Treatment Delays for Patients With Acute Ischemic Stroke in an Iranian Emergency Department: A Retrospective Chart Review

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Study objective: We evaluate the extent and nature of treatment delays and the contributing factors influencing them for patients with acute ischemic stroke, as well as main barriers to stroke care in an Iranian emergency department (ED).

Methods: A retrospective chart review was conducted on 394 patients with acute ischemic stroke who were referred to the ED of a tertiary academic medical center in northwest Iran from March 21 to June 21, 2017. The steps of this review process included instrument development, medical records retrieval, data extraction, and data verification. Primary outcomes were identified treatment delays and causes of loss of eligibility for intravenous recombinant tissue plasminogen activator (r-tPA).

Results: Of patients with acute ischemic stroke, 80.2% did not meet intravenous r-tPA eligibility; the most common cause was delayed (>4.5 hours) ED arrival after symptom onset (71.82%; n=283). Of 19.8% of subjects for whom the stroke code was activated, intravenous r-tPA was administered in only 5.3%. The average time from patients' arrival to first emergency medicine resident visit, notification of acute stroke team, presence of neurology resident, and computed tomography scan interpretation was lower for patients who met criteria of intravenous r-tPA than for those who lost eligibility for fibrinolytic therapy. The average door-to-needle time was 69 minutes (interquartile range 46 to 91 minutes).

Conclusion: Our ED and acute stroke team had a favorable clinical performance meeting established critical time goals of inhospital care for potentially eligible patients, but a poor clinical performance for the majority of patients who were not candidates for fibrinolytic therapy. [Ann Emerg Med. 2019;73:118-129.]

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0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2018.08.435

INTRODUCTION

Background

Globally, stroke is the second most common cause of death and the leading cause of long-term disability.[1,2] In 2013, it accounted for 6.5 million deaths worldwide and caused 1 of every 20 deaths in the United States. On average, every 40 seconds someone in the United States has a stroke, and someone dies approximately every 4 minutes.[3,4] Furthermore, it significantly affects patients' quality of life and also leads to immense financial burdens, projected to reach nearly $140 billion by 2030 in the United States.[5,6]

In the last few decades, there has been a tremendous effort to improve outcomes with new treatments.[7] The effectiveness of therapeutic interventions and long-term clinical outcomes are strongly time dependent.[8] Thrombolytic therapy with intravenous recombinant tissue plasminogen activator (r-tPA) is a proven intervention for patients with acute ischemic stroke,[9,10] and those treated within the first 4.5 hours of symptom onset derive more benefit than those treated later.[11] Although mechanical thrombectomy is highly effective for large-vessel occlusive stroke, a relative minority of stroke patients are eligible.[12]

Although guidelines have expanded the eligibility for intravenous r-tPA,[9] many out-of-hospital and inhospital factors impede its early administration.[13] Currently, less than 20% of eligible patients receive intravenous r-tPA,[14] and less than one third receive it within the recommended door-to-needle time of 60 minutes or less.[15]

Importance

In the last several decades, mortality rates from stroke have decreased in developed countries. However, during that period, mortality has increased in developing countries, where greater than 80% of worldwide stroke deaths occur.[16] In Iran,

Editor's Capsule Summary

What is already known on this topic

Worldwide, 80% of strokes happen in middle-income or developing countries, where few patients receive advanced care and where stroke mortality has increased over time.

What question this study addressed

In an Iranian hospital with an acute stroke team, what are the barriers to acute stroke treatment?

What this study adds to our knowledge

Only 5.3% of 394 acute ischemic stroke patients received thrombolytic drugs. Most patients (72%) present outside the window for receiving intravenous thrombolysis. When a stroke code was activated, median treatment intervals (69 minutes) only slightly exceeded recommended guidelines.

How this is relevant to clinical practice

The largest opportunity for improvement in acute stroke treatment for emergency systems resembling those in Iran is increasing public awareness of the urgency to seek treatment for stroke symptoms, followed by additional optimization of stroke code efficiency.

compared with developed countries, the incidence of stroke is higher, and the average age of onset is younger by almost 1 decade.[17] Understanding and addressing this disparity should be a public health priority.[18] To address the need for rapid evaluation and treatment, most hospitals have established multidisciplinary collaborations of clinicians as rapid response teams for guideline-based acute ischemic stroke care.[19] However, published data have shown gaps, variations, and inconsistencies in the results achieved by these teams.[20]

It is imperative to evaluate the overall performance of emergency department (ED) stroke programs to identify areas for improvement.[21,22] Moreover, because limited information is available on stroke management in developing countries,[23] the experience with implementation of acute ischemic stroke care in Iran may be informative for other similar environments with evolving health care systems that differ in structure from US and European systems.[24]

Goals of This Investigation

This study describes ED treatment delays and main barriers to implementing stroke care pathways, focusing on delays in door-to-needle times and intravenous r-tPA treatment, for patients with acute ischemic stroke who present to the ED of a midsized academic medical center in Iran.

MATERIALS AND METHODS

Study Design

We conducted a retrospective review of medical records of patients with acute ischemic stroke who were referred to the ED of Imam Reza University Hospital. This study was part of a nursing PhD dissertation approved by the institutional review board and the research ethics committee of Tabriz University of Medical Sciences. Moreover, objectives of the study were explained to the hospital officials, and permissions were obtained from them before data collection. The institutional review board waived the requirement for informed consent because this represented a retrospective review of medical records. Data extraction and abstraction were performed with methods to ensure patient confidentiality according to the Privacy Rule.

Setting

The study was conducted in the city of Tabriz, the capital of East Azerbaijan Province, located in the northwest of Iran. It is the most populated city in the Azerbaijan region (with a population of approximately 1.77 million at the study). There are 13 university hospitals, 8 private hospitals, 3 military hospitals, 3 state hospitals (2 affiliated with Iran's social security organization and 1 affiliated with Iran's Foundation of Martyrs and Veterans Affairs), and 1 Islamic Azad University–affiliated hospital (a total of 28 hospitals) in this metropolitan city.

Imam Reza University Hospital, as the largest and most well-equipped hospital in the region, is a 544-bed tertiary academic medical center with a 42-bed Level I trauma center and an ED. Annual ED visits were 111,542 in 2017, representing a 3% increase compared with the previous year. This ED was staffed by faculty emergency medicine attending physicians 24 hours a day, together with emergency medicine residents, residents from other specialties, senior medical students (interns), nurses, and nursing students. Routine challenges include prolonged throughput times and length of stay, crowding, boarding, and some ambulance diversion. In our hospital, patients were evaluated for intravenous r-tPA eligibility based on the standard inclusion and exclusion criteria considering the 4.5-hour time limit since last known wellness. A stroke code is activated according to the following process:

1. The acute ischemic stroke patient is assessed and, if he or she is eligible, the stroke code is activated by emergency medicine residents after initial ED admission diagnosis.

2. The resident-based acute stroke team works at bedside with off-site neurologist consultation.
3. Computed tomography (CT) is performed adjacent to the ED.
4. If criteria are met, the patient is transferred to the neurologic ICU.
5. Intravenous r-tPA is initiated in the neurologic ICU, where qualified nurses have access to the drug.
6. Intravenous r-tPA is administered after consent is obtained in a discussion about risks and benefits with the patient's immediate relatives.

Selection of Participants

Patients with an ED discharge diagnosis of acute ischemic stroke were included for analysis according to the following inclusion criteria: acute ischemic stroke confirmed by a stroke neurologist, and a noncontrast head CT result that ruled out another cause (such as hemorrhagic stroke).

Given the descriptive nature of this study, it was not deemed necessary to establish power, and data were collected during a 3-month period consistent with the investigators' time constraints. All charts within the study timeframe were reviewed through the electronic hospital information system, and also through manual review of paper charts because most of the patients' information was kept in a nonelectronic filing system. Figure 1 demonstrates the flow of the study.

Methods of Measurement and Data Collection and Processing

The steps of this review process were as follows: instrument (data extraction form) development, medical records retrieval, data extraction, and data verification. A researcher-made data extraction form was developed through an extensive review of the literature and specific ED guidelines in accordance with the study objectives, which included patients' demographic characteristics, disease-related characteristics, ED treatment delays, and main barriers to stroke care pathways. This structured form helped to ensure the measure of consistency and allowed no room for interpretation in data collection.

Content and face validity of the instrument were confirmed by a panel of experts that consisted of 3 emergency medicine assistant or associate professors, 5 nursing assistant or associate professors, and 5 nurses at Tabriz University of Medical Sciences. To assess the reliability of data collection, intrarater reliability measurement was computed with an intraclass correlation coefficient. To perform the intraclass correlation coefficient, the instrument was piloted on 30 predetermined and randomized charts out of study time, which were selected and recorded by the investigators for coding evaluation and calculation. The obtained intraclass correlation coefficient value for the data collection method was 0.94 (indicating an excellent reliability), with a 95% confidence interval (CI) of 0.88 to 0.97, based on a mean of multiple measurements, absolute agreement, and 2-way mixed-effects model.[25] The data from the pilot study were not included in this study because it represented an initial validation of our methods.

Because missing and incomplete data can be a concern in retrospective chart reviews, the focus was on those fields with missing data during the data verification. The overall proportions of missing data were 8.17% for the National

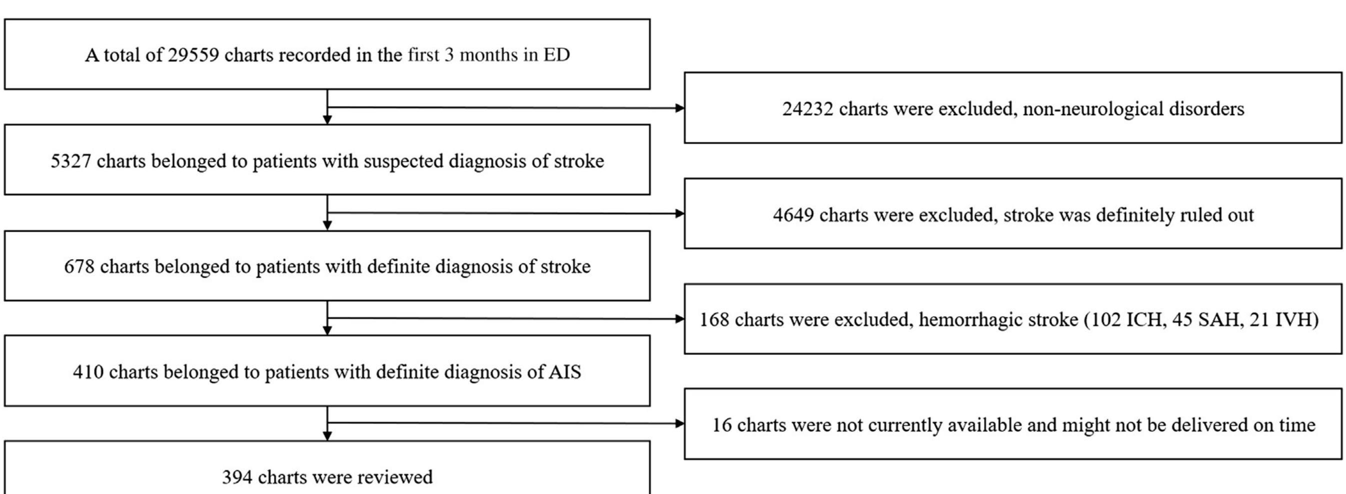

Figure 1. Flow of the study. *AIS*, Acute ischemic stroke; *ICH*, intracerebral hemorrhage; *SAH*, subarachnoid hemorrhage; *IVH*, intraventricular hemorrhage.

Institutes of Health Stroke Scale (NIHSS) score on admission or discharge and 0.01% for the modified Rankin Scale score. Missing data occurred randomly and were not likely to cause bias.[26] To ensure the quality of the data extraction, the data were manually collected by a qualified abstractor with at least 5 years' work experience in hospital and out-of-hospital emergency settings, and who was familiar with medical writing in charts. The abstractor was blinded to the purpose of the study, and 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 the evaluation of treatment delays for patients with acute ischemic stroke and ED performance in stroke door-to-needle times. Secondary outcomes were intravenous r-tPA treatment rate for eligible patients, main barriers to stroke care pathways, and disease-related characteristics of patients with acute ischemic stroke who presented to the ED.

Primary Data Analysis

Descriptive statistics for normally distributed continuous data are reported as mean with SD, and median and interquartile ranges (IQR) are reported for nonnormally distributed data. Also, the discrete variables are reported as frequency and percentage. Pairwise comparisons were applied through calculation of the mean difference with a 95% CI. Data were evaluated with R statistical software (version 3.4.2; R Core Team, Vienna, Austria).

RESULTS

Characteristics of Study Subjects

During the study (March 21, 2017, to June 21, 2017), there were 29,559 visits to our ED. Of those, 394 were included for analysis (Figure 1). The average age of patients was 68.85 years (SD 13.39 years) (range 24 to 98 years), and 53.3% (n=210) were men. Payer mix was 96.7% insured, 2.8% uninsured (covered through the Imam Khomeini Relief Foundation), 0.2% incarcerated, and 0.2% self-pay.

There was no medical history for 17.3% (n=69) of the patients. Of the 325 patients with significant medication history, 35.4% (n=115) did not bring their medications with them or did not remember their medications' names.

The rate of walk-in patients was 53.1% (n=209). Only 15.7% of patients (n=62) were admitted to a stroke unit and 39.8% (n=157) transferred out because of an insufficient hospital capacity to care for patients with acute ischemic stroke (a lack of inpatient beds). The NIHSS score was recorded for 21.3% of patients (n=84) on admission (mean 14.35 [SD 8.3]); of those, the majority had had an NIHSS score greater than 5. It was recorded for 9.4% of patients (n=37) on discharge (mean 8 [SD 5.5]). Also, a nearly 5-point decrease was observed in the mean admission and discharge NIHSS score (mean difference 4.7; 95% CI 3.3 to 6). The inpatient modified Ranking Scale score was recorded for only one patient. A stroke code was activated for 19.8% patients (n=78) with acute ischemic stroke; of these, intravenous r-tPA was only administered for 5.3% of patients (n=21). Conversely, routine antiplatelet therapy was promptly initiated for the other 373 patients. A χ^2 test of independence was performed and a significant positive correlation was found between our patients' emergency medical services (EMS) arrival status and whether the emergency medicine resident called a stroke code (χ^2 [degree of freedom=1, N=394]=50.2; $P<.001$). Other demographics and disease-related characteristics of patients are listed in Table 1. Figure 2, with error bars, illustrates ED trends of stroke patients' flow based on hospital shift work, days of the week, and weeks of the month.

In our ED, 80.2% of acute ischemic stroke patients (n=316) did not receive stroke code activation. For the 19.8% of patients (n=78) who received activation, 14.5% of codes (n=57) were canceled by the acute stroke team and only 5.3% of the total cohort (n=21) received intravenous r-tPA. Furthermore, only 11.67% of these patients (n=46) in this cohort were initially evaluated by the emergency medicine resident on their arrival. Emergency medical technicians provided out-of-hospital notification for 1.26% of patients (n=5).

The median door-to-physician time for patients with suspected acute ischemic stroke who met the entry criteria of intravenous r-tPA (n=78) was 9 minutes (IQR 0 to 19.3) compared with 20 minutes (IQR 10 to 30) for patients (n=316) who did not meet the entry criteria (mean difference 9.9 minutes; 95% CI 5.9 to 13.9 minutes). Also, CT was performed and interpreted within 33.5 minutes (IQR 17 to 61 minutes) of patient arrival if a stroke code was activated (the median door-to-CT time for patients receiving intravenous r-tPA was 29 minutes [IQR 9 to 61 minutes]); otherwise, it occurred within 75 minutes (IQR 59 to 96.5 minutes) of arrival if the patient was primarily excluded from the entry criteria of intravenous r-tPA (mean difference 39.7 minutes; 95% CI 26.8 to 52.7 minutes). The median door-to–acute stroke team notification time was 10 minutes (IQR 0 to 19.5 minutes) for eligible patients (n=78) compared with 67.5 minutes (IQR 22 to 141.5 minutes) for ineligible ones (n=316)

Table 1. Demographics and disease-related characteristics of patients presenting to the ED of Imam Reza University Hospital.

Variable	No. (%)
Sex (N=394)	
Men	210 (53.3)
Women	184 (46.7)
Education level (N=394)	
Illiterate	128 (36.7)
Primary	80 (22.9)
Secondary	47 (13.5)
Diploma	68 (19.5)
University	26 (7.4)
Place of residence (N=394)*	
City	166 (42.1)
Town	105 (26.6)
Village	123 (31.2)
Modes of arrival (N=394)	
Walk-in	209 (53.1)
Ambulance, either air or ground	185 (46.9)
EMS	66 (16.8)
Other hospitals	119 (30.2)
Side of body affected by stroke (N=394)	
Right	177 (44.9)
Left	169 (42.8)
None	45 (11.4)
Lower extremities	2 (0.6)
Both	1 (0.3)
ED treatment room (N=394)	
Medical area	311 (78.6)
Resuscitation area (top urgency)	83 (21.1)
NIHSS score on admission (N=84)	
≤5	17 (4.3)
6–10	14 (3.6)
11–25	45 (11.4)
≥26	8 (2)
SBP on arrival (N=394), mm Hg	
<90	6 (1.5)
90–120	89 (22.6)
121–140	122 (31)
141–160	88 (22.3)
161–180	56 (14.2)
181–200	14 (3.6)
>200	19 (4.8)
PR on arrival (N=394), beats/min	
<60	26 (6.6)
60–100	335 (85)
>100	33 (8.4)
Admission ward (N=117)	
Neurology	41 (10.4)
Neurologic ICU	21 (5.3)
Collateral wards	57 (14.5)
ENT	33 (8.4)
Urology	8 (2)
Orthopedic	6 (1.5)
Thoracic surgery	6 (1.5)
Pulmonary	2 (0.5)
Nephrology	1 (0.3)
Major trauma	1 (0.3)
Insurance (N=394)	
Yes	381 (96.7)
No	13 (3.3)
Marital status (N=349)	
Single	0
Married	283 (81.1)
Widow/widower	98 (28.1)
Divorced	3 (0.8)
Month of arrival (N=394)	
First	148 (37.6)
Second	121 (30.7)
Third	125 (31.7)
ESI triage (N=394)	
Level I	30 (7.6)
Level II	132 (33.5)
Level III	232 (58.9)
Status of stroke code (N=394)	
Not activated by emergency medicine resident	316 (80.2)
Activated by emergency medicine resident	78 (19.8)
IV r-tPA not administered by AST	57 (14.5)
IV r-tPA administered by AST	21 (5.3)
Diagnosis (N=394)	
Ischemic stroke	295 (74.9)
TIA	99 (25.1)
NIHSS score on discharge (N=37)	
≤5	17 (4.3)
6–10	8 (2)
11–25	12 (3.1)
≥26	0
DBP on arrival (N=394), mm Hg	
<70	85 (21.6)
70–80	136 (34.5)
81–90	81 (20.6)
91–100	62 (15.7)
>100	30 (7.6)

Table 1. Continued.

Variable	No. (%)
O_2Sat on arrival (N=394), %	
<75	5 (1.3)
75–89	29 (7.4)
90–93	141 (35.8)
>93	219 (55.6)
ED disposition situation (N=394)	
Admitted to hospital inpatient wards	119 (30.2)
DAMA	115 (29.2)
Died	3 (0.8)
Transferred to other facilities	157 (39.8)
Psychiatric hospital	153 (38.7)
Social security hospital	2 (0.5)
Military hospital	1 (0.3)
Private hospital	1 (0.3)

SBP, Systolic blood pressure; *PR*, pulse rate; *ESI*, Emergency Severity Index; *IV*, intravenous; *ENT*, ear, nose, and throat; *AST*, acute stroke team; *TIA*, transient ischemic attack*; DBP*, diastolic blood pressure; *O_2Sat*, oxygen saturation; *DAMA*, discharged against medical advice.
*Villages have a population of 100-1000, towns have a population of 1000-80,000, and cities have a population of >80,000.

(mean difference 75.4 minutes; 95% CI 57.1 to 93.6 minutes). The median door-to–intravenous r-tPA time was 69 minutes (IQR 46 to 91 minutes) (n=21). All the critical intervals and events are presented in Table 2.

The potentially eligible patients were excluded from entry criteria of intravenous r-tPA mainly because of one or more of the following: onset of symptoms greater than 4.5 hours (71.82%; n=283), older than 80 years (20.31%; n=80), wake-up stroke with unclear onset time (14.72%; n=58); minor symptoms (NIHSS score <5) (13.95%; n=55), rapidly improving stroke symptoms (clearing spontaneously) (6.59%; n=26), major symptoms and unstable medical condition (NIHSS score >25) (4.56%; n=18), current use of anticoagulant with international normalized ratio greater than 1.7 or prothrombin time greater than 15 seconds (3.29%; n=13), stroke in the previous 3 months (2.28%; n=9), major surgery in the preceding 14 days (2.04%; n=8), elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg) (1.02%; n=4), seizure at onset with postictal residual neurologic impairments (1.02%; n=4), patients' or their family members' informed refusal of intravenous r-tPA (0.51%; n=2), and history of intracerebral hemorrhage (0.26%; n=1).

LIMITATIONS

Although this study demonstrated important elements of acute stroke care in our region, it has several limitations. First, all the ED treatment times and other data collected depended on the quality of the documentation in paper charts (incomplete or inaccurate data collection, illegible handwriting, etc); there could be variation based on

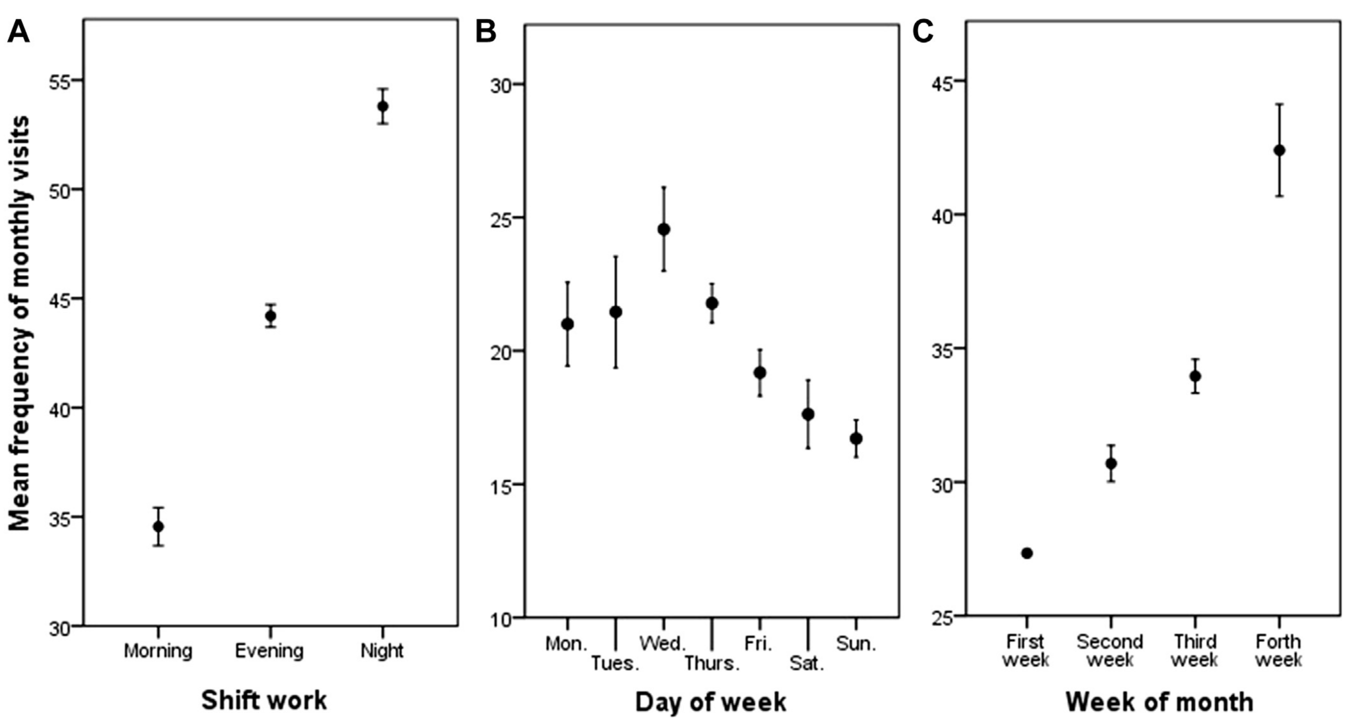

Figure 2. The mean frequency of monthly visits of acute ischemic stroke patients, with 95% CI, according to shift work (*A*), day of the week (*B*), and week of the month (*C*).

Table 2. Detailed critical intervals and events of management of patients with acute ischemic stroke in the ED of Imam Reza University Hospital, Tabriz, Iran.

Patient Category	**Patients With Suspected AIS**						**Eligible for IV r-tPA Administration**	
Events	**Patient Arrival to ED Admission (N=394)**	**ED Admission to Emergency Medicine Resident Visit (N=394)**	**Emergency Medicine Resident Visit to HIS Documentation (N=394)**	**Emergency Medicine Resident Visit to Nursing Intervention (N=394)**	**Emergency Medicine Resident Visit to the First Laboratory Test Result (N=109)**	**Emergency Medicine Resident Visit to CT Scan Result (N=95)**	**Emergency Medicine Resident Visit to Stroke Code Activation (N=78)**	**Stroke Code Activation to Initial AST Visit (N=78)**
Min–max	0 to 6	0 to 129	1 to 53	0 to 65	13 to 160	4 to 199	0 to 135	0 to 45
Median (25th–75th percentile)	3 (1 to 5)	14.4 (7 to 23)	9 (4 to 18)	0.0 (0 to 5)	62 (50.5 to 81)	49 (32 to 70)	0.0 (0 to 0)	5.5 (5 to 10.3)
ED area, median (25th to 75th percentile)								
Medical	3 (1 to 5)	17 (9 to 25)	12 (6 to 20.3)	0.0 (0 to 5)	64 (54.3 to 89.3)	51.5 (35 to 71)	0.0 (0 to 0)	5.5 (5 to 13.8)
Resuscitation	3 (2 to 5)	5.7 (4 to 14.4)	5 (3 to 16)	0.0 (0 to 0)	58 (40.5 to 74)	48 (22 to 67.5)	0.0 (0 to 0)	5 (2.8 to 10)
Pairwise differences, MD (95% CI)	0.1 (–1.2 to 1.7)	10.6 (7.3 to 13.8)	4.8 (0.8 to 8.8)	3.3 (1.5 to 5.2)	7.7 (–2.9 to 18.3)	9.7 (–3.7 to 23.2)	2.3 (–5.3 to 9.9)	–0.8 (–5.3 to 3.7)
ESI triage, median (25th to 75th percentile)								
Level I	3 (2 to 7)	5.7 (5.5 to 5.7)	5 (3 to 17)	0.0 (0 to 0)	52 (34 to 71)	50 (36.5 to 92.8)	0.0 (0 to 0.5)	5 (3.5 to 17.5)
Level II	2 (1 to 4)	14.4 (8 to 20)	10 (4 to 20)	0.0 (0 to 1.8)	62 (52 to 81.5)	49 (24 to 65)	0.0 (0 to 0)	5 (4 to 10)
Level III	3 (1 to 5)	17 (9 to 25)	8.5 (3.8 to 16.3)	0.0 (0 to 5)	65.5 (54.3 to 87.8)	47.5 (35 to 70.3)	0.0 (0 to 0)	7 (5 to 15)
Pairwise differences, MD (95% CI)								
1 vs 2	0.2 (–2 to 2.5)	–10. 4 (–15.1 to –5.6)	–2.1 (–8.1 to 3.9)	–2.5 (–5.5 to 0.5)	–14.9 (–30.6 to 0.8)	7.8 (–9.8 to 25.5)	1.2 (–3.7 to 6.2)	0.3 (–8.2 to 8.9)
1 vs 3	0.1 (–1.8 to 2)	–13.7 (–18.9 to –8.4)	–0.7 (–6.6 to 5.1)	–3.5 (–6.4 to –0.6)	–15.7 (–30.1 to –1.4)	–0.8 (–25.1 to 23.5)	–5.4 (–21.9 to 11.1)	0.9 (–5.5 to 7.2)
2 vs 3	–0.1 (–1.3 to 1.1)	–3.3 (–6.3 to –0.3)	1.3 (–3.2 to 5.8)	–1.1 (–2.8 to 0.7)	–0.8 (–12.6 to 10.9)	–8.6 (–23.6 to 6.4)	–6.6 (–15.1 to 1.8)	0.5 (–4.2 to 5.3)
Stroke code status, median (25th to 75th percentile)								
Not activated	3 (1 to 5)	15 (8 to 25)	12 (5 to 21)	0.0 (0 to 5)	61 (50 to 87)	60 (45 to 75)	–	–
Activated but canceled	2 (1 to 4)	13 (5.8 to 17)	7 (4 to 12)	0.0. (0 to 5)	63 (51 to 94)	35 (17 to 50)	0.0 (0 to 0)	5.5 (5 to 15)
IV r-tPA administered	3 (2 to 5)	12 (5 to 14.7)	5 (3.5 to 6.5)	0.0 (0 to 1)	62 (50.5 to 72.3)	20 (9 to 38)	0.0 (0 to 0)	4 (2 to 7)
Pairwise differences, MD (95% CI)								
1 vs 2	1.2 (–0.3 to 2.7)	4.6 (0.6 to 8.6)	5.5 (–1 to 12)	0.6 (–1.7 to 2.8)	–6.1 (–22.9 to 10.7)	27.9 (10.2 to 45.7)	–	–
1 vs 3	0.8 (–1.7 to 3.3)	7.6 (1.3 to 13.9)	9.3 (3.9 to 14.7)	3.3 (–0.3 to 6.9)	6.6 (–7.5 to 20.8)	40.2 (24.5 to 55.8)	–	–
2 vs 3	–0.4 (–2.1 to 1.4)	3 (–2.1 to 8.1)	3.8 (0.3 to 7.3)	2.7 (0.4 to 5.1)	12.7 (–2.5 to 27.9)	12.2 (–1.7 to 26.1)	2.5 (–6.1 to 11.1)	4.6 (–0.4 to 9.6)

HIS, Hospital information system; *MD*, mean difference.

providers' documentation skills and level of knowledge. Also, the precise out-of-hospital times, especially the time of patients' last known wellness, were not accessible in our ED charts and routinely recorded by the emergency medicine residents and acute stroke team in a dichotomous style (within/out of 4.5-hour window), and we could not independently verify their accuracy. To combat this, we optimized data quality, using predefined standardized logic, range checks, and detailed audit trails on the extracted data to prevent the potential risk of information (reviewer) bias. Another limitation was that we did not collect data on acute ischemic stroke patients' concurrent intracranial hemorrhage or hemorrhagic complications. This could have influenced inpatient NIHSS score and other outcome factors. Furthermore, we could not reliably capture outpatient follow-up. Recent stroke treatment studies have used a 90-day modified Rankin Scale score documentation as a primary outcome. We did not have those data for this

Table 2. Continued

Eligible for IV r-tPA Administration				Excluded From IV r-tPA Administration			
Initial AST Visit to Transfer Request to Neurologic ICU (N=21)	Patient Transfer Order to Neurologic ICU to Nurses' Check-in (Patient Entrance) (N=21)	Patient Entrance to Neurologic ICU to IV r-tPA Administration (N=21)	Stroke Code Activation to IV r-tPA Administration (N=21)	Emergency Medicine Resident Visit to Neurology Consultation Request (N=373)	Neurology Consultation Request to Neurology Visit (N=373)	Neurology Visit to Patient Disposition (N=373)	Patient Transfer Order to Hospital Inpatient Ward to Nurses' Check-in (Patient Entrance) (N=96)
0 to 72	0 to 45	5 to 30	10 to 95	0 to 420	0 to 555	0 to 315	0 to 1,665
25 (8 to 36)	10 (5.5 to 20)	10 (5 to 20)	62 (42.5 to 77.5)	25 (0 to 110)	65 (30 to 100)	5 (0 to 30)	337.5 (181.3 to 794.3)
30 (10 to 38)	15 (5 to 23.5)	15 (10 to 20)	70 (57 to 80)	25 (0 to 115)	65 (30 to 107.8)	5 (0 to 30)	400 (181.3 to 948.8)
25 (5.3 to 33.8)	7.5 (5 to 20)	8 (5 to 18.8)	53.5 (25 to 72.5)	30 (0 to 105)	60 (30 to 90)	5 (0 to 30)	310.5 (165 to 697.3)
4.1 (−13.7 to 21.7)	2.4 (−8.8 to 13.6)	3.2 (−3.8 to 10.3)	16.4 (−4.4 to 37.3)	3 (−17.4 to 23.4)	18.1 (0.6 to 35.5)	0.7 (−13.5 to 14.9)	95.4 (−76.2 to 266.9)
29 (10.8 to 54)	12.5 (5 to 20)	10 (6.3 to 13.8)	55 (45 to 76.3)	0.0 (0 to 108.8)	65 (28.8 to 91.8)	9.5 (0 to 21.3)	337.5 (157.5 to 986.3)
15 (5 to 33)	10 (4.5 to 20)	6 (5 to 25)	49 (18.5 to 70)	25 (0 to 105)	60 (30 to 90)	10 (0 to 40)	337.5 (176.3 to 725)
30 (12.5 to 38)	12.5 (5 to 27.8)	12.5 (10 to 18.8)	70 (56.3 to 80)	30 (0 to 118.8)	65 (30 to 115)	5 (0 to 28.8)	350 (181.3 to 802.5)
12.7 (−9.5 to 34.9)	−0.7 (−17.6 to 16.7)	−4 (−16.4 to 8.4)	9.7 (−24.6 to 44.1)	−16.8 (−52 to 18.4)	4.3 (−19.8 to 28.5)	−21.4 (−48.3 to 5.6)	46.8 (−198.6 to 292.2)
1.5 (−28.6 to 31.7)	−2.7 (−17.9 to 12.4)	−3.7 (−9.6 to 2.1)	−10 (−33.3 to 13.3)	−16.9 (−47.4 to 13.6)	−10.7 (−40.2 to 18.8)	−7.9 (−26.7 to 10.9)	32.6 (−233.3 to 298.5)
−11.2 (−29.8 to 7.4)	−2.1 (−15.6 to 11.6)	0.2 (−8.4 to 8.9)	−19.7 (−44.5 to 5)	−0.1 (−17.6 to 17.4)	−15 (−30.1 to 0.1)	13.4 (1 to 25.8)	−14.2 (−206.5 to 178.1)
–	–	–	–	40 (0 to 120)	70 (40 to 113.8)	5 (0 to 30)	364 (167.5 to 877.5)
–	–	–	–	0 (0 to 45)	30 (10 to 55)	5 (0 to 45)	335 (250 to 698)
25 (8 to 36)	10 (5.5 to 20)	10 (5 to 20)	62 (42.5 to 77.5)	–	–	–	–
–	–	–	–	44.4 (22.6 to 66.1)	47.9 (29.3 to 66.5)	−3.9 (−19.4 to 11.7)	17.6 (−220.2 to 255.3)
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–

analysis. Finally, we could not factor in the role or importance of mechanical thrombectomy in the care of these stroke patients.

DISCUSSION

Few previous studies report the timeliness of service delivery to patients with acute ischemic stroke in Iranian health care systems or in other developing countries. Our analysis demonstrated that the stroke code was not activated for the majority of acute ischemic stroke patients mostly because of delayed ED arrival after symptom onset. A minority of patients received intravenous r-tPA. These findings are consistent with those in other developing countries.[27-29] Similarly, a study in Iran showed that 68.7% of acute ischemic stroke patients did not arrive at the hospital early enough for intravenous r-tPA, and intravenous r-tPA was administered to only 3.1% of patients.[30] In another cohort study in the northeast of Iran, 85.6% of acute ischemic stroke patients did not meet the eligibility criteria because of late arrival, and only 1.2% of patients received intravenous r-tPA.[18] There is great variation in the time taken by acute ischemic stroke patients to arrive at hospitals in developing countries,[31] with the consequence that the administration rate for intravenous r-tPA is far lower than in developed countries.[27,32,33]

Despite that immediate action is of key importance to optimize stroke recovery,[34,35] some cultural, perceptual, and behavioral factors impede acute ischemic stroke patients' early presentation to the ED. These factors include 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. In our study, prolonged out-of-hospital time was common even when stroke was recognized. Our study clearly shows a strong correlation between how the patient is brought to the ED and the likelihood of calling a stroke code. It is likely that EMS activation and arrival triggers a more urgent and attentive response by emergency physicians and that the urgency of patients' condition is implied by their transport with EMS. Therefore, along with a need for rapid recognition and reaction to stroke, it is necessary to correct public attitude and misconception about the urgency of stroke symptoms. Stroke awareness programs by mass media and public "know stroke" campaigns should stress the importance of seeking immediate and timely treatment to reduce the chance of permanent damage or disability. Furthermore, EMS services are clearly underused for rapid triage and transport of stroke patients.

Although guidelines recommend a door-to-needle target time of 60 minutes for timely initiation of thrombolytic therapy after hospital arrival,[36-39] this study found a median door-to-needle time of 69 minutes, which is substantially longer than results after the implementation of the Get With the Guidelines–Stroke program in the United States,[37] the Hurry Acute Stroke Treatment and Evaluation project in Canada,[40] and the Safe Implementation of Treatment in Stroke initiative in Europe.[41] Therefore, more effort is required for stroke care responsiveness in Iran and similar settings. Vital to this effort is a clear documentation of last known wellness. A patient's eligibility for intravenous r-tPA should not dictate whether he or she receives rapid and complete assessment and documentation for stroke. As additional treatments such as thrombectomy become more widely available, dichotomizing last known wellness into "within 4.5 hours" and "outside of 4.5 hours" is not adequate.

Our study also identified specific barriers that led to much longer delays in treatment for intravenous r-tPA–ineligible patients. The main reasons behind these were as follows: delay in initial assessment by the emergency medicine resident because of undertriage, crowding, and prolonged boarding time of admitted patients in the ED medical area; examination of patients in the medical area in accordance with the "first come, first served" rule by emergency medicine residents; request for neurology consultations after performance of a CT scan; and delays in arrival of neurology residents at the patient's bedside. Neurology residents assigned a lower priority for patients who were excluded from intravenous r-tPA, resulting in their delayed presence at the patient's bedside.

We also observed a high rate of discharge against medical advice among acute ischemic stroke patients (30%), which puts them at increased risk of adverse clinical outcomes. Likewise, a previous study in Iran reported an overall rate of discharge against medical advice of 8.8%.[42] A systematic review and meta-analysis estimated the rate of discharge against medical advice from Iran hospital EDs at 11.8%.[43] In contrast, in an earlier study conducted in US hospital EDs, the rate of discharge against medical advice was reported to be approximately 0.1% to 2.7%.[44] Thus, available evidence suggests that the rate of discharge against medical advice in developing countries, and in Iran in particular, is much higher than in developed ones.[42] Some of the reasons for discharge against medical advice have been identified in previous studies.[45-48] Discharge against medical advice depends on the country and the culture of the patient, which makes it hard to compare rates cross nationally.[49] In our ED, we identified common reasons contributing to a high rate of discharge against medical advice, namely, ED crowding, long waiting times, lack of timely care and proper treatment, and lack of attention from physicians and nurses. In addition, our institution lacked available inpatient beds for all patients with acute ischemic stroke. Therefore, we triaged the patients according to need, and those with severe stroke requiring ICU admission and receiving intravenous r-tPA stayed at this institution, whereas the emergency medicine attending physician decided the necessity of others' transfer to the general neurology or neurologic ICU of another facility (Razi Psychiatric University Hospital, with 16 wards and 650 beds). The majority of these patients or their family members rejected the transfer request. This refusal was often because of their beliefs, perspectives, misconceptions, and concerns about the subsequent stigma associated with labeling of mental health problems.

In conclusion, despite major academic, managerial, and governmental efforts to improve stroke care, this study revealed that less than 1 in 5 patients with acute ischemic stroke was eligible for thrombolytic therapy, and that only

1 of every 20 patients received intravenous r-tPA for acute ischemic stroke. Delayed ED presentation represents the most clinically significant delay. For eligible patients, our ED and acute stroke team had a favorable clinical performance in terms of critical time goals of inhospital care, but performance was poor for patients who were not candidates for fibrinolytic therapy. Furthermore, given the current data, there is a clear need for mechanical thrombectomy services at our institution. Because the majority of patients with stroke code activations were intravenous r-tPA ineligible, had NIHSS scores greater than 5, and received a diagnosis of ischemic stroke, there is a great need for mechanical thrombectomy services. Thrombectomy expands the eligibility of recanalization therapy up to 24 hours in selected patients, can be performed in the setting of intravenous r-tPA administration, and is particularly useful for large-vessel occlusions with high NIHSS score. These findings support the need for an integrated multidisciplinary approach, adding endovascular providers and culture outreach specialists to our current team to improve care. More effective community-based interventions may raise awareness of the key effect of short out-of-hospital times on limiting damage, potentially reversing or stopping symptoms from developing and maximizing clinical benefits. Another opportunity is the lack of consistent interaction between our regional EMS providers and our ED that leads to extremely low rates of out-of-hospital notification. To combat this, we have instituted a continuous connection between the Tabriz EMS dispatch center and the on-call neurology resident house staff to provide prenotification for stroke.

In our system, we make the following recommendations: establishing a much more robust protocol for out-of-hospital notification and EMS direct to CT scan; administering timely intravenous r-tPA in the ED or CT-scan unit instead of in the neurologic ICU; organizing a joint collaboration among emergency medicine, neurology, and radiology departments to enhance hospital performance in stroke care; establishing mechanical thrombectomy services and integrating them into our current teamwork; and establishing clear performance goals for ED and acute stroke team and effective stroke surveillance systems for continuous data collection and quality improvement. Moreover, other strategies such as having a neurology resident in the ED at all times and appointing an emergency nursing coordinator to help patients with acute ischemic stroke fulfill benchmarks on written protocols also may improve door-to-needle times. These system improvements can address the specific opportunities identified in our analysis and will improve the quality of care for our patients.

Supervising editor: Clifton Callaway, MD, PhD

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Author contributions: HH, AS, SSV, and FAM were responsible for the original concept and study design. AS was responsible for data collection. AS, JFF, and NG were responsible for data analysis and interpretation. HH, AS, SSV, and JFF were responsible for article preparation and final critique. HH and SSV were responsible for study supervision. AS takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist. This study was extracted from Dr. Soheili's PhD dissertation, and commissioned and granted by the research deputy of Tabriz University of Medical Sciences (project no. 729).

Publication dates: Received for publication February 24, 2018. Revisions received May 27, 2018; July 24, 2018, and August 11, 2018. Accepted for publication August 16, 2018. Available online October 11, 2018.

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