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PLATELET INDEXES FOR BACTERIAL SEPSIS SEVERITY ASSESSMENT

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ABSTRACT

Sepsis is an infection-induced syndrome, mostly caused by bacteria, of organ dysfunctions caused by host response dysregulations. One of the simplest sepsis-indicator is platelet. This study aimed to determine whether platelet indexes i.e. Immature Platelet Fraction (IPF), platelet count, Mean Platelet Volume (MPV), plateletcrit (Pct), and Platelet Distribution Width (PDW), could assess sepsis severity by procalcitonin (PCT). This cross-sectional study was conducted at the Department of Clinical Pathology Adam Malik Hospital Medan from October to December 2016. Patients who had their full blood count examined with increased PCT ≥ 0.05 ng/mL were included. Sixty four of 71 patients with increased PCT were included in this study and separated into 3 groups based on their PCT levels (I = ≥ 0.05 – <2 ng/mL; II = ≥ 2 - <10 ng/mL; III = ≥ 10 ng/mL). Platelet count and plateletcrit showed a significant decrease when group I or II were compared to group III ($p < 0.05$), but when the group I was compared to the group II there was no significance. On the other hand, the other platelet indexes showed no significance amongst the groups. Higher sepsis severity based on PCT affected more of the platelet number, as the result of platelet destructions caused by pro-inflammatory cytokines and endotoxins.

Key words: Sepsis, procalcitonin, platelet indexes

INTRODUCTION

Sepsis causes significant problems in community healthcare, such as severe diseases and mortalities.[1] Even in the United States, a developed country, >200,000 cases of sepsis-related mortalities were reported each year.[2] The highest sepsis rate is found in low-to-middle income countries e.g. India and Indonesia.[3] One hundred ninety-two sepsis patients reported at hospital in Bandung in 2013.[4] Adam Malik Hospital in Medan reported 233 cases of sepsis in 2015.[5]

Infections induce pro-inflammatory responses activating the release of cytokines, such as Tumor Necrosis Factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6). These cytokines cause systemic Inflammatory Response Syndrome (SIRS).[6] TNF and IL-1 activate endothelium and increase chemokine production for activating and attracting leukocytes. TNF-α could also increase the formation of thrombin. On the other hand, IL-6 increases neutrophil productions in the bone marrow and activates coagulation cascade.[7]

Without early detection and accurate antimicrobial treatment, infection-induced inflammation will develop into sepsis. Sepsis is a life-threatening organ dysfunction that is caused by host response dysregulation towards infection.[8] Cultures are conventional laboratory methods to detect sepsis, but this method has a low specificity, time consuming (24-48 hours) and contamination vulnerable.[9,10]

One of the most popular laboratory parameters for suspecting sepsis is a prohormone of calcitonin called procalcitonin (PCT). During infections, mostly that are caused by Gram-negative bacteria, TNF-α and IL-6 together with bacteria endotoxin will induce the release of PCT in bloodstream.[11] Based on The National Institute for Health and Care Excellence (NICE), the normal PCT level cut-off for healthy people is <0.05 ng/mL12. But not all laboratory facilities in Indonesia have the devices for measuring blood PCT levels.

Another more simple parameter that has often been used in sepsis is platelet. Both pro-inflammatory cytokines and bacteria endotoxin trigger platelet activation, aggregation and adhesion, resulting in platelet sequestration and destruction.[13,14] Several platelet indexes can be measured by a hematology analyzer besides platelet counts, such as plateletcrit, IPF, MPV, and PDW.

Plateletcrit presents the mass of platelets and is affected by platelet number in the bloodstream.[15,16] One of the ways to detect bone marrow platelet production is by measuring IPF, which is the percentage of reticulated platelets that could be measured in the blood.[17] Both MPV and PDW are related to platelet morphology. Mean platelet volume expresses the average platelet size in the bloodstream and PDW is the variation of the size.[16]

The purpose of this study was to see whether these platelet indexes could assess sepsis severity that was divided based on procalcitonin (PCT) level. By studying this, could gain more information of platelet indexes that could be used to assess sepsis severity.

METHODS

The study was cross-sectional, with consecutive sampling conducted from October to December 2016 in the Department of Clinical Pathology Adam Malik Hospital in Medan. Patients were collected from the emergency room, ward, intensive care unit, a high care unit and high dependency unit of the Adam Malik Hospital.

Patients who had their venous blood drawn for full blood count and had increased PCT level were included, but the ones with dengue fever, malaria infection, Immune Thrombocytopenic Purpura (ITP) and <18- year-old of age were excluded. The full blood count was analyzed using an automated hematology analyzer Sysmex XN-1000. The patients' platelet indexes were then gathered from the result. Mini Vidas Brahms with Enzyme-Linked Fluorescence Assay (ELFA) principle was used to analyze the PCT levels. They were then separated into 3 groups according to their blood PCT levels (group I = ≥ 0.05 – <2 ng/mL; group II = ≥ 2 - <10 ng/mL; group III = ≥ 10 ng/mL).

Kruskal-Wallis test analyzed the clinical characteristics and the differences of platelet count, Pct, IPF, MPV, and PDW between the three groups. The data were considered as significant if the p-value was < 0.05.

The patients signed informed consent before their laboratory data were collected. This study had an ethical clearance approval from the Medical Faculty of North Sumatera University Health Research Ethical Committee.

RESULT AND DISCUSSION

Seven out of 71 patients were excluded since their Pct, MPV, and PDW results did not come out. Of the 64 patients, 40 (62.5%) were male, and 24 (37.5%) were female. Data with normal distribution is presented in mean (Standard Deviation (SD)) and non-normal distribution is presented in median (minimum (min.) – maximum (max.)). The mean (SD) of the patients' age was 49 years old (14.4 years). The mean (SD) of platelet count, plateletcrit, MPV were 288,828.1/µL (20,784.7/µL); 0.3% (0.2%); 10.5 fL (1.3 fL) respectively. The median (min., max.) PCT, IPF, and PDW were 21.8 ng/mL (0.17 ng/mL, 200.0 ng/mL), 4.5% (0.9%, 18.5%) and 11.8% (7.7%, 21.4%), respectively.

Table 1. The characteristics of the patients (n= 64)

Variable	Value
Gender, n (%)	
Male	40 (62.5)
Female	24 (37.5)
Age, years[a]	49.0 ± 14.4
Procalcitonin[b] (ng/mL)	21.8 (0.17-200.0)
Platelet count (/µL)[a]	288828.1 ± 20784.7
Plateletcrit (%)[a]	0.3 ± 0.2
IPF (%)[b]	4.5 (0.9-18.5)
MPV (fL)[a]	10.5 ± 1.3
PDW (%)[b]	11.8 (7.7-21.4)

The total of patients in each of the three PCT groups were 17 patients (26.5%), 23 patients (36%), 24 patients (37.5%) respectively. Differences of the platelet indexes between the 3 groups were shown in Table 2. The data showed that only the platelet count and plateletcrit had significant differences with p-value 0.043 and 0.038, respectively. As for IPF, MPV and PDW, there were no significant differences. Then continued analyzing the platelet count and plateletcrit with Post Hoc test to see the significance between 2 groups. When the group I or II were compared to the group III the results were significant, but no significance was seen when the group I was compared to the group II.

From the five platelet indexes, only platelet count, and plateletcrit showed significance when the group I or II were compared with group III. Glucu *et al.* found that the comparison of platelet count between sepsis and control was not significant, however significant between sepsis and severe sepsis.[18] Platelet count has been known to be one of the parameters in evaluating sepsis severity, such as in Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) score. Thrombocytopenia can be seen in sepsis-related organ failure.[13]

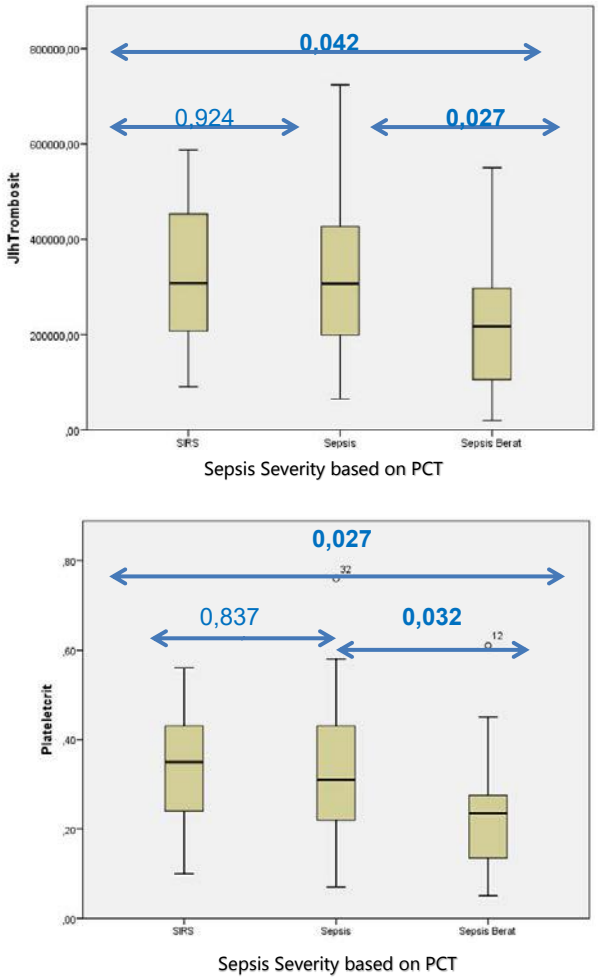

Diagram 1 and 2. These diagrams show that when platelet count and Pct of SIRS and sepsis groups were compared to severe sepsis group the result was significant

Although platelet count showed significant differences, in among groups, the data of platelet count were mostly within normal range. This might be the result of the minimal exclusion criteria in collecting samples. In a study conducted in India, patients with major trauma, operation, burn trauma and malignancy were excluded from the PCT study.[19] Another study in Iran excluded non-infectious diseases, such as immunodeficiency, pancreatitis, liver damage, cardiogenic shock and many others.[20]

There were not many studies about plateletcrit, especially its relation with bacterial sepsis. Plateletcrit reflects the total mass of platelet in circulation within 1 unit of blood volume and it is said to be relevant to hematocrit towards erythrocyte.[21]

Mean platelet volume and PDW in this study were not significantly different within groups, but MPV was slightly increased with the increasing of PCT. Cho *et al.* found that MPV did not correlate with PCT although most of the MPV values were above the normal range in increased PCT levels. The infection itself or pro-inflammatory cytokine induce the high PCT levels in sepsis and MPV may increase as a response to inflammation and thrombotic condition.[22]

Platelet distribution width pictures the platelet distribution. Activated platelets will change their morphology into a more circular shape with pseudopodia. Platelets with increased numbers and forms of pseudopodia have different sizes and affected the PDW value.[23]

Immature platelet fraction, a new platelet index, is believed to be able to reflect the percentage of immature platelet in the peripheral circulation. This study showed that IPF has no significance in differentiating the PCT groups. Research in Brazil concluded that IPF could predict sepsis development three days before the appearance of symptoms. IPF >4.7% has a 56.2% sensitivity and 90% specificity in sepsis development.[24] However, the grouping of sepsis severity was not based on PCT. The researchers in Brazil diagnosed sepsis with infection and severe sepsis with organ failure. Another study in Italy claimed that IPF did not correlate with PCT.[25]

Some literature proclaimed that the sensitivity of PCT for detecting bacteremia was relatively high although the specificity was low compared to culture.[26] In Surviving Sepsis Campaign 2016, the use of PCT in infection and sepsis was still debatable since there are a few meta-analysis showing different results.[8]

CONCLUSION AND SUGGESTION

Of all the five platelet indexes, only platelet count and plateletcrit showed significant results when compared to the group with PCT level ≥ 10 ng/mL. Platelet count has been known to be one of the parameters for assessing sepsis and the result of this study showed that platelet count could determine sepsis severity based on PCT level. Plateletcrit, as the reflection of platelet mass in the blood, showed a similar result like platelet count in this study.

Table 2. The differences of platelet indexes between the three groups of PCT levels

Variable	Procalcitonin Groups	n	Median (min.-max.)	P-value
Platelet count	I	17	308,000 (90,000-587,000)	**0.043**
	II	23	307,000 (65,000-724,000)	
	III	24	217,500 (20,000-550,000)	
Plate-letcrit	I**	17	0.4 (0.1-0.6)	**0.038**
	II	23	0.3 (0.1-0.8)	
	III	24	0.2 (0.1-0.6)	
IPF	I	17	4.5 (1.1 – 10.8)	0.644
	II	23	4.5 (0.9 – 18.5)	
	III	24	4.3 (0.9 – 10.0)	
MPV	I	17	10.3 (8.2-13.6)	0.723
	II	23	10.0 (8.4-15.0)	
	III	24	10.5 (8.5-12.3)	
PDW	I	17	11.0 (7.7-19.1)	0.804
	II	23	10.8 (8.4-21.4)	
	III	24	11.8 (7.8-16.6)	

Group I: PCT levels 0.05 s/d <2 ng/mL, group II: PCT levels ≥2 s/d <10 ng/mL and group III: PCT levels ≥10 ng/mL. Differences between 3 groups were tested with Kruskal-Wallis

This is a reflection of the platelet destruction process in sepsis when platelets are activated continuously by pro-inflammatory cytokines and endotoxins. The process will go on without the appropriate treatment and might fall into thrombocytopenia.

Further studies about the correlation between procalcitonin and sepsis severity scoring systems showed be done.

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