

## **Assessing NIHSS and MRS Scores in Patients with an Unknown Onset Time of Stroke Symptoms: A Historical Cohort Study**

**Davood Shalilahmadi<sup>1</sup>, Shahram Rafie<sup>2</sup>, Gholamreza Shamsaei<sup>3</sup>, Halleh Mirbehresi<sup>4\*</sup>**

<sup>1</sup>Assistant Professor of Neurology, Faculty of Neurology department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran  
Email: shalilahmadi@gmail.com

<sup>2</sup>Department of Neurology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran  
Email: rafie-sh@aiums.ac.ir

<sup>3</sup>Department of Neurology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran  
Email: shamsaei-gh@ajums.ac.ir

<sup>4</sup>Department of Neurology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran  
Email: hbehresi@yahoo.com

### **Abstract:**

**Aim of the research:** Acute and chronic stroke complications in patients burden the patients with expensive treatment costs. Using stroke protocol including DWI / ADC / FLAIR / GRE MRI sequences, stroke patients with an unknown onset time of symptoms can be effectively identified for intravenous thrombolytics.

**Methods:** This historical cohort study investigated stroke patients with unknown onset of symptoms undergoing MRI studies in Golestan Hospital, Ahvaz, Iran. The first study group was composed of patients with a positive DWI sequence and negative FLAIR sequences and received alteplase treatment. The second group included patients with a positive FLAIR and DWI and did not receive any thrombolytic treatment. Comparisons were made between these two groups using NIHSS score at baseline and 24 hours post-treatment and using MRS score at 3 months post-discharge. Bleeding complications were also assessed across the groups.

**Results:** The patients of two groups did not significantly differ in demographic features, which provided unbiased and more reliable findings. The majority of the risk factor variables had an even distribution in the patients of two groups. Smoking was slightly higher in the group receiving thrombolytic therapy than in the non-thrombolytic group, which was also significant. The mean NIHSS score in the group receiving thrombolytic therapy at the time of discharge was lower than their baseline mean score at admission time. Furthermore, the results in relation to the MRS index showed that at the time of discharge and 3 months after discharge, the average of this index in the group receiving thrombolytic therapy was significantly lower as compared to the non-receiving thrombolytic therapy group.

**Conclusion:** According to the results of the present study, no significant difference was present between the occurrence of death between receiving and non-receiving the thrombolytic therapy groups. However, lower values of NIHSS and MRS indicators in the survivors showed the effectiveness of this method. Therefore, it is recommended that this method has to be followed as a comprehensive disease management protocol in the early hours of the disease in patients with unknown onset of the symptoms and considered as a serious intervention that has to be done without any delay.

**Keywords:** NIHSS, MRS, wake up stroke, FLAIR

### **1. Introduction**

Stroke is the second leading cause of death worldwide, and 2019 statistics show 703 million people aged 65 years or over worldwide suffered from stroke(1). The incidence of stroke is increasing since the world population is aging (2, 3). Aging is a multifactorial process that affects the functioning of all human body systems and is associated with profound changes in the quality of life. Mentioned dramatic changes in the population's age distribution have essential effects on human health, both at the individual and national level(4).

Brain aging is associated with functional changes including genomic and epigenetic changes, disruption in protein folding mechanisms, irregular mitochondrial function and energy metabolism, disorders of ion homeostasis affecting cell signaling cascades, inflammation, and neurogenesis dysfunction, which is associated with the accumulation of molecular and cellular damage and cell death (5-8). Brain aging is one of the main effects of nerve damage and neurodegenerative diseases. According to research conducted between 1990 and 2010, the number of strokes occurring each year decreased by approximately 10% in developed countries and increased by 10% in developing

countries (9). In ischemic stroke, blood flow to a part of the brain is reduced, leading to disruption of brain tissue in a specific area. Impaired cerebral blood flow deprives neurons, glial and vascular cells of substances such as oxygen and glucose unless blood flow is restored immediately. Oxygen deprivation leads to ischemic death of brain tissue (infarction) (10).

Stroke is diagnosed in several ways: neurological examination (by NIHSS, The National Institutes of Health Stroke Scale, or NIH Stroke Scale), computed tomography (CT) scan or magnetic resonance imaging (MRI), Doppler ultrasound, and arteriography. Imaging techniques help to determine the subtypes and causes of stroke. Blood tests are not usually available to diagnose a stroke (11). Despite decades of intensive research into the underlying neurological causes in the hope of discovering new therapies and neuroprotective inhibitors, pharmacological or mechanical endovascular thrombotic interventions are the only approved treatment for stroke (12, 13). In addition, there are limited clinical applications of neuroprotection approaches, such as hypothermia therapy and transcranial magnetic stimulation (14). Currently, the only FDA-approved treatment for ischemic stroke is recombinant tissue plasminogen activating factor (rtPA), which dissolves the clot and restores blood flow (30).

Due to the short time window (less than 4.5 hours) and conditions such as increased intracerebral hemorrhage and neurotoxicity, a few percentages of patients are eligible for rtPA treatment (15). Thrombectomy is also an interventional method for removing blood clots, and recent recommendations of the American Heart Association confirm it within 24 hours (16).

Many studies are underway to extend the timing and indications for thrombolytic uptake. However, there are still concerns about treatment's side effects, such as cerebral edema and bleeding (17-19). MRI imaging is helpful for early diagnosis and treatment strategy for acute ischemic stroke. In less than 3 minutes, acute ischemic lesions can be seen as an increase in signal in the DWI sequence and a decrease in signal in the ADC sequence with a sensitivity of 88-100% and specificity of 95-100%. However, small lesions in the brainstem with mild symptoms such as ataxia or internuclear palsy may not be seen on primary MRI (20).

In 2019, 555 patients with symptoms of acute ischemic stroke were referred to Golestan Hospital, Ahwaz, Iran. 82 of them (14.7%) were treated with venous thrombolytic (Alteplase) according to the specific onset of symptoms and early referral. Unfortunately, 126 patients (22.7%) did not qualify as candidates for medication due to their unknown onset time of symptoms, and 347 (62.5%) also did not qualify as candidates for medication since more than 4.5 hours had passed after their onset of symptoms.

In 2021, according to the results in Iris Lettow et al. paper Among 503 patients randomized, 199 SAE were reported for n=110 (22%) patients. Of those patients who did suffer a SAE, 20 (10%) had a fatal outcome. Patients suffering from at least one SAE had a lower odds of reaching a favorable outcome (modified Rankin Scale score of 0-1) at 90 days (adjusted odds ratio, 0.36 [95% CI, 0.21-0.61],  $P < 0.001$ ). Higher age ( $P = 0.04$ ) and male sex ( $P = 0.01$ ) were predictors for the occurrence of SAE. SAEs were observed in about one in 5 patients, were more frequent in elderly and male patients and were associated with worse functional outcome. These results may help to assess the risk of SAE in future stroke trials and create awareness for severe complications after stroke in clinical practice.

In 2019, Ludwig Schlemm et al. said that four hundred and eighty-six patients were included in the analysis. Current smokers (133, 27.4%) were younger ( $60.1 \pm 13.0$  vs.  $67.2 \pm 10.3$  years;  $p < 0.001$ ) and less often had arterial hypertension (45.0% vs. 56.8%;  $p = 0.02$ ) or atrial fibrillation (3.8% vs. 15.3%;  $p < 0.001$ ). The acute stroke presentation was more often due to large vessel occlusion among current smokers (27.1 vs. 16.2%;  $p = 0.01$ ), and smokers had a trend towards more severe strokes (National Institutes of Health Stroke Scale score  $> 10$  in 27.1% vs. 19.5%;  $p = 0.08$ ). The treatment effect of alteplase, quantified as odds ratio for a favorable outcome (modified Rankin Scale [mRS] score at 90 days of 0 or 1), did not differ between current smokers and non-smokers ( $p$ -value for interaction: 0.59). After adjustment for age and stroke severity, neither the proportion of patients with favorable outcome, nor the median mRS score at 90 days differed between current smokers and non-smokers. When additional potential confounders were included in the model, the median mRS score was higher in current smokers than in non-smokers (cOR of better outcome for current smokers vs. non-smokers: 0.664 [0.451-0.978],  $p = 0.04$ ). Conclusions: In patients with mild to moderate MRI-proven AIS and unknown time of symptom onset with DWI-FLAIR mismatch, current smokers had worse functional outcome as compared to non-smokers. Current smoking did not modify the treatment effect of alteplase.

In 2018, Brian Silver et al. published their results about Implications of the WAKE-UP Trial. According in this paper, Alteplase has been an established treatment for stroke for over 20 years. In that time, the window for treatment has been defined as 4.5 hours based on randomized trials and systematic reviews. In population-based studies,  $\approx 1$  out of every 6 patients wakes up with stroke symptoms and has an unclear time of symptom onset.<sup>2</sup> Last seen well is used as an imperfect surrogate for determining eligibility for thrombolytic therapy. Studies have

suggested that many of these patients have likely had the event within a few hours of awakening based on imaging characteristics that match those of patients with a defined time of onset.<sup>3</sup> Both computed tomography and magnetic resonance imaging (MRI) characteristics have been used for this purpose. In the case of computed tomography, the Alberta Stroke Program Early CT Score has been used as a surrogate to define the amount of tissue injury and, by extension, the likely recency of symptoms. Small series have found favorable outcomes though these were prospective studies without randomization. In the case of MRI, the mismatch between diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) imaging has been used as a surrogate for time of onset. Specifically, abnormal signal on DWI without a corresponding abnormality on FLAIR seems to correlate with symptom onset within 4.5 hours when studying images of patients with known time of symptom onset.

In 2018, according to the results in Götz Thomalla et al. article the trial was stopped early owing to cessation of funding after the enrollment of 503 of an anticipated 800 patients. Of these patients, 254 were randomly assigned to receive alteplase and 249 to receive placebo. A favorable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 patients (41.8%) in the placebo group (adjusted odds ratio, 1.61; 95% confidence interval [CI], 1.09 to 2.36;  $P=0.02$ ). The median score on the modified Rankin scale at 90 days was 1 in the alteplase group and 2 in the placebo group (adjusted common odds ratio, 1.62; 95% CI, 1.17 to 2.23;  $P=0.003$ ). There were 10 deaths (4.1%) in the alteplase group and 3 (1.2%) in the placebo group (odds ratio, 3.38; 95% CI, 0.92 to 12.52;  $P=0.07$ ). The rate of symptomatic intracranial hemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (odds ratio, 4.95; 95% CI, 0.57 to 42.87;  $P=0.15$ ). In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days

In 2017, Götz Thomalla et al said that of 1005 patients included, diffusion-weighted imaging and fluid-attenuated inversion recovery mismatch was present in 479 patients (48.0%). Patients with daytime-unwitnessed stroke ( $n=138$ , 13.7%) had a shorter delay between symptom recognition and hospital arrival (1.5 versus 1.8 hours;  $P=0.002$ ), a higher National Institutes of Stroke Scale score on admission (8 versus 6;  $P<0.001$ ), and more often aphasia (72.5% versus 34.0%;  $P<0.001$ ) when compared with stroke patients waking up from nighttime sleep. Frequency of diffusion-weighted imaging and fluid-attenuated inversion recovery mismatch was comparable between both groups (43.7% versus 48.7%;  $P=0.30$ ). Almost half of the patients with unknown time of symptom onset stroke otherwise eligible for thrombolysis had MRI findings making them likely to be within a time window for safe and effective thrombolysis. Patients with daytime onset unwitnessed stroke differ from wake-up stroke patients with regards to clinical characteristics but are comparable in terms of MRI characteristics of lesion age.

Acute and chronic complications of a stroke in patients could have high costs on the individual and family life of the patient. Assessing hyperacute stroke protocol, which includes DWI / ADC / FLAIR / GRE MRI sequences, patients with an unknown onset time of stroke symptoms could be treated with more venous thrombolytics.

This study aimed to evaluate the possibility of increasing treatment, improving the quality of treatment, and reducing complications after acute stroke in patients due to the inclusion of patients with an unknown time of onset of stroke symptoms into the treatment cycle with an injection of Alteplase under the supervision of a medical team.

## **Objectives**

- 1.** Comparison of the decrease in NIHSS score after 24 hours post-thrombolytic-treatment in stroke patients with unknown onset of symptoms who have got thrombolytic treatment and patients who did not.
- 2.** Comparison of the decrease in NIHSS score at the time of discharge of stroke patients with unknown onset of symptoms who have got thrombolytic treatment and patients who did not receive any thrombolytic treatment.
- 3.** Comparison of MRS scores at discharge time in stroke patients with unknown onset of symptoms who have got thrombolytic treatment and patients who did not.
- 4.** Comparison of cerebral hemorrhage incidence 24 hours post-intervention in stroke patients with unknown onset of symptoms who have got thrombolytic treatment and patients who did not.
- 5.** Comparison of systemic bleeding incidence 24 hours post-intervention in patients with unknown onset of symptoms who have got thrombolytic therapy and patients who did not.
- 6.** Evaluation of anaphylaxis sensitivity response in stroke patients with unknown onset of symptoms who have got thrombolytic therapy.

7. Comparison of MRS scores at 3 months post-discharge of stroke patients with unknown onset of symptoms who have got thrombolytic treatment and patients who did not.

## 2. Methods

### 2.1 Study design, patients, and procedure:

This historical (retrospective) cohort study recruited stroke patients with an unknown onset time of symptoms who had done MRI and were referred to Golestan Hospital, Ahwaz, Iran. Patients were divided into two groups. The first group comprises patients who received alteplase treatment, as indicated for thrombolytic treatment due to ischemic lesion in diffusion-weighted sequences, but without established FLAIR finding. The second group includes patients who did not receive Alteplase, as thrombolytic treatment was not indicated due to lesion visible in fluid-attenuated inversion recovery imaging (FLAIR), visible in diffusion-weighted imaging (DWI). Comparisons were made between these two groups regarding NIHSS score at baseline and 24 hours later post-treatment, and modified Rankin scale (MRS) score 3 months post-discharge and bleeding complications.

### 2.2 Inclusion and Exclusion criteria:

Inclusion criteria were ischemic stroke patients older than 18 years with an unknown onset time of symptoms who had undergone brain MRI to evaluate the possibility of Alteplase injection. The exclusion criteria were ischemic stroke patients with a specific time of onset of symptoms.

### 2.2 Method of calculating the sample size:

As per the primary purpose of the study and in order to compare the mean NIHSS in the two groups of patients, the sample size determination formula was used to compare a quantitative index at two levels of a qualitative variable. According to similar studies carried out in this field (intravenous thrombolysis in unwitnessed stroke onset, stroke with an unknown onset time of symptom) with 95% statistical power, the first type of error of 0.05, the mean difference between the two methods equals four units, and the amount of variance equals to 20, the sample size in each group was estimated to be 16 using PASS sample size statistical software.

## 3. Statistical Analyses:

To analyze the data, statistical tests were employed to compare the means of two independent groups of t-test or their non-parametric equivalent, Mann-Whitney. Analyses were performed using SPSS software version 25, and the significance level of the tests was considered 0.05.

## 4. Results

### 4.1 Evaluation of demographic information

The results of the patients' demographic and clinical information by the group have been presented in Table 1. Based on the results of Table 1, none of the assessed variables had a significant difference between the two groups, one recipient of the thrombolytic therapy and the other non-recipient of the thrombolytic therapy.

Table 1. Evaluation of demographic and basic information of patients.

Variables	non-thrombolytic receiving group (N = 35)	Thrombolytic receiving group (N = 26)	p-value*
<b>Gender (percentage)</b>			
Female	15 (42.86%)	9 (34.62%)	0.512
Male	20 (57.14%)	17 (65.38%)	
<b>Age (years)</b>			
Standard deviation ± mean	64.22±13.45	67.61±11.59	0.170
Min-Max	31-83	44-84	
<b>Systolic blood pressure (mm Hg)</b>			
Standard deviation ± mean	156.57±29.42	163.26±23.87	0.172
Min-Max	100-220	110-210	
<b>Diastolic blood pressure (mm Hg)</b>			
Standard deviation ± mean	88.14±57.58	91.11±53.46	0.199

Min-Max	60-120	70-110	
<b>Blood sugar (mg / L)</b>			
Standard deviation ± mean	205.6±107.26	178.69±70.05	0.139
Min-Max	91-416	90-350	

\* Significance limit was calculated by independent t-test and chi-square and at 95% confidence level.

#### 4.2 Frequency of risk factors and underlying diseases

The results of the frequency in risk factors and underlying diseases are presented in Table 2. Based on the results of Table 2, the frequency of smoking between the two groups with and without thrombolytics was significant, while other risk factors did not differ significantly.

Table 2. Frequency of risk factors and underlying diseases in patients.

risk factors	non-thrombolytic receiving group (N = 35)	Thrombolytic receiving group (N = 26)	p-value*
<b>High blood pressure</b>			
No	15 (42.86%)	8 (30.77%)	0.335
Yes	20 (57.14%)	18 (69.23%)	
<b>Smoking</b>			
No	33 (94.29%)	20 (76.92%)	0.047
Yes	2 (5.71%)	6 (23.08%)	
<b>Atrial fibrillation</b>			
No	34 (97.14%)	23 (88.45%)	0.176
Yes	1 (2.86%)	3 (11.54%)	
<b>Diabetes mellitus</b>			
No	19 (54.29%)	15 (57.69%)	0.791
Yes	16 (45.71%)	11 (42.31%)	
<b>Ischemic heart disease</b>			
No	29 (84.62%)	29 (82.86%)	0.854
Yes	4 (15.38%)	6 (17.14%)	
<b>High cholesterol level</b>			
No	34 (97.14%)	22 (84.62%)	0.078
Yes	1 (2.86%)	4 (15.38%)	
<b>Previous CVA history</b>			
No	25 (71.43%)	22 (84.62%)	0.226
Yes	10 (28.57%)	4 (15.38%)	

\* Significance limit was calculated by independent t-test and chi-square and at 95% confidence level.

**4.3 Frequency of cerebral hemorrhage and death in the patients**

The frequency of cerebral hemorrhage and death in the patients by the group are presented in Table 3. According to the results of Table 3, there was no significant difference between the frequency of cerebral hemorrhage and death in the two groups, one recipient of the thrombolytic therapy and the other non-recipient of the thrombolytic therapy.

Table 3. Frequency of cerebral hemorrhage and death in the patients.

Variables	non-thrombolytic receiving group (N = 35)	Thrombolytic receiving group (N = 26)	p-value*
<b>Cerebral hemorrhage</b>			
No	33 (94.29%)	24 (92.31%)	0.758
Yes	2 (5.71%)	2 (7.69%)	
<b>Death</b>			
No	27 (77.14%)	22 (84.62%)	0.468
Yes	8 (22.86%)	4 (15.38%)	

\* Significance limit was calculated by independent t-test and chi-square and at 95% confidence level.

**4.4 Comparison of the average NIHSS score between the two groups and in each group between different periods.**

The results of comparing the average NIHSS score between the two groups and in each group at different times are presented in Table 4. Based on the results of Table 4, the average NIHSS score at any time did not differ significantly between the two groups. Also, the repeated measures analysis results showed no significant difference between different time intervals in the non-thrombolytic group. Using a post hoc test, the thrombolytic therapy receiving group differed significantly between discharge and admission times. In other words, the mean

Time	non-thrombolytic receiving group (N = 35)	Thrombolytic receiving group (N = 26)	p-value*
<b>Hospitalization time</b>	10.6±5.55	12.38±6.11	0.21
<b>24 hours after Hospitalization</b>	7.37±4.12	6.36±5.53	0.20
<b>Discharge time</b>	10.51±6.37	9.61±6.93	0.54
<b>Significance limit**</b>	0.076	0.012	

\* Significance limit was calculated by independent t-test at 95% confidence level.  
 \*\* Significance limit has been calculated by Repeated Measure test at 95% confidence level.

NIHSS score in the thrombolytic group at the time of discharge was significantly lower than at the admission time (P < 0.001).

Table 4. Comparison of the average NIHSS score between the two groups and in each group between different periods.

**4.5 Comparison of the mean MRS score across the two groups between different periods.**

Based on Table 5, the thrombolytic receiving group averaged scored at discharge (P = 0.020) and 3 months post-discharge (P = 0.03) significantly lower in modified Rankin scale than the non-thrombolytic receiving group at corresponding time points. There was a significant mean score difference between different times across each patient group using repeated measures analysis. According to analyses made by post hoc test, the patients'

baselinescores at the admission time differed significantly from discharge time (3 months after intervention),regardless of their treatment types.

Table 5. Comparison of the mean MRS score across each group at different periods.

Time	non-thrombolytic receiving group (N = 35)	Thrombolytic receiving group (N = 26)	p-value*
Hospitalization time	0.17±0.38	0.11±0.43	0.32
Discharge time	3.94±1.43	2.96±1.82	0.02
3months after discharge	2.22±1.60	1.27±1.48	0.03
Significance limit **	<0.001	<0.001	

\* Significance limit was calculated by independent t-test at 95% confidence level.  
 \*\* Significance limit has been calculated by Repeated Measure test at 95% confidence level.

### 5. Discussion

Globally, stroke is a leading cause of death and disability (21). Most cases occur in developing countries, and about 15% of acute strokes are ischemic while 45% are hemorrhagic (22). Studies demonstrate that mortality during the first 93 days of acute stroke is 43% and the rest of morbidities are mainly associated with neurological defects (23). Complications of acute stroke comprise huge treatment and rehabilitation costs and lead to the disability of a part of the useful labor of society and collectively impose an enormous burden on the health system of the country and families yearly. Unfortunately, any comprehensive study in this field has not been done yet in our country. To reduce the complications and disabilities caused by acute stroke, one of the ways that have been approved in developed countries is to set up an acute stroke care unit acquired with specially trained staff with necessary specialized training to treat acute stroke and its complications. Administration of recombinant tissue plasminogen activator during an acute thromboembolic event leads to the dissolution of the clot which redistributes blood to the tissues and re-perfuses the organs. Acute ischemic attack, acute myocardial infarction, and pulmonary embolism are fatal events that can lead to complex complications such as organ failure and death if emergency treatment will not be provided. At this time, thrombolytic administration such as tissue plasminogen activator can remove the obstruction and minimize tissue damage, and ultimately saves the patient. Since following the thrombolytic treatment, there is a risk of treatment-related bleeding therefore an effective and safe drug should be selected for each patient. For this purpose, the administration of these drugs in the management system of acute stroke treatment is very important. However, the exact impact of this part of the management system on the condition of patients' needs has to be further investigated.

NIHSS and MRS are two indicators in the acute stroke disease management system. The first of which is a stroke scale and a standard optimization tool used by physicians and other health care professionals to measure and record the rate of stroke disorders. On the other hand, the second one is an indicator of patients' performance and efficiency, which is evaluated in this system at different times. The patient's condition can be understood by evaluating these indicators, so in the present study, the results of these two indicators were reported separately for receiving thrombolytic drugs and are mentioned below.

The present study outcomes showed that there was no significant difference between demographic variables in the two groups. This was one of the advantages of this study, considering that these variables affect the disease status because it was ensured that the influential variables were evenly distributed between the two groups. Moreover, most of the variables related to risk factors had the same distribution between the two groups. Smoking was slightly higher in the thrombolytic treatment group as compared to the non-thrombolytic group, which was significant. Additionally, no significant difference was observed between the two groups in terms of cerebral hemorrhage and death outcome, which has been addressed in some other studies. However, the main results of this study indicated that the mean NIHSS score in the group receiving thrombolytic therapy at discharge was lower than at baseline. On the other hand, there was no significant difference in comparison between the two groups in any of the times, which could be due to the small sample size. Although, in the group receiving thrombolytic treatment at the time of discharge, these values are lower than at the time of referral, but in the group not receiving thrombolytic treatment, this was not the case. In conclusion, this phenomenon demonstrates the effectiveness of receiving this treatment.

Furthermore, the results in relation to the MRS index showed that at the time of discharge and 3 months after discharge, the average of this index in the group receiving thrombolytic therapy was significantly lower as compared to the non-receiving thrombolytic therapy group.

Based on results from the National Institute of Neurological Disorders and Stroke, the US Food and Drug Administration approved the use of recombinant intravenous tissue plasminogen activator in 1996. However, the accessible data do not provide conclusive evidence of the safety or efficacy of these therapies (24). The efficacy and safety of thrombolytic therapy were evaluated in a study by Sivanandy et al. (25).

The results of this study showed that the mean NIHSS was 14 at the time of hospitalization for those receiving treatment. However, the NIHSS mean was 9.89 after 24 hours of treatment and was 5.1 at the time of discharge. This proves an obvious effect of this type of treatment and these results were completely consistent with the results of the present study.

In a study conducted by Hsiao et al. (26), the effect of thrombolytic therapy on the condition of patients with stroke was investigated. One of the results of this study was the improvement of NIHSS scores during hospitalization in patients treated with thrombolytic drugs, which was significant and confirmed the results of the present study. The study concluded that rapid evaluation of patients by neurologists could reduce the complications of stroke by increasing the number of patients eligible for thrombolytic therapy.

According to a study by Menichelli et al., thrombolysis may affect the size, pattern, and nature of strokes and attains the potential to alter and improve aphasia (27). Reperfusion treatment, early improvement in NIHSS and improved aphasia are the predictors of betterment in stroke. As a matter of fact, thrombolytic drugs advance this phase through their impact on these cases. Several parameters have been identified as predictors of early outcomes in patients with acute ischemic stroke.

By utilizing the imaging options for the prospective treatment of stroke patients with unknown onset of symptoms, other studies have confirmed positive results in the use of imaging in the recovery of patients with ischemic stroke (29,28). Our study as well as some other similar studies have shown that the mismatch of the FLAIR sequence with the DWI sequence, which is a signal hyperintensity in the DWI sequence, with little or no evidence of signal hyperintensity in the T2 FLAIR sequence, may identify a group of patients with biological onset of symptoms (30) (31).

In a prospective study of stroke patients with unknown onset of symptoms, large sample of 1,005 candidates in an interventional study, DWI-FLAIR mismatch was seen in almost half of the participants (32). Several studies outcomes have shown that in patients with an indefinite time to onset of symptoms, MRI imaging can detect lesions in the stroke within the first 4.5 hours of the onset of symptoms and these outcomes are consistent with the results of our study (32). Other studies have supported this finding and mention that the prevalence of DWI-FLAIR mismatch was detected in 43.7% and 35.1% of patients, respectively (34,33).

### **Compare with other results**

In a randomized controlled trial study by Silver et al., 2018 Examining a WAKE-UP stroke, patients with acute ischemic stroke were diagnosed about 4.5 hours after admission to their hospital. The findings showed that alteplase could be given to selected patients by imaging over a long period of time, such as the imaging selection method for thrombectomy; According to the findings, the overall rate of treatment with alteplase increased by about 9 percent, and in hospitals that prescribe 20 percent of patients with alteplase, the treatment rate increases to 50 percent(35).

In the study of Rimmele et al., 2014 the clinical features and imaging of wake-up stroke were investigated. The findings of this study showed that patients who wake up with stroke symptoms represent a large group of stroke patients who are currently excluded from intravenous thrombolysis by licensing criteria. Growing evidence from clinical and imaging studies suggests that a related proportion of patients with awakening stroke may benefit from reperfusion therapy and are promising candidates for intravenous thrombolysis. Different imaging approaches have been proposed for selecting awake stroke patients for thrombolysis, including CT and multimeter MRI(36).

A multicenter controlled randomized controlled clinical trial was performed by Thomalla et al., 2014 On MRI-based thrombolysis in patients with acute stroke with an unknown time of onset of symptoms. The findings showed that the aim of WAKE-UP was to demonstrate the efficacy and safety of MRI-based intravenous thrombolysis with alteplase in patients waking up with symptoms of stroke or in patients with the onset of unknown symptoms(37).

Thomalla et al., 2018 “MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset” examined 503 patients and 254 were randomly assigned to receive alteplase and 249 to receive placebo. Optimal outcome was reported in 90 days in 131 patients in the alteplase group and in 102 patients in the placebo group (adjusted odds ratio, 1.61). The rate of symptomatic intracranial hemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (odds ratio, 4.95)(38).

Lettow et al., 2021 analyzed the effect of serious adverse events (SAE) on functional outcome and predictors of SAE in the randomized controlled WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke). Findings of the study showed that among 503 randomized patients, 199 SAE were reported for n = 110 (22%) patients. Of those patients who did suffer a SAE, 20 (10%) had a fatal outcome. Patients suffering from at least one SAE had a lower odds of reaching a favorable outcome (modified Rankin Scale score of 0-1) at 90 days (adjusted odds ratio, 0.36 [95% CI, 0.21-0.61], P <0.001). Higher age (P = 0.04) and male sex (P = 0.01) were predictors for the occurrence of SAE(39).

Schlemm et al., 2019 analyzing the effect of smoking on treatment efficacy of intravenous thrombolysis are scarce. Based on the findings of the study in patients with mild to moderate MRI-proven AIS and unknown time of symptom onset with DWI-FLAIR mismatch, current smokers had worse functional outcome as compared to non-smokers. Current smoking did not modify the treatment effect of alteplase(40).

In a Randomized, Double-blind, Placebo-Controlled Trial study by Thomalla et al., 2017 describe clinical and magnetic resonance imaging (MRI) characteristics of stroke patients with unknown time of symptom onset potentially eligible for thrombolysis from a large prospective cohort. The results showed that almost half of the patients with unknown time of symptom onset stroke otherwise eligible for thrombolysis had MRI findings making them likely to be within a time window for safe and effective thrombolysis. Patients with daytime onset unwitnessed stroke differ from wake-up stroke patients with regards to clinical characteristics but are comparable in terms of MRI characteristics of lesion age(32).

## **6. Conclusion**

Based on the present study outcomes, it can be stated that thrombolytic therapy acts as a rapid measure in patients with acute stroke by reducing complications and dysfunction in patients, and ultimately improves the condition of these candidates. According to the results of the present study, no significant difference was present between the occurrence of death between receiving and non-receiving the thrombolytic therapy groups. However, lower values of NIHSS and MRS indicators in the survivors showed the effectiveness of this method. Therefore, it is recommended that this method has to be followed as a comprehensive disease management protocol in the early hours of the disease in patients with unknown onset of the symptoms and considered as a serious intervention that has to be done without any delay.

## **7. Conflict of interest**

The authors declare that there is no conflict of interest.

## **8. Work restrictions**

According to previous guidelines (including the guideline), it has already been proven that in patients with stroke of indefinite duration having a DWI-flair mismatch in MRI, alteplase injection can be effective, but because we thought it was not ethical to study Double blind, and exclude a number of patients from receiving this drug. To be able to see if it is possible to perform a quick MRI in these patients in our center and the results are consistent with other medical centers.

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