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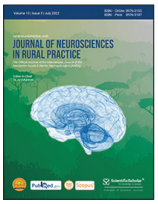

Original Article

Assessment of onset-to-door time in acute ischemic stroke and factors associated with delay at a tertiary care center in South India

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ABSTRACT

Objectives: Intravenous thrombolysis is an effective treatment of acute ischemic stroke but has a narrow therapeutic time window of 3–4.5 h. Pre-hospital delay is a major barrier to patients becoming eligible for thrombolysis. This single-center study assessed the factors causing longer onset-to-door (OTD) time to identify measures that will help decrease the delay.

Materials and Methods: Patients with acute ischemic stroke presenting to the emergency department from August to October 2022 were included in the study. The data were collected using a structured questionnaire and was completed by interviewing the patient or the caregivers. Patients were classified as early and late arrivers with the cutoff being 3.5 h. We then analyzed the relationship between early arrival and demographic factors, clinical factors, patient response factors, and logistic factors.

Results: Our study consisted of 153 patients. The average OTD time was 674.33 ± 812.713 min (median: 300; interquartile range: 151–885). The pre-hospital delay was present in 66% of patients. 16.9% of patients came beyond 24 h. In the multivariate analysis, the odds of early arrival were higher among patients who perceived their symptoms as serious (odds ratio [OR]: 18.801; confidence interval [CI]: 3.728–94.803) and lower among patients who experienced a delay in reaching due to traffic (OR: 0.085; CI: 0.008–0.873). Lack of knowledge about stroke centers among both patients and health professionals also contributed to longer OTD times. Out of 52 early arrivers, 24 received thrombolytic therapy after excluding wake-up strokes and contraindications.

Conclusion: Pre-hospital delay continues to stand in the way of patients receiving thrombolysis. Comprehensive stroke education, increasing awareness regarding stroke centers, and promoting ambulance services are some of the interventions which could help tackle the issue.

Keywords: Onset-to-door time, Pre-hospital delay, Ischemic stroke

INTRODUCTION

In 2019, stroke was the second leading cause of death (11.6% of total deaths) and the third leading cause of the disability-adjusted life years (5.7% of total DALYs) globally.[1] The number of incident stroke cases in India in 2019 was 1.29 million, and the number of deaths was 699000. It was the largest contributor to the total neurological disorder DALYs (37.9%).[2]

The National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rtPA) trial showed that patients who received alteplase were 30% more likely to have better outcomes at 3 months on assessment scales (global odds ratio for a favorable outcome was 1.7; 95% confidence interval [CI]: 1.2–1.6).[3] The Third International Stroke Trial-3 demonstrated that treatment with intravenous tPA within 1.5 h of last-seen-well was associated with a favorable outcome at 3 months compared with placebo with an odds ratio of 2.81 (95% CI, 1.75–4.50).[4]

Most studies in the published literature have focused on factors affecting door-to-needle time and on devising strategies to decrease it. However, patients with acute ischemic stroke do not even reach the hospital within the window period and, hence, miss the opportunity of becoming eligible for thrombolysis. Hence, the time taken from symptom onset to arrival at the hospital is an important area for intervention.

Hence, we initiated this single-center study to assess the time taken from the onset of symptoms to arrival at the emergency department and look into the factors causing the pre-hospital delay.

MATERIALS AND METHODS

Study design and period

This cross-sectional study was carried out from August 05, 2022, to October 05, 2022. Data collection was done

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prospectively. The data were collected specifically for this study.

Setting

This study was conducted in the department of medicine and the department of neurology of a tertiary care hospital in Kerala.

Selection criteria

All consecutive patients presenting with symptoms of acute ischemic stroke in the emergency department, irrespective of treatment received, were included in the study.

Exclusion criteria

Stroke mimics, hemorrhagic and venous infarcts, and those unwilling to provide consent were excluded

Data collection

Data from a tertiary care center located in Kerala were collected.

The hospital offers round-the-clock thrombolytic therapy for acute ischemic stroke.

Data from consecutive stroke patients were prospectively collected using a structured questionnaire. The patient or caregiver was interviewed in the local language Malayalam.

The questionnaire had questions addressing demographic details, including age and sex. Information about the time of onset of symptoms, day of onset, presenting symptoms, and risk factors with details regarding the mode of transport used by the patient to the hospital was collected. Whether they visited a local hospital before coming to our center was noted. The presence of previous stroke history and family history of stroke were inquired into. Distance from the hospital was categorized into those staying within 40 km or those staying beyond considering it takes about an hour to cover 40 km on Indian roads. The National Institutes of Health Stroke Scale (NIHSS) score was used to document stroke severity. The circulation of the brain, anterior or posterior which was predominantly affected, was noted. Knowledge about stroke, thrombolysis, and stroke helpline number (a dedicated pre-notification number for stroke) was assessed. Whether patients took their symptoms seriously or not was also asked for and recorded. The time of arrival at the hospital was obtained from the casualty out-patient ticket, and the onset-to-door (OTD) time was calculated.

Patients coming within 3.5 h were classified as early arrivers, and the rest as late arrivers considering the NINDS recommended door-to-needle time of 60 min.[5]

Statistical analysis

The entire statistical analysis was done using the Statistical Package for the Social Sciences (SPSS version 29.0, IBM Corp., Armonk, NY, USA) for MS Windows. The association between the quantitative and qualitative variables was assessed using the Mann–Whitney U test and Kruskal-Wallis test where appropriate. The association between two quantitative variables was assessed using the Chi-square test. Binary logistic regression was done to model the independent predictors of pre-hospital delay. $P < 0.05$ was considered statistically significant.

Ethical considerations

Clearance was obtained from the Institutional Ethics Committee of the hospital. Informed consent was obtained from all the participants in the study. Privacy and confidentiality of data were maintained.

OBSERVATIONS AND RESULTS

The study consisted of 153 participants who presented with acute ischemic stroke to the emergency department of the tertiary care hospital; of which 90 were male (58.8%) and 63 were female (41.2%). The mean age was 62.88 ± 13.59 years (median-64 years).

Demographic and clinical profile of patients

Demographic and clinical data of the study population are summarized in Table1. The mean OTD time was 674.33 ± 812.713 min (median: 300; interquartile range: 151–885). Out of 153, 101 (66.0%) patients were late arrivers and came after 3.5 h [Figure 1]. 15.7% of patients received thrombolysis. Other salient data is represented pictorially in Figures 2-9.

Univariate analysis

Demographic, clinical variables, patient factors, and logistic factors were compared between the group of early

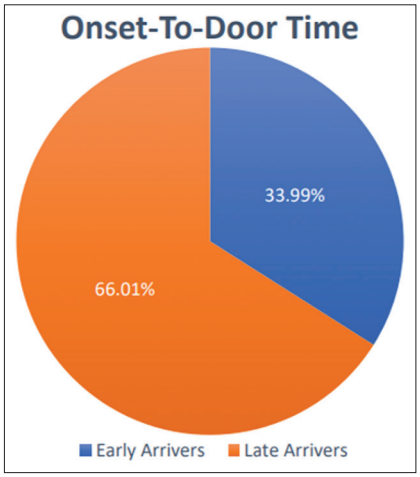

Figure 1: Proportion of patients arriving within 3.5 h.

Table 1: Demographic and clinical variables of the study participants.

Age	62.88±13.59[a]
≤45 years	17 (11.1)[b]
>45 years	136 (88.9)[b]
Gender	
Male	90 (58.8)[b]
Female	63 (41.2)[b]
Distance from onset to hospital	34.84±25.8[a]
≤40 km	100 (65.4)[b]
>40 km	53 (34.6)[b]
NIHSS	
≤15	110 (71.9)[b]
>15	43 (28.1)[b]
Marital status	
Married	143 (93.5)[b]
Single	10 (6.5)[b]
Financial status	
High SES	26 (17.0)[b]
Middle SES	17 (11.1)[b]
Low SES	110 (71.9)[b]
Place of stroke onset	
Home	129 (84.3)[b]
Office/Workplace	10 (6.5)[b]
Road	9 (5.9)[b]
Out-patient setting	4 (2.6)[b]
Chronic health-care facility	1 (0.7)[b]
Education	
≤12th grade	142 (92.8)[b]
>12th grade	11 (7.2)[b]
Mode of living	
Alone	14 (9.2)[b]
Family	137 (89.5)[b]
Friends	2 (1.3)[b]
Place of residence	
Rural	86 (56.2)[b]
Urban	67 (43.8)
Visit to a local hospital	
Yes	127 (83.0)[b]
No	26 (17.0)[b]
Time of onset	
Day	119 (77.8)[b]
Night	34 (22.2)[b]
Day of onset	
Weekday	143 (95.4)[b]
Weekend	10 (6.5)[b]
Onset-to-door time	674.33±812.713[a]
Early arrivers	52 (34.0)[b]
Late arrivers	101 (66.0)[b]
Previous history of stroke	
Present	28 (18.3)[b]
Absent	125 (81.7)[b]
Family history of stroke	
Present	25 (16.3)[b]
Absent	128 (83.7)[b]
Stroke territory	
Anterior	132 (86.3)[b]
Posterior	21 (13.7)[b]
Bystander at onset	
Family member	105 (68.6)[b]
Friend	8 (5.2)[b]
Colleague	6 (3.9)[b]
Stranger	6 (3.9)[b]
Alone	25 (16.4)[b]
Health professional	2 (2.0)[b]
Recognition of stroke	
Yes	39 (25.5)[b]
No	114 (74.5)[b]
Perceived symptoms as serious	
Yes	109 (71.2)[b]
No	44 (28.8)[b]
Knowledge about thrombolysis	
Yes	6 (3.9)[b]
No	147 (96.1)[b]
Mode of transport	
Ambulance	101 (66.0)[b]
Auto	26 (17.0)[b]
Own	24 (15.7)[b]
Vehicle taxi	2 (1.3)[b]

[a]Mean±Standard Deviation; [b]*n* (%). NIHSS: National Institutes of Health Stroke Scale, SES: Socioeconomic status

arrivers and late arrivers. These data are summarized in Table 2.

Multivariate analysis

Binary logistic regression was done to model the determinants of an early arrival (OTD time <3.5 h). The results of the multivariate analysis are summarized in Table 3.

DISCUSSION

Our study population had a median OTD time of 5 h. There seems to be an improvement in pre-hospital delay compared to the 2012 study conducted in Calicut, Kerala, where the median OTD time was 12 h.[6] The shorter delay may have been made possible by increased availability and use of ambulance services. 66% of our patients used emergency medical services (EMS) compared to 29% in the previous study. The OTD time of 5 h is also lesser than that recorded in the study conducted in Coimbatore in the neighboring state of Tamil Nadu with a median delay of 9.5 h.[7] However, 66% of the patients still arrived after 3.5 h. Among this, 17% of patients presented to the emergency department after 24 h. This is high compared to Western countries where 50–70%

Table 2: Comparison of variables between early arrivers and late arrivers.

Variable	Early arrivers (*n*=52)	Late arrivers (*n*=101)	*P*-value
Age			0.904
≤45 years	6	11	
>45 years	46	90	
Gender	36	54	0.061
Male			
Female	16	47	
Distance from onset to hospital			0.012
≤40 km	41	59	
>40 km	11	42	
Marital status			0.309
Married	47	96	
Single	5	5	
Financial status			0.988
High SES	9	17	
Middle SES	6	11	
Low SES	37	73	
Education			0.511
≤12th grade	47	95	
>12th grade	5	6	
Mode of living			0.068
Alone	3	11	
Family	47	90	
Friends	2	0	
Place of residence			0.032
Rural	23	63	
Urban	29	38	
Place of stroke onset			0.048
Home	38	91	
Office/Workplace	7	3	
Road	4	5	
Out-patient setting	2	2	
Chronic health-care facility	1	0	
Time of onset			0.855
Day	40	79	
Night	12	22	
Day of onset			0.496
Weekday	50	9	
Weekend	2	38	
Bystander at onset			0.038
Family member	33	72	
Friend	4	4	
Colleague	5	1	
Stranger	3	3	
Alone	5	20	
Health professional	2	1	
Bystander's response			<0.001
Serious	47	57	
Dismissive	0	24	
Stroke territory			0.120
Anterior	48	84	
Posterior	4	17	
Previous history of stroke			0.267
Present	7	21	
Absent	45	80	
Family history of stroke			0.816
Present	9	16	
Absent	43	86	

(Contd...)

Table 2: *(Continued)*

Variable	Early arrivers (*n*=52)	Late arrivers (*n*=101)	*P*-value
Visit to a local hospital			<0.001
Yes	33	94	
No	19	7	
Stroke diagnosed at a local hospital			<0.001
Yes	33	69	
No	0	25	
Number of institutions visited			<0.001
0	19	7	
1	32	57	
2	1	29	
3	0	8	
Recognition of stroke			0.770
Yes	14	25	
No	38	76	
Perceived symptoms as serious			<0.001
Yes	49	60	
No	3	41	
Knowledge about thrombolysis			1.000
Yes	2	4	
No	50	97	
Mode of transport			0.064
Ambulance	41	60	
Auto	5	21	
Own vehicle	6	18	
Taxi	0	2	
Delay in getting the ambulance			0.039
Yes	0	7	
No	41	53	
Delay due to traffic			0.013
Yes	1	15	
No	51	86	
Presenting symptoms			
Hemiparesis	44	73	0.088
Facial deviation	27	49	0.690
Speech disturbances	30	71	0.119
Loss of consciousness	12	13	0.106
Vertigo	6	17	0.386
Headache	7	20	0.330
Gait disturbances	5	17	0.228
Seizures	3	5	0.829
Vomiting	7	17	0.587
Blurring of vision	2	6	0.717
Risk factors			
AF	1	4	0.662
Valvular heart disease	1	5	0.664
Hypertension	34	66	0.996
CAD	15	15	0.039
Dyslipidemia	17	24	0.237
Diabetes mellitus	23	46	0.877
Smoking	10	37	0.027
NIHSS			0.005
≤15	30	80	
>15	22	21	

SES: Socioeconomic status, AF: Atrial fibrillation, CAD: Coronary artery disease, NIHSS: National Institutes of Health Stroke Scale

Table 3: Binary logistic regression model for the determinants of early arrival.

Predictor variables	β estimate	Standard error	*P*-value	Odds ratio	95% Confidence interval for EXP (B)
Onset to hospital distance	1.033	0.615	0.093	2.810	(0.841, 9.388)
NIHSS score	−0.457	0.627	0.466	0.633	(0.185, 2.163)
Place of residence	−0.019	0.560	0.973	0.981	(0.328, 2.938)
Place of stroke onset	1.489	1.309	0.255	4.434	(0.341, 57.718)
Bystander at onset	−2.558	2.619	0.329	0.077	(0.000, 13.129)
Perception of symptoms as serious	2.934	0.825	<0.001	18.801	(3.728, 94.803)
Delay in reaching due to traffic	−2.470	1.191	0.038	0.085	(0.008, 0.873)
CAD	−0.818	0.670	0.222	0.441	(0.119, 1.639)
Smoking	1.073	0.685	0.117	2.925	(0.765, 11.192)

CAD: Coronary artery disease, NIHSS: National Institutes of Health Stroke Scale

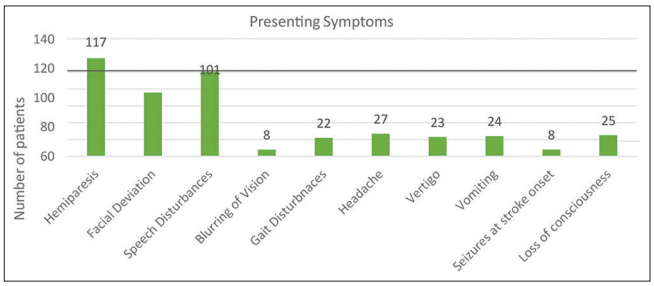

Figure 2: Symptoms of patients.

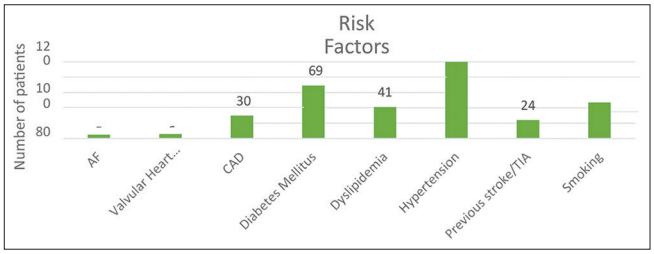

Figure 3: Risk factors for acute ischemic stroke in patients. AF: Atrial fibrillation, CAD: Coronary artery disease, TIA: Transient ischemic attack

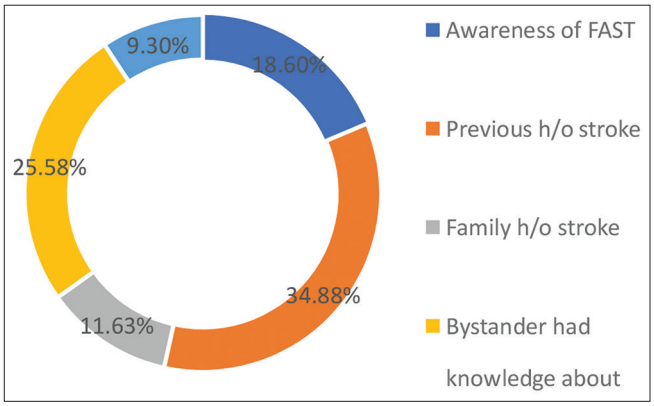

Figure 4: Sources of stroke knowledge.

of patients arrive within 3 h, and the median OTD time is 1–2.5 h.[8-11]

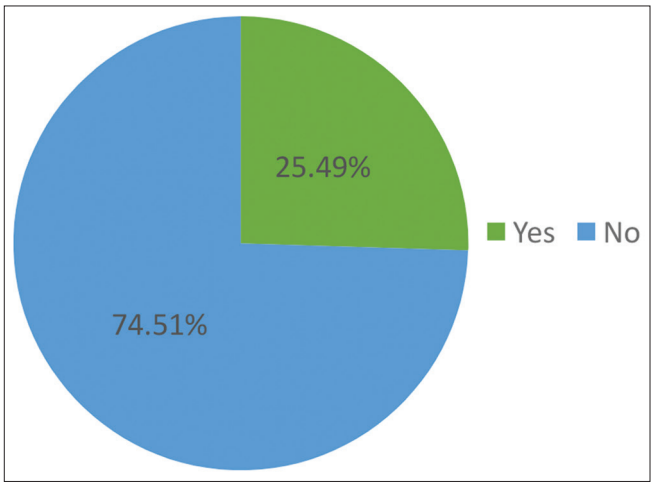

Figure 5: Proportion of patients who recognized stroke.

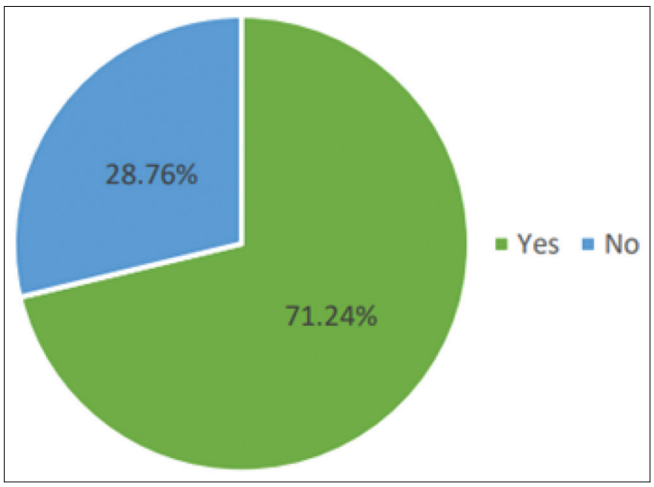

Figure 6: Proportion of patients who perceived symptoms as serious.

The most significant factors associated with pre-hospital delay in the multivariate analysis were the perception of symptoms as serious and delay in reaching due to traffic.

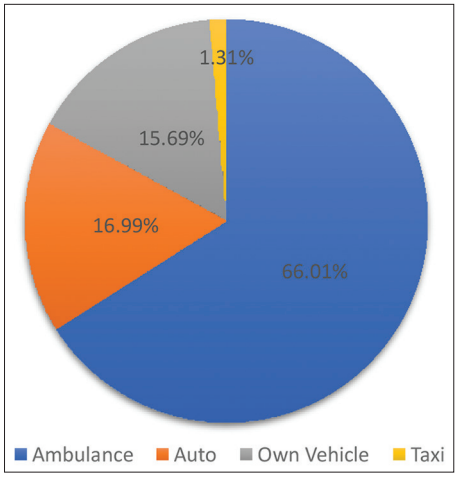

Figure 7: Mode of transport.

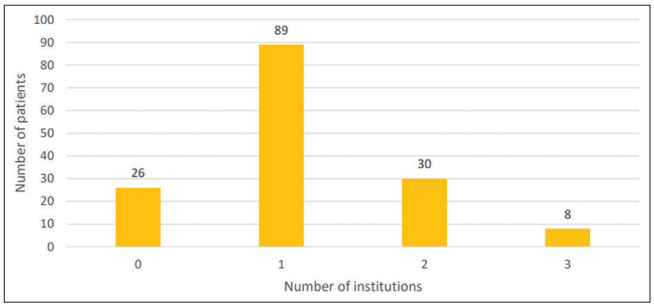

Figure 8: Number of institutions visited.

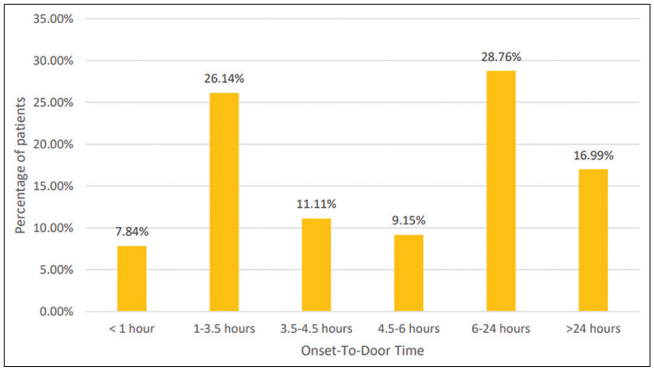

Figure 9: Division of onset-to-door time.

Failure to recognize stroke was associated with delay in many previous studies.[8,12] We found that 25.5% of patients recognized stroke, which is low compared to 70–75% in developed countries and another study in North Kerala.[7] Only 8 had knowledge about the warning symptoms of a stroke.

However, 71.2% of the study participants felt that their symptoms were serious, and this was a significant factor in early arrival.

A higher NIHSS score was seen to be associated with early arrival. This is due to an increased sense of urgency as evidenced by the fact that 80% of patients with the NIHSS scores >15 felt their symptoms were serious.

Only 3.9% of patients had knowledge about thrombolysis, which is lower than 18% in the Coimbatore study and Western countries.[8-11] None of the participants knew about the stroke helpline number, even among those who have had a stroke before, and this points to an underwhelming effort at stroke education. A study from Iran showed that the median OTD time was 2 h when the stroke helpline number was called.[13] Prenotification to the stroke team in the hospital was also associated with reduced in-hospital delay in previous studies.[12,14,15] A 11% decrease in door-to-needle time was documented when prenotification was implemented.[15]

A major cause of late arrival in the univariate analysis was a visit to a local hospital. This was documented in many previous studies as well.[7,8] Only 17% of general practitioners are aware of the window period of thrombolysis according to a study from Tamil Nadu.[15] There is also a lack of knowledge about stroke-ready hospitals among both patients and doctors. 5.2% of patients visited 3 institutions. This highlights the importance of increasing awareness about stroke centers in the state.

Stroke was not diagnosed in 19.7% of patients visiting a local hospital. This points to a need to increase awareness about the symptoms of stroke, especially posterior circulation stroke.

Those living in rural areas were found to arrive late in our study. This was seen in other studies as well.[7] Patients from rural areas were seen to have lesser urgency about their symptoms compared to urban areas. 60.6% of patients who visited a local hospital also belonged to rural areas. This signifies a need to pay special attention to rural areas with respect to stroke education. The presence of risk factors did not seem to decrease pre-hospital delay, which signifies a need to educate this high-risk population.

However, we found that neither previous history of stroke nor a family history led to early arrival, which was also seen in the other studies.[16] This suggests a disconnection between knowledge and action. Zock *et al.* found that recognition of stroke was not followed immediately by help-seeking behaviors. Personal experiences of spontaneous improvement were one reason for the wait-and-see strategy. This study also showed that most participants were not interested in stroke education unless they had a stroke themselves.[17] Another study also found that 59% of patients waited for symptoms to resolve spontaneously.[18]

Ambulance services were utilized by 66% of the population, which is greater than that reported in the 2012 Calicut study and is comparable to Western countries with a utilization rate of 60–70%.[6,7,9-11]

The use of EMSs has been well-documented to increase the odds of early arrival in previous studies.[9-11] Although we

observed a decreased OTD time in patients using ambulance services compared to those using auto, it did not produce a significant difference in arrival within 3.5 h. This is probably because most patients coming by auto live nearer to the hospital, and those living far away, use auto to visit a local hospital before finally reaching by ambulance.

However, decreased OTD time in patients using ambulance services (median 4 h) is significant since previous studies have shown that there are improved functional outcomes with early arrival irrespective of reperfusion therapy.[19] Delay in reaching due to traffic was also significantly associated with using auto as the mode of transport.

A previous study had observed that older age and female sex were associated with a shorter OTD; however, we found no correlation.[7] The presence of hemiparesis also led to shorter OTD due to the increased sense of urgency. Patients with coronary artery disease were found to arrive early, which seems to be due to the increased awareness about cardiac disease in this group.

Unlike in Western countries where living alone was an important factor leading to pre-hospital delay, the mode of living did not seem to influence OTD in our study.[11] However, being alone at the onset was found to be associated with decreased urgency and late arrival.

Stroke onset at one's office or workplace was found to be associated with early arrival. This is probably due to the presence of one's colleague as the bystander. Family members were seen to be more dismissive of patients' symptoms. However, in a study conducted in Nepal, onset at home was found to lead to early arrival.[20]

In our study, education more than 12th grade was associated with greater recognition of stroke; however, this did not equate to early arrival.

Similar causes for pre-hospital delay were found in other studies conducted in India.[6,7] This calls for a comprehensive stroke education campaign to improve patients' opportunities to avail of definitive treatment, including thrombolytic therapy and mechanical thrombectomy.

CONCLUSION

Our study highlights that onset to door time delay continues to be a major hindrance to ischemic stroke patients receiving thrombolysis. Awareness campaigns focusing on thrombolysis and stroke centers among general public and primary care physicians along with improvement in ambulance services are essential to address this lacuna in stroke care in India.

Limitations

The short duration and relatively small sample size are limitations of our study.

Ethical approval

Clearance was obtained from the Institutional Ethics Committee of the hospital.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent.

Financial support and sponsorship

The project was done as part of ICMR's short-term studentship program.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation:

The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using the AI.

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