



Challenges and Outcomes of Thrombolytic Therapy in Acute Ischemic Stroke: The Iranian Perspective

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Abstract

Background: Acute ischemic stroke (AIS) is a leading cause of mortality and long-term disability worldwide. In Iran, AIS tends to occur nearly a decade earlier than in developed nations, presenting unique challenges. Intravenous recombinant tissue plasminogen activator (IV-rtPA) is an effective thrombolytic therapy for AIS, but various factors limit its utilization.

Objectives: This study aimed to identify the barriers to the administration of IV-rtPA in AIS patients at Shahid Beheshti Hospital in Qom, Iran.

Methods: A cross-sectional descriptive-analytical study was conducted on AIS patients admitted between November 2021 and September 2022. A total of 322 patients were screened, and 178 met the inclusion criteria. Data on demographic characteristics, stroke severity (NIHSS score), comorbidities, onset-to-door time, and reasons for not receiving IV-rtPA were analyzed using SPSS version 22.

Results: Of the 178 patients, 87 (48.9%) received IV-rtPA, while 91 (51.1%) did not. The primary reasons for withholding thrombolysis were clinical improvement (37.4%), late hospital arrival beyond 4.5 hours (24.2%), lack of consent (20.9%), the physician's conservative approach (11%), and mild progression of stroke symptoms (6.6%). A significant correlation was found between NIHSS score and reasons for non-receipt of therapy ($P < 0.001$). Patients with a prior stroke history were more likely to experience delays due to a physician's conservative approach (28.6% vs. 5.7%, $P < 0.01$). Barriers to thrombolysis were also associated with lower education levels and a lack of public awareness about stroke symptoms.

Conclusions: Delayed hospital admission and lack of consent were the leading barriers to IV-rtPA administration. Public awareness campaigns emphasizing the urgency of recognizing stroke symptoms and seeking timely medical care are crucial to improving thrombolysis rates and reducing AIS-related disabilities in Iran.

Keywords: Acute Ischemic Stroke, Fibrinolytic Agents, Recombinant Tissue Plasminogen Activator, Intracranial Hemorrhage, Challenges and Outcomes

1. Background

Acute stroke is characterized by the interruption of blood flow to the brain, which can result from either a ruptured blood vessel (hemorrhagic stroke) or a blockage caused by a clot (ischemic stroke). Both conditions deprive the brain of essential nutrients and oxygen, leading to tissue damage. Notably, ischemic strokes account for approximately 87% of all stroke cases (1). Stroke is a major cause of mortality and long-term

disability, consistently ranking as a leading cause of death and varying degrees of impairment, particularly among vulnerable populations. Beyond the challenges of rehabilitation, stroke imposes significant economic and social burdens on societies worldwide. In the United States alone, its annual incidence is approximately 700,000 cases (2).

Iran currently lacks a national stroke registry, leading to significant disparities in the reported stroke cases across different regions. The incidence of stroke varies

widely, ranging from 22 to 140 cases per 100,000 population (3, 4). Compared to individuals in some developed countries, Iranians experience ischemic stroke nearly a decade earlier, contributing to a higher fatality rate. The 30-day mortality rate for stroke is approximately 10%, while 90% of survivors often face long-term disabilities (5). Intravenous recombinant tissue plasminogen activator (IV-rtPA) is a highly effective thrombolytic therapy for acute ischemic stroke (AIS). Its administration in specialized stroke centers significantly enhances survival rates and functional outcomes for patients (6, 7). The American Stroke Association (ASA) has introduced the concept of primary and comprehensive stroke centers, along with designated emergency hospitals, to ensure adequate care for stroke patients and improve the overall quality of treatment (8).

2. Objectives

This study aimed to investigate the factors contributing to the non-administration of IV-rtPA in eligible patients with AIS and to understand why many Iranian medical centers withhold this treatment from eligible patients. Our findings highlight key barriers to optimal stroke care in Iran and emphasize the urgent need for targeted interventions to improve access to evidence-based therapies.

3. Methods

This cross-sectional descriptive-analytical study was conducted at Shahid Beheshti Hospital in Qom, following approval from the ethics committee of Qom University of Medical Sciences (Approval ID: IR.MUQ.REC.1401.181). The study included patients experiencing acute strokes who were admitted to Shahid Beheshti Hospital between November 2021 and September 2022. Eligible participants were adults aged 18 years or older who met the criteria for Code Stroke activation but did not receive thrombolytic therapy. The minimum sample size was calculated based on the results of the study by Hatamabadi et al. (9) and considering the percentage of non-receipt of rTPA due to delays, which was estimated at 70%, resulting in a sample size of 322 individuals. A total of 322 patients with suspected AIS were initially screened during the study period. Of these, 178 patients met the inclusion criteria and were thoroughly examined and analyzed.

Data collected for these patients included demographic information (age and gender), National Institutes of Health Stroke Scale (NIHSS) score upon arrival, onset-to-door time (the interval between symptom onset and hospital arrival), chief complaint,

risk factors (such as a history of hypertension, dyslipidemia, diabetes mellitus, cerebrovascular disease, coronary artery disease, and smoking), initial CT scan findings, and reasons for not administering thrombolytic therapy. The collected data were analyzed using SPSS version 22 statistical software. The chi-square test was applied to analyze qualitative variables, while the *t*-test was used for quantitative variables. A *P*-value of < 0.05 was considered statistically significant for all tests.

4. Results

A total of 178 patients were analyzed, with an average age of 66.28 years (SD 12.77), ranging from 34 to 93 years. Of these, 43.3% were female, and 56.7% were male. Thrombolytic therapy was administered to 87 patients (48.9%), while 91 patients (51.1%) did not receive the treatment (Table 1). The reasons for not receiving thrombolysis included symptom improvement (37.4%), late arrival beyond 4.5 hours (24.2%), lack of consent (20.9%), the physician's conservative approach (11%), and mild stroke severity (6.6%) (Table 1). A significant relationship was found between non-receipt of thrombolysis and both age ($P < 0.001$) and education level ($P < 0.002$), with lower education associated with higher dissatisfaction (Table 2). The mean NIHSS score on admission was 10.72 (SD 3.9), with significant associations between NIHSS scores and reasons for non-receipt of IV-rtPA ($P < 0.001$) (Table 3).

Comorbidities were prevalent, with hypertension (45.5%) being the most common, followed by diabetes (30.9%), cardiovascular disease (21.3%), prior stroke (15.2%), hyperlipidemia (12.4%), and a history of smoking (7.9%). However, no significant associations were observed between the non-receipt of thrombolysis and comorbidities such as hypertension, diabetes, hyperlipidemia, cardiovascular disease, or smoking. A significant relationship was noted between a history of stroke and the physician's conservative approach to treatment ($P < 0.01$), which was cited in 28.6% of cases for patients with prior strokes, compared to 5.7% for those without (Table 3).

5. Discussion

In 1995, the U.S. Food and Drug Administration approved the use of intravenous recombinant tissue plasminogen activator (IV-rtPA) for thrombolytic treatment in patients with AIS within a 4.5-hour window (10). Approximately 33% of eligible patients did not receive IV-rtPA due to various reasons (11). In our study, the incidence of AIS was higher among males compared to females, with 43.3% (77 patients) being female and

Table 1. Baseline Demographic and Clinical Characteristics of Patients

Variables	No. (%)
Gender	
Female	77 (43.3)
Men	101 (56.7)
Education level	
Illiterate	24 (13.5)
Elementary school	68 (38.2)
High school	48 (27.0)
Some university degree	38 (21.3)
Place of residence	
Rural areas	30 (16.9)
City	148 (83.1)
Modes of arrival	
Ambulance	74 (41.6)
Personal vehicle	104 (58.4)
Marital status	
Married	169 (94.9)
Single	9 (5.1)
Causes for not receiving thrombolytic therapy	
Mild symptoms	6 (3.4)
Exceeded the golden time	22 (12.4)
Clinical improvement	34 (19.1)
Lack of consent	19 (10.7)
Conservative approach	10 (5.6)
Missing system	87 (48.9)
Past medical history	
Hypertension	
Yes	81 (45.5)
No	97 (54.5)
Hyperlipidemia	
Yes	22 (12.4)
No	156 (87.6)
Diabetes mellitus	
Yes	55 (30.9)
No	123 (69.1)
Cardiovascular disease	
Yes	38 (21.3)
No	140 (78.7)
Past stroke	
Yes	27 (15.2)
No	151 (84.8)
Smoking cigarettes	
Yes	14 (7.9)
No	140 (78.7)
Received thrombolytic therapy	
Yes	87 (48.9)
No	91 (51.1)

56.7% (101 patients) being male. A study conducted by Sharifi Razavi et al. investigated the factors influencing the duration of hospitalization for patients with AIS who received intravenous thrombolysis. Among the 173 cases analyzed, 95 patients (54.9%) were male, and 78 patients (45.1%) were female (12). Another study, conducted by Hatamabadi et al. at Mazandaran University of Medical Sciences in 2013, aimed to identify barriers to the timely initiation of thrombolytic treatment in AIS patients. The study included 151 patients, of whom 97 (64.2%) were male and 54 (35.8%) were female (9).

In this study, 91 patients (51.1%) did not receive thrombolytic therapy. The reasons for withholding thrombolytic therapy in these cases can be categorized into five groups: 37.4% (34 patients) experienced symptom improvement, 24.2% (22 patients) arrived beyond the 4.5-hour therapeutic window, 20.9% (19 patients) declined treatment due to lack of informed consent, 11% (10 patients) were affected by the physician's

conservative approach, and 6.6% (6 patients) were not treated due to the mild severity of their stroke (Figure 1). A study conducted by P.A. Barber et al. in 2001 investigated the reasons for excluding patients with AIS from receiving IV-rtPA. The study found that 27% of patients (314 out of 1,168) were hospitalized within 3 hours of symptom onset, and of these, 84 patients (26.7%) received IV-rtPA. The main reasons for exclusion in the subgroup hospitalized within 3 hours were mild symptoms (13.1%), clinical improvement (18.2%), lack of consent (13.6%), delays in conducting initial examinations (8.9%), and the presence of significant underlying conditions (8.3%) (13).

In 2019, Zhou et al. conducted a study in Hubei, China, to evaluate the utilization of thrombolytic treatment and identify barriers in patients with ischemic stroke. Among 2,096 AIS patients, only 3.8% received thrombolysis (14). Of the 709 neurologists surveyed, 66.0% reported using thrombolysis for AIS patients. The main factors contributing to the

Table 2. Comparison of the Distribution of Reasons for Not Receiving Thrombolytic Therapy in Two Groups: One with a History of Previous Disease and One Without ^a

Past Medical History	Reasons for Excluding from Not Receiving Thrombolytic Therapy					Total	P-Value
	Mild Symptoms	Exceeded 4.5-Hour Window	Rapidly Improving Symptoms	Lack of Consent	Physician's Conservative Approach		
HTN							0.196
Yes	5 (12.5)	8 (20.0)	17 (42.5)	6 (15.0)	4 (10.0)	40 (100.0)	
No	1 (2.0)	14 (27.5)	17 (33.3)	13 (25.5)	6 (11.8)	51 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	
DM							0.139
Yes	2 (7.4)	8 (29.6)	7 (25.9)	4 (14.8)	6 (22.2)	27 (100.0)	
No	4 (6.3)	14 (21.9)	27 (42.2)	15 (23.4)	4 (6.3)	64 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	
HLP							0.619
Yes	0 (0.0)	5 (38.5)	4 (30.8)	3 (23.1)	1 (7.7)	13 (100.0)	
No	6 (7.7)	17 (21.8)	30 (38.5)	16 (20.5)	9 (11.5)	78 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	
CVD							0.236
Yes	0 (0.0)	6 (28.6)	9 (42.9)	2 (9.5)	4 (19.0)	21 (100.0)	
No	6 (8.6)	16 (22.9)	25 (35.7)	17 (24.3)	6 (8.6)	70 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	
History of CVA							0.011
Yes	3 (14.3)	2 (9.5)	6 (28.6)	4 (19.0)	6 (28.6)	21 (100.0)	
No	3 (4.3)	20 (28.6)	28 (40.0)	15 (21.4)	4 (5.7)	70 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	
History of Smoking							0.794
Yes	0 (0.0)	2 (33.3)	3 (50.0)	1 (16.7)	0 (0.0)	6 (100.0)	
No	6 (7.1)	20 (23.5)	31 (36.5)	18 (21.2)	10 (11.8)	85 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	

^a Values are expressed as No. (%).

Table 3. Post Hoc Analysis of Age and National Institutes of Health Stroke Scale

Dependent Variable	Reasons for Excluding from Not Receiving Thrombolytic Therapy	Reasons for Excluding from not Receiving Thrombolytic Therapy	Mean Absolute Difference	P-Value ^a
Age	Mild symptoms	Golden time passed	9.89394	0.362
		Rapidly improving symptoms	13.16667	0.092
		Lack of consent	0.40351	1.000
		Conservative approach	-7.73333	0.706
	Golden time passed	Mild symptoms	-9.89394	0.362
		Rapidly improving symptoms	3.27273	0.845
		Lack of consent	-9.49043	0.082
		Conservative approach	-17.62727	0.002
	Rapidly improving symptoms	Mild symptoms	-13.16667	0.092
		Golden time passed	-3.27273	0.845
		Lack of consent	-12.76316	0.002
		Conservative approach	-20.90000	< 0.001
Lack of consent	Mild symptoms	-0.40351	1.000	
	Golden time passed	9.49043	0.082	
	Rapidly improving symptoms	12.76316	0.002	
	Conservative approach	-8.13684	0.394	
Physician's conservative approach	Mild symptoms	7.73333	0.706	
	Golden time passed	17.62727	0.002	
	Rapidly improving symptoms	20.90000	< 0.001	
	Lack of consent	8.13684	0.394	
NIHSS	Mild symptoms	Golden time passed	-8.84848	< 0.001
		Rapidly improving symptoms	-6.72549	0.002
		Lack of consent	-7.87719	0.001
		Conservative approach	-9.96667	< 0.001
	Golden time passed	Mild symptoms	8.84848	< 0.001
		Rapidly improving symptoms	2.12299	0.305
		Lack of consent	0.97129	0.937
		Conservative approach	-1.18181	0.948
	Rapidly improving symptoms	Mild symptoms	6.72549	0.002
		Golden time passed	-2.12299	0.305
		Lack of consent	-4.15170	0.853
		Conservative approach	-3.24118	0.171
Lack of consent	Mild symptoms	7.87719	0.001	
	Golden time passed	-9.7129	0.937	
	Rapidly improving symptoms	1.15170	0.853	
	Conservative approach	-2.08947	0.670	
Conservative approach of the doctor	Mild symptoms	9.96667	< 0.001	
	Golden time passed	1.18181	0.948	
	Rapidly improving symptoms	3.24118	0.171	
	Lack of consent	2.08947	0.670	

Abbreviation: NIHSS, National Institutes of Health Stroke Scale.

^a P < 0.05 was considered statistically significant.

underutilization of thrombolysis included delayed patient arrival, concerns about potential complications,

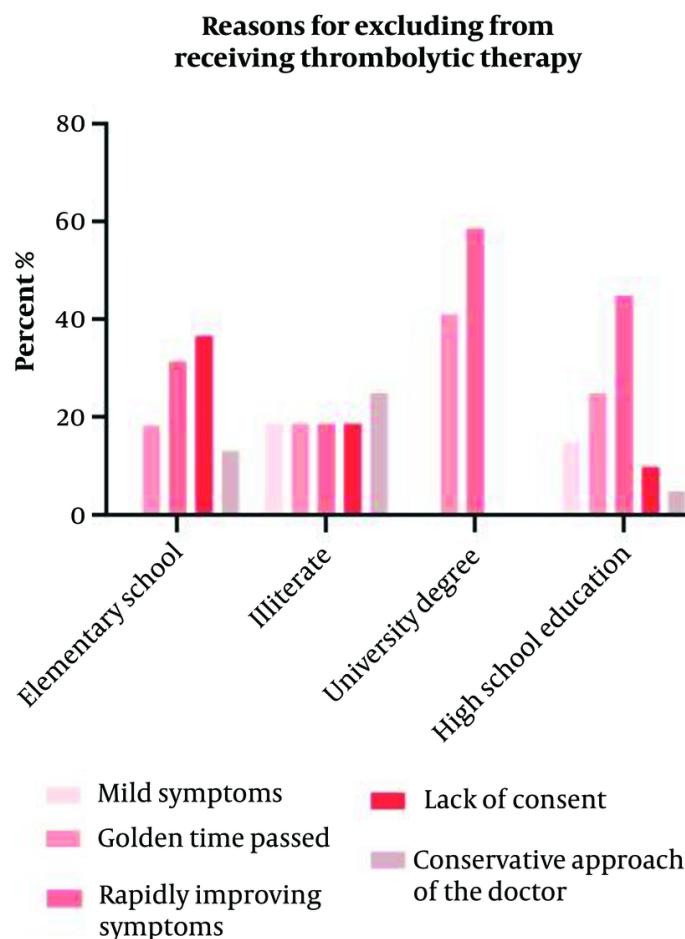


Figure 1. Reasons for excluding patients from receiving thrombolytic therapy

and the presence of mild stroke symptoms or rapid clinical improvement. The study highlighted several factors that influence the likelihood of receiving thrombolytic treatment, including early hospital admission, use of emergency medical services for transportation, absence of a prior stroke history, and a low NIHSS score (< 4). Additionally, patient education level and the experience of the neurologist were found to play significant roles in determining thrombolysis utilization (14).

In this study, the most common reason for not administering thrombolytic therapy was mild or rapidly improving symptoms, which accounted for 37.4% of cases. Patients who experienced symptom improvement had a lower average age of 62.5 years compared to other

groups. This finding suggests that the progression of AIS tends to be more favorable in younger individuals. The average age of stroke onset in Iran appears to be lower than in developed countries. Our findings are consistent with research conducted by Azarpazhooh et al., which highlights that the incidence of stroke in Iran is significantly higher than in many Western countries, with strokes occurring at younger ages (3). The results of the present study indicate that key factors preventing the administration of thrombolytic therapy in AIS patients were delayed hospital arrival and lack of consent from family members. Together, these two factors accounted for approximately 45% of the reasons for not administering IV-rtPA.

Table 4. Analysis of the Distribution of Reasons for Not Receiving r-tPA Based on Gender, Education Level, Marital Status, and Place of Residence ^a

Variables	Reasons for Excluding from Not Receiving Thrombolytic Therapy					Total	P-Value
	Mild Symptoms	Exceeded 4.5-Hour Window	Rapidly Improving Symptoms	Lack of Consent	Physician's Conservative Approach		
Gender							0.758
Female	2 (5.1)	11 (28.2)	16 (41.0)	7 (17.9)	3 (7.7)	39 (100.0)	
Male	4 (7.7)	11 (21.2)	18 (34.6)	12 (23.1)	7 (13.5)	52 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	
Education level							0.002
Illiterate	3 (18.8)	3 (18.8)	3 (18.8)	3 (18.8)	4 (25.0)	16 (100.0)	
Elementary school	0 (0.0)	7 (18.4)	12 (31.6)	14 (36.8)	5 (13.2)	38 (100.0)	
Diploma	3 (15.0)	5 (25.0)	9 (45.0)	2 (10.0)	1 (5.0)	20 (100.0)	
University degree	0 (0.0)	7 (41.2)	10 (58.8)	0 (0.0)	0 (0.0)	17 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	
Marital status							0.792
Married	6 (6.7)	22 (24.4)	33 (36.7)	19 (21.1)	10 (11.1)	90 (100.0)	
Single	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	
Location of living							0.726
Rural areas	2 (9.1)	7 (31.8)	6 (27.3)	4 (18.2)	3 (13.6)	22 (100.0)	
City	4 (5.8)	15 (21.7)	28 (40.6)	15 (21.7)	7 (10.1)	69 (100.0)	
Total	6 (6.6)	22 (24.2)	34 (37.4)	19 (20.9)	10 (11.0)	91 (100.0)	

^a Values are expressed as No. (%).

In developing countries, significant variability exists in the time it takes for AIS patients to reach hospitals. For instance, a study by Hatamabadi et al. in northern Iran reported that 68.7% of AIS patients did not arrive at the hospital within the time window necessary for IV-rtPA administration (9). In a cohort study conducted in northeastern Iran by Azarpazhooh et al., 85.6% of AIS patients were ineligible for thrombolytic therapy due to late hospital arrival (3). In contrast, our study revealed a notable finding: Approximately half of the patients examined received IV-rtPA. This proportion exceeds the results of similar studies conducted in local medical centers across Iran and is comparable to findings reported in studies conducted globally (15). In 2016, a telestroke network in the USA conducted 744 tele-consultations for emergencies and suspected strokes. Among these, 247 patients received IV-rtPA, with 33.2% experiencing positive outcomes. Of the remaining 497 patients evaluated, 244 did not have a stroke but presented with stroke-like symptoms, while 53 were diagnosed with a transient ischemic attack (TIA). Overall, 55% of eligible patients received thrombolytic therapy (16). There is a significant correlation between patients' education level and their consent to receive IV-rtPA (Table 4). Dissatisfaction with thrombolytic therapy was predominantly observed in individuals with an education level below high school. A higher level of education appears to increase the likelihood of providing informed consent. Both educational attainment and access to rapid transportation to the hospital were crucial factors influencing early hospital arrival and decision-making regarding thrombolytic therapy.

An analysis of education levels among patients revealed that 21.3% had a university education, while the

remaining 78.7% had only primary or high school education, or were illiterate. These factors contribute to a low perception of threat, a tendency to underestimate the severity of symptoms, and poor recognition of stroke warning signs. Additionally, cultural and perceptual barriers play a significant role in delaying the presentation of AIS patients to the emergency department. A 2016 review reported by the American Academy of Neurology analyzed the cases of 124 eligible AIS patients who arrived at a hospital in China within 2 hours of symptom onset. The findings revealed that only 22.6% of these patients received IV-rtPA. The most common reason for not administering thrombolytic therapy was patient or family refusal (74%), followed by physicians opting for a conservative approach (10%) and the presence of mild or rapidly improving symptoms (9%), among other factors.

The academy's assessment highlighted that the current utilization of IV-rtPA remains below expectations, raising public concern. However, it is anticipated that rapid advancements in healthcare systems and increased public awareness will significantly improve the use of thrombolytic therapy in China (17).

A significant correlation was observed between the factors contributing to the non-receipt of thrombolytic therapy and a patient's history of stroke (Table 2). Patients with a prior stroke were more likely to attribute their non-receipt of thrombolytic therapy to their physician's conservative approach (28.6% of cases) compared to those without a history of stroke (5.7%). However, this represents only one of the factors influencing non-receipt of therapy. Notably, individuals with a prior stroke history exhibited shorter time intervals between symptom onset and hospital

admission, as well as faster treatment initiation, compared to those experiencing their first stroke.

In 2013, a study conducted on 100 AIS patients at Buali Hospital in Qazvin, Iran, found that 33% had an NIHSS score of 0 - 5, while 38% had a score of 5 - 10, indicating their eligibility for thrombolytic therapy (18). In another study, the average NIHSS score recorded before treatment was 11 in 87.7% of the patients (19). A study by Atena Sharifi Razavi et al. also investigated the factors influencing hospitalization duration in AIS patients who received intravenous thrombolysis. The study reported an average NIHSS score of 10.64 ± 4.4 (12). In this study, the NIHSS was an important parameter considered. The average score was 10.7 ± 3.9 , with a minimum score of 2 and a maximum score of 28. A significant relationship was observed between the NIHSS score and the reasons for not receiving thrombolytic therapy (Table 3). The average NIHSS score in the group that did not receive thrombolytic therapy due to mild stroke severity was 3.33, which is lower than the overall average and the averages of other groups. This difference is expected and aligns with the NIHSS grading scale, where mild cases typically receive lower scores. Overall, the mean and range of NIHSS scores in this study are consistent with findings from similar studies, indicating alignment with previously reported results.

5.1. Limitations

It is important to note that the medical records section at Shahid Beheshti Hospital did not have access to documents and files for certain cases that could have been included in this study. As a result, the study was conducted using only the available and accessible records.

5.2. Conclusions

In conclusion, our study identified delayed hospital admission beyond the 4.5-hour window as the primary barrier to receiving thrombolytic therapy for AIS. Among patients presenting within 4.5 hours, key reasons for withholding thrombolysis included clinical improvement, lack of consent from patients or their families, and mild, non-disabling symptoms. Raising public awareness about the symptoms, risks, and complications of stroke is essential to encourage prompt action and reduce delays in reaching medical centers. Public education campaigns, such as 'Know Stroke' initiatives and mass media outreach, should emphasize the importance of seeking immediate and

timely treatment to minimize the risk of disability or permanent damage.

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Footnotes

Authors' Contribution: A. Kh. and G. A. participated in writing the original manuscript, analyzing the data, and conceptualizing the study. A. Kh. also played a key role in drafting and revising the manuscript. N. F. and M. A. M. played crucial roles in project supervision, coordination, patient examination, and editing the final version of the manuscript. A. M. co-contributed to data collection and manuscript review.

Conflict of Interests Statement: The authors declare that they have no competing interests.

Data Availability: The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials. Derived data supporting the findings of this study are available from the corresponding author upon request.

Ethical Approval: Ethical approval for this study was obtained from the ethics committee of Qom University of Medical Sciences (Approval ID: [IR.MUQ.REC.1401.181](#)).

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