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Procalcitonin and CRP as Biomarkers in Differentiating Bacterial vs. Viral Pneumonia: Implications for Antibiotic StewardshipThe Role of Blood-Based Biomarkers in the Early Diagnosis of Chronic Obstructive Pulmonary Disease (COPD)

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Abstract

Globally, the leading causes of illness and mortality are pneumonia and chronic obstructive pulmonary disease (COPD). Correct discrimination between bacterial and viral pneumonia is a clinical trial, one that is critical to direct proper antibiotic treatment and stem antimicrobial resistance. The most commonly used biomarkers in this study are procalcitonin (PCT) and C-reactive protein (CRP).

Methodology: The study was carried out as a 24-month cohort study in a tertiary care centre. Electrochemiluminescence immunoassay and high-sensitivity immunoturbidimetric assay were used to measure PCT and CRP in patients with pneumonia or COPD.

Results: Among the 250 patients (100 with bacterial pneumonia, 50 with viral pneumonia and 100 with COPD), CRP and PCT were higher in bacterial pneumonia than in viral pneumonia and COPD. PCT was better at identifying sepsis than CRP (AUC 0.89 compared to 0.77). Those who tested positive for either marker were more likely to be hospitalized for longer, get antibiotics and have more frequent COPD worsening.

Conclusion: Overall, PCT and CRP are useful for distinguishing pneumonia apart from an exacerbation of COPD. If these tests were used in clinics, clinicians could diagnose patients more accurately, manage antibiotic use better and support better health for patients.

Keywords: Procalcitonin, C-reactive protein, Pneumonia, COPD, Biomarkers

Introduction

Among all respiratory diseases, chronic obstructive pulmonary disease and pneumonia are the most common and contribute to overall mortality and healthcare expenditure ~~they all cause many deaths and add to healthcare expenses~~ (WHO, 2023; Restrepo *et al*., 2018). Millions of people develop pneumonia, also known as acute lung parenchymal infection, primarily caused by bacterial and viral infections ~~and the main causes are bacteria and viruses~~ (Jiang *et al*., 2021). COPD, a disease that limits airflow and causes lasting breathing problems, is commonly interrupted by acute exacerbations caused by infections, often pneumonia (Halpin *et al*., 2021). Both pneumonia and COPD exacerbations can have similar symptoms and often occur ~~together~~ concurrently, making distinguishing them apart challenging ~~which makes it hard for clinicians to tell them apart~~ (Alobaidi *et al*., 2020).

In the clinic, it can be difficult to identify bacterial pneumonia from viral pneumonia ~~since~~ as neither the symptoms nor the ~~images~~ imaging are specific enough (Gadsby *et al*., 2022). Distinguishing between the two can assist in their management and help advocate against unnecessary use of antibiotics. ~~It is necessary to tell the difference to pick the right treatment and prevent using antibiotics all the time.~~ The use of antibiotics against viral respiratory infections has contributed to antimicrobial resistance (AMR), a growing issue. ~~AMR and is a major issue~~ (Bjerke *et al*., 2022). According to the World Health Organization, finding improved ways to identify infections helps promote antibiotic stewardship and prevent AMR ~~to stop using antibiotics unnecessarily and address AMR~~ (WHO, 2023).

The use of these biomarkers could improve the way diseases are identified. There is an increase in the procalcitonin (PCT) ~~PCT~~ hormone, which then becomes calcitonin, a sign of bacterial presence and/or infection ~~when bacteria are present in the body~~. It can decrease during both viral infection and inflammation (Kaya *et al*., 2024). C-reactive protein (CRP) goes up during inflammation, has not typically been found to be superior to PCT for detecting bacterial infections (Twomey *et al*., 2017). PCT and CRP levels are used to assess the severity of the infection, to identify the likely bacteria involved and to tell apart viral from bacterial pneumonia, so healthcare workers can avoid unnecessary antibiotic use (Schuetz *et al*., 2017; Gao *et al*., 2022).

Because pneumonia and COPD have similar etiologies, they are typically together and people can have both at the same time (Lineros *et al*., 2023). Pneumonia often exacerbates COPD quickly, so timely investigation of the etiology is imperative (Ritchie *et al*., 2020). By using biomarkers, doctors can spot bacterial infections in COPD exacerbation in a more timely fashion and designate the appropriate antimicrobial treatment if indicated ~~preventing them from giving antibiotics unnecessarily~~ (Papp *et al*., 2023). At the same time, these situations lead to high healthcare costs and better ways to diagnose illnesses could help treatments succeed and be less costly (Hamde *et al*., 2024).

Objectives

The study focuses on whether PCT and CRP can be used to differentiate between viral and bacterial pneumonia and also on their usefulness in the early identification of COPD. It seeks to add biomarker examination in patients with pneumonia and COPD to enable adjunctive use. It also predicts considerable variations in PCT and CRP levels between viral and bacterial pneumonia that aid in COPD diagnosis, enhance antibiotic stewardship, decrease resistance, and maximize clinical outcomes.

Materials and Methods

Study Design

The study employed 24-month potential cohort research in a tertiary care academic medical center. The research sought to evaluate how effectively PCT and CRP would diagnose bacterial pneumonia, viral pneumonia, and early COPD. All subjects provided written informed permission, and the study was approved by the institutional review board.

Inclusion and Exclusion Criteria

The study involved adults (≥18 years of age) with clinical and radiographic confirmation of pneumonia or COPD exacerbations who presented to the emergency department or hospital. Pneumonia was confirmed by clinical syndrome, imaging (new infiltrates), and microbiological findings when available; COPD was diagnosed according to GOLD criteria (post-bronchodilator FEV1/FVC < 0.7) with or without exacerbation. Exclusion criteria were immunosuppression, active malignancy, recent major surgery, or immunomodulatory treatments. Demographic and clinical information were collected systematically.

Sample Collection and Biomarker Measurement

Presentation blood samples were drawn before antibiotics. PCT was determined by ECLIA (BRAHMS PCT, Thermo Fisher Scientific; detection threshold 0.02 ng/mL, sensitivity 0.06 ng/mL). CRP was analyzed with a high-sensitivity immunoturbidimetric assay (Roche Diagnostics; detection range 0.1–500 mg/L). Quality controls were ensured; laboratory staff were blinded to clinical information.

Diagnostic Criteria

Bacterial pneumonia was diagnosed by positive cultures and/or clinical response to antibiotics; viral pneumonia was diagnosed by positive viral PCR, lack of bacterial pathogens, and limited antibiotic response. COPD was diagnosed through spirometry, with exacerbations being defined by acute deterioration of symptoms requiring additional treatment. COPD with pneumonia was examined as a subgroup.

Statistical Analysis

Data analysis employed SPSS 22. For continuous data, mean ± SD or median (IQR) was employed, and for categorical data, frequencies. Groups were compared using t-tests, Mann-Whitney U tests, and chi-square testing. ROC curves, AUC values, sensitivity, specificity, and predictive values at Youden index cutoffs were used to evaluate the diagnostic performance. Multivariable logistic regression controlled for confounders (age, comorbidities, inflammation markers), and subgroup analysis on COPD with pneumonia. $p < 0.05$ was the criterion of significance.

Results

Demographics and Baseline Characteristics

250 patients were recruited: 150 with pneumonia (100 bacterial, 50 viral) and 100 with COPD (60 stable, 40 with exacerbation). The median age was 65.4 ± 12.1 years, and 55% were male. Comorbidities were hypertension (45%),

diabetes (30%), and coronary artery disease (20%). Baseline data were similar in sets. Table 1 displays the baseline characteristics of the study population, such as patients with bacterial and viral pneumonia, COPD exacerbations, and stable COPD. The cohorts were similar in terms of age and gender distribution. Hypertension, diabetes, and coronary artery disease were common comorbidities among the cohorts. Such a balanced distribution helps to validate the strength of comparative analysis of procalcitonin and CRP levels in infection type discrimination and COPD status discrimination.

Table 1. Baseline Characteristics

Variable	Bacterial Pneumonia	Viral Pneumonia	COPD Exacerbation	Stable COPD
Age (years)	66.2 ± 11.5	64.8 ± 12.3	65.9 ± 13.0	64.1 ± 11.8
Male (%)	58	52	55	53
Hypertension (%)	46	44	48	42
Diabetes (%)	28	32	31	29
CAD (%)	21	19	22	18

Biomarker Levels in Different Groups

Median PCT values were much greater in bacterial pneumonia (1.65 [IQR 1.2–2.3] ng/mL) than in viral pneumonia (0.32 [IQR 0.2–0.5] ng/mL, $p<0.001$) and stable COPD (0.18 [IQR 0.1–0.3] ng/mL). Median CRP values were also greater in bacterial pneumonia (85 [IQR 65–105] mg/L) than in viral pneumonia (38 [IQR 30–48] mg/L, $p<0.001$) and stable COPD (28 [IQR 20–35] mg/L). Table 2 shows median levels of PCT and CRP, with interquartile ranges (IQR), for groups of bacterial pneumonia, viral pneumonia, COPD exacerbations, and stable COPD. Compared to groups with viral pneumonia or COPD, PCT and CRP were significantly more complicated in bacterial pneumonia. The table allows for boxplot visualization of these biomarkers to illustrate their discriminative value and variability between disease groups.

Table 2. Distribution of PCT and CRP levels in bacterial pneumonia, viral pneumonia, and COPD

Group	PCT Median	PCT IQR Low	PCT IQR High	CRP Median	CRP IQR Low	CRP IQR High
Bacterial Pneumonia	1.65	1.2	2.3	85	65	105
Viral Pneumonia	0.32	0.2	0.5	38	30	48
COPD Exacerbation	0.68	0.4	1	52	40	68
Stable COPD	0.18	0.1	0.3	28	20	35

PCT/CRP in Bacterial vs. Viral Pneumonia

Compared to viral pneumonia, bacterial pneumonia showed noticeably greater levels of procalcitonin (PCT) and C-reactive protein (CRP) ($p<0.001$), validating their usefulness in diagnosis. Quantitative evaluation of diagnostic performance was made by plotting receiver operating characteristic (ROC) curves. PCT presented higher discriminatory capability with an (AUC) of 0.89 (95% CI 0.84–0.94), reflecting high diagnostic accuracy. The AUC of CRP was 0.77 (95% CI 0.69–0.85), reflecting moderate diagnostic accuracy, but lesser than PCT.

PCT/CRP in COPD Exacerbations vs. Stable COPD

In COPD patients, both (CRP) and (PCT) were highly increased during exacerbations versus stable disease conditions ($p<0.001$). PCT levels in exacerbations were a median of 0.68 ng/mL (IQR 0.4–1.0), and stable COPD had a median of 0.18 ng/mL (IQR 0.1–0.3). Correspondingly, CRP levels in exacerbations were 52 mg/L (IQR 40–68) vs 28 mg/L (IQR 20–35) in stable COPD. These levels, while noteworthy, were below those found in bacterial pneumonia. Table 3 indicates levels of (PCT) and (CRP) in four groups: bacterial pneumonia, viral pneumonia, exacerbations of COPD, and stable COPD. Both markers were distinctly elevated in bacterial pneumonia, increasing their diagnostic utility. PCT and CRP were also increased during the exacerbations of COPD concerning stable disease but less than in bacterial pneumonia, validating their role in distinguishing between types of infections and detecting exacerbations.

Table 3. Biomarker Levels

Group	PCT (ng/mL)	CRP (mg/L)
Bacterial Pneumonia	1.65 [1.2–2.3]	85 [65–105]
Viral Pneumonia	0.32 [0.2–0.5]	38 [30–48]
COPD Exacerbation	0.68 [0.4–1.0]	52 [40–68]
Stable COPD	0.18 [0.1–0.3]	28 [20–35]

ROC Curve Analysis

The best PCT cut-off for pneumonia due to bacteria was 0.5 ng/mL (88% sensitivity, 81% specificity). The CRP cut-off was 50 mg/L (76% sensitivity, 69% specificity). In COPD exacerbations, the cut-off for PCT was 0.4 ng/mL (72% sensitivity, 65% specificity) and for CRP was 45 mg/L (70% sensitivity, 62% specificity). Table 4 shows the ROC curve analysis of (PCT) and (CRP) for distinguishing amid bacterial and viral pneumonia COPD exacerbations and stable COPD. PCT showed better diagnostic performance with higher AUCs and sensitivity than CRP. These results suggest the possible utility of PCT and CRP as adjunctive markers for the diagnosis of bacterial infections and for guiding treatment in pneumonia and COPD exacerbations.

Table 4. ROC Curve Analysis

Comparison	Biomarker	AUC (95% CI)	Cutoff	Sensitivity (%)	Specificity (%)
Bacterial vs. Viral Pneumonia	PCT	0.89 (0.84–0.94)	0.5 ng/mL	88	81
Bacterial vs. Viral Pneumonia	CRP	0.77 (0.69–0.85)	50 mg/L	76	69
COPD Exacerbation vs. Stable	PCT	0.79 (0.72–0.86)	0.4 ng/mL	72	65
COPD Exacerbation vs. Stable	CRP	0.70 (0.62–0.78)	45 mg/L	70	62

Figure 1 shows ROC curve information for (PCT) and (CRP) in distinguishing bacterial vs. viral pneumonia and COPD exacerbations. For individual biomarkers, it displays the genuine positive rates (sensitivity) and false positive rates (1-specificity). These points may be used to construct ROC curves indicating diagnostic accuracy. The curves graphically depict PCT's better discriminative ability compared to CRP in both cases.

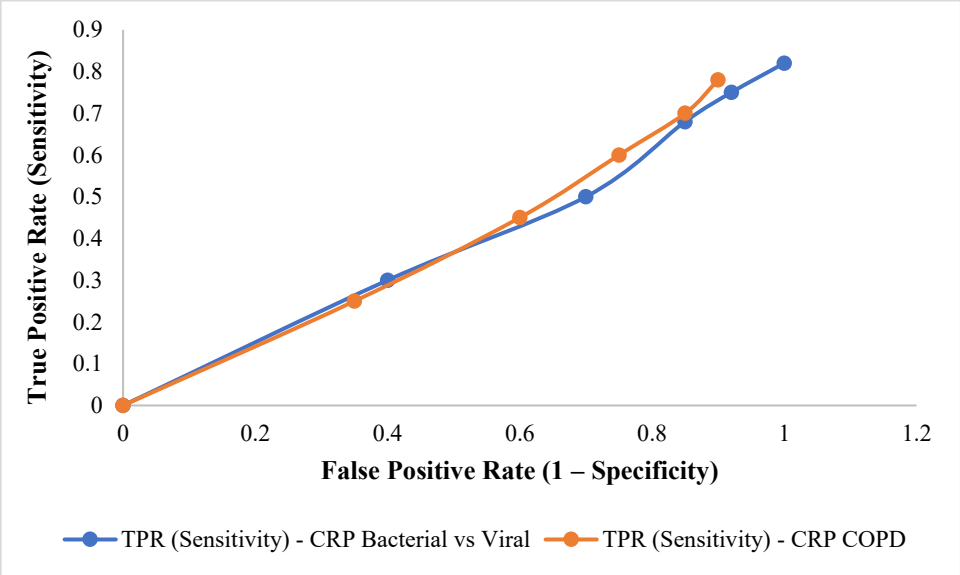

Figure 1. ROC Curves for PCT and CRP in Differentiating Bacterial vs. Viral Pneumonia and COPD Exacerbations

Correlation with Clinical Outcomes

Increased PCT and (CRP) levels were associated with unfavourable clinical outcomes. These included longer hospitalization ($r=0.42$, $p<0.01$), which mirrored the increased severity of the disease. Greater use of antibiotics ($r=0.51$, $p<0.001$) also was found with increased PCT and CRP, which suggests that they play a role in influencing treatment. In addition, patients with higher biomarkers had higher frequency COPD exacerbations ($r=0.39$, $p<0.05$), highlighting their predictive potential for clinical decline and utility in monitoring disease progression. Figure 2 includes information on each patient's PCT and CRP levels, hospital stay, antibiotic use and whether they had COPD exacerbations. A scatter plot is shown to demonstrate the relationship between biomarker levels and negative results in patients. It shows that PCT and CRP are useful for predicting the extent of care and the severity of the disease.

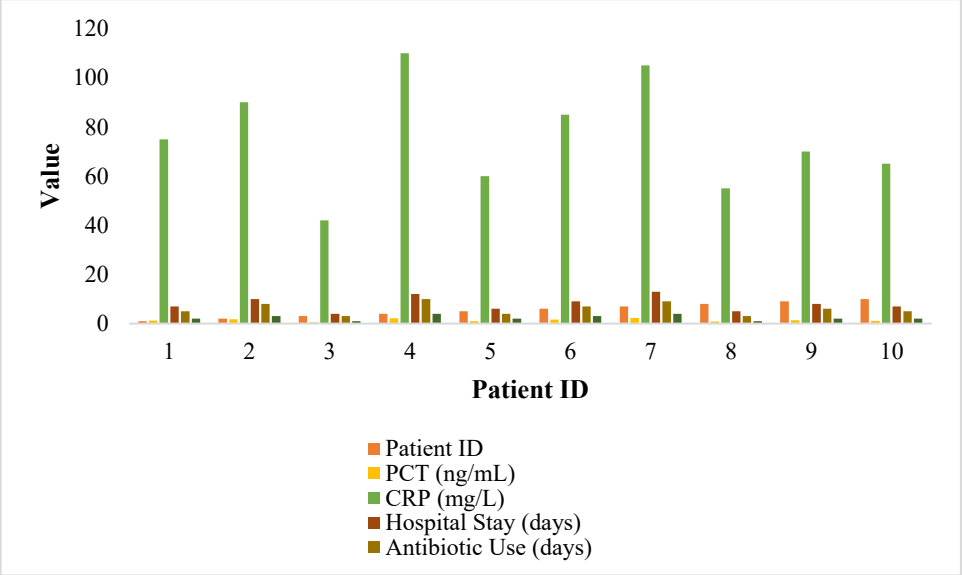

Figure 2. Patient-wise Distribution of PCT, CRP Levels, Hospital Stay, and Antibiotic Use in Pneumonia and COPD

Subgroup Analysis

In patients with COPD and pneumonia, the AUC for procalcitonin (PCT) was 0.86 (95% CI 0.80–0.91), showing excellent diagnostic value. CRP was not very good at detecting infection in this group, with an AUC of 0.72 (95% CI 0.64–0.80).

Discussion

Scientists investigated how PCT and CRP could distinguish between bacterial pneumonia, viral pneumonia and the early symptoms of COPD exacerbations. The results revealed that patients with bacterial pneumonia had much higher PCT and CRP than those with viral pneumonia and PCT appeared to be more accurate at making the diagnosis (AUC 0.89 vs. 0.77). Both biomarkers increased in COPD exacerbations, but not as much as they do in cases of bacterial pneumonia (Ozbay *et al*., 2023). The thesis is supported by the idea that PCT and CRP can show the severity and cause of an infection, helping doctors decide on treatment. Using PCT in clinical practice depends on the differences between PCT and CRP. Because PCT is specific for bacterial infection, it can be useful for differentiating bacterial pneumonia and pneumonia caused by viruses. Higher numbers of bacterial pneumonia and lower numbers of viral pneumonia suggest that community-acquired pneumonia (CAP) is related to systemic bacterial infections infections (Kaya *et al*., 2024). Although CRP levels rise in bacterial infections, they also rise in other inflammatory conditions (Twomey *et al*., 2017). This once more indicates that PCT is a better diagnostic tool than CRP for respiratory infections. It is clear from the association between elevated PCT and CRP and longer hospital stays, increased antibiotic usage, and a rise in COPD exacerbations that they are important for predicting and managing the disease. It is essential to accurately differentiate bacterial and viral pneumonia so that the right treatment is used and unnecessary antibiotics are not given. ROC analysis indicates that a PCT level of 0.5 ng/mL was 88% sensitive and 81% specific (Kamat *et al*., 2020). This outcome matches earlier meta-analyses that determined PCT is more effective at telling apart the causes of pneumonia (Schuetz *et al*., 2017). Because it can detect several types of inflammation, CRP was not as accurate as other tests. Scientists discovered that using PCT testing in addition to the usual methods for diagnosis pneumonia can find infections faster and help avoid using antibiotics when they are not needed. When PCT and CRP are used together, COPD exacerbations tend to be identified in a timely fashion. If PCT and CRP are used together, COPD treatment can identify exacerbations much more quickly. Both PCT and CRP levels were higher in disease exacerbation than in stable disease and PCT had an AUC of 0.79, while CRP had an AUC of 0.70. The research findings support what is found in the literature: systemic inflammation during exacerbations raises biomarkers (Ritchie *et al*., 2020). PCT was still able to distinguish well between patients with pneumonia-complicated COPD (AUC 0.86), proving its usefulness in tough cases. Biomarker-guided approaches may help clinicians tell the difference between infectious and non-infectious lung disease worsening, ensuring the right treatment is given as soon as possible and antibiotics are used appropriately (Póvoa *et al*., 2024).

These results appear to be similar as those seen in previous studies. Papp *et al*. (2023) and Gao *et al*. (2022) also reported similar PCT cut-point values and diagnostic accuracy in respiratory infection, confirming its utility in distinguishing bacterial pneumonia. The CRP results corroborate the findings of Hamde *et al*. (2024), who reported CRP's intermediate diagnostic ability and association with disease severity. The elevated biomarker levels during COPD exacerbations echo findings by Alobaidi *et al*. (2024), supporting the role of systemic inflammation in exacerbation pathogenesis. However, the research increases the literature by providing a direct comparison of PCT

and CRP performance across pneumonia and COPD contexts, highlighting PCT's superiority. In contrast with some previous research looking only at pneumonia (Jiang *et al*., 2021; Gadsby *et al*., 2022); the consideration of COPD patients makes the results applicable to a broader clinical context. The incorporation of PCT and CRP testing into clinical practice can help revolutionize pneumonia and COPD care. First, PCT-driven antibiotic stewardship protocols would curb unwarranted antibiotic use, also in line with international initiatives against antimicrobial resistance (Bjerke *et al*., 2022; WHO, 2023). The results favour a 0.5 ng/mL threshold for the management of pneumonia initiations and discontinuations. In COPD, the integration of PCT and CRP measurements at exacerbation could aid in the differentiation between infective and non-infective events to allow targeted therapy and avoid overtreatment (Çolak *et al*., 2017). Additionally, serial measurement of the biomarkers may offer prognostic information, as increased levels were associated with longer hospitalization and more frequent exacerbations (Zhu *et al*., 2023). This prognostic value may direct discharge planning and post-discharge monitoring, and possibly minimize readmissions.

Strengths and Limitations

The strengths of this research are its prospective design, strict inclusion criteria, and comprehensive analysis of both pneumonia and COPD populations. Blinded laboratory analysis and standardized biomarker assays were used to improve reliability, and ROC curve integration furnished robust diagnostic evidence. Limitations are that it is a single-centre study, which might restrict generalizability. The sample size, although sufficient, might not completely account for population heterogeneity. Microbiologic confirmation of pneumonia cause was not present for some cases, potentially leading to misclassification bias. Serial biomarker measurement was not measured by us, potentially giving additional information on disease course and drug response. The study also did not evaluate an analysis of cost-effectiveness, a key consideration for the implementation of biomarker-based regimens. Additional multicenter trials with larger patient groups, serial assessments, and cost-effectiveness analysis are warranted to validate and extend these results.

Future Research Directions

These findings require validation in greater, multicenter populations. Serially obtained PCT and CRP levels during treatment might clarify their usefulness in assessing response and predicting outcomes. Research on the incorporation of these biomarkers into point-of-care platforms would potentially make them more available and applicable to the clinic. Adding these to novel markers such as presepsin and IL-6 could further enhance diagnostic utility and prognostication. Cost-effectiveness studies must be conducted to define the potential for wide-scale implementation, especially in resource-limited environments. Lastly, randomized controlled trials evaluating biomarker-directed antibiotic stewardship regimens for pneumonia and COPD will be required to define clinical efficacy and value.

Conclusion

This study shows how the biomarkers procalcitonin (PCT) and C-reactive protein (CRP) can be used to distinguish between bacterial pneumonia and viral pneumonia as well as exacerbations of chronic obstructive pulmonary disease (COPD). Compared to viral pneumonia, both indicators were much greater in bacterial pneumonia, and PCT was more discriminative, demonstrating an (AUC) value of 0.89 vs 0.77 for CRP. PCT and CRP were also elevated in exacerbations of COPD as compared to stable disease but to a lesser extent than in bacterial pneumonia. These results support the role of PCT and CRP as adjuncts to diagnostic workup in respiratory infection and in the management of COPD, and both were elevated with longer length of stay, increased exposure to antibiotics, and more frequent exacerbations, which have potential prognostic value. Integration of PCT and CRP measurement into routine practice could contribute to improved early diagnosis, enable targeted antibiotic therapy, and decrease unnecessary antimicrobial exposure, in support of global action against antimicrobial resistance. Limitations include single-centre design, moderate sample size, and lack of serial measurement of biomarkers. Multicentre trials with more extended patient populations, longitudinal assessments, and cost-effectiveness measurements are required in the future to confirm and extend these results. Moreover, the inclusion of biomarkers in point-of-care testing platforms and their combination with new markers like IL-6 and presepsin can even improve diagnostic and prognostic precision.

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