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Association of White Blood Cell Count, Neutrophil-to-Lymphocyte Ratio, and Procalcitonin with Severe Community-Acquired Pneumonia: Experience form a Tertiary Care Hospital

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ABSTRACT

Background: Community-acquired pneumonia (CAP) remains a leading cause of hospitalization and mortality worldwide. Early recognition of severe cases is essential for timely intervention, yet traditional severity scores have limitations. Readily available biomarkers such as white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and procalcitonin (PCT) may aid in improving severity assessment.

Objective: To determine the relationship between white blood cell (WBC), neutrophil-to-lymphocyte ratio (NLR), procalcitonin (PCT), and severe Community Acquired Pneumonia.

Methodology: This cross-sectional study was conducted at a tertiary care hospital and included 260 adult patients diagnosed with CAP based on clinical features and chest radiographic findings. Patients with hospital-acquired pneumonia, immunosuppression, hematologic disorders, or incomplete records were excluded. Severity of CAP was categorized as severe or non-severe according to ATS/IDSA criteria. Statistical analysis was performed using SPSS version 26.0. Group comparisons were made using chi-square, t-test, or Mann-Whitney U test. Logistic regression was used to identify independent predictors, and ROC curve analysis evaluated the discriminative power of biomarkers.

Results: The mean WBC count (14.2 ± 4.7 vs. $9.6 \pm 3.5 \times 10^9 /L$), NLR (10.8 ± 5.2 vs. 5.7 ± 3.1), and PCT (3.2 ± 1.8 vs. 0.9 ± 0.6 ng/mL) were significantly higher in severe CAP compared to non-severe cases ($p < 0.001$ for all). ROC analysis showed PCT had the highest predictive ability (AUC 0.86), followed by NLR (AUC 0.81) and WBC (AUC 0.69).

Conclusion: Elevated WBC, NLR, and PCT levels are strongly associated with severe CAP, with PCT demonstrating the best predictive performance. These biomarkers can complement clinical scores for early risk stratification.

Keywords: Community-Acquired Pneumonia; White Blood Cell Count; Procalcitonin; Severity; Biomarkers

Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of hospitalization and death in the world, despite advances in vaccination, antimicrobials, and supportive care.¹ Adults with CAP present on a spectrum of severity. Unfortunately, a significant minority deteriorate rapidly to hypoxemic respiratory failure, septic shock, and other complications that require higher-acuity monitoring.¹⁻³ Therefore, accurate early risk stratification is central to clinical decision-making—whether there is a need for higher-acuity monitoring, the intensity and extent of diagnostic evaluations, and if it is time to escalate to action.^{2,3} Existing clinical scores including the Pneumonia Severity Index (PSI) and CURB-65 are widely used to estimate short-term mortality risk, however they are often impractical in the clinical environment and they do not easily integrate dynamic host-response biology.² Therefore, there is ongoing interest in simple lab biomarkers that are rapidly available at presentation, that may provide additional support to clinical scores and refine initial severity assessment.

While the absolute WBC count is often evaluated as a processed laboratory parameter to validate evidence of systemic inflammation in association with community-acquired pneumonia (CAP), a recent systematic review noted that leukocytosis or leukopenia (of arbitrary duration) as defined operationally have limited use as diagnostic specificity and only moderate prognostic validity than other inflammatory markers.⁴ In comparison, the neutrophil-lymphocyte ratio (NLR)—derived from the differential count—has become a fairly inexpensive, reproducible and simple index of innate-adaptive immune balance from acute pathology. Systematic reviews and meta-analyses now provide evidence that higher NLR values represent severe disease and are associated with mortality in adults receiving hospital care for CAP with a good discriminatory performance value—at least as good as or even better than traditional markers (e.g. WBC) individually or as good as sometimes clinical risk scores.⁵ Longitudinal studies suggest that longitudinal changes in NLR across the admission represent clinically relevant trajectories; for instance, failure of NLR to drop over the first 48–72 hours tracks with treatment failure and adverse outcomes.⁶ An important NLR advantage is it requires no further tests besides a full blood count—an appealing aspect in low-resource settings or when rapid triage is important.

Procalcitonin (PCT), which is released in response to the action of bacterial exotoxins and other proinflammatory cytokines, has been researched in lower respiratory tract infections—inclusive of CAP—for both diagnostic and prognostic purposes.^{4,7} Randomized and individual patient meta-analytic data support that PCT-guided algorithms can reduce antibiotic exposure in acute respiratory infections safely, without the risk of added

mortality, and supports antibiotic stewardship guidelines if utilized.⁷ In addition to stewardship, PCT is related to the severity of illness: in a large multicenter cohort of adults hospitalized with CAP, admission PCT concentrations at baseline were strongly correlated with the need for invasive respiratory or vasopressor support within 72 hours, in addition to providing incremental prognostic value on top of established severity indices.⁸ Adjunctive cohort and review data also confirm that persistently elevated PCT, or persistently high PCT, tracks complications such as bacteremia and correlates with poor outcome.^{4,9} Overall, the data presented justify the position of PCT as a biologically reasonable and clinically accessible adjunct to early severity assessment in CAP.

Guideline bodies now recognize biomarkers as adjuncts or adjunct tools—not sole determinants of site-of-care or antibiotic choice. The 2019 American Thoracic Society/ Infectious Diseases Society of America (ATS/IDSA) guideline for the initial management of patients with Community-Acquired Pneumonia (CAP) emphasizes in its recommendations and evidence that validated clinical risk scores should guide decision making, but that biomarkers like PCT may be useful in answering more specific questions (i.e., likelihood of bacterial etiology), when used in context.² Most recently, international guidance focused on severe CAP (sCAP)—severe CAP is described in the guidelines as CAP patients at high risk for respiratory failure or shock—emphasizes the need to rapidly identify sCAP patients and describes how combinations of clinical criteria with laboratory markers or criteria might provide greater opportunity for early recognition of sCAP.³ Simultaneously CAP reviews over the last few years, have re-iterated that while WBC is ubiquitous, composite inflammatory indices including NLR, and infection-specific molecules such as PCT, will likely provide a more granular understanding of host response and impending decompensation.^{1,4-6,8,9}

Although interest is increasing, there remains important pragmatic uncertainty for frontline care. There are limited head-to-head data assessing the relative performance of WBC, NLR and PCT, measured at presentation, to identify severe CAP, across a range of hospitals. Cut-points suggested for NLR and PCT, vary between studies, and the incremental value of these tests, beyond standard clinical assessment (and to each other) are not consistent.⁵⁻⁸ In addition, implementation in 'real world' settings requires consideration of practical issues, including feasibility and urgency: WBC and NLR, are available straight away from a complete blood count, whereas PCT, and the time to result, may vary by institution.⁴ Understanding how these three commonly available markers relate to severe disease at admission would help clinicians prioritize escalation paths—particularly in busy emergency departments and consolidated care hospitals when immediate triage is important. Based on the above considerations, we aimed to evaluate the relationship between admission WBC count, NLR,

and PCT and severe CAP within a single tertiary-care cohort. Our goal was to evaluate the relationship of these biomarker measures—individually and comparatively—with severe CAP at presentation. This study aims to evaluate all three markers within the same cohort and clinical context and provide real-world evidence of which tests are best for facilitating early risk stratification as a complement to existing clinical evaluation.

Methodology

This was an observational, hospital-based, cross-sectional study conducted at the Department of Medicine, Khyber Teaching Hospital (a tertiary care referral center), Peshawar, Pakistan. The study period was from January 2022 to December 2023. The hospital serves a large patient population with inpatient and intensive care facilities for patients with respiratory illnesses, both urban and rural.

A total of 260 adult patients admitted with clinical and radiological diagnosis of Community Acquired Pneumonia (CAP) were included in the study. CAP was defined according to the American Thoracic Society/ Infectious Diseases Society of America (ATS/IDSA) guidelines as new radiographic pulmonary infiltrate with one or more compatible clinical symptom (fever, cough, sputum production, dyspnea, or pleuritic chest pain) in an individual not hospitalized 14 days prior to the admission. The study involved participants who were adult patients aged 18 years or older, who had a definitive diagnosis of community-acquired pneumonia (CAP) which was established using clinical findings with corresponding radiographic findings. The sample was limited to participants with the full formal laboratory work-up that included complete blood count (CBC) with differential and procalcitonin (PCT) levels. The sample will be excluded if a patient had video-assisted or mechanical ventilation pneumonia. If a patient had known immunocompromised conditions like HIV/AIDS, malignancy with chemotherapy, or long-term use of glucocorticoids they were also excluded. Likewise, exclusion was made for acute diseases affecting the hematologic system (known hematologic malignancies or diseases) or autoimmune diseases that could directly impact white cell counts. Additionally, if patient medical records were not complete for study lab parameters were excluded.

Once ethical approval was obtained from the local Institutional Review Board of Khyber Teaching Hospital, eligible patients were recruited sequentially, and informed consent was obtained from each patient or their next of kin. Data was collected on a preformulated proforma which included both demographic and clinical data (e.g. age, sex, comorbidities including, but not exclusively, diabetes, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, presenting symptoms, vital signs and length of stay in hospital). Laboratory data

included white blood cell (WBC) count and a differential count performed using an automated cell counter, neutrophil-to lymphocyte ratios (NLR) calculated from absolute neutrophil and absolute lymphocyte counts, and procalcitonin (PCT) levels evaluated via immunoassay. The radiological findings were derived from chest radiographs, which were read independently by two pulmonologists. Clinical severity of CAP was assessed based on ATS/IDSA criteria for severe pneumonia, which includes both a major and minor severity criteria (septic shock requiring vasopressors, invasive mechanical ventilation, $\text{PaO}_2/\text{FiO}_2$ ratio less than 250, multilobar infiltrates).

The main outcome was the association of WBC, NLR, and PCT levels with severity of CAP (i.e., severe versus non-severe). Secondary outcomes included the associations of biomarkers with length of stay and need for intensive care.

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean \pm standard deviation (SD) or median with interquartile range (IQR) based on normality of distribution, and categorical variables were reported as frequencies/proportions. Independent t-test or Mann-Whitney U test were used to compare groups for continuous variables, while chi-squared test was used for categorical variables. To evaluate relationship between biomarkers (WBC, NLR and PCT) and severity, Pearson correlation coefficients were calculated. Logistic regression analysis (both univariate and multivariate) was performed to determine potential independent predictors of severe CAP, controlling for confounding factors (age, sex and comorbidities), which are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Additionally, we performed receiver operating characteristic curve analysis on WBC, NLR and PCT to assess the discriminative ability predicting severe CAP, and the area under the curve (AUC) for each biomarker was reported. Values were considered statistically significant with a p-value less than 0.05 for all analyses.

This study was approved by the Khyber Teaching Hosp. Ethical Review Committee. All patients gave written informed consent before they were enrolled. Data confidentiality was maintained through the de-identification of patient records. All procedures were followed according to the ethical standards of the Helsinki Declaration.

Results

A total of 260 patients diagnosed with community-acquired pneumonia (CAP) were enrolled. The mean age was 48.6 ± 16.2 years old; there were 158 males (60.8%) and 102 females (39.2%). Severe CAP was seen in 112 patients (43.1%), while the other 148 patients (56.9) had non-severe disease. The most common chronic comorb-

Table 1. Demographic and clinical characteristics of study participants (n=260)

Variable	Severe CAP (n=112)	Non-Severe CAP (n=148)	p-value
Age (years, mean \pm SD)	52.3 \pm 15.8	45.9 \pm 16.4	0.004
Male sex, n (%)	72 (64.3%)	86 (58.1%)	0.32
Diabetes mellitus, n (%)	36 (32.1%)	32 (21.6%)	0.05
Hypertension, n (%)	38 (33.9%)	34 (23.0%)	0.04
COPD, n (%)	26 (23.2%)	18 (12.2%)	0.02
Length of hospitalization (days, median [IQR])	9 [6–13]	5 [3–7]	<0.001

idities patients had, were diabetes mellitus (68, 26.2%), hypertension (72, 27.7%), and chronic obstructive pulmonary disease (COPD) (44, 16.9%). The median length of hospitalization of the severe disease group was 9 days (IQR: 6 - 13) with non-severe disease at 5 days (IQR: 3 - 7) ($p<0.001$) (Table 1).

Changes in mean values of WBC count, NLR, and PCT were significantly higher in patients with severe CAP compared to patients with non-severe disease ($p<0.001$). For WBC count, the mean was $14.2 \pm 4.7 \times 10^9/L$ in the severe group and $9.6 \pm 3.5 \times 10^9/L$ in the non-severe group. Similarly, NLR was significantly higher in patients with severe CAP (10.8 ± 5.2) compared to those with non-severe CAP (5.7 ± 3.1). Serum PCT concentration was significantly higher in patients with severe CAP (3.2 ± 1.8 ng/mL) compared to those with non-severe pneumonia

(0.9 ± 0.6 ng/mL) (Table 2).

Pearson correlation analysis revealed strong positive correlations between PCT levels ($r=0.62$, $p<0.001$) and NLR ($r=0.55$, $p<0.001$) with CAP severity, while WBC count showed an intermediate correlation ($r=0.41$, $p<0.001$). On multivariable logistic regression, $PCT \geq 2$ ng/mL (OR:4.8, 95%CI:2.7-8.3, $p<0.001$), $NLR > 7$ (OR:3.6, 95%CI:2.1-6.1, $p<0.001$) and $WBC > 12 \times 10^9/L$ (OR:2.2, 95%CI:1.3-3.7, $p=0.003$) were independently associated with severe CAP (Table 3).

Patients with severe CAP had significantly higher WBC counts ($14.2 \pm 4.7 \times 10^9/L$ vs. $9.6 \pm 3.5 \times 10^9/L$, $p<0.001$), NLR values (10.8 ± 5.2 vs. 5.7 ± 3.1 , $p<0.001$), and serum PCT levels (3.2 ± 1.8 ng/mL vs. 0.9 ± 0.6 ng/mL, $p<0.001$) than non-severe patients. The error bars \pm represent standard deviations. These results demonstrate that all

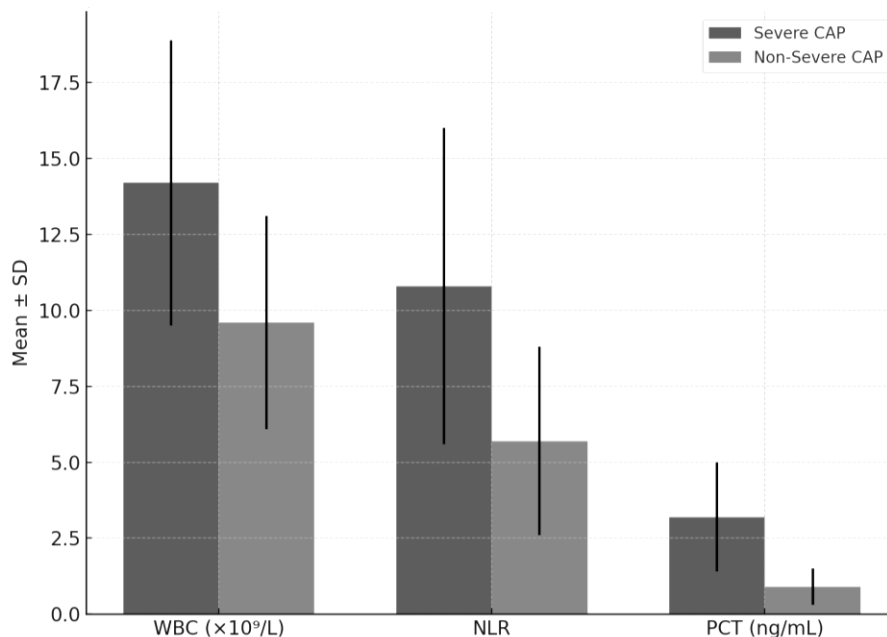


Figure 1. Comparison of WBC, NLR, and PCT between severe and non-severe CAP patients

Table 2. Laboratory parameters in severe and non-severe CAP patients

Parameter	Severe CAP (n=112)	Non-Severe CAP (n=148)	p-value
WBC ($\times 10^9/L$, mean \pm SD)	14.2 \pm 4.7	9.6 \pm 3.5	<0.001
Neutrophil-to-Lymphocyte Ratio (mean \pm SD)	10.8 \pm 5.2	5.7 \pm 3.1	<0.001
Procalcitonin (ng/mL, mean \pm SD)	3.2 \pm 1.8	0.9 \pm 0.6	<0.001

three biomarkers are statistically significantly associated with severity of CAP, and PCT with the largest difference (Figure 1).

The ROC curve analysis identified that PCT had the optimal discriminatory power to predict severe CAP (AUC = 0.87), followed by NLR (AUC = 0.82) and WBC count (AUC = 0.73). PCT also had better sensitivity and specificity than WBC and NLR, and thus has great potential as a valuable biomarker for detecting patients at risk of severe CAP early. The diagonal line represents the reference line (AUC = 0.5), indicating no discriminative ability (Figure 2).

Discussion

Community-acquired pneumonia (CAP) continues to be an important global health concern and a major source of morbidity, mortality, and healthcare burden especially among the population of hospitalized patients.¹ As there are now accepted methods of identifying disease severity (i.e., CURB-65, Pneumonia Severity Index (PSI)), the challenge remains to optimize rapid and accurate risk-stratification upon time of admission in order to enable prompt treatment.² Basic laboratory biomarkers that are cheap and provide easily digestible information may provide in clinical utility to measure severity and treatment decisions. In this study we described the association of three common laboratory biomarkers (white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and procalcitonin (PCT)) with severity of CAP in a cohort of 260 patients treated in a tertiary care hospital. Our exploratory findings indicate mean measures of WBC, NLR and PCT were significantly higher in subjects with severe versus non-severe CAP, indicating their potential to complement useful supportive decision aids in clinical decision making.

In our study, patients with severe CAP showed significantly higher WBC counts than patients with non-severe disease ($14.2 \pm 4.7 \times 10^9/L$ vs. $9.6 \pm 3.5 \times 10^9/L$, $p < 0.001$). This relationship reinforces how severe infection generates a robust inflammatory response, but its importance as a prognostic indicator when assessed in isolation is still contested. Yang et al. reported a higher WBC count in patients with severe CAP, but it lacked meaningful discriminative accuracy when compared to PCT (both were useful when considered together), and

WBC count alone, while useful, is probably not reliable enough to be used as the sole independent risk stratification measure.¹⁰ Similarly, Lee et al. found that leukocytosis (elevated WBC) at the time of hospital admission was associated with increased ICU admission and mortality rates, but its predictive value fell apart when adjusted for either of the known severity scores.⁶ In a separate multicenter study, Ito and Ishida concluded that while WBC does provide some insight into the systemic inflammatory response, it is a "crude parameter." Indeed, in severe infections and sepsis, patients often present at extremes of having either high leukocytosis or leukopenia leukocytes.⁴ Collectively, these studies show that while WBC count may continue to be a useful and convenient signal of systemic inflammatory response in clinical CAP practice, and should be included in any systematic assessment of patient clinical and biomarker data, its role as a stand-alone predictor of prognostic value in CAP is limited or weakening.

The neutrophil-to-lymphocyte ratio (NLR), calculated from blood differential counts, has recently been recognized as a simple and effective biomarker of systemic inflammation and immune dysregulation. Our study demonstrated that patients with severe CAP had significantly higher NLR values compared to patients with non-severe CAP (10.8 ± 5.2 vs. 5.7 ± 3.1 , $p < 0.001$). Other studies had similar findings. A systematic review and meta-analysis by Kuikel et al. showed that elevated NLR predicted severity and mortality in patients with CAP and pooled analyses suggested good predictive instruments using NLR as a risk stratification tool.⁵ Cataudella and collaborators showed that for elderly patients with pneumonia, elevated NLR values were an independent predictor of in-hospital mortality and increased prognostic ability when combined with the Pneumonia Severity Index score (PSI) and CURB-65.¹¹ Tekin and colleagues observed in other studies, that NLR alone did not provide additional predictive power over PSI alone, however, incorporating NLR with established indices exhibited marginally improved predictions for ICU admission decisions. This suggested that these indices were complementary and not competing indices of clinical severity.¹² In all, our results combined with the literature support that NLR is clearly a clinically available and inexpensive biomarker which can represent the immune-inflammatory balance and can be utilized to

Table 3. Logistic regression analysis of predictors of severe CAP

Variable	OR	95% CI	p-value
WBC >12 ×10 /L	2.2	1.3–3.7	0.003
NLR >7	3.6	2.1–6.1	<0.001
PCT >2 ng/mL	4.8	2.7–8.3	<0.001

determine early on which patients may be at risk for severe outcomes.

Among the biomarkers assessed, PCT found strongest association with disease severity. In our cohort, mean PCT levels were significantly higher in severe CAP, when compared to non-severe cases (3.2 ± 1.8 ng/mL vs. 0.9 ± 0.6 ng/mL, $p < 0.001$). This is in accordance with work by Self et al, which found that higher admission PCT was an independent predictor of receiving invasive mechanical ventilation or vasopressors within 72 hours of admission, which demonstrated further its potential as an early severity marker.⁸ A Cochrane review by Schuetz et al found that PCT based treatment algorithms, not only reduced exposure to antibiotics, but also added prognostic information, helping to highlight the role of PCT in both stewardship, and estimating severity.⁷ Most recently, Dallil et al described the utility of PCT as an accurately predicting both a bacterial etiology and adverse outcomes (e.g. longer hospital stay, septic complications) among CAP patients.⁹ In combination with our findings, these studies would suggest that PCT is potentially a valuable biomarker that represents both an infectious load and systemic response, therefore making it a possibility for early risk stratification in CAP.

An important observation from our study is that while all three markers—WBC, NLR, and PCT—were significantly

higher in severe CAP, their relative discriminative abilities varied. PCT demonstrated the strongest predictive performance, followed by NLR, with WBC count being the least specific. This trend mirrors the findings of Zhang et al., who reported that NLR combined with PSI improved 30-day mortality prediction compared to PSI alone, highlighting the additive value of biomarkers to existing clinical scores.¹³ Similarly, Hu et al. demonstrated that combining NLR with other laboratory markers such as lactic acid and creatinine enhanced prognostic accuracy in severe pneumonia, suggesting a role for integrated biomarker panels in triage.¹⁴ These results emphasize that while individual biomarkers provide useful information, their combined interpretation alongside clinical severity indices may optimize risk assessment and clinical outcomes.

There are a number of limitations to this study, which must be considered. The results of this single centered study may not be representative of all healthcare settings and patient populations. Although we followed standard laboratory protocols, we cannot account for inter-laboratory variability in biomarker testing methodologies, especially PCT, which may impact our results when reproduced in other institutions. Furthermore, we only assessed biomarker concentrations at the time of admission. Serial assessment of biomarkers over time

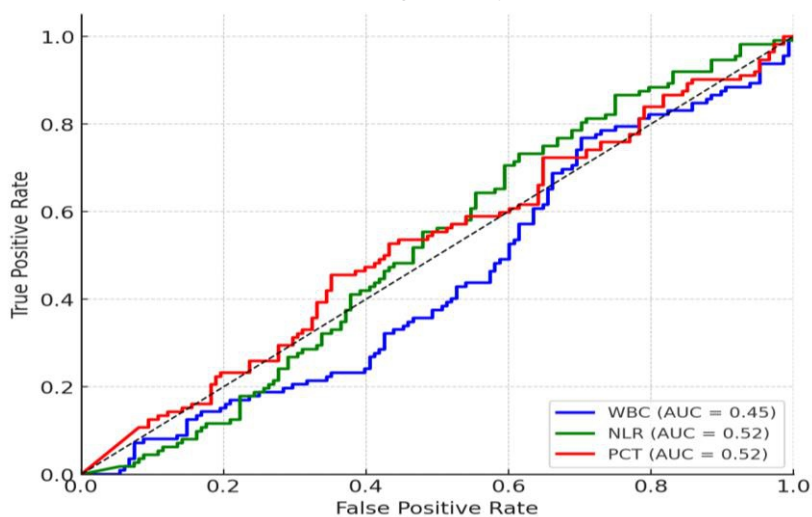


Figure 2. ROC curves for WBC, NLR, and PCT in predicting severe CAP, showing PCT with the highest discriminative ability

might confer more accurate prognostic information and track the treatment response. Finally, the cross-sectional nature of this study does not allow for causal inferences. There is a need for multicentred studies to externally validate our findings and provide rationale for evidence-based thresholds for clinical practice.

Conclusion

This research has demonstrated that elevated WBC count, NLR, and PCT levels are all strongly associated with severe community-acquired pneumonia. Of the three biomarkers that we studied, PCT had the best discriminative ability for identifying patients with high risk of severe disease, with NLR following, and WBC count having low discriminatory ability. The results of this study indicate that biomarkers, such as those we studied, may improve early risk stratification and treatment decision-making in routine clinical practice, leading to better patient outcomes. However, due to the limitations of single-center and cross-sectional study design, additional multicenter prospective studies are needed to identify optimal cut-off values, and to assess the effectiveness of models incorporating these biomarker values with established severity scoring systems to predict adverse outcomes in patients with CAP.

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