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Original Article

Time Between Symptom Onset and Emergency Department Arrival and Thrombolytic Treatment Rates in Patients with Acute Ischemic Stroke

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ABSTRACT

Objective: The objective of this research was to reveal the interval from the start of an acute ischemic stroke (AIS) to the patient's arrival at the reference center, defined as time to treatment, as well as to identify the reasons for delayed presentation when applicable. We also wanted to elucidate whether there were changes in the time to treatment in individuals with a prior diagnosis of AIS compared to those who presented with the diagnosis of AIS for the first time. Additionally, we aimed to assess the rate of thrombolytic treatment administered to the patients.

Methods: This prospective study was conducted with patients aged 18 and above diagnosed with ischemic AIS in the emergency department (ED) during a 3-month period. In total, 150 patients were included in the study. After obtaining written consent, responses of patients were recorded on the data collection form through direct communication or, in the case of those unable to respond, from their close relatives. Radiological data were obtained from hospital records. Statistical Package for the Social Sciences (SPSS) version 17.0 program was used for data analysis.

Results: Among the patients, there were 88 males and 62 females, with an average age of 71.97 ± 13.53 years. From the total group of 150 people, 105 (70%) were experiencing an acute ischemic stroke (AIS) for the first time, while 45 individuals (30%) had a history of prior AIS diagnoses. The mean time to apply to the hospital for treatment was 11.34 ± 19.63 hours. In patients with a history of prior AIS, the mean time to apply for treatment was 11.31 ± 20.2 hours. The number of patients admitted to the ED within the first 1 hour was 30 (20%), while the count of patients who were admitted to the ED within the initial 3 hours was 72 (48%). The rate of those admitted within the first 4.5 hours was 54.7%. The proportion of individuals with a university education among those who presented within the first 3 hours was higher compared to those who did not seek medical attention within the first 3 hours. No significant difference was observed in other parameters examined. The number of patients who received thrombolytic treatment was 49 (32.67%). As a reason for late admission, patients (27%) mostly stated that they waited with the idea that their symptoms would go away on their own. Those who were conscious of early application comprised only 3% of the patients.

Conclusion: The findings showed that patients were not consciously aware of the need for early presentation in the case of AIS. Furthermore, onset-to-door time remained almost the same in patients who had previously presented with AIS, and this naturally reflected on the rate of thrombolytic treatment administration. There is a need to raise awareness about this issue within the community, utilizing media outlets.

Keywords: Acute ischemic stroke, Emergency department arrival, Thrombolytic treatment

INTRODUCTION

The vast majority of AIS patients are evaluated by a clinician in the ED for the first time. Stroke refers to the sudden onset of a focal neurological syndrome developed due to cerebrovascular disease (CVD).[1] The World Health Organization (WHO) defines stroke as "the rapidly developing signs of focal or global disturbance of cerebral functions, lasting 24 hours or longer, or leading to death".[2] Stroke cases are predominantly ischemic, accounting for

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approximately 80-85%, while hemorrhagic strokes make up about 15-20%.[3] In Türkiye, CVD is the third highest cause of fatalities. Treatment possibilities for AIS were restricted before the 1990s. The primary approach included symptomatic treatment, secondary prevention, and rehabilitation treatment, and mortality rates were high. However, the mortality rate associated with stroke has been decreasing over the last 60 years. Recent studies attribute this trend to the early recognition of AIS, the development of emergency interventional treatments, and the establishment of specialized stroke centers. However, despite these advancements, stroke continues to be the leading cause of acquired long-term disabilities and the second highest cause of death, placing a significant economic strain. The United States Food and Drug Administration (FDA) gave its approval for the use of intravenous tissue plasminogen activator (IV tPA) in treating AIS in 1995.[4] In recent years, as in many countries worldwide, the administration of intravenous (IV) recombinant tissue plasminogen activator (r-tPA) for AIS has become more widespread in Türkiye.[5] In 2006, Türkiye granted the license for the utilization of IV r-tPA in the treatment of acute ischemic stroke. r-tPA, which is a serine protease, resides in the endothelial membrane and is generated by endothelial cells. It acts as a catalyst in the conversion process of plasminogen to plasmin. By further decomposing fibrin, plasmin initiates a fibrinolytic (thrombolytic) effect within the blood vessels. Twenty years after tPA was approved by the FDA, studies demonstrating the efficacy and safety of intra-arterial thrombectomy (IAT) in selected patients with AIS have increased.[6] In fact, with the introduction of mobile stroke units (MSUs) equipped with computed tomography (CT) scanners and telemedicine connections, the identification of patients and treatments has become faster today.[7] In general, the efficacy of reperfusion therapies is time-dependent.[8] For patients diagnosed with AIS, reaching a referral health center within 4.5 hours (the first 3 hours is preferred) changes the treatment protocol. Time to treatment in AIS and associated factors have been extensively studied by different centers. Nowadays, the treatment window for patients with AIS extends beyond the initial 0 to 3 hours—up to 4.5 hours for after the last period of well-being and to 6 hours for application of IAT.[9] Even with this prolonged treatment window, the impacts of both mechanical thrombectomy and IV tPA are dependent on time.[10] A primary efficiency metric for both tPA and IAT is time to treatment.[11]

MAIN POINTS

- In patients with AIS, being admitted to a health center within the first 3 hours after the onset of symptoms and being diagnosed is vital for the feasibility of thrombolytic treatment.
- There are numerous studies conducted on this topic in various countries. These studies have identified numerous factors that may affect the time to treatment in AIS cases.
- In this study, although the rate of early admission is similar, the average time to apply for treatment is higher compared to other studies. The average time to reatment remained almost the same for subsequent admissions. Based on the results of the present study, the time to treatment was only affected by education level.
- By shortening the time to visit the emergency department, thrombolytic treatment practices can become more effective.
- It is essential to raise awareness within the community about the importance of early presentation in AIS patients.

MATERIAL AND METHODS

Patients aged 18 and above who presented to our clinic within a three-month period and received a diagnosis of AIS based on the assessment by a neurology specialist and imaging techniques were included in the study. In total, 150 patients were included in the study. r-tPA was administered to eligible patients within the first 4.5 hours of illness. Patients with hemorrhagic AIS, those presenting with transient ischemic attack (TIA), and those without radiological findings in diffusion MRI were not included in the study. The researcher elucidated the aim of the study to all participants, and written informed consent was secured for their participation. The study was initiated after receiving approval from the Ethics Committee of Erzincan Binali Yıldırım University with the protocol number E-26447783-050.01.04-207602 dated October 14, 2022. Special attention was given to the documentation of factors that could influence the time of arrival at the reference hospital, such as patients' demographic characteristics, educational background, vascular area of deficits, and arrival by ambulance, during data collection. The National Institutes of Health Stroke Scale (NIHSS) was utilized for evaluating stroke severity. Responses to open-ended questions directed to the patients were collected and subsequently presented as percentages.

Statistical Analysis

The SPSS package program, version 17.0 (SPSS Inc.; Chicago, IL, USA), was employed for the analysis of data. Mean, standard deviation, median, and minimum-maximum values were used to present descriptive analyses. The chi-square test was used to compare categorical variables. A *P*-value less than .05 was considered statistically significant.

RESULTS

The study encompassed a total of 150 patients, comprising 88 males (58.67%) and 62 females (41.33%) (Table 4).

The patients had an average age of 71.97 ± 13.53 years. The average Glasgow Coma Scale (GCS) score among the patients was 14.31 ± 5.61. The mean NIHSS score was 7.93 ± 5.61. For 105 patients (70%), this was their first presentation with AIS (Table 1). The remaining 45 patients (30%) had a previous history of AIS. While 72 patients (48%) were admitted within the first 3 hours, the rate of those admitted within the first 4.5 hours was 54.7% (Table 2). The number of individuals receiving thrombolytic treatment was 49 (32.67%). The most common reason for not administering thrombolytics was delayed presentation (74%). The second most common reason was the patient's anticoagulant medication use (10%) (Table 3). Out of the participants, 101 individuals (67.33%) were brought by ambulance, while 49 individuals (32.67%) arrived on their own. Only 3 (2%) individuals were conscious about early presentation. Thirty patients (20%) arrived within the first hour. The mean time to treatment was 11.34 ± 19.63 hours. The average time for arrival is 11.33 hours for the patients presenting for the first time with AIS. In patients with a previous history of AIS, the mean time to treatment was 11.31 ± 20.2 hours. The most common reason for delayed presentation (27%) was that patients believed their symptoms would resolve on their own (Table 5). The ability to seek medical

Table 1. Patient's Data About Factors That May Affect the Time to Apply to the Hospital

		n	%
Gender	Male	88	(58.67)
	Female	62	(41.33)
First AIS presentation	Yes	105	(70.00)
	No	45	(30.00)
Educational level of the patient or the accompanying relative	Illiterate	15	(10.00)
	Primary school	27	(18.00)
	Middle school	35	(23.33)
	High school	21	(14.00)
	University	52	(34.67)
Brought by ambulance	Yes	101	(67.33)
	No	49	(32.67)
NIHSS	1-4 Light	33	(22.00)
	5-15 Moderate	103	(68.67)
	16-20 Moderate severe	9	(6.00)
	21-42 Very severe	5	(3.33)
Vascular area	MCA	68	(45.33)
	ACA	26	(17.33)
	PCA	46	(30.67)
	Widespread eclipse	10	(6.67)

N, number; MCA, middle cerebral artery, ACA, anterior cerebral artery, PCA, posterior cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Descriptives of Patient's Arrival Time to Hospital

		n	%
Admitted within the first 4,5 hours	Yes	105	(70.00)
	No	45	(30.00)
Admitted within the first 3 hours	Yes	72	(48.00)
	No	78	(52.00)
Admitted within the first 1 hour	Yes	30	(20.00)
	No	120	(80.00)
Time to treatment	First 3 hours	75	(50.00)
	3-24 hours	56	(37.33)
	More than 24 hours	19	(12.67)
Is the patient conscious about early presentation	Yes	3	(2)
	No	147	(98)
Reason for delayed presentation	Patient was unable to get an appointment at the outpatient clinic	1	(1.30)
	Patient was misdiagnosed at the initial concultation	4	(5.19)
	Patient had nobody to bring him/her to the hospital	16	(20.78)
	Patient thought the symptoms would resolve on their own	21	(27.27)
	Delay due to referral from another center	19	(24.68)
	Patient was residing in a nursing home	1	(1.30)
	Patient mistook the complaints for medication side effects	1	(1.30)
	Reluctance to come to the hospital	2	(2.60)
	Patient assumed the complaints would go away when water was poured on himself/herself	2	(2.60)
	Relatives could not identify the illness	6	(7.79)
	Living in a deserted area	2	(2.60)
	Night time prevented arrival	2	(2.60)

N, number.

Table 3. Descriptives of Patient's Trombolytic Treatment

		n	%
Thrombolytic treatment status	Yes	49	(32.67)
	No	101	
Late presentation for thrombolytic treatment	Yes	76	(50.67)
	No	73	(49.33)
Reason for failure to administer thrombolytics	Delayed presentation	74	(73.27)
	Refusal of treatment	4	(3.96)
	Anticoagulant drug use	10	(9.90)
	Low NIHHS score	9	(8.91)
	Recent surgery	2	(1.98)
	Unavailability of the medication	1	(0.99)
	Abnormalities in the hematological parameters	1	(0.99)

N, number; MCA, middle cerebral artery, ACA, anterior cerebral artery, PCA, posterior cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

attention within the first 3 hours was compared for statistical significance with factors such as the educational level of the patient or accompanying relative, whether the patient arrived by ambulance or their own vehicle, the vascular area of the deficit in the patient's brain, and the severity score of the stroke (NIHSS). A statistically significant difference was found for the educational level of the patient or accompanying relative. The proportion of individuals with a university education among those who presented within the first 3 hours was higher compared to those who did not seek medical attention within the first 3 hours. No statistically significant difference was found with respect to other parameters (Table 6).

Table 4. Descriptives of Patient's Features

	M ± SD	Median (Min-Max)
Patient age	71.97 ± 13.53	73.5 (35-95)
Mean time to treatment	11.34 ± 19.63	4 (0.25-72)
NIHSS score	7.93 ± 5.61	7 (1-42)
GCS score	14.31 ± 1.7	15 (3-15)

M, mean; min, minimum; max, maximum; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; n, number.

DISCUSSION

When the findings obtained in the present study were compared with other studies, it was observed that the rate of presentation within the first 4.5 hours was similar, but the mean time to ED presentation among patients with AIS was 11.34 ± 19.63 hours, which is higher than that reported in other studies. For instance, a study reported that, on average, it took 151 minutes from the time symptoms began to when the patient reached the emergency department.[12] This difference may be attributed to socio-cultural reasons leading to delayed presentations of the elderly patient group in our region, extending up to 48-72 hours. In the present study, 12.67% of

Table 5. Mean Time to Treatment of Patients with Respect to Other Variables

		Mean Time to Treatment	
		M ± SD	Median (Min-Max)
Educational level of the patient or the accompanying relative	Illiterate	27.93 ± 29.9	9 (1.5-72)
	Primary school	15.66 ± 22.31	6 (0.25-72)
	Middle school	9.12 ± 15.66	4 (0.25-72)
	High school	8.79 ± 16.47	4.5 (0.5-72)
	University	6.82 ± 15.48	2 (0.25-72)
Was the patient brought by ambulance	Yes	10,99 ± 19.47	4.5 (0.25-72)
	No	12.05 ± 20.16	2 (0.25-72)
Vascular area	MCA	12.01 ± 20.31	3.75 (0.25-72)
	ACA	6.47 ± 14.09	2.25 (0.5-72)
	PCA	12.25 ± 20.29	5 (0.25-72)
	Widespread eclipse	15.2 ± 24.72	3.75 (0.5-72)
NIHSS	1-4 Light	14.64 ± 20.6	5 (0.25-72)
	5-15 Moderate	11.02 ± 20006	4 (0.25-72)
	16-20 Moderate severe	8.83 ± 15.1	3 (0.5-48)
	21-42 Very severe	0.55 ± 0.27	0.5 (0.25-1)

MCA, middle cerebral artery, ACA, anterior cerebral artery, PCA, posterior cerebral artery; NIHSS, National Institutes of Health Stroke Scale; M, mean; SD, standard deviation; min, minimum; max; maximum.

Table 6. Analysis of the Statistical Significance of Factors that May Affect the Application in the First 3 Hours

		Was the patient admitted within the first 3 hours?				
		Yes (72 patients)		No (78 patients)		
		n	%	n	%	*P*
Educational level of the patient or the accompanying relative	Illiterate	2	(2.78)	13	(16.67)	**<.001**
	Primary school	8	(11.11)	19	(24.36)	
	Middle school	16	(22.22)	19	(24.36)	
	High school	10	(13.89)	11	(14.10)	
	University	36	(50.00)	16	(20.51)	
Was the patient brought by ambulance	Brought by ambulance	44	(61.11)	57	(73.08)	.118
	Not brought by ambulance	28	(38.89)	21	(26.92)	
Vascular area	MCA	32	(44.44)	36	(46.15)	.200
	ACA	17	(23.61)	9	(11.54)	
	PCA	18	(25.00)	28	(35.90)	
	Widespread Eclipse	5	(6.94)	5	(6.41)	
NIHSS	1-4 Light	15	(20.83)	18	(23.08)	.115
	5-15 Moderate	47	(65.28)	56	(71.79)	
	16-20 Moderate-severe	5	(6.94)	4	(5.13)	
	21-42 Very severe	5	(6.94)	0	(0.00)	

Chi-square test is used. N, number; MCA, middle cerebral artery, ACA, anterior cerebral artery, PCA, posterior cerebral artery; NIHSS, National Institutes of Health Stroke Scale; M, mean; SD, standard deviation; min, minimum; max, maximum; Yes, 72 patients (48%) admitted the hospital within the first 3 hours; No, 78 patients (52%) not admitted the hospital within the first 3 hours.

patients presented later than 24 hours. Mean time to treatment varies between populations and in different regions within the same country. This discrepancy could be attributed to factors such as inherited and acquired risk elements, a deficiency in understanding warning signals, and limited access to healthcare. Being aware of the factors that influence the correlation between the time of arrival at the reference hospital and stroke mortality enhances the probability of decreasing the arrival time for stroke-affected individuals, altering the clinical scenario, and attaining improved results. Knowing these variables can guide the planning of education, management, and healthcare services. In the present study, the belief among AIS patients and their relatives that pouring water on the patients would alleviate their discomfort, due to some misconceptions, was a significant reason for delayed presentation. This misconception may be due to the fact that in TIA that may have occurred in the community, symptoms in TIA may be transient, creating the perception in the community that AIS will also improve on its own over time. Other common reasons were being a referred patient and not having a relative to take the patient to the hospital. According to the results obtained, the only variable affecting presentation within 3 hours was educational level. In a similar study conducted in Romania, 55% of patients with AIS presented within the first 4.5 hours. The study identified factors contributing to delayed presentation, which included a low educational level ($P = .01$) and unemployment ($P = .033$). The research team found that the most significant factor related to delayed presentation was the educational level, with the likelihood of late presentation higher among illiterate patients. The study's results also showed that the likelihood of early presentation was higher among patients who knew they were having a stroke, while those who didn't realize their symptoms were due to a stroke tended to present late. No significant association was found between the time to treatment and the patient's age, gender, living status, and risk factors.[13] Although NIHSS is the most widely accepted and commonly used method for assessing stroke severity,[14] it was not identified as a significant variable in terms of early presentation in the present study. In another study, it was reported that 58.9% of patients arrived within 4.5 hours after the onset of symptoms.[15] Getting to the hospital independently was the sole factor positively linked with reaching the hospital over 4.5 hours subsequent to the start of a stroke, more than doubling the probability of a delayed presentation. Factors that were negatively correlated with arriving at the hospital more than 4.5 hours after the onset of a stroke a pre-existing diagnosis of atrial fibrillation, an NIHSS score of 16 points or more, and the existence of hemianopsia, facial paralysis, and sensory impairment. Factors that increased the likelihood of arriving at the

hospital 24 hours after the onset of a stroke included living alone and residing in rural areas. In conclusion, nearly one out of every three ischemic stroke patients presenting in this study reached the hospital 24 hours after the beginning of symptoms. The only factor positively associated with arriving at the hospital more than 4.5 hours subsequent to the start of a stroke was arriving at the hospital under one's own means.[16] A multitude of these elements are interlinked, and their impacts can vary based on the efficiency of various healthcare systems and the cultural, social, economic, and behavioral makeup of the population under study.[17] As a result, the rate of administering thrombolytic treatment to patients was 32.67% in the present study. 50.67% of patients had presented late for thrombolytic treatment. In a similar study conducted in 2019 at San Martino Hospital in Genova, Italy, 111 of 459 AIS patients underwent iv thrombolysis (24.4%) and 50 patients underwent mechanical thrombectomy (10.9%).[18] Until recently, despite IV-tPA being the sole treatment for AIS, only 3.2-5.2% of all AIS patients in the United States could receive IV-tPA.[19] The primary cause for the reduced treatment rate is the narrow time window for IV-tPA. As a result, the American Heart Association/American Stroke Association (AHA/ASA) expanded the IV-tPA window from 3 to 4.5 hours through amendments made in 2009.[20] This extension increased the use of IV-tPA by up to 20%.[21] Although the rates of administering thrombolytic treatment are similar in our center compared to other centers, they could be further improved.

Limitations

This study's limitations are its small participant pool and the fact that it was carried out in a single institution.

There is a need for further studies aimed at increasing public awareness in Türkiye, especially targeting high-risk patients for cerebrovascular disease (CVD). Furthermore, providing patients with more information about recognizing the disease itself can improve the time to apply to the hospital for treatment. In addition to raising public awareness about the symptoms of the disease, studies need to be carried out to announce that AIS is a disease that requires early admission to the hospital for treatment. Because it is evident that awareness of early application does not occur even in patients who have been previously treated with a diagnosis of AIS. Additionally, it may be useful to create projects for the elderly patient population, who live in rural areas and have insufficient social support and limited access to hospitals to benefit more from health services.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Erzincan Binali Yıldırım University (Date: October 14, 2022, Number:E-26447783-050.01.04-207602).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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