Predictive Value of a Rapid Immunometric NycoCard D-dimer Assay for Acute Pulmonary Embolism

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Background: The reported diagnostic performance of D-dimer assay for excluding pulmonary embolism (PE) vary widely. This study was carried out to assess the diagnostic performance of NycoCard D-dimer assay in suspected PE patients. **Objective:** To determine if a D-dimer assay can reliably exclude PE in patients with suspected PE. **Methods:** The patients evaluated for PE with a CT pulmonary angiography (CTPA) and D-dimer assay were eligible for inclusion. The electronic medical records of the patients were reviewed to analyze the diagnostic performance of NycoCard D-dimer assay for excluding acute PE. Collected data included the presence or absence of PE, D-dimer result and patient demographics. **Results:** A total of 229 consecutive patients underwent CTPA for acute PE and had a D-dimer measurement performed. Pulmonary embolisms were reported for 86/229 (37%) CTPAs. Overall, the D-dimer assay was found to have a sensitivity and specificity of 96.5% and 29.4%, respectively, for the diagnosis of PE, with a positive predictive value (PPV) and negative predictive value (NPV) of 45.1% and 93.3%, respectively. The negative predictive value in low or moderate clinical probability of PE is 95.5% (95% CI, 84.5% to 99.4%). The likelihood ratio associated with a negative D-dimer test result was 0.09 (CI, 0.02-0.38) **Conclusions:** A normal NycoCard D-dimer test result is useful in excluding PE when the clinical probability of the presence of PE is low or intermediate. An understanding of the physiological basis and limitations of D-dimer value may contribute to reduce its inappropriate use.

บทคัดย่อ: คุณค่าทางการพยากรณ์ของชุดตรวจสารโมเลกุลคู่ชนิดดี สำหรับการวินิจฉัยภาวะลิ่มเลือดอุดตันในหลอดเลือดแดงปอดเฉียบพลัน

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ภูมิหลัง: รายงานเกี่ยวกับสมรรถภาพในการวินิจฉัยของการตรวจสารโมเลกุลคู่ชนิดดีในการวินิจฉัยภาวะลิ่มเลือดอุดตันในหลอดเลือดแดงปอดเฉียบพลัน มีความแตกต่างกันมาก และชุดตรวจสำเร็จรูปที่ใช้ในแต่ละสถานพยาบาลมีความหลากหลายทั้งชนิด และหลักการของชุดตรวจแต่ละสถานพยาบาลควรประเมินสมรรถภาพในการวินิจฉัยของชุดตรวจที่ใช้ในสถานพยาบาลตนเอง **วัตถุประสงค์:** เพื่อประเมินสมรรถภาพในการวินิจฉัยของการตรวจสารโมเลกุลคู่ชนิดดีที่ใช้ในโรงพยาบาลมหาราชนครราชสีมา ในการวินิจฉัยภาวะลิ่มเลือดอุดตันในหลอดเลือดแดงปอดเฉียบพลัน **วิธีการศึกษา:** ศึกษาข้อมูลผู้ป่วยที่ได้รับการส่งตรวจเอกซเรย์คอมพิวเตอร์หลอดเลือดแดงปอดเพื่อการวินิจฉัยภาวะลิ่มเลือดอุดตันในหลอดเลือดแดงปอดเฉียบพลัน และมีผลการตรวจสารโมเลกุลคู่ชนิดดี ในโรงพยาบาลมหาราชนครราชสีมา และนำมาวิเคราะห์ทางสถิติ เพื่อประเมินสมรรถภาพในการวินิจฉัยของการตรวจสารโมเลกุลคู่ชนิดดีเพื่อการแยกโรคภาวะลิ่มเลือดอุดตันในหลอด เลือดแดงปอดเฉียบพลัน **ผลการศึกษา:** ศึกษาผู้ป่วยจำนวน 229 ราย ที่ได้รับการส่งตรวจเอกซเรย์คอมพิวเตอร์หลอดเลือดแดงปอดเพื่อการวินิจฉัยภาวะลิ่มเลือดอุดตันในหลอดเลือดแดงปอดเฉียบพลัน และมีผลการตรวจสารโมเลกุลคู่ชนิดดีในโรงพยาบาลมหาราชนครราชสีมา พบมีผู้ป่วยที่มีภาวะลิ่มเลือดอุดตันในหลอดเลือดแดงปอดเฉียบพลันจำนวน 86 ราย (ร้อยละ 37) ความไวและความจำเพาะของการตรวจสารโมเลกุลคู่ชนิดดี ในการวินิจฉัยภาวะลิ่มเลือดอุดตันในหลอดเลือดแดงปอดเฉียบพลันเท่ากับ ร้อยละ 96.5 และร้อยละ 29.4 ตามลำดับ และมีค่าการพยากรณ์ผลบวกและค่าการพยากรณ์ผลลบเท่ากับ ร้อยละ 45.1 และร้อยละ 93.3 ตามลำดับอัตราส่วน ภาวะน่าจะเป็นเมื่อผลการการตรวจสารโมเลกุลคู่ชนิดดีเป็นลบ เท่ากับ 0.09 **สรุป:** การตรวจสารโมเลกุลคู่ชนิดดี โดยใช้ชุดตรวจสำเร็จรูปที่ใช้ในโรงพยาบาลมหาราชนครราชสีมา มีประโยชน์ในการวินิจฉัยแยกโรคผู้ป่วยภาวะลิ่มเลือดอุดตันในหลอดเลือดแดงปอดเฉียบพลันกลุ่มที่มีโอกาสเป็นโรคจากการประเมินทางคลินิกต่ำ หรือปานกลาง

Introduction

Pulmonary embolism (PE) is a common and potentially fatal disease. The accurate and rapid diagnosis of PE remains difficult in clinical practice because of non-specific clinical presentation. As a result, clinicians cannot diagnose PE on the basis of clinical findings alone. Standard anticoagulation therapy for pulmonary embolism carries significant potential severe and even life-threatening side effects, so objective testing is required to establish or exclude the presence of PE.

Although pulmonary angiography is being considered as the ‘‘gold standard’’ in the diagnosis of acute pulmonary embolism, it suffers from limitation in its use as a result of being relatively expensive, time-consuming and involves radiation and contrast. Historically, radionuclide lung scan was the most common method of diagnosing acute PE. In the past decade, the computed tomography pulmonary angiogram (CTPA) has replaced the radionuclide lung scan as the primary imaging modality for the diagnosis of acute PE

PE produces a burden of clot within the circulation. When a clot breaks down, it forms fibrin degradation products (FDP), including D-dimer molecules. As a result, patients with PE are expected to have excessive numbers of D-dimer molecules in their blood. The measurement of D-dimer is widely

claimed to have potential value for excluding PE and sparing low-risk patients from further invasive workup. To limit the number of patients receiving advanced imaging, current clinical practice guidelines suggest initial D-dimer testing for those who are at low to moderate risk[1].

As a screening test, the D-dimer assay should be rapid, sensitive, and easy to perform. The reference method, enzyme-linked immunosorbent assay (ELISA), has a high sensitivity, but it is time-consuming and requires specific equipment. Standard ELISA tests therefore have a long turnaround time and are not practical for quick evaluation of patients for PE. Newer quantitative D-dimer assays are sensitive and rapid yielding test results. However, there are numerous D-dimer assays on the market and each has its own sensitivity and specificity.

The main problem of D-dimer assays is that it is not currently possible to standardize results from different assays. Previous studies in this field indicate that D-dimer assay shows significant differences between methods and that result cannot be extrapolated from one technique to another. The reported D-dimer sensitivity varies so widely (range from 48% to100%)[2,3]. Therefore, each D-dimer assay should be carefully validated separately in each hospital before implementing it as a screening test. The aim of this study is to determine if a NycoCard D-dimer assay (Nycomed Pharma, Oslo, Norway) can reliably exclude in patients with suspected PE.

Materials and Methods

The study was carried out retrospectively as patient was evaluated by NycoCard D-dimer assay and CTPA for excluding PE.

Study population

All CTPAs that had been performed at Maharat Nakorn Ratchasima Hospital in the three year period from 1st January 2014 to 31st December 2016 were identified and retrospectively reviewed on the hospital information system.

During the study period, 267 patients under-went CTPA for suspected acute PE and had a D-dimer test performed. D-dimer was measured using the NycoCard D-dimer assay. Patients were excluded if D-dimer tests were performed more than 3 days before or after CTPA or if the CT angiogram was interpreted as chronic PE or as an inconclusive study. Patients who had symptoms more than 15 days, age < 18 years and had treatment with anticoagulant for 72 hours or more also were excluded.

Sample size was estimated on the basis of our previous retrospective validation data set. We assumed and 40% prevalence of disease and a D-dimer sensitivity of 90% for acute PE. The study needs a sample size of at least 87 patients.

The result of CTPA interpreted by radiologist in the Department of Radiology and was scored as positive or negative for PE.

The cut-off level for this assay is 0.3 mg/L; a test result under 0.3 mg/L is considered to be a negative result; equal or above 0.3 mg/L is considered to be a positive result, as recommended by the manufacturer. The diagnostic value of the D-dimer assay in diagnosing PE was evaluated with CTPA as a reference.

Statistical analysis

Patient's data were entered in an Excel spreadsheet and were exported to Stata Statistical

Software version 11.0 for calculation of descriptive statistics. Descriptive statistics are presented as counts and percentages for categorical variables and mean±standard deviation (SD) for continuous variables. A comparison of categorical variables was performed using Fisher's exact test. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of D-dimer levels were calculated with 95% confidence intervals. Diagnostic performance was compared using a Fisher exact test. Values of $p<0.05$ were considered statistically significant.

Result

During the study period, a total of 229 patients met the inclusion criteria. Among them, 86 patients were diagnosed with PE by CTPA; the overall prevalence of PE was 37.6%.

The demographic and clinical characteristics of the enrolled population are shown in Table 1.

The mean age of positive and negative PE cases was 57.5±16.22 and 58.0±18.04 respectively, with statistically non-significant difference among studied cases as regards to age and sex. The majority of patient populations were female. The most common presenting symptom was dyspnea. The three most common accompanying diseases were arterial hypertension, DM, and malignant disease. None of the differences between the two study groups was significant ($P \geq 0.05$).

Table 1 Demographic Data and Clinical Characteristics of Study Population

Parameter	Positive for PE (n = 86)	Negative for PE (n = 143)	P-value
Age (mean±SD)	57.5±16.22	58.0±18.04	0.861
Sex			
Male	22 (25.6%)	54 (37.8%)	0.061
Co-morbid disease			
HT	30 (35%)	54 (37.8%)	0.674
DM	18 (20.9%)	27 (18.9%)	0.733
Malignancy	14 (16.3%)	25 (17.5%)	0.858
Fracture of lower extremities	8 (9.3%)	20 (14.0%)	0.405
CVA	4 (4.6%)	16 (11.2%)	0.098
CKD	2 (2.3%)	13 (9.1%)	0.054
CHF	2 (2.3%)	11 (7.7%)	0.139
IHD	1 (1.2%)	8 (5.6%)	0.159
Symptoms			
Dyspnea	80 (93.0%)	122 (85.3%)	0.093
Cough	25 (29.0%)	36 (25.1%)	0.540
Chest pain	17 (19.8%)	21 (14.7%)	0.361
Syncope	9 (10.5%)	8 (5.6%)	0.198
Hemoptysis	2 (2.3%)	1 (0.7%)	0.558

Table 2 Pulmonary CT Angiography Results Based on D-dimer Values

D-dimer Results	CT angiography Results	
	Positive	Negative
Positive (≥0.3 mg/L)	83	101
Negative (< 0.3 mg/L)	3	42
Total	86	143

Table 5 Pulmonary CT Angiography Results Based on D-dimer Values of low or intermediate probability patients

D-dimer Results	CT angiography Results	
	Positive	Negative
Positive (≥0.3 mg/L)	69	101
Negative (< 0.3 mg/L)	2	42
Total	71	143

Table 3 Sensitivity, specificity, NPV and PPV of D-dimer test result in relation to final diagnosis by CTPA.

	Sensitivity %(95% CI)	Specificity %(95% CI)	NPV %(95% CI)	PPV %(95% CI)
NycoCard D-dimer	96.5% (90.1-99.3)	29.4%(22.1-37.6)	93.3%(81.7-98.6)	45.1%(37.8-52.6)

Table 2 shows the diagnostic 2x2 table results for the D-dimer assay in the entire cohort.

Table 3 shows that the sensitivity of D-dimer test in diagnosis of PE was 96.5% while its specificity was 29.4% as well as its positive predictive value was 45.1% and its negative predictive value was 93.3%.

According to the Modified Wells Scoring System, 84 of the 229 patients (36.7%) were categorized as having low clinical probability of PE, 130 patients (56.8%) as having intermediate probability of PE, and 15 patients (6.5%) as having high clinical probability of PE. (Table 4)

The prevalence of PE was 9.5% in the low clinical probability, 48.5% in the intermediate clinical probability, and 100% in the high clinical probability categories (Figure 1).

Of 214 patients (93% of the cohort) who were classified as a low or intermediate pretest probability, 71 (33%) had PE. Of these 214 patients, 44 had a normal D-dimer test result; 2 of 42 patients were classified as positive for PE, Therefore, in the subgroup of patients with a low or intermediate pretest probability, the likelihood ratio associated with a negative D-dimer test result was 0.09 (95%CI, 0.02-0.38). (Table 5)

The diagnostic performance of NycoCard D-dimer test in the subgroup of patients with a low or intermediate clinical probability of PE are shown in Table 6. As expected, sensitivity and negative predictive value are high. The sensitivity is 97.2% (95% CI, 90.2% - 99.7%) and the negative predictive value is 95.5% (95% CI, 84.5% - 99.4%).

Table 4 Results of D-dimer test for cases with low, intermediate and high clinical probability in relation to final diagnosis by CTPA

D-dimer test	Pretest clinical probability					
	Low		Intermediate		High	
	PE	No PE	PE	No PE	PE	No PE
Positive	8	53	61	48	14	0
Negative	0	23	2	19	1	0

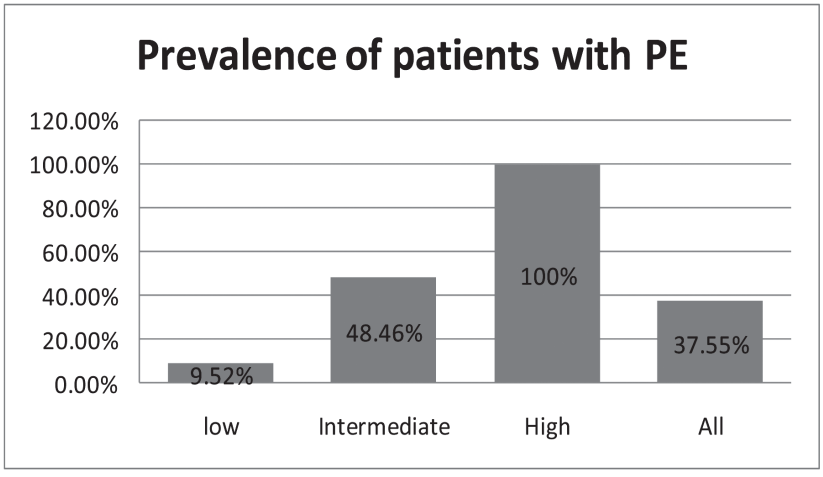

Figure 1 Percentage of patients with PE over all and by clinical risk

Discussion

Fibrin polymers are degraded by plasmin in the fibrinolytic system forming D-dimer. D-dimers are detected by immunoassays using monoclonal antibodies specific for the cross-linked D-dimer domain in fibrinogen, this specific characteristic of D-dimer explain its high sensitivity for venous thromboembolism. Three different types of D-dimer assay are available; the enzyme-linked immunosor-bentassay (ELISA), the whole-blood agglutination assay, and the latex agglutination assay. Although widely accepted as the gold standard, the ELISA is relatively expensive, time-consuming, and not widely available. A large variety of rapid D-dimer assays are now available[5,6].

Many investigators have studied the sensitivity of D-dimer assays in the evaluation of acute PE. Some of the articles published on the use of D-dimer have not clearly explained whether they used mass D-dimer or fibrinogen equivalent units (FEU) to distinguish normal from abnormal values. NycoCard D-dimer test is based upon an immunometric flow-through principle (ELISA principle) using NycoCard READER II for semiquantitative determination. D-dimer results were reported in mg/L. This estimates the concentration of the D-dimer fragments (a mass D-dimer unit) in the sample. To get the results in fibrinogen equivalent units (FEU), the result obtained must be multiplied by a factor of two.

The NycoCard D-dimer assay has been used on the basis of some previous studies describing a high diagnostic value of this assay[7]. In contrast, Rikke et al, using a NycoCard D-dimer assay, found a low sensitivity (40%) of this test for PE and suggested that it is unacceptable as a screening method[3].

It is unlikely that manufactory laboratories will repeat the studies that have been published to find

Table 6 Sensitivity, specificity, NPV and PPV of D-dimer test result in relation to final diagnosis by CTPA in cases with low or intermediate clinical probability. (95% CI)

	Sensitivity %(95% CI)	Specificity %(95% CI)	NPV %(95% CI)	PPV %(95% CI)
NycoCard D-dimer	97.2%(90.2-99.7)	29.4%(22.1-37.6)	95.5%(84.5-99.4)	40.6%(33.1-48.4)

the appropriate cut-off value of their D-dimer tests for excluding acute PE. However, the manufacturer of each test will probably provide a suggested cut-off value. What the clinician needs to do is verify that in their hands this cut-off value actually separates normal patients from patients who have disease.

Our study demonstrates the NycoCard D-dimer level is a sensitive but nonspecific test for acute PE as defined by the diagnostic reference standard, CTPA (Table 3).

For patients with low or intermediate pretest clinical probability of acute PE, NycoCard D-dimer test with a discriminated value of 0.3 mg/L have a negative predictive values of 95.5% (95% CI, 84.5% - 99.4%) (Table 6).

Our results confirm the good performance of rapid NycoCard D-dimer test. However, the results cannot be extrapolated to other assay methods.

Our data are consistent with the findings of others that a negative D-dimer result in combination with a clinical assessment of low or intermediate probability of PE reliably excludes PE[8]. For these assays, a level >500 ng/mL (fibrinogen equivalent units) is usually considered positive, and < 500 ng/mL is considered negative. Kearon[9] concluded that "the very highly sensitive D-dimer tests" (a sensitivity of about 98% or higher) can be used as a "stand-alone" test for the exclusion of pulmonary embolism. Our D-dimer assay is "the moderate to highly sensitive D-dimer tests" (a sensitivity of about 85%-98%). The negative likelihood ratio and predictive value with these tests is not high enough to "rule out" PE in all patients. Consequently, a normal result needs to be combined with another assessment that identifies patients as having a low or intermediate pretest probability for PE. An understanding of the physiological basis and limitations of D-dimer values may contribute to reduce its inappropriate use.

It would be desirable if the treating physician could identify, at presentation, those patients at high risk for a false negative D-dimer test result. Some patient characteristics, such as long duration of symptoms or the use of anticoagulant therapy, are known to be associated with lower D-dimer levels[10].

The specificity and positive predictive value of all assays were low and inadequate for the diagnosis of acute PE. Our specificity was low, which may be attributable to the greater number of inpatient data in the analysis. The majority of patients in the present study were inpatients, where it is well known that D-dimer values are specifically higher from causes other than PE[11].

A low specificity of D-dimer test seems to be accepted because it is used for ruling out PE that patients with a positive result will be examined with a confirmatory imaging. However, it is common for hospitalized patients with co-morbid disease who do not have PE to have a positive D-dimer test, leading to more imaging, which increases costs and potential harms from exposure to ionizing radiation and iodinated contrast agents[12]. Evidence from recent studies suggests that the prevalence of PE among patients who undergo diagnostic work-up CTPA has decreased from 30% to below 10%[13], possibly as a consequence of the wide availability of D-dimer that may lower physicians threshold of clinical suspicion and lead to overuse of D-dimer testing. The Pulmonary Embolism Rule-out Criteria (PERC) rule was designed to identify patients with a low clinical probability that PE can safely be excluded

without the need for D-dimer testing, thus avoiding false-positive D-dimer results[14].

Unfortunately, PERC rule is only valid in clinical settings (typically in the outpatients setting) with a low prevalence of PE[15]. In clinical settings with a higher prevalence of PE, the PERC-based approach has been shown to have a substantially poorer predictive value. Thus, it should not be used in patients with an inter-mediate or high suspicion for PE or for inpatients suspected as having PE. D-dimer test should be used with caution in patients who have factor produce false positive result. Moreover, D-dimer should never be used without a pre-test clinical probability assessment. D-dimer levels gradually increase with age; thus, the utility of the test as a diagnostic screen diminishes in elderly patients. Adjusted D-dimer levels based on certain criteria have been proposed. D-dimer levels rise with age such that using the traditional cutoff value of < 500 ng/mL (fibrogen equivalent units) results in reduced specificity of D-dimer testing in older patients (> 50 years), a population in whom PE is common. The most commonly used formula for age adjustment is: age (if over 50) x 10 = cutoff[16].

Although, there are clinical practice guidelines for physician investigating a patient suspected of having a PE[1,4], some clinicians may not have a complete understanding of the patient populations that will benefit from D-dimer screening for PE. It is recommended that a clinical probability assessment and D-dimer value should be combined and used to quantify the patient's risk of PE as low, intermediate or high.

On the basis of our results, we concluded that a negative NycoCard D-dimer test and a low to inter-mediate pretest probability of PE together are sufficient to exclude acute PE without imaging tests. On the contrary, the patients with a high pretest probability should undergo CTPA directly.

Additionally, we suggest that a management strategy of withholding anticoagulant therapy among the patients who have either a low or an intermediate pretest likelihood of PE and a negative D-dimer test is safe and clinically useful, especially when ventilation-perfusion lung scan or CTPA are not immediately available.

This study focused on patients suspected of having acute PE. Patients with chronic pulmonary embolism may have lower D-dimer values caused by clot stabilization; therefore, the D-dimer cutoff value found in our study may not be applicable to patients evaluated for chronic PE.

There were some limitations to this study. First, the study population mainly consisted of hospitalized patients with the higher prevalence of conditions associated with fibrin generation among the inpatients, such as a severe infection, cancer, myocardial infarction, trauma, fracture, or recent surgery. Including many patients with elevated D-dimer concentrations due to other causes than PE may give a false increase in sensitivity and negative predictive value because of the patient would have a D-dimer elevation above the cut-off value before the PE that have a very low chance of giving a false negative.

Second, as a result of a low specificity for the PE diagnosis, leading to a high rate of false-positive results, the clinical usefulness of the test (the proportion of negative D-dimer tests in patients with suspected of PE and in whom this diagnosis may be safely ruled out) is low.

In hospitalized population, patients with suspected PE are frequently those who are more likely than outpatients to have comorbid disease that increase D-dimer concentration. For this reason, the clinical usefulness of this test in this patient population is limited.

The clinical usefulness of NycoCard D-dimer test in this study is 36 %. Accordingly, 64% of patients with suspected PE will require further evaluation with imaging techniques for PE detection (CTPA or ventilation-perfusion lung scan). Third, patients for whom no D-dimer test result were not included. Given that these patients more frequently had a high probability of PE, the exclusion of these patients resulted in a small number of patients with a high clinical probability. The high clinical probability patients are too low to determine the safety of the test in that subgroup. Therefore, physicians should not exclude PE based on a negative D-dimer alone in high-probability patients.

Furthermore, in the present study, nearly all high probability patients had a positive result. Therefore, these patients should not be tested for D-dimer because testing results are rarely negative and the positive predictive value for PE is poor.

In the same way that previous studies have led to guidelines on the use of D-dimer assays, the findings in this study should give guidance to those who use the same type of semi quantitative immunometric D-dimer assay in clinical practice. Moreover, we believe that correct information on the best clinical use of D-dimer testing is necessary to improve its application in clinical practice.

Conclusion

The semiquantitative NycoCard D-dimer test with a discriminated value of 0.3 mg/L had high sensitivity and high negative predictive value. We concluded that a negative NycoCard D-dimer result and a low or intermediate pretest clinical probability together are sufficient to exclude acute PE.

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