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Research Article

Usefulness of D-Dimer and Pre-Test Clinical Probability Scores for the Diagnosis of Pulmonary Embolism in Critically-Ill Patients -

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ABSTRACT

Background: We aimed to investigate the usefulness of Wells score, revised Geneva score and age-adjusted D-dimer in diagnosing Pulmonary Embolism (PE) in critically-ill patients.

Methods: Retrospective study including all adult patients who underwent Computed Tomography Pulmonary Angiography (CTPA) for suspected (PE). Wells score and revised-Geneva score were calculated and D-dimer levels were recorded. D-Dimer Age Index (DDAI) was calculated as D-dimer/(D-dimer threshold according to age). Two groups were compared: Patients with PE (PE(+)) and without PE (PE(-)).

Results: Sixty-seven patients were enrolled. Pulmonary Embolism was confirmed in 27 patients (40.3 %). Wells score was significantly higher in patients with (PE) (6 [5.5-8.5] versus 4.5[3-6]; $p < 0.001$). Wells score> 4 predicted (PE) with a sensitivity of 88.9 % and a specificity of 45 %. Revised-Geneva score was significantly higher in PE(+) group (7[5-13] versus 6[5-8]; $p = 0.034$). D-dimer was checked for 53 patients (79.1 %). Only 4 (6%) patients had negative age-adjusted D-dimer. D-dimer level was significantly higher in PE(+) group (7.34[4.3-17.6] versus 3.9[1.3-6.2] mcg/ml; $p = 0.007$). Optimum cut-off of D-dimer was 4.4 mcg/ml (Youden index=0.45). DDAI was significantly higher in PE (+) group (13.5[8.6-27.1] versus 6.3[2.3-10.6]; $p = 0.006$). Optimum cut-off for DDAI was 8.4 (Youden index=0.45). Combining Wells score and age-adjusted D-dimer would have avoided (CTPA) in one patient only (6 %).

Conclusion: Wells score and revised Geneva score can be used to predict (PE) in critically-ill patients. D-dimer age index was significantly higher in patients with (PE). Combining clinical pre-test rules to age adjusted D-dimer would not have decreased the number of (CTPA).

Keywords: Pulmonary embolism; Revised geneva score; Revised wells score; D-dimer; Computed tomography pulmonary angiogram

INTRODUCTION

Pulmonary Embolism (PE) represents the third cause of cardiovascular disease-related mortality in the United States after myocardial infarction and stroke [1]. Its incidence varies between 34 and 112.3 per 100 000 and a significant increment has been reported during the last decade [2-5]. Several reasons can explain this trend including more availability of Computed Tomography Pulmonary Angiography (CTPA), better understanding of the physiopathology of the disease, establishment of pulmonary embolism rapid response team and adherence to well codified algorithms [2-9]. Critically-ill patients have increased risk of thrombo-embolic events. In fact, they are gathering numerous risk factors such as immobilization due to sedation and mechanical ventilation, indwelling venous vascular catheters, inflammatory conditions inducing endothelial injury, frequent contraindication for pharmacological prophylaxis… [7,10-12]. On the other hand, rising the suspicion of (PE) in this group of patients is always challenging, especially in sedated patient as the usual signs and symptoms suggesting the disease such as chest pain, tachypnea and cough are usually lacking [12-14]. Thereafter, pulmonary embolism is often suspected because of unexplained hypoxia or hemodynamic instability associated with deep vein thrombosis and/or right ventricular strain on echocardiogram [15]. While clinical pre-test rules such as Wells score and revised Geneva score have been largely validated in patients admitted to the emergency department or primary care facilities, several studies reported that these scores are not useful in critically-ill patients [13,15-17]. Moreover, most of the diagnostic algorithms for PE include D-dimer dosage in case of low probability to exclude pulmonary embolism and avoid unnecessary (CTPA) [15,18,19]. Recent studies suggest that the yield of D-dimer can be improved by adjusting the threshold of significance according to age [20,21]. Though the usefulness of D-dimer in critically-ill patients has been always deemed poorly contributive because of the multiple conditions interfering with the coagulation / fibrinolysis process, the value of age-adjusted D-dimer was not investigated yet. Therefore, we conducted this study to determine the usefulness of pre-test clinical rules (Wells score and revised Geneva score) as well age-adjusted D-dimer to predict pulmonary embolism in critically-ill patients.

METHODS

Settings

We conducted a retrospective observational study in a 26-beded medical-surgical intensive care unit. The study was approved by King Hamad University Hospital review board. All patients admitted between 0.1.01.2016 and 28.02.2020 were screened for inclusion. Informed consent was waived.

Patients

All adult patients (age > 18 years) admitted to our critical care department and underwent computed tomography pulmonary angiogram were included. We excluded patients who had an established diagnosis of PE before ICU admission as well as moribund patients. Patients for whom the diagnosis could not be confirmed by (CTPA) were also excluded. In case of multiple imaging tests, only the findings of the first (CTPA) were considered. The decision of performing a (CTPA) was left to the attending physician based on clinical assessment and baseline investigations. All imaging tests were reviewed simultaneously by two board certified radiologists. The diagnosis of pulmonary embolism was confirmed if the (CTPA) shows a new subsegmental or more proximal filling defect [22].

Data collection

The electronic files of all included patients were screened. The following data were collected: Demographic data (age, gender, comorbidities, cause of admission in the Intensive Care Unit (ICU), clinical findings and laboratory test results on the day of suspicion of pulmonary embolism. Symptoms rising the suspicion of pulmonary embolism were the following: 1. Tachycardia: heart rate > 90 beats per minutes for at least one hour 2. Hypoxemia: $PaO_2 < 60$ mmHg on room air or $PaO_2/FiO_2 < 250$ mmHg in patients on mechanical ventilation 3. Hemodynamic instability: Systolic Blood Pressure (SBP) < 90 mmHg or a decreased by more than 40 mmHg in hypertensive patients. Patients requiring vasopressor support or presenting with cardiac arrest were also considered as hemodynamically instable 4. Unexplained fever > 38 degrees Celsius. 5. Chest pain (pleuritic or non-pleuritic) 6. Unexplained difficult weaning from mechanical ventilation in the presence of right ventricular dysfunction.

Chest X-ray, electrocardiogram and lower limb Compression Sonography (CUS) findings were also recorded. The chest X-ray was interpreted by two board certified intensivists. Echocardiogram was performed for all patients with hemodynamic instability and whenever feasible for the other patients. Right ventricle dilation was defined as basal right ventricle / left ventricle ratio > 1 [15]. Systolic pulmonary artery pressure and left ventricular ejection fraction were also recorded.

The site of the thrombus seen on (CTPA) was recorded (saddle, mainstem, lobar, segmental or subsegmental) in all patients diagnosed with (PE) [23]. For patients without pulmonary embolism, the alternative diagnosis suggested by the imaging tests were recorded (lung consolidation, atelectasis, pleural effusion, lung mass or metastasis).

According to the hemodynamic status, the echocardiography findings and Pulmonary Embolism Severity Index (PESI) assessment, patients with pulmonary embolism were classified as high, intermediate or low risk categories [15,24].

Therapeutic interventions were recorded. Patients with high risk (PE) received thrombolysis unless contraindicated. All patients with pulmonary embolism received therapeutic anticoagulation unless contraindicated. Symptomatic treatment included fluid resuscitation, vasopressors, oxygen supply and mechanical ventilation whenever needed.

D-dimer assessment

D-dimer results were collected in all included patients whenever available. To assess whether adjusting the D-dimer level according to age would have better sensitivity and specificity for predicting pulmonary embolism in critically-ill patients with suspected (PE), a D-Dimer Age Index (DDAI) parameter was calculated according to the following formula:

DDAI = D-dimer / (D-dimer threshold according to age)

D-dimer threshold according to age was calculated as (age x 10) microgram/ml for patients with age ≥ 50 years as previously reported [20]. For patients with age below 50, the threshold was set at 0.5 microgram/ml [20].

Pre-test probability scores

The usefulness of two scores was tested to predict (PE) in critically-ill patients: Wells score [16,25] and revised Geneva score [26]. Wells score varies from 0 to 12.5 points. Pulmonary embolism was considered as unlikely if ≤ 4 and likely if > 4 [16]. Revised Geneva score varies between 0 and 22 points. Accordingly, patients were considered to have low (0 to 3 points), moderate (4 to 10 points) or high (≥ 11 points) probability of pulmonary embolism [26,27].

Outcome

For all included patient, ICU survival or death was recorded. The duration of mechanical ventilation and the ICU length of stay was also collected.

Statistical analysis

The characteristics of all included patients were described. Qualitative variables were expressed as percentages and quantitative variables were expressed as mean ± Standard-Deviation (SD) or median [Quartiles] as appropriate. Two groups were identified according to the (CTPA) findings: Patients with pulmonary embolism (PE (+) group) and those without pulmonary embolism (PE (-) group). Qualitative variables were compared with Chi2 test or Exact Fisher test as appropriate. The normal distribution of quantitative variables was first checked by Shapiro-Wilk test and then both groups were compared by using t-test or Mann-Whitney test as appropriate.

Receiver Operating Characteristic (ROC) curve were constructed to compare D-dimer and (DDAI). The optimum cut-off was then established based on Youden index. Area Under Curves (AUC) were calculated and compared by using De Longue test. Similarly, ROC curves were constructed for Wells score and revised Geneva score. Specificity and sensitivity of established threshold for each score were tested. All factors identified by univariate analysis as predictive of pulmonary embolism were integrated in a binary stepwise logistic regression to identify independent factors predicting (PE). Odds-Ratios (ORs) were calculated with the corresponding 95 % confidence interval (CI95%.) A p value < 0.05 was considered as statistically significant.

RESULTS

Baseline characteristics

During the study period, 67 patients underwent (CTPA) for suspected (PE) and were subsequently included. Mean age was 55.5 ± 18.3 years. Sex-ratio (M/F) was 0.97. Admission in the intensive care unit was required because of acute respiratory failure for 34 patients (50.7 %), cardiac arrest for 12 patients (17.9 %), septic shock for 7 patients (10.5 %) and other medical reasons for 14 patients (20.9 %). Common comorbidities were hypertension (28 patients (41.8 %)), diabetes mellitus (24 patients (35.8 %)), chronic kidney disease (6 patients (9 %)) and ischemic heart disease (5 patients (7.5 %)). Twenty-eight patients (41 %) had malignancy and 14 patients (20.9 %) were receiving chemotherapy. Mean SAPS(II) calculated following the first 24 hours of ICU admission was 45.4 ± 25. The diagnosis of (PE) was confirmed by (CTPA) in 27 patients (40.3 %).

Predictive factors of Pulmonary embolism

The diagnosis of pulmonary embolism was suspected within 2 [1-5] days of ICU admission. Main clinical symptoms rising the diagnosis were hypoxemia (38.8 %), hemodynamic instability (38.8 %), chest pain (19.4 %), unexplained failed weaning off mechanical ventilation (58.2 %) and hemoptysis (3 %). Baseline characteristics were similar between PE (+) and PE (-) groups (Table 1). Similarly, clinical findings when the diagnosis of (PE) was suspected were comparable between both groups (Table 2). Laboratory investigations did not reveal any statistically significant difference between both groups except for natremia which was significantly higher in PE (+) group (Table 3).

ECG was performed to all our patients. Sinus tachycardia was the most common findings (41 patients (61.2 %)). Right bundle brunch block was reported in 7 patients (10.4 %) and $S_1Q_3T_3$ pattern was identified in 2 patients only (3 %).

Chest X-ray was done prior to (CTPA) in all our patients. It was reported as normal in 17 cases (25.4 %). The incidence of normal chest X-ray was significantly higher in the PE (+) group than in the PE (-) group (40.7 % versus 15 %; *p* = 0.018). Lower limb compression sonography was done for 38 (56.7 %) of our patients and was positive in 12 cases (17.9 %). The deep vein thrombosis (DVT) was unilateral in 11 cases (16.4 %). The incidence of (DVT) was similar between PE (+) and PE (-) groups (8 patients (34.8 %) versus 4 patients (26.7 %) respectively; *p* = 0.728). Echocardiogram was performed in 61 patients (91 %). Median [IQR] Left Ventricular Ejection Fraction (LVEF) was 60 [55-60] %. Median [IQR] Systolic Pulmonary Artery Pressure (SPAP) was 26 [18-36] mmHg. SPAP was significantly higher in the PE (+) group (28 [24-49] versus 26 [17-33]; *p* = 0.042). The echocardiogram findings are summarized in (Table 4).

Twenty patients had (CTPA) upon admission to the (ICU) and therefore they were not on any deep vein thrombosis prophylaxis.

Table 1. Baseline characteristics of included patients.

Parameters	PE (+) group (N = 27)	PE (-) group (N = 40)	P
Age [IQR], years	55 [46-68]	57 [46-68]	0.428
Gender (M/F)	12/15	21/19	0.518
SAPS(II) [IQR]	39 [24-41]	44 [26-69]	0.300
Diabetes mellitus (n, %)	10 (37)	14 (35)	0.865
Hypertension (n, %)	12 (44.4)	16 (40)	0.718
Malignancy (n, %)	11 (40.7)	17 (42.5)	0.886
Surgery within 1 month (n, %)	9 (33.3)	8 (20)	0.219

Footnotes: SAPS(II) Simplified Acute Physiology Score (II); IQR: Interquartile

Table 2: Clinical findings on pulmonary embolism suspicion.

Parameters		Total (N = 67)	PE (+) group (N = 27)	PE (-) group (N = 40)	p
Symptoms	Pain (n/%)	13 (19.4)	6 (22.2)	7 (17.5)	0.632
	Hypoxemia (n/%)	54 (80.6)	23 (92)	31 (93.9)	0.582
	Shock (n/%)	35 (52.2)	15 (55.6)	20 (51.3)	0.732
	Hemoptysis (n/%)	2 (3)	2 (5)	0 (0)	0.353
	Failed weaning (n/%)	39 (58.2)	15 (55.6)	24 (60)	0.718
SBP [IQR], mmHg		109 [80-124]	109 [83-124]	108 [79-127]	0.879
DBP [IQR], mmHg		60 [47-70]	60 [50-70]	59 [46-73]	0.999
HR [IQR], beat per minute		110 [90-130]	114 [99-130]	110 [89-129]	0.462
RR [IQR] breath per minute		26 [20-32]	26 [22-33]	27 [20-32]	0.688
SpO_2 [IQR], %		95 [92-99]	95 [89-98]	96 [92-100]	0.435
GCS [IQR]		15 [8-15]	15 [10-15]	14 [7-15]	0.119
Temperature [IQR], degrees Celsius		37 [36.7-37.3]	37 [36.8-37.6]	37 [36.6-37.2]	0.292

Footnotes: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; RR: Respiratory Rate; GCS: Glasgow Coma Scale; SpO_2: Pulse Saturation in Oxygen; IQR: Interquartile

Table 3: Comparison of laboratory investigations between PE (+) group and PE (-) group.

Parameters	PE (+) group (N = 27)	PE (-) group (N = 40)	P
Leucocytes [IQR] (/mm^3)	13000 [9510-15300]	10930 [6362-14415]	0.190
Hemoglobin [IQR] (g/dl)	10.1 [8.4-11.8]	11.3 [9.2-13.7]	0.106
Platelets count [IQR] (G/L)	190 [164-366]	221 [165-340]	0.873
Sodium [IQR] (mmol/l)	**140 [137-145]**	**137 [134-141]**	**0.04**
Potassium [IQR] (mmol/l)	4.1 [3.8-4.5]	3.9 [3.5-4.6]	0.612
Urea [IQR] (mmol/l)	7.3 [4.6-14]	7.1 [5-11.1]	0.853
Creatinine [IQR] (micromole/l)	70[56-153]	92 [63-133.5]	0.378
CRP [IQR] (mg/l)	73.7 [48.3-130.5]	63.5 [26-138]	0.721
PaO_2/FiO_2 ratio [IQR] (mmHg)	170 [102-248]	161 [121 – 220]	0.941
Lactate [IQR] (mmol/l0	2.8 [1.5-6]	2.3 [1.2-4]	0.202
Troponin [IQR]	0.13 [0.02-0.79]	0.04 [0.01-0.59]	0.110
BNP [IQR]	134 [49-274]	58 [27-129]	0.144

Footnote: CRP: C-Reactive Protein; FiO2: Inspiratory Fraction Of Oxygen; BNP: B-Type Natriuretic Peptide

Table 4: Echocardiogram findings in PE (+) and PE (-) groups.

Parameters	PE (+) group (N = 26)	PE (-) group (N = 35)	p
LVEF [IQR], %	60 [55-60]	55 [55-60]	0.240
SPAP [IQR], mmHg	28 [24-49]	26 [17-33]	**0.042**
Core pulmonale (n/%)	4 (15.4)	3 (8.6)	0.409

Pharmacological prophylaxis with unfractionated heparin or low molecular weight heparin was comparable between PE (+) and PE (-) groups (respectively 15 (55.6 %) patients and 18 (45 %) patients; $p = 0.397$). The remaining patients had mechanical prophylaxis with compression devices with no difference between the two groups (respectively 5 (18.5 %) patients and 9 (22.5 %) patients; $p = 0.694$).

Characteristics of patients with pulmonary embolism

The thrombus was lobar in 12 cases (44.4 %), segmental in 11 cases (40.7 %) and sub-segmental in 4 cases (14.8 %). Pulmonary embolism was bilateral in 16 patients (59.3 %). Fifteen (55.6 %) patients had acute circulatory failure requiring norepinephrine infusion. However, massive PE was considered in only 4 patients who subsequently received thrombolysis. No sub-massive PE was identified. Eighteen patients (66.7 %) were on mechanical ventilation when the diagnosis of pulmonary embolism was suspected. Pulmonary Embolism Severity Index (PESI) was 124 [99 – 153]. Twenty-four patients (88.9 %) received therapeutic anticoagulation with unfractionated heparin. Anticoagulation was contraindicated for 3 patients (11.1 %) who subsequently underwent inferior vena cava filter insertion.

Prediction of pulmonary embolism by pre-test probability scores

Wells score was significantly higher in patients with pulmonary embolism than in patient without pulmonary embolism (6 [5.5-8.5] versus 4.5 [3-6]; $p < 0.001$). Moreover, "*(PE) as the first diagnosis or equally likely*" as one of Wells score criteria was verified in 62 patients (92.5 %). Revised Geneva score was significantly higher in PE (+) group than in PE (-) group (7 [5-13] versus 6 [5-8]; $p = 0.034$). The incidence of pulmonary embolism was significantly higher in patients with likely (PE) according to Wells score and similarly, the incidence of PE was significantly increasing according to the revised Geneva score probability classes (Table 5). However, 3 patients (8.5 %) had (PE) while they were classified as unlikely (PE) according to simplified Wells score and 2 patients (7.4 %) had (PE) while they were considered at low probability according to revised Geneva criteria. Receiver Operating Characteristics (ROC) curves showed no significant statistical difference between the area under curve for revised Geneva and Wells score (respectively 0.65 ± 0.07 CI95% [0.53-0.77] and 0.75 ± 0.06 CI95% [0.63-0.87]; $p = 0.068$) (Figure 1).

The analysis of the ROC curve for Wells score showed that a score > 4 predicts pulmonary embolism with a sensitivity of 88.9 % and a specificity of 45 %.

The analysis of the ROC curve for revised Geneva score showed that a score > 3 predicts pulmonary embolism with a sensitivity of 92.6 % and a specificity of 15 % whereas a score > 10 predicted (PE) with a sensitivity of 37 % and a specificity of 92.5 %.

A statistically significant correlation was found between Wells score and revised Geneva score (r = 0.736; $p < 0.001$) (Figure 2).

Prediction of pulmonary embolism by D-dimer dosage

D-dimer dosage was available in the records of 53 patients (79.1 %). Only 4 (6%) patients had negative D-dimer based on the age predicted threshold. One of them (25 %) had pulmonary embolism confirmed by (CTPA). D-dimer serum level was significantly higher in patients with pulmonary embolism (7.34 [4.3-17.6] versus 3.9 [1.3-6.2] mcg/ml; $p = 0.007$). Similarly, the D-dimer age index was significantly higher in the PE (+) group (13.5 [8.6-27.1] versus 6.3 [2.3-10.6]; $p = 0.006$). ROC curve analysis showed that the area under curve was similar between D-dimer and DDAI (respectively 0.70 ± 0.07 95% CI [0.57-0.82] and 0.71 ± 0.07 95%CI [0.57 – 0.83]; $p = 0.941$) (Figure 3).

Optimum cut-off of D-dimer based on maximal Youden index was 4.4 mcg/ml (Youden index = 0.45). A D-dimer level > 4.4 mcg/ml predicts pulmonary embolism with a sensitivity of 77.3 % and a specificity of 67.7 %. Optimum cut-off for D-dimer age index was 8.4 (Youden index = 0.45). An index > 8.4 predicts pulmonary embolism with a sensitivity of 77.4 % and a specificity of 77.2 %.

Combining D-dimer and clinical prediction rules to predict pulmonary embolism

Among the 53 patients with available D-Dimer, 37 (69.8 %) patients were considered to likely have (PE) according to Wells score. The frequency of patients with positive D-dimer according to age was comparable between patients with likely and those with unlikely (PE) (respectively 34 patients (91.9 %) and 15 patients (93.8%); $p = 0.814$). Only one patient (1.9 %) was unlikely to have PE with negative D-dimer according to age and therefore (CTPA) could have been avoided. The D-dimer levels were comparable between patients with likely and unlikely (PE) diagnosis (respectively 4.9 [3-10.5] versus 3.9 [1.5-11.3]; $p = 0.462$). Similarly, (DDAI) was similar between the two groups (respectively 9.7 [5.6-15.4] versus 7.8 [2.6-15.4]; $p = 0.427$).

According to revised Geneva score, 8 (15.1 %) patients were at low risk, 33 (62.3 %) patients were at moderate risk and 12 (22.6 %) patients were at high risk of PE. Among the 4 patients with negative D-dimer according to age, 2 patients (6.1 %) were at moderate risk and 2 other patients (16.7 %) were at high risk of pulmonary embolism according to revised Geneva score. All patients at low risk of PE had positive D-dimer and therefore, no (CTPA) could have been avoided.

Independent factors predicting pulmonary embolism

Multivariate analysis showed that independent factors predicting pulmonary embolism were normal chest X-ray, revised Geneva score, systolic pulmonary artery pressure and D-Dimer age index (Table 6).

Table 5: Pre-test probability scores in patients with and without pulmonary embolism.

Parameters		PE (+) group (N = 27)	PE (-) group (N = 40)	p
Revised Geneva score	Low (n/%)	2 (7.4)	7 (17.5)	**0.004**
	Moderate (n/%)	14 (51.9)	30 (75)	
	High (n/%)	11 (40.7)	3 (7.5)	
Wells score	Likely (n/%)	24 (88.9)	22 (55)	**0.003**
	Unlikely (n/%)	3 (8.5)	18 (45)	
Revised Geneva score [IQR]		7 [5-13]	6 [5-8]	**0.034**
Wells score [IQR]		6 [5.5-8.5]	4.5 [3-6]	**< 0.001**

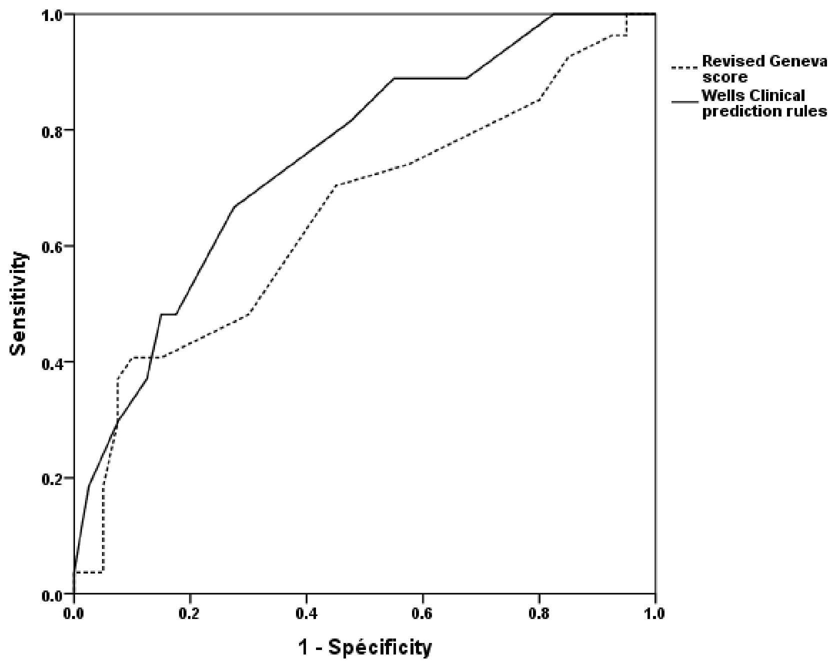

Figure 1: Receiver Operating Characteristics (ROC) curve assessing the yield of wells and revised geneva scores in predicting pulmonary embolism in critically-ill patients.

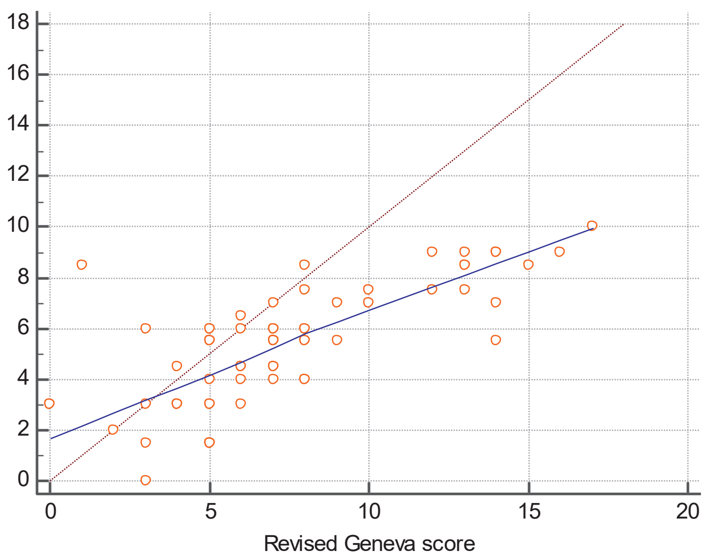

Figure 2: Correlation between Wells score and Revised Geneva score.

Outcome

Thirty-five patients died in the ICU (52.2 %). The ICU mortality was similar between PE (+) and PE (-) groups (respectively 51.9 and 52.5 %; p = 0.958). The median ICU Length of Stay (LOS) was 12 [4-25] days. The LOS was comparable between PE (+) group and PE (-) group (15 [5-28] versus 9 [4-24] days respectively; p = 0.315). The median duration of mechanical ventilation was 8 [2-22] days. This duration was comparable between PE (+) and PE (-) groups (13 [2-25] versus 6 [2-21] days respectively; p = 0.522).

DISCUSSION

Our study showed a significant correlation between Wells and revised Geneva scores in critically-ill patients with suspected pulmonary embolism. Both were significantly higher in patients with than those without (PE). However, 8.5 % had (PE) while considered unlikely according to Wells score and 7.4 % had (PE) while they were at low probability according to revised Geneva score. These findings are concordant with the initial studies that have assessed the usefulness of a dichotomized model of Wells score [25,28]. In fact, *Wells et al.* [25] reported in a validation study including 1260 patients that the

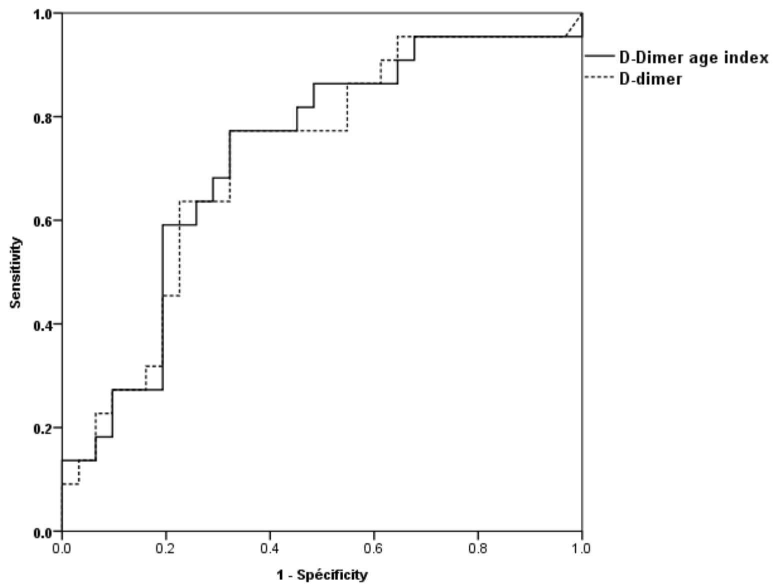

Figure 3: Receiver Operating Characteristics (ROC) curve assessing the yield of D-dimer and D-dimer age index in predicting pulmonary embolism in critically-ill patients..

Table 6. Multivariate analysis of predictive factors of pulmonary embolism.

Factors	OR	P	CI95%	
			Min	Max
Revised Geneva score	**1.5**	**0.007**	**1.1**	**2.1**
Wells score	0.8	0.729	0.3	2.6
SPAP	**1.1**	**0.018**	**1.1**	**1.2**
D-dimer	0.8	0.268	0.6	1.2
DDAI	**1.1**	**0.022**	**1.1**	**1.2**
Normal chest X-ray	**10.5**	**0.028**	**1.3**	**84.8**

incidence of (PE) in the ''PE unlikely group'' was 7.8 % while it was 40.7 % if PE was deemed likely. Similarly, *Wolf et al* [28] reported that the incidence of PE was only 3 % if the simplified Wells score was ≤ 4 while it was 28 % in the other cases. Our findings also corroborate previous results assessing the prevalence of pulmonary embolism according the revised Geneva score classes. In fact, *Le Gal et al* [27] reported that (PE) was seen in 8 %, 28 % and 74 % in patients with low, intermediate and high probability classes respectively. However, available data in the literature suggest that these scores are not reliable in critically-ill patients [13,29]. In a retrospective study including 138 patients, *Girardi et al* [13] reported that 26.8 % of the patients considered unlikely for PE had proven filling defect in (CTPA) and 30.6 % of patients with low probability according to revised Geneva score had confirmed (PE). These findings contrasting our results can be explained by several factors. First, only 21 of our patients (31.3 %) were considered unlikely to have (PE) according to Wells score while this category represented 71 % of *Girardi's* series. The analysis of the different Wells score components in *Girardi et al* study revealed that the criteria '' *Pulmonary embolism as the first diagnosis or equally likely*'' was considered in only 16.7 % of all cases which may reflect that the score might be under estimated in the unlikely (PE) group. Second, 28 (41.8 %) of our patients had active malignancies which has led to increased number of patients with likely (PE) according to Wells score and moderate/high probability risk according to revised Geneva score.

D-dimer is commonly requested to investigate thromboembolic events, especially in patients presenting to the emergency department with suspected diagnosis of deep vein thrombosis or pulmonary embolism [30,31]. It is a cross-linked fibrin degradation product that reflects a local or a widespread activation of the coagulation cascade followed by an activation of the fibrinolysis [32]. Several conditions such as pregnancy, old age, malignancy and liver failure, are known to be associated with increased D-dimer [32-35]. In the ICU settings, other common conditions including ischemic stroke, acute bleeding, infection, disseminated intravascular coagulation, renal failure… are also associated with increased D-dimer with no associated (VTE) [34,36,37]. Recent data suggest that age adjustment of the D-dimer threshold increased the percentage of patients for whom (PE) can be safely excluded from 6.4 to 29.7 % [20]. However, to the best of our knowledge, such strategy has not been tested yet in critically-ill patients. Our results show that both D-dimer and (DDAI) were significantly higher in PE (+) group than in PE (-) group. However, only DDAI was identified as independent factor predicting pulmonary embolism in multivariate analysis. In fact, this index could have more benefit than the usual age-adjustment as it allows adjusting the D-dimer threshold even for patients younger than 50 years. While applying the strategy of assessing age-adjusted D-dimer in patients with low pre-test probability would lead to decreased number of unnecessary (CTPA) in critically-ill patients needs to be investigated by further studies. In fact, only 4 of our patients (6%) had D-dimer level below the age-adjusted threshold. Moreover, following such diagnostic strategy would have avoided one (CTPA) (1.9 %) if Wells score was applied and none if revised Geneva score was applied.

Although our study is one of the rare studies assessing the usefulness of pre-clinical rules along with age-adjusted D-dimer in critically-ill patients, several limitations need to be highlighted. First, our study has a limited sample size as only 67 patients were included. This could be explained by the low incidence of pulmonary embolism in intensive care units. In fact, available data in the literature suggest that the incidence ranges between 0.5 and 1.9 % only [12,38]. Second, we included only patients with PE confirmed by (CTPA). Other diagnostic modalities were not included given the retrospective methodology and the lack of registry for pulmonary embolism. Finally, 41.8 % of our patients had malignancy. This group of patient is at high risk of thromboembolic events with frequently significant increase of D-dimer level even in the absence of any thromboembolic event [35]. Therefore, further studies are warranted to investigate the usefulness of D-dimer and clinical pre-test rules in critically-ill patients with malignancies.

CONCLUSION

Our study showed that Wells score and revised Geneva score can be used to predict pulmonary embolism if critically-ill patients. D-dimer and D-dimer age index are both significantly higher in patients with (PE). Combining clinical pre-test rules to age adjusted D-dimer would not have decreased the number of referrals for (CTPA).

AUTHOR CONTRIBUTION

All the authors equally contributed in the design, data collection, data analysis and drafting the manuscript. The submitted manuscript was approved by all authors.

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