TURKISH JOURNAL OF EMERGENCY MEDICINE

Original Article

Access this article online

Quick Response Code:

Website: www.turkjemergmed.com

DOI: 10.4103/2452-2473.357344

Current status of acute ischemic stroke management in Iran: Findings from a single-center study

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Abstract:

OBJECTIVES: This study investigated the current status of acute ischemic stroke (AIS) management in an Iranian emergency department (ED).

METHODS: A descriptive study using a retrospective chart review was conducted on medical records of 270 patients with AIS who presented to the ED of a tertiary university hospital in the northeast of Iran from March 22 to September 22, 2019. The steps of this review process included instrument identification, medical records retrieval, data extraction, and data verification.

RESULTS: Of patients with AIS, 88.9% (n = 240) did not receive stroke code activation. For the 11.1% of patients (n = 30) who received activation, 7% of codes (n = 19) were canceled by the acute stroke team and IV recombinant tissue plasminogen activator (r-tPA) was only administered for 4.1% of patients (n = 11). ED arrival outside 4.5 h from symptom onset was the main barrier to IV r-tPA administration for 83.8% of potentially eligible patients with AIS (n = 217). The median door-to-needle time was 70 min (interquartile range: 47–90 min).

CONCLUSIONS: There was a better clinical performance in terms of critical time goals in potentially eligible patients with AIS if managed with stroke team activation compared to no stroke team activation.

Keywords:

Acute ischemic stroke, emergency department, fibrinolytic therapy, Iran

Submitted: 23-04-2022
Revised: 15-07-2022
Accepted: 16-07-2022
Published: 30-09-2022

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Introduction

Stroke is the third leading cause of death globally behind cardiovascular disease and cancer[1] and accounts for the fourth leading cause of death in the United States (US).[2] According to the American Heart Association, in 2019, stroke accounted for 1 of every 19 deaths in the US.[3] With the aging population, the prevalence of patients with stroke is projected to increase and lead to an additional 4 million Americans aged 18 years or older with stroke in 2030 relative to 2010.[4] These figures are staggering and yet, there is an even higher incidence of stroke in low-and middle-income countries.[5] In fact, 87% of the 5.7 million stroke patients who died in 2005 were from low-and middle-income countries.[6] According to the World Bank Group, Iran is a middle-income country and recent reports indicate that 139/100,000 individuals in Iran suffer from new strokes annually, which is higher than most western countries.[7]

How to cite this article: Askari-Majdabadi H, Basereh Z, Soheili A, Powers K, Soleimani M, Mirmohammdkhani M, *et al.* Current status of acute ischemic stroke management in Iran: Findings from a single-center study. Turk J Emerg Med 2022;22:213-20.

Box-ED Section

What is already known on the study topic?

- Stroke is the third leading cause of death globally behind cardiovascular disease and cancer.
- Although there is no definitive cure for acute ischemic stroke (AIS), intravenous recombinant tissue plasminogen activator (IV r-tPA) has an impressive impact on the management of patients with AIS.
- Time is the biggest challenge of this treatment method and the success of treatment and resultant patient outcomes depend on timely diagnosis of AIS and early administration of IV r-tPA.

What is the conflict on the issue? What is its importance for readers?

- Few studies have tracked the stroke system performance measures for patients in Iran and other developing countries.
- It is essential to evaluate the performance of stroke emergency programs in Iran to identify insufficiencies that affect timely provision of emergency services to patients with AIS.

How is this study structured?

- The present single-center study was conducted on medical records of 270 patients with AIS who presented to the ED of a tertiary university hospital in the northeast of Iran.

What does this study tell us?

- The stroke code was activated for a small proportion of patients with AIS and only a minority of these patients received IV r-tPA.
- The low rate of stroke code activation and IV r-tPA administration in our study was primarily due to an absence of early recognition of stroke symptoms and delayed ED presentation after symptom onset.
- There was a better clinical performance in terms of critical time goals for in-hospital care for potentially eligible patients with AIS if managed with stroke team activation compared to no stroke team activation.

Despite recent advances in the treatment of stroke, it remains a major cause of mortality and morbidity in adults.[8] Although there is no definitive cure for acute ischemic stroke (AIS), using intravenous recombinant tissue plasminogen activator (IV r-tPA) can have an impressive impact on the management of patients with AIS and greatly reduces the burden of the disease.[9] Time is the biggest challenge of this treatment method and the success of treatment and resultant patient outcomes depend on timely diagnosis of AIS and early administration of IV r-tPA.[10] Specifically, IV r-tPA is an effective AIS treatment when administered within 4.5 h of symptom onset[11] and prehospital or in-hospital delays may lead to the loss of opportunity for optimal use.[12]

Given the importance of time in reperfusion of ischemic brain tissue, most hospitals have created multidisciplinary rapid response teams to provide timely emergency services to patients with AIS. However, many studies have shown deficiencies and inconsistencies in achieving the desired outcomes.[13,14] It is essential to evaluate the performance of stroke emergency programs in order to identify insufficiencies and the underlying components that affect timely provision of emergency services to patients with AIS. This study investigated the current status of AIS management in an emergency department (ED) at Sabzevar Vasei Hospital in Iran. Considering the lack of sufficient and reliable information on the status of guideline-based AIS care in Iran, our findings can be informative for other similar middle-income countries with evolving health care systems that differ in structure from US and European systems.

Methods

Study design and setting

A descriptive study using a retrospective chart review was conducted on medical records of patients with AIS who presented to the ED of Vasei University Hospital in Sabzevar, Iran.

This hospital is a 220-bed tertiary academic medical center with a 19-bed ED that had 93,198 ED visits in 2019. The ED is staffed by faculty emergency medicine attending physicians 24 h a day, as well as senior medical students (interns), nurses, and nursing students. In this ED, patients with AIS are evaluated for IV r-tPA eligibility based on standard inclusion and exclusion criteria, within a 4.5-h window from their last known well time. The eligible patients are managed in a step-by-step approach as illustrated in Figure 1.

Selection of participants

Patients with an ED discharge diagnosis of AIS were included for analysis according to the following inclusion criteria: AIS confirmed by a stroke neurologist and a noncontrast brain CT result that ruled out other causes (such as hemorrhagic stroke).

Methods of measurement and data collection and processing

Given the descriptive nature of this study, it was not deemed necessary to establish power, and data were collected during a 6-month period consistent with the investigators' time constraints from March 22, 2019, to September 22, 2019. All medical records within the study timeframe were reviewed manually because the

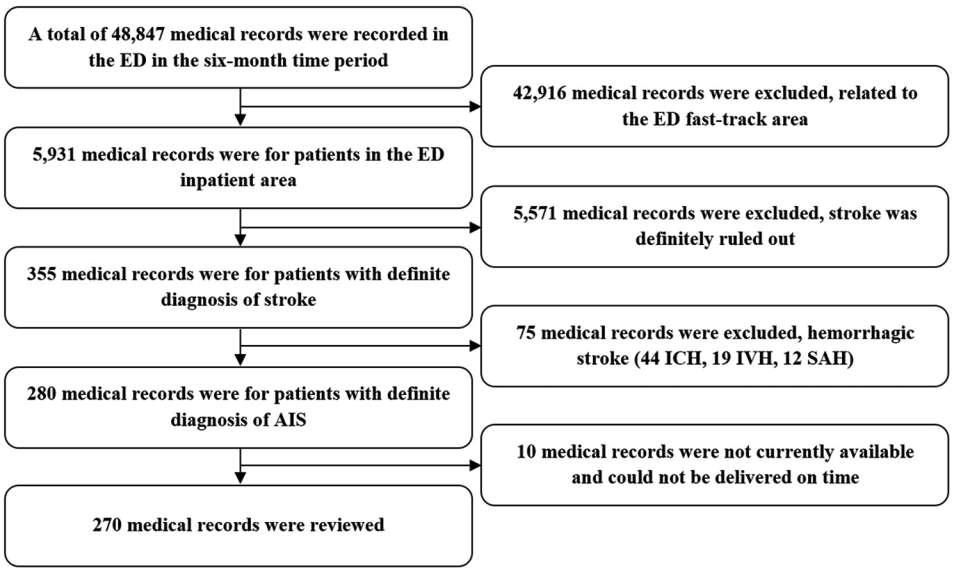

Figure 1: The AIS eligible patients' step-by-step management approach. AIS: Acute ischemic stroke

patients' information was kept in a nonelectronic filing system. Figure 2 demonstrates patient selection and the flow of the study.

A data extraction form developed by Hassankhani *et al*. based on an extensive review of the literature and specific ED guidelines for stroke management[14] was used for collecting data. Use of this structured instrument helped ensure the measure of consistency, minimized the possibility of interpretation in data collection, and included patients' demographic characteristics, disease-related characteristics, in-hospital stroke management times, and main barriers to stroke care pathways. Content and face validity of the instrument were established by Hassankhani *et al*. using a qualitative "expert panel" approach. In their study, the intra-rater reliability of data collection method was evaluated and the reported intraclass correlation coefficient (ICC) value was 0.94 (indicating an excellent reliability) with a 95% confidence interval (CI) of 0.88–0.97. In the present study, the instrument was piloted on 30 randomized medical records and intra-rater reliability measurement was computed with an ICC. The obtained ICC value was 0.89 indicates a high intra-rater reliability (CI 95% of 0.83–0.91) based on a single rater, absolute agreement, and two-way mixed effects model.[15] The data of the pilot study were not included in results because it represented an initial validation of our methods.

To ensure the quality of the data extraction, the data were manually collected by a trained abstractor who was (a) blinded to the purpose of the study, and (b) familiar with the site's medical record documents and documentation. Since missing, conflicting, and/or ambiguous chart elements can be a concern in retrospective chart reviews, any discrepancies during the coding process were reviewed and clarified jointly by the research team. The data were collected in a secure onsite location to avoid the loss of charts and confidential information. Moreover, the data were entered without patients' names, addresses, and other identifying features to ensure anonymity.

Outcome measures

The primary outcome of the study was to evaluate the current status of AIS Management and our ED performance in stroke door-to-needle (DTN) times. Secondary outcomes were to determine stroke code activation rate, IV r-tPA administration rate for eligible patients, contributing factors of treatment delays, disease-related characteristics of patients with AIS, and main barriers to stroke care pathways.

Statistical analysis

Descriptive statistics for normally distributed continuous data are reported as mean with standard deviation (SD). Median and interquartile ranges (IQR) are reported for nonnormally distributed data. The discrete variables are reported as frequency and percentage. As the data were not normally distributed based on the results of Kolmogorov–Smirnov test ($P < 0.05$) and a histogram normal curve (was not concentrated and symmetrical), the nonparametric Mann–Whitney U test was used for statistical analysis. Data were evaluated with IBM SPSS software (version 25; SPSS, Chicago, IL). A $P < 0.05$ was considered statistically significant.

Ethical considerations

The study was part of a nursing master thesis approved by the institutional review board and the research ethics committee of Semnan University of Medical Sciences

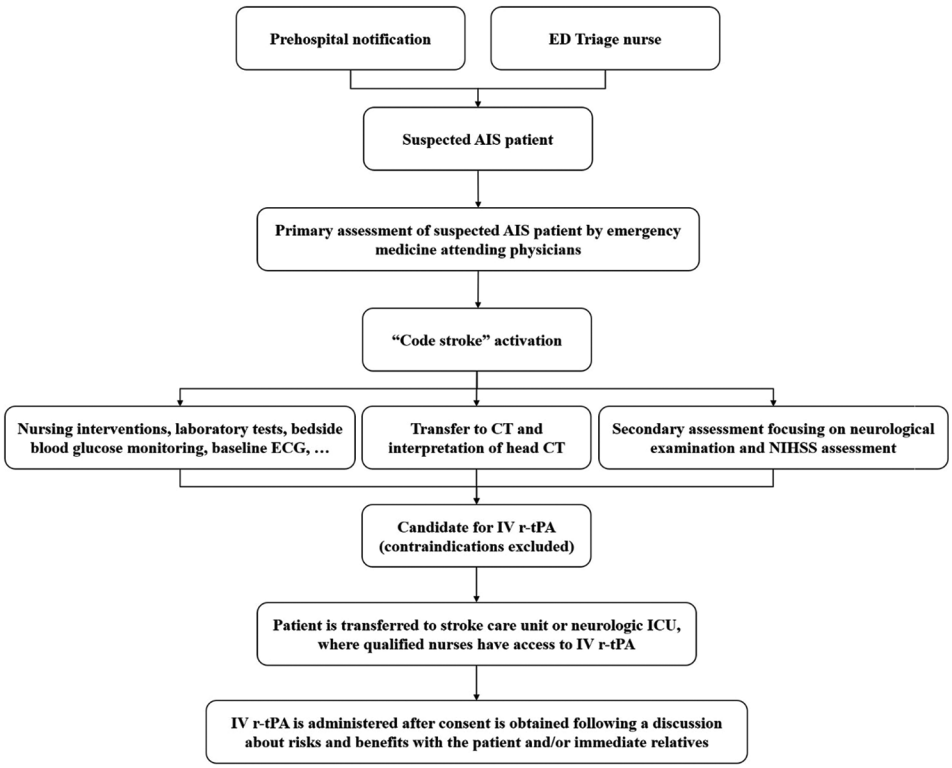

Figure 2: Our hospital's protocol for stroke code activation and IV r-tPA administration. IV r-tPA: Intravenous recombinant tissue plasminogen activator

(date of the ethical approval: June 2, 2020. number of the ethical approval: IR.SEMUMS.REC.1399.074). The objectives of the study were explained to officials of the Vasei University Hospital. The institutional review board waived the requirement for informed consent because this study involved a retrospective review of medical records. Data extraction and abstraction were performed with methods to ensure patient confidentiality according to the Privacy Rule (the data were collected in a secure onsite location to avoid the loss of medical records and provided without patients' names, addresses, and other identifying information).

Results

Of 48,847 ED visits during the study period, 270 medical records were included for analysis [Figure 1]. The mean age of patients was 68.62 years (SD 13.66 years; range, 17–96 years), and 56.3% (n = 152) were male. In addition, all of the patients were insured.

The rate of walk-in patients was 58.5% (n = 158). Emergency medical technicians provided out-of-hospital notification for 7.4% of patients (n = 20), which implies that emergency medical services (EMS) are clearly underused for rapid triage and transport of stroke patients in our region. No patient was transferred out and only 1.1% of patients with AIS (n = 3) were admitted to a non-stroke medical unit.

The National Institutes of Health Stroke Scale (NIHSS) score was recorded for 5.5% of patients (n = 15) at admission (median 7 [IQR: 6–16]); of those, the majority had an NIHSS score >5. The NIHSS score was recorded for 1.8% of patients (n = 5) at discharge (median 8 [IQR: 2.5–20]). Similarly, the modified Rankin Scale (mRS) score was recorded for only 1.8% (n = 5) at admission (median 0.5 [IQR: 0.5–4.5]) and 0.7% (n = 2) at discharge (median 4.5 [IQR: 4–5]). Moreover, 88.9% of patients with AIS (n = 240) did not receive stroke code activation. For the 11.1% of patients (n = 30) who received stroke code activation, 7% (n = 19) were canceled by the acute stroke team and IV r-tPA was only administered to 4.1% (n = 11). Conversely, routine antiplatelet therapy was promptly initiated for the other 259 patients. Other demographic and disease-related characteristics of patients are listed in Table 1.

In patients who received IV r-tPA, the median DTN time was 70 min (IQR: 47–90 min). The acute stroke team achieved a DTN time of 60 min or less in 4 out of 11 patients and a DTN time of 45 min or less just in 2 out of 11 patients. Since mechanical thrombectomy was not available at the hospital, none of the patients with AIS underwent mechanical thrombectomy or other emergency endovascular treatments.

A Mann–Whitney U-test across ED throughputs indicated that the majority of stroke-related performance

Table 1: Demographic and disease-related characteristics of study participants

Variable	*n* (%)	Variable	*n* (%)
Gender (*n*=270)		Insurance (*n*=270)	
Male	152 (56.3)	Yes	270 (100)
Female	118 (43.7)	No	0
Education level (*n*=86)		Month of arrival (*n*=270)	
Illiterate	50 (58.1)	1st month	45 (16.7)
Primary	23 (26.7)	2nd month	43 (15.9)
Secondary	11 (12.8)	3rd month	48 (17.8)
Diploma	1 (1.2)	4th month	46 (17)
University	1 (1.2)	5th month	50 (18.5)
		6th month	38 (14.1)
Marital status (*n*=270)		Place of residence (*n*=270)	
Single	9 (3.3)	City	165 (61.1)
Married	253 (93.7)	Village	105 (38.9)
Widow/widower	8 (3)		
Modes of arrival (*n*=270)		BS on ED arrival (261)	
Walk-in	158 (58.5)	<50	0
Ambulance, either air or ground	112 (41.5)	51-100	41 (15.7)
EMS	80 (29.6)	101-150	114 (43.7)
Other hospitals	32 (11.9)	151-200	59 (22.6)
		>200	47 (18)
Side of body affected by stroke (*n*=270)		Status of "stroke code" (*n*=270)	
Right	90 (33.3)	Not activated by EM physician	240 (88.9)
Left	96 (35.6)	Activated by EM physician	30 (11.1)
Both	6 (2.2)	IV r-tPA not administered by AST	19 (7)
None	73 (27)	IV r-tPA administered by AST	11 (4.1)
Lower extremities	5 (1.9)		
ED treatment room (*n*=270)		ESI triage (*n*=270)	
Medical area	265 (98.1)	Level 1	9 (3.8)
Resuscitation area (top urgency)	5 (1.9)	Level 2	194 (81.9)
		Level 3	34 (14.3)
NIHSS at admission (*n*=15)		NIHSS at discharge (*n*=5)	
≤5	3 (20)	≤5	2 (40)
6-10	6 (40)	6-10	2 (40)
11-25	5 (33.3)	11-25	0
≥26	1 (6.7)	≥26	1 (20)
SBP (mmHg) on ED arrival (*n*=270)		DBP (mmHg) on ED arrival (*n*=270)	
<90	6 (2.2)	<70	22 (8.1)
90-120	62 (23)	70-80	153 (56.7)
120-140	89 (33)	80-90	55 (20.3)
140-160	45 (16.7)	90-100	35 (13)
160-180	43 (15.9)	>100	5 (1.9)
180-200	15 (5.6)		
>200	10 (3.6)		
PR (bpm) on ED arrival (*n*=270)		O2Sat (%) on ED arrival (*n*=264)	
<60	14 (5.2)	<75	2 (0.8)
60-100	234 (86.7)	75-89	14 (5.3)
>100	22 (8.1)	89-93	66 (25)
		>93	182 (68.9)
Admission ward (*n*=258)		ED disposition situation (*n*=270)	
Neurology ward	229 (88.8)	Admitted to our hospital inpatient wards	258 (95.6)
Stroke care unit	12 (4.7)	DAMA	9 (3.3)
Neurological ICU	14 (5.4)	Died	1 (0.4)
Medical ward	3 (1.1)	Discharged	2 (0.7)
		Transferred to other facilities	0

ESI: Emergency severity index, NIHSS: National Institutes of Health Stroke Scale, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, O_2Sat: Oxygen saturation, PR: Pulse rate, BS: Blood sugar, ICU: Intensive care unit, DAMA: Discharged against medical advice, EM: Emergency medicine, ED: Emergency department, EMS: Emergency medical services, IV r-tPA: Intravenous recombinant tissue plasminogen activator, AST: Acute stroke team

time intervals (except door to admission time) were significantly faster and more favorable in potentially eligible patients with AIS who were managed with stroke team activation compared to ineligible AIS patients with no stroke team activation ($P < 0.05$). The results of Mann–Whitney *U*-test, which was applied to analyze critical time intervals among different status of "Stroke Code," are also summarized in Table 2.

The exact time of "symptom onset" and "last known well" time was not available in the patients' medical records. This critical event was merely documented as a dichotomous entry of (a) ED presentation within 4.5 h or (b) ED presentation outside 4.5 h after symptom onset or last known well.

The potentially eligible patients were excluded from entry criteria of IV r-tPA and the initially activated stroke codes were canceled mainly because of one or more of the following: delayed ED presentation after symptom onset (83.8%; $n = 217$), minor (NIHSS score <5) or rapidly improving symptoms (17.8%; $n = 46$), major symptoms and unstable medical condition (NIHSS score >25) (11.6%; $n = 30$), current use of anticoagulant with international normalized ratio >1.7 or prothrombin time >15 s (3.9%; $n = 10$), recent major surgery in the preceding 14 days (1.9%; $n = 5$), ischemic stroke within 3 months (1.5%; $n = 4$), elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg) (1.2%; $n = 3$), and patients' or their family members' informed refusal of IV r-tPA (0.4%; $n = 1$).

Discussion

To the best of our knowledge, few studies have tracked the stroke system performance measures for patients in Iran and other developing countries. Our analysis revealed that the stroke code was activated for a small proportion of patients with AIS and only a minority of these patients received IV r-tPA (i.e., 1 in 9 patients with AIS were potentially eligible for IV r-tPA, and only 1 of almost every 25 patients with AIS received IV r-tPA). The low rate of stroke code activation and IV r-tPA administration in our study was primarily due to delayed ED presentation after symptom onset. These findings are consistent with previous studies in Iran and other developing countries. For example, a retrospective chart review conducted at a hospital in northwest of Iran reported that 80.2% of patients with AIS did not meet IV r-tPA eligibility, mostly because of delayed ED arrival after symptom onset and of 19.8% for whom the stroke code was activated, IV r-tPA was administered in only 5.3%.[14] Another cohort study in the northeast of Iran also demonstrated that 85.6% of patients with AIS did not meet the IV r-tPA eligibility, mainly because of late arrival and only 1.2% of patients received IV r-tPA.[16] Similarly, the proportion of patients with AIS receiving IV r-tPA in Asia[17] and other developing countries[18] is far lower than in developed countries mostly because of delayed ED arrival after symptom onset.

The early presentation of patients with AIS to the EDs in our country and similar developing countries may be impeded by cultural, perceptual, and behavioral factors such as poor recognition of stroke symptoms, tendency to minimize the importance of symptoms, low threat perception among the public, and lack of rapid transportation to the hospital. Therefore, along with a need for rapid recognition and reaction to stroke, it is necessary to educate the public and dispel misconceptions about the urgency of stroke symptoms.[14]

Table 2: Critical time intervals and events for management of patients with acute ischemic stroke in emergency department of Vasei University Hospital

Statistics	Median (25^{th}-75^{th} percentile)	Status of "stroke code"		
		Not activated (*n*=240)	Activated (*n*=30)	*P*
ED throughput intervals				
Door to admission	7 (4-13) (*n*=248)	7 (4-13) (*n*=220)	8 (5-18) (*n*=28)	0.1
Door to first EM visit	5 (2-5) (*n*=241)	5 (2-5) (*n*=213)	2 (2-5) (*n*=28)	0.04
First EM visit to CT scan	26 (20-65) (*n*=232)	31 (20-89) (*n*=204)	18 (15-20) (*n*=28)	<0.001
Door to CT scan time	31.5 (25-74.5) (*n*=224)	40 (25-95) (*n*=196)	20 (19-25) (*n*=28)	<0.001
CT scan to first neurologist visit	65 (15-130) (*n*=227)	75 (25-140) (*n*=201)	15 (10-27.5) (*n*=26)	<0.001
First neurologist visit to r-tPA administration	20 (15-25) (*n*=11)	-	20 (15-25) (*n*=11)	-
Door to needle (IV r-tPA) time	70 (47-90) (*n*=11)	-	70 (47-90) (*n*=11)	-

All times are reported in minute. ED: Emergency department, EM: Emergency medicine, IV r-tPA: Intravenous recombinant tissue plasminogen activator, CT: Computed tomography

Community-level efforts using mass media and public "know stroke" campaigns are vital to improve awareness of stroke symptoms. These efforts should be designed to specifically target the public, physicians, hospital personnel, and EMS personnel to stress the importance of seeking immediate treatment and using the EMS system in order to decrease stroke onset to ED arrival times and increase proportion of patients receiving IV r-tPA.[19]

In our study, the median DTN time was 70 min which is substantially longer than the results achieved after the implementation of the Get With the Guidelines (GWTG)-Stroke program in the US,[20] the Hurry Acute Stroke Treatment and Evaluation project in Canada,[21] and the Safe Implementation of Treatment in Stroke initiative in Europe.[22] Recent studies have found that delayed DTN times in patients with AIS who were treated with IV r-tPA were significantly associated with poor clinical outcomes,[23] higher all-cause mortality at 1 year, and higher likelihood of all-cause readmission at 1 year.[24] This evidence propelled the American Stroke Association to set more aggressive targets for timely treatment with IV r-tPA. The primary goals of phase III of the GWTG-Stroke program are to achieve DTN times within 60 min for 85% or more of AIS patients treated with IV r-tPA, with secondary goals of decreasing DTN times to 45 min (in 75% or more) and 30 min (in 50% or more).[19] Therefore, further clinical, managerial, and governmental efforts are required for stroke care responsiveness in Iran and similar settings.

Furthermore, given the current data, the majority of patients who received a diagnosis of AIS were IV r-tPA ineligible, aged 18 years or older, and had NIHSS scores of 6 or greater, making them suitable candidates for thrombectomy. Despite a clear need for mechanical thrombectomy services at our institution, mechanical thrombectomy services were unavailable not only at our hospital but also unavailable at any other hospital in nearby cities and provinces. As a result, none of the patients with AIS underwent mechanical thrombectomy or other emergency endovascular treatments.

Specific to the stroke care system at our hospital site, we make the following recommendations to other low-to middle-income countries with similar systems and barriers: establishing a more robust protocol for out-of-hospital notification and EMS direct to computed tomography (CT) scan; administering IV r-tPA in the ED or CT scan unit instead of neurologic intensive care unit; organizing a joint collaboration among emergency medicine, neurology, and radiology departments to enhance hospital performance in stroke care; establishing mechanical thrombectomy services and integrating endovascular providers into the current teamwork; and establishing clear performance goals for the ED and acute stroke team with effective stroke surveillance systems for continuous data collection and quality improvement. Moreover, appointing an emergency nursing coordinator to help patients with AIS fulfill benchmarks on written protocols may also improve DTN times.

Limitations

Our study has several limitations worth noting. First, the data quality and completeness depended on the quality of the documentation in paper-based medical records; there could be variation based on providers' documentation skills and level of knowledge. While recent stroke treatment studies have used the NIHSS score with a 90-day mRS score documentation as a primary outcome, the NIHSS and mRS scores were not documented in sufficient numbers to allow for a reliable description of the current situation. In addition, we could not factor in the role or importance of mechanical thrombectomy in the care of these patients. Last, we could not reliably capture outpatient follow-up.

Conclusions

Our analysis revealed that the acute stroke team achieved a DTN time of 60 min or less in 4 out of 11 patients who received IV r-tPA, and the DTN time was 45 min or less in 2 out of 11 patients. Further, ED providers and the acute stroke team had better clinical performance in terms of critical time goals for in-hospital care for potentially eligible patients with AIS who were managed with stroke team activation compared to ineligible ones with no stroke team activation. This suggests that stroke team activation is associated with more rapid diagnostic and therapeutic interventions for potentially eligible patients with AIS and improves care performance.

Acknowledgments

The authors would like to thank all those who spent their valuable time participating in this research project, and we are also immensely grateful to the "anonymous" reviewers.

Author contributions statement (CReDiT)

HAM and AS: Conceptualization (lead); methodology (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal). ZB and MS: writing – original draft (lead); writing – review and editing (equal). MM: Software (lead). ZB and KP: Review and editing (equal). ZB and TAS: Investigation; writing – review and editing (supporting). MS: Conceptualization (supporting); writing – original draft (supporting). AS did the overall supervision of the whole study and all authors had made substantial contribution to the study. All authors have read and approved the final manuscript before submission.

Conflicts of interest

None Declared.

Ethics approval

Ethical approval for this study was obtained from the Research Ethics Committee of Semnan University of Medical Sciences. Date of the ethical approval: June 2, 2020. Number of the ethical approval: IR.SEMUMS.REC.1399.074.

Funding
This study is funded by the research deputy of Semnan University of Medical Sciences (Project No. A-10-78-8). The funding sources had no role in the study design, in the gathering, analysis, and interpretation of data, in the report's writing, and in the decision to submit the manuscript for publication. The corresponding author affirms that he had complete access to all the data in the study and had final responsibility for the decision to submit for publication.

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