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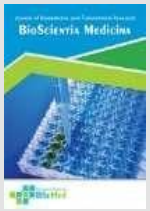

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Procalcitonin Outperforms NLR as a Sepsis Predictor in Pneumonia Patients: A Cross-Sectional Study from a Tertiary Hospital in Padang, Indonesia

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A B S T R A C T

Background: Pneumonia remains a significant cause of morbidity and mortality worldwide, with sepsis being a severe complication. Early identification of sepsis is crucial for prompt treatment and improved outcomes. This study aimed to evaluate the performance of procalcitonin (PCT) and neutrophil-lymphocyte ratio (NLR) as predictors of sepsis in pneumonia patients at a tertiary hospital in Padang, Indonesia. **Methods:** A cross-sectional study was conducted on 110 adult pneumonia patients admitted to Dr. M. Djamil General Hospital Padang between 2022 and 2023. Data on demographics, clinical characteristics, NLR, and PCT levels were collected from electronic medical records. Sepsis was defined according to established clinical criteria. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of NLR and PCT in predicting sepsis. **Results:** The study population had a mean age of 57.72 ± 14.41 years, with 56.4% being male. Of the 110 patients, 73.6% had community-acquired pneumonia (CAP) and 26.4% had hospital-acquired pneumonia (HAP). Sepsis was present in 55.5% of the patients. The median NLR and PCT levels were significantly higher in the sepsis group compared to the non-sepsis group (NLR: 14 vs. 6.6, p=0.002; PCT: 2.17 vs. 0.24, p=0.000). ROC analysis showed that PCT had a higher area under the curve (AUC) compared to NLR (0.724 vs. 0.676), indicating better diagnostic accuracy. The optimal cut-off point for PCT was 0.455, with a sensitivity of 65.6% and specificity of 65.3%. For NLR, the cut-off point was 10.375, with a sensitivity of 63.9% and specificity of 63.3%. **Conclusion:** PCT demonstrated superior diagnostic accuracy compared to NLR in predicting sepsis among pneumonia patients in this study. However, NLR remains a valuable tool, especially in resource-limited settings where PCT testing may not be readily available.

1. Introduction

Pneumonia, an acute infection affecting the lung parenchyma, remains a significant global health challenge, contributing substantially to disease burden and mortality worldwide. It stands as the leading cause of death from infectious diseases, affecting individuals across all age groups, but with a particular impact on the elderly and those with underlying health conditions. The global pneumonia burden underscores its significance as a major public health concern. In Indonesia, pneumonia presents a considerable public health challenge, exhibiting a prevalence of 2.21% across all age groups. Notably, the highest prevalence is observed in older age groups (44-64 years, 64-74 years, and ≥75 years), underscoring the vulnerability of this population segment. The disproportionate impact on older individuals emphasizes the need for targeted interventions and care strategies for this demographic. Sepsis, a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection, frequently arises as a severe complication of pneumonia. The global incidence of sepsis has been on the rise, posing a formidable

challenge to healthcare systems worldwide. The increasing prevalence of sepsis necessitates heightened awareness and proactive measures to mitigate its impact on patient outcomes.[1-4]

Early recognition and prompt treatment of sepsis are of paramount importance in improving patient outcomes and reducing mortality rates. The time-sensitive nature of sepsis management underscores the need for rapid diagnostic tools and effective therapeutic interventions. Consequently, extensive research has been dedicated to identifying biomarkers that can aid in the early diagnosis of sepsis, enabling timely and targeted interventions. Procalcitonin (PCT), a precursor of the hormone calcitonin, has emerged as a promising biomarker for bacterial infections and sepsis. PCT levels exhibit a rapid increase in response to bacterial infections, establishing it as a valuable tool for the early detection and monitoring of sepsis. The responsiveness of PCT to bacterial infections highlights its potential for guiding clinical decision-making in the context of sepsis management.[5-7]

Another readily accessible biomarker is the neutrophil-lymphocyte ratio (NLR), derived from routine complete blood counts. NLR reflects the interplay between innate and adaptive immune responses, and its elevation has been associated with heightened inflammation and adverse prognoses in various infectious diseases, including pneumonia. The association of NLR with inflammatory states and disease outcomes underscores its potential role as a prognostic indicator. While both PCT and NLR have demonstrated promise as sepsis biomarkers, their comparative diagnostic performance in pneumonia patients remains an area of ongoing investigation. Evaluating the relative efficacy of these biomarkers is crucial for informing clinical practice and optimizing sepsis management strategies.[8-10] In this study, we undertook an evaluation of the accuracy of PCT and NLR in predicting sepsis among pneumonia patients admitted to Dr. M. Djamil General Hospital, a tertiary care center in Padang, Indonesia.

2. Methods

This study employed a cross-sectional design, conducted at Dr. M. Djamil General Hospital, a tertiary referral hospital located in Padang, Indonesia. The study period spanned from July 2023 to December 2023. Ethical approval for the study was obtained from the hospital's ethics committee (approval number not provided). The cross-sectional design allowed for the collection of data at a single point in time, providing a snapshot of the prevalence and association of variables within the study population. Dr. M. Djamil General Hospital, as a tertiary referral hospital, serves a diverse patient population, potentially enhancing the generalizability of the study findings.

The study population comprised adult patients (age > 18 years) admitted to the inpatient wards with a confirmed diagnosis of pneumonia. The diagnosis of pneumonia was established based on a combination of clinical and radiological findings, adhering to the guidelines set forth by the Indonesian Ministry of Health. To ensure the specificity of the study population, exclusion criteria were applied. Patients with a history of malignancy, fourth-degree burns, or extrapulmonary infections were excluded from the study. The inclusion of adult patients with pneumonia allowed for the investigation of the diagnostic performance of PCT and NLR in a clinically relevant population. The exclusion criteria aimed to minimize the potential confounding effects of other medical conditions on the relationship between the biomarkers and sepsis.

Data for the study were collected retrospectively from electronic medical records, a method that capitalizes on the availability of comprehensive patient information within the hospital's digital record-keeping system. The following data elements were extracted for each patient; Demographics: Age and gender were recorded as fundamental patient characteristics; Pneumonia Type: The type of pneumonia, classified as either community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP), was documented. This distinction is crucial as

the etiology and clinical course of CAP and HAP can differ significantly; Sepsis Status: The presence or absence of sepsis was determined according to the Sepsis-3 criteria, a widely recognized clinical definition of sepsis; Laboratory Data: Neutrophil count, lymphocyte count, NLR, and PCT level were retrieved from laboratory reports. NLR was calculated as the ratio of neutrophil count to lymphocyte count, providing a measure of the balance between innate and adaptive immune responses.

The measurement of PCT and NLR was conducted using standard laboratory techniques. PCT levels were determined using commercially available assays, while NLR was calculated based on the neutrophil and lymphocyte counts obtained from complete blood counts. The use of standardized laboratory procedures ensured the accuracy and reliability of the biomarker measurements.

Data analysis was performed using IBM SPSS Statistics 26 software, a comprehensive statistical package widely used in healthcare research. Descriptive statistics were employed to summarize patient characteristics, providing a clear overview of the study population. Continuous variables were presented as mean ± standard deviation or median (interquartile range), depending on the distribution of the data. Categorical variables were presented as frequencies and percentages, facilitating the interpretation of categorical data. The diagnostic performance of NLR and PCT in predicting sepsis was evaluated using receiver operating characteristic (ROC) curve analysis, a robust method for assessing the discriminatory ability of diagnostic tests. The area under the ROC curve (AUC) served as a measure of overall diagnostic accuracy, with higher AUC values indicating better discriminatory power. In addition to AUC, sensitivity, specificity, and optimal cut-off points were determined for both biomarkers. Sensitivity represents the proportion of true positives correctly identified by the test, while specificity represents the proportion of true negatives correctly identified. The optimal cut-off point is the threshold value that maximizes the combined sensitivity and specificity. Comparisons between groups were performed using appropriate statistical tests, depending on the nature of the data. The independent t-test was used for normally distributed data, while the Mann-Whitney U test was employed for non-normally distributed data. The chi-square test was used to analyze the relationship between categorical variables. A p-value of <0.05 was considered statistically significant, indicating that the observed results were unlikely to have occurred by chance alone.

3. Results

Table 1 presents the baseline characteristics of the 110 pneumonia patients included in the study, comparing those with sepsis (n=61) to those without sepsis (n=49). The table also provides p-values to indicate the statistical significance of any differences observed between the two groups. The proportion of males and females in the sepsis and non-sepsis groups was similar, with no statistically significant difference observed (p=0.191). This suggests that gender was not a significant factor in the development of sepsis in this study population. The mean age of patients in both groups was comparable (57.84 ± 15.49 years in the sepsis group vs. 57.57 ± 13.09 years in the non-sepsis group, p=0.924), indicating that age was not a significant predictor of sepsis in this study. A statistically significant difference was found between the two groups regarding the type of pneumonia (p=0.032). A higher proportion of patients with sepsis had hospital-acquired pneumonia (HAP) (34.4%) compared to those without sepsis (16.3%). Conversely, community-acquired pneumonia (CAP) was more prevalent in the non-sepsis group (83.7%) compared to the sepsis group (65.6%). This suggests that HAP may be associated with a higher risk of developing sepsis compared to CAP. The median NLR was significantly higher in the sepsis group (14) compared to the non-sepsis group (6.6) (p=0.002). This finding supports the notion that NLR is a potential marker of inflammation and could be useful in identifying patients at risk of sepsis. Similarly, the median PCT level was significantly higher in the sepsis group (2.17

ng/mL) compared to the non-sepsis group (0.24 ng/mL) (p=0.000). This confirms previous findings that PCT is a sensitive marker of bacterial infection and sepsis.

Table 1. Baseline characteristics of the study population and their association with sepsis.

Variable	Patients with pneumonia (n=110)	Sepsis (n=61)	Non-sepsis (n=49)	p-value
Gender				0.191
Male	62 (56.4%)	31 (50.8%)	31 (63.3%)	
Female	48 (43.6%)	30 (49.2%)	18 (36.7%)	
Age (years)	57.72 ± 14.41	57.84 ± 15.49	57.57 ± 13.09	0.924
Pneumonia type				
CAP	81 (73.6%)	40 (65.6%)	41 (83.7%)	0.032
HAP	29 (26.4%)	21 (34.4%)	8 (16.3%)	0.032
NLR	10.56 (0.06-97)	14 (0.13-97)	6.6 (0.79-48)	0.002
PCT (ng/mL)	0.50 (0.02-115.94)	2.17 (0.02-115.94)	0.24 (0.04-88.31)	0.000

Table 2 presents the diagnostic performance of NLR and PCT in predicting sepsis among the study population. The table provides the area under the receiver operating characteristic curve (AUC), 95% confidence interval (CI), cut-off value, sensitivity, and specificity for each indicator. The AUC is a measure of the overall diagnostic accuracy of a test. It ranges from 0.5 to 1, with 0.5 indicating no discriminatory ability and 1 indicating perfect discrimination. In this study, PCT had a higher AUC (0.724) compared to NLR (0.676), suggesting that PCT has a better overall accuracy in predicting sepsis. The 95% CI provides a range of values within which the true AUC is likely to lie. The narrower the CI, the more precise the estimate of the AUC. The 95% CI for PCT (0.630-0.818) was narrower than that for NLR (0.573-0.780), indicating a more precise estimate of the AUC for PCT. The cut-off value is the threshold value used to classify patients as having or not having sepsis. The optimal cut-off value is the one that maximizes the combined sensitivity and specificity. The optimal cut-off value for PCT was 0.455 ng/mL, while the cut-off value for NLR was 10.375. Sensitivity is the proportion of patients with sepsis who are correctly identified by the test. PCT had a slightly higher sensitivity (65.6%) compared to NLR (63.9%). Specificity is the proportion of patients without sepsis who are correctly identified by the test. PCT also had a slightly higher specificity (65.3%) compared to NLR (63.3%).

Table 2. Diagnostic performance of NLR and PCT in predicting sepsis.

Indicator	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
NLR	676	0.573-0.780	10.375	63.9	63.3
PCT	724	0.630-0.818	455	65.6	65.3

Figure 1 displays the Receiver Operating Characteristic (ROC) curves for NLR (Figure 1A) and PCT (Figure 1B) in predicting sepsis among pneumonia patients. The ROC curve is a graphical representation of the diagnostic ability of a test. It plots the true positive rate (sensitivity) against the false positive rate (1-specificity) at various threshold settings; A. NLR: The ROC curve for NLR shows a moderate ability to discriminate between patients with and without sepsis. The curve rises above the diagonal line, indicating that NLR has some predictive value. However, the curve is not very steep, suggesting that

the discriminatory power of NLR is not very high; B. PCT: The ROC curve for PCT shows a better discriminatory ability compared to NLR. The curve is steeper and closer to the upper left corner of the graph, indicating a higher true positive rate and a lower false positive rate. This suggests that PCT is a more accurate predictor of sepsis compared to NLR. The AUC is a numerical representation of the overall diagnostic accuracy of a test. It ranges from 0.5 to 1, with 0.5 indicating no discriminatory ability and 1 indicating perfect discrimination. The AUC for PCT (0.724) is higher than that for NLR (0.676), confirming that PCT has a better overall accuracy in predicting sepsis.

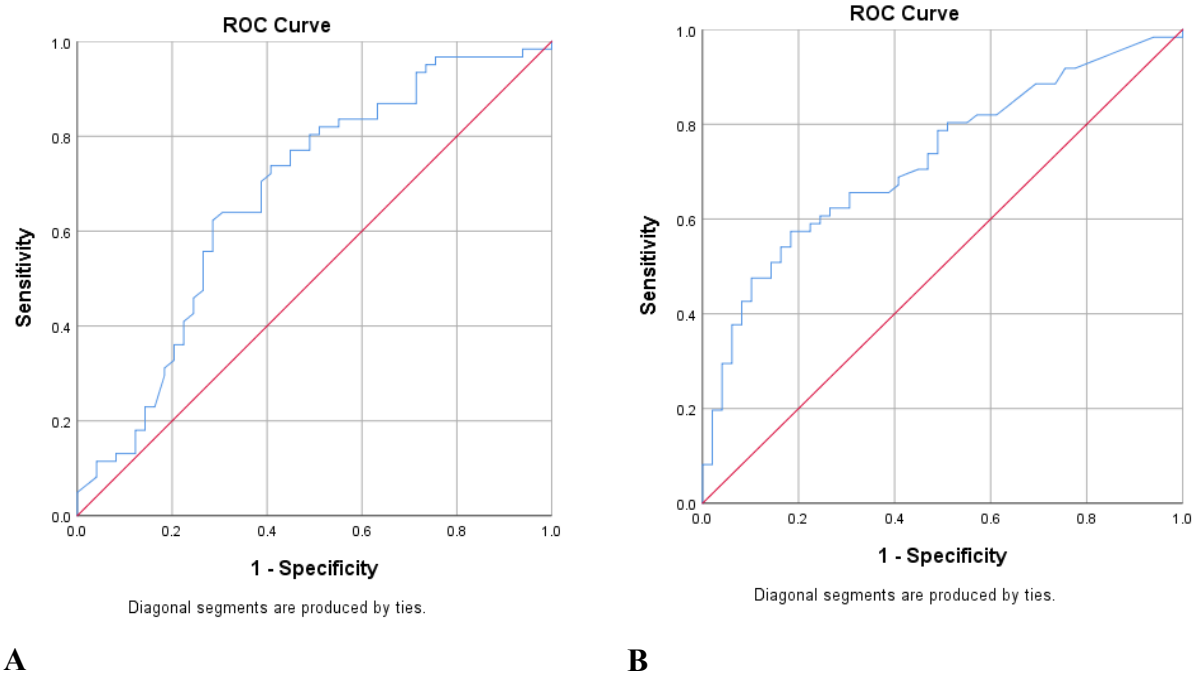

Figure 1. ROC Curve. A. NLR; B. PCT.

4. Discussion

Our study's findings align with a growing body of research that underscores the value of procalcitonin (PCT) as a reliable biomarker for sepsis. PCT is a prohormone, a precursor to the hormone calcitonin, which is primarily produced by the parafollicular cells (also known as C cells) of the thyroid gland. While calcitonin plays a crucial role in calcium homeostasis, PCT's biological function under normal physiological conditions remains somewhat elusive. However, in response to bacterial infections, PCT production increases dramatically, not just in the thyroid, but in various tissues and organs throughout the body. This systemic response to infection has propelled PCT to the forefront of sepsis diagnostics. The precise mechanisms that drive the surge in PCT production during sepsis are complex and not yet fully elucidated. However, current understanding suggests that bacterial endotoxins, such as lipopolysaccharide (LPS), and pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), play pivotal roles. These molecules, released by immune cells in response to bacterial infection, act as potent stimuli for PCT production. LPS, a major component of the outer membrane of Gram-negative bacteria, is a particularly potent inducer of PCT. It binds to Toll-like receptor 4 (TLR4) on immune cells, triggering a cascade of signaling events that ultimately

lead to the activation of transcription factors, such as nuclear factor-kappa B (NF-κB), which promote the expression of PCT. Pro-inflammatory cytokines, such as TNF-α and IL-6, further amplify this response, creating a positive feedback loop that drives PCT production. In contrast to bacterial infections, viral infections typically do not induce a significant increase in PCT levels. This differential response is attributed to the distinct mechanisms by which bacterial and viral pathogens interact with the immune system. Viral infections primarily activate the interferon pathway, which does not appear to have a major influence on PCT production. PCT levels rise rapidly in response to bacterial infection, typically within 2-4 hours of onset. This rapid kinetics makes PCT an ideal marker for early detection of sepsis, allowing for timely intervention and potentially improving patient outcomes. PCT levels generally correlate with the severity of infection, providing valuable information for risk stratification and guiding treatment decisions. Higher PCT levels are often associated with more severe infections and worse prognosis. PCT exhibits high specificity for bacterial infections, minimizing false positives due to viral infections or non-infectious inflammatory conditions. This specificity is crucial for avoiding unnecessary antibiotic use and minimizing the risk of antibiotic resistance. PCT levels can be used to monitor the response to treatment and predict outcomes in sepsis patients. Decreasing PCT levels generally indicate a favorable response to therapy, while persistently elevated levels may suggest treatment failure or the development of complications. In our study, PCT demonstrated superior diagnostic accuracy compared to NLR, as evidenced by a higher AUC in ROC curve analysis. The AUC for PCT was 0.724, indicating good discriminatory ability. The optimal cut-off point of 0.455 ng/mL for PCT provides a practical threshold for clinical decision-making. PCT levels above this cut-off should raise a strong suspicion of sepsis, prompting further investigation and treatment. Our findings are consistent with previous studies that have demonstrated the value of PCT as a sepsis biomarker in various clinical settings. PCT has been shown to be useful in the diagnosis of sepsis in both adults and children, in both community-acquired and hospital-acquired infections, and in both immunocompetent and immunocompromised patients. The use of PCT as a sepsis biomarker has the potential to significantly impact clinical practice. By enabling early detection and risk stratification, PCT can guide treatment decisions, improve patient outcomes, and reduce healthcare costs. PCT's rapid response to bacterial infection allows for early detection of sepsis, even before the development of overt clinical signs and symptoms. This early detection can facilitate prompt initiation of appropriate therapy, potentially preventing the progression to severe sepsis or septic shock. PCT levels correlate with the severity of infection, allowing for risk stratification of sepsis patients. This information can help clinicians identify patients who are at higher risk of adverse outcomes and may benefit from more aggressive treatment. PCT can be used to guide antibiotic therapy in sepsis patients. PCT-guided antibiotic stewardship has been shown to reduce antibiotic use without compromising patient outcomes. This is important for minimizing the risk of antibiotic resistance and preserving the effectiveness of antibiotics for future generations. PCT levels can be monitored to assess the response to treatment in sepsis patients. Decreasing PCT levels generally indicate a favorable response to therapy, while persistently elevated levels may suggest treatment failure or the development of complications. This information can help clinicians adjust treatment strategies as needed. The utility of PCT extends beyond the general diagnosis and management of sepsis. PCT has been shown to be a useful tool in differentiating bacterial from viral Lower Respiratory Tract Infections (LRTIs), aiding in the judicious use of antibiotics. In pneumonia, PCT levels can help distinguish between bacterial and viral etiologies, guiding appropriate antimicrobial therapy. PCT is particularly valuable in the Intensive Care Unit (ICU), where critically ill patients are at high risk of developing sepsis. Serial PCT measurements can help

monitor the progression of infection, assess the response to treatment, and identify patients who may benefit from more aggressive interventions. In immunocompromised patients, who may present with atypical or masked signs of infection, PCT can provide an early warning sign of sepsis. This is crucial as delayed diagnosis and treatment in this population can lead to rapid deterioration and poor outcomes. PCT has shown promise in the early diagnosis of Surgical Site Infections (SSIs), allowing for prompt intervention and potentially reducing the morbidity and mortality associated with these infections. PCT is increasingly being used in the evaluation of neonatal sepsis, where early diagnosis is critical. PCT levels can help distinguish between true sepsis and other inflammatory conditions that may mimic sepsis in neonates. The increasing prevalence of antibiotic resistance is a major global health threat. The overuse and misuse of antibiotics are key drivers of resistance. PCT-guided antibiotic stewardship has emerged as a promising strategy to optimize antibiotic use and minimize the development of resistance. PCT can be used to guide the initiation, duration, and de-escalation of antibiotic therapy in sepsis patients. Studies have shown that PCT-guided antibiotic stewardship can safely reduce antibiotic use without compromising patient outcomes. This approach is particularly valuable in settings where antibiotic resistance is prevalent. PCT has become an indispensable tool for clinicians in various healthcare settings. Its ability to provide rapid, reliable, and actionable information has transformed the way we approach the diagnosis and management of sepsis. In the EDEmergency Department (ED), where rapid assessment and triage are essential, PCT can help identify patients with suspected sepsis who require immediate attention and intervention. This can expedite the initiation of appropriate therapy and potentially improve outcomes. In primary care settings, PCT can aid in the early detection of bacterial infections, guiding the appropriate use of antibiotics and reducing the risk of unnecessary prescriptions. This can contribute to antibiotic stewardship efforts and minimize the development of resistance. On hospital wards, PCT can be used to monitor the progression of infection, assess the response to treatment, and identify patients who may benefit from more aggressive interventions. This can help optimize resource allocation and improve patient care. In post-operative care, PCT can be used to detect early signs of infection, allowing for prompt intervention and potentially reducing the risk of complications. The early and accurate diagnosis of sepsis, facilitated by PCT, can lead to significant cost savings in healthcare. By reducing the length of hospital stays, minimizing the need for intensive care, and preventing complications, PCT can contribute to a more efficient and cost-effective healthcare system. Studies have shown that PCT-guided antibiotic stewardship can reduce antibiotic use and healthcare costs without compromising patient outcomes. This is particularly important in an era of rising healthcare expenditures.[11-13]

The neutrophil-lymphocyte ratio (NLR), a simple calculation derived from routine complete blood counts, has emerged as a readily available and cost-effective biomarker with potential applications in various inflammatory and infectious conditions, including sepsis. NLR reflects the balance between neutrophils, the key effector cells of the innate immune system, and lymphocytes, the central players in the adaptive immune response. In sepsis, the innate immune system is rapidly activated to combat the invading pathogens, leading to an increase in neutrophil production and mobilization. Simultaneously, lymphocyte activity may be suppressed due to various factors, including the effects of stress hormones and the redirection of resources towards the innate immune response. This dynamic interplay between neutrophils and lymphocytes results in an elevated NLR, making it a potential indicator of systemic inflammation and infection. Sepsis is characterized by a dysregulated host response to infection, leading to a complex interplay of pro-inflammatory and anti-inflammatory processes. The innate immune system, the body's first

line of defense against infection, is rapidly activated in sepsis, leading to the release of various inflammatory mediators, such as cytokines, chemokines, and reactive oxygen species. Neutrophils, the most abundant type of white blood cells, play a crucial role in the innate immune response. They are recruited to the site of infection, where they phagocytose and kill invading pathogens. In sepsis, the increased demand for neutrophils leads to their accelerated production and release from the bone marrow. This, coupled with the activation and mobilization of existing neutrophils, results in an elevated neutrophil count. On the other hand, lymphocyte activity may be suppressed in sepsis due to several factors. Stress hormones, such as cortisol, can induce lymphocyte apoptosis (programmed cell death). Additionally, the redirection of resources towards the innate immune response may limit the availability of resources for lymphocyte proliferation and activation. The combined effect of increased neutrophils and decreased lymphocytes results in an elevated NLR. This elevation reflects the shift in the immune balance towards the innate arm of the immune system, a hallmark of sepsis. NLR is readily available from routine complete blood counts, which are commonly performed in clinical practice. This makes NLR a highly accessible biomarker, even in resource-limited settings. Additionally, the calculation of NLR is simple and does not require specialized equipment or expertise, making it a cost-effective option for sepsis screening. NLR can be elevated early in the course of sepsis, even before the development of overt clinical signs and symptoms. This early detection can facilitate prompt initiation of appropriate therapy, potentially improving patient outcomes. NLR can be monitored serially to assess the progression of infection and the response to treatment. Decreasing NLR values may indicate a favorable response to therapy, while persistently elevated or increasing values may suggest treatment failure or the development of complications. Studies have shown that NLR can predict mortality and other adverse outcomes in sepsis patients. Higher NLR values are often associated with worse prognosis. NLR can be influenced by various factors other than infection, such as stress, trauma, surgery, and medications. This can lead to false positives, potentially limiting its diagnostic accuracy. NLR values can vary depending on the laboratory methods used and the patient population studied. This can make it challenging to establish universal cut-off values for NLR in sepsis diagnosis. Pre-existing medical conditions, such as diabetes, chronic kidney disease, and autoimmune diseases, can affect NLR values. This can complicate the interpretation of NLR in patients with complex medical histories. In our study, NLR had a lower AUC compared to PCT, indicating lower overall diagnostic accuracy. The AUC for NLR was 0.676, suggesting moderate discriminatory ability. However, NLR remains a valuable tool, particularly in resource-limited settings where PCT testing may not be readily accessible. The NLR cut-off point of 10.375 identified in this study can be used to guide clinical suspicion of sepsis and prompt further investigation or treatment. Our findings are consistent with previous studies that have evaluated the diagnostic performance of NLR in sepsis. NLR has been shown to be a useful marker for sepsis screening, but its accuracy may be lower compared to other biomarkers, such as PCT. Despite its limitations, NLR can be a valuable tool for clinicians in various healthcare settings. In the ED, where rapid assessment and triage are essential, NLR can be used as a quick and inexpensive screening tool for sepsis. Elevated NLR values can raise suspicion of sepsis and prompt further investigation and treatment. In primary care settings, NLR can be used to assess the risk of infection in patients presenting with non-specific symptoms. Elevated NLR values may warrant further evaluation and monitoring. On hospital wards, NLR can be monitored serially to assess the progression of infection and the response to treatment. This information can help clinicians adjust treatment strategies as needed. In post-operative care, NLR can be used to detect early signs of infection, allowing for prompt intervention and potentially reducing the risk of complications. NLR has shown

promise in risk stratification of sepsis patients. Studies have demonstrated that higher NLR values are associated with increased risk of mortality and other adverse outcomes, such as organ failure and the need for intensive care. This information can help clinicians identify patients who may benefit from more aggressive treatment and closer monitoring. NLR has also shown potential as a prognostic marker in sepsis. Studies have demonstrated that NLR can predict mortality and other adverse outcomes, such as organ failure and the need for intensive care. This information can help clinicians make informed decisions about treatment strategies and resource allocation. The utility of NLR extends beyond the general assessment of sepsis. NLR has been associated with adverse outcomes in patients with cardiovascular disease, including acute coronary syndrome and heart failure. Elevated NLR values may indicate increased inflammation and risk of complications. NLR has been shown to be elevated in patients with pneumonia and other respiratory infections. It can be used to assess the severity of illness and predict outcomes. NLR has been investigated as a potential marker of inflammation in inflammatory bowel disease (IBD). Elevated NLR values may correlate with disease activity and predict complications. NLR has been associated with prognosis in various types of cancer. Elevated NLR values may indicate a more aggressive disease course and poorer outcomes. NLR has been linked to adverse outcomes in patients with chronic kidney disease. Elevated NLR values may reflect increased inflammation and risk of cardiovascular events. NLR, while not as specific as PCT, can still provide valuable information for clinical decision-making. Its accessibility and ease of calculation make it a useful tool for clinicians in various healthcare settings. NLR can be used as a quick and inexpensive triage tool to identify patients who may be at higher risk of infection or complications. NLR can be monitored serially to assess the progression of infection or inflammation and the response to treatment. NLR can provide prognostic information, helping clinicians make informed decisions about treatment strategies and resource allocation. As research on NLR continues to evolve, there is growing interest in its potential role in personalized medicine. The ability of NLR to reflect the individual's immune status and predict outcomes may pave the way for tailored treatment strategies based on NLR values.[14-16]

Our study explored the potential influence of gender and age on the susceptibility to sepsis in pneumonia patients. Interestingly, we found no statistically significant association between either gender or age and the presence of sepsis. This observation contrasts with some previous studies that have reported a higher incidence of sepsis in males and older individuals. The reasons for these discrepancies may be multifaceted, potentially stemming from differences in study populations, methodologies, and the complex interplay of factors that contribute to sepsis development. While some studies have suggested a potential link between male gender and increased sepsis risk, our findings did not corroborate this association. Sex hormones, such as estrogen and testosterone, have been implicated in immune responses. Estrogen is generally considered to have immunoprotective effects, while testosterone may be immunosuppressive. However, the exact role of sex hormones in sepsis susceptibility is complex and not fully understood. There may be gender-specific genetic variations that influence the immune response and susceptibility to infections. However, more research is needed to explore this potential link. Lifestyle and behavioral factors, such as smoking and alcohol consumption, may differ between genders and could influence sepsis risk. However, our study did not specifically collect data on these factors. The prevalence of certain comorbidities, such as cardiovascular disease and diabetes, may differ between genders and could influence sepsis risk. However, our study did not specifically analyze the impact of comorbidities on sepsis development. Females have two X chromosomes, one of which is randomly inactivated in each cell. This process, known as X-chromosome inactivation, can lead to mosaicism,

where different cells express different X-linked genes. Some of these genes may be involved in immune responses, and their differential expression could influence sepsis susceptibility. The gut microbiome, the community of microorganisms that reside in the digestive tract, plays a role in immune function. There are known differences in gut microbiome composition between males and females, which could potentially influence sepsis susceptibility. Exposure to environmental toxins and pollutants may differ between genders due to occupational or lifestyle factors, and could potentially influence sepsis risk. The relationship between age and sepsis is complex and influenced by various factors, including immunosenescence, the gradual decline in immune function that occurs with aging. Immunosenescence can lead to impaired innate and adaptive immune responses, making older individuals more susceptible to infections and less able to mount an effective response to sepsis. However, our study did not find a significant association between age and sepsis. The mean age of our study population was 57.72 years, which may not be representative of the broader population. The age range of our participants may not have been wide enough to capture the full spectrum of age-related changes in immune function. Older individuals often have multiple comorbidities that can increase their risk of sepsis. However, our study did not specifically analyze the impact of comorbidities on sepsis development. Frailty, a state of increased vulnerability to stressors, is common in older adults and can increase the risk of sepsis. However, our study did not specifically assess frailty in our participants. Malnutrition is common in older adults and can impair immune function, increasing the risk of sepsis. However, our study did not specifically assess nutritional status in our participants. Older individuals often take multiple medications, some of which can impair immune function and increase sepsis risk. However, our study did not specifically analyze the impact of medications on sepsis development. Social isolation and loneliness are common in older adults and can negatively impact immune function, potentially increasing sepsis risk. However, our study did not specifically assess social factors in our participants. It is important to recognize that gender and age are just two of many factors that can influence sepsis susceptibility. Other factors, such as genetics, comorbidities, lifestyle, and environmental exposures, also play a role. The complex interplay of these factors makes it challenging to isolate the specific contribution of gender and age to sepsis risk. While our study did not find a significant association between gender or age and sepsis, it is important for clinicians to remain vigilant for signs and symptoms of sepsis in all patients, regardless of their gender or age. Early detection and prompt treatment are crucial for improving outcomes in sepsis. Assess each patient's individual risk factors for sepsis, including comorbidities, medications, and functional status. Be alert for subtle signs and symptoms of sepsis, such as changes in mental status, vital signs, and laboratory values. Initiate appropriate treatment promptly, including antibiotics, fluids, and supportive care. Monitor patients closely for response to treatment and reassess their condition regularly.[17,18]

Our study revealed a noteworthy finding regarding the relationship between pneumonia type and the risk of septic shock. Contrary to traditional assumptions, we observed no significant association between the type of pneumonia (community-acquired pneumonia [CAP] vs. hospital-acquired pneumonia [HAP]) and the development of septic shock. This suggests that the risk of progressing to septic shock may be similar in both CAP and HAP patients, underscoring the critical importance of vigilance and early intervention regardless of the pneumonia type. Traditionally, HAP has been considered to carry a higher risk of complications, including sepsis and septic shock, compared to CAP. HAP is often caused by more virulent and resistant pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus* (MRSA). These pathogens are more likely to cause severe infections and are often more challenging to

treat due to antibiotic resistance. HAP typically occurs in patients who are already hospitalized and may have underlying health conditions, such as chronic obstructive pulmonary disease (COPD), diabetes, or immunosuppression. These comorbidities can compromise the immune system and increase susceptibility to severe infections. Hospitalized patients are exposed to a variety of healthcare-associated pathogens, including those that are resistant to multiple antibiotics. This increases the risk of acquiring infections with difficult-to-treat pathogens. Hospitalized patients often undergo invasive procedures, such as intubation and mechanical ventilation, which can increase the risk of pneumonia and other infections. Our findings challenge the traditional paradigm that HAP is inherently associated with a higher risk of septic shock compared to CAP. Advances in the management of CAP, including the development of new antibiotics and improved supportive care, have led to better outcomes and reduced complications. This may have narrowed the gap in the risk of septic shock between CAP and HAP. The increasing prevalence of antibiotic resistance in HAP pathogens has made it more challenging to treat these infections effectively. This may have contributed to a higher risk of complications, including septic shock, in HAP patients. The prevalence of comorbidities, such as COPD, diabetes, and immunosuppression, is increasing in the general population. This may have led to a higher proportion of CAP patients with underlying health conditions that increase their risk of septic shock. Improvements in infection control practices and antibiotic stewardship programs may have contributed to a reduction in the incidence of HAP and its associated complications. Clinicians should maintain a high index of suspicion for septic shock in all pneumonia patients, regardless of the pneumonia type. Early recognition and prompt intervention are crucial for improving outcomes. Clinicians should carefully assess each patient's individual risk factors for septic shock, including comorbidities, pathogen virulence, and antibiotic resistance patterns. This information can help guide treatment decisions and prioritize patients for closer monitoring. Septic shock requires early and aggressive treatment, including antibiotics, fluids, and supportive care. Clinicians should not delay treatment based on the assumption that CAP is less likely to progress to septic shock compared to HAP. Judicious use of antibiotics is essential to minimize the development of antibiotic resistance. Clinicians should follow antibiotic stewardship guidelines and de-escalate antibiotic therapy when appropriate.[19,20]

5. Conclusion

Our study underscores the superior accuracy of procalcitonin (PCT) compared to the neutrophil-lymphocyte ratio (NLR) in predicting sepsis among pneumonia patients. PCT's rapid response to bacterial infections, correlation with infection severity, and high specificity make it an ideal marker for early sepsis detection and monitoring. However, NLR remains a valuable tool, especially in resource-limited settings where PCT testing may be unavailable. Our findings also challenge the traditional assumption that hospital-acquired pneumonia (HAP) carries a higher risk of septic shock than community-acquired pneumonia (CAP). This highlights the need for vigilance and early intervention in all pneumonia patients, regardless of the type. Further research is needed to explore the complex interplay of factors influencing sepsis susceptibility, including gender, age, genetics, comorbidities, and environmental exposures. Our study contributes to a growing body of evidence supporting the use of PCT and NLR as valuable tools for sepsis prediction and management in pneumonia patients. These findings have significant implications for clinical practice, guiding early intervention, optimizing treatment strategies, and improving patient outcomes.

6. References

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