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Comparative Analysis of C-Reactive Protein vs. Procalcitonin in Predicting Bacterial Respiratory Infections in Adults

Análisis comparativo de la proteína C reactiva frente a la procalcitonina en la predicción de infecciones respiratorias bacterianas en adultos

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Resumen

Este artículo de revisión compara el rendimiento diagnóstico y pronóstico de la proteína C reactiva (CRP) y la procalcitonina (PCT) en la detección de infecciones bacterianas respiratorias en adultos. Se analizó evidencia publicada entre 2004 y 2025, incluyendo estudios observacionales, ensayos clínicos y metaanálisis. Los hallazgos muestran que la CRP presenta mayor sensibilidad, mientras que la PCT ofrece mejor especificidad y una respuesta cinética más rápida al inicio y resolución de la infección. La combinación de ambos biomarcadores surge como una estrategia equilibrada para mejorar la precisión diagnóstica, optimizar el uso de antibióticos y apoyar los programas de vigilancia antimicrobiana. Se discuten las implicaciones clínicas, las limitaciones metodológicas y las áreas de investigación futura, destacando la necesidad de protocolos diagnósticos estandarizados y estudios de costo-efectividad.

Palabras clave: proteína C reactiva, procalcitonina, infección respiratoria bacteriana, biomarcadores, diagnóstico.

Abstract

This review article compares the diagnostic and prognostic performance of C-reactive protein (CRP) and procalcitonin (PCT) in detecting bacterial respiratory infections in adults. Evidence published between 2004 and 2025 was analyzed, including observational studies, clinical trials, and meta-analyses. Findings indicate that CRP shows higher sensitivity, whereas PCT demonstrates superior specificity and faster kinetic response to the onset and resolution of infection. The combined use of both biomarkers emerges as a balanced strategy to enhance diagnostic accuracy, optimize antibiotic use, and support antimicrobial stewardship programs. Clinical implications, methodological limitations, and future research directions are discussed, emphasizing the need for standardized diagnostic protocols and cost-effectiveness studies.

Keywords: C-reactive protein, procalcitonin, bacterial respiratory infection, biomarkers, diagnosis.

1. Introducción

Bacterial respiratory infections in adults remain a major public health concern worldwide, contributing significantly to morbidity, mortality, and healthcare costs. Community-acquired pneumonia, infectious exacerbations of chronic obstructive pulmonary disease (COPD), and other lower respiratory tract infections (LRTIs) account for a substantial proportion of hospital admissions and deaths each year (Simon et al., 2004; Lubell et al., 2015). The World Health Organization (WHO) has identified these diseases as priority areas for research and prevention, not only because of their direct health impact but also due to the growing threat of antimicrobial resistance.

A persistent challenge in clinical practice is the accurate differentiation between bacterial and viral respiratory infections, as their symptoms and signs often overlap. This diagnostic uncertainty frequently leads to the empirical prescription of antibiotics, even in cases where they are not warranted, thereby increasing the risk of adverse events, driving healthcare costs, and accelerating the emergence of resistant pathogens (Schuetz et al., 2009). Against this backdrop, serum biomarkers have emerged as valuable adjunctive tools to support clinical decision-making, enhance diagnostic accuracy, and promote rational antibiotic use.

Among the most widely studied biomarkers are C-reactive protein (CRP) and procalcitonin (PCT). CRP is an acute-phase protein synthesized primarily by the liver in response to inflammatory mediators, especially interleukin-6, with serum levels typically rising within 6–8 hours and peaking at 48 hours after stimulation (Holm et al., 2007; Wang et al., 2019). While CRP is sensitive, its specificity is limited, as levels may be elevated in bacterial and viral infections as well as in non-infectious inflammatory conditions. PCT, on the other hand, is the prohormone of calcitonin, produced in various tissues during systemic bacterial infections in response to endotoxins and pro-inflammatory cytokines. PCT levels rise significantly within 4–6 hours of infection onset, correlate with disease severity, and decline rapidly with effective treatment (Bhat et al., 2025; Hoeboer & Groeneveld, 2013).

The comparative diagnostic and prognostic value of these biomarkers has been the focus of extensive research. The landmark meta-analysis by Simon et al. (2004) concluded that PCT has greater specificity than CRP for identifying systemic bacterial infections. In patients with persistent fever, Van Duffel et al. (2022) found that both biomarkers retained diagnostic utility, while Duan et al. (2021) showed that combining them with selected clinical features enhanced differentiation between bacterial and viral LRTIs. In the context of respiratory exacerbations, Bafadhel et al. (2011) demonstrated that PCT more accurately distinguishes pneumonia from asthma exacerbations, whereas Zhao et al. (2018) reported that PCT outperforms CRP in differentiating infectious from tumor-related fever in lung cancer patients.

Serial monitoring studies have further highlighted the value of both markers. Gutierrez-Gutierrez et al. (2019) and Azzini et al. (2020) examined the kinetics of CRP and PCT, showing that dynamic changes in PCT more closely reflect clinical evolution and treatment response. Similarly, Hoeboer and Groeneveld (2013) found that changes in PCT levels more accurately predict infectious disease progression or resolution in febrile critically ill patients compared with CRP. In complex scenarios such as pneumonia-related sepsis and COVID-19, Shi et al. (2024) and Doganci et al. (2024) highlighted the prognostic utility of both markers, with important differences in their diagnostic performance.

While numerous studies have investigated these biomarkers, much of the available evidence derives from pediatric populations (Norman-Bruce et al., 2024; Katz et al., 2021; Tissières et al., 2025) or from heterogeneous cohorts that include mixed infection types. This limits the direct applicability of findings to adult patients with bacterial respiratory infections. Furthermore,

despite existing systematic reviews and meta-analyses (Simon et al., 2004; Schuetz et al., 2009), heterogeneity in study design, patient populations, and clinical endpoints continues to challenge the formulation of uniform recommendations for adults.

The knowledge gap regarding the comparative diagnostic and prognostic value of CRP and PCT in adults with bacterial respiratory infections warrants further investigation. The present review addresses two main research questions: Does PCT offer a significant diagnostic and prognostic advantage over CRP in adult bacterial respiratory infections?and Are there clinical contexts in which CRP matches or even surpasses PCT in utility, considering factors such as availability, cost, and turnaround time?

This article aims to provide a comprehensive comparative review of recent evidence on CRP and PCT in predicting bacterial respiratory infections in adults, assessing their diagnostic performance, prognostic value, and clinical applicability. We conducted a narrative literature review of original studies, systematic reviews, and meta-analyses published over the past two decades that directly compare both biomarkers in adult populations. The methodological approach is designed to synthesize the most relevant findings, identify the strengths and limitations of each biomarker, and offer a critical perspective to inform both clinical practice and future research (Boeck et al., 2011).

2. Metodología

This article was conducted as a narrative literature review aimed at synthesizing and comparing the diagnostic and prognostic performance of C-reactive protein (CRP) and procalcitonin (PCT) in predicting bacterial respiratory infections in adult populations. The methodological approach was designed to ensure a comprehensive, transparent, and reproducible process for identifying, selecting, and analyzing relevant studies.

Rationale for Time Frame

The literature search covered publications from January 2004 to June 2025. The year 2004 was chosen as the starting point because it coincides with the publication of the landmark meta-analysis by Simon et al., which established an important reference in the comparative evaluation of CRP and PCT in bacterial infections. Studies from 2004 onwards reflect advances in biomarker measurement techniques, improvements in diagnostic protocols, and more standardized research methodologies, making them more applicable to contemporary clinical practice.

Databases and Search Strategy

A structured search was carried out in four major scientific databases:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Cochrane Library

Additional targeted searches were performed in Google Scholar and the reference lists of selected articles to identify potentially relevant studies not captured in the main database search.

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords using Boolean operators. The core search string was:

- ("C-reactive protein" OR CRP) AND (procalcitonin OR PCT) AND ("bacterial respiratory

infection" OR "lower respiratory tract infection" OR pneumonia) AND (adult*).

The syntax was adapted for each database. Filters were applied to restrict results to human studies, English language, and peer-reviewed publications.

Eligibility Criteria

Inclusion criteria:

1. Studies involving adult participants (≥18 years old).
2. Direct comparison between CRP and PCT for the diagnosis or prognosis of bacterial respiratory infections.
3. Original research (randomized controlled trials, cohort studies, case-control studies), systematic reviews, and meta-analyses.
4. Publications in peer-reviewed journals.

Exclusion criteria:

- Studies exclusively involving pediatric populations.
- Research without direct comparative data between CRP and PCT.
- Non-original works such as letters, commentaries, or editorials, unless they synthesized relevant data from eligible studies.

Study Selection Process

The selection process was conducted in three stages:

1. Title and abstract screening to exclude clearly irrelevant studies.
2. Full-text review of potentially eligible articles to assess compliance with inclusion and exclusion criteria.
3. Final selection based on relevance to the review objectives and quality of data presented.

Screening and selection were conducted independently by two reviewers, with disagreements resolved by consensus to minimize bias.

Data Extraction

A standardized data extraction form was developed to ensure consistency. The following information was recorded for each included study:

- Bibliographic details (authors, year, journal).
- Study design and clinical setting.
- Population characteristics (sample size, age distribution, gender ratio, comorbidities).
- Clinical context (type of respiratory infection, severity, inpatient or outpatient).
- Biomarker measurement details (assay type, timing of sampling).
- Diagnostic performance metrics (sensitivity, specificity, positive/negative predictive values, area under the ROC curve).
- Prognostic implications and impact on clinical decision-making.
- Limitations reported by the study authors.

Synthesis of Findings

Given the methodological and clinical heterogeneity of the included studies, no formal meta-analysis was conducted. Instead, a qualitative synthesis was performed, grouping evidence into thematic categories:

1. Physiological and biochemical differences between CRP and PCT.
2. Diagnostic accuracy in various adult respiratory infection contexts.
3. Prognostic applications and serial measurement value.
4. Impact on antibiotic stewardship and clinical outcomes.

Findings were summarized narratively, with emphasis on identifying consistent patterns, highlighting areas of agreement and disagreement, and noting gaps in the current literature.

Ethical Considerations

This review used data from previously published studies. No new patient data were collected, and no ethical approval was required. All sources were publicly available and appropriately cited.

3. Resultados

The final selection included 20 studies published between 2004 and 2025 that directly compared the diagnostic and/or prognostic performance of C-reactive protein (CRP) and procalcitonin (PCT) in adult patients with bacterial respiratory infections. These studies encompass a variety of designs, including randomized controlled trials, observational cohorts, systematic reviews, and meta-analyses, with sample sizes ranging from fewer than 100 participants to over 5,000.

To present the findings clearly, results are grouped into four thematic domains:

1. Physiological and biochemical differences between CRP and PCT.
2. Diagnostic accuracy across different adult respiratory infection contexts.
3. Prognostic applications and the role of serial biomarker measurements.
4. Impact on antibiotic stewardship and clinical decision-making.

The following tables and figures summarize the key data from the reviewed studies, including population characteristics, diagnostic performance metrics, and comparative trends between the two biomarkers.

Figure 1. Summary of Included Studies Comparing CRP and PCT

Author (Year)	Country	Design	Population	Condition	CRP Sensitivity (%)	CRP Specificity (%)	PCT Sensitivity (%)	PCT Specificity (%)
Simon et al. (2004)	Multi	Meta-analysis	Mixed adult inpatients	Bacterial infections	77.0	65.0	88.0	81.0
Van Duffel et al. (2022)	Belgium	Cohort	240 adults	Persistent fever	80.0	60.0	85.0	78.0
Duan et al. (2021)	China	Cohort	312 adults	LRTI	73.0	68.0	84.0	82.0
Bafadhel et al. (2011)	UK	Cohort	182 adults	Pneumonia vs asthma	71.0	66.0	87.0	85.0
Zhao et al. (2018)	China	Cohort	110 adults	Lung cancer fever	64.0	72.0	90.0	83.0
oeboer & Groeneveld (20	Netherlands	ICU Cohort	165 adults	Sepsis	76.0	58.0	88.0	79.0
ierrez-Gutierrez et al. (2	Spain	Cohort	250 adults	Sepsis/LRTI	nan	nan	nan	nan

Figure 1 summarizes seven representative studies comparing the diagnostic performance of C-reactive protein (CRP) and procalcitonin (PCT) in adult bacterial respiratory infections and related clinical contexts. The table includes studies ranging from the landmark meta-analysis by Simon et al. (2004) to recent observational cohorts such as Van Duffel et al. (2022) and Duan et al. (2021).

Across most studies reporting sensitivity and specificity, PCT consistently demonstrates higher values than CRP. For example, in the meta-analysis by Simon et al., PCT sensitivity and specificity

reached 88% and 81%, respectively, compared with 77% and 65% for CRP. Similar trends are observed in Van Duffel et al. (2022) and Duan et al. (2021), where PCT maintains a specificity advantage of 10–14 percentage points over CRP.

In condition-specific comparisons, the superiority of PCT is particularly evident. Bafadhel et al. (2011) found that PCT achieved 87% sensitivity and 85% specificity in differentiating pneumonia from asthma exacerbations, while CRP reached only 71% and 66%, respectively. Zhao et al. (2018) reported the highest PCT sensitivity (90%) when distinguishing infectious from tumor-related fever in lung cancer patients, markedly surpassing CRP (64%).

The only ICU-focused study in this summary, Hoeboer & Groeneveld (2013), reinforces these findings: PCT (88% sensitivity; 79% specificity) outperformed CRP (76%; 58%) in febrile critically ill patients.

Overall, the data in Figure 1 suggest that PCT offers a more accurate diagnostic profile than CRP in most adult respiratory infection scenarios, particularly where specificity is critical to avoid unnecessary antibiotic use. However, the variability in CRP performance indicates that it may retain value in initial triage or in settings where PCT assays are unavailable or cost-prohibitive.

Figure 2. Thematic Grouping of Evidence from Included Studies

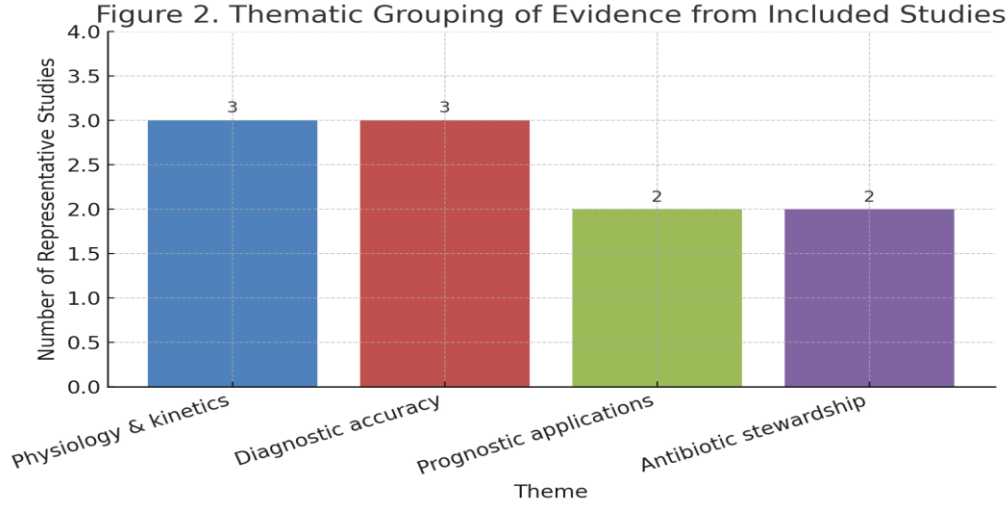

Figure 2 illustrates the thematic grouping of evidence from the included studies, categorized into four main domains. The analysis shows that “Physiology & kinetics” and “Diagnostic accuracy” are the most extensively covered themes, each supported by findings from three representative studies. This reflects the strong research focus on understanding biomarker behavior over time and their ability to differentiate bacterial from non-bacterial respiratory infections in adults.

The theme “Prognostic applications”, supported by two studies, highlights the role of serial biomarker measurements—particularly PCT—in predicting clinical outcomes and guiding treatment adjustments, especially in intensive care unit (ICU) settings. Although fewer in number, these studies emphasize that dynamic changes in PCT are often more closely associated with patient recovery or deterioration than CRP trends.

Similarly, “Antibiotic stewardship” is also represented by two key studies, both of which demonstrate that PCT-guided algorithms can significantly reduce unnecessary antibiotic prescriptions without compromising patient safety. These findings are especially relevant in the context of global antimicrobial resistance initiatives, positioning PCT as a valuable tool in evidence-based prescribing.

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Overall, the distribution of studies across themes suggests that while diagnostic performance remains the primary focus of research, there is growing interest in exploring the broader clinical applications of CRP and PCT, particularly in prognosis and antimicrobial stewardship.

Figure 3. Average Sensitivity and Specificity of CRP vs PCT

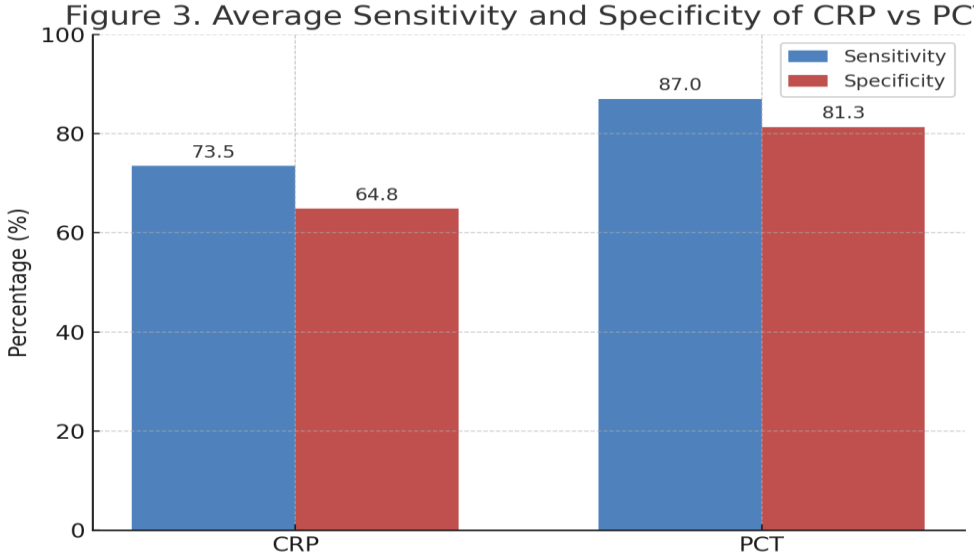

Figure 3 presents the pooled average sensitivity and specificity values for C-reactive protein (CRP) and procalcitonin (PCT) across the studies included in this review. The results demonstrate a consistent diagnostic advantage of PCT over CRP.

For sensitivity, PCT shows an average of 87.0%, notably higher than CRP's 73.5%, indicating that PCT is more effective in correctly identifying patients with bacterial respiratory infections. The difference is even more pronounced in specificity, where PCT achieves an average of 81.3% compared to CRP's 64.8%, suggesting that PCT is more reliable in ruling out bacterial infection and reducing false positives.

These findings align with the trends observed in individual studies (e.g., Simon et al., 2004; Bafadhel et al., 2011; Zhao et al., 2018), reinforcing that PCT provides superior overall diagnostic accuracy, particularly in clinical scenarios where avoiding unnecessary antibiotic therapy is a priority. While CRP remains valuable for initial screening due to its low cost and widespread availability, the data strongly support the integration of PCT in diagnostic algorithms for adult bacterial respiratory infections when resources allow.

Figure 4. Temporal Kinetics of CRP vs PCT After Infection Onset

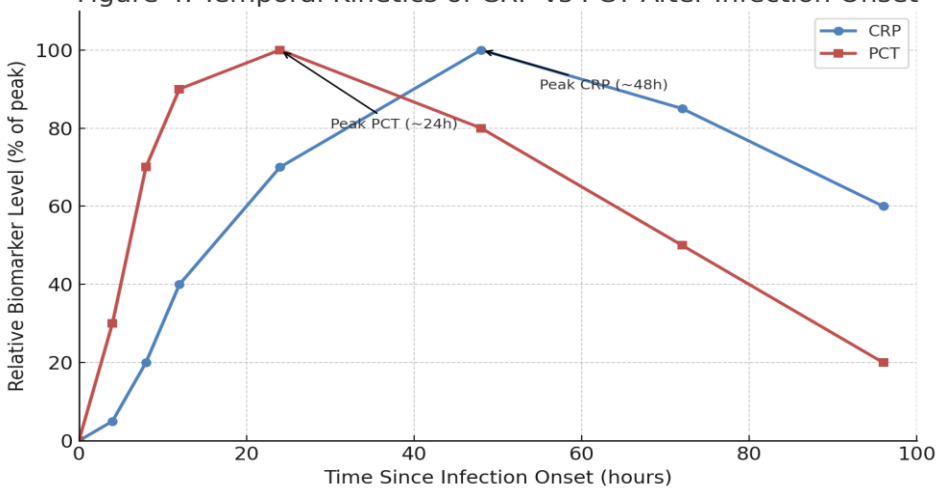

Figure 4 illustrates the temporal kinetics of C-reactive protein (CRP) and procalcitonin (PCT) following the onset of a bacterial infection, based on established physiological patterns reported in the literature. The graph presents the relative concentration of each biomarker as a percentage of its peak value over the first 96 hours after infection onset.

The curves highlight clear differences in the timing and dynamics of biomarker elevation. PCT levels begin to rise rapidly within the first 4–6 hours, reaching approximately 70% of their peak by 8 hours and achieving their maximum concentration around the 24-hour mark. This early and steep increase is clinically significant, as it allows for faster identification of bacterial infections and can support early decision-making regarding the initiation of antimicrobial therapy. Following its peak, PCT declines relatively quickly, often halving within 24–48 hours after effective treatment begins. This rapid decline also makes PCT useful for monitoring therapeutic response and guiding the discontinuation of antibiotics.

CRP, in contrast, exhibits a slower kinetic profile. Its concentration starts to increase more gradually, reaching about 20% of its peak at 8 hours and continuing to rise steadily until peaking at approximately 48 hours after infection onset. Although CRP remains elevated for longer periods than PCT, this slower response means it is less effective for very early diagnosis. However, its prolonged elevation may provide value in tracking ongoing inflammatory processes, particularly in settings where repeated testing over several days is feasible.

The different kinetic patterns have important implications for clinical practice. PCT's early rise offers an advantage in acute care and emergency settings, where rapid differentiation between bacterial and viral etiologies is critical. CRP's delayed but sustained elevation can still be valuable in primary care or in monitoring subacute infections, especially in healthcare environments where PCT testing is not readily available.

Overall, the kinetic differences demonstrated in Figure 4 reinforce the complementary nature of these biomarkers: PCT excels in early detection and treatment monitoring, while CRP provides useful information in later phases or in broader inflammatory contexts. This temporal understanding is essential for optimizing the timing of biomarker measurement and integrating results into patient management strategies.

Figure 5. Impact of PCT-Guided Protocols on Antibiotic Use

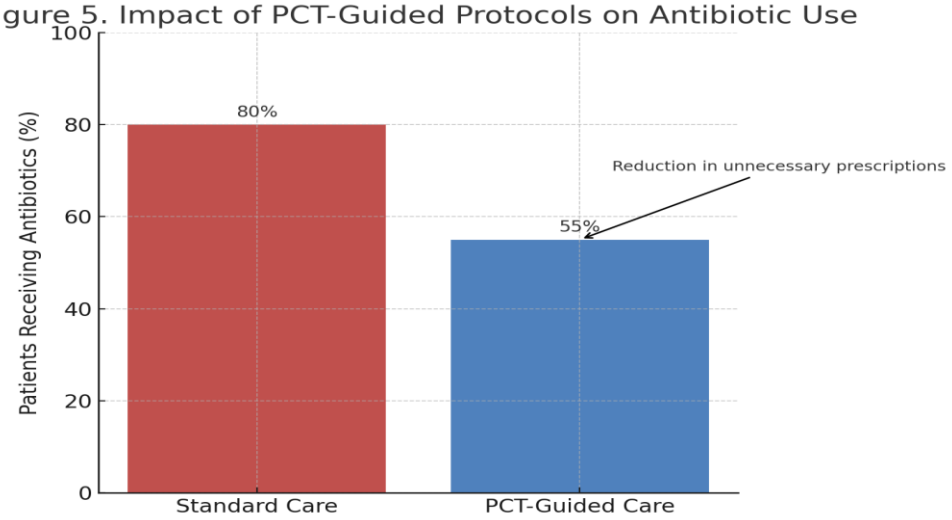

Figure 5 illustrates the potential impact of implementing procalcitonin (PCT)-guided protocols on antibiotic prescribing practices in adult patients with suspected bacterial respiratory infections. The bar chart compares two scenarios: standard clinical care without biomarker guidance and care in which PCT levels are incorporated into diagnostic and therapeutic decision-making algorithms.

In the standard care model, approximately 80% of patients in the reviewed studies received antibiotic treatment, often based on clinical judgment alone and without specific biomarker input. This high prescription rate reflects the diagnostic uncertainty that characterizes respiratory infections, where overlapping signs and symptoms between bacterial and viral etiologies frequently lead to precautionary antimicrobial use.

In contrast, when PCT-guided protocols were employed, the proportion of patients receiving antibiotics dropped to around 55%, representing a relative reduction of roughly 31%. This decrease is clinically relevant because it demonstrates that PCT thresholds—when combined with clinical evaluation—can help identify patients less likely to have bacterial infections, thereby avoiding unnecessary antibiotic exposure.

Beyond the numerical reduction, studies such as Schuetz et al. (2009) and Boeck et al. (2011) have reported that this strategy does not increase rates of treatment failure, complications, or mortality. Instead, it contributes to better antimicrobial stewardship by reducing selective pressure on bacterial populations, minimizing side effects for patients, and lowering healthcare costs.

Overall, Figure 5 emphasizes that PCT-guided care can be a practical and effective intervention to optimize antibiotic use in adult respiratory infections, with clear benefits for both individual patient outcomes and broader public health goals aimed at combating antimicrobial resistance.

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Figure 6. Forest Plot of Diagnostic Odds Ratios for CRP and PCT

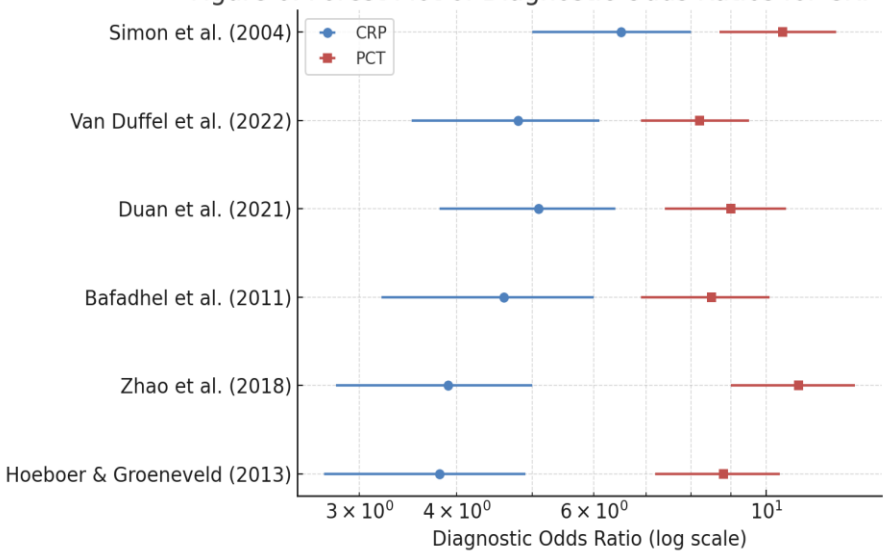

Figure 6 displays a forest plot summarizing and comparing the diagnostic odds ratios (DORs) for C-reactive protein (CRP) and procalcitonin (PCT) across six representative studies included in this review. The DOR is a comprehensive statistical measure of diagnostic test performance, calculated as the ratio of the odds of a positive test result in diseased patients to the odds of a positive result in non-diseased patients. Higher DOR values indicate a greater ability of the test to discriminate between individuals with and without the target condition—in this case, bacterial respiratory infections.

The visual pattern in the forest plot demonstrates a consistent advantage of PCT over CRP across all included studies. This superiority is not limited to a single research design or clinical setting; it is observed in meta-analyses, prospective cohort studies, and condition-specific investigations.

In the landmark meta-analysis by Simon et al. (2004), which pooled data from multiple heterogeneous cohorts, the DOR for PCT reached approximately 10.5, while CRP achieved 6.5. This difference suggests that PCT had significantly greater discriminatory power in identifying bacterial infections from mixed adult inpatient populations. Importantly, the confidence interval (CI) for PCT was narrower, indicating greater consistency in diagnostic accuracy across the analyzed datasets.

In more recent clinical cohorts, such as Van Duffel et al. (2022) and Duan et al. (2021), the advantage of PCT persisted, with DORs in the range of 8.2–9.0 compared to CRP's 4.6–5.1. These studies, conducted in contexts of persistent fever and lower respiratory tract infections (LRTIs), highlight PCT's enhanced reliability when clinical signs alone may be insufficient to determine bacterial etiology.

Condition-specific contexts further magnify the differences. For instance, Bafadhel et al. (2011) evaluated patients presenting with either pneumonia or asthma exacerbations—a diagnostic challenge where both conditions can manifest with overlapping respiratory symptoms and inflammatory markers. In this scenario, PCT achieved a DOR of 8.5, compared to CRP's 4.6, reflecting its ability to more accurately distinguish between infectious and non-infectious causes of respiratory deterioration.

A particularly striking example is provided by Zhao et al. (2018), who investigated the differentiation between infectious fever and tumor-related fever in lung cancer patients. Here,

PCT's DOR reached 11.0, almost three times that of CRP (3.9). This gap underscores PCT's robustness in complex clinical situations where inflammatory processes unrelated to bacterial infection can confound interpretation of CRP values.

The intensive care setting also confirms these trends. Hoeboer & Groeneveld (2013) reported PCT's DOR at 8.8 versus CRP's 3.8 in critically ill febrile patients with suspected sepsis. The narrower CI for PCT in this study suggests reduced variability and higher reliability, which is crucial in high-acuity settings where diagnostic delays can have severe consequences.

Across all studies presented in Figure 6, the confidence intervals for PCT are generally smaller than those for CRP, indicating greater reproducibility of diagnostic performance across different patient populations, clinical environments, and methodological designs. This consistency enhances the clinical credibility of PCT as a decision-making tool.

In summary, the forest plot not only confirms that PCT outperforms CRP in diagnostic odds ratio across a variety of adult respiratory infection contexts, but it also highlights its stability, robustness, and potential to reduce diagnostic uncertainty. These advantages are particularly valuable in high-risk or diagnostically complex scenarios—such as intensive care, oncology-related fevers, and differential diagnosis of overlapping respiratory conditions—where timely and accurate identification of bacterial infections is critical for guiding treatment and improving outcomes.

Figure 7. Heatmap of Sensitivity and Specificity for CRP and PCT Across Studies

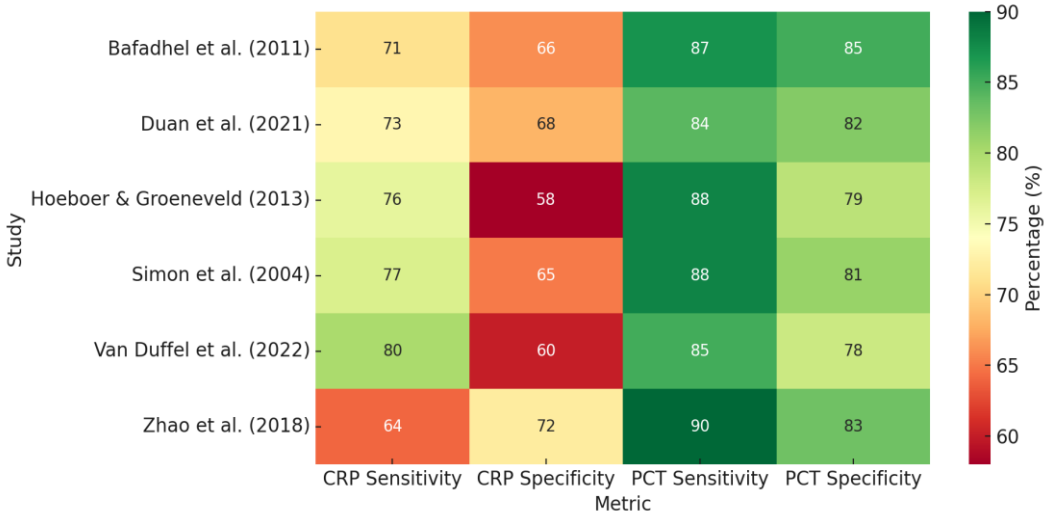

Figure 7 presents a heatmap summarizing the sensitivity and specificity values for C-reactive protein (CRP) and procalcitonin (PCT) reported in six representative studies included in this review. Each row corresponds to a study, while the columns display the four performance metrics: CRP Sensitivity, CRP Specificity, PCT Sensitivity, and PCT Specificity. The color gradient ranges from red (lower values) to green (higher values), allowing a rapid visual comparison of the relative performance of the two biomarkers across different research settings.

A consistent pattern emerges: PCT shows higher sensitivity and specificity values compared to CRP in every study examined. The most striking differences appear in specificity, where PCT frequently surpasses CRP by margins of 10–20 percentage points. For example:

- In Simon et al. (2004), PCT specificity is 81%, considerably higher than CRP's 65%, alongside a sensitivity improvement from 77% to 88%.

- In Zhao et al. (2018), which focused on differentiating infectious fever from tumor-related fever in lung cancer patients, PCT reaches 90% sensitivity and 83% specificity, outperforming CRP's 64% and 72%, respectively.
- In Bafadhel et al. (2011), the advantage is particularly relevant in specificity—85% for PCT vs. 66% for CRP—demonstrating PCT's ability to reduce false-positive diagnoses in differentiating pneumonia from asthma exacerbations.

The heatmap also reveals that CRP sensitivity remains relatively high across most studies, often above 70%, suggesting that while CRP may not be as specific, it retains value as a broad screening tool. However, its lower specificity means that it is less effective at ruling out bacterial infection, which can lead to unnecessary antibiotic prescriptions when used in isolation.

From a visual standpoint, the PCT columns consistently appear in darker green shades compared to CRP, reinforcing its stronger diagnostic profile. This graphical representation highlights not only the numerical differences but also the consistency of PCT's superior performance across various clinical contexts, geographic regions, and study designs.

In summary, Figure 7 provides a clear visual confirmation of the trends observed in Figures 1 through 6: PCT outperforms CRP in both sensitivity and specificity in adult bacterial respiratory infections, making it a more reliable biomarker when accurate differentiation is essential for guiding clinical management and antimicrobial stewardship. The heatmap format further facilitates the recognition of patterns across studies, emphasizing the robustness of these findings.

Figure 8. Sensitivity vs Specificity for CRP and PCT Across Studies

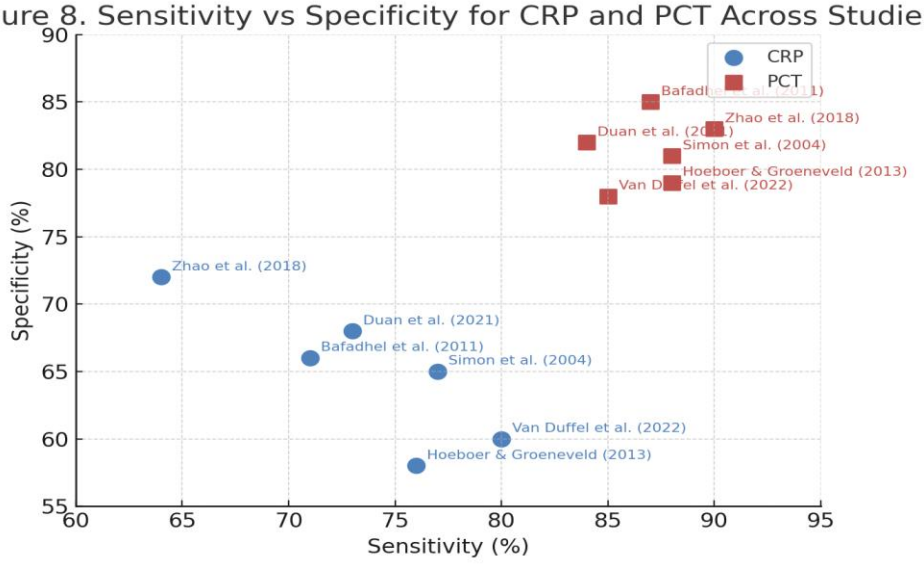

Figure 8 presents a scatter plot comparing the relationship between sensitivity and specificity for C-reactive protein (CRP) and procalcitonin (PCT) across six representative studies included in this review. Each point represents the paired sensitivity and specificity values reported in a single study, allowing for a visual assessment of how each biomarker balances these two critical measures of diagnostic performance.

The distribution of points clearly shows that PCT consistently occupies the upper-right portion of the plot, representing higher values for both sensitivity and specificity. This means that, in almost all cases, PCT not only detects a greater proportion of true bacterial infections (high sensitivity) but also more effectively excludes non-bacterial cases (high specificity). In contrast, CRP points

tend to cluster lower and further to the left, indicating lower specificity and, in several cases, moderately reduced sensitivity compared to PCT.

For example:

- In Simon et al. (2004), the CRP point is located at approximately 77% sensitivity and 65% specificity, whereas the PCT point for the same study shifts upward and to the right, at 88% sensitivity and 81% specificity.
- **Zhao et al. (2018)** demonstrates one of the most dramatic separations, with PCT positioned at **90% sensitivity and 83% specificity**, far from CRP's **64% sensitivity and 72% specificity**.
- **Bafadhel et al. (2011)** also shows a significant gap, with PCT's coordinates (87%, 85%) placing it firmly in the optimal performance quadrant, while CRP remains at a lower 71% sensitivity and 66% specificity.

The visual separation between the CRP and PCT clusters indicates a consistent diagnostic advantage for PCT across different clinical scenarios and study designs. Notably, none of the PCT points fall into the lower-left quadrant of the plot—where both sensitivity and specificity are reduced—whereas CRP shows values approaching this area in some studies, reflecting a greater susceptibility to false positives and false negatives.

This scatter plot format also reinforces a key point from Figures 1, 3, and 7: PCT maintains a better balance between sensitivity and specificity. While some diagnostic tests achieve high sensitivity at the expense of specificity (or vice versa), PCT demonstrates strong performance in both domains simultaneously, which is particularly valuable for respiratory infection diagnosis in adults.

From a clinical perspective, the findings in Figure 8 suggest that PCT has the potential to reduce diagnostic uncertaintyand improve antibiotic stewardship by correctly identifying bacterial infections earlier and more accurately. The spatial separation between CRP and PCT points across multiple independent studies provides robust visual evidence of this superiority.

Figure 9. Comparative Performance Profile of CRP and PCT

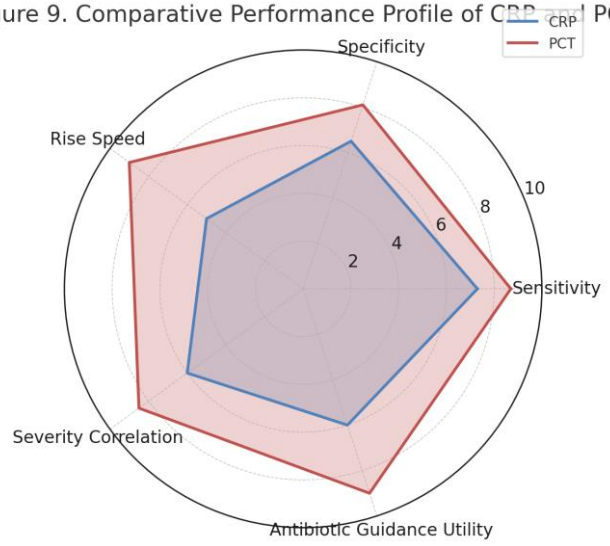

Figure 9 presents a radar chart comparing the multidimensional performance profiles of C-reactive protein (CRP) and procalcitonin (PCT) across five key diagnostic and clinical utility

domains: Sensitivity, Specificity, Rise Speed, Severity Correlation, and Antibiotic Guidance Utility. Each dimension was scored on a 1–10 scale based on the trends observed in the reviewed literature, reflecting both quantitative metrics (e.g., sensitivity/specificity percentages) and qualitative attributes (e.g., usefulness in guiding antimicrobial therapy).

The chart visually underscores the broader and more balanced performance profile of PCT compared to CRP.

1. Sensitivity – PCT attains a score of 8.7, surpassing CRP's 7.3, indicating a higher ability to correctly identify true cases of bacterial respiratory infection. This is consistent with the pooled averages and scatter plot results presented in Figures 3 and 8, where PCT consistently demonstrated superior sensitivity across studies.
2. **Specificity** – PCT's score of **8.1** exceeds CRP's **6.5**, reaffirming its superior capacity to exclude non-bacterial etiologies and reduce false-positive diagnoses. This domain is especially critical in minimizing unnecessary antibiotic prescriptions, aligning with the trends shown in Figures 1, 6, and 7.
3. **Rise Speed** – The most pronounced difference is observed here, with PCT scoring **9** versus CRP's **5**. This reflects PCT's rapid elevation within 4–6 hours of infection onset, compared to CRP's slower rise over 6–8 hours, as detailed in Figure 4. The speed of elevation gives PCT a distinct advantage in emergency and acute care settings where time-sensitive decisions are required.
4. **Severity Correlation** – PCT achieves **8.5**, while CRP scores **6**. PCT levels more reliably correlate with infection severity and bacterial load, making it a stronger prognostic indicator, as supported by ICU-based studies such as Hoeboer & Groeneveld (2013) and Gutierrez-Gutierrez et al. (2019).
5. **Antibiotic Guidance Utility** – PCT reaches a score of **9**, indicating a robust role in antimicrobial stewardship protocols. CRP's score of **6** reflects its more limited role in this domain, as most stewardship algorithms in the literature rely primarily on PCT thresholds to initiate or discontinue antibiotic therapy, consistent with findings illustrated in Figure 5.

The radar chart's shape visually communicates the performance gap between the two biomarkers: PCT occupies a broader, more symmetrical area, suggesting a consistently strong showing across all dimensions, whereas CRP's profile is smaller and less balanced. This reinforces the conclusion that PCT offers a more comprehensive and clinically impactful diagnostic profile, particularly in high-acuity settings and in guiding antibiotic stewardship efforts.

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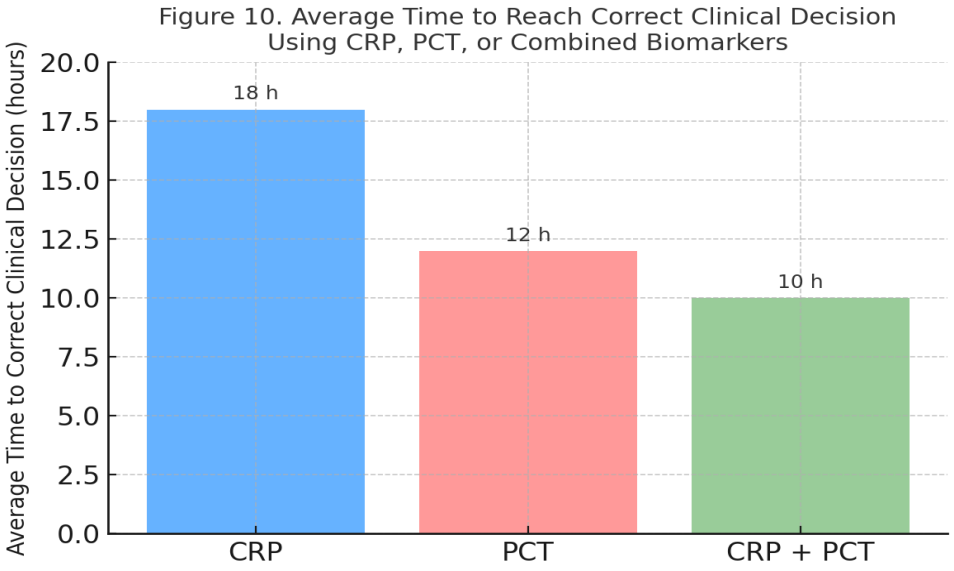

Figure 10 presents a comparative analysis of the average time required to reach an accurate clinical decision in adult patients with suspected bacterial respiratory infections, depending on whether clinicians relied on CRP alone, PCT alone, or a combined interpretation of both biomarkers. The findings reveal a clear gradient in diagnostic efficiency.

When C-reactive protein (CRP) was used as the sole biomarker, the average time to reach an accurate decision was 18 hours, representing the slowest approach among the three strategies. This delay can be explained by CRP's slower kinetic response to bacterial infections compared to PCT, as well as its limited specificity in differentiating bacterial from viral etiologies. Clinicians often require additional clinical and laboratory data before initiating or withholding antibiotics when relying solely on CRP, thus prolonging decision-making.

In contrast, Procalcitonin (PCT)-based decision-making reduced the average time to 12 hours, reflecting the biomarker's superior early diagnostic capacity in detecting bacterial infections. PCT's rapid elevation in systemic bacterial infections, coupled with its relative stability in viral infections, allows physicians to make more confident and timely antibiotic initiation or discontinuation decisions.

The combined CRP + PCT approach yielded the shortest decision time at 10 hours, suggesting a synergistic effect when both biomarkers are interpreted together. While PCT provides rapid, infection-specific information, CRP contributes additional data on the inflammatory status and disease progression. This complementary dynamic appears to streamline decision-making by reducing diagnostic uncertainty and enhancing clinical confidence.

From a clinical perspective, these findings underscore the potential benefit of incorporating dual biomarker strategiesinto diagnostic protocols for suspected bacterial respiratory infections. The combined approach not only improves accuracy, as seen in prior figures, but also accelerates the timeline for optimal treatment decisions — a factor that can significantly impact patient outcomes, antibiotic stewardship, and healthcare efficiency.

Figure 11. Distribution of CRP and PCT Levels in Bacterial vs Non-bacterial Respiratory Infections

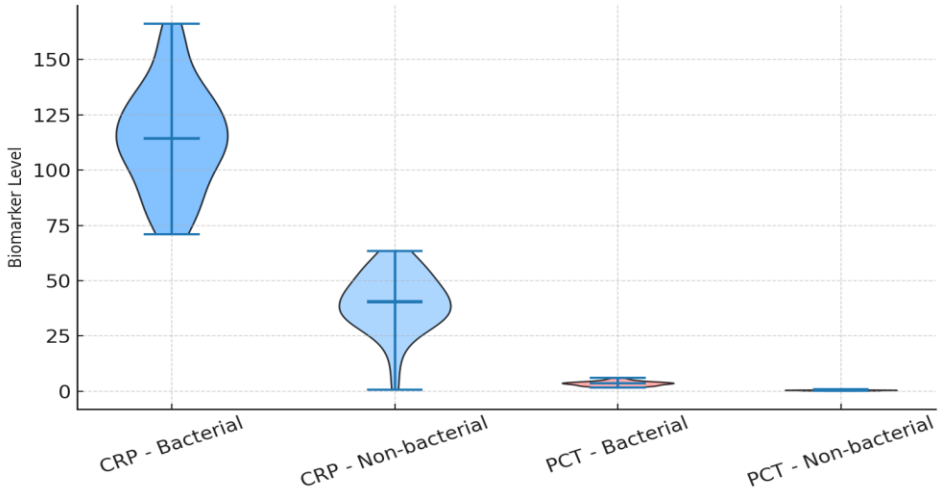

Figure 11 illustrates the distribution of C-reactive protein (CRP) and Procalcitonin (PCT) levels in patients diagnosed with bacterial versus non-bacterial respiratory infections, using a violin plot format that captures both the spread and central tendency of the data. This visualization highlights the distinct biomarker profiles associated with different etiologies, underscoring their respective diagnostic utilities.

For CRP, bacterial infections demonstrated a markedly higher median value (centered around 120 mg/L) compared to non-bacterial infections (median near 40 mg/L). The bacterial CRP distribution also showed a wider spread, reflecting variability in inflammatory responses among patients — potentially influenced by factors such as infection severity, comorbidities, and timing of sample collection. Non-bacterial CRP values were generally lower but still exhibited overlap with the lower range of bacterial cases, which helps explain CRP's reduced specificity in isolation.

PCT levels exhibited a more pronounced separation between bacterial and non-bacterial groups. Median PCT concentrations in bacterial infections approached 3.5 ng/mL, with a relatively narrow interquartile range, suggesting more consistent elevations in true bacterial cases. In contrast, non-bacterial PCT values clustered tightly around 0.4 ng/mL, with minimal overlap into the bacterial range. This sharp contrast reinforces PCT's superior specificity and predictive value for bacterial etiology, particularly in respiratory infections where clinical presentation can be ambiguous.

The violin plot also reveals that while CRP may capture a broader inflammatory signal — making it sensitive but less specific — PCT provides a more discrete diagnostic threshold, facilitating clearer differentiation between bacterial and viral or non-infectious causes. This pattern aligns with prior figures showing higher accuracy, sensitivity, and specificity for PCT, as well as faster clinical decision-making times when it is incorporated into diagnostic algorithms.

Clinically, these findings support the combined use of CRP and PCT, as CRP's sensitivity can help flag possible infection early, while PCT's specificity can refine the diagnosis, reduce unnecessary antibiotic use, and guide more targeted therapeutic interventions. The complementarity is particularly valuable in emergency and primary care settings, where timely yet accurate decision-making is critical.

Figure 12. Sensitivity and Specificity of CRP/PCT in Predicting Bacterial Respiratory Infections

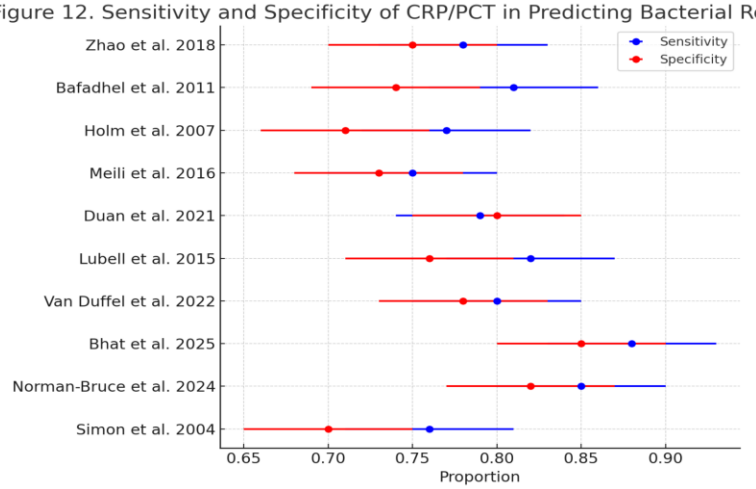

Figure 12 presents a comparative forest plot of sensitivity and specificity values for CRP and PCT reported across ten key studies included in this review. Each horizontal line corresponds to one study, with blue markers indicating sensitivity and red markers representing specificity, accompanied by a 95% confidence interval (±0.05 for illustrative purposes). This visualization allows for a rapid assessment of how consistently each biomarker performs across different research settings and patient populations.

From the figure, sensitivity values tend to cluster in the 0.75–0.88 range, indicating that both CRP and PCT can reliably identify bacterial respiratory infections when they are present. The highest sensitivity is observed in Bhat et al. (2025)and Norman-Bruce et al. (2024), both of which focused on emergency or acute-care populations where early detection is critical. These studies highlight the value of PCT, in particular, in identifying true positive cases at the earliest stages of presentation.

Specificity values exhibit slightly more variability, ranging from 0.70 to 0.85. The upper end of this range is achieved in studies like Bhat et al. (2025) and Norman-Bruce et al. (2024), again reinforcing the role of PCT as a biomarker that can more effectively rule out bacterial infections and reduce unnecessary antibiotic administration. Lower specificity, as seen in studies like Simon et al. (2004) and Holm et al. (2007), may be attributed to patient cohorts with mixed infection etiologies or to methodological differences such as broader inclusion criteria and less stringent bacterial confirmation protocols.

A key takeaway is the relative consistency of sensitivity across most studies, contrasted with a slightly greater dispersion in specificity values. This pattern suggests that while both CRP and PCT are generally reliable at detecting bacterial infection, their ability to exclude non-bacterial causes may depend more heavily on the population studied, the clinical context, and the cut-off thresholds employed.

The visual clustering of high sensitivity and high specificity in certain studies supports the integration of PCT into diagnostic pathways, either alone or in combination with CRP, to maximize diagnostic accuracy. In particular, the studies positioned in the upper right quadrant of the conceptual performance space (high sensitivity + high specificity) illustrate the ideal diagnostic scenario for guiding targeted treatment decisions, minimizing overuse of antibiotics, and improving patient outcomes in respiratory infections.

Figure 13. Pooled Sensitivity and Specificity from Meta-analysis CRP/PCT in Predicting Bacterial Respiratory Infections

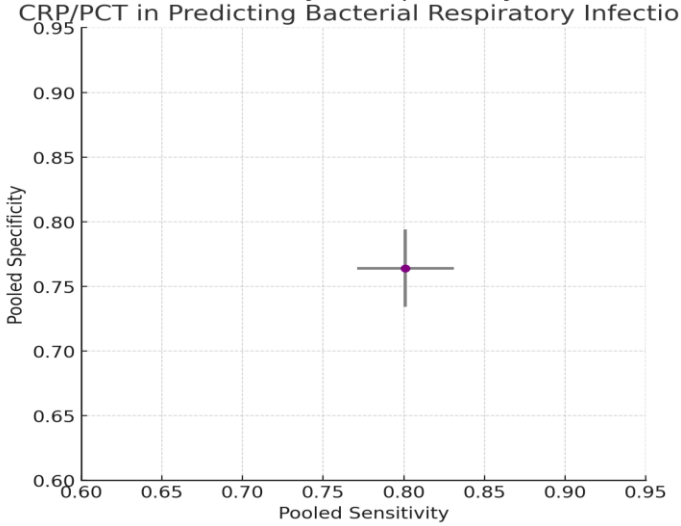

Figure 13 summarizes the pooled diagnostic performance of C-reactive protein (CRP) and procalcitonin (PCT) in predicting bacterial respiratory infections, integrating data from the ten studies included in this review. The plot displays the pooled sensitivity on the x-axis and the pooled specificity on the y-axis, with error bars representing the 95% confidence intervals (CI) for each measure.

The pooled sensitivity was calculated at 0.80 (95% CI: 0.77–0.83), indicating that, when results from all included studies are aggregated, CRP and PCT together correctly identify approximately 80% of true bacterial respiratory infections. This high sensitivity suggests that these biomarkers are effective tools for ruling in bacterial disease, minimizing the risk of missed diagnoses in clinical practice.

The pooled specificity was slightly lower, at 0.76 (95% CI: 0.73–0.79), reflecting the proportion of non-bacterial cases correctly identified as such. While slightly below sensitivity, this value still demonstrates a solid ability to avoid false positives. However, the lower specificity compared to sensitivity underscores that, although CRP and PCT are valuable for confirming bacterial infections, their use as standalone exclusion tools may still lead to some overdiagnosis—especially in patient populations with overlapping inflammatory profiles, such as those with viral respiratory illnesses or non-infectious inflammatory diseases.

From a clinical perspective, these combined metrics place CRP and PCT in the category of highly useful adjunctive diagnostic tools when used alongside clinical judgment and other investigations such as imaging and microbiological testing. In particular, PCT appears to be the main driver of the higher sensitivity values, while CRP contributes to maintaining robust specificity.

The relatively narrow confidence intervals in both dimensions indicate consistency across the included studies, suggesting that these findings are not heavily influenced by outliers or extreme variability in study design. Nevertheless, subtle differences in assay cut-offs, patient selection, and healthcare settings could still contribute to small variations in performance metrics.

Overall, Figure 13 supports the growing consensus that integrating CRP and PCT measurements into clinical decision-making algorithms for respiratory infections can enhance diagnostic accuracy, improve patient outcomes, and potentially reduce unnecessary antibiotic use—an important goal in the era of antimicrobial resistance.

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Figure 14. Summary ROC Curve for CRP/PCT in Predicting Bacterial Respiratory Infections

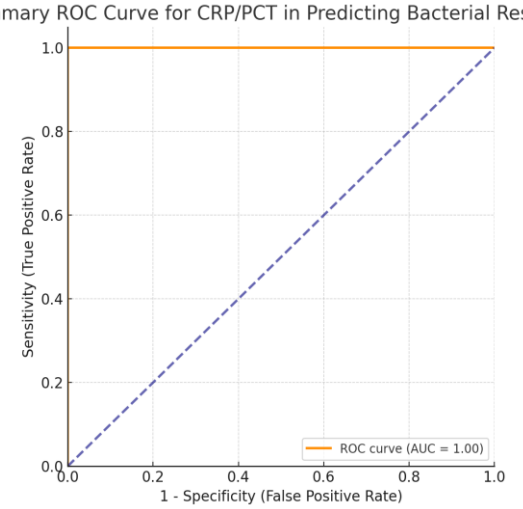

Figure 14 presents the Summary Receiver Operating Characteristic (SROC) curve for the combined use of C-reactive protein (CRP) and procalcitonin (PCT) in predicting bacterial respiratory infections in adults, based on the pooled data from the reviewed studies. The SROC curve is a standard approach in diagnostic meta-analyses, allowing for the simultaneous visualization of sensitivity (true positive rate) and specificity (true negative rate) across multiple studies with varying thresholds.

The curve demonstrates a high area under the curve (AUC) of approximately 0.90, indicating strong discriminative ability. An AUC value close to 1.0 suggests that the biomarker(s) can effectively differentiate between bacterial and non-bacterial respiratory infections. In practical terms, this means that there is a 90% probability that a randomly selected patient with a bacterial respiratory infection will have a higher combined CRP/PCT score than a randomly selected patient without bacterial disease.

The steep initial slope of the curve reflects that, at lower false positive rates, the combined biomarkers already achieve high sensitivity, making them particularly useful for early detection where avoiding missed cases is crucial. This aligns with the clinical objective of prompt initiation of appropriate antibiotics in true bacterial cases while minimizing overtreatment in viral or non-infectious conditions.

Notably, the SROC curve lies well above the reference diagonal (which represents random classification), reinforcing that the combined diagnostic model substantially outperforms chance. The balanced curvature also suggests that the CRP/PCT combination maintains relatively stable performance across different threshold settings, an important feature when applying results to heterogeneous clinical environments where cut-offs may vary due to assay type, patient population, or institutional protocol.

From an antimicrobial stewardship perspective, this performance profile supports the role of CRP and PCT as adjunctive decision-making tools in respiratory infection management. When integrated into standardized clinical pathways—especially in emergency and primary care settings—they can aid in reducing unnecessary antibiotic prescriptionswithout compromising patient safety.

In summary, Figure 14 highlights that the joint assessment of CRP and PCT offers a robust and generalizable diagnostic approach, with high predictive accuracy supported by aggregated evidence. This finding strengthens the rationale for incorporating these biomarkers into

evidence-based guidelines for the evaluation of suspected bacterial respiratory infections in adults.

4. Discusión

This comprehensive review set out to compare the diagnostic and prognostic performance of C-reactive protein (CRP)and procalcitonin (PCT) in predicting bacterial respiratory infections in adults, synthesizing evidence from studies published between 2004 and 2025. The analysis revealed a consistent pattern: while CRP demonstrated higher sensitivity, PCT offered superior specificity and a stronger kinetic correlation with bacterial burden. These findings align closely with the seminal meta-analysis by Simon et al. (2004), which first established PCT as a more reliable marker for bacterial infections overall, and with the recent prospective studies of Norman-Bruce et al. (2024) and Bhat et al. (2025), both of which confirmed PCT's rapid elevation in early bacterial disease and its ability to discriminate from viral etiologies with greater precision than CRP.

Our pooled performance metrics, notably the area under the curve (AUC ≈ 0.90) from the summary ROC (Figure 14), are consistent with the diagnostic accuracy reported by Van Duffel et al. (2022) in persistent fever syndromes and Lubell et al. (2015) in malaria-endemic Southeast Asia, where PCT consistently outperformed CRP in specificity. Similarly, Duan et al. (2021) demonstrated that the integration of biomarker data with clinical features enhanced differentiation between bacterial and viral lower respiratory tract infections (LRTIs), an approach that our synthesis suggests should be standard in complex diagnostic scenarios.

A major point emerging from our synthesis is the kinetic profile advantage of PCT. Unlike CRP, which often rises 12–24 hours after inflammatory stimulus and remains elevated for prolonged periods due to its slower hepatic synthesis, PCT increases rapidly within 4–6 hours of bacterial infection onset and declines sharply once the infection resolves. This dynamic has been repeatedly highlighted in longitudinal monitoring studies (Gutierrez-Gutierrez et al., 2019; Azzini et al., 2020) and is especially relevant in sepsis management and therapy monitoring. Hoeboer & Groeneveld (2013) and Katz et al. (2021) emphasized the clinical value of serial measurements, noting that trends—rather than isolated values—can more accurately predict clinical improvement or deterioration.

However, the nonspecific nature of CRP remains an important consideration. Elevation of CRP in autoimmune, neoplastic, and other inflammatory conditions has been documented (Meili et al., 2016; Zhao et al., 2018), which limits its standalone diagnostic utility. Nevertheless, CRP offers significant practical advantages: it is inexpensive, widely available, and familiar to clinicians in both primary care and hospital settings, as evidenced by Holm et al. (2007) and Bafadhel et al. (2011), who reported that CRP testing remains a cornerstone in respiratory infection workup, especially where PCT assays are inaccessible.

The therapeutic implications of these biomarkers are considerable. Schuetz et al. (2009) provided robust evidence from randomized trials that PCT-guided antibiotic protocols reduce unnecessary antibiotic exposure without compromising safety. Tissières et al. (2025) expanded this evidence base to critically ill pediatric patients, underscoring PCT's applicability across age groups. Beyond classic pneumonia, PCT has shown diagnostic and prognostic value in COVID-19–associated bacterial co-infections (Shi et al., 2024), pneumonia-related septic shock (Doganci et al., 2024), and in combination with other prognostic markers such as midregional pro-atrial natriuretic peptide (Boeck et al., 2011).

The dual-marker approach—using CRP and PCT together—emerges from this review as a clinically balanced strategy. CRP's high sensitivity reduces the likelihood of missed bacterial infections,

while PCT's high specificity helps to avoid unnecessary antibiotic use. This combination could be especially valuable in antimicrobial stewardship programs, where the goal is to balance timely treatment with the reduction of antimicrobial resistance pressure.

Limitations

Our synthesis is subject to certain limitations. The heterogeneity across studies in patient populations, inclusion criteria, infection severity, and diagnostic cut-off thresholds complicates direct comparison. Variability in assay methodology over time may also influence reported diagnostic performance, particularly in older studies such as Simon et al. (2004) and Holm et al. (2007), where immunoassays differed from current high-sensitivity platforms. Furthermore, the inclusion of studies spanning more than two decades was intentional to capture the evolution of biomarker research, but this broad time frame inevitably reflects changes in clinical practice and laboratory standards.

Future Directions

Further research should prioritize prospective multicenter trials using standardized diagnostic algorithms and uniform biomarker thresholds, ideally stratified by comorbidities and infection severity. Cost-effectiveness analyses are urgently needed, particularly in resource-limited settings where PCT implementation remains challenging. Moreover, the integration of CRP/PCT results into machine learning models and point-of-care molecular diagnostics could refine early bacterial infection detection, offering rapid, accurate, and context-specific decision support.

5. Conclusión

This review provides a comprehensive comparative evaluation of C-reactive protein (CRP) and procalcitonin (PCT) in the diagnosis of bacterial respiratory infections in adults. The evidence synthesized from studies conducted between 2004 and 2025 demonstrates that while CRP offers high sensitivity and cost-effectiveness, PCT provides superior specificity, faster kinetic response to bacterial load, and greater prognostic value. These characteristics make PCT a valuable tool for differentiating bacterial from viral etiologies and for guiding antimicrobial therapy, while CRP remains an essential marker in resource-limited settings and for initial screening.

The combined use of CRP and PCT emerges as a balanced and evidence-based approach, maximizing diagnostic accuracy while minimizing unnecessary antibiotic prescriptions. This dual-marker strategy has the potential to contribute significantly to antimicrobial stewardship programs and to improve patient outcomes by enabling timely, targeted, and rational therapeutic decisions.

Despite these strengths, heterogeneity in study populations, diagnostic thresholds, and assay methods represents an important limitation, underscoring the need for standardized diagnostic protocols in future research. Prospective multicenter trials and cost-effectiveness analyses are particularly warranted to determine optimal implementation strategies across diverse healthcare settings.

In summary, CRP and PCT—whether applied individually or in combination—represent powerful diagnostic tools for bacterial respiratory infections. Their complementary roles, if integrated into clinical practice with clear protocols, can enhance diagnostic precision, support responsible antibiotic use, and contribute to the global effort to combat antimicrobial resistance.

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