Original Article

Combined analysis of C-reactive protein in pleural fluid and serum is effective in the differential diagnosis of exudative pleural effusions

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Background: Exudative pleural effusion (EPE) is one of the common pleural manifestations of various diseases. Differential diagnosis of EPE is imperative clinically as it identifies different causes of EPE, thereby, enabling effective treatments. Thoracoscopy is a useful tool for differential diagnosis of EPE; however, some patients refuse thoracoscopic examination due to its invasive nature. In addition, the specificity and sensitivity of existing routine tests of EPE are unsatisfactory. Therefore, there is a great need to establish an effective method for the differential diagnosis of EPE.

Methods: This study was a single-institution retrospective analysis of diagnostic efficiency of C-reactive protein (CRP) and procalcitonin (PCT) between March 2018 and September 2018. A total of 87 patients diagnosed with EPE were enrolled. All participants underwent diagnostic thoracentesis. The EPE was examined using biochemical, routine, microbiological, and cytological methods. Pathological cytology detection was necessary for those suspected of malignant PE. Benign PE originates in patients with pneumonia, empyema, and tuberculosis. The levels of CRP and PCT in EPE and serum were measured before treatment. Correlation analysis and receiver-operating characteristic (ROC) curve analysis were conducted to determine the underlying relationship between levels of CRP and PCT, and for differential diagnosis.

Results: The ROC analysis showed that the sensitivity and specificity for the analysis of pleural fluid CRP (p-CRP) were higher (cut-off: 17.55 pg/mL; sensitivity: 75.00%, specificity: 83.90%) than that of serum CRP (s-CRP, cut-off: 23.90 pg/mL; sensitivity: 71.00%, specificity: 80.4%) in the differential diagnosis for EPE. However, the analysis of pleural fluid PCT (p-PCT) and serum PCT (s-PCT) did not demonstrate correlations with EPE. Combined analysis of p-CRP (cut-off: 17.55 mg/dL) with s-CRP (cut-off: 23.9 pg/mL) showed the highest diagnostic accuracy (88.4%) in diagnosing infectious EPE.

Conclusions: The data support the close relationship between combined analysis of p-CRP with s-CRP and effective and accurate differential diagnosis of EPE, due to its higher sensitivity and specificity. However, as a highly sensitive marker for diagnosing bacterial infections, neither s-PCT nor p-PCT, showed correlations with the differential diagnosis of EPE.

Keywords: C-reactive protein (CRP); procalcitonin (PCT); pleural effusion (PE); empyema; diagnostic effectiveness

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Introduction

As a common clinical manifestation of pleural-related diseases, there are several diseases that may cause exudative pleural effusion (EPE) (1). Its differential diagnosis depends on comprehensive routine examinations of EPE, including biochemical examination, enzymology, infection index, and pathological cytology (2). However, the sensitivity and specificity of the above tests are still controversial (3,4). The etiology of exudative effusion with lymphocyte predominance, which is difficult to diagnose, depends on medical pleural biopsy or even surgical thoracoscopy. However, the application of thoracoscopy in differential diagnosis of EPE is clinically limited as some patients refuse the test due to its invasive nature, potential risk of anesthesia, and expensive medical costs. Besides, the duration of these invasive operations may be prolonged due to the series of complicated diagnostic tests. Invasive examination-based biochemical and etiological tests fail to reach a diagnostic consensus in the differential diagnosis between tuberculosis (TB)- and bacteria-oriented EPE, and in turn lead to a detainment of interventions in early stage. For patients with malignant pleural disease, prompt diagnosis assists in minimizing the abuse of antibiotics and reducing medical costs, while the utilization of pathological cytology often needs repeated tests of pleural extraction, which may delay the treatment. Therefore, rapid diagnosis and the administration of corresponding therapies for the pleural effusion (PE) in an accurate and effective manner maximizes patient benefit.

It has been widely accepted that the analysis of CRP and PCT levels in serum is useful to diagnose systemic and focal inflammatory disease. Some researchers have investigated the roles of CRP and PCT in differentiating the etiology of EPE (5). The CRP is an acute-phase protein that is synthesized primarily by hepatocytes in response to various stimuli from either infectious or non-infectious origin (6). The expression of CRP in PE is closely related to the level of serum CRP (s-CRP), which is mainly due to the release of inflammatory factors stimulating the expression of CRP in local capillaries of the pleural cavity. The synthesized CRP translocate into the pleural cavity, leading to permeability change in pleura and the formation of EPE (7). Meanwhile, PCT is a prohormone of calcitonin that is secreted by C-cells of the thyroid gland in response to physiological hypercalcemia. Escalation of PCT is now regarded as a useful serological biomarker of bacterial infection (8). In recent years, some multi-center clinical studies have explored the diagnostic effectiveness of PCT in serum or PE, but have drawn conflicting conclusions, leading to a controversial status for the diagnostic role of pleural PCT (9,10).

This study aimed to evaluate the effectiveness of CRP and PCT in diagnosing EPE and to compare the pleural fluid concentrations of CRP and PCT in EPE patients with various pathologies, including benign and malignant. The sensitivity and specificity of the analysis of CRP and PCT were determined. We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/atm-21-3383)

Methods

Study design

This study was a retrospective analysis of the database of maintained medical records at the Department of Pulmonary and Critical Care Medicine, Xijing Hospital, Fourth Military Medical University. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective clinical study and meta-analysis was approved by the institutional review board of Xijing Hospital, Fourth Military Medical University (KY20202098-C-1). Individual consent for this retrospective analysis was waived. Between September 2018 and July 2019, we enrolled and analyzed a total of 87 patients aged ≥18 years with EPE according to Light's criteria. All participants underwent thoracentesis. A malignant PE was confirmed with cytological cells, and some participants with malignant PE but negative cytology were diagnosed by histopathological biopsy of the pleura or other organs. The etiologies of PE were mainly classified into four categories: malignant, TB, parapneumonic effusion, and empyema. Our clinicians provided a comprehensive diagnosis of empyema or parapneumonic effusion according to the participant's medical history, clinical manifestations, physical signs, appearance of PE, routine tests, and other results. The TB EPE was diagnosed if one of the following was positive: granulomatous inflammation seen on the pleural biopsy specimen, acid-fast staining, mycobacterium TB culture, or Gene-Xpert/TB-DNA-PCR positive.

All cases were divided into two main categories: infectious or non-infectious effusions. The diagnosis was made by physicians based on test results and response to treatments.

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Procedures

Each participant underwent thoracentesis, and all pleural fluid samples were subjected to routine examinations (e.g., pH, Rivalta test, total red blood cell, white blood cell, lymphocyte and neutrophil count and ratio), biochemical examinations (total protein and glucose), enzymology tests [lactate dehydrogenase (LDH), adenosine deaminase (ADA)], and microbiological examinations. To detect bacterial infections, smear tests and bacterial culture were conducted. Acid-fast staining, tuberculosis-DNA-polymerase chain reaction (TB-DNA-PCR), and Gene-Xpert were used for TB detection. Pathological cytology was used to distinguish EPE from benign or malignant origins.

Measurement of CRP and PCT levels

Pleural fluid and peripheral blood (4 mL for each) was obtained and centrifuged at 3,500 rpm for 5 min at 4 ℃, and the supernatants were collected. The levels of CRP and PCT were determined with "The One Step Test for CRP/PCT kit (colloidal gold)", measured by a Getein1100 fluorescence immunity analyzer (Getein Biotech, Inc., Nanjing, China) with a functional assay sensitivity of 0.1 ng/mL. The analyses were performed according to the manufacturers' instructions.

Statistical analysis

Data were presented as means ± standard deviation (SD) for normally distributed data and as medians with interquartile ranges in parentheses for skewed data. The chi-square test was used to compare the rates. Receiver-operating characteristic (ROC) curves were generated by plotting sensitivity against 1-specificity, and the area under the curve (AUC) with 95% confidence intervals (CI) was calculated. The Youden index was used to identify the cut-off values with potential diagnostic significance. After data collection, statistical analysis of the data was performed using the software SPSS version 21.0 (SPSS Inc., IBM Corp., Chicago, IL, USA), and P values <0.05 were considered statistically significant.

Results

Clinical and biological characteristics of participants

A total of 87 patients were enrolled and analyzed in this study. According to the type of disease, participants were divided into four groups. The benign group included 56 cases: TB (n=33, 58.92%), parapneumonic (n=17, 30.35%), and empyema (n=6, 10.71%). Although parapneumonic and empyema were differentiated in this study, in recent literature they have been grouped together under the term "pleural infection" because both conditions are treated in the same manner. Diagnosis of these 2 diseases depends on the comprehensive judgment of clinicians. There were 31 cases of malignancy. The clinical data of the biological features participants are shown in *Table 1*. This study included 62 men and 25 women with no significant difference in each group. The average age of all participants was 56 years. There were no differences in terms of age and gender between the four groups (*Table 1*).

General characteristics of EPE

There were significant differences in the number of white blood cell (WBCs) among the four groups: the highest was in the empyema group [56,742×10^6/L (16,212–24,6200)×10^6/L], followed by the TB group [1,889×10^6 (180–7,310)×10^6], and parapneumonic [1,359×10^6/L (150–9,100)×10^6/L], and the lowest was in the tumor group [1,290×10^6 (33–8,242)×10^6] (*Table 1*). There were also significant differences in the number of red blood cells (RBCs) among the four groups. Empyema and parapneumonic groups had relatively higher RBCs [6,050×10^6 (1,000–59,500)×10^6 and 5,000×10^6 (400–260,000)×10^6], while the TB and malignant groups had relatively low RBC counts [2,890×10^6 (0–112,500)×10^6 and 2,800×10^6 (0–54,500)×10^6] (*Table 1*). There were also significant differences in the ratios of lymphocytes and neutrophils. The malignant and TB groups had higher lymphocyte cell numbers and ratio [70.5% (12–93%) and 88.5% (28–98%)], while those of empyema and parapneumonic groups were lower [38% (7–97%) and 8% (2–26%), respectively] (*Table 1*). In contrast, the malignant and TB groups had lower neutrophil cell numbers and ratio [26 (7–88%) and 12% (1–72%), respectively], whereas the neutrophil cell numbers and ratio were higher [62% (3–93%) and 92% (74–98%), respectively] in the empyema and parapneumonic groups (*Table 1*).

The biochemical analysis showed that protein, LDH, and ADA were significantly different among the 4 groups. The level of ADA in the TB group [57.50 (20.27–79.05)) was much higher followed by that in the parapneumonic and malignant groups [20.85 (15.17–27.53) and 18.60

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Table 1 Baseline demographic data and pleural fluid characteristics

Variable	Malignant	Tuberculosis	Parapneumonic	Empyema	P value
Age (y, median; range)	65 [21–87]	56 [19–95]	55 [15–77]	65 [36–66]	0.07
Male, n (%)	21 (67.74)	25 (75.76)	11 (64.71)	5 (83.33)	0.857
PE conventional analysis					
WBC ($\times 10^6$/L)	1,290 (33–8,242)	1,889 (180–7,310)	1,359 (150–9,100)	56,742 (16,212–246,200)	<0.001
RBC ($\times 10^6$/L)	2,890 (0–112,500)	2,800 (0–54,500)	6,050 (1,000–59,500)	5,000 (400–260,000)	<0.006
Lymphocytes (%)	70.5 [12–93]	88.5 [28–98]	38 [7–97]	8 [2–26]	<0.001
Neutrophils (%)	26 [7–88]	12 [1–72]	62 [3–93]	92 [74–98]	<0.001
PE biochemical analysis					
Total protein (mean ± SD, g/L)	41.91±8.82	45.87±11.69	39.41±10.21	50.46±6.49	0.02
Glucose (mmol/L)	5.68±2.26	4.17±2.73	6.32±1.86	5.31±0.32	0.082
LDH (IU/L)	298 (189.5, 729)	243.66 ± 112.23	497 (236, 713)	790 (449, 2,427)	<0.001
ADA (IU/L)	18.60 (9.8, 29.5)	57.50 (20.27, 79.05)	20.85 (15.17, 27.53)	3.88 (1.00–4.86)	<0.001

Data are presented as the mean ± SD for normally distributed data or as the median (interquartile ranges) for skewed data; the tuberculosis group (n=33), parapneumonic (n=17), and empyema (n=6). PE, pleural effusion; WBC, white blood cell; RBC, red blood cell; ADA, adenosine deaminase; LDH, lactate dehydrogenase.

(9.8–29.5), respectively]. The level of ADH in the empyema group was the lowest [3.88 (1.00–4.86)]. The levels of LDH in the empyema and parapneumonic groups were higher [790 (449–2,427) and 497 (236–713), respectively].

Pleural fluid levels of CRP and PCT

The pleural fluid CRP (p-CRP) levels were significantly higher in the empyema and parapneumonic groups, while lower in the tuberculous and malignant groups (*Figure 1A*). However, there were no significant differences between empyema and parapneumonic [54.9 (28.75–77.85) *vs.* 57.25 (40.7–191.63)], as well as tuberculous and malignant groups. Unlike p-CRP, there were higher levels of s-CRP in benign groups (TB, empyema, and parapneumonic) of than that in the malignant group [12.9 (5.45–34.70)] (*Figure 1B*), but there was no significant difference between TB [44.9 (20.35–108.35)], parapneumonic group [93.9 (40.13–162.63)], and empyema [116 (49.60–176.73)]. Interestingly, pleural fluid PCT (p-PCT) level was similar among 4 groups (*Figure 1C*). As a classical marker of bacterial infection, PCT level was higher in the parapneumonic effusion group compared with that in the TB and malignant groups, while there was no significant increase in the empyema group (*Figure 1D*). Notably, the levels of s-/p-CRP and s-PCT were significantly different between the 4 groups, while p-PCT was not. Both s-CRP and p-CRP were the highest in the empyema group, followed by the parapneumonic effusion group and TB group, with the lowest in the malignant group. The s-PCT was higher in the parapneumonic effusion and empyema groups, and lower in the TB and malignant groups. There were no significant differences in p-PCT among the four groups (*Table 2*).

The diagnostic accuracy of different marker

The diagnostic performance of s-CRP and p-CRP values determined from ROC analysis are shown in *Figure 2*. The results showed that the AUC of s-CRP was 0.81 (P<0.001) and AUC of pleural CRP was 0.783 (P<0.001). The p-CRP represents a very useful marker for the differentiation of malignant from infectious effusions. Using a cut-off point of 17.55 pg/mL, p-CRP presented 75.00% sensitivity and 83.90% specificity for differential diagnosis of malignant from benign (*Table 3*). For s-CRP, at the cut-off point of 23.90 pg/mL, s-CRP presented 71.00% sensitivity and 80.40% specificity for the diagnosis of malignant (*Table 4*). The combination of p-CRP and s-CRP yielded the highest diagnostic accuracy (88.4%) and higher specificity (72.4%) in diagnosing infectious PE (*Table 5*).

The analysis of p-PCT and s-PCT showed that both of

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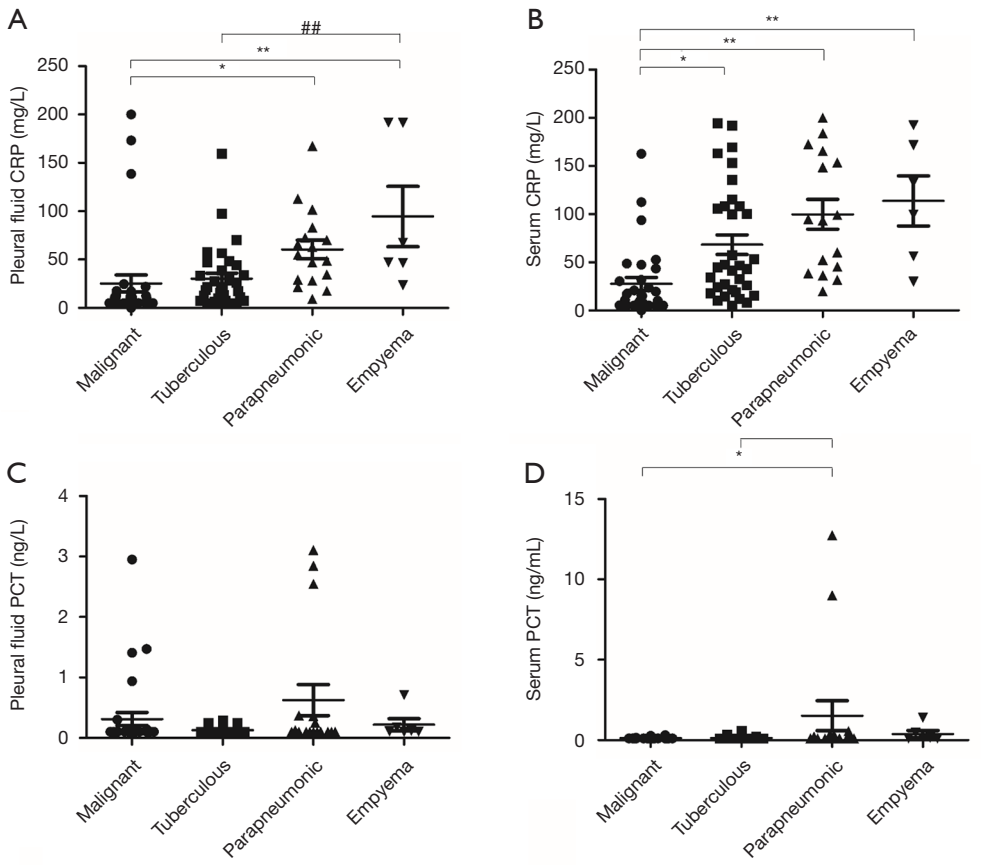

Figure 1 CRP and PCT of pleural fluid and serum levels in the different diagnostic subgroups. (A) p-CRP, (B) serum CRP, (C) p-PCT, and (D) s-PCT levels in the different diagnostic subgroups. Individual values are plotted. Bars represent the means of the values, and p-values are shown between groups with statistically significant differences. *P<0.05, **P<0.01, *vs.* Malignant group. ##P<0.01, *vs.* Tuberculous group. CRP, C-reactive protein; PCT, procalcitonin; p-CRP, pleural fluid CRP; p-PCT, pleural fluid PCT; s-PCT, serum PCT.

Table 2 Levels of CRP and PCT in the pleural fluid and blood

Parameters	Malignant	Tuberculosis	Parapneumonic	Empyema	P value
CRP (mg/L)					
Pleural effusion	11.10 (5, 14.5)	19 (8.75, 41.65)	54.9 (28.75, 77.85)	57.25 (40.7, 191.63)	<0.001
Serum	12.9 (5.45–99.10)	44.9 (20.35, 108.35)	93.9 (40.13, 162.63)	116 (49.60, 176.73)	<0.001
PCT (ng/mL)					
Pleural effusion	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.365)	0.115 (0.1, 0.305)	0.094
Serum	0.1 (0.1, 0.1025)	0.1 (0.1, 0.1)	0.14 (0.1, 0.355)	0.125 (0.1, 0.6925)	0.011

Data are presented as the mean ± SD for normally distributed data or as the median (interquartile ranges) for skewed data. CRP, C-reactive protein; PCT, procalcitonin.

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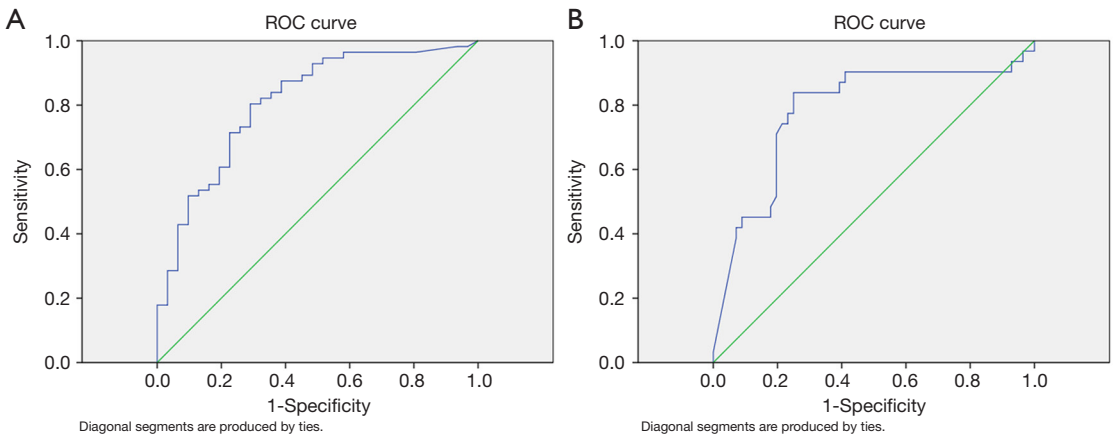

Figure 2 ROC curve for the diagnosis of EPE. ROC analysis curves of p-CRP and s-CRP levels for differentiating malignant from infectious effusions. (A) ROC curve of s-CRP levels for differentiating parapneumonic pleural effusions, and (B) ROC curve of p-CRP levels for differentiating parapneumonic pleural effusions. The AUC for p-CRP is 0.810 (P<0.001), and for s-CRP is 0.783 (P<0.001). AUC, area under the curve; ROC, receiver operating characteristic; p-CRP, pleural fluid C-reactive protein; s-CRP, serum C-reactive protein; EPE, exudative pleural effusion.

Table 3 Diagnostic performance of pleural effusion CRP based on the ROC analysis

Parameters	Optimal cut-off point (pg/mL)	Sensitivity	Specificity	+LR	–LR	PPV (%)	NPV (%)	AUC	Accuracy (%)
Malignant *vs.* benign	17.55	0.75	0.839	4.69	0.30	89.36	65	0.783	78.16
Malignant *vs.* TB	17.55	0.75	0.839	3.76	0.30	80.00	67	0.783	71.88
Malignant *vs.* EM and PE	17.55	0.96	0.839	2.44	0.05	81.48	96.30	0.884	62.96
TB *vs.* EM and PE	45.35	0.788	0.696	3.48	0.30	72.73	77.42	0.796	75.47

EM, empyema; PE, parapneumonic; TB, tuberculosis; +LR, positive likelihood ratio; –LR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

Table 4 Diagnostic performance of serum CRP based on the ROC analysis

Parameters	Optimal cut-off point (pg/mL)	Sensitivity	Specificity	+LR	–LR	PPV (%)	NPV (%)	AUC	Accuracy (%)
Malignant *vs.* benign	23.90	0.71	0.804	2.76	0.36	83.02	66.67	0.810	76.74
Malignant *vs.* TB	23.90	0.700	0.727	1.07	0.41	72.73	33.33	0.768	41
Malignant *vs.* EM and PE	26.70	0.71	0.952	2.44	0.3	70.97	95.65	0.897	81.48
TB *vs.* EM and PE	28.45	0.364	0.952	0.61	0.67	48.78	92.31	0.681	59.24

EM, empyema; PE, parapneumonic; TB, tuberculosis; +LR, positive likelihood ratio; –LR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; ROC, receiver operating characteristic curve; CRP, C-reactive protein; PCT, procalcitonin.

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Table 5 Diagnostic performance of s-CRP and p-CRP combinations

Cut-off value (p-CRP, 17.55 pg/mL + s-CRP, 23.90 pg/mL)	Sensitivity (%)	Specificity (%)	+LR	−LR	PPV (%)	NPV (%)	Accuracy (%)
Malignant *vs.* benign	88.40	72.40	3.20	0.16	67.4	80.8	81.9
Malignant *vs.* TB	72.00	80.77	3.74	0.35	78.26	75	76.47
Malignant *vs.* EM and PE	95.24	80.77	4.95	0.06	80.00	95.45	87.23
TB *vs.* EM and PE	95.24	28.00	4.95	0.45	52.63	95.45	58.70

EM, empyema; PE, parapneumonic; TB, tuberculosis; +LR, positive likelihood ratio; −LR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

the AUCs were <0.5 (data not shown), which suggests that both p-PCT and s-PCT are not useful for differentiating malignant from other types of effusions. However, p-PCT may be a useful marker in differentiating parapneumonic effusion from other types of effusions (excluding empyema).

Discussion

The manifestation of EPE is clinically common in pleura of patients with various respiratory disorders, and its diagnosis mainly depends on PE-based examinations, including routine, biochemical, enzymological, tumor marker and pathological cytology analysis (11,12). However, the sensitivity and specificity of these tests are less than satisfactory. Pathological diagnosis, depending on pleural biopsy and other invasive operations, is regarded the golden criteria in identifying the nature of pleural lesions, although the intolerance for invasive thoracoscopy and the potential presence of underlying complications undermine its extensive clinical application, and its alternatives such as cytological examination may lead to misdiagnosis or missed diagnosis. Therefore, there exists a necessity to establish a diagnostic method with relatively high sensitivity and specificity. Additionally, the differential diagnosis of TB pleurisy and parapneumonic PE often represents a quandary for physicians, which results in the abuse of antibiotics on the one hand, and pleural hypertrophy on the other, especially in a country with high incidence of tuberculosis, such as China.

The peptide precursor for calcitonin released by the C-cells of the thyroid gland, PCT, is often used to distinguish bacterial infections from other diseases (13). The diagnostic value of PCT in PE and serum has previously been investigated by several research groups; however, the results have been somewhat contradictory. For example, Porcel *et al.* proposed that PCT has no value for the differential diagnosis of PEs (9), while Lin *et al.* found that either PE or s-PCT were effective in diagnosing parapneumonic PE (14). Furthermore, Khosla *et al.* investigated the diagnostic value of PCT in distinguishing infectious and noninfectious etiologies of PE, and the analysis results showed that PCT is a novel biomarker for diagnosing infectious PE (10). Faced with these contradictory outcomes, herein we examined the relationship between p-PCT and s-PCT levels in EPE from different groups and explored the various causes of PEs. Interestingly, p-PCT level was similar in all four groups. As a classical marker of bacterial infection, s-PCT level was higher in the parapneumonic effusion group than that in the TB and malignant groups, but it was difficult to explain its absence of rapid increase in empyema group. The underlying mechanism may lie in the fact that those patients had received antibiotics and other treatments which can influence the expression of inflammatory factors both in serum and pleura. In the present study, we found that there was no significant difference in p-PCT between four groups. Overall, it was unclear whether p-PCT or s-PCT is of no diagnostic value for judging the etiology of PE disease, which may be related to the location of PCT secretion and the way of PCT entering the thoracic cavity. It may also be due to the disintegration of a mass of necrotic cells in the pleural cavity, releasing many inflammatory cytokines, and in turn affecting the metabolism of PCT in PE.

For the classical inflammatory indicator, CRP, its expression in PE might largely depend on its infiltration from thoracic wall vessels into the pleural cavity, while there was a positive correlation between CRP in PE and s-CRP (15). Similar to other previous studies, we found that p-CRP levels were higher in infectious PEs, especially in parapneumonic effusion and empyema compared with non-infectious effusions. This result indicated the promising value of p-CRP measurement in differentiating benign

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and malignant PEs. It is worth noting that combinative examination of p-CRP and s-CRP can distinguish pleural fluid from benign and malignant diseases with a higher accuracy than examination of either p-CRP or s-CRP alone. To evaluate the diagnostic value of two kinds of CRPs, we performed ROC analysis, revealing that the combination of PE CRP and s-CRP was more valuable and effective than p-CRP or s-CRP alone, which further improved the diagnostic sensitivity, specificity, and accuracy.

However, there were several limitations in the present study. Firstly, the gold standard for diagnosing pleural diseases with lymphocyte predominance is pleural biopsy. However, most of the participants in this study did not undergo the examination due to various factors, such as their refusal, clinical limitations, and expense-related inevitable issues. The clinical diagnosis mainly depends on the comprehensive interpretations of physicians based on symptoms, signs, and various existing laboratory results. Secondly, some malignant participants may have had obstructive pneumonia, but we did not have a more accurate grouping, which may also have affected the analysis results. In summary, our results showed that combined analysis of CRP in serum and PE may be useful for differential diagnosis of EPE with higher diagnostic accuracy, sensitivity, and specificity.

Conclusions

The data supported the close relationship between combined analysis of p-CRP with s-CRP and effective and accurate differential diagnosis of EPE, due to its higher sensitivity and specificity. However, as a highly sensitive marker for diagnosing bacterial infections, neither p-PCT nor s-PCT showed correlations with the differential diagnosis of EPE.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-3383

Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-3383

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-3383). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee of Xijing Hospital, Fourth Military Medical University (KY20202098-C-1). Individual consent for this retrospective analysis was waived.

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