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Original Article

Pre-Hospital Delaying Factors in Patients of Acute Ischemic Stroke who are Candidates for Thrombolytic Therapy

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ABSTRACT

***Objective*:** To identify and statistically evaluate pre-hospital delaying factors for thrombolysis in Acute Ischemic Stroke (AIS).
***Study Design*:** Cross-sectional study.
***Place And Duration OF Study*:** Emergency/Neurology Department, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Dec 2020 to Mar 2021.
***Methodology*:** Patients older than 18 years and who reported to the emergency/Neurology clinic with stroke symptoms were included in the study. The patients or their relatives were interviewed with a detailed questionnaire that recorded patients' National Institute of Health Stroke Scale and other socio-demographic variables. In addition, the patients were grouped based on time of arrival to the hospital: Early (<4.5 hours) and Late (>4.5 hours), and the variables recorded were compared with each other.
***Results*:** Of 98 patients, 71(72.5%) arrived early, and 27(27.5%) arrived late. Seventy patients (72%) were male, and 28(28%) were female. Only 18 patients availed of the ambulance service, whereas the rest of the study participants reached the hospital using private transportation.
***Conclusion*:** Female gender, NIHSS score of 10 or below and using transport other than ambulance adversely affect the hospital arrival time of acute ischemic stroke patients.

Keywords: Acute Ischemic Stroke (AIS), Intravenous thrombolytic therapy (IVT), National Institute of Health Stroke Scale (NIHSS), Pre-hospital delay.

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INTRODUCTION

Stroke is among the leading causes of mortality and long-term disability worldwide. Acute Ischemic Stroke (AIS) is the most common type among all types of strokes, accounting for about 80% of the total incidence of strokes. Studies have shown that the initial 4.5 hours after the onset of symptoms are crucial for the patient as this is when Intravenous Thrombolysis (IVT) has proved to be an effective therapy.[1-3] Hence, emergency clinicians have to be mindful of the time of administration of the thrombolytic therapy after initiation of symptoms as it is an important factor for a good clinical outcome for patients of acute ischemic stroke.[4,5]

Despite thrombolytic therapy being approved by the FDA for patients of acute ischemic stroke, the population of AIS patients who avail of this treatment option is very low6. Studies have shown that patients who benefit from the therapy are the ones who get thrombolytic administered within a narrow "therapeutic window" that is limited to 3-4 hours only; hence, to get successfully treated by thrombolysis, the patient must reach an emergency facility of the hospital within 3 hours of the onset of stroke symptoms.[7,8] Due to the delay in arrival at the hospital after the onset of stroke, the number of patients treated with thrombolytic therapy is very low. Studies have shown that delay in reaching the hospital in time is one of the reasons for mortality and lifelong physical disability in most patients.[9,10] Delays may also be caused after reaching the hospital, where the health care professional may fail to recognise the symptoms of stroke in a patient. In this study, we aimed to investigate the factors causing a pre-hospital delay in acute ischemic stroke patients.

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METHODOLOGY

The cross-sectional study was conducted at Pak Emirates Military Hospital, Rawalpindi, from 16th December 2020 to 26th March 2021. A sample size of 98 patients was calculated with taking an expected percentage of acute ischemic stroke patients who arrived later than 4.5 hours as 42%.[9]

Inclusion Criteria: This study included patients older than 18 years who presented to the Emergency

Department and the Outpatient Clinic of Neurology Department within 24 hours with symptoms compatible with acute ischemic stroke.

Exclusion Criteria: Patients who have had recurrent strokes, strokes with intracerebral haemorrhage and strokes after arriving at the hospital (in-hospital stroke) were excluded from the study.

In this study, the investigator selected a sample based on subjective judgement rather than selecting participants randomly. Since the clinicians and investigators had to rely on their judgement to choose among the patients to participate in this study (survey and questionnaire), the sampling technique used in the study was a non-probability purposive sampling technique. On arrival of the patients, the onset of stroke was recorded as the time of appearance of symptoms of a stroke. For patients who arrived at the hospital in an unconscious state, the time when they were last seen awake was recorded as the time of onset of stroke, and for patients who woke up with symptoms, the time of onset was taken as the time at which the patient went to sleep. The information about the onset of stroke symptoms was collected via an in-person interview that was requested to be taken by the patient's relative if they consented to participate in the study. The interview contained a detailed questionnaire regarding stroke risk factors, patient demographics and initiation of symptoms. The relatives were also asked if the arrival to this tertiary care setup was direct or from another hospital. If it was indirect, the name of the previous hospital and duration of stay was recorded. The patient's relatives were also inquired if the patient had been administered thrombolytic therapy in the previous hospital. Means of transportation the study participant took to reach the hospital were also recorded (by ambulance or other private vehicles). The distance of the route taken was determined using regional road maps.

Non-contrast computed tomography (CT) was used to distinguish between ischemic vs. hemorrhagic stroke. Clinical diagnosis in the emergency department was made based on the National Institute of Health Stroke Scale (NIHSS), whereby stroke symptoms, time of arrival to the hospital, gender, age, level of education and socioeconomic status of the patient were determined. For study purposes, we classified NIHSS into two major categories,> ten and <10. Patients with >10 were classified as severe cases.

Time of onset of stroke was divided into two groups within a day: A Morning interval reporting between 07:00-19:00 and a Night interval reporting between 19:00-07:00. At the time of discharge, neurological deficits were assessed for each study participant by using a Modified Rankin Scale (mRS) score. Based on this score, the participants were further classified as having good functional outcomes (mRS <2) or bad functional outcomes (mRS >2). In addition, the level of the patient's education was also recorded.

Similarly, patients were also classified based on income/socioeconomic status and were grouped as either low, medium or high income as perceived by the patient himself/herself. Based on arrival at the hospital, the study participants were classified as early arrival (<4.5 hours) and late arrival (> 4.5 hours). Based on this grouping, factors that affected the time of arrival at the hospital were evaluated and compared statistically.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Independent sample t-test was applied to explore the inferential statistics. Chi-square test was applied to explore the inferential statistics.The p-value lower than or up to 0.05 was considered as significant.

RESULTS

The study included 98 patients who fulfilled the inclusion criteria, of which 70(72%) were male, and 28 (28%) were female. The mean age of the participants was 55±14.5 years (range: 35-86). Out of these 98 patients, 71 patients (72.5%) reported to the hospital within the first 4.5 hours after the onset of symptoms of stroke and the rest reported after 4.5 hours time window (Table-I).

Table-I: Study participants on the basis of time of Arrival to the Hospital (n=98)

Time of Arrival	n(%)
Early Arrival (<4.5 hours)	71(72.5%)
Late Arrival (>4.5 hours)	27(27.5%)

Among the two groups based on the time of the day (morning interval 07:00-19:00 and night interval 19:00-07:00), stroke symptoms were most commonly seen and reported by the patients admitted in the morning interval. Among our study participants, 68 patients (69.4%) reported to the hospital in the daytime, and one symptom common in most of them was hemiparesis. Other stroke symptoms evaluated upon arrival at the hospital were hemianesthesia, hemianopia, aphasia and dysarthria (Table-II).

Table-II: Stroke Related Features that were Recorded After Admission to the Hospital (n=98)

Patients' Stroke Related Features	n(%)
Time Frame of Onset of Symptoms	
Morning (07:00-19:00)	68(69.4%)
Night (19:00-07:00)	30(30.6%)
Stroke Symptoms	
Hemiparesis	78(79.6%)
Hemianesthesia	36(36.7%)
Hemianopia	21(21.5%)
Aphasia	52(53.1%)
Dysarthria	16(16.32%)
Stroke Risk Factors	
Hypertension	82(83.7%)
Smoking	51(52.04%)
Diabetes	66(67.3%)
Hyperlipidemia	25(25.5%)
Coronary artery disease	58(59.2%)
Atrial Fibrillation	19(19.4%)
Family history of stroke	76(77.6%)
Mean of Transportation to the Hospital	
Ambulance	18(18.37%)
Other Private Means	80(81.63%)
Prior admission to the hospital (YES/NO)	16(16.33%)
If yes: Prior administration of intravenous thrombolytic therapy.	4(4.08%)
Modified Rankin Score (mRS) at the time of Discharge	
<2	56(57.14%)
>2	42(42.86%)

Information about risk factors and other comorbidities was also recorded in an in-person interview with the patient's relatives. On evaluation, hypertension was identified as the most prevalent risk factor in the study population, with 83.7% of the patients reporting it. Out of 98 study partici-pants, only 16(16.33%) patients were indirectly brought to the emergency clinic and Neurology Clinic of Pak Emirates Military Hospital, i.e., these 16 patients were previously admitted to another hospital after the onset of stroke symptoms. Out of these 16 patients, only four knew about the application of thrombolytic therapy priorly.

For multivariable analysis, effective variables like age, gender, means of transportation and NIHSS variables were included. The results are presented in Table-III, where the patients' clinical features and social demographic features were compared. Distance covered in relation to time to reach hospital is shown in the Figure.

DISCUSSION

In this study, we closely examined the effect of factors causing a delay in the arrival of patients to the hospital after the onset of stroke symptoms. Our study found that 71(72.5%) patients could report to the emergency ward of Pak Emirates Military Hospital within 4.5 hours after initiating stroke symptoms.

Table-III: Association of Time of Admission with Patients' Characteristics (n=98)

		Time of Admission		*p*-value
		<4.5 hours (n=71)	>4.5 hours (n=27)	
Distance covered to reach hospital	Mean±SD	7.78±6.07	8.62±6.89	0.401
	Median (IQR)	6.00(3.00)	8.00(4)	
Mann Whitney U test				853.500
Stroke Risk Factors				
Hypertension		56(78.9%)	26(96.3%)	0.037*
Smoking		32(45.1%)	19(70.4%)	0.025*
Diabetes		46(64.8%)	20(74.1%)	0.381
Hyperlipidemia		18(25.4%)	7(25.9%)	0.954
Coronary artery disease		33(47.9%)	25(88.9%)	0.000*
Atrial Fibrillation		11(15.5%)	8(29.6%)	0.114
Family history of stroke		52(73.2%)	24(88.9%)	0.097
Means of Transportation to the Hospital				
Ambulance		16(22.5%)	2(7.4%)	0.084
Other private means		55(77.5%)	25(92.6%)	
Prior admission to the hospital (YES/NO) If yes: Prior administration of intravenous thrombolytic therapy		12(16.9%) 59(83.1%)	4(14.8%) 23(85.2%)	0.805
mRS at the Time of Discharge				
<2		48(67.6%)	8(29.6%)	0.001
>2		23(32.4%)	19(70.4%)	
NIHSS				
<10		52(73.2%)	3(11.1%)	<0.001
>10		19(26.8%)	24(88.9%)	

Among stroke risk factors, hypertension, smoking, and coronary artery disease were the factors which were significantly associated with the time of admission.

These factors' frequency was higher among patients with delayed admission time. Other significant factors associated with the time of admission were the mRS score at the time of discharge and the NIHSS score.

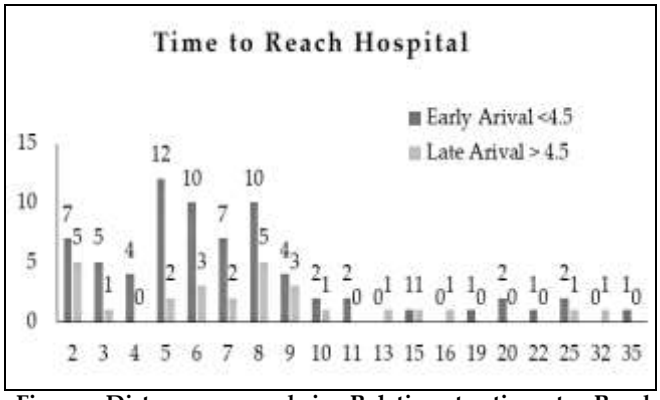

Figure: Distance covered in Relation to time to Reach Hospital (n=98)

An ecological study showed that people residing in a deprived urban area have an increased pre-hospital delay, concluding that there is an association between area-level socioeconomic status and pre-hospital delay.[11] Although we did not assess the association of area of living and socioeconomic status of patients about the pre-hospital delay, however, in this study, 92.85% of patients belonged to the low-middle class, and 92.6% of the patients among those who reached the hospital late used other private means of transportation rather than an ambulance, which may result in late arrival as well.

In resource-limited/low-middle-income countries like Nepal, the rate of pre-hospital delay is relatively high, and in a previous study only 20% arrived on time; some of the major reasons that were associated were heavy traffic, lack of medical infrastructure, unavailability of ambulance services etc.[12] When we compare the percentage of patients who arrived early (within 4.5 hours) in our study, it was quite higher compared to the study from Nepal. i.e., 72.44%.

The literature reported that a distance of >20 km was associated with delayed arrival to the emergency.[13,14] In our study, the mean distance to travel among patients in the delayed group was 8.62±6.89 Km. The maximum distance covered by the patients to reach the hospital in this study was 35 km which may be considered a contributing factor to late arrival at the hospital for emergency treatment. Although our study does not address these factors as causes of time delay, lack of awareness of the patient's condition, non-availability of ambulance services and misdiagnosis of the patients have also been recognised as causative factors for delay in many previous studies.[15,16] In some literature, gender has also been associated with the time of arrival at the hospital. In some studies, it has been concluded that the female gender negatively impacts the time of arriva.[17,18] In contrast, other studies conclude that gender has no association with the time of arrival at the hospital.[19] In our study, this has been observed that the female gender is strongly associated with the delay in arrival at the hospital.

In this study, it was observed that in the delayed group, patients had significantly higher mRS and NIHSS scores. Gaurav Nepal from Nepal also reported higher mRS and NIHSS scores in the late group in his study, which is in line with the results of our study showing higher mRS and NIHSS scores in the delayed group.[20]

Despite all the above discussion, an important point is that the time taken to reach the hospital varies depending on the country's geographical, sociodemographic, and organisational variables and development stage.

CONCLUSION

On analysis of the results and statistics comparing the social demographic and clinical features of the patients, this can be concluded that female gender, low NIHSS score (<10) and using transport other than an ambulance cause delayed hospital arrival of acute ischemic stroke patients.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

KA: & KHN: Data acquisition, data analysis, data interpretation, approval of the final version to be published.

WUH: Study design, drafting the manuscript, concept, critical review, approval of the final version to be published.

RMW: Critical review, drafting the manuscript, interpretation of data, approval of the final version to be published.

Authors agree 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.

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