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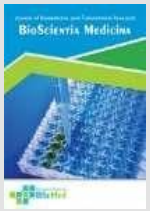

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Risk Factors of In-Hospital Mortality of Ischemic Stroke Patients in Gunung Jati General Hospital

El Alsha Andini[1*], Raditya Dewangga[1], Adrialmi[2]

[1]General Practitioner, Gunung Jati General Hospital, Cirebon, Indonesia

[2]Department of Neurology, Gunung Jati General Hospital, Cirebon, Indonesia

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***Corresponding author:**
El Alsha Andini

E-mail address:
elalshaandini@gmail.com

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A B S T R A C T

Background: Stroke is the leading cause of death and the most significant contributor to disabilities worldwide. Predicting the mortality of stroke patients and giving optimal care remain challenges in developing countries like Indonesia. In this study, we aimed to identify factors associated with in-hospital mortality after acute ischemic stroke. **Methods:** The study conducted a retrospective cohort of cerebral infarct patients administered in 2022 to Gunung Jati General Hospital, West Java, Indonesia. This study included hospitalized patients with a clinical history of stroke confirmed by a CT scan or MRI. The clinical data, radiology, and laboratory tests were collected at admission or within 24 hours after admission. **Results:** This study involved a total of 92 ischemic stroke patients with a median age of 62. The most prevalent comorbidities were dyslipidemia (93.5%), hypertension (83.7% of patients), and concomitant infection (50%). Patients who experienced in-hospital mortality had a significantly higher number of comorbidities, such as chronic kidney disease, concomitant infection, and atrial fibrillation. Statistically higher neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were also shown in non-survived patients. Ischemic stroke patients with concomitant infection and atrial fibrillation, respectively, had 6.679 (aOR: 6.679, 95% CI 1.802-27.029) and 6.904 times (aOR: 6.904, 95% CI 1.290-36.959) greater to have in-hospital mortality. **Conclusion:** Concomitant infection and atrial fibrillation were associated with in-hospital mortality in ischemic stroke patients at Gunung Jati General Hospital. The findings indicated the importance of identifying timely management for improving better outcomes.

1. Introduction

According to the 2017 Global Burden of Disease study, stroke affects 104.2 million people worldwide, where 82.4 million of them suffer from ischemic stroke. Stroke is the second most common cause of death and the most significant contributor to disabilities after coronary heart disease, causing nearly 50% of patients to have chronic disabilities. In Indonesia, stroke is the third leading cause of death, with 138,268 fatalities.[1] Surveys conducted in 2007, 2013, and 2018 show that the prevalence of stroke in Indonesia remains high.[2]

Previous studies revealed that stroke tends to be more severe and resulting in higher mortality in women.[3,4] In addition, length of stay, vital signs, age, hypertension, diabetes mellitus, previous stroke, aspiration pneumonia, and pre-existing heart disease showed an association with mortality in stroke patients.[5,6] Previous research has shown that inflammation markers were associated with atherosclerotic events and became an early predictor of severity and poor short-term prognosis in ischemic stroke since inflammation plays an essential role in the pathophysiology of stroke.[5,7]

Predicting the mortality of stroke patients, identifying those at high risk, and providing them with optimal care remain challenges in developing countries like Indonesia. In addition, limited data on

stroke mortality predictors were available in our region. The study aimed to identify factors associated with in-hospital mortality after acute ischemic stroke.

2. Methods

The study conducted a retrospective cohort of ischemic stroke patients administered in 2022 to Gunung Jati General Hospital, west Java Province, Indonesia. The sampling method was consecutive sampling. This study included patients aged ≥18 years who were hospitalized with a clinical history of stroke confirmed by head CT scan or MRI. Patients discharged from the hospital by their intention during treatment were excluded. The study recorded baseline characteristics, including age, gender, cardiovascular risk factors, other possible risk factors, and laboratory data. History taking, physical examination, electrocardiography, laboratory examinations, and radiology examinations were conducted at hospital admission. The clinical data and laboratory tests were collected during admission or within 24 hours after admission.

The diagnosis of hypertension was based on documented medical history, the use of antihypertensive medication, and the presence of high systolic or diastolic blood pressure based on European Society of Cardiology guidelines.[8] Diabetes mellitus was diagnosed according to documented medical history, such as using hypoglycemic agents or laboratory criteria based on the American Diabetes Association (ADA) 2021 guideline.[9] Dyslipidemia was defined based on laboratory criteria according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III).[10]

Data were analyzed using SPSS version 26 (IBM, New York, USA). Continuous variables were expressed using either the mean and standard deviation (SD) or the median and minimum-maximum values depending on the normality of data distribution, respectively. Categorical variables were expressed as frequency and percentages. NLR (Neutrophil-to-lymphocyte ratio), MLR (Monocyte-to-lymphocyte ratio), and PLR (Platelet-to-lymphocyte ratio) levels were subsequently divided into tertiles. Comparisons between groups were made using the student's t-test or Mann-Whitney U-test for continuous variables and Pearson's Chi-square or Fisher's exact test for categorical variables.

Multivariable binary logistic regression analysis was performed. This analysis was adjusted for age, sex, and other potential confounding factors, including all variables with a p-value less than 0.25 in the initial univariate analysis. The selection of variables for retention was based on a p-value of <0.05. The results were presented as odds ratios (OR) and 95% confidence intervals (CI).

The study protocol received ethical clearance from the ethical committee of the Gunung Jati General Hospital No.041/LAIKETIK/KEPPKRSGJ/VI/2023. The patient or their family signed the medical records to be used for research in the hospital's general consent.

3. Results

This study involved a total of 92 ischemic stroke patients. Clinical characteristics of the ischemic stroke patients are shown in Table 1. Most of the patients were male, involving 69.6% of the cases. The primarily affected age group was the elderly population, with a median age of 62 years. The most prevalent comorbidities were dyslipidemia (93.5%), hypertension (83.7%), diabetes mellitus (43.5%), and concomitant infection (50%). The median NLR was 4.09 (0.94-53.83), PLR was 16384.84 (3836.93-252777.78), and MLR was 0.30 (0.11-1.88).

As indicated in Table 2, patients who experienced in-hospital mortality had notable comorbidities such as chronic kidney disease (CKD), concomitant infection, and atrial fibrillation (AF). Statistically higher NLR and PLR (below tertile 3) were also shown in non-survived patients. Ischemic stroke patients with concomitant infection and atrial fibrillation, respectively, had 6.679 (aOR: 6.679, 95% CI 1.802-27.029) and 6.904 times (aOR: 6.904, 95% CI 1.290-36.959) greater to have in-hospital mortality.

Table 1. Demographic and clinical characteristics of survived versus non-survived ischemic stroke patients.

Variables	Total (n=92)	In hospital-mortality		p-value
		Yes (n = 19)	No (n = 73)	
Age, median (min-max)	62 (24-80)	60 (30-80)	62 (24-79)	0.950
Male, n (%)	64 (69.6)	14 (73.7)	50 (68.5)	0.661
Hypertension, n (%)	77 (83.7)	13 (68.4)	64 (87.7)	0.075
Diabetes mellitus, n (%)	40 (43.5)	10 (52.6)	30 (41.1)	0.366
Dyslipidemia, n (%)	86 (93.5)	16 (84.2)	70 (95.9)	0.100
Chronic kidney disease, n (%)	12 (13)	6 (31.6)	5 (8.2)	0.015
Concomitant infection, n (%)	46 (50)	16 (84.2)	30 (41.1)	0.001
Congestive heart failure, n (%)	8 (8.7)	2 (10.5)	6 (8.2)	0.667
Atrial fibrillation, n (%)	8 (8.7)	5 (26.3)	3 (4.1)	0.009
Previous history of ischemic stroke n (%)	10 (10.9)	1 (5.3)	9 (12.3)	0.681
Neutrophil-to-lymphocyte ratio, median (min-max) (%)	4.09 (0.94-53.83)	9.37 (1.12-53.83)	3.87 (0.94-35.20)	0.006
Monocyte-to-lymphocyte ratio, median (min-max) (%)	0.30 (0.11-1.88)	0.36 (0.11-1.13)	0.28 (0.11-1.88)	0.107
Platelet-to-lymphocyte ratio, median (min-max) (%)	16384.84 (3836.93–252777.78)	25840.00 (3836.93-252777.78)	15399.24 (5121.95-116176.47)	0.031
Length of stay, days	4 (1-17)	4 (2-17)	4 (1-13)	0.412

Table 2. Multivariate logistic regression analysis

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Hypertension	0.305	0.092-1.004	0.051			
Dyslipidemia	0.229	0.042-1.239	0.087			
Chronic kidney disease	5.154	1.436-18.500	0.012			
Concomitant infection	7.644	2.046-28.568	0.002	6.679	1.802-27.029	0.005
Atrial fibrillation	8.333	1.783-38.953	0.007	6.904	1.290-36.956	0.024
NLR Tertiles 2 (3.28-6.66)	1.286	0.263-6.289	0.756			
NLR Tertiles 3 (>6.66)	6.000	1.482-24.299	0.012			
PLR Tertiles 2 (12687.5-23421.05)	2.077	0.470-9.187	0.335			
PLR Tertiles 3 (> 23421.05)	4.500	1.094-18.503	0.037			

4. Discussion

The present study explored the risk factor of in-hospital mortality among ischemic stroke patients in secondary referral hospitals in developing countries. The majority of patients exhibited modifiable risk factors, including dyslipidemia, hypertension, and diabetes mellitus. This finding is consistent with previous studies and aligns with the high prevalence of non-communicable diseases in the country.[5,6,11]

Half of the patients in this study also had concomitant infection. Infection and inflammation are potential contributors to adverse outcomes following ischemic stroke. The infection could directly or indirectly exacerbate stroke outcomes and systemic inflammation, potentially causing secondary neurologic injury. Consequently, various inflammatory markers also have been associated with unfavorable outcomes. In the prior study, mortality was associated with admission white blood cell count, fever, and positive cultures in ischemic stroke patients who underwent thrombectomy.[12] One study compared stroke with and without urinary tract infection (UTI) found that significantly higher post-stroke complication, the length of LOS, and median 3-month mRS (higher disability), and lower median 3-month Barthel index (lower independence) in the UTI group.[13] Stroke-associated pneumonia also appeared to have longer LOS and lower functional outcomes.[14]

This present study found a significantly higher number of NLR and PLR in patients with in-hospital mortality. NLR was significantly associated with severe stroke and poor short-term prognosis and functional outcomes in previous studies.[5,7] NLR was also found to be linked with more severe cerebral edema, early

neurological deterioration, and poor long-term prognosis in stroke patients.[15] Meta-analysis of eighteen studies had shown the association between PLR and poor functional outcome, poor early neurological improvement, radiological bleeding, and mortality among stroke patients.[16]

PLR and NLR stand out as a valuable biomarker due to its cost-effectiveness and availability. Blood neutrophils have been shown to disrupt vascular remodeling during recovery by producing neutrophil extracellular traps (NETs), increasing pro-inflammatory responses, causing endothelial dysfunction and subsequent atherosclerosis, and contributing to destabilization and rupture of atherosclerosis plaque. Neutrophils play a role in ischemia–reperfusion injury (IRI), where stroke continues to progress despite occlusion resolution, and the no-reflow phenomenon, where blood flow is not restored despite occlusion removal. Platelets' involvement in the formation of NETs may contribute to these phenomena.[7,16]

We found higher mortality in ischemic stroke patients with presenting atrial fibrillation. A previous study that compared ischemic stroke with AF versus ischemic stroke with sinus rhythm (SR) showed a significantly higher mortality rate in the first year after stroke in AF groups. The worse prognosis in the AF group was observed to be related to older age and multi-comorbidities in those groups.[17]

CKD also notably showed higher in patients with in-hospital mortality in this study. Patients face a 30-fold increased risk of stroke morbidity and a case mortality rate of nearly 90%. CKD and stroke exhibit a mutual and bidirectional interaction involving cerebro-renal physiological events. CKD patients also tend to have other comorbidities, like hypertension and diabetes.[18]

Several limitations should be acknowledged in this study. Firstly, the retrospective study analysis may have relied on examining existing patient records. Consequently, there was a constraint in the available data, limiting the exploration of numerous predictors of mortality in acute ischemic stroke, including factors like stroke territory, severity, and complications. The recruitment of participants from a single hospital may introduce selection bias. Additionally, the evaluation was limited to the hospitalization period, restricting the predictive value of NLR and other variables for the long-term prognosis of ischemic stroke.

5. Conclusion

Concomitant infection and atrial fibrillation were associated with in-hospital mortality in ischemic stroke patients at Gunung Jati General Hospital. The findings indicated the importance of identifying timely management for improving better outcomes.

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