Predictors of Early Neurological Deterioration Following Intravenous Thrombolysis: Difference between Risk Factors for Ischemic and Hemorrhagic Worsening

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Abstract

Background: Prevention of early neurological deterioration (END) is becoming an important therapeutic target in acute ischemic stroke management. The aim of the study is to ascertain the causes and predictors of early neurological deterioration following thrombolysis and determine the predictive value of IScore. Methods: In this single center prospective study, we analyzed clinical, imaging and outcome data in 168 patients thrombolyzed intravenously ≤4.5 hours from onset of stroke. Early neurological deterioration was defined as worsening ≥2 points in the NIHSS score at 24 hours. Results: END occurred in 34 patients (20%) and caused significantly worse short term outcome. Ischemic END (ENDi) (n = 23) was twice as common as symptomatic hemorrhage (ENDh) (n = 11). Ischemia progression (n = 15) was the most common cause. Early malignant edema was another major cause. On multivariate analysis, significant predictors (p <.05) were proximal artery occlusion [all END (p <.001), ENDi and ENDh], previous ischemic insults (all END) and raised diastolic blood pressure (ENDh). ENDi was more common in those with carotid artery occlusion, large vessel disease and previous ischemic insults. ENDh was more common in those with raised diastolic blood pressure and NIHSS-ASPECTS mismatch. For patients with NIHSS <14, IScore >105 and for NIHSS ≥14, IScore >175 was associated with higher risk of END. Conclusion: END occurs in one fifths of patients after intravenous thrombolysis; ENDi outnumbers ENDh. Proximal artery occlusion is a major predictor for END. Potentially modifiable risk factors include admission hyperglycemia and elevated blood pressures. Distinct factors characterize ENDh and ENDi and can guide prevention and management strategies. IScore identifies patients at risk for END.

Keywords: Acute ischemic stroke, early neurological deterioration, intravenous thrombolysis, IScore

Introduction

The use of intravenous thrombolysis (IVT) using recombinant tissue plasminogen activator (rt-PA) has revolutionized acute ischemic stroke (AIS) care since its inception in 1996 and introduction of intra-arterial revascularization using mechanical thrombectomy has further improved outcome. Even though the majority of patients exhibit improvement, a significant fraction of patients show no improvement or deteriorate following IVT. Early neurological deterioration (END) has been reported to occur in 5% to 40% of patients with AIS, depending on definition used and length of the observation period and portends markedly increased morbidity and mortality.[1] The most critical period is the first 24 hours after thrombolysis; intensive monitoring of neurological status, blood pressure monitoring and glycemic control are carried out to ensure patient stability and prompt early recognition of deterioration. There is a lack of clarity regarding the causes of END following IVT; symptomatic intracranial hemorrhage is the best studied. However recent studies have emphasized the importance of ischemia progression and further studies are needed to elucidate the underlying mechanisms and pathophysiology. Early detection and prevention of END is emerging as one of the important therapeutic targets in acute ischemic stroke management.[2]

There is a scarcity of validated scores to predict early neurological deterioration after thrombolysis. The ischemic stroke predictive risk score (IScore) is a developed and validated scoring system for the prediction of short- and long-term mortality after stroke which has also been validated to predict intracerebral hemorrhage after thrombolysis and occurrence of END within the acute stroke stage.[3-5] Most of the variables used to compute the IScore are known to be associated with END after thrombolysis. However no studies have assessed the utility of IScore to predict END following thrombolysis.

We aim to study the incidence, causes, predictors and associated factors of early neurological deterioration following...
intravenous thrombolysis in acute ischemic stroke, determine the difference between predictive factors for ischemic and hemorrhagic worsening and determine whether IScore can be used to predict early neurological deterioration in thrombolysis patients.

**Materials and Methods**

**Study design**

This is a single center prospective cohort study evaluating patients undergoing intravenous thrombolysis for acute ischemic stroke in a tertiary care setting. We collected data about demographic and clinical variables. Written informed consent was obtained from all patients. The study was approved by the institutional ethics committee.

**Study population**

Our hospital is a large public, referral and teaching hospital serving both urban and rural population of multiple districts in the southern part of India. Suspected acute ischemic stroke patients were evaluated in the emergency department and transferred to neurology intensive care unit if found eligible for thrombolysis.

Acute ischemic stroke patients treated with intravenous recombinant tissue plasminogen activator (r-tPA) in the Neurology Intensive Care Unit from April 2019 to March 2021 were included in the study. Patients who underwent mechanical thrombectomy were excluded as factors related to the procedure may contribute to neurological deterioration in such patients.

Suspected acute ischemic stroke patients, who presented within 4.5 hours of last known well were evaluated emergently with clinical examination, random blood glucose measurements, CT brain and CT angiogram of carotid and vertebral circulation. Stroke severity was assessed using NIHSS score. MRI brain was obtained whenever clinically indicated. Patients who were ≥18 years of age, had measurable neurological deficits with NIHSS score ≥4 or major deficits such as severe aphasia, complete hemianopia or limb weakness limiting sustained effort against gravity and had hemorrhage excluded on CT brain were taken up for intravenous thrombolysis as per current guidelines.[6] CT brain was evaluated to calculate ASPECTS (Alberta Stroke Program Early CT score) and patients with extensive areas of frank hypodensity were excluded from thrombolysis. Intravenous labetalol and nitroglycerin infusion were used for blood pressure control and patients whose blood pressure could not be maintained below 185/110 mm Hg were not thrombolized. Close monitoring of neurological status, blood pressure and vital signs was continued for 24 hours after thrombolysis. NIHSS score was determined at admission, 2 hours after IV thrombolysis, at 24 hours and at the time of deterioration, if any.

**Clinical, imaging and outcome variables**

Baseline characteristics of patients including age, gender, vascular risk factors, presence of cardiac disease, atrial fibrillation, previous stroke or transient ischemic attack (TIA), random blood glucose at admission, blood pressure levels, hemoglobin levels, platelet count, onset to thrombolysis time, door to needle time, severity of stroke, clinico-radiological dissociation (NIHSS ≥8, ASPECTS >8) and stroke subtypes were studied.

CT angiogram of the carotid and vertebral circulation was obtained to look for large vessel occlusion. Proximal occlusion was defined as occlusion of the M1 segment of the middle cerebral artery (MCA), M2 segment of MCA or the basilar artery. CT brain was repeated at time of deterioration if any and follow up MRI brain was done at 24 hours. If MRI could not be done, follow up CT brain was obtained. The follow up imaging was evaluated for infarct location, hemorrhagic transformation, new ischemic changes and development of cerebral edema. Stroke etiology was classified as per TOAST criteria into large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology.

Modified Rankin scale (mRS) at 3 months was used to assess the outcome of the patients. Poor outcome was defined as mRS >2. Length of hospital stay and in-hospital mortality were secondary outcome measures assessed.

**Definition of END**

Early neurological deterioration is defined as worsening ≥2 points in the NIHSS score at 24 hours (END). The cause of deterioration is determined and is classified into hemorrhagic (ENDh), ischemic (ENDi) and systemic factors (early aspiration, fever).

Patients were classified as ENDh if symptomatic intracerebral hemorrhage (sICH) occurred. sICH is suspected in patients who develop sudden neurologic deterioration, a reduction in level of consciousness, new headache, nausea and vomiting, or a sudden rise in blood pressure. sICH was defined as any hemorrhage associated with worsening of ≥2 point on the NIHSS score. Patients were classified as ENDi if no hemorrhage was detected on follow up imaging and included patients with progression of ischemia, early recurrent ischemic stroke, unexplained deterioration, early malignant edema and post-stroke seizures. Early malignant edema was considered if there was brain swelling and midline shift along with decline in level of consciousness. Early recurrent ischemic stroke was defined as the occurrence of new neurological symptoms along with development of corresponding ischemic lesions on follow-up imaging.

**IScore calculation**

The 30-day IScore for each patient was calculated using a previously reported method.[10] In brief, IScore uses 10 variables including age, sex, stroke severity and subtype, history of atrial fibrillation, congestive heart failure, cancer, kidney disease on dialysis, hyperglycemia on admission, and dependency before the stroke for the calculation of risk score. For the IScore calculation, the stroke severity was categorized into 4 groups
based on the NIHSS score: NIHSS score of 23 or higher (very severe), NIHSS score of 14-22 (severe), NIHSS score of 9-13 (moderate), and an NIHSS score of 8 or lower (mild).

**Statistical analysis**

The baseline clinical and imaging variables are presented using standard descriptive statistics. We compared the demographic, clinical, imaging and outcome variables and IScore in patients with END and without END. The patients with ENDi and ENDh subgroups were compared to determine differences in the clinical presentation and outcomes. Categorical variables are expressed as number of patients (percentage %) and continuous variables as mean ± standard deviation and non-normally distributed variables as median (interquartile range). The Chi square test was used for comparing categorical variables. The student’s t test and Mann Whitney U test were used to compare continuous variables. Statistical significance was determined using P value < 0.05. Significant univariate factors associated with END were entered in a multivariate logistic regression to determine independent predictors of END.

The relation between IScore and END was examined using student’s t test. For prediction of END using IScore, stroke severity was categorized into two groups based on NIHSS Score: mild-moderate <14, severe-very severe ≥14. ROC (receiver operated curve) analysis was done to determine the optimal IScore that predicts END in the 2 subgroups. Statistical analysis was done using SPSS version 22.

**RESULTS**

During the study period, 185 patients received intravenous thrombolysis with rt-PA; 17 had to be excluded due to incomplete data (incomplete follow up imaging/clinical details-7, CT angiogram not available -10). The final analysis included 168 patients. Median NIHSS was 10 (6, 14) at admission and 7 (4, 14) at 24 hours. 55 (33%) patients had proximal occlusion on CT angiogram. Large vessel disease (42%) was the most common etiologic subtype of stroke.

**Pretreatment variables associated with END**

Univariate analyses of pre-treatment clinical and imaging characteristics between no END and all END, ENDi and ENDh are presented in Table 1. All END was associated with personal history of diabetes, previous ischemic insults, admission hyperglycemia, elevated systolic and diastolic blood pressure, proximal occlusion on CTA, internal carotid artery occlusion, NIHSS-ASPECTS dissociation and stroke due to large vessel disease.

We also identified some differences between ENDh and ENDi subgroups. Internal carotid artery occlusion, previous ischemic insults and stroke due to large vessel disease was associated with ENDi whereas NIHSS-ASPECTS mismatch was protective for ENDi. Elevated blood pressure and requirement of intravenous antihypertensives to control blood pressure was strongly associated with ENDh. Personal history of having diabetes and prolonged door-needle-time was associated with ENDh. Admission hyperglycemia and proximal occlusion was associated with both subgroups.

On multivariate analysis, proximal occlusion and previous ischemic insults were significant predictors of all END. Proximal occlusion and elevated diastolic blood pressure predicted ENDh whereas proximal occlusion predicted ENDi. Independent predictors of END are summarized in Table 2.

**Vascular and Follow up Imaging variables associated with END**

Arterial occlusion on CT angiogram involved the internal carotid artery with or without tandem occlusion of MCA in 17 patients, M1 segment of MCA in 34 patients, M2 segment of MCA in 16 patients and basilar artery in 5 patients. Follow up MRI brain was evaluated in 143 patients and CT brain in 25 patients. There were 143 anterior circulation strokes and 25 posterior circulation strokes. Univariate analyses of vascular and follow up imaging variables between no END and END groups are described in Table 3.

**Causes of END**

Early neurological deterioration occurred in 34 patients (20.2%); ENDi accounted for 13.7% cases and ENDh 6.5%. No systemic causes for END were identified. When the length of observation was increased to 5 days, total deterioration increased to 43 (25.6%), 6 additional cases due to malignant edema and 3 due to aspiration. The causes of END are summarized in Table 4.

The most common mechanism for ENDi was presumed extension of ischemia. Of the 11 patients who had presumed progression of ischemia in the involved MCA territory, new ischemic changes on follow up imaging was confirmed in 4 patients. 2 patients with ICA occlusion had extension of infarction to the ACA territory and 3 had worsening due to worsening small vessel ischemia (2 in internal capsule and 1 in pons). Early malignant edema (cerebral edema and mass effect with malignant MCA infarction) caused deterioration in 5 (3%) patients. The other mechanisms included 1 patient with RHD and AF who had recurrence in the opposite MCA territory and 1 patient had post stroke seizure. Parenchymal hematoma accounted for majority of ENDh (73%).

**Outcome**

Patients with early neurological deterioration had significantly worse short term outcomes with longer hospital stay (OR 23.94, CI: 3.15-82.69) and greater in-hospital mortality (OR 23.76, CI: 4.84-116.59). Patients with END also had significantly poor mRS at 3 months (OR for death or disability 14.3, CI: 4.8-43.2). Prognosis was equally dismal for ENDi and ENDh.

**IScore to predict END**

IScore was significantly higher (p <.001) in deteriorated patients than in patients without END (149 ± 33 vs119 ± 39). No differences were identified between ENDi and ENDh. On
multivariate analysis, IScore was independently associated with END after adjusting for other factors contributing to END (p = 0.002). An ROC analysis was done [Figure 1]. For patients with NIHSS <14 (125 patients), IScore >105 predicted END with sensitivity 91%, specificity 96% and positive predictive value (PPV) 30% and negative predictive value (NPV) 96%. For patients with NIHSS ≥14 (33 patients), IScore >175 predicted END with sensitivity 82%, specificity 92% and PPV 50% and NPV 92%.

Table 1: Demographic and clinical variables associated with END

| Variable                                      | No END n=134 | All END n=34 | P     | ENDi n=23 | P     | ENDh n=11 | P     |
|-----------------------------------------------|--------------|--------------|-------|-----------|-------|-----------|-------|
| A. Patient history                            |              |              |       |           |       |           |       |
| 1. Age                                        | 60±12.5      | 65±12.9      | 0.07  | 63±12     | 0.39  | 67±13     | 0.08  |
| 2. Sex (Male)                                 | 90 (67)      | 24 (71)      | 0.70  | 17 (74)   | 0.52  | 7 (64)    | 0.81  |
| 3. Hypertension                               | 68 (51)      | 22 (65)      | 0.14  | 16 (70)   | 0.09  | 6 (55)    | 0.80  |
| 4. Diabetes mellitus                          | 35 (26)      | 16 (47)      | 0.02* | 9 (39)    | 0.19  | 7 (64)    | 0.01* |
| 5. Hyperlipidemia                             | 37 (28)      | 14 (41)      | 0.12  | 10 (43)   | 0.12  | 4 (36)    | 0.53  |
| 6. Cardiac disease                            | 19 (14)      | 8 (24)       | 0.18  | 5 (22)    | 0.35  | 3 (27)    | 0.24  |
| 7. Previous ischemic stroke/TIA               | 7 (5)        | 7 (21)       | 0.004*| 5 (22)    | 0.01* | 2 (18)    | 0.08  |
| 8. Atrial fibrillation                        | 16 (12)      | 4 (12)       | 0.97  | 2 (8.7)   | 0.65  | 2 (18)    | 0.54  |
| 9. Smoking                                    | 41 (31)      | 14 (41)      | 0.24  | 9 (39)    | 0.41  | 5 (45)    | 0.30  |
| B. Pretreatment characteristics              |              |              |       |           |       |           |       |
| 1. NIHSS (IQR)                                | 10 (6,13)    | 12 (9,15)    | 0.98  | 12 (10,15)| 0.25  | 13 (10,16)| 0.91  |
| 2. Blood glucose at presentation (mg/dl)      | 139±45       | 168±61       | 0.002*| 167±59   | 0.02* | 169±66   | 0.04* |
| 3. Systolic blood pressure (mmHg)             | 158±32       | 170±38       | 0.04* | 164±35   | 0.39  | 185±41   | 0.01* |
| 4. Diastolic blood pressure (mmHg)            | 90±15.4      | 101±25       | 0.002*| 94±17    | 0.28  | 117±33   | <.001*|
| 5. Intravenous antihypertensive before thrombolysis | 44 (33)   | 16 (47)     | 0.12  | 8 (35)    | 0.85  | 8 (73)    | 0.01* |
| 6. Onset-to-needle time (minutes)             | 203±46       | 212±41       | 0.33  | 207±42   | 0.69  | 220±41   | 0.22  |
| 7. Door-to-needle time (minutes)              | 70±32        | 77±24        | 0.42  | 68±23    | 0.41  | 89±29    | 0.04* |
| 8. Proximal Occlusion                         | 31 (23)      | 24 (71)      | <.001*| 16 (70)   | <.001*| 8 (73)   | <.001*|
| 9. Internal Carotid artery occlusion          | 9 (7)        | 8 (24)       | 0.004*| 7 (30)    | <.001*| 1 (9)    | 0.76  |
| 10. CT ASPECTS ≤7                            | 24 (14)      | 8 (24)       | 0.45  | 6 (26)    | 0.35  | 2 (18)   | 0.97  |
| 11. NIHSS-ASPECTS dissociation                | 30 (22)      | 14 (41)      | 0.03* | 8 (35)    | 0.69  | 6 (55)   | 0.02* |
| C. TOAST classification                       |              |              |       |           |       |           |       |
| 1. Large artery atherosclerosis               | 48 (36)      | 22 (65)      | 0.002*| 16 (70)   | 0.002*| 6 (55)   | 0.21  |
| 2. Cardioembolic                              | 18 (13)      | 6 (18)       | 0.30  | 4 (17)   | 0.61  | 2 (18)   | 0.66  |
| 3. Small vessel disease                       | 37 (28)      | 5 (15)       | 0.12  | 3 (13)   | 0.13  | 2 (18)   | 0.49  |
| D. Outcome                                    |              |              |       |           |       |           |       |
| 1. Length of stay <5 days                     | 65 (49)      | 1 (3)        | <.001*| 1 (4)    | <.001*| 0        | <.001*|
| 2. In-hospital mortality                      | 2 (1.5)      | 9 (26)       | <.001*| 6 (26)   | 0.001*| 3 (27)   | 0.002*|
| 3. mRS at 3 months (poor)                     | 46 (34)      | 30 (88)      | <.001*| 21 (91)  | <.001*| 9 (82)   | <.001*|

Numbers in brackets are percentages. *P<0.05, †P<0.001

Table 2: Predictors for END on multivariate analysis (P<0.05)

| Variable                                      | Adjusted odds ratio (CI)* | P     |
|-----------------------------------------------|---------------------------|-------|
| All END                                       |                           |       |
| Proximal Occlusion                            | 8.99 (3.10-26.12)         | 0.001 |
| Previous ischemic insults                     | 4.66 (1.02-21.42)         | 0.03  |
| ENDh                                          |                           |       |
| Proximal Occlusion                            | 3.79 (1.22-13.99)         | 0.04  |
| Elevated Diastolic blood pressure             | 1.08 (1.00-1.18)          | 0.03  |
| ENDi                                          |                           |       |
| Proximal Occlusion                            | 4.80 (1.56-14.79)         | 0.006 |

*CI: 95% confidence intervals upper-lower

Figure 1: ROC analysis for IScore. AUC (area under curve) = 0.82 for NIHSS <14 and 0.85 for NIHSS ≥14

**DISCUSSION**

In this study, defining END as worsening of NIHSS score by 2 or more points in 24 hours, we found END in 20.2%. This is consistent with previous studies using NIHSS worsening ≥2 criteria which have reported END ranging from 4.4 to 31.9% depending on length of observation. There has been much discussion about the optimal NIHSS change required...
to define END, the most popular definition being 4 or more NIHSS aggravations between the time of initial treatment and the following 24 hours. However, studies have shown that neurological deterioration with 2 or more NIHSS aggravations more accurately predicted in-hospital mortality. We have used this definition of END to enable early recognition of this devastating complication thus facilitating decompressive hemicraniectomy, rescue thrombectomy and intensive hemodynamic management.

In our study, presumed ischemia progression in the involved arterial territory (47%) emerged as the most common cause of ENDi as well as all END. Early malignant edema (14.7%) was the other major cause of END. This proportion is consistent with other studies which have reported intracerebral hemorrhage in 20-30%, malignant edema in 6-24% and ischemia progression in 47-80% of END. [8,9,11-14]

Significant imaging findings associated with END in our study were cortical location of infarcts and proximal arterial occlusion. Cortical location of infarcts was associated with greater CTP mismatch and worse outcomes after thrombolysis compared to lacunar infarcts in an recent large study. In accordance with evidence from previous studies, proximal arterial occlusion was a significant independent predictor for all END as well as ENDi. [12-14,16] Mechanisms of ischemia progression contributing to END after IV r-tPA include failed recanalization, proximal extension of thrombus, distal thrombus migration, arterial re-occlusion and recurrent embolic events and endovascular therapy may be of benefit (Hermes meta-analysis). [17]

In keeping with previous reports, diabetes, admission hyperglycemia and elevated blood pressure were found to be associated with END in our study.[11-13,16] Surveys from our region have shown that our population differs from Western populations in having higher vascular risk factors.[18] Three or more risk factors were identified in 23% of our patients but there was no significant difference between END and no END group. We found elevated diastolic blood pressure to be independent predictor for ENDh which is well supported by previous studies.[19] The prolonged door-to-needle time noticed in ENDh group can be attributed to the time required to control blood pressure.

ENDi differed significantly from ENDh, occurring more frequently in patients with carotid artery occlusion, stroke due to large artery atherosclerosis and patients with previous ischemic insults; in comparison ENDh occurred in patients with elevated diastolic blood pressure and NIHSS-ASPECTS dissociation. Several studies have substantiated the finding that stroke due to large artery atherosclerosis is more common in

### Table 3: Imaging variables associated with END

| Variable                                      | No END n=134 | END n=34 | P   | Odds Ratio (CI) |
|-----------------------------------------------|--------------|----------|-----|-----------------|
| Site of Arterial Occlusion on CT angiogram    |              |          |     |                 |
| Internal Carotid artery*                      | 9            | 8        | 0.003 | 4.63 (1.62-13.20) |
| M1 segment of MCA                             | 14           | 20       | <.001 | 12.25 (5.08-29.50) |
| M2 segment of MCA                             | 13           | 3        | 0.87  |                 |
| Basilar artery                                | 4            | 1        | 0.98  |                 |
| Follow up Imaging                             |              |          |     |                 |
| A. Arterial territory                         |              |          |     |                 |
| Anterior circulation                         | 112          | 31       | 0.26  |                 |
| Vertebral-basilar                            | 22           | 3        | 0.28  |                 |
| B. Location of ischemic changes              |              |          |     |                 |
| Cortical involvement                         | 64           | 26       | 0.003 | 3.77 (1.59-8.93)  |
| Subcortical                                   | 48           | 5        | 0.02  | 3.23 (1.18-8.91)  |
| Brainstem                                     | 20           | 2        | 0.16  |                 |
| Cerebellum                                    | 2            | 1        | 0.57  |                 |
| C. Intracerebral haemorrhage                 | 9            | 11       | <.001 | 6.64 (2.47-17.81) |
| Hemorrhagic infarction                        | 8            | 3        | 0.54  |                 |
| Parenchymal hematoma                          | 1            | 8        | <.001 | 40.12 (4.9-141.12) |
| D. New ischemic changes                      | 4            | 9        | <.001 | 10.02 (2.81-35.36) |
| E. Cerebral edema                             | 12           | 5        | 0.32  |                 |

*Includes 4 patients with tandem occlusion (END group: n=4). †Odds ratio (95% confidence interval) for significant factors on univariate analysis

### Table 4: Causes of END

| Etiology                                      | Patients (Number) |               |
|-----------------------------------------------|-------------------|---------------|
| 1. Ischemic END (ENDi) n=23                   |                   |               |
| a. Progression of ischemia                   | 16                |               |
| b. Early malignant edema                     | 11                |               |
| c. Post stroke seizures                      | 2                 |               |
| d. Re-infarction in other territory          | 1                 |               |
| 2. Symptomatic Intracranial haemorrhage (ENDh) n=11 | 8                 |               |
| a. Parenchymal hematoma                      | 8                 |               |
| b. Hemorrhagic infarction                    | 3                 |               |
ENDi.[9,13] Internal carotid artery occlusion has been determined to be predominantly associated with ischemic END due to distal embolism in a recent study evaluating IVT in patients with minor stroke and isolated internal carotid occlusion as well as a multicentric study from France evaluating minor stroke and large vessel occlusion.[20,21]

In a large study from Japan, comparison of patients with ischemic END and hemorrhagic END revealed that severe stroke symptoms and pretreatment with antplatelets were associated with ENDh, whereas extensive early ischemic changes and large artery occlusions were associated with ENDi.[22] We were able to demonstrate that NIHSS-ASPECTS dissociation that is, an absence of early ischemic changes in severe stroke is associated with ENDh. Studies have found that higher ASPECTS predicts greater recanalization and clinical aspects mismatch predicts penumbra which responds to revascularization lowering the risk of ENDi.[23,24]

There are no previous studies confirming the association between ENDi and prior ischemic insults. A likely explanation is that large artery atherosclerosis and vascular risk factors which are associated with ischemia progression also predisposes to recurrent strokes. We did not find any association between AF, CHF or cardiac disease and END. AF is a risk factor for END due to recurrent ischemic stroke and contributed to END by this mechanism in 1 patient.[25] We did not find a relationship between NIHSS and END, but lower NIHSS and higher NIHSS have both been related to END.[13,16]

Prevention of END should become a priority in post revascularization management. Early use of antithrombotics has resulted in greater sICH.[26] Improved availability of mechanical thrombectomy, decompressive hemi‑craniectomy and intensive stroke unit care is essential. Our study has shown that IScore >175 in patients with severe stroke and >105 in patients with mild‑moderate stroke can predict END. This can facilitate triage and transfer of patients administered IVT in primary care settings to referral centers capable of rescue thrombectomy and decompressive hemicraniectomy. Further large scale studies are needed to confirm this.

Our study had several limitations. Majority of patients reaching the emergency department were referred from peripheral hospitals and used their own conveyance due to limited ambulance services. These factors contributed to prolonged onset to thrombolysis time. Our study population is also distinct in having a large number of vascular risk factors and hence our study may not be generalizable to other populations. MRI at admission could not be done for majority of patients and there may be differences inherent to the imaging methods when comparing pre and post treatment scans. Collateral circulation, infarct area and post treatment vascular imaging assessments could not be obtained. Imaging factors which contribute to deterioration were not included in the predictive score.

In spite of these limitations we were able to derive several conclusions. END occurs in one fifth of patients after intravenous thrombolysis and resulted in significant disability and in-hospital mortality; ENDi outnumbers ENDh. Proximal artery occlusion is a major predictor. Several potentially modifiable risk factors were also identified. ENDi was more common in those with carotid artery occlusion, large artery atherosclerosis and previous ischemic insults. ENDh was more common in those with raised diastolic blood pressure and NIHSS-ASPECTS mismatch. Use of IScore identifies patients at risk for END.

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Conflicts of interest There are no conflicts of interest.

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