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Factors Related to Early Versus Late Hospital Arrival in Acute Ischemic Stroke

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ABSTRACT

Background: **The onset-to-arrival time affects the decision of intravenous thrombolysis therapy which is associated with stroke's prognosis. This study aimed to evaluate factor associated with early and late arrival of patients with Acute Ischemic Stroke and the effect on patients' outcomes.**

Materials and Methods: **Patients confirmed with acute ischemic stroke in central stroke centers were included in a prospective study. The patients were grouped into early arrivers (less than 4.5 hours) and late arrivers (at and after 4.5 hours). Patients' data were obtained from the stroke registry system.**

Results: **In Summary, Higher initial NIHSS, less than 15 km from the hospital, a history of CVA, Diabetes, Abnormal blood pressure, EMS transportation, Atrial fibrillation, and current use of anticoagulants, Not using opium, and not smoking was significantly associated with early arrival time. Normal blood pressure AF was a negative and significant (p-value=0.001, Odds ratio: 0.38) predictor of the late arrival. Normal blood pressure was a positive and significant (p-value<0.001, Odds ratio: 4.762) predictor of the late arrival.**

Conclusion: **Some baseline factors are associated with the onset-arrival time of patients with ischemic stroke.**

Keywords:. Early hospital arrival, fibrinolysis, factor, late hospital arrival, stroke.

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I. Introduction

Stroke is the fifth leading cause of death in the United States [1]. Rapid diagnosis and prompt treatment of stroke improves the outcome. The American Heart Association's (AHA) guidelines for the early management of patients with acute ischemic stroke emphasizes the importance of rapid symptom recognition and rapid prehospital management [2].

To date, the gold standard treatment for an ischemic stroke is intravenous (IV) recombinant tissue plasminogen activator (rt-PA) that should be administered in the first 4.5 hours of onset and endovascular reperfusion therapy which should be performed in the first 6 hours of onset in order to improve the outcome [2]-[5].

The therapeutic time window is narrow and any delay in arrival at stroke centers is the main reason why patients miss these rescue therapies. Early arrival of patients (less than 6 hours) to stroke centers is associated with shorter hospitalization and favorable outcomes [6].

Some studies have been conducted to determine the factors associated with stroke onset-arrival time. So far, factors associated with early hospital arrival in the literature are female sex, lower age, not living alone, lower consciousness, history of coronary artery disease, transport by EMS, daytime onset, atrial fibrillation, and higher initial NIHSS scores [7]-[11]. Symptom onset at home, a history of diabetes, and visiting a local doctor before attending the hospital have been associated with late hospital arrival [11], [12].

The aim of this study is to evaluate factors associated with both early and late hospital arrival in two major university stroke centers. In addition, we have evaluated the outcomes correlated to early or late arrival time.

II. Materials and Methods

A. Study Population

In this cross-sectional study, patients who arrived at the Emergency Departments of two central university stroke centers from March 2022 to February 2023 were enrolled. We studied patients with acute ischemic stroke who arrives at hospital within 24 hours the of onset of symptoms. Acute Ischemic Stroke was diagnosed based on imaging modalities including Brain CT scan and/or Brain MRI (DWI). Patients who arrived after 24 hour of stroke onset and those referred from other hospitals and cities were excluded from the study. Data were obtained from the acute national stroke registry system and hospital medical records.

B. Variables and Groups

The onset-to-arrival time (time between onset of symptoms and arrival at the hospital), baseline data, distance between event location and hospital, BMI, initial National Institute of Health Stroke Scale (NIHSS) score at the hospital, Modified Rankin Score (mRS) before the event, mean blood pressure, history of CVA, diabetes, atrial fibrillation, serum lipid profile, current use of anticoagulants, opium use and cigarette smoking, mode of transportation, duration of hospitalization in stroke unit and discharge status were collected in data form.

Distance from hospital was divided into 2 groups (≤ 15 km and > 15 km). Severity of stroke was determined as NIHSS score between 0 and 42 based on initial signs. Patients' total function before the event of stroke was reported as "The Modified Rankin Score" (mRS), which is a 6-point disability scale with possible scores ranging from 0 to 5. Mode of transportation was classified into emergency medical services (EMS) vs. non-EMS (e.g., private car, taxi, walking).

Favorable outcome was considered by patients' arrival in less than 4.5 hours (rTPA golden time window). Therefore, subjects were categorized into the early group (time between symptom onset and hospital arrival ≤4.5 hours) and the late group (time between symptom onset and hospital arrival >4.5 hours).

C. Statistical Analysis

Assuming a confidence level of 0.05, the sample size was estimated to be 245. Results for qualitative and quantitative variables were presented as number (%) and mean± standard deviation (SD), respectively. Independent sample t-test or Mann-Whitney U test was used for continuous variables and $\chi 2$ test or Fisher's exact test was used for categorical variables to compare variables between the early and late arrival groups. P value of <0.05 was considered statistically significant. Data analysis was performed using SPSS V.23 software.

D. Ethics

This research has been approved by the local Ethics Committee of the Vice Chancellor for Research and technology. We followed the Helsinki rules.

III. Results

A. Baseline Characteristics

Of 245 patients with acute stroke included in the study, 144 patients (58.77%) were referred to the Emergency Department of Stroke Center I, and 101 patients (41.22%) were referred to the Emergency Department of Stroke Center Ⅱ.

The mean age of patients was 67.08 ±13.79 years. Of total patients, 47.3% (n = 116) were women and 52.7% (n = 129) were men. Results showed that 59.2% (n = 145) of patients arrived early (≤4.5 hr.) at the hospital. Regarding mode of transportation, 55.5% (n = 136) of patients were transferred to the hospital by EMS and 44.5% (n = 109) by non-EMS transportation.

Thirteen patients (5.3%) died, and 232 patients (94.7%) were discharged from hospital. Study variables are described in Table I.

B. Factors associated with Arrival Time

1) Univariate analysis

Mean NIHSS score was 12.71 ± 5.32 for patients with early arrival, and 10.46 ± 4.94 for patients with late arrival. Higher initial NIHSS score was significantly associated with early hospital arrival (p-value=0.001). Age and BMI were not associated with early or late arrival. MRS was not associated with onset-arrival time (p-value=0.118).

Chi-square test was performed to observe the association between hospital arrival and gender, distance from hospital, abnormal blood pressure, diabetes mellitus, history of CVA, atrial fibrillation, lipid profile, current use of anticoagulants,

mode of transportation, opium usage, cigarette smoking.

Distance was significantly associated with onset to arrival time (X2(1) = 6.18, p-value=0.013). Regarding distance from the hospital, 62.1% (n=90) early arrived patients had less than 15 km from hospital.

Abnormal blood pressure was significantly associated with early arrival (X2(1) = 25.05, p-value<0.001). In early arrived patients, 84.1% (n=122) had an abnormal blood pressure.

Diabetes was associated with early arrival of patients to the hospital (X2(1) = 7.72, p-value=0.005). In early arrived patients, 73.1% (n=106) were diabetic.

Also in early arrived patients, 73.1% (n=106) had had a history of CVA. CVA was significantly associated with early arrival (X2(1) = 7.72, p-value=0.005). EMS transportation was significantly associated with early arrival (X2(1) = 6.18, p-value=0.013). In patients with an early arrival to the hospital, 62.1% (n=90) were transported using EMS.

Atrial fibrillation (X2(1) = 7.72, p-value=0.005) and current use of anticoagulants (X2(1) = 5.43, p-value=0.020) were also significantly associated with early arrival.

Not using opium, and not smoking was significantly associated with early arrival (X2(1) = 4.37, p-value=0.037). In early arrived patients, 91%(n=132) did not report use of opium and did not report smoking.

Regarding the patients' prognosis, early arrival time had significantly decreased the Hospital Length of Stay (LOS) (P-value= 0.048). Then again early arrival reduced the rate of mortality at the time of discharge, but this was not significant. Data is shown in Table I.

Multivariate analysis

A logistic regression was performed to assess the multiple association between late arrival and patients' AF, blood pressure (normal or abnormal), mode of transportation and cigarette smoking.

TABLE I: STUDY VARIABLES

-	Early Arrival (≤4.5 hr)		Late Arrival (>4.5 hr)		P-Value
	Frequency (%)	Mean ± SD	Frequency (%)	Mean ± SD	
Age (year)	-	66.21 ± 14.92	-	68.34 ± 11.93	0.217
BMI (kg/m^2)	-	26.45 ± 3.87	-	25.78 ± 3.20	0.138
Initial NIHSS	-	12.71 ± 5.32	-	10.46 ± 4.94	0.001
Gender Male Female	 74 (57.4%) 71 (61.2%)	-	 55 (42.6%) 45 (38.8%)	-	0.541
Distance from Hospital ≤15 km >15km	 90 (66.2%) 55 (50.5%)	-	 46 (33.8%) 54 (49.5%)	-	0.014
Mean Blood Pressure Normal Abnormal	 23 (33.8%) 122 (68.9%)	-	 45 (66.2%) 55 (31.1%)	-	<0.001
History of CVA Yes No	 106 (65.4%) 39 (47%)	-	 56 (34.6%) 44 (53%)	-	0.006
Diabetes Yes No	 106 (65.4%) 39 (47%)	-	 56 (34.6%) 44 (53%)	-	0.006
AF Yes No	 106 (65.4%) 39 (47%)	-	 56 (34.6%) 44 (53%)	-	0.006
Lipid Profile Normal Abnormal	 66 (61.1%) 79 (57.7%)	-	 42 (38.9%) 58 (42.3%)	-	0.603
Current use of anticoagulants Yes No	 68 (68%) 77 (53.1%)	-	 32 (32%) 68 (46.9%)	-	0.024
Opium use Yes No	 13 (41.9%) 132 (61.7%)	-	 18 (58.1%) 82 (38.3%)	-	0.050
Cigarette Smoking Yes No	 13 (41.9%) 132 (61.7%)	-	 18 (58.1%) 82 (38.3%)	-	0.050
Mode of Transport EMS Other	 90 (66.2%) 55 (50.5%)	-	 46 (33.8%) 54 (49.5%)	-	0.014
Discharge status Expired Alive	 5 (38.5%) 140 (60.3%)	-	 8 (61.5%) 92 (39.7%)	-	0.150
Hospital Length of Stay (LOS) (day)	-	10.76 ± 10.59	-	14.02 ± 13.84	0.048

BMI: Body Mass Index; NIHSS: National Institutes of Health Stroke Scale; MBP: Mean Blood Pressure; CVA: cerebrovascular accident; AF: Atrial Fibrillation; EMS: emergency medical service. Data are presented with number (%) or mean± standard deviation.

AF was a negative and significant (p-value=0.001) predictor of the late arrival of stroke patients to the hospital. The odds ratio indicates that AF decreased the odds of arriving late by a factor of 0.38. Mode of transportation was another negative, but non-significant (p-value=0.310) predictor of the late arrival. EMS transportation decreased the odds of late arrival by a factor of 0.538.

Normal blood pressure was a positive and significant (p-value<0.001) predictor of the late arrival. The odds ratio indicates that for patients with a normal blood pressure, the odds of arriving late was increased by a factor of 4.762. Cigarette smoking was a positive but non-significant (p-value=0.370) predictor of the late arrival of stroke patients. The odds ratio indicates that cigarette smoking, increased the odds of late arrival by a factor of 2.41.

IV. Discussion

In this study we evaluated the factors related to early and late arrival at the hospital after ischemic stroke. The findings of our study showed that higher Initial NIHSS, altered blood pressure, history of CVA, Diabetes Mellitus, atrial fibrillation, transport by EMS, distance less than 15 kms from hospital, and use of anticoagulants were significantly correlated with early arrival at our center, while opium use and cigarette smoking were significantly correlated with late arrival. Age, gender, BMI, and lipid profile showed no significant association with onset-arrival time.

Regarding EMS transportation and early arrival, the association between EMS transportation and early arrival was like previous studies [7], [13]-[16]. These results enhance the significant role of EMS in transporting the patients with alarming signs of stroke to the nearest qualified stroke centers during the golden time. Nonetheless, the use of EMS might not be applicable for all setups since it is dependent on the region, distance, and emergency transport system. This also indicates the role of education for EMS team to be sensitive for recognizing any early sign of stroke to deliver the patients to the nearest stroke center as soon as possible. Furthermore, public awareness of stroke has been reported to be effective for the call of early emergency service [15].

Our results also indicated that there are significant correlations between early arrival time and high mean blood pressure, diabetes mellitus and history of stroke. It is assumed that patients with these conditions already have frequent visits to the hospital, and are highly alert and aware of the threats, which results in earlier arrival to the hospital in the case of acute events. In addition, high blood pressure causes stress which can be a factor associated with earlier hospital arrival. This was in line with studies in which the history of cardiovascular diseases and CVA were reported as effective factors [13]. The association between early arrival time with current anticoagulant usage, and atrial fibrillation was also noted in our results, as in most previous reports [7], [17]. To explain, stroke caused by AF (cardiac embolism mechanism) usually presents suddenly and more severely [18]. These characteristics may cause patients or witnesses to seek medical assistance earlier. The association between current anticoagulant usage and early hospital arrival could as well be explained this way. In a similar study by [9], atrial fibrillation, coronary heart disease, sudden presentation of symptoms, feelings of anxiety, led to the arrival of patients within 3 hours. These findings were in parallel with our study. On the contrary, opium usage and cigarette smoking were significantly associated with late (>4.5 hrs.) hospital arrival. This might be due to poor health-consciousness. These patients might also have more ambiguous symptoms, and not be correctly interpreted as an acute cerebrovascular event.

We found no significant relationship between BMI, Serum lipid profile with either early or late hospital arrival. Also, our study did not report any correlation between gender and patients' arrival time. Similar findings regarding gender are supported by [19]. While in a study by [7], male sex tended to be related with early hospital arrival. In contrast, in another study by [20] female sex has been related with early hospital arrival [7], [10]. These paradoxical results with no rational justifications might show that the effects are not the case and that this might be just an incidental finding.

As opposed to [20] and [21] where increased pre-stroke mRS score was associated with early arrival, in our study, the baseline functional status of the (evaluated by mRS) was not associated with onset-arrival time in our study.

In this study higher NIHSS score was a significant contributor to early arrival time associated with early arrival. The Mean NIHSS score in patients with early arrival was 12.71 ± 5.32. In line with our study, [20] found that Higher NIHSS score was associated with early arrival .In a prospective multicenter study, authors reported that early arrival of less than 3 hours is associated with greater NIHSS score greater than 7 hours. Higher NIHSS contributes to more severe symptoms which causes higher awareness of patients and care givers along with more anxiety to seek for help. Lower NIHSS means less severe symptoms; as a result, patients may be unable to interpret these symptoms as stroke, which finally contributes to a significant delay [22].

In our study, early arrival time significantly decreased the Hospital Length of Stay (LOS); whereas the decrease in the mortality rate was not significant. In a similar study by [23], early-arrival group showed a better functional outcome. This finding highlights the value of these types of studies to evaluate the factors affecting patients' arrival and to identify the modifiable factors. Changing the modifiable factors and public education will eventually improve the outcome of acute ischemic stroke.

Our study is the first report on this issue in this geographical region. Also, we have provided a thorough view of factors affecting both early and delayed arrival time. The strength of our study is that multiple centers which are first-line stroke centers located in central districts of the capital, were included. Therefore, the findings of this study could be generalized to some extent. However, the study has some limitations in a sense that not all baseline factors have been taken into consideration. In addition, long term impact of early and late arrival on therapeutic outcomes and prognosis has not been evaluated so far.

We recommend public awareness of modifiable factors such as EMS transport and actions to be taken to educate people regarding atypical symptoms of stroke and the importance of immediate referral and seeking medical assistance. These endeavors will affect the arrival time to the hospital, which subsequently improves the prognosis.

V. Conclusion

Some factors are associated with early and late arrival time. We suggest measures to be taken to educate people on atypical symptoms of stroke and the importance of immediate referral to the hospital.

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Conflict of Interest

Authors declare that they do not have any conflict of interest.

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