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Acute Pulmonary Thromboembolism Retrospective Auditory - The Benefits of Clinical Predictive Tools

Bruno Sousa Dos Santos[1,2,*], Maya Wielert[3], Ieva Krieva[1,2], Kathryn Mullan[4], Sandra Seimane[2], Aleksejs Visnakovs[2], Olegs Sabelnikovs[1,5]

[1]Department of Anesthesiology, Faculty of Medicine, Riga Stradins University, Riga, Latvia
[2]Department of Emergency, Riga East Clinical University Hospital (RECUH), Riga, Latvia
[3]Faculty of Medical, University of Lübeck, Lübeck, Germany
[4]Department of Medicine, Altnagelvin Area Hospital, Derry/Londonderry, Northern Ireland, UK
[5]Department of Anesthesiology, Pauls Stradins Clinical University Hospital, Riga, Latvia

Abstract Several studies in recent years have identified the importance of developing a more standardized diagnostic approach to patients suspected of acute pulmonary embolism (PE). Still many doctors prefer a theoretical approach to the diagnosis of PE without the use of pre-test clinical predictive tools. Through the process of audit, we collected data available from the files of patients who underwent computer tomography pulmonary angiography (CTPA) and tested this data within the pre-test probability tool "Wells criteria score". Additionally, other important variables that were previously validated as well as those with possible diagnostic value were also analysed, as these may prove to be useful indicators to further develop the pathway towards a more efficient diagnosis of PE. The results within this study were compared to similar studies. With the aim of understanding the possible benefits of a more purposely structured approach, this study ultimately intends to support the development of PE protocols towards a more standardized approach to its diagnosis. Subsequently, it seeks to promote improvement in patient safety and accuracy in diagnosis as well as clinical decision-making. The main results in this study show a clear correlation between Wells criteria score risk levels with an increased predictive likelihood of a positive PE. Dyspnea and chest pain proved to be the most frequent clinical findings outside wells criteria. The age-adjusted D-dimer in this study data demonstrated to be a candidate for further evaluation with great potential for clinical application. Electrocardiogram S1Q3T3 findings displayed a specificity of 92,86% and positive predictive value 69,70%. The conclusion of this study reveals that a standardized approach that includes Wells criteria together with an age-adjusted D-dimer may avoid unnecessary steps and examinations in diagnosis of PE, namely that of D-dimer tests and CTPA.

Keywords Pulmonary Embolism, Thromboembolism, DVT, Wells, D-dimer, Electrocardiogram, Angiography

1. Introduction

Epidemiology: Deep vein thrombosis/pulmonary embolism (DVT/PE) is the third most common disease among cardiovascular diseases, and its overall incidence ranges from 1/1000 to 2/1000 per year [1], [2]. In Europe, there is an estimated 684 000 DVT cases and 434 723 PE cases per annum with the death toll from venous thromboembolism reaching 543 454 per annum. The same study estimates a death toll of 370 012 in the six European countries which were involved in the study. Of these cases, only 7% were diagnosed and possibly received appropriate treatment. The remaining 93.0% were only confirmed postmortem. In effect, they either went undiagnosed and therefore untreated (59.0%) or suffered sudden fatal PE (34.0%) [3], [4].

PE pathogenesis: PE occurs due to the formation of a thrombus which subsequently travels to the pulmonary arteries. Virchow's triad states the main risk factors of thrombus formation, it consists of: (1) venous stasis or blood flow alterations, (2) vascular endothelial injury and (3) inherited or acquired hypercoagulability state [5], [6].

Clinical presentations in PE: PE can manifest with a wide variety of clinical presentations. A study by P. D. Stein et al. showed the following frequencies of the most common clinical presentations: dyspnea at rest or with exertion was present in 73.0% of cases, pleuritic pain in 66.0%, calf or thigh pain and/or swelling in 44.0%, cough in 37.0%, orthopnea in 28.0%, wheeze in 21.0% and hemoptysis was present in 13.0% of cases [7]. Conversely, some patients exhibit severe clinical presentations such as

sudden death or shock as well as atypical symptoms, while others remain entirely asymptomatic [7]–[10].

1) *Diagnostic approach to PE:* Approach to PE is mostly done by theoretical "unstructured" approach and confirmed by CTPA after a positive D-dimer test result is carried out in the emergency department (ED) of Riga East Clinical University Hospital (RECUH). A study done by C. R. Weiss et al. reports that a great percentage of doctors at other centers also prefer an "unstructured" approach for pre-test assessment (72.5%). Only 22.9% reported to use validated predictive tools and/or guidelines. However, 93.0% were aware of the updated guidelines and 44.2% reported to use them in practice on a daily basis [11].
2) The challenges of implementing algorithms for the diagnosis of PE have always been present within everyday clinical practice. The use of combined algorithms has proved beneficial. Well validated algorithms often contain: (1) a clinical pre-test probability tool (for instance Wells criteria score), (2) a D-dimer test, and (3) a CTPA [2], [12], [13].

Clinical predictive tools: The pre-test probability tools for the diagnosis of PE have been compared in different studies. Wells criteria score and Geneva score are among the most commonly used tools by physicians and recommended by several guidelines in the approach to the diagnosis of PE [2], [13]. From these pre-test probability tools, Wells criteria is the most frequently used [2]. Based on this information and the caveat that today's doctors are currently more familiar with the Wells criteria, we have selected Wells criteria as the pre-test probability tool to be used in our study.

Wells score criteria (Table 1.): The Wells score consists of one subjective criterion "PE is the first diagnosis, or equally likely" and six objective criteria of varying weight. Different amounts of points are assigned to the positive criteria. The sum total of these points allows patients to be categorized into a three-level pre-test probability/risk: low (<2 points); intermedium (2 to 6 points); and high (>6 points). Wells score can also be interpreted as a two-level probability/risk: low (≤4 points) and high (>4 points). In this study, we have used the three-level score.

Table 1. The Wells score criteria with respective points for each criterion.

Wells score criteria	
Criteria	Points
Clinical signs and symptoms of DVT	3
PE is the first diagnosis, or equally likely	3
Heart Rate > 100 beats per min	1.5
Immobilization ≥ 3 days, or surgery in the previous 4 weeks	1.5
Previous, objectively diagnosed PE or DVT	1.5
Hemoptysis	1
Malignancy with treatment within 6 months or palliative	1
DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism.	

D-dimer test: The use of D-dimer levels adjusted to the patients' age in patients ≥50 years old, also known as "age-adjusted D-dimer", has been thought to be beneficial by means of increasing specificity without effecting sensitivity. It demonstrated sensitivities of >97% and higher specificities when compared to the standard cut-off value of a standard D-dimer test (0.50 mcg/mL). The D-dimer test has a tendency to be elevated within this age group (≥50 years old) due to a natural increase in fibrinogen concentration, known and unknown malignancies and age related increase in inflammation, among other reasons [14]. Note that this approach is mainly accepted for hemodynamic stable patients at a low and/or intermediate risk [2], [13], [15], [16].

Electrocardiography (ECG): In the presence of PE diagnosis, T-wave inversion, T-wave flattening, sinus tachycardia and ST-segment changes are among the most common acute changes on ECG when compared to the previous ECGs [17]. Besides these cited findings, ECG changes that indicate Right Ventricular Dysfunction (RVD) including S-wave on lead 1, Q-wave on lead 3 and T wave-inversion on lead 3 (S1Q3T3) are also considered at RECUH when suspicion of PE.

2. Chapters

2.1. Aims of the Research

1) This study intends not only to contribute to a more standardized diagnostic approach to suspected PE in the studied center, but also to put forth results to the greater scientific community with the hope of informing future studies in this clinical field.
2) Study's hypothesis: Reduction of excessive examinations and improvement in patients' safety can be achieved by including a clinical predictive tool (in this study Wells criteria) and/or an age-adjusted D-dimer test.
3) Additionally, we would like to evaluate the benefits of ECG findings, as the ECG is one of the most frequently used diagnostic tests in the emergency settings when a patient presents with chest related symptoms.

2.2. Tasks

1) To analyse the data of patients who underwent CTPA for suspected PE from the 2014 archive at Riga East Clinical University Hospital, Riga, Latvia.
2) To compare the statistical analysis of potential relevant data in the diagnosis of PE with previous published studies and clinical guidelines.
3) To discuss possible benefits of using international recommended clinical predictive scores (Wells criteria in this study) for the pre-test probability of PE, age-adjusted D-dimer and the ECG S1Q3T3 findings.

3. Methods

3.1. Sample

This is a retrospective study done with data collected from patients that underwent CTPA for suspected PE at the emergency department (ED) of RECUH from January to September of 2014.

3.2. Flowchart Data

220 patients out of 249 were included in this study. 29 patients were excluded due to incomplete or unclear data.

3.3. Clinical Presentations

The most common clinical presentations were divided into positive and negative PE groups, the relative frequencies and odds ratio (OR) were calculated, as well as its significance between the groups.

For the clinical presentations of blood pressure and arterial oxygenation saturation % (SpO2) the median/mean values and its significance between positive and negative PE groups were calculated.

3.4. Wells Criteria Score

First, for each patient included in this study the pre-test probability (risk levels) by the Wells criteria risk score was calculated. The Wells criteria score is represented in Table 1 and its risk levels described on page 3.

Second, the patients were stratified according to their CTPA result (positive/negative for PE) and their risk level according to the Wells criteria. For each group, the relative frequency of PE was calculated and the correlation between Wells risk levels and the likelihood ratio of a positive result for PE was analyzed.

3.5. D-dimer / Age-adjusted D-dimer

The standard threshold for the D-dimer test is set at 0.05 mcg/mL regardless of the patient's age. To assess the individual threshold for age-adjusted D-dimer, a calculation was done for each patient of 50 years of age or above. The age-adjusted D-dimer test threshold was calculated using the following formula [16]:

Formula 1

Age-adjusted D-dimer test: (1) Age x 0.010 = mcg/mL

Individual D-dimer results were statically analyzed and stratified by the Wells criteria score risk levels. The correlations between D-dimer values and patients of 50 years of age or older for positive and negative PE groups were evaluated.

3.6. Electrocardiography S1Q3T3 Finding

The predictive value of S1Q3T3 findings on a ECG as an indicator for RVD in PE was estimated for this population.

3.7. Statistical Analysis

Categorical data was compared by the Chi-square test. Continuous data was tested for "skewness" by Shapiro-Wilk test. Mann-Whitney U test was applied to compare means/medians in continuous skewed variables. Spearman's correlation coefficient was used for continuous skewed variables. Statistical significances were calculated at $p \leq 0.05$, and all data analyze was performed using the software SPSS by IBM, version 23.

4. Results, Interpretation, Discussion

4.1. Demographic Data

From a total of 220 CTPA validated cases that are included in this study, 100 (45.5%) cases are male and 120 (54.5%) cases are female. The mean age (Standard deviation [SD]) for the positive PE cases was 77.88 (± 9.11) for females and 64.46 (± 16.83) for males. 71/220 (32.3%) of cases proved to be positive for PE in CTPA while 149/220 (67.7%) of cases were negative.

4.2. Clinical Presentations Results, Its Significance and Discussion

Table 2 shows the relative frequencies of the most common clinical presentations within positive and negative PE groups. The included symptoms and signs (clinical presentations) on this study were identified as the most common triggers for patients seeking medical care and/or the likelihood of being admitted to the ED.

Dyspnea proved to be the most frequent clinical presentation for both groups. In the positive PE group, dyspnea showed a relative frequency of 90.1% compared to the negative PE group (63.7%), odds ratio [CI 95%] = 5.21 [2.23-12.19], with the statistical significance between the groups being $p < 0.001$.

Previous studies showed similar results. Miniati et al. reports sudden onset of dyspnea present in 78% of cases with positive PE (n=281; 74-82 [95% CI]) [18]. Stein et al. describe 79% of cases having dyspnea at rest or exertion [7]. In both studies dyspnea was the most frequent symptom on admission. This corresponds with our results where dyspnea represented the most frequent symptom in cases of positive PE independently of the different dyspnea forms. Thus, it can be denoted that dyspnea plays an important role in identifying patients with possible PE in clinical practice.

Table 2. Clinical presentations relative frequencies association to positive and negative PE by CTPA results.

Clinical presentation	Positive PE by CTPA	Negative PE by CTPA	*OR* [95% CI]	*p* Value (X^2)
Dyspnea	64/71 (90.1)	93/146 (63.7)	5.21 [2.23-12.19]	< .001
Tachypnea (≥20 times per min)	34/67 (50.7)	50/137 (36.5)	1.79 [0.99-3.24]	.052
Non-specific chest pain	32/70 (45.7)	45/146 (30.8)	1.89 [1.05-3.40]	.032
Syncope	13/71 (18.3)	40/149 (26.8)	0.61 [0.30-1.23]	.116
Cough	12/71 (16.9)	20/148 (13.5)	1.30 [0.60-2.84]	.506
Anxiety	37/71 (52.1)	98/147 (66.7)	0.54 [0.31-0.97]	.038
Breathing related chest pain	13/71 (18.3)	11/149 (7.4)	2.81 [1.19-6.64]	* .020
Body Temperature >37.5 °C	5/19 (26.3)	14/19 (73.7)	0.95 [0.30-2.97]	* .000
ECG atrial fibrillation	21/71 (30.0)	48/144 (33.3)	0.86 [0.46-1.59]	.625
Hypotension	15/37 (40.5)	22/37 (59.5)	1.57 [0.76-3.26]	.220
Hypertension	26/93 (28.0)	67/93 (72.0)	0.72 [0.40-1.30]	.307
Clinical presentation	Median "Mean ± SD" (Range) *n*=70	Median "Mean ± SD" (Range) *n*=148	U	*P* value
Systolic blood pressure in mmHg	131.19 "129.19 ± 29.72" (40 - 180)	138.00 "137.90 ± 32.03" (67 - 250)	4538.00	.140
Diastolic blood pressure in mmHg	79.50 "74.80 ± 16.34" (20 - 108)	80.00 "76.75 ± 18.41" (25 - 126)	4909.50	.533
Mean average blood pressure in mmHg	96.67 "92.93 ± 19.70" (26.67 – 126.67)	98.50 "97.13 ± 21.51" (41.00 – 162.67)	4672.50	.243
Clinical presentation	Median "Mean ± SD" (Range) *n*=69	Median "Mean ± SD" (Range) *n*=145	U	*p* value
Arterial oxygen saturation in %	94.00 "92.86 ± 4.45" (99 - 78)	95.00 "93.82 ± 5.05" (71 – 100)	4009.00	.018

X^2: Chi-square test; * Fisher's Exact Test (Significance 2-sided); U: Mann Whitney U test;

PE: Acute Pulmonary Thromboembolism; CTPA: Computer Tomography Pulmonary Angiography; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism. SD: Standard deviation; df: degrees of freedom

Table 2 shows the most common clinical presentations for patients with PE and their relative frequencies for positive and negative PE groups, statistical significance, and odds ratio between the groups.4.3. Wells Score Criteria Results, Its Significance and Discussion.

Breathing related chest pain/pleuritic chest pain was present with a significant relative frequency of 18.3% in positive PE cases when compared to the negative PE cases (7.4%), odds ratio [CI 95%] = 2.81 [1.19-6.64], with the statistical significance between the groups being p = 0.020 (Fischer's Exact Test).

Similarly, non-specific chest pain is significantly more frequent in the positive PE cases (45.7%) than in the negative cases of PE (30.8%), odds ratio [CI 95%] = 1.89 [1.05-3.40], with the statistical significance between the groups being p = 0.032.Chest pain is reported by Miniati et al. in 39% of the cases with positive PE (n=140; 34-44 [95% CI]) and by Stein et al. to be present in 47% (pleuritic chest pain) and 17% (non-pleuritic) [7], [18]. When comparing the data to this study, it shows that the symptom of chest pain is of statistical and clinical significance and one of the main symptoms in patients with PE. Moreover, it is imperative to highlight that non-specific chest pain shows the highest frequencies and statistical significance in our study. However, chest pain in its generalised form is among the leading symptoms for patients with positive PE, and it is the second most frequently reported symptom after dyspnea.

Tachypnea (≥ 20 breaths per minute) occurred in 50.7% of patients with PE and in 36.5% of patients with a negative CTPA result, odds ratio [CI 95%] = 1.79 [0.99-3.24], with the statistical significance between the groups being p = 0.052.

Syncope showed a relative frequently of 18.3% for the

positive PE group and of 26.8% for the negative PE group, odds ratio [CI 95%] = 0.61 [0.30-1.23], with the statistical significance between the groups being p = 0.116.

16.9% of patients with PE complained of cough while 26.8% without PE also had cough, odds ratio [CI 95%] = 1.30 [0.60-2.84], with the statistical significance between the groups being p = 0.506.

Anxiety was present with a relative frequently of 52.1% in PE cases and 66.7% for the negative PE group, odds ratio [CI 95%] = 0.54 [0.31-0.97], with the statistical significance between the groups being p = 0.038.

26.3% of positive PE cases and in 73.7% of negative PE cases presented with a body temperature >37 ºC, odds ratio [CI 95%] = 0.95 [0.30-2.97], with the statistical significance between the groups being p = 0.000 (Fischer's Exact Test).

Patients with PE showed hypotension in 40.5% of the cases. In patients without PE hypotension was present with a relative frequency of 59.5%, odds ratio [CI 95%] = 1.57 [0.76-3.26], with the statistical significance between the groups being p = 0.220.

Conversely, hypertension occurred with a relative frequently of 28.0% for the positive cases of PE and of 72.0% for negative PE cases, odds ratio [CI 95%] = 0.72 [0.42-1.30], with the statistical significance between the groups being p = 0.307.

Systolic blood pressure of positive PE cases exhibited a median value of 131.19 mmHg and mean value of 129.19 ± 29.72 [Mean ± SD] with a range of 40.00 – 180.00 mmHg. The negative group for PE showed a median value of 138.00 mmHg and a mean value of 137.90 ± 32.03 [Mean ± SD] with a range of 67.00 – 250.00 mmHg. Mann Whitney U test showed for systolic blood pressure a result of U= 4538.00, with the statistical significance between the groups being p = 0.140.

Diastolic blood pressure showed a median value of 79.50 mmHg and a mean value of 74.80 ± 16.34 [Mean ± SD] for the positive cases of PE with a range of 20.00 – 108.00 mmHg. The negative group for PE showed a median value of 80.00 mmHg and a mean value of 76.75 ± 18.41 [Mean ± SD] with a range of 25.00 – 126.00 mmHg. Mann Whitney U test for systolic blood pressure showed a result of U= 4909.50, with the statistical significance between the groups being p = 0.533.

Altogether, the mean average blood pressure had a median value of 96.67 mmHg and a mean value of 92.93 ± 19.74 [Mean ± SD] with a range of 26.67 – 126.67 mmHg for positive PE cases. The negative group for PE showed a median value of 98.50 mmHg and a mean value of 97.13 ± 21.51 [Mean ± SD] with a range of 41.00 – 162.67 mmHg. Mann Whitney U test showed for systolic blood pressure clinical presentation a result of U= 4672.50, with the statistical significance between the groups being p = 0.243.

The statistical analysis of arterial oxygen saturation % (SpO2) proved a significant difference between the medians of the positive and negative PE groups, with the positive group for PE having a lower median when compared to the negative group. In numbers, the positive group presented a median of 94.00% SpO2 and a mean value of 92.86 ± 4.45 [Mean ± SD] with the range of 99.00 – 78.00 % SpO2. Conversely, the median for the negative PE group was 95.00% SpO2 and the mean value 93.82 ± 5.05 [Mean ± SD] with the range of 71.00 – 100.00 % SpO2. Mann Whitney U test was performed for arterial oxygen saturation with a result of U= 4009.00, showing the following statistical significance between the groups p = 0.018.

Kline et al. reported arterial oxygen saturation (%) and in-hospital complications for patients with PE as follows: for SpO2 < 95% nine out of ten (90%) patients had in-hospital complications and for SpO2 ≥ 95% 31 out of 86 (36.05%) patients had in-hospital complications. Mortality for patients with SpO2 < 95% was 20% within 30 days, compared to only 2% for patients with SpO2 ≥ 95% [19].

Table 3 shows the "Wells criteria relative frequencies and comparison between positive and negative PE for the studied population".

Table 3. Wells criteria calculation relative frequencies results evaluation between positive and negative PE by CTPA.

Wells score criteria	Positive PE by CTPA *n*=71	Negative PE by CTPA *n*=149	*OR [CI 95%]*	*p* value (X^2)
Clinical signs and symptoms of DVT. *n* (%)	36 (50.7)	34 (22.8)	3.48 [1.91-6.35]	< .001
PE is 1st diagnosis or equally likely. *n* (%)	68 (95.8)	122 (81.9)	5.02 [1.47-17.15]	* .005
Heart Rate > 100/min. *n* (%)	31 (43.7)	49 (32.9)	1.59 [0.89-2.83]	.120
Immobilization ≥ 3 days, or surgery in the previous 4 weeks. *n* (%)	17 (23.9)	22 (14.8)	1.82 [0.90-3.69]	.096
Previous, objectively diagnosed PE or DVT. *n* (%)	22 (31.0)	15 (10.1)	4.01[1.93-8.35]	< .001
Hemoptysis. *n* (%)	4 (5.6)	5 (3.4)	1.72 [0.45-6.61]	* .474
Malignancy with treatment within 6 months or palliative. *n* (%)	10 (14.1)	8 (5.4)	2.89 [1.09-7.68]	.027

* Fisher's Exact Test (Exact Significance 2-sided);

PE: Acute Pulmonary Thromboembolism; CTPA: Computer Tomography Pulmonary Angiography; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism.

Table 3 Shows the Wells score criteria "clinical presentations", their relative frequencies for positive and negative PE groups, statistical significance, and odds ratio between the groups.

For the criterion "Clinical signs and symptoms of DVT" the positive cases of PE were significantly more frequent (50.7%) than the negative cases of PE (22.8%), odds ratio [CI 95%] = 3.48 [1.91-6.35], with the statistical significance between the groups being $p < 0.001$.

For the criterion "Previous, objectively diagnosed PE or DVT" the positive cases of PE were significantly more frequent (31.0%) than the negative cases of PE (10.1%), odds ratio [CI 95%] = 4.01[1.93-8.35], with the statistical significance between the groups being $p < 0.001$.

Within Wells score criteria for our studied population the criteria that showed greater statistical significance were "Clinical signs and symptoms of DVT" and "Previous, objectively diagnosed PE or DVT".

"Clinical signs and symptoms of DVT" had a relative frequency of 50.7%. This frequency proved to be similar to other previous reported studied data, for instance as by Posadas-Martínez et al., where the relative frequency for "Clinical signs and symptoms of DVT" was reported to be 62.3% for positive PE patients and 2% for negative PE patients.

The same study reported "Previous, objectively diagnosed PE or DVT" with a relative frequency of 13.1% for positive PE patients and 4.9% for negative PE patients. Additionally, Posadas-Martínez et al., reported "Immobilization ≥ 3 days, or surgery in the previous 4 weeks" with the highest relative frequency of 74.3% for positive PE patients and 62% for negative PE patients [20]. Comparable relative frequencies are present for our studied population.

For the criterion "Malignancy with treatment within 6 months or palliative" the positive cases of PE were significantly more frequent (14.1%) than the negative cases of PE (5.4%), odds ratio [CI 95%] = 2.89 [1.09-7.68], with the statistical significance between the groups being $p = 0.027$. This criterion has been suggested to be relevant, especially due to the strong evidence of the pathophysiologic - hypercoagulability states in cancer patients. PE accounts for the second most common cause of death in cancer patients. Undergoing chemotherapy also increases the risk of thrombosis [21].

For the criterion "PE is 1st diagnosis or equally likely" the PE positive cases were significantly more frequent (95.8%) than the negative cases of PE (81.9%), odds ratio [CI 95%] = 5.02 [1.47-17.15], with statistical significance between the groups $p = 0.005$ (Fischer's Exact Test).

"PE is 1st diagnosis or equally likely" is the subjective criterion that has been most criticized. On the other hand, in a multivariable regression analysis it also has shown to be one of the most important criteria of the Wells score.

The physician's decisions to validate this criterion have been influenced by the presence of one or more criteria of the Wells score [22].

We believed that in our data the criterion "PE is 1st diagnosis or equally likely" in general does not derive from the physician being influenced by the presence of other criteria in the score tool, but instead from the clinical suspicion of a positive PE diagnosis to be likely present. This is supported by the fact that most of the physicians in the studied center were not using a score system but an unstructured theoretical approach to the diagnosis of PE instead. Additionally, all our patients underwent CTPA with query PE. However, we could not say if this was performed before or after a D-dimer test. Nevertheless, a D-dimer test was done at RECUH for most cases suspicious of PE.

The criterion that did not reach statistical significance was that of hemoptysis; despite this, its clinical significance remains, especially given that its presence may be an indicator of a more severe pulmonary thromboembolism. Hemoptysis itself with or without the presence of a positive PE can be a life-threatening complication [2], [23].

We found hemoptysis with a relative frequency of 5.6% in patients with a positive and 3.4% with a negative CTPA result for PE, odds ratio [CI 95%] = 1.72 [0.45 – 6.61], with the statistical significance between the groups being $p < 0.474$ (Fischer's Exact Test).

A heart rate > 100/min was reported in 43.7% of positive PE cases and in 32.9% of patients negative to PE, odds ratio [CI 95%] = 1.59 [0.89 – 2.83], with the statistical significance between the groups being $p < 0.120$.

The criterion "Immobilization ≥ 3 days or surgery in the previous 4 weeks" was present in 23.9% positive to PE and in 14.8% negative to PE, odds ratio [CI 95%] = 1.82 [0.90 – 3.69], with the statistical significance between the groups being $p < 0.096$.

Table 4 shows the Wells criteria risk score calculation by risk levels and the respective PE results. This assessment gave us the following results: As the risk level increases the predictive likelihood of a positive PE also increases, with the statistical significant likelihood ratio being (2df, n=220) = 27.154, $p < 0.001$.

Wells criteria and other similar clinical predictive tools have been widely validated and their performances have been compared. Most studies indicate similar results between the different clinical predictive tools in the pre-test probability calculation for patients suspected of PE. Their benefits have been reported and recommended by international guidelines [2], [13], [22], [24]. Likewise, our data shows the higher the Wells criteria risk level that a patient is assigned to, the higher the likelihood of a positive PE result.

Table 4. Well's criteria risk levels calculation for positive and negative PE by CTPA results.

Wells criteria risk levels	Cases per risk. *n*	Positive PE by CTPA. *n* (%)	Negative PE by CTPA. *n* (%)
Low risk	22	1 (4.5)	21 (95.5)
Intermediate risk	139	36 (25.9)	103 (74.1)
High risk	59	34 (57.6)	25 (42.4)

N = 220; PE: Acute Pulmonary Thromboembolism; CTPA: Computer Tomography Pulmonary Angiography.

Table 4 Shows the Well's criteria risk levels stratification of the 220 patients, risk levels relative frequencies stratified by for positive and negative PE by CTPA results.

4.4. D-dimers Results Evaluation, Its Significance and Discussion

4.4.1. D-dimer Demographic Results

D-dimer results with a cutoff value of 0.50 mcg/mL were elevated in 209/220 (95%) of the cases and not elevated in 2/220 (0.9%) of the cases. In 9/220 (4.1%) cases D-dimer were not taken.

4.4.2. D-dimer Results Stratified by Positive and Negative PE Groups

For the positive cases of PE, D-dimer had a minimum value of 1.35 mcg/mL, a maximum value of 36.72 mcg/mL, a mean value of 13.80 ± 11.3 [Mean ± SD] mcg/mL, and a median value of 9.25 mcg/mL.

For negative cases of PE, D-dimer had a minimum value of 0.17 mcg/mL, a maximum value of 35.13 mcg/mL, a mean value of 7.58 ± 8.22 [Mean ± SD] mcg/mL, and a median value of 4.05 mcg/mL. These results can be seen in Table 5.

4.4.3. D-dimer Results Stratified by Wells Criteria Risk Score Levels and PE Groups

On Table 5, D-dimer test results were stratified according to Wells criteria score risk levels with the following results:

For the low risk level 22/22 (100%) patients had elevated D-dimer. From these one case (4.5%) was positive for PE and 21 (95.5%) of cases were negative for PE.

For the intermediate risk level in 132/139 (95%) patients D-dimer were elevated, in 2/139 (1.4%) D-dimer were below the standard threshold, and in 5/139 (3.6%) D-dimer were not taken. From all 139 cases in the intermediate risk level 36 (25.9%) were positive and 103 (74.1%) were negative for PE.

For the high risk level, D-dimer were elevated in 55/59 (93.2%) of the patients and not taken in 4/59 (6.8%) of the patients. From these 59 cases, 34 (57.6%) were positive for PE and 25 (42.4%) of cases were negative for PE.

4.4.4. D-dimer Values Stratified by Wells Criteria Risk Groups based on CTPA Results for PE

For the low risk group based on Wells criteria, CTPA results presented 21/22 cases negative to PE confirmed by CTPA, from these a minimum D-dimers value of 0.63 mcg/mL and a maximum D-dimer value of 35.13 mcg/mL with a range of 34.50 and a mean value of 9.72 ± 9.39 [Mean ± SD]. For the positive PE cases, 1/22 positive PE case confirmed by CTPA with a D-dimer value of 14.99 mcg/mL.

For the medium-risk group based on Wells criteria, CTPA results presented 99/134 cases negative to PE confirmed by CTPA, from these a minimum D-dimer value of 0.17 mcg/mL and a maximum D-dimer value of 35.13 mcg/mL with a range of 34.96 and a mean value of 7.74 ± 8.55 [Mean ± SD]. For the positive PE cases, 35/134 positive PE case confirmed by CTPA, from these a minimum D-dimer value of 1.35 mcg/mL and a maximum D-dimer value of 36.72 mcg/mL with a range of 35.37 and a mean value of 14.99 ± 12.00 [Mean ± SD].

For the high-risk group based on Wells criteria, CTPA results presented 24/55 cases negative to PE confirmed by CTPA, from these a minimum D-dimer value of 1.01 mcg/mL and a maximum D-dimer value of 15.51 mcg/mL with a range of 14.50 and a mean value of 5.03 ± 4.50 [Mean ± SD]. For the positive PE cases, 31/55 positive PE case confirmed by CTPA, from these a minimum D-dimer value of 2.01 mcg/mL and a maximum D-dimer value of 35.13 mcg/mL with a range of 33.12 and a mean value of 12.43 ± 10.03 [Mean ± SD].

Table 5. D-dimer values by Wells criteria risk groups based on CTPA results for PE.

	D-dimer Results (mcg/mL)				
	CTPA results (*n*)	Min	Max	Mean ± SD	Range
Low Risk	Negative PE (*n*=21)	0.63	35.13	9.72 ± 9.39	34.50
	Positive PE (*n*=1)	14.99	14.99	14.99 ± 0	0
Medium Risk	Negative PE (*n*=99)	0.17	35.13	7.74 ± 8.55	34.96
	Positive PE (*n*=35)	1.35	36.72	14.99 ± 12.00	35.37
High Risk	Negative PE (*n*=24)	1.01	15.51	5.03 ± 4.50	14.50
	Positive PE (*n*=31)	2.01	35.13	12.43 ± 10.03	33.12

PE: Acute Pulmonary Thromboembolism; CTPA: Computer Tomography Pulmonary Angiography. SD: Standard deviation

Table 5 shows the descriptive statistics of D-dimer results stratified by Wells criteria risk levels.

4.4.5. D-dimer Test Result Significance for the Outcome of CTPA Findings in the High-risk Group

From the results in the high-risk group (by Wells criteria risk score) we found no correlation between an elevated D-dimer alone and the occurrence of PE, with statistical significance, Fisher's Exact test, p = 0.630.

Following guideline recommendations, the use of a D-dimer test in high risk patients is often not recommended; instead the patient should undergo CTPA directly [2], [13].

Our data in Table 5 supports such an approach. We have identified the minimum value found in the high-risk group in our studied population to be 1.01 mcg/mL. At a cut of value of 0.50 mcg/mL these patients would have been considered to have an elevated D-dimer value and therefore, it is likely they would have been sent to CTPA after these results.

4.4.6. D-dimers Test Result Correlation to Age in Patients 50 Years Old and Older

The Figure 1 shows the results of a Spearman's correlation coefficient that was computed separately for positive and negative PE by CTPA groups for patients 50 years old or older, aiming to finding a correlation between age and D-dimer test result values. .

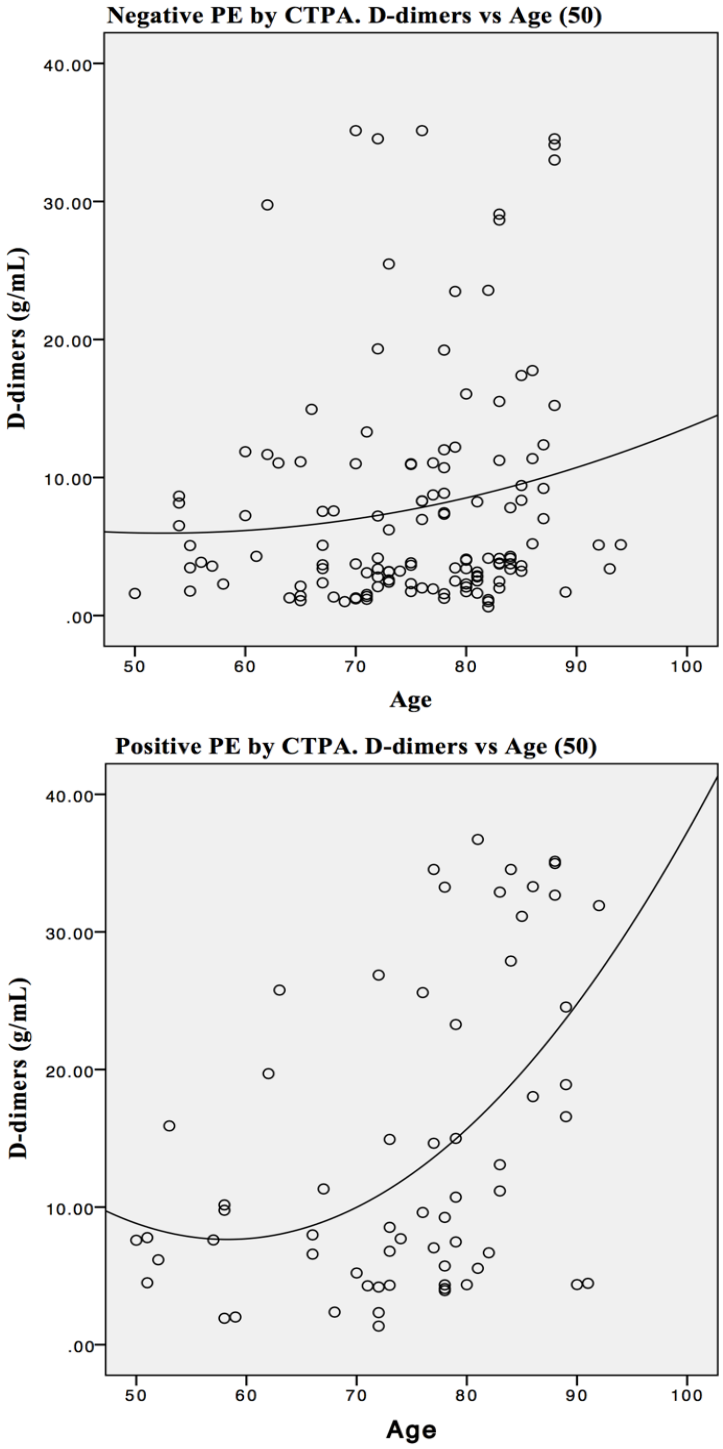

Figure 1. Shows a Spearman's correlation coefficient correlation between d-dimer test value results and patients age (≥ 50). PE: Acute Pulmonary Thromboembolism; CTPA: Computer Tomography Pulmonary Angiography.

For the positive PE group, the results show a moderate positive correlation between age and the quantitative value of D-dimer that was found, with statistical significance, rs = 0.425, N = 67, (2-tailed), $p < 0.001$.

For the negative PE group, the correlation is only very weak positive with statistical significance, rs = 0.172, N = 131, (2-tailed), p = 0.005.

The elevated D-dimer in the positive group is largely related to the presence of PE in its actual form. In addition, there may be a possible physiologic increase, as well as the likely presence of DVT as part of the PE pathophysiology. The positive but weak correlation between age (≥ 50 years old) and increase in D-dimer value seen in patients without PE, can perhaps be explained by the presence of DVT or/and the presence of a physiologic increase in D-dimer.

Of note, several studies have reported a similar positive correlation between D-dimer value and patient age. This may result in a higher number of patients with elevated D-dimer values above the conventional threshold, who ultimately acquire a negative PE result in CTPA [16], [25], [26].

4.4.7. Age - Adjusted D-dimer Correlation to Age in Patients 50 Years Old and Older

Following the above mentioned correlation in point 2.3.5. between D-dimer and age, we also tested our data for age adjusted D-dimer from 50 years and older with the previous mentioned formula (1). Adjusting the D-dimer threshold to age resulted in only one case out of a total of one hundred and ninety four cases (1/194) where otherwise considered elevated D-dimer fell under the upper limit threshold. This patient had a negative result for PE in CTPA. No patient with PE had a D-dimer value below the age-adjusted threshold. This may allow theoretical support to implement a threshold for D-dimer results based on age-adjusted D-dimer instead of the standard laboratory threshold. Age-adjusted D-dimer has been recommended by several studies and has shown great efficacy specifically in the exclusion of false positive PE patients [15], [16], [27].

4.5. Electrocardiography Results for Right Ventricular Dysfunction (RVD) "S1Q3T3" Predictive Value and Discussion

RVD analysis of ECG resulted in 33/205 (16.1%) cases with positive ECG S1Q3T3 findings. Of this 23/33 (69.7%) cases were positive for PE in CTPA. Among the 172/205 (83.9%) cases with negative ECG S1Q3T3 findings, 130/172 (75.6%) had a negative result for PE in CTPA. S1G3T3 findings in ECG had a sensitivity of 35.38%, a specificity of 92.86%, a positive predictive value of 69.70%, and a negative predictive value of 75.58% for PE. Previous studies reported S1Q3T3 findings in PE patients to be associated with a worse form of PE and poor prognosis of a patient. It has also been suggested to be a good predictor when compared to cardiac enzyme markers or brain natriuretic peptide. Additionally, ECG is widely available and inexpensive [28], [29].

This study demonstrates significant specificity for S1Q3T3 findings when a diagnosis of PE is suspected. Given that this finding is associated with more severe forms of PE, we recommend its use in light of its positive predictive value. However, while we can recommend ECG findings to rule out PE, we leave it open to discussion and further study. Furthermore, for patients entering the ED with an ECG performed in the ambulance with concurrent syncope, hypotension or other signs and symptoms of more severe forms of PE; we believe that the ECG findings S1Q3T3 to be of great value in influencing the subsequent actions of the physician.

5. Conclusions

1. Analysis of our data revealed increased significance for some clinical presentations. Dyspnea and chest pain were found to be the most relevant clinical findings outside of Wells criteria.
2. This study demonstrates that the data, when tested according to international guidelines and with respective comparison to similar studies, holds value in informing the development of our current approach to PE diagnosis.
3. The use of a Wells criteria pre-test probability tool and an age-adjusted D-dimer test has been shown to be pertinent in the process of optimizing the diagnostic process in PE.

In patients with a high risk pretest probability, a CTPA is indicated, without prior D-dimer testing. It is believed that this avoids excessive D-dimer testing and shortens the time to diagnosis. Conversely, for those patients with low risk pre-test probability by Wells criteria, our data indicates that there is scope to reduce the number of CTPA examinations performed in this patient group.

This is supported by the evaluation of Wells criteria in our study which highlights the positive correlation between higher risk levels and the prevalence of a positive PE result.

Age-adjusted D-dimer evaluation supports its use over the traditional laboratory cutoff of 0.50 mcg/mL, however this approach should be prospectively evaluated.

An approach including Wells criteria and age-adjusted D-dimer cutoff test may avoid unnecessary steps and examinations.

The clinical relevance of electrocardiogram S1Q3T3 positive findings demonstrated by this study is replicated in several earlier studies. We believe there is a growing pool of evidence justifying the inclusion of these readily-available investigation in future diagnostic approaches. Ultimately, due to its positive predictive value, future evaluation is recommended.

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