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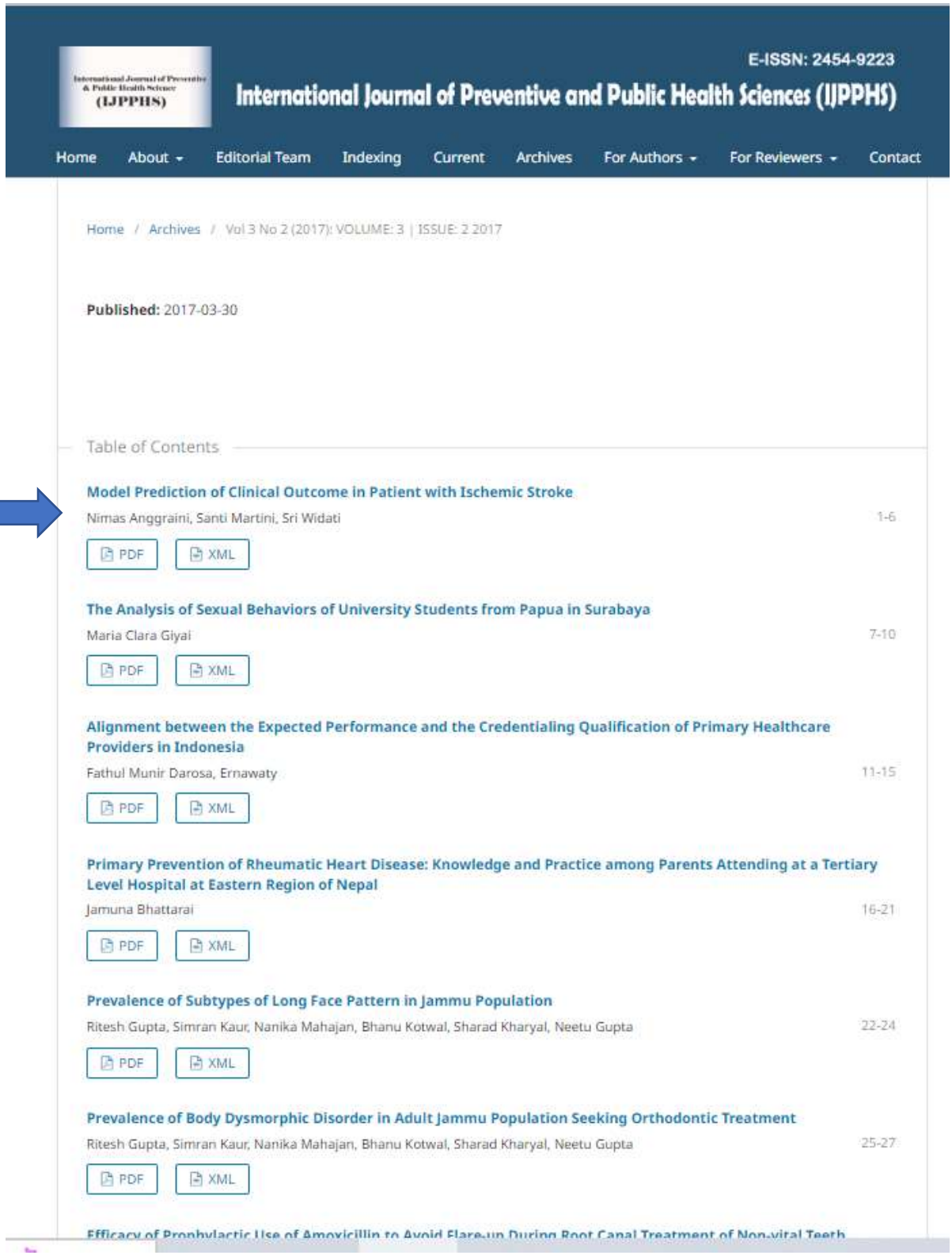

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Original Article

# Model Prediction of Clinical Outcome in Patient with Ischemic Stroke

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## ABSTRACT

**Introduction:** The increasing of life expectancy driven by the success of national development leads to an epidemiological transition to non-communicable diseases (NCDs). The number of morbidity caused by NCD and accidents is expected to increase significantly, and this incidence is related to the increased of risk factors due to lifestyle changes in the community. Stroke is the second leading cause of death worldwide and is a major cause of disability globally.

**Purpose:** The purpose of this study is to develop a model prediction of clinical outcomes in patients with ischemic stroke.

**Materials and Methods:** A case-control study was conducted. A total of 110 patients had been included in the study divided into 55 case groups and 55 control groups. Data analysis was performed using SPSS version 21 software program.

**Results:** The results of the study indicated 10 variables to be continued into multiple logistic regression ($P < 0.25$), namely: Age ($P = 0.163$), gender ($P = 0.000$), history of hypertension ($P = 0.038$), heart abnormalities ($P = 0,039$), history of stroke/transient ischemic attack ($P = 0.196$), blood pressure ($P = 0.169$), total cholesterol ($P = 0.004$), triglycerides ($P = 0.035$), blood glucose level ($P = 0.132$), and therapeutic time window ($P = 0.146$). Meanwhile, there were three variables that qualified to be used as a predictors model for clinical outcomes of ischemic stroke in the form of 0.477–0.035*total cholesterol+0.07*triglyceride+0.007* blood glucose levels.

**Conclusion:** This study can be an input in the development of the epidemiological science of NCD, especially stroke. It thus can provide an input on appropriate promotive and preventive measures to reduce the number of disability and death from stroke.

**Key words:** Clinical outcome, Ischemic stroke, Predictor

## INTRODUCTION

The increasing of life expectancy driven by the success of national development and the expanding modernization in Indonesia leads to an epidemiological transition to non-communicable diseases (NCDs). The number of morbidities caused by NCD is expected to increase significantly. The incidence is related to the increased risk factors due to lifestyle changes in the community.[1] The World Health Organization shows that 57 million deaths occur in the world in 2008, and 36 million were caused by NCD. Stroke is the second leading cause of death worldwide and is a major cause of disability globally.[2]

In Indonesia, since 1995–2007, the proportion of non-communicable disease had increased significantly from 41.7% to 59.5%. Stroke was positioned in the first rank of 10 most degenerative diseases with a mortality rate of 12.68% in 2009. East Java was one of the provinces that experienced a significant increase in stroke from 2007 to 2013 compared to other provinces which also had the highest stroke prevalence. Stroke is a NCD that can affect the quality of life (health-related quality of life) for patients that can be discharged from the hospital to recover.

There are many factors which can affect the outcomes and levels of improvement after experiencing ischemic stroke.[3] Outcome of stroke is generally described in terms of mortality and functional status after experiencing stroke. A decrease in ability can occur due to loss of consciousness as well as malfunction of certain areas of the brain that caused by disruption of blood flow or the rupture of blood vessels in that certain areas.[4] The goal of stroke management is to reduce

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morbidity, reduce mortality, and reduce disability rates. One of the various attempts that plays an important role to achieve these goals is the introduction of symptoms of stroke and early treatment starting from the medication of pre-hospital quickly and precisely. The treatment of acute stroke is also influenced by knowledge at the community level about the risk factors for stroke and healthcare workers regarding the concept that stroke is a disease which needs emergency treatment. The philosophy "time is brain and the golden hour" given the common understanding that stroke disease is a medical emergency, it will play a role in saving lives and preventing long-term disability.[5,6]

## MATERIALS AND METHODS

This research was a type of analytic observational studies with case-control study design. The source of population was obtained from medical record of ischemic stroke patient in Syarifah Ambami Rato Ebu Hospital during January–December 2016 period with the total of 324 respondents and with these following inclusion criteria: (1) Assessment data on medical record were well completed, (2) determination of diagnosis performed by neurologist of Syarifah Ambami Rato Ebu Hospital, and (3) medical record of ischemic stroke patients who were inpatient at Syarifah Ambami Rato Ebu Hospital.

The sample size was determined using Lemeshow 1997, and it obtained 110 respondents, with ratio 1:1 which consists of 55 groups as control and 55 groups as case using single-blind method. Bivariate analysis was performed using Chi-square test with $P < 0.25$ on categorical variable (age, gender, history of stroke/transient ischemic attack (TIA), history of hypertension, history of diabetes mellitus, heart abnormality, and therapeutic time window) and implementing independent *t*-test with $P < 0.25$ on numerical variable (blood pressure, blood cholesterol levels, and blood glucose levels).

Multivariate analysis continued using multiple logistic regression with a significance level of 95% ($\alpha = 0.05$). Data were analyzed using SPSS 21. The research ethics was conducted by the Health Research Ethics Committee Faculty of Public Health of Airlangga University.

## RESULTS

Based on the results of the study, it was known that the average respondent in the group with moderate clinical outcome was 49 ± 11.488 years old. Most respondents 63.6% were between 46 and 83 years old and 52.7% of them are female. In groups with severe clinical outcomes, the average respondent was 53 ± 10.347 years old. Most respondents of 69.1% were aged between 46 and 83 years and female were 50.9%. The result of bivariate analysis using Chi-square test showed $P = 0.163$ (age) and 0.000 (gender), so the variable of age and gender was candidate of clinical outcome model of stroke outcome because $P < 0.25$.

Based on the results of the study, it was found that some of the respondents 58.2% in the group with moderate clinical outcome had a history of hypertension, most of the respondents 83.6% had no history of diabetes mellitus, 65.5% had no heart disorder, and 78.2% had no history stroke/TIA. In the group with severe clinical outcome, most of the respondents 61.8% had a history of hypertension, 74.5% had no history of diabetes mellitus, 61.8% had no cardiac lesion, and 72.7% had never experienced stroke/TIA. The result of bivariate analysis using Chi-square test showed $P = 0.038$ (history of hypertension), $P = 0.039$ (heart abnormality), and $P = 0.196$ (history of stroke/TIA) so that history of hypertension, heart abnormality, and history of stroke/TIA were the candidate model of clinical outcome of stroke for $P < 0.25$. While the history of diabetes mellitus variable showed $P = 0.880$, it was not a candidate of prognosis outcome indicator of stroke because $P > 0.25$.

Regarding the results of the study, it was found that the average respondent in the group with moderate clinical outcome was hospitalized with blood pressure of 157/87 ± 25.142 mmHg, total cholesterol of 173 ± 28.995 mg/dl, triglyceride of 134 ± 12.984 mg/dl, and blood glucose level of 154 ± 65.247 mg/dl. In groups with severe clinical outcomes, the average respondents entered the hospital with a blood pressure of 163/89 ± 24.735 mmHg, total cholesterol of 189 ± 37.135 mg/dl, triglyceride levels of 127 ± 22.722 mg/dl, and blood glucose level of 187 ± 91.623 mg/dl.

In the group with moderate clinical outcome, some of the respondents were hospitalized with blood pressure of 160–230 mmHg (50.9%), total blood cholesterol level of <200 mg/dl (78.2%), blood triglyceride of <160 mg/dl (74.5%), and blood glucose level of <200 mg/dl (78.2%). In groups with severe clinical outcome, some of the respondents were hospitalized with blood pressure of 160–230 mmHg (54.5%), total blood cholesterol levels of <200 mg/dl (58.2%), blood triglyceride levels of <160 mg/dl (50.9%), and blood glucose level of <200 mg/dl (63.6%). Based on the results of analysis, it was known that $P = 0.169$ (blood pressure), $P = 0.004$ (total cholesterol), $P = 0.035$ (triglyceride), and $P = 0.132$ (blood glucose level), so the variable of blood pressure, total cholesterol, triglyceride, and blood glucose level was candidate of prediction model of clinical outcome because $P < 0.25$.

Based on Table 1, it was known that some respondents in a group with mild clinical outcome got health service >6 h, i.e., 47.3%. In groups with severe clinical outcome, some of the respondents received health care >6 h (50.9%). The results of bivariate analysis using Chi-square showed $P = 0.146$, so therapeutic time window was a prospective model of clinical outcome of stroke because $P < 0.25$.

Multivariate test showed that there were three influential variables and an model prediction of clinical outcomes in patients with ischemic stroke in the form of 0.477–0.035*total cholesterol+0.07*triglyceride+0.007*GDA.

## DISCUSSION

The decline of the vascular system increases with age, and stroke is twice as often experienced when a person is >55 years.[2] From the results of this study, there was no significant effect between ages with clinical outcome of stroke. This was not in accordance with a study conducted by Adja in 2015 which found out that older patients had a higher incidence and an increased prevalence of ischemic stroke with worse functional outcomes compared to younger patients.[7] In other studies, it was also explained that age differences correlated with clinical deterioration, wherein clinical worsening groups had an older age averagely, since in older age, there was more than one risk factor that could aggravate clinical outcomes such as

**Table 1:** Distribution of clinical outcomes in ischemic stroke patients

| Variable | Clinical outcome | | *P* value |
|---|---|---|---|
| | Severe outcome (%) | Moderate outcome (%) | |
| Age (years) | | | |
| 27–45 | 17 (30.9) | 20 (36.4) | 0.163 |
| 46–83 | 38 (69.1) | 35 (63.6) | |
| Total | 55 (100) | 55 (100) | |
| Gender | | | |
| Male | 27 (49.1) | 26 (47.3) | 0.000 |
| Female | 28 (50.9) | 29 (52.7) | |
| Total | 55 (100) | 55 (100) | |
| History of hypertension | | | |
| Yes | 34 (61.8) | 32 (58.2) | 0.038 |
| No | 21 (38.2) | 23 (41.8) | |
| Total | 55 (100) | 55 (100) | |
| History of diabetes mellitus | | | |
| Yes | 14 (25.5) | 9 (16.4) | 0.880 |
| No | 41 (74.5) | 46 (83.6) | |
| Total | 55 (100) | 55 (100) | |
| Heart abnormality | | | |
| Yes | 21 (38.2) | 19 (34.5) | 0.039 |
| No | 34 (61.8) | 36 (65.5) | |
| Total | 55 (100) | 55 (100) | |
| History of stroke/TIA | | | |
| Yes | 15 (27.3) | 12 (21.8) | 0.196 |
| No | 40 (72.7) | 43 (78.2) | |
| Total | 55 (100) | 55 (100) | |
| Blood pressure (systole) | | | |
| 160–230 mmHg | 30 (54.5) | 28 (50.9) | 0.169 |
| 140–159 mmHg | 16 (29.1) | 17 (30.9) | |
| 100–139 mmHg | 9 (16.4) | 10 (18.2) | |
| Total | 55 (100) | 55 (100) | |
| Blood pressure (diastole) | | | |
| 70–90 mmHg | 39 (71) | 34 (61.9) | |
| 91–120 mmHg | 16 (29) | 21 (38.1) | |
| Total | 55 (100) | 55 (100) | |
| Total cholesterol | | | |
| ≥200 mg/dl | 23 (41.8) | 12 (21.8) | 0.004 |
| <200 mg/dl | 32 (58.2) | 43 (78.2) | |
| Total | 55 (100) | 55 (100) | |
| Triglycerides | | | |
| ≥160 mg/dl | 27 (49.1) | 14 (25.5) | 0.035 |
| <160 mg/dl | 28 (50.9) | 41 (74.5) | |
| Total | 55 (100) | 55 (100) | |
| Blood glucose level | | | |
| ≥200 mg/dl | 20 (36.4) | 12 (21.8) | 0.132 |
| <200 mg/dl | 35 (63.6) | 43 (78.2) | |
| Total | 55 (100) | 55 (100) | |
| Therapeutic time window (h) | | | |
| >6 | 28 (50.9) | 26 (47.3) | 0.146 |
| 3–6 | 15 (27.3) | 16 (29.1) | |
| <3 | 12 (21.8) | 13 (23.6) | |
| Total | 55 (100) | 55 (100) | |

*$P<0.25$. TIA: Transient ischemic attack

hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, and an increased of inflammatory process in old age.[8]

Table 1 showed a significant effect of sex on clinical outcomes of stroke. The results were consistent with research conducted by Spaander in 2017 that explained that women were more susceptible to the alteplase process, thus accelerating the process of recanalization that could affect the functional outcome after stroke attacked. This was caused by the distribution of groups were almost identical. so it could illustrate the influence of female sex on the clinical outcomes of stroke. It might also be related to the age of the majority of respondents who were in the elderly age range that would affect the level of estrogen hormone in female respondents. Another mechanism that also explained the differences in endogen fibrinolysis due to sex hormone differences between men and women had an indirect effect on the control of the fibrinolytic system due to low levels of platelet inhibitors.[9,10] Other studies have also discussed gender differences in stroke outcomes, based on several animal experiments that estrogen level is one of the most important factors associated with worsening brain tumor ischemia.[11]

Hypertension is the most important risk factor for all types of stroke, both ischemic stroke and bleeding stroke. From the results of this study obtained, there was a significant influence between history of hypertension to clinical outcome of stroke. The results were consistent with studies conducted by Ingeman *et al*. 2017 who reported an association between hypertension history with stroke outcome despite using different tools (mrS score).[9] This was related to the uncontrolled blood pressure in patients who had a history of previous hypertension so that it could affect the healing process when an ischemic stroke was striking. Other studies conducted by Chamorro suggested that a complete improvement in ischemic stroke would be facilitated by an inadequate reduction in blood pressure when cerebral edema was developing and resulting in adequate cerebral perfusion pressure which was associated with the history of previous blood pressure conditions.[12]

Based on the results of the study in Table 1, there was no significant effect of a history of diabetes mellitus to the clinical outcome of stroke. The results were not in accordance with previous studies conducted by Kooten and quoted by Adja in 2015 that they found 43% of patients who affected by acute phase of stroke with hyperglycemia and more than half of them had experienced diabetes or had latent diabetes.[7,10] The study also found a significant relationship between hyperglycemia and worsening stroke outcome. This happened because the distribution of respondents were almost heterogen. In addition, the previous study also did not include some other factors that could also be a factor that affected the outcome of stroke.

The presence of cardioembolic was the most common cause of ischemic stroke associated with worsening stroke outcome compared to other ischemic stroke types.[10] In this study, it found that there was significant effect between heart abnormalities on stroke outcome. These results were in accordance with the results of research conducted by Scheitz *et al*. in 2012 which explained that increased levels of cTnT affected the prognosis of patients with stroke in the short term.[11] The cTnT level was related to the presence of abnormalities in a person's heart.

Based on the results of the study, it found that there was no significant effect between the history of stroke/TIA and clinical outcomes of stroke. These results did not match with some studies that found an association between a history of stroke and a clinical outcome of stroke. One of the studies was conducted by Scheitz *et al.* (2012), suggesting that the risk of recurrent stroke and/or death was higher in the minor ischemic stroke (moderate ischemic stroke) despite the significant differences only in death. The apparent prognostic differences might be due to good prognosis in patients with *Amaurosis fugax* among patients with TIA.[11]

The increasing risk of stroke occurred along with the increasing in blood pressure, it was estimated that the risk of stroke might increase of 1.6 times per rising of 10 mmHg systolic blood pressure, and about 50% of stroke attacks could be prevented by blood pressure control.[8] Based on the results of the study, it was found that there was no significant influence between the states of blood pressure when hospitalized to the clinical outcomes of ischemic stroke. This was in contrast to some studies that reported that if hypertension was not lowered during an acute stroke, it could affect on brain edema. Systolic blood pressure in the poor outcome group was higher than in the good outcome group.[13] This occurred because there was no significant difference in blood pressure conditions when viewed from the distribution of respondents in both groups where the majority of both respondents had a blood pressure of 160–230/70–90 mmHg.

Blood pressure affected the events of stroke and affected the process of ischemia through the regulation of cerebral blood flow (CBF). Increased blood pressure during acute stroke was often a brain autoregulation mechanism to suffice brain blood flow in the ischemic area. This autoregulation was influenced by sympathetic inactivity of blood vessels, arterial $CO_2$ pressure, blood pressure-lowering drugs, and the presence of chronic hypertension. Systolic pressure described the phase of heart muscle contraction, whereas diastolic pressure described the relaxation phase. Systolic pressure affected the content of cardiac output pumped by the heart and diastolic pressure reflected the volume of blood to be pumped in the left ventricle, so the blood vessel was clogged, autoregulation mechanism would raise systolic blood pressure and lower diastolic blood pressure so that CBF would remain constant in the area of the ischemic brain through the collateral system.[10]

Based on the results of the study, it was found that there was significant influence between cholesterol levels in the blood both total cholesterol and triglycerides to clinical outcomes of stroke. The increasing of total cholesterol levels and low-density lipoprotein (LDL) was closely related to the occurrence of atherosclerosis. High LDL cholesterol was a risk of ischemic stroke. The events of stroke were increased in patients with total cholesterol levels above 240 mg/dl. The increasing in lipoprotein (a)/Lp was also a risk of heart disease and stroke. LP (a) was a particle of LDL, and its increase would trigger the occurrence of thrombosis by the mechanism of inhibiting plasminogen activator.[14] Plaque that was not well calcified in the blood vessels had the potential to develop into the acute coronary syndrome, where acute coronary syndromes suffered by patients would lead to higher susceptibility, resulting in worse patient outcomes.[11]

The result showed that there was no significant effect between random blood sugar levels when hospitalized with

clinical outcomes of stroke. This was not in accordance with some studies that explained that the increase in blood sugar levels might occur in the first 48 h in patients with acute phase stroke whether the patients diagnosed with diabetes mellitus or not, affecting the mortality and morbidity of patients. These factors were associated with worsening outcomes in ischemic stroke in many studies performed both in humans and animal experiments.[15,16] In lacunar stroke, the association between hyperglycemia and stroke outcomes was inconsistent and different in people who receiving low-molecular-weight heparin treatment. Hyperglycemia was known to increase the size of the infarct area. In a study conducted that patients with hyperglycemia at imbalance perfusion, magnetic resonance imaging showed increased lactate production and was associated with worsening outcomes.[14] Other studies also explained significant difference of the average of blood sugar level among total dependency outcome, severe dependency outcome, and moderate dependency outcome of acute ischemic stroke according to Barthel index.[17]

Ischemic stroke had a variety of etiologies but principally was caused by atherothrombosis or embolism, which would interfere with or terminate CBF. If CBF drops to <10 ml/mg/min, there would be a failure of homeostasis, which would cause rapid calcium influx and protease activity, that was a cascade or an excitotoxic chain process and ultimately the death of neurons. If a CBF disorder occurred between 15 and 30 ml/100 mg/min, then the ischemic state could be restored if the therapy was performed early on. There was no significant effect of therapeutic time window on clinical outcome of stroke. This was not in accordance with research conducted by Adja in 2015 which explained that patients who came at >6 h had more clinical worsening than patients who came on the onset of <6 h. In this research most of the respondents got health services >6 h since they complained the symptoms. The most of the respondents got health services >6 h since they complained the symptoms. The meta-analysis study of 9 studies conducted by Saini (2009) and cited by Adja (2015) found that patients who came within 8–72 h of onset of stroke experienced significant clinical and statistically deterioration. The worsening of acute stroke at the beginning of its development (within 48–72 h of onset) was potentially serious and had long-term clinical implications of deterioration for the patient. Underlying mechanisms included the presence of systemic factors, proliferative blood vessel occlusion, cerebral edema, hemorrhagic transformation, and seizures.[7,18,19]

Regarding on Table 2, the multivariate analysis using multiple logistic regression, the most influencing factors on clinical outcomes of stroke in ischemic stroke patients were total cholesterol, triglyceride levels, and blood glucose levels when hospitalized to the hospital. Total cholesterol levels had odds ratio (OR) value of 1.036 (95% confidence interval [CI] = 1.012–1.060) which indicated that elevated total blood cholesterol was a risk factor that worsened the clinical outcomes of stroke patients when discharged from the hospital. The triglyceride level had an OR value of 0.932 (95% CI = 0.899–0.966) indicating that elevated triglyceride levels in the blood were a protective factor against clinical outcomes of stroke patients when discharged from the hospital and the blood glucose level had OR value of 1.007 (95% CI = 1.000–1.014) which showed that elevated random blood sugar levels were a risk factor that worsened the clinical outcome of stroke patients when discharged from the hospital.

**Table 2:** Multiple logistic regression model prediction of clinical outcome

| No | Variable | *P* value | B | OR | CI 95% |
|---|---|---|---|---|---|
| 1 | Total cholesterol | 0.003 | 0.035 | 1.036 | 1.012–1.060 |
| 2 | Triglyceride | 0.000 | –0.070 | 0.932 | 0.899–0.966 |
| 3 | Blood glucose level | 0.049 | 0.007 | 1.007 | 1.000–1.014 |

OR: Odds ratio, CI: Confidence interval

These three factors were indicators in the preparation of the clinical outcomes prediction model of stroke and produce the following models: 0.477–0.035*total cholesterol+0.07*triglyceride+0.007*blood glucose levels. This prediction model could predict the clinical outcomes of stroke in ischemic stroke patients and might be applied when giving discharge planning - when patients were planned to discharge from the hospital - which described about the condition of the patients at home.

### Limitations of the Study

Limitations in this study were the model formed that could not produce sensitivity and specificity so that required further analysis to analyze it.

## CONCLUSION

Regarding the analysis results, it obtained a predictive model of clinical outcomes of stroke in ischemic stroke patients that the total cholesterol, triglyceride levels, and blood glucose levels were: 0.477–0.035*total cholesterol+0.07*triglyceride+0.007*blood glucose levels so that the socialization of all layers of society, both health workers and the general public to increase understanding of the importance of prehospital stroke treatment was very important to reduce mortality and disability caused by stroke.

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