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Original Article

# Performance of the Quantitative Latex Immunoturbidimetric D-dimer Assay for the Diagnosis of Acute Pulmonary Embolism at Rafik Hariri University Hospital

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**Abstract**

**Background and aims:** The diagnostic workup for pulmonary embolism (PE) includes D-dimer assay and computed tomographic angiography. Several D-dimer assays have been approved for PE diagnosis with different sensitivity and specificity. We aimed to study the sensitivity and specificity of the quantitative latex agglutination D-dimer assay used in a referral teaching hospital in Lebanon for the diagnosis of acute PE.

**Methods:** Using a retrospective chart review, we studied 300 patients who had D-dimer test at Rafik Hariri University Hospital in the period between January 1, 2012 and December 31, 2013. Accordingly, 93 patients had a CT angiography after being suspected to have acute PE. A statistical table 2*2 was used to compare the results of CT angiography and D-dimer test.

**Results:** Thirteen patients (13.97%) had PE and 60 patients (64.51%) had positive D-dimer test. Quantitative latex agglutination D-dimer assay had a sensitivity of 69%, specificity of 36%, and negative predictive value of 88%. False positive ratio was also 64%. Moreover, the receiver operating characteristic (ROC) curve was obtained with an area under the curve measuring 0.527.

**Conclusion:** Quantitative latex agglutination D-dimer assay has a high negative predictive value; thus, it can exclude a PE diagnosis if it is associated with low clinical pretest probability.

**Keywords:** Pulmonary embolism, D-dimer, Latex agglutination, Lebanon

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## Introduction

Pulmonary embolism (PE) is defined by the presence of a material in the pulmonary artery or one of its branches causing its obstruction and leading to hemodynamic and respiratory consequences.[1] The incidence of PE is 3-6 per 10 000 adults each year, which becomes more common with age in men and mortality can reach 25% if left untreated.[2] Clinical impression alone has a sensitivity and specificity of 85% and 51%, respectively, for acute PE.[3] This emphasizes the need for additional diagnostic evaluation whenever acute PE is suspected.

Whenever PE is suspected, the pretest clinical probability should be performed using the Wells score. Based on this scoring system and the clinical status of the patient, clinicians will use different tools for PE diagnosis including D-dimer assay, chest CT angiography, and trans-thoracic echocardiography.[4]

The US Food and Drug Administration approved the use of enzyme-linked immunosorbent assay (ELISA) and latex turbidimetric methods for the diagnostic workup of PE. The negative predictive value of the high-sensitive D-dimer assay reaches 94%; thus, it is useful only in ruling out PE when it is negative.[5]

The latex method is based on the occurrence of an agglutination reaction between D-dimer antigen that is found in the blood sample and the polystyrene particles that are linked to a monoclonal antibody (DD5) to the cross-linkage region of D-dimer. This reaction is then detected turbidimetrically via the increase in turbidity.[5]

ELISA assays are the reference standard for D-dimer quantitation. These assays consist of a labeled antibody added to microtiter wells that contain antibody-antigen complex. This complex is formed after binding D-dimer antigen found in the blood sample to the antibody coated to the wells. A colorimetric reaction will finally determine the quantity of bound labeled substance.[5]

Many variables may affect the D-dimer value including the age, presence of cancer or any liver disease, being pregnant, having *disseminated intravascular coagulation* (DIC) or simply a *deep vein thrombosis* (DVT), and so on. All these variables may give a falsely high D-dimer value; hence, positive results will not be diagnostic.

The selected cutoff value used in excluding PE can produce a difference in specificity. The study of Yamaki et al showed that the selection of a higher cutoff point can increase specificity from 48% to 78% only in the low pretest probability group compared to the intermediate-high risk group where no significant change was seen.[6]

Levels of D-dimer decrease to 25% of the initial value 1-2 weeks after clinical presentation; consequently, PE cannot be excluded if the patient presents after 1 week following onset of symptoms, and this can explain some of the false negative results.[7] False negative results can also be seen in patients with factor XIII deficiency due to the lack of cross-linkage.

Anticoagulation therapy is the other factor that can give false negative results. The use of heparin decreases D-dimer levels by 25%, which results in a decrease in sensitivity from 95.6% to 89.4%.[8]

Multiple research have been conducted worldwide to study the sensitivity and specificity of D-dimer for the diagnosis of PE. They have found that different assays of D-dimer have different results and have shown that D-dimer has a high negative predictive value for PE if it is used in cases where there is low clinical probability.[7]

Hence, we chose to study the sensitivity and specificity of D-dimer for the diagnosis of PE as defined by CT angiography findings at Rafik Hariri University Hospital (RHUH) where they use the latex agglutination D-dimer assay. Further, we aimed to see if our results are compatible with the results of studies conducted outside Lebanon. And if the results are not satisfying, our main objective was to encourage this hospital to use a more sensitive and specific test such as ELISA.

## Materials and Methods

We performed a retrospective chart review of one Lebanese referral teaching hospital (Rafik Hariri University Hospital – RHUH) for the period from January 1, 2012 through December 31, 2013. We recorded all patients who had a D-dimer test along with CT angiography when PE was suspected. Specifically, the database contains information concerning patient's age, D-dimer value, CT angiography result, and variables that can affect the end result. This study was approved by RHUH Institutional Review Board. Moreover, no conflict of interests has been declared by the authors.

All cases who had D-dimer test along with CT angiography, when PE was suspected, were enrolled in this study. Cases who were diagnosed with PE by another diagnostic tool were excluded. Patients who had only CT angiography without D-dimer test were also excluded.

It is worth to note that 300 patients had D-dimer test during this period and they were studied to know why this test was used without further investigations.

The technique of CT angiography used at RHUH: A regular CT chest protocol is used with a timing of 13 to 15 minutes after intravenous injection of contrast with 3 mm slice thickness.

The reference range used for D-dimer assay is 63.8- 246.4 µg/L (Advanced D-dimer, Dade Behring Diagnostics, Marburg, Germany) or 0-0.5 µg/mL (Tina-quant D-dimer BM, F. Hoffman-La Roche Ltd., Basel, Switzerland). Both assays are quantitative latex immunoturbidimetric used in the period of our study.

## Statistical Analysis

The D-dimer assay results were compared with the CT angiographic diagnoses in a statistical table 2*2 (Table 1). To find the statistical parameters, the following formulas were used:

Sensitivity = A/A+C

Specificity = D/B+D

Youden index = Sensitivity (%) + Specificity (%) - 100

Positive predictive value = A/A+B

Negative predictive value = D/C+D

Positive likelihood ratio = sensitivity/ 1- specificity

Negative likelihood ratio = 1- sensitivity/ specificity

The results were also computed by IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA) for further analysis.

## Results

Patients' sociodemographic characteristics are summarized in Table 2.

From 300 patients who had D-dimer test, only 93 patients met the inclusion criteria mentioned above. Out of these 93 patients, 14% had PE and 65% had positive D-dimer test. Note that all patients diagnosed with PE were followed by a pulmonologist.

The statistical analysis was performed based on the statistical table 2*2 (Table 3).

Sensitivity= (9/13) *100=69.23%

Specificity= (29/80) *100=36.25%

Youden index= Sensitivity (%) + specificity (%) – 100= 69.23 + 36.25 – 100 = 5.48

Positive predictive value= (9/60) *100=15%

Negative predictive value= (29/33) *100=87.87%

Positive likelihood ratio= (0.6923/ 1-0.3625) =1.09

Negative likelihood ratio = (1-0.6923/ 0.3625) =0.85

From 51 patients who had positive D-dimer test with negative PE, 22 patients had one of the variables that can lead to false positive results including cancer, liver disease, trauma, disseminated intravascular coagulation (DIC), and pregnancy. False positive ratio= (51/80) *100=63.75%.

**Table 1.** Statistical Table 2*2

| | CT positive for PE | CT negative for PE |
|---|---|---|
| D-dimer positive | A | B |
| D-dimer negative | C | D |

**Table 2.** Patients' Sociodemographic Characteristics

| | Number (%) | CT angiography positive for PE |
|---|---|---|
| Mean age (+/- SD) | 50.3 (+/- 26.5) years old | 58.6 (+/- 27.2) years old |
| Male | 140/300 (47%) | 10/13 (77%) |
| Female | 160/300 (53%) | 3/13 (23%) |

SD=Standard deviation. CT=Computed tomography. PE=Pulmonary embolism

**Table 3.** Diagnosis of Acute Pulmonary Embolism

| | CT Positive for PE | CT Negative for PE | Total |
|---|---|---|---|
| D-dimer positive | 9 | 51 | 60 |
| D-dimer negative | 4 | 29 | 33 |
| Total | 13 | 80 | 93 |

CT, Computed tomography; PE, Pulmonary embolism

Logistic regression analysis showed a positive correlation between these variables and D-dimer result with R value ranging between 0.3 and 0.4. The receiver operating characteristic (ROC) curve was obtained with an area under the curve measuring 0.527.

From 300 patients who had D-dimer test, 35 patients had surgery during their hospital stay. From these 35 patients, 27 had positive D-dimer test (77.14%), while none of them had a diagnosis of acute PE.

The majority of these patients were followed by a pulmonologist (93% of 300 patients).

## Discussion

The analysis of the data gathered in this study demonstrated that quantitative latex agglutination D-dimer assay was slightly sensitive with high negative predictive value and low specificity. This was also reflected in the obtained low Youden index.

However, by comparing our results with those of previous studies, we notice a discrepancy between the values. The sensitivity in our study was lower than that in earlier studies, which is around 95%.[9-11] Note that one of these studies had used the pulmonary angiogram as a diagnostic reference standard.[9] The specificity in our study and in the other studies is found to be in a similar range.[10,11]

The results may seem different, but it is all the same spirit. This discrepancy can be due to the huge difference in the population size; 93 patients in our study versus 1355 in the study of Froehling et al[11] who used CT angiography of the chest as a diagnostic reference standard.

The quantitative latex agglutination D-dimer assay had a high negative predictive value (87.87%) in our study. Thus a combination of a negative quantitative latex agglutination D-dimer assay and a low pretest clinical probability is likely sufficient to exclude a diagnosis of acute PE without further investigations; therefore, it will lead to decreased radiation exposure. However, our study did not aim to test this hypothesis that would require another prospective study for confirmation.

Concerning the false positive result, 22 patients were found to have a variable that might result in a false positive result. The remaining patients (29 patients) may have had any of the variables that could affect the D-dimer result but none of these variables were found during the chart review of these patients. Note that 16 patients of the 22 had cancer, one patient was pregnant, 2 patients had trauma, 2 patients had liver disease (hepatitis C and liver failure), and one patient had DIC.

Concerning the percentage of surgical patients who had positive D-dimer test without further investigations (77, 14%), these patients may have had a low pretest clinical probability and the D-dimer assay was used to exclude a diagnosis of PE based on their high negative predictive values. However, it is known that surgical intervention may falsely increase the D-dimer value by itself and having a positive result in the post-operative period may be misleading more than being helpful in PE diagnosis.

Therefore, we had to ask about the cost-effectiveness of this test in the post-operative period if PE was suspected and this high percentage was worrisome since these patients did not have further tests to rule out PE despite the high level of D-dimer that might be explained simply by the recent surgical event. From this perspective, we strongly advice that the clinical probability of PE is carefully assessed before doing a proper investigation even if it is a simple laboratory test such as D-dimer assay.

During our study, we noticed that a pulmonary consultation was done for the majority of patients including the PE patients and the patients who had positive D-dimer without further investigations. Probably, the assessment of patients by a pulmonary rehabilitation team played an important role in discontinuing any further tests despite the positive result of D-dimer that could be correlated with

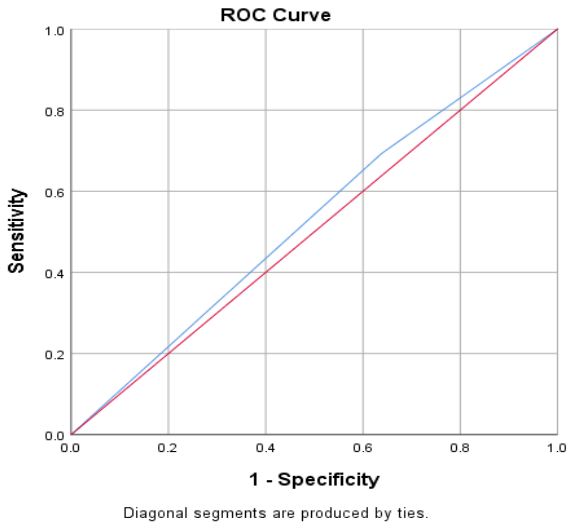


**Figure 1.** Receiver operating characteristic (ROC) curve with an area under the curve measuring 0.527

any variables found in patients.

This is the first study that was done in RHUH to test the performance of quantitative D-dimer latex immunoturbidimetric assay and no published study about this subject was found in Lebanon.

Several limitations are found in our study. The first we know is the retrospective design that is used. Second, CT angiography is not the gold standard for acute PE diagnosis since it may miss subsegmental pulmonary emboli. Third limitation is the limited number of patients who were enrolled. Fourth, we did not do a comparison between two different assays (latex versus ELISA). Fifth, all patients who were included in our study were hospitalized ones; however, the diagnosis of thrombosis in this setting was complicated by the fact that D-dimer antigen levels were commonly elevated for various reasons in hospitalized patients, which limited its value for exclusion of venous thromboembolism.

In this study, we showed that quantitative latex agglutination D-dimer assay was slightly sensitive and also had a high negative predictive value for excluding acute PE. However, specificity was low. Using this test alone with low pretest clinical probability was sufficient in ruling out the disease. Therefore, we should emphasize the clinical presentation and risk factors of each patient whenever PE is suspected.

Nevertheless, sensitivity of the quantitative latex agglutination D-dimer assay for the diagnosis of acute PE was lower compared to the reported sensitivity of the quantitative rapid ELISA.[12] Despite difference in the sensitivity between the two previously mentioned D-dimer assays, it seems inappropriate to recommend the use of ELISA instead of the quantitative latex agglutination assay since many studies have demonstrated that these two assays can be comparable in sensitivity and specificity [7]. Therefore, another study on the same population is needed to compare both tests and further studies on a greater number of patients are also recommended.

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