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Predictors of the functional outcome after thrombolysis in an Egyptian patients' sample

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Abstract

Background: About 6.2 million individuals worldwide and approximately 200 Egyptians/100,000 citizens have cerebrovascular stroke annually, and only less than 1% of stroke patients received intravenous (IV) thrombolysis in 2014. Outcome of the ischemic stroke after IV thrombolysis varies, and there is lack of data about the predicting factors that contributes to the outcome of ischemic strokes after IV thrombolysis in Egypt.

Objective: The aim of this work is to study the predictors of the functional outcome of ischemic cerebrovascular stroke after IV thrombolysis in Egyptian patients.

Patients and methods: This is a prospective study that includes acute ischemic stroke patients who received IV thrombolysis at the Alexandria University Hospital during the year from February 2017 to February 2018, and they were evaluated initially by Rapid Arterial Occlusion Evaluation (RACE) scale and followed-up serially for 6 months after thrombolysis using the National Institutes of Health Stroke Scale (NIHSS) and modified ranking score (mRS).

Results: Forty-five patients are included; 56% had favorable functional outcome (mRS 0–2) after 6 months, 68% had ≥ 4 points improvement in NIHSS after 6 months, and 13% had hemorrhagic conversion with 18% mortality rate. High initial RACE scale and long hospital stay are associated with poor functional outcome 6 months after thrombolysis.

Conclusion: Stroke severity demonstrated by high initial RACE and the duration of hospital stay are the two most significant predictors with an impact on the functional outcome of ischemic cerebrovascular stroke after thrombolysis.

Keywords: Stroke, Thrombolysis, rTPA, NIHSS, mRS, RACE, Predictors of stroke outcome

Introduction

About 200 Egyptians/100,000 citizens have cerebrovascular stroke annually, and the majority of cerebrovascular strokes are ischemic (85–87%) in nature [1–3].

Stroke is the second worldwide most common cause of mortality, and the third being disability-adjusted life years (DALYs) lost. Moreover, low- and middle-income countries account for 86% of all stroke mortality and over 87% of DALYs lost from stroke [4, 5].

Optimal treatment involves the administration of recombinant tissue plasminogen activator (rtPA) as early as possible within a window period of 4.5 h after the onset of clinical symptoms. In Egypt, the frequency of thrombolysis is very low, less than 1% of the ischemic stroke patients in 2014. Major reasons include the financial aspect, the pronounced delay in pre-hospital delivery, and in-hospital management of acute stroke [6].

The clinical outcome of acute ischemic stroke (AIS) after rtPA varies a lot, and to early predict the course

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and outcome of the ischemic stroke after IV, thrombolysis can help in making decisions regarding the treatment protocol followed for each individual patient [7, 8].

One of the adverse events that could occur and lead to a worse outcome is the hemorrhagic transformation in ischemic stroke area. Many studies presented some risk factors for hemorrhagic conversion after thrombolysis like advanced age, increased onset-to-treatment times, higher National Institutes of Health Stroke Scale (NIHSS; stroke severity), dense middle cerebral artery (MCA) sign or early infract signs on computer tomography (CT) brain imaging, and hyperglycemia and hypertension before or after tPA administration [9, 10].

On the other hand, there is a lack of similar data in Egypt in literature. Thus, the aim of this work is to study the clinical functional outcome of AIS after thrombolysis in Egyptian patients and the predicting factors contributing to that outcome.

Methods

This is a single-armed prospective cohort study conducted at Alexandria University Hospital and included all acute ischemic stroke (AIS) patients who presented to the hospital within the time window (4.5 h from stroke symptoms' onset) and were 18 years old or more and candidates for IV thrombolysis throughout the year from February 2017 to February 2018. Due to the small number of acute ischemic stroke patients arriving to hospitals within the first 4.5-h window period of stroke, the sample size was not determined before the start of the current study. Instead, duration of a year was set to recruit all stroke patients that would receive rtPA in such period.

All patients with absolute contraindication to rtPA were excluded. These absolute contraindication includes significant head trauma or prior stroke in the previous 3 months, suggestive symptoms of subarachnoid hemorrhage, arterial puncture at non-compressible site in previous 7 days, history of previous intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, recent intracranial or intraspinal surgery, persistent elevated blood pressure (systolic > 185 mmHg or diastolic > 110 mmHg), active internal bleeding, acute bleeding diathesis including platelet count < 100,000/mm^3, heparin received within 48 h, current use of anticoagulants with international normalized ratio (INR) > 1.7 or PT > 15 s and current use of direct thrombin inhibitors or direct factor Xa inhibitors, blood glucose concentration < 50 mg/dL, and CT brain demonstrating a multilobar infarction with hypodensity > 1/3 cerebral hemisphere [11].

Patients with relative contraindications for rtPA, including minor or rapidly improving stroke symptoms spontaneously, pregnancy, seizure at onset, major surgery or serious trauma within the previous 14 days, recent gastrointestinal or urinary tract hemorrhage within the previous 21 days, recent acute myocardial infarction within the previous 3 months, were evaluated according to risk versus benefit in every individual situation according to the consultants' opinions [11].

Ethical committee approval and written informed consent from all the subjects or their surrogates were obtained. All patients in this study were subjected to rapid clinical assessment on admission including complete history taking with special emphasis on the stroke risk factors—as hypertension, diabetes, smoking, dyslipidemia, cardiac risk factors or previous history of stroke, or transient ischemic attack (TIA); neurological examination and assessment of stroke severity by the National Institutes of Health Stroke Scale (NIHSS) [12] (scores ranging from 0 to 42); the Rapid Arterial Occlusion Evaluation (RACE) scale [13, 14] (scores ranging from 0 to 9); and the Field Assessment Stroke Triage for Emergency Destination (FAST-ED) [15] (scores ranging 0 from to 9), with higher scores indicating more severe strokes in all the previously mentioned scales.

Also, the patients underwent initial brain imaging either CT (using a Brilliance 64-slice CT scanner (Philips Healthcare, Netherlands)) or magnetic resonance imaging with diffusion weighted image (MRI with DWI) (using a Philips Achieva 1.5 T MRI scanner (Philips Healthcare, Netherlands)), and all CT brain scans done initially were assessed by the Alberta Stroke Program Early CT Score (ASPECTS) [16] before rtPA administration and to determine the dose of rtPA to be used according to the extent of the hypodensity area demonstrated on the initial CT brain. Assessment of vital signs and initial laboratory investigations like complete blood picture (CBC), INR, and random blood glucose were also sought for all patients.

They received IV thrombolysis at Alexandria University Stroke Unit at Elhadara and Smouha hospitals. Communication with the neurological experts using telemedicine to provide the rtPA service 24 h/7 days with optimal care was sought. Two doses of rtPA were used: the standard 0.9 mg/kg and a lower dose of 0.6 mg/kg. rtPA with low dose was considered in patients who had relative contraindications for rtPA or presented with more than one of the following factors: hospital arrival 3 h or more after the onset of stroke symptoms, old age (> 80 years), multiple risk factors/comorbidities that indicated possible unhealthy vasculature and consequently high risk of hemorrhage, high initial NIHSS or signs of large vessel occlusion, and low Alberta Stroke Program Early CT Score (ASPECTS) on CT brain (less than 7).

All patients were monitored closely during and following the rtPA infusion and unless it was indicated—like in case of worsening of the stroke symptoms,

development of headache or peripheral bleeding, and follow-up CT brain was done 24 h after tPA to exclude hemorrhagic conversion of the ischemic stroke before the initiation of antiplatelets. Other investigations were done to the patient to assess the possible etiology of the ischemic stroke as electrocardiography (using Fukuda M-E Cardisuny C110 ECG machine (Fukuda Denshi Company, Japan)), echocardiography (using Philips HD11 Ultrasonography machine (Philips Healthcare, Netherlands)), and carotid doppler (using Philips clear-vue 350 Ultrasonography Machine (Philips Healthcare, Netherlands)) and/or CT brain angiography (using a Brilliance 64-slice CT scanner (Philips Healthcare, Netherlands)).

The patients were evaluated serially for 6 months after thrombolysis during their hospital stay and via their follow-up visits at the clinic using the NIHSS and modified ranking score (mRS) at 24 h after IV thrombolysis, upon the patients' discharge from the hospital, and at the end of the third and sixth month post-thrombolysis. FAST-ED and RACE scales were used initially to assess the severity of stroke and correlate the stroke severity with the outcome of ischemic stroke, while follow-up of the stroke manifestation and the functional outcome were achieved by using the NIHSS and mRS.

Statistical analysis

Data were analyzed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) Statistics for Windows software version 20.0 (released 2011 by IBM Corporation which is headquartered in Armonk, New York, USA), and several factors were studied to assess their impact on the functional outcome after 6 months using statistical tests like Mann Whitney test, Kruskal Wallis test, Spearman coefficient, Friedman test, and linear and logistic regression analyses. The level of statistical significance was expressed as Pearson's value (P value), with the P value considered statistically significant whenever it was ≤ 0.05.

Results

The study included 45 ischemic stroke patients. The median age of the patients was 59 years (mean 60.13 ± 10.5 years). Only 4 patients had stroke at a young age at the age of or below 45 years old. Other stroke risk factors reported in the study sample together with the ischemic stroke clinical presentation are demonstrated in Table 1.

The number of modifiable risk factors ranged from 0 to 5 risk factors per patient, with a median of 2 risk factors per patient (mean ± SD is 2.11 ± 1.11). Only 6 patients were found on daily antiplatelets use prior to the onset of their stroke.

The initial CT brain was unremarkable in 34 patients, while it revealed old strokes—whether subclinical or was

Table 1 Demographic data, stroke risk factors, and clinical presentation in the study sample ($n = 45$)

	***n* (%)**
Age (years)	
Mean ± SD.	60.13 ± 10.50
Median (min.–max.)	59 (29–84)
Sex	
Male	20 (44.4%)
Female	25 (55.6%)
Risk factors of stroke	
Hypertensives	26 (57.8%)
Diabetics	17 (37.8%)
Smoker	
Non-smoker	32 (71.1%)
Smoker	11 (24.4%)
Ex-smoker	2 (4.4%)
Dyslipidemics	5 (11.1%)
Cardiac risk factors	
Arterial fibrillation (AF)/ arrhythmias	14 (31.1%)
Known AF	7 (15.6%)
Newly discovered AF after the stroke onset	7 (15.6%)
Myocardial infraction (MI)	5 (11.1%)
Structural cardiac risk factors	
Hypokinesia/akinesia	10 (22.2%)
Intracardiac myxoma	1 (2.2%)
Intracardiac Thrombus	1 (2.2%)
Valvular (RHD)	9 (20%)
Ejection fraction (EF) < 40%	7 (15.6%)
Previous history of stroke/TIA	10 (22.2%)
History of TIA	5 (11.1%)
History of stroke	5 (11.1%)
Clinical presentation	
Weakness	
Hemiparesis	34 (75.6%)
Hemiplegia	11 (24.4%)
Speech disorder (aphasia/dysphasia)	12 (26.7%)
Gaze deviation	14 (31.1%)
Bulbar	41 (91.1%)
Dysarthria/facial palsy	31 (68.9%)
Deglutition weakness/choking	10 (22.2%)
Hemisensory affection	6 (13.3%)
Cerebellar ataxia	2 (4.4%)
Initial CT brain	
Unremarkable	34 (75.6%)
MCA sign	2 (4.4%)
Old strokes	9 (20%)

SD standard deviation, *min.* minimum, *max.* maximum, *TIA* transient ischemic attack, *CT* computer tomography, *n* number

associated with corresponding history of clinical stroke—in 9 patients. MCA hyperdense sign was apparent in the initial CT brain scans of 2 patients.

The median onset-to-hospital-arrival time was 180 min with a range of 60–240 min. The median door-to-needle (DTN) time was 50 min, and the minimum DTN time was 25 min with 82.2% of the patients having a door-to-needle time of 60 min or less. The median onset-to-tPA time was 235 min (3 h 55 min), with a range of 120–270 min (2–4 h 30 min). Twenty-seven patients received rtPA dose of 0.6 mg/kg (60% of the patients), and 18 patients received rtPA of 0.9 mg/kg (40% of the patients).

Upon admission, the patient was evaluated before administration of rtPA and further investigations were done during the hospital stay and the follow-up period as demonstrated in Table 2. The commonest stroke type was cardioembolic (15 patients; 33.3%) followed by lacunar (12 patients; 26.7%), atherosclerotic (10 patients; 22.2%) then undetermined stroke type (8 patients; 17.8%), with the majority of patients (43 patients; 95.6%) having anterior circulation strokes.

Adverse events encountered are as follows: mortality (8 patients; 18%), midline shift (9 patients; 20%), hemorrhagic transformation (6 patients; 13%), intubation (6 patients; 13%), peripheral bleeding as hematuria or unilateral ear bleeding (3 patients; 6.7%), and skin rash (1 patient; 2.2%).

Throughout the study, there was a dropout of 8 patients of whom 3 patients died during hospitalization out of malignant MCA stroke with midline shift > 10 mm within the first 36 h, bilateral brainstem stroke (basilar artery occlusion), and cardiogenic shock due to decompensated heart failure. Another five outpatient deaths occurred during the follow-up period. Causes of death included causes related to the high disability, sepsis including aspiration pneumonia, and warfarin toxicity.

Regarding the functional outcome assessed via mRS, the median mRS was 4 following the rtPA administration by 24 h, 3 upon discharge, and 2 at 6 months post-thrombolysis. Significant change in the mRS upon discharge from its value after 24 h was illustrated (P = 0.034). Also a significant decline in the mRS after 6 months in comparison to the initial mRS after 24 h was detected (P = 0.030) (Table 3). Fifty-six percent of the patients had favorable functional outcome identified as mRS = 0–2 after 6 months (Fig. 1).

Statistically significant descends in NIHSS were found along the different time intervals (24 h upon discharge and 3 and 6 months later) when each was compared to the initial NIHSS and when the rates of change between the different periods were compared (Table 3) (Fig. 2).

The female gender was significantly associated with the rate of change of NIHSS after 6 months (Fig. 3), with a significantly higher mean change in the female patients 7.27 ± 3.98 in comparison to the male patients 5.47 ± 1.77 (P = 0.024). However, no such association was revealed with the mRS after 6 months.

There was a positive strong correlation between poor mRS outcome after 6 months and the length of hospital stay; stroke severity manifested as high initial NIHSS, FAST-ED, and RACE and old age of the patients (Table 4). Also, the rate of change of mRS at 6 months from that at 24 h after rtPA (Δ mRS 24 h–6 months) showed significant negative correlational relationships with each of the initial NIHSS and RACE scores and the length of hospital stay, which means that the higher the initial NIHSS and RACE or the longer the hospital admission, the smaller the change in the mRS after 6 months was.

There were significant associations between poor functional outcome (mRS after 6 months) and the occurrence of hemorrhagic transformation or midline shift and large vessel occlusive ischemic stroke types. Moreover, a significant association between the rate of change of the mRS after 6 months (Δ mRS 24 h–6 months) and the occurrence of intracerebral hemorrhagic transformation and midline shift was revealed, with the rate of diminution of the mRS being minimal or even reversed—indicating worsening of the mRS—in the patients with hemorrhagic transformation (P = 0.021) or midline shift (P = 0.014) (Table 5).

Modified ranking score (mRS) after 6 months was also found to have a significant negative correlation with the systolic blood pressure on admission; the lower the blood pressure, the poorer the mRS became after 6 months (r_s = − 0.305, P = 0.042).

There is a significant reverse correlation between the duration of the hospital stay and the rate of change of the NIHSS upon discharge and 6 months after rtPA administration and the rate of change of the mRS after 6 months as well. That means the longer the hospital stay, the smaller the change in these disability and functional scores was from their initial values.

The length of the hospital stay was found to be positively and strongly correlated with the initial FAST-ED (r_s = 0.421, P = 0.004) and RACE scores (r_s = 0.431, P = 0.003) and reversely correlated with the ASPECT score on the initial CT brain (r_s = − 0.303, P = 0.043).

Furthermore, univariate logistic regression analysis confirmed the significant impact of each of the following independent variables on the mRS outcome after 6 months: initial FAST-ED, initial RACE, initial NIHSS, length of hospital stay, large vessel occlusion strokes, and the occurrence of midline shift. However, the multivariate regression analysis revealed only a significant

Table 2 Patient assessment and hospital factors pre- and post-thrombolysis in the study sample ($n = 45$)

	Median (min.–max.)
Onset-to-hospital-arrival time	
Mean ± SD	171.8 ± 43.22
Median (min.–max.)	180 (60–240)
Initial FAST-ED	
Median (min.–max.)	3 (1–7)
Initial RACE	
Median (min.–max.)	4 (2–9)
ASPECT score	
Median (min.–max.)	10 (8–10)
Systolic BP (mmHg)	
Median (min.–max.)	140 (100–220)
Diastolic BP (mmHg)	
Median (min.–max.)	80 (60–140)
Random blood glucose (mg/dL)	
Median (min.–max.)	156 (88–558)
INR	
Median (min.–max.)	1.06 (0.90–1.34)
Platelets (× 10^3 μL)	
Median (min.–max.)	226 (102–402)
Hemoglobin (g)	
Median (min.–max.)	13 (9.5–17)
Door to needle (min)	
Mean ± SD	53.67 ± 19.32
Median (min.–max.)	50 (25–120)
Onset-to-TPA time (min)	
Mean ± SD	225.7 ± 36.6
Median (min.–max.)	235 (120–270)
Hospital stay (days)	
Median (min.–max.)	5 (2–68)
	***n* (%)**
Stroke type	
Cardioembolic LVO	15 (33.3%)
Atherosclerotic LVO	10 (22.2%)
Small vessel stroke	12 (26.7%)
Undetermined cause	8 (17.8%)
Carotid dopplex (of symptomatic side) ($n = 43$)	
Normal	24 (55.8%)
Atherosclerosis without or with stenosis < 50	16 (37.2%)
Stenosis ≥ 70%	1 (2.3%)
Total occlusion	2 (4.7%)
Carotid dopplex (of asymptomatic side) ($n = 43$)	
Normal	30 (69.8%)
Atherosclerosis without or with stenosis < 50	11 (25.6%)
Stenosis ≥ 50 to < 70%	1 (2.3%)
Stenosis ≥ 70%	1 (2.3%)

SD standard deviation, *FAST-ED* Field Assessment Stroke Triage for Emergency Destination, *RACE* Rapid Arterial Occlusion Evaluation, *MCA* middle cerebral artery, *ASPECT* Alberta stroke program early CT score, *BP* blood pressure, *INR* International normalized ratio, *TPA* tissue plasminogen activator, *LVO* large vessel occlusion, *n* number

impact of the initial RACE on the mRS after 6 months, denoting that stroke severity is highly associated with poor functional outcome (mRS) 6 months after thrombolysis (Table 6).

Discussion

Various studies used different measures to assess the outcome of stroke after IV thrombolysis. However, most of the studies included the mRS in their assessment and used it either alone or besides other measures as NIHSS, 4-point improvement in NIHSS, Barthel Index, and Glasgow Outcome Scale [17]. The present study utilized mRS, Δ change of NIHSS, and 4-point improvement in NIHSS as tools to assess the clinical outcome of AIS.

Among all patients studied, favorable functional outcome (mRS 0–1) after 6 months was encountered in 49% of the patients and mRS of 0–2 after 6 months as well was found in 56% of the patients. Significant changes in mRS were observed upon discharge and after 6 months, each being compared to mRS after the first 24 h. The patients showed significant changes in NIHSS at 24 h, upon discharge, and 3 months and 6 months after tPA administration, with a median initial NIHSS of 10 that decreased to 1 after 6 months. Mortality was encountered in 18% of all patients in this current study.

A meta-analysis included 12 trials (7012 patients) showed mRS of 0–2 at the final follow-up in 46·3% of the patients—with the highest benefit found in patients treated within the first 3 h, mortality in 19% and symptomatic intracerebral hemorrhage (SICH) in 7·7% that accounted for most of the early deaths [18]. Several studies showed approximate similar results as well [19–22].

The studied sample had higher percentage of females. It may be attributable to the risks related to pregnancy and the postpartum state, sex hormone, the use of hormonal contraceptives, and the longer life span of women [2, 23–26]. Also, a significant association relationship was found between the female gender and rate of change of the NIHSS, indicating that women showed significantly more descends in the NIHSS compared to men. This differs from studies in Turkey and North America

Table 3 Comparison between the different periods according to NIHSS and mRS throughout the follow-up duration

	Initial (*n* = 45)	After 24 h (*n* = 45)	Upon discharge (*n* = 42)	After 3 months (*n* = 38)	After 6 months (*n* = 37)	Fr	*P*
NIHSS							
Min.–Max.	5.0–18.0	0.0–19.0	0.0–18.0	0.0–18.0	0.0–18.0	120.215*	< 0.001*
Mean ± SD	10.16 ± 3.69	7.67 ± 5.19	5.48 ± 5.04	3.63 ± 4.79	3.27 ± 4.65		
Median	10.0	7.0	4.0	2.0	1.0		
p_1		**0.006***	**< 0.001***	**< 0.001***	**< 0.001***		
p_2					**0.003***		
mRS							
Min.–Max.		0.0–5.0	0.0–6.0	0.0–6.0	0.0–6.0	12.918*	0.005*
Mean ± SD.		3.11 ± 1.45	2.62 ± 1.80	2.60 ± 2.19	2.56 ± 2.27		
Median		4.0	3.0	2.0	2.0		
P_1			**0.034***	**0.079**	**0.030***		
P_2					**0.967**		

Fr Friedman test, Sig. bet. periods was done using post hoc test (Dunn's)
NIHSS National Institutes of Health Stroke Scale, *mRS* modified ranking score
P = *P* value for comparing between the different periods
P_1 = *P* value for comparing between the *initial* and each periods
P_2 = *P* value for comparing between *upon discharge* and after 6 months
*Statistically significant at $P \leq 0.05$

where Keheya and colleagues and Williams and colleagues, respectively, found that the female gender was associated with less-favorable functional outcome among ischemic stroke patients due to more severe strokes and older age at stroke onset and that also females were at higher risk for ischemic strokes among patients with symptomatic intracranial atherosclerosis [24, 26–29].

On the contrary, Pu and colleagues reported no gender differences in outcomes among ischemic stroke Chinese patients with intracranial atherosclerosis after adjusting the other risk factors. Another global study found no significant difference between males and females regarding the impact of disability due to stroke measured by disability-adjusted life-years (DALYs) and healthy years lost due to disability (YLDs) [24, 30, 31]. The differences between the current study and the other various studies may be explained by differences in the study design, the genetic background of the study population, or variations in risk factors among males and females. Anatomical differences including the cerebral collateral arteries between men and women or among different races were recently suggested but still unclear [24].

The present study found that the hospital stay duration was significantly and reversely correlated with the rate of change in NIHSS and mRS after 6 months. Approximately two-thirds of the patients were discharged

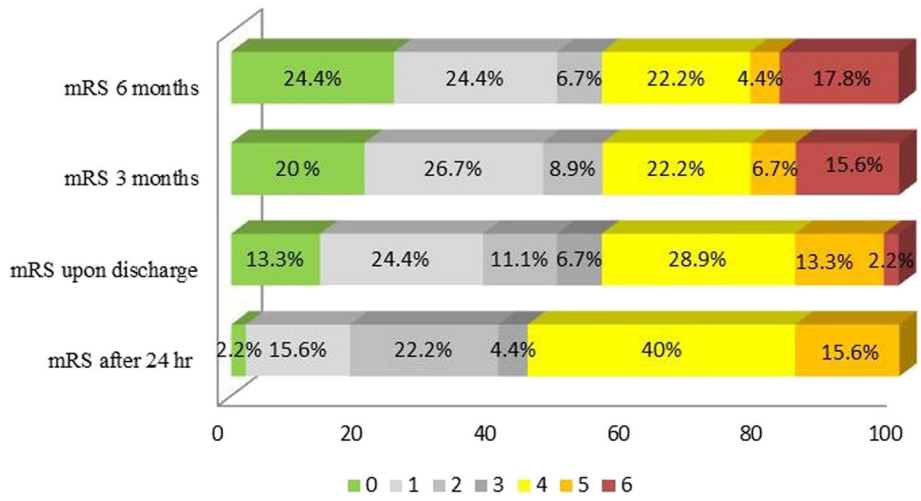

Fig. 1 Percentages of each mRS value among the group of patients studied at different time periods

Fig. 2 The median NIHSS along the different periods in the total sample and in each group

within the first week after admission. Kasemsap and colleagues demonstrated that long hospital stay in AIS patients was found to be associated with intravenous thrombolysis, AF, pneumonia and urinary tract infection regardless of age, stroke severity, or comorbidities [32]. Fjærtoft and colleagues in a 5-year-prospective study suggested that stroke unit care together with early supported discharge (ESD) of AIS patients reduced mortality and increased functional outcome [33].

The present study showed no significant correlation between the onset-to-tPA time and the outcome after 6 months. This may be attributed to the small size sample of this study and the diversity of data. Several studies demonstrated that shortening the door-to-needle time is associated with early recanalization, better functional outcomes, and decrease in-hospital stay length [18, 34–36].

Thirteen percent of all patients included in this current study (6 patients) had intracerebral hemorrhagic transformation whether asymptomatic or symptomatic. Symptomatic intracerebral hemorrhage (SICH) with neurological deterioration with increase of 4 or more points in the NIHSS was encountered in only one patient within the first 36 h after tPA administration. Frequencies of SICH vary in different studies from the National Institute of Neurological Disorders and Stroke Trial (NINDs) to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) according to the definition selected (1.7–10.3%) [10, 37–40]. Chang and colleagues found that more than 80% of SICH occurred within less than 12 h after tPA administration [41]. Paciaroni and colleagues and several similar studies demonstrated that large lesion, cardioembolic strokes, high blood glucose levels, low platelet count, and treatment with thrombolysis are predictors of hemorrhagic transformation in AIS patients [42–44].

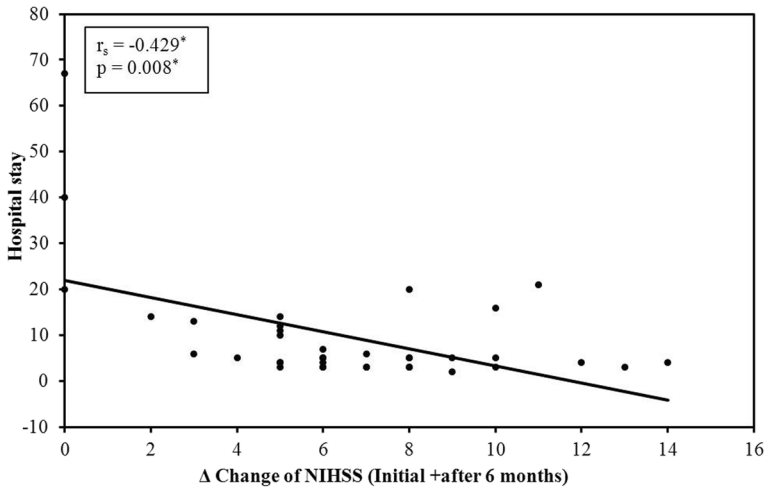

Fig. 3 Correlation between Δ change of NIHSS (initial-after 6 months) with hospital stay

Table 4 Correlation between patients' age, initial stroke assessment scales, onset-to-tPA and hospital stay durations, and the functional outcome of AIS

	Δ Change of:						mRS after 6 months	
	Δ NIHSS (initial–upon discharge)		Δ NIHSS (initial–after 6 months)		Δ mRs (after 24 h–after 6 months)			
	r_s	*P*	r_s	*P*	r_s	*P*	r_s	*P*
Age (years)	− 0.008	0.960	0.058	0.731	− 0.258	0.087	0.367*	0.013*
***n* of risk factors**	− 0.062	0.697	0.010	0.952	− 0.066	0.667	0.155	0.310
Initial FAST-ED	0.032	0.842	0.212	0.208	− 0.198	0.192	0.506**	0.000**
Initial RACE	− 0.137	0.386	0.029	0.863	− 0.406*	0.006*	0.677**	0.000**
Initial NIHSS	0.144	0.362	0.306	0.066	− 0.305*	0.042*	0.548**	0.000**
Onset-to-presentation time	− 0.272	0.081	− 0.215	0.202	− 0.144	0.347	0.199	0.190
Onset to tPA	− 0.262	0.094	− 0.197	0.242	− 0.204	0.178	0.283	0.059
ASPECT score	0.071	0.656	− 0.132	0.437	0.052	0.732	− 0.216	0.155
Hospital stay	− 0.427*	0.005*	− 0.429*	0.008*	− 0.359*	0.016*	0.558**	0.000**

Δ Change rate of change, *n* number, *NIHSS* National Institutes of Health Stroke Scale, *mRS* modified Ranking score, *FAST-ED* Field Assessment Stroke Triage for Emergency Destination scale, *RACE* Rapid Arterial oCclusion Evaluation Scale, *tPA* tissue plasminogen activator, *ASPECT* Alberta stroke program early CT score
r_s Spearman coefficient
*Statistically significant at $P \leq 0.05$
**Statistically significant at $P \leq 0.01$

Table 5 Correlation between gender, stroke type, hemorrhagic conversion of stroke and midline shift, and the functional outcome of AIS

	Δ Change of NIHSS (initial–after 6 months)			mRS after 6 months				Δ Change of mRS (after 24 h–after 6 months)		
	Mean ± SD	Test of sig.	*P*	Mean ± SD	Median	Test of sig.	*P*	Mean ± SD	Test of sig.	*P*
Sex										
Male	5.47 ± 1.77	*U* = 92.0*	0.024*	2.80 ± 2.42	3	*U* = 272	0.607	0.35 ± 1.14	*U* = 214.50	0.402
Female	7.27 ± 3.98			2.36 ± 2.18	1			0.72 ± 1.57		
Initial CT brain (MCA sign)										
Negative	6.58 ± 3.39	*U* = 10.0	0.450	2.51 ± 2.25	2	*U* = 55.50	0.517	0.60 ± 1.40	*U* = 20.50	0.201
Positive	5.0			3.50 ± 3.54	3.5			0.50 ± 0.71		
Anterior vs. posterior circulation										
Anterior circulation	6.39 ± 3.27	*U* = 2.636	0.104	2.51 ± 2.25	2	*U* = 55.50	0.517	0.58 ± 1.40	*U* = 33.50	0.618
Posterior circulation	12.0			3.50 ± 3.53	3.5			0.0 ± 1.41		
TOAST classification										
Cardioembolic LVO	8.11 ± 4.68	*H* = 4.645	0.200	3.73 ± 2.34	4	*H* = 14.27*	0.003*	0.20 ± 1.82	*H* = 4.787	0.188
Atherosclerotic LVO	4.88 ± 2.70			3.30 ± 2.21	4			0.50 ± 1.65		
Small vessel stroke	6.50 ± 1.83			0.67 ± 1.15	0			0.92 ± 0.79		
Undetermined cause	6.50 ± 3.74			2.25 ± 1.75	1			0.75 ± 0.71		
Hemorrhagic transformation										
Negative	6.76 ± 3.34	*U* = 46.50	0.354	2.28 ± 2.22	1	*U* = 176.50*	0.045*	0.72 ± 1.41	*U* = 49.50*	0.021*
Positive	4.75 ± 3.40			4.33 ± 1.86	4.5			− 0.50 ± 0.55		
Midline shift										
No midline shift	7.06 ± 3.08	*H* = 5.020	0.081	2.03 ± 2.16	1	*H* = 9.129*	0.010*	0.83 ± 1.38	*H* = 8.583*	0.014*
Midline shift < 5	4.60 ± 3.58			4.43 ± 1.40	4			− 0.57 ± 0.79		
Midline shift > 5	0.0			5.50 ± 0.71	5.5			− 0.50 ± 0.71		

U Mann Whitney test, *H* Kruskal Wallis test, *AIS* acute ischemic stroke, *Δ Change* rate of change, *NIHSS* National Institutes of Health Stroke Scale, *mRS* modified Ranking score, *CT* computed tomography, *MCA* middle cerebral artery, *TOAST classification* trial of ORG 10172 in acute stroke treatment classification, *LVO* large vessel occlusion
P = *P* value for comparing between the different categories
* Statistically significant at $p \leq 0.05$

Table 6 Factors affecting the Δ change of NIHSS and mRS after 6 months and mortality (using regression analysis)

	Δ Change of NIHSS after 6 months		mRS after 6 months		Mortality	
	Univariate		Univariate		Univariate	
	P	B (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Dose (0.9)	**0.617**	− 0.565(− 2.8 to − 1.70)	**0.541**	0.685 (0.204 to 2.302)	**0.111**	0.168 (0.019 to 1.50)
Age (years)	**0.629**	− 0.025 (− 0.130 to 0.08)	**0.054**	1.070(0.999 to 1.145)	**0.173**	1.059 (0.975 to 1.15)
No of risk factors	**0.855**	0.081 (− 0.816 to 0.98)	**0.306**	1.277 (0.800 to 2.038)	**0.195**	1.50 (0.811 to 2.78)
Initial FAST − ED	**0.906**	0.346 (− 0.429 to 1.12)	**0.011***	1.943*(1.163 to 3.245)	**0.181**	1.43 (0.845 to 2.43)
Initial RACE	**0.958**	− 0.017 (− 0.653 to 0.6)	**0.001***	2.638*(1.507 to 4.617)	**0.066**	1.57 (0.971 to 2.54)
Initial NIHSS	–	–	**0.005***	1.354*(1.098 to 1.668)	**0.184**	1.153 (0.935 to 1.42)
Onset-to-presentation time	**0.340**	− 0.013 (− 0.042 to 0.02)	**0.181**	1.010 (0.995 to 1.025)	**0.958**	1.0 (0.983 to 1.019)
Onset to tPA	**0.313**	− 0.017 (− 0.050 to 0.02)	**0.154**	1.013 (0.995 to 1.032)	**0.997**	1.00 (0.979 to 1.021)
ASPECT score	**0.233**	− 1.012 (− 2.72 to 0.685)	**0.551**	0.764 (0.316 to 1.848)	**0.442**	0.670 (0.241 to 1.862)
Hospital stay	**0.001***	− 0.139*(− 0.21 to − 0.06)	**0.012***	1.174*(1.036 to 1.331)	**0.179**	1.035 (0.985 to 1.087)
SBP on admission	**0.424**	0.016 (− 0.024 to 0.06)	**0.062**	0.975 (0.950 to 1.001)	**0.193**	0.976 (0.941 to 1.012)
DBP on admission	**0.575**	0.021(− 0.053 to 0.09)	**0.063**	0.952 (0.904 to 1.003)	**0.183**	0.954 (0.891 to 1.02)
RBS on admission	**0.260**	− 0.007(− 0.019 to 0.01)	**0.201**	1.004 (0.998 to 1.010)	**0.113**	1.005 (0.999 to 1.012)
Sex (females)	**0.109**	1.80 (− 0.422 to 4.034)	**0.503**	0.667(0.203 to 2.184)	**0.266**	0.409 (0.085 to 1.97)
Initial CT brain (MCA sign)	**0.491**	0.469(− 0.89 to 1.836)	**0.872**	1.263 (0.074 to 21.54)	**0.788**	0.872 (0.320 to 2.37)
Stroke type (cardioembolic LVO)	**0.614**	− 0.369 (− 1.84 to 1.10)	**0.013***	18.33*(1.868 to 179.8)	**0.099**	0.222 (0.037 to 1.3)
Anterior vs. posterior circulation	**0.100**	5.611 (− 1.12 to 12.3)	**0.872**	1.263(0.074 to 21.54)	**0.266**	5.14 (0.286 to 92.3)
Hemorrhagic transformation	**0.264**	− 2.0(− 5.59 to 1.58)	**0.069**	8.0 (0.850 to 75.28)	**0.299**	2.750 (0.408 to 18.5)
Midline shift	**0.012***	− 2.96*(− 5.24 to − 0.69)	**0.013***	16.0*(1.788 to 143.1)	**0.151**	2.486 (0.717 to 8.62)
	#Multivariate		**#Multivariate**		**#Multivariate**	
	P	B (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Hospital stay	**0.048***	− 0.131*(− 0.261 to − 0.001)				
Initial RACE			**0.048***	3.954*(1.010 to 15.481)		

B Beta constant, *OR* odd`s ratio, *CI* confidence interval
#All variables with $p < 0.05$ was included in the multivariate
*Statistically significant at $p \leq 0.05$
Δ Change rate of change, *NIHSS* National Institutes of Health Stroke Scale, *mRS* modified Ranking score, *CT* computed tomography, *FAST-ED* Field Assessment Stroke Triage for Emergency Destination scale, *RACE* Rapid Arterial oCclusion Evaluation Scale, *tPA* tissue plasminogen activator, *ASPECT* Alberta stroke program early CT score, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *RBS* random blood glucose, *MCA* middle cerebral artery, *LVO* large vessel occlusion

The current study showed a significant inverse association between the occurrence of hemorrhagic transformation or the midline shift and the functional outcome (mRS) after 6 months. This was consistent with other studies that showed an adverse outcome associated with parenchymal hematoma [42, 45].

Different rtPA doses did not show a significant impact on the functional outcome after 6 months whether demonstrated via mRS after 6 months or the rate of change of NIHSS after 6 months, and that was consistent with some published studies. A meta-analysis which included ten cohort studies with 4389 sum patients revealed no statistically significant difference regarding the efficacy-favorable functional outcome, modified ranking scale 0–1 at 3 months, and safety (incidence of symptomatic intracranial hemorrhage (SICH) and mortality within 3 months) between the standard- and low-dose IV-tPA groups [46].

Another study showed no statistically significant difference among the different doses of tPA used in Chinese stroke patients regarding the incidence of sICH and mortality [47]. The ENCHANTED trial showed as well no significant difference between the two doses regarding the efficacy, yet the lower dose significantly showed lesser complications (SICH).

A similar non-randomized study by Ong and colleagues compared the different doses of tPA (0.6, 0.7, 0.8, and 0.9 mg/kg) with regard to the efficacy and safety via assessing the early neurological improvement (ENI) and the early neurological deterioration (END) at 24 h and mRS at 6 months. He defined the ENI as > 8 points improvement of the NIHSS—compared with the

baseline—at 24 h after rtPA or NIHSS improvement to 0 or 1 toward the end of tPA infusion and END as > 4 points increase in NIHSS within 24 h after rtPA infusion compared with baseline NIHSS. There was no significant difference regarding the ENI and END among the low doses and the standard dose of rtPA in the acute phase. However, significant poorer functional outcome (mRS = 3–6) at 6 months was demonstrated in the standard dose of rtPA. This was consistent with the finding of the current study in that the different doses of tPA differed in their outcome after 6 months but not at the acute phase.

Ong and colleagues explained that the poor functional outcome was associated with the severity of stroke (high initial NIHSS), stroke type (large vessel strokes), and diabetes mellitus [48]. Similarly, Huang and colleagues demonstrated that patients with lower pre-thrombolysis NIHSS score, no prior history of diabetes, no leukoaraiosis, lower pre-thrombolysis blood glucose, and systolic blood pressure had a better outcome [49]. Also, Koennecke and colleagues found that poor outcome at discharge from the stroke unit was associated with age, prestroke disability, ICH, diabetes, hypertension, atrial fibrillation, previous stroke, stroke severity, and pneumonia [50].

The present study showed that poor mRS outcome after 6 months was associated with old age, stroke severity manifested as high initial NIHSS, RACE and FAST-ED scores, large vessel occlusive stroke types, the occurrence of hemorrhagic transformation or midline shift, and long hospital stay. However, after analyzing the similar factors with multivariate regression, the duration of hospital stay had a significant impact on the rate of change of NIHSS after 6 months and stroke severity demonstrated by high initial RACE had a significant impact on the mRS after 6 months.

The current study may have certain limitations like the small number of the patients and all subjects being recruited from one region. So, it is possible that there may be other factors with an impact on the clinical outcome of AIS treated with IV rtPA thrombolysis, but their effect got obscured by these limitations. Several pre-hospital factors contributed to these limitations as decreased awareness of the population of the variety of stroke symptoms and the urgency to attend to hospital within the first 4.5-window period. Also, the transportation delay caused by traffic, lack of inter-hospitals' communications to deliver the patient to an equipped stroke center, or delay within the emergency services due to impaired triaging system or crowded emergency room (ER) is an important pre-hospital factor. The current study encourage the use of telemedicine and recommend to exert more effort regarding increasing the population's awareness about stroke, educational programs for the emergency services, and enhancing the inter-hospital communication services.

Conclusion

Stroke severity demonstrated by high initial RACE and the duration of hospital stay are the two most significant predictors with an impact on the functional outcome of ischemic cerebrovascular stroke after thrombolysis.

Abbreviations

AF: Atrial fibrillation; AIS: Acute ischemic stroke; ASPECTS: Alberta Stroke Program Early CT Score; CBC: Complete blood picture; CT: Computer tomography; DALYs: Disability-adjusted life years; DBP: Diastolic blood pressure; DTN: Door to needle; ENCHANTED: Enhanced Control of Hypertension and Thrombolysis Stroke Study; END: Early neurological deterioration; ENI: Early neurological improvement; ESD: Early supported discharge; FAST-ED: Field Assessment Stroke Triage for Emergency Destination; IBM: International Business Machines; INR: International normalized ratio; IV: Intravenous; MCA: Middle cerebral artery; MI: Myocardial infraction; MRI with DWI: Magnetic resonance imaging with diffusion weighted image; mRS: Modified ranking score; NIHSS: National Institute of Hospital Stroke Scale; NINDs: National Institute of Neurological Disorders and Stroke Trial; RACE: Rapid Arterial Occlusion Evaluation; rtPA: Recombinant tissue plasminogen activator; SBP: Systolic blood pressure; SICH: Symptomatic intracerebral hemorrhage; SITS-MOST: Safe Implementation of Thrombolysis in Stroke-Monitoring Study; SPSS: Statistical Package for the Social Sciences; YLDs: Years lost due to disability; Δ: Rate of change

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Authors' contributions

HME revised the results and the manuscript and is the corresponding author. DHS provided the idea of the research and revised the results. AME revised the radiological data in the research. HSA did the follow-up of the participants and data collection and sorting, demonstrated some of the results in the form of figures, and wrote the manuscript. The authors have read and approved the final manuscript.

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Availability of data and materials

The research data supporting the results reported in the article is totally available upon request from the authors.

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee (EC) of the Alexandria Faculty of Medicine which is constituted and operates according to the International Conference on Harmonisation-Good Clinical Practice ICH GCP guidelines (Food and Drug Administration guideline) and applicable local and institutional regulations and guidelines which govern the EC operation. The approval was obtained by the monthly meeting of EC on October 2017.

Informed written consents from stroke patient who participated in the study were obtained from all participants

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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