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NEUTROPHIL PLATELET RATIO ON ADMISSION AS A PREDICTOR OF SEPSIS SEVERITY

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Abstract

Background: Neutrophils play a critical role in the immune response, platelets for regulating coagulation and inflammatory responses. This study aims to investigate relationship between Neutrophil Platelet Ratio (NPR) and severity of sepsis, that can be used as biomarker for predicting severity and mortality of sepsis patients.

Methods: This study was a cohort-retrospective study at Wahidin Sudirohusodo Hospital. We included patients ages over 18 years with sepsis and septic shock diagnosed. NPR is calculated by dividing neutrophil by platelet, data were analyzed using Mann-Whitney test.

Results: Data analysis was performed on 66 subjects with Sepsis and Septic Shock patients (33 each group). Average NPR in sepsis patients was 0.11 ± 0.12 and septic shock patients 0.11 ± 0.20 with p-value of 0.455 indicates that no significant difference. The average NPR in patients who survived was 0.11 ± 0.10 , while patients who didn't survive was also 0.11 ± 0.20 with p-value 0.09. Relationship between NPR and mortality in patients during the 7-day treatment with p-value of 0.002, means NPR has a relationship with risk of death in sepsis patients in 7-day care.

Conclusion: Our study found that High NPR is related to mortality within 7 days treatment, but NPR at admission hasn't been proven as a predictor of sepsis severity.

Keywords: Sepsis, Septic Shock, Neutrophil, Platelet, NPR

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and septic shock is defined as a subset of sepsis characterized by profound circulatory and cellular metabolic abnormalities that substantially increase mortality.⁽¹⁾ Early identification and prompt early management upon the onset of sepsis will provide a better outcome. In emergency situations, during hospitalization and in outpatient care, hemograms is represent one of the most cost-effective and accessible minimally invasive tests, proving to be valuable in the management of the disease.^(2,3)

Hemogram-derived ratios (HDR), including Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), Monocytes-Lymphocyte Ratio (MLR), Neutrophil-Platelet Ratio (NPR) and Systemic Immune-Inflammation Index (SII), can serve as surrogate markers of systemic inflammation and various studies have shown that these markers can be very useful and reliable markers of inflammation and predictors of severity and mortality.^(4,5) Immune dysfunction and coagulation dysfunction accompany the entire process of sepsis occurrence and development. Neutrophils and lymphocytes are immune cells that play an important role in the immune response. Platelets are key factors that affect coagulation function and inflammatory response.⁽⁶⁾ In several studies, NPR levels were significantly associated with mortality and the relationship remained significant even after multivariable adjustment.⁽⁷⁾

Based on the relationship that can be associated with neutrophil and platelet values to an inflammatory process, it is suspected that it can also predict the severity of sepsis. Among all sepsis biomarkers that have been studied, routine blood parameters, especially Neutrophil-Platelet Ratio, can represent a valuable examination, because routine blood represents the most frequent first-line laboratory test performed in all clinical facilities, this test is also easy to do, cheap, and available in all health facilities. Therefore, this study aims to determine the relationship between NPR and the severity of sepsis, so that it can be an effective and efficient biomarker in predicting the severity and mortality of sepsis patients.

Material and Methods

This study worked with an analytic observational study with a cohort-retrospective design with Sepsis Patients in Dr. Wahidin Sudirohusodo Hospital. Wahidin Sudirohusodo Hospital is located in Makassar City, South Sulawesi Indonesia. Makassar has a population of approximately 1.5 million people. This hospital is the biggest hospital in the city and also the main referral for emergency patients with internal diseases where many cases of sepsis are often reported. This study was conducted from July 2024 until the minimum sample size was reached. The study population were patients who admitted to the emergency of Dr. Wahidin Sudirohusodo Hospital and met the inclusion and exclusion criteria. Subjects were included in this study if they met the following criteria ages over 18 years old and have been diagnosed with sepsis and septic shock. All of the subjects agreed to complete of examinations and signed an informed consent. The exclusion criteria were subjects with comorbidity of chronic liver disease and a history of long-term consumption of antiplatelets.

Independent variable included Neutrophil Platelet Ratio obtained from the results of routine blood test then the value calculated by dividing the neutrophil count by platelet count (N/P) and Sepsis Severity. Dependent variables is severity of sepsis is divided based on sepsis (Mean Arterial Pressure ≥ 65 mmHg) and septic shock (Mean Arterial Pressure < 65 mmHg), and also survival and non survival. We considered possible confounders in our analysis.

Sampling was carried out by consecutive sampling, subjects who met the inclusion and exclusion criteria were included in the study. The Criteria objectives of Sepsis in this study were patients who have been diagnosed if there is an acute increase in SOFA score ≥ 2 . Septic shock is a condition that meets the criteria for sepsis and requires vasopressors to maintain the patient's mean arterial pressure (MAP) ≥ 65 mmHg and serum lactate levels ≥ 2 mmol/L [1,2]. Severity of sepsis is divided based on sepsis (MAP ≥ 65 mmHg) and septic shock (MAP < 65 mmHg). We collect data of demographic variables such as sex, age, and comorbidities. We also collect data of routine blood test results that issued by clinical pathologist. Then NPR is calculated by dividing the neutrophil count by platelet count (N/P). Sample size was calculated using a single proportion and we get the minimum sample size was 43 patients. A total of 66 samples were collected met the inclusion and exclusion criteria.

Statistical Analysis :

Data were analyzed using Statistical Product and Service Solution (SPSS) version 25. The analysis method consists of descriptive methods and statistical tests. The statistical tests utilized were Independent Sample T-test and Mann-Whitney tests. Statistical test results were considered significant if the p-value was <0.05 . The results obtained will be presented in the narrative form which is complemented by tables and figures.

Ethical Consideration :

This study was approved by the Ethics Committee for Biomedical Research in Humans, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. Based on recommendation letter Number : 597/UN4.6.4.5.31/PP36/2024, with protocol number : UH24060400. All subjects were ≥ 18 years age and asked to give informed consent before participating in the study, for subjects who were not able to give informed consent, we explained the consent to the family or guardians of the subjects.

Results

This study consisted of 66 participants who met the study criteria. Thirty five participants (53%) were male, while 31 participants (47%) were female. The participants ranged in age from 21 to 83 years, and 54 subjects among them was age <60 years (81.8%). Based on the number of comorbidities in sepsis patients with <2 comorbidities, there were 38 (66.7%), while comorbidities ≥ 2 in sepsis patients were 22 (33.3%). Based on the source of infection, it can be seen that the source of infection is from the respiratory system as many as 30 subjects (45.45%) followed by skin and soft tissue infections 22 subjects (33.33%), gastroenterological infections 9 subjects (13.6%), urinary tract 5 subjects (4.13%). Subjects with sepsis and septic shock conditions were 33 subjects in each group. The range of NPR value was 0.005 - 0.294 with a mean of 0.03 ± 0.047 . Based on the mortality category, non survival subjects was found to be higher in 40 subjects (60.61%) compared to survival subjects in 26 subjects (39.39%). (Table 1).

Table 1. Subject's characteristics of Sepsis Patients in Wahidin Sudirohusodo Hospital, 2024 (n=66)

Variable	Variable	n (%)	Min	Max	Mean	SD
Gender	Male	35 (53)				
	Female	31 (47)				
Age			21	83	52.09	15.23
	≤ 60 years old	54 (81.8)				
	> 60 years old	12 (18.2)				
Number of Comorbidities	< 2 comorbid	38 (66.7)				
	≥ 2 comorbid	22 (33.3)				
Source of Infection	Respirology	30 (45.45)				
	Gastroenterology	9 (13.6)				
	Urology	5 (4.13)				
	Skin and Soft Tissue	22 (33.33)				
Laboratorium Results	Neutrofil count		4283	43846	16705.65	10204.76
	Platelet count		20000	544000	249800	125300
	NPR		0.005	0.294	0.03	0.047
SOFA score	≤ 8	48 (72.72)				
	> 8	18 (27.27)				
Mortality	<i>Survival</i>	26 (39.39)				
	<i>Non Survival</i>	40 (60.61)				

NPR: Neutrophil Platelet Ratio; SOFA: Sequential Organ Failure Assessment.

Table 2. Data and Analysis of Relationship between NPR and Severity of Sepsis Patients in Wahidin Sudirohusodo Hospital, 2024

Severity Variable	NPR		
	Median (Min - Max)	Mean \pm SD	<i>p</i> -Value
Sepsis (n=33)	0.06 (0.01 – 0.51)	0.11 \pm 0.12	0.455*
Septic Shock (n=33)	0.05 (0.01 – 1.19)	0.11 \pm 0.20	

Mann-Whitney Test (p<0.05)

In Table 2, relationship between Neutrophil Platelet Ratio (NPR) in sepsis and septic shock, according to the data, the average neutrophil-platelet ratio in sepsis patients was 0.11 ± 0.12 and did not differ in septic shock patients, namely 0.11 ± 0.20 . The p-value of 0.455 indicates that there is no statistically significant difference. This indicates that the NPR in this study has not provided a strong enough difference to distinguish between sepsis and septic shock.

Table 3. Data and Analysis of Relationship between NPR and Mortality within 7 Days Treatment of Sepsis Patients in Wahidin Sudirohusodo Hospital, 2024

Mortality Variable	NPR		
	Median (Min – Max)	Mean \pm SD	<i>p</i> -Value
Survival (n=26)	0.05 (0.02 – 0.50)	0.11 \pm 0.10	0.090*
Non Survival (n=40)	0.10 (0.01 – 1.19)	0.11 \pm 0.20	
Day of Care Non Survival Patients (n=40)			
< 7 days (n=19)	0.06 (0.02 – 1.19)	0.14 \pm 0.25	0.002*
\geq 7 days (n=21)	0.02 (0.01 – 0.51)	0.06 \pm 0.11	

Mann-Whitney Test (p<0.05)

In Table 3, analysis of data reveals that difference of NPR between survival and non survival sepsis patients. The data show that the average NPR in patients who survived was 0.11 ± 0.10 , while in

patients who did not survive was also 0.11 ± 0.20 . The p-value of 0.090 indicates that the difference in the average NPR between survival and non-survival was not statistically significant. But the results of the analysis also showed a relationship between NPR and mortality in sepsis patients during the 7-day treatment period. The data show that the average NPR in patients who died <7 days was 0.14 ± 0.25 , while in patients who died after 7 days of treatment the average NPR of the group was 0.06 ± 0.11 . The p-value of 0.002 indicates that the difference in the average NPR between mortality during 7-day care of sepsis patients is statistically significant, that means NPR has a relationship with the risk of death in sepsis patients in 7-day care.

Discussion

Studies analyzing the relationship between neutrophil platelet ratio and sepsis severity are very limited. NPR has been shown to predict in-hospital mortality outside of sepsis. However, the role of neutrophils in thrombosis is increasingly recognized and more is known about the immunomodulatory properties of platelets such that they interact with each other during infection, inflammation and thrombosis by modulating the function of each platelet.⁽⁸⁾

In a study conducted by Zhang Y et al examined the combined value of NLR and NPR in 1263 sepsis patients. The study explained that based on multivariate analysis, the NPR value increased in non-survivor patients with a p-value of 0.001, where a statistically significant difference was obtained.⁽⁹⁾

Single neutrophils, lymphocytes or platelets are influenced by many factors, so that when examined alone they have minimal correlation with the severity of patients with sepsis. In addition, due to the release of large amounts of inflammatory mediators and cytokines in sepsis, the body's response to infection is uncontrolled, and the balance between pro-inflammatory and anti-inflammatory is damaged, resulting in an increased in neutrophils and increased platelet consumptions. When combining hemogram derivatives, it can reflect the balance between innate and adaptive immunity, but many factors such as sepsis treatment, focus of infection, comorbidities and patient immunity can each affect neutrophils and platelets so that there is no significant difference in NPR in the two groups.⁽⁶⁾

In this study, based on the mortality rate analyzed by the Mann-Whitney test, the average NPR in survival was 0.11, while in patients who not survival, the average NPR also was 0.11. However, the p-value of 0.090 indicates that the difference in the average NPR between patients who survival and not survival was not statistically significant. This means that the NPR in this study has not proven a strong or significant relationship with the risk of death in sepsis patients in this study. However, we also analyzed patient mortality during 7 days of treatment, the average NPR value in patients who died <7 days was 0.14 ± 0.25 , while in patients who died after 7 days of treatment, the average NPR of the group was 0.06 ± 0.11 . The p-value of 0.002 indicates that the difference in the average NPR between mortality during 7 days of treatment of sepsis patients is statistically significant. This is in line with the study conducted by Zhang Y, et al who studied 1263 sepsis patients, 179 of whom died within 28 days of treatment, it was found that NPR correlated with patient mortality within 28 days of treatment with a p-value <0.001. In the study of Yeter H et where the relationship between mortality and suppression of NPR levels was not statistically significant. Where NPR is the ratio of neutrophils to platelets in peripheral blood. Sepsis triggers an irregular immune response involving inflammation and coagulation pathways. Inflammation and infection can directly activate platelets, causing platelet aggregation, adhesion to the endothelium, and release of inflammatory mediators and promoting further coagulation activation, so it can be said that platelets play a key role in the pathogenesis of inflammation-induced coagulation activation. Meanwhile, thrombocytopenia is common in sepsis due to increased platelet consumption in microthrombi, decreased production, and immune damage.^(10,11)

Although elevated NPR levels are associated with worse outcomes and increased mortality in cardiovascular disease, auto-inflammatory diseases, and malignancies, the relationship with sepsis may be more complex. First, platelet count changes are often seen in the ICU setting rather than in the ED, especially in sepsis, and thrombocytopenia often occurs during sepsis progression rather than on admission, necessitating serial platelet counts. Second, platelets are essential for coagulation and may contribute to disseminated intravascular coagulation. Third, it is known that platelets are one of the important factors of immunity, reacting to infection and contributing to pathogen killing and tissue repair as part of the innate immune response. During sepsis, neutrophils and lymphocytes rapidly respond to infection. Due to the mechanisms mentioned above, NPR with sepsis may differ from the association of this biomarker with other diseases.^(10,12)

Our results support that NPR levels are associated with early mortality in patients with septic shock. However, the relationship between sepsis severity and NPR levels did not reach statistical significance, this may also be influenced by various confounding factors such as previous treatment history and location of infection experienced by the sepsis patients studied.^(10,12)

Limitations

The limitations of this study are that this study has a limited sample and this study is a retrospective cohort study but the cause and effect of the relationship between NPR and the severity of sepsis patients can be biased and due to other things that are also confounding factors in influencing NPR levels. In addition, this study was only conducted at the time of initial hospital admission, but no serial examination of NPR values was carried out, and no assessment of the length of hospitalization, history of initial management, history of antibiotic use in sepsis patients studied which can be used as a consideration of prognosis in sepsis severity.

Conclusion

Our study found that NPR is related to in-hospital mortality within 7 days for sepsis patients in Wahidin Sudirohusodo Hospital. High NPR value indicate an increased risk of death, but NPR value at admission in this study has not been proven as a predictor of sepsis severity.

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