



## An increase in mean platelet volume (MPV) as a predictor of mortality in children with sepsis

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### ABSTRACT

Submitted: 2021-09-11  
Accepted : 2021-12-10

Sepsis is associated with increased morbidity and mortality in children worldwide, mainly in developing countries. This fatal risk emphasizes the importance of finding accessible and inexpensive parameters to be used as predictors for mortality in children with sepsis. The aim of this study was to determine the role of increased mean platelet volume (MPV) as a predictor for mortality in children with sepsis. A case control study was applied using medical records of all in-patients aged 1 mo -18 y diagnosed with sepsis at Dr. Sardjito General Hospital, Yogyakarta from January 2015-December 2016. Bivariate and multivariate analyses by Chi-square and logistic regression to evaluate the correlations between increased MPV within the first 24-72 h ( $\Delta$ MPV>0) and mortality were applied. Eighty-one eligible subjects met the inclusion/exclusion criteria with the mortality was 52%. Chi-square analysis showed significant correlations between increased MPV and mortality ( $p=0.005$ ). Multivariate analysis showed increased MPV within the first 24-72 h after sepsis diagnosis as a predictor for mortality after controlling for sex and AKI (adjusted OR 3.851; 95% CI:1.354-10.948;  $p= 0.011$ ). In conclusion, an increase in MPV within the first 24-72 h after diagnosed is an independent predictor for mortality in children with sepsis.

### ABSTRACT

Kejadian sepsis berhubungan dengan peningkatan morbiditas dan mortalitas anak-anak di seluruh dunia, khususnya di negara berkembang. Risiko fatal ini menekankan pentingnya menemukan parameter yang murah dan mudah diakses untuk digunakan sebagai prediktor kematian pada anak dengan sepsis. Penelitian bertujuan mengkaji peran peningkatan rerata *platelet volume* (MPV) sebagai prediktor mortalitas pada anak dengan sepsis. Penelitian ini merupakan penelitian kasus kontrol menggunakan rekam medis seluruh pasien rawat inap anak umur 1 bulan-18 tahun di RSUP Dr. Sardjito, Yogyakarta yang didiagnosis sepsis dari Januari 2015-Desember 2016. Analisis bivariat dan multivariat dengan uji *Chi-square* dan regresi logistik dilakukan untuk menentukan korelasi antara peningkatan MPV dalam 24-72 jam pertama ( $\Delta$ MPV>0) dengan mortalitas. Sebanyak delapan puluh satu subjek memenuhi kriteria inklusi/eksklusi dengan kematian sebesar 52%. Uji *Chi-square* menunjukkan korelasi signifikan antara peningkatan MPV dengan mortalitas ( $p=0,005$ ). Analisis multivariat menunjukkan peningkatan MPV dalam 24-72 jam pertama sejak diagnosis sepsis ditegakkan sebagai prediktor mortalitas setelah mengontrol variabel jenis kelamin dan *acute kidney injury*/AKI (*adjusted* OR 3,851; 95%CI: 1,354-10,948;  $p= 0,011$ ). Dapat disimpulkan bahwa peningkatan MPV dalam 24-72 jam pertama setelah penegakkan diagnosis merupakan prediktor independen untuk mortalitas anak dengan sepsis.

### Keywords:

children;  
mean platelet volume;  
mortality;  
sepsis

## **INTRODUCTION**

Sepsis is a life-threatening organ dysfunction caused by a dysregulated immune system due to infection.<sup>1</sup> Sepsis affects millions of people worldwide each year, and is associated with high morbidity, mortality, and health-maintenance costs. Sepsis is also a major cause of infant and child mortality worldwide. The incidence of sepsis increased in recent years, especially in developing countries.<sup>2</sup> Based on epidemiological studies in the United States, the incidence of severe sepsis involved 0.56 cases per 1000 population per year, with a mortality reaching 10.3% (more than 4383 deaths per year).<sup>3</sup> The incidence of sepsis in the Pediatric Intensive Care Unit (PICU) Dr. Cipto Mangunkusumo Hospital (RSCM), Jakarta was 19.3% with a mortality rate 10%.<sup>4</sup> High mortality rate encourages applied research to discover easily accessible and inexpensive methods that can be widely used to know the severity of sepsis when diagnosed so an optimal management approach can be developed to reduce mortality.

Mean platelet volume (MPV) is a simple and accurate marker of functional status and size of the platelets. Some research hypothesized that cytokines such as interleukin 3 (IL-3) and IL-6 in sepsis patients will affect megakaryocytes ploidy that leads to the production of more reactive and larger platelets, so MPV will increase.<sup>5,6</sup> In healthy populations, MPV has an inverse correlation with the number of platelets, but biological effects, clinical significance, and its association with sepsis is still not clearly understood.

Previous study explains that the measurement of the MPV can be used

as predictors of mortality in patients with sepsis and critical illness.<sup>7-12</sup> Study on the role of MPV as a predictor of mortality in children with sepsis is still rarely conducted. The procedure of MPV measurement is very simple and does not require high cost. This study aimed to determine the MPV role as a predictor of mortality in children with sepsis.

## **MATERIALS AND METHODS**

### **Design of study**

We conducted a prognostic study with matched case control design at Dr. Sardjito General Hospital, Yogyakarta by reviewing medical records. Subjects were patients aged 1 mo-18 y who were diagnosed with sepsis based on Indonesian Pediatric Society 2016 criteria<sup>1</sup> and were hospitalized in the Pediatric Intensive Care Unit (PICU) since January 2015 to December 2016, with performed blood cultures and MPV measurement.

### **Protocol of study**

Mean platelet volume value came as part of complete blood count measurement using a quantitative automated hematology analyzer which analyzed at the clinical pathology laboratory of Dr. Sardjito General Hospital. Mean platelet volume measurement was taken at diagnosis and within 24-72 h thereafter. Mean platelet volume values were recorded from the medical record. Subjects were excluded if there was comorbidity such as hematologic abnormalities (leukemia, immune thrombocytopenic purpura, essential thrombocytosis, abnormal platelet

function, aplastic anaemia), asplenia, chronic diseases, organ transplantation, malignancies, congenital abnormalities, immunosuppressive drugs or discharge against medical advice.

The case group was children based on inclusion and exclusion criteria who died during hospitalization, and the control group was children who were survived, match by age. The data taken including age, gender, nutritional status, number of leukocytes, MPV value at the time diagnosed as sepsis ( $MPV_1$ ), MPV values within 24-72 h after diagnosed ( $MPV_2$ ), changes in the value MPV within 24-72 h after diagnosed ( $\Delta MPV$ ), the number of platelets, acute kidney injury (AKI),<sup>13</sup> disseminated intravascular coagulation (DIC),<sup>14</sup> septic shock<sup>15</sup> and the outcomes (dead or alive). Mean platelet volume values taken were the result of blood sample analysis in the clinical pathology laboratory that were written in medical records or tracked from clinical laboratory installation. If there were more than one examination within the time range (24-72 h), the MPV value that was recorded is the latest MPV. Mean platelet volume is considered high when MPV value  $> 10.4$  fl, and increased when  $\Delta MPV > 0$  ( $MPV_2 - MPV_1 > 0$ ). Other data were taken from examination performed within 72 h after sepsis diagnosis.

### Statistical analysis

Descriptive analysis was conducted to describe the basic characteristics of the subjects and the data was displayed in the form of proportions. Bivariate analysis by Chi-square test was conducted to determine any correlation

between an increase in MPV ( $\Delta MPV > 0$ ), thrombocytopenia, leukopenia, age, gender, AKI, DIC and septic shock with mortality. Multivariate analysis by logistic regression was performed for an increase in MPV ( $\Delta MPV > 0$ ) and confounders with p value  $< 0.25$  to determine the adjusted OR. This study was approved from the Medical Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/ Dr. Sardjito General Hospital, Yogyakarta (ref. number KE/FK/0546/EC/2017).

### RESULTS

Within 2 years (January 1<sup>st</sup>, 2015 - December 31<sup>th</sup>, 2016) there were 81 subjects who met the study criteria. Subjects' characteristics are shown in Table 1. Median of age was 25-month (1-205-month), with higher proportion of patients younger than 5 years old (66,7% versus 33,3%). Diseases related to the occurrence of sepsis in this study include pneumonia (28.4%), dengue shock syndrome (24.7%), intracranial infection (19.8%), surgery (9.9%), gastrointestinal infections (4.9%), skin infections (3.7%), and typhoid fever (1.2%). Pneumonia is most prevalent in the case group (43.9%), while dengue shock syndrome is most prevalent in the control group (30.0%). Positive culture was found in 65.4% of the subjects. The most common pathogens are *Streptococcus viridans* (17.3%), *Klebsiella pneumoniae* (11.8%), *Candida sp.* (10.9%), *Acinetobacter baumannii* (9.1%), *E. coli* (9.1%), *Enterobacter cloacae* (5.5%), and *Pseudomonas aeruginosa* (5.5%).

TABLE 1. Basic characteristics of subjects

Characteristics	Died (n = 41) n (%)	Alive (n = 40) n (%)	Total (n = 81) n (%)
Age			
• <5 years	27 (65.9)	27 (67.5)	54 (66.7)
• ≥ 5 years	14 (34.1)	13 (32.5)	27 (33.3)
Gender			
• Boys	24 (58.5)	34 (85.0)	58 (71.6)
• Girls	17 (41.5)	6 (15.0)	23 (28.4)
Underlying diseases			
• Surgical cases	1 (2.4)	7 (17.5)	8 (9.9)
• Non-surgical cases	40 (97.6)	33 (82.5)	73 (90.1)
• Pneumonia	18 (43.9)	5 (12.5)	23 (28.4)
• Dengue shock syndrome	8 (19.5)	12 (30.0)	20 (24.7)
• Intracranial infection	8 (19.5)	8 (20.0)	16 (19.8)
• Gastrointestinal infections	1 (2.4)	3 (7.5)	4 (4.9)
• Skin infections (burns, cellulitis, abscesses)	1 (2.4)	2 (5.0)	3 (3.7)
• Typhoid fever	0 (0.0)	1 (2.5)	1 (1.2)
• > 1 source of infection	4 (9.8)	2 (5.0)	6 (7.4)
Wasted or severely wasted	13 (31.7)	9 (22.5)	22 (27.2)
Positive culture	20 (48.8)	33 (82.5)	53 (65.4)
• Blood	0 (0.0)	5 (12.5)	5 (6.2)
• Feces	1 (2.4)	0 (0.0)	1 (1.2)
• Respiratory tract	7 (17.1)	10 (25.0)	17 (21.0)
• Others	1 (2.4)	1 (2.5)	2 (2.5)
• > One kind of sample	11 (26.8)	17 (42.5)	28 (34.6)

This study showed that  $MPV_1$  and  $MPV_2$  values had no effect on mortality, while an increase in MPV ( $\Delta MPV > 0$ ) did have a significant effect on mortality ( $p = 0.005$ ) (TABLE 2). The results of the bivariate analysis of other variables also shown in TABLE 2. Thereafter, multivariate analysis by logistic regression was performed for an increase in MPV ( $\Delta MPV > 0$ ) and confounders with  $p$  value  $< 0.25$  to

determine the adjusted OR. Confounders which included was female gender, leukopenia, AKI, DIC, and septic shock. We obtained adjusted OR of  $\Delta MPV > 0$  based on reference model (model 1) was 4.144 (95% CI 1.328 to 12.933;  $p = 0.014$ ) (Table 3). After analyzed for the best model that would be used based on its validity and precision, we obtained final adjusted OR of  $\Delta MPV > 0$  was 3.851 (95% CI 1.354 to 10.948;  $p = 0.011$ ) (TABLE 3).

TABLE 2. Result of bivariate analysis on the factors that affect mortality in sepsis

Variables	Died (n = 41) n (%)	Alive (n = 40) n (%)	p*
MPV <sub>1</sub>			
>10.4 fl	10 (24.4)	15 (37.5)	0.202
≤10.4 fl	31 (75.6)	25 (62.5)	
MPV <sub>2</sub>			
>10.4 fl	19 (46.3)	11 (27.5)	0.079
≤10.4 fl	22 (53.7)	29 (72.5)	0.005
ΔMPV increased	28 (68.3)	15 (37.5)	0.875
Aged <5 years	27 (65.8)	27 (67.5)	0.008
Female gender	17 (41.5)	6 (15.0)	0.118
Leukopenia	4 (9.7)	9 (22.5)	0.745
Thrombocytopenia	18 (43.9)	19 (47.5)	0.352
Wasted or severely wasted	13 (31.7)	9 (22.5)	0.000
Acute kidney injury (AKI)	21 (51.2)	5 (12.5)	0.002
Disseminated intravascular coagulation (DIC)	24 (58.5)	10 (25.0)	0.005
Septic shock	28 (68.3)	18 (45.0)	0.034

TABLE 3. Validity and precision of potential models based on multivariate analysis by logistic regression

Model	OR	95%CI	OR changes from reference model (%)	Precision	p
Model 1 or reference model (controlling for gender, leucopenia, AKI, DIC and septic shock)	4.144	1.328-12.933	-	11.605	0.014
Model 2 (controlling for gender, AKI, DIC and septic shock)	3.926	1.275-12.089	5.3	10.814	0.017
Model 3 (controlling for AKI, DIC and septic shock)	3.609	1.220-10.677	12.9	9.457	0.020
Model 4 (controlling for gender, AKI and septic shock)	4.413	1.477-13.190	6.5	11.713	0.008
Model 5 or final model (controlling for gender and AKI)	3.851	1.354-10.948	7.1	9.594	0.011
Model 6 (controlling for gender)	3.859	1.458-10.211	6.9	8.753	0.007
Model 7 (Unadjusted)	3.590	1.434-8.988	13.4	7.554	0.006

## DISCUSSION

In the present study, we have evaluated the MPV role as a predictor of mortality in children with sepsis. The bivariate analysis showed there was no correlation between MPV<sub>1</sub>, MPV<sub>2</sub> and mortality in children with sepsis (p = 0.202 and p = 0.079 respectively), while an increase in MPV within 24-72

h after diagnosed as sepsis (ΔMPV > 0) is associated with higher mortality (p = 0.005). After conducting multivariate analysis, we obtained adjusted OR for ΔMPV>0 was 3.851 (95% CI 1.354 to 10.948; p = 0.011).

Sepsis causes immune dysregulation resulting in the release of various pro-inflammatory cytokines that affect megakaryocytes. Sepsis also



leads to increase growth factors such as thrombopoietin which regulates megakaryocytes proliferation and differentiation.<sup>16</sup> As the result, the young platelets which are larger and more active are released.<sup>17,18</sup> These large platelets are characterized by an increase in MPV. Furthermore, an increase in MPV also indicates that the platelets are more active functionally, metabolically and enzymatically than the small ones. This difference is due to an increase in the content of alpha granules and dense granules, thromboxane A2 intracellular, and pro-coagulation surface proteins such as P-selectin and glycoprotein IIa/IIIa.<sup>10</sup>

The results of this study are similar to several previous study, which showed that MPV increased significantly within 72 h after admission in the group of deceased patients caused by sepsis ( $p = 0.001$ ).<sup>10</sup> Similarly, the study by Erdogan concluded that there was no correlation between mortality and MPV value obtained at admission and 48 h later in critically ill children ( $p = 0.480$  and  $p = 0.213$  respectively), but an increase in MPV within 48 h after treatment in the pediatric intensive care unit is associated with higher mortality ( $p < 0.001$ ).<sup>19</sup> Therefore, serial MPV measurements may help to predict poor outcome in pediatric patients with sepsis to optimize the treatment and reduce mortality.

Another factor associated with mortality in children with sepsis is the presence of AKI (OR 6.129; 95%CI 1.844 to 20.369;  $p = 0.003$ ). This is consistent with a previous study that concluded AKI as a risk factor of mortality in children with severe sepsis (OR 2.5; 95%CI 1.5 to 4.2;  $p = 0.001$ ).<sup>20</sup> Septic patients with AKI are associated with poorer outcome due to organ dysfunction, so that the risk of death is greater. Meanwhile, the influence of gender on mortality was not statistically significant (OR 3.157; 95%CI 0.944 to 10.562;  $p = 0.062$ ).

The mortality rate of sepsis based

on this study is 50.6%. This result is consistent with a previous study that showed the mortality rate in children with sepsis who were hospitalized at PICU Dr. Sardjito General Hospital from July to November 2012 was 52%.<sup>21</sup> The diagnosis of sepsis is confirmed by PELOD-2 score with cut-off  $\geq 11$  which is associated with an increase in mortality  $\geq 30.5\%$ .<sup>1</sup>

Most subjects were aged  $< 5$  years (66.7%) with the youngest only 1 month old. Research determined the maturity of immune system depends on the age, so the younger patients had lower maturity to eliminate pathogens thereby increasing the risk of sepsis.<sup>22</sup> In this study, there was no age difference in the case group or control group. This finding is similar to Saraswati's study which reported that the ages  $< 5$  y.o. are not proved to be a risk factor for mortality in children with sepsis.<sup>4</sup> However, the proportion of children aged 1-12 mo in case group was higher than the control group, although the finding was not statistically significant (46.3% versus 35.0%,  $p = 0.299$ ).

We found male predominance with ratio of 2.5:1. However, the proportion of female subjects in the case group was higher than the control group (41.5% vs. 15.0%). This finding is consistent with the results of Pietropaoli's study that concluded although the incidence of sepsis was greater in male patients, still females with severe sepsis/septic shock have higher mortality risk (OR 1.11; 95%CI 1.04 to 1.19;  $p = 0.002$ ).<sup>23</sup> Positive culture found in this study was similar to a previous study that found etiological pathogens in as many as 40-60% cases.<sup>24</sup>

This study has several limitations. The retrospective design by reviewing medical records gave us difficulties to obtain complete information. Mean platelet volume data also were obtained retrospectively, so the timing of blood sampling was different in all subjects and we could not control the time interval

between blood sampling and laboratory processing. One previous study showed that the duration of blood sample in ethylenediaminetetraacetic acid (EDTA) tube can affect MPV results, so the measurement processing should be done within one h after blood sampling.<sup>25</sup>

## CONCLUSION

Elevation MPV within 24-72 h after being diagnosed ( $\Delta$ MPV>0) predict poor outcome in pediatric patients with sepsis.

## ACKNOWLEDGEMENTS

We would like to thank Christopher Erik Hookom for assisting in manuscript preparation.

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