Association between Prehospital Delay Status and Stroke Severity in Acute Ischemic Stroke: Shift-Analysis Approach

Su Jung Lee
Department of Nursing, Chuncheon Sacred Heart Hospital, Chuncheon-si, Republic of Korea

*Corresponding author: Su Jung Lee, Department of Nursing, Chuncheon Sacred Heart Hospital, 77, Sakju-ro, Chuncheon-si, Gangwon-do 24259, Republic of Korea, Tel: +82-33-240-5846, Fax: +82-33-255-6244; E-mail: sujunglee.95@gmail.com

Received date: March 01, 2018; Accepted date: April 10, 2018; Published date: April 17, 2018

Copyright: © 2018 Lee SJ. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Objective: We investigated the association between stroke severity and pre-hospital delay of patients with an Acute Ischemic Stroke (AIS).

Method: A consecutive 1,412 patients with AIS enrolled in the acute stroke registry were included in the final study. Stroke severity was assessed by National Institute of Health Stroke Scale (NIHSS) score. A pre-hospital delay between less than 3 h and 3 h or more was compared using Pearson’s chi-square for categorical variables and Student’s t-test or Mann-Whitney U test for continuous variables, as appropriate. Association between initial NIHSS score and pre-hospital delay was plotted with Spearman’s correlation analysis. We used the analysis of variance or Kruskal-Wallis test and chi-squared test to compare the baseline characteristics according to NIHSS tertile. We analysed the variables associated with the higher shift of NIHSS tertile using an ordinal logistic regression analysis.

Results: Increased stroke severity decreased the pre-hospital delay (Spearman’s rho=-0.216, p<0.001). Age (common odds ratio (cOR), 1.03; 95% confidence interval (CI), 1.02-1.03; p<0.001), history of previous stroke (cOR, 1.56; 95% CI, 1.25-1.94; p<0.001) and pre-hospital delay ≥ 3 h (cOR, 0.48; 95% CI, 0.39-0.59; p<0.001) were associated with higher shift of NIHSS tertiles in univariable ordinal logistic regression analyses. In multivariable model, pre-hospital delay ≥ 3 h is a negative predictor for higher shift of NIHSS tertile (cOR, 0.49; 95% CI, 0.39-0.61; p<0.001).

Conclusion: As the stroke severity increased, onset-to-hospital arrival time was decreased in AIS patients. Therefore, the findings suggest the need for development of individualized educational programs for each stroke patient.

Keywords: Stroke; Severity of illness index; Time factors

Introduction

Stroke is the second leading cause of death and 6.7 million people died of stroke in 2015 according to the World Health Organization [1]. In Korea, stroke is the third major cause of death, after cancer and cardiovascular disease [2]. It is an important factor contributing to the increased burden of medical expenses due to high rates of disability and complications [3]. The acute phase treatment of ischemic stroke involves mainly intravenous thrombolysis with recombinant tissue type plasminogen activator and endovascular treatment via mechanical thrombectomy, resulting in improvement of neurological symptoms after ischemic stroke, the degree of disability and prognosis after 3 months [4]. Based on the recommendations of European Cooperative Acute Stroke Study III trial, the time window for rtPA administration in patients with Acute Ischemic Stroke (AIS) has been increased to 4.5 h [5]. However, less than 10% of patients are treated with rtPA following ischemic stroke [6,7]. Pre-hospital delay from symptom onset to hospital arrival is one of the key factors determining the choice of intravenous thrombolytic therapy or intravascular surgery during the acute period. In addition, minimizing onset-to-door time cannot be overstated because cutting the time from cerebral arterial occlusion to recanalization is crucial for recovery of ischemic penumbra and is the most important treatment strategy for rapid recovery of patients with stroke symptoms [8].

Several studies investigated the factors associated with pre-hospital delay in AIS patients, including gender, educational and income levels, cohabitation with family, mode of transportation to hospital, regional differences between urban and rural areas, history of previous stroke, and stroke awareness of care givers [9]. In some studies, pre-hospital delay was longer with a lower National Institutes of Health and Stroke Scale (NIHSS) score [10-12]. Initial stroke severity is one of the most important predictors of post-stroke prognosis. However, Strambo et al. [13] reported that a third of all patients with a lower initial NIHSS score showed a poor prognosis at 3 months after stroke suggesting the need for rapid transfer to a specialized stroke center upon detection of neurological symptoms regardless of their severity. The severity of stroke depends on factors such as hyperglycemia, atrial fibrillation, previous myocardial infarction, and hypertension and therefore, accurate assessment of severity is critical for the management of patients with stroke [14]. Thus, we sought to assess whether stroke severity was associated with pre-hospital delay in AIS patients.
Methods

Study design

This study is a retrospective case-controlled observational study.

Setting and sample

We used a single-center registry database containing prospective demographic and clinical data of patients diagnosed with AIS, who were admitted to hospital within 7 days of stroke symptom onset (January 2011-December 2016). We found that 1,618 consecutive patients with a transient ischemic attack (TIA) and ischemic stroke were eligible for inclusion in the study. TIA was defined by rapid development of clinical signs associated with focal or global disturbance of cerebral function lasting fewer than 24 h, without any apparent nonvascular cause [15] in addition to the absence of documented diffusion-restrictive lesion on brain MRI. Acute ischemic stroke was defined as a sudden loss of focal cerebral function that persisted more than 24 h and relevant symptoms of stroke, which were detected as diffusion restrictive lesions on brain MRI. We excluded (1) 18 patients aged less than 19 years, (2) 96 patients who were admitted to the hospital after 7 days of symptom onset, (3) 48 patients transferred from other hospitals, (4) 25 patients with a hemorrhagic stroke, and (5) 37 patients with missing clinical information. A total of 1,412 subjects with TIA or AIS were included in the final analysis.

Ethical consideration

Written informed consent was obtained from all the patients and corresponding caregivers. This study was approved by the Institutional Review Board of the participating medical center (IRB No. 2017-65).

Measurements

Prehospital delay

It is difficult to determine the precise onset of a stroke if subjects experienced a stroke during sleep or in the absence of a witness or bystander during stroke onset. Thus, we divided the timing of the stroke symptom onset into two cases. First, if the time of stroke symptom onset is clear, the pre-hospital delay was defined as the time from the clear onset to hospital arrival. Second, if the stroke onset was unclear, pre-hospital delay was defined starting with the initial recognition of stroke symptoms until hospital arrival. Pre-hospital delay was divided into <3 h and ≥3 h.

Clinical parameters

NIHSS consists of 11 items: level of consciousness, horizontal eye movement, visual field test, facial palsy, motor power of arm and leg, limb ataxia, sensory response, language, speech, extinction and inattention. The score ranges from 0 to 42 points and increased scores indicate the severity of neurological symptoms [16]. We used the initial NIHSS score for admission to emergency department.

Stroke subtypes were based on The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [17]. We merged stroke associated with other determined and undetermined etiologies into one group. Risk factor such as hypertension, diabetes, hyperlipidemia and smoking were defined previously [18].

Data collection

We used the ischemic stroke registry data for this analysis. Patients with AIS within 7 days of symptom onset were prospectively included in this registry. Well-trained neuro-physicians retrieved information regarding stroke severity and mechanisms, and acute treatment and laboratory results, automatically from the electronic medical records.

Data analysis

Descriptive comparison of <3 h and ≥3 h of prehospital delay was conducted using Pearson's chi-square test for categorical variables and Student's t-test or Mann-Whitney U-test for continuous variables, as appropriate. Association between initial NIHSS score and pre-hospital delay was plotted with Spearman's correlation analysis. We compared the baseline characteristics according to NIHSS tertiles using analysis of variance or Kruskal-Wallis test and chi-squared test. We analysed the variables associated with the shift to higher NIHSS tertile using univariable ordinal logistic regression analysis, and expressed these associations as a common odds ratio (cOR). Multivariable ordinal logistic analyses were performed via a tiered approach. Initially, the association between prehospital delay (≥3 h) and a higher shift of NIHSS tertile was represented as crude cOR, and was adjusted for age, gender and stroke subtype. All variables with a p<0.05 in univariable ordinal logistic regression analysis were selected as covariates in the final multivariable ordinal logistic regression model. We performed these analyses using IBM SPSS Statistical Software 24.0 (IBM SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the participants

The mean age of the participants was 69.3 ± 12.5 years and the male ratio was 57.6% (814 out of 1,412). The median pre-hospital delay was 6.1 (1.6-31.4) h. Thirty-two percent (511/1412) of the total subjects visited a hospital within 3 h of symptom onset. The proportion of patients with diabetes and dyslipidemia differed between the two groups. Small-vessel occlusion (SVO) was the predominant stroke subtype in study participants. The proportion of cardioembolic (CE) stroke was higher in the group with a pre-hospital delay <3 h than in the group ≥3 h (Table 1).

|                          | Over 3 h (n=901) | Within (n=511) | 3 h | P value |
|--------------------------|------------------|----------------|-----|---------|
| Female                   | 392 (43.5)       | 206 (40.3)     | 0.243 |
| Age, years               | 69.8 ± 12.3      | 68.8 ± 13.0    | 0.271 |
| History of previous stroke | 234 (26.0)        | 134 (26.2)     | 0.917 |
| Hypertension             | 591 (65.6)       | 351 (68.7)     | 0.236 |
| Diabetes                 | 329 (36.5)       | 155 (30.3)     | 0.019 |
| Dyslipidemia             | 172 (19.1)       | 126 (24.7)     | 0.014 |
| Current Smoking          | 255 (28.3)       | 126 (24.7)     | 0.138 |
| Stroke subtype (TOAST)   | <0.001           |                |      |
| TIA                      | 73 (8.1)         | 72 (14.1)      |      |
| LAA                      | 233 (25.9)       | 143 (28.0)     |      |
Stroke severity and relationship with pre-hospital delay

As shown in Figure 1, the Spearman’s correlation between initial stroke severity (NIHSS score) and pre-hospital delay indicates that increased severity of stroke gradually decreased the pre-hospital delay (Spearman’s rho=-0.216, p<0.001). NIHSS is an interval variable and left-shifted variable. Thus, we divided these scores into tertiles (0-1, 2-4, 5 or more). Table 2 lists the differences in demographic, clinical and laboratory parameters by NIHSS tertile. Advanced age, male sex, previous history of stroke and short pre-hospital delay were associated with high NIHSS tertiles. In addition, as the stroke severity increased, the proportion of large artery atherosclerosis (LAA) and CE strokes increased gradually.

### Table 1: Baseline characteristics (N=1,412).

| SVO | 451 (50.1) | 147 (28.8) |
| CE  | 81 (9.0)   | 104 (20.4)  |
| SOE/SUE | 63 (7.0) | 45 (8.8) |
| NIHSS, median (IQR) | 2 (1–4) | 4 (1–12) | <0.001 |
| NIHSS, mean ± SD | 3.4 ± 4.2 | 6.9 ± 7.0 | <0.001 |
| Thrombolysis | 9 (1.0) | 126 (24.7) | <0.001 |

### Table 2: Baseline characteristics (N=1,412).

| Variable | Tertile 1 | Tertile 2 | Tertile 3 |
|----------|-----------|-----------|-----------|
| Age, years | 66.7 ± 13.2 | 69.6 ± 12.0 | 71.9 ± 11.8 | <0.001 |
| Female | 225 (44.0%) | 185 (41.9%) | 188 (41.0%) | 0.607 |
| History of previous stroke | 112 (21.9%) | 104 (23.5%) | 152 (33.1%) | <0.001 |
| Hypertension | 337 (65.9%) | 280 (63.3%) | 325 (70.8%) | 0.054 |
| Diabetes | 165 (32.3%) | 176 (39.8%) | 143 (31.2%) | 0.012 |
| Dyslipidemia | 113 (22.1%) | 96 (21.7%) | 89 (19.4%) | 0.542 |
| Current Smoking | 134 (26.2%) | 124 (28.1%) | 123 (26.8%) | 0.813 |
| Stroke subtype (TOAST) | 114 (22.3%) | 15 (3.4%) | 16 (3.5%) | <0.001 |
| TIA | 82 (16.0%) | 93 (21.0%) | 201 (43.8%) |
| LAA | 243 (47.6%) | 264 (59.7%) | 91 (19.8%) |
| CE | 34 (6.7%) | 43 (9.7%) | 108 (23.5%) |
| SOE/SUE | 38 (7.4%) | 27 (6.1%) | 43 (9.4%) |
| Thrombolysis | 9 (0.0%) | 13 (2.9%) | 122 (26.6%) | <0.002 |
| Prehospital delay | 163 (31.9%) | 100 (32.6%) | 248 (54.0%) | <0.001 |

Results of univariable ordinal logistic regression analysis are displayed in Table 3. Age (cOR, 1.03; 95% confidence interval [CI], 1.02-1.03; p<0.001), history of previous stroke (cOR, 1.56; 95% CI, 1.25-1.94; p<0.001), pre-hospital delay ≥ 3 h (cOR, 0.48; 95% CI, 0.39-0.59; p<0.001) were associated with a shift in NIHSS tertiles. In addition, elevated WBC count, TG, BUN, admission serum glucose and systolic blood pressure were associated with a higher shift of NIHSS tertile in univariable analyses. After adjusting for age, gender, stroke severity and several laboratory parameters, pre-hospital delay ≥ 3 h (versus pre-hospital delay <3 h) was associated with a lower shift of NIHSS tertile (cOR, 0.49; 95% CI, 0.39-0.61; p<0.001; Table 4).

### Figure 1: Relationship between stroke severity and prehospital delay (symptom onset to admission time, h).
Table 2: Characteristics of each group according to the NIHSS tertile (N=1,412).

| Blood Cell | 3 h or more | Within 3 h | Within 3 h
|------------|-------------|------------|-------------
| WBC, x10⁹/L | 7.3 ± 2.3 | 7.7 ± 2.7 | 8.5 ± 3.5 |
| Hb, g/dL | 13.7 ± 1.9 | 13.8 ± 1.8 | 13.6 ± 2.1 |
| Hct, % | 40.9 ± 17.8 | 40.3 ± 5.0 | 40.0 ± 6.4 |
| Total Cholesterol, mg/dL | 169.7 ± 42.8 | 172.5 ± 44.1 | 167.9 ± 43.1 |
| TG, mg/dL | 136.3 ± 92.9 | 130.8 ± 79.6 | 113.0 ± 85.4 |
| HDL-C, mg/dL | 46.0 ± 11.5 | 45.9 ± 11.1 | 48.1 ± 11.7 |
| LDL-C, mg/dL | 99.8 ± 31.6 | 104.5 ± 36.2 | 98.5 ± 34.7 |
| BUN, mg/dL | 16.8 ± 7.9 | 17.1 ± 10.0 | 18.9 ± 10.0 |
| Cr, mg/dL | 1.1 ± 1.05 | 1.0 ± 0.7 | 1.0 ± 0.5 |
| Glucose fasting, mg/dL | 119.1 ± 49.0 | 123.5 ± 52.3 | 129.8 ± 55.7 |
| INR | 1.0 ± 0.3 | 1.0 ± 0.2 | 1.1 ± 0.5 |
| BPsys, mm Hg | 141.6 ± 25.9 | 143.9 ± 25.7 | 175.2 ± 44.1 |
| BPdia, mm Hg | 83.1 ± 13.7 | 94.3 ± 16.5 | 119.1 ± 49.0 |

Note: BPdia: Diastolic Blood Pressure; BPsys: Systolic Blood Pressure; BUN: Blood Urea Nitrogen; CE: Cardioembolism; Cr: Creatinine; Hb: Hemoglobin; Hct: Hematocrit; HDLC: High Density Lipoprotein Cholesterol; INR: International Normalized Ratio; LAA: Large Artery Artherosclerosis; LDLC: Low Density Lipoprotein Cholesterol; NIHSS: National Institute Of Health Stroke Scale; TG: Triglycerides; TIA: Transient Ischemic Attack; TOAST: Trial of Org 10172 in Acute Stroke Treatment; SOE: Stroke of Other Determined Etiology; SUE: Stroke of Undetermined Etiology; SVO: Small Vessel Occlusion; WBC: White Blood Cell

Table 3: Common odds ratios for higher shift of NIHSS tertile in univariable ordinal logistic regression analysis.

| Prehospital delay ≥ 3 h | cOR (95% CI) | P value |
|------------------------|-------------|---------|
| Crude analysis | 0.48 (0.39-0.59) | <0.001 |
| Model 1 | 0.46 (0.38-0.57) | <0.001 |
| Model 2 | 0.46 (0.38-0.57) | <0.001 |
| Model 3 | 0.46 (0.37-0.58) | <0.001 |
| Model 4 | 0.49 (0.39-0.61) | <0.001 |

Note: CI: Confidence Interval; cOR: Common Odds Ratio; NIHSS: National Institute of Health Stroke Scale

Table 4: Common odds ratios for higher shift of NIHSS tertile in multivariable ordinal logistic regression analysis.

Model 1 adjusted for age;
Model 2 adjusted for variables included in the Model 1 plus sex;
Model 3 adjusted for variable included in the Model 2 plus stroke subtype.
scores of 5 or higher, and that patients with stroke due to SVO had a longer pre-hospital delay compared with those diagnosed with CE. Accordingly, it is crucial to manage the risk factors for stroke and the presence of vulnerable plaque [20]. Several factors underscore the need for prompt arrival at a hospital even if the stroke symptoms are mild or minor.

The results of this study underscore the need for efforts to improve public awareness of stroke symptoms as well as the awareness of stroke as an emergency situation. The present study found that the incidence of LAA and CE subtypes of cerebral infarction according to the TOAST classification, was relatively higher in the group with NIHSS scores of 5 or higher, and that patients with stroke due to SVO had a longer pre-hospital delay compared with those diagnosed with CE stroke. These findings are in line with previous study findings [21].

A notable finding in the study was that pre-hospital delay did not differ according to the previous history of stroke. Survivors of stroke or a TIA showed an increased risk for subsequent stroke, which was associated with a higher severity of disability and risk of death compared with patients sustaining stroke for the first time [22]. Accordingly, it is crucial to manage the risk factors for stroke and educate patients regarding warning symptoms and emergency treatment. However, recent data obtained from stroke units at acute hospitals nationwide in Korea show that 56% of stroke patients and guardians and 77% of community residents participated in stroke education programs [23]. Therefore, systematic education should be more aggressively provided to groups at highest risk for stroke, i.e., stroke survivors and their guardians.

According to the guidelines of the American Stroke Association, the acronym FAST (face, arm, speech and time) has been used to detect the signs of stroke [24]. In Korea, since 2009, efforts have been made to increase public awareness of stroke symptoms through a campaign of "Stroke, Suddenly Five." A previous study, which investigated the factors driving patients with acute stroke and TIA to a hospital between 2004 and 2009, showed that patients experiencing unilateral paralysis and language disorders had a shorter pre-hospital delay, whereas those experiencing headache and visual disorders had a longer pre-hospital delay [25]. The current study is not completely consistent with the previous report, although the importance of education of mild or rare symptoms in the prevention of pre-hospital delay cannot be overstated.

In addition, the NIHSS is a scale reflecting stroke severity, but symptoms of stroke in the anterior cerebral artery are scored higher and therefore, patients with stroke in the posterior cerebral artery scored lower on the scale [26,27]. Because the primary symptoms of stroke associated with the posterior cerebral artery, such as double vision, visual field defect, ataxia, and headache, constitute a relatively small proportion of the NIHSS score, and patients often do not understand the stroke symptoms, it is possible that stroke location may determine the extent of pre-hospital delay. However, this supposition remains inconclusive based on the current study because information on the location of stroke was not examined.

Hematological testing according to the NIHSS score indicates differences in WBC, TG, and BUN. WBC levels are associated with edema following inflammatory cell infiltration into the brain, hemorrhagic transformation after stroke, and increased mortality rate [28]. Moreover, it is vital to closely monitor the changes in BUN, i.e., as a marker of impaired renal function because renal function deteriorates with the worsening of stroke and the glomerular filtration rate (GFR) decreases in most stroke patients. The classification of NIHSS scores revealed significantly higher systolic BP in the group with worsening neurological impairment. Brown DW et al. reported that systolic BP is a predictor of stroke and an independent factor associated with increased risk of fatal stroke in both men and women [29]. Accordingly, nurses should be aware of the importance of controlling systolic BP in stroke patients and closely monitor systolic BP.

The present study has the following limitations. First, the study was a retrospective analysis of stroke patients admitted to a single university hospital. As regional and hospital conditions may affect the clinical features of stroke, it is difficult to generalize the findings to the entire population of stroke patients. Second, the location of stroke and the extent of stenosis in the involved vessels, which affect stroke severity, were unavailable. Third, we did not investigate additional factors that may affect pre-hospital delay, such as patient transport means, the level of knowledge of patients and guardians, or whether the patient lived with family members. Hence, the study cannot address the effect of such factors on pre-hospital delay. Despite the limitations, the study findings are of great significance in continuously managing stroke risk factors and severity not perceived by patients. In addition, the findings suggest the need for education on stroke prevention and comprehensive self-management of health.

Conclusion

The study demonstrated that pre-hospital delay in many patients is influenced not only by physical factors as living with family and the distance to hospital, but also by potential severity, confirming the importance of clinical factors. Therefore, there is a need for prospective studies to determine whether nursing education for hospitalized patients diagnosed with AIS reduces the delay in hospital arrival and for improved patient outcomes following stroke recurrence.

References

1. Media Centre Fact Sheets (2017) Cardiovascular diseases [Internet]. World Health Organization.
