

The Impact of Onset to Hospital Admission Time on Clinical Outcome in Patients with Ischemic Stroke without Reperfusion Therapy

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Objective: The narrow therapeutic window after stroke onset is a major concern in stroke treatment, especially in developing countries. This study aimed to investigate the correlation between onset to hospital admission time and clinical outcome in patients with ischemic stroke who did not receive reperfusion therapy. **Method:** A total of 313 patients with ischemic stroke were recruited in this retrospective cohort study. Data were obtained from the electronic stroke registry of Bethesda Hospital Yogyakarta, Indonesia. Ischemic stroke was diagnosed by well-trained neurologists and confirmed by brain CT-scan. Clinical outcome was assessed using the modified Rankin scale. Predictors of clinical outcome were assessed. Data analysis was conducted using multiple logistic regression. **Results:** The incidence of disability and death were 30.4% (95/313) and 7.6% (24/313) respectively. Multiple logistic regression analysis showed onset to hospital admission time greater than 6 hours (OR: 4.56; 95% CI:2.372-8.792; $p < .001$) was an independent factor to a significant increase in disability risk. However, longer onset to hospital admission time did not significantly increase the risk of death. Age and complications were independent predictive factors of both disability (OR: 2.36; 95% CI:1.357-4.125; $p = .002$) and OR: 12.4; 95% CI:2.443-62.968; $p = .002$, respectively) and mortality (OR: 3.66; 95% CI:1.147-11.711; $p = .028$) and OR: 58.8; 95% CI:10.353-333.983; $p < .001$, respectively). **Conclusion:** Shorter onset to hospital admission time could save ischemic stroke patients from disability.

Keywords: Stroke, Hospital Admission Time, Treatment Outcome, Indonesia.

Introduction

Stroke is one of the most common causes of disability and death worldwide¹⁻⁴. Since it is said "time is brain", early stroke treatment has become critical to prevent disability and mortality^{5,6}. The establishment of intravenous recombinant tissue-type plasminogen (rt-PA) greater than 3 hours after

stroke onset has been shown to improve clinical outcome^{7,8}. The narrow time frame limits the use of this therapy as its benefits become attenuated with increasing time from stroke onset to treatment^{9,10,11-13}. Moreover, most patients who are admitted within 3 hours of stroke onset are still unable to receive this treatment due to eligibility criteria^{14,15}.

The efficacy of stroke therapy strongly depends on the time

interval from symptom onset to treatment. Previous studies which included stroke patients who received reperfusion therapy, showed that early hospital arrival after stroke onset improves functional outcome and reduces mortality¹⁶. However, data on the outcome for early stroke treatment on patients who did not receive reperfusion therapy are scarce^{6,17}. To address this issue, we investigated the time from stroke onset to hospital admission in patients with acute ischemic stroke. We aimed to evaluate the clinical outcome based on the time interval from symptom onset to hospital admission in patients who did not receive reperfusion therapy.

Materials and Methods

Study design

In this retrospective cohort study, we analyzed data from the electronic stroke registry of Bethesda Hospital Yogyakarta, Indonesia. Each subject had been followed up from day 1 of admission until they were discharged from the hospital. Trained stroke neurologists performed emergency evaluations and initiated the optimal stroke treatment as early as possible. Stroke was diagnosed upon admission by the sudden onset of nonconvulsive and focal neurological deficits with reference to the findings of either brain computed tomography, magnetic resonance imaging, or both.

Study subjects

Subjects with ischemic stroke who met the following criteria were included in the study: (i) ischemic stroke patients age greater than 18 years; (ii) hospitalized at Bethesda Hospital, Yogyakarta, Indonesia between January 2015 to December 2017; (iii) did not receive reperfusion therapy and (iv) complete data recorded in the electronic stroke registry. The exclusion criteria were: (i) incomplete data; (ii) discharge against medical advice; (iii) received reperfusion therapy and (iv) transferred to another hospital.

Clinical assessments

Demographic characteristics including comorbidity, complication, diagnosis, onset time, and hospital admission time were collected. Ischemic stroke diagnosis was established using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification with the subtypes of: (i) large-artery atherosclerosis; (ii) cardioembolism;

(iii) small vessel occlusion; (iv) stroke of other determined etiology, and; (v) stroke of undetermined etiology¹⁸. Subjects were classified into 2 age groups based on the Indonesian Ministry of Health's regulation of the geriatric age limit in Indonesia, less than 60 years of age and greater than or equal 60 years of age. Based on stroke history, the subjects were divided into those with first-time stroke and those with recurrent stroke.

Comorbidities evaluated in this study included hypertension, dyslipidemia, ischemic heart disease (IHD), and atrial fibrillation. Hypertension was diagnosed by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or consuming antihypertensive drugs. Dyslipidemia was defined as low density lipoprotein cholesterol level >140 mg/dL, high density lipoprotein cholesterol <40 mg/dL, triglyceride level >200 mg/dL, and/or total cholesterol level >200 mg/dL. IHD included confirmed stable angina pectoris by cardiac stress test; confirmed unstable angina pectoris, ST-elevation myocardial infarction (STEMI), and non-STEMI by electrocardiography (ECG). Atrial fibrillation (AF) was defined as an irregular heart beat confirmed by ECG test with typical P-wave findings.

Complications assessed in this study included urinary tract infection (UTI), pneumonia, gastrointestinal bleeding, and decubitus ulcer. UTI was defined as an infection of any part in the urinary tract during hospitalization confirmed by physical examination and urinalysis. Pneumonia was defined as pulmonary infection confirmed by physical examination, blood test and chest radiograph. Gastrointestinal bleeding was defined as bleeding of any part in the gastrointestinal tract with hematemesis and/or melena. Decubitus ulcer was defined as any discoloration of the skin and the presence of a wound in the skin and underlying soft tissues covering bony area compromised by pressure.

Time from stroke onset to hospital admission and study outcome

The time between stroke onset and hospital arrival was calculated as the onset of symptoms to hospital admission time. This study categorized 5 clinically relevant groups according to their onset to hospital admission time as follows: <3 hours, 3-6 hours, greater than 6-12 hours, greater than 12-24 hours, and greater than 24 hours. The clinical outcome was determined using the modified Rankin Scale (mRs) at the time of discharge from hospital. The patients were categorized into 3 groups: no

disability (mRs 0-2), with disability (mRs 3-5) and death (mRs 6).

Statistical analysis

Univariate analysis was used to examine the demographic characteristics. Bivariate analysis was conducted by analyzing disability and death status with age, gender, stroke history, presence of comorbidity, presence of complications, and stroke onset. To identify the independent factors associated with the clinical outcome, multivariate logistic regression model analyses were performed using baseline clinical characteristics and stroke features. Statistical analysis was performed using SPSS® Version 18 software.

Results

From January 2015 to December 2017, a total of 1657 patients with ischemic stroke were admitted in Bethesda Hospital Yogyakarta, Indonesia. Three hundred and thirteen stroke patients without reperfusion treatment were included in this study. Characteristics of patients included in the study are presented in Table 1. There were more patients greater than 60 years of age (58.5%) and more male patients (58.5%), with most patients were admitted within 24 hours of stroke onset. There were 65.5% of patients who were admitted with a first-time stroke; 68.1% had comorbidities; 93.3% had no complications; and 62% of patients admitted did not suffer from disabilities at discharge.

Table 1. Subjects Characteristics

| Characteristics | Ischemic Stroke | |
|------------------|-----------------|-------|
| | n | % |
| Age | | |
| ≤60 years | 130 | 41.5% |
| >60 years | 183 | 58.5% |
| Gender | | |
| Male | 183 | 58.5% |
| Female | 130 | 41.5% |
| Onset | | |
| <3 hour | 25 | 8.0% |
| 3-6 hour | 85 | 27.2% |
| >6-12 hour | 51 | 16.3% |
| >12-24 hour | 43 | 13.7% |
| >24 hour | 109 | 34.8% |
| Previous stroke | | |
| First Stroke | 205 | 65.5% |
| Recurrent Stroke | 108 | 34.5% |
| Comorbidity | | |
| Yes | 213 | 68.1% |
| No | 100 | 31.9% |

| | | |
|-----------------|-----|-------|
| Complication | | |
| Yes | 21 | 6.7% |
| No | 292 | 93.3% |
| Outcome | | |
| No disability | 194 | 62% |
| With disability | 95 | 30.4% |
| Death | 24 | 7.6% |

Table 2. Analysis on Subjects Ischemic stroke with Disabilities.

| Characteristic | Multivariate Analysis | | |
|-------------------|-----------------------|--------------|---------|
| | OR | OR (95% CI) | p-value |
| Onset | | | |
| <3 hour | | | |
| 3-6 hour | 1.54 | 0.037-0.725 | .262 |
| >6-12 hour | 4.56 | 2.372-8.792 | < .0001 |
| >12-24 hour | 4.07 | 2.190-7.573 | < .0001 |
| >24 hour | 5.94 | 1.368-25.851 | < .0001 |
| Age >60 years | 2.36 | 1.357-4.125 | < .0001 |
| Male | 1.30 | 0.773-2.193 | .321 |
| Recurrent Stroke | 1.00 | 0.579-1.732 | .996 |
| With Comorbidity | 1.61 | 0.936-2.780 | .085 |
| With Complication | 12.4 | 2.443-62.968 | < .0001 |

Table 3. Analysis on Subjects Ischemic stroke with Mortality

| Characteristic | Multivariate Analysis | | |
|-------------------|-----------------------|----------------|---------|
| | OR | OR (95% CI) | p-value |
| Onset | | | |
| <3 hour | | | |
| 3-6 hour | 2.45 | 0.502-11.994 | .267 |
| >6-12 hour | 2.04 | 0.178-24.228 | .561 |
| >12-24 hour | 0.22 | 0.027-1.815 | .160 |
| >24 hour | 3.54 | 0.429-29.338 | .240 |
| Age >60 years | 3.66 | 1.147-11.711 | < .0001 |
| Male | 1.50 | 0.550-4.099 | .428 |
| Recurrent Stroke | 0.75 | 0.273-2.103 | .594 |
| With Comorbidity | 2.50 | 0.905-6.924 | .077 |
| With Complication | 58.8 | 10.353-333.983 | < .0001 |

After multivariate adjustment, onset to hospital admission time greater than 6 hours, age greater than 60 years, and patients with complication were independent predictive factors of disability. Age greater than 60 years had the lowest risk of disability of the other significant factors (OR: 2.36; 95%CI: 1.357-4.125). Among the statistically significant factors, patients with complications had the highest risk of disability (OR: 12.4; 95%CI: 2.443-62.968). Patients who were admitted to the hospital after 6 hours had approximately five times the risk of disability (OR: 4.56; 95%CI: 2.372-8.792). Each odd ratio

(OR) shown above is relative to the less than 3 hours from stroke onset group.

In the group that died, the statistically significant factors were age greater than 60 years and patients with complication ($p < .0001$). For all groups, onset to hospital admission time was not predictive of mortality from ischemic stroke. The multiple regression analysis for patients who died are shown in Table 3. Age greater than 60 years and patients with complication were independent predictive factors of mortality (OR: 3.665; 95%CI: 1.147-11.711). The patients with the presence of complication had the highest risk of mortality (OR: 58.8; 95%CI: 10.353-333.983).

Discussion

Through multiple logistic regression analysis, we determined that hospital admission greater than 6 hours after stroke onset was associated with disability (mRs 3-5). This association was independent of age, gender, previous stroke, comorbidity and complication. Onset of stroke and hospital admission time did not have any effect on mortality at any time interval. However, age and presence of complication were independent predictive factors of mortality.

Hospital admission time after ischemic stroke onset has been known to be an important factor influencing the clinical outcome and prognosis¹⁹. Previous studies reported that earlier hospital arrival correlated with poorer clinical outcome, as patients with more severe symptoms have a tendency to get to the hospital earlier²⁰⁻²³. Nonetheless, patients with the most severe stroke have are more likely to survive with early admission¹⁷.

Thrombolytic therapy on early treatment of ischemic stroke has been proven to give patients a favorable outcome particularly in large artery atherosclerosis and cardioembolism²⁴. However, because of the narrow therapeutic window and contraindications, thrombolytic therapy is often withheld^{15,25}. Matsuo et al. showed that regardless of thrombolytic therapy and stroke severity, faster hospital admission was associated with a more favorable clinical outcome, including neurological improvement and good functional outcome¹⁵. The above results were mirrored in our study as favorable functional outcomes more frequently occurred in patients who were admitted to hospital within 6 hours after stroke onset regardless of patient's background characteristics.

Denti et al. investigated patients with ischemic stroke without thrombolytic therapy and found that early hospital admission time was associated with a reduced risk of 1-month mortality, but no association was observed for disability¹⁷. Their study found no correlation between survival and functional recovery. In contrast, the present study showed older age and the presence of complications, but not hospital admission time, as significant risk factors of mortality. In a previous population-based study, older age was a strong predictor of mortality after stroke²⁶. Moreover, elderly patients have a higher prevalence of disorders such as atrial fibrillation, hypertension, coronary heart disease, a history of stroke and a smoking habit²⁷.

In the present study, patients with complications such as UTI, pneumonia, gastrointestinal bleeding, and decubitus ulcer were 58 times more at risk of mortality. Up to one-third of stroke patients suffered from pneumonia. An earlier study reported that mortality of stroke complicated by pulmonary infection increased the risk of mortality three times²⁸. UTI and decubitus ulcer increased duration of hospital stay, health care costs, the risk of bacteremia and exposure to intravenous antibiotics. UTI and decubitus ulcer were also associated with decreased neurological status, poor clinical outcomes, and higher mortality risk. Gastrointestinal bleeding after the onset of stroke can lead to reduced hemoglobin concentration, neurological damage, poor functional results and death²⁹.

The association between onset to hospital admission time and clinical outcomes was also found in patients with strokes caused by large artery atherosclerosis or small-vessel occlusion¹⁵. In terms of early stroke treatments besides thrombolytic therapy, control of hypertension and blood glucose level, early use of anti-platelet agents, adequate nutrition, neuroprotective statins and treatment of arrhythmia are known to favorably impact prognosis. The benefit of these treatments may also increase with shorter times from stroke onset to treatment to improve collateral flow or microcirculation and early protection of neuron from ischemic insult. Early stroke treatments also contribute to decreased morbidity and mortality after acute ischemic stroke^{15,24}.

This cohort study was based in a single hospital, so potential confounding factors related to process of care limit the extent to which our results can be generalized. However, this study includes the strengths of provision of stroke care by expert neurologists and no missing baseline data. A potential limitation

is the short-time interval between stroke and the clinical outcome assessment. This study only measures mRs as clinical outcome during hospital stay. The mid and long-term prognosis and outcome should be measured and analyzed so the mid- and long-term treatment outcome could also be better understood.

Conclusion

In conclusion, this study demonstrated that early hospital admission after stroke onset is associated with a more favorable functional outcome. Specifically, if a patient is admitted after 6 hours of ischemic stroke onset, the likelihood of being discharged with disability increases.

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