Reliability of D-Dimer test results in deciding the necessity of performing CTA in high risk population to establish the diagnosis of PE

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Abstract
Purpose: To evaluate the reliability of D-Dimer test results in the diagnosis of PE in high risk patients.

Patients and methods: This prospective study was conducted on 98 patients. Mean age was 50 years; age range was 17–88 years. All patients underwent D-Dimer assay. Multidetector CT Angiography (MDCTA) was performed on 128 row multi-slice scanner. Statistical analysis of D-Dimer test values was attempted to assess its diagnostic reliability. Patients were further stratified into two groups: patients with positive D-Dimer test and patients with negative D-Dimer test, and cut-off value patients with negative D-Dimer test and cutoff value was estimated for D-Dimer test results.

Results: Statistical analysis of D-Dimer test values yielded sensitivity 100%, specificity 28% with 100% negative predictive value (NPP) and low positive predictive value (26%). Likelihood ratios were NLR <0.1 and PLR <1. Cutoff value for D-Dimer test results in correlation with CT Angiography results, was 1.45 μg/ml, with diagnostic sensitivity 87% and diagnostic specificity 57%. PLR was 0.43 and NLR was 0.13.

Conclusion: Negative D-Dimer test is a reliable diagnostic modality to rule out the need for CT Angiography in patients at high risk population of PE. However, positive test results cannot confirm the diagnosis and further testing is warranted.

1. Introduction

Pulmonary Embolism (PE) is a well known disease, considered as one of two clinical presentations of the same pathology: venous thromboembolism (VTE), and deep vein thrombosis (DVT) (1). DVT affecting the legs accounts for about 90%
of pulmonary embolism (2). Acute pulmonary embolism is the third cardiovascular emergency condition that follows myocardial infarction and stroke (3). The importance of PE is attributed to being a preventable cause of death in hospitalized patients (4). Moreover, it is rapidly fatal in 10% of cases. Death occurs in about 5% of cases after the onset of treatment and about one-third of the patients develop complications as pulmonary hypertension (5).

Patients susceptible for PE include those with previous VTE, oncology, recent surgery, prolonged bed rest, estrogen therapy and old aged patients. Yet, 25% of PE are idiopathic cases (4,6). The clinical probability of PE can be achieved by combination of multiple variables. These variables include clinical signs and symptoms, and laboratory tests together with clinical scores (7): Wells score (8), Revised Geneva e (9) and Miniati scores or Pisa score (10); of which the most widely used is Wells score (11).

The most significant symptoms for diagnosis of acute PE are as follows: sudden onset of dyspnea, chest pain and fainting especially when associated with specific ECG and chest X-ray findings (12). Other signs and symptoms include haemoptysis, DVT, tachycardia and tachypnea with low oxygen saturation (2). However, clinical diagnosis of PE remains a clinical suspicion that requires further investigation (12). Consequently, patients with high clinical probability based on clinical pre-test, need confirmatory test while those with low probability need exclusionary test (13,14).

The diagnosis of PE with ventilation/perfusion scintigraphy is based on functional parameter changes, when perfusion defect is detected in normally ventilated areas which is termed ventilation/perfusion mismatch. Pulmonary CTA diagnosis of PE is established through the direct detection of thrombus within the affected vessel (3). Thus, ventilation–perfusion scan is non-diagnostic in up to 70% of cases (15).

Catheter pulmonary angiography was considered the reference standard for diagnosis of PE; however, its use is limited because it is an invasive diagnostic procedure (16). MDCT Angiography is now the non-invasive diagnostic modality of choice in patients not having history of renal failure or allergy in contrast agents (17). However, because of the cost of CT examination, exposure to radiation and contrast media, it should be limited to cases only in need, in order to reduce number of negative pulmonary angiograms (18).

Immunoturbidimetric assays are a new generation of rapid, automated, quantitative D-Dimer tests based on agglutination of microlatex particles which are coated with monoclonal antibodies that are specific for D-Dimer (19). It is the primary diagnostic test in cases of low to moderate clinical suspicion (2). Plasma D-Dimer concentrations above 0.5 µg/ml have 95% sensitivity and 55% specificity for VTE (16).

Therefore, the aim of this study was to evaluate the reliability of D-Dimer test results in the diagnosis of PE in high risk patients without the need of further investigation by CT Angiography.

2. Patients and methods

2.1. Patients

This prospective research was conducted in the period between January 2014 and March 2015 for cases referred from Oncology, Cardiology and Surgery Departments. The study was carried out on 98 patients referred with clinical probability of Pulmonary Embolism (PE), from which informed consent was waived. They were classified into 3 groups of high risk patients (Table 1): 39 patients (39.8%) with history of malign tumor, 36 patients (36.7%) had recent surgery, and 23 patients (23.5%) were being treated for cardiac disease. Mean age was 50 years; age range was 17–88 years. 55 were males (56%) and 43 were females (43.9%).

2.2. Inclusion criteria

Referral based on clinical examination with symptoms and signs suggestive of pulmonary embolism and/or history of DVT or PE. 98 patients underwent D-Dimer assay preceding or following CTA within the range of 24 h, and positive D-Dimer threshold was greater than 0.5 µg/ml.

2.3. Exclusion criteria

High risk cases who performed CT Angiography but did not perform D-Dimer test for whom the referring clinician assumed false positive D-Dimer because of repeated catheterization and hemodynamic instability. Also, patients with history of contrast medium allergy, renal failure or intravenous line inaccessibility for whom CT Angiography was contraindicated.

2.4. Methods

Multidetector Pulmonary CT Angiography (MDCTA) was performed on a Multidetector CT scanner (128 row multi-slice volume scanner, Philips Healthcare, Best, Netherlands) with 0.8-s helical rotation speed, 1.25-mm collimation, and a pitch of 3:1. Patients were injected with 100 mL of iopamidol diluted with saline chaser dose to 120 mL total volume at a rate of 3 mL/s using automated bolus-triggering technique. Imaging began 20 s after initiation of contrast infusion.

2.5. D-Dimer assay

D-Dimer assay was done by using STA Liatest kit (Diagnostica Stago, Asnieres, France). Blood for D-Dimer assay was collected in 0.109 mol/L (3.2%) trisodium citrate anticoagulant according to the standards of National Committee for Clinical Laboratory guidelines. Samples were centrifuged for 15 min at 2500 g. Processing and analysis of samples were done within 1–2 h of collection by using STA-R coagulation analyzer (Diagnostica Stago). This

<table>
<thead>
<tr>
<th>Patient category</th>
<th>No.</th>
<th>%</th>
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<tbody>
<tr>
<td>Oncology</td>
<td>57</td>
<td>37.5%</td>
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<tr>
<td>Surgery</td>
<td>56</td>
<td>36.8%</td>
</tr>
<tr>
<td>Cardiology</td>
<td>39</td>
<td>25.7%</td>
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<tr>
<td>Total</td>
<td>152</td>
<td>100</td>
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</table>

No. = number, % (percent).
Reliability of D-Dimer test results

Analyzer utilizes an immunoturbidimetric analysis for quantitative assessment of D-Dimer in plasma. The results were expressed as micrograms for each milliliter D-Dimer unit (DDU). D-Dimer value less than 0.5 μg/ml DDU was interpreted as normal value, and D-Dimer value greater than or equal to 0.5 μg/ml DDU was interpreted as positive D-Dimer test.

3. Statistical analysis

Statistical analysis was performed by using the program Statistical Package for the Social Sciences (SPSS) Version 20.0 for Windows. Statistical analysis of D-Dimer test values was attempted to assess its diagnostic reliability. Specificity, sensitivity, positive and negative predictive values and likelihood ratios were estimated. Patients were further stratified into two groups: patients with positive D-Dimer test and patients with negative D-Dimer test. Continuous variables were compared using the Student’s t-test and cutoff value was estimated for D-Dimer test results.

4. Results

A total of 98 patients included in our study were evaluated for pulmonary embolism using CT Angiography as the gold standard test; 20 of which (20.4%) were diagnosed as positive PE and 78 (79.6%) were negative. D-Dimer assay results were 76 (77.55%) diagnosed as positive and 22 (22.44%) were negative for PE (Table 2).

Statistical analysis of D-Dimer test values yielded sensitivity 100%, specificity 28% with 100% negative predictive value (NPP) and low positive predictive value (26%). Likelihood ratios demonstrate that D-Dimer test is reliable to rule out PE (NLL <0.1); however, the likelihood of positive CT Angiography when D-Dimer assay is positive is very low (PLR <1) (Table 3).

Cutoff value for D-Dimer test results in correlation with CT Angiography results, was 1.45 μg/ml., with diagnostic sensitivity 87% and higher diagnostic specificity 57%. Yet, at this value positive likelihood ratio was 0.43 which still means that positive D-Dimer test has a poor likelihood of positive CT Angiography. Meanwhile negative likelihood ratio was 0.13, confirming the strong negative predictive value of D-Dimer test (Table 4).

5. Discussion

CTA is now recognized as the diagnostic modality of choice to establish the diagnosis of PE (20). CT outstands any other imaging modality by its capability of detecting abnormality in both mediastinum and pulmonary parenchyma (21,22). This is because a variety of serious conditions have been detected in patients clinically at-risk of PE, for example, pneumothorax and aortic dissection (23,24).

With the advent of MDCT, strategies have been adopted to achieve optimal vascular enhancement; for example the use of a bolus test dose or automated bolus triggering technique (25), which we implemented in our study. Single breath-hold scanning significantly decreases respiratory motion artifacts in dyspneic patients (26). Similarly, reduced temporal resolution and ECG gating eliminated or significantly decreased artifacts from cardiac pulsation (27,28). This explains the reason for CT being overwhelmingly the diagnostic modality of choice for diagnosis of PE.

The diagnosis of pulmonary embolism was confidently diagnosed by Multidetector CT Angiography (MDCTA) that was carried out for 98 patients included in our study; 20 cases (20.4%) were diagnosed as positive PE. The location of thrombus in the main pulmonary artery, lobar, segmental and subsegmental pulmonary artery branches was precisely reported (Figs. 1–3) as well as of intracardiac (Fig. 2d) and IVC thrombosis (Fig. 3d), in addition to associated parenchymal findings such as pulmonary consolidation and pleural effusion (Figs. 1–3) and right ventricular dysfunction with subsequent flattening of interventricular septum and contrast reflux into the IVC and hepatic veins (Fig. 2e and f).

In our study cohort, 76 cases (77.55%) were diagnosed as negative on MDCTA evaluation and received no treatment for PE. Anticoagulant therapy can be safely stopped after negative CT Angiography for PE, as only 1 % of cases were reported in the literature to have recurrent thromboembolism within the next three months (29,30).

All negative cases for PE on MDCTA yielded negative D-Dimer test (Table 2); consequently, D-Dimer test results

<table>
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<th>Table 2 D-Dimer assay and MDCTA results.</th>
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<tbody>
<tr>
<td><strong>D-Dimer test</strong></td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>Positive</td>
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<tr>
<td>Negative</td>
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<td>Total</td>
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No. = number, % (percent), (+ ve) = positive, (− ve) = negative.

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<tr>
<th>Table 3 Statistical analysis of D-Dimer assay results.</th>
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<tr>
<td><strong>Value</strong></td>
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<tr>
<td>Sensitivity</td>
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<tr>
<td>Specificity</td>
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<tr>
<td>PPV</td>
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<tr>
<td>NPV</td>
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<tr>
<td>PLL</td>
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<td>NLL</td>
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</table>

PPV = positive predictive value, NPV = negative predictive value, PLL = Likelihood ratio. NLL = Negative likelihood ratio. % (percent).

<table>
<thead>
<tr>
<th>Table 4 Statistical analysis of D-Dimer test results at cutoff value 1.45 μg/ml.</th>
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<tbody>
<tr>
<td><strong>Value</strong></td>
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<tr>
<td>Sensitivity</td>
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<td>Specificity</td>
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<td>PLL</td>
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<td>NLL</td>
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PPV = positive predictive value, NPV = negative predictive value, PLL = Likelihood ratio. NLL = Negative likelihood ratio. % (percent).
showed 100% sensitivity and 100% negative predictive value (NPV) on statistical analysis (Table 3). This was also reported by a similar study conducted on oncologic patients (31), reporting NPV and sensitivity as 97% and 98%, respectively; and in agreement with another study (32), which suggested that it is possible to avoid unnecessary MDCTA by clinical correlation with D-Dimer test results.

On the contrary, 56 out of 76 high risk cases that were diagnosed as positive D-Dimer assay were diagnosed as negative for PE on MDCTA (Table 2), resulting in low specificity and positive predictive value, 28% and 26%, respectively (Table 3). In an attempt to calculate the diagnostic reliability of positive D-Dimer test, we estimated the cutoff value of the test results (1.45 μg/ml); however, the increase in specificity was not satisfactory to rely on positive results to establish the diagnosis, as positive likelihood ratio was 0.43 (Table 4). This means that increasing the threshold of positive test result to higher than the standard value (0.5 μg/ml) still yields false positive results.

Therefore, we can deduce that our findings are in agreement with previous studies which stated that D-Dimer test is not reliable in cases with high clinical probability (18,33,34).

Based on the results of this study, negative D-Dimer assay in high risk patients can only rule out the necessity of further testing for PE. Yet, positive D-Dimer assay, even with higher thresholds for positive results, can neither confirm nor exclude the possibility of PE and further testing is required. Unless contraindicated, MDCTA is the imaging modality of choice for diagnosis of PE and once confirmed, anticoagulant therapy should be started. Our recommendation is concordant with that of previously published international recommendations as the primary diagnostic modality of choice in patients with a positive D-Dimer or high clinical susceptibility (1,35).

Our results could be limited by selection bias followed in our methodology where cases were confined to high risk group of patients only. Another limitation of the current study is the relative small number of patients lacking a broad range of statistical confirmation.
Fig. 2  Female patient, 55 years old, presented with cardiogenic shock. After ICU admission and tracheostomy, she was referred for MDCTA. Findings: Axial (a), coronal (b) sagittal oblique (c) images show the following: acute thrombus is impacted in the distal end of the main pulmonary artery, and scattered thrombi are seen within the left lower lobe posterior segmental and lingular subsegmental branches. Axial (d) shows the following: significant dilatation of the right atrium with intra-atrial filling defect (1.5 cm) in diameter representing a thrombus (arrow); associated left basal small atelectasis is noted. Axial (e and f) show the following: right sided cardiac dysfunction is demonstrated in the form of flattening of the interventricular septum (arrow in e) and reflux of CM into the IVC with dilated hepatic veins (f).
In conclusion, MDCTA is the primary modality of choice for diagnosis of PE; yet, the request for CT examination should be in correlation with clinical probability and D-Dimer test results. Negative D-Dimer test is a reliable diagnostic modality to rule out the need for CT Angiography in patients at high risk population of PE. However, positive test results cannot confirm the diagnosis and further testing is warranted.

Conflict of interest

The authors declare that there are no conflict of interests.

References

(2) Lapner ST, Kearon C. Diagnosis and management of pulmonary embolism. BMJ 2013:346–757.


Kearon C. Diagnosis of pulmonary embolism. CMAJ 2003;168:183–94.


Sadigh G, Kelly AM, Cronin P. Challenges, controversies, and hot topics in pulmonary embolism imaging. AJR 2011;196:497–515.


Woodard PK. Pulmonary arteries must be seen before they can be assessed (editorial). Radiology 1997;204:11–2.


