Infection and Drug Resistance

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ORIGINAL RESEARCH

Diagnostic Utility of Pleural C-Reactive Protein and Procalcitonin for Parapneumonic Pleural Effusion: A Head-to-Head Comparison Study

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Introduction: The diagnostic utility of pleural fluid C-reactive protein (CRP) and procalcitonin (PCT) for parapneumonic pleural effusion (PPE) is a subject of ongoing investigation. There remains lack studies comparing their diagnostic accuracy in a head-to-head manner. Furthermore, the incremental diagnostic value of their combination over a single marker and the net benefit of them remains unknown.

Methods: This prospective study enrolled participants presenting with undiagnosed pleural effusion, subsequently measuring their pleural levels of CRP and PCT. A diagnostic model that integrated both biomarkers was constructed using logistic regression analysis. The diagnostic performance and net benefit of CRP, PCT, and the composite model were assessed through receiver-operating characteristic (ROC) curve analysis and decision curve analysis (DCA).

Results: The study included 32 PPE patients and 121 patients without PPE. The area under the ROC curve (AUC) for CRP was 0.73 (95% confidence interval [CI]: 0.63–0.83), with a sensitivity of 0.71 (95% CI: 0.55–0.87) and a specificity of 0.68 (95% CI: 0.59–0.77) at a threshold of 10 mg/L. In contrast, the AUC for PCT was 0.58 (95% CI: 0.46–0.69), with sensitivity and specificity rates of 0.50 (95% CI: 0.33–0.67) and 0.65 (95% CI: 0.56–0.74) at a threshold of 0.1 ng/mL, respectively. Notably, the AUC for the diagnostic model was comparable to that of CRP alone at 0.73 (95% CI: 0.63–0.82). DCA showed that applying CRP provided a net clinical benefit, while PCT did not.

Conclusion: Pleural fluid CRP possesses moderate diagnostic capability for PPE, while PCT exhibits limited diagnostic utility. Additionally, the combined application of CRP and PCT does not confer any significant enhancement in diagnostic accuracy over the use of CRP alone.

Keywords: C-reactive protein, diagnostic test accuracy, parapneumonic pleural effusion, procalcitonin

Introduction

Pleural effusion is an important clinical manifestation associated with a variety of pathological conditions, including tuberculous pleurisy, malignancy, heart failure, and pneumonia.[1–3] Among these, pleural effusion arising from pneumonia is specifically referred to as parapneumonic pleural effusion (PPE).[4] Epidemiological studies indicate that between 10% and 60% of patients with community-acquired pneumonia (CAP) develop pleural effusion during the course of their illness.[5–7] Furthermore, pleural effusion serves as a significant prognostic indicator in patients diagnosed with pneumonia.[8–10] In cases involving undiagnosed pleural effusion, the prompt and accurate diagnosis of PPE is imperative for effective treatment, thereby enhancing patient outcomes.[4]

The established diagnostic gold standards for PPE include pleural fluid microbiological culture, biopsy, and thoracoscopy.[11,12] However, microbiological culture presents significant limitations, as it is both time- and labor-intensive,

Received: 29 August 2024
Accepted: 29 January 2025
Published: 17 February 2025

hindering the timely diagnosis and treatment of affected patients. Moreover, the sensitivity of microbiological culture is approximately 50%, and the potential for specimen contamination further diminishes its specificity.[3,11,13] Thoracoscopy, while offering a high diagnostic yield for PPE, is an invasive procedure that carries the risk of operation-related complications, such as bleeding and infection, particularly in vulnerable patient populations. Furthermore, the invasive nature of thoracoscopy and biopsy may preclude their application in individuals with coagulation disorders.[12] In instances where microbiological and biopsy findings yield negative results, empiric antimicrobial therapy may be considered; however, this approach raises concerns regarding the potential for antibiotic resistance, complicating future therapeutic interventions. In contrast, pleural fluid biomarkers offer a promising alternative diagnostic modality for PPE, as they are characterized by lower costs, shorter turnaround times, ease of performance, observer independence, and a less invasive profile, thereby positioning them as a valuable tool in this clinical context.[14,15]

Among the array of pleural biomarkers, C-reactive protein (CRP) and procalcitonin (PCT) have emerged as the most extensively investigated.[15] Systematic reviews and meta-analyses aggregating published data with considerable heterogeneity have demonstrated that CRP exhibits moderate diagnostic accuracy for PPE, whereas PCT is characterized by low diagnostic accuracy.[15–18] However, it is noteworthy that few studies have performed direct comparisons of the diagnostic efficacy of PCT and CRP for PPE in a head-to-head manner.[19–21] The inferences drawn from non-head-to-head comparisons warrant circumspection, as the existing studies differ significantly in their design, participant demographics, and clinical contexts, factors which may introduce confounding variables and potentially undermine the validity of the conclusions. Furthermore, the potential additive effect of combining CRP and PCT in enhancing the diagnostic precision for PPE remains to be elucidated. In light of these considerations, the objective of this study was to conduct a head-to-head comparison of the diagnostic accuracies of CRP and PCT for PPE. Additionally, this study sought to explore whether the integration of these biomarkers could enhance the diagnostic accuracy of either CRP or PCT. This investigation adhered to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines.[22]

Methods

Participants and Diagnostic Criteria

The participants in the current investigation were derived from the SIMPLE study, a prospective and pre-registered research initiative aimed at evaluating the diagnostic accuracy of biomarkers in individuals presenting with undiagnosed pleural effusion.[23] Comprehensive details of this study, including the established inclusion and exclusion criteria, specimen collection protocols, contextual setting, and data acquisition methodologies, have been documented in our prior publications.[24,25] In summary, we systematically recruited patients with undiagnosed pleural effusion who sought care at the Department of Respiratory and Critical Care Medicine at the Affiliated Hospital of Inner Mongolia Medical University during the period from September 2018 to July 2021. Exclusion criteria were rigorously applied and included the following characteristics: individuals younger than 18 years, pregnant women, patients with a known etiology upon admission (eg, prior lung cancer diagnosis or trauma-induced pleural effusion), individuals who developed pleural effusion during their hospital stay, and those lacking a clearly defined etiology prior to discharge.

Upon enrollment, comprehensive clinical data were systematically recorded, and a pleural fluid specimen was obtained prior to any therapeutic intervention. Following centrifugation, the supernatant of the pleural fluid was meticulously collected and preserved at temperatures ranging from −80°C to −70°C for subsequent analysis.

Diagnostic Criteria

PPE was diagnosed through a combination of microbiological culture, Gram staining, pleural biopsy revealing neutrophil infiltration, the presence of pus cells, imaging characteristics indicative of loculation, and pertinent clinical findings, notably the therapeutic response to antibiotic treatment. In contrast, tuberculous pleural effusion (TPE) was identified via a positive *Mycobacterium tuberculosis (Mtb)* culture of pleural fluid, acid-fast bacilli staining, or pleural biopsy demonstrating granulomatous inflammation, while excluding other granulomatous diseases. For patients with a high clinical suspicion of TPE, it was common practice to initiate anti-tuberculosis therapy, with subsequent follow-up assessments; a positive response to this treatment regimen was also interpreted as indicative of TPE.

Furthermore, pleural effusion secondary to heart failure (HF) was diagnosed based on transudative fluid characteristics, as evidenced by ultrasound and chest X-ray findings reflecting bilateral pleural effusion, alongside biochemical assays, such as serum natriuretic peptide levels, and echocardiographic indicators, including increased cardiac size and diminished left ventricular ejection fraction. The patient's response to anti-heart failure medications also contributed to the diagnostic consideration. Malignant pleural effusion (MPE) was diagnosed primarily through cytological analysis of the effusion and histopathological examination of pleural biopsy specimens. In situations where there was a high suspicion of MPE but cytology results were negative and pleural biopsy was not conducted, a diagnosis of MPE could nevertheless be established if a primary malignancy was detected, provided that alternative etiologies for the pleural effusion were systematically excluded. Importantly, the diagnostic process involved the collaboration of two clinicians, Z.D. Hu and L. Yan, who were blinded to the levels of CRP and PCT prior to arriving at the conclusive diagnosis.

Pleural Fluid CRP and PCT Assays

In December 2021, we conducted a systematic assessment of pleural fluid levels of CRP and PCT. The measurement of PCT was performed utilizing Beckman DXI800, while CRP levels were determined using Beckman AU5800. Importantly, the laboratory personnel involved in the testing of CRP and PCT were blinded to the clinical characteristics of the patients to prevent bias. The coefficients of variation (CV) for CRP were found to be 6.25% at a concentration of 0.48 mg/L and 0.31% at 9.18 mg/L. In the case of PCT, the CVs were reported as 1.74% at 11.5 ng/mL and 1.40% at 57.0 ng/mL, indicating a high level of precision in the assays conducted.

Statistical Analysis

Due to the data-driven nature of this study, we did not establish a predetermined sample size prior to participant enrollment.[23] The Kolmogorov–Smirnov test was employed to assess the normal distribution of continuous variables. For continuous variables exhibiting a skewed distribution, we reported the median and interquartile range (IQR). Conversely, continuous variables demonstrating normal distribution were expressed using the mean and standard deviation. To compare continuous variables with normal distribution, we utilized the independent Student's *t*-test or one-way ANOVA. For continuous variables with skewed distribution, the Mann–Whitney *U*-test or Kruskal–Wallis *H*-test were applied for comparative analysis. Categorical variables were assessed using the Chi-square test or Fisher's exact test.

A diagnostic model was constructed utilizing a logistic regression approach. Spearman correlation analysis was conducted to analyze the relationship between CRP and PCT. The diagnostic accuracy of CRP and PCT for PPE was assessed through receiver operating characteristic (ROC) curves, with areas under the ROC curves (AUC) serving as indicators of overall diagnostic performance for PCT, CRP, and the proposed model. The thresholds established for calculating sensitivity and specificity were 10 mg/L for CRP and 0.1 ng/mL for PCT, reflecting widely accepted standards in extant literature.[16,17]

Positive and negative likelihood ratios (PLR and NLR) were computed based on the aforementioned thresholds. Decision curve analysis (DCA) was applied to ascertain the net benefit associated with the determination of CRP and PCT levels. All statistical analyses were executed utilizing R (version 4.0.5) and Stata (version 16), with a p-value of less than 0.05 denoting statistical significance.

Results

Participant Characteristics

Figure 1 illustrates the flowchart delineating the participant selection process for this study. A total of 170 individuals were initially recruited; however, 17 participants were subsequently excluded, resulting in a final cohort of 153 participants included in the data analysis. The study population comprised 32 patients with PPE and 121 patients with non-PPE. Among the non-PPE group, the distribution of effusion types included 66 patients with MPE, 20 patients with TPE, 23 patients with pleural effusion secondary to HF, and 12 patients with other classifications of pleural effusion. The comprehensive characteristics of the participants are detailed in Table 1.

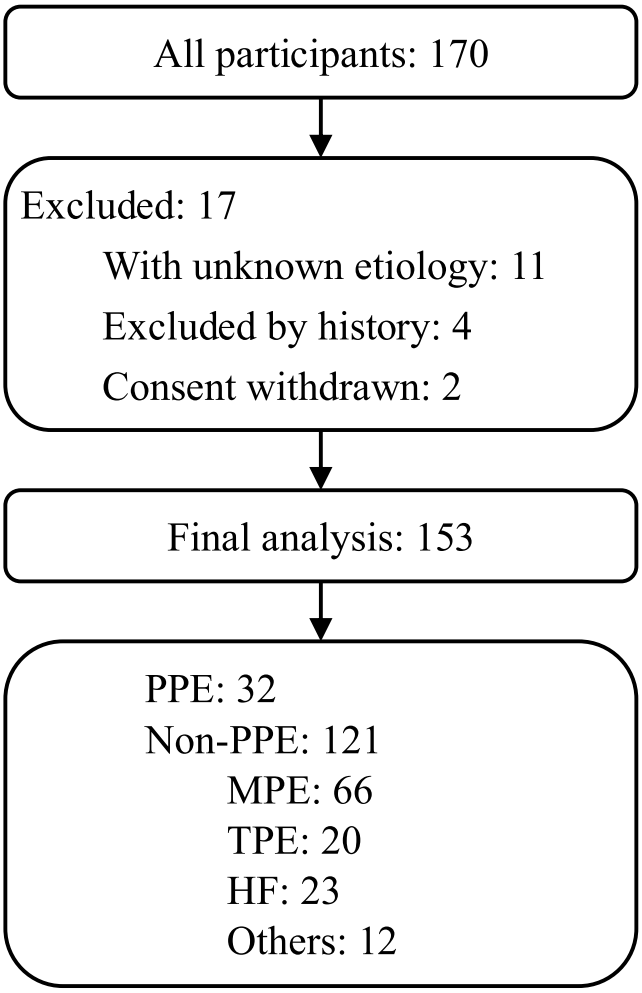

Figure 1 A flowchart of the participant selection process.
Abbreviations: PPE, parapneumonic pleural effusion; MPE, malignant pleural effusion; TPE, tuberculous pleural effusion; HF, heart failure.

Comparison of CRP and PCT Levels Between Patients With PPE and Non-PPE

The comparative analysis of CRP and PCT levels in pleural fluid from patients exhibiting PPE as opposed to those without PPE is depicted in Figure 2. It is important to note that due to insufficient pleural fluid samples, measurements for CRP and PCT were not available for 18 and four participants, respectively. The median CRP concentration was observed to be markedly elevated in

Table 1 Characteristics of the Participants in the Pleural Fluid

	PPE (n=32)	Non-PPE (n=121)	*p*
Age (years)	69 (60–75)	73 (66–80)	0.042
Sex, n (%)			0.066
Female	6 (19)	46 (38)	
Male	26 (81)	75 (62)	
WBC (10^6/mL)	1279 (449–2442)	818 (414–1338)	0.112
LDH (U/L)	291 (174–620)	196 (120–376)	0.024
ADA(U/L)	15 (6–34)	8 (5–13)	0.008
Glucose (mmol/L)	5.4 (3.9–6.4)	5.8 (4.8–6.7)	0.112
Protein (g/L)	37 (23–43)	34 (22–41)	0.511

Abbreviations: PPE, parapneumonic pleural effusion; WBC, white blood cell; LDH, lactate dehydrogenase; ADA, adenosine deaminase.

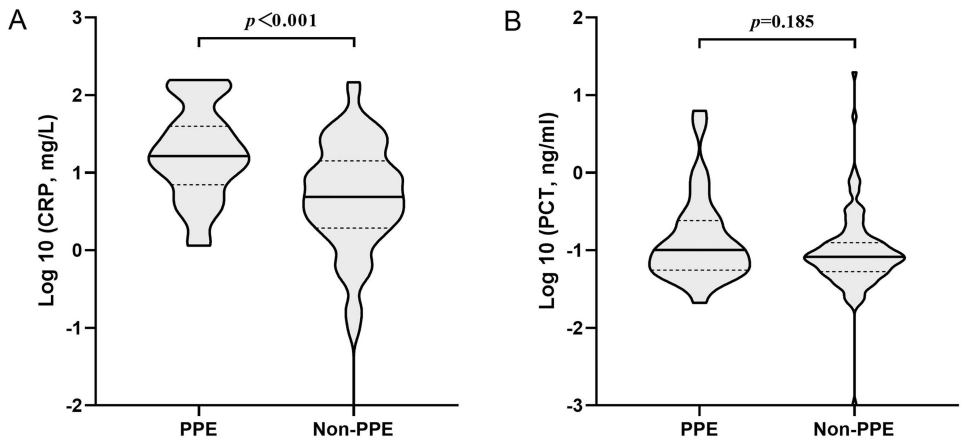

Figure 2 Comparison of pleural fluid CRP (**A**) and PCT (**B**) levels between PPE and non-PPE. Data were log-transformed.
Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; PPE, parapneumonic pleural effusion.

the PPE group, recording a median level of 16.3 mg/L (IQR: 8.0–39.7) compared to 4.9 mg/L (IQR: 2.0–13.3) in the non-PPE group, with this difference reaching statistical significance ($p < 0.001$ via the Mann–Whitney *U*-test). In contrast, the median PCT levels were 0.10 ng/mL (0.06–0.22) for PPE patients and 0.08 ng/mL (0.05–0.12) for non-PPE patients, a difference that did not attain statistical significance ($p = 0.185$, Mann–Whitney *U*-test).

Additionally, a positive correlation between pleural CRP and pleural PCT levels was identified, with a correlation coefficient of 0.37 ($p < 0.001$). In a subset of patients, serum CRP levels were also assessed, revealing median concentrations of 7 mg/L (IQR: 3–21) in pleural samples and 17 mg/L (IQR: 6–41) in serum samples. This discrepancy was statistically significant ($p < 0.001$, Mann–Whitney *U*-test). Moreover, a strong positive correlation was established between serum CRP and pleural CRP levels, evidenced by a correlation coefficient of 0.87 ($p < 0.001$, assessed using Spearman correlation analysis).

Diagnostic Accuracy of CRP and PCT

Figure 3 illustrates the ROC curves for CRP and PCT in the diagnosis of PPE. The AUC for CRP was determined to be 0.73 (95% CI: 0.63–0.83), with a sensitivity of 0.71 (95% CI: 0.55–0.87) and a specificity of 0.68 (95% CI: 0.59–0.77) at

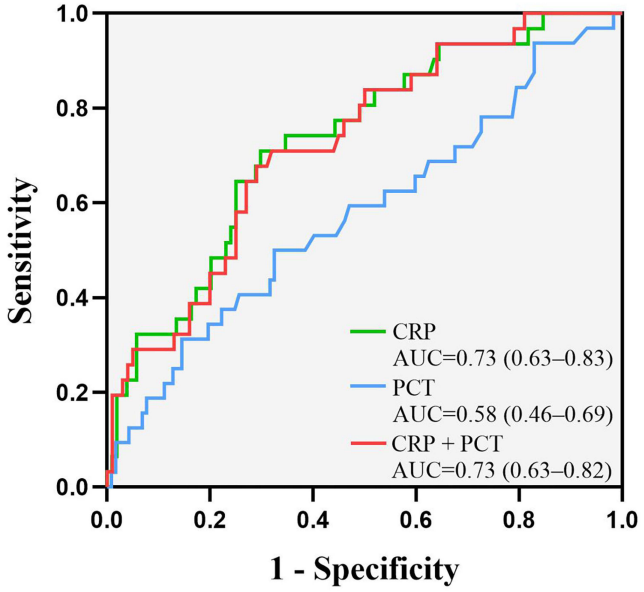

Figure 3 Receiver operating characteristic curves of CRP and PCT for parapneumonic pleural effusion.
Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; AUC, the area under the curve; CI, confidence interval.

https://doi.org/10.2147/IDR.S493610

Table 2 Diagnostic Accuracy of Pleural Fluid CRP, PCT, and Their Combination for PPE

Diagnostic Metrics	CRP	PCT	PCT + CRP
Threshold	10 mg/L	0.1 ng/mL	0.18
AUC (95% CI)	0.73 (0.63–0.83)	0.58 (0.46–0.69)	0.73 (0.63–0.82)
Sensitivity (95% CI)	0.71 (0.55–0.87)	0.50 (0.33–0.67)	0.74 (0.59–0.90)
Specificity (95% CI)	0.68 (0.59–0.77)	0.65 (0.56–0.74)	0.55 (0.45–0.65)
PLR (95% CI)	2.24 (1.56–3.21)	1.43 (0.93–2.18)	1.65 (1.22–2.23)
NLR (95% CI)	0.42 (0.24–0.75)	0.77 (0.53–1.12)	0.47 (0.25–0.88)
PPV (95% CI)	0.40 (0.27–0.53)	0.28 (0.16–0.40)	0.34 (0.23–0.45)
NPV (95% CI)	0.89 (0.82–0.96)	0.83 (0.75–0.90)	0.87 (0.79–0.96)

Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; AUC, the area under the curve; CI, confidence interval; PLR, positive Likelihood ratio; NLR, negative Likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

a threshold of 10 mg/L. In contrast, the AUC for PCT was found to be 0.58 (95% CI: 0.46–0.69), with sensitivity and specificity values of 0.50 (95% CI: 0.33–0.67) and 0.65 (95% CI: 0.56–0.74), respectively, at a threshold of 0.1 ng/mL.

Subsequently, we implemented a logistic regression model to integrate pleural fluid levels of CRP and PCT, yielding the equation LogitP = −1.641 + 0.023 × CRP (mg/L) – 0.129 × PCT (ng/mL). The AUC for this model was calculated to be 0.73 (95% CI: 0.63–0.82), which did not demonstrate a statistically significant improvement over the AUC for CRP (p = 0.691) but was significantly superior to that of PCT ($p = 0.011$). Table 2 presents the sensitivities, specificities, PLR, NLR as well as the positive and negative predictive values for CRP, PCT, and the logistic regression model in the context of PPE diagnosis.

Furthermore, we employed DCA to evaluate the net clinical benefit associated with CRP and PCT measurements. The decision curves for both markers, as depicted in Figure 4, indicated that the decision curve for CRP notably exceeds the reference lines, whereas the decision curve for PCT remained in closer proximity to these reference lines.

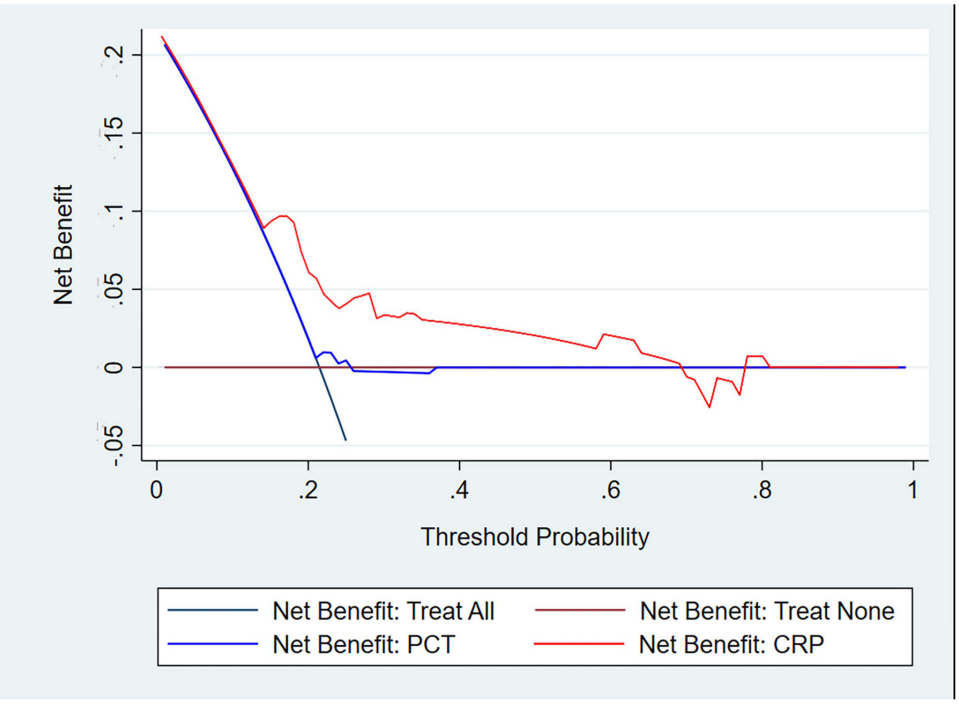

Figure 4 Decision curves of CRP and PCT for parapneumonic pleural effusion.

Discussion

This investigation demonstrated that patients with PPE exhibited significantly elevated levels of CRP in comparison to non-PPE patients, whereas PCT levels were found to be comparable between the two groups. We conducted a thorough evaluation of the diagnostic accuracy and net benefit of both CRP and PCT utilizing ROC curve analysis and DCA. Furthermore, a logistic regression model was employed to determine whether the integrative use of CRP and PCT could yield superior diagnostic accuracy relative to the utilization of a single biomarker. The findings of our study indicate that pleural CRP has moderate diagnostic accuracy and net benefit for the diagnosis of PPE, while PCT demonstrates limited diagnostic accuracy and net benefit in this context.

Numerous studies have explored the diagnostic accuracy of pleural fluid CRP and PCT in the context of PPE, yet the findings have exhibited considerable variability. Previous systematic reviews and meta-analyses have suggested that CRP demonstrates moderate diagnostic accuracy for PPE, while PCT is characterized by low diagnostic accuracy in this regard.[15–18] Our findings align with the conclusions drawn from these prior systematic investigations. However, our study possesses several methodological strengths compared to earlier research. Primarily, we employed a prospective design and performed a head-to-head comparison of the diagnostic accuracies of PCT and CRP. The prospective nature of our data collection reduces the potential for recall bias and enhances the representativeness of our study population, thereby increasing the reliability of our conclusions in comparison to earlier studies. To the best of our knowledge, only two prior studies have conducted a direct comparison of the diagnostic accuracy of pleural CRP and PCT for PPE.[20,26] Our findings are consistent with the results reported by these investigations. Furthermore, we analyzed whether a combination of CRP and PCT could enhance the diagnostic accuracy compared to each biomarker in isolation. Our results indicated that the composite model of CRP and PCT yielded an AUC similar to that of CRP alone, suggesting that PCT does not augment the diagnostic capability of CRP. Notably, both this study and previous research have identified a significant positive correlation between pleural fluid CRP and PCT,[20] which underscores the partial overlap in their diagnostic value. This observation may partially elucidate why combining CRP and PCT does not yield an improvement in diagnostic accuracy over a single biomarker. Lastly, we assessed the net clinical benefit of CRP and PCT utilizing DCA, which demonstrated that CRP provides a net benefit for patients with undiagnosed pleural effusion, whereas PCT does not exhibit a discernible advantage. To our knowledge, this is the first study to evaluate the net benefit of PCT alongside CRP in this clinical context.

Our investigation demonstrated that the AUC for CRP in diagnosing PPE was 0.73, suggesting that CRP exhibits moderate diagnostic accuracy for this condition. The PLR and NLR serve as critical diagnostic metrics that reflect the efficacy of an index test in confirming or excluding the presence of a target disease. A PLR exceeding 10 is indicative of a strong capacity to rule in the disease, while an NLR below 0.1 signals a robust ability to rule it out.[27] At a CRP threshold of 10 mg/dL, the observed PLR and NLR were 2.24 (95% CI: 1.56–3.21) and 0.42 (95% CI: 0.24–0.75), respectively. These findings suggest that pleural CRP, when used in isolation, is insufficient for either confirming or excluding the diagnosis of PPE. Therefore, the interpretation of CRP results should be conducted in conjunction with a comprehensive assessment, including the patient's history of presenting illness, clinical signs and symptoms, past medical history, laboratory findings, and diagnostic imaging evaluations. Moreover, our study revealed that the combination of PCT and CRP yielded an AUC comparable to that of CRP alone, indicating that PCT does not enhance the diagnostic performance of CRP. In terms of clinical utility, CRP demonstrates a greater potential for stratifying PPE cases, while PCT exhibits limited utility in this context.[15] Consequently, the simultaneous measurement of CRP and PCT is not advocated, and CRP should be preferred as the diagnostic biomarker of choice.

Our study has some limitations. First, the sample size in our study is relatively small. Particularly, only 32 PPEs were included. Second, because pleural fluid pH could not be measured in our hospital, we could not stratify PPE and analyze the value of CRP and PCT in distinguishing complicated PPE from uncomplicated PPE. Third, the participants in our study had a higher median age than previous studies, and age can affect the diagnostic accuracy of pleural biomarkers.[28,29] Therefore, it should be cautious to generalize our findings to clinical settings with young patients. Fourth, the diagnostic model with CRP and PCT has not been validated externally. Fifth, we used stored pleural fluid to determine CRP and PCT, but the long-term stability of CRP and PCT in stored pleural fluid specimens is unclear. However, our previous study indicated that carcinoembryonic antigen is stable at temperatures between −80 to −70 °C for approximately two years.[25] Therefore, we speculate that CRP and PCT are also stable under such conditions.

This study has several notable limitations that warrant discussion. First, the sample size is relatively small, with only 32 cases of PPE included in the analysis. Second, the inability to measure pleural fluid pH at our institution hindered our capacity to stratify cases of PPE and to evaluate the efficacy of CRP and PCT in distinguishing between complicated and uncomplicated forms of PPE. Third, the median age of participants in this study was higher than that reported in previous investigations, which suggests that age may influence the diagnostic accuracy of pleural biomarkers.[28,29] This discrepancy necessitates caution when extrapolating our findings to clinical populations consisting of younger patients. Fourth, the diagnostic model incorporating CRP and PCT has not undergone external validation, which limits the robustness of our conclusions. Finally, while we analyzed stored pleural fluid specimens to determine CRP and PCT levels, the long-term stability of these biomarkers in such samples remains indeterminate. However, previous research from our group has indicated that carcinoembryonic antigen remains stable when stored at temperatures between −80 and −70 °C for approximately two years.[25] Therefore, we postulate that CRP and PCT may exhibit similar stability under these conditions.

Conclusions

In conclusion, the measurement of CRP in pleural fluid demonstrates a moderate diagnostic utility for the identification of PPE. Conversely, PCT exhibits a limited diagnostic efficacy in this context and does not enhance the diagnostic performance of CRP. Consequently, the prevailing evidence does not advocate for the concurrent evaluation of CRP and PCT. Therefore, CRP emerges as the preferred biomarker for the diagnosis of PPE.

Data Sharing Statement

Data for this analysis cannot be publicly available due to ethical restrictions.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Inner Mongolia Medical University Hospital (No. 2018011). Signed informed consent forms were obtained from all individual participants included in the study. All patient details were de-identified. We performed this study following the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Scientific Project of Inner Mongolia Healthcare Committee (202201340). The funder played no role in the study design, data analysis, paper preparation and submission.

Disclosure

The authors have no conflicts of interest to declare.

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