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Predictors o f Unfavorable Functional Outcome in Ischemic Stroke Patients After Intravenous Thrombolytic Therapy

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Abstract

Background: Acute ischemic stroke (AIS) is one of the major causes of disability and death worldwide. Currently, intravenous administration of recombinant tissue plasminogen activator (rt-PA), initiated within 4.5 hours after symptom onset, is the standard therapy for AIS. We aimed to predict the 30-day functional outcome of AIS patients who received alteplase in comparison with non- thrombolyzed patients and to evaluate the predictors of the unfavorable outcome after 30 days.
Methods: All the data of 80 AIS patients who received rt-PA during the period from 2019 to 2021 were prospectively collected and analyzed. For comparison, 80 patients who received regular treatment,rather than rt-PA within the first 24 h, were selected to match the alteplase group as regards the baseline data and included in the study as a control group. The functional outcome of the thrombolyzed patients after 30 days was evaluated in comparison with controls by using a modified ranking scale.
Results: After a 30-day follow-up period, the mortality rate was slightly higher among the rt-PA group (12.5%) in comparison with the control group (10%), however, this difference was not significant. Intracranial hemorrhage (ICH) was significantly higher in the alteplase group than in non- thrombolyzed patients (13.8% vs 3.8%). More patients had a favorable outcome (mRS = 0–2) in the rt-PA group than in the control group (28.7% vs 15%). Age, high baseline blood glucose level, systolic blood pressure, NIHSS score on admission and after 24h, body mass index (BMI) (≥ 30), AF, cardioembolic stroke and occurrence of ICH stroke were significant predictors of functional outcome after IV thrombolysis. Gender, hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, smoking, Ischemic heart disease, previous stroke or transient ischemic attack (TIA) and timing of initiation of thrombolytic therapy had a non-significant effect.
Conclusion: After 30-day follow-up period, rt-PA had a significant more increase of favorable functional outcome with increased risk of ICH. Older age, baseline hyperglycemia, high SPB, high NIHSS (either on admission or after 24h), obesity, cardioembolic stroke subtype, history of AF and occurrence of ICH were significant predictors of unfavorable functional outcome after thrombolysis.

Keywords: Thrombolytic therapy, rt-PA, Functional outcome, mRS, Stroke.

Introduction

Acute ischemic stroke (AIS) is one of the major causes of disability and death worldwide [1]. Over the last four decades, the stroke incidence in low- and middle-income countries has more than doubled [2]. Stroke is a major health problem in the Egyptian population. Egypt is the most populated country in the Middle East with over 98 million inhabitants. However, there are few demographic stroke studies, mostly obtained through door to door surveys in some governorates [3]. They revealed an overall crude stroke prevalence of 613/10,0000 and crude incidence rate of 202/10,0000 [4].

Intravenous (IV) recombinant tissue plasminogen activator (IV rt-PA) is currently the only proven effective medication for the treatment of AIS with promising adjuvant medications currently under investigation [5]. Recent advances in endovascular thrombectomy have broadened therapeutic options in specific patient populations, with modern treatment strategies utilizing advanced imaging modalities to extend the window for treatment. Nevertheless, in developing countries, especially, with the lack of facilities, intravenous thrombolytic therapy (IVT) still is the only available effective pharmacologic approach in selected patients with AIS [6].

Utilization of reperfusion therapies for stroke remains <1% in Egypt [7]. The challenge of deciding IV rt-PA in any given patient involves weighing its risks and benefits [8].Therefore, this study was designed to evaluate the short term outcome of AIS patients who received thrombolytic therapy regardsing mortality, ICH, and functional outcome in relation to non-thrombolyzed patients and to evaluate the factors which could be useful in predicting a possible unfavorable functional outcome at 30 days.

Methods

This prospective study included 80 AIS patients treated with IV rt-PA (group I) in the neurology intensive care unit (ICU) and stroke unit, Zagazig University Hospitals, during the period between February 2019 and February 2021. The patients who received rt-PA were diagnosed according to the World Health Organization (WHO) criteria [9]. The inclusion and exclusion criteria were used according to the guidelines, and IV treatment with alteplase (0.9 mg/kg up to a maximum of 90 mg, 10% of the total dosage as a bolus and the rest over 1 h) was initiated within 4.5 h of the onset of symptoms. For comparison, 80 AIS patients who received regular treatment within the first 24 h were also included as control group (group II). They were selected to match the case group as regards the baseline characteristics. Written informed consent was taken from the patients or their family members to participate in the study

We recorded the medical history prior to the stroke and analyzed the following variables: age, gender, histories of vascular risk factors including hypertension, diabetes mellitus, previous stroke or transient ischemic attacks (TIA), current or former smoking, and hyperlipidemia, obesity (identified by body mass index ≥ 30), ischemic heart disease, and atrial fibrillation (AF), either as a history of AF or AF diagnosed during the index admission by electrocardiography. Baseline glycemia, body temperature, blood pressure levels, complete blood count, liver and kidney function test, coagulation profile, and lipid profile were also recorded. Stroke severity on

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admission and 24 h was ascertained by a neurologist experienced in NIHSS. Furthermore, Acute ischemic stroke subtypes were determined by using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [10].

All patients presented with acute stroke were subjected to CT brain on admission to exclude patients with stroke mimic or primary intracranial hemorrhage and after 24 h to assess ICH following thrombolytic therapy. Magnetic resonance imaging (MRI) of the brain was done in suspected brain stem lesions, early ischemic stroke, and when follow-up CT brain is free.

Outcome measures

Our study evaluated functional outcome as assessed on the modified Rankin scale (mRS) at 30 days after stroke onset, via telephone or face to face by a neurologist. A good functional outcome was defined as mRS of 0-2 points, whereas a poor outcome was defined as mRS ≥ 3 points.

Statistical analysis

All data were collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(**Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by t test or Mann Whitney, paired by paired t or Sign test. P value was set at <0.05 for significant results and <0.001 for highly significant results.

Results

Table 1 shows demographic and baseline characteristics among studied groups. There was no significant difference between the patients who received rt-PA and those who received regular treatment as regards age, sex, risk factors, clinical data, severity of stroke (NIHSS), or subtype of stroke (TOAST).

Table 2 shows a significant increase of ICH among the rt-PA group (group I) compared to controls (group II) (13.8% vs 3.8%, $P < 0.05$). 28.7% of the alteplase patients had a favorable functional outcome compared to 15% of the controls ($P < 0.05$). The death rate was higher in the alteplase group compared to controls, however, this difference was non-significant (12.5% vs 10%, P>0.05). Among our 80 patients who were treated with thrombolysis (group 1), alteplase was given within 3 h in 45 patients, while in the other 35 patients, alteplase was initiated 3–4.5 h of stroke onset. Older age, higher admission blood sugar, SBP, baseline and 24-hour NIHSS score had a highly significant effect on the functional outcome.

AF, obesity (BMI≥30), cardioembolic stroke and occurrence of ICH were significantly associated with unfavorable outcome. There was a non-significant association between the outcome and DM, hypertension, hyperlipidemia, previous TIA or stroke, ischemic heart, smoking and timing of initiation of thrombolytic therapy.

Table 1 Baseline characteristics of both studied groups

	Group I, N=80	Group II, N=80	P value
Demographic data			
Age (Mean ± SD)	67.7± 9.5	69.3± 11.6	0.47
Gender, n(%)			
Female	26(32.5%)	29(36.3%)	0.37
Male	54(67.5%)	51(63.7%)	
Risk factors			
Hypertension, n (%)	56(70%)	60(75%)	0.91
Diabetes, n (%)	44(55%)	44(55%)	1.00
AF, n (%)	24(30%)	25(31.3%)	1.00
Ischemic heart, n (%)	16(20%)	20(25%)	0.71
Smoking, n (%)	32(40.0%)	17(33.3%)	0.62
Obesity (BMI≥30), n (%)	40(50%)	35 (43.7%)	0.428
Hyperlipidemia, n (%)	36(45%)	32(40%)	0.80
Previous stroke, n (%)	8(10%)	10(12.5%)	0.617
Previous TIA, n (%)	10(12.5%)	12(15%)	0.646
Clinical data			
SBP (Mean ± SD)	153.56 ± 16.03	155.94 ± 24.01	0.463
DBP (Mean ± SD)	92.25 ± 9.52	94.0 ± 12.26	0.315
RBS (Mean ± SD)	186.03 ± 86.07	169.7 ±71.2	0.097
Body temperature (Mean ± SD)	37.1± 0.28	37.1± 0.5	0.75
Admission NIHSS (Mean ± SD)	11.16±4.84	12.4±4.9	0.48
Stroke subtypes (TOAST criteria)			
Large artery atherosclerosis, n (%)	43(53.7%)	46(57.5%)	0.77
Cardioembolic, n (%)	27(33.7%)	21(26.3%)	
Small artery, n (%)	7(8.8%)	8(10.0%)	
Undetermined, n (%)	3(3.8%)	5(6.2%)	

P > 0.05 = non-significant
SD=standard deviation, AF=atrial fibrillation, BMI=body mass index, TIA=Transient ischemic attack, SBP=systolic blood pressure, DBP=diastolic blood pressure, RBS=random blood sugar, NIHSS= National Institute of Health Stroke Scale TOAST=trial of ORG 10172 in acute stroke treatment, h=hours

Table 2 Outcome among both studied groups

Outcome	**Group I** (TPA)	**Group II** (non-TPA)	**P value**
24 h NIHSS (Mean ± SD)	9.2±6.1	12.3±5.7	**<0.001****
ICH, n(%)	11(13.8%)	3 (3.8%)	**0.04***
Outcome 30 days			
Favorable (mRS ≤ 2), n(%)	23(28.7%)	12(15%)	**0.035***
Unfavorable (mRS >2), n(%)	57(71.3%)	68(85%)	
Mortality, n(%)	10 (12.5%)	8 (10%)	0.617

*p<0.05 is statistically significant **p≤0.001 is statistically highly significant
NIHSS= National Institute of Health Stroke Scale, ICH=intracerebral hemorrhage, mRS= modified rankin scale

Table 3 Thirty days outcome among thrombolyzed AIS patients in relation to baseline characteristics

	Favorable, N=23	**Unfavorable,** N=57	**P value**
Demographic data			
Age (mean±SD)	63±10.7	69.5 ±8.3	**0.00****
Gender, n%			
Female	8(34.8%)	18(31.6%)	0.49
Male	15(65.2%)	39(68.4%)	
Risk factors			
Hypertension, n%	13(56.5%)	43(75.5%)	0.16
IHD, n%	5(21.7%)	11(20.7%)	0.804
Diabetes, n%	10(43.5%)	34(59.6%)	0.14
AF, n%	3 (13%)	21 (36.8%)	**0.035***
Smoking, n%	11(47.8%)	21(36.9%)	0.45
Obesity(BMI≥30) , n%	6 (26.1%)	34 (59.6%)	**0.007***
Previous stroke, n%	1 (4.3%)	7 (12.3%)	0.284
Previous TIA, n%	2 (8.7%)	8(14%)	0.513
Hyperlipidemia, n%	11 (36.7%)	25 (50.0%)	0.296
Clinical data			
SBP(mean±SD)		157.8± 16.3	**0.00****
DBP(mean±SD)	148.3± 14.4	92.36 ±9.91	0.895
RBS(mean±SD)	92.07 ± 8.99	193.5±79.4	**<0.001****
NIHSS on admission (mean±SD)	136±45.3	12.7±4.3	**<0.001****
NIHSS after 24h (mean±SD)	7.4±2.8	11.3±5.9	**<0.001****
ICH, n%	3.8±2.6	10 (17.5%)	**0.02***
	0 (0.0%)		
Stroke subtypes (TOAST)			
Large artery atherosclerosis, n%	13(56.5%)	30(52.6)	**0.02***
Cardioembolic, n%	3(13.0%)	24(42.1%)	
Small artery, n%	6(26.1%)	1(1.8%)	
Undetermined, n%	1(4.3%)	2(3.5%)	
rt-PA timing			
(<3h) , n%	15(65.2%)	30(52.6%)	0.304
(3 – 4.5h) , n%	8 (34.8%)	27(47.4%)	

P<0.05 is statistically significant **p≤0.001 is statistically highly significant
SD=standard deviation, AF=atrial fibrillation, BMI=body mass index, TIA=Transient ischemic attack, SBP=systolic blood pressure, DBP=diastolic blood pressure, RBS=random blood sugar, NIHSS= National Institute of Health Stroke Scale TOAST=trial of ORG 10172 in acute stroke treatment, h=hours, rt-PA=recombinant tissue plasminogen activator.

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Discussion

Regarding risk factors of ischemic stroke; this study reported that the most common risk factors in both groups were hypertension (70%), diabetes mellitus (DM) (55%), and atrial fibrillation (AF) (30%) in rt-PA group versus 75%, 55%, and 31.3%, respectively in control group. However, in a recent Egyptian study conducted by **Aref et al.,** DM was the most prevalent risk factor, followed by hypertension, and followed by dyslipidemia [11].

Our study has demonstrated that use of intravenous thrombolytic therapy for acute ischemic stroke is associated with better neurological and functional outcomes, and significantly reduce the effect of stroke morbidity; this was in agreement with several studies that supported the short- and long-term outcome benefits of IV rt-PA like the large third international stroke trial (The IST-3 Collaborative Group)[12].

In this study, there was treatment benefit with alteplase over placebo with early neurological improvement evidenced by significant reduction in NIHSS after 24 hours in rt-PA group. These data were in accordance to results obtained by **Agarwal et al.,** who reported improvement in the 24-hour NIHSS among patients treated with alteplase compared with the placebo group [13].

Our results demonstrated that thrombolysis significantly increased the incidence of the favorable functional outcome as assessed by mRS 30 days after stroke onset, which is evidenced by the fact that only 15% of non-thrombolysed patients versus 28.7% of thrombolysed patients had good functional outcome (mRS 0-2). **Li et al.** reported that 57.4% of patients who received alteplase had good functional outcomes at 14 days follow-up by mRS [14]. While, **Das et al.** reported that favorable functional outcome at 6 months occurred in 23.33% of thrombolysed AIS patients which is lower than our results [15]. The variation in improvement rates between studies may be due to the differences in mean ages, initial NIHSS, and dose of IV rt-PA as well as the variability in the time of follow up.

This current study revealed that within 30 days after stroke onset, a total of 18 patients died in both groups. The death rate was slightly higher among rt-PA (group I) with 10 patients died (12.5 %) versus 8 patients (10%) in control group. Our results agreed with results of that study conducted by **Chao et al.** which reported slightly higher mortality rate (12.8%) within three months among Chinese AIS patients who received standard dose of alteplase [16]. The authors suggested that reduction of the dose from 0.9 to 0.72 mg/Kg may reduce the mortality down to 6.9 %, as the patients in this study who were treated with a low dose (0.55–0.84 mg/kg) had a lower hemorrhagic transformation rate, hence a lower mortality rate, and also a better functional outcome, especially in patients older than 70 years [16]. Our results differs from some previous studies like that of **Hacke et al.,** and **Ghosh et al**. as regards mortality rates [17,18]. They reported that mortality did not differ significantly between alteplase and placebo groups**.** The variation in mortality rates between studies may be due to the difference in mean ages, initial NIHSS, as well as the differences in stroke subtypes included in the studies according to TOAST criteria classification.

Hemorrhagic complications after reperfusion therapies include a broad spectrum of severity between small petechial hemorrhagic infarcts (HIs) to parenchymal hematomas (PHs). Intracranial hemorrhage (ICH), especially with PH, is associated with increased morbidity and mortality [19]. This study found that ICH was significantly higher in the alteplase group with 11 patients (13.8%) developed ICH (asymptomatic, symptomatic) versus three patients (3.8%) who received regular treatment. Of these eleven patients who developed post-thrombolysis ICH in our study, five patients (6.3%) were symptomatic (sICH), and 7.5% were asymptomatic. Almost similar results reported by **Emberson and colleagues,** in their meta-analysis study which found that alteplase increased the likelihood of sICH as it occurred in 6.8 % of patients assigned alteplase versus 1.3 % of patients assigned control [20]. In a recent study by **Tork et al.**, post-thrombolysis ICH reported in 8.7 % of patients, with 2.7% were symptomatic and 6 % were asymptomatic [21]. The higher percentage of post rt-PA ICH reported in our study could be explained by higher percentage of our patients had severe stroke on admission as assessed by NIHSS. Higher NIHSS score increases the risk of hemorrhages since severe ischemic stroke is reflected by large areas of injured brain tissue, including injured blood vessels, which are prone to bleeding after rt-PA treatment. Additionally, we also found that the poor functional outcome 30 days post-stroke was significantly associated with the occurrence of post-thrombolysis ICH. Despite an increase in the rates of early ICH, treatment with intravenous rt-PA improve clinical outcome of AIS patients. Some previous studies recommend using low dose alteplase (0.6mg/kg) in order to reduce risk of post-thrombolysis ICH especially for populations at a higher bleeding risk, such as East Asians, or for patients who are eligible for endovascular treatment [22,23,24].

There are various factors which were reported to be predictors of the outcome in AIS patients. The clinical characteristics of patient, such as age, gender, severity of stroke, diabetes, hypertension, and cardiovascular comorbidities, etc, are the known risk factors of stroke and also predictors of poor outcome in untreated patients [25].

In the present study, we analyzed these risk factors and their relation with the functional outcome at 30 days after thrombolytic therapy. As regards the demographic data of the studied patients, we found that the mean age was 67.7± 9.5 with 67.5% male predominance in rt-PA group. Among our 80 alteplase patients, the age showed highly significant association with the 30-day functional outcome, as the patients who had favorable outcome were younger (mean ± SD = 63±10.7) than those with unfavorable outcome (69.5 ±8.3). These findings are in agreement with results of

Bhardwaj et al. study which found that advanced age correlates significantly with poor outcome at 3 months in AIS patients who received IV rt-PA [25]. Additionally, many previous studies reported that younger age is one of few independent good prognostic factors [26, 27]. On the other hand, it has been reported that age did not change the effect of alteplase on odds of good outcome [26]. Additionally, recent Egyptian studies like that conducted by **Tork et al**. and that study conducted by **Mohamed et al**. did not show significant correlations between age and functional outcome [21, 28].

Regarding gender, our findings agreed with that of **El-sayed et al**. study which found no significant relation between gender and functional outcome [29]. On the other hand, **Liu et al.** reported that women had a poorer functional outcome after IV rt-PA compared with men [30]. While, in another previous study, male gender was significant predictor of poor functional outcome at 3 months [31]. This could be because of sex disparities in fibrinolytic factors or that women are particularly liable to depression after stroke, and this is related to greater stroke severity [32]. However, the effect of sex and age on the outcome is still uncertain and a matter of controversy [28].

The therapeutic time window was set at 3 hours or less after stroke onset, which was revised to 4.5 hours in 2013 according to the American Heart Association/American Stroke Association (AHA/ASA) guidelines for the early management of patients with acute ischemic stroke [33]. The earlier the administration of rt-PA, the better the outcome even with this therapeutic time window [33]. Among our 80 patients who were treated with thrombolysis (group I), alteplase was given within 3 hours in 45 patients (56.3%), while in the other 35 patients (43.7%) alteplase was initiated 3-4.5 hours of stroke onset. This study revealed that 47.4% of those patients with unfavorable functional outcome had their rt-PA initiated after three hours of stroke onset. However, these differences were statistically non-significant. Our findings are in line with results of previous studies like that of **Tork et al.**, **Elsayed et al** and **Huang et al** [21,29,34]. On the other hand, **Hacke et al**. concluded that IV alteplase given 3 to 4.5 h after stroke onset in their study was associated with a modest but significant improvement in the clinical outcome than the reported previously among patients treated within 3 h. However, the authors recommended that patients should be treated with alteplase as early as possible, and having more time does not mean we should be allowed to take more time [17]. The impact of time-to-treatment on outcome after thrombolysis depends on several factors, including the pattern of arterial occlusion, efficacy of collateral circulation, and size of irreversible ischemia [35]. The non-significant association between the outcome and timing of rt-PA reported in our study could be attributed to the fact that IV rt-PA was initiated within less than three hours of stroke onset in the majority of our patients.

Regarding the relation between outcome in our alteplase patients and various risk factors; we found that obesity significantly affect 30-day functional outcome with 59.6% of those who developed unfavorable outcome were obese (BMI 30 or above). Our results are in agreement with results of previous studies like that of **Mohamed et al** and **Sarikaya et al.** [28,36]. Several reasons might explain the unfavorable clinical outcome in obese patients with stroke treated with thrombolytic therapy. First, obesity has been shown to be associated with a pro-inflammatory and pro-thrombotic state thus potentially hampering the clot-dissolving effect of alteplase [36]. Furthermore, obesity is closely associated with the metabolic syndrome [37]. Additionally, in obese patients, the dose of alteplase might have been insufficient because the maximum dose is limited at 90 mg. In contrast to our results, **Kim et al**. suggest that obesity is associated with a good outcome after stroke [44]. However, the authors suggested the good outcome in AIS patients was not because the patients were obese, but rather because those patients were younger or more likely to have less severe stroke that is associated with a non-cardioembolism mechanism [38].

Previous studies have reported that stroke patients with atrial fibrillation (AF) mostly present with large cortical infarcts, and less frequently with lacunar infarcts compared with patients without AF due to the lack of collateral vessels which develop and compensate for acute arterial occlusion in patients with gradual occlusion of arteries, such as in atherosclerosis of cervical or cerebral arteries[18]. The exact mechanisms of AF effect on the outcomes of stroke patients were not clear, it was suggested that stroke patients with AF may have large and old thrombi, which are not sensitive to the treatment of thrombolytic therapy [39].Our study found significant relation between AF and the poor functional outcome in ischemic stroke treated with IV thrombolysis, and that was in agreement with many previous studies [21,40].On the other hand, there were studies showed significant correlation between AF and favorable functional outcome after receiving IV rt-PA [41, 42], while other studies found a non-significant effect of AF on the outcome[18,28].

Apart from obesity and AF, results of this study did not show any significant relation between other risk factors and functional outcome of AIS patients treated with IV thrombolysis. These results agreed with some previous studies like that conducted by **Bhardwaj and colleagues**, which found that risk factors such as hypertension, diabetes, dyslipidemia, smoking, alcohol intake, history of stroke, coronary artery disease, and valvular heart disease did not influence outcome in patients of AIS receiving rt-PA [25]. While, **Tork et al**. found significant negative correlation between DM and hypertension and the functional outcome among AIS patients after receiving IV rt-PA [21].

As regards the baseline clinical data of thrombolysed patients on admission; this study found that admission hyperglycemia (HG) was significantly associated with poor functional outcome. This could be because the increased glucose levels in stroke patients can alter the blood barrier permeability, exacerbate the thromboinflammatory cascade, induce acidosis, increase oxidative stress response, and increase the risk of intracerebral hemorrhage [43]. Moreover, in IV thrombolytic patients, the HG can reduce the fibrinolytic activity of t-PA by increasing the production of plasminogen activator inhibitor (PAI)-1[44].Our findings are in agreement with many previous studies like **Das et al.**, **Ahmed et al.**, and **Tsivgoulis et al.** [15,26,45]

The correlation of baseline systolic blood pressure (SBP) with outcome of AIS patients underwent thrombolysis has been discussed in several studies. Some previous studies suggested that higher SBP on admission was associated with poor outcomes [46, 47,48]. Additionally, a recent meta-analysis study conducted by **Lei et al.** suggested that lower baseline SBP may be positively associated with a greater chance of good outcome and less chance of intracranial hemorrhage in AIS patients treated with thrombolytic therapy [49]. Our study also detected similar findings regarding the admission SBP, however, diastolic blood pressure (DBP) did not show significant relationship with the post-thrombolysis outcome. On the other hand, some other previous studies reported non-significant effect of baseline blood pressure on the outcome of AIS patients treated with alteplase like that study conducted by **Bhardwaj et al.** [25].

The National Institutes of Health Stroke Scale (NIHSS) is a score of severity of the stroke. We have found that patients with higher NIHSS score on admission had poor functional outcome 30 days after treatment with IV alteplase. These findings again are consistent with previous studies that showed that higher NIHSS score at the time of presentation was associated with poor outcome [21,25,28,29]. Different from our findings, **Emberson and colleagues** did not find clear evidence that stroke severity modified the effect of IV thrombolysis [20]. Moreover, the **IST-3 collaborative group** reported that significant trends towards larger effect of treatment on more severe stroke as assessed by NIHSS [12].

Many previous studies reported that the NIHSS score 24 h after receiving IV rt-PA is considered to be a strong independent predictor of the functional outcome, its increase is associated with poor functional outcome and vice versa [21,50,51]. Thus highly suggests that the initial clinical improvements in the first hours or 24 h after receiving IV rt-PA is of great importance in determining the final degree of patient dependency in the future [21]. This study also found highly significant association between NIHSS 24 h after thrombolysis and 30-day functional outcome of AIS patients.

Regarding the effect of stroke subtypes, according to TOAST criteria, on the AIS outcome; In spite of the controversy about cardioembolic (CE) stroke responses to IV rt-PA in many previous studies, IV alteplase was recommended for patients with AIS of all types [52]. Some previous studies have demonstrated that responses to rt-PA therapy may be different according to stroke subtypes [53, 54], and some other studies have shown no difference in functional outcomes between stroke subtypes [28, 29]. Our study found that CE stroke had worse functional outcome, 30 days following thrombolytic therapy, compared with other stroke subtypes. This is in agreement with previous studies like that recent study which was conducted by **Esmael et al.** [55].These findings could be attributed to the development of large embolus size, large infarct size, and frequent hemorrhagic transformation associated with CE stroke, thus producing more disabling strokes. On the contrary, **Vaclavik et al.** reported better functional outcome of CE strokes treated by intravenous thrombolysis in comparison to other stroke subtypes [56].

Conclusion

We can conclude that after 30 days of follow-up, rt-PA had significant increase of favorable functional outcome with increased risk of ICH than controls, and a non-significant difference of the mortality rate.

Declarations

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