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Review Article

CLINCAL PROBABILITY ASSESSMENT AND D-DIMER TEST ARE THE FIRST STEP IN THE DIAGNOSIS OF PULMONARY EMBOLISM

*Ercia Maria da Conceicao Sequeira and Prof. Wang Zhong Ping

Second Department of Respiratory Medicine, Yan'an Hospital Affiliated to Kunming Medical University Yunnan, 10678, P.R. China

ABSTRACT

Pulmonary embolism (PE) is the most common preventable cause of death among hospitalized patients, estimated to be responsible for approximately 100,000 to 200,000 deaths in the United States each year. The clinical presentations vary from asymptomatic patient to the severity of the condition. The diagnosis is the pillars and even with a well-trained professional doctor such as internist or emergency specialist, sometimes they are confused to make the appropriate diagnosis of PE because the symptoms and signs are similar to the other diseases. This is most common when the patient comes in with chronic disease on exacerbation. There are several methods used to make the diagnosis such as the clinical probability assessment, noninvasive laboratory test and invasive test. Various studies consider clinical probability assessment and D-dimer test are becoming the standard of care at many institutions for the evaluation of patients with suspected PE, which help guide clinicians in their work-up of PE. Prompt recognition and treatment are essential for minimizing the mortality and morbidity associated with PE. This article will review the clinical probability assessment and D-dimer test as a primary test in an investigation for pulmonary embolism.

Keywords: Pulmonary embolism, Diagnosis, Clinical probability, D-dimer.

INTRODUCTION

Pulmonary embolism causes a number of complications that affect respiratory and cardiovascular system, which is determined primarily by its hemodynamic impact. In part of respiratory system led to impaired gas exchange and pulmonary functions, the cardiac and hemodynamic effects of an embolism are related to three factors: the degree of reduction of the cross sectional area of the pulmonary vascular bed, preexisting status of the cardiopulmonary system, and physiologic consequences of both hypoxic mediated and neurohumorally mediated vasoconstriction[1]. PE is under diagnosed in the wards, especially when the patients is present with symptoms and signs that are similar to their own basic disease for the first time at emergency, therefore the diseases remain a major health problem.[2] Venous thromboembolisms including pulmonary embolism and deep vein thrombosis are diseases that manifests in similar clinical presentations which is ranked as the third most common cardiovascular disease in developed countries.[3, 4] Diagnostic strategy should be based on clinical evaluation of the probability of PE and D-dimer test, if these assessments show in high probability then additional testing is necessary to make the accuracy diagnosis of PE.[2]

Clinical Probability Assessment:

Clinical probability assessment has become an important step in the investigation of patients with clinically suspect of PE. Standardized prediction rules involve baselines clinical symptoms and signs, risk factor for VTE, personal history and laboratory test. These tests permit the classification of patient's conditions into different categories of clinical pre-test probability of PE. According to the systematic review and meta-analysis study, Ceriani E, *et, al*., identified 9 clinical prediction rules where 29 studies representing 31215 patients from Embase, Medline and the Cochrane database who were suspected with PE. This study was grouped in three levels bases on Wells or revise Geneva or version (original or simplified) scores. The proportion of patients confirmed with PE was expected to be approximately 10% in the low probability category, 30% in the intermediate probability category, and 65% in the high-clinical probability category. If Patients were in two levels scores base on Wells scores and Charlotte rules, then the proportion of PE is approximately 12% and 50%. The types of patients were either outpatients or inpatient and showed the accuracy of assessing PE are similar in schemes three versus two levels based on the assessment clinical probability.[5, 6] The clinical probability of PE was evaluated in 41 patients suspected pulmonary embolism using seven scoring system such us Geneva score, revised Geneva score, simplified Geneva score, Wells score, simplified Wells score, simplified Charlotte rule and Pisa model (Table). The final diagnosis was based on multislice CT pulmonary angiography (CTPA).The result showed that from the suspected 41 patients, 24 patients (58.5%) had pulmonary embolism with CTPA positive. The Pisa model ($P \leq 0.001$) has a high score in correlation with the result of CTPA, followed by the original Geneva score and the Wells score ($P \leq 0.001$). The highest score of sensitivity was shown by simplified Wells score (0.92), while the Pisa model had the highest specificity (0.82) and the highest overall accuracy (0.76). The strength of this study is evident based on the Pisa model having the best correlation with the CTPA result, one downfall was that without CTPA the Pisa model will not be in the highest score compared with other models.[7] The evaluation and demonstrations of accuracy of pretest probability assessment for PE

using clinical gestalt vs clinical prediction rules, which from data synthesis demonstrate that the clinical gestalt strategy according to the classification pretest categories were used in 7 studies: low (8%-19%), moderate (26-47%) and high (46-91%), respectively. While the clinical prediction rule classified in low (3%-28%), moderate (16-46%), high (38-98%) bases on 10 studies. A clinical prediction rule is when the accuracy of detecting PE and can be used even by a personal health care worker who has less clinical experience .[8] On the contrary, clinician gestalt estimate of pretest probability for pulmonary embolism was accurate for pulmonary embolism but not for acute coronary syndrome based on receiver operating curve analysis.[9] The implicit evaluation of pre-test probability was demonstrated to be relatively accurate in the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study.[10, 11] However, physician experience is the main tool to rule out the empirical clinical probability correctly. Clinical prediction rules are available for the diagnosis of PE.

Different probability scores for pulmonary embolism are calculated for each patient:

The original Geneva score (Wicki criteria)[12] :

Variable	Score
Age	
60-79 years	1
80+ years	2
Previous venous thromboembolism	
Previous DVT or PE	2
Previous surgery	
Recent surgery within 4 weeks	3
Heart rate	
Heart rate >100 beats per minute	1
PaCO2 (partial pressure of CO2 in arterial blood)	
<35 mm Hg	2
35-39 mm Hg	1
PaO2 (Partial pressure of O2 in arterial blood)	
<49 mm Hg	4
49-59 mm Hg	3
60-71 mm Hg	2
72-82 mm Hg	1
Chest X-ray findings	
Band atelectasis	1
Elevation of hemidiaphragm	1
<5 Points indicates a low probability of PE.	
5-8 Points indicates a moderate probability of PE.	

>8 Points indicates a high probability of PE.

Table 1: The original Geneva score.

The revised Geneva score [13]:

Variable	Score
Age 65 years or over	1
Previous DVT or PE	3
Surgery or fracture within 1 month	2
Active malignant condition	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate 75-94 beats per minute	3
Heart rate 95 or more beats per minute	5
Pain on deep palpation of lower limb and unilateral edema	4

0-3 Points indicates low probability. 4-10 Points indicates intermediate probability. 11 Points or more indicates high probability.

Table 2: The revised Geneva score

The simplified Geneva score[14] :

Variable	Score
Age >65	1
Previous DVT or PE	1
Surgery or fracture within 1month	1
Active malignancy	1
Unilateral lower limb pain	1
Hemoptysis	1
Pain on deep vein palpation of lower limb and unilateral edema	1
Heart rate 75-94 bpm	1
Heart rate greater than 94 bpm	+1

Patients with a score of 2 or less are considered unlikely to hava a current PE. Heart rates of 75-94 bpm receive 1 point, while heart rates higher than 94 bpm receive a further point (i,e., 2 points in total).

Table 3: The simplified Geneva score.

Well score[15] :

Clinical signs and symptoms of PE probability	points
Evidence of DVT (leg swelling and pain with palpation)	3.0
Heart rate higher than 100 beats per minute	1.5
Previous objectively diagnosed DVT or PE	1.5
Immobilization for three or more consecutive days or surgery in previous four weeks	1.5
Hemoptysis	1.0
Malignancy	1.0
Pulmonary embolism as a highly likely diagnosis	3.0

DVT, deep venous thrombosis.

Probability of pulmonary embolism : <2 point = low; 2-6 points = moderate and >6 = high

Table 4: Well score.

Simplified Wells score[14]:

As the simplified Geneva score, the simplified Wells scoring system replaced the weighted scores for each parameter with a 1 point score for each parameter present. PE is considered unlikely if the score is ≤ 1 and is likely if the score is >1 (Table 1, Table 2, Table 3, Table 4).

Simplified Charlotte rule[16]:

If any two boxes are checked the patient is considered high risk.

- Age > 50.
- HR > systolic blood pressure (SBP).
- Surgery in the past month.
- Unilateral leg swelling.
- Hemoptysis.
- Unexplained room air pulse oximetry <95%.

Pisa model[17]:

Positive variable included age (57-67 years, 68-74 years, >75 years), male gender, immobilization, history of DVT, sudden onset of dyspnea, chest pain, fainting or syncope, hemoptysis, unilateral leg swelling and ECG with acute cor pulmonale. Negative variable are history of cardiovascular disease, history of pulmonary disease, orthopnea, fever > 38°C (100.4°F), wheezes, and crackles. Two calculator based on the Pisa model are available online. One calculator model uses chest X-ray findings (Pisa model 1).[18, 19] The other model does not need chest X-ray findings (pisa model 2) (this model was used)[20, 21] The score is calculated as a percentage and the probability of PE is classified as follows:

Slight risk if score ≤10, moderate risk if score = 11-50, substantial risk if score $= 51 - 80$ and high risk if score ≥80.

D-dimer test:

D-dimer is a fibrin degradation product (FDP), a small protein fragment presents in the blood after a blood clot is degraded by fibrinolysis and represent an excellent noninvasive triage test in patients with suspected PE. The D-dimer essay rise in the presence of thrombosis or disseminated intravascular coagulation.[22] With its high negative predictive value, the D-dimers represent an excellent noninvasive triage test in patients with suspected PE. A large variety of D-dimer assays have been evaluated and it appears that their diagnostic performances varied substantially from one assay to another.[23] Arnaud Perrier *et. al*, after > 10 years of intensive research, plasma D-dimer measurement is increasingly accepted as a first line test in patients with suspected pulmonary embolisms.[24] D-dimer test was the fastest adoption test that was used in suspected patients with deep venous thrombosis, due to clinicians being less fearful of a false negative result in that context when a potentially fatal disease such as pulmonary embolism is suspected.[25-28] The D-dimer tests can be divided into two main groups: rapid enzyme-linked immunosorbent assays (ELISAs) and modern latex agglutination tests which have important differences in performance characteristics. The study showed that the Rapid enzyme-linked immunosorbent assays (ELISAs) have very high sensitivity but low specificity, while modern latex agglutination tests tend to be somewhat less sensitive but more specific. A recent study demonstrated that latex agglutination tests have lower specificities as an ELISA assays so their performance characteristics tend to be similar.[27] In total, 2017 D-dimer test evaluations for DVT and 111 for PE were analyzed. Several studies designed comparisons between sensitivities and specificities characteristics which were associated with systematic differences in diagnostic accuracy. The sensitivities of the D-dimer enzyme-linked immunofluorescence assay (ELFA) (DVT 96%; PE 97%), Microplate enzyme-linked immunosorbent assay (ELISA) (DVT 94%; PE 95%), and latex quantitative assay (DVT 93%; PE 95%) were superior to those of the whole-blood D-dimer assay (DVT 83%; PE 87%), latex semi quantitative assay (DVT 85%; PE 88%) and latex qualitative assay (DVT 69%; PE 75%). The latex qualitative and whole-blood D-dimer assays had the highest specificities (DVT 99%, 71%; PE 99%, 69%).[29]Prospective study compared blood samples used for D-dimer test by five different latex agglutination assays with pulmonary angiography as diagnostic endpoint of pulmonary embolism. Angiographic evidence of PE was found in 34% (35/103) of patients. The latex agglutination assays had sensitivities of 97 to 100% and specificities of 19 to 29%. The negative predictive value was 94 to 100%. While, the five D-dimer assay were negative in up to 55% of patients with normal pulmonary angiography. The negative predictive value in these patients was 100% by all five agglutination assays tested. In patients with recent surgery, malignancy, or abnormalities in total bilirubin test, the D-dimer test tend to be positive. The latex agglutination assays for D-dimer considers as a clinical useful test in the diagnostic of an acute pulmonary embolism in the absence of recent surgery, malignancy or liver disease and when the pulmonary angiography is used as the diagnostic endpoint.[30] In the retrospective validation analysis of three large cohorts, the age-adjusted D-dimer cutoff would have increased by about 20% the number of patients in whom the D-dimer test was considered negative without increasing the false-negative rate when compared with the usual 500µg/l cutoff. The results were particularly appealing in patients older than 80

years,the age adjusted cutoff allowed an increase in the proportion of patients with a negative D-dimer result from 9% to 21% without any false negative test.[30] However, in older patients D-dimer test increases, which makes it less useful to rule out pulmonary embolism in this advanced age.[31-36] A D-dimer concentration below the conventional cut-off point of 500µg/l combined with a "low/intermediate" or "unlikely" clinical probability can safely rule out the diagnosis in about 30% of patients with suspected pulmonary embolisms.[37-39] The need for a better noninvasive diagnostic approach have resulted in reevaluation of the D-dimer (D-D) assay in patients with suspected acute pulmonary embolisms.[40]

CONCLUSION

Pulmonary embolism is a potential fatal disease, difficult to diagnose particularly in elderly patients. The clinical evaluation is the key step in rising the awareness of the disease and setting up appropriate diagnostic strategies. The basic step in the approach of diagnostic strategy for PE depends on the pretest clinical probability and performing a D-dimer test. The clinical probability assessment and D-dimer test are safe, efficient and included in noninvasive methods. PE can be excluded in patients with a low or intermediate or unlikely clinical probability and a normal D-dimer test. Additional imaging test is required for those who present a high or likely clinical probability and positive D-dimer test.

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