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Pre-Hospital and In-Hospital Delay in Acute Ischemic Stroke Patients in Indonesia: A Multi-center Study

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ABSTRACT

Little is known regarding pre-hospital and in-hospital delays in acute ischemic stroke (AIS) patients in Indonesia. This study evaluated the nature of these delays and identified factors causing pre-hospital delays among AIS patients in Indonesia. This was a prospective, multicenter, observational study conducted among adult AIS patients in three hospitals in the city of Surabaya between March 15 and August 15, 2019. Baseline characteristics and the pre- and post-arrival time intervals of the patients to the study sites were collected and analyzed. Multiple logistic regression analyzes with a stepwise forward model were performed to evaluate the factors contributing to pre-hospital delay. A total of 126 patients were recruited for this study. The mean age was 58.56 ± 10.71– years–old. The mean time of pre-hospital delay and mean time to the computed tomography scan were 1,004 ± 1,116.09 and 189 ± 166.44 min, respectively. Eighteen out of 126 patients (14.29%) presented to the hospitals within 4.5 h of the intravenous thrombolysis (IVT) time window. However, only three patients (2.38%) ultimately received IVT. Wake-up stroke (odds ratio [OR] = 17.865; p = 0.019), unaware of the gravity of the symptoms (OR = 11.025; p = 0.007), unaware of stroke symptoms (OR = 7.880; p = 0.003) and referral patient (OR = 7.819; p = 0.008) were significantly associated with pre-hospital delay. Pre-hospital delay of AIS was patients very common and may represent the most challenging problem to improve stroke care in Indonesia. Wake-up stroke, a lack of patient understanding in recognizing stroke symptoms, and an ineffective referral system were the most prominent risk factors for pre-hospital delay in Indonesian AIS patients.

Keywords: Acute ischemic Stroke, Fibrinolysis, Stroke, Patient, Indonesia

INTRODUCTION

Stroke is a major cause of death and disability in many countries particularly in Asia (Chen *et al*., 2007; Venketasubramanian, *et al* 2017). In Indonesia, stroke was the first leading cause of death between 2007 and 2017, with incidence increasing by 29.2% over the 10 years (Gani, 2018). Among the stroke cases, 67.1% and 32.9% were ischemic and hemorrhagic strokes, respectively (Yudiarto *et al*., 2014). Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) or alteplase, is the cornerstone of acute ischemic stroke (AIS) management through its ability to restore blood flow to the ischemic area (Emberson *et al*., 2014; Powers *et al*., 2018). Despite its proven efficacy and safety, the therapeutic window of 4.5 hours for rt-PA presents a challenge to any health system to maximize its benefits. The use of IVT for managing AIS remains low even in developed countries with advanced healthcare systems. A recent survey of 44 European countries suggested that only 7.3% of incident ischemic stroke patients received IVT. This rate varies significantly from country by country with the highest rate of 20.6% in the Netherlands and rates of 9.2 and 11.7% in France and the UK, respectively (Aguiar de Sousa *et al.*, 2019). Data on IVT usage rates in developing countries with limited organized stroke care are generally much lower ranging from < 1% to 4.76% depending on the level of stroke care organization in the country (Abd-Allah & Moustafa, 2014; Ghandehari, 2013; Suwanwela, 2018; Wasay *et al.*, 2010). Low public awareness of stroke, poorly developed emergency medical services (EMS), and limited coordination in the referral system are common causes of late hospital arrival in these countries. Cost of therapy, limited availability of neurologists, limited access to computed tomography (CT) scanners, and a lack or scarcity of stroke care facilities are the key factors for delays in the timely management of stroke upon hospital arrival. Taken together, these issues represent major obstacles to IVT use in developing countries (Pandian *et al.*, 2017; Sharma *et al.*, 2012). Notably, the contribution of these factors varies from country to country, as each country's health system has different challenges. Data regarding pre-hospital and in-hospital delay along with factors contributing to the delays in AIS treatment are scarce in Indonesia. Therefore, the availability of such data should be useful for relevant health authorities and hospital systems to improve stroke care in the nation.

MATERIAL AND METHODS

Objectives

We captured all key time intervals for pre-hospital and in-hospital delays. The time from onset of symptoms to emergency department arrival (T-ED) was collected for pre-hospital delay. Four time intervals were used for in-hospital delay, including 1) T-triage, indicating the time from ED arrival to completion of the initial patient assessment 2) T-CT, indicating the time from ED arrival to completion of the CT scan, 3) T-lab, indicating the time from ED arrival to the completion of laboratory tests and 4) T-IVT, indicating the time from ED arrival to the start of IVT for those receiving IVT. In addition, we identified the risk factors causing pre-hospital delay among AIS patients.

Study design and participants

This study was a prospective, observational study conducted among adults (age ≥ 18 years) with AIS (International Classification of Diseases, 10th revision codes 163.9) who presented to the EDs of three participating hospitals in Surabaya city, Indonesia, between March and August 2019. These study sites were Dr. Soetomo General Hospital (SGH), Universitas Airlangga Hospital (UAH), and Hajj General Hospital Surabaya (HGH). SGH is a 1,300-bed, tertiary-care hospital with 20 neurologists and three CT machines. UAH is a 200-bed, secondary-care, university-affiliated hospital with eight neurologists and two CT machine. HGH is a 362-bed, secondary-care hospital with five neurologists and one CT machine. SGH and UAH have alteplase in the hospital formulary whereas, HGH does not have adequate human resources or facilities to support thrombolysis therapy. As a result, HGH did not have alteplase in the hospital formulary and could only provide supportive care and referral for AIS patients. Patients who provided informed consent were included in the study. Patients with neurologic deficits other than stroke were excluded.

Data collection

After obtaining consent from the patients, data were collected through interviews, the medical chart, and the hospital database, where appropriate. Demographic data consisted of age, gender, educational status, comorbidities, history of stroke, distance from the onset location to the hospital, mode of transportation and referral from another hospital. Detailed information related to the AIS event consisted of time of onset, presence of a witness, wake-up stroke, stroke risk factors, reason for pre-hospital delay, the NIH Stroke Scale/Score (NIHSS) score on admission and use of IVT.

Data analysis

Descriptive analysis was used to assess the participant's characteristics, such as the demographic and clinical data. All time intervals are expressed as mean ± standard deviation and median (25th–75th percentile). Patients were divided into two groups to identify pre-hospital delay factors; 1) those who arrived at a study site within 3.5 h (early arrivers) and 2) those who arrived at a study site after 3.5 h (late arrivers). The chi-Square test was used to analyze categorical variables in the early versus late arriver comparisons. The Kolmogorov-Smirnov test was used to test the normality of the data. The independent-sample *t*-test and the Mann-Whitney test were used to compare mean differences of all time intervals between early and late arrivers.

Table I. Baseline characteristics of overall study population, early arrivers (pre-hospital delays of ≤ 3.5 h) and late arrivers (pre-hospital delays of > 3.5 h).

Total n = 126	n (%)	n (%) ≤ 3.5 h	n (%) > 3.5 h	p value[a]
Age, year (mean ± SD = 58.56 ± 10.71)				
Age ≤ 65 years	98 (77.78)	10 (55.55)	63 (58.33)	0.825
Age > 65 years	28 (22.22)	8 (44.45)	45 (41.67)	
Gender				
Male	73 (57.94)	11 (61.11)	87 (80.56)	0.066
Female	53 (42.06)	7 (38.89)	21 (19.44)	
Education				
No education or with elementary level	34 (26.98)	4 (22.22)	30 (27.78)	0.623
Junior high-school or higher level	92 (73.02)	14 (77.78)	78 (72.22)	
Distance from onset location to study sites (kilometres, km)				
> 15 Km	6 (4.76)	0 (0.00)	6 (5.56)	0.306
≤ 15 Km	120 (95.24)	18 (100.00)	102 (94.44)	
Witnesses				
Alone	4 (3.17)	0 (0.00)	4 (3.70)	0.407
Joint family or colleague	122 (96.83)	18 (100.00)	104 (96.30)	
Transportation				
Private vehicle	64 (50.79)	6 (33.33)	56 (51.85)	0.146
Public transportation	62 (49.21)	12 (66.67)	52 (48.15)	
Onset Time				
Day	48 (38.10)	11 (61.11)	67 (62.04)	0.940
Night	78 (61.90)	7 (38.89)	41 (37.96)	
NIHSS (mean ± SD = 8.25 ± 4.13)				
≤ 14	115 (91.27)	15 (83.33)	100 (92.59)	0.198
> 14	11 (8.73)	3 (16.67)	8 (7.41)	
Wake-up stroke	45 (35.71)	1 (5.56)	44 (40.74)	0.004
Referral patient	50 (39.68)	3 (16.67)	47 (43.52)	0.031
Stroke history	38 (30.16)	4 (22.22)	34 (31.48)	0.428
Hypertension	118 (93.65)	17 (94.44)	101 (93.52)	0.881
Diabetes	62 (49.21)	9 (50.00)	53 (49.07)	0.942
Dyslipidemia	52 (41.27)	6 (33.33)	46 (42.59)	0.460
Atrial fibrillation	3 (2.38)	0 (0.00)	3 (2.78)	0.474
Coronary Artery Disease	5 (3.97)	2 (11.11)	3 (2.78)	0.094
Heart failure	3 (2.38)	0 (0.00)	3 (2.78)	0.474
Cardiomegaly	2 (1.59)	0 (0.00)	2 (1.85)	0.561
Smoking	35 (27.78)	7 (38.89)	28 (25.93)	0.256
Unaware of stroke symptoms	64 (50.79)	5 (27.78)	59 (54.63)	0.035
Unaware of the gravity of symptoms	39 (30.95)	2 (11.11)	37 (34.26)	0.049
Communication barrier with caregiver or family	22 (17.46)	1 (5.56)	21 (19.44)	0.151
Trial of self-medication	5 (3.97)	0 (0.00)	5 (4.63)	0.352

a: χ^2 testing for significant differences among groups; Risk factors in patients can be more than one.

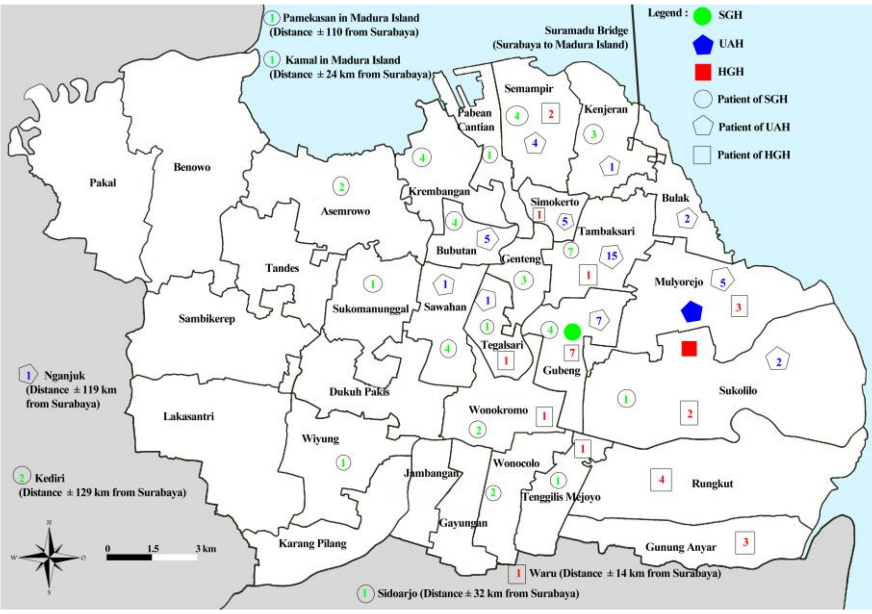

Figure 1. Geographical location of stroke cases and study sites indicating distance of onset location to the study sites

Univariate and multivariate logistic regression analyzes were used to identify predictors that affected pre-hospital delay. Variables were eliminated in a stepwise forward mode with the likelihood ratio to solve multicollinearity and interaction problems. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The adjusted OR was calculated by multiple logistic analyzes with $P < 0.05$ considered as statistically significant. Data were analyzed using SPSS 21 software for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS AND DISCUSSION

Baseline characteristics

A total of 126 patients who met the inclusion criteria and provided informed consent were enrolled in this study including 50, 49, and 27 patients from SGH, UAH and HGH, respectively (Table I). The mean age of the participants was 58.56 ± 10.71–years–old and more than two–thirds were < 65–years–old. The sex distribution was almost equal. The top five most–common risk factors of ischemic stroke in the study population were hypertension (93.65%), diabetes (49.21%), dyslipidemia (41.27%), smoking (27.78%), and coronary artery disease (3.97%). About one–third of the population experienced a recurrent stroke while two–thirds experienced the first stroke at the time of inclusion in the study. About one–third of the patients developed wake-up stroke. The mean NIHSS score at admission was 8.25 ± 4.13 while the majority of the patients (87.30%) had NIHSS scores on admission of ≤ 14. Approximately 95% of the patients resided within 15-km radius of the hospitals. Based on geographical location (Figure 1), 61 patients did not present at the ED of the nearest study site but went to a site that was farther away. (Figure 1). No one came to the ED through the EMS. Almost 40% of the patients were referrals from other health care. As SGH is a referral center, it received disproportionately more referral patients compared to UAH and HGH (p=0.001). (Supplementary Table S1)

Key time intervals pre- and post-hospital arrival

The median (25^{th}–75^{th} percentile) of T-ED, T-triage, T-CT, and T-lab were 635 (353.25–1.071.75), 5 (4–10), 139 (96–215) and 123.5 (95.25–180.75) min, respectively. Eighteen (14.29%) patients (early arrivers) arrived within the IVT time window. The early arrivers had significantly less delay on T-ED and T-lab with a median (25^{th}–75^{th} percentile) of 121 (60–164) vs 719 (460–1.177) ($p < 0.001$) and 99 (68–127) vs 133 (98–184) min ($p = 0.001$) than the late arrivers, respectively. A similar delay pattern was observed in all three hospitals with the longest delay in T-ED followed by T-CT (Supplementary S4–6) (Table III).

Table II. Factors contributing to delayed arrival by univariate and multivariate logistic regression analyses.

	Crude OR	(95% CI)	p value	Adjusted OR	(95% CI)	p value
Referral patient	3.852	1.053-14.088	0.041	0.041	1.720- 35.554	0.008
Wake-up stroke	11.687	1.500-91.059	0.019	17.865	2.037-156.673	0.009
Unaware of stroke symptoms	3.131	1.043-9.393	0.042	7.880	2.055-30.227	0.003
Unaware of the gravity of symptoms	4.169	0.909-19.114	0.066	11.025	1.949-62.369	0.007

OR: odds ratio; CI: confidence interval; Ref: reference group; p value by Wald test; Eliminated by stepwise forward LR mode in multivariate logistic regression analyses

Table III. Comparison between early-arrivers and late-arrivers.

Time interval		T pre-hospital delay	T Triage	T CT	T Lab
Target (min)		≤ 210	≤ 10	≤ 25	-
Total patient	Mean ± SD	1.004±1.116.09	9.29±13.54	189±166.44	173.24±208.18
	Median (25th–75th percentile)	635 (353.25-1.071.75)	5 (4-10)	139 (96-215)	123.5 (95.25-180.75)
Early-arrived patient	Mean ± SD	115.33±62.03	7.11±6,67	190.67±153.53	103.11±42.46
	Median (25th–75th percentile)	121 (60-64)	5 (4-7)	154 (99-243)	99 (68-127)
Late-arrived patient	Mean ± SD	1.152.08±1.139.76	9.66±14.33	188.72±168.49	184.93±222.05
	Median (25th–75th percentile)	719 (460–1177)	5 (4–10)	136 (95–215)	133 (98–184)
p value		< 0.001	0.238	0.962	0.001

Qualification and use of IVT

Among 18 (14.29%) early arrivers, ten, five and three cases presented at HGH, UAH, and SGH, respectively. However, only three (2.38%) patients at SGH received IVT, and all cases received standard-dose alteplase. Detailed information on the time intervals of these patients is presented in Supplementary Table 3. Ten (7.93%) patients did not receive IVT at HGH due to the inability to adequately monitor the patients administered IVT. This was due to an inadequate number of CT scanners and a shortage of neurologists at the time of the study. Five (3.97%) patients did not receive IVT due to contraindications in three cases and delayed notification to the neurology department in two cases.

Risk factors for pre-hospital delay

Univariate logistic regression analysis showed that referral patients (OR = 3.852; p = 0.041), unaware of stroke symptoms (OR = 3.131; p = 0.042), and wake-up stroke (OR = 1.687; p = 0.019) were significantly associated with a pre-hospital delay > 3.5 hours (Supplementary Table S2). After adjustment in the multivariate logistic regression analysis, wake-up stroke (OR = 17.865; p = 0.019), unaware of the gravity of symptoms (OR = 11.025; p = 0.007), unaware of stroke symptoms (OR = 7.880; p = 0.003), and referral patient (OR = 7.819; p = 0.008) were significantly associated with pre-hospital delay > 3.5 h (Table II).

The demographics of our study population were consistent with national data on stroke patients. Stroke patients in Indonesia tend to be younger than stroke patients in Western studies but similar to other Asian nations (Chen *et al.*, 2007; Venketasubramanian *et al.*, 2017). Consistent with national health statistics, very high rate of hypertension, diabetes, dyslipidemia, and smoking are present in this population (WHO, 2012; Yudiarto *et al.*, 2014).

Similar to previous studies conducted in Indonesia and other developing countries, a small proportion of patients with stroke arrived at the hospital within the IVT time window but only 2.38% receive IVT (Abd-Allah & Moustafa, 2014; Ghandehari, 2013; Machin & Hamdan, 2018; Suwanwela, 2018; Wasay *et al.*, 2010).

Table IV. Time interval of alteplase patient

Time interval (min)	All alteplase cases		Case 1	Case 2	Case 3
	Mean ±SD	Median (25^{th} – 75^{th} percentile)			
T pre-hospital delay	76.67±30.91	60 (55–90)	50	60	120
T Triage	3.33±1.70	4 (2.5–4.5)	5	4	1
T CT	36.67±8.06	32 (31–40)	32	30	48
T Lab	72.67±33.83	55 (49–87.5)	43	120	55
T DTN	45.67±11.44	45 (38.5–52.5)	32	45	60

Interestingly, this low rate of early arrival occurred despite almost all cases living within a 15 km radius of the study sites. Several factors play rolet in this issue. First, the majority of the cases did not recognize the stroke symptoms and were unaware of the gravity of the symptoms. Most cases lost time by observing their symptoms at home. Once a decision was made to go to the hospital, almost all cases used either private or public transportion despite the availability of EMS. The hospital destination that the patient or caregiver chose often added to lost time as 40% of the cases went to small community hospitals or clinics. This chain of events ultimately led to the disqualification of most patients when they finally arrived at our study. Notably, about one–third of the study population had a stroke history. This would theoretically increase the patient awareness of symptoms and increase the likelihood of seeking hospital care. Unfortunately, pre-hospital delay data indicated that this may not be the case. This finding emphasizes the need to improve the quality of patient education after stroke to ensure the urgency to seek medical help.

About 35% of the case were wake-up strokes in our study and it was a strong predictor of pre-hospital delay. This may be because the time of onset of wake-up stroke is defined as when a patient goes to sleep or is last known to be awakened without symptoms. As the study sites did not use magnetic resonance imaging (MRI) mismatch to determine the onset time of wake-up stroke, almost all patients with wake-up stroke were too late for IVT.

The T-CT scan appeared to be the bottleneck upon arrival to the study sites. While the generally recommended T-CT is < 25 min (Potter *et al.*, 2019), the median T-CT was 154 and 32 min for early arrivers and those receiving IVT. The significant delay in T-CT in this study reflected the discrepancy in the demand and supply for CT scanning in the study settings. The situation varied among centers. HGH had only one CT scanner. SGH and UAH were able to perform CT scans in a timely fashion as there were more CT machines at these sites. As a result, the availability of CT machines is a key area for improvement.

All time intervals of cases receiving IVT were significantly shorter, which allowed rapid administration of IVT promptly. All cases shared two common key factors during patient and caregiver interviews, which were awareness of stroke symptoms by the witnesses in all three cases and direct transportation of the patients to a study site with stroke care capability. Hospital delay was minimized with an early arrival as staff neurologists realized the potential candidates for IVT and had ample time to coordinate with other departments to manage the cases. A "fast track" pathway was activated for these patients which resulted in the timely management of AIS with IVT. As almost all cases of stroke occurred in the presence of a witness, a public awareness campaign may have a widespread impact on shortening hospital delays.

Our study suggests that "referral patients" are a major factor for pre-hospital delay compared to previous studies in Indonesia (Machin & Hamdan, 2018). We were able to extend this finding by identifying areas to improve pre-hospital and in-hospital delays during stroke case. Based on our analysis, five key areas of improvement are needed. First, a public campaign to raise awareness of stroke symptoms should be conducted and reinforced on a wide scale. Second, the city of Surabaya has an EMS system but no patients called the service due to a lack of awareness of its existence. An effective EMS in developed and developing country substantially reduces prehospital delays and improves the likelihood of early arrival and timely treatment (Gu *et al.*, 2019; Minnerup *et al.*, 2014). Therefore, the EMS should be promoted. As 40% of patients went to a small hospital lacking stroke care capability, an attempt to educate the public regarding the centers that are capable of providing stroke care is another important element to improve the timely transportation of stroke patients. Third, coordination with other hospitals that have adequate facilities is needed to shorten the referral process (Manners *et al.*, 2019; Meretoja *et al.*, 2014; Powers *et al.*, 2018). Fourth, improved availability of human resources (neurologists) and facilities (CT machines/stroke units) should be a top priority, particularly as stroke is the leading cause of death in the Indonesian population. Fifth, improving the coordination between triage staff and neurologists and implementing a "fast track" may help minimize in-hospital delays.

Some limitations of our study should be discussed. All study sites were located in the city of Surabaya. In addition, due to limited time and manpower, we only included a small number of patients. Thus, our results may have limited generalizability in other regions of Indonesia, particularly the more rural areas. Studies based on a nationwide registry may be needed to characterize the characteristics and magnitude of this important health problem. Some limitations in our analysis should be mentioned. T-ED may have been overestimated with large number of wake-up stroke patients and the lack of MRI mismatch to detect onset in those cases. Patient selection bias was unavoidable, as we only enrolled subjects who provided consent to participate in the study. In addition, we conducted the interview on the day that the patient's condition improved and some detailed information may not have been accurately captured after the fact. We did not follow and collect patient outcomes at discharge. Therefore, we did not have information on the outcomes of these patients. Additional factors were not collected, such as NIHSS at onset, NIHSS on the last day of in-patient treatment, type of symptoms/signs, and patient's financial situation. Nevertheless, we believe that our findings are useful for policymakers and health authorities in Indonesia and potentially other developing countries with similar healthcare contexts.

CONCLUSION

Pre-hospital delay of AIS was very common and may represent the most challenging problem to improve stroke care in Indonesia. Wake-up stroke, a lack of patient understanding in recognizing stroke symptoms, and an ineffective referral system were the most prominent risk factors for pre-hospital delay in Indonesian AIS patients. Time to complete the CT scan represented a bottleneck for in-hospital delays. Based on this finding, attempts to increase public awareness of stroke symptoms, improved the utilization of the EMS system, improved human resources and facilities, and better coordination inside and between hospitals are keys to improving in the early management of AIS in Indonesia.

ETHICAL APPROVAL

This study protocol was approved by the Faculty of Dentistry/Faculty of Pharmacy Mahidol University Institutional Review Board (REC number: 0517.0319/EC683), the Ethics Committees of Dr. Soetomo General Hospital Surabaya (REC number: 1021/KEPK/III/2019), Universitas Airlangga Hospital (REC number: 105/KEH/2019), and Hajj General Hospital Surabaya (REC number: 070/78/03.2/2019). This study was completed following the 2013 Declaration of Helsinki.

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