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RESEARCH

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Analysis of predictors of hemorrhagic transformation after reperfusion therapy with recombinant tissue plasminogen activator in patients with acute ischemic stroke: a single-center experience

Mahmoud H. Nassar[1], Amany F. Elrefaey[1], Khalil M. Abbas[2], Ehab S. Mohamed[1] and Osama A. Ragab[1*]

Abstract

Background Hemorrhagic transformation (HT) is a serious complication of thrombolytic therapy for acute ischemic stroke, limiting its indications and affecting treatment plans and clinical prognosis. Identifying risk factors for HT could help improve the risk–benefit ratio of thrombolytic therapy. We aimed to analyze the predictors of HT after reperfusion therapy with recombinant tissue plasminogen activator (rTPA) in patients with acute ischemic stroke. This study included 115 patients who received rTPA. All patients underwent history taking, clinical examination, neurological examination including Glasgow Coma Scale and National Institutes of Health Stroke Scale scores (NIHSS), radiological investigation, and cardiac investigation. Patients were followed up strictly every 2 h for 1st 24 h then for two weeks clinically using the NIHSS and radiologically using CT or MRI to detect HT.

Results Patients with HT represented 21.7% of all patients receiving rTPA, while symptomatic intracranial hemorrhage (sICH) represented 6.9%. Patients with HT had significantly higher blood pressure, respiratory rate, atrial fibrillation rate, NIHSS score, INR, prothrombin time, neutrophil-to-lymphocyte ratio (NLR), and lower platelet count, LDL level, higher Fazekas score, lower ASPECT score, and prolonged onset-to-needle time.

Conclusion Predicting HT in acute ischemic stroke patients is crucial for optimizing management and potentially improving outcomes. In our study, six predictors were associated with HT: higher respiratory rate, higher atrial fibrillation rate, higher NLR, lower LDL level, higher Fazekas score, lower ASPECT score, and onset-to-needle time greater than 180 min.

Keywords Hemorrhagic transformation, Acute ischemic stroke, rTPA

Background

Hemorrhagic transformation (HT) is one of the main adverse complications of acute ischemic stroke (AIS) which can occur spontaneously after physiological reperfusion as the natural course of AIS or after thrombolytic therapy with recombinant tissue plasminogen activator (rTPA) and/or mechanical reperfusion therapies such as thrombectomy [1]. The incidence of symptomatic HT

*Correspondence:
Osama A. Ragab
osama.ragab@med.tanta.edu.eg
[1] Neurology Department, Tanta University, Tanta, Egypt
[2] Public Health Department, Tanta University, Tanta, Egypt

ranges from 0.6 to 20%, and in autopsy studies, the incidence is much higher [2].

Unfortunately, less than 5–20% of all ischemic stroke patients are eligible for rTPA treatment due to the narrow time window for administration. Outside of this time window, the risk of parenchymal hematoma increases significantly [3].

The incidence of HT after reperfusion therapy is 10 times higher compared to the incidence after spontaneous reperfusion and increases with time (the later the reperfusion, the higher the HT rate), stroke severity assessed with the National Institutes of Health Stroke Scale (NIHSS), high systolic blood pressure, acute high glucose level, antiplatelet or dual antiplatelet usage before the event, obesity, lower platelet count, and the presence of other comorbidities (atrial fibrillation, hypertension, and diabetes mellitus) [4].

The classification of HT after thrombolytic therapy is typically based on two main factors: the radiographic appearance of the hemorrhage and the presence of associated neurological deterioration. The radiographic classification distinguishes between hemorrhagic infarction, which represents petechial hemorrhage within the area of infarction, and parenchymal hematoma, representing a well-defined area of hemorrhage with or without mass effect [5]. We aimed to analyze the predictors of HT after reperfusion therapy with recombinant tissue rTPA in patients with AIS in our stroke center.

Methods

The duration of this study was 12 months, starting from June 2021 to May 2022. The total number of patients included in this study who received rTPA was 115.

Inclusion criteria included all patients aged 18 years or more who presented with their first-ever acute cerebral ischemic stroke documented by cranial computed tomography (CT) and/or brain magnetic resonance imaging (MRI) and received rTPA according to guidelines [6]. Patients with previous history of cerebrovascular stroke were excluded from the study. We divided patients into two groups: group A, which represented rTPA treated patients with HT, and group B, which represented rTPA treated patients without HT.

All patients underwent history taking, clinical examination neurological examination including Glasgow Coma Scale (GCS) [7] and NIHSS [8], and routine laboratory investigations included complete blood count, prothrombin time and activity, international normalized ratio, liver and renal function tests, lipid profile, and random blood sugar. Additionally, specific laboratory tests such as serum ferritin, protein C and S, homocysteine, antithrombin III, and factor V Leiden were performed when deemed necessary based on individual patient requirements and finally neutrophil/lymphocyte ratio (NLR) [9].

Radiological investigation including computed tomography (CT) brain using the Alberta Stroke Program Early CT Score (ASPECTS) for all patients [10]. ASPECT score is a scoring system used to assess the extent of early ischemic changes in the middle cerebral artery territory on noncontract CT, on the other hand patients with posterior circulation stroke PC-ASPECT score was applied [11]. Magnetic resonance imaging (MRI) of the brain was performed in patients whose CT scans did not show positive findings, or in those who presented with symptoms and signs suggestive of cerebral ischemic stroke involving the cerebellum or brain stem, such as vertigo, or in cases of suspected metabolic disturbances. This was done to exclude stroke mimics or other medical conditions and confirm the diagnosis of acute cerebral ischemic stroke. Leukoaraiosis was evaluated and scored according to The Fazekas scale visual rating scale [12]. It is commonly used in the evaluation of small vessel disease, which is a condition associated with cerebrovascular pathologies and cognitive impairment. The scale is scored based on the extent and distribution of white matter lesions in the periventricular and deep white matter regions. A score of 0 indicates no or minimal lesions, while a score of 3 represents the most severe level of white matter lesion burden.

Diagnostic tests were performed to evaluate vascular and cardiac factors contributing to stroke. These included sonography of extracranial vessels and transcranial Doppler sonography to detect extracranial and intracranial vessel stenosis. Cardiac investigations comprised electrocardiography (ECG) for all patients and transthoracic or transesophageal echocardiography to determine potential cardiac sources of stroke.

Patients underwent stringent follow-up during the first 24 h after receiving rTPA, with assessments conducted every 2 h using the GCS, NIHSS score, and monitoring of vital signs. A non-contrast CT scan of the brain was performed 24 h after rTPA administration or earlier if clinical deterioration occurred to detect the presence of HT. The European Cooperative Acute Stroke Study II (ECASS II) score was used to classify the type of HT [13, 14]. Patients were subsequently followed up for a period of 2 weeks.

Ethical considerations included obtaining written informed consent from first-degree relatives of all studied patients. The study was approved by the Ethics Committee of the Faculty of Medicine (approval code: 34,621/4/21).

Statistical analysis of the data was performed using SPSS version 24, a software developed by IBM in Illinois, Chicago, USA. The statistical tests used in this study

included the independent-samples t-test to compare means between two groups, the Chi-square test for categorical variables to compare between different groups, Fisher's exact or Monte Carlo correction when more than 20% of the cells had an expected count less than 5 for the Chi-square test, the Mann–Whitney test for abnormally distributed quantitative variables to compare between two studied groups, and regression analysis to assess the influence of one or more independent variables on a dependent variable.

Results

The current study included 115 patients with AIS who were treated with rTPA. Twenty-five patients developed HT (group A), while the remaining patients did not develop HT (group B). There were no statistically significant differences between the two groups regarding age, sex, residence, and smoking status, as demonstrated in Table 1.

The results of the study indicate that patients who developed HT after receiving rTPA were more likely to exhibit certain clinical characteristics compared to those who did not develop HT. Specifically, patients with HT had a higher prevalence of atrial fibrillation, elevated systolic and diastolic blood pressure, increased respiratory rate, and higher stroke severity as assessed by the NIHSS score. Additionally, these patients experienced a longer time interval before receiving rTPA treatment. Conversely, there were no statistically significant differences observed between the two groups concerning the prevalence of hypertension, diabetes mellitus, ischemic heart disease, valve replacement, random blood sugar levels, heart rate, and Glasgow Coma Scale scores (Table 2).

The study results highlight several significant differences in laboratory parameters between patients who developed HT after receiving rTPA and those who did not. Notably, the group of patients with HT exhibited lower platelet counts, elevated neutrophil-to-lymphocyte ratios, prolonged coagulation parameters as evidenced by higher international normalized ratio (INR) and prothrombin time (PT) values, decreased low-density lipoprotein (LDL) levels, and lower ASPECTS score. Conversely, there were no statistically significant differences observed between the two groups concerning hemoglobin levels, total leukocyte counts, urea, creatinine, triglycerides, and total cholesterol levels (Table 3).

Regarding the site of infarction and TOAST classification of stroke between both groups, the study results did not show significant differences between studied

Table 1 Sociodemographic characteristics of both groups

	Group A ($n=25$)	Group B ($n=90$)	*P* value
Age			
Range	35–85	40–84	0.058
Mean ± SD	67.96 ± 9.9	63.65 ± 9.92	
Sex			
Male (*n*/%)	14 (56.0%)	52 (57.8%)	0.874
Female (*n*/%)	11 (44.0%)	38 (42.2%)	
Residency			
Rural (*n*/%)	16 (64.0%)	48 (53.3%)	0.967
Urban (*n*/%)	9 (36.0%)	42 (46.6%)	
Smoker (*n*/%)	11 (44.0%)	34 (37.8%)	0.573

Group A: hemorrhagic transformation patients of rTPA group. Group B: non-hemorrhagic transformation patients of rTPA group

Table 2 Clinical characteristics of both groups on admission

	Group A ($n=25$)	Group B ($n=90$)	*P* value
HTN (*n*/%)	15 (60.0%)	56 (62.2%)	0.840
DM (*n*/%)	10 (40.0%)	30 (33.3%)	0.536
AF (*n*/%)	14 (56.0%)	31 (34.4%)	0.012
IHD (*n*/%)	8 (32.0%)	19 (21.10%)	0.256
Valve replacement. (*n*/%)	0 (0.0%)	5 (5.6%)	0.354
Bp (systolic)			
Range	130–220	120–200	0.010
Mean ± SD	165.6 ± 25.1	151 ± 15.47	
Bp (diastolic)			
Range	80–130	60–110	0.003
Mean ± SD	101.6 ± 14.3	91.61 ± 10.16	
RBS			
Range	84–380	89–370	0.119
Mean ± SD	205.04 ± 93.61	170.56 ± 69.6	
HR			
Range	60–105	86–110	0.820
Mean ± SD	81.28 ± 9.46	81.66 ± 6.55	
RR			
Range	14–21	14–22	0.002
Mean ± SD	17.44 ± 2.1	15.88 ± 1.59	
GCS			
Range	10–15	13–15	0.841
Mean ± SD	14.89 ± 0.74	14.92 ± 0.4	
NIHSS			
Range	7–20	5–22	0.005
Mean ± SD	13.52 ± 3.454	11.27 ± 3.496	
Time of receiving rTPA			
< 180 min	7 (28.0%)	61 (67.8%)	< 0.001
> 180 min	18 (72.0%)	29 (32.2%)	

HTN, hypertension; DM, diabetes mellitus; AF, atrial fibrillation; IHD, ischemic heart disease; BP, blood pressure; RBS, random blood sugar; HR, heart rate; RR, respiratory rate; GCS, Glasgow Coma Scale; NIHSS, National Institutes for Health Stroke Scale; group A, hemorrhagic transformation patients of rTPA group; group B, non-hemorrhagic transformation patients of rTPA group

Table 3 Laboratory and radiological findings of both groups on admission

	Group A (*n* = 25)	Group B (*n* = 90)	*P* value
Hb (gm/dl)			0.241
Range	9–14.4	8.5–15.3	
Mean ± SD	11.7 ± 1.3	12.1 ± 1.5	
PLT (cu mm)			0.001
Range	123,000–363000	140,000–403000	
Mean ± SD	189,320.0 ± 55,241.68	254,133.3 ± 64,892.34	
TLC (cu mm)			0.207
Range	3000- 19,000	3400–13400	
Mean ± SD	7216.0 ± 3481.46	7512.22 ± 2319.04	
N/L ratio			
Range	4.05–8.86	1.22–3.90	0.001
Mean ± SD	6.20 ± 1.3	2.52 ± 0.65	
INR			0.001
Range	1–1.5	1–1.6	
Mean ± SD	1.23 ± 0.15	1.09 ± 0.13	
PT (s)			
Range	11–18	11–17	0.001
Mean ± SD	14.36 ± 1.76	12.87 ± 1.38	
Urea (mg/dl)			
Range	25–97	19–88	0.388
Mean ± SD	65.28 ± 20	52.8 ± 17.11	
Creatinine (mg/dl)			
Range	0.6–2.2	0.7–2.6	0.907
Mean ± SD	1.1 ± 0.4	1.074 ± 0.23	
TG (mg/dl)			
Range	39–207	38–320	0.590
Mean ± SD	114.7 ± 48.5	109.89 ± 52.04	
Cholesterol (mg/dl)			
Range	70–340	66–380	0.583
Mean ± SD	200.64 ± 71.71	212.72 ± 83.59	
LDL (mg/dl)			
Range	38–82	92–160	0.001
Mean ± SD	53.92 ± 9.82	115.56 ± 15.03	
Fazekas score			0.039
Range	1–3	1–2	
Mean ± SD	1.91 ± 0.73	1.4 ± 0.39	
ASPECTS			
Range	7–10	8–10	0.047
Mean ± SD	8.9 ± 1.08	9.38 ± 0.54	

Hb, hemoglobin; Plt, platelet count; TLC, total leucocytic count; NLR, neutrophil lymphocytic ratio; INR, international normalized ratio; PT, prothrombin time; TG, triglyceride; LDL, low-density lipoprotein; ASPECT score, Alberta Stroke Program Early (non-contrast) CT score-group A, hemorrhagic transformation patients of rTPA group; group B, non-hemorrhagic transformation patients of rTPA group

patients according to site of infarction, while cardioembolic stroke was more prevalent in patient with HT after thrombolytic therapy (Table 4).

The study findings revealed that a substantial proportion, 21.7% (25 out of 115 patients), experienced HT, while a smaller yet significant subset of 6.96% (8 out of 115 patients) developed sICH. Notably, among the patients who manifested HT, a minority of 28% (7 out of 25) exhibited this complication within the initial 12-h window. The preponderance, accounting for 68% (17 out of 25), experienced HT during the subsequent 12- to 24-h interval, whereas a marginal 4% (1 out of 25) developed HT beyond the 24-h mark. Furthermore, the study employed the European Cooperative Acute Stroke Study II (ECASS II) classification to characterize the hemorrhagic subtypes. The results demonstrate that 4.3% of the patients exhibited hemorrhagic infarction type 1 (HI-1), while 6% manifested hemorrhagic infarction type 2 (HI-2). Concurrently, parenchymal hematoma type 1 (PH-1) and type 2 (PH-2) were observed in 5.2% and 6% of the patients, respectively. A substantial majority, constituting 92.1% (106 out of 115 patients), survived the follow-up period. However, a notable 2.6% (3 out of 115 patients) died secondary to the deleterious effects of HT. Concurrently, 5.2% (6 out of 115 patients) experienced mortality attributable to etiologies distinct from HT (Table 5).

Our results elucidated the lack of a statistically significant association between the anatomical site of cerebral infarction and the propensity for HT in the rTPA treatment group. This finding suggests that the localization of the ischemic insult, per se, does not confer a differential susceptibility to the development of HT in the context of thrombolytic intervention (Fig. 1). Further analysis found no relationship between the total percentage of infarct sources and the occurrence of HT among patients undergoing rTPA administration (Fig. 2).

The logistic regression analysis findings, as depicted in Table 6, demonstrate significant associations between HT and respiratory rate (RR), atrial fibrillation (AF), neutrophil-to-lymphocyte ratio (N/L R), LDL cholesterol level, ASPECTS score and time of receiving rTPA > 180 min (Fig. 3).

Discussion

Hemorrhagic transformation represents a significant adverse complication in the clinical trajectory of acute ischemic stroke management, serving as a potent predictor of mortality and disability among patients undergoing reperfusion therapy. The findings of our study have illuminated the identification of several salient risk factors as harbingers of early HT in patients with AIS treated with rTPA. Notably, higher respiratory rates, the presence of atrial fibrillation, elevated neutrophil-to-lymphocyte ratios, lower low-density lipoprotein (LDL) levels, higher Fazekas score diminished ASPECTS Scores, and

Table 4 Site and etiological classification of infarction of both groups

	Group A ($n=25$)	Group B ($n=90$)	*P* value
Site of infraction			
Total MCA (*n*/%)	7 (28.0%)	14 (15.6%)	0.504
Partial MCA (*n*/%)	12 (48.0%)	31 (34.4%)	
Basal ganglia (*n*/%)	2 (8.0%)	5 (5.6%)	
Internal capsule (*n*/%)	1 (4.0%)	9 (10%)	
ACA (*n*/%)	0 (0.0%)	4 (4.4%)	
PCA (*n*/%)	0 (0.0%)	3 (3.3%)	
Cerebellar (*n*/%)	0 (0.0%)	8 (8.9%)	
Brain stem (*n*/%)	1 (4.0%)	7 (7.8%)	
Thalamus (*n*/%)	1 (4.0%)	9 (10%)	
Insula (*n*/%)	1 (4.0%)	0 (0.0%)	
TOAST classification (n/%)			
Cardio embolic (*n*/%)	14(56.0%)	34(37.8%)	0.043
Large artery atherosclerosis (*n*/%)	11(44.0%)	49(54.4%)	
Small vessel disease (*n*/%)	0(0.0%)	3(3.3%)	
Other determined etiology (*n*/%)	0(0.0%)	2 (2.2%)	
Undetermined etiology (*n*/%)	0(0.0%)	2 (2.2%)	

MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; group A1, hemorrhagic transformation patients of rTPA group; group A2, non-hemorrhagic transformation patients of rTPA group

Table 5 Percentage, timing and type of hemorrhagic transformation and mortality in patients with hemorrhgic transformation

	N/% (All patients = 115)
HT patients	25 (21.7%)
Timing HT	
0–12 h	7 (28%)
12–24 h	17 (68%)
> 24 h	1 (4%)
Type of HT (ECASS II)	
HI-1	5 (4.3%)
HI-2	7 (6%)
PH-1	6 (5.2%)
PH-2	7 (6%)
Hospital mortality during follow-up period	
Due to HT	3 (2.6%)
Due to other causes	6 (5.2%)

HT, hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hematoma; hrs, hours; ECASS-II, intravenous alteplase in acute ischemic stroke; European Cooperative Acute Stroke Study-II; group A1, hemorrhagic transformation patients of rTPA group; group A2, non-hemorrhagic transformation patients of rTPA group

prolonged onset-to-needle times exceeding 180 min emerged as significant predictors of HT in our cohort.

Several studies have reported different incidences of HT in patients with acute ischemic stroke that performed reperfusion therapies. In a multi-centric study conducted by Liu et al. [15] that included 538 patients with ischemic stroke receiving thrombolysis, 17.4% ($n=94$) were diagnosed with HT on brain computed tomography within 36 h after stroke onset, and half of them (47/94 patients) had symptomatic HT. Another study proposed two distinct categories of HT following AIS. The first category, termed early HT, occurs within the initial 18–24 h and is hypothesized to be primarily driven by factors such as reactive oxygen species, blood-borne matrix metalloproteinase-9 (MMP-9) enzyme, and brain-derived MMP-2 enzyme. In contrast, delayed HT, occurring after the 18–24-h window, is postulated to stem from brain-based factors, including MMP-9 and MMP-3 enzymes, other proteolytic enzymes, vascular alterations, and neuroinflammatory processes within the brain parenchyma [16].

Strbian et al. [17] elucidated the temporal patterns of sICH, demonstrating that while most cases occurred within the initial 24 h, a significant proportion, ranging from 10 to 15%, manifested beyond the 24-h mark. Corroborating these findings, the NINDS trial in 2012 revealed that all fatal sICH events transpired within the first 24 h, with a striking 80% occurring within the first 12 h. These studies underscore the critical importance of vigilant monitoring and timely intervention in the acute phase following thrombolytic therapy, as the risk of potentially life-threatening hemorrhagic complications remains elevated, particularly within the initial 24-h window.

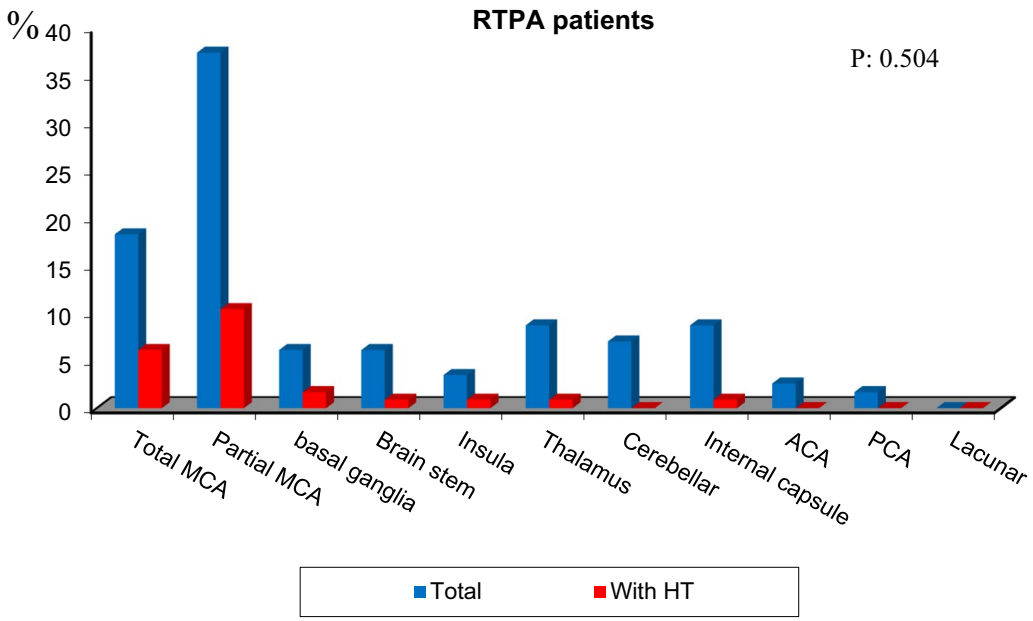

Fig. 1 Correlation between site of infarction and hemorrhagic transformation in rTPA patients

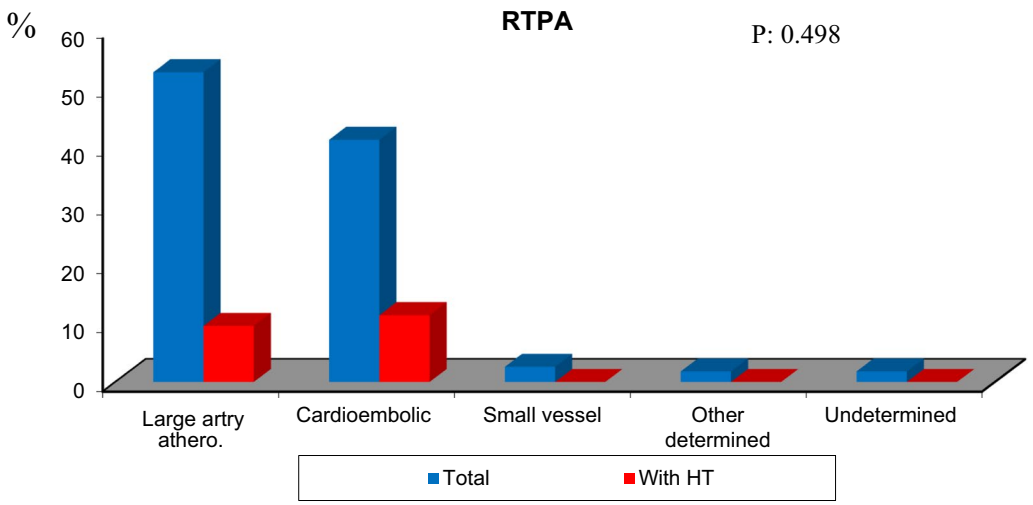

Fig. 2 Correlation between TOAST classification and hemorrhagic transformation in rTPA patients

The pathogenesis of HT following rTPA therapy is proposed to be a multifactorial process, wherein not only the restoration of reperfusion, but also the dysregulation of extracellular proteolysis within the neurovascular unit matrix contribute to its exacerbation. Notably, the effects of rTPA on MMP activity have been implicated as a potential mechanistic underpinning of this phenomenon. Compelling evidence suggests that rTPA potently induces the release of MMP-9 from human neutrophils, thereby potentially compromising the integrity of the neurovascular unit and precipitating hemorrhagic complications [18]. Furthermore, the pathophysiological cascade following recanalization encompasses the activation of platelets, coagulation factors, and the innate and adaptive immune systems, collectively exacerbating the injury sustained during the ischemic insult. Alteplase can potentiate HT through non-fibrinolytic mechanisms, including the activation of the immune system [3].

Additionally, alteplase activates platelet-derived growth factor-CC (PDGF-CC), an agonist of platelet-derived growth factor receptor alpha (PDGFRα) on astrocyte end-feet. This signaling cascade can promote BBB

Table 6 Multivariate logistic regression for prediction of hemorrhagic transformation in patient taking rTPA

	OR	95% CI		*P* value
		Lower	Upper	
SBP	0.543	0.154	2.531	0.693
DBP	0.714	0.365	1.842	0.791
RR	0.365	0.157	0.572	0.001
AF	0.607	0.324	0.827	0.021
Platelet count	2.315	0.854	5.321	0.631
N / L R	0.569	0.415	0.762	0.001
INR	0.754	0.586	3.210	0.960
PT	0.587	0.327	2.412	0.796
LDL	2.514	1.638	5.142	0.017
NIHSS at arrival time	0.745	0.359	3.654	0.265
Fazekas score	0.373	0.082	0.524	0.01
ASPECTs	0.191	0.057	0.643	0.008
Time of receiving rTPA > 180 min	0.513	0.351	0.896	0.017

SBP, systolic blood pressure; DBS, diastolic blood pressure; RR, respiratory rate; AF, atrial fibrillation; INR, international normalized ratio; N/L R, neutrophil/lymphocyte ratio; PT, prothrombin time; LDL, low-density lipoprotein; ASPECT score, Alberta Stroke Program Early (non-contrast) CT score; NIHSS, National Institutes for Health Stroke Scale

disruption and HT, as PDGFRα activation triggers the upregulation of MMPs. Moreover, alteplase binds to the lipoprotein receptor (LRP) on neurons and perivascular astrocytes, inducing the expression of MMP-3 and MMP-6, further contributing to the degradation of the neurovascular unit [19].

The temporal dynamics of HT following thrombolytic treatment unveil distinct pathophysiological mechanisms at play. Early HT, manifesting within the initial 36 h after intervention, is hypothesized to be a direct consequence of the reperfusion process itself. Conversely, HT occurring beyond the 36-h mark is posited to be correlated with a delayed disruption of BBB [4].

In the present study, there was association between atrial fibrillation or cardioembolic source of infarction and HT in patients received rTPA. Tu et al. [20] revealed that atrial fibrillation is associated with higher volumes of more severe baseline hypoperfusion, leading to greater infarct growth, more frequent severe HT. The present study unveils a significant association between elevated respiratory rates and the occurrence of HT in patients receiving rTPA therapy. This observation may be attributable to the underlying pathophysiological mechanisms linking tachypnea to rapid atrial fibrillation, characterized by a heart rate exceeding 110 beats per minute. The complex interplay between respiratory dysfunction,

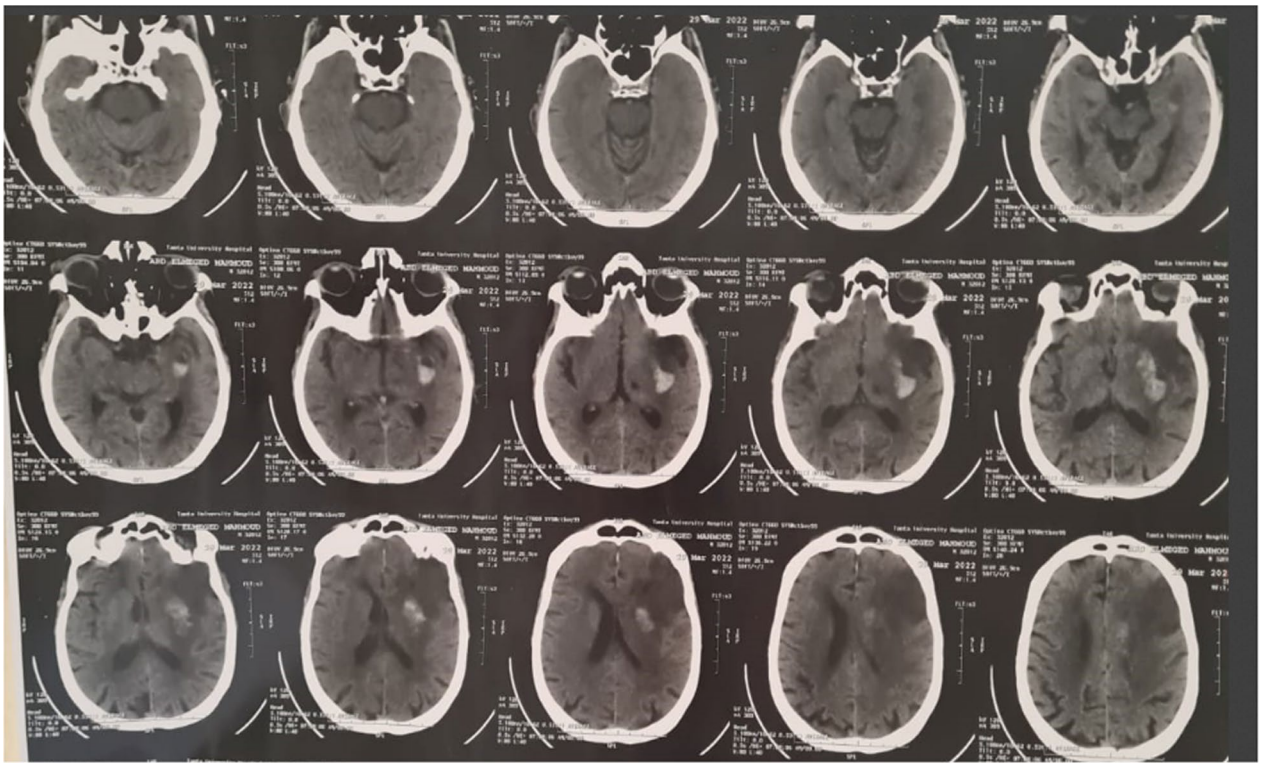

Fig. 3 Male patient aged 63 years old. CT brain shows left partial middle cerebral artery. Infraction with (HI-2)

impaired gaseous exchange, and the ensuing compensatory mechanisms can precipitate a cascade of events culminating in tachyarrhythmias, such as rapid atrial fibrillation [21].

There was a significant association between lower low-density lipoprotein (LDL) levels and HT) in patients who received rTPA treatment. A study by Yang et al. [21] analyzed the lipid profiles of 348 acute ischemic stroke (AIS) patients, and HT was observed in 35 patients. Compared to the non-HT group, the HT group had lower levels of total cholesterol and LDL. This finding suggests that an adequate level of lipids may help maintain the integrity of small cerebral vessels, while excessively low lipid levels can compromise the integrity of small vessels, leading to blood extravasation through the unstable endothelial cells in these vessels.

The present study revealed a significant association between HT in patients receiving rTPA and higher NLR. This finding is consistent with the work of Sharma et al. [22] who reported that a high NLR ($\geq$4.255) was significantly associated with HT in AIS patients treated with intravenous thrombolysis. They explained that disruption of BBB and focal inflammation of the infarcted lesion have been correlated with HT, as neutrophils play a role in BBB disruption in AIS. Zhang et al. [23] found that an NLR with a cutoff value of 7.5–11 was a predictor of HT rate and 3-month mortality in AIS patients, irrespective of country and sampling time.

The current study also revealed a significant association between needle time exceeding 180 min and HT after thrombolysis. This observation aligns with the findings of Lei et al. [24] who reported a higher bleeding risk in patients receiving thrombolysis within 3–6 h compared to those receiving thrombolysis within 3 h. A meta-analysis by Sun et al. [25] reported that longer time from stroke onset to treatment is associated with increased risk of sICH.

Furthermore, there was an association between the severity of AIS document by NIHSS score at arrival and HT in patients receiving rTPA. Iancu et al. [26] found that the NIHSS score was significantly higher in rTPA patients with HT compared to rTPA patients without HT. Lei et al. [21] multi-center survey of acute stroke patients undergoing thrombolysis with rt-PA demonstrated that the NIHSS score is an independent risk factor for HT, and an increase of 1 point in the NIHSS score indicates a 1.38% increase in the risk of bleeding.

Previous research on leukoaraiosis and HT following thrombolytic therapy has predominantly converged on a consensus: severe leukoaraiosis augments the risk of HT or sICH after thrombolysis [27]. Our study findings corroborate this conclusion. Leukoaraiosis is postulated to be a manifestation of chronic endothelial dysfunction, potentially predisposing individuals to bleeding complications and disruption of the blood–brain barrier integrity [28].

In the present study, lower ASPECTS scores were associated with HT in patients receiving rTPA. Supporting our results, De Andrade et al. [29] reported that a low ASPECTS is a predictive factor for hemorrhagic transformation after thrombolytic therapy. The rationale behind this observation is that ASPECTS is used to score AIS patients based on the extent of early ischemic changes across ten brain regions, and the number and degree of affected regions are closely related to the occurrence of HT in AIS patients. Chang et al. [30] results indicated that lower ASPECTS scores were associated with higher rates of HT and that from all studied scores, the predicted value of ASPECTS score is the best for prediction of After rTPA therapy.

This study has some important limitations. Firstly, it was conducted at a single center. This design can limit how well the findings apply to other populations or healthcare settings. Secondly, the study included only 115 patients who received rTPA. While this may be sufficient for the main analysis, the sample size might be considered small for subgroup analyses or investigating rare events. Finally, the evaluation of leukoaraiosis using the Fazekas scale and the ASPECTS assessment may be susceptible to variability between raters due to potential subjectivity and the relation of microbleeds and infarction volume with HT were not evaluated. We hope that in the foreseeable future, a valid predictive tool for hemorrhagic transformation will become clinically available, thereby enhancing the application of thrombolytic therapy and subsequently improving outcomes.

Conclusion

The precise prediction of HT in patients with AIS is of paramount importance in clinical practice, as it facilitates the optimization of management strategies and potentially enhances overall outcomes. The present study has elucidated several pivotal predictors of HT in stroke patients receiving rTPA therapy. Notably, elevated respiratory rates, the presence of atrial fibrillation, heightened neutrophil-to-lymphocyte ratios, diminished low-density lipoprotein levels, higher Fazekas score, reduced ASPECT scores, and prolonged onset-to-needle times exceeding 180 min emerged as significant harbingers of HT in this patient cohort.

Abbreviations

AF	Atrial fibrillation
AIS	Acute ischemic stroke
ASPECT	Alberta Stroke Program Early CT Score
BBB	Blood brain barrier
CT	Computed tomography
DM	Diabetes mellitus

ECG	Electrocardiography
EXASS II	The European Cooperative Acute Stroke Study
GCS	Glasgow Coma Scale
HI-1	Hemorrhagic infarction type
HI-2	Hemorrhagic infarction type 2
HT	Hemorrhagic transformation
HTN	Hypertension
INR	International normalized ratio
LDL	Low density lipoprotein
MMP	Matrix metalloproteinase
MRI	Magnetic resonance image
NIHSS	National Institutes of Health Stroke Scale scores
NLR	Neutrophil lymphocyte ratio
PDGF	Platelet derived growth factor
PH-1	Parenchymal hematoma type 1
PH-2	Parenchymal hematoma type 2
PT	Prothrombin time
RBS	Random blood sugar
RR	Respiratory rate
rTPA	Recombinant tissue plasminogen activator
sICH	Symptomatic intracranial hemorrhage

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Author contributions
All authors have participated in designing the study, acquisition of data, data interpretation and revising. MN recruited patient and carried out clinical, neurological evaluation and participated in interpretation of the study results. AE recruited patients and carried out clinical, neurological evaluation and participated in interpretation of the study results. KA carried out statistical analysis and participated in results analysis and manuscript writing recruited the patient and carried out clinical, neurological evaluation, participated in interpretation of the study results and editing the manuscript. OR recruited the patient and carried out clinical, neurological evaluation, participated in interpretation of the study results and editing the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials
All raw data will be available on the editor request.

Declarations

Ethical approval and consent for participation
Ethical considerations included obtaining written informed consent from first-degree relatives of all studied patients. The study was approved by the Ethics Committee of the Faculty of Medicine (approval code: 34621/4/21).

Consent for publication
Not applicable.

Competing interests
The authors have no conflict of interest to disclose.

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