% cases. In CT scan of head, 88% had anterior circulation, 7% had posterior circulation stroke and 5% cases had both circulation involvements. Forty five percent were categorized as lacunar, 36% as large artery and 19% as cardio-embolic ischemic stroke. NIHS score varied from 3-18 and it characterized stroke as mild in 29%, moderate in 53% and severe stroke in 18% cases. Early onset seizures (EOS), fever within first 72 hours was noted in 12% and 13% respectively. The mean blood sugar level at admission was 146.93 $\pm$ 88.2 mg/dl.

Early 7-day mortality rate was 13 per 100 patients in the present study. Eight patients (61.53%) were male and five patients (38.5%) were female with mean age 77.12 $\pm$ 6.37 years and 65 $\pm$ 7.2 years in respective group. In the expired group, history of smoking and alcohol consumption was present in 23.1% and 46.2% patients respectively. Hypertension was detected in 92.3% (JNC 7 Grade I- 30.76% & II- 61.53%). Hyperglycemia (i.e. admission blood sugar level > 140 mg/dl) was found in 46.15%, early onset seizures in 7.69%, fever in 61.5% and high hematocrit level noted in 7.69% cases respectively. Early neurological deterioration was noted in 76.9% patients (Table 1). In 76.9% patients who died had massive cerebral infarction (3 of them having hemorrhagic transformation) and in three (23.1%) patients cardiac disorders i.e. tachycardia-01, ST elevated MI – 02, were the terminal event. Univariate analysis revealed a significant correlation of early mortality with neurological deficit (NIHS score), hypertension, atrial fibrillation, fever at admission and early deterioration of neurological status. Other factors i.e. age, sex, history alcohol consumption, smoking, diabetes, Coronary artery disease, early onset seizure, hematocrit, blood sugar level at admission, and dyslipidemia had no effect on day-7 mortality. Multivariate analysis was done to asses relationships with age, fever, hypertension and NIHS score and only NIHS score was significantly correlated with early mortality after acute ischemic stroke (Table 2).

| Table 1. Risk factors in expired and discharged patients. | | | | |
|---|---|---|---|---|
| Risk factors | Expired | Discharged | OR | p value |
| Age (>65) | 11(84.6%) | 52(59.8%) | 2.99 | 0.84 |
| Smoking | 10(76.9%) | 56(64.4%) | 0.79 | 0.37 |
| Alcohol | 6(46.2%) | 37(42.5%) | 0.06 | 0.80 |
| Hypertension | 12(92.3%) | 60(69%) | 3.05 | 0.04 |
| Diabetes | 0 | 19(21.8%) | 3.50 | 0.06 |
| CAD | 2(15.4%) | 13(14.9%) | 0.76 | 0.38 |
| AF | 6(46.2%) | 17(19.5%) | 4.52 | 0.03 |
| Dyslipidemia | 7(53.8%) | 46(52.9%) | 0.004 | 0.94 |
| Fever | 5(38.5%) | 8(9.2%) | 8.64 | 0.013 |

| | | | | |
|---|---|---|---|---|
| Early onset Seizure | 1(7.7%) | 11(12.6) | 0.26 | 0.60 |
| NIHSS Severe (>15) | 9(69.2%) | 12(13.8%) | 20.95 | 0.001 |
| Early neurological deterioration | 10(76.9%) | 0 | 74.35 | 0.001 |

Significance at 0.05 level (X2 test) CAD- Coronary Artery Disease

AF- Atrial Fibrillation

**Table 2. Evaluation of independent predictors of early mortality by multivariate analysis.**

| Variables | p value | OR | 95.0% CI for OR | |
|---|---|---|---|---|
| | | | lower | upper |
| AGE | 0.222 | 3.461 | 0.464 | 27.149 |
| Hypertension | 0.101 | 2.186 | 0.75 | 22.84 |
| Fever | 0.224 | 3.747 | 0.496 | 19.79 |
| NIHSS score | 0.001 | 19.811 | 3.19 | 89.22 |

OR Odds Ratio

## DISCUSSION

Numerous clinical variables have been identified as predictor of prognosis in ischemic stroke like advancing age and severity of neurological deficits at onset which consistently correlated with mortality and morbidity,[17]other factors i.e. gender, hypertension, cardiac diseases including atrial fibrillation, hyperglycemia, vascular territory, hyperdense sign on CT scan, though found unfavorable, but no definite relation could be established.[18] Only few studies have analyzed data for early 7-day mortality and a mortality rate of 5% to 6.9%[5-8] is reported.

In our study age and sex were not related to 7-day mortality. Also, no relation was noted to risk factors of smoking, alcohol intake, coronary artery disease, diabetes mellitus, and blood sugar levels at admission, hematocrit and hyperlipedemia. In the expired group 61.5% had severe stroke and 38.5% moderately severe stroke respectively. A positive correlation with early mortality was noted with severity of stroke (i.e. high NIHS score: p < 0.001, OR=19.811, 3.19-89.22). Silver et al[19] noted that early mortality in stroke had a bimodal distribution with 1st peak with in seven days and 2nd peak between second and third week. Death due infarction had a peak between 3rd and 6th day. This early death was related to initial stroke severity and not to the age and sex of the patient. Saposnik et al[7] also noted that early mortality was related to severity of illness at onset and early deterioration in neurological status and not to age and sex of the patient. This disparity was due to that some earlier studies either ignored stroke severity or early deterioration in their analysis or due to masking the effect of age and sex by stronger markers (stroke severity and neurological deterioration) of mortality.[7]

The effect of early onset seizures (EOS) on mortality is not clear. In present study 13% patients had EOS within 72 hours of ictus. Only one (7.6%) patient in expired group had EOS. There was no effect of EOS (P>0.60) on early 7-day mortality. In Copenhagen study[20] 4.27% cases had seizures within 14 days with 66% of them were in first 24 hours. Patients with EOS had severe stroke and a high mortality rate of 50% as compared to 20% in patients without EOS. However, multiple logistic regression analysis, with mortality as a dependant factor, showed no effect of EOS on in hospital mortality instead EOS was related to stroke severity. Lobovitz et al[21] reported increased early mortality at 48 hours in patients having EOS (30.8%) versus those without EOS (7.4%: p< 0.01). However, this study included both ischemic and hemorrhagic stroke and multivariate analysis did not include stroke subtypes. Vermio et al[22] in a retrospective study reported higher mortality in univariate and multivariate analysis but the onset of seizures was not classified. Only Arboix et al[23] noted that EOS was associated with a high in hospital mortality on both univariate and multivariate analysis.

Only 38.5% patients in expired group and 9.2% patients in discharged group had fever. We further analyzed in the expired group and showed that two patients each had urinary tract infections and lower respiratory tract infections and one had both. In the present study, presence of fever was statistically significant in relation to early mortality (p<0.013). This adverse affect of rise of temperature in early stage was noted in other studies as well.[24-27] Reith et al[24] reported that high body temperature (with in 24 hours of onset) was related to initial stroke severity (SSC p<0.009), infarct size (p<0.0001), mortality (p<0.02) and outcome in survivors (p<0.003).

Wang et al[26] in a retrospective study of 509 patients of ischemic stroke noted higher in hospital and late (1-year) mortality in patients with hyperthermia (>37.5°C) and lower morbidity and mortality in hypothermic (>36.5°C) independent of other variable. Hajat et al[25] in a meta-analysis reported significant higher combined probability values for both mortality and morbidity. Greer et al[27]in meta-analysis in patient with strokes and other neurological injuries also confirm worse outcome in those having fever /higher body temperature was associated with worse outcome in all types of neurological injuries including ischemic strokes regardless of the measures used.

In the study group hypertension was noted in 72% cases. It was present in 92.3% cases that expired with grade-II

in 61.5% (8/13) and grade-I in 30.76% (4/13) patients (p < 0.04). The relationship of hypertension on subsequent prognosis has shown adverse prognosis,[28,29] good prognosis,[30,31] no effect[32] and a U shaped effect high and low systolic and diastolic BP with optimal BP around 180 mms of Hg and a fall of 20 mms within first day was associated with poor prognosis.[33] In this study 4 patients died within 48 hours (mortality rate of 0.9%). However, 07 day mortality was not mentioned. IST trial confirmed this U shaped relation with the optimal blood pressure was around 150 mms Hg[34] but not in GAIN International Trial.[35]

Early neurological deterioration, having potentially serious short and long term morbidity and mortality, is common in acute ischemic stroke. Thanvi et al[36] in a review on the subject reported END to be related to the initial severity of stroke, non embolic stroke, large vessel occlusion, anterior circulation stroke, hyperglycemia and history of diabetes mellitus, both to high blood pressure at admission or a base line blood pressure below 100/70 mms of Hg, atrial fibrillation, large infarct (>33% of MCA territory), hyper dense middle cerebral artery sign and degree of cerebral edema. Age, gender and level of pre stroke independence were not related to END. In the present study END was noted in 79.9% cases as compared to 17.4% cases in discharge group (p<0.001). END was statistically related to the severity of neurological deficit, and presence of hypertension, fever and hyperglycemia at onset.

A higher 7-day mortality rate of 13% was noted in present study in contrast to 5% to 6.9% reported by other workers.[5-8] Saposnik et al[8] noted that group having access to organized care had a lower mortality rate. The risk adjusted mortality rates were 2.0% (in stroke unit), 3.2% (assessment by stroke team), 7.8% (occupational therapy or physiotherapy) and 22.5% (none of these) respectively. Further, stratified analysis by level of consciousness and stroke severity showed that access to escalated level of care, improved survival 7-day. In multivariate analysis, organized care was the independent predictor of 7-day mortality after adjusting for age, sex, stroke severity, neurological worsening, administration of antiplatelet agents and other comorbid conditions. Also, an inverse relationship was found with physician experience in stroke management and early stroke mortality. A meta-analysis,[37] showed a 18% relative reduction in mortality, reduction in death or dependence or need of institutional care when treated in stroke unit in comparison to a general medical ward (Level 1 Evidence). The absolute changes showed a 3% reduction in all cause mortality, a 3% reduction in need of nursing home care and a 6% increase in numbers of survivors. The benefit extended to all patients irrespective of

age, gender, type and severity of infarcts. Ours is a recently established neurology unit. The patients were treated in ICU for an average of 4 days however the care could not have been of the same standard of a Stroke unit. There has been considerable evolution in the treatment of acute ischemic stroke in recent years like thrombolytic therapy or endovascular therapy after intravenous tissue-type plasminogen activator.[38] Other aggressive therapies to decrease secondary brain edema such as early decompressivehemicraniectomy for large hemispheric strokes and use of hyperosmolar agents such as mannitol and hypertonic saline have also developed.[39] Thrombolytic therapy for stroke is yet to be introduced in Bharatpur. In addition most of the cases were admitted after 2-3 days of ictus depriving them of benefit of aspirin therapy within 48 hours as shown in CAST[40] and IST trial.[41]

The limitation of the study of being an observational study with less number of cases, newly established neurological centre with limited trained manpower, late presentation of the patients and no facility of thrombolytic therapy. It is hoped that the ongoing study, started after establishing the neuro-ICU and a stroke team, will address to these limitation.

## CONCLUSIONS

A mortality rate of 13 percent was noted by 7th day. In univariate analysis, a positive correlation was noted with stroke severity, early neurological deterioration, hypertension, atrial fibrillation and fever at onset whereas in multivariate analysis only NIHS score was significantly correlated with early mortality after acute ischemic stroke.

## ACKNOWLEDGEMENT

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