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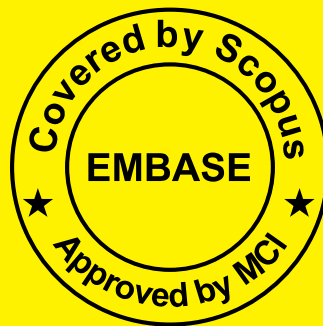


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Indicator of Dyslipidemia for Ischemic Stroke in Elderly with Hypertension

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ABSTRACT

Elderly with hypertension have a greater risk for ischemic stroke. It can be caused by dyslipidemia which is an abnormal amount of lipids in the blood such as increased levels of total cholesterol, LDL cholesterol, triglycerides and decreased levels of HDL cholesterol. The aim of this study is to analyze the indicator of dyslipidemia for ischemic stroke in elderly with hypertension. This study is an observational studies of analytical epidemiology with case control study design. The subject of study is the occurrence of ischemic stroke in elderly with hypertension who were admitted to outpatient installation RSU Haji Surabaya. The sample size for case and control samples were 74 patients. Samples were taken using simple random sampling methods. The data of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides from patient medical records were analyzed using bivariate analysis ($p=0.25$) is selected as a candidate for the multivariate analysis with multiple logistic regression ($p=0.05$). Total cholesterol, LDL cholesterol and triglycerides are selected as a candidate ($p=0.00$, $p=0.18$, $p=0.18$). The results showed that the most influential independent variables and became a model to predict the incidence of ischemic stroke in RSU Haji Surabaya was elevated total cholesterol ($p=0.03$; OR=4.87; 95% CI=1.10-21,53). It was concluded that total cholesterol had an effect on the incidence of ischemic stroke in RSU Haji Surabaya. Self-awareness is required to perform blood cholesterol screening as a prevention efforts, especially for elderly with hypertension because of greater risk for ischemic stroke.

Keywords: *ischemic stroke, dyslipidemia, elderly, hypertension, cholesterol*

INTRODUCTION

Non-Communicable Diseases (NCDs) are the cause of death around the world. The cases keep increasing and kill 38 million lives annually. As many as 85% of cases occurred in developing countries, including Indonesia. NCDs in Indonesia are estimated to reach 71% of total deaths [1].

Stroke is a non-communicable disease that notoriously becomes worldwide problem since it is worlds number three cause of death, after heart disease

and cancer. In developing countries, it accounts for 85% of deaths and 87% lifelong disabilities [2].

Indonesia is a developing country in Asia which ranks first as the country with the highest number of stroke patients. It is predicted that 500,000 Indonesians suffer from stroke every year, with about 25% of people dying and 75% having minor or severe disabilities [3].

Based on the report of the results of basic health research in Indonesia, the increase in stroke prevalence diagnosed by health workers in 2007 reached 8.3/1000 population and in 2013 reached 12.1/1000 population. One province with a higher prevalence of stroke than the national average is the province of East Java, which is 16/1000 population. Higher than in 2007 of 7.7/1000 population [4].

Stroke is generally classified into ischemic stroke with 80-85% of cases and hemorrhagic stroke with 15-20% of cases [5]. In Indonesia, ischemic stroke is the most

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common type of stroke that is 52.9% of cases [6]. Age is one of the most influential risk factors for ischemic stroke. Because along with increasing age, the greater the risk of a person suffering from ischemic stroke. This is due to degeneration of organ function in the body that is the decrease of blood flow to the brain resulting in the occurrence of stroke [7]. Based on Law Number 13 Year 1998 about the welfare of the elderly, it is explained that the elderly is someone who reached the age of 60 years and over [8].

The results of basic health research in 2013 it is known that the top 10 diseases in the elderly are dominated by the class of cardiovascular disease and the highest is hypertension, because the elderly will naturally experience a decrease in the degree of health. Uncontrolled hypertension or a history of hypertension in the elderly can lead to stroke. The prevalence of stroke in the diagnosed age group increased or experienced the highest symptoms at age ≥ 75 years and increased along with the age of a person [4].

World Population Prospects stated that the world's elderly population is increasing by 7.2% in 2013 and is predicted to increase to 9.6% by 2050. In Indonesia, there is also a potential fairly rapid increase of percentage in the elderly compared to other ages since 2013 as much as 8.9% until 2050 as much as 21.4%, and in contrast at age of 0-14 and 15-59 the percentage tends to decrease [9].

Stroke can be caused by dyslipidemia which is an abnormal state that is present in the blood. Dyslipidemia is indicated by increased levels of total cholesterol, *Low Density Lipoprotein* (LDL), triglycerides, and decreased levels of *High Density Lipoprotein* (HDL) [10].

Total cholesterol is an overall amount of HDL cholesterol level, LDL cholesterol and 20% triglycerides [11]. Total cholesterol level is associated with stroke because it is the risk factor for ischemic stroke [12]. An increase of 1 mmol/L can increase the risk as much as 25% [13]. That increase results in atherosclerosis which plays part in the occurrence of ischemic stroke [7, 11].

Dyslipidemia is a major risk factor for the atherothrombotic vascular disease, including ischemic stroke. Drug therapy is needed in the treatment of dyslipidemia, as well as slowing the progression of atherosclerosis, stabilizing rupture-prone plaque, reducing the risk of arterial thrombosis, and improving prognosis. But first, a diagnosis and an evaluation of

blood cholesterol levels is needed, consisting of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides [5]. The aim of this study is to analyze indicator of dyslipidemia for ischemic stroke in elderly with hypertension, especially in RSU Haji Surabaya.

METHOD

This research is an observational study of analytical epidemiology. Case control study design was conducted from November 2016 until January 2017 in Outpatient Installation RSU Haji Surabaya. The case population is the whole occurrence of ischemic stroke in elderly with hypertension. The control population is the whole occurrence other than ischemic stroke in elderly with hypertension. Samples are determined by the inclusion criteria of patients who perform complete blood cholesterol tests. To minimize the bias, exclusion criteria were set which are patients diagnosed with Hemorrhagic Stroke, Diabetes Mellitus and Coronary Heart Disease (CHD). The ratio of sample size for case and control is 1:1 so the total samples were 74 patients. Samples were taken using simple random sampling methods, lottery all the registration numbers of patients undergoing treatment by 2015. The data of total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides from patient medical records were collected using case data form and control data form.

The data were processed and analyzed with univariate, bivariate and multivariable analysis. Univariate analysis was conducted to examine the distribution of respondents data on the research. The results are presented in narrative and table format. To find the independent variable that qualified to become the candidate of multivariable analysis, selection with bivariate analysis ($p < 0,25$) was conducted. The influential variables to see the effect of independent variable to the dependent variable was determined by multivariable analysis with Multiple Logistic Regression Test ($p < 0,05$).

RESULTS AND DISCUSSIONS

Table 1 showed the distribution of gender that the more than half (54.1%) were male respondents. Analysis of the gender of the respondents in this study showed that the majority of ischemic stroke respondents were male, which is similar to what has been reported in previous studies that more than 50% of patients with

ischemic stroke are male [14, 15]. This is because women are protected by the hormone estrogen so as to avoid heart disease and stroke. However, after entering the age of the elderly and experiencing the menopause, women's risks become equal to male. Many menopausal women in Canada die from stroke and heart disease each year compared to cancer [16]. Men with hypertension were 23.07 times more likely to have a stroke than women [17]. Gender is one of the risk factors that cannot be controlled and potentially effect on the incidence of stroke [18].

Table 1: Distribution of gender

Gender	Ischemic stroke	Without ischemic stroke	N (%)
	n (%)	n (%)	
Male	20 (54,1)	20 (54,1)	40 (54,1)
Female	17 (45,9)	17 (45,9)	34 (45,9)

Table 2 showed the total cholesterol, LDL cholesterol and triglycerides are selected as a candidate ($p=0.00$, $p=0.18$, $p=0.18$) for the multivariable analysis. There are 3 variables that become candidates as indicator of dyslipidemia for ischemic stroke in elderly with hypertension in RSU Haji Surabaya.

Table 2: Candidates of multivariable analysis

Variabels	p-value	Results
Total cholesterol ≥ 200 mg/dl	0,00	candidate
LDL cholesterol ≥ 130 mg/dl	0,18	candidate
HDL cholesterol < 30 mg/dl	0,63	not a candidate
Triglycerides ≥ 150 mg/dl	0,18	candidate

The results presented in bivariate analysis of total cholesterol for ischemic stroke in elderly in RSU Haji Surabaya is eligible to be included in multivariable analysis. The results is similar with a study by Hakim (2013) which showed a significant association ($p=0.03$) between total cholesterol levels and the incidence of stroke. High total cholesterol can lead to plaque buildup in the arteries that supply blood to the brain causing stroke [20].

Total cholesterol can also affect the clinical outcomes of patients with ischemic stroke [21]. High total cholesterol levels can worsen the clinical outcomes of stroke due to the oxidation of cholesterol that can

initiate inflammatory processes and lead to plaque buildup in blood vessel walls that can inhibit blood flow in the arteries [22]. In contrast, in some cases high total cholesterol levels can also produce better clinical outcomes as they are affected by the protective effects of statin use in the acute phase of stroke [23]. These results are supported by Muhammad *et al.* (2014) who stated that patients with high total cholesterol levels have good clinical outcomes because cholesterol can serve as a buffer to neutralize free radicals and prevent the destruction of nerve cell tissue.

A study by Hakim (2013) in Dr. Kariadi Semarang and a study by Wu (2013) in China found significant results that showed a relationship between LDL cholesterol levels and the incidence of ischemic stroke. LDL cholesterol has a tendency to stick to blood vessel walls to form plaque that can narrow the blood vessels. Blockage mainly occurs in small blood vessels that supply nutrition to the heart and brain. Plaque on the vessels can detach and clog blood flow to the brain. Uneven blood vessels can also cause the formation of blood clots in the vessels. It can block the flow to the brain and cause stroke [26]. A decrease in LDL cholesterol by 1 mmol would decrease the fatal stroke by 17% [27].

A Study by Soebroto (2010) in RS Dr. Moewardi Surakarta, Muliawati (2015) in RSUP Dr. Kariadi Semarang and Sumiyah (2016) in RSD dr. Soebandi Jember showed that there is no specific relationship between LDL cholesterol levels and the incidence of ischemic stroke. The difference is caused by the difference of sample used in previous research that is on ischemic stroke and hemorrhagic stroke, history of ischemic stroke patients with diabetes mellitus complication and most of respondents who are ischemic stroke patients with productive age of ≤ 55 years.

The results presented in bivariate analysis of HDL cholesterol for ischemic stroke in elderly in RSU Haji Surabaya is not eligible for entry in multivariable analysis. This is because HDL cholesterol can also be pro-inflammatory and pro-atherogenic in stroke patients, which causes patients with normal HDL levels to have a poor clinical outcome [22]. HDL cholesterol levels can be increased by reducing weight, increasing physical exercise, and quitting smoking [31]. HDL cholesterol can be a risk factor for ischemic stroke [32]. One way that can be done to prevent for ischemic stroke is to increase HDL

cholesterol levels. HDL cholesterol acts as a “vacuum cleaner” that sucks in excess of cholesterol as much as possible. HDL cholesterol takes excess cholesterol from the cells and tissues and bring it back to the liver [33].

The difference results showed a significant relationship between HDL cholesterol level and the incidence of stroke [19]. The study by Yeh *et al.* (2013) in Taiwan and Sohail *et al.* (2013) in Pakistan stated that patients with low HDL (≤ 35 mg/dl) had greater stroke severity and poor clinical outcomes. Low HDL cholesterol levels can increase the risk of blood clots in the carotid arteries, causing a risk of stroke. Low HDL cholesterol levels have the same danger of having too high cholesterol levels of LDL [36].

The 33-years study with 7579 female patients and 6372 male patients showed that elevated triglyceride levels contribute in increasing the risk of ischemic stroke in men and women [37]. The high triglycerides and low HDL cholesterol were associated with an increased incidence of ischemic stroke in both genders [38]. A cohort study by Nodestgaard *et al.* (2007) it was seen that there was an increased risk of stroke associated with blood fat levels called triglycerides. The high triglycerides can increase risk factors for ischemic stroke three to four times greater [40]. Increased triglyceride levels also make LDL cholesterol toxic to artery walls and reduce the beneficial effects of HDL cholesterol [41].

Triglycerides formed as a result of the metabolism of foods in the form of fat and also in the form of excessive carbohydrates and protein are not entirely needed as an energy source [42]. A study by Wardaini (2012) stated that triglycerides are not associated with ischemic stroke. Patients with obese often have high triglyceride levels and these conditions can lead to elevated risk of heart disease or stroke [44].

Table 3 showed that the most influential independent variables and became a model to predict the incidence of ischemic stroke in elderly with hypertension in RSU Haji Surabaya is total cholesterol. This is evidenced by the results of statistical analysis are significant with $p=0.03$ ($p<0.05$). Total cholesterol with OR=4.87 which means that the possibility of elderly with hypertension with total cholesterol level ≥ 200 mg/dl will suffer an ischemic stroke 4.87 times greater when compared with elderly with hypertension with total cholesterol of <200 mg/dl.

Table 3: Indicator of dyslipidemia for ischemic stroke in elderly with hypertension

Variabel	B	OR	95% CI	p-value
Total cholesterol ≥ 200 mg/dl	1,58	4,87	1,10-21,53	0,03
LDL cholesterol ≥ 130 mg/dl	0,16	0,85	0,19-3,74	0,83
Triglycerides ≥ 150 mg/dl	1,08	2,96	0,78-11,21	0,11
Constant	-1,64			0,01

Multivariable analysis showed that total cholesterol level becomes the most influential cholesterol test, thereby it is used as an indicator for ischemic stroke, especially in elderly with hypertension. Many studies have shown that high total cholesterol levels are often associated with the risk of stroke [45]. Increased total cholesterol levels in the blood will lead to the formation of plaque in the blood vessels causing a stroke [7].

The patients with ischemic stroke with a total cholesterol level of ≥ 200 mg/dl had a 3.584 times greater risk of having poorer clinical outcomes compared to patients with normal total cholesterol levels [46]. A study by Karunawan *et al.* (2016) in RS Bethesda Yogyakarta obtained significant results ($p=0,00$) on the correlation of total cholesterol level with functional outcome of ischemic stroke patients. In addition, high total cholesterol levels can also worsen the clinical outcomes of stroke. The cause is the oxidation of cholesterol can initiate the inflammatory process and the formation of plaque on blood vessel walls that can inhibit blood flow in the arteries [22]. A study by Khalil *et al.* (2013) in Egypt, it is known that the Relative Risk of total cholesterol in ischemic stroke patients with hypertension is 3.35 which means the possibility of patients with high total cholesterol levels accompanied by hypertension to have ischemic stroke is 3.35 times greater when compared to hypertensive patients with low total cholesterol levels. The results were obtained from 63.81% of ischemic stroke patients aged ≤ 65 years. Total cholesterol levels and the disability outcomes also showed a significant association of acute ischemic stroke patients [49].

Based on modified levels of stroke risk factors it was found that high total cholesterol levels increased the relative risk of death by 3.9 times. As a correlation between the severity rating system of each dyslipidemia and other modifiable risk factors and patterns it was found

that APACHE II scores correlated positively with high total cholesterol levels and strongly correlated positively with age. At the same time, according to Glasgow Coma Scale (GCS) mortality is positively correlated with high total cholesterol [48].

The difference results showed a high total cholesterol was associated with reduced stroke severity and resulted in better clinical outcomes because it was influenced by the protective effects of statin use in the acute phase of stroke [23]. High total cholesterol levels have good clinical outcomes because cholesterol can serve as a buffer to neutralize free radicals and prevent damage to nerve cell tissues [24].

CONCLUSIONS

It can be concluded that the indicator of dyslipidemia for ischemic stroke in elderly with hypertension in RSU Haji Surabaya is total cholesterol level with $OR=4.87$. The hospitals can perform routine total cholesterol tests for patients diagnosed with ischemic stroke, so as to control the occurrence of recurrent strokes and other comorbid complications that can worsen the condition of the patient. The public should have self-awareness is required to perform blood cholesterol screening as a prevention efforts, especially for elderly with hypertension because of greater risk for ischemic stroke.

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