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Short-term outcome in ischemic stroke patients after thrombolytic therapy

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Abstract

Background: Stroke represents the second leading cause of death in the world after myocardial infarction. Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (alteplase, rt-PA) is the only pharmacological therapy that was approved for treatment within 4.5 h of acute ischemic stroke (AIS) onset. We aimed to predict the 3-month outcome of AIS patients who received alteplase regarding mortality, spontaneous intra-cerebral hemorrhage (sICH), and functional outcome in comparison with non-thrombolyzed patients and to evaluate the predictors of the outcome after 3 months.

Methods: All the clinical, National Institute of Health Stroke Scale (NIHSS) scores, radiological, and laboratory data of 40 AIS patients and received rt-PA during the period from 2016 to 2018 were collected and analyzed retrospectively. For comparison, 40 patients, as a control group, were selected to match the alteplase group as regards the baseline data and received regular treatment, rather than rt-PA within the first 24 h, that were obtained. The outcome of the thrombolyzed patients after 3 months was evaluated in comparison with controls by using a modified ranking scale.

Results: After a 90-day follow-up period, the death rate was slightly higher among the rt-PA group (7.5%) in comparison with the control group (5%). sICH occurred in 7.5% of the patients in the alteplase group and in 5% of the non-thrombolyzed patients; however, this difference was not significant. More patients had a favorable outcome (mRS = 0–2) in the rt-PA group than in the control group (65% vs 60%, OR 1.38, 95% CI 0.50–3.6, $P = 0.51$). NIHSS score on admission, body mass index (BMI) (≥ 30), and previous transient ischemic attacks (TIA)/ previous ischemic stroke were significant predictors of outcome after IV thrombolysis. Age, sex, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, smoking, atrial fibrillation (AF), stroke subtype, size of infarction, and hyperdense middle cerebral artery had a non-significant effect.

Conclusion: After 3 months of follow-up, rt-PA had a non-significant more increase of favorable outcome with increased risk of sICH and death than controls. Baseline NIHSS, BMI, and history of TIA or previous ischemic stroke were significant predictors of outcome after thrombolysis.

Keywords: Ischemic stroke, Thrombolytic therapy, Outcome

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Background

Acute ischemic stroke is among the most common causes of disability and death. About 16% of the patients have a fatal outcome, and 20% have a serious long-term disability and left dependent on caregivers for their daily activity [1, 2].

Recombinant tissue plasminogen activator (rt-PA), as the primary thrombolytic agent, has been proved effective and beneficial in patients with AIS and recommended by many guidelines worldwide [3]. Alteplase was associated with reduced progression in lesion visibility 24 to 48 h post-treatment using brain CT or MRI [4]; however, a large number of patients eligible for thrombolysis are currently not receiving rt-PA. The challenge of deciding IV rt-PA in any given patient involves weighing its risks and benefits [5].

This study aimed to evaluate the 3-month outcome of AIS patients who received thrombolytic therapy regarding mortality, sICH, and functional outcome in relation to non-thrombolyzed patients and to evaluate the predictors of the outcome after thrombolysis.

Methods

This retrospective study is concerned with all the data of the 40 acute ischemic stroke (AIS) patients treated with IV rtPA (group I) in the neurology intensive care unit (ICU). The clinical, radiological, and laboratory data were obtained from the www.sits.eu and the registry of neurology ICU. The patients who received rt-PA were diagnosed according to the World Health Organization (WHO) criteria [6]. The inclusion and exclusion criteria were used according to the guidelines, and IV treatment was within 4.5 h of the onset of symptoms [1]. One patient with missing data and without well-documented on-site evaluation of examination and brain imaging and two patients with missing 3-month function outcome evaluation were excluded.

Clinical, radiological, and laboratory data of AIS patients who received regular treatment within the first 24 h, during the period from February 2016 to February 2018, were also obtained from the registry of ICU and stroke unit. Forty patients were included as a control group (group II). They were selected to match the case group as regards the baseline characteristics.

Clinical assessment included detailed medical history with special attention to past medical history to establish the presence of any risk factor: hypertension (HTN), diabetes mellitus (DM), dyslipidemia, smoking, obesity (identified by body mass index ≥ 30) [7], previous transient ischemic attacks (TIA), previous ischemic stroke, atrial fibrillation (AF), and other cardiovascular diseases. Complete general and neurological examinations were reviewed including the Glasgow Coma Scale (GCS) [8] to assess the consciousness level and the National Institute of Health Stroke Scale (NIHSS) [9] to assess the stroke severity and stroke subtypes classified according to the TOAST criteria [10].

Complete blood count, liver and kidney function test, random plasma glucose level, coagulation profile, and lipid profile were reviewed.

All patients presented with cerebral stroke were subjected to CT brain on admission to exclude patients with stroke mimic or primary intracranial hemorrhage and after 24 h to assess sICH of rt-PA. The CT brain was evaluated for the presence of any signs of early infarction [11], hyperdense middle cerebral artery (HMCA) sign [12], and estimating the size of infarction according to the rules [13]. The size was classified as small, medium, and large [14]. 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. Cardiac evaluation including ECG and echocardiography was available.

There was no significant difference between the patients who received rt-PA and those who received regular treatment as regards age, sex, regard risk factors, HTN, DM, hyperlipidemia, AF, current cigarette smoking, previous stroke and/or TIA, and mean body mass index, clinical data, severity of stroke (NIHSS), level of consciousness (GCS), subtype of stroke (TOAST), or radiological findings (Table 1).

The case and control groups were followed up for 3 months to assess mortality, sICH, and short-term functional outcome using the modified Rankin Scale (mRS). Scores on the mRS range from 0 (no symptoms at all) to 6 (death); a score of 2 or less indicates a favorable outcome, and 3–5 indicates an unfavorable outcome [9].

Statistical analysis

All data were collected and statistically analyzed using IBM SPSS 23.0 for Windows (SPSS Inc., Chicago, IL, USA) and NCSS 11 for Windows (NCSS, LCC, Kaysville, UT, USA). According to the type of data, quantitative variables were expressed as the mean ± SD and median range. The qualitative data were expressed as a number or percentage. Difference and association of qualitative variables were statistically tested for significance using the chi-square test, Fisher exact test, and odds ratio (95% confidence interval). Differences between the quantitative independent groups were tested using the t test or *Friedman test of significance. P* > 0.05 was considered non-statistically significant. $P < 0.05$ and $P < 0.01$ were considered significant and highly significant, respectively

Results

Table 2 shows a non-significant increase of sICH among the rt-PA group (group I) compared to controls (group II) (7.5% vs 5.0%, OR 1.524, 95% CI 0.252–9.21, P >

Table 1 Baseline characteristics of both studied groups

	Group I, N = 40	Group II, N = 40	Test	P value
Demographic data				
Male sex, n (%)	22 (55)	22 (55)	$X^2 = 0.00$	1.0
Age (mean ± SD)	63.8 ± 11.8	64.9 ± 11.4	$t = 0.424$	0.672
Risk factors				
Hypertension, n (%)	25 (62.5)	26 (65.0)	$X^2 = 0.05$	0.816
Diabetes mellitus, n (%)	13 (32.5)	12 (30)	$X^2 = 0.06$	0.809
Hyperlipidemia, n (%)	14 (35.0)	13 (32.5)	$X^2 = 0.05$	0.813
Atrial fibrillation, n (%)	7 (17.5)	9 (22.5)	$X^2 = 0.312$	0.567
Current Smoking, n (%)	11 (27.5)	9 (22.5)	$X^2 = 0.267$	0.606
Previous stroke/TIA, n (%)	7 (17.5)	8 (20.0)	$X^2 = 0.082$	0.775
Body mass index (mean ± SD)	28.12 ± 3.8	28.15 ± 4.1	$t = 0.03$	0.978
Clinical data				
Laterality (right), n (%)	19 (47.5)	19 (47.5)	$X^2 = 0.000$	1.0
Cranial nerve, n (%)	24 (60)	27 (67.5)	$X^2 = 0.487$	0.485
Incoordination, n (%)	8 (20)	7 (17.5)	$X^2 = 0.082$	0.775
Sensory affection, n (%)	23 (57.5)	20 (50)	$X^2 = 0.453$	0.501
Motor deficit, n (%)	29 (72.5)	30 (75.0)	$X^2 = 0.07$	0.799
Anti-hyperlipidemic drugs, n (%)	8 (20.0)	8 (20.0)	$X^2 = 0.00$	1.0
Previous antiplatelet, n (%)	7 (17.5)	6 (15.0)	$X^2 = 0.09$	0.762
Systolic BP (mean ± SD)	146.8 ± 18.3	149.8 ± 20.1	$t = 0.699$	0.784
Diastolic BP (mean ± SD)	91.3 ± 13.4	90.8 ± 10.7	$t = 0.184$	0.854
Blood glucose (mean ± SD)	131.9 ± 44.3	120.4 ± 28.4	$t = 1.38$	0.171
Admission GCS, range (mean ± SD)	11–15 (14.5 ± 0.93)	10–15 (14.6 ± 1.17)	$t = 0.63$	0.528
Admission NIHSS, range (mean ± SD)	3–21 (11.95 ± 5)	4–26 (11.88 ± 6.4)	$t = 0.06$	0.952
TOAST stroke subtype, n (%)				
Large artery	16 (40.0)	15 (37.5)	$X^2 = 0.61$	0.894
Cardioembolic	7 (17.5)	5 (12.5)		
Small vessel	12 (30.0)	14 (35.0)		
Others	5 (12.5)	6 (15.0)		
CT findings				
Size, n (%)				
Large	6 (15)	7 (17.5)	$X^2 = 0.214$	0.899
Medium	21 (52.5)	19 (47.5)		
Lacunar	13 (32.5)	14 (35)		
Laterality (right), n (%)	21 (52.5)	21 (52.5)	$X^2 = 0.00$	1.0
Hyperdense MCA sign, n (%)	9 (22.5)	9 (22.5)	$X^2 = 0.00$	1.0

$P > 0.05$ = non-significant
BP blood pressure, *GCS* Glasgow Coma Scale, *MCA* middle cerebral artery, *TIA* transient ischemic attack, *SD* standard deviation

0.05). Sixty-five percent of the alteplase patients had a favorable outcome compared to 60% of the controls (OR 1.38, 95% CI 0.53–3.6, $P > 0.05$). The death rate was higher in the alteplase group compared to controls (7.5% vs 5%, OR 1.52, 95% CI 0.25–9.5). Among our 40 patients who were treated with thrombolysis (group 1), alteplase was given within 3 h in 28 patients (group 1a), while in the other 12 patients, alteplase was initiated 3–4.5 h of stroke onset (group 1b). The death rate was higher among group 1b (16.7%) than among group 1a (3.6%). The unexpected non-significant higher percentage of group 1b (83.3%) had a favorable outcome compared with group 1a (57.1%) (Table 3). Younger age and male sex had a non-significant effect on the outcome.

Table 2 Outcome at 3 months among both studied groups

Outcome 3 months	Group I		Group II		X^2	OR (95% CI)	P value
	No.	%	No.	%			
sICH	3	7.5	2	5	0.21	1.52 (0.25–9.21)	0.64
Favorable (mRs ≤ 2)	26	65.0	24	60.0	0.64	1.38 (0.53–3.6)	0.51
Unfavorable (mRs 3–5)	11	27.5	14	35.0		0.71 (0.28–1.8)	0.52
Death (mRS = 6)	3	7.5	2	5.0		1.52 (0.25–9.2)	0.52

OR (95% CI) odds ratio with 95% confidence interval, *mRS* modified Rankin Scale, *sICH* spontaneous intra-cerebral hemorrhage

There was a non-significant association between the outcome and DM, hypertension, AF, hyperlipidemia, and smoking. Higher admission blood sugar, SBP, and DBP had a non-significant effect. TIA and previous ischemic stroke were associated with a favorable outcome, however higher death rate. Increased body weight and baseline INHSS score had a significant effect on death and unfavorable outcome (Table 4).

Discussion

Recombinant tissue plasminogen activator (rt-PA), as the primary thrombolytic agent, has been proved effective and beneficial in patients with AIS and recommended by many guidelines worldwide [3]. Alteplase was associated with reduced progression in lesion visibility 24 to 48 h post-treatment using brain CT or MRI [4]. However, a big number of patients eligible for thrombolysis are currently not receiving rt-PA. The challenge of deciding IV rt-PA in any given patient involves weighing its risks and benefits [5].

This study aimed to predict the 3-month outcome of 40 AIS patients who received thrombolytic therapy regarding mortality, sICH, and functional outcome in relation to non-thrombolyzed 40 matched patients. There was no significant difference between the patients who received rt-PA and those who received regular treatment as regards the baseline data.

The current study revealed that after 90 days, a total of five patients died in both groups. The death rate was slightly higher among group I on alteplase (7.5%) in comparison with group II (5%) (OR 1.52, 95% CI 0.25–9.2, P = 0.5). Two patients in group I (due to sICH as a complication of alteplase) and one patient in group II died within the first 7 days. It has been [9] found that mortality did not differ significantly between the alteplase and placebo groups. In the first week, the death rates were 2.9% in their alteplase group and 3.2% in the placebo group. After 90 days of follow-up, the death rates were

6.7% and 7.7%, respectively. This agreement is due to the nearly similar mean age of the patients included in their study (64.9 years) and our patients (63.8 years), the mean NIHSS of the patients (10.7 vs 10.4), and the same time window of 4.5 h. A more recent study [15] reported a 9.26% death rate among the alteplase group patients after 3 months of follow-up, however, with the exclusion of large vessel occlusion. The Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study group Chao et al. [16] reported a 12.8% mortality rate within 3 months among Chinese AIS patients who received a standard dose of alteplase and suggested that reduction of the dose from 0.9 to 0.72 mg/kg may reduce the mortality down to 6.9%. The analysis of the SITS-MOST study [17] revealed a death rate of 15.5% among AIS patients who were treated with rt-PA within 3 h of stroke onset. In another study [18], the mortality rate was not significantly different between the treated rt-PA patients and control (16.3% vs 11.8%) at 3 months follow-up. The IST-3 collaborative group [19] also reported higher percentages of deaths among the alteplase and control groups (27% in both groups); however, their follow-up period extended to 6 months. They found that more deaths occurred within 7 days in the rt-PA group (11%) than in the control group (7%), but between 7 days and 6 months, there were fewer deaths in the rt-PA group than in the control group. A meta-analysis [20] data for total deaths by the end of follow-up showed that 19.1% allocated rt-PA and 18.5% allocated control died. Their higher percentages may be due to the heterogeneity of the analyzed studies and variability of the follow-up periods.

The variation in mortality rates may be due to the difference in the mean ages, initial NIHSS, the extended window in some studies, and the extended time of follow-up [20].

Symptomatic intracerebral hemorrhage (sICH) is one of the major causes of an increase of > 4 points of the

Table 3 Relation between the onset of treatment of intravenous rt-PA and outcome

Time to treatment	Favorable, N = 26		Unfavorable, N = 11		Death, N = 3		Test	P value
	No.	%	No.	%	No.	%		
Group Ia (< 3 h) (n = 28)	16	57.1	11	39.3	1	3.6	7.52	0.02 S
Group Ib (3–4.5 h) (n = 12)	10	83.3	0	0.0	2	16.7		

Table 4 Three months outcome among thrombolyzed AIS patients in relation to baseline characteristics

	Favorable, N = 26, n (%)	Unfavorable, N = 11, n (%)	Death, N = 3, n (%)	Test	P value
Risk factors					
Male sex, n = 22	15 (68.2)	5 (22.7)	2 (9.1)	X^2 = 0.646	0.724 NS
Diabetes mellitus, n = 13	7 (53.8)	5 (38.5)	1 (7.7)	X^2 = 1.21	0.524 NS
Hypertension, n = 25	17 (68.0)	6 (24.0)	2 (8.0)	X^2 = 0.411	0.81 NS
Atrial fibrillation, n = 7	6 (85.7)	1 (14.3)	0 (0.0)	X^2 = 4.57	0.102 NS
Hyperlipidemia, n = 14	9 (64.3)	3 (21.4)	2 (14.3)	X^2 = 1.61	0.45 NS
Cigarette smoking, n = 11	7 (63.6)	4 (36.4)	0 (0.0)	X^2 = 1.58	0.46 NS
Previous stroke/TIA, n = 7	5 (71.4)	0 (0.0)	2 (28.6)	X^2 = 7.41	**0.03 S**
Age (mean ± SD)	62.1 ± 12.2	66.8 ± 11.1	68 ± 10.8	F = 0.821	0.45 NS
Baseline NIHSS (mean ± SD)	10.35 ± 4.81	13.96 ± 3.51	15.24 ± 4.82	KW = 2.51	**0.04 S**
Admission RBS (mean ± SD)	145.3 ± 75.1	177.3 ± 61.7	182.2 ± 67.1	F = 1.17	0.56 NS
SBP (mean ± SD)	144.2 ± 14.2	155.5 ± 23.4	136.7 ± 25.2	F = 2.1	0.143 NS
DBP (mean ± SD)	83.3 ± 11.5	89.2 ± 12.3	98.2 ± 14.7	F = 2.45	0.1 NS
Body mass index (mean ± SD)	27.2 ± 3.4	30.2 ± 3.5	29.7 ± 5.9	F = 3.24	**0.04 S**
TOAST classification					
Large vessel, n = 16	10 (62.5)	5 (31.3)	1 (6.2)	X^2 = 0.218	0.9 NS
Cardio-embolic, n = 7	5 (71.4)	2 (28.6)	0 (0.0)	X^2 = 1.24	0.46 NS
Small vessel, n = 12	9 (75)	2 (16.7)	1 (8.3)	X^2 = 1.01	0.6 NS
Others, n = 5	1 (20)	3 (60)	1 (20)	X^2 = 5.17	0.08 NS
CT findings					
Size, n (%)					
Large, n = 6	2 (33.3)	3 (50)	1 (16.7)	X^2 = 3.91	0.418 NS
Medium, n = 21	14 (66.7)	6 (28.6)	1 (4.8)		
Lacunar, n = 13	10 (76.9)	2 (15.4)	1 (7.7)		
HMCAS, n = 9	5 (55.6)	3 (33.3)	1 (11.1)	X^2 = 0.505	0.78

TIA transient ischemic attack, *NIHSS* National Institute of Health Stroke Scale, *RBS* random blood sugar, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HMCAS* hyperdense middle cerebral artery sign

NIHSS score from the baseline after thrombolysis [3]. This study found that hemorrhagic transformation occurred in 7.5% of the patients in the alteplase group and in 5% of the patients who received regular treatment. However, this difference was not significant. It has been found that alteplase increased the likelihood of sICH [21]. In previous studies [15, 17, 19, 22], after 3 months of follow-up from rt-PA, the rate of sICH varied between 3.4 and 14.2%. A lower percentage of sICH (2.4% for alteplase patients vs 0.2% for placebo patients) has been reported [9]. The rate of sICH in the current study is very close to the results of the IST-3 [19] which reported sICH in 7% of the patients with thrombolysis and only 1% among the placebo group.

Despite an increase in the rates of early sICH and deaths, treatment with intravenous rt-PA may improve clinical outcomes at the end of follow-up. Our results revealed that more patients had a favorable outcome (mRS = 0–2) in the rt-PA group than in the control group (65% vs 60%, OR 1.38, 95% CI 0.50–3.6, P = 0.51) by the end of 90 days. According to Wardlaw et al. [20], this deference is equivalent to 50 more patients per 1000 alive and with favorable outcome 3 months after alteplase.

The first randomized study, the National Institute of Neurological Disorders and Stroke (NINDS), in 1995 [23] demonstrated that intravenous rt-PA was safe and effective in treating AIS within 3 h of onset. The number of patients with favorable outcomes 3 months after stroke was higher in the rt-PA group than in the control group (39% vs 26%, OR 1.7, 95% CI 1.2–2.6). The favorable outcome in the NINDS trial was defined as mRS = 0–1 which may explain its low percentages in both groups. Hacke et al. [9] also defined favorable outcome as a score of 0–1 on mRS and reported that 52.4% of the patients in the altaplase group had favorable outcomes as compared with 45.2% in those in the placebo group, representing an absolute improvement of 7.2% (OR 1.34, 95% CI 1.02–1.76).

Independency as defined by mRS of 0–2 at 3 months, in the SITS-MOST study, was 50.4% in AIS patients treated with intravenous alteplase within 3 h of stroke onset [17]. The Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study group [16] reported 48.7% of the patients who received standard dose had a mRS of 0–2 at 3 months follow-up. The IST-3 collaborative group [19] found that 37% of the patients in the rt-PA group versus 35% in the control group were alive and independent (OR 1.13, 95% CI 0.95–1.35, P = 0.18) as measured by a commonly used variant of mRS 0–2; however, the follow-up period extended to 6 months and 53% of the patients were older than 80 years of age. In a systematic review and meta-analysis [20] results for 7012 patients, rt-PA significantly increased the odds of being alive and independent at the final follow-up as 46.3% of rt-PA patients versus 42.1% of the control group had favorable outcomes (OR 1.17, 95% CI 1.06–1.29, P > 0.001). However, in some patients, intravenous alteplase window was extended up to 6 h after stroke onset, and the follow-up periods were variable. In a recent study, at 3 months, a high percentage of the patients (76.54%) had a favorable clinical outcome after intravenous alteplase in ischemic stroke patients without large vessel occlusion [15]. Among the Egyptian patients, at 3 months from onset, 52% of the alteplase patients versus 48% of the control patients had favorable outcomes with no statistical difference between both groups [24].

The therapeutic time window was still set at 3 h or less after stroke onset, which was revised to 4.5 h in 2012. The earlier the administration of rt-PA, the better is the outcome even within this therapeutic time window [25]. Emberson et al. [21] reported that when estimated in the predefined subgroups of treatment delay, alteplase significantly increased the odds of a good outcome when given within 3 h (OR 1.75; P < 0.001) and after 3 up to 4.5 h (OR 1.26, P < 0.0132) compared to patients with a window extended to 4.5–6 h. A meta-analysis study [20] found that there were slightly fewer deaths by the end of follow-up in patients treated with alteplase within 3 h equivalent to 15 fewer deaths per 1000, but slightly more deaths in those treated after 3 h, equivalent to an excess of 18 per 1000 patients in comparison with controls. As regards the favorable outcomes compared to controls, 90 per 1000 patients' allocated rt-PA within 3 h and only 18 per 1000 treated after 3 h had favorable outcomes.

Among our 40 patients who were treated with thrombolysis (group I), alteplase was given within 3 h in 28 patients (group Ia), while in the other 12 patients, alteplase was initiated 3–4.5 h of stroke onset (group Ib). The death rate was higher among group 1b (16.7%) than among group 1a (3.6%). The unexpected non-significant higher percentage of group 1b (83.3%) had favorable outcomes compared with group 1a (57.1%). Hacke et al.

[9] 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, 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. The findings of an updated analysis from SITS-ISTR [26] reported 60% of the patients treated within 3–4.5 h versus 57% of those who were treated within 3 h of stroke were functionally independent at 3 months. However, 12% of both groups had died by 3 months of follow-up. Another observational study [27] found a death rate of 11.8% and 11.1% in the patients who received alteplase within 3 h and those who delayed to 3–4.5 h, respectively. The 3-month outcome was favorable for patients who delayed to 3–4.5 h (62.7%) compared with patients treated within 3 h (58.4%). The higher death rate among group 1b of our study may be attributed to the increased risk of IV alteplase complications beyond 3 h of its administration, and in spite of that follow-up after 3 months, they had better outcomes.

Female sex and older age had a non-significant effect on the outcome 3 months after IV alteplase. The effect of sex and age on the outcome is uncertain and a matter of controversy [3, 17, 19–22]. The mean baseline NIHSS among our thrombolyzed patients with favorable outcomes was significantly lower than those with unfavorable outcomes. Similar differences were reported in other studies [4, 15, 20, 22]. Stroke severity as measured by NIHSS score has been proved as a strong predictor of the risk of death and functional outcome [9, 17] as well as for successful recanalization [28]. On the other side, Emberson et al. [21] did not found such clear evidence; moreover, the IST-3 collaborative group [17] reported significant trends towards a larger effect of treatment on more severe stroke as assessed by NIHSS. We found significantly higher mean BMI among deceased patients and those with unfavorable outcome compared to patients with favorable outcomes. Higher body weight has been reported as a significant predictor of sICH [17], mortality, and functional outcome [27, 29]. Chwojnieki et al. [18] found no statistical association between BMI and death rate. Unlike previous studies [15, 19, 28] which reported no significant effect of previous stroke/TIA on the outcome, we found a significant association between previous stroke/TIA and increased death rate and favorable outcomes. We were in agreement with a previous study [18] that the increased death rate. DM, hypertension, AF, hyperlipidemia, and smoking had a non-significant effect on the outcome in the current study, as did the mean admission RBS, SBP, and DBP. This finding agreed with those of previous studies [22, 28, 30]. The significant effect of these factors as

predictors for the outcome has been documented but varied from a study to another [9, 15, 17, 18].

In spite of the controversy about cardioembolic stroke and the concerns of thrombolysis in patients with small vessel disease, IV alteplase was recommended for patients with AIS of all types [3]. Association between a favorable outcome and small vessel disease [31] and cardioembolic stroke [22] was reported. Our study revealed a non-significant association between the subtypes of AIS, according to TOAST classification, and functional outcomes. The non-significant association has been found previously [23, 24, 32]. We found that patients with hyperdense middle cerebral artery (HMCA) and those with a large-sized infarction had unfavorable outcomes; however, the association did not reach significance. HMCA sign has been recorded as a factor of a high incidence of unfavorable outcome [33] and used as an item of thrombotic stroke instrument designed to predict poor outcomes [34]. A recent meta-analysis [35] found that patients with an initial HMCAS were 1.56-fold more likely to have unfavorable outcomes than those who did not present with this sign. Our patients with poor outcomes after 3 months of IV alteplase were found to have a higher mean stroke volume compared to patients with favorable outcomes; however, the difference was not significant. The same finding was reported recently [15]. Lacunar infarction usually had a favorable outcome [3], and the larger the size of ischemic cerebral stroke, the more unfavorable outcome [14].

The limitations of our study were that it was performed in a single center, in which a small number of AIS patients had received rt-PA. Besides the small number, all patients were less than 80 years old except for one patient who was above 80 years.

Conclusion
We can conclude that after 3 months of follow-up, rt-PA had a non-significant increase of favorable outcomes with increased risk of sICH and death than controls.

Abbreviations
IV: Intravenous; alteplase, rt-PA: Recombinant tissue plasminogen activator; AIS: Acute ischemic stroke; sICH: Spontaneous intra-cerebral hemorrhage; NIHSS: National Institute of Health Stroke Scale; BMI: Body mass index; TIA: Transient ischemic attacks; HTN: Hypertension; DM: Diabetes mellitus; AF: Atrial fibrillation; ICU: Intensive care unit; DBP: Diastolic blood pressure; GCS: Glasgow Coma Scale; HMCA: Hyperdense middle cerebral artery; MRI: Magnetic resonance imaging; mRS: Modified Rankin Scale

Authors' contributions
WSM, ASA, AEA, and ELA carried out this work. WSM designed the study, had done the statistical analysis, and wrote the manuscript. WSM and ASA did the literature search and coordinated the research team. AEA, WSM, and ELA collected the patients, gathered the clinical data, and reviewed the manuscript. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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