A Prospective Study of Deteriorating Acute Ischemic Stroke in Non-Thrombolysed Patients

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Abstract

Context: Progression of stroke is likely multifactorial; however, risk of deterioration in acute ischemic stroke can be predicted in great majority of cases at admission by careful close observation. Aims: To study the causes of neurological deterioration of non-thrombolysed stroke patients. Settings and Design: This was a prospective observational study of non-thrombolysed stroke patients admitted at the Stroke ICU of a teaching hospital in Kerala, India for a period of one year from between January 2017 to January 2018. Methods and Material: All stroke patients with first episode of acute ischemic stroke were admitted and evaluated for neurologic deterioration (defined as an increase in National Institute of Health Stroke Scale Score (NIHSS score) by 2 or more points, after admission during the first week). Results: 80 out of 320 patients with acute stroke patients developed neurological deterioration and were analyzed for clinical, biochemical and radiological features associated with deterioration. Clinical features - Stroke severity (high NIHSS Score), altered consciousness at admission, persistent gaze deviation, bulbar dysfunction, atrial fibrillation, recent myocardial infarction, systemic diseases (hypertension, hepatic and renal dysfunction) and deep vein thrombosis were associated with deterioration. Biochemical features - Uncontrolled blood sugar and hyponatraemia were associated with deterioration. Imaging features - ASPECT score less than 7, large infarct at admission, dense MCA sign, hemorrhagic transformation, proximal large vessel occlusion and lack of correlation between clinical deficits with initial CT picture were associated with higher risk of deterioration. Conclusion: Each stroke case needs prompt individualized evaluation and management. Interventions based on pathophysiology identified by imaging features and patient’s clinical condition and management of systemic diseases and complications will improve the outcome. Keywords: Stroke, deterioration, clinical, imaging features, predictors.

INTRODUCTION

Stroke incidence and mortality are higher in Asian countries than in western countries [1]. Based on few epidemiological studies in India, the crude prevalence rate of stroke was reported between 44 and 842 strokes per 100,000 persons, and annual incidence rate is between 13 and 124 strokes per 100,000 persons [2]. Trivandrum stroke registry, which is based on a community study in our district, in south India, recorded an adjusted annual incidence rate of 135 per 100 000 (95% confidence interval between 123 and 146) [3]. About one third of ischemic stroke patients deteriorate after admission to a hospital. It is associated with serious consequences on the short term (morbidity and death) and long term disability [4, 5]. Different studies have pointed out different markers to predict the deterioration and outcome in acute ischemic stroke. They include stroke severity on admission [6-8], the presence of large vessel occlusion [4, 9-11], history of coronary artery disease or myocardial infarction [12, 13], presence of Atrial Fibrillation [4], diabetes mellitus [4, 12-15], acute or chronic hyperglycemia [12, 13, 15, 17, 18], elevated blood pressure [19, 20], early recurrent ischemic stroke [21] and symptomatic hemorrhagic transformation [16, 22]. Advances in brain and vascular imaging have provided insight into the underlying causes of deterioration, enabling clinicians to use preventive and therapeutic interventions, specifically targeted at them like endovascular early revascularization (intra-arterial thrombolysis,
angioplasty, mechanical thrombectomy and extended window mechanical thrombectomy), endarterectomy and early de-compressive craniectomy [4]. The present study was conducted to study the causes of neurological deterioration of non-thrombolysed stroke patients at the Stroke Intensive Care Unit (ICU) of a teaching hospital in Kerala, India.

**MATERIALS AND METHODS**

This was a prospective observational study of non-thrombolysed stroke patients admitted at the Stroke ICU of a teaching hospital in Kerala, India for a period of one year from between January 2017 to January 2018 with the approval of the college Ethics Committee. All patients admitted with first episode of acute ischemic stroke were admitted and treated as per American Stroke Association (ASA) protocol. Neurologic deterioration was defined as an increase in National Institute of Health Stroke Scale Score (NIHSS score) by 2 or more points, after admission during the first week (5). They were included in the study. Informed consent was obtained in all cases.

**INCLUSION CRITERIA**

- Patients admitted with a diagnosis of first episode of acute ischemic stroke were included.
- A deterioration in National Institute of Health Stroke scale score (NIHSS) equal to or more than two points after admission during the first week of admission were included in the study.

**EXCLUSION CRITERIA**

- Thrombolysed patients were excluded. Thrombolysis was not done for these patients because of medical or personal reasons (financial, unwillingness)
- Hemorrhagic stroke and stroke mimics.
- Strokes secondary to systemic illness/infections.
- Cases of hypotension leading to global ischemia.
- Recurrent stroke
- Severe stroke at admission (NIHSS > 20) because they carry high risk for further deterioration.

The baseline characteristics of these patients were noted at the time of admission - vascular risk factors, clinical features (vitals, level of consciousness, NIHSS score) and radiological features. Alberta Stroke Program Early Computed Tomogram Score (ASPECTS) scoring was done in all cases. Biochemical parameters (blood sugar, urea, serum creatinine, electrolytes, serum lipid profile, platelet count, prothrombin time, activated partial thromboplastin time (APTT), liver function test) and blood counts were done in all cases. HBA1C level was assessed in all diabetic patients.

These patients were monitored carefully for any evidence of deterioration. Blood pressure, oxygen saturation, and electrocardiogram (ECG) were monitored continuously. Neck vessel Doppler scan was done for all patients. Cardiac evaluation, X-ray chest and echo cardiogram were done within 24 hours for all. Computed Tomogram Angiogram (CTA) of brain and neck vessels were done when Doppler of neck vessels showed stenosis or occlusion to assess site of occlusion and collateral flow.

Swallowing function was evaluated in all patients and nasogastric tube was inserted in cases with swallowing difficulty. Endotracheal intubation was resorted to, as and when required. Prevention of bedsore was done by using air bed, frequent change of posture, passive physiotherapy. Foley’s catheter was put for all patients who had altered sensorium or unable to pass urine. Spouse and family members were interviewed to get the relevant clinical details - the onset time and symptoms, past illnesses and drug history. A standard 5-point questionnaire with one point for each question was presented to patient or to spouse/caregiver when patient was aphasic or unable to cooperate (What is stroke / Risk factors of stroke / Symptoms of stroke / How long to continue drugs /Stroke helpline number). This questionnaire was used to identify their awareness regarding stroke, risk factors of stroke, the frequency of checking and degree of control of risk factors, life style, and stroke prevention. They were taught stroke prevention measures, patient care and community rehabilitation.

Any deterioration in sensorium (quantified by Glasgow Coma Scale (GCS) score) or worsening of deficit (NIHSS Score increase by 2 points or more) was considered as deteriorating stroke. These patients were further evaluated clinically and investigated as follows – repeat imaging [CT brain with CT Angiogram or Magnetic Resonance Imaging (MRI) brain with Magnetic Resonance Angiogram(MRA)], biochemical parameters (blood sugar, electrolytes, renal function, hepatic function, coagulation parameters, C-reactive protein) and cultures were sent to rule out infections and further managed based on etiology. Patients with large Middle cerebral artery (MCA) infarcts were closely monitored for deterioration and neurosurgery team was alerted for possible early craniectomy. Antiepileptic drugs were started in case of seizures or electroencephalogram (EEG) showing any evidence of Non Convulsive Status epilepticus. Disability was assessed using Modified Rankin Scale (MRS) at the time of discharge and at three month follow up. The data was recorded systematically and analyzed.

**RESULTS**

**Age and gender**

Out of 320 patients admitted to stroke ICU with first acute ischemic stroke, 80 patients (25%) who deteriorated satisfied the inclusion criteria. The mean age of the deteriorated stroke patients was 61.5 ± 24.5 years with a range of 36 to 91 years. The age
distribution of patients is shown in Figure 1. There were 54 (67.5%) males and 26 (32.5%) females.

![Age distribution of deteriorated patients](image)

**Economic status**
45 (56.3%) patients belonged to middle income group, 34 (42.5%) in low income and 1 (1.2%) in high income group according to the modified Kuppuswami scale [51].

**Education**
56 (70%) patients had less than primary education, 19 (23.75%) had secondary education and 5 (6.25%) were graduates.

**Stroke awareness questionnaire**
All performed very poorly. (Score < 1 in 68 patients, 1 in 12 patients).

**Time to door**
Time to door was calculated as the time from last seen normally /symptom onset to hospital door in hours.

Only 3 (3.75 %) reached hospital within 3 hours, only 18 (22.5%) reached hospital before 4.5 hours of the onset of symptoms. The time to door details is shown in table 1.

Table-1: Time to door details of deteriorated patients

| Time to door (hours) | Frequency (n=80) | Percent |
|----------------------|------------------|---------|
| Less than 3 hours    | 3                | 3.3     |
| 3 to 4.5 hours       | 15               | 18.7    |
| 4.5 to 6 hours       | 40               | 50      |
| 6hours to 24 hours   | 22               | 28      |

**Risk factors**
Hypertension – 68 (85%) patients were known hypertensives. Regular monitoring and treatment was observed only in 12 patients (15%). Only 10% had awareness regarding hypertension and complications.

Diabetes Mellitus – 34 patients (42.5%) were diabetic, only one patient (2.9%) had diabetic awareness regarding control of blood sugar, importance of regular monitoring and complications of diabetes.

Dyslipidemia – 50 patients (62.5%) had dyslipidemia (high LDL cholesterol, low HDL cholesterol). Of this, 36 also had hypertriglyceridemia.

Tobacco smoking – 33 (41.3%) were smokers. Out of them, 25 (75%) were current and 8 (25%) were former smokers who stopped within the last 5 years. None of the female patients were smokers.

Alcohol use – 4 patients (5%) were heavy alcoholics, 34 (30%) were social drinkers and 52 (65%) were non alcoholics, which included all the 26 females.

Cardiac illness – 25 patients (31.25%) had already diagnosed coronary artery disease. 7 patients (8.8%) had rheumatic heart disease (RHD). 45 patients (56.3%) had no diagnosed cardiac illness at admission. The details of cardiac co-morbidities are shown in table 2.

Cardiac Risk Factors | Frequency (n=80) |
|---------------------|-----------------|
| Lone AF             | 3               |
| CAD                 | 23              |
| CAD + AF            | 2               |
| RHD                 | 4               |
| RHD + AF            | 3               |
| No known cardiac illness | 45 |
| **Total**          | **80**         |

Transient Ischemic Attacks (TIA) – 14 patients (17.5%) had TIA within one week prior to admission.

Peripheral vascular disease ((PVD) – PVD was detected in 2 patients (2.5%).

COPD – 4 (5%) deteriorated patients had COPD.

Drug default - 77% patients were not regular in monitoring their vascular risk factors (hypertension, diabetes mellitus and dyslipidemia) and had defaulted their medications.

Family history of vascular disease 49 (61.3%) patients. had first degree relatives with stroke or CAD
Stroke symptoms
11 Patients (13.8%) had wake up stroke, 42 (52.5%) had onset of symptoms in morning hours (before 12 noon); and 27 (33.8%) had onset in the afternoon hours (after 12 noon).

Vascular Territory affected
76 patients (95%) had anterior circulation stroke. 34 patients (42.5%) had right MCA territory stroke (left hemiplegia) and 42 patients (52.5%) had left MCA territory stroke (right hemiplegia +/- aphasia), and 4 patients (5%) had posterior circulation stroke (Table 3).

Table 3: Vascular Territory affected

| Territory                  | Frequency (n=80) | Percent |
|----------------------------|-----------------|---------|
| Right MCA (Left hemiplegia) | 34              | 42.5    |
| Left MCA (Right hemiplegia)| 42              | 52.5    |
| Posterior circulation      | 4               | 5       |

Level of consciousness at admission
28 patients (35%) were drowsy at admission. 52 patients (65%) were fully conscious at presentation, but sensorium worsened with worsening of deficit in 48 patients.

Persistent gaze deviation to one side
7 out of the 76 MCA territory stroke patients had persistent gaze deviation towards the lesion side at admission along with altered consciousness, and they all had large infarcts (ASPECT score less than 7) and all deteriorated. In NIHSS it is one component, but it was strikingly associated with large infarcts and deterioration.

Blood pressure at admission.
Joint National Committee (JNC – 8) classification of hypertension is as follows: <120/80 = normal; 120-139/80-89 – Pre hypertension; 140-159/90-99- Stage 1 hypertension; >160/>100 – Stage 2 hypertension.Among the 80 patients deteriorated, 14 had pre-hypertension, 7 had stage 1 hypertension and 59 had stage 2 hypertension.

Table 3: Causes of neurologic deterioration

| Causes of deterioration                  | Frequency | Percent |
|-----------------------------------------|-----------|---------|
| Cerebral Causes                         |           |         |
| Brain edema                             | 72        | 90      |
| Extension of infarct                    | 70        | 87.5    |
| Haemorrhagic transformation             | 17        | 21.25   |
| Seizure                                 | 9         | 11.25   |
| Aspiration pneumonia                    | 50        | 62.5    |
| Metabolic factors                       | 32        | 40      |
| Cardiac illness (CAD, RHD, AF)          | 9         | 11.25   |
| Deep vein thrombosis                    | 4         | 5       |
| Pulmonary Embolism                      | 2         | 2.5     |
| Infections (Urinary tract infection, sepsis) | 1       | 1.25    |
Cerebral causes – brain edema, extension of infarct and hemorrhagic transformation – contributed to deterioration, along with seizures in 9 cases. There was one case of non-convulsive status epilepticus detected by EEG monitoring.

**Initial Imaging findings in deteriorated patients (at admission)**

In our study, ASPECT score at admission CT, was less than or equal to 7 in 60 (75%) patients and ASPECT score was > 7 in 20 (25%) deteriorated patients (Table 6). Internal carotid artery (ICA) occlusion or near total occlusion was identified in 4 patients, and M1 or M2 segment of MCA occlusion confirmed on CT or MR angiogram in 38 patients with deterioration.

| Initial imaging findings | No. of patients |
|--------------------------|-----------------|
| Large infarct - ASPECT Score 7 or less than 7. (hypo density in 3 or more parts, of 10 parts of MCA territory) | 60 |
| Dense MCA sign/MCA dot sign. | 3 |
| Hypo attenuation involving cortex and sub cortical areas (superficial MCA and deep perforator territories of MCA) | 6 |
| Extensive bilateral small vessel ischemic changes | 5 |
| Multiple infarcts involving watershed zones. | 3 |
| ICA occlusion on CT angiogram/ carotid Doppler | 4 |

**Hemorrhagic transformation**  
17 cases (15 anterior circulations and 2 posterior circulations) suffered hemorrhagic transformation of infarct (Table 7). Smokers more frequently developed hemorrhagic transformation.

| Etiologic causes of hemorrhagic transformation | Frequency (n=17) |
|---------------------------------------------|-----------------|
| Large infarct – ASPECTS (equal to or less than 7) | 12 |
| Current heavy smokers | 6 |
| Uncontrolled blood pressure | 5 |
| Uncontrolled blood sugars | 4 |
| CAD. Acute MI | 4 |
| Atrial fibrillation | 3 |
| Uraemia | 2 |
| Dual Antiplatelets (Aspirin + Clopidogrel) | 2 |
| Post circulation stroke - Top of basilar syndrome | 2 |
| Dense MCA sign | 1 |
| Hepatic failure | 1 |

**Seizures**  
Following features were identified in 9 patients who developed seizures (Table 8).

| Etiologic factors | Frequency (n=9) |
|------------------|-----------------|
| Large infarcts (cortical/extension to cortex) | 9 |
| Atrial fibrillation with embolic CVA | 5 |
| Very low serum sodium < 120meq/L | 4 |
| Uncontrolled diabetes (very high blood sugar) | 2 |
| CAD, recent myocardial infarction, cardiac failure | 2 |
| Haemorrhagic transformation of infarct | 1 |
| ICA occlusion –with deterioration of stroke | 1 |
| Status epilepticus | 1 |
| Heavy smoker | 1 |
Metabolic Causes

Metabolic causes contributed for deterioration in 32 patients. The metabolic abnormalities are shown in table 9

Table-9: Metabolic abnormalities in deteriorated patients

| Metabolic abnormalities | Frequency (n=32) | Percent |
|-------------------------|-----------------|---------|
| Hyponatremia            | 27              | 84.3    |
| Uncontrolled blood sugar| 5               | 15.6    |
| Renal dysfunction       | 5               | 15.6    |
| Hepatic dysfunction     | 1               | 3.13    |

Hyponatremia

27 patients had hyponatremia during hospital stay. It was found in patients with large infarcts, between 2nd and 14th day in majority and correlated with the size of infarct. Large infarcts were associated with hyponatremia, and all had altered sensorium and 4 patients with very low sodium of less than 120 millieq/L developed seizures. Hyponatremia was reversible by early identification and appropriate management. Of the 9 patients who died during hospital stay, 6 had hyponatremia.

Outcome

There was significant disability in great majority at discharge, though notable improvement occurred on follow up. The Modified Rankin Scale (MRS) Score at discharge and at 3 months follow up is shown in Table 10. 9 patients died during hospital stay, and one patient died during the three month follow-up. The person who died during follow-up had MRS of 5 at discharge, and had CAD and old myocardial infarction. Majority showed improvement in their disability score at 3 months.

Table-10: MRS score at discharge and at 3 months follow up

| MRS     | At Discharge | At 3 Months |
|---------|--------------|-------------|
|         | No. of patients | Percentage | No. of patients | Percentage |
| 2 or <2 | 2             | 2.5%        | 12             | 15%        |
| 3       | 7             | 8.75%       | 30             | 37.5%      |
| 4       | 37            | 46.25%      | 24             | 30%        |
| 5       | 25            | 31.25%      | 4              | 5%         |
| 6 (DEATH) | 9         | 11.25%      | 10             | 12.5%      |

(MRS Score: 1.No disability despite symptoms; 2. Slight disability, able to carry out all ADL;3.Moderate disability, require some help, walk independently; 4. Moderate to severe disability, unable to walk; 5.severe disability, bedridden, need constant nursing care; 6.Death).

Mortality

A total of 9 patients died. (8 patients died during the initial admission and 1 patient died after discharge). All patients who died had large infarcts with mass effect and deteriorated early. Multiple factors contributed to their deterioration and death (Table 11). The one patient who died after discharge had CAD, DM, HT, Old myocardial infarction (MI) and experienced sudden death, due to MI / arrhythmia.

Table-11: Factors that contributed to deterioration and death in 9 patients

| ASPECT score | Mass effect | Hemorrhagic transform alia | Seizure | Necrosis | Aspiration | Hyponatremia | High blood pressure | Uncontrolled DM | Smoker | DVT, Pul embolism | MI | CAD | ICA occlusion |
|--------------|-------------|---------------------------|---------|---------|------------|--------------|---------------------|----------------|--------|------------------|----|-----|-------------|
| 1            | 7           | +                         | +       | +       | -          | +            | +                   | +              | +      | -                |    |      |             |
| 2            | 6           | +                         | +       | +       | +          | -            | -                   | -              | -      | +                |    |      |             |
| 3            | 8           | +                         | +       | +       | -          | +            | -                   | -              | -      | +                |    |      |             |
| 4            | 7           | +                         | +       | +       | +          | +            | -                   | -              | -      | +                |    |      |             |
| 5            | 6           | +                         | +       | +       | -          | +            | +                   | +              | +      | -                |    |      |             |
| 6            | 5           | +                         | +       | +       | +          | +            | +                   | -              | +      | -                |    |      |             |
| 7            | 6           | +                         | +       | +       | +          | +            | +                   | -              | -      | -                |    |      |             |
| 8            | 9           | +                         | +       | +       | +          | +            | -                   | +              | +      | -                |    |      |             |
| 9            | 6           | +                         | +       | +       | +          | +            | +                   | +              | +      | -                |    |      |             |
**DISCUSSION**

In this prospective observational study, 80 cases (25%) of 320 total cases of first ischemic stroke of moderate and moderately severe degree, deteriorated after admission in the first week. Severe strokes with NIHSS score ≥ 20 were excluded as severe stroke carry high risk of progressive deterioration and bad outcome. Awareness regarding stroke, and vascular risk factors were very poor irrespective of formal education or economic strata in the group deteriorated.

Kerala state has a higher prevalence of vascular risk factors, compared to national average [24, 25, 26, 27, 28, 29]. Among our deteriorated stroke patients, 85% were hypertensives, 42.5% were diabetics, 62.5% had dyslipidemia and 41.3% were smokers. Only 18 patients (22.5%) arrived at the hospital before 4.5 hours. Lack of awareness regarding early symptoms, importance of transient symptoms as harbinger of a major stroke, early treatment options, limited access to newer imaging techniques, unaffordable cost, lack of universal health insurance coverage, influence of alternative systems of medicine contributed to delayed arrival to a stroke care center. There is lack of well-equipped acute stroke care units and rehabilitation centers at rural areas. Newer treatment options are available only in urban centers, where infrastructure is very limited.

**Neurologic deterioration & Outcome**

In this prospective observational study, neurologic deterioration was seen in 25% of first acute ischemic stroke cases (80 out of 320 patients). In the previous studies, the prevalence varied between 13% and 38% [30]. In European progressing stroke studies, early neurologic deterioration was seen in 26% of patients in first 3 days after acute ischemic stroke and any neurologic worsening (transient or persistent for at least three days) occurred in 33% [31]. In a recent Chinese study, 32% of first ever stroke showed early neurologic deterioration [5]. Early neurological deterioration (END) was defined as an increment in motor power of at least one point or total NIHSS score deterioration of ≥2 points within the first week after admission. During acute phase, deterioration was a strong predictor of short term and long term unfavorable outcome (functional disability and mortality) in patients with first ever ischemic stroke [5].

In the current study, of the 320 first ever acute ischemic stroke cases, 80 patients (25%) deteriorated. 9 of them (11.3%) died (MRS 6) during hospital stay, and one more died at three months follow up. 77.6% (MRS - 4 and 5) were left with severe disability, with inability to walk at discharge. At 3 months, of the 70 patients who survived, 28 were unable to walk independently, 30 required some help for activities of daily living (MRS - 3), again proving that deterioration after the admission is associated with early worsening and long term disability in survivors.

**Factors at admission predictive of deterioration**

They were grouped as clinical, radiologic and biochemical features.

**Clinical features at admission predictive of deterioration**

a. **NIHSS Score at admission** – Higher the NIHSS score at admission, more severe is the stroke and higher is the chance of deterioration. In one study, patients with an initial NIHSS score less than or equal to 7 experienced lower frequency of worsening (14.8%) than those with a score > 7 (65.9%), with a dichotomy in early outcome surrounding an initial NIHSS score of 7 [32]. Siegler [33], reported that a worsening of NIHSS Score ≥ 2 points after admission is a sensitive indicator of poor outcome. In our study also, deteriorated stroke had moderate and moderate to severe stroke at admission (NIHSS score of 5 to 20) - NIHSS score of 5 to 9 in 27 patients, 10 to 15 in 51 patients, and 16 to 20 in 2 patients. Severe stroke with NIHSS score > 20 were excluded in our study.

b. **Altered sensorium (drowsiness) at admission** – Altered sensorium suggests large area affection, brain edema and mass effect or hemorrhagic transformation and was predictive of deterioration. Altered sensorium due to post ictal stage, non-convulsive status epilepticus, and metabolic encephalopathy need exclusion. In our study, 28 patients (35%) were drowsy at admission.

c. **Persistent gaze deviation, towards the lesion** suggestive of gaze pathway affection in cortex or sub cortical regions (suggestive of large infarct) was associated with deterioration. In present study, 28 patients (35%) had altered sensorium (drowsiness) at admission.

d. **Proximal large vessel occlusion** - High NIHSS score cannot predict proximal large vessel occlusion with certainty. Patients with low NIHSS score at admission also can have proximal large vessel stenosis or occlusion. Hence acute stroke imaging algorithm should include head and neck CT angiogram, along with non-contrast CT [38]. CT angiogram has better resolution than MR angiogram. Doppler study of neck vessels, CT or MR Angiogram, ultrasound or MR plaque imaging to identify vulnerable plaques are all important in acute stroke evaluation.

e. **Atrial fibrillation** was associated with neurologic deterioration in 8 patients. They carry high risk of recurrent embolism and hemorrhagic transformation. Three out of 8 patients with atrial fibrillation had hemorrhagic transformation. They also can develop recurrent embolism or hypotension which can lead to deterioration. Atrial
f. **Myocardial Infarction** – Evidence of recent myocardial infarction was there in 6 patients (2 patients also had atrial fibrillation), and both myocardial infarction and atrial fibrillation in 2 patients who deteriorated. They carried high risk of embolic stroke, hemorrhagic transformation and deterioration. One previous study found that coronary artery disease was associated with poor long term outcome [37]. Such patients require cardiac evaluation to assess the embolic risk early. They need repeat imaging of brain, in case of any neurologic deterioration. One of our patients with CAD recovered from acute stroke with severe disability, succumbed to CAD and sudden death one month after discharge.

g. **Dual antiplatelets, anticoagulants and fibrinolytics** used were associated with high risk of hemorrhagic transformation, especially in large infarcts. 2 patients with CAD on dual antiplatelet therapy with aspirin and clopidogrel developed hemorrhagic transformation. 1 patient with hepatic dysfunction and 2 patients with renal dysfunction also deteriorated with hemorrhagic transformation of infarct. They carry increased risk of hemorrhagic transformation due to their effect on coagulation system.

h. **Seizures** – Seizures were present in 9 patients (11.23%) and it contributed to deterioration. One patient with altered sensorium and hyponatremia (< 120meq/L) had non convulsive status epilepticus, and was detected by bed side EEG monitoring. Embolic stroke, involvement of cortex and hemorrhagic transformation carried increased risk of seizures. Severe hyperglycemia and hyponatremia were the metabolic causes identified in our patients with seizures. Seizures are common in large cortical infarcts and they account for early neurologic deterioration in about 5% of ischemic stroke patients [48].

i. **Persistently elevated BP** was associated with risk of worsening brain edema, hemorrhagic transformation and deterioration in deficit and sensorium. This occurred in 2 of our patients with renal dysfunction.

j. **Bulbar dysfunction and Aspiration pneumonia** – Evidence of tracheal aspiration and pneumonia was present in 50 (62.5%) patients. Dense hemiplegia with bulbar dysfunction and altered sensorium increase the risk of aspiration pneumonia. Protection of airway is very important in them. Presence of bilateral infarcts, and extensive bilateral small vessel ischemic changes in imaging increased the risk of prolonged bulbar dysfunction (pseudo bulbar) and associated complications. Swallowing function needs to be assessed daily, as per American Academy of Neurology guidelines, before starting oral feeds. Asymptomatic aspiration was also common.

k. **Older age and high BMI** were independent predictors in long term outcome in some studies [5]. Wang et al. reported old age as an independent predictor of disability and death [39]. As age advances, reduced cerebro-vascular reserve and multiple co-morbidities increase the risk. But we could not find such an association. 49 (61%) patients were above 69 years of age

l. **Tobacco smoking** was detected in 41.3% of patients who deteriorated after admission. Tobacco smoke induces inflammation, endothelial dysfunction, vasoconstriction and increased thrombotic tendency. It also increases the risk of subarachnoid hemorrhage. Two fifths of all stroke deaths under the age of 65 years are linked to smoking [40].

m. **DVT and pulmonary embolism** – Prevention of DVT and pulmonary embolism is an important priority and must be started early with physiotherapy, pneumatic compression devices and prophylactic heparin. Of our patients deteriorated, 4 had evidence of DVT and 2 developed pulmonary embolism. Daily monitoring for calf pain, asymmetric edema, tenderness and local rise of temperature of calf are helpful signs. Doppler ultrasound study of leg veins upto IVC can detect DVT in majority of cases.

n. **Malignant MCA infarct**–Large MCA infarct with early evidence of brain edema and mass effect need early neurosurgery consultation and decompressive craniectomy to save life in selected patients. We had 3 cases that underwent hemicraniectomy, two improved to MRS score 3 at 3 months follow up, and the other was left with severe disability (MRS 5). Hemicraniectomy performed early, within 48 hours significantly reduces mortality, and improves functional outcome in selected patients [41].

Biochemical parameters at admission predictive of deterioration

a. **Blood sugar and Hba1c at admission** – Very high blood sugar (> 400mg%, with elevated Hba1C > 9%) values were present in 6 of 36 (16.6%) deteriorated diabetic patients. 20 had blood sugar values between 200 and 399 mg% at admission. Diabetes is reported as independent predictor of deterioration in many studies [12, 42, 43]. Diabetic microangiopathy and chronic
hypertension impair micro vascular function, reducing the potential for collateral development. This leads to reduced oxygen delivery and regional metabolic disturbances, which may aggravate cellular damage by enhancing brain edema and free radical injury [46, 47].

b. Hyponatremia – Hyponatremia was seen in 27 patients with deterioration, was more with large infarcts and occurred from 3rd to 14th day of infarct; it was associated with altered sensorium. There were seizures in four patients with serum sodium value < 120meq/L. Prompt identification of cause and management is critical. SIADH was more common than cerebral salt wasting, which was seen in only one patient. Volume status (degree of hydration) is the clue.

Radiological features at admission predictive of deterioration
a. Initial CT brain - ASPECTS score - ASPECTS is a 10 point quantitative score used to assess early ischemic changes on non-contrast CT head [23]. In our study, ASPECT score at admission CT was less than or equal to 7 in 60 deteriorated patients (75%), and ASPECT score was more than 7 in 20 (25%) deteriorated patients. Many studies showed a linear inverse relationship between ASPECT score and risk of deterioration [44, 45]. Two of our patients who arrived early in less than 2 hours of onset of symptoms had ASPECTS score of 10. There was no evidence of even early changes of infarct; however they developed full blown MCA infarct within 24 hours. MRI Diffusion Weighted imaging could be beneficial in such patients as MRI can pick up acute infarcts as early as 30 minutes.

b. Proximal large artery stenosis or occlusion
Patchy hypo densities involving cortical, sub cortical and deep perforator regions, in MCA territory, or dense MCA sign/MCA dot sign, superficial and deep watershed area infarcts suggest possible proximal ICA or stem occlusion of MCA with some collateral flow. (Figure 2-4). Large vessel occlusion and failure of collaterals is the most common mechanism of neurologic deterioration (END) (4). Angiogram and penumbra imaging (MRI perfusion diffusion mismatch) are the guides for intervention. Percentage stenosis of ICA also can be calculated with ultrasound study. CT Angiogram or DSA is confirmatory.
c. **Hemorrhagic transformation of infarcts** this is more common with large infarcts, embolic strokes and patients following thrombolysis or coagulopathy. In the present study, there were 17 cases with hemorrhagic transformation. (Figure 5,6) Other causes of hemorrhagic transformation include embolic stroke, on dual antiplatelets, renal dysfunction, hepatic dysfunction and patients with uncontrolled hypertension. Hemorrhagic transformation range from small asymptomatic petechiae, to large hematoma with mass effect.

d. **Diffuse bilateral subcortical and periventricular hypo densities** suggesting diffuse small vessel disease, also carried higher risk of deterioration because of bilateral disease, poor reserve, and high risk for pseudo bulbar dysfunction, tracheal aspiration and pneumonia. MRI can show micro hemorrhages also.

e. **Multiple infarcts** in different vascular territories, bilateral infarcts, and wedge shaped infarct, hemorrhagic transformation – all suggest possible embolic etiology.

f. **Clinico-radiologic dissociation**
Lack of correlation between clinical deficit with initial CT picture, deficit with lack of imaging correlate initially (early CT), deficit with small
infarct or multiple watershed infarcts or small infarct with altered sensorium (seizures and metabolic causes ruled out) often suggest proximal large vessel occlusion and higher risk of deterioration. Such patients need further imaging-Doppler, MRI (DWI, FLAIR, MR/ CT perfusion, MR Angiogram or CT Angiogram).

LIMITATIONS OF THE STUDY
Small sample size is the major limitation in our study. A larger sample size comparing deteriorated to non-deteriorated patients shall provide more information regarding the causes of deterioration.

CONCLUSIONS
Progression of stroke is likely multifactorial; however, risk of deterioration in acute ischemic stroke can be predicted in great majority of cases at admission by careful close observation of clinical, biochemical and imaging characteristics, and by performing necessary investigations early. High NIHSS score, alteration in sensorium at arrival, persistent gaze deviation, and early features of raised intracranial pressure were predictive of deterioration in our study. Clinico-radiologic dissociation features at admission like focal deficit with normal early CT, or deficit/ altered sensorium with only minor imaging finding in initial CT brain scan, which cannot be explained by a small infarct were associated with high risk of deterioration. In such scenarios MRI Angiogram or CT angiogram may be more beneficial. High blood sugars and hyponatremia were the metabolic factors associated with deterioration. Imaging features like large infarct with early edema and mass effect features of proximal large artery stenosis and bilateral extensive small vessel ischemic changes were associated with deterioration. In conclusion, each stroke case needs prompt individualized evaluation and management. Interventions based on pathophysiology identified by imaging features and patient’s clinical condition and management of systemic diseases and complications will improve the outcome.

REFERENCES
1. Ramakant P, Verma AK, Misra R, Prasad KN, Chand G, Mishra A, Agarwal G, Agarwal A, Mishra SK. Changing microbiological profile of pathogenic bacteria in diabetic foot infections: time for a rethink on which empirical therapy to choose? Diabetologia. 2011 Jan 1;54(1):58-64.
2. Pandian JD, Sudhan P. Stroke epidemiology and stroke care services in India. Journal of stroke. 2013; 15(3):128-134.
3. Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja PN, Nayak SD, Sarma PS, Radhakrishnan K. Incidence, types, risk factors, and outcome of stroke in a developing country: the Trivandrum Stroke Registry. Stroke. 2009 Apr 1;40(4):1212-8.
4. Thanvi B, Treadwell S, Robinson T. Early neurological deterioration in acute ischaemic stroke: predictors, mechanisms and management. Postgraduate Medical Journal. 2008 Aug 1;84(994):412-7.
5. Geng HH, Wang Q, Li B. Early neurological deterioration during the acute phase as a predictor of long-term outcome after first-ever ischemic stroke. Medicine (Baltimore). 2017;96(51):e9068.
6. Bustamante A, García-berrocoso T, Rodriguez N. Ischemic stroke outcome: A review of the influence of post-stroke complications within the different scenarios of stroke care. Eur J Intern Med. 2016;29:9-21.
7. DeGraba TJ, Hallenbeck JM, Pettigrew KD, Dutka AJ, Kelly BJ. Progression in acute stroke: value of the initial NIH stroke scale score on patient stratification in future trials. Stroke; a journal of cerebral circulation. 1999; 30(6):1208–12.
8. Siegler JE, Boehme AK, Kumar AD, Gillette MA, Albright KC, Beasley TM. Identification of modifiable and non-modifiable risk factors for neurologic deterioration after acute ischemic stroke. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association. 2013; 22(7):e207–13.
9. Miyamoto N, Tanaka Y, Ueno Y, Kawamura M, Shimada Y, Tanaka R. Demographic, clinical, and radiologic predictors of neurologic deterioration in patients with acute ischemic stroke. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association. 2013; 22(3):205–10.
10. Tei H, Uchiyama S, Ohara K, Kobayashi M, Uchiyama Y, Fukuzawa M. Deteriorating ischemic stroke in 4 clinical categories classified by the Oxfordshire Community Stroke Project. Stroke; a journal of cerebral circulation. 2000; 31(9):2049–54.
11. Weimar C, Mieck T, Buchthal J, Ehrenfeld CE, Schmid E, Diener HC. Neurologic worsening during the acute phase of ischemic stroke. Archives of neurology. 2005;62(3):393–7.
12. Davalos A, Toni D, Iweins F, Lesaffre E, Bastianello S, Castillo J. Neurological deterioration in acute ischemic stroke: potential predictors and associated factors in the European cooperative acute stroke study (ECASS) I. Stroke; a journal of cerebral circulation. 1999; 30(12):2631–6.
13. Miyamoto N, Tanaka Y, Ueno Y, Kawamura M, Shimada Y, Tanaka R. Demographic, clinical, and radiologic predictors of neurologic deterioration in patients with acute ischemic stroke. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association. 2013; 22(3):205–10.
14. Weimar C, Mieck T, Buchthal J, Ehrenfeld CE, Schmid E, Diener HC. Neurologic worsening during the acute phase of ischemic stroke. Archives of neurology. 2005; 62(3):393–7.
15. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Effect of blood pressure and diabetes on stroke in progression. Lancet. 1994; 344(8916):156–9.
16. Grotta JC, Welech KM, Fagan SC, Lu M, Frankel MR, Brott T. Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. Stroke: a journal of cerebral circulation. 2001; 32(3):661–8.
17. Leigh R, Zaidat OO, Suri MF, Lynch G, Sundararajan S, Sunshine JL. Predictors of hyperacute clinical worsening in ischemic stroke patients receiving thrombolytic therapy. Stroke: a journal of cerebral circulation. 2004; 35(8):1903–7.
18. Ogata T, Yasaka M, Wakugawa Y, Ibayashi S, Okada Y. Predisposing factors for acute deterioration of minor ischemic stroke. Journal of the neurological sciences. 2009; 287(1–2):147–50.
19. Suri MF, Suarez JI, Rodrigue TC. Effect of treatment of elevated blood pressure on neurological deterioration in patients with acute intracerebral hemorrhage. Neurocrit Care. 2008;9(2):177-82.
20. Toyoda K, Fujimoto S, Kamouchi M, Iida M, Okada Y. Acute blood pressure levels and neurological deterioration in different subtypes of ischemic stroke. Stroke. 2009; 40(7):2585–8.
21. Awadh M, MacDougall N, Santosh C, Teasdale E, Baird T, Muir KW. Early recurrent ischemic stroke complicating intravenous thrombolysis for stroke: incidence and association with atrial fibrillation. Stroke. 2010; 41(9):1990–5.
22. Georgiadis D, Engelter S, Tettenborn B, Hunger Stroke. 2010; 41(9):1990–5.
23. Cloft HJ. Death and destruction in the intra-arterial battle with acute ischemic stroke. AJNR Am J Neuroradiol. 2009; 40:2988–93
24. Hacke W, Furlan AJ, Al-Rawi Y. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomized, double-blind, placebo-controlled study. Lancet Neurol. 2009; 8:141–50.
25. Wang D, Hao Z. Acute ischemic stroke in the elderly Chinese: Risk factors, Hospital Management and one year outcome. ClinNeurol Neurosurgery. 2011; 113:442-6.
26. WHO Tobacco knowledge summaries 2016. (Tobacco and stroke-http://apps.who.int/iris/bitstream/10665/250278/1/WHO-NMH-PND-CIC-TKS-16.1-eng.pdf)
27. Treadwell SD, Thanvi B. Malignant middle cerebral artery (MCA) infarction: pathophysiology, diagnosis and management: Postgrad Med J. 2010 Apr; 86(1014):235–42.
28. Roguery, Rodriguez- campello. Acute stroke unit care and early neurologic deterioration in ischemic stroke, j. neuro.2008; 255:1012-7.
29. Tanaka R, Ueno Y, Miyamoto N. Impact of diabetes and pre diabetes on the short term results of a community-based study in Kerala, India. Indian J Med Res. Jan. 2010; 131:53-63.
prognosis in patients with acute ischemic stroke. J Neurol Sci 2013; 332:45-50.
44. Hill MD, Buchan AM. Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. CMAJ. 2005; 172:1307.
45. Schröder J, Thomalla G. A Critical Review of Alberta Stroke Program Early CT Score for Evaluation of Acute Stroke Imaging. Front Neurol. 2017 Jan 12; 7:245.
46. Pulsinelli W. Pathophysiology of acute ischaemic stroke. Lancet. 1992; 339:533–6.
47. Toni D, De Michele M, Fiorelli M. Influence of hyperglycemia on infarct size and clinical outcome of acute ischemic stroke patients with intracranial arterial occlusion. J Neurol Sci. 1994;123:129–33
48. Johnston KC, Li JY, Lyden PD. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. RANTTAS Investigators. Stroke. 1998;29:447–53
49. Berrouschot J, Sterker M, Bettin S. Mortality of space-occupying (‘malignant’) middle cerebral artery infarction under conservative intensive care. Intensive Care Med. 1998;24:620–3
50. Rajajee V, Kidwell C, Starkman S. Early MRI and outcomes of untreated patients with mild or improving ischemic stroke. Neurology. 2006;67:980–4
51. Saleem SM. Modified Kuppuswamys Scale Updated For Year 2018. Paripex-Indian Journal of Research. 2018 May 18;7(3).