ORIGINAL ARTICLE

D-dimer testing for safe exclusion and risk stratification in patients with acute pulmonary embolism in primary care

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Background: Safe exclusion and risk stratification are currently recommended for the initial management of patients with acute pulmonary embolism (APE). The aim of this study was to assess the safe exclusion and risk stratification value of D-dimer (DD) for APE when tested at the beginning of admission. **Materials and Methods:** All consecutive Chinese APE patients and controls were recruited from January 2010 to December 2012. All measurements of serum indexes were made in duplicate and blinded to the patients' status. All the 40 patients with the first episode of APE were confirmed by multi-detector computed tomographic pulmonary angiography. The plasma prothrombin time (PT), activated partial thromboplastin time, thrombin time, fibrinogen, and DD levels were measured within 24 h of admission. We used the Mann-Whitney U-test to determine the differences between groups and drew receiver operator characteristic curve to evaluate the indexes' value in the APE screening. **Results:** The PT and DD in the APE group were significantly higher than those in the disease control group ($P < 0.05$). Taking PT and DD as the useful screening tests for APE and AUC was 0.765 and 0.822, respectively. DD yielded the higher screening efficiency, with DD >1820 μg/L as cut-off value, the sensitivity, specificity, positive and negative predictive value was 82.5%, 75.2%, 56.9%, and 91.6%, respectively. **Conclusion:** The patients with APE showed significant higher DD levels compared with disease controls, suggesting a negative qualitative DD test result can safely and efficiently exclude APE in primary care.

Key words: Acute pulmonary embolism, coagulation indicators, D-dimer, risk stratification

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INTRODUCTION

Acute pulmonary embolism (APE) is a relatively common life-threatening cardiovascular emergency with a wide spectrum of clinical presentations and associated with significant morbidity and mortality.[1,2] For many doctors, especially those in the primary health-care institutions, patients with unexplained shortness of breath or pleuritic chest pain pose a diagnostic dilemma.[3] As the condition is insidious, and the clinical presentations of APE are much complicated without specificity, the disease is diagnosed only after the patients have irreversible visual impairment, finally affecting the rate of missed disease diagnosis and misdiagnosis rates.[4] So, the choice of screening and risk stratification indexes has important clinical roles in estimating the danger of APE, early diagnosis and therapy.[5-7] Considering D-dimer (DD) has been clinically used to exclude deep vein thrombosis and pulmonary embolism,[8-12] we measured the plasma prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (Fib), and DD levels within 24 h of admission in 40 consecutive patients with the first episode of APE and 101 cases of the non-APE patients, to select the appropriate risk assessment and screening indicators.

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MATERIALS AND METHODS

Acute pulmonary embolism group

All the 40 consecutive patients with the first episode of APE (median: 56 years; range: 38-84; 12 females, 28 males) who visited the Emergency Department of the

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First Affiliated Hospital, College of Medicine, Zhejiang University, from January 2010 to December 2012 and confirmed by dynamic computed tomographic angiography of the pulmonary vasculature (dynamic CTPA) were retrospectively analyzed.

Disease control group

101 cases of non-APE patients (median: 51 years; range: 35-78; 37 females, 64 males), including 32 lung cancer patients, 16 tuberculosis patients, 36 pneumonia patients, and 17 chronic obstructive pulmonary disease patients were included in the study.

The study was conducted in compliance with the World Medical Association Declaration (1975) of Helsinki and was approved by the Ethics Committee at our Institution.

The serum levels of coagulation indicators were quantified from venous blood samples, which were drawn in the hospital's Emergency Department immediately after admission and determined with the Sysmex coagulation analyzer 7000 (Sysmex CA-7000). All the measurements of PT, APTT, TT, Fib, and DD were made in duplicate and blinded to the patients' clinical or preclinical status, and performed using blood collection system (Becton Dickinson, Franklin Lakes, USA), Sysmex CA-7000 instrument (Sysmex, Kobe, Japan), and Siemens reagents (Siemens, Marburg, Germany).

Statistical analysis

All statistical analyses were performed using the SPSS version 20.0 for windows (SPSS Inc., Chicago, IL, USA). Data were presented as median (range). Comparison between two independent groups was done using the Mann-Whitney U-test. $P < 0.05$ was considered statistically significant.

RESULTS

When compared with the disease control group, the difference in the admission level of DD, PT, TT, and Fib in all the 40 APE patients was statistically significant ($P < 0.05$). Compared with the healthy control group, the difference in the admission level of DD, PT, and APTT in APE patients was statistically significant ($P < 0.05$), as shown in Table 1. The receiver operator characteristic (ROC) curve was also employed to evaluate the value of screening of DD and PT, as shown in Figure 1. ROC curve analysis showed that the area under the ROC curve (AUROC) of DD, PT, APTT, TT, and Fib was 0.822, 0.765, 0.580, 0.612, and 0.347, respectively, as shown in Table 2. We found that an 1820 μg/L cut-off level of DD provided the best discrimination between the APE cases and non-APE cases. The cut-off level, sensitivity, specificity, positive and negative predicted values for each coagulation indicator were shown in Table 2.

Table 1: Median (range) of coagulation indicators in groups and *P* value compared to APE group

Group	APE group (*n* = 40)	Disease control group (*n* = 101)	*P*
Age, years	56 (38-84)	51 (35-78)	0.294
Gender (male/female)	28/12	64/37	0.557
PT (s)	15.2 (10.1, 29.4)	11.7* (9.6, 29.5)	<0.001
APTT (s)	30.2 (20.2, 60.2)	28.6 (19.7, 70.2)	0.140
TT (s)	18.4 (14.9, 22.1)	17.8* (14.8, 23.1)	0.038
Fibrinogen (g/L)	2.8 (1.3, 7.5)	3.5* (1.2, 8.9)	0.005
D-dimer (μg/L)	3610 (620, 16,610)	750* (90, 10,450)	<0.001

*Compared with APE group, the difference was statistically significant ($P < 0.05$), APTT = Activated partial thromboplastin time; TT = Thrombin time; PT = Prothrombin time; APE = Acute pulmonary embolism

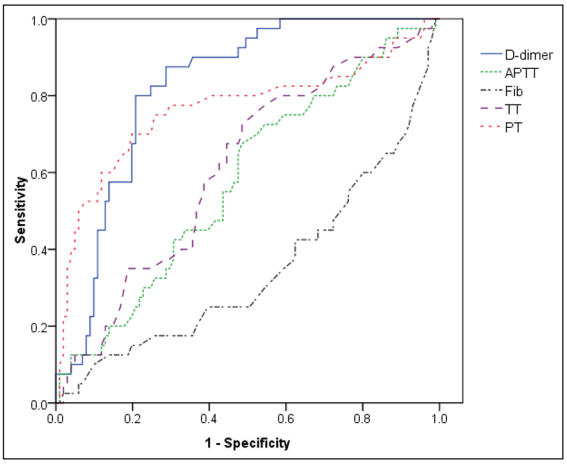

Figure 1: Receiver operating characteristic curve of indexes for prediction of acute pulmonary embolism. The area under the receiver operating characteristic curve of D-dimer, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (Fib) was 0.822, 0.765, 0.580, 0.612, and 0.347, respectively

DISCUSSION

APE is a common cardiovascular emergency which can lead to pulmonary hypertension and right ventricular failure as a consequence of pulmonary arterial bed occlusion.[13] As the clinical feature of APE may be relatively mild, it is frequently overlooked. As a result, many patients are misdiagnosed or never diagnosed, and doctors do not always get another chance.[14] For these reasons, stratification of patients with suspected APE between a high probability of having the condition compared with a low probability is particularly important.[15,16] Currently, most experts recommend using multi-detector (MD) CTPA (MD-CTPA), radionuclide pulmonary ventilation/perfusion imaging, and color Doppler ultrasonography as valuable methods for diagnosing.[17,18] MD-CTPA as the gold diagnostic criteria is the most accurate test to diagnose APE and now regarded as the imaging test of first choice.[19,20] However, since MD-CTPA is an invasive examination and needs higher technology requirement, while radionuclide pulmonary ventilation/perfusion

Table 2: The sensitivity, specificity, PPV, NPV, AUC, 95% CI, and *P*-value of AUC for each coagulation indicator

Test	Cut-off value	AUC	APE group (n = 40)		Disease control group (n = 101)		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
			True positive	False negative	True negative	False positive				
PT (s)	12.7	0.765 (0.664, 0.867) P<0.001	28	12	81	20	70.0	80.2	58.3	87.1
APTT (s)	28.5	0.580 (0.477, 0.682) P=0.140	29	11	46	55	72.5	45.5	34.5	80.7
TT (s)	17.8	0.612 (0.511, 0.713) P=0.038	30	10	49	52	75.0	48.5	36.6	83.1
Fibrinogen (g/L)	1.3	0.347 (0.242, 0.453) P=0.005	40	0	1	100	100.0	0.9	28.6	100.0
D-dimer (μg/L)	1820	0.822 (0.753, 0.891) P<0.001	33	7	76	25	82.5	75.2	56.9	91.6

PPV = Positive predictive value; NPV = Negative predictive value; AUC = Area under the curve; ROC = Receiver operating characteristic; CI = Confidence interval; APTT = Activated partial thromboplastin time; TT = Thrombin time; PT = Prothrombin time; APE = Acute pulmonary embolism

imaging and color Doppler ultrasonography were expensive diagnostic methods,[21-23] these examinations are of limited popularization in the primary health-care institutions in developing countries, such as China.

DD is a fibrin degradation product formed by the breakdown of fibrin *in vivo* by specific enzymes, and widely used as a diagnostic tool in low- and moderate-risk patients with suspected venous thromboembolism.[24] The study shows that the levels of DD and PT in APE patients were significantly tighter than those in controls. By comparing the AUROC, we found that the DD has higher identified diagnosis values compared with PT. Among the 40 APE patients, the sensitivity of DD is 82.5%, but specificity is correspondingly low (75.2%). Sensitivity and specificity are not so directly applicable for the clinical decision. In the evaluation of the diagnostic screening value of DD, we also calculated the positive predictive value (PPV) and the negative predictive value (NPV) which were most relevant for clinical decision making. The choice of cut-off level influences the PPV and NPV, and the ideal requirements (both PPV and NPV are 100%) are most often unattainable. Thus, a higher cut-off level would reduce the PPV and increase the NPV. The final choice of cut-off level rests on clinical considerations. In the present context, the clinical decision is to make a judgment on the risk of bad things - APE happening. The chosen cut-off level favors the negative decision: Patients whose serum DD level <cut-off (i.e., negative results) could be excluded from the high-risk groups. For example, when DD was "negative" (i.e., below 1820 μg/L), such test results correctly predicted "non-APE" in 91.6% of subjects with a negative test, and those patients can be classified, respectively, as being at very low risk or low risk of having APE, and there is no need to do additional investigations by imaging. A negative qualitative DD test result can safely and efficiently exclude pulmonary embolism in primary care. As a consequence, the PPV was only 56.9%, namely only 56.9% subjects with DD levels >1820 μg/L would be correctly diagnosed with APM.

CONCLUSION

In conclusion, the DD levels in patients with APE were higher than those in disease controls, suggesting the potential of using these tests for both diagnosis and screening. Especially, for the primary health-care institutions, unable to carry out expensive and complicated imaging examinations, DD testing may be a highly effective and noninvasive approach, reducing the patient's financial and mental burden.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

ZY contributed in the conception of the work, conducting the study, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. YC contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the

work. QX contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. ZS contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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