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CORRELATION BETWEEN INTERLEUKIN-17, INTERLEUKIN-10 LEVELS, MEAN PLATELET VOLUME TO PLATELET COUNT RATIO AND APACHE II SCORE IN SEPSIS

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Abstract. Background: *We used the Acute Physiology and Chronic Health Evaluation II (APACHE II) score to gauge the severity of sepsis. It was based on 12 physiological and laboratory measurements taken in the first 24 hours in the intensive care unit. The severity of sepsis correlates with the pro-inflammatory cytokine interleukin-17 (IL-17) and the anti-inflammatory cytokine interleukin-10. The mean platelet volume to platelet count (MPV/PC) ratio acts as a marker of inflammation in sepsis.* ***Objective:*** *The aim of this study is to prove the correlation between pro-inflammatory cytokines, anti-inflammatory cytokines, and markers of inflammation with APACHE II scores in septic patients.* ***Materials and methods:*** *A cross-sectional analytical observational study involving 35 sepsis patients was conducted. The enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of IL-17 and IL-10, and a hematology analyzer was used to determine the MPV/PC ratio. The Pearson and Spearman correlation tests were used to analyze the data.* ***Results:*** *The mean level of IL-17 was 432.51 ± 355.92 pg/ml, IL-10 was 3.09 ± 1.04 pg/ml, and the MPV/PC ratio was 4.90 ± 2.89. The study found significant correlations between IL-17 levels, IL-10 levels, MPV/PC ratio, and the APACHE II score (r = 0.721, p = 0.00), (r = 0.430, p = 0.01), and (r = 0.408, p = 0.01), respectively.* ***Conclusion:*** *There was a strong positive correlation between IL-17 levels and APACHE II scores, and a moderate positive correlation between IL-10 levels, MPV/PC ratio, and APACHE II scores.*

Key words: *sepsis, Interleukin-17, Interleukin-10, MPV/PC ratio, APACHE II*

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INTRODUCTION

Sepsis is an infection accompanied by life-threatening organ dysfunction caused by an unfavorable response from the body, according to the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) in 2016 [1]. Interleukin-17 (IL-17) has a controversial nature as a pro-inflammatory cytokine that can exacerbate and protect against sepsis [2].

Interleukin 10 is a major immunoregulator in sepsis [3], while MPV/PC ratio is easy to use as an indicator of inflammation [4]. One of the prognostic scoring systems for assessing the severity of sepsis used in Indonesia is the APACHE II [5]. The APACHE II score is used for determining mortality in the intensive care unit (ICU). Hosseini and Ramazani stated in their study that the intensive care unit (ICU) uses the APACHE II score to determine mortality. In 2016, Hosseini and Ramazani conducted a study that showed a significant difference between patients who survived and those who did not in the ICU, as indicated by the APACHE II score and the SOFA score ($P < 0.0001$, $P = 0.001$). The AUC for APACHE II was 73%, and for SOFA it was 63.4% [6].

According to research by Wu et al., patients with sepsis produce more IL-10 and less IL-12 in response to lipopolysaccharides (LPS) when IL-17 is absent [7]. IL-17 is an important regulator of the inflammatory response and plays a role in innate and adaptive immunity. IL-17 worsens the immune imbalance and causes high mortality [7, 8]. Matsumoto et al. stated that levels of cytokines IL-1β, IL-6, IL-8, MCP-1, IL-10, and plasminogen activator inhibitor-1 (PAI-1) increased during the acute phase in both critical and non-critical patients. Levels of IL-10 (days 1, 2, and 4), IL-6 and PAI-1 (days 2 and 4), and IL-8 (day 4) in critically ill patients increased significantly compared to non-critical patients [9]. Oh et al. found that either MPV or platelet count by itself could not predict shock or death within 28 days in septic patients. However, MPV to platelet count ratio (MPV/PC) in the first 24 hours was a good indicator of death within 28 days in patients with severe sepsis [10]. There are still differences in research results, so we want to prove the correlation between IL-17, IL-10, the MPV/PC ratio, and the APACHE score in patients with sepsis.

MATERIALS AND METHODS

Study subjects

This study is an analytical observational study with a cross-sectional design in sepsis patients at Dr. Kariadi Hospital, Semarang. The inclusion criteria were (1) diagnosed as sepsis using SOFA score criteria within 24 hours of ICU care and (2) aged between 18 and 74 years old. Exclusion criteria were (1) patients with a history of congenital and coronary heart disease, (2) a history of autoimmune disease, and (3) patients with malignancy. This study had been approved by the Health Research Ethics Commission of Dr. Kariadi Hospital, Number 671/EC/KEPK-RSDK/2020.

Data collection

The study focused on the demographics and clinical examination of sepsis patients, taking into account factors such as age, sex, history of disease, and laboratory biochemistry testing. The APACHE II score was calculated by looking at 12 common physiological and laboratory tests, including complete blood count, markers for kidney function, liver function, and blood gas analysis from each patient.

Detection of IL-17 and IL-10

Serum IL-17 and IL-10 levels were determined using the sandwich enzyme-linked immunoassay (ELISA) principle from Elabscience® USA in the GAKI laboratory, Faculty of Medicine, Universitas Diponegoro Semarang. Every procedure was carried out according to instructions.

RESULTS

According to the inclusion and exclusion criteria, a total of 35 patients with sepsis were included. The data analyzed included IL-17, IL-10, MPV/PC ratio and APACHE scores. The Shapiro-Wilk test was used to test the normality of the data. The IL-10 data and APACHE scores exhibited a normal distribution. The IL-17 and MPV/PC ratio data were not normally distributed; after data transformation, the IL-17 and MPV/PC ratio data were normally distributed. We analyzed the data using Pearson's test method. The table below displays the characteristics of the data.

These data show that the percentage of males (48.57%) is comparable to that of women (51.43%), and the mean age is 53 years. We conducted a data normality test using the Shapiro-Wilk test. IL-10 data and APACHE score were normally distributed. IL-17 and MPV/PC ratio data were not normally distributed; however, after data transformation, both IL-17 and MPV/PC ratio data became normally distributed. We analyzed the data using the Pearson test. Table 2 illustrates the correlation between IL-17, IL-10, MPV/PC ratio and APACHE score in sepsis patients. Below, we include a scatter plot illustrating the correlation between IL-17, IL-10, MPV/PC ratio, and APACHE score.

DISCUSSION

This study included 35 septic patients who met the inclusion and exclusion criteria. The male and female populations are comparable, with 18 males (51.42%) and 17 females (48.57%). This result is different from that of Lat et al., which states that a higher percentage of male patients are admitted to the intensive care unit

Table 1. Research subject characteristics data

Variable (n= 35)	n (%)	Mean ± SD	Median (min-max)
Age (years)		52.57 ± 13.99	56 (19-74)
Gender Male Female	 17 (48.57) 18 (51.43)		
Body mass index (kg/m^2)		23.04 ± 4.43	23.5 (16.4-34.5)
Systolic (mmHg)		119.94 ± 24.54	119 (53-185)
Diastolic (mmHg)		75.57 ± 15.66	75 (42-110)
Temperature (°C)		38.15 ± 1.18	38.5 (36-40)
Glasgow Coma Scale		8.49 ± 3.75	8 (3-15)
Hemoglobin (g/dL)		11.43 ± 2.51	12 (7-16)
Red distribution width/ RDW		16.40 ± 3.82	15.2 (12.0-29.7)
Leukocytes (x103/µL)		16.13 ± 9.03	14.2 (1,5-37.9)
Platelet (x103/µL)		286.86 ± 152.17	280 (94-626)
MPV (fL)		10.2 ± 1.02	10.3 (8.2-12.7)
MPV/PC ratio		4.89 ± 2.89	3.9 (1.4-11.1)
Interleukin-17 (pg/mL)		432.51 ± 355.92	312.7 (21.2-1214.8)
Interleukin-10 (pg/mL)		3.09 ± 1.04	3.1 (1.2-4.9)
APACHE II Score		21.77 ± 3.26	22 (16-29)

SD, standard deviation; min, minimum; max, maximum

Table 2. Correlation between levels of IL-17, IL-10, MPV/PC ratio, and APACHE II scores in patients with sepsis

Variable	APACHE II Score	
	r	p
Interleukin-17 (pg/mL)	0.721	0.000
Interleukin-10 (pg/mL)	0.430	0.010
MPV/PC ratio	0.408	0.015

APACHE: acute physiology and chronic health evaluation; MPV/PC ratio: mean platelet volume to platelet count ratio; Pearson test, $p < 0.05$; r, correlation coefficient.

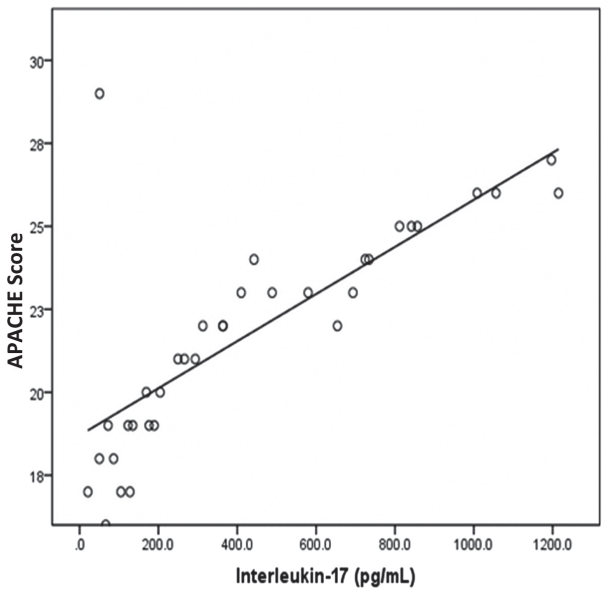

Fig. 1. Scatter graph of the correlation between IL-17 and APACHE II score

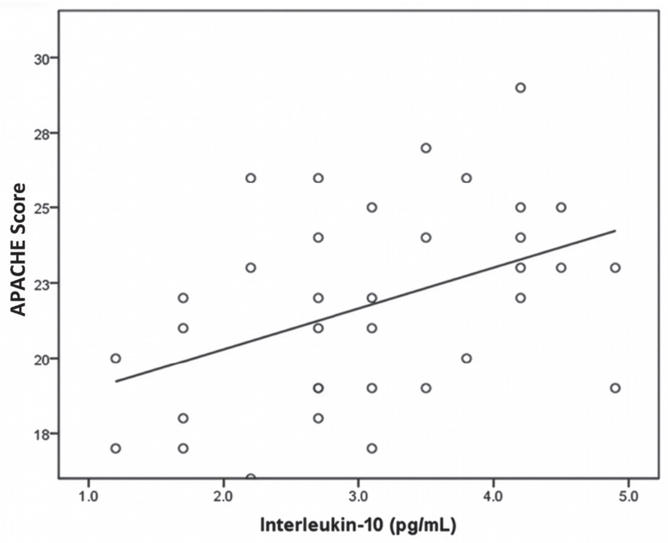

Fig. 2. Scatter graph of the correlation between IL-10 and APACHE II score

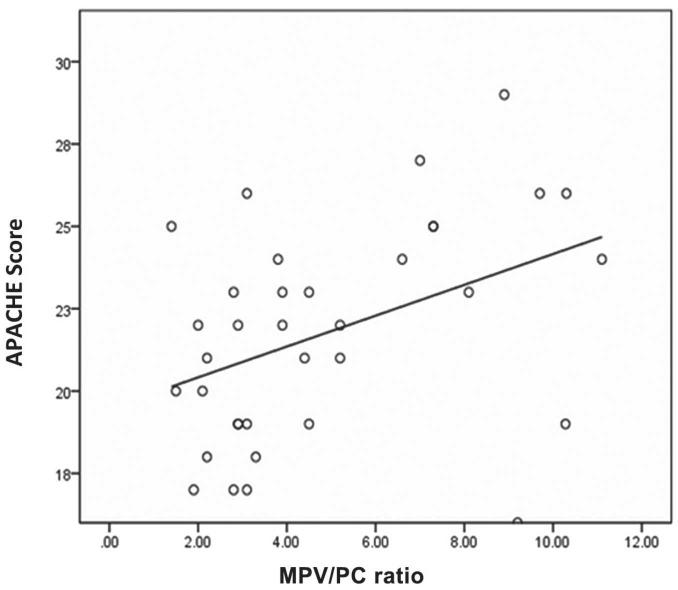

Fig. 3. Scatter graph of the correlation between MPV/PC ratio and APACHE II score

than female patients. This is possible because estrogen may have a protective effect on critical illness in women [11]. Research by Bosch et al. showed that low dihydrotestosterone (DHT) and high estradiol levels in women were protective against septic shock [12]. The results of this study are comparable to those of Nasir et al. (2015), where there was no significant difference in 97 septic patients, consisting of 52 men (54%) and 45 women (46%) [13].

The results of this study showed that there was a strong positive correlation between IL-17 and APACHE II scores. A study by Ahmed Ali et al. also found that IL-17 was the only marker amongst all evaluated in the study markers. The median level of IL-17 was 72 pg/mL in patients with sepsis and 37 pg/mL in individuals without sepsis (p = 0.000; OR, 3.2). The increase in IL-17 levels is in line with the severity of sepsis and complications that occur [14]. Research by Li et al. also showed a positive correlation between interleukin-17 levels in sepsis and complications (685.27 ± 122.91 pg/ml) compared to controls (162.96 ± 25.19 pg/ml; p < 0.01) [15]. Inflammation and decreased immunity result from the host's inability to resist infection, leading to sepsis [16]. In response to infection or injury, the host immune system produces cytokines, which are chemokines that are involved in the intricate pathophysiology of sepsis [17, 18]. IL-17, as a pro-inflammatory cytokine, provides a protective effect against infections caused by bacteria, fungi, viruses, and parasites [19, 20]. Several studies have shown that high levels of IL-17 are linked to a higher risk of sepsis. IL-17 levels may be used as a new way to predict how sepsis will get worse and as a target for treatment [21].

In line with the research of Matsumoto et al. , this study found a moderately positive relationship between IL-10 levels and APACHE II scores. This is because IL-10 levels were significantly higher in critically ill patients in the ICU compared to those who were not critically ill on days 1, 2, and 4 [9]. L'Heureux et al. showed that the increase in IL-10 levels that occurred in the first 48 hours of sepsis had a significant difference between survivors and patients who died [22]. In contrast to the study of Angurana et al., who showed that there was a negative correlation of IL-10 in children with sepsis (r = -0.257, p = 0.09) [23]. Interleukin-10 is an anti-inflammatory cytokine that can stop inflammation in sepsis [24]. IL-10 is an immunoregulatory cytokine, with elevated levels typically linked to a state of homeostatic immunological tolerance or a counterregulatory response, serving as negative feedback for elevated pro-inflammatory cytokines [25]. Excessive levels of IL-10 in sepsis may lead to functional immunosuppression and result in uncontrolled infection. Immunosuppression in sepsis leads to an increased risk of death and secondary infection [26]. Iskander et al. stated that sepsis is always in a state of mixed antagonist response syndrome (MARS), where both pro-inflammatory and anti-inflammatory cytokines are increased [27].

A systemic immune response in sepsis after a septic stimulus is a hyperinflammatory response in the form of SIRS. This occurs when the blood releases an excessive amount of pro-inflammatory cytokines. Compensatory anti-inflammatory response syndrome (CARS) is the term for the production of anti-inflammatory cytokines that occur when the immune response enters the hypo-inflammatory phase. Between SIRS and the CARS zone, there is a brief interval for the mixed anti-inflammatory response syndrome (MARS). During this time, there is a balance between circulation that causes inflammation and circulation that stops it [27].

The results of this study showed a moderately positive correlation between MPV/PC ratio and APACHE II scores. This study is in line with the results of research by Vélez-Páez et al., who showed a significant difference in MPV/PC ratio in septic patients who survived than those who died on the first day ($p = 0.001$) and on the second day ($p = 0.014$) [28]. The study by Oh et al. also found that the ratio of MPV/PC ratio on the first day of sepsis could predict death after 28 days of treatment (HR: 1.032; 95% CI: 1.012-1.054; $p = 0.002$) [10].

Dysregulation of the hemostatic system closely relates to the severity of sepsis. In sepsis, abnormal changes in coagulation can cause microvascular changes, organ failure, and death. This can lead to disseminated intravascular coagulation (DIC) [29, 30]. Early detection of progression in severe sepsis is useful for risk stratification, monitoring disease progression, and progressing therapy [30]. Platelets play an important role in thromboembolic, inflammatory, and immunomodulatory processes [31, 32]. Approximately 40% of patients with severe sepsis have a platelet count < 80,000/mm^3 [32]. Platelets express a signaling receptor, the toll-like receptor (TLR), which functions to stimulate pro-inflammatory cytokines. The number of platelets in people with sepsis caused by Gram-positive bacteria dropped in the first three days. After that, the number of platelets in people with sepsis caused by Gram-negative and fungal platelets also dropped after three days [33].

The MPV value is a measure of the mean platelet volume, and its increase reflects platelet reactivity. Patients with localized bacterial infections showed normal MPV values, but about half of septic patients displayed elevated MPV values. The MPV/PC ratio can serve as an indicator of pro-inflammatory cytokines in sepsis, according to research by Aydemir et al. [33].

CONCLUSION

IL-17 levels and APACHE II scores have a strong positive correlation, while the MPV/PC and IL-10 levels have a moderately positive correlation with APACHE II scores. The limitation of this study is that it didn't look at things that might change the APACHE II score, such as age, high blood pressure, acute kidney injury, acute respiratory distress syndrome, stroke, asthma, beta-blocker drug use, head injury, and sedative drug use. In order to divide the study population by age and ensure that its age range is not too wide, more research is required. Future research will focus more on the duration of specimen collection for IL-17, IL-10, MPV, and platelet count. It can also be conducted on other pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α.

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Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki. This study had been approved by the Health Research Ethics Commission of Dr. Kariadi Hospital, Number 671/EC/KEPK-RSDK/2020.*

Informed Consent from Participants: *Informed consent was obtained from all participants included in the study.*

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