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Stroke Thrombolysis in the Elderly: A Moroccan Retrospective Study

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Abstract **Original Research Article**

***Background*:** Age increases the risk of mortality and poor prognosis following a stroke. The benefits of intravenous thrombolysis (IVT) in elderly patients have been well established. However, the outcomes in daily clinical practice may differ from those reported in other studies. The objectives of our study are to evaluate the effectiveness and safety of thrombolysis in elderly stroke patients and provide local data that can inform clinical practices in similar settings and raise awareness about specific challenges in treating elderly patients with ischemic stroke. ***Methods*:** We conducted a retrospective, cross-sectional, descriptive, and analytical study in the neurology department of Hassan II University Hospital in Fez, Morocco, from May 2015 to March 2021. All elderly patients aged ≥ 80 years within 6 h of onset who received intravenous thrombolysis were recruited. The primary outcomes were the rate of hemorrhagic transformation, NIHSS score at 24 h after IV thrombolysis and the rate of death within the first 7 days. Secondary outcomes were functional status at 3 months, assessed using the modified Rankin Scale (mRS). Our results were interpreted in light of the main studies in the literature. ***Results*:** 41 patients (58.5 % female, aged 84 ± 3.5 y.o) all received IV thrombolysis (tenecteplase 85.4% vs alteplase 14.6%) were included. The mean NIHSS score before IV thrombolysis was 13 (range, 3-20) and that 24 h after IV thrombolysis was 10 (rang, 1-19). Hemorrhagic transformations occurred in 31.7% of the patients within 7 days after onset (9.8% HI1, 9.8% HI2, 2.4% PH1, 9.8% PH2), and all of these cases were asymptomatic. The rate of death within the first 7 days was 22%. Among living patients, the median three months mRS was 3. The mortality rate at three months was 26.8% (n=11). However, there was no significant association between these outcomes and the occurrence of ICH after IVT. ***Conclusion*:** Despite the higher mortality rate in our sample, IV thrombolysis does not predict death. There was no statistically significant association between hemorrhagic transformation and disability or death rates at 3 months, suggesting the involvement of other factors. The fact that elderly patients are at high risk for stroke-related death and disability makes them an important target group for acute treatment.

Keywords: Elderly, Thrombolysis, Acute Ischemic Stroke, Alteplase, Tenecteplase.

INTRODUCTION

Moroccan demographic characteristics are shifting with a remarkable expansion in the elderly population. Prolonged life expectancy at older ages has led to the growing size of the elderly population and therefore stroke patients.

Thrombolysis is an effective acute treatment for eligible stroke patients. However, age has an impact on the outcomes following acute ischemic stroke and IV thrombolysis.

The benefits of thrombolysis in the elderly are well documented in clinical trials [1, 2]; however, real-world outcomes can differ due to comorbidities, frailty, and age-related conditions. These factors may limit both the accessibility and effectiveness of intravenous thrombolysis (IVT) in routine clinical practice, particularly in elderly patients who may face treatment delays, a higher risk of complications, and logistical challenges in receiving timely stroke care.

Additionally, these conditions may wrongly influence practitioners to avoid IVT in eligible elderly patients, driven by concerns about increased risks or poor outcomes. Consequently, some patients who meet the criteria for thrombolysis may be excluded from potentially beneficial treatment, resulting in missed opportunities to improve recovery. This underscores the

need for more real-world data to guide clinical decisions and optimize care for this population.

The trials of Bluhmki *et al.,* 2020 had shown that Alteplase has a positive benefit-risk profile among patients aged >80 years when administered according to other regulatory criteria [1].

Furthermore, the risk-benefit profile of tenecteplase thrombolysis is preserved in patients aged ≥80 years, which supports intravenous tenecteplase as an alternative to alteplase in these patients [2].

Thrombolysis is a critical treatment for ischemic stroke; however, its application in elderly patients remains challenging. Our study provides valuable insights into the effectiveness and safety of this intervention in a Moroccan context, where managing older adults is crucial. Our results are based on a series of 41 patients treated at our stroke unit, providing pertinent local data that can inform clinical practices in similar settings across Africa and beyond.

METHODS

Study Design

- Conducted a retrospective, cross-sectional, descriptive, and analytical study in the neurology department of Hassan II University Hospital in Fez, Morocco, from May 2015 to March 2021 (almost six years).

Setting

- The study was carried out in the stroke unit of the neurology department at Hassan II University Hospital, which provides a suitable environment for treating acute ischemic stroke and transient ischemic attacks (TIA).

Participants

- Included all patients aged over 80 years with acute ischemic stroke or TIA who received intravenous thrombolysis and were admitted within 6 h of stroke onset.
- Excluded three groups of patients: those with stroke mimics, those not treated with thrombolysis, and those who underwent thrombectomy.
- Focused on evaluating the short-term outcomes of patients who received thrombolysis without other interventions.
- All the patients have meet the criteria of 3 months follow up.

Variables

- Collected data on demographic characteristics, clinical presentation, treatment details, and outcomes.

Data Sources/Measurement

- Data were collected from existing medical records stored in the hospital's local register.
- Information was entered into Excel spreadsheets and analyzed using the Statistical Package for the Social Sciences (SPSS) software.
- A 95% confidence interval was used, with a significance level set at 0.05.

Statistical Analysis

- Various statistical methods and tests were applied based on sample size and the nature of the variables.

Bias

- Efforts were made to minimize bias by using clear inclusion and exclusion criteria and collecting data from reliable medical records.

Study Size

- The final study included a total of 41 elderly patients who met the inclusion criteria and were treated with intravenous thrombolysis.

Quantitative Variables

- NIHSS scores were measured on admission and 24 h post-thrombolysis.
- Hemorrhagic transformation was classified based on CT findings and ECASS-II criteria.
- Modified Rankin Scale (mRS) scores were recorded to assess functional outcomes at 3 months.
- Mortality data were collected within one week post-stroke and at 3 months.

Definitions and Classifications

- Neurological worsening during hospitalization was defined as an NIHSS score increase of 3 points or more from the admission score.
- Symptomatic intracranial hemorrhage (sICH) was defined as clinical deterioration with an NIHSS score increase of 4 points or more, with hemorrhage likely causing the deterioration.
- Intracerebral hemorrhage (ICH) was classified according to the European Cooperative Acute Stroke Study II (ECASS-II) criteria [3].
- Intracranial collaterals were graded based on the Miteff scoring system [4].

Imaging Protocol

- Baseline head CT with angiography (CTA) was performed for all patients, with follow-up scans routinely done 24 h after thrombolysis and whenever hemorrhage was suspected.

Treatment Protocol

- Patients were treated with IV alteplase at a dose of 0.9 mg/kg or IV tenecteplase at a dose of 0.25 mg/kg of body weight.

Stroke Etiology

- Stroke Etiology was determined by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and classified as large artery atherosclerosis, cardioembolism, small vessel disease, other, or unknown [5].

Outcome Measures

- Primary outcomes included the NIHSS score 24 h after thrombolysis, the rate of hemorrhagic transformations, and mortality within the first week.
- Secondary outcomes were assessed using the modified Rankin Scale (mRS) score and the mortality rate at 3 months.

Ethical Considerations

- Data collection complied with global ethical standards regarding patient confidentiality and data protection.

RESULTS

Participants

A total of 41 patients with ischemic stroke were treated with intravenous thrombolysis. Among them, 24 (58.5%) were female and 17 (41.5%) were male. The average age was 84 years (range, 80-92 years).

Descriptive data

Hypertension was the most prevalent condition, present in 51.2% of our patients, followed by diabetes and ischemic cardiomyopathy, each present in 7.3% of cases [Table 1].

The mean NIHSS (National Institutes of Health Stroke Scale) score prior to the administration of intravenous thrombolysis (IVT) was 13, with scores ranging from 3 to 20. Most patients exhibited moderate to severe stroke symptoms. The majority of our patients exhibited moderate-to-severe stroke symptoms at onset [Table 2].

All patients had an ASPECT score of 7 or higher, with the majority (39.0%) having a score of 10. Regarding the occlusion sites on CTA, a significant portion (29.3%) occurred in the M1 segment, 19.5% in the M2 segment, and 2.4% were in the basilar artery. However, in nearly half of the cases, the occlusion could not be visualized and the decision to administer IVT was based on the radio-clinical mismatch. Of the patients, 92.7% had good-to-moderate intracranial collaterals (grades 3 or 2 on the Miteff scoring system).

Table 1: The demographic and clinical history characteristics of the study population

Features	Total sample
Average age (years)	84 ± 3.5
Females	58.5
Hypertension	51.2
Diabetes	7.3
Ischemic cardiomyopathy	7.3
Previous TIA/stroke/ALI	4.9
Hypercholesterolemia	2.4
Smoking habit	2.4

Data are presented as % unless otherwise indicated.
NIHSS, National Institutes of Health Stroke Scale/Score; TIA, transient ischemic attack; ALI, Acute limb ischemia.

Table 2: The stroke severity of the study population

NIHSS on admission	N (%)
0-4	1 (2.4)
5-15	31 (75.6)
16-20	9 (22)

Treatment Details

35 patients (85.4%) received tenecteplase, while six patients (14.6%) received Alteplase as IV thrombolytic agents.

The mean time-to-needle was 3 h and 42 min. The maximum time from symptom onset to treatment was 5 h and 45 min, whereas the minimum time was 1 h. Most patients (80.49%) received intravenous thrombolysis within the 4.5-h window.

The analysis of stroke etiologies revealed that a significant proportion, 39% of strokes, were attributed to cardioembolism mainly due to atrial fibrillation. Large artery atherosclerosis was identified in 29.3% of the cases. In contrast, lacunar strokes accounted for only 4.9% of the cases [Table 3].

Table 3: The stroke causes of the study population

Aetiologies	Total sample
Cardioembolism	39%
Large artery atherosclerosis	29.3%
Lacunar	4.9%
Cryptogenic	26.3%

Outcome Data

NIHSS score at 24 hours

Seventeen patients (41.5%) had a significant reduction (≥4 points) in their NIHSS score within the first 24 h after IV thrombolysis. Furthermore, the overall NIHSS scores improved significantly by an average of 2.9 points ($p < .001$, t-test) after IV thrombolysis, with a mean NIHSS score of 10 and scores ranging from 1 to 19 [Figure 1].

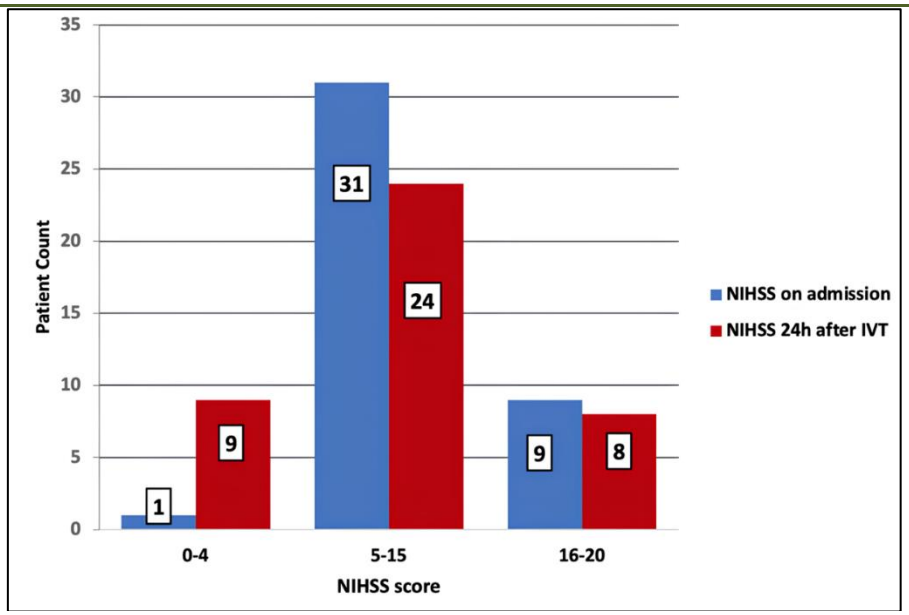

Figure 1: The NIHSS Profile of our Patients Prior and 24 h After IV Thrombolysis (IVT).

The blue columns represent NIHSS scores on admission prior to IVT and the red columns the NIHSS 24 h after IVT. This chart demonstrates that many patients with moderate stroke symptoms on admission showed improvement after IVT, shifting to minor stroke symptoms. However, the severe stroke group remained almost unchanged.

Hemorrhagic Transformation within the first week

Thirteen patients (31.7%) experienced intracranial hemorrhagic transformations within the first seven days after stroke onset. However, no cases of symptomatic intracranial hemorrhage (SICH) were noted in the entire population [Table 4].

Table 4: Rate of hemorrhage transformation within 3 months of follow-up

Hemorrhagic transformation*	%
Hemorrhagic infarction type 1	9.8%
Hemorrhagic infarction type 2	9.8%
Parenchymal hematoma type 1	2.4%
Parenchymal hematoma type 2	9.8%
sICH	0%

* Based on the European Cooperative Acute Stroke Study (ECASS II) classification

sICH: symptomatic Intracerebral Hemorrhage

Early Mortality/Disability and mortality at 3 months

Thirteen patients (31.7%) had no or mild disability, which is classified as a modified Rankin Scale score (mRs) of 0-2. This suggests that over one third of the patients had a relatively good outcome in terms of disability. In contrast, the median mRS score was 4 and the overall mortality rate at three months was 26.8%. Notably the majority of these deaths (22%) occurred within the first week of stroke onset. However, there was no significant association between intracranial hemorrhage (ICH) and death within the first week (Fisher exact test, $p = 0.294$). Furthermore, these deaths were not significantly associated with the occurrence of parenchymal hematoma type 2 (Fisher exact test, $p = 0.204 > 0.05$).

The occurrence of ICH, especially PH2, negatively affected disability outcomes at 3 months (mRS); however, neither of these associations were statistically significant (Mann-Whitney U test: $p = 0.382$ for ICH, $p = 0.483$ for PH2).

DISCUSSION

Interpretation of Findings in Relation to Other Studies

Population aging is challenging for healthcare systems because of the increasing demand for acute stroke treatment especially in older patients.

Prior studies such as Weber *et al.*, [6], showed that older patients still had a lower probability of receiving stroke unit treatment, although several studies have shown that stroke unit treatment reduces death or institutionalization [7]. In addition, the benefit of intravenous thrombolysis is preserved in patients with acute ischemic stroke (AIS) over the age of 80 years [8, 9].

This benefit was clearly observed in the Bluhmki study [1] which included Individual patient data from 7 randomized trials of alteplase (0.9 mg/kg) versus placebo or open control for AIS, and the European SITS-UTMOST registry database [10]. Although, the 90-day mortality was lower among patients aged <80 years versus ≥80 years, alteplase versus placebo was associated with a higher proportion of good stroke outcome and similar 90-day mortality. The odds of good stroke outcome following alteplase use were independent of age. Good outcomes were reported in almost half of the patients who received alteplase in routine practice [1].

Similar outcomes were observed with Tenecteplase in the Xiong trial [2]. Thrombolysis using 0.25 mg/kg Tenecteplase was comparable with alteplase in achieving excellent functional outcome within 4.5 h of symptom onset, with a similar safety profile in patients over 80 years old who did not undergo endovascular thrombectomy.

Comparison with Our Findings

Our data demonstrated similar outcomes to prior trials [1, 2], with a significant improvement in the NIHSS score following IV thrombolysis. In addition, the overall mortality rate at three months was elevated to 26.8%, which is consistent with the results of other studies. However, we found that hemorrhagic transformation did not affect the occurrence of unfavorable outcomes 3 months after IV thrombolysis. This finding aligns with those of previous studies, suggesting that age-related factors, such as frailty and comorbidities, play a significant role. Older patients tend to have higher rates of complicated medical conditions. Therefore, there are several reasons unrelated to hemorrhagic complications of IV thrombolysis that could explain the poor outcomes in elderly patients.

Debate on Thrombolysis in Minor Strokes especially in the elderly

Despite the efficacy of thrombolysis, recent debate has emerged regarding its use in minor ischemic strokes, especially in elderly patients.

In a recent prospective observational study [11], conducted at the Haukeland University Hospital, thrombolysis with alteplase was linked to better short-term outcomes in elderly patients with major ischemic stroke.

However, for patients with minor ischemic stroke (NIHSS score <3 on admission), thrombolysis was associated with worse short-term outcomes [11].

The first limitation of this study was its observational nature which could be associated with unknown biases that influence the choice of treatment and patient monitoring standards. The second was the use of an NIHSS score threshold of 3 to define a minor ischemic stroke. Other limitations were the unknown reasons for not administering thrombolysis and lack of investigation into thrombolysis in the extended time window.

Further studies showed no difference between thrombolysis and dual antiplatelet therapy (DAPT) in acute minor cerebral infarction related to functional outcomes [12-14].

A recent randomized clinical trial conducted by Chen *et al.*, in 2023 [15] found that DAPT was not inferior to alteplase in patients with an NIHSS score ≤5, regardless of age. The authors suggested that early deterioration in the thrombolysis group compared with that in the DAPT group could be attributed to thrombus progression. Alteplase has a short half-life, whereas DAPT provides a continuous antiplatelet effect and may prevent stroke recurrence [15]. The absence of vessel imaging data in some patients weakens the data analysis in this trial, particularly because previous studies suggest a potential benefit of alteplase or tenecteplase in patients with minor ischemic stroke and large artery occlusion [16-18]. Further data will be provided in the TEMPO-2 trial (NCT02398656), on tenecteplase vs standard of care in minor stroke cases with large artery occlusion.

Strengths and Limitations

Our study's strength lies in its real-world data contribution, offering insights into thrombolysis in the elderly in a Moroccan context. However, limitations include its retrospective design, which may introduce data collection biases. The absence of a control group and the small sample size may limit the generalizability of the findings.

CONCLUSION

Despite the higher mortality rate observed in older population, thrombolysis does not predict mortality. Given that elderly patients are at higher risk of stroke, they represent a crucial target group for acute treatment. Therefore, the decision to administer thrombolytic therapy should not be based on the patient's age but should be individualized to consider the overall clinical context, risks and benefits.

What is already known on this topic:

- Intravenous thrombolysis (IVT) is effective in improving outcomes for ischemic stroke patients, but its benefits in elderly patients are debated due to higher risks of complications.
- Comorbidities, frailty, and age-related conditions can limit the accessibility and effectiveness of intravenous thrombolysis (IVT) in elderly patients, resulting in treatment delays, increased risks of complications, and logistical challenges in accessing care
- Data on IVT outcomes in elderly patients are mostly from high-income countries, with limited evidence from low- and middle-income regions like Morocco.

What this study adds:

- Offering valuable insights into the effectiveness and safety of thrombolysis in elderly patients within a Moroccan context, highlighting the importance of managing older stoke patients.
- Enhancing the understanding of the clinical implications of thrombolysis for this population, based on a series of 41 patients treated at our stroke unit.
- Providing relevant local data that can inform clinical practices and raise awareness about the

outcomes of IVT in elderly populations in similar contexts.

Competing Interests: The authors declare no competing interest.

Authors' Contributions

- **Study Conception and Design:** [Walid Sadki].
- **Data Collection:** [Walid Sadki, Boutayna Touiti, Naima Chtaou].
- **Data Analysis and Interpretation:** [Walid Sadki].
- **Manuscript Drafting:** [All authors].
- **Manuscript Revision:** [All authors].
- **Approval of the Final Version:** [All authors approved the final version of the manuscript].

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