Diagnostic Performance of D-dimer in Predicting Pulmonary Embolism in Tuberculosis Pleural Effusion Patients.

Xiao-Ming Li
Shanghai Jiaotong University School of Medicine Xinhua Hospital https://orcid.org/0000-0002-0262-6731

Ya-Jing Qin
Weifang Respiratory Disease Hospital

Wen-Jing Ye
Shanghai Jiaotong University School of Medicine Xinhua Hospital

Xi Chen
Shanghai Jiaotong University School of Medicine Xinhua Hospital

De-Zhi Sun
Weifang Respiratory Disease Hospital

Xue-Jun Guo
Shanghai Jiaotong University School of Medicine Xinhua Hospital

Wen Gu (guwen@xinhuamed.com.cn)
Shanghai Jiaotong University School of Medicine Xinhua Hospital https://orcid.org/0000-0003-1414-0605

Research article

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Abstract

Background: Tuberculosis pleural effusion patients always have elevated D-dimer levels. How D-dimer performance in predicting pulmonary embolism in TPE population is unclear. The aim of this study was to assess the diagnostic performance of D-dimer for pulmonary embolism in TPE population and explore the potential mechanism of PE in TPE patients.

Methods: We retrospectively analyzed patients who were admitted to Xinhua hospital and Weifang Respiratory Disease Hospital with a final diagnosis of TPE between March 2014 and January 2020. Data including demographics, history, symptoms, D-dimer, C-reactive protein (CRP), white blood cell (WBC) and erythrocyte sedimentation rate (ESR) as well as the cytokines such as IL-6, IL-8, TNF-α, IL-2 receptor of the first blood test, imaging results including computed tomography pulmonary angiography (CTPA) and compression ultrasound (CUS) with Doppler were collected and analyzed.

Results: 248 patients (male=170, female=78) at the age of 43±20.6 years were final included in this study. Elevated D-dimer (≥0.5mg/L) was detected in 186/248 (75%) patients. 150 patients received CTPA examination. PE was diagnosed in 29/150 (19.3%) patients. Among the TPE population, PE patients had significantly higher DD level than that of non-PE patients (2.26±0.96 mg/L VS 1.06±0.73 mg/L) (P□0.05). An optimized cut off value for D-dimer in predicting PE in TPE was 1.18 mg/L, with a sensitivity of 89.7% and a specificity of 77.8 % (area under curve was 0.893; 95% CI: 0.839-0.947; P□0.01). PE patients had lower median WBC and IL-8 values (5.14□10^9/L VS 6.1□10^9/L, P□0.05 ; 30.2 pg/ml VS 89.7 pg/ml, P□0.05) but higher median IL-2 receptor value (1964.8 pg/ml VS 961.2 pg/ml, P□0.01) than that of non-PE patients.

Conclusions: D-dimer is still an objective biomarker to predict PE in TPE patients. In order to avoid unnecessary radiological test, the cut off value of D-dimer in TPE patients should be set at 1.18 mg/L. In addition, the imbalance of prothrombotic and antithrombotic cytokines may partly attribute to the formation of pulmonary embolus in TPE patients.

Background

Tuberculosis (TB) is the major cause of death from infectious disease worldwide. Tuberculosis pleural effusion (TPE) is one of the most common form of extrapulmonary TB which caused by Mycobacterium infection in pleural space [1]. Its frequency varies in accordance with the tuberculosis burden in different regions. As reported, it is less than 10% in low tuberculosis burden countries while over 40% in counties with high tuberculosis burden. TPE has a morbidity of 6.5–8.7% in China which accounts for the major portion of pleural effusion especially in young adults [2].

D-dimer, as an essential biomarker for the diagnosis of pulmonary embolism (PE), is increased in pleural effusion and plasma of TPE patients. As previously study, D-dimer may be considered as a useful biomarker for TPE diagnosis [3]. It is well established that PE should be ruled out if the patients have

normal D-dimer level [4]. PE has the similar symptoms, such as chest pain and shortness of breath, with TPE. While together with positive D-dimer, whether to do further imaging tests to confirm the PE diagnosis is a dilemma for clinicians.

In order to assess the diagnostic performance of D-dimer for pulmonary embolism in TPE population and explore the potential mechanism of PE in TPE patients, we analyzed the clinical data of TPE patients in our hospital and want to make contributions to guide clinical decision-making.

Methods

Patients

We retrospectively analyzed patients who were admitted to the Department of Respiratory Medicine, Xinhua Hospital Affiliated to Shanghai Jiao Tong University school of Medicine and Department of Respiratory and Critical Care Medicine, Weifang Respiratory Disease Hospital in China, with a final diagnosis of TPE between March 2014 and January 2020. Patients were excluded if they with the conditions which may influence the D-Dimer levels such as active tumor, hepatic insufficiency, renal insufficiency and pregnant.

This study is a retrospective study. It only collects the clinical data of patients, does not interfere with the treatment plan of patients, and does not bring any risk to patients' physiology. We did our best to protect the information provided by patients without disclosing their personal privacy. All the protocols were approved by The Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. (NO. XHEC-D-2020-183)

Data Collection

According to the medical record, data regarding patients' characteristics such as age, sex, previous medical history, current symptoms, D-dimer, C-reactive protein (CRP), white blood cell (WBC) and erythrocyte sedimentation rate (ESR) as well as the cytokines such as IL-6, IL-8, TNF-α, IL-2 receptor of the first blood test were collected and analyzed. Imaging results including computed tomography pulmonary angiography (CTPA) and compression ultrasound (CUS) with Doppler were collected and analyzed.

Statistical Analyses

SPSS version 22.0 (IBM Corporation, New York) was used for statistical analysis. student t test and non-parametric test were used for parametric continuous and nonparametric continuous variables, respectively. Using receiver operating curve (ROC) analysis to evaluated the threshold value of D-dimer in differentiating PE from non-PE in TPE patients. Statistical significance was set at $P < 0.05$.

Results

A total of 255 patients were final diagnosed of TPE between March 2014 and January 2020 in the department of Respiratory medicine of our hospital. We excluded 7 patients (active tumor = 1, hepatic insufficiency = 4, renal insufficiency = 1, pregnant = 1) who with conditions that may influence the D-dimer. 248 patients (male = 170, female = 78) at the age of 43 ± 20.6 years were final included in this study. Elevated D-dimer (≥ 0.5 mg/L) was detected in 186/248 (75%) patients. 150 patients received further radiological examination (CTPA). PE was diagnosed in 29/150 (19.3%) patients. Figure 1 shows the flow of participants through the study and Table 1 outlines the characteristics of the patients enrolled in the analysis.

Table 1
Characteristics of the study population (n = 248)

Characteristic	Count (%) or Mean (SD)
Male	170 (68.5%)
Female	78 (31.5%)
Age (years)	43 (20.6)
Symptoms	
Cough	185 (74.6%)
Fever	128 (51.6%)
Chest pain	126 (50.8%)
Dyspnea	123 (49.6%)
Expectoration	100 (40.3%)

In TPE population the D-dimer levels of PE patients were significantly higher than that of non-PE patients (2.26 ± 0.96 mg/L VS 1.06 ± 0.73 mg/L) (P□0.05) (Fig. 2). In order to different PE from non-PE, we calculated the ROC curve. The area under ROC curve (AUC) was 0.893 (95% confidence interval: 0.839–0.947; P□0.01) (Fig. 3). The ROC curve analysis suggested the best cut off point for D-dimer in predicting PE in TPE was 1.18 mg/L, with a sensitivity of 89.7% and a specificity of 77.8%.

PE patients had lower median WBC and IL-8 values (5.14□10^9/L VS 6.1□10^9/L, P□0.05; 30.2 pg/ml VS 89.7 pg/ml, P□0.05) but higher median IL-2 receptor value (1964.8 pg/ml VS 961.2 pg/ml, P□0.01) than that of non-PE patients. Other inflammatory biomarkers and cytokines such as ESR, CRP, IL-6, TNF-α had no significant differences in PE group when compared with non-PE group. (Table 2)

Table 2
Biochemical characteristics of patients with confirmed diagnosis (median, range)

	PE	Non-PE	P value
ESR (mm/h) (n = 150; 29/121)	54.5(2-120)	44(1-120)	0.127
CRP (mg/L) (n = 150; 29/121)	39.1(1.39–200)	37(2.46–196)	0.538
WBC (10^9/L) (n = 150; 29/121)	5.14(3.05–10.5)	6.1(2.1–12.5)	0.022*
IL-8 (pg/ml) (n = 109; 22/87)	30.2(7.97–58.1)	89.7(5-354)	0.028*
IL-6 (pg/ml) (n = 109 ;22/87)	22.3(8.74-40)	21.5(5-59.4)	0.487
IL-2 receptor (pg/ml) (n = 109 ;22/87)	1964.8(618–5444)	961.2(463–5444)	0.005**
TNF-α(pg/ml) (n = 109; 22/87)	32.8(10.9–66.5)	50.6(7.52–201)	0.102
*P□0.05,**P□0.01			

Discussion

The current study investigated the plasma levels of D-dimer and their diagnostic performance in predicting PE in TPE patients. Our results indicated that most (75%) of the TPE patients had D-dimer levers higher than 0.5 mg/L. Furthermore, in TPE with PE patients D-dimer levels are significantly higher than that of patients without PE. With the cut off value of 1.18 mg/L, D-dimer showed a high sensitivity of 89.7% and specificity of 77.8% in predicting PE.

Pulmonary embolism (PE) due to endogenous or exogenous thrombosis in pulmonary arterial trunk or its branches is a potentially life-threatening disease [5]. An accurate and prompt diagnosis is essential to reduce the mortality. D-dimer is formed when cross-linked fibrin is broken down, in patients who are suspected of having PE, the plasma D-dimer levels correlate with the probability of having PE [6]. In order to increase the specificity of D-dimer testing and avoid unnecessary, costly even potentially harmful CTPA test, the 2019 ESC Guidelines endorse using clinical pretest probability (C-PTP) together with D-dimer level to rule out PE instead of a fixed cut-off level [7]. However, recently studies suggested that strategies using clinical probability and D-dimer have limited diagnostic performance when PE with complications. As Goodacre and colleagues reported, in pregnancy, the YEARS/D-dimer strategy had a sensitivity of 58.3% and a specificity of 44% while the Geneva/D-dimer strategy had a sensitivity of 75% and a specificity of 20.8% for PE [8]. According to our study, the most common symptoms of TPE are cough (74.6%), fever (51.7%), chest pain (50.8%) and dyspnea (49.6%). Chest pain, hemoptysis, dyspnea is the PE triad without specificity [9]. When PE co-occurred with TPE, the symptoms are confusing. It is difficult to distinguish PE from the TPE patients by using symptoms. Furthermore, fever, chest pain and dyspnea often accelerate the heart rate which may increase the wells score [10]. When together with the elevated D-dimer level, the clinical decision may incline to let patients do the further radiological test. Increased wells

score influenced by complications may partly explain the limited diagnostic accuracy of the C-PTP/D-dimer strategy for PE in patients with complications.

Although D-dimer levels elevated in most of the TPE patients, it is also an objective biomarker to rule-out non-PE patients. According to receiver operating curve analysis of this study, area under the curve of D-dimer was 0.893 which indicated a significant statistical correlation between D-dimer and PE among TPE patients. In this cohort, when using the threshold level of 0.5 mg/L, D-dimer showed a high sensitivity of 100%, but a very low specificity of nearly 0%. At a D-dimer level of 1.18 mg/L, the sensitivity was 89.7% while the specificity reached to 77.8% which indicates high value of D-dimer in predicting PE in TPE patients.

According to this study, the morbidity of PE in TPE patients is no less than 19.3%, which is higher than that in normal population [11]. To elucidated the underlying mechanism, we compared inflammatory biomarkers between different patients. The inflammation processes of TPE are orchestrated by cytokines and chemokines. Cytokines and chemokines also participate in all stage of embolism from the early endothelial dysfunction to the late formation of embolus [12]. Maria and colleagues reviewed recent studies and revealed that cytokines including IFNγ, IL-6, CCL2, IL-17A, IL-9, IL-1β and TGF-β exert prothrombotic effects while other cytokines such as IL-10, TNF-α and IL-8 appear to promote thrombus resolution in late phase of venous thromboembolism [13]. In addition, another study revealed that IL-8 enhances thrombus resolution through neovascularization and neutrophil recruitment [14]. The limitation of these studies is that most of the subjects are experimental models. Study on human is scarce. In currently study, IL-8 level and WBC count of PE patients were significantly lower than that of non-PE patients which indicated dysfunction of antithrombotic cytokine in PE patients. While IL-2 receptor was significantly higher in PE patients than that in non-PE patients. This result was consistence with the study of Mirjana which revealed a positive correlation between IL-2R and anti-annexin A5 antibodies, a risk factor of embolism, in primary antiphospholipid syndrome (PAPS) patients with pulmonary embolism [15]. Nonetheless, IL-6, TNF-α, ESR and CRP showed no significant differences between PE and non-PE patients in this study. Interestingly, none of the patients in this study who underwent deep vein ultrasound of the lower extremity had deep venous thromboembolism (DVT) (data not shown). Whether TPE only promotes local venous thrombosis is worth further study. Our study sheds light on the role of cytokines in PE among TPE patients. Prospective large-scale studies are needed to determine whether there are cytokines induced procoagulant and anticoagulant dysfunction in patients with TPE.

There are several limitations of our study that must be addressed. First, the small number of patients must be emphasized bearing the risk of a sample size error. Second, our used D-dimer cut-out level of 0.5 mg/L was not age-adjusted, for the case collection time span was from 2014 to 2020, most of the early cases received CTPA test when D-dimer was more than 0.5 mg/L. Third, retrospective design of the study limited the richness of the research. Information associated with clinical pretest probability was not record or we could study the C-PTP/D-dimer strategies' diagnostic performance in predicting PE among

TPE patients. A prospective, ideally designed study, with physicians randomly blinded to routinely collected D-dimers would be required to solve the above problems.

Conclusions

Most of the TPE patients has elevated plasma D-dimer level. Among TPE patients, plasma D-dimer levels of PE patients are higher than that of non-PE patients. In order to avoid unnecessary radiological test, the rule-out cut off value of D-dimer in TPE patients should be set at 1.18 mg/L. The imbalance of prothrombotic and antithrombotic cytokines may partly attribute to the formation of pulmonary embolus in TPE patients.

Abbreviations

CRP：C-reactive protein；CTPA：computed tomography pulmonary angiography；ESR：erythrocyte sedimentation rate；PE：pulmonary embolism；ROC：receiver operating curve；TB：Tuberculosis；TPE： Tuberculosis pleural effusion； WBC：white blood cell；

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. It was a retrospective study, and verbal informed consent was obtained from all the participants, the method of which was approved by the ethics committee.

Consent for publication

Not applicable.

Availability of data and materials

Please contact Xiaoming Li.

Competing interests

The authors declared no competing interests

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Authors’ contributions

XML conceived the study and participated in its design and performance, the statistical analysis, and in drafting and revising the manuscript. YJQ conceived the study and participated in its design and performance, the statistical analysis, and in drafting and revising the manuscript. WJY participated in the study design and performance, statistical analysis, and in drafting and revising the manuscript. XC conceived the study and participated in its design and performance. DZS conceived the study and participated in its design and performance. XJG conceived the study and participated in its design and coordination and in revising the manuscript. WG conceived the study and participated in its design and coordination and in revising the manuscript. All authors have read and approved the manuscript, and ensured that this is the case.

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References

1. Shaw JA, Diacon AH, Koegelenberg CFN. Tuberculous pleural effusion. Respirology. 2019; (10):962–971.
2. Antonangelo L, Faria CS, Sales RK. Tuberculous pleural effusion: diagnosis & management. Expert Rev Respir Med. 2019;(8):747–759.
3. Shen Y, Yang T, Jia L, Wang T, Chen L, Wan C, et al. A potential role for D-dimer in the diagnosis of tuberculous pleural effusion. Eur Rev Med Pharmacol Sci. 2013;17(2):201–5.
4. Kearon C, de Wit K, Parpia S, Schulman S, Afilalo M, Hirsch A, et al. PEGeD Study Investigators. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. N Engl J Med. 2019;381(22):2125–34.
5. Keller K, Beule J, Balzer JO, et al. D-Dimer and thrombus burden in acute pulmonary embolism. Am J Emerg Med. 2018;36:1613–8.
6. Kohn MA, Klok FA, van Es N. D-dimer interval likelihood ratios for pulmonary embolism. Acad Emerg Med. 2017;24:832–7.
7. Konstantinides S. 2019 ESC guidelines on pulmonary embolism: Novelties and unanswered questions. Eur J Intern Med. 2020. PMID: 32088099.
8. Goodacre S, Nelson-Piercy C, Hunt BJ, Fuller G. Accuracy of PE rule-out strategies in pregnancy: secondary analysis of the DiPEP study prospective cohort [published online ahead of print, 2020 Apr 9]. Emerg Med J. 2020. doi:10.1136.
9. de Winter MA, van Bergen EDP, Welsing PMJ, Kraaijeveld AO, Kaasjager KHAH, Nijkeuter M. The Prognostic Value of Syncope on Mortality in Patients With Pulmonary Embolism: A Systematic Review and Meta-analysis. Ann Emerg Med. 2020;S0196-0644(20)30216-X. doi:10.1016/j.annemergmed.

10. Aslam HM, Naeem HS, Prabhakar S, Awwal T, Khalid M, Kaji A. Effect of Beta-blockers on Tachycardia in Patients with Pulmonary Embolism. Cureus. 2019;11(12):e6512. doi:10.7759/cureus.6512.
11. Paul JD, Cifu AS. Management of Acute Pulmonary Embolism. JAMA. 2020;324(6):597–598. doi: 10.1001/jama.2020.3905. PMID: 32780129.
12. Ramji DP, Davies TS. Cytokines in atherosclerosis: Key players in all stages of disease and promising therapeutic targets. Cytokine Growth Factor Rev. 2015;26:673–85.
13. Najem MY, Couturaud F, Lemarié CA. Cytokine and chemokine regulation of venous thromboembolism. J Thromb Haemost. 2020;18(5):1009–19. doi:10.1111/jth.14759.
14. Henke PK, Wakefield TW, Kadell AM, Linn MJ, Varma MR, Sarkar M, et al. Interleukin-8 Administration Enhances Venous Thrombosis Resolution in a Rat Model. J Surg Res. 2001;99:84–91.
15. Bećarević M, Ignjatović S, Majkić-Singh N. Deterioration of thromboses in primary antiphospholipid syndrome: TNF-alpha and anti-annexin A5 antibodies. Clin Lab. 2012;58(9–10):1079–84.

Figures

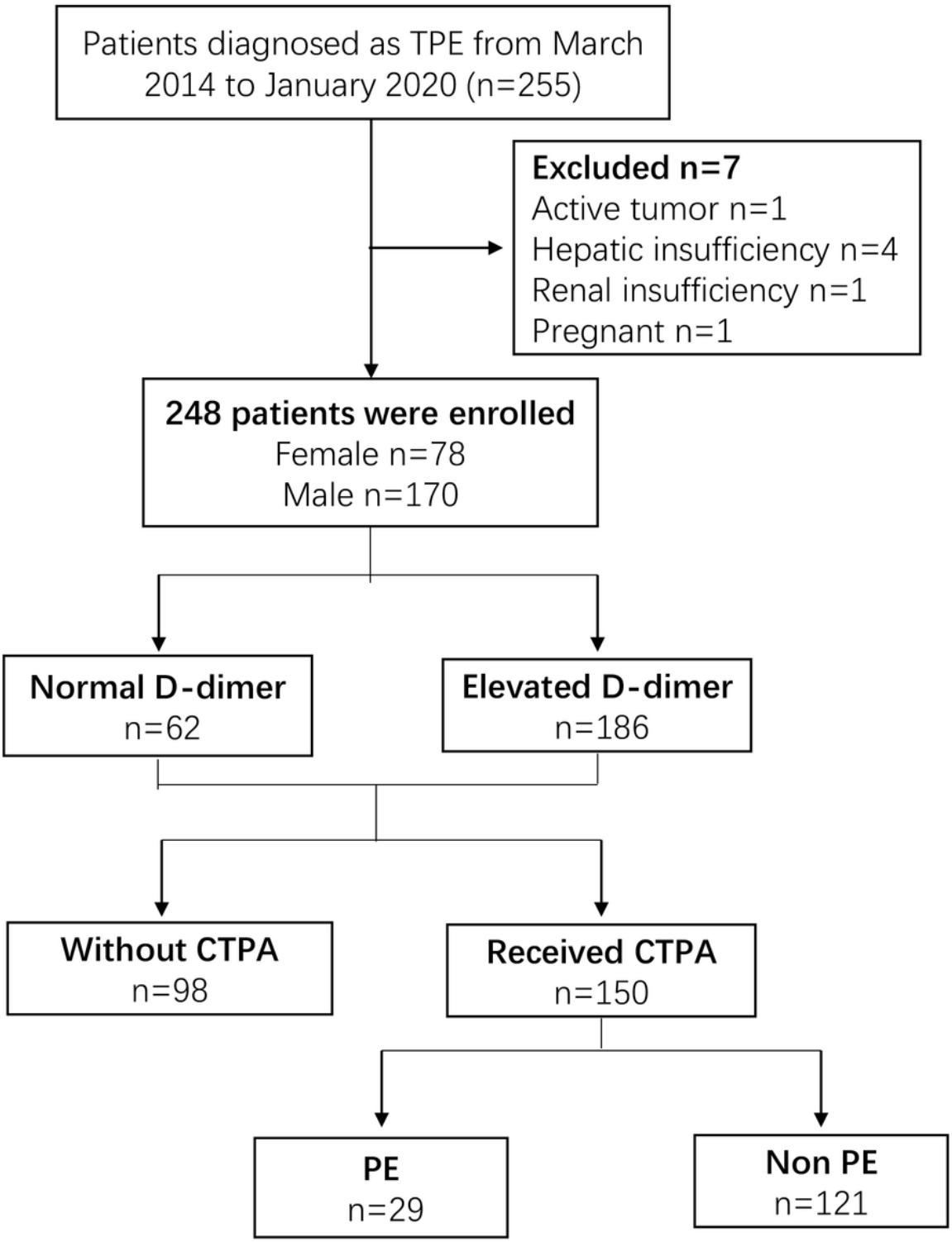

Figure 1

Flow chart of participants through the study. PE, pulmonary embolism; CTPA, computed tomography pulmonary angiogram.

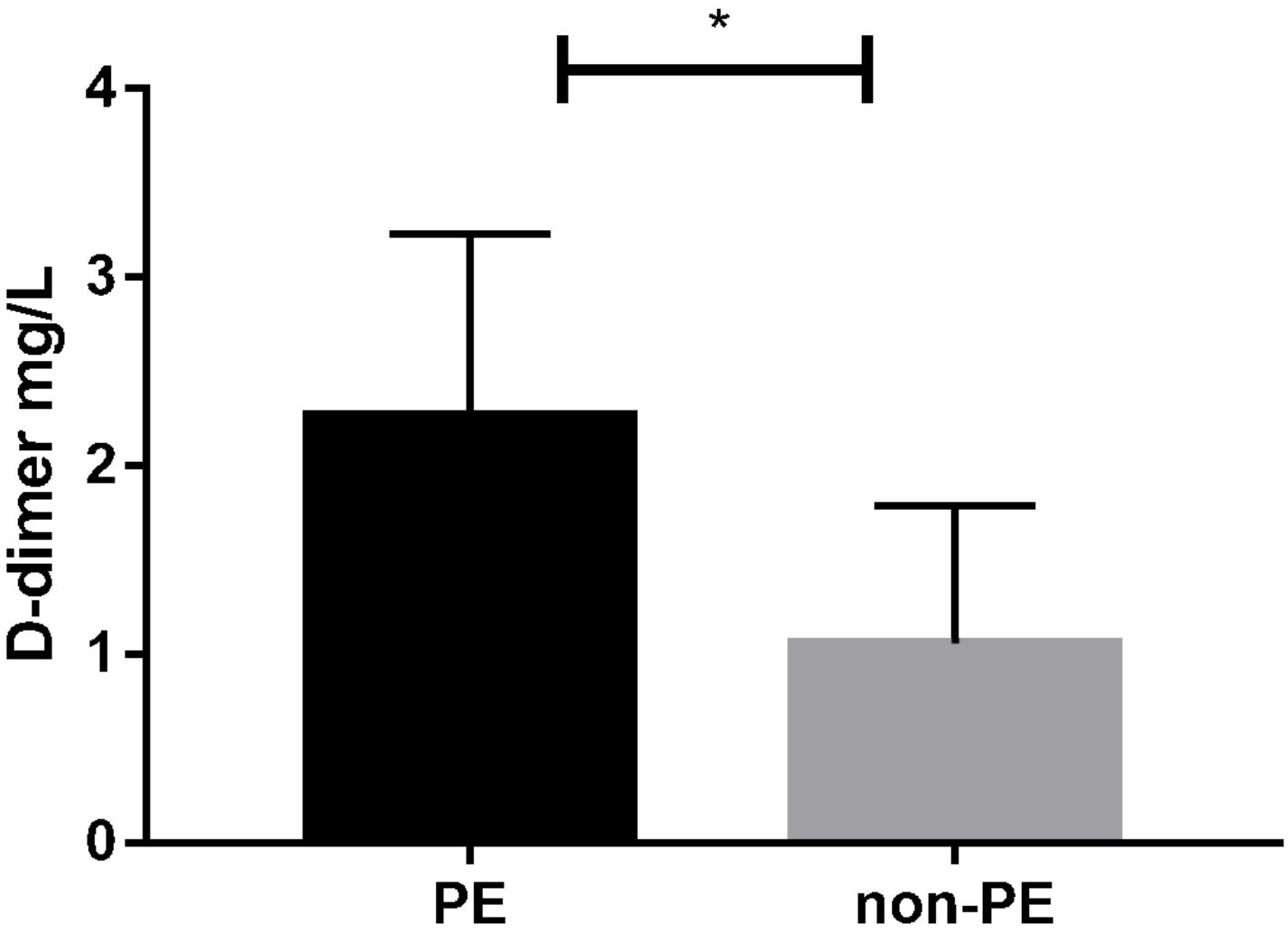

Figure 2

Plasma D-dimer levels in PE and non-PE among TPE patients. *P□0.05 .

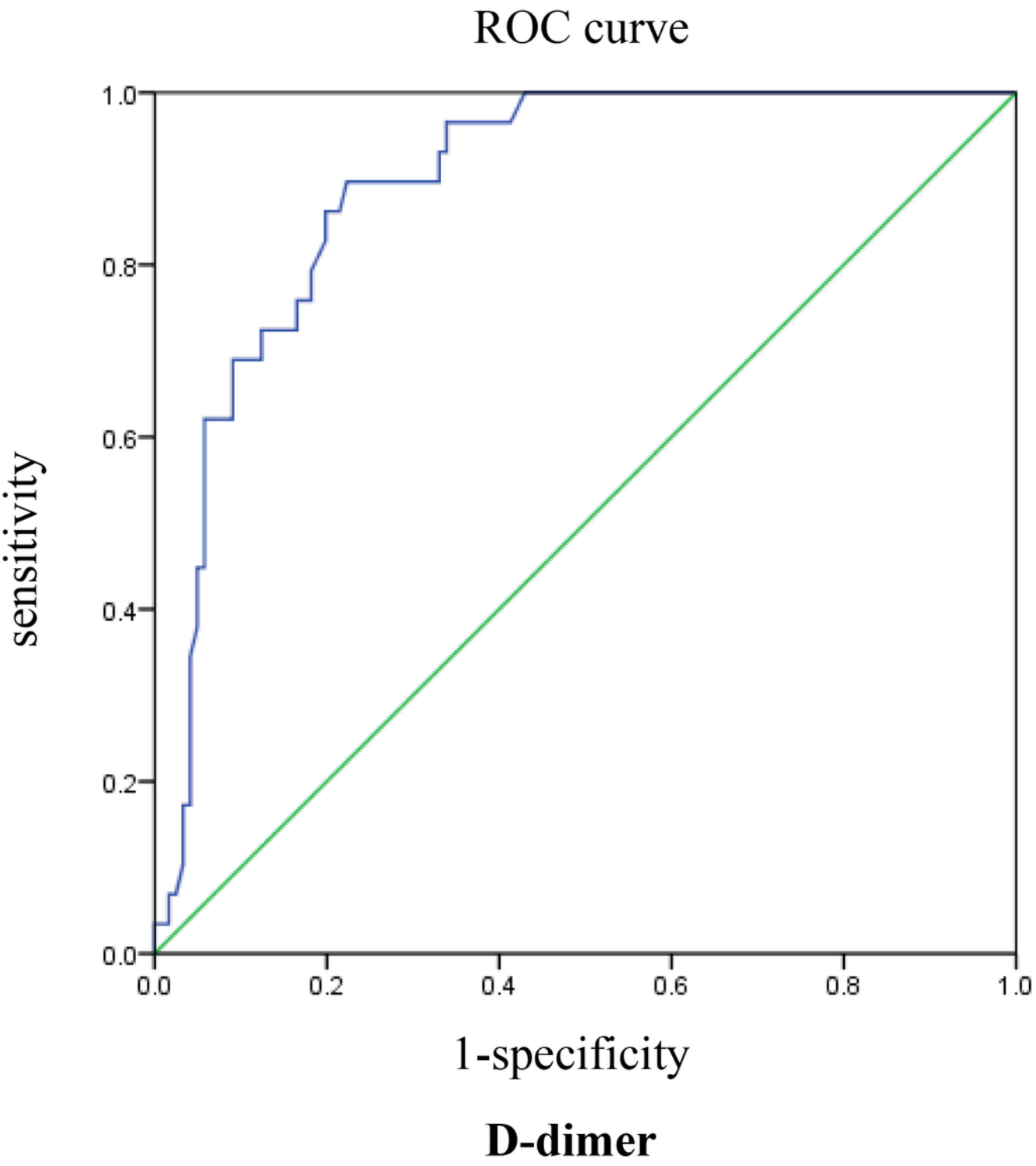

Figure 3

Receiver operating characteristic curves of D-dimer for differential diagnosis of PE (n = 29) versus Non-PE (n = 121) among TPE patients. The area under the receiver operating characteristics curve was 0.893.