Differences in Neutrophil Lymphocyte Ratio (NLR) between Sepsis and Septic Shock Patients in a Tertiary Hospital in Indonesia

Intanri Kurniati,[1] Ferdian Syukri Arisqan,[2] Utari Gita Mutiara[2]
[1]Department of Clinical Pathology, Faculty of Medicine, University of Lampung, Lampung, Indonesia
[2]Faculty of Medicine, University of Lampung, Lampung, Indonesia

Abstract

Sepsis is a severe medical condition characterized by organ dysfunctions resulting from the body's response to an infection. Septic shock is a complication of sepsis that involves circulatory, cellular, and metabolic disturbances. The body's response to infection is typically marked by an increase in neutrophils and a decrease in lymphocytes, leading to increased Neutrophil Lymphocyte Ratio (NLR). This study aimed to investigate the differences in NLR between sepsis and septic shock patients treated at Dr. H. Abdul Moeloek Provincial Hospital, Lampung, Indonesia. This study utilized a comparative analytic study approach with a cross sectional design. A total of 96 sepsis patients who met the inclusion and exclusion criteria treated during the period January 2018–December 2020 at Dr. H. Abdul Moeloek Provincial Hospital, Lampung, Indonesia, were included in this study. The study found that most of sepsis patients showed an increase in neutrophils (89.58%), a decrease in lymphocytes (94.79%), and elevated NLR values (87.5%). The mean NLR value of septic shock patients (20.10±5.89) was significantly higher than that of sepsis patients (18.01±1.35) (p=0.025). It indicates that the NLR value increases significantly in patients who develop septic shock compared to those with sepsis alone. The findings suggest that NLR could be a potential biomarker for septic shock diagnosis. However, the effectiveness of NLR in predicting the severity of sepsis and determining the risk of mortality in these patients still needs to be examined by conducting studies that involve a larger sample size.

Keywords: Neutrofil Lymphocyte Ratio (NLR), sepsis, septic shock

Introduction

Sepsis is among the most common health issues among populations experiencing severe clinical infections. It is characterized by typical inflammatory responses, such as vasodilation, leukocyte accumulation, and increased microvascular permeability in tissues far from the infection site's source.[1] In 2016, the International Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) suggested the term sepsis-3 to describe the sepsis condition. According to that, sepsis is defined as a life-threatening organ dysfunction caused by a body's response to an infectious disorder. Sepsis shock is a severe form of sepsis accompanied by hypotension despite adequate fluid resuscitation. It requires vasopressors to maintain a mean arterial pressure of ≥65 mmHg or a lactate concentration in the blood of >2 mmol/L (>18 mg/dL).[2,3]

A study conducted in 2009 across 16 countries in Asia, including Indonesia, discovered that the incidence of severe sepsis and septic shock in intensive care units (ICUs) was 10.9%, with a mortality rate of 44%. Similarly, a study at RSCM Jakarta in 2012 found that out of 84 intensive care cases, 23 were diagnosed with severe sepsis and septic shock, and the mortality rate reached 47.8%.[4]

Leukocytes play a crucial role in the systemic inflammatory response, particularly in severe infections, trauma, and shock.[5] During systemic inflammation, the number of neutrophils tends to increase, while the number of lymphocytes tends to decrease, resulting in an increased of neutrophil lymphocyte ratio (NLR). The neutrophil lymphocyte ratio (NLR) is determined by comparing the absolute neutrophil count to the absolute lymphocyte count, which can be obtained by examining the leukocyte count in the blood sample.[6,7] Sepsis may cause a rise in the NLR value due to increased lymphocyte cell apoptosis. In addition, septic shock is known to cause a considerable decrease in lymphocyte

Corresponding Author:
Ferdian Syukri Arisqan,
Faculty of Medicine, University of Lampung, Dr. Harun II street Number 77 Kota Baru Bandar Lampung
Email: ferdiansyukria@gmail.com

count, leading to a significant increase in the NLR value.

Previous studies have demonstrated that the NLR value can serve as a valuable prognostic marker for sepsis patients in the ICU. However, research has yet to be conducted on NLR values in sepsis patients in Lampung, specifically at Dr. H. Abdul Moeloek Hospital. This is a significant gap, given that the NLR value has the potential to support early, affordable, and rapid diagnosis of shock sepsis. Thus, this study aims to investigate the differences in NLR values between patients with sepsis and septic shock at RSUD Dr. H. Abdul Moeloek Lampung.

Methods

This was a comparative analytic study with a cross sectional design. This study was conducted at Dr. H. Abdul Moeloek Hospital Lampung between December 2020 to January 2021, using medical record data from January 2018 to December 2020.

The inclusion criteria for this study were adult patients (≥18 years old) diagnosed with sepsis and septic shock, with complete blood test results recorded in their medical records. They agreed to participate by signing an informed consent form. Sepsis was diagnosed based on a SOFA score ≥2. Septic shock was diagnosed based on SOFA score ≥2 and lactate levels ≥2 mmol/L (>18 mg/dL), as well as a requirement for vasopressors to maintain mean arterial pressure of ≥65 mmHg. The exclusion criteria were pregnant females, patients with immunocompromised conditions such as liver failure, autoimmune disease, hematological cancer, and AIDS, and patients with severe illnesses such as metastatic cancer, stroke, coma, and advanced heart failure.

This study uses consecutive sampling methods, meaning that all patients who met the inclusion and exclusion criteria were enrolled. Ninety-six patients who met the criteria were included in the study and were divided into two groups based on disease severity: the sepsis group, consisting of 77 patients, and the septic shock group, consisting of 19 patients. Personal medical history, age, clinical signs, symptoms, and laboratory blood test results were collected from all subjects from their medical records. All data were analyzed using SPSS for Windows (version 24.0, Chicago, Illinois, USA). Quantitative data were expressed as mean with standard deviation, while qualitative data were expressed as frequency and percentage. The difference in

Table 1 General Characteristics of Subject

Variables	Frequency	Percentage (%)
Gender		
Male	53	55.21
Female	43	44.79
Age (years±SD)	54.68±15.67	
18–25	4	4.17
26–35	8	8.33
36–45	11	11.46
46–55	23	23.96
56–65	24	25.00
>65 years	26	27.08
Neutrophil		
Neutropenia	0	0
Normal	10	10,42
Neutrophilia	86	89,58
Lymphocyte		
Lymphopenia	91	94,79
Normal	5	5,21
Lymphocytosis	0	0
NLR		
<5	12	12.5
>5	84	87.5

NLR values between sepsis and septic shock patients was analyzed using an independent t-test with a significant level (α) of 5%.

This research has undergone ethical review and obtained an ethical clearance letter from the Health Research Ethics Committee, Faculty of Medicine, University of Lampung, with letter number 30906/UN26.18/PP.05.02.00/2020.

Results

This study includes 96 patients with sepsis diagnosis according to ICD X: A41.9. Most of the subjects in this study were male (55.21%) with an average age of 54.68±15.67 years. The age distribution was dominated by individuals over 45 years old, and the older the age group, the higher the number of subjects. As predicted earlier, most of the subjects showed an increase in the number of neutrophils (89.58%), a decrease in lymphocytes (94.79%), and an increase in NLR value (87.5%) (Table 1).

Table 2 Difference of NLR Value Between Sepsis and Septic Shock

Variables	Total (n=96)	Sepsis (n=77)	Septic shock (n=19)	p
Neutrophils (%)	88 (52–97)	84 (75–96)	90 (52–97)	0.183
Lymphocyte (%)	6 (1–42)	10 (1–23)	6 (2–42)	0.247
NLR	18.45±1.51	18.106±1.35	20.10±2.89	0.025*

Note: * showed a significant difference between sepsis and septic shock at α=5%

The neutrophil count showed no significant difference between sepsis and septic shock. Similarly to the neutrophil count, lymphocyte count also did not show a significant difference between these two groups. The study also found that most patients had an NLR value higher than the normal NLR range, averaging 18.45±1.51. The NLR values were significantly higher in patients with septic shock (20.10±5.89) compared to those in the sepsis group (18.01±1.35) (p=0.025) (Table 2).

Discussion

Leukocyte count has long been used as a diagnostic parameter for sepsis or septic shock. However, not all septic patients exhibit abnormalities in their leukocyte count, as some may have normal leukocyte counts.[8-10] In recent years, researchers have sought new variables that might be more accurate in diagnosing sepsis. One such promising variable is the LNR value.

This study involved 96 subjects, most of whom were sepsis patients (80.21%), while the remaining had septic shock (19.79%). These findings align with Huang et al.'s study, which found that the number of sepsis patients was higher than that of septic shock patients (23 vs. 22, respectively).[17] Another study by Nainggolan et al. reported a higher prevalence of sepsis (59.7%) than septic shock (40.3%).[18] As Martin notes, intensive care services are typically required when shock sepsis accounts for over 50% of patients.[19]

The study also found that sepsis was more prevalent among older individuals (Table 1), consistent with previous research such as the study by Starr and Saiyo.[13,14] One possible explanation for this discrepancy is the influence of estrogen, a hormone known to have a protective effect against infection, sepsis, and trauma. Estrogen is involved in increasing various anti-inflammatory cytokines, including IL-4 and IL-10, which can indirectly stimulated antibody production.

The study also found that sepsis was more prevalent among older individuals (Table 1), which is consistent with previous research such as the study by Starr and Saiyo. In the United States, over half of sepsis cases are diagnosed in patients aged 65 years and above, with higher mortality rates than younger patients. Sepsis poses a more significant threat to geriatric patients because aging weakens their immune systems, making them more susceptible to infections and sepsis (Tamba Doang). Both innate and adaptive immune responses decline with age, which can contribute to increased infections among the elderly. The reduction in adaptive immune responses is associated with decreased immune function and a decline in the number of cells involved in the body's immune system. Specifically, the number of B cells and generation of T cells decreases with aging, reducing response to new pathogens. However, the ability to mount an efficient response to pathogens remains intact.[14]

Most of the samples in this study had neutrophilia and lymphopenia (Table 1). This study also revealed that the neutrophil count of the subject was overall elevated, while the lymphocyte count was decreased, but similar in sepsis and septic shock (Table 2). Neutrophilia is a characteristic feature of sepsis caused by bacterial invasion, which triggers the mobilization and rapid migration of immune cells (neutrophils) from the bone marrow to the circulation, resulting in a shift to the left.[16] Conversely, lymphopenia is often observed in severe systemic inflammation such as sepsis, involving marginalization and redistribution of lymphocytes in the lymphatic system, leading to accelerated of apoptosis. The apoptosis process is initiated when macrophages release proapoptotic agents such as TNF-α, Nitrite oxide (NO), and glucocorticoids, which suppress lymphocyte production.[13,17]

This study also found an increase in NLR values, with significantly higher values in

patients with septic shock than those with sepsis alone (Table 2). This finding suggests that NLR may have potential value in assessing the severity of sepsis. These results are consistent with a study by Zahorec, which investigated the relationship between lymphocyte and neutrophil counts during systemic inflammatory responses and found that the ratio of lymphocyte to neutrophil counts is a reliable, fast, and simple method for evaluating inflammatory stress.[20] This is also supported by research conducted at Dr. Hasan Sadikin General Hospital Bandung in 2013, which showed a relationship between NLR and SOFA scores in ICU patients, where systemic inflammatory conditions such as sepsis were marked by an increase in NLR and organ failure was marked by an increase in SOFA scores.[21]

This study has some limitations, as it relied on secondary data from medical records, which may have been affected by the quality of documentation by healthcare providers. As a result, the researchers needed help understanding the variables studied comprehensively. There were also limitations in collecting medical record data, which often needed to be completed, especially regarding the history and physical examination record.

In conclusion, NLR is a simple parameter that can be easily measured through a complete blood count, a standard and required test for all hospitalized patients. The NLR values in shock septic were significantly higher than those with sepsis alone. Therefore, it has the potential to be widely utilized in assessing the severity of sepsis or septic shock. However, more extensive studies are necessary to confirm the effectiveness of NLR in predicting the severity of sepsis and determining the risk of mortality in these patients by involving a larger sample size.
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