

Relationship between Interleukin-18 (IL-18) level and Mean Platelet Volume (MPV) with ischemic stroke event in Sanglah General Hospital, Bali, Indonesia



Anak Agung Ngurah Subawa,^{1*} Dewa Putu Gde Purwa Samatra,²
Desak Gde Diah Dharma Santhi¹

ABSTRACT

Background: Long-term stroke risk factors may lead to inflammation of endothelial vessels characterized by migration of macrophages and T-lymphocytes in blood vessel walls by releasing Interleukin-18 (IL-18) cytokines and causing changes in Mean Platelet Volume (MPV) values. This study aims to determine the relationship between IL-18 and MPV levels with ischemic stroke event in Sanglah General Hospital Denpasar.

Methods: A matched-pair case-control study design was conducted in this study. The number of stroke and control samples were 33 people, respectively, and the dependent variable was an ischemic stroke, following MPV and IL-18 as dependent variables. Free T-2 sample test used to compare MPV in each group while the Mann-Whitney test used to compare the interleukin levels

of the two groups. Data were analyzed using SPSS version 20 for Windows.

Results: The MPV value of ischemic stroke patients was significantly higher (8.5 ± 1.19 fL), whereas the MPV value at control was 0.00 ± 0.44 fL ($p < 0.05$). The levels of IL-18 were statistically significantly higher in stroke patients (450.71 ± 278.82 pg/ml) compared with controls (221.46 ± 127.83 pg/ml) ($p < 0.05$). With the Spearman correlation test, there was a significant moderate negative correlation between MPV value and ischemic stroke ($r = -0.357$; $p = 0.003$) as well as IL-18 and ischemic stroke ($r = -0.492$; $p = 0.000$).

Conclusion: Our study suggests that there was a significant relationship between MPV and IL-18 value and ischemic stroke event at Sanglah General Hospital, Bali, Indonesia

Keywords: IL-18, Ischemic Stroke, MPV, Sanglah General Hospital

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¹Department of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Denpasar, Bali

²Department of Neurology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Denpasar, Bali

*Correspondence to:
Anak Agung Ngurah Subawa,
Department of Clinical Pathology,
Faculty of Medicine, Universitas
Udayana, Sanglah General Hospital,
Denpasar, Bali
drsubawa@yahoo.com

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INTRODUCTION

Stroke is a rapidly growing clinical syndrome due to focal and global brain disorders with symptoms that last for 24 hours or more and can cause death without any other apparent cause other than vascular abnormalities.^{1,2} Factors associated with the incidence of stroke divided into two, namely, risk factors that can't be modified and modifiable risk factors.³ Based on the previous study by Guzik A and Bushnell C in 2017, every year, there are 10 million people worldwide suffered a stroke.⁴ stroke has become a health problem because it is known for causing the primary disability in old and younger age. Each year, 795,000 people experience a new or recurrent stroke. About 610,000 of them suffered the first attack, and 185,000 were recurrent attacks.⁵ The incidence rate of men against women at age 55-64 years was 1.25, at age 65-74 years was 1.50, at age 75-84 years was 1.07 and at age ≥ 85 years was 0.76.⁵ According to a study by Kusuma Y et al., stroke, along with hypertension, ischemic heart disease, and other heart diseases,

is also the primary non-contagious disease of the cause of death in Indonesia.⁶

Thrombosis is a significant complication of the process of atherosclerosis involving platelet activation, and aggregation that develops from atherosclerotic plaque ulceration.⁷ Atherothrombosis leads to local occlusion and embolism in the distal region with clinical manifestations that can be seen in ischemic Stroke.⁷ Several studies have shown that MPV correlates with platelet function and platelet activation.^{8,9} This condition can be assessed by thromboxane synthesis, beta-thrombomodulin release, expression of procoagulant function or molecular adhesion.¹⁰ A previous study has explained the association of MPV with cardiovascular disease, especially the coronary heart, and it is known that platelet activation and aggregation play a role in the formation of a thrombus.¹¹ Research by Slavka G et al. found that MPV values could be a predictive parameter for all vascular death and ischemic heart disease.¹² While Khode V et al. argues, that large

MPV as a predictor of major cardiovascular events in acute coronary syndromes.¹³

Mean Platelet Volume (MPV) is a platelet activation that plays a role in the pathogenesis of ischemic Stroke.⁹⁻¹¹ Platelet volume was associated with shorter bleeding time, and mean platelet volume (MPV) was considered a determinant for platelet activity levels.¹⁴ Platelets have been known to play a role in the pathogenesis of atherosclerotic complications and thrombus formation.¹⁵ Greisenegger S et al. suggest there is an increase in mean platelet volume (MPV) in patients with acute myocardial infarction and acute cerebral ischemia.¹⁵ The rise in MPV is associated with a poor prognosis in acute ischemic stroke.¹⁵ Bath P et al. conducted the study and concluded that MPV is an independent predictor of stroke risk among individuals with a history of stroke or TIA (Transient Ischaemic Attack).¹⁶ MPV measurements can add useful prognostic information to physicians in treating patients with a cerebrovascular history.^{15,16} MPV is related to the severity of the acute ischemic stroke and has high effectiveness to distinguish a mild and mild ischemic stroke.¹⁴

Based on those mentioned above, this study aims to determine the relationship between MPV and IL-18 level to the ischemic stroke event occur in Sanglah General Hospital, Bali, Indonesia.

MATERIAL AND METHODS

The design of this study was a matched-pair case-control study. The study began with the identification of cases of individuals accompanied by the effects (Stroke). At the same time, the control group was the same or near-same age group with the case, but without any result. Eligible patients are selected consecutively (continuous sampling) until the number of samples is met. This study was conducted in September through December 2016

with a total sample of 33 patients with ischemic Stroke in Sanglah General Hospital Denpasar who meet the inclusions criteria, and 33 control groups were donors' blood in Bali Blood Transfusion Unit.

A total of 66 people consisted of 33 subjects suffering from ischemic stroke and 33 healthy subjects as control who participated in this study. The data taken include age, gender, and MPV value. The population of this study was young ischemic infarction sufferers who met the inclusion criteria and filled out the informed consent form. Inclusion criteria include patients with ischemic stroke of young age (aged 40-64 years), diagnosis by history, general physical examination, neurological physical examination and as the gold standard is a CT scan of the head, patients with acute ischemic infarction stroke are determined based on the period of attack or onset from 24 hours to 48 hours. Exclusion criteria are patients with febrile, sepsis, acute and chronic kidney disease, acute or chronic liver disease, and malignant disease.

All blood samples for MPV value examination were taken from patients with ischemic infarct stroke. Blood samples for MPV examination were taken using a tube with EDTA preservatives while for IL-18 examination plasma was used for the remaining MPV examination. Plasma on IL-18 probe was stored in cooler temperature - 40°C and continued by ELISA examination and mentioned in pg/ml.

Statistical analysis used was the normality test with Kolmogorov-Smirnov followed by an independent parametric test of T-Test.

RESULTS

The mean age of the subjects in the group of ischemic stroke patients was 56.15±8.38 years old. According to gender, the female in the stroke group was accompanied by 10 patients (30.31%) and 23 patients (69.69%) as male (Table 1). Moreover, based on the age group, most of the respondents in the treatment group were in the range of 61-65 years old (42.43%), followed by 46-50 years old (27.27%), 56-60 years old (18.18%), 40-45 years old (9.09%), and 51-55 years old (3.03%) (Table 1).

There was a significant difference between the mean value of MPV in the group of ischemic stroke patients (8.5±1.19 fL) compared with the control group (8.0±0.44 fL) (p=0.030) (Table 2). Besides, a significant difference was also found for the IL-18 evaluation between ischemic stroke group (450.71±278.82 pg/ml) and control group (21.46±127.83 pg/ml) (Table 2).

A Spearman correlation test was conducted between MPV and IL-18 to determine the relationship with the ischemic stroke event at Sanglah

Table 1 Baseline characteristic of respondents in the treatment group

Variable	n (%)	Mean±SD
Age (Years)		56.15±8.38
Age Group		
40-45	3 (9.09)	
46-50	9 (27.27)	
51-55	1 (3.03)	
56-60	6 (18.18)	
61-65	14 (42.43)	
Gender		
Female	10 (30.31)	
Male	23 (69.69)	

Table 2 The MPV value and IL-18 levels between groups

Group	Mean	SD	P
MPV (fL)			
Ischemic Stroke	8.50	1.19	0.030
Control	8.00	0.44	
IL-18 (pg/ml)			
Ischemic Stroke	450.71	278.82	0.000
Control	21.46	127.83	

Table 3 Relationship of MPV and IL-18 with ischemic stroke incident

Parameters	R-Value	P
MPV	-0.357	0.003
IL-18	-0.492	0.000

General Hospital. The study found that there was a significant moderate negative correlation between MPV ($r=-0.357$; $p=0.003$) and IL-18 ($r=-0.492$; $p=0.000$) to the ischemic stroke event (Table 3).

DISCUSSION

According to the present study conducted, the researchers obtained results that show relationships between both MPV and IL-18 toward ischemic stroke incident. Previous research by Dherma found the average age of ischemic stroke patients was 57.59 ± 11.53 years, gender in a woman who suffered a stroke as much as 55%, and MPV value in the group of stroke patient was 10.23 ± 0.60 fL.¹⁷ While research by Rosmiati found the MPV value the first three days of the beginning of the disease is 8.9 fL and on the fifth day, the disease increased to 9.4 fL.¹⁸

Mean Platelet Volume is a marker of platelet function and is associated with the indicator of platelet activity which includes aggregation and release of A2, platelet factor 4, and thrombo-globulin.¹⁹ Platelets play a significant role in maintaining the integrity of blood vessels through hemostatic. Platelet volume is associated with shorter bleeding time, and mean platelet volume (MPV) has been considered a determinant for platelet activity levels.¹⁴

Bath P et al. conducted the study and concluded that MPV is an independent predictor of stroke risk among individuals with a history of stroke or TIA (Transient Ischaemic Attack).¹⁶ MPV measurements can add useful prognostic information to physicians in treating patients with a cerebrovascular history.¹⁶ Research by Ghahremanfard F

concluded that MPV is related to the severity of the acute ischemic stroke and has high effectiveness to distinguish a mild and mild ischemic stroke.¹⁴ Similarly, research by Arikanogulu et al. found there is a relationship between MPV and CRP in Stroke, MPV and CRP patients are higher in patients with ischemic stroke who die than in survivors where MPV and CRP may be an indication of signs of death in stroke patients.²⁰

Concerning the current study, MPV levels indeed become a crucial factor that could determine ischemic stroke events in patients. This study finds the mean value of MPV in the group of ischemic stroke patients was 8.5 ± 1.19 fL, while the MPV value in the control group was 8.0 ± 0.44 . Therefore, it can be concluded that this result correlates with many previous studies mentioned above. Another factor IL-18 is a member of the IL-1 cytokine superfamily, which is an essential regulator of the natural and adaptive immune response.²¹ Interleukin-18 is expressed by various cells and tissues including alveolar macrophages, dendritic cells, Kupffer cells, keratinocytes, osteoblasts, adrenal cortical cells, intestinal epithelial cells, microglia cells and synovial fibroblasts.²¹ The expression of IL-18 is found in chronic inflammatory diseases mediated by Th1, autoimmune disease, various types of malignancies and some infectious diseases.²¹ IL-18 exhibits various physiological functions including a role in inducing IFN- γ production, regulation of ligand Fas expression in NK cells, promoting ligand-mediated cytotoxicity Fas of Th1 cells, and nuclear translocation of NF- κ B. Also, IL-18 is capable of inducing TNF- α , IL-1 β , and chemokines, thus contributing to local and systemic inflammatory processes. The expression of IL-18 is found in chronic inflammatory diseases mediated by Th1, autoimmune disease, metabolic disease, various types of malignancies and some infectious diseases.²²⁻²⁴ IL-18 plays a protective role in bacterial infections, fungi, viruses and intracellular parasites.²⁰

This study shows there was a significant difference in IL-18 levels in ischemic stroke patients compared with healthy people. This following Zaremba J and Losy J studies that carried out the IL-18 research in 23 coronary stroke patients on the first day, the results were higher compared with 15 healthy people as controls.²⁵ Using correlation analysis of Spearman, there is a relationship between IL-18 levels with ischemic stroke incident with the p-value of 0,000 (<0.050).²⁵ The similar result was shown by a relationship between MPV and ischemic stroke incident with a p-value of 0.03.

Our study found that the mean level of IL-18 in the ischemic stroke group was higher compared with the control group. It can be seen from the

result that in this study there was a significant difference in IL-18 levels in ischemic stroke patients compared with healthy people as controls according to Zaremba studies IL-18 in 23 ischemic stroke patients whose blood was drawn on the first day the results were higher compared with 15 healthy people as controls.²⁵

Clinical application from this research is for the patient above 40-year-old, we suggest to do routine complete blood count examination. Through the CBC examination, we can monitor the MPV level if the level above the reference range, we can recommend antiplatelet medication such as plasmin. Beside of that, CBC is an inexpensive and straightforward examination, and also easy to interpret. As compared with other markers of platelet activity, which require special hemostasis laboratories, because of the stringent requirement for nearly perfect phlebotomy, blood-processing procedures, platelet isolation, and specialized equipment, MPV is a practical and prognostically important biomarker of ischemic stroke disease. A formal comparison of MPV and other novel biomarkers is needed to characterize its relative clinical utility.

CONCLUSION

We conclude that there was a significant difference between treatment and control group in both MPV and IL-18 value. In addition, a significant relationship was also found between MPV and IL-18 value to the ischemic stroke event at Sanglah General Hospital, Bali, Indonesia

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

ETHICS CONSIDERATION

Ethics approval has been obtained prior to the study being conducted by Ethic Committee, Faculty of Medicine, Universitas Udayana and Sanglah General Hospital.

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AUTHOR CONTRIBUTION

All of authors are equally contribute to the study from the conceptual framework, data gathering,

data analysis, until reporting the the results of study through publication.

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