Clinical application of the Innovance D-dimer assay in the diagnosis of acute pulmonary thromboembolism

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Abstract. Patients with acute pulmonary thromboembolism (APTE) have a high short-term mortality rate. The current study aimed to investigate the use of D-dimer in the diagnosis of APTE in suspected APTE patients. All suspected APTE patients were classified into diagnosis or control groups according to the results of a computed tomography pulmonary angiogram. Mann-Whitney U and Kruskal-Wallis H tests were used to evaluate the association between D-dimer values and APTE. Area under the curve (AUC) values and the Youden Index were used to determine D-dimer cut-off levels for the prediction of APTE. The data of 112 suspected APTE patients (54.8% women; mean age, 70.5 years) were analyzed prospectively. There were no significant differences in age (74.5 vs. 73.5 years, P=0.538) or gender distribution (female ratio 56.5 vs. 53.0%, P=0.847) between the diagnosis and control groups. The incidence of symptoms including dyspnea (67.4 vs. 33.3%; P<0.01), chest distress (47.8 vs. 25.8%; P<0.05) and elevated D-dimer (8.49 vs. 0.97 mg/l; P<0.001) were significantly higher in patients with APTE compared with the control group. D-dimer values >3.32 mg/l fibrinogen equivalent units (FEU) were indicative of APTE and the Youden Index was 0.69. The maximum AUC was 0.87 (95% CI: 0.79-0.92), the sensitivity and specificity were 89.13 and 80.30%, respectively, the positive and negative likelihood ratios were 4.53 and 0.14, respectively, and the positive and negative predictive values were 75.90 and 91.40%, respectively. A D-dimer value <0.60 mg/l FEU was the optimal threshold for excluding APTE diagnosis, with a sensitivity of 100.0% and a specificity of 28.79%. The positive and negative likelihood ratios were 1.40 and 0.00, respectively, and the positive and negative predictive values were 49.50 and 100.00%, respectively. Thus, D-dimer levels, combined with clinical assessment, yield high sensitivity and specificity in diagnosing APTE.

Introduction

Pulmonary thromboembolism (PTE) is a pulmonary circulation dysfunction caused by thrombotic occlusion of the pulmonary artery (1-3). Acute PTE (APTE) is a cardiovascular emergency associated with high morbidity and mortality (4-9). Computed tomography pulmonary angiogram (CTPA) is the gold standard for APTE diagnosis, with a sensitivity of 90% and a specificity of 78-100% (10-12). However, CTPA is an expensive procedure and has some technical limitations, which restrains its clinical application in many hospitals. A plasma D-dimer test is commonly the first step in patient APTE risk assessment, and is considered to have clinical value (13-15).

D-dimer is a soluble degradation product of crosslinked fibrin under the action of the fibrinolytic system. An elevated concentration of D-dimer is often suggestive of secondary fibrinolytic hyperthyroidism (15). The high negative predictive value of plasma D-dimer makes it an important criterion for excluding PTE diagnosis. However, since elevated concentrations of D-dimer are associated with a variety of diseases, its diagnosis specificity for PTE is poor (16-18). Previous studies have suggested that high plasma D-dimer levels combined with clinical assessment (e.g. Wells' criteria) can improve the specificity of PTE diagnosis (19,20). However, no consistent standard has been established for the critical value of plasma D-dimer (21). The medical decision level (MDL) of test items is often used to determine the standard, and the receiver operating characteristic (ROC) curve is commonly used to determine the MDL (22,23).

In the current prospective study, Wells' clinical assessments were performed for suspected APTE patients who

were admitted to the Respiratory Medicine Department of the Hospital of Xinjiang Production and Construction Corps (Urumqi, China). An Innovance assay was used to determine plasma D-dimer levels, and patients were divided into a diagnosis group and a control group according to the results of CTPA and their medical history. The MDL of plasma D-dimer levels in the diagnosis of APTE was also analyzed using an ROC curve, in order to establish a critical value for D-dimer.

Materials and methods

Study protocol. The current study was a prospective analysis of 112 patients with suspected APTE, who were treated in the Respiratory Medicine Department of the Hospital of Xinjiang Production and Construction Corps between August 2012 and November 2014. The present study was approved by the Ethics Committee of Xinjiang Production and Construction Corps Hospital. Written informed consent was obtained from all patients prior to initiation of the study. The diagnosis and treatment process of this disease was in line with previous studies (14,24,25). All clinically evaluated patients with suspected APTE underwent CTPA and other laboratory tests within 24 h of admission, and before treatment was administered.

Enrolled subjects. The inclusion criteria for patients with suspected APTE were as follows: i) Clinical manifestations that included unexplained sudden onset of chest pain, dyspnea, hemoptysis, coughing, asphyxia, cyanosis, hypoxemia, palpitations, syncope or shock; ii) the presence of typical risk factors of pulmonary embolism, including deep vein thrombosis (DVT), prolonged bed rest, chronic heart and pulmonary disease, fracture history, history of surgery, cancer, childbirth or oral contraceptives. The inclusion criteria for first onset of APTE cases were as follows: i) If patients were diagnosed with APTE and had no previous history of APTE, ii) if this disease was diagnosed within 14 days of onset, and thrombolytic therapy was effective.

All of the patients with suspected APTE were divided into the diagnosis group (first onset of APTE patients) and the control group (excluded APTE diagnosis patients) according to their CTPA examination and medical history. Patients with chronic PTE and recurrent PTE were excluded, as were deceased patients who were diagnosed with APTE without CTPA examination.

Wells' criteria scores were used to evaluate the pre-test probability for APTE (Table I) (26). These scores were judged by two physicians, and if inconsistencies were present, the final judgment was made by a third physician. Patients with a score of >4 were assessed as high suspected APTE; patients with a score of ≤4 were assessed as low suspected APTE.

Laboratory parameters. Plasma D-dimer levels were evaluated using an automated latex-enhanced quantitative immunoturbidimetric assay, performed with a Sysmex CA-1500 instrument (Sysmex Corporation, Kobe, Japan). The Innovance D-Dimer kit and its quality control materials and calibrators were produced by Siemens AG (Munich, Germany). According to the manufacturer's instructions, a value of 0.5 mg/l fibrinogen equivalent units (FEU) was selected as the threshold for

excluding thromboembolic diseases. The subjects were segregated on the basis of their serum D-dimer levels into those with positive (>0.5 mg/l FEU) or negative (≤0.5 mg/l FEU) values.

Cardiac Troponin I (cTnI) levels were determined using the ADVIA Centaur CP Immunoassay System (Siemens AG), with a cut-off value of 0.04 ng/ml (positive cTnI ≥0.04 ng/ml, negative cTnI <0.04 ng/ml).

Technical examinations. CTPA was performed with a 640-MDCT scanner (Aquilion One TSX-301A; Toshiba Medical Systems Corporation, Otawara, Japan). The patients received 100 ml iopamidol (Isovue 370; Bracco S.p.A., Milan, Italy) at an intravenous flow rate of 4 ml/sec, followed by flushing with 50 ml normal saline solution. Imaging was performed 15-20 sec after contrast administration, determined with a precise contrast tracking system (SureStart; Toshiba Medical Systems Corporation). The diagnostic criteria of APTE were based on previous studies (27,28).

Color Doppler ultrasound (GE Healthcare Bio-Sciences, Pittsburgh, PA, USA) was used to detect the formation of DVT. The diagnostic criteria were based on a previous study (29). Echocardiographic detection (color Doppler ultrasound; GE Healthcare Bio-Sciences) was used to evaluate the function of the right ventricle. The criteria of right ventricular dysfunction were based on previous studies (4,6) and included right ventricular enlargement (end diastolic diameter >30 mm or right/left ventricular diastolic diameter ratio >0.6), right ventricular hypokinesia, abnormal movement of the ventricular septum and right pulmonary arterial hypertension (>30 mmHg). Patients were diagnosed with right ventricular dysfunction if more than one of these symptoms was detected.

The risk stratification criteria for APTE are shown in Table II. There were three categories for stratification: Hemodynamic instability, such as the presence of shock and hypotension (systolic blood pressure <90 mmHg or blood pressure decreased by 40 mmHg for 15 min); right ventricular dysfunction; and biochemical markers that suggested myocardial injury, such as positive cTnI.

Statistical analysis. SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) and MedCalc 15.2.2 (MedCalc Software bvba, Ostend, Belgium) software packages were used for data processing. Quantitative data were analyzed using the chi-squared test. Measurement data are presented as the mean ± standard deviation. The Mann-Whitney U test was used to compare results between two groups and the Kruskal-Wallis H test was used to compare the results of multiple groups. $P<0.05$ was considered to indicate a statistically significant difference. The plasma D-dimer data of the APTE diagnosis group and the control group were used to produce an ROC curve. The AUC was calculated and the optimal threshold in the diagnosis of APTE was determined as the MDL for D-dimer, which was the evaluated as the critical value.

Results

Patient grouping. Between August 2012 and November 2014, a total of 112 patients were included in this study. They were divided into a diagnosis group (first onset APTE patients,

Table I. Wells' criteria scores for PTE.

Category	Characteristic	Points
Risk factors	Previous history of DVT or PTE	1.5
	Immobilization for 3+ days or surgery within last 4 weeks	1.5
	Anti-tumor therapy or tumor metastases within last 6 months	1.0
Symptoms and signs	Hemoptysis	1.0
	Heart rate more >100 beats/min	1.5
	DVT symptoms or signs	3.0
Clinical judgment	High possibility of PTE diagnosis	3.0

PTE, pulmonary thromboembolism; DVT, deep vein thrombosis.

Table II. Acute pulmonary thromboembolism risk stratification.

		Risk stratification index	
Early death risk	Shock or hypotension[a]	Right ventricular dysfunction	Myocardial injury
High risk	+	+	+
Moderate risk	-	+	+
Moderate risk	-	-	+
Moderate risk	-	+	-
Low risk	-	-	-

[a]Patients are always classified as high risk if shock or hypotension are present.

n=46, 41.1%) and a control group (n=66, 58.9%). The characteristics of the two groups are shown in Table III. There were no significant differences in the age (74.5 vs. 73.5 years; P=0.538) or gender distribution (female ratio 56.5 vs. 53.0%, P=0.847) between the diagnosis and control groups.

Patient characteristics. The occurrence of dyspnea (67.4 vs. 33.3%; P<0.01) and chest distress (47.8 vs. 25.8%; P<0.05) was significantly higher in the diagnosis group than the control group. For the risk factors, the frequency of coronary heart disease (39.1 vs. 15.2%; P<0.01) and diabetes (26.1 vs. 10.6%, P<0.05) was significantly higher in the diagnosis group compared with the control group, while the occurrence of chronic lung disease was significantly lower in the diagnosis group (19.6 vs. 39.4%; P<0.05). The frequency of DVT in the diagnosis group was significantly higher than the control group (22.7 vs. 0%; P<0.001). A $S_IQ_{III}T_{III}$-type ECG result was also significantly more frequent in the diagnosis group than the control group (13.0 vs. 6.3%; P<0.05).

Wells' criteria scores. In the diagnosis group, 25 (54%) patients were classified as low suspected APTE, with Wells' criteria scores of 2.90±0.74; 21 (46%) patients were classified as high suspected APTE, with Wells' criteria scores of 4.67±0.43. The plasma D-dimer levels of both subgroups are shown in

Fig. 1. There was no significant difference in plasma D-dimer level between the low suspected APTE group and the high suspected APTE group (P=0.68).

Risk stratification. According to the risk stratification results, there were 6 high-risk patients (13%), 29 moderate-risk patients (63%) and 11 low-risk patients (24%) in the diagnosis group. The plasma D-dimer levels in those patients are shown in Fig. 2. No significant difference in D-dimer levels was found between the groups (P=0.29).

Plasma D-dimer levels. The plasma D-dimer level of all patients in the diagnosis group was >0.50 mg/l FEU. The concentration distributions ranged from 0.60 to 40.00 mg/l FEU, with a median of 8.49 mg/l FEU and a mean of 11.13±10.29 mg/l FEU. In the control group, the plasma D-dimer level of some patients was lower than 0.5 mg/l FEU, although the concentration distributions ranged from 0.10 to 25.29 mg/l FEU, with a median of 0.95 mg/l FEU and a mean of 2.80±4.55 mg/l FEU. The D-dimer level was significantly higher in the diagnosis group than the control group (P<0.001; Fig. 3).

ROC curve analysis. Analysis of the ROC curve showed an AUC of 0.87 for the prediction of APTE by D-dimer level (95% CI 0.79-0.92). Plasma D-dimer values >3.32 mg/l FEU were indicative of APTE. The Youden Index cut-off value for D-dimer predicting APTE was 0.69. Its sensitivity was 89.13%, specificity was 80.30%, positive predictive value was 75.90% and negative predictive value was 91.40%. The positive and negative likelihood ratios were 4.53 and 0.14, respectively. A plasma D-dimer value <0.60 mg/l FEU was the optimal critical value to exclude APTE diagnosis. A D-dimer value of 0.60 mg/l FEU was the optimal threshold to exclude APTE. A D-dimer value <0.60 mg/l FEU was used to exclude APTE, and the sensitivity, specificity, positive and negative predictive values were 100.00, 28.79, 49.50 and 100.00%, respectively. The positive and negative likelihood ratios were 1.40 and 0.00, respectively. The ROC curve is shown in Fig. 4.

Discussion

Elevated plasma D-dimer levels are associated with a variety of diseases, such as thrombosis, inflammation, malignant tumor, liver disease, trauma and cardiovascular disease (17,20,22).

Table III. Characteristics of the diagnosis and control groups.

Parameter	Diagnosis group (n=46)	Control group (n=66)	P-value
Gender (women), % (n)	56.5 (26)	53 (35)	0.847
Age, years (range)	74.5 (64.8-81.0)	73.5 (66.8-79.0)	0.538
Symptoms			
Dyspnea, % (n)	67.4 (31)	33.3 (22)	0.001[b]
Chest distress, % (n)	47.8 (22)	25.8 (17)	0.043[b]
Cough, % (n)	39.1 (18)	54.5 (36)	0.127
Chest pain, % (n)	19.6 (9)	9.1 (6)	0.158
Syncope or collapse, % (n)	13.0 (6)	3.0 (2)	0.062
Hemoptysis, % (n)	10.9 (5)	15.2 (10)	0.583
Pulmonary infarction triad, % (n)	4.3 (2)	0 (0)	0.167
Risk factors			
Aging, % (n)	87.0 (40)	74 (54)	0.603
Hypertension, % (n)	50.0 (23)	33.3 (22)	0.083
Coronary heart disease, % (n)	39.1 (18)	15.2 (10)	0.004[b]
Diabetes, % (n)	26.1 (12)	10.6 (7)	0.041[b]
Smoking, % (n)	23.9 (11)	33.3 (22)	0.302
Chronic lung disease, % (n)	19.6 (9)	39.4 (26)	0.038[b]
Pulmonary infection, % (n)	17.4 (8)	43.5 (20)	0.183
Prolonged bed rest, % (n)	13.0 (6)	7.6 (6)	0.354
Atrial fibrillation, % (n)	6.5 (3)	6.1 (4)	1.000
Trauma/fracture, % (n)	4.3 (2)	0 (0)	0.167
Surgery, % (n)	4.3 (2)	4.5 (3)	1.000
Malignant tumor, % (n)	4.3 (2)	7.6 (5)	0.698
Cerebral infarction, % (n)	2.2 (1)	3.0 (2)	1.000
Long-distance travel (sedentary), % (n)	2.2 (1)	0 (0)	0.411
Oral contraceptives, % (n)	2.2 (1)	0 (0)	0.411
Deep vein thrombosis, %[a]	22.7 (10/44)	0 (0/57)	0.000[b]
$S_I Q_{III} T_{III}$-type electrocardiogram, % (n)	13.0 (6)	6.3 (1)	0.019[b]

[a](Number of patients diagnosed with deep vein thrombosis/number of cases treated with lower extremity venous Doppler ultrasonography). Continuous variables are described by the median, 25 and 75th percentile if they had a skewed distribution (skewness >1). Nearly normally distributed variables are presented as the mean ± standard deviation. Discrete variables are described through relative and absolute frequencies. Discrete variables were tested with the Chi-squared test and contingency tables; continuous variables with skewed distribution were analyzed with the Mann-Whitney U test. [b]$P<0.05$ vs. control group.

Previous studies have suggested that plasma D-dimer is an important indicator to exclude DVT and PTE, as its negative predictive value is more than 99%, but its diagnosis specificity is only 40-43% (19,20,30). Patients in the current study were admitted to hospital with respiratory diseases as their main symptoms. All suspected APTE patients were evaluated by physicians, and were divided into a diagnosis group and a control group according to CTPA examination. The results demonstrated that the plasma D-dimer levels of patients in the diagnosis group were higher than those of patients in the control group. Analysis of the ROC curve suggested that plasma D-dimer values >3.32 mg/l FEU were indicative of APTE, with a Youden Index of 0.69. The sensitivity and specificity were 89.13 and 80.30%, respectively.

The signs and symptoms of APTE lack specificity. Wells' clinical assessment was performed on all patients, firstly after admission and then after APTE diagnosis by CTPA examination. The results showed that 54% of patients in the diagnosis group were considered to have low suspected APTE, and the remaining patients were assessed as high suspected APTE. There was no significant difference between the Innovance assay-measured plasma D-dimer levels in the low suspected and high suspected APTE groups. This suggested that the symptoms and signs of APTE lacked specificity, and that the Wells' score has some subjective factors. Although patients were assessed as low suspected APTE by their Wells' scores, a diagnosis of APTE should not be dismissed in order to avoid misdiagnosis. In 46 first onset APTE patients, the most common risk factors were aging, hypertension, coronary heart disease and diabetes. Therefore, particular care should be taken in diagnosing ATPE in elderly patients with hypertension, coronary heart disease or diabetes, even if a Wells' clinical assessment gives a low suspected APTE result.
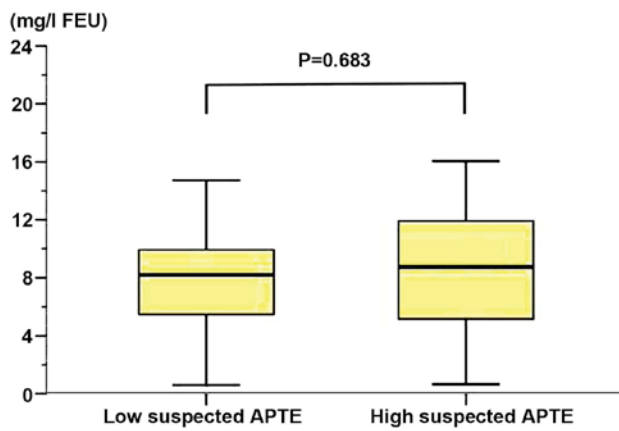
Figure 1. Plasma D-dimer levels of patients with low and high suspected ATPE. FEU, fibrinogen equivalent units; ATPE, acute pulmonary thromboembolism.
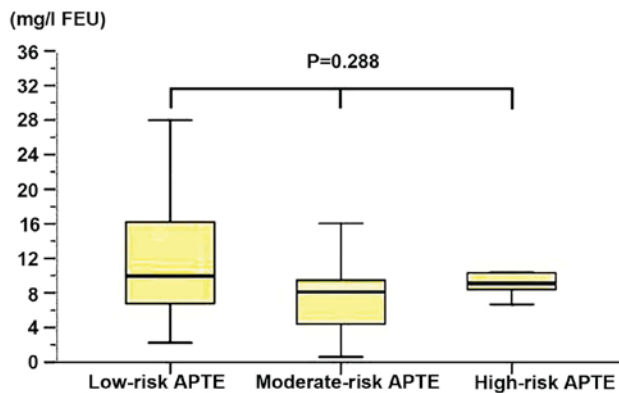

Figure 2. Plasma D-dimer levels of patients in low-, moderate- and high-risk APTE groups. FEU, fibrinogen equivalent units; ATPE, acute pulmonary thromboembolism.
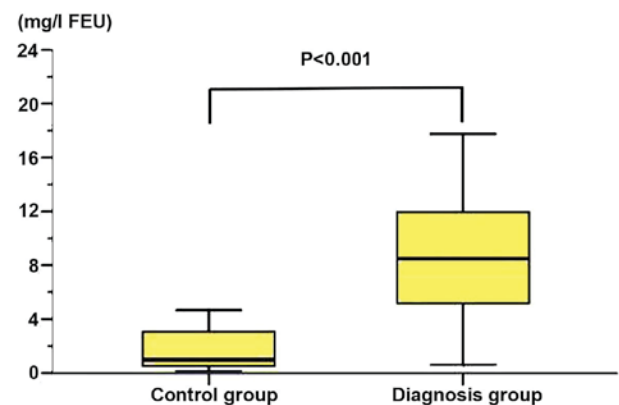

Figure 3. Plasma D-dimer levels of patients in the control and diagnosis groups. Continuous variables were analyzed with the Mann-Whitney U test on skewed distributions. FEU, fibrinogen equivalent units.
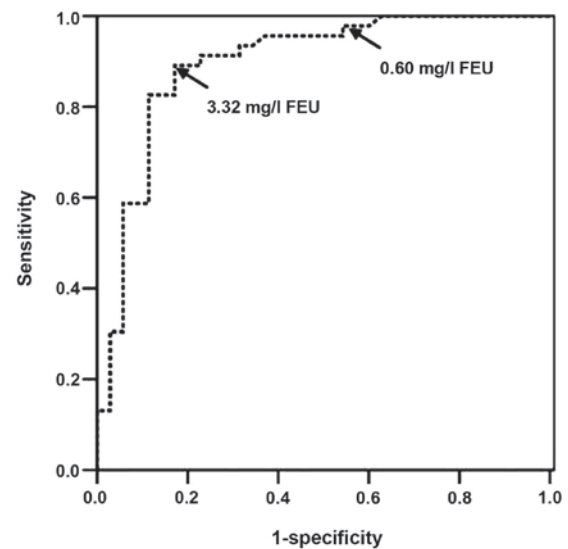

Figure 4. Receiver operating characteristic curve to test the effectiveness of D-dimer in the diagnosis of acute pulmonary thromboembolism. Area under the curve is 0.87 and Youden Index is 0.69. FEU, fibrinogen equivalent units.

Common symptoms in first onset APTE patients in the current study were dyspnea, chest distress, coughing and chest pain. However, there were only two patients displaying a typical pulmonary infarction triad (dyspnea, chest pain and hemoptysis). Dyspnea was the most common symptom, displayed by 67% of APTE patients to varying degrees. However, dyspnea is also the most common symptom of acute exacerbation of chronic obstructive pulmonary disease (COPD), which could lead to misdiagnosis.

In the current study, venous pressure Doppler ultrasonography was performed on 44 first onset APTE patients. The results showed that 10 of the patients had DVT (23%), suggesting the formation of DVT may be associated with the pathogenesis of APTE. Previous results have suggested that the coincidence of pulmonary embolism and DVT is 44% (23).

The control group in the present study consisted of patients with a suspected ATPE diagnosis following clinical evaluation, but for whom an APTE diagnosis was then excluded by CTPA examination. The Innovance-determined plasma D-dimer levels were significantly higher in the diagnosis group than the control group. This suggested that plasma D-dimer level had a high diagnostic value for APTE after clinical evaluation. An ROC curve of Innovance-determined plasma D-dimer levels in the diagnosis of APTE was established based on the plasma D-dimer levels of the diagnosis and control groups. The results showed that 3.32 mg/l FEU plasma D-dimer was the optimal critical value (or MDL) in APTE diagnosis, and its sensitivity and specificity were 89.13 and 80.30%, respectively. Thus, plasma D-dimer level can serve as a report limit in the diagnosis of APTE in respiratory medicine. A limitation of the present study was that the number of cases used was small. Further research with a lager sample size is required to confirm the results demonstrated in the present study. In conclusion, Innovance-determined plasma D-dimer level, combined with clinical assessment, has high sensitivity and specificity in the diagnosis of APTE.

Acknowledgements

References

1. Goldhaber SZ and Elliott CG: Acute pulmonary embolism: Part I: Epidemiology, pathophysiology, and diagnosis. Circulation 108: 2726-2729, 2003.
2. Goldhaber SZ, Visani L and De Rosa M: Acute pulmonary embolism: Clinical outcomes in the international cooperative pulmonary embolism registry (ICOPER). Lancet 353: 1386-1389, 1999.
3. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM and Melton LJ III: Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. Arch Intern Med 158: 585-593, 1998.
4. Chalikias GK, Tziakas DN, Stakos DA and Konstantinides SV: Management of acute pulmonary embolism: A contemporary, risk-tailored approach. Hellenic J Cardiol 51: 437-450, 2010.
5. Hsu JT, Chu CM, Chang ST, Cheng HW, Cheng NJ, Ho WC and Chung CM: Prognostic role of alveolar-arterial oxygen pressure difference in acute pulmonary embolism. Circ J 70: 1611-1616, 2006.
6. Ohigashi H, Haraguchi G, Yoshikawa S, Sasaki T, Kimura S, Inagaki H, Hachiya H, Hirao K and Isobe M: Comparison of biomarkers for predicting disease severity and long-term respiratory prognosis in patients with acute pulmonary embolism. Int Heart J 51: 416-420, 2010.
7. Schellhaass A, Walther A, Konstantinides S and Böttiger BW: The diagnosis and treatment of acute pulmonary embolism. Dtsch Arztebl Int 107: 589-595, 2010.
8. Konstantinides S and Goldhaber SZ: Pulmonary embolism: Risk assessment and management. Eur Heart J 33: 3014-3022, 2012.
9. Kucher N and Goldhaber SZ: Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. Circulation 108: 2191-2194, 2003.
10. Quiroz R, Kucher N, Zou KH, Kipfmueller F, Costello P, Goldhaber SZ and Schoepf UJ: Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: A systematic review. JAMA 293: 2012-2017, 2005.
11. Schoepf UJ: Diagnosing pulmonary embolism: Time to rewrite the textbooks. Int J Cardiovasc Imaging 21: 155-163, 2005.
12. Delgado Almandoz JE, Schaefer PW, Kelly HR, Lev MH, Gonzalez RG and Romero JM: Multidetector CT angiography in the evaluation of acute blunt head and neck trauma: A proposed acute craniocervical trauma scoring system. Radiology 254: 236-244, 2010.
13. Wilson DB and Gard KM: Evaluation of an automated, latex-enhanced turbidimetric D-dimer test (advanced D-dimer) and usefulness in the exclusion of acute thromboembolic disease. Am J Clin Pathol 120: 930-937, 2003.
14. van Belle A, Büller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, Kramer MH, Kruip MJ, Kwakkel-van Erp JM, Leebeek FW, *et al*: Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 295: 172-179, 2006.
15. Wells P: Overview and comparison of D-dimer assay kits for DVT and PE. Clin Adv Hematol Oncol 2: 160,178, 2004.
16. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, Forgie M, Kovacs G, Ward J and Kovacs MJ: Excluding pulmonary embolism at the bedside without diagnostic imaging: Management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 135: 98-107, 2001.
17. Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, Biel RK, Bharadia V and Kalra NK: D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: A systematic review. Ann Intern Med 140: 589-602, 2004.
18. Carrier M, Righini M, Djurabi RK, Huisman MV, Perrier A, Wells PS, Rodger M, Wuillemin WA and Le Gal G: VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. Thromb Haemost 101: 886-892, 2009.
19. Jain S, Khera R, Suneja M, Gehlbach B and Kuperman E: Role of D-dimer assays in the diagnostic evaluation of pulmonary embolism. Am J Med Sci 350: 501-507, 2015.
20. Becattini C, Lignani A, Masotti L, Forte MB and Agnelli G: D-dimer for risk stratification in patients with acute pulmonary embolism. J Thromb Thrombolysis 33: 48-57, 2012.
21. Gupta RT, Kakarla RK, Kirshenbaum KJ and Tapson VF: D-dimers and efficacy of clinical risk estimation algorithms: Sensitivity in evaluation of acute pulmonary embolism. AJR Am J Roentgenol 193: 425-430, 2009.
22. Ghanima W, Abdelnoor M, Holmen LO, Nielssen BE, Ross S and Sandset PM: D-dimer level is associated with the extent of pulmonary embolism. Thromb Res 120: 281-288, 2007.
23. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, *et al*: Guidelines on the diagnosis and management of acute pulmonary embolism: The task force for the diagnosis and management of acute pulmonary embolism of the European society of cardiology (ESC). Eur Heart J 29: 2276-2315, 2008.
24. Tapson VF: Acute pulmonary embolism. N Engl J Med 358: 1037-1052, 2008.
25. Mos IC, Klok FA, Kroft LJ, DE Roos A, Dekkers OM and Huisman MV: Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: Systematic review and meta-analysis. J Thromb Haemost 7: 1491-1498, 2009.
26. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, Turpie AG, Bormanis J, Weitz J, Chamberlain M, *et al*: Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: Increasing the models utility with the SimpliRED D-dimer. Thromb Haemost 83: 416-420, 2000.
27. Weiss CR, Scatarige JC, Diette GB, Haponik EF, Merriman B and Fishman EK: CT pulmonary angiography is the first-line imaging test for acute pulmonary embolism: A survey of US clinicians. Acad Radiol 13: 434-446, 2006.
28. Winer-Muram HT, Rydberg J, Johnson MS, Tarver RD, Williams MD, Shah H, Namyslowski J, Conces D, Jennings SG, Ying J, *et al*: Suspected acute pulmonary embolism: Evaluation with multi-detector row CT versus digital subtraction pulmonary arteriography. Radiology 233: 806-815, 2004.
29. Kearon C, Ginsberg JS and Hirsh J: The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 129: 1044-1049, 1998.
30. Keller K, Beule J, Schulz A, Coldewey M, Dippold W and Balzer JO: D-dimer for risk stratification in haemodynamically stable patients with acute pulmonary embolism. Adv Med Sci 60: 204-210, 2015.