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Correlation Between Neutrophil to Lymphocyte Ratio (NLR) and Procalcitonin Levels in Sepsis Pneumonia Patients

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ABSTRACT

Introduction: According to the World Health Organization's global health estimates, lower respiratory infections are the fourth leading global cause of deaths and the deadliest communicable disease, causative for three million deaths worldwide in 2016. Despite the introduction of antibiotic therapies in the 1950s, pneumonia mortality has not decreased substantially, and sepsis, septic shock or acute pulmonary failure (eg acute respiratory distress syndrome, ARDS) are frequent secondary complications. To improve management and treatment of pneumonia, supporting microbiological and virological tests from throat swabs, sputum or blood cultures might be indicated to identify the responsible pathogen(s) and to allow targeted antimicrobial or antiviral therapy. To determine the relationship between procalcitonin level and neutrophil to lymphocyte ratio in sepsis pneumonia patients.

Method: This study was conducted with an observational analytic design conducted in a cross-sectional manner, from January 2023 to December 2023. The subjects of this study were taken from the population of sepsis pneumonia patients who were hospitalized at intensive care unit, were found to be 132 samples. Data included procalcitonin level and neutrophil to lymphocyte ratio from laboratory findings, were analyzed with univariate and bivariate method to assess the relationship between procalcitonin level and neutrophil to lymphocyte ratio.

Results: In this study, white blood cell, neutrophil and neutrophil/lymphocyte ratio values were found to be significantly higher in patients with elevated procalcitonin. Among the 132 samples, the mean of procalcitonin level was between $\geqslant$ 2 to 10 (39,39%) and neutrophil to lymphocyte ratio was between $\geqslant$ 11 to 17 (50%).

Conclusion: There was no significant relationship between procalcitonin level and neutrophil to lymphocyte ratio in sepsis pneumonia patient at intensive care unit in Adam Malik Hospital Medan (P value 0.816).

Keywords

Sepsis, Pneumonia, Neutrophil to Lymphocyte Ratio, Procalcitonin, Intensive Care Unit

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INTRODUCTION

The World Health Organization (WHO) explains that there were 48.9 million cases and 11 million sepsis-related deaths worldwide in 2017, which accounted for nearly 20% of global deaths. The incidence of sepsis in the United States reaches 300 cases per 100,000 people and is the leading cause of death in critical condition patients with more than 210,000 deaths each year.

The incidence of sepsis doubled in the United States from 2002 to 2008, likely due to the increase in chronic diseases, increased antibiotic resistance, use of immunosuppressive drugs and chemotherapy.[1]
Sepsis is a severe systemic inflammatory state of the body due to an uncontrolled hyperinflammatory response that is a form of response to pathogen invasion. Sepsis is commonly found in patients admitted to the Intensive Care Unit (ICU) with high variability in outcome. Sepsis patients may die due to disease progression to severe sepsis that progresses to septic shock or due to multiple organ failure (MOF) accompanied by decreased immunity.[1,2]

As many as 10% of patients admitted to the ICU are sepsis patients and there are 750,000 sepsis patients hospitalized per year with a mortality rate of >200,000 patients per year. Mortality rates for severe sepsis range from 15%-40% and mortality rates for septic shock range from 20%-72%. The high mortality rate due to sepsis, severe sepsis, and septic shock requires early identification as well as appropriate and immediate therapy to prevent further deterioration of the patient's condition.[2]

Pneumonia is the most common primary infection in sepsis, followed by infections of the abdomen, genitourinary tract, skin and soft tissues. Sepsis is one of the frequent complications of pneumonia, in addition to emphysema, lung abscess, pneumothorax and respiratory failure. Severe sepsis occurs in community-acquired pneumonia and pneumonia associated with hospitalization; health care-associated pneumonia is the most common cause of sepsis with almost half of all cases accompanied by intra-abdominal and urinary tract infections. On blood culture, only a few of the cases were found to have gram-positive bacteria and the rest were found to have gram-negative bacteria culture.[3]

The incidence of pneumonia is more common in developing countries. Pneumonia affects around 450 million people every year. Based on RISKESDAS data in 2018, the prevalence of pneumonia based on health worker diagnosis was around 2% while in 2013 it was 1.8%. Based on data from the Ministry of Health 2014, the number of pneumonia patients in Indonesia in 2013 ranged from 23-27% and mortality from pneumonia was 1.19%. In 2010, pneumonia was included in the top 10 hospital inpatient diseases in Indonesia with a crude fatality rate (CFR) or the mortality rate of a certain disease in a certain period of time divided by the number of cases was 7.6%.[4]

Sepsis can result from community acquired, hospital acquired, and healthcare associated infections, with pneumonia accounting for more than 50% of the sepsis incidence in patients admitted to the ICU. Biomarkers of inflammation such as PCT and NLR have been proposed as indicators of systemic inflammation and infection. Because PCT and NLR levels both have high accuracy in cases of systemic bacterial infection and predict pneumonia sepsis mortality. However, until now there are no journals or studies that correlate and compare the accuracy of NLR with Procalcitonin.

METHOD

A cross-sectional study was conducted at the ICU of H. Adam Malik Hospital in 2023. Patients diagnosed with pneumonia-related sepsis were enrolled. The NLR was calculated from complete blood counts, while Procalcitonin levels were measured using standard laboratory techniques.

Demographic data including age, gender, and underlying health conditions were also collected. The correlation between NLR and Procalcitonin levels was analyzed using Spearman's correlation coefficient.

RESULTS

The highest age was ≥ 60 years as many as 53 people (40.15%), the second highest age was age 46-59 years as many as 42 people (31.85%). and the least age was age ≥ 19-30 years as many as 15 people (11.36%). and the most gender was male as many as 81 people (61.37%).

Based on table 2 below, it is known that the most NLR is critical inflammation in the value of procalcitonin is shock sepsis and sepsis / other infections as many as 22 patients (16.64%), followed by mild to moderate in sepsis / other infections as many as 12 patients (9.09%).

Table 1. Demographic features of pneumonia sepsis patients

Characteristic	n	%
Age		
≥ 19-30 years old	15	11,36
31-45 years old	22	16,64
46-59 years old	42	31,85
≥60 years old	53	40,15
Gender		
Laki-Laki	81	61,37
Perempuan	51	38,63

NLR Features Of Sepsis Pneumonia Patients

Table 2. NLR Features Of Pneumonia Sepsis Patients

Rasio NLR	n	%
Reverse Severe (0,1 – 0,7)	2	1,52
Normal (1 – 2)	2	1,52
Low Inflammation (2 – 3)	5	3,79
Mild to Moderate Inflammation (3 – 7)	20	15,15
Moderate Inflammation (7 – 11)	20	15,15
Critical Inflammation (>17)	66	50,00
Severe Inflammation (11 – 17)	17	12,88
Procalcitonin Features Of Sepsis Pneumonia Patients	132	100

Based on table 3 below, the most common description of procalcitonin values in sepsis patients was in category sepsis/other infections, 52 patients (39.39%).

Table 3. Procalcitonin Features Of Pneumonia Sepsis Patients

Nilai Prokalsitonin	n	%
Normal (< 0,5)	18	13,64
Sepsis (> 2)	7	5,30
Sepsis Berat (2 – 10)	16	12,12
Sepsis/ Infeksi Lain (0,5 – 2)	52	39,39
Syok Sepsis (>10)	39	29,55
Procalcitonin Features Of Pneumonia Sepsis Patients	132	100

DISCUSSION

Sepsis affects both genders, but there is a prominent male predominance among sepsis patients. Several studies have consistently shown that men are more frequently diagnosed with sepsis compared to women. For example, a study analyzing data from 19 hospitals in South Korea found that 56.7% of sepsis patients were male.[5]

Similarly, a large-scale analysis of 34 studies involving 498,146 septic adult patients revealed male predominance, with 54-61% of patients being male.[6] A systematic review and meta-analysis study conducted by Shankar-Hari on rehospitalization rates and risk factors in sepsis survivors, advanced age, male gender, comorbidities and disease severity showed inconsistent associations with rehospitalization rates of sepsis patients. Sepsis, a life-threatening organ dysfunction caused by an unregulated host response to inflammation,1 is a leading cause of death in intensive care units (ICUs) and accounts for one in five deaths worldwide.2-4 Sepsis is a heterogeneous disease that affects men more often than women.[5] Evaluating whether outcomes differ by gender is a recognized health research priority.[6]

It has been hypothesized that gender may exert a prognostic effect on sepsis outcomes. Biological mechanisms regarding the relationship between sex hormone metabolism and immune response are known to support this hypothesis.[6-9] However, individual studies evaluating the relationship between sex and sepsis outcomes report conflicting and imprecise findings.[7]

Sepsis is a critical condition that disproportionately affects the elderly, with most septic patients being over 65 years old. Studies show that nearly 60% of sepsis cases occur in this age group, highlighting the

vulnerability of older adults to this severe infection.[10,11] The incidence and severity of sepsis increases with age due to factors such as comorbidities, institutionalization, and decreased immune function.[12]

Sepsis is a frequent complication of (CAP).[7] However, it is a multifactorial process that requires management to ensure appropriate care according to each patient's needs.[8] A recent multicenter study found that age is an independent risk factor for mortality in sepsis, with therapy rapidly administered within the first six hours of resuscitation being associated with reduced mortality in very elderly patients (⩾80 years).[9] In a Spanish multicenter cohort study of 4070 patients hospitalized with (CAP), 38% presented with severe sepsis (organ dysfunction).[7] where age ⩾65 years, chronic obstructive pulmonary disease, renal disease, and alcohol abuse were independent risk factors. In contrast, previous antibiotic therapy and diabetes mellitus were protective risk factors. Despite the increased risk of infectious diseases due to age-related vulnerability, there is a dearth of data on sepsis in very old patients with (CAP).[12]

Aging is associated with an increased prevalence of chronic conditions. Age-related changes in the immune system increase susceptibility to infectious diseases and sepsis. In this study, sepsis affected 71% of very old patients with (CAP), 7% went into septic shock, and 11% of those with sepsis required ICU treatment. The prevalence of sepsis in our patients with CAP was almost double that previously reported by Montull et al. (38% of severe sepsis in patients with CAP).[7] However, we used the current definition of Sepsis-3 with a change in SOFA score ⩾2 we included nursing home residents and focused on very old patients. In our study, we also observed an uncommon presentation of pneumonia in patients with and without sepsis. Interestingly, very old patients with sepsis showed less pleuritic pain and more mental status changes than patients without sepsis. These findings confirm the results of previous studies, which showed that in elderly patients, (CAP) can present without fever, cough or pleuritic pain but with altered mental status, sudden decline in functional capacity, and worsening of previous comorbidities.[13]

Clinicians should be vigilant in diagnosing pneumonia in elderly patients to reduce complications associated with delayed initiation of empiric antimicrobial therapy.[14] NLR is a significant marker to indicate critical inflammation in sepsis and pneumonia. Studies have shown that NLR is a simple, cost-effective, and rapidly available biomarker that correlates well with other inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT).[15-17] In patients with community-acquired pneumonia (CAP), a high NLR has been associated with increased severity and poor outcomes, including higher mortality rates.[18]

The neutrophil to lymphocyte ratio (NLR), calculated as a simple ratio between the number of neutrophils and lymphocytes measured in peripheral blood, is a biomarker that combines two sides of the immune system: the innate immune response, mainly due to neutrophils, and adaptive immunity, which is supported by lymphocytes.[19] Neutrophils are responsible for the first line of host immune response against invading pathogens, through different mechanisms, including chemotaxis, phagocytosis, release of reactive oxygen species (ROS), granular proteins, and cytokine production and liberation.[2]

Neutrophils also play an important regulatory role in adaptive immunity and are key effector cells during the systemic inflammatory response (SIRS). As regulators of innate immunity, neutrophils recruit, activate, and program other immune cells, secreting an array of pro-inflammatory and immunomodulatory cytokines and chemokines capable of enhancing the recruitment and effector functions of other immune cells, such as dendritic cells (DCs), B cells, NK cells, CD4, CD8, and γδ T cells, and mesenchymal stem cells. An increase in the number of isolated neutrophils, and, consequently, an increase in NLR, can be observed in several conditions: bacterial or fungal infections.[4,6] acute stroke.[5] myocardial infarction.[6] atherosclerosis.[7] severe trauma.[8] cancer.[9] postoperative complications.[12] and any condition characterized by tissue damage that activates SIRS. This is because the initial hyperdynamic phase of infection is characterized by a proinflammatory state, mediated by neutrophils and other inflammatory cells.[4] SIRS is associated with suppression of neutrophil apoptosis, which increases neutrophil-mediated killing as part of the innate response.[4] Thus, NLR is often characterized by increased neutrophils and decreased lymphocytes.

NLR is a cheap and easy-to-perform biomarker that can reflect the balance between both aspects of the immune process.[1] acute and chronic inflammation and.[2] adaptive immunity. Although there is no fixed cut-off value available, changes in NLR values that occur over time are a sign of impaired immune system. However, NLR can be considered a strong prognostic marker in assessing disease severity and a predictor of mortality, but still taking into account the effects of confounding and considering the disease-specific context, comorbid diseases and therapeutic strategies. Further age-adjusted case control studies may also be helpful in identifying the range of normality of NLR values. Furthermore, NLR values should also be adjusted based on disease severity, to aid the performance of this promising biomarker.

Procalcitonin (PCT) is a valuable biomarker for diagnosing sepsis, as it is specific for bacterial infections and can help distinguish sepsis from other inflammatory conditions. Elevated (PCT) levels are strongly associated with sepsis, with various studies highlighting its diagnostic accuracy. For example, a study on neonatal sepsis found that (PCT) had a sensitivity of 88.46% and specificity of 87.88%, outperforming C-reactive protein (CRP) in diagnostic accuracy.[20]

Procalcitonin is a calcitonin prohormone released by parenchymal cells, including liver cells, kidney cells, adipocytes, and muscle cells in response to bacterial toxins; conversely, procalcitonin is reduced in patients with viral infections. (PCT) is released into the bloodstream of healthy individuals at levels less than 0.05 ng/L. Once stimulated by bacterial endotoxin, the plasma concentration of (PCT) increases within 2-3 hours after bacterial invasion. (PCT) levels peak after 6-12 hours and remain high for 48 hours before dropping to baseline levels within the following 2 days. The rapid and persistent response to systemic inflammation caused by bacteria highlights the role of (PCT) as a marker of sepsis. (PCT) can remain in circulation for 7 days, but once inflammatory signals such as bacterial endotoxins are removed, its half-life is about 20-35 hours. In comparison, (CRP) can be detected 4-6 hours after inflammation and peaks after 36-50 hours with its half-life of 19 hours after the stimulus is removed. [21,22]

(PCT) guided discontinuation of antibiotic therapy was shown to reduce antibiotic exposure and lower the risk of poor outcomes in patients with lower respiratory tract infections (LRTIs) compared to standard antibiotic treatment guidance in several randomized trials. In addition, data from meta-analyses of randomized clinical trials have confirmed the safety-grade benefit of (PCT) guided antibiotic discontinuation. However, the mechanisms underlying this survival benefit remain unclear. The use of (PCT) as a reference for early discontinuation of antimicrobials in medically stable, non-febrile sepsis patients showed significant clinical benefit. The (PCT) guideline approach is associated with lower infection-related adverse events, lower 28-day mortality, shorter LOT, earlier hospital discharge, and decreased hospitalization costs. These benefits may have a major impact on public health, especially in countries with high antimicrobial consumption.[23]

The value of NLR is affected by various comorbidities, which can significantly affect its prognostic and diagnostic utility in various medical conditions. In patients with stable ischemic heart disease (SIHD), diabetes was identified as a major comorbidity that significantly overlaps with severe coronary artery disease (CAD) and increased NLR values.[25] In the context of non-small cell lung cancer (NSCLC) with pulmonary comorbidities, NLR was found to be a negative prognostic factor for overall survival, suggesting that pulmonary conditions may influence NLR values.[26] For patients with diffuse large B-cell lymphoma (DLBCL), the Charlson Comorbidity Index (CCI) was used to assess the impact of comorbidities, revealing that higher CCI scores were associated with worse outcomes and higher NLR values.[27]

In COVID-19 patients, comorbidities such as cardiovascular disease (CVD) were shown to increase NLR, which was associated with an increased risk of cardiovascular events during follow-up.[28] In addition, severe COVID-19 patients with higher CCI scores showed increased NLR values, which is a significant predictor of mortality.[29,30] In acute ischemic stroke (AIS) patients, comorbidities such as metabolic syndrome and diabetes are associated with higher NLR values, which correlate with the incidence of early-onset delirium.[31] Furthermore, in patients undergoing radical resection for non-B, non-C hepatocellular carcinoma (NBNC-HCC), factors such as body mass index (BMI), diabetes, and metabolic syndrome were found to influence NLR values and postoperative disease-free survival.[32] Overall,

comorbidities such as diabetes, pulmonary conditions, cardiovascular disease, and metabolic syndrome significantly affect the NLR value, thus affecting its prognostic and diagnostic relevance across different diseases.

CONCLUSION

The high number of septic pneumonia patients who are male can be a consideration for clinicians in assessing the diagnosis and severity of mortality when patients present with clinical and supporting symptoms that suggest pneumonic sepsis. Special attention and considering comorbidities to elderly patients can be used as a reference in the management of sepsis pneumonia patients who come to health facilities, in addition, advanced age can be a risk factor for the possibility of patients being readmitted due to recurrent sepsis pneumonia or a decline in condition after out of the intensive care room.

Patients with clinical and radiological findings that suggest a diagnosis of sepsis pneumonia should consider the NLR value as a reference for mortality. Where the NLR number in laboratory examinations which shows a value of 11-17 is the highest number of patients treated in intensive care, therefore ordinary ward patients who show an NLR Critical Inflammation value can be made a priority for intensive care. Procalcitonin values that are not too high still indicate a blood infection and require more serious treatment, this means that the clinician who assesses the patient's laboratory results still needs to consider the need for intensive care even though the procalcitonin value still shows a value of $\geq$ 2-10.

DECLARATIONS

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CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest in this report.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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