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Correlation of Platelet-Lymphocyte Ratio (PLR) as 28-Days Sepsis Mortality Predictor in Intensive Care Unit of RSMH Palembang

Tiara Santi Rizal[1*], Fredi Heru Irwanto[2], Rizal Zainal[3], Mgs Irsan Saleh[4]

[1] Fellowship of Anesthesiology and Intensive Therapy, Faculty of Medicine, Sriwijaya University /RSUP Dr. Mohammad Hoesin Palembang
[2,3] Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Sriwijaya University /RSUP Dr. Mohammad Hoesin Palembang
[4] Department of Pharmacology, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia

***Corresponding author:**
Tiara Santi Rizal

Fellowship of Anesthesiology and Intensive Therapy, Faculty of Medicine, Sriwijaya University
/ RSUP Dr. Mohammad Hoesin Palembang

Email :
tiarashanty222@gmail.com

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ABSTRACT

Introduction. Inflammatory and anti-inflammatory response are important in pathophysiology and mortality of sepsis. Platelet as first lineinflammatory marker was found increasing during early phase of infection. Decrease in lymphocyte was caused by disrupted balancebetween inflammatory and anti-inflammatory response. Platelet-to- lymphocyte ratio (PLR) is a cheap and accessible biomarker of sepsis mortality. This study aims to find the sensitivity and specificity of PLR as mortality predictor of sepsis in 28 days.

Methods. This observational analytic study with retrospective cohort design was conducted to 91 sepsis patients in intensive care unit of Dr. Mohammad Hoesin Palembang Central Hospital between January and December 2019. Samples were secondarily collected from medical record during June-July 2020. Data was analyzed using chi-square test, cog regression test, and ROC curve analysis.

Results. The result found 50 patients (54,9%) died in 28 days. Morbidity score (Charlson) was the only statistically significant mortality parameter (p=0,009). The study reported PLR cut-off point of >272,22. The sensitivity and specificity of PLR as 28-days sepsis mortality predictor are 84% and 80,49% respectively.

Conclusion. PLR is alternatively reliable mortality predictor in sepsis patient, accounted to its relatively high sensitivity and specificity.

Keywords: 28 Days Mortality, Intensive Care Unit, Lymphocyte, Platelet, PLR, Sepsis

Introduction

Sepsis is a complex and multifactorial syndrome that occurs due to the body's response to infection, where the response tends to be dangerous.1,2 Sepsis is also a major cause of morbidity and mortality in the world, it is caused by dysregulation of the body's immune system in response to infection. Although various pathophysiologic based sepsis management strategies have been implemented, the mortality rate remains high, around 300 deaths per 100,000 population. [3]

Inflammatory and anti-inflammatory responses play an important role in the pathophysiological process of sepsis, which is strongly associated with an increased risk of mortality. The diagnosis of sepsis and its severity is aggravated by the varied and non-specific signs and symptoms of sepsis. However, early diagnosis and assessment of the severity of sepsis are essential. The goal is to immediately initiate specific treatment. [4]

Death in sepsis is associated with Multiple Organ Dysfunction Syndrome (MODS), caused by microvascular thrombosis and endothelial dysfunction, resulting in tissue hypoxia. The degree of organ damage can be assessed by several scoring systems based on clinical examinations, laboratory data, and therapeutic interventions. The scoring system that is often used is The Sequential Organ Failure Assessment (SOFA). A high SOFA score is associated with an increased likelihood of death. The SOFA score requires several clinical examination variables and laboratory data such as PaO2, platelet count, creatinine level, and bilirubin level.[5]

Other than SOFA, the assessment should also be combined with the Acute Physiology and Chronic Health Evaluation (APACHE) score to get a better prognosis result compared to just examining one of them. APACHE is used within the first 24 hours when the patient is admitted to the ICU to describe the patient's morbidity, assess severity of disease, and risk of death. This score is commonly used in intensive care units but requires several laboratory examinations that are complex and require adequate time, facilities and funds. It also lacks practicality and some assessment parameters are not available at all levels of health services.[6]

There are several biomarkers that are often used to predict the mortality of ICU patients, such as differential counting, CRP, procalcitonin. Seligman and Afifi published procalcitonin and CRP as biomarkers that can predict mortality rates.[7,8] However, these tests are expensive and not all hospitals can do it.

In the last few decades, various studies have been carried out to treat this condition, with the aim of establishing appropriate therapy management, preventing complications that may occur, and reducing mortality. In the treatment of sepsis, a marker that can estimate the severity of the disease and a predictor of mortality is needed, this is useful for seeing the patient's life expectancy, and deciding the next patient's management.[9]

Currently, many studies are reported regarding the pathogenesis of sepsis and the purpose of new biomarkers and predetermined parameters. However, despite these innovations, the degradation in anticipation of disease mortality has not been achieved. One reason is the inadequate parameters of effective, reproducible and inexpensive follow-up. [10] Several studies have reported that platelets and lymphocytes have an important role in the inflammatory process. In addition, platelets also play a role in the immunomodulatory process, by initiating the release of inflammatory cytokines and interacting with various types of bacteria and immune cells, including neutrophils, T lymphocytes, lymphocytes, natural killer (NK). Platelets are identified as the first-line indicator in detecting and acting against various pathogens. Platelets are the ones that respond to damage signals in blood vessels and in the extracellular space. Data have shown that during the early phase of bacterial infection, there is a large increase in the number of platelets in the bloodstream, which then decrease excessively. Decreased platelet count usually occurs in patients with sepsis and septic shock. Decreased platelet counts in sepsis are associated with an imbalance between central production and peripheral overconsumption of platelets.[11,12]

Platelet lymphocyte ratio (PLR) is a value that can be used as a biomarker and can be easily calculated based on a simple laboratory from the results of a complete blood count. The PLR relationship in particular during the systemic inflammatory response was first introduced by Demirag in a patient who had undergone vascular surgery. They demonstrated that increasing PLR levels directly correlated with mortality.[13]

Shen et al showed that platelets and lymphocytes play an important role in the inflammatory process. Therefore, PLR is assessed as a prognostic predictor of mortality in septic patients.[3] Mathews et al assessed that an increase in PLR could predict mortality in intensive care. [9] This study showed mortality with a sensitivity of 89.9% and a specificity of 71.8%. The Baran and Birol study showed that the increase in PLR of patients with suspected Early-Onset Sepsis (EOS) had a sensitivity of 88.9%, a specificity of 84.7% [14]

Zheng et al have also shown that increased PLR can predict mortality for hepatocellular carcinoma and critical patients with acute kidney injury.[15,16] While Furuncuoglu Y et al assessed that PLR and mortality are correlated so that a high PLR ratio is associated with high mortality rates. This study showed that an increasing trend of PLR is associated with worsening clinical conditions and increased mortality in subjects.[17]

In recent years, PLR has received a lot of attention from several studies, because it can act as an indicator of inflammation in a wide spectrum of diseases, such as myocardial infarction, acute kidney injury, hepatocellular carcinoma and non-small cell lung cancer. Increased PLR is thought to be a predictor of long-term mortality and not just a marker of acute medical conditions.[15-21] In addition, PLR is considered inexpensive and results are quickly obtained and helps determine high-risk patients and also to follow up on clinical improvement objectively and to predict mortality in patients.[17,22]

In sepsis, mostly 28 days leading to mortality is considered the most appropriate and a significant endpoint, and is widely used in clinical trials. This is done for several reasons, one of which is a requirement by the Food and Drug Administration and other licensing authorities. This period is considered to be an effective time period for assessing the efficacy of the drug. Shorter time spans may not be sufficient to demonstrate the true benefit of a drug, whereas with longer time spans the effect of the drug itself becomes increasingly difficult to distinguish from other causes of death, particularly those associated with comorbidities.[23]

Methods

This study is an observational analytic study using a retrospective cross-sectional design that aims to determine the correlation between the platelet lymphocyte ratio in predicting mortality in septic patients. The data were taken from the medical records of patients in the medical record installation of RSMH Palembang during June-July 2020. The study population was all sepsis patients who were treated in the intensive care unit of RSMH Palembang during the period January 2019 to December 2019.

The inclusion criteria in this study were patients who had complete medical record data, were treated in the intensive care room of RSMH Palembang, both surgical and medical cases that met the criteria for a sepsis diagnosis, and aged 18 years - 65 years. Meanwhile, the patient exclusion criteria were patients with incomplete data and patients with active bleeding, malignancy, acute coronary syndrome, or a history of platelet abnormalities such as ITP.

Samples were collected using purposive sampling method, that is all patients who met the inclusion criteria and exclusion criteria were included as samples until the minimum sample size (51) was met.

Data taken from medical records included identity (name, age, gender), diagnosis, length of stay, SOFA score, and platelet and lymphocyte values on the first day of admission to the intensive care room. The PLR value is then calculated. Samples were also stratified by death and life outcomes for 28 days from admission. Patients discharged before 28 days were contacted by telephone to confirm an outcome within 28 days.

The collected data was processed using SPSS ver 22.0 and Medcalc. Correlation of subject characteristics to mortality in septic patients was analyzed using a simple cog regression test, with statistical decisions if p value <0.05 (statistically significant). The cut-off point value of the PLR value of septic patients on mortality was analyzed using the Receiver Operating Characteristics (ROC) curve so that the cut-off point values and the values of sensitivity, specificity and AUC were obtained as predictors of 28-day mortality in septic patients. The correlation between PLR value and mortality in sepsis patients was analyzed using the chi-square test with statistical decisions if p value <0.05 (statistically significant) and correlation strength (r), the direction of correlation, based on Guillford's (1956) criteria, namely 0.0 - <0.2 = very weak; 0.2 - <0.4 = weak; 0.4 - <0.7 = moderate; 0.7 - <0.9 = strong; 0.9 -1.0 = very strong.

Results

The sample involved in this study was 91 people with the characteristics described in table 1. Sixty patients (65.9%) were male and 31 were female (34.1%). A total of 74 samples were in the age range 18-65 years (81.3%), while the remaining 17 samples (18.7%) were> 65 years old. The average age of the sample in this study was 52 years.

The majority of patients had comorbid factors (74.4%) as evidenced by the number of comorbid scores 1. Sepsis in the largest sample originated from gastrointestinal tract infections, namely 39 people (42.9%), followed by respiratory tract infections as many as 36 people (39, 6%), and the rest (17.6%) came from other focal infections. Meanwhile, based on the type of case, it was found that most of the samples were in the surigkal case group as many as 63 people (69.2%), and the rest (30.8%) came from medical cases.

Based on the treatment room and length of treatment, it was found that the majority of the samples came from the GICU treatment room (50.5%) and the average length of treatment was 8 days with the longest treatment time being 46 days and the shortest being 0 days. A total of 72 people (79.11%) received care outside the intensive care room ≥ 1 day before being transferred to the intensive room, while the rest were treated outside the intensive room for <1 day.

Table 1. General Characteristics

Characteristics	Total (%)	Percent (%)
Age		
- 18-65 years	74	81,3
- >65 years	17	18,7
Mean±sd(Min-Max)	52±15,43 (18-82)	
Sex		
- Male	60	65,9
- Female	31	34,1
Hospital Room Origin		
- P1	8	8,8
- GICU	46	50,5
- ICU IGD	37	40,7
Comorbid Score		
- 0	19	20,9
- 1	72	79,1
Type of Disease		
- Respiratory tract infection	36	39,6
- Gastrointestinal tract infection	39	42,9
- etc	16	17,6
Length of Care Before Intensive		
- < 1 hari	19	20,9
- ≥ 1 hari	72	79,1
Length of Intensive Care Mean±sd(Min-Max)	8,32±7,91 (0 – 46)	
Type of Case		
- Medical	28	30,8
- Surgical	63	69,2

Platelet, lymphocyte and Platelet Lymphocyte Ratio (PLR) values are presented in Table 2. The mean platelet values were 288,604 + 157,183.67 with a minimum platelet value of 50,000 and a maximum of 761,000, the mean lymphocyte value was 10.30 + 7.02 with a

minimum value of 2 and a maximum of 39, while the mean platelet lymphocyte ratio (PLR) value was 353.61 + 205.17 with a minimum value of 25.45 and a maximum of 985.

Table 2. Value of Platelet, Lymphocyte and Platelet Lymphocyte Ratio (PLR)

Platelet, Lymphocyte, and Platelet Lymphocyte Ratio (PLR)	N	Mean ± sd	Min – Max
Platelet	91	288.604 ± 157.183,67	50.000 – 761.000
Lymphocyte	91	10,30 ± 7,02	2 – 39
PLR	91	353,61 ± 205,17	25,45 – 985

*Descriptive analysis using SPSS 22.0

Based on patient outcomes at 28 days, the samples were classified into dead and alive groups. As many as 54 people (54.9%) died within 28 days, while 41 people (45.1%) were alive. The results of the study are presented in table 3.

Table 3. Distribution of the Frequency of Mortality in Sepsis Patients

Mortality	Total (%)	Percent (%)
Dead	54	54,9
Alive	41	45,1
Total	91	100,0

*Descriptive analysis using SPSS 22.0

Table 4 shows the relationship between age, gender, comorbid score, hospital room origin, length of stay before intensive care, source of infection, and type of case with patient mortality. Of these variables, only the comorbid score (p = 0.00) and the type of case (p = 0.02) had a statistically significant relationship with mortality.

The comorbid score had an RR = 3.89 with 95% CI (1,400-10,805). This result means that septic patients who have a comorbid score of 1 have a risk of death by 3.89 times compared to patients who have a comorbid score of 0. Meanwhile, the RR value on the relationship between the type of case variable and mortality is 1.629. This value indicates that the medical case group had a mortality risk of 1.629 times compared to the surgical patient group.

Cut off point values and sensitivity, specificity, AUC Platelet Lymphocyte Ratio (PLR) as predictors of 28-day mortality in septic patients were obtained from analysis using

the ROC curve. The PLR cut off point value as a predictor of 28-day mortality in septic patients was> 272.22. The ROC curve is presented in Figure 1.

Based on the curve, it is known the sensitivity, specificity and AUC values of PLR as predictors of 28-day mortality in septic patients as described in table 5. PLR is known to have a sensitivity of 84%, specificity of 80.49%, with an Area under the ROC curve (AUC) by 89.1%.

Table 4. Correlation of Variables with Mortality in Sepsis Patients at 28 Days

Variable	Mortality		Total n (%)	*p value*	RR 95% CI
	Yes n (%)	No n (%)			
Sex					
Male	31 (51,7)	29 (48,3)	60 (100,0)	0,514	0,843
Female	19 (61,3)	12 (38,7)	31 (100,0		0,581-1,222
Total	50 (54,9)	41 (45,1)	91 (100,0)		
Comorbid Score					
Skor 1	46 (67,6)	22 (32,4)	68 (100,0)	0,000	3,890
Skor 0	4 (17,4)	19 (82,6)	23 (100,0)		1,400-10,805
Total	50 (54,9)	41 (45,1)	91 (100,0)		
Hospital Room Origin					
P1	4 (50,0)	4 (50,0)	8 (100,0)	0,641	
GICU	24 (52,2)	22 (47,8)	46 (100,0)		
ICU IGD	22 (59,5)	15 (40,5)	37 (100,0)		
Total	50 (54,9)	41 (45,1)	91 (100,0)		
Length of care before intensive	9 (47,4)	10 (52,6)	19 (100,0)		0,832
< 1 day	41 (56,9)	31 (43,1)	72 (100,0)	0,626	0,497 - 1,392
≥ 1 day					
Total	50 (54,9)	41 (45,1)	91 (100,0)		
Source of Infection					
Respiratory tract infection	21 (66,7)	12 (33,3)	36 (100,0)	0,119	
Gastrointestinal tract infection	21 (53,8)	18 (46,2)	39 (100,0)		
Etc	5 (31,3)	11 (68,8)	16 (100,0)		
Total	50 (54,9)	41 (45,1)	91 (100,0)		
Type of Case					
Medical	21 (75,0)	7 (25,0)	28 (100,0)	0,020	1,629
Surgical	29 (46,0)	34 (54,0)	63 (100,0)		1,157 – 2,295
Total	50 (54,9)	41 (45,1)	91 (100,0)		

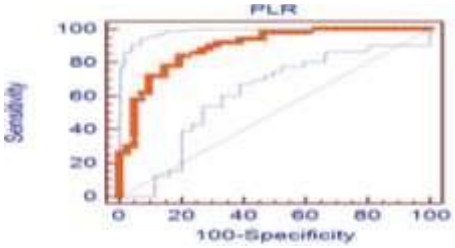

Figure 1. ROC curve PLR as a predictor of 28-day mortality in septic patients

Table 5. Diagnostic Value of Platelet-to-Lymphocyte Ratio (PLR)

Diagnostic Value	Value	95% Confidence Interval
- Sensitivitas	84%	70,9 - 92,8
- Spesifisitas	80,49%	65,1 - 91,2
- AUC	89,1%	80,9 - 94,7
- *Cut off point*	>272,22	

*ROC Curve analysis using Medcalc

Analysis using the chi square test regarding the correlation of the platelet lymphocyte ratio (PLR) to the mortality of septic patients is shown in Table 6. There is a significant relationship (p = 0.001) between the PLR value and the mortality of septic patients within 28 days. This relationship has a RR of 4.305 with a value of 95% CI (2.021 - 9.169). This means that septic patients who have a PLR value> 272.22 have a risk of 4.305 times to experience death compared to septic patients who have a PLR value <272.22. The strength of correlation is known through the contingency coefficient value. The correlation value obtained is r = 0.542. Based on Guillford's criteria (1956), the value range from 0.4 to 0.7 indicates moderate correlation strength with positive correlation direction, the more septic patients who have PLR values> 272.22, the 28-day mortality rate of septic patients increase.

Table 6. Value of Cut off Point Platelet Lymphocyte Ratio (PLR) on mortality in sepsis patients

Platelet Lymphocyte Ratio (PLR)	Mortality		Total	*p value*	RR (95%CI)	*R*
	Dead	Alive				
PLR > 272,22	42 (84,0)	8 (16,0)	50 (100,0)	0,001	4,305 (2,021 - 9,169)	0,542
PLR < 272,22	8 (19,5)	33 (80,5)	41 (100,0)			
Total	50 (54,9)	41 (45,1)	91 (100,0)			

Chi square test p> 0.05 = not statistically significant, p <0.05 = statistically significant,
RR <1 protective factor, RR> 1 risk factor, RR = 1 no correlation
R value of correlation strength, range of r values: * 0-0.3 (low), ** 0.3-0.7 (moderate), ***> 0.7 (high)

Discussion

Based on the study, from 91 samples, it was found that the average age was 52 years with a minimum age of 18 years and a maximum age of 82 years, the largest age was in the range 18-65 years, namely 74 people (81.3%) and aged> 65 years as many as 17 people (18.7%), with a mean age of 52 years. These results are consistent with research conducted by Djordjevic in 2018 where mortality was higher in the older age group. The higher incidence and mortality of sepsis in old age is due to factors, old age is more often accompanied by chronic disease, decreased organ function and age-related immunity, known as immunosenescence.[24] Similar results were obtained in a study in Thailand where the group with the highest number of sepsis patients was in the age range 18-60 years, with a mean age of 57 years.24 Study by Ki, et al in Korea showed 61.3% of patients were over 65 years of age.[25] Research in Taiwan showed a significantly higher incidence of sepsis at> 85 years of age, approximately 30-fold higher, reported from an evaluation of Taiwan's 10-year health insurance claims data. [24-27]

The results of the analysis of this study indicate that there is no significant relationship between age (p value = 0.188) and 28 days mortality in septic patients. The results of the study by Martin-Loeches et al showed that the overall 28-day mortality was 39.6% (n = 590) and was significantly higher in the very old group (≥ 80 years) than in the old group (65-79 years). However, this study did not include patients under 65 years of age. Angus et al reported that the mortality rate increases with increasing age of the patient, with a significant peak of nearly 40% in patients older than 85 years, as well as the results of the study by Wang et al which showed a significant increase in 28-day mortality in patients aged> 65. years. 28,29

Based on this study, there were 60 male samples who died as many as 31 patients (51.7%) while 19 patients (61.3%) were female. The results of statistical tests using the chi square obtained p value = 0.514 with an alpha value of 0.05 ($p < \alpha$), meaning that there is no statistically significant relationship between sex and mortality in septic patients. The value of RR = 0.843 and 95% CI (0.581 - 1.222) means that female patients can reduce the risk of death of sepsis patients by 0.843 times compared to male sex.

Based on the theory, it is known that the incidence and mortality of sepsis patients is higher in men than women. There are studies where hormones affect immune function where androgen hormones have a suppressive effect on the immune response and vice versa hormones in women have a protective effect. On the other hand, a study conducted by Anthony et al

suggested that mortality was higher in women than in men. But apart from this study, gender was not directly related to septic shock and sepsis.[27]

Previous studies have shown that sepsis is more common in men than in women.[30] Similarly, studies in Thailand showed that 53% of all sepsis patients studied were male. Men have a higher risk of sepsis than women in some previous studies, although there have also been some studies suggesting otherwise.[27,31] Although lifestyle factors may be an unmeasured confounding factor for this association, sex hormones have many potential effects on multiple organs, including cardiovascular function and immune function. In men, a higher concentration of cytokines is found after induction of endotoxemia which suppresses cell-mediated immune responses, whereas estradiol (a female hormone) increases the responsiveness of mononuclear cells after exposure to lipopolysaccharides, thereby protecting women in the early stages of the disease course.[31]

The comorbid score proved to be significant in the mortality of septic patients at 28 days. The mortality of sepsis cases is known to be 54.9% greater in patients with comorbid co-morbidities. More than half of the septic patients who died had at least one chronic medical condition according to a study conducted by Ergun (2011), it was found that there was a significant difference from the Charlson Comorbidity Index (CCI) to 28-day mortality with a p value <0.001. Other studies have also suggested that consistently increased mortality rates in patients with zero to low, moderate, and high CCI predict 28-day mortality in septic patients.[32] An earlier study showed that the incidence was seen to increase with increasing age, and a higher increase was found in the comorbid > 0 group. The most common comorbidity are cancer, liver disease and AIDS. This study also demonstrated an increase in bacteremia and organ dysfunction in comorbid patients.33 Other studies have suggested that an increase in comorbidity is found to be directly proportional to an increase in age, which is also an independent risk factor for septic mortality.[34] The study by Paoli et al. worse consisted of patients with comorbidities such as cardiovascular disease, chronic renal failure and active cancer.[35] Many studies have demonstrated a role for type 2 diabetes mellitus, hematologic malignancies, cirrhosis of the liver, atrial fibrillation, and coronary heart disease in individual susceptibility to infection.[32,36]

The origin of the hospital room and length of stay were found to be insignificant for the incidence of mortality in septic patients within 28 days. However, several studies have shown an association between length of stay in the intensive care unit and mortality from sepsis. A study reported that the length of stay in the intensive care unit is directly proportional to the

mortality rate in sepsis patients. According to Zhang et al, patients who were treated for <6 hours in the ER before transfer to the ICU had a mortality rate of 21.4%. This number is smaller than sepsis patients who are treated longer outside the intensive care room. The crude mortality rate rates for sepsis patients who were admitted to the ER for 6-24 hours and> 24 hours were 31.9% and 31.8%, respectively.[37]

Previous studies found an association between length of stay outside the intensive care unit and mortality from sepsis. Sepsis is a severe condition that requires special supportive therapy and close monitoring in the intensive care setting. Patients with sepsis should be observed for signs of worsening hemodynamic status and respiratory dysfunction. The risk of organ failure is quite high in sepsis patients. These conditions cause septic patients to require supportive therapy such as mechanical ventilation, renal replacement therapy, and vasopressors. The intensive care room is equipped with trained health personnel and adequate equipment to treat sepsis patients who are in critical condition. Therefore, sepsis patients need to be immediately transferred to the intensive care unit for special treatment.[37]

The length of stay for patients in the intensive care unit varied from 0 to 46 days, with a mean length of stay of 8.32 days. Previous studies said about 46% of sepsis patients who were hospitalized were admitted through the emergency department. The study also stated that the average length of hospitalization for sepsis patients was 5.1 days. Other studies reported that the average length of stay in septic patients was longer than that of non-septic patients (8.4 days vs 4.8 days).[38,39] Long treatment duration compared to other diseases was associated with multiple organ failure and risk of death. which can occur in septic patients. Other factors such as age, immunity status, comorbidities, and characteristics of infection also influence the prognosis and length of stay of patients with sepsis.[40]

The correlation between source of infection or type of disease and mortality in septic patients was analyzed using the chi square test. The results of the analysis were presented that of the 36 patients who had the main type of disease with respiratory problems 24 people died (66.7%), 21 people (53.8%) had respiratory infections, while the patients were included in other disease groups are 5 people (31.3%). These results are consistent with studies reported by previous studies regarding predictors of mortality in septic patients in intensive care units. The study stated that the majority of sepsis patients who originated from respiratory infections died (71.7%). This number was the highest in the study, followed by other cases with a mortality percentage of 59.3%. Similar to this study, statistically this study did not find a significant relationship between the source of infection and mortality in septic patients ($p = 0.261$).[41]

In previous studies, the potential source of infection in most cases (one third of cases) was the respiratory tract, followed by genitourinary infections and surgical procedure-related infections.[33] Other studies have also shown that the most common source of infection in sepsis is the respiratory tract.[42] Respiratory, gastrointestinal, genitourinary tract , and skin and soft tissue are common sources of septic infection, with pneumonia as the most common cause of sepsis.[43] The mucosa is a highly organized structure that lines body cavities such as the respiratory, urogenital, and intestinal tracts. The mucosa facilitates various functions such as absorption of water, nutrients and gases, as well as immune function. The mucosa also bridges between the external environment and the host tissue. The combined surface area of the digestive and respiratory tracts exceeds even the surface dimensions of the largest organ, the skin, which can also be the largest source of infection. [44]

Another variable that is significant for the mortality of septic patients at 28 days is the case type variable. The incidence of sepsis is higher in patients with chronic medical conditions that impair immune function, especially in patients with cancer, acquired immunodeficiency syndrome (AIDS), diabetes, and chronic obstructive pulmonary disease (COPD), patients taking immunosuppressive drugs and hemodialysis patients. A study examining a nationally representative sample of US hospital discharge records estimated the incidence rate of sepsis to be 755 per 100,000 patients with COPD.[20-24] In addition, the largest mortality was in medical cases of septic patients in intensive care units, possibly due to patients not receiving prompt and precise management. [45,46]

A previous study compared risk factors and mortality in patients with surgical and medical sepsis. This study involved 556 samples and 418 of them were medical sepsis patients. Even so, the risk of death was reported to be higher in patients with surgical sepsis than medical sepsis.[47] Meanwhile, another study stated that 58.5% of patients with surgical sepsis died within 28 days.[48]

Table 5 shows the PLR diagnostic value based on ROC as a predictor of 28-day mortality in septic patients. Platelets play a role in the immune modulator process, by promoting the release of inflammatory cytokines and interacting with various types of bacteria and immune cells, including neutrophils, T lymphocytes, lymphocytes, natural killer (NK). Platelets are identified as first-line indicators of detection and action against pathogens, as well as ones that respond to damage signals in blood vessels and in the extracellular space. Data have shown that during the early phase of bacterial infection, there is a large increase in the number of platelets in the bloodstream, which then reduces excessively.[12]

The lowest lymphocyte value in the sample was 2 and the highest was 39. The patient's lymphocyte mean was 10.3. Overall, the lymphocyte levels of the patients in this study were classified as low (lymphophenia). Sepsis can create an imbalance between pro-inflammatory and anti-inflammatory processes through a series of immunological responses. This condition causes apoptosis of immune cells such as T-helper, T-cytotoxic, dendritic cells, and B lymphocyte cells which lead to complete immune suppression.[49]

According to previous studies, lymphocyte levels tend to be low in the early phase of sepsis and will be in the same range of values within 28 days. Lymphopenia indicates a poor prognosis in septic patients, as revealed in another study which states that patients with lymphopenia require more ICU care, have a higher incidence of septic shock, have a higher 28-day mortality rate, and have a higher SOFA score. higher than in patients with normal lymphocyte levels.[49] Previously, other studies reported a similar case in which persistent lymphophenia (up to day 4) in septic patients was associated with death and was a risk factor for secondary infection.[50]

PLR is a marker used as a predictor of mortality in septic patients. In this study, the mean PLR level of the patients was quite high (353.6), with the lowest level of 25.45 and the highest level of 985. High PLR levels were associated with mortality in septic patients. This statement is supported by previous studies. One study reported PLR levels higher than 250 were significantly associated with hospitalized patient mortality ($p < 0.001$).[3] Other investigators examined predictors of outcome in 392 severely ill patients, including patients with sepsis. One of the predictors studied was PLR. According to the study, the mean PLR level in patients who died was 225.11 and the highest level was 410.4. However, this value is considered insignificant ($p = 0.848$).[24]

Platelets play an important role in immunomodulatory and inflammatory processes. Platelets induce the release of inflammatory cytokines and directly interact with bacteria and cells in the body, including neutrophils, T lymphocytes, NK cells, and macrophages. These immune cells play a role in the exacerbation of inflammation. Meanwhile, low lymphocyte levels indicate suppression of the immune response and inflammation. This means that a high platelet count indicates a severe degree of inflammation, while a low lymphocyte level is associated with a low body immune response to infection. Therefore, elevated PLR levels are associated with excessive systemic inflammation and can lead to worsening of certain diseases, including sepsis. This condition will produce a poor prognosis.[3]

The mortality in this study reached more than half of the study sample. As many as 50 people (54.9%) died within 28 days of being diagnosed with sepsis, while the remaining 41 people (45.1%) survived. Sepsis is a life-threatening condition characterized by organ dysfunction caused by dysregulation of the body's response to infection.[40]

A study in 2017 stated that as many as 46.4% (about 5 million people) of the total sepsis patients worldwide experienced death, to be precise about 148 deaths per 100,000 population. Meanwhile, another study reported that 67.5% of sepsis patients admitted to the ICU died. Furthermore, the study describes old age (> 60 years) as a significant risk factor affecting the death of sepsis patients. As many as 79.5% of the total patients who died were patients aged> 60 years.[41,51]

Most deaths in septic patients were reported due to discontinuation of certain treatments due to the patient's comorbid conditions or due to the patient's poor prognosis (44%) and septic shock (40%).[52] In sepsis, changes in the function of endothelial cells, phagocytes, lymphocytes, and regulation immunity as a whole. Shifts in hemostatic balance leading to procoagulation conditions are caused by changes in tissue factors, antithrombin, protein C, and fibrinolysis inhibition. This condition ultimately leads to thrombus formation and paradoxical failure of hemostasis.[8]

Based on this research, the cut off point value of PLR as a predictor of 28 days mortality in septic patients was> 272.22. Research that specifically discusses the PLR cut-off value as a predictor of 28-day mortality in septic patients is still very limited. In research by Zheng, et al in 2017, the cut off values were obtained using the curve fitting method, which are as follows; low PLR group (PLR <90) was 17.6%, medium PLR group (PLR 90-311) was 22.6% high PLR group (PLR> 311) was 22.6%. U shaped relationship was observed between PLR and mortality 90 days, and patients in the moderate PLR group (90-311) had a lower 30-day mortality rate when compared to the high PLR group and the low PLR group. In the PLR cut-off relationship with the 30-day mortality in septic patients, very low PLR (<101.2; P = 0.001) was associated with an increased risk, whereas a slightly increased risk was associated with a very high PLR (> 330.2; P = 0.088) after adjustment on confounding factors.[53]

Diagnostic test sensitivity is the ability of the diagnostic variable to detect true positives, which is a description of the test's ability to accurately identify samples with certain conditions. Different from sensitivity, specificity is the ability of a diagnostic variable to predict accurately a sample that does not have certain conditions (true negative). In this study, what is meant by sensitivity is the ability of PLR to accurately predict the death of septic patients who are

admitted to the intensive care unit within 28 days, meaning that a high PLR is associated with a high 28-day mortality rate. Meanwhile, what is meant by specificity is the PLR's ability to predict septic patients in the intensive care unit who will not die within 28 days, that is, a low PLR value will be associated with a low mortality rate for septic patients.[54]

In this study, the sensitivity and specificity values of PLR in predicting mortality of septic patients who were admitted to the intensive care unit within 28 days were found to be 84% and 80.49%, respectively. This value is high and proves that PLR can predict the death of sepsis patients who are treated in the intensive care unit quite well. High sensitivity and specificity values for PLR were also reported by Arcagok et al (2019) who examined PLR as a predictor of neonatal sepsis. According to the study, PLR had a sensitivity value of 88.9% and a specificity of 84.7%.[55]

Several previous studies also support the findings obtained in this study. Research by Shen et al (2019) which is a secondary study with 58.000 samples reported that high PLR levels are associated with mortality in septic patients. The PLR value that was considered significant was >200.[3] Meanwhile, a previous retrospective study compared PLR levels in surviving and deceased septic patients. The result, from 330 samples, 66.4% of patients who died had PLR levels higher than those who survived. [56]

Through this study, PLR was found to have a comparable prognostic value and even better when compared to other predictors of sepsis mortality. One study reported the sensitivity and specificity of NLR in predicting the prognosis of sepsis. According to the study, the NLR examined on the first day had a sensitivity of 87.5% and a specificity of 90% in predicting sepsis mortality. These results indicate that NLR is a good prognostic marker in predicting death in septic patients. [57]

Schuetz et al (2017) tested procalcitonin as a predictor of mortality in severe septic patients. The study stated that the sensitivity and specificity of procalcitonin in predicting death in septic patients within 30 days were 77% and 39%, respectively. We agreed that procalcitonin was a significant independent predictor of mortality in septic patients. Another marker used as a predictor of death in septic patients is the level of CRP (c-reactive protein). Ryu et al (2019) concluded that CRP was not good enough as an independent predictor of 28-day mortality in septic patients. The sensitivity and specificity values of CRP reported by Ryu et al were 52.5% and 56.4%, respectively.[58,59]

Therefore, it can be concluded that PLR as a prognostic test to predict mortality of septic patients within 28 days has a good sensitivity and specificity when compared with other

biomarkers. The low price and the availability of PLR examination facilities at the hospital make PLR a good alternative examination for sepsis patients.

Conclusion

Platelet lymphocyte ratio (PLR) has a sensitivity value of 84% and a specificity of 80.49% as a predictor of 28-day mortality in septic patients who are admitted to the ICU RSMH Palembang. From the results of the ROC analysis, the platelet lymphocyte ratio has an AUC of 89.1, which means that PLR can be used as a marker to predict mortality in patients with good categories as a predictor of 28 days mortality in septic patients who are admitted to ICU RSMH Palembang Cut off point or cut off point of PLR as a predictor of 28-day mortality in septic patients is located at a value> 272.22. There is a correlation between platelet lymphocyte ratio (PLR) in predicting 28 days mortality in septic patients, which is positive with moderate correlation (r = 0.542). The results of the analysis with simple cox regression showed that the correlation between PLR and patient mortality was statistically significant (p value = 0.001) with a value of $\alpha = 0.05$ ($p < \alpha$). The RR value was 4.305 (95% CI = 2.021–9.169). also showed that patients with PLR values> 272.22 had a 4.305 times risk of experiencing mortality within 28 days compared to patients who had PLR levels <272.22. Platelet lymphocyte ratio (PLR) can be used as a prognostic screening tool in predicting mortality of patients diagnosed with sepsis in the ICU because it has a significant correlation (r = 0.542). Prospective studies with repeated sampling are needed to obtain more accurate results and to know when the PLR value is most significant in predicting mortality in septic patients.

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