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Delays in receiving Alteplase and related factors in patients with stroke referred to Shahid Beheshti Hospital in Kashan-Iran in 2020-2021

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Abstract:

BACKGROUND: The benefits of using Alteplase are time-dependent. This study aimed to evaluate delays between the onset of symptoms and the administration of Alteplase and related factors in patients with acute ischemic stroke (AIS).

MATERIALS AND METHODS: In this cross-sectional study, 60 AIS patients receiving Alteplase were selected by census sampling from July 2020 to July 2021 from the eligible patients referred to Shahid Beheshti Hospital in Kashan, Iran. The data collection tool was a researcher-made questionnaire containing demographic information, time periods from the onset of symptoms to the injection of Alteplase, and associated factors. The required information was collected from the patients, their relatives, their health records, and Kashan Emergency Medical Service (EMS) information system. Data were analyzed in SPSS-16.

RESULTS: Eighty-five percent of the 60 patients participating in the study were transferred to the hospital by EMS ambulances. The mean time intervals between different phases were as follows: Onset-To-Door (OTD) time 81.35 ± 33.76 minutes; Door-To-CT (DTC) scan time 16.12 ± 17.46 minutes; Door-To-Needle (DNT) time 51.30 ± 26.14 minutes; and the overall Onset-To-Needle (ONT) time 133.75 ± 39.17 minutes. Also, the mean ONT in people transferred by EMS was about 129 minutes, and the longest prehospital delay in these patients was related to the time between the arrival of the EMS ambulance to the hospital. Marital status and geographical location where the stroke had occurred showed a significant relationship with prehospital delay and pre-hospital notification (PHN) by EMS But there was no relationship between underlying diseases or economic status and prehospital delays; also, the patient's diastolic blood pressure at the time of receiving Alteplase showed a significant relationship with in-hospital delay.

CONCLUSION: The findings of the study showed that the majority of people trust and use EMS ambulances to transfer to the hospital and the time spent in different stages, from the onset of symptoms to the injection of the thrombolytic drug, was in an acceptable range in the patients.

Keywords:

Ischemic stroke, time-to-treatment, tissue plasminogen activator

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Introduction

Stroke is the second most common cause of death in the world and the fourth leading cause of death in the United States.[1] About 85% of all strokes are ischemic.[2] In these patients, maintaining brain tissue perfusion by intravenous thrombolysis with the help of drugs such as Alteplase or endovascular thrombectomy within an appropriate time frame is critical. Alteplase is a tissue plasminogen activator compound that breaks down plasminogen into plasmin, destroys plasmin fibrin, and resolves thrombosis. Plasmin is rapidly inactivated by antiplasmin and has a short half-life.[3] Treatment with

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alteplase within 3 hours is significantly more effective than 3–4.5 hours, and a time interval of more than 3 hours increases the risk of death within 3 months as well as symptomatic intracerebral hemorrhage within 36 hours.[4] Furthermore, treatment after 4.5 hours has been associated with an increased risk of intracranial hemorrhage and an 85% increase in death within 90 days after the stroke.[5] Therefore, the effectiveness of Alteplase is highly dependent on time, so the earlier is treatment started, the better will be the effect.[6,7]

Some studies, such as Nepal's (2019) study, only evaluated prehospital delay among the study patients and found that education higher than high school, onset of symptoms during the day, awareness of stroke treatment, direct presentation, location distance less than 20 km, stroke detection, facial deviation, speech disturbances, and rushing to ED after onset of symptoms was associated with early admission.[8] Falat (2019) also examined only the prehospital period and the factors affecting it.[9] Some other studies have only examined the inhospital interval and the factors affecting this time. Kamal and Chai examined the Door-to-Needle (DNT) time and the factors affecting it in general.[10,11] Therefore, studies that have comprehensively evaluated all prehospital and inhospital times were very limited

On the other hand, different studies have reported different results regarding the time intervals from the onset of stroke symptoms to receiving Alteplase. Vidale *et al*.(2016), Iglesias Mohedano *et al*. (2017), Alkhotani *et al*. (2022) estimated the Onset-to-Needle Time (ONT) to be 240, 145, and 156 minutes on average.[12-14]Also, Ding *et al*. (2019) reported the mean delay in receiving Alteplase in people who went directly to the studied hospitals as 164.7 minutes.[15]

Considering to these factors; the importance of time in patients receiving Alteplase, the difference in the results of the studies conducted in relation to the mean delay in receiving alteplase, the focus of some of the studies on only one of the time intervals (prehospital and inhospital), and the SAMA code (a special care system for patients with ischemic stroke, that has been implemented in Kashan since 2016) however, delays in the reperfusion of patients has not yet been evaluated All these issues prompted the research team to conduct a more comprehensive study (evaluating all time intervals) during the COVID-19 pandemic. This study aimed to evaluate delays between the onset of symptoms and the administration of Alteplase and related factors in patients with acute ischemic stroke (AIS).

Materials and Methods

Study design and setting

This cross-sectional study after obtaining permission from the ethics committee (IR.KAUMS.NUHEPM.REC.1399.028) to access the samples and collect their information, the head of the department was first asked to inform the researcher if an eligible patient presented to the hospital to receive Alteplase, and the researcher (first author) attended the patient's bedside to collect information. The researcher talked to the patients/patient caregivers (in case the patients were unable to respond) about the objectives, reason, and methods of the study and obtained their written or oral (in case of unwillingness to attend the hospital due to COVID-19 conditions) informed consent for participation. The required information was collected using a researcher-made questionnaire.

Participants and sampling

In this study, all patients receiving alteplase from July 2019 to July 2019 (during the Covid-19 epidemic) in Shahid Beheshti Hospital, Kashan, Iran, as the only center for Alteplase injection to acute ischemic patients, were examined by census method. According to the inclusion and exclusion criteria, 60 patients were included in the study. The inclusion criteria were being at least 18 years old, willing to participate in the study, having a definitive diagnosis of AIS by a neurologist, and receiving Alteplase. The exclusion criteria were not being able to access the time frames intended by the researcher and having a stroke inside the hospital.

Data collection tools and technique

The questionnaire had three parts, including demographic information (age, sex, marital status, occupation, education, monthly income, nationality, place of residence, and the number of children), the time intervals in question, including ONT, the time from the onset of symptoms to contacting EMS, from contacting EMS to ambulance arrival, from ambulance arrival to arriving at Shahid Beheshti Hospital, Onset-To-Door (OTD) time, Door-To-CT (DTC) time, CT-To-Needle (CTN) time, DTN time, and total time (or ONT), and the associated factors, including underlying diseases, history of stroke, history of COVID-19, way of transfer to the hospital, day of the stroke during the week, hour of onset of stroke symptoms, EMS sending notification to the hospital (SAMA code in triage), and geographical location where the stroke had taken place.

The questionnaire items were read for the patients/caregivers to answer, and the form was completed using the information available in the patients' health records at Shahid Beheshti Hospital. Also, part of the questionnaire that was related to the patients transferred by EMS ambulance was completed using the information available in the EMS system of Kashan City. To ensure the accuracy of the information obtained from the patients (or their caregivers) and the EMS system,

they were matched with the information entered into the patients' records at Shahid Beheshti Hospital. The validity of the questionnaire was approved by 17 specialists (ten faculty members of the School of Nursing and Midwifery, the head nurse of the general ward and two nurses of this ward, the deputy, the training specialist, and two EMS technicians and operators). The reliability of the questionnaire was also confirmed based on its objectivity.

Ethical considerations

Ethical approval of the research was obtained from the ethics committee of Kashan University of Medical Sciences (IR.KAUMS.NUHEPM.REC.1399.028) and then coordinated with the hospital manager to conduct the research. Informed consent was obtained from the participants after explanations about the research, and the confidentiality of the information was assured to the participants. Honesty, justice, beneficence, non-maleficence, and respect for human rights and dignity were observed throughout the research process.

Statistical analysis

The collected data were entered into and analyzed by SPSS-16 software (Inc., IBM., USA). For the descriptive analysis of the data, the mean and standard deviation of the intended time intervals were obtained and the frequency and ratio of the qualitative variables were calculated. As for inferential statistics, the Kruskal-Wallis, Mann-Whitney, and Spearman-Brown tests were used to examine the relationship between the variables and the different time intervals. The level of statistical significance was set at *P* values less than 0.05.

Results

Among the 60 patients with AIS referred to Shahid Beheshti Hospital of Kashan who received Alteplase during the researcher's intended period, 36 (60%) were males and 24 (40%) were females. Their mean age was 66.53 ± 14.81 (range: 24–101) years. Other demographic data are presented in Table 1.

Table 2 shows that ONT was 133.75 minutes, and the longest delay was related to the prehospital period (81.35 minutes), and in patients transferred by EMS ambulance, the longest delay was related to the time between ambulance arrival on site and arrival at the hospital (35.24 minutes).

Regarding the factors related to delay in arriving at the hospital and receiving Alteplase, the results showed that the effect of the variable of marital status on OTD was statistically significant, with OTD being significantly shorter in married patients compared to single ones.

Table 1: The frequency distribution of the demographic characteristics of the participants by group

Variable	Number (percentage)
Marital status	
Married	40 (66.7)
Single	3 (5)
Divorced and widowed	17 (28.3)
Education	
Illiterate	26 (43.3)
High school	22 (36.7)
Diploma	8 (13.3)
University	4 (5.17)
Occupation	
Employee and retiree	18 (30)
Self-employed	21 (35)
Housewife	21 (35)
Place of residence	
Kashan	36 (60)
The suburbs of Kashan	24 (40)
Nationality	
Iranian	56 (93.3)
Non-Iranian	4 (6.7)
Financial status (Based on the opinion of patients)	
Favorable	2 (3.3)
Average	7 (11.7)
Unfavorable	51 (85)

The effect of the variable of geographical location where the stroke had taken place on OTD was statistically significant in all the patients receiving the drug. The OTD of patients whose geographical location of stroke was in the city of Kashan was significantly shorter than the patients whose geographical location of stroke was in the suburbs of Kashan ($P < 0.05$) [Table 3]. Spearman's test did not show a significant relationship between the quantitative variables, including age and number of children, and the time of arrival at the hospital.

Regarding the inhospital delay of patients receiving Alteplase referred to Shahid Beheshti Hospital in Kashan during the study period, the results showed that the EMS pre-hospital notification (PHN) played an effective role in reducing the duration of inhospital delay ($P = 0.011$) [Table 4].

Discussion

This study aimed to evaluate the delay between the onset of symptoms and the administration of Alteplase in patients with ischemic stroke and its related factors. The findings showed that the mean ONT was 133 minutes, which is less than the 4.5 hours recommended by global guidelines.[16] This time interval was shorter in the study by Katsanos *et al*.(2020) compared to our results.[17] Liu *et al*.(2018), Ding *et al*.(2019), and Alkhotani *et al*.

Table 2: Frequency distribution of different time intervals between the onset of symptoms to receiving Altplase in participants

Time Intervals	Number	Minimum time (minute)	Maximum time (minute)	Mean±SD
All participants				
Onset-To-Door time (OTD)	60	27	165	81.35±33.76
Door-To-CT time (DTC)	60	2	92	16.12±17.46
CT-To-Needle Time (CTN)	60	4	230	36.73±29.84
Total time/Onset-To-Needle Time (ONT)	60	55	220	133.75±39.17
Transferred by EMS ambulances to the hospital				
Onset of symptoms to contacting EMS	51	4	124	34.24±31.80
Contacting EMS to ambulance arrival	51	2	24	10.45±4.73
Ambulance arrival to arriving at Shahid Beheshti Hospital	51	5	67	35.24±12.83
Onset-To-Door time (OTD)	51	40	165	80.67±32.01
Total time/Onset-To-Needle Time (or ONT)	51	70	220	129.51±36.38
People not taken directly to the hospital				
Onset-To- a non-hospital medical center	8	15	60	26.88±14.38
Duration of staying at a non-hospital medical center	8	20	90	40±23.90
Onset-To-Door time (OTD)	8	27	135	83.38±40.03
Transferred by vehicle other than EMS ambulances to the hospital				
Onset-To-Door time (OTD)	9	27	140	85.22±44.39

(2022) reported longer times.[14,15,18] Ding *et al*.(2019) stated the reason for the increased delay in receiving Alteplase as inter-hospital transfers.[15]

The results of the present study also showed that the mean ONT in people transferred by EMS was about 129 minutes. The highest prehospital delay in these patients was related to the time between the arrival of an EMS ambulance on site and arrival at the hospital. Numerically, however, this interval was close to the time from the onset of stroke symptoms to calling EMS. Limited studies have been conducted to investigate the time intervals associated with prehospital emergency services. Lee *et al*.(2021) conducted a study on all patients with AIS and estimated the time interval from the onset of the first abnormal symptom to calling EMS as very close to our study (34 minutes). They suggested that this time interval had become longer (48 minutes) during the COVID-19 pandemic.[19] Therefore, in addition to emphasizing public training programs to help identify the symptoms of acute stroke and the critical role of time for these patients, more focus should be placed on retraining programs for emergency medical technicians to increase the speed of action on site, because delays must be reduced as best as possible.

In this study, the mean OTD was about 81 minutes; in those transferred by EMS ambulance, it was about 80 minutes. Efforts to increase public awareness and improve life support by ambulance EMS technicians before arriving at the hospital can be effective in reducing delays in treating patients.[20]

Furthermore, the mean inhospital delay was 51 minutes, and the longest time spent in the hospital was the CT-To-Needle time, which are shorter than the Stroke Association guidelines.[16] The results obtained by Xian *et al*.(2017) were in line with our findings,[21] while Hassankhani *et al*.(2019) and Man *et al*.(2020) found longer times than those recommended in the guidelines [22,23] and Lee *et al*.(2021) obtained a shorter time (47 minutes).[19] Ghadimi *et al*.(2021) also reported a much shorter inhospital delay (17 minutes).[24] Nevertheless, the researchers acknowledged that the inhospital delay could be reduced to 20 minutes.[25] Although according to the results of the current study, inhospital delays are within acceptable limits, since rapid drug injection and reducing inhospital delays are associated with a reduction in mortality within a year,[23] hospital guidelines should focus on reducing inhospital delays to less than 20 minutes. The reason is that every minute of delay in treating patients with AIS is associated with a reduced chance of survival, increased risk of intracerebral hemorrhage, and worsening of the patients' activity and daily life conditions.[26] When the medical staff inside the hospital receive the patient's initial report, they should try to make arrangements in the hospital so that action can be taken more quickly after the patient arrives.[20] Not waiting for the test results (except in patients who have taken anticoagulants), injection of Alteplase in the CT scan ward and devising specific protocols for the rapid control of blood pressure can be effective in reducing inhospital delays.[27]

The results also showed that the mean DTC time (16 minutes) was shorter than the time recommended in similar studies. In these studies, the time interval from reaching the hospital to performing CT is recommended to be $\leq$ 25 minutes.[16,28] This finding can be due to the implementation of measures such as transferring patients

Table 3: Frequency distribution of Onset-To-Door Time related factors in participants

Variable		Number (percent)	Mean±SD	Test type and result
Gender	women	24 (40)	79.46±32.25	0.87*
	men	36 (60)	82.61±35.08	
Marital status	Married	40 (66.7)	76.45±34.88	0.013*
	single	20 (33.3)	91.15±29.74	
education	< Diploma	26 (43.3)	87.23±36.53	0.67**
	Diploma	30 (50)	77.90±32.35	
	University	4 (6.7)	69.00±22.82	
Occupation	Employee and retiree	18 (30)	79.06±35.67	0.95**
	Self-employed	21 (35)	82.00±33.69	
	Housewife	21 (35)	82.67±33.65	
Nationality	Iranian	56 (93.3)	81.5±33.53	0.83*
	Non-Iranian	4 (6.7)	79.25±41.97	
Financial status	Favorable	3 (3.3)	75.00±21.21	0.98
	Average	7 (11.7)	82.86±26.12	
	Unfavorable	51 (85)	81.39±35.35	
History of Underlying Diseases	No	6 (10)	79.67±3034	0.68**
	One didease	9 (15)	77.22±33.27	
	> One didease	45 (75)	82.40±34.85	
History of previous stroke	yes	13 (21.7)	79.92±28.81	0.88*
	no	47 (78.3)	81.74±35.25	
First action after the onset of the first worrying symptoms	Transfer to hospital	3 (5)	96.67±40.41	0.34**
	contacting to 115	46 (76.7)	77.26±31.05	
	Transfer to other medical centers	11 (18.3)	94.27±41.43	
The onset of symptoms over the weekend	yes	11 (18.3)	73.82±34.35	0.31*
	no	49 (81.7)	83.04±33.72	
Stroke location	home	56 (93.3)	82.43±34.48	0.33*
	outdoors	4 (6.7)	66.25±16.01	
Geographical location of stroke	Kashan	38 (63.3)	74.42±30.37	0.04*
	The suburbs of Kashan	22 (36.7)	93.32±36.53	
Being alone when a stroke occurs	yes	4 (6.7)	98.75±21.36	0.12*
	no	56 (93.3)	80.11±34.23	
Transfer by EMS	yes	51	80.67±32.01	0.94*
	no	9	85.22±44.39	

Variable	Mean±SD	Number (percent)	The correlation coefficient	Test type and result
Age (years)	66.53±14.81	60 (100)	-0.06	0.64***
Number of children	4.43±2.4	60 (100)	-0.15	0.24***

*Mann-Whitney *U*,** Kruskal–Wallis test, ***Spearman Correlation Coefficient

with EMS stretcher to the CT scan unit, performing CT scan without contrast injection, having a full-time AIS nurse on site, and sending PHN through the EMS system at Shahid Beheshti Hospital to reduce delays in treatment. Nevertheless, Qhadimi *et al*.(2021) reported a DTC time of 10.60 minutes.[24]

Although prehospital delays are not negligible, less recent and up-to-date studies have examined these delays in Alteplase-receiving patients, and most studies have only examined inhospital delays. The analyses of the factors related to prehospital delays have shown no significant relationships between underlying diseases or economic status and prehospital delays. Meanwhile, Nepal (2019) reported that history of diabetes and income below $1,000 lead to increased prehospital delays.[8] One of the reasons for these disparate results is that the insurance coverage system in Nepal is limited and transfer by EMS and seeking hospital care are costly, which have led Nepalese to use EMS less for patient transfer. In Iran, however, EMS transfer is free, and Alteplase is injected at lower costs in public hospitals.

Another study in Chicago reported a significant relationship between the variables of being female, older age, and race with prehospital delays.[29] Our data did not show a significant relationship between the mentioned variables. Wang *et al*.(2022) also stated in a study that there is no relationship between age and delay in treating patients with acute stroke.[30] Zhu *et al*. (2020) suggested that using EMS leads to faster patient transfer.[31] Revathi *et al*.(2023) also stated that the use of buses and taxis has significantly increased the delay in reaching the hospital.[32] The present study, however, found that patient transfer by EMS or other vehicles does not make a significant difference in prehospital delays.

Table 4: Frequency distribution of Door-To-Needle Time (DNT) related factors in participants

Categorized variables		Number (percent)	Mean±SD	Test type and result
Availability of altplas for infusion	Yes	58 (96.7)	49.76±24.27	0.06*
	No	2 (3.3)	96.00±50.91	
Inform ems to the hospital (sama code in triage)	Yes	44 (73.3)	44.93±19.74	0.011**
	No	7 (11.7)	64.00±43.07	
	No transferred by EMS	9 (15)	72.56±26.05	
Patient seizures at the time of admission	Yes	2 (3.3)	40.50±21.92	0.69*
	No	58 (96.7)	51.67±26.35	
Quantitative variables	**Mean±SD**	**Number (percent)**	**The correlation coefficient**	**Test type and result**
Systolic blood pressure at the time of admission	29.18±143.95	60 (100)	-0.11	0.93***
Systolic blood pressure at the time of Alteplase injection	22.21±143.88	60 (100)	-0.02	0.84***
Diastolic blood pressure at the time of Alteplase injection	12.31±86.30	60 (100)	-0.27	0.03***
Blood sugar level at the time of admission	77.08±160.10	60 (100)	-0.14	0.27***

*Mann-Whitney *U*, **Kruskal–Wallis test, ***Spearman Correlation Coefficient

One of the reasons for this finding could be the long time taken for emergency medical technicians to arrive on site in the present study.

Bahnasy *et al*.(2019) showed that variables such as living in rural areas and remote places are effective factors in prehospital delays,[33] as in line with the results of our study, because factors such as lack of ambulances, distance from the ambulance, and the distance to Shahid Beheshti Hospital (the only hospital that injects Alteplase in Kashan) from the surrounding villages lead to increased prehospital delays.

According to the present findings, PHN by the EMS center before the patients' arrival at the hospital was effective in reducing inhospital delays, which is in line with the results of some studies.[34-38] For example, Rostanski *et al*. (2017) admitted that PHN reduces inhospital delays by 10 minutes.[39] Based on the protocols provided by the American Heart Association, the EMS center sends out information to prepare the specialist, nurse, and CT scan ward.[16] Kashan hospitals also observe this protocol. After informing the hospital through the EMS center, the emergency supervisor will make the necessary arrangements with the neurology resident, AIS nurse, and the CT scan ward to reduce the waste of time.

The patients transferred to the hospital by EMS ambulance had a statistically significant shorter DTC time than those transferred by other vehicles. Tong (2018) also showed that patient transfer with the help of EMS reduces inhospital delays.[40] PHN by EMS and the preparedness of the CT Scan ward have helped achieve these outcomes.

In the present study, the patients' diastolic blood pressure at the time of injection of Alteplase showed a negative correlation with inhospital delays. Carrera (2019) also showed that people who had high blood pressure before taking Alteplase and used antihypertensive drugs had more inhospital delays than other patients; however, this difference was not statistically significant.[41] Mowla *et al*. (2017) also found that high blood pressure is a major factor contributing to inhospital delays.[42]

Limitations and recommendation

One of the limitations of this study was the incomplete report forms at the EMS center. Another limitation of the research is that some patients living in the suburbs of Kashan went to the medical center in Qom, which was beyond the control of the researchers It is suggested that managerial and supervisory solutions be considered to improve the conditions and eliminate the deficiencies in the treatment system, and on the other hand, a wider study should be done on this issue at the country level.

Conclusions

Due to the significant effect of time on the outcomes of Alteplase therapy as well as the irreversible effects of delay on the patient outcomes and the importance of each minute of time in the results of the treatment, efforts should be made to reduce the discussed time intervals, even if only by 1 minute. Although the different time intervals from the onset of symptoms to receiving the drug were generally less than the recommended standards in the present study, the time intervals from the onset of stroke symptoms to calling EMS, from the arrival of the ambulance on site to arrival at the hospital, and the time from CT scan to receiving Alteplase suffered the longest delays. These findings demonstrate the need to further work on these intervals through educational and research programs. Therefore, in prehospital and inhospital settings, educational and research programs should focus on promoting public awareness and also increasing the skills and speed of emergency medical technicians and nurses. Research on the duration of OTD after educating the public through the media is

suggested, with emphasis on communities such as schools, universities, barracks, and factories.

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Conflicts of interest

There are no conflicts of interest.

References

1. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: A systematic analysis for the global burden of disease study 2016. Lancet Neurol 2019;18:439-58.
2. Kottapally M, Josephson SA. Common neurologic emergencies for nonneurologists: When minutes count. Cleve Clin J Med 2016;83:116-26.
3. Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, *et al*. Ischaemic stroke. Nat Rev Dis Primers 2019;5:70.
4. Chen X, Shen Y, Huang C, Geng Y, Yu Y. Intravenous thrombolysis with 0.9 mg/kg alteplase for acute ischaemic stroke: A network meta-analysis of treatment delay. Postgrad Med J 2020;96:680-5.
5. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683-90.
6. Zhou Y, Yang T, Gong Y, Li W, Chen Y, Li J, *et al*. Pre-hospital delay after acute ischemic stroke in Central Urban China: Prevalence and risk factors. Mol Neurobiol 2017;54:3007-16.
7. Ajmi SC, Advani R, Fjetland L, Kurz KD, Lindner T, Qvindesland SA, *et al*. Reducing door-to-needle times in stroke thrombolysis to 13 min through protocol revision and simulation training: A quality improvement project in a Norwegian stroke centre. BMJ Qual Saf 2019;28:939-48.
8. Nepal G, Yadav JK, Basnet B, Shrestha TM, Kharel G, Ojha R. Status of prehospital delay and intravenous thrombolysis in the management of acute ischemic stroke in Nepal. BMC Neurol 2019;19:155.
9. Fladt J, Meier N, Thilemann S, Polymeris A, Traenka C, Seiffge DJ, *et al*. Reasons for prehospital delay in acute ischemic stroke. J Am Heart Assoc 2019;8:e013101.
10. Chai E, Li C, Jiang L. Factors affecting in-hospital delay of intravenous thrombolysis for acute ischemic stroke: A retrospective cohort study. Medicine (Baltimore) 2019;98:e15422.
11. Kamal N, Sheng S, Xian Y, Matsouaka R, Hill MD, Bhatt DL, *et al*. Delays in door-to-needle times and their impact on treatment time and outcomes in get with the guidelines-stroke. Stroke 2017;48:946-54.
12. Vidale S, Arnaboldi M, Bezzi G, Bono G, Grampa G, Guidotti M, *et al*. Reducing time delays in the management of ischemic stroke patients in Northern Italy. Int J Cardiol 2016;215:431-4.
13. Iglesias Mohedano AM, García Pastor A, Díaz Otero F, Vázquez Alen P, Vales Montero M, Luque Buzo E, *et al*. Efficacy of new measures saving time in acute stroke management: A quantified analysis. J Stroke Cerebrovasc Dis 2017;26:1817-23.
14. Alkhotani A, Alharbi Y, Alghamdi H, Alshareef H, Abdulmuttalib JA, Alsulami A, *et al*. Time window for acute stroke treatment: Current practice in King Abdullah Medical City Specialist Hospital in Makkah, Saudi Arabia. Cureus 2022;14:e28878.
15. Ding Y, Ji Z, Ma L, Zhai T, Gu Z, Niu J, *et al*. Interhospital transfer on intravenous thrombolysis in patients with acute ischemic stroke in three Chinese municipal stroke centers. J Thromb Thrombolysis 2019;48:580-6.
16. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 Update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-418.
17. Katsanos AH, de Sa Boasquevisque D, Al-Qarni MA, Shawawrah M, McNicoll-Whiteman R, Gould L, *et al*. In-Hospital delays for acute stroke treatment delivery during the COVID-19 pandemic. Can J Neurol Sci 2021;48:59-65.
18. Liu Z, Zhao Y, Liu D, Guo ZN, Jin H, Sun X, *et al*. Effects of nursing quality improvement on thrombolytic therapy for acute ischemic stroke. Front Neurol 2018;9:1025.
19. Lee SH, Mun YH, Ryoo HW, Jin SC, Kim JH, Ahn JY, *et al*. Delays in the management of patients with acute ischemic stroke during the COVID-19 outbreak period: A multicenter study in Daegu, Korea. Emerg Med Int 2021;2021. https://doi.org/10.1155/2021/6687765.
20. Toyoda K, Koga M, Iguchi Y, Itabashi R, Inoue M, Okada Y, *et al*. Guidelines for intravenous thrombolysis (Recombinant tissue-type plasminogen activator), the third edition, March 2019: A guideline from the Japan stroke society. Neurol Med Chir (Tokyo) 2019;59:449-91.
21. Xian Y, Xu H, Lytle B, Blevins J, Peterson ED, Hernandez AF, *et al*. Use of strategies to improve door-to-needle times with tissue-type plasminogen activator in acute ischemic stroke in clinical practice: Findings from target: Stroke. Circ Cardiovasc Qual Outcomes 2017;10:e003227.
22. Hassankhani H, Soheili A, Vahdati SS, Mozaffari FA, Fraser JF, Gilani N. Treatment delays for patients with acute ischemic stroke in an Iranian emergency department: A retrospective chart review. Ann Emerg Med 2019;73:118-29.
23. Man S, Xian Y, Holmes DN, Matsouaka RA, Saver JL, Smith EE, *et al*. Association between thrombolytic door-to-needle time and 1-year mortality and readmission in patients with acute ischemic stroke. JAMA 2020;323:2170-84.
24. Ghadimi N, Hanifi N, Dinmohammadi M. Factors Affecting Pre-Hospital and In-Hospital Delays in Treatment of Ischemic Stroke; a Prospective Cohort Study. Arch Acad Emerg Med 2021;9:e52.
25. Mikulik R, Bar M, Cernik D, Herzig R, Jura R, Jurak L, *et al*. Stroke 20 20: Implementation goals for intravenous thrombolysis. Eur Stroke J 2021;6:151-9.
26. Darehed D, Blom M, Glader E-L, Niklasson J, Norrving B, Eriksson M. In-hospital delays in stroke thrombolysis: Every minute counts. Stroke 2020;51:2536-9.
27. Tran D, Zhu Z, Shafie M, Abcede H, Stradling D, Yu W. Three easily-implementable changes reduce median door-to-needle time for intravenous thrombolysis by 23 minutes. BMC neurology 2019;19:300.
28. Polineni SP, Perez EJ, Wang K, Gutierrez CM, Walker J, Foster D, *et al*. Sex and Race-Ethnic Disparities in Door-to-CT Time in Acute Ischemic Stroke: The Florida Stroke Registry. Journal of the American Heart Association 2021;10(2047-9980 (Electronic)):e017543.

29. Potisopha W, Vuckovic KM, DeVon HA, Park CG, Hershberger PE. Sex Differences in Prehospital Delay in Patients With Acute Stroke: A Systematic Review. The Journal of cardiovascular nursing 2020;35:E77-e88.
30. Wang HY, Gu HQ, Zhou Q, Jiang YY, Yang X, Wang CJ, *et al*. Thrombolysis, time-to-treatment and in-hospital outcomes among young adults with ischaemic stroke in China: findings from a nationwide registry study in China. BMJ open. 2022;12(6):e055055.
31. Zhu Y, Zhang X, You S, Cao X, Wang X, Gong W, *et al*. Factors Associated with Pre-Hospital Delay and Intravenous Thrombolysis in China. Journal of stroke and cerebrovascular diseases: The official journal of National Stroke Association. 2020;29:104897.
32. Revathi S, Kavitha MS, Shankar V. Factors Associated with Prehospital Delay in Patients with Acute Stroke in South India. Indian journal of community medicine: Official publication of Indian Association of Preventive & Social Medicine 2023;48:82-90.
33. Bahnasy WS, Ragab OAA, Elhassanien ME. Stroke onset to needle delay: Where these golden hours are lost? An Egyptian center experience. Eneurologicalsci 2019;14:68-71.
34. Leung WCY, Teo KC, Kwok WM, Lam LHC, Choi OMY, Tse MMY, *et al*. Pre-hospital stroke screening and notification of patients with reperfusion-eligible acute ischaemic stroke using modified Face Arm Speech Time test. Hong Kong medical journal = Xianggang yi xue za zhi. 2020;26:479-85.
35. Sangari A, Akhoundzadeh K, Vahedian M, Sharifipour E. Effect of pre-hospital notification on delays and neurological outcomes in acute ischemic stroke. Australasian emergency care 2022;25:172-5.
36. Siarkowski M, Lin K, Li SS, Al Sultan A, Ganshorn H, Kamal N, *et al*. Meta-analysis of interventions to reduce door to needle times in acute ischaemic stroke patients. BMJ open quality 2020;9.
37. Acar BA. Impact of emergency room meetings on improvement of door-to-needle times in acute ischemic stroke patients: A single center's experience. Northern clinics of Istanbul 2018;5:282-7.
38. Verma A, Jaiswal S. Bringing Down the Door-to-needle Time: Patient Thrombolysed in 6 Minutes-A Case Report. Perm J 2021;25:20.239.
39. Rostanski SK, Shahn Z, Elkind MS, Liberman AL, Marshall RS, Stillman JI, *et al*. Door-to-needle delays in minor stroke: a causal inference approach. Stroke 2017;48:1980-2.
40. Tong X, Wiltz JL, George MG, Odom EC, Coleman King SM, Chang T, *et al*. A Decade of Improvement in Door-to-Needle Time Among Acute Ischemic Stroke Patients, 2008 to 2017. Circulation Cardiovascular quality and outcomes. 2018;11:e004981.
41. Carrera JF, Sorace BJ, Worrall BB, Southerland AM, Chiota-McCollum NA. Delay to Tissue Plasminogen Activator in Hypertensive Stroke Patients: An Analysis of Delay Duration Across Agents. Journal of stroke and cerebrovascular diseases: The official journal of National Stroke Association. 2020;29:104525.
42. Mowla A, Doyle J, Lail NS, Rajabzadeh-Oghaz H, Deline C, Shirani P, *et al*. Delays in door-to-needle time for acute ischemic stroke in the emergency department: A comprehensive stroke center experience. J Neurol Sci. 2017;376:102-5.