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Original Research Article

THE DIFFERENCE IN NEUTROPHIL-LYMPHOCYTE RATIO (NLR), PLATELET-LYMPHOCYTE RATIO (PLR), AND LACTATE LEVELS BETWEEN SEPSIS AND SEPTIC SHOCK PATIENTS WHO DIED IN THE ICU

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ABSTRACT

Introduction: Sepsis and septic shock are organ dysfunctions caused by the dysregulation of the body's response to infection and are the most common causes of death. **Objective:** This study aims to describe the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lactate levels in patients with sepsis and septic shock who died in the Intensive Care Unit (ICU). **Methods:** An observational retrospective study was conducted by examining the medical record data of sepsis and sepsis shock patients who were hospitalized in the ICU of Dr. Soetomo General Academic Hospital Surabaya from January to December 2019. **Results:** The study sample was 28 patients: 16 with sepsis and 12 with septic shock. Fifteen patients (53.6%) were women. The patients' mean age was 53.18 ± 13.61 years, and most patients (8 patients, 28.6%) belonged to the late adult age group (36-45 years). The most common comorbidities were diabetes mellitus and hypertension (30.8%). The highest incidence of infection in both groups occurred in the lungs (42.9%). Most of the patients had high SOFA scores, in the moderate (7-9) to severe (≥ 10) category (39.3%). Almost all patients (82.1%) were treated for less than one week. The hematological examination within the first 24 hours showed a leukocyte value of 16,995 (Leukocytosis) and a platelet value of 279,500 (Normal). The NLR of septic shock patients (31.38±55.61) was higher than the NLR of sepsis patients (23.75±22.87). The PLR of septic shock patients (534.02±1000.67) was lower than the PLR of patients (802.93±1509.89). Lastly, the lactate levels in septic shock patients (3.84±1.99) were higher than in sepsis patients (1.97±1.06). **Conclusion:** There were no significant differences in the NLR and PLR values between sepsis and septic shock patients, but there were significant differences in their initial lactate levels.

Keywords: Died; ICU; Lactate Levels; Neutrophil-Lymphocyte Ratio; Platelet-Lymphocyte Ratio; Sepsis; Septic Shock

ABSTRAK

Pendahuluan: Sepsis dan syok sepsis merupakan disfungsi organ akibat gangguan regulasi respon tubuh terhadap infeksi dan menjadi penyebab kematian terbanyak. **Tujuan:** Penelitian ini bertujuan mengetahui gambaran rasio neutrofil-limfosit, rasio trombosit-limfosit, dan kadar laktat pada pasien sepsis dan syok sepsis yang meninggal di *Intensive Care Unit* (ICU). **Metode:** Studi observasional retrospektif dilakukan pada rekam medis pasien sepsis dan syok sepsis yang meninggal di *ICU* RSUD Dr. Soetomo Surabaya Januari-Desember 2019. **Hasil:** Sampel penelitian sejumlah 28 pasien, yaitu 16 pasien sepsis dan 12 pasien syok sepsis. Lima belas pasien (53,6%) adalah perempuan. Rata-rata usia pasien adalah 53,18 ± 13,61 tahun dan sebagian besar pasien (8 pasien, 28,6%) merupakan kelompok usia dewasa akhir (36-45 tahun). Komorbid paling sering ditemukan yaitu diabetes melitus dan hipertensi (30,8%). Kejadian infeksi terbanyak di kedua kelompok terjadi pada organ paru-paru (42,9%). Sebagian besar pasien memiliki skor SOFA terbanyak ditemukan dalam kategori sedang (7-9) hingga berat (≥ 10) (39,3%). Hampir semua pasien (82,1%) dirawat selama kurang dari 1 minggu. Hasil pemeriksaan hematologi dalam 24 jam pertama, memiliki nilai leukosit sebesar 16.995 (Leukositosis) dan nilai trombosit sebesar 279.500 (Normal). Rata-rata NLR pasien syok sepsis (31,38±55,61), lebih tinggi dari rata-rata NLR pasien sepsis (23,75±22,87). Rata-rata PLR pasien syok sepsis (534,02±1000,67), lebih rendah dari rata-rata PLR pasien (802,93±1509,89). Kadar laktat pasien syok sepsis (3,84±1,99) lebih tinggi dari rata-rata kadar laktat pasien sepsis (1,97±1,06). **Kesimpulan:** Tidak ada perbedaan bermakna pada nilai NLR dan PLR antara pasien sepsis dan syok sepsis, namun terdapat perbedaan bermakna pada kadar laktat awal antara pasien sepsis dan syok sepsis.

Kata kunci: Meninggal; ICU; Kadar Laktat; Rasio Neutrofil-Limfosit; Rasio Trombosit-Limfosit; Sepsis; Syok Sepsis

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INTRODUCTION

Sepsis and septic shock are major health problems related to infection and are the most common causes of death in the intensive care unit. The annual global incidence rate of sepsis in hospitals has reached 31.5 million cases, of which 19.4 million cases are severe sepsis and 5.3 million caused patient deaths (1). Another study in 2002 in 24 countries in the European continent found that 29.5% of severe sepsis and septic shock cases were from 198 Intensive Care Units (ICU). The high mortality rate of patients with sepsis and septic shock poses a challenge for medical personnel regarding the speed and accuracy of the initial management of sepsis, especially while still in the Emergency Unit. The Indonesian Ministry of Health (2017) stated that the mortality rate for patients with severe sepsis in intensive care had reached 32.2% and 54.1% in cases of septic shock (2).

Sepsis is a syndrome caused by the dysregulation of the body's response to infection, resulting in organ dysfunction. Infection is the body's systemic inflammatory response, which consists of releasing pro-inflammatory cytokines. Early recognition of systemic inflammation as a marker of sepsis can guide early treatment and reduce the potential for widespread metabolic/cellular disturbances and the development of septic shock.

Organ dysfunction can be identified by the Sequential Organ Failure Assessment (SOFA) Score. Sepsis is diagnosed if a patient's total SOFA score is ≥ 2 and a patient is said to be in septic shock if a vasopressor is needed to maintain a Main Arterial Pressure or MAP of ≥ 65 mmHg and serum lactate level ≥ 2 mmol/L. A SOFA score of 2 reflects a mortality of approximately 10% in the general hospital population with suspected infection. This mortality rate increases to 40% when the patients experience septic shock (3).

Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) are new inflammatory biomarkers that can act as indicators of sepsis development. Additionally, a hematological profile can be used to determine the early signs of infection and assess treatment response. NLR and PLR are indices used as prognostic tools in several clinical conditions, including sepsis. NLR is a new inflammatory biomarker that indicates shock in septic patients (4). NLR also has a positive, though weak correlation, with the prognostic Sequential Organ Failure Assessemnt score (SOFA) at admission (5,6). Other studies have also shown that a high PLR is associated with an increased mortality rate for sepsis patients (7).

Identifying the factors affecting organ dysfunction precisely and quickly through periodic examinations can shorten the diagnosis time and instigate prompt treatment, thus reducing mortality sepsis and septic shock patients. Based on this background, we conducted a study that described the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lactate levels in patients with sepsis and septic shock. This study aims to determine the differences in neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lactate levels in sepsis and septic shock patients who died in the ICU.

METHODS

This observational retrospective study was conducted on all patients with sepsis and septic shock who died at ICU Dr. Soetomo General

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Academic Hospital Surabaya. This study used the total sampling method to collect secondary data from the medical records of adult sepsis patients aged ≥ 18 years with a diagnosis of sepsis or septic shock who died in the ICU of Dr. Soetomo General Academic Hospital Surabaya from January 1st, 2019, to December 31st, 2019. The data consists of sociodemographic characteristics (age and gender), comorbidities, underlying disease, length of treatment, early SOFA score, hematology profile (early leukocyte and thrombocyte count), and early NLR, PLR, and lactate levels. The NLR is calculated by dividing the neutrophil count by the absolute lymphocyte count. PLR is calculated by dividing the platelet count by the absolute lymphocyte count. The exclusion criteria in this study were patients who were forcibly discharged and patients with incomplete or missing data.

A total of 28 patients met this study's inclusion criteria, consisting of 16 patients with sepsis and 12 patients with septic shock. Data analysis was conducted using SPSS 23.0 for Windows, a descriptive statistical program, and a comparative test analysis. After the normality test was conducted using Kolmogorov's Smirnov/Shapiro-Wilk test, an unpaired T-test/Mann-Whiteney was performed to determine the mean difference of early NLR, early PLR, and early lactate value in the two patient groups. In the statistical test results, p <0.05 indicated a significant difference between the two groups. This research obtained ethical permission and was approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya (0883/LOE/301.4.2/IV/2022).

RESULTS AND DISCUSSION

Table 1. Distribution of Patient Characteristics

Variable	Description		Mean/ Median
	Group	N (%)	
Gender	Male	13 (46.4)	
	Female	15 (53.6)	
Age*	26-35	2 (7.1)	
	36-45	8 (28.6)	53.18 ± 13.61 (30-78)
	46-55	5 (17.9)	
	56-65	7 (25)	
	>65	6 (21.4)	
Comorbidities	**With comorbidities**	**14 (50)**	
	Heart disease	2 (7.7)	
	Diabetic	8 (30.8)	
	Hypertension	8 (30.8)	
	Autoimmune -Disease	1 (3.8)	
	Stroke	3 (11.5)	
	Kidney failure	3 (11.5)	
	Malignancy	1 (3.8)	
	Without comorbidities	**14 (50)**	
*Note: One patient can have more than 1 comorbidity			
Early SOFA score*	Mild (< 7)	6 (21.4)	
	Moderate (7-9)	11 (39.3)	8.46 ± 2.63
	Weight (≥ 10)	11 (39.3)	
- Septic			7.75 ± 2.73
- Septic Shock			9 ± 2.50
Underlying Disease	Lung	12 (42.9)	
	Cardiovascular	3 (10.7)	
	Urinary Tract	6 (21.4)	
	Digestive tract	2 (7.1)	
	Skin. Bone & Soft Tissue	4 (14.3)	
	Gynaecology	1 (3.6)	
Treatment Length**	< 1 week	22 (82.1)	
	1-2 weeks	3 (10.7)	1 (1-22)
	> 2 weeks	2 (7.1)	
Early Leukocyte **			16.995 (5.250-38.340) / Leucocytosis
Early Thrombocyte**			279.500 (86.000-878.000) / Normal

Note:
* Variable data is normally distributed (based on the results of the Shapiro Wilk Test: p > 0.05) presented in the mean value and standard deviation (SD)
**Variable data is not normally distributed (based on the results of the Shapiro Wilk Test: p <0.05) presented in the median value (min-max)

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The sample in this study were patients with sepsis and septic shock diagnosed clinically and through laboratory-based testing for the SOFA score. The total subjects during the study period were 28 patients who met the inclusion criteria. The 28 patients were divided into two groups: the sepsis group, with 16 patients, and the septic shock group, with 12 patients. The distribution of the patients' general characteristics is shown in Table 1 below.

The results revealed that there were more female patients than male patients, with 15 female patients (53.6%) and 13 male patients (46.4%). In theory, it states that differences regarding sex in sepsis sufferers may occur due to significantly higher levels of anti-inflammatory mediators in women, contributing to their better prognosis. Studies have shown that men diagnosed with sepsis have high TNF-α (pro-inflammatory) levels and significantly low IL-10 (anti-inflammatory) levels, while the opposite is true in women. The increased production of IL-10 until day five after sepsis diagnosis in women is likely to inhibit the production of other inflammatory cytokines from macrophages that are activated by T-helper cells, which has protective abilities and increase the survival rate in septic conditions. Another study also showed that low 5a-DHT (dihydrotestosterone) and high estradiol levels protected host cells after adverse circulatory conditions, such as septic shock (8).

However, in this study, data for the sex characteristic did not allow the authors to identify the cause of this increase in sepsis and septic shock incidence in female patients. This result may be due to differences in each individual's other vulnerability risk factors (such as nutritional status). It may also be due to the level of care, which is one of this research's limitations. Thus, further research is needed.

The mean age of the patients was 53.18 ± 13.61 years, where the lowest age was 30 years, and the highest was 78 years. A total of 8 patients (28.6%) were in the late adult age group (36-45 years). Individuals in late adulthood are more often treated in health services. Moreover, in this age range, there may also be a decrease in the body's defense system, causing the body to be more susceptible to diseases (9).

The most common comorbidities found in patients with sepsis and septic shock were diabetes mellitus and hypertension (30.8%). The number of comorbidities that increase the risk of death for sepsis patients varies, depending on the underlying infection or pathogen causing the etiology (10). However, factors regarding infecting pathogens based on culture results were not investigated in this study, which is another limitation of this study. The number of comorbidities a patient has can also increase the development of sepsis, although not all comorbidities can increase the risk of death (11–13).

Next, most patients had high SOFA scores in the moderate (7-9) to severe (≥ 10) category (39.3%). This indicates that most patients diagnosed with sepsis in the ICU of Dr. Soetomo General Academic Hospital Surabaya were in quite bad condition, which may be related to the patient's conditions as referral patients. The mean initial SOFA score of sepsis and septic shock patients was 8.46 ± 2.63. Meanwhile, the average SOFA score of sepsis patients was lower than that of septic shock patients, at 7.75 ± 2.73, and septic shock patients at 9 ± 2.50. This is because patients with septic shock need vasopressors to maintain Main Arterial Pressure or MAP ≥ 65 mmHg, which can lead to high SOFA values in

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the criteria for assessing cardiovascular function in septic shock patients (14).

The highest incidence of infection (underlying disease) in both groups occurred in the lungs or respiratory system (42.9%). A theory explains that the incidence of septic shock caused by an infection of the respiratory system is influenced by the length of stay and the use of a ventilator (15). The use of the same ventilator for a long time also increases the opportunity for the development of various pathogens that can cause nosocomial infections. However, this study did not collect data regarding the use of ventilators. Nevertheless, special attention regarding the condition of the treatment room is required to reduce the chance of septic shock and reduce mortality.

Next, almost all patients (82.1%) were treated for less than one week. Other research shows that the results of a patient's diagnosis, when admitted to the hospital can affect the treatment duration, and no other risk factors affect the treatment duration of more than five days (16). From the data from this study, it was also found that there were no septic shock patients who underwent treatment for >2 weeks in the hospital. This is probably because the patient's condition was already severe when admitted and treated in the ICU at Dr. Soetomo General Academic Hospital Surabaya. The incidence of septic shock can affect survival time during treatment. However, data regarding patient referrals or patient conditions before being referred from previous health facilities were not investigated in this research, which is a limitation of this study.

The haematological examination from the first 24 hours found a leukocyte value of 16,995 (leucocytosis). The high leukocyte value is caused by increased leukocyte activity within 24-48 hours from increased levels of pro-inflammatory cytokines. The body's immune response is only balanced if anti-inflammatory cytokines match cytokine production within 24 hours after the pathogen infection. Meanwhile, the platelet count of patients with sepsis and septic shock was 279,500 (Normal), where the lowest value was 86,000, and the highest value was 878,000. This may be because not all sepsis patients experienced complications with DIC (Disseminated Intravascular Coagulation). According to the 2005 PAPDI guidelines regarding laboratory results on assessing the body's haemostatic function due to DIC, even if all patients experience complications of DIC, the platelet count can appear normal in both the compensation and hyper-compensation phases (17).

Table 2. The Comparison of NLR, PLR, and Lactate Levels in Sepsis and Septic Shock Patients

Variable	Septic N = 12	Septic Shock N = 16	p-Value
NLR	23.75 ± 22.87	31.38 ± 55.61	0.908
PLR	802.93±1509.89	534.02±1000.67	0.246
Lactate	1.97 ± 1.06	3.84 ± 1.99	0.002

Note: Asymp. Sig. (2-tailed) *p Value* < 0.05 was considered to have a significant difference between the two groups

Based on the test results in Table 2, there is no significant difference in the NLR (p-value = 0.908) and PLR (p-value = 0.246) in sepsis and septic shock patients. This may be due to the initial process of pathogenesis in sepsis and septic shock, where there is an inflammatory process in which neutrophils, lymphocytes, and platelets can still increase or decrease. When the body responds to inflammation through T lymphocytes that secrete Th1 substances to release proinflammatory cytokines, IFN γ will also stimulate macrophages to release IL1 and TNF α. This results in increased levels of proinflammatory cytokines. However, the body's immune response can become unbalanced if anti-

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inflammatory cytokines does not match cytokine production within the first 24 hours of pathogen infection. This condition can cause the infection to spread throughout the body, resulting in systemic inflammation and sepsis. Then, within 24-48 hours of pathogen exposure, the influence of various mediators and cytokines causes the endothelium to become increasingly stressed, such that the vascular wall loses its function and elasticity, giving rise to signs of septic shock (18–20).

Other results in Table 2 showed a significant difference between the average initial lactate levels in sepsis and septic shock patients. In septic shock patients, the average was 3.84 ± 1.99, whereas, in septic patients, the average lactate level was lower at 1.97 ± 1.06 (p = 0.002). This is because a physiological response in the body leads to lactic acid acidosis. The level of lactic acid in the blood increases in septic conditions through a different mechanism than septic shock. Hyperlactatemia in sepsis is caused mainly by excessive hypermetabolism and lactate clearance that does not match the body's metabolism (21–23). Increased lactate in sepsis can occur due to the increased production of leukocytes and phagocytes, increased production of lactic acid in the lungs, increased production of lactic acid in the splanchnic area due to dysoxia, multiorgan disorders that produce lactic acid, and increased activity of phosphofructokinase. In septic shock, similar conditions, other than hypermetabolism, occur due to extensive tissue hypoxia (22,24).

To overcome this condition, septic shock patients are recommended to be given vasopressor therapy to maintain MAP and monitor lactate levels repeatedly (3,25). However, data related to adherence to sepsis bundle therapy and septic shock in the patients in this study sample were considered homogeneous, which is a limitation of this study. We hope there will be several follow-up studies that can improve this study and fill the research gaps in this topic.

CONCLUSION

The results showed no difference in NLR and PLR between sepsis and septic shock patients. However, there was a significant difference between lactate levels in sepsis and septic shock patients. Patient mortality due to sepsis is still relatively high, especially for patients with septic shock. A multicenter prospective study in Indonesia with serial measurements over a longer period is needed to better understand the characteristics of sepsis and septic shock patients.

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Conflict of Interest

The authors stated that there is no conflict of interest in this study.

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Authors' Contributors

All authors have contributed to all processes in this research.

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