**Original Research**

# THE COMBINATION OF NLCR AND PLR ENHANCES THE SEPSIS-3 STRATEGY

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## ABSTRACT

*According to Sepsis-3, antibiotics should be administered in the first hour of diagnosis of sepsis. Still, there is difficulty in differentiating between bacterial and nonbacterial infections and a lack of a rapid diagnostic tool to distinguish them. This study evaluated the diagnostic value of NLCR and PLR in suspected bacterial sepsis. The diagnostic value of PLR in adult bacterial sepsis patients has never been studied. This study was a retrospective study from the medical record of Dr. Hasan Sadikin Hospital Bandung. All patients at age ≥ 18 years diagnosed with sepsis based on ICD-10 code and qSOFA ≥ 2 were included. We calculated sensitivity, specificity, NPV, PPV, positive LR, and AUC of NLCR and PLR. There were 177 patients included in this study. The sensitivity of NLCR was 69.5%, specificity was 34.7%, NPV was 56.9%, PPV was 47.9%, and LR+ was 1.06, while the sensitivity of PLR was 62.2%, specificity was 38.9%, NPV was 54.4%, PPV was 46.8%, and LR+ was 1.02. We obtained cut-off values for NLCR 11.06, AUC 0.500, PLR 222.41, and AUC 0.497. The low value of AUC NLCR and PLR was due to prior antibiotic use. The combination of NLCR and PLR had higher positive LR (1.16) and specificity (54.7%), and also, according to NLCR, we had the highest sensitivity (69.5%). The combination of NLCR and PLR enhances the sepsis-3 strategy because it can be used as screening tools for bacterial sepsis, and antibiotics can also be administered in the first hour of managing sepsis, particularly in the emergency ward.*

***Keywords:*** *Bacterial sepsis; diagnostic value; infectious disease; NLCR; PLR*

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**Highlights:**

1. The combination of NLCR and PLR will improve the ability to distinguish infection rather than noninfection in the emergency setting for early antibiotic prescribing as well as the sepsis-3 strategy.
2. The diagnostic value of PLR in adult bacterial sepsis patients has never been studied.

## INTRODUCTION

Sepsis is a severe condition of organ dysfunction resulting from dysregulated host response to infection (Singer et al. 2016). Sepsis is one of hospitalized patients' most common causes of mortality (Kumar et al. 2011). The burden of sepsis was around US$ 130 million in 100,000 patients (Purba et al. 2020).

According to Sepsis-3, broad-spectrum antibiotics should be administered in the first hour of diagnosis of sepsis (Lehman 2019). Early broad-spectrum antibacterial agents are recommended to improve survival (Dellinger et al. 2013). However, sepsis management is still challenging, particularly in distinguishing between infection of bacterial and nonbacterial (Ljungström et al. 2017).

Positive microbiological culture is the gold standard in diagnosing sepsis, although it takes time. When a patient has received antibiotics, it can lead to false negatives (Davis 2005). Moreover, bacterial sepsis is rarely proven by culture. Only 30-40% of cases are positive in blood culture (Singer et al. 2016). Therefore, simple and novel diagnostic tools are needed to help distinguish bacterial sepsis.

Recently, the neutrophil-to-lymphocyte count ratio (NLCR) has been identified as a cost-economic, simple, and fast laboratory tool which can contribute to determining bacterial sepsis (Luhulima et al. 2017). A previous retrospective study stated that NLCR was a better parameter in diagnosing bacterial sepsis compared to others, i.e., leukocyte and CRP (C-reactive protein) (de Jager et al. 2010). Meanwhile, PLR had prognostic indicators of cancer and adverse cardiovascular events, also useful systemic inflammatory markers (Shen et al. 2019). PLR also be used in predicting neonatal sepsis (Arcagok & Karabulut 2019, Can et al. 2018). The studies on the diagnostic value of PLR and NLCR are still limited, particularly in adult bacterial sepsis. Therefore, this study evaluated the diagnostic value of NLCR and PLR in suspected bacterial sepsis.

## MATERIALS AND METHODS

### Study design and patients

The study was conducted retrospectively from medical records in a tertiary hospital, Dr. Hasan Sadikin Hospital Bandung, West Java, Indonesia, from 1 January to 31 December 2019. This study was undergone into several steps until extracting the included data. The population of this study was the patient admitted to the hospital and diagnosed with sepsis based on the ICD-10 code. We accessed the hospital information system to achieve the list of sepsis patients according to the ICD-10 (code: A40-A41.9). We screened and included the medical record if it met the criteria as (1) adult patient (age $\geq$ 18 years), (2) quick Sequential Organ Failure Assessment (qSOFA) score $\geq$ 2, (3) performed routine blood examinations, with culture at the time diagnosis sepsis established or at the first admission with diagnosis sepsis. We excluded patients with a clinical history of HIV infection (Human Immunodeficiency Virus), hematologic disease, oncology disease, autoimmune disease, hepatic cirrhosis, invasive fungal infection, and drug-induced thrombocytopenia, and medication history of immunosuppressant.

We hand-searched the included medical record and extracted information for the demographic characteristic (age, sex), type of ward, previous antibiotic use, clinical source of sepsis, complete blood count data, and bacterial culture data. We also accessed the laboratory information system to obtain the complete blood count and bacterial culture if not present in the medical record. Bacterial sepsis was described as: (1) infection of bacteria that is defined by qSOFA $\geq$ 2 according to Sepsis-3 criteria, and (2) proven-positive culture from any suspected source of infection (blood, sputum, pus, urine, and body fluid). In this study, contaminant bacteria such as *Bacillus species* (other than *B. anthracis*), *Corynebacterium species* (other than *C. jeikeium)*, *Propionibacterium acnes*, *Clostridium perfringens*, *Coagulase-negative staphylococci* and *Viridans group streptococc*i in blood culture and sputum did not include as pathogen bacteria (Weinstein 2003).

We also examined the quality of cultured sputum from Gram stain using the Bartlett Scoring (Bartlett et al. 1998). Only epithelial cells reported below 10 per HPF were included in this study. Meanwhile, from complete blood count data, we performed calculations of NLCR and PLR. NLCR was obtained by dividing the number of absolute neutrophil counts (cells/$mm^3$ or uL) with the number of absolute lymphocyte counts (cells/$mm^3$ or uL). A value of NLCR greater than ten was considered a cut-off value for bacterial sepsis (Ljungström et al. 2017). PLR was obtained by dividing the number of platelet counts (cells/$mm^3$ or uL) with the number of absolute lymphocyte counts (cells/$mm^3$ or uL). We used the cut-off value of PLR greater than 200 for bacterial sepsis (Shen et al. 2019).

The study was authorized by the health research ethics committees of Dr. Hasan Sadikin General Hospital, Bandung, West Java No. LB.02.01/X.6.5/306/2020. No individual consent was collected since the data were derived from the hospital- and laboratory information systems.

**Statistical analysis**

Data on age, type of ward, previous antibiotic use, and clinical source of sepsis were summarized as frequencies and percentages. Absolute lymphocyte count, absolute neutrophil count, leukocyte, NLCR, and PLR were summarized as median (interquartile range/IQR). We performed two analyses: (1) determining the optimal cut-off value (COV) of NLCR and PLR based on this study using receiver operating characteristics curves (ROC), (2) accessing the diagnostic performance of multiple combinations between NLCR and PLR using previously reported COV and this study COV, to obtain the sensitivity, specificity, negative predictive value, positive predictive value, and positive likelihood ratio against culture among suspected bacterial sepsis.

## RESULTS

We observed 566 patient records through the hospital-information system with the ICD-10 code of sepsis. This study's suspected bacterial sepsis was 31.3% (177 out of 566 patient records). The positive culture-proven among the suspected bacterial sepsis was 46.3% (82 out of 177 patient records) (Figure 1).

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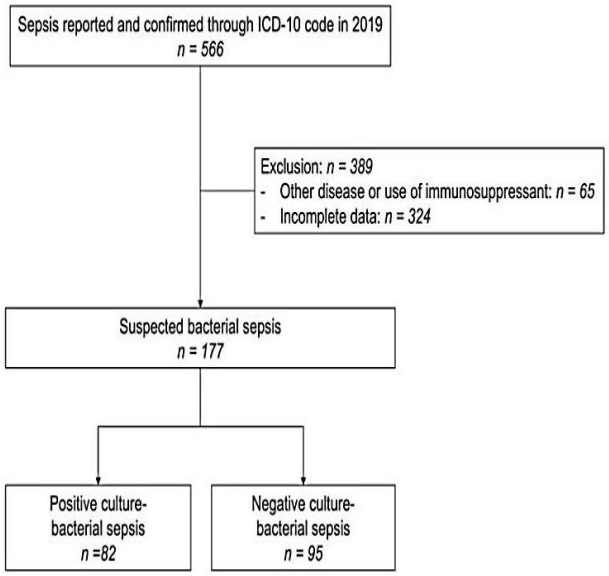


Figure 1. Flowchart of patient selection

The patients' characteristics of suspected bacterial sepsis are shown in Table 1. Admission during diagnosis of sepsis was most commonly from the emergency ward (70.7% vs. 77.9%), previous antibiotic use (34.1% vs. 35.8%), and lung mainly was the focus of infection (52.4% vs. 60%). Skin and soft tissue infection, as the focus of infection, had a chance of having positive-culture results; in contrast to gastrointestinal, which tends to be a negative-culture result in bacterial sepsis ($p<0.05$). The hematology results among positive-culture and negative-culture bacterial sepsis are shown in Table 2. Higher IQR of WBC, PLT, NLCR, and PLR was found in negative-culture bacterial sepsis.

There were 277 specimens collected from the positive-culture bacterial sepsis patients. Among this group, pus and body fluid specimens showed high positivity of culture growth, 85.7% and 55.6%, respectively. Meanwhile, blood as the primary specimen, which commonly indicates the presence of bacteremia, only showed positivity of 21.2%. We observed a discrepancy between clinical suspicion of focus of sepsis with specimens being cultured, i.e., the focus of lung infection observed in 100 patients, but the number of sputum being submitted for culture was 52 specimens (52%). Overall, the positivity of culture among all the specimens was 37.5% (Table 3).

We evaluated and calculated this study's optimal COV of NLCR and PLR. The area under receiver operating characteristics (AUROC) curves of the NLCR against culture-proven bacterial sepsis were 0.500 (0.414-0.585). Meanwhile, the AUROC of the PLR against culture-proven bacterial sepsis was 0.497 (0.412-0.583) (Figure 2). From this analysis, the optimal COV of NLCR and PLR were 11.06 and 222.41, respectively. We calculated the diagnostic performance of NLCR and PLR using different COV against culture-proven bacterial sepsis. The sensitivity of NLCR and PLR using different COV was moderate, ranging between 57.3% and 69.5%. The specificity of NLCR and PLR using different COV was low, ranging between 34.7% and 43.2%. The sensitivity and specificity of NLCR and PLR could be improved by combining two variables with optimal COV, as observed in this study (COV NLCR of 11.06 and PLR of 222.41). Using this combination, this variable's sensitivity and specificity against culture-proven bacterial sepsis were achieved at 52.4% and 54.7%, respectively. This combination also affected the improvement of PPV and LR+ (Table 4).

Table 1. Patient characteristics of suspected bacterial sepsis

| Characteristic | Positive-culture bacterial sepsis (n=82) | | Negative-culture bacterial sepsis (n=95) | | Total (n=177) | | p-value* |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Age (years) | | | | | | | 0.066 |
| 20 - 30 | 10 | 12.2 | 9 | 9.5 | 19 | 10.7 | |
| 31 - 40 | 8 | 9.8 | 7 | 7.4 | 15 | 8.5 | |
| 41 - 50 | 12 | 14.6 | 9 | 9.5 | 21 | 11.9 | |
| 51 - 60 | 20 | 24.4 | 36 | 37.9 | 56 | 31.6 | |
| 61 - 70 | 21 | 25.6 | 12 | 12.6 | 33 | 18.6 | |
| > 70 | 11 | 13.4 | 22 | 23.1 | 33 | 18.6 | |
| Gender | | | | | | | 0.563 |
| Female | 45 | 54.9 | 48 | 50.5 | 93 | 52.5 | |
| Male | 37 | 45.1 | 47 | 49.5 | 84 | 47.5 | |
| Admission during the diagnosis of sepsis | | | | | | | 0.220 |
| Non-intensive ward | 10 | 12.2 | 13 | 13.7 | 23 | 13 | |
| Intensive care unit | 14 | 17.1 | 8 | 8.4 | 22 | 12.4 | |
| Emergency unit | 58 | 70.7 | 74 | 77.9 | 132 | 74.6 | |
| Previous antibiotic used[$] | | | | | | | 0.836 |
| Yes | 28 | 34.1 | 34 | 35.8 | 62 | 35 | |
| No | 24 | 29.3 | 24 | 25.3 | 48 | 27.1 | |
| Unknown | 30 | 36.6 | 37 | 38.9 | 67 | 37.9 | |
| The focus of infection[#] | | | | | | | |
| Lung | 43 | 52.4 | 57 | 60.0 | 100 | 56.5 | 0.312 |
| Gastrointestinal | 8 | 9.8 | 22 | 23.2 | 30 | 16.9 | 0.018 |
| Genitourinary | 8 | 9.8 | 5 | 5.3 | 13 | 7.3 | 0.253 |
| Skin and soft tissue | 26 | 31.7 | 13 | 13.7 | 39 | 22.0 | 0.004 |
| Others | 7 | 8.5 | 1 | 1.1 | 8 | 4.5 | 0.025 |

([$]), The antibiotic treatment is being given before the diagnosis of sepsis;
([#]), multiple foci of infection per patient possible; (*), significant p<0.05

Table 2. Hematology results among suspected bacterial sepsis

| Hematology | Positive-culture bacterial sepsis (n=82) | | Negative-culture bacterial sepsis (n=95) | | p-value* |
|---|---|---|---|---|---|
| | IQR | Range | IQR | Range | |
| WBC (cells/uL) | 10852.50 | 1100-51950 | 11400 | 1050-48740 | 0.921 |
| ANC (cells/uL) | 10880.33 | 754.80-44157.5 | 10001.90 | 955.5-39605.5 | 0.962 |
| ALC (cells/uL) | 1014.28 | 194.8-3146.5 | 1003.90 | 42-5977.5 | 0.634 |
| PLT (cells/uL) | 193250 | 30000-588000 | 212000 | 24000-671000 | 0.817 |
| NLCR | 13.93 | 1.97-96 | 24.08 | 1.58-98 | 0.992 |
| PLR | 293.6 | 31.89-1923.21 | 495.43 | 33.41-1619.05 | 0.951 |

abbrev: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; IQR, inter-quartile range; NLCR, neutrophil-to-lymphocyte count ratio; PLT, platelet count; PLR, platelet-to-lymphocyte ratio; WBC, white blood cell count

Table 3. The positivity of culture among bacterial sepsis patients

| Type of specimen | Number of specimens being cultured | Positivity of culture | |
|---|---|---|---|
| | | n | % |
| Blood | 156 | 33 | (21.2) |
| Urine | 25 | 11 | (44) |
| Sputum | 52 | 25 | (48.1) |
| Pus | 35 | 30 | (85.7) |
| Body fluid* | 9 | 5 | (55.6) |
| Total | 277 | 104 | 37.5 |

(*), Body fluid was from pleural fluid, double lumen catheter, bullae, and cerebrospinal liquid

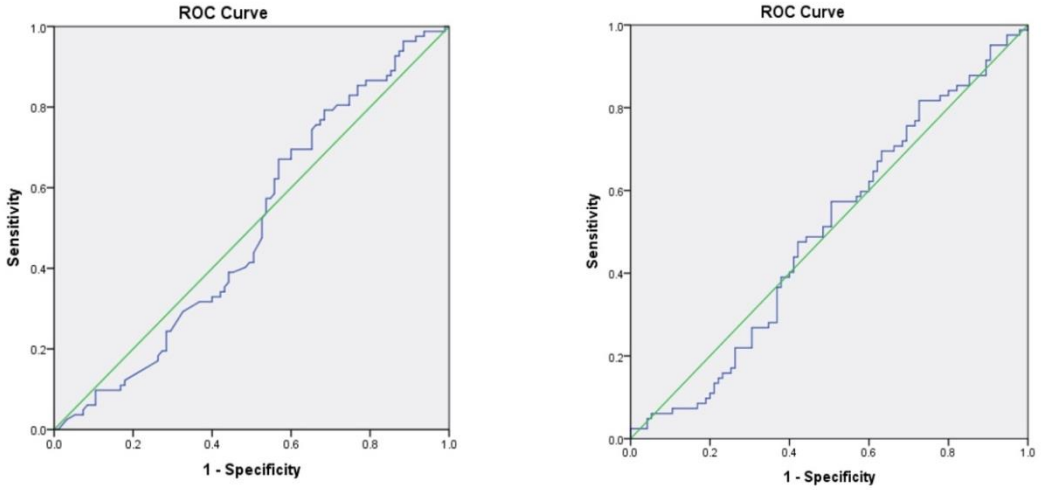


Figure 2. ROC curves of NLCR (A) and PLR (B)

Table 4. Diagnostic value of NLCR, PLR, Combination NLCR, and PLR

| | Sensitivity % | Specificity % | PPV % | NPV % | LR+ |
|---|---|---|---|---|---|
| NLCR > 10 | 69.5% | 34.7% | 47.9% | 56.9% | 1.06 |
| NLCR > 11.06 | 67.1% | 40% | 49.1% | 58.5% | 1.12 |
| PLR > 200 | 62.2% | 38.9% | 46.8% | 54.4% | 1.02 |
| PLR > 222.41 | 57.3% | 43.2% | 46.5% | 53.9% | 1.01 |
| NLCR > 10 and PLR > 200 | 52.4% | 50.5% | 47.8% | 55.2% | 1.06 |
| NLCR > 11.06 and PLR > 222.41 | 52.4% | 54.7% | 50% | 57.1% | 1.16 |

Abbrev: NLCR, neutrophil-to-lymphocyte count ratio; NPV, negative predictive value; LR+, likelihood ratio positive; PLR, platelet-to-lymphocyte ratio; PPV, positive predictive value

## DISCUSSION

Sepsis is a severe condition of organ dysfunction resulting from dysregulated host response to infection. According to Sepsis-3, broad-spectrum antibiotics should be administered in the first hour of diagnosis of sepsis (Singer et al. 2016). Early identification and management of sepsis are essential in lowering mortality (Visveswari et al. 2019). As a result, biomarkers have been developed for rapid laboratory diagnosis of sepsis (Zhang et al. 2016). NLCR and PLR are simple, fast, and cheap tools to help diagnose bacterial sepsis (Luhulima et al. 2017).

Neutrophilia and lymphopenia were both associated with bacteremia. Response of immune to infection is an increase in neutrophil count resulting from rapid movement of neutrophils from the marginated pool within the bone marrow and reduced apoptosis of neutrophils (Westerdijk et al. 2019). The lymphocyte count is also decreased by increased apoptosis of lymphocytes and migration of activated lymphocytes to inflammatory tissues (Westerdijk et al. 2019). Lymphocytes and platelet also play critical roles in the inflammatory process (Shen et al. 2019). Inflammation causes accelerated proliferation of megakaryocytes and thrombocytosis. Also, decreased lymphocytes and increased platelet were connected to aggregation and inflammation (Arcagok & Karabulut 2019). PLR also had prognostic indicators in various diseases, such as myocardial infarction, hepatocellular carcinoma, non-small cell lung cancer, and acute kidney injury (Shen et al. 2019).

We performed a diagnostic evaluation for NLCR and PLR as additional modalities for diagnosing bacterial sepsis. NLCR and PLR were found above 10 and 200 in both positive and negative culture bacterial sepsis. Previous studies have shown various sensitivity, specificity, NPV, and PPV for both NLCR and PLR. However, this study has used a similar cut of value (COV) for NLCR and PLR (Arcagok & Karabulut 2019, Ljungström et al. 2017, Luhulima et al. 2017, Mandal & Valenzuela 2018, Marik & Stephenson 2020, Zhang et al. 2016). For example, we used the COV NLCR of 10, which resulted in a sensitivity of 69.5%, and specificity of 34.7%, compared with a previous study using similar COV resulted in a

sensitivity of 64.7% and specificity of 60.8% (Ljungström et al. 2017). Other studies about the diagnostic value of PLR in adult patients were rare. PLR has been studied in neonatal sepsis. PLR value in neonates with definite early-onset sepsis had high sensitivity (91.3%) and specificity (97.6%) (Arcagok & Karabulut 2019).

The difference in diagnostic value is influenced by: (1) disease definition; (2) time of performing the gold standard test, e.g., culture; and (3) previous history of antibiotic. Different guidelines for determined Sepsis, i.e., Sepsis-2 and Sepsis-3, have resulted in different performance characteristics, as described previously. However, we consider the time of performing the gold standard and the history of antibiotics essential in this diagnostic testing. In this study, we found that antibiotic usage occurred in 35% of all subjects included, which was similar to that of previous research, which stated that 32.8% of the patients who had received prior antibiotic therapy were given antibiotics in the first hour of arrival (Abe et al. 2019). As our hospital is a tertiary hospital, we received a referral from primary and secondary care whose patients had already been given prior antibiotics.

A previous study revealed that among patients with sepsis who did not receive antibiotics, the positivity of blood culture was 50.6% and in those who were already receiving antibiotics was only 27.7%. Antibiotic therapy while obtaining blood cultures is associated with losing pathogens (Scheer et al. 2019). In this study, the positivity of the whole culture was 37.5%, and the blood culture was 21.2%. The time of performing culture was also crucial, as we found many patients whose culture was not tested, primarily in patients with lung infection (52 sputum cultures from 100 patients), but we did not explore the reason. Other potential factors may contribute: (1) inadequate sample collection, (2) patients with the chronic obstructive pulmonary disease often have squamous metaplasia of bronchial cells, (3) unidentified an-aerobic and atypical bacteria such as *Chlamydia pneumoniae, Legionella* species, and *Mycoplasma pneumoniae* (Madison & Irwin 2004).

Our study has two limitations. First, we have limited access to information about patients (the name and period of antibiotic used). Second, inadequate culture specimen and unidentified an-aerobic and atypical bacteria examination.

Despite the low-performance characteristics, we observed the additional value of the combination between NLCR and PLR in bacterial sepsis. Based on this study, most patients have been diagnosed with sepsis in the emergency ward (74.6% of all subjects), meaning sepsis treatment should be initiated in the emergency department (Hall et al. 2011).

**Strength and limitation**

The study provides important information on the diagnostic value of NLCR and PLR in suspected bacterial sepsis, which can aid in the early diagnosis and treatment of sepsis.The combination of NLCR and PLR had higher positive LR and specificity, which may improve the accuracy of diagnosis.The study was conducted in a single hospital, which may limit the generalizability of the results to other settings.

## CONCLUSION

The combination of NLCR and PLR had higher positive LR and specificity and, according to NLCR, had the highest sensitivity. Therefore, it enhances the sepsis-3 strategy and can be implemented in emergency wards as a direct screening of suspected bacterial sepsis. This also becomes an essential tool as consideration for clinicians when providing empiric antibiotics in the first hour of managing sepsis, as well as the role of clinical pathway and antimicrobial stewardship program in the hospital.

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**Conflict of interest**

None.

**Funding disclosure**

None.

**Author contribution**

EHP, ENA, US and AKS conceptualized, wrote, and revised the manuscript. YH reviewed, finalized the manuscript and managed the administration.

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