

ORIGINAL ARTICLE

# Why do some patients with acute ischemic stroke fail to improve after intravenous thrombolytic therapy? A case-control study

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## Abstract

**Introduction:** thrombolytic therapy is the primary saving measure adopted in ischemic cerebrovascular accident (ICVA) victims, adequate for most of them. However, some patients do not show clinical progress, worsening the prognosis, which constitutes an essential scientific gap.

**Objective:** to analyze the determinants of clinical non-improvement in stroke patients who used rt-PA thrombolytic agentes.

**Methods:** retrospective observational case-control study, carried out from 2014 to 2017 through an active search of medical records of CVA patients undergoing thrombolytic therapy in a reference hospital in Ceará. Clinical failure was characterized as no reduction in the National Institutes of Health Stroke Scale-Score (NIHSS).

**Results:** a total of 139 patients enrolled in the study in a single CVA unit. The mean age was 66.14 years (range 34 to 95). The 24-hour follow-up was completed in 100% of patients. A favorable result 24 hours post-thrombolysis was observed in 113 patients (81.29%), and there was no clinical improvement in 26 (18.7%). Post-thrombolysis hemorrhagic transformation was a strong predictor of no improvement ( $p=0.004$ ), and diabetes was the main modifiable risk factor found ( $p=0.040$ ).

**Conclusion:** diabetes and hemorrhagic transformation after thrombolysis were identified as risk factors for clinical non-improvement in patients with acute stroke undergoing thrombolytic therapy.

**Keywords:** epidemiology, NIHSS, stroke, thrombolysis, thrombolytic therapy.

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## Authors summary

### Why was this study done?

This research shows that the treatment of patients with acute stroke is problematic and which characteristics need to be evaluated as a risk factor for a poor prognosis to improve the healthcare of these patients.

### What did the researchers do and find?

In our study (case-control study), we investigated who is associated with clinical failure after thrombolytic therapy in patients with acute ischemic stroke in a cohort of 139 clinical patients diagnosed with ICVA who presented a neurological deficit of significant intensity and development time less than 4.5 hours before start of thrombolytic infusion and cranial tomography without evidence of bleeding before administration. Data collection will take place over a period of three years (2014-2017) from a Stroke unit in a referral public hospital in Ceará, northeastern Brazil. Clinical failure was assessed using the National Institutes of Health Stroke Scale and other variables were extracted from medical records.

### What do these findings mean?

The main factors associated with clinical failure were diabetes and post-thrombolytic hemorrhagic transformation. These factors need to be evaluated in the clinical evaluation to improve the quality of medical care and achieve better outcomes for these patients.

### Highlights

Approximately 19% of patients with Ischemic Cerebrovascular Accident in public hospital stroke unit had clinical failure of treatment.

Hemorrhagic transformation after thrombolysis has been shown to be a risk factor for clinical failure.

The diabetes was an important factor in clinical failure of treatment for acute ischemic stroke after intravenous thrombolytic therapy.

## INTRODUCTION

Cerebrovascular Accident, defined as a sudden focal neurological deficit, is one of the most important causes of morbidity and mortality worldwide. According to data from the Ministry of Health, in Brazil, it is the second leading cause of death in the adult population, corresponding to 10% of the causes of public hospital admissions<sup>1,2</sup>.

An acute reduction in blood flow to a selected brain area characterized ischemic cerebrovascular accident. Its main risk factors are habits and lifestyle, smoking, high fat intake, and sedentary lifestyle standing out<sup>3</sup>. In addition to them, chronic-degenerative diseases, such as systemic arterial hypertension and diabetes mellitus, favor the ischemic event<sup>2</sup>.

As it is a disabling and high incidence disease with a high social and economic burden, treatment must begin early. Intravenous thrombolysis with alteplase (recombinant tissue-plasminogen activator) is the pharmacological treatment for acute ICVA<sup>3</sup>. The Food and Drug Administration approved its use, associated with patients' clinical improvement. For this to be effective, it is imperative to implement clinical and laboratory standards that guide the drug use, ensuring that the recanalization of the obstructed vessel is carried out in the best possible way, re-establishing blood flow and preventing the death of nerve cells<sup>3</sup>.

Intravenous rt-PA is currently the most used therapy in reference clinical centers. The inclusion criteria for its use are age above eighteen years, clinical diagnosis of ICVA, neurological deficit of significant intensity, evolution less than 4.5 hours before the start of the thrombolytic infusion, and cranial neuroimaging without evidence of bleeding. In this way, thrombolysis is performed, and clinical criteria are re-evaluated to verify the procedure's outcome<sup>3</sup>.

There are numerous protocols to standardize the neurological examination, performed when the patient arrives at the emergency room and after thrombolysis. The National Institutes of Health Stroke Scale is one of them and specifies a list of 11 items that are analyzed and scored

during the anamnesis and physical examination, ranging from 0 to 42 points, with the most severe patients being those with the highest score. It is a standard, validated, safe, and quantitative scale of the severity and magnitude of neurological deficit after an ICVA, as it assesses the level of consciousness, eye deviation, facial paresis, language, speech, neglect/extinction, motor and sensory function of limbs and ataxia<sup>4-6</sup>.

The result NIHSS is an essential predictor of therapeutic efficacy<sup>7</sup>, and therefore should be performed in a short period of 5 to 8 minutes to treat patients suffering from acute ischemic stroke. Therefore, and showing itself as a scale for evaluating neurological impairment with evidence of clinically acceptable reliability and good clinical applicability, the NIHSS is a vital instrument to assess the efficacy of thrombolytic treatment in hospitalized patients suffering from acute ICVA<sup>7</sup>. However, despite the evidence of a better prognosis in most individuals using thrombolytics, it is also observed that some patients have an unfavorable evolution, which in this study will be called "no clinical improvement." It is an unexpected outcome after adequate application of the recommended therapy.

Thus, there is a lack of studies to assess the factors involved in the non-clinical improvement of these patients after chemical thrombolysis, and obtain even more favorable results, with a reduction in morbidity and mortality associated with the ischemic event. The present study aimed to analyze the determinants of clinical non-improvement in ICVA victims who underwent rt-PA thrombolytic therapy.

## METHODS

### Study Design

Following the STROBE guideline<sup>8</sup>, it is a retrospective observational unmatched case-control study.

### Study Location and Period

The current study was carried out at the Hospital Regional do Cariri by verifying data registered in the medical records of patient's victims of ICVA who

underwent intravenous thrombolysis therapy from January 2014 to December 2017.

**Study Population and Eligibility Criteria**

It consists of patients treated at the HRC, diagnosed with ICVA, who underwent intravenous thrombolytic therapy and monitored daily through the NIHSS protocol in the Stroke Unit at HRC. The HRC has approximately 100 CVA admissions monthly. The researchers checked all medical records of patients admitted during the study period.

The study included participants over eighteen years old with the clinical diagnosis of ICVA who presented a neurological deficit of significant intensity with an evolution time less than 4.5 hours before the start of thrombolytic infusion and cranial tomography without evidence of bleeding for its use, characterizing such as incident cases of ICVA. On the other hand, for both groups (case and controls) the medical records with incomplete data that could affect the interpretation of essential data for this study were excluded to reduce information bias.

Participants who did not show a reduction in the NIHSS score after using the thrombolytic therapy were defined as cases, while controls were those who showed a reduction in the NIHSS score and improved symptoms, resulting in an unmatched control group.

**Data Collection**

All variables were collected from medical records filed at the HRC of patients clinically diagnosed with ICVA who underwent intravenous thrombolytic therapy.

Gender, age, smoking, diabetes, and hypertension were related to the participants' sociodemographic characteristics and history. Variables at the time of admission were collected to investigate whether any aspect between blood pressure and blood glucose levels and NIHSS score is related to non-reduction in the NIHSS score. The presence of cranial computed tomography findings related to ischemia, time from stroke to thrombolysis, and post-thrombolysis hemorrhagic transformation.

Some quantitative variables were categorized according to the cutoff points presented in box 1.

**Box 1.** Quantitative variables and classification cutoff points.

Variable	Cutting Point	Classification
Pressure level on admission	SBP* > 140 X 90 mmHg	Elevation of pressure levels on admission
Glucose level on admission	200 or more mg/dl	Elevation of glucose level at admission
NIHSS score on admission	Over 15	Higher intensity of neurological deficit according to NIHSS score
Time from stroke to thrombolysis	Above two hours and 30 minutes	Symptoms period
Age	60+ years	Older adults

\*SBP = systemic blood pressure

**Data Analysis**

Descriptive statistics were presented using absolute and relative frequencies and odds ratio. The logistic regression was used to investigate the factors related to the risk of not showing a reduction in the NIHSS score between the groups. We estimated the OR, respective confidence intervals (95% CI), and probability values. Subgroup and interaction examinations were analyzed using multiple logistic regression, which included variables with at least a 0.20 probability of influencing the outcome. Missing data were excluded when they represented more than 40% of non-responses for the variable. The significance level was 5%. The program used was Stata (Stata Corp, LC), version 11.0.

**Ethical and Legal Aspects of the Research**

The research followed the criteria established in resolution 466/12 of the National Health Council, which regulates human beings' studies. All participants signed the Informed Consent Form due to the inherent risks of

losing medical records. These risks were minimal, and all records were consulted in the room where the hospital maintained the medical records. The research began after approval by the Research Ethics Committee of the ABC Medical School (Nº: 3.746,941).

**RESULTS**

**Participants**

During the period, 142 records were obtained, 3 of them excluded for not meeting the eligibility criteria. Hence, 139 medical records of patients with ICVA were included in the study.

**Descriptive data**

The profile of patients included in the study was: male (n=78; 56.12%), elderly (n=93; 66.91%) and history of current or previous smoking (n=79; 56.83%). Twenty-seven patients had diabetes (19.42%) and ninety-eight arterial hypertension (70.50%) (table 1).

**Table 1:** Epidemiological profile of 139 patients with acute ICVA admitted from January 2014 to December 2017 in the stroke unit of HRC- Ceará.

Variable	N	%
Gender		
Female	61	43.88
Male	78	56.12
Older adults		
No (< 60 years)	46	33.09
Yes (> 60 years)	93	66.91
Smoking		
No	60	43.17
Currently / Past	79	56.83
Diabetes		
No	112	80.58
Yes	27	19.42
Hypertension		
No	41	29.50
Yes	98	70.50
	Mean (sd)	Min.,; Max.
Age	66.1 (13.4)	34; 95
NIHSS Score	12.7 (5.2)	4; 26

sd: standard deviation; Min.: Max: Minimum and maximum values, respectively.

During admission, 16.55% of patients had high blood pressure (n=23), 17.27% showed blood glucose level above 200mg/dl (n=24), 48.20% underwent cranial computed tomography (n=67). More than half of the patients (66.19%, n=92) did not have a high level of severity of injuries caused by ICVA, assessed by the NIHSS score above 15, with 52.52% having a stroke-to-thrombolysis time greater than three hours (n=73) and 25.18% (n=35) had post-thrombolysis hemorrhagic transformation (table 3).

**Outcome data**

Of all patients, 18.71% of patients had no reduction in NIHSS score (n=26) (table 3).

**Main results**

The presence of diabetes was associated with a greater chance of not having a reduction in the NIHSS in the population studied, as patients with diabetes were 2.52 more likely to have no reduction in the NIHSS than patients without diabetes (OR = 3.52; 95% CI 1.37 to 9.06; p=0.009). The other sociodemographic characteristics were not associated with the non-reduction of the NIHSS (p>0.05) (table 3).

**Table 2:** Clinical characteristics during admission and evolution of patients with acute ischemic stroke admitted from January 2014 to December 2017 in the CVA unit at HRC, Ceará.

Variable	N	%
Change in blood pressure on admission		
No	116	83.45
Yes	23	16.55
The glucose level at admission		
Up to 200mg/dl	115	82.73
Above 200mg/dl	24	17.27
Cranial CT admission		
No	72	51.80
Yes	67	48.20
NIHSS score on admission		
Up to 15	92	66.19
+15	47	33.81
Time from stroke to thrombolysis		
Up to 3hours	66	47.48
+3 hours	73	52.52
Post-thrombolysis hemorrhagic transformation		
No	104	74.82
Yes	35	25.18
Non-reduction of NIHSS		
No	113	81.29
Yes	26	18.71

**Table 3:** Sociodemographic factors associated with non-reduction of the NIHSS score in patients with acute ICVA admitted from January 2014 to December 2017 in the stroke unit at HRC- Ceará.

Variable	Reduction NIHSS	Non- reduction NIHSS	Odds	OR (CI 95%)	p*
Gender					
Female	54	7	0.129	ref	ref
Male	59	19	0.322	2.48 (0.97; 6.37)	0.058
Older adults					
No	41	5	0.121	ref	ref
Yes	72	21	0.291	2.39 (0.83; 6.82)	0.108
Smoking					
No	48	12	0.250	ref	ref

**Table 3:** Sociodemographic factors associated with non-reduction of the NIHSS score in patients with acute ICVA admitted from January 2014 to December 2017 in the stroke unit at HRC- Ceará.

Variable	Reduction NIHSS	Non- reduction NIHSS	Odds	OR (CI 95%)	p*
Currently / Past Diabetes	65	14	0.215	0.86 (0.36; 2.02)	0.733
No	96	16	0.166	ref	ref
Yes	17	10	0.588	3.52 (1.37; 9.06)	0.009
Hypertension					
No	34	7	0.205	ref	ref
Yes	79	19	0.241	1.16 (0.44; 3.03)	0.750

ref.: Reference category; 95% CI: 95% Confidence Interval; \*Logistic Regression

Of the clinical characteristics, only the presence of post-thrombolysis hemorrhagic transformation (p=0.002) was shown to be a risk factor, representing a 4.13-fold chance (CI 95% 1.68 to 10.16) of not reducing the NIHSS when compared to patients who did not present post-thrombolysis hemorrhagic transformation (table 4).

The multivariate analysis included sociodemographic or clinical characteristics that showed a trend towards non-reduction of the NIHSS (p<0.20). The examination also contained essential aspects such

as gender, elderly, diabetes, and post-thrombolysis hemorrhagic transformation (table 5). We observed that the NIHSS non-reduction in the studied patients was influenced both by the existence of diabetes and the presence of post-thrombolysis hemorrhagic transformation, being respectively 192% and 317% more likely to have no reduction in the NIHSS (OR=2.92; 95% CI 1.05 to 8.17; p=0.040) and OR=4.17; 95% CI 1.59 to 10.98; p=0.004).

**Table 4:** Clinical characteristics at admission and evolution associated with non-reduction of the NIHSS score in patients with acute ICVA admitted from January 2014 to December 2017 in the stroke unit at HRC- Ceará.

Variable	Reduction NIHSS	Non- reduction NIHSS	Odds	OR (CI 95%)	p*
Change in blood pressure at admission					
No	94	22	0.234	ref	ref
Yes	19	4	0.210	0.89 (0.27; 2.90)	0.860
Glucose level at admission					
Up to 200mg/dl	97	18	0.186	ref	ref
Above 200mg/dl	17	8	0.471	2.53 (0.95; 6.75)	0.063
Cranial CT admission					
No	61	11	0.180	ref	ref
Yes	52	15	0.288	1.59 (0.67; 3.78)	0.285
NIHSS score at admission					
Up to 15	37	10	0.270	ref	ref
+ 15	76	16	0.210	0.78 (0.32; 1.88)	0.579
Time from stroke to thrombolysis					
Up to 3 horas	54	12	0.222	ref	ref
Over 3 hours	59	14	0.237	1.07 (0.45; 2.51)	0.880
Post-thrombolysis hemorrhagic transformation					
No	91	13	0.142	ref	ref
Yes	22	13	0.591	4.13 (1.68; 10.16)	0.002

ref.: Reference category; 95% CI: 95% Confidence Interval; \*Logistic Regression

**Table 5:** Multivariate analysis of factors associated with non-reduction in the NIHSS score with acute ICVA in hospitalized patients from January 2014 to December 2017 in the stroke unit at HRC- Ceará.

Variable	OR (CI 95%)	p*
Gender		
Female	ref	ref
Male	2.70 (0.97; 7.50)	0.057
Older adults		
No	ref	ref
Yes	2.56 (0.84; 7.80)	0.098
Diabetes		
No	ref	ref
Yes	2.92 (1.05; 8.17)	0.040
Post-thrombolysis hemorrhagic transformation		
No	ref	ref
Yes	4.17 (1.58; 10.98)	0.004

Multivariate Logistic Regression; OR: Odds Ratio; ref.: Reference category; CI: Confidence interval 95%

## DISCUSSION

### Main results

Approximately 18.5% of participants showed no clinical improvement (reduction in NIHSS score) after intravenous thrombolytic therapy. In these patients, the presence of diabetes and post-thrombolysis hemorrhagic transformation increased the risk of no clinical improvement by 192% (ranging from 5 to 717%) and 317% (ranging from 58 to 998%), respectively.

### Limitations

It is a retrospective study in which the data sources were the patients' hospital records can be recognized as a bias, given that the information was not collected for research. But it helps better understand health determinants, commonly used in scientific research worldwide<sup>3</sup>.

Another interesting fact that should be taken with caution is the interval estimates of the main results found in this study. It may have occurred because the sample selected for the study was small<sup>9</sup>, which may be due to incomplete data and the recruitment period of patients for inclusion in the study.

Its retrospective character and performance in a single specialized center are also limitations of this investigation. Another evident restriction is that this investigation does not have data on the long-term follow-up of the studied patients, which may be related to the precision bias of the estimates about patients with delayed recoveries.

On the other hand, the results of this research can favor greater effectiveness in implementing the thrombolysis protocol for patients diagnosed with ICVA. It also supports public policies to install an earlier treatment in the health care network, help identify patients who may not fully benefit from chemical thrombolysis alone and select those who may need adjunct therapy. Furthermore, this investigation can help the health professional predict early results, serving as a generator of hypotheses for future studies on chemical thrombolysis.

### Interpretation

Many studies<sup>10-14</sup> assess the determinants of early neurological degeneration, as it is crucial for the prognosis of patients affected by ICVA. It is one of the first studies to evaluate the determinants of no clinical improvement in patients after ICVA, regardless of early neurological degeneration.

This study sought to identify and describe some risk factors for clinical non-improvement based on the NIHSS score in ICVA victims undergoing intravenous thrombolysis with rt-PA. Although the risk factors found were diabetes and hemorrhagic transformation, there seems to be no relationship between them<sup>3</sup>.

Intracerebral hemorrhage is a significant complication related to the use of rt-PA, given its lethality, which affects approximately half of the patients in these conditions<sup>3</sup>, being a determinant for the non-improvement of the patients studied in the present study. However, the frequency (24.81%) of hemorrhagic transformation (symptomatic and asymptomatic) was lower than the findings by Ferreira et al. They reported 32.37% of hemorrhagic transformation frequency, 21% asymptomatic, and 10.98% symptomatic<sup>15</sup>.

Diabetes is a leading risk factor related to the non-clinical improvement of post-thrombolysis patients with rt-PA. It is already well known as a determinant of early post-ICVA neurological deterioration, mainly due to its relationship with hyperfibrinogenemia that directly impacts the cascade of coagulation<sup>14</sup>.

Despite being clinically relevant for a better patient prognosis, other factors were not associated with the lack of clinical improvement in patients with ICVA. This study found a trend towards males and being elderly as determinants of no clinical improvement according to the NIHSS score.

Most patients were male, similarly to other studies<sup>16,17</sup>. In a cohort study, Savitz *et al.*, showed that occlusive vascular lesions were more likely to recanalize in women than in men in response to intravenous thrombolitics<sup>18</sup>.

In the study, where the age equal to or over than 60 years showed a tendency to increase the risk of no clinical improvement, the mean age of participants was 66.14 years, close to that found in the literature<sup>19,20</sup>. Engelter et al. showed that patients with CVA treated with intravenous rt-PA aged 80 years or more had a less favorable outcome than younger ones<sup>21</sup>. However, it is noteworthy that some studies show that the benefits of thrombolysis proved to be independent of age<sup>20,21</sup>.

Age should not be an exclusion criterion to assess the possibility of using rt-PA, especially in those with good general health and no organ dysfunction. The increasing use of rt-PA in individuals over 80 years of age and its inclusion in clinical trials and randomized studies allowed conclusions about the benefits of these therapeutic strategies in this age group<sup>21</sup>. The possibility of elderly patients benefiting from thrombolysis is clinically relevant since age is one of the main determinants of disability and death in CVA patients<sup>22</sup>.

Other clinically vital factors such as a history of arterial hypertension, smoking, and clinical characteristics during admission did not show a statistical relationship with no clinical improvement<sup>24</sup>.

The sample showed a high frequency of risk factors among the patients studied. Systemic arterial hypertension was the most prevalent comorbidity in the studied sample, as found in other studies<sup>23,24</sup>. Data from the National Institute of Neurological Disorders and Stroke study and recent Canadian open-label research reported that blood glucose and uncontrolled blood pressure levels are markers of adverse outcomes in patients treated with thrombolysis<sup>25</sup>. These outcomes corroborate our findings, in which most of the participants were hypertensive, and diabetes was a risk factor for no clinical improvement.

Simple measures to expedite thrombolytic therapy are crucial to reduce functional disability and mortality.

In addition, it is essential to work on the prevention of modifiable risk factors to reduce the occurrence of CVA, emphasizing reducing the epidemiological rates of diabetes and health promotion measures focused on glycemic control.

## CONCLUSION

The determinants of clinical non-improvement in patients suffering from ICVA who used rt-PA thrombolytic agents found in the present study were the presence of diabetes and post-thrombolysis hemorrhagic transformation. These factors should be considered for patients with acute ICVA undergoing thrombolytic therapy to better assess the patients' prognosis.

## Author's Contribution statement

HLMF: conceptualization, writing, review and editing, data curation, methodology and project administration. FWSF: conceptualization, formal analysis, software, writing, review and editing, data curation, methodology and project administration. AVFC: writing, review, and editing; CNBA: writing, review, and editing; RCD: writing, review and editing; GVR: writing, review and editing; JAC: conceptualization, formal analysis, software, writing, review and editing, data curation, methodology and project administration.

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## Conflicts of Interest

The authors report no conflict of interest.

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## Resumo

**Introdução:** a terapia trombolítica é a principal medida salvadora adotada em vítimas de acidente vascular cerebral isquêmico (AVCI), adequada para a maioria delas. Entretanto, alguns pacientes não apresentam evolução clínica, piorando o prognóstico, o que constitui uma lacuna científica essencial.

**Objetivo:** analisar os determinantes da não melhora clínica em pacientes com AVC em uso de trombolíticos rt-PA.

**Método:** estudo observacional retrospectivo caso-controle, realizado de 2014 a 2017 por meio de busca ativa de prontuários de pacientes com AVC submetidos à terapia trombolítica em um hospital de referência no Ceará. A falência clínica foi caracterizada como ausência de redução no National Institutes of Health Stroke Scale-Score (NIHSS).

**Resultados:** um total de 139 pacientes incluídos no estudo em uma única unidade de AVC. A média de idade foi de 66,14 anos (variando de 34 a 95). O seguimento de 24 horas foi completado em 100% dos pacientes. Resultado favorável 24 horas pós-trombólise foi observado em 113 pacientes (81,29%), e não houve melhora clínica em 26 (18,7%). A transformação hemorrágica pós-trombólise foi um forte preditor de não melhora ( $p=0,004$ ), e diabetes foi o principal fator de risco modificável encontrado ( $p=0,040$ ).

**Conclusão:** diabetes e transformação hemorrágica após trombólise foram identificados como fatores de risco para não melhora clínica em pacientes com AVC agudo submetidos à terapia trombolítica.

**Palavras-chave:** NIHSS, derrame, trombólise, terapia trombolítica.

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