Outcomes of Stroke Patients Undergoing Thrombolysis in Sri Lanka; an Observational Prospective Study From a Low-middle Income Country

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Abstract

Background

Stroke related deaths are relatively higher in low- and middle-income countries where only a fraction of eligible patients undergo thrombolysis. There is also limited evidence on post-thrombolysis outcomes of patients from Asian countries in these income bands.

Methods

This is a single center prospective observational study of a patient cohort with acute ischaemic stroke, undergoing thrombolysis with alteplase (low and standard dose), over a 24-month period in 2019/2020. Demographic, clinical (including scoring systems for functional impairment) and imaging data of all patients were recorded prior to thrombolysis, within 24-hours post-thrombolysis and at 3-months follow up. Incidence of symptomatic intracranial haemorrhages and all-cause mortality by 3 months was also recorded.

Results

Eighty-nine patients (males – 61, 69%, mean age: 60 years ± 12.18) were recruited. Time from symptom onset to reperfusion was 174 minutes ± 56.50. Ten (11%) patients died and 19 (21%) developed symptomatic intracranial haemorrhages (sICH) by 3 months. Functional independence at 3 months (measured by Barthel index, National Institutes of Health Stroke Score – NIHSS, or modified Rankin scale - mRS) was independently associated with NIHSS on admission (p<0.05). Thrombolysis with low dose alteplase was associated with better NIHSS or mRS scores (p<0.05) at 3 months compared to standard dose.

Conclusions

On admission NIHSS is predictive of functional independence at 3 months and reducing the time from symptom onset to thrombolysis, may further improve outcomes. The preliminary observations on low dose alteplase efficacy must be confirmed by a randomized controlled trial in the local population.

Background

Globally, age standardized stroke mortality has declined from 2005–2017, but most of these deaths still occur in middle – and low- income countries\(^1\). Interestingly, age standardized stroke prevalence has been increasing since 2005 in middle income countries. Age standardized stroke related disability adjusted life years lost (DALYs) has been declining in countries across all income bands, probably reflecting advances in stroke care and therapy in the last 15 years, but there is still a huge discrepancy between high – income countries and others\(^1\). Overall, these numbers suggest a global inequality in resource distribution leading to suboptimal care and more deaths in stroke patients from less affluent countries. Thrombolysis with intravenous alteplase (a recombinant tissue plasminogen activator – rtPA) is one of the most
important therapies in acute stroke management, but remains out of reach for many eligible candidates in lower-middle income countries (as low as 2% of stroke patients receive thrombolysis according to some studies)\(^2\)\(^3\), partly due to unavailability of the drug, public unawareness and also due to lack of infrastructure (roads and transportation, paramedic services) which prevents patients reaching hospitals within the specified time window\(^2\). In addition, most of these countries have no locally developed guidelines to manage acute stroke patients, have fewer hospitals with dedicated stroke units and have less accessible brain imaging when adjusted for the sizes of their populations\(^4\). Also in clinical research, data on experience with rtPA in stroke care are limited from low-middle-income Asian countries compared to high income countries\(^5\).

Sri Lanka is a low-middle income country with a population of approximately 22 million, with a dual public and private health care system. The public healthcare system is free for all citizens (funded by taxpayer) but accessibility is a problem due to huge demand and overcrowding. By 2018, there were only 38 neurologists in the public health system, thrombolysis with rtPA was available in only 14 state hospitals and mechanical thrombectomy was available in only one hospital\(^6\). Thrombolysis is available in several private hospitals in a few main cities, and a private hospital in Colombo has been providing endovascular treatment since 2013. Thrombolysis with rtPA first started in Sri Lanka in 2008 but less people received this service as it was limited to neurology units in the National Hospital of Sri Lanka (NHSL-C), located in the commercial capital of Colombo. Also, most people could not get into the hospital in time due to lack of a paramedic and ambulance service and the distance from hospital, further complicated by traffic congestion. Since then, this service have expanded to more centers outside of Colombo, more trained neurologists joined the workforce and an island-wide paramedic and ambulance service had started since 2016\(^7\). However, there is no data on the success of rtPA therapy, its complications and functional improvement observed on follow up from Sri Lanka.

The aim of this study is to a) describe the outcomes (functional independence at 3 months post-thrombolysis) and complications (death and intracranial haemorrhage) of a cohort of patients that underwent thrombolytic therapy at the National Hospital of Sri Lanka over a 24-month period, and b) identify demographic, clinical, haematological, biochemical, imaging and treatment (low vs. high dose alteplase) related factors associated with a better outcome. We hypothesized that low dose alteplase will be as good as high dose alteplase in improving functional independence without any difference in complication rates. The decision to give high or low dose alteplase to a patient was determined by the pre-existing policy of the participating neurology units, and therefore, this is not an interventional study.

**Methods**

This is an observational prospective study carried out at the National Hospital of Sri Lanka in Colombo (NHSL-C) between 2019 January – 2020 December. The study was carried out according to STROBE guideline and extension. This hospital, located in the commercial capital and the most densely populated district of Sri Lanka, is the country’s largest and premier public health hospital. NHSL-C has three
neurology units offering thrombolytic therapy and all of them were involved in this study. All adult consenting patients (> 18 years of age) with acute ischmeic stroke who were eligible for thrombolytic therapy according to American Heart Association/American Stroke Association (AHA/ASA) guidelines (2019 update) were included in the study if they had no contraindications for thrombolysis.

Of the three Neurology units at NHSL-C, one unit used low dose alteplase (0.7 mg/kg of actual body weight, with a maximum dose of 90 mg) as per pre-existing unit policy at the time of the study. Other two units used alteplase 0.9 mg/kg of actual body weight (maximum dose – 90 mg). Hence the dose of alteplase received by a patient was determined by where the patient was admitted to and not as part of this study (the patient would have received the same treatment regardless of recruitment to this study). The demographic (e.g., age, gender), clinical (past medical history, details of current presentation including time elapsed since onset of symptoms to admission or reperfusion), biochemical, haematological and imaging (non-contrast CT of head prior to thrombolysis) data for were recorded for all patients, before and after thrombolysis. The definitions used for each data item are further explained in supplementary table 1. When a laboratory investigation was repeated, the earliest available results after the onset of symptoms was recorded. The National Institutes of Health Stroke Score (NIHSS) and modified Rankin Scale (mRS) for dependence was calculated on admission prior to thrombolysis. The Alberta Stroke Programme early CT score (ASPECTS) was calculated using the pre-thrombolysis non-contrast CT scan of the head. Following risk assessment tools to predict the risk of symptomatic intracranial haemorrhages (sICH) were also calculated: Hemorrhage after thrombolysis (HAT score), DRAGON score, SEDAN score, Stroke Prognostication using Age and NIH Stroke Scale (SPAN-100 index), The Cucchiara score, STARTING-SICH is a nomogram and Safe Implementation of Treatments in Stroke Monitoring Study score (SITS-MOST). After thrombolysis, all patients were monitored in a high dependency unit at least for 24 hours with strict blood pressure control. Anticoagulant plus antithrombotic agents as well as invasive procedures (intra-arterial catheters, nasogastric tube insertion) were avoided as much as possible within the first 24 hours post-thrombolysis. A follow-up non-contrast CT head was done 24 hours after the alteplase infusion and the NIHSS was repeated. If a patient developed sudden neurologic deterioration, a decline in level of consciousness, new onset headache, nausea and vomiting, or a sudden rise in blood pressure post-thrombolysis, non-contrast CT head was repeated urgently.

The primary outcomes of interest were NIHSS at 24 hours and 3 months post thrombolysis (dichotomized as favourable and non-favourable: 0–1 or > 1), mRS at 3 months (dichotomized as independent and dependent: 0–2 or 3–5) and Barthel Index (12) at 3 months (dichotomized as independent or dependent: <60 or > 60). Duration of hospital stay was also recorded. All-cause mortality and sICH at three months was recorded as complications. The occurrence of an sICH was recorded if either of the NINDS, ECASS 2 or SITS-MOST definitions for ICH were met.

Data were analysed with Statistical Package of Social Science (SPSS version 21, IBM, USA). Descriptive statistics were summarized as measures of central tendency (mean / median) and dispersion (standard
deviation or interquartile range) according to normality of distributions. Statistically significant differences were explored with independent T test or linear regression for continuous variables and with chi square test for categorical variables (unadjusted analysis). Any variables found to be significant in the unadjusted analysis were further explored with logistic regression (adjusted analysis). Cut-off for statistical significance was p < 0.05.

**Results**

Eighty-nine patients with ischaemic stroke, who were eligible for rTPA were recruited (mean age: 60 years ± 12.18, males = 61, 69%). The demographic characteristics, clinical characteristics on admission, within 24 hours and 3 months after thrombolysis are summarised in Tables 1–4. Time from onset of symptom onset to admission, time from admission to the CT scan and time from symptom onset to reperfusion were 115 ± 58.28, 34 ± 33.27 and 174 ± 56.50 respectively (in minutes) for the entire cohort. 37 patients (43%) were reperfused within 3 hours while the remainder were reperfused between 3 -4.5 hours since the onset of symptoms. The median duration of hospital stay was 10 ± 7.74 days. The average NIHSS and the mRS was 13 ± 5.21 and 04 ± 1 respectively on admission. The average NIHSS 24 hours post-thrombolysis was 12 ± 8.73 and at 3 months it was 7 ± 6.80. The modified Rankin scale and Barthel index at 3 months follow up was 1 ± 1.415 and 77 ± 22.55 respectively for the entire cohort. Ten (11%) patients died (7 patients due to intracranial haemorrhages, 2 due to pneumonia and 1 due to cardiac cause : 5 patients within first week due to sICH, 3 patients within one week to one month = 2 patients due to sICH and one due to cardiac cause, 2 patents within one month to 3 months due to pneumonia) and 19 (21%) developed symptomatic intracranial haemorrhages (sICH) by 3 months (18, 20% of these were within 7 days of thrombolysis, while 1, 1% was between 8–30 days post thrombolysis). In addition to sICH, 13 (14.9%) patients developed mild systemic bleeding following thrombolysis and none developed orolingual angioedema.
Table 1
Clinical and demographic characteristics of eligible patients

| Characteristic                                      | Mean ± SD | Category                        | Number (%) |
|-----------------------------------------------------|-----------|---------------------------------|------------|
| **Age (years)**                                     | 60 ± 12.17| Less than 45                    | 13 (14.6)  |
|                                                     |           | 45–55                           | 11 (12.4)  |
|                                                     |           | 55–65                           | 26 (29.2)  |
|                                                     |           | 65–75                           | 33 (37.1)  |
|                                                     |           | More than 75                    | 6 (6.7)    |
| **Gender**                                          | NA        | Male                            | 61 (68.5)  |
|                                                     |           | Female                          | 28 (31.5)  |
| **BMI**                                             | 24 ± 3.90 | Less than 18                    | 1 (1.12)   |
|                                                     |           | 18–23                           | 36 (40.4)  |
|                                                     |           | 23–30                           | 46 (51.6)  |
|                                                     |           | 30–35                           | 5 (5.6)    |
|                                                     |           | More than 35                    | 1 (1.12)   |
| **Cardiovascular comorbidities***                   | NA        | No                              | 15 (16.9)  |
|                                                     |           | Yes                             | 74 (83.1)  |
| **Smoking**                                         | NA        | Non- or former smoker           | 69 (77.5)  |
|                                                     |           | Current smoker                  | 20 (22.5)  |
| **Alcohol Use (within last year)**                  | NA        | Non-user or < 90g per week      | 77 (86.5)  |
|                                                     |           | > 90 g per week                 | 12 (13.5)  |
| **Aspirin use (regularly for last 2 weeks)**        | NA        | No                              | 49 (55.1)  |
|                                                     |           | Yes                             | 40 (44.9)  |
| **Clopidogrel use (regularly for last 2 weeks)**    | No        | 66 (74.2)                       | 66 (74.2)  |
|                                                     | Yes       | 23 (25.8)                       | 23 (25.8)  |
| **Anticoagulant use**                               | NA        | No                              | 84 (94.4)  |
|                                                     | Yes       | 5 (5.6)                         | 5 (5.6)    |

*Includes diabetes mellitus, hypertension, previous stroke, ischaemic heart disease, heart failure, atrial fibrillation.
| Characteristic   | Mean ± SD | Category | Number (%) |
|-----------------|-----------|----------|------------|
| Statins use     | NA        | No       | 37 (41.6)  |
|                 |           | Yes      | 52 (58.4)  |

*Includes diabetes mellitus, hypertension, previous stroke, ischaemic heart disease, heart failure, atrial fibrillation.
Table 2
Investigation and assessment scores on admission (pre-thrombolysis)

| Characteristic                               | Mean ± SD  | Category | Number (%) |
|----------------------------------------------|------------|----------|------------|
| Serum glucose on admission (mg / dL)         | 166 ± 69.66| 50–200   | 66 (74.2)  |
|                                              |            | 200–350  | 19 (21.3)  |
|                                              |            | >350     | 4 (4.5)    |
| Systolic blood pressure on admission (mm/Hg) | 162 ± 26.37| < 90     | 0 (0.0)    |
|                                              |            | 90–140   | 19 (21.3)  |
|                                              |            | 140–160  | 27 (30.3)  |
|                                              |            | 160–185  | 26 (29.2)  |
|                                              |            | >185     | 17 (19.1)  |
| Diastolic blood pressure on admission (mm/Hg) | 96 ± 14.49 | < 60     | 0 (0.0)    |
|                                              |            | 60–80    | 10 (11.4)  |
|                                              |            | 80–90    | 27 (30.7)  |
|                                              |            | >90      | 51 (58.0)  |
| On admission mRS                             | 04 ± 1     | 1        | 3 (3.4)    |
|                                              |            | 2        | 11 (12.5)  |
|                                              |            | 3        | 20 (22.7)  |
|                                              |            | 4        | 46 (52.3)  |
|                                              |            | More than Four | 8 (9.0) |
| On admission NIHSS                           | 13 ± 5.21  | 0–4      | 4 (4.7)    |
|                                              |            | 4–8      | 13 (15.1)  |
|                                              |            | 8–12     | 18 (20.9)  |
|                                              |            | 16–20    | 27 (31.4)  |
|                                              |            | 20–24    | 18 (20.9)  |
|                                              |            | 24–28    | 6 (7.0)    |

mRS = modified Rankin scale, NIHSS = National Institutes of Health Stroke Score, ASPECTS = Alberta Stroke Programme early CT score, INR = International normalized ratio, eGFR = estimated glomerular filtration rate. Haematocrit level = The normal haematocrit for men is 40 to 54%; for women it is 36 to 48%.
| Characteristic                                           | Mean ± SD | Category  | Number (%) |
|---------------------------------------------------------|-----------|-----------|------------|
| On admission CT scan ASPECTS                           | 9 ± 0.88  | >28       | 0 (0.0)    |
| On admission CT scan leukoariosis                      | NA        | Present   | 29 (32.6)  |
|                                                          |           | Not present | 60 (67.4)  |
| On admission CT scan hyperdense cerebral artery sign   | NA        | Present   | 12 (13.5)  |
|                                                          |           | Not present | 77 (86.5)  |
| Platelet count on admission                            | NA        | < 150,000 | 6 (6.7)    |
|                                                          |           | 150,000–300,000 | 65 (73.0) |
|                                                          |           | > 300,000 | 18 (20.2)  |
| On anticoagulant/s with INR ≤ 1.7                       | NA        | Yes       | 5 (5.6)    |
|                                                          |           | No        | 84 (94.4)  |
| eGFR on admission                                       | NA        | > 90      | 41 (41.6)  |
|                                                          |           | 60–90     | 39 (44.3)  |
|                                                          |           | 30–60     | 5 (5.7)    |
|                                                          |           | 15–30     | 3 (3.4)    |
|                                                          |           | < 15      | 0 (0.0)    |
| Haematocrit level on admission                          | NA        | Low       | 10 (11.2)  |
|                                                          |           | Normal    | 73 (82.0)  |
|                                                          |           | High      | 6 (6.7)    |
| Serum albumin level on admission (g/L)                  | NA        | > 35      | 45 (51.1)  |
|                                                          |           | < 35      | 44 (48.9)  |
| Stroke vascular territory                               | NA        | Anterior  | 82 (92.1)  |
|                                                          |           | Posterior | 7 (7.9)    |

mRS = modified Rankin scale, NIHSS = National Institutes of Health Stroke Score, ASPECTS = Alberta Stroke Programme early CT score, INR = International normalized ratio, eGFR = estimated glomerular filtration rate. Haematocrit level = The normal haematocrit for men is 40 to 54%; for women it is 36 to 48%.
Table 3
Post-thrombolysis functional assessment

| Characteristic                        | Mean ± SD | Category          | Number (%) |
|---------------------------------------|-----------|-------------------|------------|
| NIHSS at 24 hours                     | 12 ± 8.73 | NA                | NA         |
| Duration of hospital stay (days)      | 10 ± 7.74 | NA                | NA         |
| NIHSS at 3 months                     | 7 ± 6.80  | Favourable (0–1)  | 26 (33.3)  |
|                                       |           | Unfavourable (> 2)| 52 (66.7)  |
| mRS at 3 months                       | 1 ± 1.41  | Independent (0–2) | 51 (63.8)  |
|                                       |           | Dependent (3–5)   | 29 (36.2)  |
| mRS at 3 months                       | 1 ± 1.41  | Favourable (0–1)  | 37 (46.3)  |
|                                       |           | Unfavourable (2–5)| 43 (53.8)  |
| BI at 3 months                        | 77 ± 22.55| Independent (> 60)| 58 (72.5)  |
|                                       |           | Dependent (< 60)  | 22 (27.5)  |

mRS = modified Rankin scale, NIHSS = National Institutes of Health Stroke Score, BI = Barthel index

Table 4
Post thrombolysis complications

| Characteristic                        | Category                      | Number (%) |
|---------------------------------------|-------------------------------|------------|
| Death at 3 months                     | No                            | 79 (88.7)  |
|                                       | Yes                           | 10 (11.3)  |
| Cause of death at 3 months            | Death due to ICH              | 7 (70%)    |
|                                       | Death due to other causes     | 3 (30%)    |
| Symptomatic ICH                       | No                            | 70 (78.7)  |
|                                       | Yes                           | 19 (21.3)  |

ICH = Intracranial haemorrhage

In the unadjusted analysis as shown in Table 05, several variables had a statistically significant association with a Barthel index > 60 at 3 months (independent function), a favourable NIHSS score at 3 months and a modified Rankin scale of 0–2 (independent function) at 3 months (p < 0.05). However, in the adjusted analysis, a Barthel index greater than 60 at 3 months was only associated with the NIHSS on admission and the modified Rankin scale on admission. NIHSS at 3 months was only associated with NIHSS on admission and the presence / absence of leukoaraiosis on the pre-thrombosis CT-scan.
Modified Rankin scale at 3 months was only associated with the NIHSS on admission. There were no significant associations for the duration of hospital stay in the adjusted analysis.
Table 5
Associations for functional outcomes, duration of hospital stay and complications at 3 months post-thrombolysis.

| Variable                              | P value against each outcome |
|---------------------------------------|-----------------------------|
|                                       | Barthel index at 3 months   | Modified Rankin Scale at 3 months | NIHSS at 3 months | Duration of hospital stay | Intracranial Haemorrhage at 3 months | Death at 3 months |
| History                               |                             |                                 |                   |                          |                                      |                  |
| Age*                                  | NS                          | NS                              | NS                | NS                       | NS                                   | NS               |
| BMI*                                  | NS                          | NS                              | NS                | NS                       | < 0.001**                           | < 0.001          |
| Time to admission*                    | 0.019                       | 0.012                           | 0.016             | NS                       | NS                                   | NS               |
| Time to reperfusion*                  | NS                          | NS                              | 0.014             | NS                       | NS                                   | NS               |
| Cardiovascular comorbidities#         | NS                          | NS                              | NS                | NS                       | NS                                   | NS               |
| Smoking                               | NS                          | NS                              | NS                | NS                       | NS                                   | NS               |
| On aspirin                            | NS                          | NS                              | NS                | NS                       | NS                                   | NS               |
| On clopidogrel                        | NS                          | NS                              | NS                | NS                       | NS                                   | NS               |
| On statins                            | NS                          | NS                              | NS                | NS                       | NS                                   | NS               |
| Examination and investigations        |                             |                                 |                   |                          |                                      |                  |
| Vascular territory of stroke         | NS                          | NS                              | NS                | NS                       | NS                                   | NS               |
| On admission NIHSS*                   | < 0.001**                   | < 0.001**                       | < 0.001**         | 0.044                    | NS                                   | NS               |
| On admission mRS*                     | < 0.001**                   | 0.001                           | 0.014             | NS                       | NS                                   | NS               |

*continuous variables – evaluated with independent T test, NS – non-significant, ** associations that remained significant in the adjusted analysis, BMI – body mass index, SBP – Systolic blood pressure, DBP – Diastolic blood pressure, CT – Computed tomography, rTPA – recombinant tissue plasminogen inhibitor, NIHSS – National Institutes of Health Stroke Score, mRS – modified Rankin Scale, eGFR- estimated glomerular filtration rate, MCA – middle cerebral artery, INR – international normalised ratio, #Cardiovascular comorbidities – includes diabetes mellitus, hypertension, previous stroke, ischaemic heart disease, heart failure, atrial fibrillation, ASPECTS - Alberta Stroke Programme early CT score, NS – Not significant
| Variable                  | P value against each outcome |
|--------------------------|------------------------------|
| CT- ASPECT score*        | NS NS NS NS NS 0.001 NS     |
| CT – MCA hyperdense sign | 0.011 NS 0.025 NS 0.003** 0.040 |
| CT - Leukoaraiosis       | NS 0.002 < 0.001** NS NS NS |
| Glucose*                 | NS NS NS NS NS NS NS       |
| SBP *                    | NS NS NS NS NS NS NS       |
| DBP *                    | NS NS 0.021 0.017 NS NS NS |
| Platelet count           | NS NS NS NS NS NS NS       |
| INR < 1.7                | NS NS NS NS NS NS NS       |
| eGFR                     | NS NS NS NS NS NS NS       |
| Serum albumin            | 0.004 < 0.001 0.006 0.005 NS |
| Haematocrit              | NS NS NS 0.019 NS NS NS NS |
| Treatment                |                            |
| Low vs. high dose rTPA   | NS 0.031** < 0.001** NS NS NS |

*continuous variables – evaluated with independent T test, All other categorical variables were evaluated with chi square test, NS – non-significant, ** associations that remained significant in the adjusted analysis, BMI – body mass index, SBP – Systolic blood pressure, DBP – Diastolic blood pressure, CT – Computed tomography, rTPA – recombinant tissue plasminogen inhibitor, NIHSS – National Institutes of Health Stroke Score, mRS – modified Rankin Scale, eGFR- estimated glomerular filtration rate, MCA – middle cerebral artery, INR – international normalised ratio. #Cardiovascular comorbidities – includes diabetes mellitus, hypertension, previous stroke, ischaemic heart disease, heart failure, atrial fibrillation, ASPECTS - Alberta Stroke Programme early CT score, NS – Not significant

As for complications, there were no significant associations for death in the adjusted analysis while lower BMI and a hyperdense middle cerebral artery sign on pre-thrombolysis CT were independently associated with intracranial haemorrhage at 3 months (p < 0.05). Of the multiple scoring systems that were evaluated for their predictive capacity to identify an sICH, only the SEDAN score was significantly high in people with intracranial haemorrhages (compared to those without) in this cohort (mean score of 1.61 vs. 2.47, p = 0.011). However, this result was influenced by a single outlier with ICH who had a very high SEDAN score.
Low dose rTPA was statistically significantly associated with a lower NIHSS at 24 hours and 3 months post thrombosis (p < 0.001) as well as a lower modified Rankin score at 3 months (p = 0.031). However, compared to high dose rTPA, it did not result in less deaths, less intracranial haemorrhages (or any other episodes of major or minor bleeds), a shorter hospital stay or an improved Barthel's index at 3 months.

**Discussion**

This prospective observational study of patients with acute ischaemic stroke who were eligible for thrombolysis in a resource limited setting in Sri Lanka showed that nearly 10% died and that nearly 20% developed intracranial haemorrhages within 3 months of thrombolysis. Both on admission NIHSS and mRS were associated with functional dependence at 3 month follow up. Low dose rTPA administration was associated with a better NIHSS and mRS score at 3 months but it did not influence complications such as death or ICH, or shorten the hospital stay.

The age distribution and NIHSS on admission in the patient cohort of this study were comparable to those observed in other prospective studies on thrombolysis for stroke as detailed in supplementary table 2. However, the time from symptom onset to thrombolysis was comparatively higher (Supplementary Fig. 1). This may be due to delays in getting to hospital due to not using paramedic services, traffic congestion, living further away from the hospital or a combination of this factors. This study did not explore the reasons for delay in hospital admission, and also did not capture the people who came after the 4.5-hour time window to compare with, but this highlights the need for more qualitative and quantitative data to explore the reasons for delays in getting to hospital. Earlier thrombolytic treatment reduces in-hospital mortality and symptomatic intracranial haemorrhages while increasing functional independence following treatment \(^2^3\), and it’s important that patients in resource limited settings can tap in to these benefits by timely access to healthcare.

A favourable outcome in terms of functional independence at 3 months post-thrombolysis in our patient cohort was associated with the on-admission mRS and NIHSS while the 3-month NIHSS was also associated with the presence of leukoaraiosis on the pre-thrombolysis CT scan. These observations agree with that of several previous studies \(^2^4\)–\(^2^9\). However, other studies have also found different associations for functional dependence/independence at 3 months such as major neurological improvement at 24 hours \(^2^4\), pre-thrombolysis random blood glucose level \(^2^4,2^5\), blood pressure on admission \(^2^9\), cardiac ejection fraction \(^2^9\), time to thrombolysis \(^2^5\), patient age \(^2^4,2^6\), ASPECT Score on admission \(^2^6\), hyperdense MCA sign \(^3^0,3^1\), having an anterior circulation stroke \(^2^9\) and past history of stroke / CHADS score \(^2^9\). Some of these associations may be attributable to the variation in samples size and differences in baseline demographic and clinical characteristics (e.g., past history of co-morbidities) of individual cohorts. However, the time to admission (and thrombolysis) was associated with several outcome indicators in the unadjusted analysis in our cohort also. This association was insignificant in the adjusted analysis probably because as discussed above, due to the overall delay in getting admitted or treated compared to other studies. This should not be erroneously interpreted as time to admission (or thrombolysis) not
having an impact on post-thrombolysis functional outcome. The overall variation in predictors across studies from different countries suggest that aiming to develop a universal system to predict post-thrombolysis functional improvements may be less relevant and instead clinicians should focus on establishing locally adapted, evidence based approaches to improve outcomes of their patients.

As for complications, the percentage suffering from post-thrombolysis sICHs were relatively higher in our cohort (supplementary Fig. 3) but the mortality was similar that observed in much larger international cohorts\(^\text{18, 32}\) (supplementary Fig. 4). This may be because we defined sICHs according to three different definitions (ECASS 2, SITS-MOST and NINDS trial definitions) and meeting any one of these definitions were considered as a positive case. Of these, SITS-MOST definition which only considers large parenchymal haemorrhage type 2 as sICH has had a good association with poor outcome and mortality in previous studies\(^\text{33}\), but we could not do a head-to-head comparison of these definitions due to low number of events observed. Previous studies have found several associations for post-thrombolysis sICH including age, current or historical antiplatelet / anticoagulant use\(^\text{29, 34, 35}\), serum triglyceride and fibrinogen level\(^\text{29, 36}\), statin use\(^\text{37, 38}\), hypertension or hyperglycaemia on admission\(^\text{29}\), NIHSS on admission\(^\text{29}\), anterior circulation stroke\(^\text{29}\), leukoaraiosis on CT\(^\text{28}\), ASPECT score and comorbidities such as atrial fibrillation\(^\text{29}\), renal impairment\(^\text{39}\), heart failure\(^\text{29}\) or a CHADS2 score > 2\(^\text{29}\).

Some of these associations have been confirmed in a meta-analysis\(^\text{40}\). Interestingly, in this study we found a strong and independent association of lower BMI and sICH. This has not been observed before and currently we are unable to explain this observation, except that this observation should be confirmed in a larger cohort. Even though we found that hyperdense middle cerebral artery sign is significantly associated sICH (relative risk of 3.74) several studies and meta-analysis have concluded that the association is not statistically significant\(^\text{30, 41, 42}\).

Whether low dose alteplase is comparable to standard dose in efficacy and safety in Asian patients remains controversial\(^\text{43}\). The use of low doses of rtPA was proposed in Asian countries due racial differences related to the functionality of fibrinogen and coagulation factors which potentially increased the risk of intracerebral haemorrhage\(^\text{43}\). Our observation was that low dose alteplase may be associated with better functional outcomes, but did not necessarily had a better safety profile with regard to deaths and sICH, as expected. Supplementary table 3 illustrates studies comparing low dose vs standard dose which mostly shows no difference for efficacy and safety outcomes. A previous meta-analysis had concluded that there is no association between alteplase dose and favourable outcome and mortality, but that the low dose may be associated with a lower incidence of sICH\(^\text{44}\). From a cost perspective, alteplase used in Sri Lanka is made in India and a 20 mg vial costs USD 355 while a 50 mg vial costs USD 692. If the low dose is as effective as the standard dose this could be considerably cost saving in a resource limited setting.

This study has several limitations; firstly, we recruited from a single centre which affects the generalisability of studies to the whole of Sri Lanka. Yet NHSL-c is one of the few centres where thrombolysis is available in the country and all other centres where thrombolysis is available also do
have similar facilities and are supervised consultant neurologists. Secondly, Sri Lankan data may not be
generalisable to other countries but as shown above in the discussion, the heterogeneity of associations
for outcomes and complications highlight the need for locally relevant datasets than extrapolating
findings from other countries. Thirdly, the sample size is small despite recruiting all eligible patients from
all neurology units in the largest hospital in Sri Lanka located in the most populous district of the country
over a 24-month period. This highlights a greater problem in gaining access to services within the critical
time window for thrombolysis which may be influenced by patient-dependent (e.g., unawareness) and -
independent factors (e.g., lack of infrastructure for faster transport of critically ill patients). Exploring
reasons for this was beyond the scope of this study. Finally, comparison of low dose vs. standard dose alteplase should ideally be done as a randomised blinded controlled trial for conclusive results.

**Conclusion**

This single centre prospective observational study of patients undergoing thrombolysis, the first of its
kind from Sri Lanka, a low-middle income country, shows that better NIHSS and mRS scores on
admission to be independently associated with functional independence at 3 months post-thrombolysis.
Notably the time to thrombolysis in this cohort was higher compared to similar studies in other countries
which is a concern as it may indicate problems with accessing services within the critical time window.
Observations show that low dose rTPA may lead to better functional outcomes at 3 months with a similar
safety profile compared to standard dose in Sri Lankan patients, but this needs to be confirmed in a
randomised controlled trial.

**Abbreviations**

DALYs = Disability adjusted life years lost

rtPA. = recombinant tissue plasminogen activator

NHSL-C = National Hospital of Sri Lanka in Colombo

AHA/ASA = American Heart Association/American Stroke Association

NIHSS = National Institutes of Health Stroke Score

mRS = modified Rankin Scale

ASPECTS = Alberta Stroke Programme early CT score

sICH = Symptomatic intracranial heamorrhages

HAT score = Hemorrhage after thrombolysis

SPAN-100 index = Stroke Prognostication using Age and NIH Stroke Scale
Declarations

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Author's contribution =

1) Conception and design of the study = HMMTBH. CR. AMBDA. SBA. SS. BS. AF
2) Acquisition and analysis of data = HMMTBH. CR. AMBDA. SBA. SS. BS. AF
3) Drafting a significant portion of the manuscript or figures = HMMTBH. CR. AMBDA. SBA. SS. BS. AF
4) Correction of the manuscript = HMMTBH. CR. AMBDA. SBA. SS. BS. AF

All authors have read and approved the manuscript.

Conflicts of interest =

Nothing to report

Ethical approval and consent to participate =

Ethical clearance for this study was obtained from the "Ethics review committee of National hospital of Colombo" (Reference number = AAJ/ETH/COM/2018/DEC).

The study was carried out according to relevant guidelines and regulations.

The study was carried out according to STROBE guideline and extension.

Written informed consent was obtained from all patients or next of kin for those unable to give consent.

Availability of data and material =

The data set for this publication is available upon request from the authors.
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