Original Article

A study of modified Wells score for pulmonary embolism and age-adjusted D-dimer values in patients at risk for deep venous thrombosis

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Abstract

Aims: Pulmonary embolism (PE) is the most severe complication of deep venous thrombosis (DVT). This study was designed to evaluate the usefulness of modified Wells score combined with age-adjusted D-dimer cut-off levels as a clinical pre-test probability assessment for predicting PE in patients 'at risk for DVT.' **Methods:** This was a cross-sectional study including 200 in-patients at risk for DVT. Patients were categorized as 'pulmonary embolism unlikely' or 'pulmonary embolism likely' using modified Wells score and underwent D-dimer testing. PE was considered excluded in patients classified as unlikely with normal D-dimer levels, whereas the rest of the patients underwent computed tomography pulmonary angiogram (CTPA). **Results:** Out of 200 patients, 163 patients (81.50%) were 'pulmonary embolism unlikely,' whereas 37 patients (18.50%) were 'pulmonary embolism likely.' Of 163 patients categorized as 'pulmonary embolism unlikely,' 67 patients (41.5%) had normal D-dimer values and were excluded from CTPA. PE was detected in 24.2% of the patients who underwent CTPA. **Conclusion:** The combined strategy using modified Wells score and age-adjusted D-dimer cut-off value has 100% sensitivity and a negative predictive value and can be used to safely exclude PE in in-patients.

Keywords: Deep venous thrombosis, D-dimer, pulmonary embolism, wells score

Introduction

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are separate but related aspects of the same dynamic disease process termed venous thromboembolism (VTE). The manifestation spectrum of PE ranges from silent to a massive and sometimes suddenly fatal event. Acute PE is the third most common cardiovascular disease after acute coronary syndrome and stroke. Patients admitted with an acute medical illness are at increased risk for VTE during and following hospital admission as compared to the general population. It is considered the most common preventable cause of death among hospitalized patients. Prompt diagnosis and appropriate treatment of PE can dramatically reduce mortality and morbidity among patients; therefore, the importance of its early detection in the primary care setting cannot be under-estimated. However, PE appears to be one of the most missed diagnoses in primary care. In the recent years, extensive research has been devoted to developing non-invasive and cost-effective diagnostic strategies for PE, considering that angiography is costly and invasive. This study was designed to evaluate the usefulness of modified Wells score combined with age-adjusted D-dimer cut-off levels as a clinical pre-test probability assessment for predicting PE in patients 'at risk for DVT.'

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Methods

Patients

Between November 2018 and March 2020, 200 patients meeting the inclusion criteria and admitted under the Department of

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Medicine of Lady Hardinge Medical College and associated Dr. Ram Manohar Lohia Hospital were enrolled. Patients were eligible if they were 18 years and above with either diagnosed DVT based on lower limb Doppler ultrasonography or a Wells score for DVT of 1–8. Patients with previously diagnosed PE or chronic thromboembolic pulmonary hypertension (CTEPH) were excluded from the study. Ethics committee approval was obtained on 26-10-2018.

Clinical decision rule and D-dimer assay

Modified Wells criteria for PE as shown in Table 1 were applied for classifying patients as 'pulmonary embolism likely' and 'pulmonary embolism unlikely.'

For patients who are PE unlikely, a normal D-dimer value effectively excludes PE, and no further testing was performed. In contrast, an elevated D-dimer value required further testing and these patients underwent CTPA.

For patients who are PE likely, a normal D-dimer is not as helpful for excluding the diagnosis. Although a negative D-dimer result does reduce the likelihood of PE, it does not reduce it sufficiently to rule out the diagnosis. These patients were further investigated using CTPA.

D-dimer test was performed using a Liatest D-Di Plus kit on an STA Compact coagulation analyzer (Stago) for all the patients.

A D-dimer cut-off value of <500 ng/mL was taken for patients with an age of 50 years and below. For patients with an age over 50 years, the age-adjusted cut-off was calculated applying the most commonly used formula: Age (if over 50 years) x 10 = cut-off value in ng/mL (fibrinogen equivalent units).

Radiological evaluation

Computed tomography pulmonary angiography was performed using multi-detector-row systems. The pulmonary arteries were evaluated up to and including the sub-segmental vessels from the level of the aortic arch to the lowest hemi-diaphragm. PE was diagnosed if the contrast material outlined an intra-luminal defect or if a vessel was totally occluded by a low-attenuation material on at least two adjacent slices.

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD and median. Qualitative variables were correlated using Fisher's exact test. Spearman correlation coefficient was used to find out the strength of correlation between two variables. Diagnostic test was used to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Inter-rater kappa agreement was used to find out the strength of agreement of D-dimer and Wells score with PE. A *P* value of <0.05 was considered statistically significant.

Results

A total of 200 admitted patients fulfilling the inclusion criteria were taken for study, whose age distribution varied from 18 years to 92 years. The mean age observed was 55.16 + 16.8 years. Maximum patients were in the age group of 51 to 60 years (28%). Out of 200 cases, 119 patients (59.50%) were males and 81 patients (40.50%) were females. The most common admitting diagnosis was pneumonia present in 35 patients (17.5%), followed by DVT present in 31 patients (15.5%), heart failure in 30 patients (15%), and stroke in 28 patients (14%), as shown in Table 2. The average duration of hospital stay among the patients was observed to be 8 days with a minimum of 3 days and a maximum of 48 days of hospital stay. The risk factors had a variable distribution among the study population with multiple risk factors being present in many individuals as shown in Table 3. Out of 200 patients included in the study, 31 patients had DVT,

Table 1: Wells criteria

Clinical variable	Score
Clinical symptoms of DVT (leg swelling, pain on palpation)	3.0
Other diagnosis less likely than PE	3.0
Heart rate >100	1.5
Immobilization (≥3 days) or surgery in the past 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Modified Wells criteria interpretation	
PE likely	>4.0
PE unlikely	≤4.0

Table 2: Characteristics of patients included in study

Characteristics	Total population (*n*=200)
Age (years, Mean±SD)	55.16±16.8 years
Gender, N (M/F)	119/81
Admitting diagnosis, *n* (%)	
Pneumonia	35 (17.5)
DVT	31 (15.5)
Heart failure	30 (15)
Stroke	28 (14)
Others	76 (38)
Duration of hospital stay (days, Mean±SD)	9.46±5.12

Table 3: Distribution of risk factors among patients with DVT and 'at risk for DVT'

Risk Factors, *n* (%)	DVT patients (*n*=31)	'At risk for DVT' patients (*n*=169)
Smoking	7 (22.58)	47 (27.81)
OCP intake	0 (0)	0 (0)
Surgery (<4 weeks)	2 (6.45)	5 (2.96)
Lower limb fracture	3 (9.68)	8 (4.73)
Immobilization (>3 days)	31 (100)	169 (100)
History of venous thromboembolism	1 (3.23)	0 (0)
Malignancy	1 (3.23)	0 (0)

while the remaining 169 patients were 'at risk for DVT' with a Wells score for DVT of 1–8. Immobilization (≥3 days) was the most common risk factor present in 31 patients (100%) with DVT and 169 patients (100%) 'at risk for DVT.' The second most common risk factor found was smoking, which was present in 7 patients (22.58%) with DVT and 47 patients (27.81%) 'at risk for DVT.' Similarly, the most common risk factor found in patients with PE was immobilization (100%), and it was followed by smoking as the second most common risk factor (13.33%).

Assessment of clinical probability of PE

The modified Wells score for PE was calculated for all the 200 patients, based on which they were classified as 'pulmonary embolism unlikely' with a score of 4 or less points and 'pulmonary embolism likely' with a score of more than 4 points. A total of 163 patients (81.50%) were categorized as 'pulmonary embolism unlikely,' while 37 patients (18.50%) were categorized as 'pulmonary embolism likely.' Out of 163 patients with 'pulmonary embolism unlikely,' 96 patients had elevated D-dimer values, while the remaining 67 patients had normal D-dimer values. In the study, it was found that elevated D-dimer values were significantly associated with patients with 'pulmonary embolism likely' ($P < 0.0001$). Also, a significant positive correlation was observed between modified Wells score for pulmonary embolism and D-dimer values (correlation coefficient 0.216, *P* value 0.0021).

Diagnosis of PE

Out of 200 patients, CTPA was indicated in 133 patients who were 'pulmonary embolism likely' or had elevated D-dimer values, while the remaining 67 patients who were 'pulmonary embolism unlikely' and had normal D-dimer values were not investigated further and PE was considered ruled out. Only 62 patients underwent CT pulmonary angiography, while in the rest 71 patients, CTPA could not be performed due to renal insufficiency (n = 53), deteriorating clinical conditions or expiry prior to CTPA (n = 16) and lost to follow-up (n = 2). Of 62 patients, 47 patients (23.50%) had normal CTPA, while 15 patients (7.50%) had evidence of pulmonary embolism on CTPA. In the study, it was observed that patients categorized as 'PE likely' were significantly associated with the presence of PE on CTPA (*P* value 0.035); also, patients with DVT were significantly associated with an increased frequency of PE on CTPA (*P* value 0.002), as shown in Table 4.

Table 4: Association of D-dimer, modified Wells score and LL Doppler with CTPA

Total CTPA (*n*=62)	Normal CTPA (*n*=47)	Positive CTPA (*n*=15)	*P*
D-dimer			
Elevated	46	14	0.428
Normal	1	1	
Modified Wells score			
PE Likely (>4)	18	11	0.035
PE Unlikely (≤4)	29	4	
LL Doppler			
DVT	15	12	0.002
Normal study	32	3	

The sensitivity, specificity, PPV, and NPV of age-adjusted D-dimer cut-off values for the diagnosis of PE were observed to be 93.33%, 2.13%, 23.33%, and 50%, respectively, while those of modified Wells score for PE were 73.33%, 61.7%, 37.93%, and 87.88%, respectively. The combined approach had a sensitivity of 100%, a specificity of 2.13%, a PPV of 24.59%, and an NPV of 100% for the diagnosis of PE, as shown in Table 5.

Discussion

DVT of the lower limbs is associated with increased risk of PE. However, symptoms may vary from patient to patient and are frequently subtle and non-specific. The role of primary care physicians is crucial for the early detection of PE to prevent mortality and morbidity among patients. This study was designed to evaluate the usefulness of age-adjusted D-dimer cut-off levels combined with modified Wells score as a clinical pre-test probability (PTP) assessment for predicting PE in patients 'at risk for DVT.'

In the present study, immobilization (>3 days) was found to be the most common risk factor present in patients with DVT and PE (100%). A study done by Arnaud Perrier *et al.*[1] including 965 patients with suspected PE revealed immobilization as the most common risk factor.

In our study, 31 patients (15.5%) were detected with DVT, while 169 patients (84.5%) had normal lower limb Doppler ultrasonography. PE was detected in 44.4% of patients with DVT and 8.6% of patients without DVT who underwent CTPA. Patients with DVT had an increased frequency of PE on CTPA with a significant *P* value of 0.002. In another study done by Parakh R *et al.* including 1,552 patients with clinically suspected DVT, 744 patients (47.9%) had DVT detected by radionuclide venography, of which 70% had proximal DVT.

Table 5: Sensitivity, specificity, PPV and NPV of age-adjusted D-dimer, modified Wells score and combined approach for predicting PE using CTPA as gold standard

Diagnostic test	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
D-dimer (ng/ml)	93.33% (68.05%–99.83%)	2.13% (0.05%–11.29%)	23.33% (13.38%–36.04%)	50% (1.26%–98.74%)
Wells score for PE	73.33% (44.90%–92.21%)	61.7% (46.38%–75.49%)	37.93% (20.69%–57.74%)	87.88% (71.80%–96.60%)
Wells score and D-dimer for PE	100% (78.20%–100.00%)	2.13% (0.05%–11.29%)	24.59% (14.46%–37.29%)	100% (2.50%–100.00%)

A high-probability lung scan was noted in 39.5% of patients with radionuclide venography-proven DVT, while in patients without radionuclide venography-proven DVT, 4.5% had high-probability lung scan[2].

In the present study, PE was detected in 12.1% of patients with 'pulmonary embolism unlikely' and 37.9% of patients with 'pulmonary embolism likely' who underwent CTPA. In a similar study done by P Page *et al.*[3] including 3306 patients, PE was detected in 12.1% of patients with 'pulmonary embolism unlikely' and 37.1% of patients with 'pulmonary embolism likely.' Also, significant association was observed between patients categorized as 'pulmonary embolism likely' and frequent detection of pulmonary embolism on CTPA (*P* value 0.035). A significant positive correlation was also observed between modified Wells score for PE and age-adjusted D-dimer values (correlation coefficient 0.216, *P* value 0.0021).

In our study, PE was detected in 24.2% of the study population who underwent CTPA. This is comparable to the study conducted by Parakh R *et al.*[2] in which 21.2% of patients with suspected lower limb DVT had high-probability lung scan for PE. In another study done by Arnaud Perrier *et al.*[1] including patients with suspected PE, 23% of patients had PE on CT scan.

In the present study, the sensitivity, specificity, PPV and NPV of age-adjusted D-dimer cut-off values for the diagnosis of PE were observed to be 93.33%, 2.13%, 23.33%, and 50%, respectively, while those of modified Wells score for PE were 73.33%, 61.7%, 37.93%, and 87.88%, respectively. In a study conducted by Adam L. Sharp *et al.*,[4] the sensitivity and specificity of age-adjusted D-dimer cut-off values for the diagnosis of PE were found to be 93% and 64%, respectively. In a systematic literature review done by Anne R Bass *et al.*,[5] the sensitivity of the modified Wells score in hospitalized patients was found to be 72.1% and the specificity was found to be 62.2%. In another study done by Zhao C *et al.*,[6] the sensitivity, specificity, PPV, and NPV for the diagnosis of PE of the combination of 2 level Wells score with age-adjusted D-dimer cut-off values were observed to be 97.4%, 62.3%, 35.5%, and 99.1%, respectively. This is similar to our study, in which the combined approach had a sensitivity of 100%, a specificity of 2.13%, a PPV of 24.59%, and an NPV of 100% for the diagnosis of PE.

To conclude, PE is one of the biggest masqueraders in medicine and a preventable cause of death; therefore, early diagnosis is of paramount importance while simultaneously avoiding the risks of unnecessary testing. The combined strategy using modified Wells score and age-adjusted D-dimer cut-off value has 100% sensitivity and NPV and can be used to safely exclude PE in in-patients. This study provides a platform to design a larger study to evaluate the usefulness of various non-invasive and cost-effective diagnostic tests for PE.

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Conflicts of interest

There are no conflicts of interest.

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