Original Article

Relationship Between White Blood Cell, Neutrophil-to-Lymphocyte Ratio, Procalcitonin, and Severe Community-Acquired Pneumonia in a Private Tertiary Hospital

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ABSTRACT

Background: Studies have tried to determine the diagnostic value of serum inflammatory biomarkers in patients with community-acquired pneumonia (CAP) to help guide clinical decision making. This study aimed to determine the relationship between white blood cell (WBC), neutrophil-to-lymphocyte ratio (NLR), procalcitonin (PCT), and severe CAP.

Methodology: This study reviewed records of patients aged 18 years and above diagnosed with CAP from January 2022 to January 2024 at Perpetual Help Medical Center—Las Piñas. Data collected were demographics, WBC and neutrophil and lymphocyte counts, procalcitonin, and CURB-65 scores. Receiver operating characteristic (ROC) curve analysis was done to determine the best cut-off for WBC, NLR, and procalcitonin in diagnosing severe CAP (CURB-65 score 3 to 5). Pearson correlation test was used to determine pairwise correlations between WBC, NLR, and procalcitonin.

Results: A total of 120 patients were included. The mean WBC count and mean NLR were higher among patients with elevated PCT than those with normal PCT (15.2 ± 5.8 vs 10.7 ± 3.7; p <0.001 and 18.6 ± 17.9 vs 8.6 ± 7.9; p = 0.005, respectively). The prevalence of severe pneumonia was higher in patients with elevated PCT than those with normal PCT (65.8% vs 12.8%; p <0.001). Procalcitonin level at a threshold of 0.5 ng/mL showed the highest sensitivity (90%, 95% confidence interval [CI] 0.77 to 0.97) and best test performance (area under the ROC 0.79, 95% CI 0.72 to 0.86) in diagnosing severe pneumonia. The mean NLR was weakly correlated with WBC (r = 0.300; p = 0.002). The mean PCT was moderately correlated with WBC (r = 0.637, p = 0.04) and NLR (r = 0.750, p = 0.03).

Conclusions: Procalcitonin shows acceptable performance in diagnosing severe pneumonia. This study also suggests a significant correlation between WBC, NLR, and PCT. Multicenter studies are recommended to better generalize the results to the larger population.

Keywords: pneumonia, neutrophil/lymphocyte ratio, procalcitonin, CURB-65

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INTRODUCTION

Community-acquired pneumonia is a leading cause of mortality and morbidity worldwide.[1] The incidence of CAP in the Philippines is 4,205 patients per 100,000 discharges.[2] CAP, a type of lower respiratory tract infection (LRTI), is diagnosed by the presence of infiltrates on chest imaging in patients with fever, dyspnea, cough, and sputum.[1] Clinical signs and symptoms of bacterial and viral LRTIs are often indistinguishable. Microbiologic testing is helpful but often takes days until a pathogen is identified.[3] Nowadays, biomarkers combined with clinical risk scores are used to identify specific patients at risk, assess the severity of illness and prognosticate patients, and guide antibiotic therapy.[4]

Researchers have explored the prognostic value of serum inflammatory biomarkers like white blood cell (WBC) and procalcitonin (PCT) in CAP patients.[5,6,7] The WBC subpopulation is of note in the systemic inflammatory response to infection, with neutrophilia and lymphocytopenia recognized as possible markers in infectious disease management.[4] The neutrophil-to-lymphocyte ratio (NLR), a ratio between neutrophil and lymphocyte counts, is a biomarker which relates the innate and adaptive immune response supported by neutrophils and lymphocytes, respectively.[8] An increased NLR is associated with a high CURB-65 score, intensive care unit admission, and mortality.[4]

Procalcitonin, another serum biomarker, helps differentiate bacterial infection from other causes of infection or inflammation and is widely used to guide antibiotic therapy in LRTI patients. It is generally used to determine the need to continue antibiotic therapy.[1] Non-infectious conditions may also elevate PCT levels. These conditions include trauma, burn, medullary C-cell carcinoma, small cell carcinoma of the lung and bronchial carcinoid, immunomodulatory therapy, cardiogenic shock, during peritoneal dialysis, and in some patients with cirrhosis or chronic kidney disease. Clinicians must take note of the above conditions that might affect PCT levels.[9]

Several studies have tried to determine the relationship of NLR and PCT to CAP, separately, with promising results.[6,7] However, there are also studies on both NLR and procalcitonin showing no significant relationship with CAP.[5] This study aimed to determine the correlation between WBC, NLR, PCT, and severe CAP in patients admitted in Perpetual Help Medical Center – Las Piñas. Further, optimal cut-off values for WBC, NLR and PCT to diagnose severe CAP were determined. CURB-65 (confusion, uremia, respiratory rate, BP, age ≥65 years) was used to classify pneumonia as severe. Capelastegui et al. reported that patients with CURB-65 score of more than two are high risk for mortality and should be managed as having severe pneumonia.[10] No local data has yet examined the relationship between WBC, NLR and PCT in severe CAP.

METHODOLOGY

Research design
The study used a cross-sectional, records-based design.

Study site
Perpetual Help Medical Center – Las Piñas is a tertiary hospital which caters to patients with CAP.

Target population
The research included patients aged 18 years old and above who were admitted in Perpetual Help Medical Center – Las Piñas, with a diagnosis of CAP from January 2022 to January 2024.

Inclusion/exclusion criteria
Cases of CAP were identified based on the diagnosis of the treating physicians as reflected in the medical record. Excluded from this study were patients with a history of tumors, burns, trauma, surgery, kidney disease, inflammatory diseases, immunosuppression, extrapulmonary infections, or CAP but with no procalcitonin results upon admission. Likewise, patients who were diagnosed with COVID-19 and pulmonary tuberculosis were excluded.

Study procedure
The investigator obtained permission to access medical records of adult patients who were diagnosed with CAP in Perpetual Help Medical Center – Las Piñas. Simple random sampling was done. Each eligible patient was assigned a number and a table of random numbers was used to select participants for the study.

The researcher reviewed medical records to fill-up the data collection tool. Data on patient demographics, neutrophil and lymphocyte counts, and PCT levels on the first day of admission were collected. NLR was measured by dividing the number of neutrophils by the number of lymphocytes. CURB-65 scores were computed using data upon admission. Severe CAP was identified in patients with a CURB-65 score of greater than two.

Patients were divided into two groups: those with normal PCT levels and those with elevated PCT levels.

Sample size calculation
To answer the primary objective of determining the correlation between WBC, NLR, and PCT, the minimum sample size for a two-tailed correlational analysis was calculated. Based on 95% confidence interval, mean effect size of 0.25,5 with 80% power, at least 120 patients were needed. This was also sufficient to detect a medium effect size of 0.5 in an independent t-test with 80% power and 95% confidence interval. Calculations were done using G*Power software v3.1.9.7. Based on patient census, the study site had enough number of patients to meet the sample size for the study.

Data processing and encoding
Data was encoded in a tabulated form using SPSS for Windows version 20.

Data analysis
Data was analyzed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as means ± standard deviations and counts (percentages). Chi-square test was used to compare categorical data. Independent Student's t-test was used to compare mean WBC, neutrophil, lymphocyte, and NLR by PCT level. Analysis of the area under the receiver operating characteristic (AUROC) curves was used to determine the best cut-off value for WBC, NLR, and PCT to diagnose severe CAP. The optimal cut-off was defined as the point where sensitivity and specificity values were the closest to the value of the area under the ROC, with minimal difference between them. Pearson correlation test was used to determine pairwise correlations between WBC, NLR and PCT. A p value of <0.05 was considered statistically significant.

Ethical Considerations
This research adhered to the Declaration of Helsinki and was approved by the University of Perpetual Help System—Jonelta Institutional Ethics Review Board (UPHS-IERB 2023-022 RP).

A waiver of written and verbal informed consent was requested from the IERB. The protocol was eligible for waiver or alteration of all required elements of informed consent.

RESULTS
A total of 120 patients with CAP were included, with 60.8% showing elevated PCT. The mean age was 68.2 ± 15.5 years among those with elevated PCT and 68.7 ± 16.4 years among those with normal PCT (p = 0.921). A comparison of patients' demographics and blood parameters in those with normal and elevated PCT are detailed in Table 1.

Among those with elevated PCT, 54.8% were male compared to 42.5% in the normal PCT group (p = 0.152). The mean WBC count was significantly higher among those with elevated PCT than those with normal PCT (15.2 ± 5.8 vs 10.7 ± 3.7; p <0.001). The mean neutrophil count was significantly higher among those with elevated PCT than those with normal PCT (84.0 ± 8.7 vs 75.2 ± 11.9; p <0.001). The mean lymphocyte count was significantly lower among those with elevated PCT than those with normal PCT (8.6 ± 7.0 vs 14.7 ± 9.7; p = 0.001) . The mean NLR was significantly higher among those with elevated PCT than those with normal PCT (18.6 ± 17.9 vs 8.6 ± 7.9; p = 0.005). The prevalence of severe CAP (CURB-65 score 3 to 5) was significantly higher in those with elevated PCT than those with normal PCT (65.8% vs 12.8%; p <0.001).

Table 1. Demographic data and blood parameters of patients diagnosed with CAP, with normal and elevated PCT levels

	Procalcitonin ≤0.5 ng/mL (normal)	Procalcitonin >0.5 ng/mL (elevated)	p-value
Total number of participants	47 (39.2)	73 (60.8)	
Age	68.7 ± 16.4	68.2 ± 15.5	0.921
Sex			
Male	20 (42.5)	40 (54.8)	0.152
Female	27 (57.5)	33 (45.2)	
WBC count, x $10^3/mm^3$	10.7 ± 3.7	15.2 ± 5.8	<0.001
Neutrophil count, %	75.2 ± 11.9	84.0 ± 8.7	<0.001
Lymphocyte count, %	14.7 ± 9.7	8.6 ± 7.0	0.001
NLR	8.6 ± 7.9	18.6 ± 17.9	0.005
CURB-65			
Less than 3	41 (87.2)	33 (45.2)	<0.001
3 to 5	6 (12.8)	40 (65.8)	

WBC, white blood cell; CURB-65, confusion, uremia, respiratory rate, blood pressure, age ≥65 years

Table 2. AUROC curve analysis for the prediction of severe CAP (CURB-65 score 3 to 5)

	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
WBC count, x $10^3/mm^3$	13.5	0.64 (0.54 to 0.74)	0.71 (0.61 to 0.81)	0.68 (0.54 to 0.81)
NLR	10.7	0.51 (0.45 to 0.57)	0.59 (0.53 to 0.65)	0.55 (0.45 to 0.65)
PCT, ng/ml	0.5	0.90 (0.77 to 0.97)	0.55 (0.43 to 0.67)	0.79 (0.72 to 0.86)

AUROC, area under the receiver operating characteristic curve; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio, PCT, procalcitonin

Table 3. Correlation between WBC, NLR, and PCT

	WBC	NLR	PCT
WBC	…	…	…
NLR	r = 0.300 p-value = 0.002	…	…
PCT	r = 0.637 p-value = 0.04	r = 0.750 p-value = 0.03	…

WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio, PCT, procalcitonin

In the AUROC analysis (Table 2) for diagnosing severe CAP, the WBC cut-off value was 13.5 x 103/mm3 (AUC 0.68, 95% CI 0.54 to 0.81), the NLR cut-off value was 10.7 (AUC 0.55, 95% CI 0.45 to 0.65), and the PCT cut-off value was 0.5 ng/mL (AUC 0.79, 95% CI 0.72 to 0.86). Procalcitonin showed the highest sensitivity (90%, 95% CI 0.77 to 0.97) and best test performance (AUC 0.79, 95% CI 0.72 to 0.86) in diagnosing severe CAP. However, its specificity was lowest (55%, 95% CI 0.43 to 0.67).

In Table 3, the mean NLR was significantly but weakly correlated with WBC (r = 0.300, p = 0.002). The mean PCT was significantly and moderately correlated with WBC (r = 0.637, p = 0.04) and NLR (r = 0.750, p = 0.03).

DISCUSSION

Community-acquired pneumonia is an acute infection of the pulmonary parenchyma.[2] Clinical features of bacterial and viral LRTIs are similar and cannot be solely distinguished by features alone.[1] Viral pathogens are increasingly being recognized as common causes of CAP, sometimes surpassing bacterial cases with the aid of modern diagnostic panels.[7] However, these tests are costly. In our institution, the cost of PCT testing is five times more than CBC. It also takes time before the clinician gets the results. This is probably why antibiotic therapy is essentially empirical in most cases of pneumonia.[8] Studies have been done to determine the use of biologic markers in predicting the severity of illness, for prognostication in patients with CAP. and to guide antibiotic therapy.[4,5] In this retrospective cross-sectional study, WBC, neutrophil, NLR, and CURB-65 scores were found to be significantly higher in patients with elevated procalcitonin, while lymphocyte count was significantly lower in those with elevated procalcitonin. In a study done by Cil et al., WBC, neutrophil, and NLR were also found to be significantly higher in patients with elevated procalcitonin.[5]

Our study showed a weak correlation between NLR and WBC. PCT was significantly and moderately correlated with WBC and NLR. This is supported by previous studies done by Beyaz et al. and Huang et al.,[6,7] wherein a positive correlation was found between PCT and NLR. However, this study finding differs from a study done by Cil et al. wherein no significant correlation was found between PCT and NLR.[5]

The WBC cut-off value was determined to be 13.5 x $10^3/mm^3$ (AUC 0.68), NLR cut-off 10.7 (AUC 0.55), and PCT cut-off 0.5 ng/ml (AUC 0.79) in this study. Procalcitonin showed the highest sensitivity (90%) and best test performance (AUC 0.79) in diagnosing severe pneumonia, while Cil et al. found the highest AUC with neutrophil counts.[5]

Findings on the correlation of PCT with NLR and WBC were different among different studies. In a study by Beyaz et al.[6] PCT and NLR were observed to be correlated in pneumonia patients. However, Cil et al. found no correlation between PCT and NLR.[5] Our study found significant correlations between WBC, NLR, and PCT suggesting that these markers could reflect the magnitude of inflammatory response in CAP patients, with PCT showing the highest sensitivity and best test performance in diagnosing severe CAP. These biomarkers may be used with PCT instead of PCT alone. However, in our country where most patients have budget constraints, because of the correlations seen between NLR, WBC, and PCT, NLR may be used since it is cheaper than serum procalcitonin.[12]

There are a few limitations to the study. Because data was secondarily obtained from records, the quality of data cannot be fully assured. The study does not differentiate between viral and bacterial pneumonia since culture studies and viral panel results were not collected. Patients with viral pneumonia who were classified as severe CAP might have distorted the results. The use of CURB-65 to determine pneumonia severity might have caused misclassification bias. Patients with higher-risk CAP without requested procalcitonin were excluded from the study, hence, possibly affecting the generalizability of results.

Despite these limitations, this study still provides valuable insights on the relationship between WBC, NLR, PCT, and severe CAP. To the best of our knowledge, there is no previous research in the Philippines with regard to their relationship. Further studies can be done in a multicenter approach to better generalize the results to a larger population. We recommend that WBC, NLR, PCT be used as an adjunct to CURB-65 in determining pneumonia severity. Other scoring systems may be utilized to further support the diagnosis of severe pneumonia.

CONCLUSION

Evaluating PCT and complete blood count parameters particularly WBC and NLR may assist clinicians in diagnosing and managing patients with severe CAP. With the significant correlations of the biomarkers and the high cost of PCT, WBC and NLR may be cheaper alternatives in some clinical settings. The high sensitivity of PCT may assist the clinician to consider the severity of patient's infection but complete assessment is best due to its low specificity.

Statement of Authorship

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Due to a technical error, the manuscript underwent single-anonymous rather than double-anonymous review. The reviewers confirmed that their review of the manuscript was unbiased and they had no conflicts of interest in reviewing the article.