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ORIGINAL ARTICLE

Role of the Fibrinogen Degradation Products and D-Dimer in the Differential Diagnosis of Pulmonary Tuberculosis and Community-Acquired Pneumonia

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SUMMARY

Background: **Differential diagnosis between pulmonary tuberculosis (TB) and community acquired pneumonia (CAP) is often difficult. Pulmonary TB could induce a systemic hypercoagulable state. The present study aims to investigate whether fibrinogen degradation products (FDP) and D-dimer play a diagnostic role for pulmonary TB.**
Methods: **We retrospectively analyzed the clinical and laboratory characteristics of 192 patients with activated pulmonary TB and 110 patients with CAP. The serum levels of FDP and D-dimer were detected and the diagnostic ability was evaluated.**
Results: **The serum levels of FDP and D-dimer were significantly higher in patients with pulmonary TB compared to CAP (both $p < 0.05$). ROC curve analyses showed that the diagnostic value of FDP in pulmonary TB was noticeably higher than that of D-dimer ($p = 0.0197$). Combined detection of FDP and D-dimer may slightly improve the sensitivity of diagnosis for pulmonary TB from CAP. However, the AUC showed no significant differences from FDP alone ($p = 0.416$).**
Conclusions: **The serum level of FDP and D-dimer are useful laboratory markers that can be used to distinguish patients with pulmonary TB from patients with CAP.**
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KEY WORDS

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INTRODUCTION

Pulmonary TB remains a public health problem worldwide. According to the World TB Day 2016 report, an estimated 9.6 million people developed tuberculosis worldwide in 2014, of whom 1.5 million died. Of the estimated 480,000 cases of multidrug-resistant tuberculosis, three quarters remained undetected and untreated. Tuberculosis is now the leading cause of death by infectious disease worldwide, surpassing malaria and HIV [1]. The initial symptoms of pulmonary TB are similar to those of CAP. It is often difficult to distinguish pulmonary TB from CAP in clinical settings [2,3]. Currently available diagnostic methods such as the acid-fast ba-

cilli test and microbiological and histological examination of biopsied tissue play a limited role in differentiating pulmonary TB from CAP [4-6].

Studies have shown that patients with pulmonary infection might have coagulation disorders, which include increased procoagulant activity, decreased expression of anti-coagulant factors, and suppression of the fibrinolytic system [7-9]. Acute lower respiratory tract infection may be associated with activation of coagulation in the circulation, as reflected by elevated plasma levels of fibrinogen [10-12]. However, in patients with pulmonary TB, the coagulation disorders were significantly different [13].

Both FDP and D-dimer levels are major markers of coagulation disorders, especially the thromboembolic disorders [14,15]. Low levels of FDP and D-dimer can be detected in healthy individuals, and significantly higher levels are observed in patients with deep venous thrombosis, disseminated intravascular coagulation, myocardial infarction, cancer, and infections [16,17]. However, the levels of FDP and D-dimer in pulmonary TB and CAP have not been studied fully. In the present study, we analyzed the levels of FDP and D-dimer in the peripheral blood of patients with pulmonary TB and CAP and assessed their value in the differential diagnosis.

MATERIALS AND METHODS

Patients

This retrospective study reviewed the clinical data of 192 patients with active pulmonary TB and 110 patients with CAP in the First Affiliated Hospital of Anhui Medical University and Anhui Chest Hospital between January 2013 and December 2016. This study was approved by the Ethics Committees of the Faculty of Medicine (Anhui Medical University, China), and informed consent was obtained from all subjects before collection of blood.

Diagnosis for pulmonary TB was based on microbiological analysis of sputum. All the patients with pulmonary TB were sputum acid-fast bacilli (AFB) smear-positive. Patients were considered to have bacterial CAP when 1) clinical signs and new infiltration on chest radiograph were evident and completely resolved after treatment with the appropriate antibiotics, 2) sputum or lavage fluid cultures were M. tuberculosis-negative during clinical follow-up, and 3) viral pathogens were not detected.

Exclusion criteria included use of antibiotics for more than 24 hr at the time of enrollment. Chronic inflammatory conditions, current steroid therapy, anticoagulant therapy or change to other diagnosis such pulmonary embolism or cancer during follow-up.

The measurement of FDP and D-dimer

After the first evaluation, venous blood was drawn for biochemical examination. Samples were stored at -80°C until testing was performed in series. FDP and D-dimer levels were measured by a quantitative latex assay (STA-LIAtest D-DI; Diagnositica-Stago, Asnieres, France) on an STA-R analyzer (Diagnostica-Stago) according to the manufacturer's instructions. The linear ranges, as given by the manufacturer, lie between 0.00 and 5.00 μg/mL for FDP and 0.00 and 0.50 μg/mL for D-dimer.

Statistical analyses

The analyses were performed using the SPSS 22.0 software package. Data are presented as the mean ± standard error (SE) for normally distributed data. Differences in continuous variables between groups were determined using Students's *t*-test or the Mann-Whitney *U*-test. Correlation between FDP and D-dimer was analyzed using Pearson's correlation test. ROC curve analysis was performed to identify the most useful cutoff levels for FDP and D-dimer to identify the great sum of sensitivity and specificity for distinguishing pulmonary TB from CAP. The ability of FDP and D-dimer to distinguish pulmonary TB from CAP was compared using the area under the curve (AUC). A p-value of < 0.05 was considered statistically significant.

RESULTS

Study population

Among the 192 patients with pulmonary TB who participated in the present study, 119 were male and 73 were female, with a mean age of 59.41 ± 17.54 (range, 16 - 94 years). Regarding the 110 patients with CAP, 58 were male and 52 were female, with a mean age of 61.96 ± 16.17 (range, 15 - 97 years). Baseline clinical characteristics are listed in Table 1.

FDP and D-dimer levels in pulmonary TB and CAP

The levels of FDP and D-dimer were determined in all samples. We found FDP and D-dimer levels in pulmonary TB to be 7.35 ± 0.77 μg/mL and 2.49 ± 0.26 μg/mL respectively, while they were 3.95 ± 0.56 μg/mL and 1.57 ± 0.29 μg/mL in patients with CAP ($p < 0.000$ and $p = 0.025$, respectively, Figure 1). Furthermore, there was strong positive correlation between FDP and D-dimer in the CAP group ($r = 0.510$, $p < 0.000$, Figure 2) and pulmonary TB group ($r = 0.855$, $p < 0.000$), respectively.

Diagnostic accuracy of discriminating pulmonary TB from CAP

The ROC curves for the analyses of FDP and D-dimer in patients with pulmonary TB were plotted (Figure 3). The AUC of FDP (0.696, 95% CI: 0.640 - 0.747) was significantly higher than that of D-dimer (0.653, 95% CI: 0.596 - 0.707, $p = 0.0197$, Table 2). When FDP and D-dimer were combined, the AUC was 0.703 (95% CI: 0.648 - 0.754), which showed no significant differences from FDP alone ($p = 0.416$, Table 2).

The resulting ROC-AUCs, sensitivities, and specifici-

Table 1. Baseline clinical characteristics of the study population.

Symptoms	CAP (n = 110)	Pulmonary TB (n = 192)	p-value
Cough	75 (68.18%)	136 (70.83%)	0.629
Fever	36 (32.72%)	54 (28.13%)	0.400
Night sweats	6 (5.45%)	34 (17.71%)	0.003
Weight loss	11 (10%)	39 (20.31%)	0.020
Hemoptysis	16 (14.54%)	21 (10.94%)	0.357
Chest pain	14 (12.73%)	11 (5.73%)	0.034
Symptom duration > 2 weeks	45 (40.91%)	150 (78.16%)	< 0.001

Chi-square test or Pearson's test was performed. Values are presented as number (percentage).

Table 2. The ROC analysis of D-dimer and FDP in the diagnosis of pulmonary TB.

Items	FDP	D-dimer	Combination
Optimal cutoff	3.550 µg/mL	1.625 µg/mL	-
Sensitivity (%)	61.500	47.900	66.700
Specificity (%)	70.000	77.300	67.300
Younden's index (%)	0.315	0.252	0.340
SE	0.0311	0.0323	0.0307
AUC (95% Cl)	0.696 (0.640 - 0.747)	0.653 (0.596 - 0.707)	0.703 (0.648 - 0.754)
p-value	0.4167 (vs. combination) 0.0197 (vs. D-dimer)	0.0341 (vs. combination)	-

Table 3. Positive rates of FDP and D-dimer in pulmonary TB and CAP groups [case (%)].

Groups	Case (n)	FDP [n (%)]	D-dimer [n (%)]
Pulmonary TB	192	118 (61.45)	92 (47.90)
CAP	110	33 (30.00)	25 (22.70)

Chi-square test or Pearson's test was performed. Pulmonary TB group vs. CAP group: FDP ($\chi^2 = 27.683$, $p < 0.001$) and D-dimer ($\chi^2 = 18.697$, $p < 0.001$).

ties at the best cutoffs are summarized in Table 2. The sensitivity and specificity of these two markers were different when they were applied separately in the diagnosis of pulmonary TB. FDP showed the higher sensitivity (0.615) and specificity (0.700). When the detection of FDP was combined with that of D-dimer, the sensitivity increased to 0.667 (Table 2). The established cutoffs for discriminating pulmonary TB from CAP were 3.55 mg/L for FDP and 1.625 µg/L for D-dimer. When the cutoff values were applied, 118 (61.45%) and 92 (47.90%) cases showed statistically significant differences from those in the CAP group (both $p < 0.001$, Table 3).

DISCUSSION

The present study demonstrated for the first time that the levels of FDP and D-dimer are significantly higher in patients with activated pulmonary TB than in patients with CAP. FDP has been demonstrated to have a more effective diagnostic value in pulmonary TB. Further-

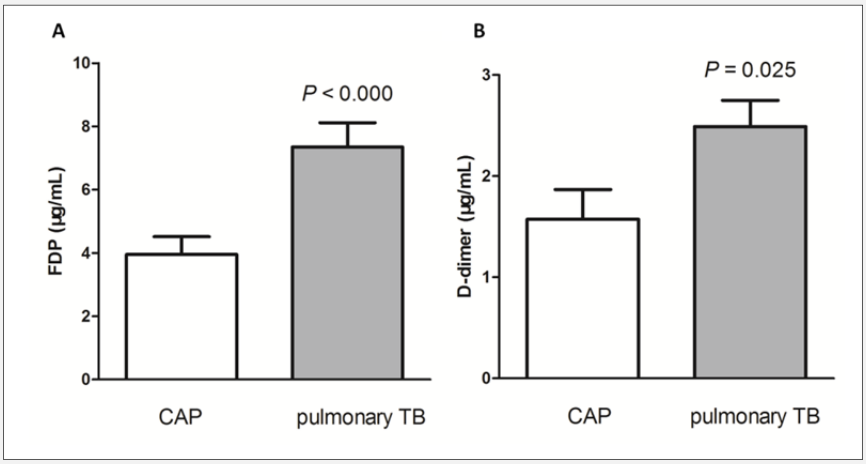

Figure 1. The serum levels of FDP (A) and D-dimer (B) in the peripheral blood of patients with pulmonary TB compared to the levels in patients with CAP.

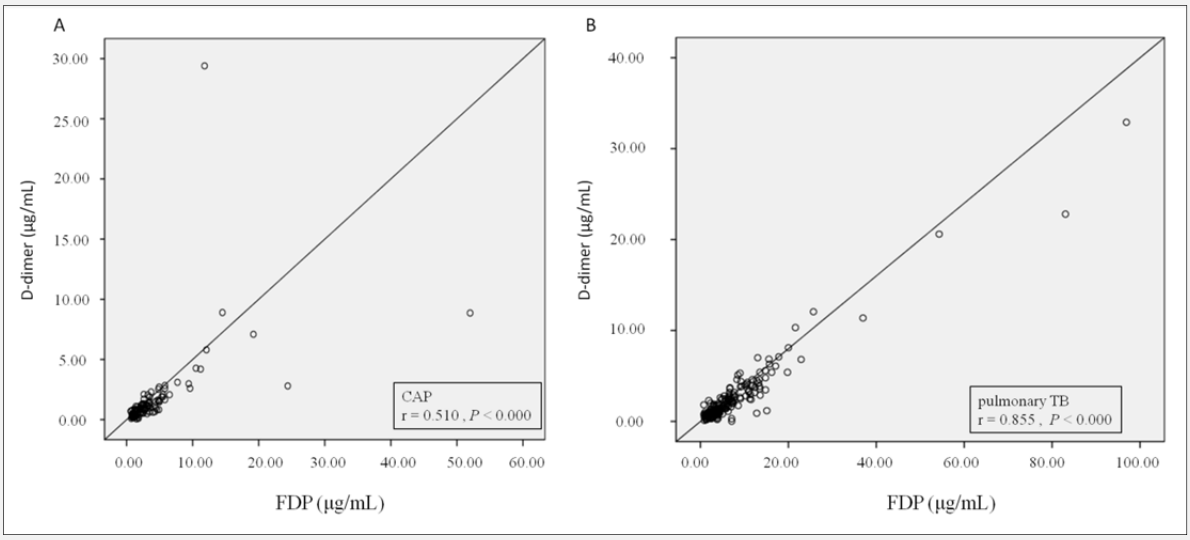

Figure 2. The correlation between FDP and D-dimer in the CAP group (A. r = 0.510, p < 0.000) and pulmonary TB group (B. r = 0.855, p < 0.000).

more, FDP combined with that of D-dimer could increase the sensitivity of diagnosis for pulmonary TB. Accumulating evidence supports the conclusion that hemostatic changes occur during severe pulmonary infections. These changes include increased procoagulant activity, decreased expression of anticoagulant factors, and suppression of the fibrinolytic system [18,19]. D-dimer is a specific marker of cross-linked fibrin used in the diagnosis of disseminated intravascular coagulation and pulmonary thromboembolism. High D-dimer levels

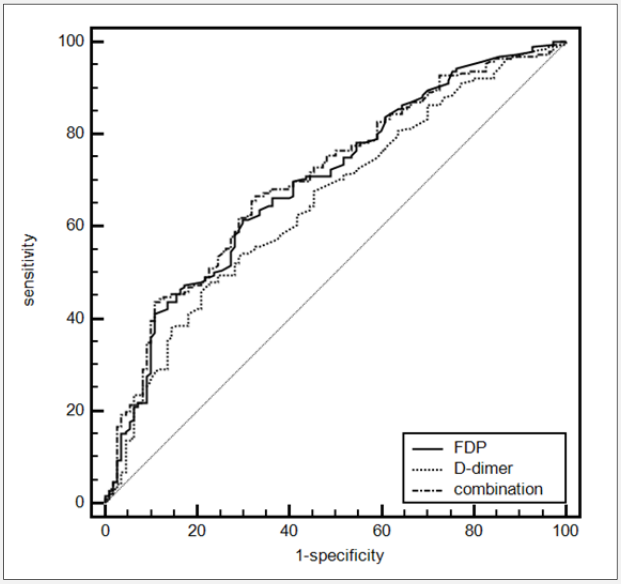

Figure 3. ROC curves of FDP and D-dimer as well as the combination of two markers in patients with pulmonary TB vs. patients with CAP.

may indicate microvascular thrombosis and severity of disease [20]. Shilon Y et al. found D-dimer levels to be correlated with severity of patients with CAP [21]. Kager M et al. found the serum level of D-dimer was significantly higher in patients with pulmonary TB than healthy controls [22]. The current study, covered 192 cases patients with pulmonary TB. Results indicated that D-dimer was markedly higher in pulmonary TB than in those with CAP. These results indicate that D-dimer may play an important role in the occurrence and development of pulmonary TB.

FDP is a product of the degradation of fibrinogen and fibrin, and it is an indicator of enhanced primary and second fibrinolysis [23]. The levels of FDP in pulmonary TB have only rarely been studied. Liu et al. found that FDP levels in the pulmonary TB were higher than healthy donors [24]. In our present study, with a larger sample pool, we demonstrate that the levels of FDP are significantly higher than in patients with CAP. In the current study, we showed a positive linear correlation between serum levels of D-dimer and FDP. The significant association of these two factors has also been reported in other studies [25,26].

ROC analysis has been used extensively to compare the diagnostic value of these two markers. There has been little research into the role of D-dimer in the differential diagnosis of pulmonary TB. Shen Y reported that D-dimer might be useful as a simple marker of tuberculous pleural effusion [27]. In the present study, the ROC curve showed a sensitivity of 0.479 and a specificity of 0.773 for serum D-dimer in the diagnosis of pulmonary TB, and FDP showed a sensitivity of 0.615 and a specificity of 0.773. The significantly higher AUC suggests that FDP may be a better marker of diagnosis of pulmonary TB than D-dimer. Furthermore, combination of FDP and D-dimer could slightly increase the sensitivity to 0.667 for diagnosis of pulmonary TB, but there were no significant differences in AUC between the combination and using either marker alone. These results indicate that a combination of FDP and D-dimer may have a better diagnostic performance for pulmonary TB. Several limitations of this study must be addressed. First of all, our study is an observation study, we did not further investigate the mechanism of how M. tuberculosis affects the fibrinolytic system in patients with pulmonary TB. Secondly, our results may be further confirmed if recurrent pulmonary TB patients were involved in this study.

CONCLUSION

In summary, the current study showed that the combination of FDP and D-dimer derived from a blood sample during the initial stage of diagnosis is a very useful marker for distinguishing patients with pulmonary TB from those with CAP.

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Ethical Approval:
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent:
Informed consent was obtained from all individual participants included in the study.

Declaration of Interest:
The authors declared that they have no conflicts of interest with regard to this work.

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