# DETERMINING THE PROPORTION OF ISCHEMIC STROKE PATIENTS PRESENTING TO RMI WHO ARE CANDIDATES FOR THROMBOLYSIS

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## ABSTRACT

**Introduction:** Ischemic Stroke associated mortality and morbidity severely and detrimentally effects a person's life and hence it is proposed as the most feared vascular event (1). Recombinant tissue plasminogen activator (rt-PA) is a standard therapy approved for acute ischemic stroke (2). Medical history of the patient suffering a stroke is usually a complicated clinical picture which makes the decision to utilize rt-PA even more complex (9). It is this complexity that has created a reticence in the local medical community towards prompt acute stroke care.

**Materials & Methods:** The study used a quantitative cross-sectional design. Standard thrombolytic checklist was used to structure a questionnaire supplemented by the standard NIHSS scoring to complete the expanded criteria on the checklist. Informed consent was obtained, and the respondents were assured of the confidentiality of the information they provided.

SAMPLE All patients admitted in Ward H in RMI with Acute Ischemic Stroke were tested against the inclusion and exclusion criteria and 92 were selected for the study.

**Results:** The time limit for thrombolysis set via international guidelines is less than 4.5 hours and this disqualified 70 of the 90 patients in the study. Close next is a persistent high blood pressure which accounted for 18 patients. Low serum glucose (11%), evidence of hemorrhage on a CT scan (14%) and recent stroke or head trauma (8%) also showed significant frequencies. The numbers for bleeding risk, including the use of anticoagulants were exceptionally low. Patients with rapidly improving stroke symptoms were the biggest proportions of relative contraindications at 21% of the total. Patients with only minor and isolated insults accounted for 16% of the patients with relative contraindications. Seizure at the onset of stroke symptoms was found in 18 of the 90 patients. The additional criteria is for patients who had arrived in the hospital between 3 and 4.5 hours. 22% of the patients had an NIHSS score of >25. Only 3 patients qualified based on the additional criteria.

**Limitations:** The main weakness is the small sample size as well as relying on the patient reported timing of the onset of symptoms. Furthermore, if patients were not literate, for the NIHSS score they were shown pictorial representations of scenes to describe and that was used to gauge the impact of the stroke on their cognitive abilities.

**Conclusions:** Given the devastating and permanent disability 9% of the acute ischemic stroke patient received at RMI represent a major proportion. It presents a unique opportunity to the hospital to establish a stroke unit or another organizational solution with treatment with intravenous rt-PA in the emergency department (ED), followed by transportation to a semi-intensive stroke care unit.

**Keywords:** Thrombolytics, thrombolysis, thromboembolism, checklist, rt-PA, recombinant tissue plasminogen activator, ischemic, stroke, Peshawar, Rehman Medical Institute, RMI

## INTRODUCTION

Stroke, and its most common variant Ischemic Stroke has a devastating multi-faceted effect on an individual's life. Not only with its associated mortality but the morbidity severely and detrimentally effects a person's life and hence it is proposed as the most feared vascular event[1]. Recombinant tissue plasminogen activator (rt-PA) is a standard therapy approved for acute ischemic stroke[2].

Initially there were studies done that established the effectiveness of rt-PA for acute ischemic stroke if given with 3 hours of onset of symptoms[3-5]. As rt-PA is a potent thrombolytic it comes with its own linked risks so a criterion was established to limit its use in only suitable patients. Subsequent studies expanded the role of rt-PA to upto 4.5 hours after symptoms started but it was associated with more adverse events[6-8]. This led to even more restrictions on top of the stringent criteria for rt-PA administration.

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Moreover, medical history of the patient suffering a stroke is usually a complicated clinical picture which makes the decision to utilize rt-PA even more complex[9]. It is this complexity that has created a reticence in the local medical community towards prompt acute stroke care.

No large scale epidemiological studies are available to determine the true incidence of stroke in Pakistan. Estimated annual incidence is 250/100,000, translating to 350,000 new cases every year[10]. At a major university hospital with a busy Neurology service in Karachi, 519 patients with stroke were admitted over a 22 month period[11]. In a retrospective analysis of patients admitted with stroke in two major hospitals over an 8 years period, 796/12,454 (6.4%) of consecutive cases admitted in medical units had stroke[12].

Rehman Medical Institute is a tertiary care facility in Peshawar and is held as the premier private sector hospital of the region that caters to the needs of not only patients from the city of Peshawar but also to patients from the whole province and Afghanistan as well.

It is imperative to establish whether patients suffering an acute ischemic stroke coming to RMI are candidates for prompt thrombolytic therapy and to recommend measures to provide international standard care to these patients.

### *Rationale*

To determine the proportion of stroke patients who have suffered an acute ischemic stroke and are candidates for Thrombolytic therapy as per international guidelines. This study would serve to form the basis for the establishment of stroke specific care in the hospital

## METHODOLOGY

The project was set in Rehman Medical Institute, Peshawar, KPK Pakistan from August 15th to December 10th 2017. The population included patients admitted in the medical ward in RMI with acute ischemic stroke. The study used a quantitative cross-sectional design. Standard thrombolytic checklist was used to structure a questionnaire supplemented by the standard NIHSS scoring to complete the expanded criteria on the checklist. Informed consent was obtained, and the respondents were assured of the confidentiality of the information they provided.

### Inclusion Criteria

1. Patients who have a radiologically established ischemic infarct whether on CT or MRI
2. Diagnosis of new Acute Ischemic Stroke by a consultant Neurologist

### Exclusion Criteria

1. Patients with Age ≤ 18 years
2. Patients with a recognized diagnosis of a disease that would explain the symptoms without thromboembolism as a cause for them
3. Non-availability of a first degree relative in case the patient cannot answer the questions
4. Patients with a Hemorrhagic conversion of an Acute Ischemic Infarct as established by a Consultant Neurologist
5. Thrombolytic therapy initiated at another facility for the same episode

### Sample Size

Calculated using the WHO sample size calculation formula: $n = z^2 * p * (1-p) / d^2$

"n" is the preferred sample size (to be calculated)

"z" is the level of confidence measure which is set at 1.96

"p" is the prevalence found in a previously conducted study (13) which is 0.048

"d" is the margin of error which is set at 0.05

$$n = \frac{3.8416 * (0.048 * (1 - 0.05))}{0.05 * 0.05} = 70.21830144$$

### Data Analysis

Latest version of SPSS was used to establish the relative proportion of Acute Ischemic Stroke patients with frequencies of those who qualify for the Thrombolytic therapy. Those who do not qualify will be stratified based on whether they fail the Absolute or the Relative Contraindications in the list and to establish the same for the Expanded Criteria. Furthermore, positive and negative frequencies of each individual criterion on the standard Thrombolytic Checklist are established.

### Ethical Issues

1. Informed verbal consent was obtained
2. Reassurance of the respondents for confidentiality of all received information

**KEYWORDS**: Thrombolytics, thrombolysis, thromboembolism, checklist, rt-PA, recombinant tissue plasminogen activator, ischemic, stroke, Peshawar, Rehman Medical Institute, RMI

## RESULTS

After reviewing the patient records available in the hospital, we had anticipated that we would be able to accrue at least 100 patients in the time frame of the study. As the frequency of the incidence of strokes is random, coupled with other outside factors like the local public holidays we were able to collect data from 92 patients after a stringent application of the inclusion and exclusion criterions.

| Absolute Contraindications | | Count |
|---|---|---|
| Stroke or head trauma in the previous 3 months | yes | 7 |
| | no | 83 |
| Previous intracranial hemorrhage | yes | 3 |
| | no | 87 |
| Intracranial neoplasm, arteriovenous malformation, or aneurysm | yes | 1 |
| | no | 89 |
| Recent intracranial or intraspinal surgery | yes | 1 |
| | no | 89 |
| Arterial puncture at a non-compressible site in the previous 7 days | yes | 0 |
| | no | 90 |
| Symptoms suggestive of subarachnoid hemorrhage | yes | 2 |
| | no | 88 |
| Persistent blood pressure elevation (systolic >185 mmHg or diastolic >110 mmHg) | yes | 18 |
| | no | 72 |
| Serum glucose <50 mg/dL (<2.8 mmol/L) | yes | 10 |
| | no | 80 |
| Active internal bleeding | yes | 1 |
| | no | 89 |
| Acute bleeding diathesis, including but not limited to conditions defined in 'Hematologic' | yes | 0 |
| | no | 90 |
| Platelet count <100,000/mm3 | yes | 1 |
| | no | 89 |
| Current anticoagulant use with an INR >1.7 or PT >15 seconds | yes | 0 |
| | no | 90 |
| Heparin use within 48 hours and an abnormally elevated aPTT | yes | 0 |
| | no | 90 |
| Using direct thrombin or direct factor Xa inhibitor with evidence of anticoagulant effect by lab tests | yes | 0 |
| | no | 90 |
| Evidence of hemorrhage | yes | 13 |
| | no | 77 |
| Extensive regions of obvious hypodensity consistent with irreversible injury | yes | 4 |
| | no | 86 |

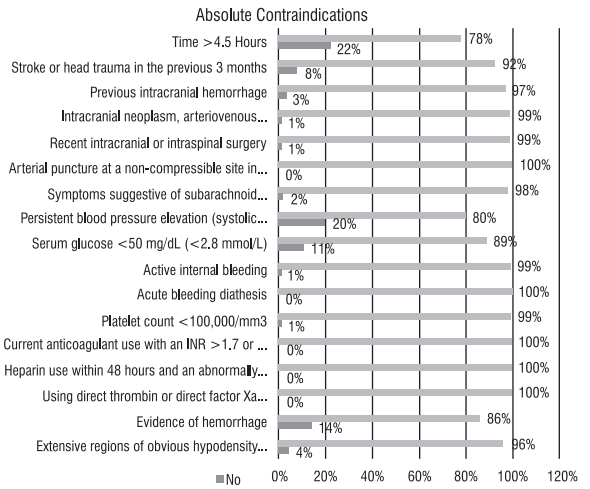
We gathered our data from the acute ischemic stroke patients who had arrived at RMI from the August to mid of December,2017. Of the 92 questionnaires only 2 were excluded for being incomplete and 90 were used for data analysis and results.

We analyzed the data from the questionnaires and divided our results into patients who qualified for thrombolysis, ie they had no absolute contraindication for it. And another group who had some relative contraindication for it. Both of these were then divided into whether they qualified the additional criteria set for if the patient had arrived between 3-4.5 hours after symptoms onset. The data was put into SPSS version 23 and analyzed.

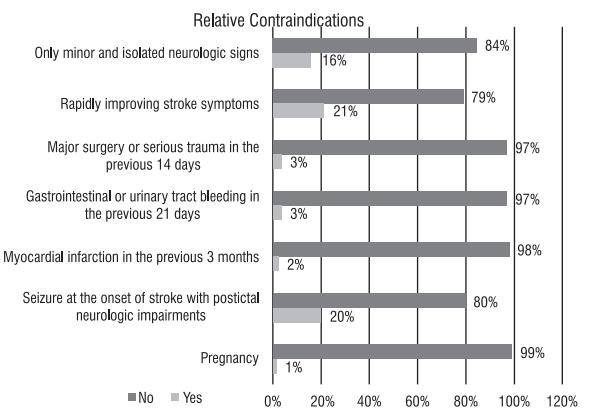
Patients disqualified from thrombolysis based on the absolute criteria show great variation. The time limit for thrombolysis set via international guidelines is less than 4.5 hours and this disqualified 70 of the 90 patients in the study.

Close next is a persistent high blood pressure which accounted for 18 patients.

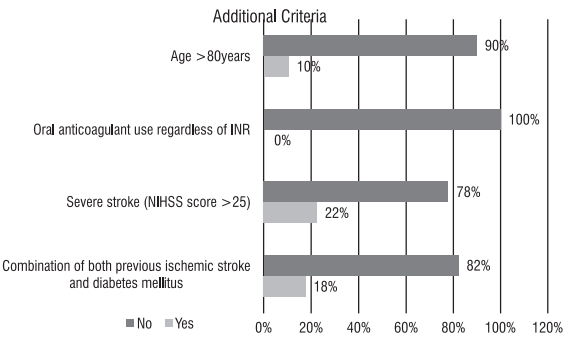
Low serum glucose (11%), evidence of hemorrhage on a CT scan (14%) and recent stroke or head




| Relative Contraindications | | Count |
|---|---|---|
| Only minor and isolated neurologic signs | yes | 14 |
| | no | 76 |
| Rapidly improving stroke symptoms | yes | 19 |
| | no | 71 |
| Major surgery or serious trauma in the previous 14 days | yes | 3 |
| | no | 87 |
| Gastrointestinal or urinary tract bleeding in the previous 21 days | yes | 3 |
| | no | 87 |
| Myocardial infarction in the previous 3 months | yes | 2 |
| | no | 88 |
| Seizure at the onset of stroke with postictal neurologic impairments | yes | 18 |
| | no | 72 |
| Pregnancy | yes | 1 |
| | no | 89 |




| Additional Criteria | | Count |
|---|---|---|
| Age >80 years | yes | 9 |
| | no | 81 |
| Oral anticoagulant use regardless of INR | yes | 0 |
| | no | 90 |
| Severe stroke (NIHSS score >25) | yes | 20 |
| | no | 70 |
| Combination of both previous ischemic stroke and diabetes mellitus | yes | 16 |
| | no | 74 |




trauma (8%) also showed significant frequencies.

The numbers for bleeding risk, including the use of anticoagulants were exceptionally low. None of the patients studied were on anticoagulants with the prescribed criteria.

Patients with rapidly improving stroke symptoms are not ideal candidates for thrombolysis and they accounted for the biggest proportions of relative contraindications at 21% of the total. The same applies to patients with only minor and isolated insults, they accounted for 16% of the patients with relative contraindications.

Seizure at the onset of stroke symptoms was found in 18 of the 90 patients.

The additional criteria is for patients who had arrived in the hospital between 3 and 4.5 hours. They need to qualify an additional set of limits before thrombolysis.

None of the 90 patients we studied were on oral anticoagulants.

22% of the patients had an NIHSS score of >25. These patients could only be thrombolysed if they had arrived in <3 hours. Another contraindication for this population of patients is the presence of both diabetes and previous ischemic stroke. Proportion of patients in this condition were found to be 18%.

Overall only 3 patients qualified through this criteria of which 1 patient also had a relative contraindication while the other 2 had no contraindications at all.

## DISCUSSION

The study focused on the patients suffering an acute ischemic stroke event that presented to the Rehman Medical Institute. It was the primary goal to establish the proportion of cases that could have been thrombolysed according to the international guidelines.

In the 120 days of the study we had an average of 0.8 patient income per day who qualified for our study after the inclusion exclusion criteria were applied. This correlates almost exactly with a study at a major university hospital with a busy Neurology service in Karachi, 519 patients with stroke were admitted over a 22 month period[11].

Our primary finding is that of the 90 patients, 8 patients had no absolute contraindication to thrombolysis. Of these 8 patients, 6 arrived in the ER in less than 3 hours of symptoms onset and a further 2 arrived in ER in less than 4.5 hours. The latter group had to qualify the additional criteria to qualify for thrombolysis.

Apart from these an additional 6 patients had relative but no absolute contraindication to thrombolysis. Of these six, 2 patients qualified through the additional criteria.

That means almost 9% of the patients received with ischemic stroke could receive thrombolysis and an additional 6.6% can receive the same but with some caution.

The greatest limiter according to our study was the time limit for thrombolysis. 70 out of the 90 patients we studied had arrived in the hospital later than 4.5 hours. Of these 73 had arrived in less than 3 hours and a further 3 arrived between 3 and 4.5 hours. This means 78% with acute ischemic stroke reach the hospital later than the proscribed limit for thrombolysis. This suggests an absence of awareness amongst the local population regarding the signs and symptoms of stroke as well as the urgency of the diagnosis.

Hypertension presents a risk factor with considerable burden of cardiovascular disease as published previously in a study in Pakistan[13]. Our data shows 20% of the patients with a persistently high blood pressure which presents a relative contraindication to the use of thrombolytics which can present an additional risk for bleeding risk.

Due to the small study population we were not able to gauge the impact of anticoagulant medications. Indeed, of the study group none were on warfarin, had used heparin recently or any of the new medications like direct factor 10 inhibitors. Only one patient presented with a low platelet count. We expect these factors to play a role in a study with a larger sample.

Of the factors studied in the relative contraindication group signs and symptoms of a minor stroke or rapidly improving stroke were of great value with 16% and 21% respectively. Conversely adverse signs like seizure at stroke symptom onset was seen in 18 patients which constitutes 20% of the total.

The strengths of this study include standardization using an internationally accepted checklist, on site verification of diagnosis by a consultant neurologist as well as radiographic examination by the same. Localization of the NIHSS questionnaire was done by translating the english words and phrases to their equivalent in the national Urdu language. Our sample is from a multiethnic population and our stroke burden correlates well with a similar study done in Pakistan[11].

Our main weakness is the small sample size as well as relying on the patient reported timing of the onset of symptoms. Furthermore, if patients were not literate, for the NIHSS score they were shown pictorial representations of scenes to describe and that was used to gauge the impact of the stroke on their cognitive abilities.

This study represents a framework which can be expanded easily to multiple centers to give a region centric representation of the opportunities for the establishment of ischemic stroke treatment solutions.

## CONCLUSIONS

Given the devastating and permanent disability 9% of the acute ischemic stroke patient received at RMI represent a significant proportion. It presents a unique opportunity to the hospital to establish a stroke unit or another organizational solution with treatment with intravenous rt-PA in the emergency department (ED), followed by transportation to a semi-intensive stroke care unit. This offers a safe and effective solution to provide intravenous thrombolysis to acute stroke as per the study done by A Semplicini et al (14). Another clinical study has already shown that patients with ischemic stroke can safely be submitted to thrombolytic therapy in the setting of a hospital with experience in the treatment of acute stroke, even without a neuro-intensive care unit (15). Concrete steps need to be taken in this regard considering the burden of acute ischemic stroke.

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