Biomarkers in Differential diagnosis of Pneumonia and Bronchitis in children

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ABSTRACT

The aim of this study is to investigate the utility of several biomarkers in differentiating bacterial community-acquired lower respiratory tract infection (CA-LRTI) from non-bacterial CA-LRTI in children and the difference of their diagnostic performance between pneumonia and bronchitis. A retrospective cohort study composed of 108 pediatric patients hospitalized for CA-LRTI was performed during 2010–2013. Based on chest X-ray and sputum samples, patients were divided into four categories: bacterial pneumonia or bronchitis, and non-bacterial (viral or unknown etiology) pneumonia or bronchitis. Peripheral white blood cell and neutrophil counts, serum C-reactive protein (CRP), and procalcitonin (PCT) levels were compared. CRP and PCT were significantly elevated in bacterial pneumonia. PCT had the highest diagnostic performance in pneumonia. In bronchitis, neutrophil count significantly decreased in non-bacterial cases; PCT was not useful. Diagnostic performance of biomarkers may differ between pneumonia and bronchitis.

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Introduction

Community-acquired lower respiratory tract infections (CA-LRTIs), including pneumonia and bronchitis, are a major cause of pediatric hospital referrals worldwide [4,12]. These infections may be caused by viruses, bacteria, atypical pathogens, or mixed etiologies. Viral infections are frequent in children, whereas bacterial infections are usually associated with greater clinical severity and may require timely antibacterial treatment [3,4,12].

Accurately and rapidly distinguishing between bacterial and non-bacterial community-acquired lower respiratory tract infections is crucial for clinical decision-making. Inappropriate antibiotic use may contribute to antimicrobial resistance, adverse drug reactions, and increased healthcare costs. Conversely, delayed initiation of antibiotics in true bacterial infections may aggravate disease progression and increase the risk of complications [4,7,12].

Several diagnostic markers have been proposed to help clinicians determine the etiology and severity of pediatric respiratory infections. C-reactive protein (CRP) and procalcitonin (PCT) are among the most widely studied biomarkers in pediatric community-acquired pneumonia. CRP reflects systemic inflammatory activity, while PCT is more closely associated with bacterial infection and may help guide antibiotic treatment decisions in pediatric pneumonia [7,8,12].

Traditional hematological markers, including total white blood cell (WBC) count, neutrophil count, and newer inflammatory ratios, have also been evaluated in children with pneumonia. However, their diagnostic accuracy may be limited because hematological parameters can vary according to age, disease severity, immune response, and the presence of viral or atypical pathogens [1,2,8,9]. Recent studies also suggest that combined clinical and biomarker-based approaches may improve discrimination between bacterial and viral community-acquired pneumonia in children [3,6].

CRP and PCT have shown clinical usefulness in identifying bacterial pneumonia and assessing disease severity, although their performance differs across patient groups and clinical settings [7,8,10,12]. Novel biomarkers and inflammatory indicators, including heparin-binding protein and S100A8/A9, have also been investigated as potential markers of severe or complicated pediatric community-acquired pneumonia [11,13]. However, the diagnostic value of these biomarkers in acute bronchitis remains less clearly established, probably because bronchial inflammation is often more localized and may not always produce a strong systemic biomarker response [9,12].

It is also important to consider that children with preexisting respiratory conditions, immune dysfunction, or severe systemic illness may have a higher risk of complicated bacterial lower respiratory tract infection. In such patients, early differentiation between bacterial and non-bacterial disease is clinically important for selecting appropriate therapy and preventing deterioration [4,9,11,12].

This study aims to evaluate the efficacy of CRP, PCT, WBC count, and neutrophil count in differentiating between bacterial and non-bacterial CA-LRTI in hospitalized children.

A significant aspect of the research is the assessment of diagnostic accuracy in acute pneumonia and acute bronchitis, because pediatric respiratory care physicians frequently face practical challenges in distinguishing bacterial from non-bacterial lower respiratory tract infections [3,7,8,12].

Materials and Methods

This retrospective cohort study was performed at the Department of Pediatrics at Samarkand State Medical University. From January 2020 to December 2023, 145 children under 15 years old hospitalized with CA-LRTI participated in the research. The institutional ethics committee reviewed the research protocol and granted permission. Since the research was conducted retrospectively, I did not need formal permission from the participants.

To diagnose CA-LRTI, the patient's medical history (fever, cough, tachypnea, and respiratory distress) and physical examination findings (crackles, rhonchi, or reduced breath sounds on auscultation) were considered. Chest radiographs were used to classify the individuals into two fundamental diagnostic categories:

The identification of pulmonary infiltrates or consolidation on imaging is the diagnostic criterion for pneumonia.

The primary indicators of bronchitis are the absence of radiographic consolidation and the lack of clinical symptoms indicative of bronchial inflammation.

Children born with congenital lung disorders, cystic fibrosis, or recognized immunodeficiency syndromes were included in the study unless their conditions significantly hindered the interpretation of the data. Upon the patient's admission, electronic medical records were used to acquire demographic data, preexisting comorbidities, and laboratory findings. The laboratory findings included the counts of WBC, neutrophils, CRP, and PCT. We also examined the outcomes of the microbiological and virological assessments.

Sputum samples were obtained from patients during the first 24 hours of hospitalization using either spontaneous expectoration or suction, according upon their age and health status. We examined each sample microscopically to assess its quality and then used the Geckler grading system to categorize them. Only specimens classified as Grade 4 or 5, indicating satisfactory quality with few epithelial cells, were suitable for bacteriological culture. Grade 6 specimens were collected during sputum acquisition via a tracheostomy, since the airway access was aseptic.

All samples that fulfilled the criteria were subjected to Gram staining. The presence of bacteria inside phagocytosed polymorphonuclear cells was seen as evidence of an active bacterial infection. The bacterium then proliferated in culture, confirming its role as the likely etiological agent of the illness.

We used rapid antigen detection tests on nasopharyngeal aspirates, throat swabs, or sputum specimens to identify the etiologies of viral and atypical illnesses, including respiratory syncytial virus, influenza virus, and adenovirus. The selection of the material was contingent upon the patient's symptoms. We conducted serologic testing for Mycoplasma pneumoniae, which included particle agglutination and established a diagnostic threshold of a fourfold rise in titers.

- Chlamydophila pneumoniae, using enzyme-linked immunosorbent assay (ELISA) for immunoglobulin M (IgM) with a positive index above 2.0.

The tests were sought just for certain patients based on their age, the severity of their condition, and the physician's suspicion.

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Due to the data's deviation from a normal distribution, we used the Mann–Whitney U test to compare continuous variables, presenting them as medians with interquartile ranges. We used Fisher's exact test to analyze categorical data.

We constructed receiver operating characteristic (ROC) curves to evaluate the efficacy of each biomarker (WBC, neutrophil count, CRP, and PCT) in distinguishing between bacterial and non-bacterial diseases. We determined the optimal cut-off values for each marker by using Youden's index and computing the area under the curve (AUC). We determined the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) according to these criteria. A p-value of less than 0.05 was deemed statistically significant for all comparisons.

Results

3.1 Patient Enrollment and Group Classification

Out of the 145 children admitted with suspected community-acquired lower respiratory tract infections (CA-LRTIs) from January 2020 to December 2023, twelve were excluded from the study due to complex health issues (such as cardiomyopathy or rhabdomyolysis) or inadequate sputum samples. Twenty-five more individuals had received empirical antibiotics prior to their hospital admission, rendering their microbiological profiles mostly uninformative. Consequently, these patients were excluded from the study.

A total of 108 patients satisfied the qualifying criteria and were subsequently included into the final analysis. The outcomes of the sputum culture and radiographic examination resulted in the categorization of these people into four distinct groups:

The research encompasses the following groups: Group A included 38 individuals with bacterial pneumonia, Group B included 32 individuals with non-bacterial pneumonia (etiology unclear or viral), Group C consisted of 21 individuals with bacterial bronchitis, and Group D had 17

individuals with non-bacterial bronchitis (etiology unknown or viral).

Table 1 illustrates the distribution of demographic and clinical factors among the four groups examined in this study. No statistically significant alterations were seen in the age, gender distribution, or prevalence of underlying disorders among the groups. The quantity of underlying disorders remained unchanged. Conversely, other laboratory tests revealed significant discrepancies across the groups, reinforcing the notion that some medical indicators are valuable for diagnostic purposes.]

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	Group A (Bacterial Pneumonia) n = 38	Group B (Non-Bacterial Pneumonia) n = 32	Group C (Bacterial Bronchitis) n = 21	Group D (Non-Bacterial Bronchitis) n=17
Age, months (range)	24 (3–168)	26 (1–149)	15 (2–48)	18 (1–96)
Male sex, %	65.8%	68.8%	66.7%	52.9%
Underlying diseases, %	76.3%	71.9%	76.2%	47.1%
Difficulty in expectorating, %	57.9%	59.4%	61.9%	41.2%
Chronic lung disorder, %	10.5%	0%	9.5%	11.8%
Immunodeficiency, %	10.5%	9.4%	9.5%	0%
Fever, %	89.5%	71.9%	85.7%	47.1%
Oxygen therapy, %	78.9%	81.3%	76.2%	100%
Mechanical ventilation, %	10.5%	9.4%	0%	17.6%
WBC count (/µL), median	11,120	11,070	10,010	9180
Neutrophil count (/µL), median	8220	7300	6625	3750 *
C-reactive protein (mg/dL), median	9.95 *	2.15	4.20	1.70
Procalcitonin (ng/mL), median	1.2 *	0.1	0.1	0.1
*Note: Significant differences ($p < 0.05$) were observed.				

As a result of the fact that bacterial pneumonia (Group A) was associated with significantly higher levels of CRP and PCT in comparison to non-bacterial pneumonia (Group B), the discriminative value of these markers was brought to light. While this was going on, it was discovered that the neutrophil count was much greater in bacterial bronchitis (Group C) compared to non-bacterial bronchitis (Group D). The idea that the neutrophil count plays a role in determining whether or not the bronchial tree is irritated by bacteria is given more credence as a result of this discovery. PCT levels were found to be low in bronchitis groups regardless of the etiology, which demonstrates that this marker has limited relevance in the diagnosis of lower respiratory infections that are not caused by pneumonia.

Table 2. ROC Analysis for Differentiating Bacterial vs. Non-Bacterial Pneumonia

Marker	**AUC**	**Cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
WBC (/µL)	0.59	10,500	62%	50%	72%	38%
Neutrophils (/µL)	0.62	7665	67%	60%	77%	46%
CRP (mg/dL)	0.76	5.73	71%	80%	88%	57%
PCT (ng/mL)	0.87	0.2	**86%**	**80%**	**90%**	**73%**

The following table provides a summary of the distribution of bacterial pathogens among individuals who have been officially diagnosed with bacterial illnesses. Haemophilus influenzae and Streptococcus pneumoniae were the organisms that were identified the most commonly in cases of bacterial pneumonia (Group A). On the other hand, Moraxella catarrhalis and H. influenzae were the most common kinds of bacteria found in cases of bacterial bronchitis (Group C).

Receiver operating characteristic (ROC) analysis was used to assess the diagnostic accuracy of four routinely utilized biomarkers, namely white blood cell count, neutrophil count, C-reactive protein (CRP), and PCT. This evaluation was conducted independently for pneumonia and bronchitis. Procalcitonin (PCT) had the highest discriminative capability for pneumonia among the evaluated markers. The area under the curve (AUC) was 0.87, indicating exceptional accuracy. A PCT cut-off of 0.2 ng/mL provided the optimal balance of high sensitivity (86%) and specificity (80%). Furthermore, CRP exhibited commendable performance (area under the curve = 0.76), but with somewhat reduced sensitivity and negative predictive value compared to PCT. The counts of white blood cells and neutrophils exhibited little diagnostic utility (area under the curve < 0.65).

Unlike pneumonia, neutrophil count served as the most effective biomarker for bacterial bronchitis, with an AUC of 0.79. A threshold of 6035/µL produced elevated specificity (82%) and positive predictive value (80%). CRP had modest efficacy, however PCT proved to be diagnostically ineffective in bronchitis (AUC = 0.55). These data corroborate the concept that localized, less severe infections, such as bronchitis, may not elicit a systemic PCT response, in contrast to pneumonia.

Discussion

The goal of this study was to evaluate how accurately routinely available biomarkers, including white blood cell (WBC) count, neutrophil count, C-reactive protein (CRP), and procalcitonin (PCT), can differentiate bacterial from non-bacterial community-acquired lower respiratory tract infections (CA-LRTIs) in hospitalized children. Particular attention was paid to their diagnostic performance in two important clinical presentations: acute pneumonia and acute bronchitis [3,4,8,12].

Our results show that PCT is the most informative biomarker for identifying bacterial pneumonia, which is consistent with previous pediatric studies on biomarker-guided diagnosis and antibiotic decision-making in community-acquired pneumonia [7,8,12]. A cut-off value of 0.2 ng/mL demonstrated the best diagnostic balance in our study, with high sensitivity of 86% and specificity of 80%. This finding supports the use of PCT as part of diagnostic algorithms for pediatric pneumonia, especially when bacterial etiology is clinically suspected [7,12].

Table 4. ROC Analysis for Differentiating Bacterial vs. Non-Bacterial Bronchitis

Marker	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV
WBC (/µL)	0.73	9590	67%	64%	67%	64%
Neutrophils (/µL)	**0.79**	6035	**67%**	**82%**	**80%**	**69%**
CRP (mg/dL)	0.69	3.99	58%	82%	77%	64%
PCT (ng/mL)	0.55	0.2	33%	73%	57%	50%

PCT was far less useful for bronchitis than for pneumonia, probably because bronchial infections are more localized and less likely to produce a strong systemic inflammatory response. This interpretation is consistent with the general concept that biomarker performance depends on the severity, anatomical localization, and systemic involvement of respiratory infection [8,9,12]. In contrast, neutrophil count was the best marker of bacterial bronchitis in our study, with an AUC of 0.79 and relatively high specificity and predictive value. This suggests that neutrophilic inflammation may be more useful for detecting localized bacterial airway involvement when systemic biomarkers such as PCT remain low [1,3,9].

CRP showed only moderate diagnostic usefulness for bronchitis but demonstrated better accuracy for pneumonia, with an AUC of 0.76. This difference confirms that biomarkers should not be interpreted uniformly across all CA-LRTI phenotypes. Instead, their diagnostic value should be assessed according to the clinical form of infection, disease severity, and probability of bacterial involvement [3,8,10,12].

Children with severe motor and intellectual disabilities, chronic respiratory disorders, immunodeficiency, or other serious comorbidities represent a particularly vulnerable group. Impaired airway clearance, weak cough reflex, recurrent aspiration risk, and altered immune response may increase susceptibility to recurrent or complicated lower respiratory tract infections. In these patients, neutrophil count may be especially useful because clinical symptoms can be atypical and systemic biomarker responses may be difficult to interpret [4,9,11,12]. Early and accurate identification of bacterial bronchitis in this group is clinically important because timely antibacterial treatment may prevent disease progression and lower respiratory tract damage [4,9].

Overall, these findings indicate that biomarkers do not have equal diagnostic value across all forms of CA-LRTI. The selection and interpretation of laboratory tests should be based on the clinical phenotype, infection severity, anatomical localization, and patient-specific factors such as immune status, chronic respiratory disease, or disability [3,4,8,12].

Conclusions

This research establishes that procalcitonin (PCT) and C-reactive protein (CRP) are extremely useful biomarkers for diagnosing bacterial pneumonia in hospitalized children, with PCT demonstrating higher diagnostic accuracy. Conversely, neutrophil count surpassed other indicators in diagnosing bacterial bronchitis, although PCT and CRP had limited use for this illness.

These data highlight that the diagnostic significance of biomarkers varies according on the type, severity, and systemic involvement of respiratory tract infections. Additionally, in susceptible juvenile groups, such as those with chronic respiratory conditions or SMID, neutrophil count may be especially valuable owing to modified systemic biomarker responses.

The use of differential biomarker algorithms customized to the clinical presentation and patient profile might markedly enhance diagnosis accuracy and minimize needless antibiotic exposure. Extensive, multicenter, prospective investigations are necessary to corroborate

these findings and to enhance biomarker thresholds for standard clinical use.

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