

UNIVERSITY OF MEDICINE AND PHARMACY

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FACULTY OF GENERAL MEDICINE

**DEPARTMENT XV: ORTHOPEDICS-TRAUMATOLOGY,
UROLOGY, RADIOLOGY AND MEDICAL IMAGING**

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PhD thesis

-ABTRACT-

**RISK FACTORS AND PREDICTORS OF HEMORRHAGIC
TRANSFORMATION AND MORTALITY IN ACUTE ISCHEMIC
STROKE AFTER THROMBOLYSIS AND MECHANICAL
THROMBECTOMY**

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**Timișoara
2024**

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1. General part

Stroke, the second most common cause of death and a major contributor to disability worldwide, accounts for 11.6% of all fatalities (1). It also ranks third in terms of combined disability and mortality, representing 5.7% of total disability-adjusted life-years (DALYs). The prevalence of strokes is on the rise globally, primarily driven by the growing elderly population. In Europe, Romania stands out as the country with the highest rates of new stroke cases and stroke-related deaths, as indicated by the 2015 statistical reports (2). It is worth noting that this medical condition also carries a significant financial burden (3).

Ischemic stroke accounts for 87% of all strokes, while the remaining 13% is due to hemorrhagic strokes, both of which can lead to life-threatening complications, including death (4). The growing incidence of strokes prioritizes the need for researchers and healthcare providers to understand risk factors, to optimize treatment regimens in order to reduce effects and stroke consequences (5, 6).

Recognizing stroke symptoms and signs as soon as possible is crucial, according to the national current guidelines and protocols for the initial care of acute ischemic stroke (AIS) patients (7). So, management of acute stroke, like meeting the time targets for allowing patients with AIS to be admitted as soon as possible to hospital for increasing the rate of cerebral reperfusion or to identified risk factors or predictors for adverse complications of acute ischemic stroke like hemorrhagic transformation (HT), plays a vital role in achieving this goals.

Of greatest importance is the prompt and comprehensive management of acute stroke, as it is a critical condition that requires collaboration across multiple disciplines to optimize patient outcomes (both in terms of survival and functional recovery of AIS patients) (8). In the traditional way, the closest cooperation has been between the neurologists, the neurosurgeons and the radiologists, but implementing an interdisciplinary "stroke code" protocol involving the emergency physicians can shorten hospital admission delays by almost 30 minutes and achieve acute management time targets for cerebral reperfusion: < 4.5 h or < 6 h (7). The target < 4.5 h from the onset of AIS symptoms it is recommended for administer intravenous thrombolysis, as long as there are no contraindications. Additionally, endovascular treatment, such as mechanical thrombectomy with a stent retriever and aspiration catheter, should be performed within 6 hours from symptom onset, regardless of whether intravenous thrombolysis has been given (7, 9).

Encounter of stroke in emergency departments (EDs) is a typical neurological emergency. However, there is a notable lack of information on the correlation between prolonged ED times stays, particularly for critically ill patients, and outcome, such as mortality or hemorrhagic transformation, for this patients. Findings from various studies have been

inconsistent, with some indicating a link between ED length of stay and outcomes (10, 11), while others do not (12, 13).

Hemorrhagic transformation, a significant complication of acute ischemic stroke (14), can occur spontaneously, as a result of natural reperfusion, or after treatments such as intravenous thrombolysis (IVT) (with rt-PA: recombinant tissue plasminogen activator) and/or endovascular treatment (EVT) such as mechanical thrombectomy (MT) (15). The occurrence of hemorrhagic transformation can vary, with an average time frame of 6 days according to recent research (range 1–27 days) according to a recent research (16). In clinical practice, it is referred to as early hemorrhagic transformation if it happens within 18-24 hours and late hemorrhagic transformation if it develops after 18-24 hours (17).

It is therefore imperative to explore methods to anticipate early HT or potentially minimize complications that could impact prognosis and lead to higher mortality rates in acute ischemic stroke patients, regardless of whether they undergo intravenous thrombolysis or mechanical thrombectomy. In addition, it is essential to understand both modifiable factors, such as comorbidities and emergency department time goals, and non-modifiable factors, such as age, genetic predisposition and gender. Equally important is the assessment of predictors to improve the overall outcome and quality of life of these patients. However, more studies in larger cohorts need to be conducted to establish the role of these risk factors and acute ischemic stroke, as information on their role is insufficient.

Thus, ***the motivation of this study*** is to identify the risk factors and predictors associated with early-HT and in-hospital all-cause mortality, as well as to analyze whether ED time targets in the acute management of stroke patients are key roles in the evolution and management of these patients, with a view to their possible use for improving outcomes, increasing the use of cerebral reperfusion therapy, with impact on minimizing disability and mortality.

The novelty and importance of this study is due to the comprehensive, interdisciplinary approach (involving Radiology Department, Emergency Department and Neurology Department) of the acute management of patients with AIS to identify risk factors and predictors of worse outcomes. A better understanding of the factors involved in early hemorrhagic transformation or related to mortality in these patients will contribute to the development of therapeutic strategies and their management with impact on reducing mortality or adverse complications by identifying those at risk of worsening outcomes.

2. Special part

Although new approaches to identifying predictors and risk factors in acute stroke outcomes are currently available in the literature, there is still a lack of data on their involvement in haemorrhagic transformation and mortality associated with acute ischemic stroke during thrombolysis.

Thus, this research aims to provide answers to the following questions:

- ❖ Which risk factors can be predictors in patients with acute ischemic stroke of hemorrhagic transformation after cerebral reperfusion therapies?
- ❖ Which risk factors and acute stroke management time targets can be predictors for mortality in patients with acute ischemic stroke?
- ❖ Can these risk factors become reliable predictors in detecting worsening prognosis of patients with AIS?
- ❖ Are certain acute ischemic stroke management times, such as onset-to-door time, door-to-physicians, and door-to-CT, related to stroke outcome in stroke patients during thrombolysis?

Type of study: retrospective, analytical and interdisciplinary (Radiology Department, Emergency Department and Neurology Department).

Populations studied:

- ❖ Patients with AIS in window time of intravenous thrombolysis and mechanical thrombectomy, selected and diagnosed according to "The World Health Organization's definition of stroke (introduced in 1970 and still used) defined as a "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death (unless interrupted by surgery or medication), with no apparent cause other than that of vascular origin" (18, 19) and according to reperfusion therapy protocol (9, 20).
- ❖ From the group of patients that perform reperfusion therapy, one patient with aortic pathologies, and acute ischemic stroke that performed mechanical thrombectomy via transbrachial approach was selected for presentation as a case report.

Study background: The following premises formed the basis of the current research:

- ❖ While stroke is the second leading cause of death and a major cause of disability in the world, with an ever-increasing incidence every year, while causing an increase in overall mortality from cardiovascular disease, the present study attempts to analyze the factors of risk and predictors of adverse complications and mortality after reperfusion therapy (intravenous thrombolysis or mechanical thrombectomy).
- ❖ Several studies have been conducted on the risk factors involved in the evolution and outcomes of acute ischemic stroke (21, 22), but there is a lack of information in the specialized literature regarding the prediction and role of certain factors in hemorrhagic transformation and mortality in patients with AIS.

General objectives:

The aim of this current study was to identify a link between:

- ❖ Risk factors - like factors/conditions present in the patient -associated with increased risk of hemorrhagic transformation after acute ischemic stroke

And

- ❖ Predictors - like characteristics/ complications that occur during the acute ischemic stroke event- of early hemorrhagic transformation as well as of all-cause mortality following reperfusion therapy.

Specific objectives:

- ❖ Associations between risk factors and early- HT in patients with acute ischemic stroke;
- ❖ Evaluation of the incidence of early HT in patients with AIS treated with reperfusion therapy (intravenous thrombolysis or mechanical thrombectomy);
- ❖ Correlations between acute stroke management times, risk factors and in hospital all - cause mortality associated with acute ischemic stroke.

Studied parameters:

➤ **Clinical evaluation:** age (> 18 years old), gender, smoking (defined as current use of >1 cigarette per day), alcohol consumption, body mass index (BMI) (calculated according to the following formula: $BMI = \text{weight (kg)} / \text{height}^2 (\text{m}^2)$), history of arterial hypertension (already under treatment with antihypertensive drugs or blood pressure value > 140/90 mmHg at least twice before stroke or), history of diabetes mellitus (already under treatment with antidiabetics drugs or glucose level > 200 mg/dL postprandial), clotting parameters (international normalized ratio (INR), prothrombin time (PT), partial prothrombin time (aPTT)), hyperlipidemia and the presence/absence of atrial fibrillation. These data were recorded at the time of admission for all patients.

➤ **Hemodynamic risk parameters:** heart rate (HR), systolic and diastolic blood pressure (SBP, respectively DBP).

➤ **Stroke severity indicators:** The National Institutes of Health Stroke Scale - NIHSS, The Alberta Stroke Program Early CT score - ASPECTS.

At the time of admission NIHSS was performed, and also at 1 h, 2 h, and at 24 h. NIHSS were represented by the following values (23):

- 0 = no stroke symptoms,
- 1–4 = minor stroke symptoms,
- 5–15 = moderate stroke symptoms,
- 16–20 = moderate/severe stroke symptoms,
- 21–42 = severe stroke symptoms.

The ASPECTS consists of a 10-point quantitative score, as follow: 1 point is subtracted from 10 for any evidence of early ischemic change for each of the defined regions. Cerebral infarction in all 10 regions is indicated by a score of 0. Low ASPECTS (<7) indicate large infarctions associated with increased stroke severity and increased risk of HT (24).

- **Acute stroke time management:** onset-to-ED door time as recommended < 4.5 hours (or of no more than 3 hours for the second study), a door-to-physician time of less than 10 minutes, a door-to-CT time of less than 25 minutes, a door-to-CT-results time of less than 45 minutes, and a door-in-door-out time of no more than 120 minutes.

- **Hemorrhagic Transformation:** has been observed to occur within a range of 1 to 27 days, with an average timeframe of approximately six days. We considered as early hemorrhagic transformation when it occurs at less than 18–24 h, and late hemorrhagic transformation when it develops after more than 24 h (17).

The European Cooperative Acute Stroke Study researchers have developed based on CT scans two distinct stages of hemorrhagic transformation (HT): the presence of detectable petechiae is categorized as hemorrhagic infarction (HI), while more severe manifestations manifest as parenchymal hematoma (PH), with or without any accompanying mass effect (25).

- **Clinical Risk Factors of HT:** focus on hypertension, hyperglycemia, advanced age, gender, stroke severity scores, low platelet counts, smoking and alcohol consume.

The first part of the personal research: "PERSONAL STUDY: ANALYSIS OF RISK FACTORS AND PREDICTORS OF EARLY HEMORRHAGIC TRANSFORMATION AFTER REPERFUSION THERAPY IN PATIENTS WITH ACUTE ISCHEMIC STROKE" (26) aimed to identify risk factors as well as predictors of early HT as important tools to improve outcomes clinical conditions of these patients and their quality of life. This study has some major findings. One of the main findings of this study was the identification of certain risk factors as predictors of early HT in AIS patients treated with cerebral reperfusion therapies such as: male sex, high blood pressure and high glycemic values. Another major finding showed that higher NIHSS values and lower ASPECTS scores were associated with increased risk of early HT. In addition, from the results of our study, 20.37% of patients (n = 43; age: median 70.00 years; 51.2% male) had early HT, which represents a relatively high incidence of early HT in this study group compared to other clinical trials.

The second part of the research: " COLLABORATIVE RESEARCH: PREDICTORS FOR MORTALITY IN PATIENTS WITH ACUTE ISCHEMIC STROKE" (8) is based on a study carried out in collaboration with ED from Timiș Municipal Emergency Hospital and which study purpose is to evaluate timeliness of ED interventions and their impact on the administration of intravenous thrombolysis after initial admission of patients with acute ischemic stroke in an ED from a hospital without stroke team/neurology and assess the impact on of AIS management times on all-cause mortality during hospitalization for AIS.

This study noted that the mean door-to-CT time was 52 minutes, which is double the recommended target time of less than 25 minutes, correlated significant with death outcome for all patients included. Also highlight the importance to the achievement of all of the ED time

targets for AIS management, and that a reduce of door-to-CT time can influence all-cause mortality in these patients.

The third part of the personal research: "OUR EXPERIENCE AND LITERATURE REVIEW - MECHANICAL THROMBECTOMY VIA TRANSBRACHIAL APPROACH IN THE EMERGENCY MANAGEMENT OF ACUTE ISCHEMIC STROKE PATIENTS WITH AORTIC PATHOLOGIES" (27) analyzes a case chosen for its complexity determined by the association of two pathologies with high cerebrovascular risk, arterial hypertension, poorly medicated, and the existence of an undiagnosed coarctation of the aorta until the moment of mechanical thrombectomy and advancement with the guide catheter. Due to the discovery of an aortic coarctation that greatly influences the emergency management of a patient with AIS, and that the clasically transfemoral approach is not recommended, our first attempt, consequently, a transbrachial approach was performed, resulting in complete revascularization of the occluded arterial territory. The evolution of this case demonstrates that during MT, it is crucial to optimize all strategies that have the potential to prevent delays and ensure prompt initiation of stroke treatment.

Starting from this complex case report, in this part of our research, we also conducted a review of the case reports of patients with different aortic pathologies and AIS reperfusion therapy performed by MT via transbrahial approach (TBA) from the literature.

In addition, from our experience and from literature review, in young hypertensive patients, unresponsive to antihypertensive treatment and admitted to the emergency department with acute stroke symptoms, we believe that the identification of an aortic pathology is essential. However, whether these patients should be routinely screened for aortic pathologies remains a matter of debate.

The present study divided the selection of patients into two distinct categories: AIS patients in time of cerebral reperfusion therapy (<4.5 h from stroke symptoms onset), that were selected from the database of the Timis County Clinical "Pius Brinzeu" Emergency Hospital and from patients with symptoms of AIS selected from the patients adress from ED of the Timis Municipal Clinical Emergency Hospital to our hospital for cerebral reperfusion. These two studies were conducted from January 2019 until December 2022.

Consecutive patients were chosen based on inclusion / exclusion criteria in this research study through a retrospective investigation that adhered to specific scientific objectives.

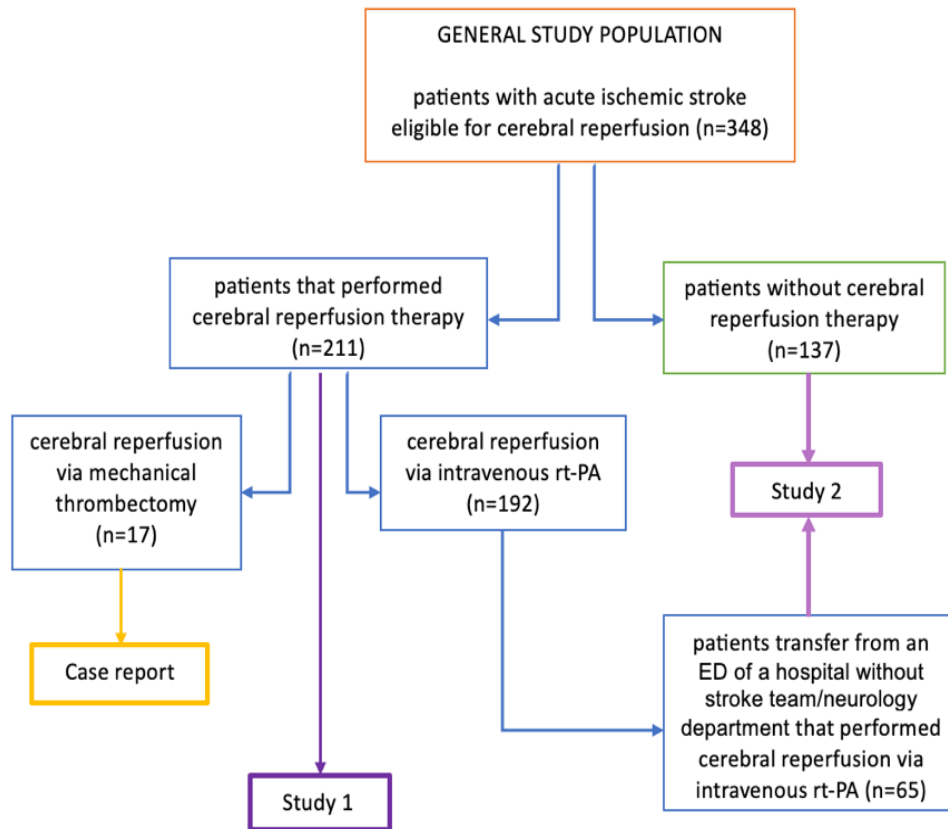


Figure 1. Selection of study population

This research study was approved by the Ethics Committee of the Timis County Clinical Emergency Hospital and Timis Municipal Clinical Emergency Hospital. The present research conformed to the Declaration of Helsinki and all patients included in this research provided written informed consent.

3. Results

Study 1

From a total of 557 patients screened for eligibility to perform reperfusion therapy, only patients ($n = 211$) that received intravenous thrombolytic therapy ($n = 192$) or endovascular treatment through mechanic thrombectomy ($n = 17$) were included in the final sample of this study.

Among 211 consecutive patients included in the final sample, 43 (20.37%; age: median 70.00 years; 51.2% males) had early HT and 168 (79.63%; age: median 68.00

years; 61.3% males) were without early HT. Patients with early HT were older compared with patients without early HT, but no statistically significant difference ($p = 0.843$) was observed between the groups. They also tended to have a higher BMI compared to the other group (without early HT) ($p = 0.764$). Regarding gender, no difference between groups was observed ($p = 0.231$). Although no statistically significant differences were observed between the two groups. Moreover, 37.2% of the patients from the early-HT group ($n = 16$) had atrial fibrillation previously, compared with 28.6% ($n = 48$) from the group without early HT ($p = 0.272$). No statistically significant difference was observed between groups for alcohol consumption ($p = 0.433$), smoking ($p = 0.839$), platelets count ($p = 0.279$), hemoglobin ($p = 0.527$), creatinine ($p = 0.098$), and INR ($p = 0.538$).

The values of ASPECTS at admission and ASPECTS at 24 h are significantly lower in patients with early HT (Mann–Whitney test, $p = 0.045$ and $p < 0.001$, respectively). NIHSS values at admission, at 1 h, 2 h, and 24 h are significantly increased in those with early HT (Mann–Whitney test, $p < 0.001$, $p = 0.040$, $p = 0.032$, and $p = 0.007$, respectively).

By applying the chi-square test to analyze the incidence of early HT after the two types of reperfusion therapy (fibrinolytic and endovascular treatment), no statistically significant differences were observed in the study sample between them ($p = 0.089$).

In order to identify the independent risk factors for hemorrhagic transformation, we employed a multivariate logistic regression. The odds ratio and 95% confidence interval were calculated. The independent factors that increase the risk for hemorrhagic transformation were male gender by 2.7-fold, presence of baseline high blood pressure by 2.4-fold, and high glycemic values by 1.2-fold.

In order to identify the scoring systems that are predictive of the hemorrhagic transformation, a multivariate logistic regression was employed. Higher values of ASPECTS at 24 h decrease the risk of hemorrhagic transformation by 0.6-fold. Higher values of NIHSS at 24 h increased the risk of hemorrhagic transformation by 1.18-fold.

Age values are insignificantly increased in the case of patients with early hemorrhagic transformation (Mann-Whitney test, $p=0.843$). BMI values are insignificantly increased in the case of patients with early-hemorrhagic transformation (Mann-Whitney test, $p=0.764$). DBP values are also not statistically significantly increased in the case of patients with early-hemorrhagic transformation (Mann-Whitney test, $p=0.767$). The number of platelets is insignificantly increased in the case of those with early-hemorrhagic transformation (Mann-Whitney test, $p=0.279$). Hemoglobin and serum creatinine are both non-significantly elevated in those patients with early hemorrhagic transformation (Mann-Whitney test, $p=0.527$ and $p=0.098$).

Study 2

In this study, a total of 202 patients who had experienced an acute stroke were included in the cohort. Among these patients, 51.98% (n=105) were women. Thrombolysis was performed by only 32.18% (n=65) of the patients. The most common symptom observed in patients with AIS was right hemiparesis, which was present in 71 patients (35.14%). At the other extreme, headaches was the least common symptom, reported by only seven patients (3.47%). Arterial hypertension was found to be the most prevalent risk factor for stroke, affecting 82.18% of the patients. This was followed by diabetes mellitus, which was present in 26.73% of the patients, and smoking, which was reported by 18.32% of the patients.

Among all the patients with AIS symptoms admitted to our ED, 35.15% summarizing a number of 71 patients unfortunately passed away during their hospitalization. Additionally, ten of all patients remained with dependent disability, while the majority, 59.90% (n=121), were discharged without any disability.

When analyzing patient survival, we conducted logistic regression analysis to compare the cumulative survival curves of individuals who received intravenous rt-PA with those who did not. Our findings indicate that the mean number of hospitalization days is only marginally higher for the group that did not receive rt-PA, rendering it insignificant ($p=0.455$)

When analysis ED time targets and death outcome it was observed a statistically significant correlation between symptoms onset-to-ED door time and death outcomes ($p=0.016$) and between door-to-CT time ($p=0.037$).

3. Case report and original research: our experience and literature review

Mechanical thrombectomy via the transbrachial approach is a very rare option used in cases of patients with aortic pathologies and acute ischemic stroke due to the insufficient evidence in the literature, the difficulty from a technical point of view and the result of this technique influenced by the complications that frequently accompany it.

Background: Only a few cases of patients with aortic pathologies and acute ischemic stroke where MT via TBA were reported in the literature, and its application in the emergency management of AIS has still not been dealt with in detail.

Objectives: Out of a need to clarify and clearly emphasize the effectiveness of this approach in emergency MT via TBA in patients with AIS and aortic pathologies, this literature review and case report has the following objectives: the first one is the presentation of an emergency MT via transbrachial approach performed in a 44-year-old patient with AIS and diagnosed aortic coarctation during transfemoral approach (TFA), with successful reperfusion

in our department and the second one is to review the cases reports of patients with different aortic pathologies and AIS reperfusion therapy performed by MT via TBA from the literature.

Methods: A total of nine cases (one personal case and eight published cases) were revised in terms of aortic pathologies type, reperfusion therapy type, and the complication of both mechanical thrombectomy and local transbrachial approach.

Results: Mechanical thrombectomy through the transbrachial approach was the first choice in more than half of these cases (55.55%, n = 5 cases) in the treatment of acute ischemic stroke in the presence of previously diagnosed aortic pathologies. In one-third of all cases (33.33%, n = 3, our case and 2 case reports from the literature), the transbrachial approach was chosen after attempting to advance the guiding catheter through the transfemoral approach and intraprocedural diagnosis of aortic pathology. In only one case, after an ultrasound evaluation of the radial artery that showed a monophasic flow, MT was performed via TBA. Local transbrachial complication was reported in one case, and in two other cases, it was not stated if there were such complications. Hemorrhagic transformation of AIS was reported in two cases that underwent MT-only cerebral reperfusion via TBA, one with acute aortic dissection type A and our case of previously undiagnosed aortic coarctation. In the cases in whom short and long-term follow-up was reported, the outcome of treatment, which was not exclusively endovascular (77.77% cases with only MT and 33.33% with association of first thrombolysis and after MT), was good (six from nine patients). In two case reports, the outcomes were not stated, and one patient died after a long hospitalization in the intensive care unit from respiratory complications (our patient).

Conclusions: Being a clinical emergency, acute ischemic stroke requires urgent medical intervention. In patients with aortic pathologies, where acute ischemic stroke emergency care is a challenge, mechanical thrombectomy via the transbrachial approach is a safe alternative method for cerebral reperfusion.

4. General conclusions

- Our first study identified male gender, hypertension and elevated blood glucose values as predictors of early HT in AIS patients treated with cerebral reperfusion therapies.
- Both higher NIHSS values and lower ASPECTS scores were associated with an increased risk of early HT.
- 20.37% of patients from our first study group had early HT, which represents a relatively high incidence compared to other clinical trials.

- Among the independent risk factors for early HT found in our study after performing a multivariate logistic regression analysis, the ED admission high values of blood pressure increased the risk by 2.4-fold and high values of blood glucose by 1.2-fold.
- We demonstrate that AIS patients undergoing cerebral reperfusion methods that present a high value of blood pressure and blood glycemia on admission to the ED, as well as the male gender require special attention.
- These risk factors can be used as early warning indicators for medical staff to assess the risk of early haemorrhagic transformation after AIS for both methods of cerebral reperfusion (intravenous thrombolysis with Actilyse and /or mechanical thrombectomy).
- It is of critical importance to identify predictors of HT in patients with AIS receiving reperfusion therapies in order to minimize the risk of negative outcomes. Predictive models could be used in the future for the selection of patients with low risk of complications time-of-onset independent.
- When we analyze the impact of ED time targets on the administration of rt-PA treatment, we found that none of the following factors had a statistically significant effect: door-to-CT, door-to-physician, door-to-transfer time, NIHSS score upon admission to the Neurology department or NIHSS score after 24 hours.
- It is worth noting that the average door-to-CT time in our second study was 52 minutes, which is double the recommended target time of less than 25 minutes.
- In our second research, we observed a significant correlation between meeting ED time targets and patient mortality, specifically about the time it takes to perform a CT scan after arriving at the hospital.
- Based on our findings, it is recommended that hospitals without a dedicated stroke unit reevaluate their management of AIS cases by prioritizing the achievement of ED time targets. This will not only have an impact on interhospital transfers but also the overall outcome of AIS patients.

- The data from our all studies provide a practical basis for medical staff to monitor patients' risk factors for early HT and perform timely target medical interventions to improve outcomes for these patients.

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