

# Sepsis Due to Bacterial Infection: An Analysis based on Ratio Count of Neutrophil – Lymphocyte

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## Abstract

Sepsis due to bacterial infection is a serious medical emergency and requires prompt and proper handling. Various parameters such as white blood cells count, CRP, and PCT level are used as a marker of sepsis due to bacterial infection. Sepsis is a condition of systemic inflammation with infection. Physiological response to systemic inflammation involves an increased level of neutrophils and a reduction of lymphocyte count; therefore, combining both parameters seems logical, and NLCR could be a simple and even better marker in predicting sepsis. This research aimed to determine the sensitivity and specificity of the NLCR test in patients with sepsis due to bacterial infection. This research was conducted by observing 70 sepsis patients aged 14-70 years at a private hospital in Bekasi and UKI general hospital in July-September 2015 through medical records. This research was an observational study with a cross-sectional design. The result of this research showed ROC curve for NLCR test with sensitivity 97.8 % , specificity 84.0 % , and cut off  $\geq 6.4$  (AUC: 0.94, p-value <0.05). In conclusion, the NLCR is an ideal and efficient marker to diagnose sepsis due to bacterial infection with good sensitivity and specificity tests.

**Keywords:** Sepsis, NLCR, Sensitivity, Specificity.

## INTRODUCTION

Sepsis is a severe health problem and is a medical emergency. Sepsis can cause death if there is a delay in the diagnosis and improper management of sepsis. Sepsis caused by bacterial infection can progress rapidly and progressively from mild to severe disease accompanied by shock and multiorgan failure [1]. The mortality rate caused by sepsis in Indonesia is very high. Namely, 56.83% (Yogyakarta), 54.17% (Palembang), and in Solo (2004), 83.1% of sepsis patients died [2]. An ideal sepsis marker is needed, namely a marker that is very distinctive and sensitive, as well as fast and very efficient in its use, directly proportional to the emergency, and has an affordable price.

Bacterial culture is the gold standard for determining bacterial infections [3]. However, the examination of bacterial culture has a weakness; the cost examination of bacterial culture is quite expensive, and the test takes a long time. The fastest cultural results are known for more than 24 hours [4]. A bacterial culture examination is carried out before giving antibiotics to patients suspected of bacterial infection. Because the culture results are long while patients with sepsis require fast and precise diagnosis and treatment, it is necessary to use a septic marker that can show accurate results with a short examination time and sound sensitivity and specificity of the test.

Several markers of sepsis are currently used to diagnose sepsis, namely Procalcitonin (PCT), IL-6 levels, and C-Reactive Protein. However, these two markers have a high examination cost and become an obstacle to examination,

especially in developing countries [5]. De Jager et al. explained that in a retrospective study, the neutrophil-lymphocyte count ratio is a simple and excellent test in diagnosing sepsis due to bacterial infection compared to routine parameters such as white blood cell count and CRP [6]. Michal Holub's research obtained the results of the neutrophil-to-lymphocyte Ratio (NLCR) diagnostic test with a sensitivity of 91% and a specificity of 96% for sepsis due to bacterial infection [7]. CRP has a sensitivity of 98.5% and a specificity of 75.0% [8]. There are markers of other sepsis, such as PCT, with a sensitivity of 85.0% and a specificity of 91.0% [9].

NLCR is a combination of the ratio of neutrophils and lymphocytes that can be a good marker of sepsis because in sepsis due to bacterial infection, there is a high level of endotoxin in the patient's blood and causes an increase in circulating neutrophils in the blood and a decrease in lymphocyte levels [10]. Based on the description of the background of the problem above, the problem can be formulated as follows: a) Can the neutrophil-lymphocyte count ratio (NLCR) be used as a marker of sepsis due to bacterial infection? b) What is the sensitivity and specificity of the neutrophil-lymphocyte count ratio as a marker of sepsis due to bacterial infection? The study aims to examine the neutrophil-lymphocyte count ratio as a marker of sepsis due to bacterial infection.

## LITERATURE REVIEW

Infection is a condition where various microorganisms enter the human body. Microorganisms that multiply rapidly in the human body can cause tissue damage

that causes infectious diseases [11]. Infectious diseases in humans will form an injury that can trigger an inflammatory reaction [12]. Inflammation is an attempt by the body to eliminate and eradicate the causative organism. Inflammatory responses in the human body can be acute and chronic [11; 12]. Acute inflammation may be confined to a single injury site or widespread, causing signs and symptoms of systemic inflammation. The clinical manifestation of systemic inflammation is called systemic inflammatory response syndrome (SIRS) [13].

Inflammation is a protective tissue response to injury or tissue damage that serves to destroy the agent causing harm to the tissue. In an inflammatory state, the body will produce various kinds of inflammatory mediators, such as interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interferon-gamma (IFN- $\gamma$ ). These inflammatory mediators play a role in the pathogenesis of infectious diseases [14]. Sepsis is still the cause of death in the Intensive Care Unit in hospitals domestically and abroad. Impairment and organ failure are common in patients with systemic inflammatory responses syndrome (SIRS) and sepsis [15].

SIRS is a collection of symptoms caused by ischemia, inflammation, trauma, infection, or a combination of these symptoms. SIRS cannot always be correlated with infection. The clinical manifestations of SIRS are as follows; Temperature > 38°C or < 36°C; b) Heart rate > 90 beats/minute; c) Respiration > 20 breaths/minute or Pa CO<sub>2</sub> < 32 mmHg; d) Leukocyte count > 12,000/mm<sup>3</sup> or <4000/mm<sup>3</sup>, or there are >10% immature cell forms. Sepsis is a systemic inflammatory response syndrome evidenced by infection in a specific organ based on positive culture results at that site or clinical suspicion of infection [15; 16]. Severe sepsis is sepsis associated with organ dysfunction (Multi Organ Dysfunction Syndrome/Multi-Organ Failure), hypoperfusion disorders, hypotension, and oliguria or anuria. Septic shock is a subset of severe sepsis characterized by impaired tissue perfusion and persistent hypotension, despite adequate fluid resuscitation. There were new diagnostic criteria for sepsis, namely biomolecular markers such as procalcitonin (PCT) and C-reactive protein (CRP), as an initial step in the diagnosis of sepsis [17].

The etiology of sepsis due to bacterial infection is the most common Gram harmful bacteria with a percentage of 60% to 70% of cases. Gram-negative bacteria produce various products that can trigger the release of inflammatory mediators. Lipopolysaccharide (LPS) is a complex glycoprotein endotoxin that is the outermost component of Gram-negative bacteria. LPS attaches to CD14, monocytes, macrophages, and neutrophils mediated by plasma proteins. The structure of lipid A in LPS plays a role in the emergence of reactions in the host body, such as stimulating tissue inflammation, fever, and shock in infected patients. LPS can directly activate the cellular and humoral immune systems, which can cause septicemic symptoms [18; 19]. Bacteria that invade the human body will activate the immune system in the body. The activated cellular immune system is monocytes, macrophages, neutrophils, and eosinophils. The activated humoral immune system is a complement, c-reactive protein (CRP), and cytokines. T lymphocytes act as cellular immunity, and B lymphocytes act as humoral immunity. If the immune system fails to overcome the infection, an inappropriate immune reaction will occur [20; 21].

The sepsis pathophysiology is caused by complex interactions between microbial marker molecules, leukocytes, humoral factors, and vascular endothelium. Bacterial infectious diseases can cause an inflammatory reaction as a direct immune response to bacterial infection. In the early

stages of the interaction of the body's response with SIRS, it is characterized by the production of local cytokines as a tissue inflammatory response so that it can repair tissue damage and activate RES. The inflammatory reaction in sepsis is mediated by crucial mediators such as TNF- (Tumor Necrosis Factor- $\alpha$ ) and IL-1 $\beta$  [22]. Other cytokines that cause inflammation in sepsis are IL-1, IL-6, and IFN- $\gamma$ . IFN- $\gamma$  is a pleomorphic cytokine essential in stimulating macrophages to express TNF- $\alpha$ , IL-1, IL-6, and IL-8 in the host response to sepsis and septic shock [22].

The pro-inflammatory cytokines TNF- $\alpha$ , IL-1, and IFN- $\gamma$ , play a role in helping cells to destroy infecting microorganisms. TNF- $\alpha$  and IL-1 play a role in the occurrence of fever and the release of stress hormones (norepinephrine, vasopressin, glucocorticoids) and activation of the renin-angiotensin-aldosterone system [12]. IL-6, a pro-inflammatory cytokine, is produced by activated macrophages in the acute phase, but IL-6 can act as an anti-inflammatory cytokine when made from activated Th2 cells [12; 14]. The acute phase response to sepsis is characterized by a decrease in pro-inflammatory mediators and the release of endogenous antagonists to maintain the body's immune response. A study on sepsis patients found that the role of sepsis degree was the IL-1 $\beta$  and IL-10 balance [17]. If IL-10 is more dominant, it will trigger the maturation of B cells. Then B cells will differentiate into plasma cells that produce IgG [20; 21].

IgG has effective opsonin properties. Together with phagocytic cells, monocytes, and macrophages, NK cells will bind through the Fc receptor so that there will be damage to blood vessel cell walls through the ADCC (Antibody-Dependent Cellular Cytotoxicity) process [22]. Increased levels of complement C3a, which has anaphylatoxin properties, can cause vascular dilatation so that resistance decreases and vascular permeability increases, resulting in plasma extravasation. Complement C3b is attached to the target cell wall to form labile bonds, membrane binding proteins together with IgG form opsonization through NK cells which are effector cells, so that that cell lysis will occur through the ADCC process. As a result of this process, there will be a decrease in blood pressure to shock [21; 13].

In the body's effort to react to sepsis, T lymphocytes will release substances from Th1 that function as immunomodulators: IFN- $\gamma$ , IL-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Th2 lymphocytes, in addition to expressing IL-6, also play a role in the secretion of IL-4, IL-5, and IL-10. Interleukin 1 receptor antagonists (IL-1ra), IL-4, and IL-10 play a role in modulating and repressing the exaggerated response. In sepsis, there is an increase in the levels of IL-1 $\beta$  and TNF- $\alpha$  in the patient's serum. IL-1 $\beta$  acts as a significant immuno-regulator that contributes to the activation of T lymphocytes and prostaglandin E<sub>2</sub> (PG-E<sub>2</sub>) formation and stimulates the expression of intercellular adhesion molecule -1 (ICAM-1). Increased ICAM-1 will cause adhesion of inflammatory cells, including macrophages and neutrophils. ICAM-1 causes neutrophils sensitized by GM-CSF to adhere to endothelium efficiently [23; 24].

Neutrophils will be secreted first in a state of infection, so neutrophil levels are very high during sepsis. The interaction between neutrophils and endothelium goes through the stages of neutrophil transmigration through the endothelial wall [25]. Neutrophils adhering to endothelium will release lysozyme, which will cause endothelial wall lysis and damage cell walls and genes that can cause cell death. Neutrophils will also carry super oxidants, free radicals that affect oxygenation in the mitochondria of cells. This process results in vascular disorders (vascular leak), causing multiple organ damage. Besides being driven by the vascular leak, multiorgan failure is also caused by thrombosis and

coagulation in small blood vessels resulting in septic shock [19].

There is a new theory of sepsis that the role of the pro-inflammatory reaction is not dominant, so a concept is proposed, namely Compensatory Anti-Inflammatory Response (CARS) and Mixed Antagonist Response Syndrome (MARS) [26]. The local inflammatory response due to infection with microorganisms causes the systemic distribution of pro-inflammatory mediators and systemic distribution of anti-inflammatory mediators. Both distributions induce SIRS (pro-inflammatory), CARS (anti-inflammatory), and MARS (a mixture of SIRS and CARS). It can lead to homeostasis (balanced CARS and SIRS), apoptosis (death with minimal inflammation), organ dysfunction (predominant SIRS phase), and organ system suppression (predominant CARS phase). From this study, it can be concluded that an inflammatory response does not entirely cause sepsis, but sepsis can be an immunosuppressive condition based on the loss of the ability of delayed-type hypersensitivity reactions and the ability to eliminate infection [24; 26].

Neutrophils are the most abundant peripheral blood leukocytes and have an affinity for immune complexes and the ability to phagocytize. About 50% of neutrophils are in the peripheral blood, attached to the walls of blood vessels (marginal pool). Neutrophils enter tissues by migrating in response to chemotactic factors [27]. These cells have a short life span, about 10 hours in circulating blood. Neutrophils have a dense nucleus consisting of two to five lobes and a pale cytoplasm with irregular borders and contain many red, pink-blue (azurophilic), or gray-blue granules. The granules are divided into primary granules that appear in the promyelocyte stage and secondary (specific) granules that appear in the myelocyte period and are dominant in mature neutrophils.

Lymphocytes are an important component of the immune response. Lymphocytes are derived from hemopoietic stem cells. Lymphocytes play a specific role in the immune system. Specific immunity is only directed against certain antigens, namely the antigen, which is the ligand. In addition, the specific immune response also creates an immunological memory that will react quickly if the host is exposed to the same antigen again [28]. In acquired immunity, antibodies and effector lymphocytes specific to the stimulated antigen will be formed, resulting in antigen elimination. Cells that play a role in acquired immunity are APC (antigen-presenting cell) antigen-presenting cells, T lymphocytes, and B lymphocytes [25; 28]. T lymphocytes and B lymphocytes play a role in cellular and humoral immunity, respectively. Mature lymphocytes are small mononuclear cells with a slightly blue cytoplasm. Most of the peripheral blood lymphocytes are T cells, as much as 70%. The normal lymphocyte count in adult blood is  $1.5 - 3.5 \times 10^9/L$  or 20% - 40% of the leukocyte count [28].

The neutrophil-lymphocyte count ratio is a straightforward calculation by dividing the absolute number of neutrophils by the complete number of lymphocytes. One of the physiological responses of the immune system to systemic inflammation is an increase in the number of neutrophils and a decrease in the number of lymphocytes [29]. Zahore et al. documented that the NLCR value is a parameter that can be easily measured to indicate the severity of systemic inflammation and sepsis [30]. NLCR is also a helpful parameter in detecting bacteremia in emergency treatment and a diagnostic marker that is inexpensive and easy to assess because it does not require special tools to measure it.

The immune response to the inflammatory process in patients given endotoxemia, after 4-6 hours, there will be a decrease in lymphocytes (85) and an increase in neutrophils

(300%). In sepsis, IL-6, produced by macrophages, stimulates the production of neutrophil cells from progenitor cells in the bone marrow, resulting in increased neutrophil production (neutrophilia). Neutrophils are also the initial immune response to infections that occur in the body because neutrophils are many peripheral blood leukocytes [29; 30].

The decrease in lymphocytes (lymphocytopenia) in sepsis is due to the increased secretion of glucocorticoid hormones induced by TNF- $\alpha$ . Glucocorticoid hormones affect aspects of the immunologic and inflammatory response. This glucocorticoid hormone also interferes with the production of lymphocytes in the lymph nodes, although the mechanism is unclear [30]. An increase in the neutrophils number and a decrease in the number of lymphocytes causes an increase in the absolute ratio of neutrophils and lymphocytes in patients with a systemic inflammatory reaction. In septic patients the neutrophil-lymphocyte count ratio is 6.2 [7; 31]. In sepsis, the key inflammatory mediators are TNF- $\alpha$  and IL-1 $\beta$ . Several pro-inflammatory cytokines released by the body during sepsis are IL-1, IL-6, and IFN- $\gamma$ . TNF increases sepsis, increasing several stress hormones such as adrenaline, renin-angiotensin-aldosterone, vasopressin, and glucocorticoids [21; 30].

The increase in stress hormones also affects the decreased production of eosinophils (eosinopenia) and the migration of eosinophils to the site of inflammation. The increase in glucocorticoid hormones also suppresses the production of lymphocytes in the lymph nodes so that in sepsis, lymphocytopenia occurs through an unclear mechanism. The inflammatory mediator IL-1 $\beta$  in macrophages signals T lymphocyte activation, so IL-1 $\beta$  acts as a significant immuno-regulator. IFN- $\gamma$  is a pleomorphic cytokine essential in activating microbial phagocytosis mechanisms through macrophage stimulation. Macrophages are mononuclear phagocytic cells that produce IL-6 to initiate the formation of acute-phase proteins, namely CRP. C-reactive protein can activate complements in the body. IL-6 and Colony Stimulating Factor can also stimulate the production of neutrophils from progenitor cells in the bone marrow, so neutrophilia occurs in sepsis. The physiological response of the immune system in sepsis is an increase in the number of neutrophils and a decrease in lymphocytes. It is due to changes in the dynamics and regulation of apoptosis in systemic inflammation [29; 30].

A delay in the process of neutrophil apoptosis can cause a prolongation of the function of neutrophils in the inflammatory process and will prolong the process of toxic metabolic elaboration. Conversely, increased lymphocyte apoptosis will result in a decrease in inflammatory effectors and also immunosuppression. An increase in the neutrophils number and a reduction in the number of lymphocytes will cause an increase in the absolute ratio of neutrophils and lymphocytes [30]. In sepsis with bacterial infection, PCT levels increased due to CT-mRNA stimulation. Procalcitonin secretion is influenced by the pro-inflammatory cytokines IL-1 $\beta$ , TNF-, and IL-6 [8]. In this study, bacterial culture was also carried out, which is the gold standard in determining sepsis due to bacterial infection.

## RESEARCH METHOD

The type of research conducted in this study is a comparative observational study, and there is no specific treatment for the sample. This study was conducted on adult SIRS and sepsis patients who met the criteria for sample acceptance and were treated in the ICU and inpatients at a private hospital in Bekasi and a general hospital at the Christian University of Indonesia. The number of sepsis patients and suspected SIRS at UKI RSU and Bekasi Private Hospital in 2014 were 159. The sample in this study was blood from patients with SIRS and sepsis, and blood with EDTA is

intended for complete blood counts and peripheral blood smears. Specimens such as blood, sputum, pus, and urine will be cultured. The results of the examination of vital signs and laboratories were taken from the medical records of patients who met the criteria for receiving SIRS samples or suspected sepsis. In this study, there were 70 samples with the following details; 50 data that met the study criteria (inclusion data), 6 data that did not meet the study criteria (exclusion data), and 14 harmful control data (sepsis not caused by bacterial

infection). The research and data collection was carried out in the Medical Records of the Indonesian Christian University General Hospital and Private Hospitals in Bekasi from July – September 2015. The diagnostic value of the NLCR test on culture as the gold standard was determined by the sensitivity and specificity parameters of the NLCR test in patients with sepsis who were treated with sepsis. Can be determined in the table 2 x 2.

**Table 1: NLCR Diagnostic Test Assessment**

Culture NLCR	Positive	Negative	Total
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

From the table above, the results of the NLCR test can be calculated compared to culture as the gold standard, as follows:

Sensitivity =  $a : (a+c)$

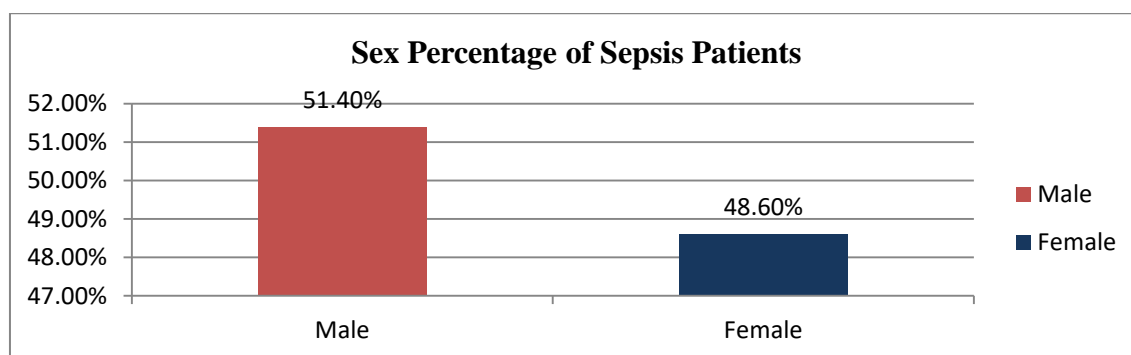
Specificity =  $d : (b+d)$

In this study, the researcher used the ROC (Receiver Operator Curve) contained in the IBM SPSS Statistic 22 application to determine the cut-off point of the diagnostic test in the form of a graph depicting the trade-off between sensitivity and specificity. Samples in the study will be taken from male and female patients with an age range of 14 years to 70 years. Patients must meet at least two or more SIRS symptoms. Then a complete blood count, peripheral blood smear, neutrophil and lymphocyte count ratio, and bacterial culture will be performed. A positive bacterial culture result is the gold standard for sepsis and a marker for the presence of infection-causing bacteria. Negative bacterial culture results in

SIRS patients will be excluded if there is no definite diagnosis. However, if there is an actual diagnosis, such as peritonitis, appendicitis, and pancreatitis, then the data will be considered as true unfavorable and are pure SIRS patients without being caused by bacterial infection. The data that has been collected will be processed and analyzed for research purposes.

## RESULT AND DISCUSSION

In this study, 70 samples of SIRS patients met the criteria for receiving SIRS samples or suspected sepsis. Of the 70 samples, 36 patients (51.4%) were male, and 34 (48.6%) were female.

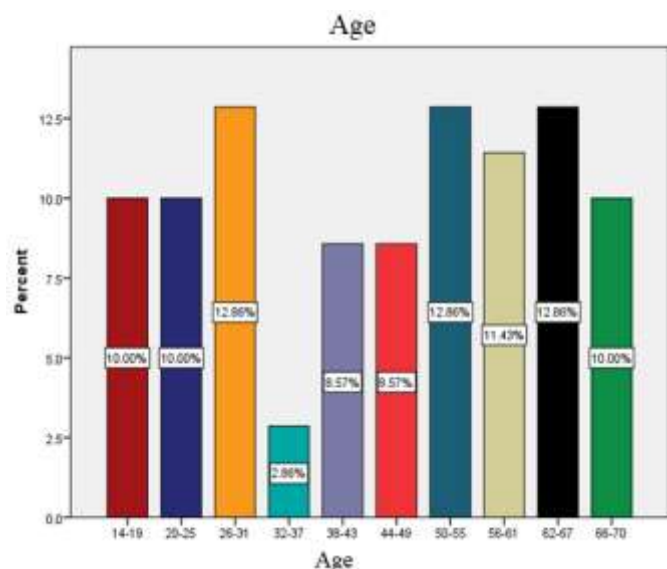


**Figure 1: Sex percentage of patients with sepsis**

From the 70 research samples, it was found that the age range that suffered the most SIRS or suspected sepsis was

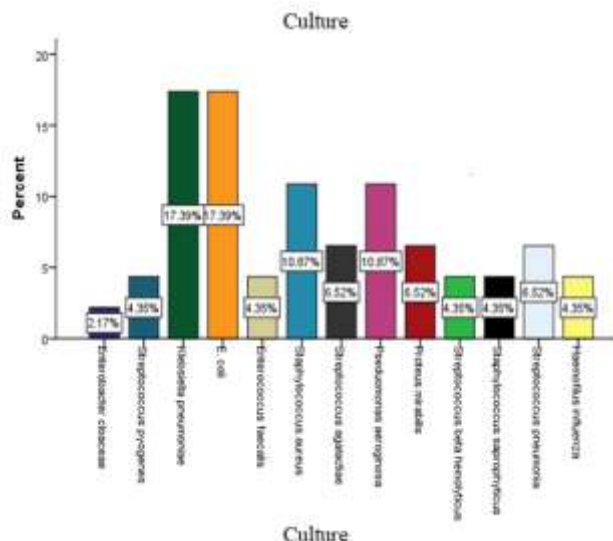
the age range 26-31, the age range 50-55, and the age range 62-67, with a percentage of 12.86% each.





**Figure 2: A bar chart of the age range of patients with sepsis**

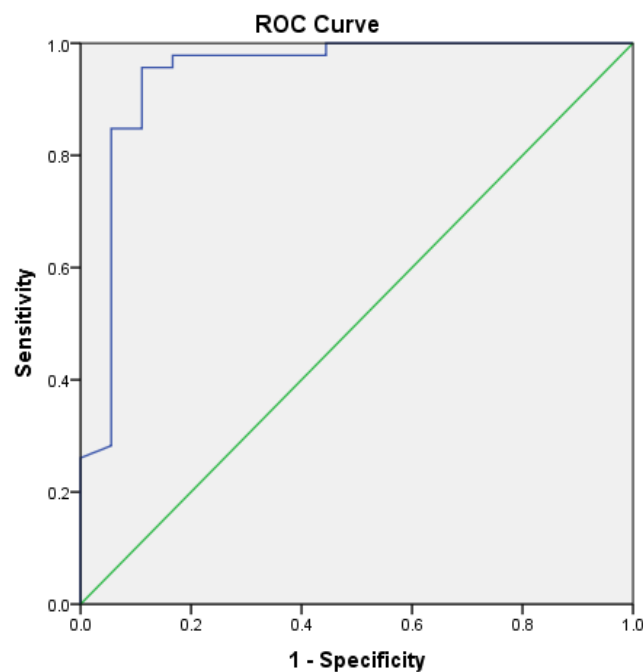
In this study, the inclusion sample was 50 patients with sepsis (71.43%) from 70 research samples. Total positive cultures from 50 samples were 46 patients (92.0%), with the most common types of bacteria causing *Klebsiella pneumonia* (17.39%), *Escherichia coli* (17.39%), *Pseudomonas aeruginosa* (10.87%), *Staphylococcus aureus* (10.87%), and *Streptococcus pneumoniae* (6.52%).



**Figure 3: Percentage of germs that cause sepsis**

The highest percentage of patients with sepsis caused by *Klebsiella pneumonia* infection was found in the age range of 14-43 years, as much as 75%. Patients with sepsis caused by *Escherichia coli* infection were dominant in the age range of 41 - 70 years with a percentage of 75%. Negative culture results were four patients (8%), but in these patients, there were clinical data and a definite diagnosis that supported the suspicion of sepsis, so in this study, the data were considered as the inclusion sample.

In this study, six samples were excluded (8.57%) from 70 research samples because the bacterial culture was not examined as the gold standard. 14 (20%) of the 70 study samples were negative control samples, namely non-bacterial sepsis, such as in patients with Dengue Hemorrhagic Fever, Herpes Simplex Virus, and Hepatitis B. The sensitivity and specificity of NLCR in patients with sepsis were calculated based on the ROC curve. On the ROC curve, the best results were sensitivity of 97.8%, specificity of 84.0%, AUC (Area Under Curve) 0.94 with a cut-off of the number of NLCR 6.4 with p-value <0.05.



Diagonal segments are produced by ties.

**Figure 4: ROC NLCR Curve in Sepsis Patients**

Sepsis is a systemic inflammatory response due to a severe infection. Sepsis is one of the medical emergency problems, so a diagnosis with a high index of suspicion is needed, taking a careful medical history, physical examination, and appropriate laboratory tests.

Of the 50 samples of research data that matched the inclusion criteria for sample acceptance, there were 46 patients with positive culture results (92.0%) and negative culture results in 4 patients (8%). These data suggest that the significant etiology of sepsis is the presence of bacterial infection.

In this study, the bacteria that caused sepsis were *Klebsiella pneumonia* (17.39%), *Escherichia coli* (17.39%), *Pseudomonas aeruginosa* (10.87%), *Staphylococcus aureus* (10.87%), and *Streptococcus pneumoniae* (6.52%). All of these bacteria were Gram-negative except for *Staphylococcus aureus* and *Streptococcus pneumoniae*.

According to A. Guntur H in the Textbook of Internal Medicine Volume III states that Gram-negative bacteria are the most significant etiology of sepsis, which is 60-70% [20]. It is because Gram-negative bacteria's lipopolysaccharide (LPS) endotoxin can directly activate the cellular and humoral immune systems, leading to the development of septicemic symptoms. Gram-negative bacterial endotoxin lipopolysaccharides play a role in stimulating the release of inflammatory mediators responsible for sepsis [21].

The NLCR number diagnostic test results in patients with sepsis on the results of bacterial culture with the best cut-off at the number of NLCR was 6.4 with a sensitivity of 97.8% and a specificity of 84.0%. The results of the NLCR diagnostic test in this study support the results of previous studies conducted by Michal Holub (2011) and Okashah et al. (2014). In Michal Holub's research (2011), the cut-off number of NLCR is 6.2, with a sensitivity of 91.0% and specificity of 96.0% for bacterial infections [7]. It was found that the cut-off of NLCR 6.2 with sensitivity (88.0%) and specificity (75.0%) for sepsis due to bacterial infection [31]. The difference in cut-off in this study is thought to be due to differences in characteristics, the number of study samples, and different study locations.

In this study, a cut-off of NLCR 6.4 supports the theory that there is an increase in the number of NLCR in patients with sepsis caused by bacterial infection. One of the body's physiological responses to systemic inflammation is an increase in the number of neutrophils and a decrease in the number of lymphocytes [24; 25]. The increase in the neutrophils number is due to the presence of IL-6, produced by macrophages in sepsis which stimulates the production of neutrophil cells so that the number of neutrophils increases (neutrophilia) [28]. The decrease in the number of lymphocytes in sepsis is caused by the increased secretion of glucocorticoid hormones and suppresses the production of lymphocytes in the lymph nodes, resulting in lymphocytopenia [29]. An increase in the number of neutrophils and a decrease in the number of lymphocytes can lead to an increase in the absolute ratio of neutrophils to lymphocytes (NLCR) compared to patients without a systemic inflammatory reaction [29].

## CONCLUSION

From the results of research and data analysis that has been carried out in this study, it can be concluded that the best sensitivity of the diagnostic test NLCR (Neutrophil-Lymphocyte Count Rate) in patients with sepsis due to bacterial infection was obtained at 97.8% at the cut off of the number of NLCR 6.4. The best specificity of the NLCR diagnostic test (Neutrophil-Lymphocyte Count Rate) in patients with sepsis due to bacterial infection was 84.0% at the cut-off of the NLCR count 6.4. Based on the information above, it can be concluded that the neutrophil-lymphocyte count ratio (NLCR) can be an ideal, efficient, and inexpensive marker for diagnosing sepsis in patients with sepsis due to bacterial infection, with a very high test sensitivity and high test specificity. For this reason, further research with a broader sample on the NLCR benefits as a marker of sepsis due to bacterial infection is needed. In addition, it is also necessary to examine the type of leukocyte count to see the number of NLCR in patients suspected of sepsis due to bacterial infection to establish a diagnosis of sepsis with an NLCR number 6.4 so that fast and appropriate sepsis management can be carried out and can reduce the risk of mortality and morbidity due to sepsis.

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