

Diagnosis of Parapneumonia Pleural Effusion With Serum and Pleural Effusion Activin A

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Abstract

Background

We aimed to evaluate the diagnostic value of Activin A levels in serum and pleural effusion on parapneumonic pleural effusion (PPE).

Methods

We collected serum and pleural effusion from 86 PPE and 37 non-PPE (NPPE) patients. Including Activin A, levels of biomarkers as lactate dehydrogenase (LDH), procalcitonin (PCT) and C-reactive protein (CRP) were measured. All factors were calculated for association with days after admission. The diagnostic potential of biomarkers on PPE was considered by receiver operating characteristic (ROC) curve analysis.

Results

Levels of Activin A in serum and pleural effusion of PPE patients were significantly higher than those of the NPPE patients. Moreover, concentrations of Activin A in pleural effusion showed a more obvious relevant days after admission. ROC curve analysis found that Activin A in pleural effusion had AUCs of 0.899 with 93% sensitivity and 84% specificity for PPE diagnosis.

Conclusion

Activin A in pleural effusion correlated with disease severity could act to diagnosis PPE.

Key Messages

- Higher concentrations of Activin A in pleural effusion were associated with days of admission in PPE patients.
- Elevated levels of Activin A in pleural effusion exhibited 93% sensitivity and 84% specificity in diagnosis of PPE.
- Pleural fluid Activin A level had higher AUC and better accuracy in the diagnosis of PPE.

Background

Approximately, pleural effusion concomitantly appeared in 40% of patients with pneumonia [1]. The timely and accurate diagnosis of parapneumonic pleural effusions (PPE) based on pneumonic etiologies is crucially important. Compared with patients without PPE, pneumonia patients with PPE are suffering from higher mortality and longer hospital stays [2]. Besides suitable antibiotics, systemic treatment and essential drainage intervention are frequently needed in PPE patients. So, it's critical to earlier investigate the presence and pathogen of PPE in order to take corresponding measures.

Traditionally, it's necessary to distinguish exudate and transudate of pleural effusion via the quantifying ratio of lactate dehydrogenase (LDH) and albumin in pleural effusion to serum for Light's Criteria Rule [3]. Moreover, the consider factors of PPE involve neutrophilic exudates with low glucose, elevated LDH, procalcitonin (PCT), C-reactive protein (CRP) and pleural effusion pH. These actors were used clinically with multiple sensitivities and specificities, but none of them are impeccable [4].

As a foremost member of the transforming growth factor- β (TGF- β) superfamily, activin A was recognized in several physiological functions including inflammation and tissue repair [5]. Nowadays, activin A was described as

proinflammatory and anti-inflammatory actions participated in immune response of diseases [6]. Sideras et al., found overexpression of activin A induced pathological variation of acute lung injury (ALI)/ acute respiratory distress syndrome (ARDS) in vivo. Furthermore, therapeutic neutralization of activin-A attenuated the pathogenicity of ALI [7]. Indeed, activin A was confirmed as the activator of interleukin 6 (IL-6), tumor necrosis factor- α (TNF)- α in acute inflammatory [8]. Conversely, activin A play anti-inflammatory action by suppressing IL-6-mediated signaling and secreting interleukin 1 (IL-1) receptor antagonist [9,10]. Functionally, activin A as a remarkable biological actor in asthma, chronic obstructive lung disease (COPD) and lung cancer were supported in recent studies [11,12]. In our previous study, we found that levels of serum Activin A were increased in COPD patients with skeletal muscle wasting [13]. Furthermore, we recently identified that higher expression of serum Activin A was associated with poor prognosis of Community-Acquired Pneumonia (CAP) (not yet published). Not surprisingly, the clinical roles of Activin A in pulmonary infectious diseases are needed to be paid attention. However, the investigation of Activin A in pleural effusion is unclear.

In the present study, we aimed to evaluate the clinical value of Activin A level in serum and pleural effusion on diagnostic potency of PPE.

Methods

Study population

This study was carried out between Jan 2017 and Feb 2021 in Yixing people's hospital affiliated Jiangsu University. This study was approved from the institutional review boards (IRBs) at the Yixing People's Hospital. And all participants consent to participate in the study with their written name. 86 patients diagnosed with PPE aged ≥ 18 years were enrolled. And enrolled subjects were excluded from the following criteria, as (1) age < 18 years; (2) pregnancy; (3) malignant tumor; (4) serious renal or heart or liver diseases. 37 patients with non-parapneumonic effusion (NPPE) were also selected into our study. All participants were categorized as PPE and NPPE groups.

Data collected

We recorded the related clinical characteristics and laboratory parameters from peripheral venous blood and pleural effusion within 24 h after admission. Basic parameters including white blood cell counts (WBC), CRP, PCT and LDH were collected.

Definition of PPE

PPE as a type of pleural lesions was diagnosed according to the criteria [14]. In this study, enrolled patients without PPE was classified as NPPE, including malignant pleural effusion, transudate pleural effusion and other pathogenesis.

Assessment of Activin A in blood and pleural effusion

The peripheral venous blood between 6 am and 7 am and pleural effusion within 24 h after admission were prepared to check the concentrations of Activin A by using enzyme-linked immunoassays (ELISA) kits (R&D Systems, USA) according to the manufacturer's recommendations.

Statistical analysis

Categorical variables between groups were compared using by χ^2 test via SigmaStat software. Receiver operating characteristic (ROC) curves were presented. The Univariate analyses of continuous variables were performed using the nonparametric Mann-Whitney U test.

Results

Characteristics of enrolled patients.

We enrolled 86 patients diagnosed with PPE and 37 with NPPE. Among the NPPE group, 16 were confirmed as malignancy pleural effusion with pleural cytology report, 17 were diagnosed with transudate pleural effusion and 4 were linked to other pathogenesis. Table 1 showed the baseline characteristics in the two groups. There were no significant differences in clinical presentation, including age, gender, smoking, blood pressure, respiratory rate, heart rates and so on.

Table 1
Characteristics of enrolled patients with parapneumonic and non-parapneumonic pleural effusion.

| | PPE | NPPE | <i>P</i> value |
|--|----------------|----------------|----------------|
| | n = 86 | n = 37 | |
| Gender (male) (n (%)) | 24 (27.9 %) | 13 (35.1 %) | 0.34 |
| Age (years old) | 62 (52, 76) | 63 (51, 74) | 0.65 |
| Smoking | 37 (43 %) | 20 (54 %) | 0.21 |
| Fever episode (n (%)) | 48 (55.8 %) | 22 (59.5 %) | 0.18 |
| Systolic blood pressure (mmHg) | 164 (102, 196) | 171 (112, 197) | 0.23 |
| Diastolic blood pressure(mmHg) | 87 (78, 108) | 92 (81, 120) | 0.34 |
| Pulse rate (times/minute) | 92 (72, 121) | 94 (63, 127) | 0.42 |
| Respiratory rate (times/minute) | 17 (15, 22) | 19 (17, 23) | 0.37 |
| Days of admission (days) | 9 (7, 14) | 13 (11, 17) | 0.11 |
| In hospital mortality (n (%)) | 4 (4.6 %) | 2 (5.4 %) | 0.28 |
| PPE, Parapneumonic effusion; NPPE, Non-parapneumonic effusion. | | | |

Factors In Serum And Pleural Effusion

We investigated the common biomarkers including WBC counts, CRP, PCT and LDH in blood sample, and found that there were differences between PPE and NPPE patients. Moreover, inflammatory factors including WBC counts and LDH in pleural effusion were also significantly different between the two groups. (Table 2) Furthermore, Figs. 1 showed that the higher levels of Activin A were present not only in serum but also in PPE, which indicated the closed association between Activin A and PPE. In order to deeply understand the clinical value of Activin A, we evaluated the biomarkers in correlation with days after admission in PPE patients. With age and gender adjustments, we confirmed that only concentrations of Activin A in pleural effusion were associated with days of admission in PPE patients. (Table 3)

Table 2
Levels of biomarkers in patients with parapneumonic and non-parapneumonic pleural effusion.

| | PPE | NPPE | Pvalue |
|--|--------------------|--------------------|----------|
| | n = 86 | n = 37 | |
| Serum | | | |
| WBC ($\times 10^9/L$) | 16.1 (10.5, 20.4) | 8.6 (4.3, 13.2) | 0.005* |
| N (%) | 82.5 (72.1, 87.3) | 77.6 (62.3, 83.6) | 0.18 |
| CRP (mg/L) | 173 (137.3, 268.4) | 64.2 (13.2, 121.8) | < 0.001* |
| PCT (ng/mL) | 0.38 (0.17, 2.97) | 0.07 (0.03, 0.23) | < 0.001* |
| LDH (U/L) | 103 (78.6, 142.3) | 110 (88.1, 178.2) | 0.203 |
| Activin A (ng/mL) | 33.6 (9.31, 50.7) | 7.82 (0.71, 17.11) | < 0.001* |
| Pleural effusion | | | |
| WBC ($\times 10^6/L$) | 2.35 (1.31, 10.21) | 0.42 (0.11, 0.87) | < 0.001* |
| N (%) | 81.4 (57.2, 88.5) | 11.4 (3.7, 24.8) | < 0.001* |
| CRP (mg/L) | 102 (85.6, 174.9) | 32.7 (8.41, 82.44) | < 0.001* |
| PCT (ng/mL) | 0.33 (0.09, 1.02) | 0.05(0.02, 0.13) | < 0.001* |
| LDH (U/L) | 326 (147, 628) | 76.3 (48, 151.3) | < 0.001* |
| Activin A (ng/mL) | 27.1 (8.66, 30.3) | 1.29 (0.33, 8.06) | < 0.001* |
| PPE, Parapneumonic effusion; NPPE, Non-parapneumonic effusion; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; LDH, lactate dehydrogenase. *p < 0.05 | | | |

Table 3
The correlation between days of admission and inflammatory biomarkers in serum and pleural fluid in parapneumonic effusion patients.

| | serum | | | | | | pleural effusion | | | | | |
|--|--------|-------|-------|--------|-------|-----------|------------------|--------|--------|--------|-------|-----------|
| | WBC | N % | CRP | PCT | LDH | Activin A | WBC | N % | CRP | PCT | LDH | Activin A |
| r | -0.203 | -0.34 | -0.26 | 0.504 | 0.263 | 0.682 | -0.121 | -0.252 | -0.092 | 0.466 | 0.358 | 0.852 |
| P value | 0.392 | 0.28 | 0.274 | 0.013* | 0.245 | 0.003* | 0.613 | 0.351 | 0.03* | 0.026* | 0.121 | < 0.001* |
| PPE, Parapneumonic effusion; NPPE, Non-parapneumonic effusion; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; LDH, lactate dehydrogenase. *p < 0.05 | | | | | | | | | | | | |

Predictive roles of Activin A in serum and pleural on PPE

It's necessary to earlier definite PPE associated with clinical options and prognosis. We evaluated the efficacy of Activin A in predicting PPE by assessing ROC curve. Figure 2 showed that Activin A levels in pleural effusion exhibited 93% sensitivity and 84% specificity in diagnosis of PPE. Table 4 showed that pleural effusion Activin A had an AUC of 0.899 (95% confidence interval 0.813–0.965), and serum Activin A had an AUC of 0.862 (95% confidence interval 0.733–0.95). Pleural

effusion CRP and PCT had AUC of 0.813 and 0.782, respectively. And blood CRP and PCT had AUC of 0.756 and 0.821, respectively. (Table 4) Together, pleural effusion Activin A level had higher AUC and better accuracy in the diagnosis of PPE.

Table 4
The diagnostic value of inflammatory biomarkers in parapneumonic fluid.

| | AUC | P value | 95% confidence interval | | Sensitivity | Specificity |
|------------------|-------|----------|-------------------------|-------|-------------|-------------|
| | | | Lower | Upper | | |
| Serum | | | | | | |
| CRP | 0.756 | 0.006* | 0.649 | 0.860 | 0.73 | 0.67 |
| PCT | 0.821 | 0.004* | 0.722 | 0.923 | 0.75 | 0.74 |
| Activin A | 0.862 | 0.002* | 0.733 | 0.950 | 0.89 | 0.81 |
| Pleural effusion | | | | | | |
| CRP | 0.813 | 0.003* | 0.711 | 0.906 | 0.84 | 0.74 |
| PCT | 0.782 | 0.001* | 0.662 | 0.883 | 0.86 | 0.82 |
| Activin A | 0.899 | < 0.001* | 0.813 | 0.965 | 0.93 | 0.84 |

PPE, Parapneumonic effusion; NPPE, Non-parapneumonic effusion; CRP, C-reactive protein; PCT, procalcitonin. *p < 0.05

Discussion

To the best of our known, it's firstly to assess concentrations of Activin A both in serum and in pleural effusion for diagnosis of PPE. In the present study, elevated levels of serum and pleural effusion Activin A were appeared in PPE compared with NPPE patients. Furthermore, increased levels of Activin A in pleural effusion were determined to be associated with days after admission. Pleural effusion Activin A had acceptable sensitivity and specificity diagnose PPE.

As a consequence of pressure, transudative effusion outcome in the pleural space. Coupled with increased inflammatory cells in the pleura, pleural effusion as an exudative effusion developed with the complex etiological factors [15]. In addition to malignancy, tuberculous-induced pleural effusion was rich in lymphocytes [16]. However, PPE from bacteria is abundant supply of neutrophils. Unluckily, morbidity and mortality are higher in patients with pneumonia and pleural effusion than in individuals without pleural effusion [17]. Radiological and ultrasonic test is commonly accepted to determine pleural effusion. Popular biomarkers of inflammatory as CRP and PCT in serum and pleural effusion were used to predict PPE [18]. Falguera et al., found pleural effusion CRP contributed to the diagnosis and assessment of severity of PPE [19]. Although CRP has value in predicting inflammation severity, the non-specific characteristic is regrettable [20]. Our study also found the clinical effects of CRP on PPE diagnosis with moderate accuracy. In the previous study, PCT concentrations in serum and pleural effusion showed predictive roles in PPE patients [21]. However, unexpected sensitivity and specificity of PCT in diagnosis of PPE was concluded in a meta-analysis study [22]. Our data found levels of PCT in serum levels in serum and in pleural effusion predicted PPE with AUC value (0.821 and 0.782). In our study, we firstly confirmed Activin A in serum and pleural effusion had predictive ability of PPE, with higher AUC value (0.862 and 0.899). Previous studies confirmed the abnormal expression of Activin A in serum were found in various pulmonary diseases [23,24]. Consisted with lower cut-off values of CRP and PCT, concentrations of Activin A in pleural effusion not in serum could be more suitable for diagnosing PPE with better sensitivity and specificity.

Activin A was proved to be participated in development of pulmonary inflammation [25]. The biological functions of Activin A as a key regulator of other inflammatory cytokines including TNF- α , interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) were confirmed in inflammatory response [26,27]. The clinical investigation found that a higher concentration of Activin A in

bronchoalveolar fluid (BALF) could predict poorer mortality in ARDS patients [28]. Our previous study found that compared with healthy individuals, patients with chronic obstructive pulmonary disease have elevated levels of serum Activin A correlated with TNF- α expression [13]. Furthermore, we recently revealed that increased levels of Activin A in serum not influenced by etiology play a more a more effective predictor of hospital mortality in CAP patients (not yet published). However, to our known, there's no associated report about Activin A in pleural effusion with pulmonary inflammation, especially with PPE. The forecast role of Activin A in pleural effusion is unclear. It's necessary to observe the clinical value of Activin A in PPE.

Once diagnosed, therapeutic strategy including enough antibiotics and proper drainage is necessary. The patients with severe cases of PPE always suffered from the longer days after admission with standard treatments regimens. Therefore, it's essential to proactively determine the severity of their condition, in order to identify patients who would need aggressive interventions earlier. In this study, all PPE patients were made in drainage as standard therapy. In order to evaluate the association between Activin A and disease severity, we used the number of days after admission to represent severity of PPE. The data of our study confirmed that Activin A in pleural effusion correlating with days of admission is just an appropriate indicator of severity in PPE.

As a retrospective study, our study faced some limitations. First, numbers of NPPE patients are fewer, and it's difficult to classify subgroup analyses with different pathogen of pleural effusion. Second, meanwhile, we have not compared the levels of Activin A in BALF, serum and pleural effusion. Third, levels of Activin A in pleural effusion at different time points after admission were unknown.

Conclusions

The present study revealed that Activin A concentration in pleural effusion exhibited capacity for diagnosis of PPE and for gauging the severity of the disease. Our data supported a close relationship between levels of Activin A and local inflammation in the pleura. Whether it is suitable to distinguish PPE from multiple etiologies of pleural effusion needs further investigation.

Abbreviations

PPE

parapneumonic pleural effusion; NPPE:non- parapneumonic effusion; LDH:lactate dehydrogenase; PCT:procalcitonin; CRP:C-reactive protein; ROC:receiver operating characteristic; TGF- β :transforming growth factor- β ; ALI:acute lung injury; ARDS:acute respiratory distress syndrome; IL-6:interleukin 6; TNF- α :tumor necrosis factor- α ; IL-1:interleukin 1; COPD:chronic obstructive lung disease; CAP:community-acquired pneumonia; WBC:white blood cell counts; BALF:bronchoalveolar fluid.

Declarations

Ethics approval and consent to participate

This study was approved from the institutional review boards (IRBs) at the Yixing People's Hospital. And all participants consent to participate in the study with their written name.

Consent for publication

All authors provided consent for publication.

Availability of data and material

The authors confirmed the availability of supporting data and materials. All data generated or analysed during this study are included in this published article.

Competing interests

The authors ensure the availability of supporting data and materials.

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Authors' contributions

Conceptualization, H.D; and X.H.J; Methodology, G.H.Z; and Y.S; Software, R.H.C; Formal Analysis, Y.D; Investigation, Z.W.T; Writing—Original Draft Preparation, X.H.J; Writing—Review and Editing, H.D. All authors have read and agreed to the published version of the manuscript. All authors read and approved the manuscript.

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Figures

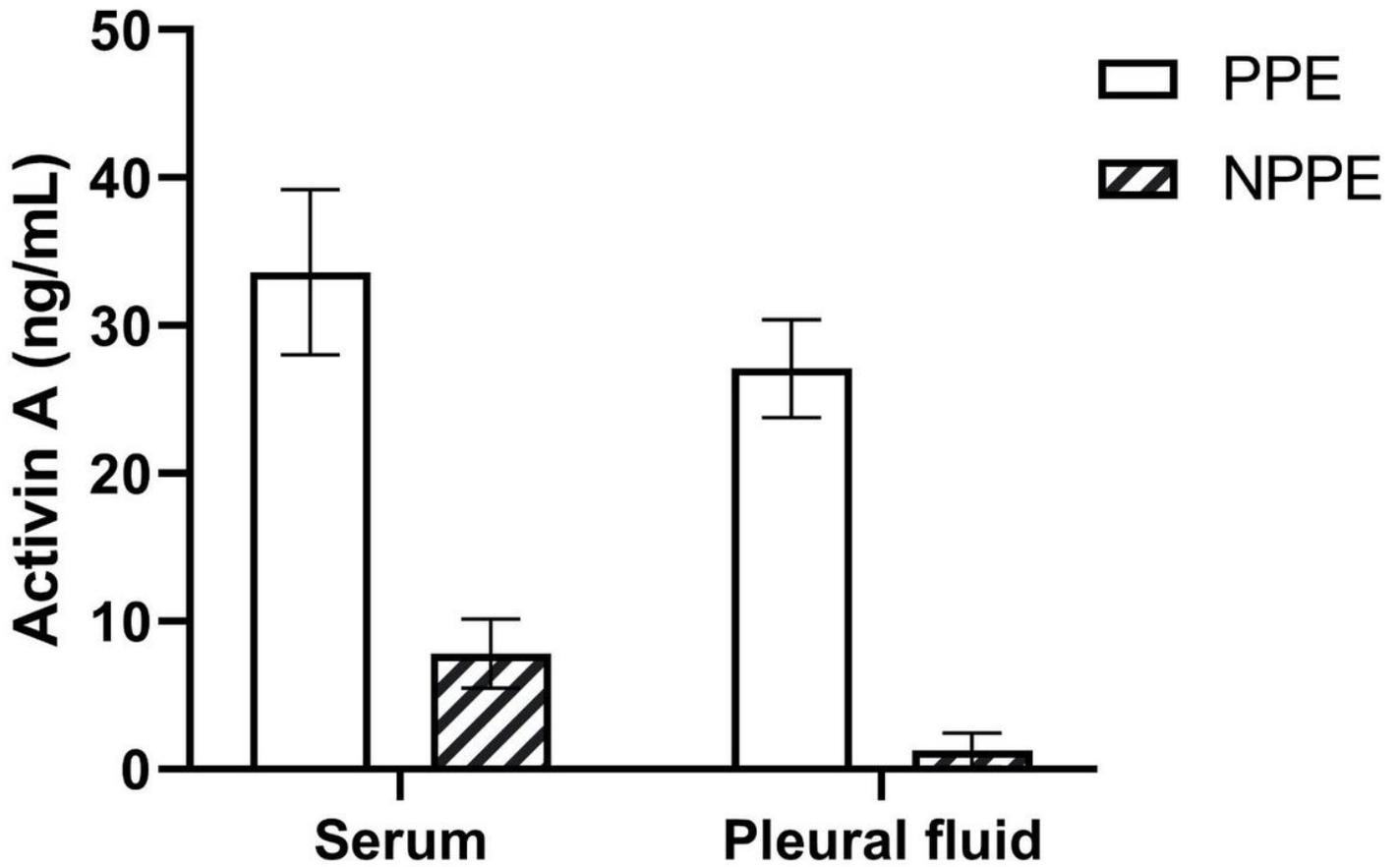


Figure 1

Levels of Activin A in parapneumonia pleural effusion and non- parapneumonia pleural effusion patients. Increased concentrations of Activin A were confirmed in serum and pleural effusion of PPE patients than those of NPPE patients. PPE, Parapneumonic effusion; NPPE, Non-parapneumonic effusion. *p <0.05

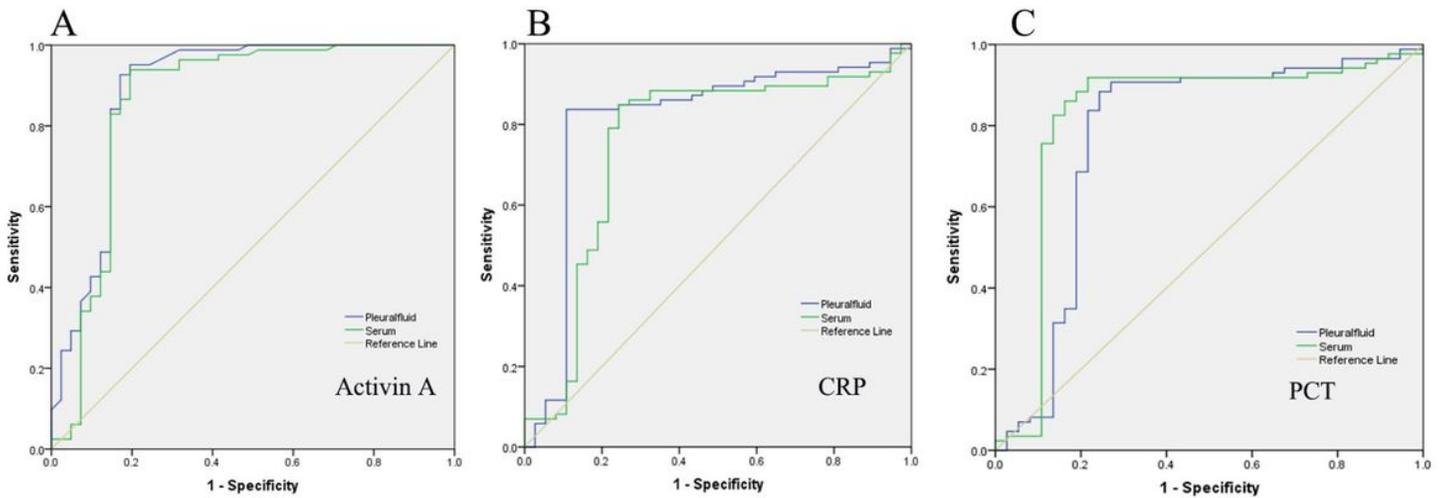


Figure 2

Receiver operating characteristic (ROC) curve of biomarkers in diagnosis of parapneumonic pleural effusion. A. The diagnostic role of Activin A in serum and pleural effusion on PPE. B. The ROC of CRP in diagnosis of PPE. C. The ROC of PCT in diagnosis of PPE. CRP, C-reactive protein; PCT, procalcitonin.