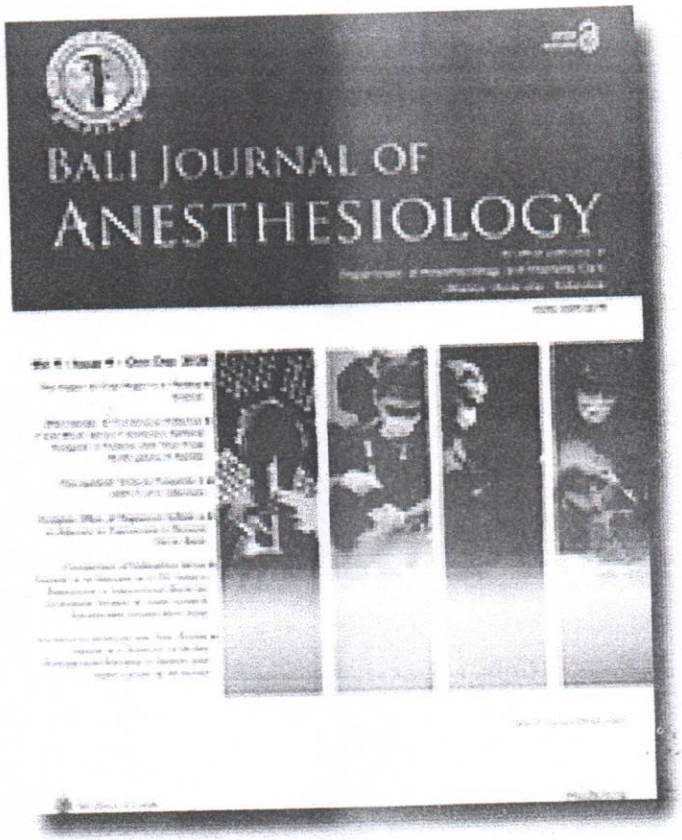
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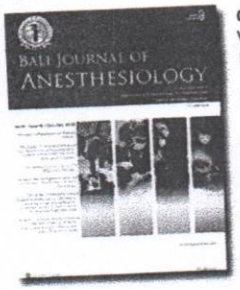

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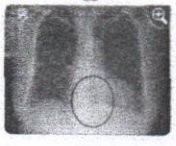

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Original Article

Immature Granulocyte and Mean Platelet Volume as a Predictor of 30-Day Postoperative Mortality in Patients with Sepsis Caused by Peritonitis

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Abstract

Background: Prompt and reliable identification and risk stratification in sepsis patients are needed to reduce the risk of mortality. Immature granulocytes (IG) and mean platelet volume (MPV) are considered as the predictors of 30-day mortality in sepsis patients. This study aims to analyze the relationship between IG and MPV with 30-day mortality following emergency laparotomy in patients with sepsis due to peritonitis. **Materials and Methods:** In this observational retrospective study, IG, MPV value, and 30-day mortality were obtained from the medical records of sepsis patients due to peritonitis who underwent an emergency laparotomy that met the inclusion criteria. We recorded the patients' data that met the inclusion criteria from the medical records that consisted of age, sex, diagnosis, sequential organ failure assessment score, and routine laboratory examination at the time of admission. Then, we analyzed each variable to determine the valid predictors of mortality. **Results:** From a total of 107 patients, the mortality rate was 34.58%. IG of day 1 (cutoff = 1.05), MPV of day 3 (cutoff = 10.35), and mean difference of platelet volume between day-0 and day-3 (cutoff = 0.35) were valid predictors for 30-day mortality ($P = 0.004$, $P = 0.006$, and $P < 0.001$, respectively). The mean difference of platelet volume day-0 and day-3 had the highest sensitivity and specificity, which was 67.6% and 72.9%, respectively. **Conclusion:** The number of IG on day-1, MPV on day-3, and mean difference of platelet volume between day-0 and day-3 are the valid predictors of mortality in sepsis patients due to peritonitis who underwent emergency surgery within 30 days.

Keywords: Immature granulocyte, mean platelet volume, peritonitis, sepsis

Introduction

Sepsis is a life-threatening state of organ dysfunction caused by immune dysregulation against infection.[1] The epidemiological burden of sepsis globally is difficult to be determined, but sepsis is estimated to affect more than 30 million people worldwide each year and potentially causes around 6 million deaths.[2] A research conducted in seven countries by collecting the data from 1979 to 2015 showed 288 cases of sepsis and 148 cases of severe sepsis per 100,000 people/year with in-hospital mortality rates were 17% for sepsis and 26% for severe sepsis.[3] Another study found that 27.08% of all patients with sepsis had severe sepsis with 40%–60% mortality.[4]

Peritonitis is one of the most common causes of sepsis. Research on critical surgical patients with severe sepsis showed that the most infection site (72.3%) was the abdomen.[5] A study on 675 sepsis patients that needed surgical site control showed 389 patients (57.6%) experiencing intra-abdominal sepsis.[6] The high mortality rate in sepsis patients can be caused by several factors, including low awareness, late identification, and inappropriate management of the disease.[7-9]

Some biomarkers of organ dysfunction occur in patients with sepsis, especially in septic shock, and these markers are related to the severity and mortality of sepsis.[9-13] Thrombocytopenia is a common condition and a multifactorial phenomenon

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that occurs during sepsis.[14] When thrombocytopenia occurs, younger platelets are released into the blood, and these platelets are larger and more active, so mean platelet volume (MPV) increases. An increase in MPV indicates a platelet diameter that can be used as a marker for platelet activation, endothelial damage, and thrombotic and inflammatory conditions.[15-18] Previous studies have shown that patients who died of sepsis had a more considerable increase in MPV values and increased MPV from baseline is an independent risk factor for 28-day mortality in patients with sepsis.[15] MPV has the potential to be used as an easily accessible prognostic marker of sepsis.[18]

Although several markers have been investigated, only a few can be applied clinically due to the complexity of sepsis, and easy identification of markers is needed to provide adequate treatment for patients with sepsis.[19] There were no studies that analyzed the MPV and immature granulocytes (IG) as the predictors of mortality in patients with sepsis caused by peritonitis who underwent surgery. This study set goals to compare the significance of IG and MPV by diagnostic testing to predict the sepsis prognosis due to peritonitis in patients undergoing emergency surgery.

Materials and Methods

This was a retrospective study conducted in Dr. Soetomo General Hospital in Surabaya, Indonesia. After the approval of our Institutional Ethics Committee (1903/KEPK/III/2020 dated on March 20, 2020), we collected the data of the patients diagnosed with peritonitis and presented with sepsis who underwent emergency laparotomy from the medical records between May and December 2019.

We employed all-inclusive sampling for subject selection. Patients who met the following criteria were enrolled in the study protocol: aged ≥18 years old, diagnosed with peritonitis who underwent emergency laparotomy, presented with sepsis at the time of admission with the suspected source of infection (peritonitis), and ≥2 quick sequential organ failure assessment (SOFA) criteria based on the 3rd International Consensus Definition for Sepsis and Septic Shock 3. The exclusion criteria were the patient with incomplete medical record and conditions that cause the increase of IG and MPV, such as blood cell malignancy, an autoimmune disease, an immunocompromised condition, and history of drugs consumption (anti-platelet such as clopidogrel) before admission.

We recorded the patients' data that met the inclusion criteria from the medical records that consisted of age, sex, early diagnosis, infection site, SOFA score, routine laboratory examination at the time of admission in the emergency room (d0), day-1 (d1) postlaparotomy, and day-3 (d3) postlaparotomy, and patient's outcome between day-3 and day-30 postlaparotomy. Then, patients were divided into two groups: the survivor group (Group S) and the nonsurvivor group (Group NS). SOFA score was used to determine the outcome and correlate with IG and MPV as a predictor of mortality in sepsis patients.

Statistical analysis was performed with the SPSS statistics software version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.). Continuous variables were expressed as mean ± standard deviation or median (range) where appropriate, and categorical variables were expressed as the absolute number and proportions. Logistic regression was performed to see the most influential subvariables and receiver operating characteristic (ROC) curve plotting to determine IG and MPV cutoff value as a predictor of mortality. The cutoff value was calculated to get the best sensitivity and specificity. $P < 0.05$ was considered statistically significant.

Results

A total of 107 participants were enrolled in this study, with a mortality rate of 34.6%. Demographic, clinical, and laboratory characteristics in each group are shown in Table 1. In this study, we did not find any significant differences in sex, age, and BMI between nonsurvivor and survivor group. The median of days in mechanical ventilation was longer in nonsurvivor than in the survivor group.

Logistic regression analysis to analyze the correlation between SOFA score, IG, and MPV with 30 days-mortality is shown in Table 2. IG day 0, day 1, and day 3, ΔIG day 3-day 0, MPV day 3, and ΔMPV day 3-day 0 were further analyzed with ROC curves to determine the cutoff value, as shown in Figure 1 and Table 3. According to the ROC curve, all of these parameters were significant as a predictor of 30 days-mortality. Upon diagnostic testing [Table 4], only IG-d1, MPV-d3, and ΔMPV d3-d0 were valid as a predictor for 30-days mortality in sepsis patients, which were shown with McNemar test and κ-value of >0.05. In this study, ΔMPVd3-d0 >0.35 ($\times 10^3/mm^3$) was the best predictor for sepsis-related mortality in 30 days with the highest sensitivity (67.6%) and specificity (72.9%).

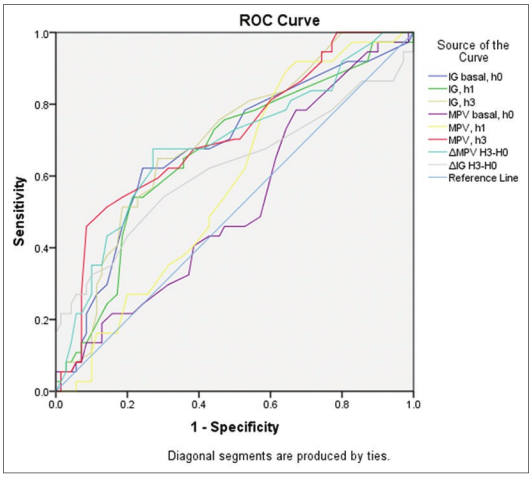

Figure 1: Receiver operating characteristic curves for immature granulocytes and mean platelet volume to predict 30 days-mortality in sepsis patients with peritonitis who underwent emergency laparotomy

Table 1: Demographic, clinical, and laboratory characteristics comparison

	Group NS	Group S	*P*
Number of patients	37 (34.6)	70 (65.4)	
Sex, *n* (%)			0.174*
Male	29 (78.4)	46 (65.7)	
Female	8 (21.6)	24 (34.3)	
Age (years)	60 (18-80)	48 (18-83)	0.076**
BMI (kg/m^2)	24.2 (17.3-31.2)	23.9 (14.5-45.4)	0.639**
Infection site, *n* (%)			
Perforated appendicitis	8 (21.6)	44 (62.9)	0.015*
Gastric perforation	15 (40.5)	16 (22.9)	
Others	14 (37.8)	10 (14.3)	
Comorbidities, *n* (%)			
Diabetes mellitus	9 (24.3)	11 (15.7)	0.277*
Hypertension	11 (29.7)	19 (27.1)	0.777*
COPD	4 (10.8)	4 (5.7)	0.340*
Osteoarthritis	4 (10.8)	2 (2.9)	0.089*
Gastritis	1 (2.7)	3 (4.3)	0.681*
Malignancy	3 (8.1)	3 (2.9)	0.221*
Coronary disease	0	1 (1.4)	0.465*
Asthma	1 (2.7)	0	0.167*
No comorbidity	11 (29.7)	31 (44.3)	0.142*
LOS (days)	7 (4-15)	8 (4-20)	0,165**
MV (days)	7 (0-14)	1 (0-8)	<0.001**
SOFA score	11 (6-12)	5 (0-8)	<0.001**
Laboratory values			
Hb d0 (g/dL)	10.8 (±2.3)	11.9 (±2.7)	0.041***
WBC d0 (10^3/mm^3)	11.2 (4.3-36.5)	13.4 (0.9-38.4)	0.130**
Platelet d0 (10^3/mm^3)	324.0 (87.0-643.0)	271.0 (37.0-801.0)	0.911**
Albumin d0 (10^3/mm^3)	2.8 (±0.5)	3.1 (±0.5)	0.001***
IG d0 (10^3/mm^3)	1.5 (0.2-9.0)	0.6 (0.2-5.5)	0.002**
IG d1 (10^3/mm^3)	1.7 (0.2-15.0)	0.7 (0.3-14.0)	0.005**
IG d3 (10^3/mm^3)	1.9 (0.5-9.6)	0.8 (0.3-5.9)	0.001**
ΔIG d3-d0	0.3 ([-1.9]-2.9)	0.1 ([-1.1]-1.3)	0.043**
MPV d0 (10^3/mm^3)	10.04±0.94	9.93±0.96	0.568***
MPV d1 (10^3/mm^3)	10.16±0.69	9.94±1.01	0.242***
MPV d3 (10^3/mm^3)	10.69±0.80	10.02±0.94	<0.001***
ΔMPV d3-d0	0.6 ([-0.7]-2.0)	0.05 ([-8.5]-2.0)	0.001**

Data for age, body mass index, length of stay, days on mechanical ventilation, SOFA score, and laboratory values are expressed as mean±standard deviation or median (range). *Chi-square test, **Mann–Whitney U-test, ***T2-independent test. BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, LOS: Length of stay, MV: Mechanical ventilation, SOFA: Sequential organ failure assessment, Hb: Hemoglobin, WBC: White blood cells, IG: Immature granulocytes, MPV: Mean platelet volume, Δ: Difference

Table 2: Logistic regression analysis for the independent predictors of 30 days mortality

	Odds ratio	*P*
SOFA score	2.309	<0.001*
IG d0	1.378	0.036*
IG d1	0.867	0.120*
IG d3	1.271	0.049*
ΔIG d3-d0	2.216	0.032*
MPV d0	1.131	0.566*
MPV d1	0.766	0.241*
MPV d3	2.361	0.001*
ΔMPV d3-d0	2.567	0.001*

*Logistic regression analysis. SOFA: Sequential organ failure assessment, IG: Immature granulocytes, MPV: Mean platelet volume, Δ: Difference

Discussion

Sepsis is a health problem that affects all age groups worldwide and is a complication of peritonitis which can cause multiple organ failure and death.[20] This mortality rate varies and depends on the severity of the disease, incidence rate, and organ failure, so that early detection of severe sepsis or septic shock is needed not only for risk stratification but also in monitoring the efficacy of treatment and disease progression.[15]

In this study, mortality in patients with sepsis due to peritonitis who underwent emergency laparotomy was 34.58%. This mortality rate is in line with previous studies with settings that similar to this study. In another study, a 30-day mortality rate during hospital stay was 40%, and this mortality rate was

Table 3: The cutoff point for immature granulocytes and mean platelet volume in predicting 30 days mortality in sepsis patients with peritonitis

	AUROC	*P*	Cutoff
IG d0	0.678 (0.568-0.787)	0.003*	0.95
IG d1	0.665 (0.555-0.774)	0.005*	1.05
IG d3	0.703 (0.602-0.804)	0.001*	1.15
ΔIG d3-d0	0.619 (0.496-0.741)	0.044*	0.15
MPV d3	0.711 (0.607-0.815)	<0.001*	10.35
ΔMPV d3-d0	0.688 (0.579-0.798)	0.001*	0.35

AUROC: Area under the receiver operating characteristic curve, IG: Immature granulocytes, MPV: Mean platelet volume, Δ: Difference, *significant if $P<0.05$

Table 4: Immature granulocytes and mean platelet volume predictive performance for 30-day mortality in sepsis patients with peritonitis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	McNemar test	κ
IG d0	67.6	62.9	51.0	78.6	0.034	0.279
IG d1	64.9	64.3	49.0	77.6	0.073	0.271
IG d3	67.6	62.9	51.0	78.6	0.034	0.279
ΔIG d3-d0	62.2	57.1	43.4	74.1	0.023	0.175
MPV d3	62.2	65.7	48.9	76.7	0.143	0.262
ΔMPV d3-d0	67.6	72.9	56.8	81.0	0.143	0.262

PPV: Positive predictive value, NPV: Negative predictive value, IG: Immature granulocytes, MPV: Mean platelet volume, Δ: Difference

significantly increased in patients with septic shock.[21] Death in sepsis patients that occurred in the initial phase is caused by multiple organ failure due to primary infection, while in the final phase is mostly caused by secondary infection due to immunosuppression in the clinical course of sepsis.[22,23]

In this study, older age was significantly associated with mortality within 30 days ($P = 0.015$). Some studies suggest that old age (geriatrics) can be an independent risk factor for predisposing to severe sepsis.[24] There were several reasons why older people were more likely to develop infections. It has been established that immune function decreases with age; also known as immunosenescence, which makes older people vulnerable to an increased risk of infection and more severe and prolonged infections. The elderly were more susceptible to infection due to the process of body changes and decreased organ function and the presence of comorbid diseases. The diagnosis of sepsis in the elderly is even more difficult because the elderly provide responses and clinical symptoms of sepsis that are less clear, and sometimes accompanied by delirium.[25]

The median SOFA score in the nonsurvivor group was significantly higher than in the survivor group. This finding was in accordance with previous research that stated that significantly high-SOFA scores were found in many of the nonsurvivor groups.[11,26] SOFA scores at initial hospital admission and changes in SOFA scores during treatment have good accuracy in predicting hospital mortality. Furthermore, SOFA scores are an accepted method for determining risk stratification and prognosis for severe sepsis patients at hospital admission.[27,28]

The mean Hb at admission in the nonsurvivor group was significantly lower than in the survivor group, and both groups had anemia. These results were similar to the study by Jung *et al*.,[29] which states that the percentage of patients with 90-day mortality increases with decreasing initial hemoglobin levels and initial hemoglobin levels independently associated with 90-day mortality and mortality increases proportionately with decreasing hemoglobin levels. Low hemoglobin levels at hospital admission indicate inadequate tissue oxygenation. They may reflect more severe inflammation compared to patients with septic shock with normal hemoglobin levels.[29] Anemia in sepsis can be caused by several mechanisms, including a systemic inflammatory response process. It may cause a decrease in red blood cell production, and destruction of red blood cells due to hemolysis and bleeding due to disseminated intravascular coagulation. The combination of anemia and changes in oxygen consumption induced by sepsis can increase tissue oxygenation disorders, resulting in cellular hypoxia, cell dysfunction, and can end in multiple organ dysfunction syndromes, so that mortality increases.[30]

The mean albumin at admission in the nonsurvivor group was lower than the survivor group. This result was in accordance with the previous study, where albumin results significantly lower in the group of nonsurvived patients.[15] Takegawa *et al*.[31] reported that the value and change of albumin in a short time reflects the risk of death in clinical and surgical patients undergoing treatment in the intensive care unit (ICU). Progressive decreases in serum albumin caused by the decreased synthesis in the liver have effects on colloidal osmotic pressure and carriers of endogenous or exogenous compounds. Therefore, they can dynamically change the permeability of blood vessels, which may contribute to death.

The IG count on day 0, 1, and 3 in the nonsurvivor patients was significantly higher than the survivors. Similarly, the Δ IG day 3-day 0 was significantly higher in the nonsurvivor group. This result was similar to the study by Nierhaus *et al*.[32] in sepsis patients treated at the ICU. They reported a difference of IG in between survivor and nonsurvivor groups, in the period 15 (days 10–14 treatment; area under curve [AUC] = 0.617, $P = 0.042$) and the period 20 (days 15–21 treatment; AUC = 0.682, $P < 0.001$), but they stated that IG did not have prognostic power in predicting mortality despite the significant difference. This discrepancy occurred because the number of patients with infection relatively increased in the final period (day 10–21) due to several noninfectious patients who left the ICU early, so the balance of the two groups studied was leaning toward the infected population.

We found that the cutoff value of first day's IG as a predictor of mortality in septic patients due to peritonitis was 1.05, with a sensitivity of 64.9% and specificity of 64.3%. Previous studies had shown that IG could significantly distinguish the sepsis

group with complicated severe sepsis with a cutoff of 0.5% and can differentiate better than leukocytes, C-reactive protein (CRP), and procalcitonin.[33]

This study shows that the MPV value of day 3 was valid as a predictor of mortality in sepsis patients due to peritonitis performed by emergency laparotomy. This finding was in line with a study by Vardon-Bounes *et al*.[14] which showed that MPV values were significantly correlated with mortality, particularly the MPV value on the 10th day can predict 90-day survival of sepsis patients. Several previous studies have also shown that MPV increments are statistically significant in the first 3 days in Gram-positive sepsis patients and can predict 28-day mortality in septic shock.[15,34]

This study shows that the value of ΔMPV d3-d0 ≥0.35 is a valid predictor of mortality in sepsis patients due to peritonitis underwent emergency laparotomy. This finding was in line with a study by Kim *et al*.[15] based on the multivariate analysis shown that ΔMPV was an independent predictor of 28-day mortality after confounding factors were adjusted (hazard ratio = 1.44; 95% confidence interval = 1.01–2.06; $P = 0.044$), so an increase in MPV in the first 72 h of hospital admission was a poor predictor of 28-day mortality in sepsis patients.[15] Daily monitoring of MPV values can stratify the risk of death in sepsis patients due to the changes in MPV during the 1st week after the onset of sepsis due to MPV values that do not return to baseline or normal values correlated with unfavorable outcomes.[14]

Increased MPV indicates platelet diameter, which can be used as a marker for platelet activation, endothelial damage, and thrombotic and inflammatory conditions.[15,17,18] The size of the MPV is a picture of the proinflammatory and prothrombotic conditions of the body. Large platelets are more functional, metabolic, and enzymatic active than platelets with smaller MPVs, so large platelets have more significant prothrombotic potential. Furthermore, the inflammatory process can induce procoagulant changes and cause embolization which is the most common cause of death in patients with systemic infections. MPV can be considered as an integrative measure of the inflammatory process and the destructive state of hypercoagulation in critical illness. Thus, the relationship between increased MPV and mortality in patients with sepsis can occur partly explained by this idea.[15]

This study still has several limitations that might affect the results of the study. Patients were selected from a single health center with a retrospective design, so it may not cover the general population. Since this is a retrospective study, no further investigation was carried out on the confounding factors that may influence the IG and MPV values. The serological marker evaluations such as CRP, calcitonin, or lactate are not evaluated because they are not routinely carried out in our hospital.

Conclusion

We found that the IG on day-1, MPV on day-3, and mean difference of platelet volume between day-0 and day-3 are valid predictors of mortality in sepsis patients due to peritonitis who underwent emergency surgery within 30 days. IG and MPV are easy, fast screening tool in stratifying the risk of mortality in sepsis patients due to peritonitis underwent emergency surgery.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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