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High Neutrophil - Signal Fluorescence Intensity (NE-SFL) Values as Predictor of Sepsis Occurrence in Adult Patients

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KEYWORDS

Sepsis, NE-SFL

ABSTRACT:

Background: Sepsis is a systemic response to infection. Neutrophils play a crucial role in fighting microbial infections, thereby reducing the presence of pathogenic organisms within the body. Neutrophil - Signal Fluorescence Intensity (NE-SFL) is one of the parameters that make up the cell population data (CPD). This parameter can be obtained using the Sysmex XN hematology instrument. NE-SFL helps measure neutrophil immaturity and activation. Specifically, high fluorescence intensity indicates increased DNA or RNA content, reflecting significant cytokine production.

Objective: To determine the significance of elevated NE-SFL as a predictor of sepsis in adult patients.

Methods: This study is an analytical observational research with a case-control design involving 77 individuals. The study was conducted from September 2022 to March 2023 at Prof. Dr. I. G. N. G. Ngoerah Denpasar Hospital.

Results: The study included 37 sepsis patients and 40 non-sepsis patients. Data analysis revealed that sepsis patients had higher NE-SFL values than non-sepsis patients, with a p-value of 0,000. Based on the ROC curve, the NE-SFL cutoff value as a predictor of sepsis was 46,4 (95% CI: 0,743-0,440, $p < 0,001$). The odds ratio (OR) of NE-SFL for sepsis was 24,286 (95% CI: 7,345-80,297, $p < 0,001$). Neutrophil - Signal Fluorescence Intensity was considered meaningful as a predictive model for sepsis in adult patients.

Conclusion: In this study, neutrophil - Signal Fluorescence Intensity can be used as a predictor of sepsis in adult patients

1. INTRODUCTION

Sepsis is a medical emergency that describes the body's systemic immune response to infection (Urrechaga, 2020a). An underlying disease always accompanies sepsis, either organ system disorders or post-surgical disorders (Merry et al., 2021). The course of sepsis caused by bacteria begins with an infection process characterized by the onset of bacteremia, which then develops Systemic Inflammatory Response Syndrome (SIRS) and ends with Multiple Organ Dysfunction Syndrome (MODS) (Triana & Widodo, 2020). In 2016-2020 at RSUP Prof. Dr. I.G.N.G. Ngoerah Denpasar. It was found that 3% of 8,923 patients experienced sepsis (Farha et al., n.d.). The microorganisms that cause sepsis most often found in adults are gram-negative bacteria, such as E. Escherichia coli (Guntur, 2008).

Generally, the immune response to infection optimizes the ability of immune cells (neutrophils, lymphocytes, and macrophages) to exit the circulation and enter the site of infection. Ultimately, neutrophils are activated and release nitric oxide, a potent vasodilator, which can allow neutrophils and fluid to extravasate into the infected extravasculature, leading to septic shock. 10. Neutrophils are essential in fighting microbial

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infections caused by large amounts of proteolytic enzymes, thereby reducing these pathogens.

At R.S.U.P. Prof. Dr. I.G.N.G. Ngoerah Denpasar, the criteria for diagnosing sepsis use criteria quick SOFA score, symptoms or signs corresponding to systemic Inflammatory Response Syndrome (SIRS) such as temperature >38.3O C or <36O C, pulse >90 times/minute, respiration >20 times/minute, hyperglycemia without diabetes mellitus, acute loss of consciousness, leukocytosis, or SOFA score 16. An increase in the SOFA value above the normal can be diagnosed as sepsis. Increasing SOFA values are associated with mortality 9. Examinations that can determine the etiology of infection are positive blood cultures. Blood specimens, urine, cerebrospinal fluid, abscesses, and visible skin lesions must be cultured to determine the microorganism type. Blood cell count, platelet count, prothrombin time and partial thromboplastin, fibrinogen, D-dimer, blood gas analysis, kidney and liver profile, and calcium ion can also be checked. (Garna, 2012)

Over the last few decades, the Sysmex X.N. The hematology examination tool has experienced rapid development, one of which is the discovery of new parameters, namely Cell population data (C.P.D.). Cell population data provides quantitative information regarding neutrophils' morphological and functional characteristics through Neutrofil – signal fluorescence intensity (NE-SFL) analysis. These parameters will be obtained immediately after a complete blood examination (Park et al., 2015). Therefore, NE-SFL can be used as an additional parameter cheaper than other laboratory tests, and the test results will be faster. (Park et al., 2015)

Neutrofil–signal fluorescence intensity emerged as a valuable parameter for the early diagnosis of sepsis in adult patients. This examination uses an optical signal method presented in three axes: white blood cells, differential fluorescence (W.D.F.), and channel scattergram. Neutrofil–signal fluorescence intensity measures neutrophil immaturity and activation. In particular, high fluorescent intensity indicates increased cellular content of R.N.A. and D.N.A., reflecting substantial cytokine production. Biban et al. said that, as a first responder during the response of the innate immune system against organism attack and activation of cell morphological characteristics, NE-SFL can be helpful in the early detection of sepsis. (Biban et al., 2021)

This study aims to determine the cut-point value of NE-SFL. Also, to prove that a high NE-SFL value can predict sepsis in adult patients at R.S.U.P. Prof. Dr. I.G.N.G. Ngoerah Denpasar.

2. METHODS

2.1 Time and place of research

This is an analytical observational approach case-control study in patients diagnosed with sepsis (SOFAScore) and healthy people with a complete blood count (NE-SFL) for screening blood donors. This research was conducted at RSUP by Prof. Dr. I.G.N.G. Ngoerah Denpasar from September 2022 to March 2023.

This research has received feasibility approval from the Udayana Medical Faculty Research Ethics Committee Unit Number: 2031/UN14.2.2.VII.14/LT/2023.

2.2 Population and Sample

The study population was all patients diagnosed with sepsis who were treated at RSUP Prof. Dr. I.G.N.G. Ngoerah Denpasar. The sample for this study is an accessible population that meets the inclusion criteria, taken using techniques of consecutive sampling until the total number of research subjects is 77 samples. The inclusion criteria for the sepsis group in this study were adult patients diagnosed with sepsis (SOFAScore) who are being treated at RSUP Prof. Dr. I.G.N.G. Ngoerah Denpasar and carried out a complete blood examination for the period September 2022 to March 2023. The exclusion criteria for this study were medical record data and results of complete blood examinations of sepsis patients that were incomplete or could not be read by the equipment. Meanwhile, the inclusion criteria for non-septic patients are healthy people who do screening blood donation atRSUP Prof. Dr. I.G.N.G. Ngoerah Denpasar, and the exclusion criteria are the results of a complete blood test of healthy people that is incomplete or cannot be read by the instrument.

NE-SFL examination data is taken from the base Sysmex XN tool, while demographic data and examination of patient vital signs were taken from medical record data.

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2.3 Operational definition of research variables

Adult patients diagnosed with sepsis by the doctor in charge of the patient based on the PPK KSM Internal Medicine RSUP Prof. Dr. I.G.N.G. Ngoerah Denpasar is related to sepsis. The diagnosis of sepsis is fulfilled if 2 of the 3 symptoms meet the criteria quick SOFA (qSOFA) or the presence of two criteria Systemic inflammatory response syndrome (SIRS) is fulfilled.

Neutrophil – signal fluorescence intensity (NE-SFL) is one of the parameters in cell Population Data (CPD) on the Sysmex XN-3000 instrument.Neutrofil–signal fluorescence intensity measures neutrophil immaturity and activation. As the first responder during the response to the innate immunity system against invading organisms and activation of cell morphological characteristics, NE-SFL can be helpful for the early detection of sepsis.

Non-septic patients are the ones who do screening blood donation at RSUP Prof. Dr. I.G.N.G. Ngoerah Denpasar.

2.4 Data analysis

Research participants were grouped into two, namely sepsis and non-septic. All data will be analyzed in descriptive form. The normality test analysis used in this research Kolmogorov Smirnov (data distribution is said to be normally distributed if the p-value is> 0.05). To analyze the value cut-off NE-SFL parameters in sepsis and non-septic patients, they were analyzed using receiver operating characteristics (ROC). Risk analysis used the logistic regression method to examine the role of NE-SFL on the incidence of sepsis in adult patients by controlling for confounders (age, gender, and vital signs) in the study. This analysis will later produce a value odds ratio (OR), which has been controlled for confounding variables in the research. Statistical results are significant when the p-value is <0.05.

The entire data analysis process is processed using the SPSS for Windows software version 23.0.

3. RESULT

The research participants were 77 patient samples who met the inclusion criteria, consisting of 37 sepsis patients and 40 healthy people who had complete blood tests using the Sysmex XN-3000 at Prof. Hospital. Dr. Dr. I.G.N.G. Available in September 2022 to March 2023.

Differences in the characteristics of septic, non-septic patients and the total sample based on age, temperature, pulse, respiration, blood pressure and gender can be seen in Table 1.

Table 1. Differences in Characteristics of Sepsis, Non-Sepsis Patients and the Total Sample

Variable	Status			P Score
	Sepsis	Non sepsis	Total	
Age	60.92 ±15.06	33.48 ±6.14	39 (20-88)	0.000
Temperature	36.60 (35.00-38.90)	36.15 (35.80-36.80)	36.40 (35.00-38.90)	0.000
Pulse	92.62 ±19.37	95 (83-100)	92 (36-128)	0.919
Breath	21.38 ±4.02	20 (18-22)	20 (12-30)	0.568
Systole	102.78 ±26.69	115 (110-120)	110 (60-180)	0.000
Diastole	64.67 ±15.23	80 (70-90)	80 (35-90)	0.000
Gender,(N%)				
Man	21 (56.80)	26 (65.00)		0.459
Woman	16 (43.20)	14 (35.00)		

The results of data analysis showed that there were significant differences in age, temperature, systole and diastole. Sepsis patients were more likely to be found in older age, 60.92 ± 15.06, with the median of the entire sample being 39 years. The body temperature of sepsis patients showed higher than the control group by median

36.60 (35.00-38.90) degrees Celsius. Systolic blood pressure in sepsis patients was found to be lower than non-septic patients with a standard deviation value

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102.78 ±26.69. There was also a significant difference in diastolic blood pressure in the sepsis group with a standard deviation of 64.67 ± 15.23 compared to the non-septic group with a median of 80 (70-90) mmHg. There were no significant differences in pulse, respiration and gender between the sepsis and non-septic groups (p>0.05).

Table 2. AUC and Cut off value of NE-SFL in sepsis patients

AUC	CI Lower bound	95% Upper bound	*Cut off*	Sensitivities	Specificity	P
0.844	0.743	0.944	46.400	81,1%	85%	0.000

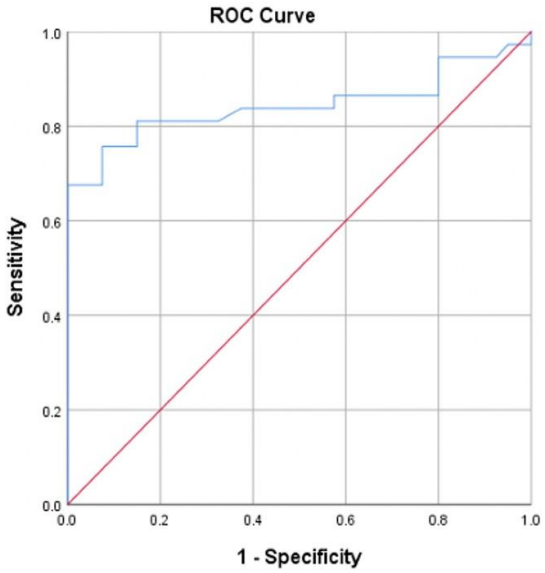

Figure 1. Curvereceiver operating characteristic (ROC) NE-SFL as a predictor of sepsis

To determine the NE-SFL value which is used as a predictor of sepsis, a cut point (cut off point) through receiver of curve (ROC) as in Figure 1. Table 2 shows Area under the curve (AUC) and cut off value of NE-SFL against sepsis in adult patients. The AUC value of NE-SFL was 0.844, considered significant as a predictive model for sepsis in adult patients with a cutoff point namely 46,400.

Test results chi-square which shows NE-SFL as a predictor of sepsis, is shown in table 3.

Table 3. NE-SFL as a predictor of sepsis

Variable	Status		P	OR	CI 95%	
	Sepsis	Non Sepsis			Lower Bound	Upper Bound
NE-SFL						
>46,4	30 (81.100)	6 (15.000)	0.000	24.286	7.345	80.297
<46,4	7 (18.900)	34 (85.000)				

Test results chi-square showed that NE-SFL was a significant predictor of sepsis (OR=24.286; 95%CI=7.345-80.297; p=0.000). The OR value of 24.286 shows that patients with high NE-SFL have a

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24-fold higher chance of suffering from sepsis than patients with low NE-SFL.

4. DISCUSSION

This study suggests that NE-SFL may be helpful for early detection of sepsis (and septic shock), consistent with the function of neutrophils as first responders during the innate immune system response to foreign organisms and the morphological characteristics of activated cells (Biban et al., 2021). Our results agree with Biban's research in 2021, where the NE-SFL parameter shows a higher value in sepsis patients than in the control group, so the NE-SFL parameter can be used as a predictor of sepsis. In accordance with (Park et al., 2015), NE-SFL may be useful for detecting sepsis, along with other surrogate sepsis biomarkers currently available. Take it all reported that NE-SFL parameters were significantly higher in 40 adults with sepsis compared to the control group. According to (Biban et al., 2021), the NE-SFL value was significantly higher in patients with septic shock than those without sepsis. (Biban et al., 2021; Urrechaga et al., 2017)

This study shows that NE-SFL parameters can help clinicians confirm and diagnose adult sepsis patients early. The sooner sepsis is detected, the better the prognosis for the patient. According to (Urrechaga, 2020b), the results of his research explained that the NE-SFL parameter is essential in quickly and reliably detecting patients at risk of sepsis. One of the leading causes of high mortality in sepsis patients is delay in treatment. Each hour of delay in starting therapy results in an increase in sepsis-related mortality of approximately 7-10% (Urrechaga, 2020b). Because sepsis is a time-dependent process, the first 12 hours are critical for prognosis patient (Urrechaga et al., 2017). Prompt diagnosis and appropriate antibiotic therapy are essential to prevent death and disability. Suppose sepsis is detected too late or antibiotic treatment is not started promptly. In that case, the patient's condition can worsen to severe sepsis or even septic shock, which is more deadly as severity increases. Thus, rapid detection of sepsis is essential to prevent adverse outcomes and reduce mortality by promptly initiating treatment before permanent damage occurs. (Urrechaga, 2020b)

This study shows sepsis patients have a higher NE-SFL value than non-septic patients, as indicated by a p-value <0.05. According to the ROC curve, the value is found to be cut off. The best NE-SFL as a predictor of sepsis is 46.4. According to chi-square test results, NE-SFL is a significant predictor of sepsis because high NE-SFL results mean a 24-fold higher chance of sepsis than patients with low NE-SFL. Based on the results of research conducted by (Shen et al., 2017), neutrophils are activated when bacterial infections occur, especially in cases of sepsis. The research used the Sysmex XN tool hematology analyzer, which can provide information on neutrophil activity through NE-SFL (Park et al., 2015). Marull et al. NE-SFL is a reliable marker for sepsis with a value cut-off NE-SFL of 49,9 ch. (Urrechaga et al., 2019) evaluated the NE-SFL using the Sysmex XN analyzer, finding differences when comparing the median NE-SFL of the sepsis and control groups. Neutrofil–signal fluorescence intensity (NE-SFL) was found to be increased in patients with sepsis. (Urrechaga et al., 2019)

This research has limitations namely timeline Changes in NE-SFL values in sepsis patients could not be evaluated in this study because samples were not taken every day in sepsis patients.

5. CONCLUSION

Neutrofil – signal fluorescence intensity (NE-SFL) is considered significant for predictive models for the occurrence of sepsis in adult patients, so this can be a basis for clinical consideration as an early marker for faster treatment in patients with high NE-SFL values.

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