

Correlation between Mean Platelet Volume and Procalcitonin in Sepsis Patients

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ABSTRACT

Sepsis is a clinical condition of potentially life-threatening organ dysfunction caused by the host's response to infection. Delayed diagnosis and treatment of sepsis lead to worsening of the disease, which can lead to circulatory collapse, multiple organ failure, and death, therefore accurate and timely diagnosis can prevent death. Procalcitonin (PCT) is the most widely used, studied, and promising marker for the diagnosis of sepsis. Recent studies have shown that procalcitonin plays an important role in the clinical diagnosis of sepsis because it can differentiate sepsis from SIRS. Most studies found an increase in the Mean Platelet Volume (MPV) in septic patients, both neonates, and adults. The MPV value can be used as a parameter to assess the prognosis of septic patients. This cross-sectional analytical study was conducted on 21 septic patients at Dr. M. Djamil Hospital, Padang from January 2020 to April 2021. Mean platelet volume values were determined using an automatic hematology analyzer based on the formula made by the device. Procalcitonin levels were measured using the enzym-linked immunofluorescent assay method. Data were analyzed by Pearson correlation test and $p < 0.05$ was significant. The mean age of the research subjects was 54 years and the range was 22-77 years. The number of male and female research subjects in this study was almost the same, consisting of 10 male (48%) and 11 female (52%) patients. The average MPV was 10.59(0.56) fL and the median procalcitonin was 9.35(2.08-200) ng/mL. Pearson correlation test showed that MPV was positively correlated with procalcitonin with moderate correlation ($r=0.435$, $p=0.049$). There was a moderate positive correlation between MPV and procalcitonin in septic patients.

Keywords: Mean platelet volume, procalcitonin, septic patients

INTRODUCTION

Sepsis is a clinical condition of potentially life-threatening organ dysfunction caused by the host's response to infection. Sepsis and septic shock are major health problems in millions of people worldwide every year. It was estimated to increase in the last 20 years by 400,000-500,000 annually in the United States.^{1,2} Delayed diagnosis and treatment of sepsis lead to worsening disease, resulting in circulatory collapse, multiple organ failure, and death. Therefore, accurate and timely diagnosis can prevent death.^{3,4}

Procalcitonin (PCT) is the most widely used, studied, and promising marker for sepsis diagnosis. Procalcitonin is a calcitonin prohormone that is produced in response to endotoxins or mediators released due to bacterial infection and is strongly correlated with the extent and severity of bacterial infections.⁵ Recent studies have shown that procalcitonin plays an important role in the clinical diagnosis of sepsis because it can differentiate sepsis from SIRS. This marker has better accuracy than the

previous marker, but it has a fairly expensive price and is not available in all health facilities, especially in developing countries. Therefore, it is necessary to have a simple and inexpensive marker that can predict sepsis well and is easy to use in daily practice.^{6,7}

Most studies found an increase in the Mean Platelet Volume (MPV) in septic patients, both neonates, and adults. The MPV value can be used as a parameter to assess the prognosis of sepsis patients. An MPV value of 9.7 fL (femtoliter) at the time of diagnosis of sepsis was associated with a threefold increase in mortality.^{3,8} Mean platelet volume measurement has been carried out since the 1970s and is now used as a routine test; however, it is still rarely studied in relationship with sepsis. The MPV is an indication of the size of the circulating platelets in the peripheral blood. An increase in MPV indicates increasing in platelet production, young platelets with a larger size, as compensation for the accelerated platelet production.^{3,9}

The study of Cho *et al.* found a positive correlation between MPV and procalcitonin in

patients with definitive infection, MPV increased significantly with an increase in procalcitonin >1.0 ng/mL.¹⁰ Research by Ginting *et al.* found a strong correlation between MPV and procalcitonin ($r=0.702$, $p<0.001$), suggesting that MPV can be used as a simple parameter to diagnose sepsis.¹ Meanwhile, research by Dursun *et al.* in Turkey found a weak correlation between MPV and procalcitonin ($r=0.243$, $p<0.001$) in pediatric sepsis; while Wilar *et al.* found no relationship between increased MPV and mortality in neonatal sepsis.^{3,11} Some studies give different results, most studies show an increase in MPV values. Mean platelet volume values have a fairly good relationship with sepsis, both diagnostic and prognostic. Periodic measurement of MPV values can also provide prognostic information. The MPV is one of the promising parameters in the assessment of the state of sepsis. Further research is needed to study the role of MPV as a prognostic factor in sepsis.¹²

METHODS

This study was an analytic study with a cross-sectional design on 21 patients diagnosed with sepsis by clinicians and conducted at the Central Laboratory of Dr. M. Djamil Hospital, Padang, and the treatment room of Dr. M. Djamil Hospital from January 2020 to April 2021. The study sample was part of the population that met the inclusion and exclusion criteria. The inclusion criteria of this study were; samples with a diagnosis of sepsis sent to the laboratory for hematological test and procalcitonin, patients aged 18 years, treated for 24-48 hours with a diagnosis of sepsis. The exclusion criteria were patients receiving cytotoxic therapy, history of malignancy, kidney failure, kidney damage, liver, burns, pulmonary embolism, heart failure, and diseases with platelet disorders based on medical record data.

A whole blood specimen with K2EDTA anticoagulant was used for the MPV test and serum was used for the procalcitonin test. A mean platelet volume test was carried out using an automated hematology analyzer. Mean platelet volume was calculated indirectly using a formula; plateletcrit (%) divided by the number of platelets (mm^3) multiplied by 107. Plateletcrit and platelets were analyzed using the impedance principle. The procalcitonin assay combines the one-step sandwich immunoassay method with final detection using fluorescence (ELFA).

The research data were analyzed using a computer program. Categorical data were provided

in frequency, and numerical data were provided as mean (standard deviation) and median (minimum-maximum value). Mean platelet volume and procalcitonin data were analyzed for the normality test of data distribution using the Shapiro-Wilk test. The normality test showed that MPV data were normally distributed but procalcitonin data were not normally distributed. Log transformation was performed and the procalcitonin data were then normally distributed. Therefore, a Pearson correlation test was performed between MPV and procalcitonin logs. A correlation was stated as significant if the p-value <0.05.

This research was conducted after obtaining ethical clearance from the Health Research Ethics Commission of the Dr. M. Djamil Hospital, Padang with number 05/KEPK/2021.

RESULTS AND DISCUSSIONS

The study of 21 treated sepsis patients who met the inclusion and exclusion criteria to determine the correlation between MPV values and procalcitonin levels obtained the basic characteristics as presented in Table 1.

Table 1. The basic characteristic of data

Variable	f(%)	Mean (SD)
Gender		
Male	10(48)	
Female	11(52)	
Age (year)		54(17)

There was almost the same number of male and female research subjects, consisting of 11 males (52%) and 10 females (48%) with the average age of the study sample being 54 years with an age range of 22-77 years. This result was slightly different from the study of Kim *et al.*, which reported a higher number of female (51%) sepsis patients compared to male (49%) patients. A study by Ginting *et al.* also found higher sepsis cases in females (52 %) compared to males (48%).^{1,13}

Different results were obtained by Djuang *et al.* and Wilar *et al.* in which the number of males and females differed greatly.^{3,14} Research by Haryono *et al.* found the same percentage of male and female patients.¹⁵

The mean age of septic patients in this study was close to the results of a study by Indramila *et al.*, Intansari *et al.*, Bounes *et al.*, and Yang *et al.*, which reported the mean age of 53 years, 53 years, 66 years, and 69 years, respectively.¹⁶⁻¹⁹

Research in the United States in 1979-2000 on the epidemiology of sepsis found that the average age for female septic patients was 62.1 years and for male 56.9 years with a greater number of male patients. Research in 2008 found no differences or only slight differences between the two gender.²⁰ Age is an independent risk factor for mortality in patients with severe sepsis, old age is more susceptible to infection due to decreased organ function and the presence of comorbid diseases.²¹

The incidence of sepsis increases in the elderly, which occurs around the age of 65 years and is caused by comorbidities, obesity, repeated hospitalization, and immune system disorders. Disorders of the immune system with increasing age result in decreased chemotaxis and phagocytic functions of neutrophils and macrophages, reducing the number of naive B cells and T cells, thereby reducing the ability to react quickly to pathogens.^{22,23} The incidence of sepsis in neonates is influenced by various factors such as preterm birth, surgical delivery, maternal fever, invasive procedures, and low birth weight.^{8,24}

Gender differences affect the immune response in sepsis. The immune response is correlated with steroid hormones, especially estradiol and progesterone, which can inhibit the inflammatory response and increase non-inflammatory mediators and enhance humoral and cellular immune responses. Females have higher concentrations of steroid hormones than males.²⁵

The average MPV values and procalcitonin levels can be seen in Table 2. A total of 2 research subjects (10%) had MPV values within the normal range <10 fL. A total of 9 subjects (43%) had procalcitonin levels at high risk of developing severe sepsis ($PCT \geq 2$ -<10 ng/mL) and 12 subjects had procalcitonin levels most likely severe sepsis or septic shock ($PCT \geq 10$ ng/mL).

Table 2. Mean platelet volume value and procalcitonin value

Variable	Mean (SD)	Median (min-maks)
MPV (fL)	10.59 (0.56)	10.5(9.9-12.1)
Procal citonin (ng/mL)	44.11(62.98)	9.35(2.08-200)

This study found an increase in MPV of 10.59(0.56), similar to a finding in a study by Ginting *et al.* which obtained an average MPV value of 10.97(0.63) fL and a study by Bounes *et al.*, which also obtained a median MPV of 10.5 fL with the lowest

value of 10.4 fL and the highest value of 10.7 fL.^{1,18} The average MPV in this study increased from the reference value range due to the inflammatory response producing platelet-activating factor that can activate platelets to eliminate bacteria, resulting in accelerated platelet destruction due to sepsis. Increased consumption of platelets causes the production and activation of platelets to increase, resulting in larger platelet. The MPV value reflects the overall platelet size.¹¹

The median level of procalcitonin in this study was 9.35 ng/mL with the lowest level of 2.08 ng/mL and the highest level of 200 ng/mL. This increase was also obtained by Cho *et al.* and Djuang *et al.*^{10,14} Procalcitonin will increase infections caused by bacteria. Macrophages will synthesize proinflammatory cytokines in response to infection. The body's tissue response to infection will also stimulate the synthesis of Tumor Necrosis Factor (TNF- α). The body's tissue needs TNF- α to synthesize procalcitonin. Several studies have shown that procalcitonin is rarely elevated in viral infections. This might be due to the stimulation of macrophages to synthesize interferon-alpha, which will prevent the synthesis of TNF- α .^{26,27}

Mean platelet volume and procalcitonin data were tested for normality using Shapiro-Wilk. The results showed that MPV data had a normal distribution, while procalcitonin data had abnormal distribution. Log transformation was then performed for procalcitonin, and normal data distribution was obtained. The correlation between MPV and log procalcitonin was analyzed by the Pearson correlation test. Based on the correlation test, there was a moderate positive correlation between MPV and log procalcitonin ($r=0.435$) ($p<0.05$) (Fig. 1).

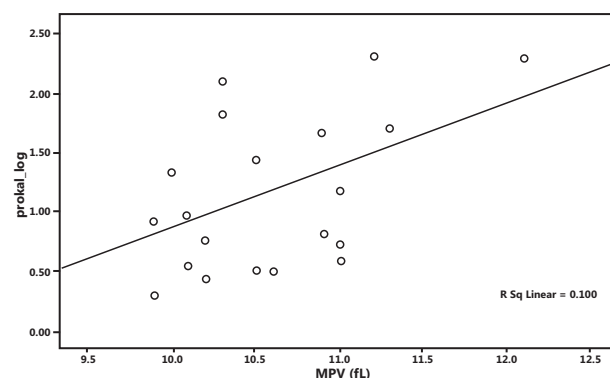


Figure 1. Correlation between MPV value and procalcitonin

The results of this study differed from the results of a study by Ginting *et al.*, which found a strong correlation between MPV and procalcitonin

($r=0.702$, $p<0.001$).¹ Therefore, MPV can be used as a simple parameter to diagnose sepsis, possibly influenced by the research method used. The difference was due to the use of a greater number of research subjects, differentiation of moderate and severe sepsis, and culture tests carried out on research subjects.

A study by Cho *et al.* found a positive correlation between MPV and procalcitonin in patients with definitive infection, with a significant increase of MPV along with an increase in procalcitonin >1.0 ng/mL.¹⁰ The study of Djuang *et al.* also found an increase in MPV along with an increase in procalcitonin in patients with bacterial sepsis.¹⁴ An increase in MPV indicates a proinflammatory and thrombotic condition involving a number of inflammatory mediators, cytokines, and endothelial dysfunction. However, research by Dursun *et al.* in Turkey found a weak correlation between MPV and procalcitonin ($r = 0.243$, $p<0.001$) in pediatric sepsis; while Wilar *et al.* found no relationship between increased MPV and mortality in neonatal sepsis.^{3,11}

This difference in results might be influenced using different research subjects and many factors that influence the incidence of sepsis in neonates, including preterm birth, surgical delivery, and low birth weight.

The study of Bounes *et al.* in ICU patients in France obtained an increase in MPV in the first 15 days with a cut-off value of > 11.6 fL as a predictive factor of death within 90 days in septic shock patients.¹⁸ This suggests that MPV is one of the important factors associated with mortality, as a response to reduced platelets during septic shock, triggering megakaryocytes to release immature platelets into the circulation. Continuous MPV monitoring can be one of the parameters to determine the prognosis of death in septic shock.

The infection itself or proinflammatory cytokines induces high procalcitonin levels in sepsis and MPV may be elevated in response to inflammation and thrombotic conditions.¹¹ The MPV value can be used as a parameter to assess the prognosis of sepsis patients. An MPV value of 9.7 fL at the time of diagnosis of sepsis was associated with a threefold increase in mortality.^{3,8}

No classification of research subjects based on the degree of risk of sepsis remained the limitation in this study, making it unable to determine the correlation between MPV and the degree of sepsis to predict the prognosis of sepsis and include culture as the gold standard in the diagnosis of sepsis.

CONCLUSIONS AND SUGGESTIONS

The MPV had a moderate positive correlation with procalcitonin in septic patients at Dr. M. Djamil Hospital. Further research with the classification of research subjects based on the degree of sepsis was required to determine the correlation between the mean platelet volume and procalcitonin in assessing the prognosis in septic patients.

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