

## Are There Standardized Cutoff Values for Neutrophil-Lymphocyte Ratios in Bacteremia or Sepsis?

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Bacteremia and sepsis are common causes of morbidity and mortality worldwide, with incorrect or delayed diagnoses being associated with increased mortality. New tests or markers that allow a more rapid and less costly detection of bacteremia and sepsis have been investigated. The aim of this study was to clarify the cutoff value of the neutrophil-lymphocyte ratio (NLR) according to procalcitonin (PCT) level in the decision-making processes for bacteremia and sepsis. In addition, other white blood cell subgroup parameters, which are assessed in all hospitals, for bacteremia and sepsis were explored. This retrospective study included 1,468 patients with suspected bacteremia and sepsis. Patients were grouped according to the following PCT criteria: levels <0.05 ng/ml (healthy group), 0.05–0.5 ng/ml (local infection group), 0.5–2 ng/ml (systemic infection group), 2–10 ng/ml (sepsis group), and >10 ng/ml (sepsis shock group). One important finding of this study, which will serve as a baseline to measure future progress, is the presence of many gaps in the information on pathogens that constitute a major health risk. In addition, clinical decisions are generally not coordinated, compromising the ability to assess and monitor a situation. This report represents the first study to determine the limits of the use of NLR in the diagnosis of infection or sepsis using a cutoff value of <5 when sufficient exclusion criteria are used.

**Keywords:** Procalcitonin (PCT), neutrophil-lymphocyte ratio (NLR), bacteremia, sepsis

### Introduction

Bacteremia and sepsis are common causes of morbidity and mortality worldwide, with incorrect or delayed diagnoses being associated with increased mortality. Most cases of bacteremia and sepsis are caused by bacterial or fungal infections, with positive culture and drug sensitivity testing considered the gold standard [9]. Recently, new tests or markers that allow more rapid and less costly detection of bacteremia and sepsis have been investigated. Several studies have shown that procalcitonin (PCT, the precursor of calcitonin), C-reactive protein (CRP), and mean platelet volume (MPV) could be useful predictors [7, 8].

The total leukocyte and neutrophil counts have historically been used as markers of infection. An association was found between infection, and monocyte and lymphocyte counts, as well as specific associations between these two

counts [3, 20]. In 1922, Simon [17] coined the term “septic factor” to describe the association between neutrophilia, and considered this factor useful for the diagnosis of pyogenic infection. The neutrophil-lymphocyte ratio (NLR) is a simple biomarker of inflammation. Several studies have reported that an elevated NLR (in the peripheral blood) is associated with a poor prognosis [2, 5, 6, 10, 11, 15, 19, 22]. However, the ideal cutoff is controversial, with studies citing NLR values of 3 and 5 as appropriate [21]. However, to date, no NLR cutoff value for bacteremia and sepsis has been established.

The aim of this study was to clarify the cutoff value of NLR according to PCT level in the decision-making processes for bacteremia and sepsis. In addition, other white blood cell (WBC) subgroup parameters, which are assessed in all hospitals, for bacteremia and sepsis were explored.

## Materials and Methods

This was a laboratory-based study without participant involvement or observation. All data, including specimen sources and patient information, were carefully analyzed and recorded from laboratory request forms. This retrospective study included 1,468 patients with suspected bacteremia and sepsis. Inclusion criteria included undergoing concurrent PCT, CRP, and hemograms. The exclusion criteria were neutropenia, thrombocytopenia, leucopenia, hematological malignancy, trauma, metabolic disease, chronic and/or intracellular bacterial (brucellosis, salmonellosis, and tuberculosis) infections, granulomatous chronic diseases, pregnancy or post-partum period (6 months), and chronic renal failure. Patients were grouped according to the following criteria: PCT levels <0.05 ng/ml (healthy group (HG)), PCT levels of 0.05–0.5 ng/ml (local infection group (LIG)), PCT levels of 0.5–2 ng/ml (systemic infection (SIG)), PCT levels of 2–10 ng/ml (sepsis group (SG)), and PCT levels >10 ng/ml (sepsis shock group (SSG)).

Blood samples were collected in a hematologic sample tube containing anticoagulant, and the following hematology parameters were investigated using the Cell-Dyn 3700 SL hematology analyzer (Abbott Laboratories, North Chicago, IL, USA): WBCs, neutrophils (NEU), and lymphocytes (LYM). The NEU:LYM ratio (NLR) was calculated using NEU/LYM.

Venous blood was withdrawn for each patient without using anticoagulants. After clotting, each sample was immediately analyzed in terms of CRP and PRC levels. CRP levels were measured using a nephelometric method with an IMAGE 800 analyzer (Beckman Coulter Inc., Brea, CA, USA). PRC was measured using the mini VIDAS immunoanalyzer (bioMérieux, Marcy L'Etoile, Craponne, France). The cutoff concentration measured by the assay was 8 µg/ml (95th percentile) for CRP. These values were considered the cutoffs for healthy individuals on the basis of the manufacturer's instructions.

SPSS Statistics Base 17.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. The mean values of measured variables were compared using the "test for the significance of a difference between two means." For the diagnostic evaluation of the biological markers, the sensitivity and specificity of each cutoff point for each marker was recorded. Reference intervals were calculated according to the percentile method (CLSI C28-A3). Comparisons of the diagnostic accuracy of these markers were conducted using receiver operator characteristic (ROC) curve analyses by calculating

the area under the curve (AUC). *P*-values <0.05 were considered to indicate statistical significance.

## Results

In this study, all patients with a PCT result were evaluated according to the exclusion criteria, after which 701 (47.8%) patients aged 18 years or older were selected. According to statistical analysis, sociodemographic (age average, gender, male-female rates, *etc.*) variables have no significant effect on NLR. PCT, CRP, WBC, NEU, LYM, and NLR values as means ± standard deviation [interquartile range] (variance) were calculated as follows: 7.7 ± 24.5 [3.3] ( $\sigma = 598.1$ ), 85.1 ± 97.6 [107.2] ( $\sigma = 9439.1$ ), 11.5 ± 7.3 [6.4] ( $\sigma = 53.7$ ), 8.7 ± 6.9 [5.4] ( $\sigma = 47.2$ ), 1.8 ± 1.5 [1.4] ( $\sigma = 2.1$ ), and 8.1 ± 9.8 [7.2] ( $\sigma = 98.9$ ), respectively.

The correlation levels between PCT and CRP, WBC, and NLR were 0.2245, 0.2332, and 0.2582, respectively ( $p < 0.001$ ). The concordance correlation coefficients between PCT and CRP, WBC, and NLR were 0.0453, 0.1666, and 0.1982, respectively. PCT was considered as a reference control and the CRP, WBC, and NLR bias correction factors (accuracy) were 0.2021, 0.6451, and 0.8512, respectively. Of all the evaluated parameters, NLR showed a strong, statistically significant correlation, a high concordance correlation coefficient, and the highest accuracy.

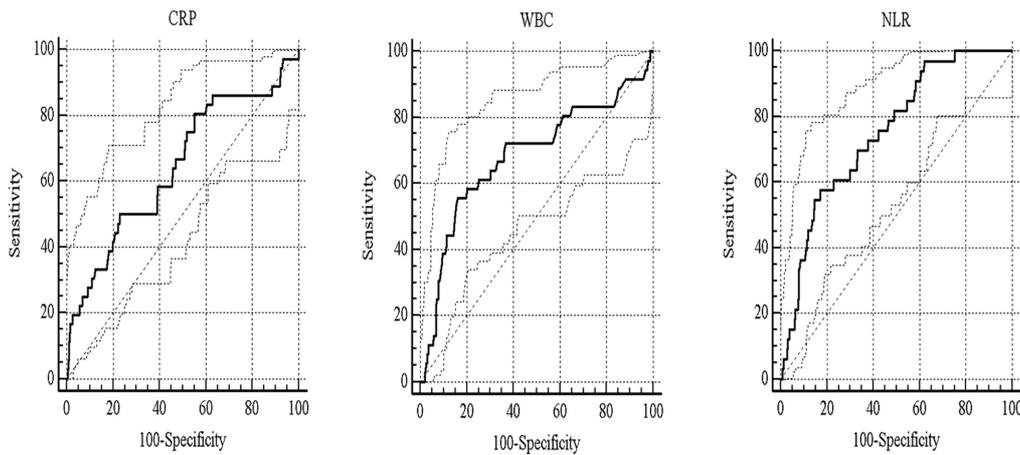
The CRP, WBC, and NLR sensitivity and specificity values were similar after ROC analysis using PCT as a reference. However, NLR had the highest values in terms of sensitivity, specificity, and statistical significance (Table 1). The ROC curves for CRP, WBC, and NLR are shown in Fig. 1.

The PCT, CRP, WBC, and NLR values differed significantly among the determined groups. All evaluated parameters are shown according to infection status. The NLR cutoff values for the HG, LIG, SIG, SG, and SSG groups could be considered to be <5, ≥5–<10, ≥10–<13, ≥13–<15, and ≥15, respectively. However, it was not possible to distinguish between HG and the other groups in terms of the CRP and WBC values because these were higher than the normal range (Table 2).

**Table 1.** ROC analysis results for CRP, WBC, and NLR.

|     | Sensitivity | Specificity | AUC   | 95% CI      | <i>p</i> -value |
|-----|-------------|-------------|-------|-------------|-----------------|
| CRP | 50.1        | 76.8        | 0.643 | 0.600-0.685 | 0.0065          |
| WBC | 55.4        | 81.3        | 0.682 | 0.642-0.721 | 0.0008          |
| NLR | 57.8        | 83.9        | 0.751 | 0.713-0.786 | 0.0001          |

AUC, Area under the ROC curve; CI, Confidence interval (binominal exact).



**Fig. 1.** ROC curves for CRP, WBC, and NLR.

**Discussion**

An increase in WBC is typically associated with infection, and leucopenia can occur during severe infections. However, several studies found that WBC had low diagnostic performance for infection [16, 12]. PCT was a better marker of infection [13], and its accuracy for diagnosing bacterial infections and sepsis increased proportionally with the serum PCT level. Manufacturers use various PCT cutoff values to indicate different health statuses. Based on the manufacturer’s recommendations, levels <0.05 ng/ml indicate a healthy subject, levels between 0.05 and 0.5 ng/ml indicate local infections, levels between 0.5 and 2 ng/ml indicate systemic infections, levels between 2 and 10 ng/ml indicate sepsis, and levels >10 ng/ml indicate septic shock. However, the use of PCT is limited, as it is unable to distinguish sepsis from other inflammatory conditions.

Hemocytometers are available in most hospitals and produce important laboratory data. However, data on WBC subgroups alone are not sufficient as they can indicate only bacterial or viral infection. Leukocytosis, predominantly NEU, has been described, but NEU, LYM, and NLR cutoff

values are not adequately discussed in the literature in terms of bacteremia and sepsis. Most predictive values discussed in the literature concerned other clinical issues, such as mortality, morbidity, and complications related to the results. Xiao *et al.* [21] reported that an NLR of  $\geq 3$ –5 ng/ml could be a useful predictor of the prognosis of patients with hepatocellular carcinoma after liver transplantation. In the present study, we argued for NLR cutoff values to be set according to PCT, and aimed to clarify the relationships between NEU, LYM, and NLR levels and sepsis.

The rapid or specific detection of infection at an early stage remains a challenge in medicine. This study showed that measurement of NEU and LYM levels and calculation of NLR values in critically ill patients were important. Indeed, accurate NLR cutoff values could be used to guide the appropriate use of antibiotics. We believe that an NLR value  $\geq 5$  may be a more convenient marker than CRP, due to its improved ability to detect bacterial infections at lower cost. Our results confirmed a correlation between the mean PCT level and NLR in patients with suspected infection in all study groups.

This observation was possibly due to the presence of

**Table 2.** Distribution of PCT, CRP, WBC, and NLR values in the HG, LIG, SIG, SG, and SSG groups.

| Group                        | n (%)       | PCT <sup>a</sup> | CRP <sup>b</sup> | WBC <sup>c</sup> | NLR           | NLR cutoff <sup>d</sup> |
|------------------------------|-------------|------------------|------------------|------------------|---------------|-------------------------|
| HG                           | 203 (28.88) | 0.04 ± 0.01      | 29.34 ± 41.98    | 9,117 ± 2,832    | 4.19 ± 4.36   | <5                      |
| LIG                          | 242 (34.59) | 0.15 ± 0.07      | 70.19 ± 66.94    | 10,543 ± 4,976   | 5.68 ± 8.99   | $\geq 5$ –<10           |
| SIG                          | 113 (16.13) | 1.08 ± 0.44      | 121.25 ± 102.09  | 13,914 ± 10,724  | 11.78 ± 14.04 | $\geq 10$ –<13          |
| SG                           | 81 (11.56)  | 4.64 ± 2.13      | 137.97 ± 114.09  | 13,048 ± 7,768   | 13.16 ± 6.38  | $\geq 13$ –<15          |
| SSG                          | 62 (8.84)   | 34.34 ± 31.89    | 161.13 ± 145.65  | 16,014 ± 11,686  | 16.87 ± 9.55  | $\geq 15$               |
| <i>p</i> -value <sup>e</sup> |             | <0.001           | <0.001           | <0.05            | <0.001        |                         |

<sup>a</sup>ng/ml; <sup>b</sup>mg/l; <sup>c</sup>Count in mm<sup>3</sup>; <sup>d</sup>Recommended cutoff values; <sup>e</sup>One-way ANOVA.

local infections, which were more readily detected by NLR than NEU, LYM, or CRP. However, there are disadvantages for using NLR in the diagnosis of sepsis. For example, elevated NLR levels are associated with trauma, surgery, pancreatitis, and rheumatic disorders [1, 4, 14, 18]. Therefore, the specificity of NLR for an infection could be low or high. In the present study, detection of NLR was associated with a moderate sensitivity (57.8%) and high specificity (83.9%) for diagnosing sepsis in critically ill patients.

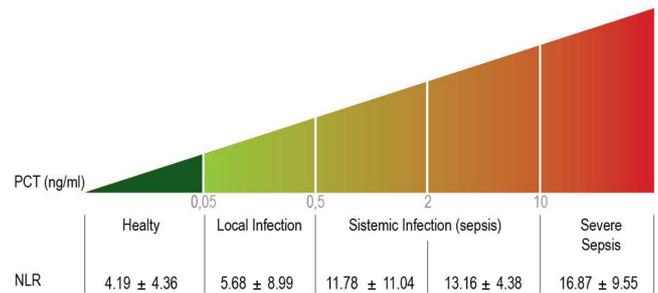
The patients in this cohort with low NLR values (*i.e.*, <5) were not diagnosed with infection. However, when the test was applied to all ICU patients, the prevalence of sepsis on the NLR should be considered. Moreover, when elevated NLR levels return to normal or decrease below normal in patients with sepsis, this can indicate either the disappearance of sepsis or an improvement in the patient's condition. However, a prospective study is needed to confirm these recommendations.

Our findings from an appropriate patient sampling set indicate that NLR and PCT results may help to define bacteremia and/or sepsis. However, PCT is not applicable in all hospitals, because some lack the necessary equipment and its cost-effectiveness is questionable. Therefore, NLR could be considered a novel marker of bacteremia and/or sepsis. However, physicians involved in the treatment and decision-making processes should exercise caution when applying exclusion criteria (Fig. 2).

If reliable laboratory data are not collected, the correct clinical course cannot be determined. However, if reliable laboratory data and information regarding indications are available, but no effort is made to clarify the data, then this could result in misleading of health professionals. Therefore, the mottos, "Think globally, act regularly" and "Act regularly, practice fundamentally," should be followed by health professionals in their efforts to keep infection under control. Continuous monitoring of laboratory data, and education of health professionals and the general public are necessary for selection of the correct therapy, with the aim of reducing the incidence of infection.

This study had several limitations. Patient records, and data on previous antibiotic use, previous interventions, or biochemical analyses (leukocytes on urinalyses) were not available. The data provided included only the results of routine microbiology assessments.

In conclusion, determining the scale of the problem is essential for the monitoring of, and formulating effective responses to, bacteremia and sepsis by healthcare institutions. One important finding of this study, which will serve as a baseline to measure future progress, is the presence of



**Fig. 2.** Vidas B·R·A·H·M·S PCT cutoff and NLR values according to infection status.

many gaps in the information on pathogens that constitute a major health risk. In addition, clinical decisions are generally not coordinated, compromising the ability to assess and monitor a situation. This report represents the first study to determine the limits of the use of NLR in the diagnosis of infection or sepsis using a cutoff value of <5 when sufficient exclusion criteria are used.

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