Diagnosis of Pulmonary Embolism in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: a Cross-sectional Study

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JMF, HMC and BLF have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and have drafted the submitted article.

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ABSTRACT

Introduction: Pulmonary embolism (PE) remains a frequent complication in patients with Chronic Obstructive Pulmonary Disease (COPD). It is unclear the extent to which the traditional risk stratifying scores for PE are accurate in this population.

Methods: Cross sectional study of adult patients with COPD and suspected PE included in an Institutional Registry of Thromboembolic Disease at a tertiary teaching hospital in the city of Buenos Aires, Argentina. We estimated the area under the receiver operating characteristic curves (AU-ROC), sensitivity and specificity of the Wells and Geneva scores using a positive computed tomography angiography as the gold standard for PE. We also estimated the sensitivity and specificity for the presence of isolated dyspnea at presentation, without other cardinal symptoms of acute exacerbation of COPD.

Results: A total of 168 patients were included, of which 22% had confirmed PE. The AUC was 0.66 (95% CI 0.56-0.76) and 0.54 (95% CI 0.45-0.67) for the Wells and Geneva, respectively. Considering the most widely used cut-off points, the sensitivity and specificity were 24% and 90% for the Wells and 59% and 43% for the Geneva score, respectively. Isolated dyspnea on presentation had a sensitivity of 92% and specificity of 37%.

Conclusions: Both Wells and Geneva scores exhibit poor diagnostic accuracy for the diagnosis of PE in patients with COPD. The presence of isolated dyspnea on presentation could be an easy to

identify criteria for the initial triage in this population. Further validation of our findings remains warranted.

Keywords: Chronic Obstructive Pulmonary Disease – Pulmonary Embolism – Clinical Epidemiology – Exacerbation

Short Title: "PE Diagnosis in COPD exacerbations"

INTRODUCTION

Acute exacerbations of Chronic Obstructive Pulmonary Disease (AE-COPD) are the second cause of emergency department admission and are associated with significant impairment in the quality of life of patients with COPD.[1] The underlying etiology of AE-COPD remains unknown in up to 30% of the cases.[2-4] According to a recent review, the prevalence of pulmonary embolism (PE) can reach up to 16.1 (95% CI 8.3%-25.8%) in patients presenting with unexplained AE-COPD.[5] In patients with COPD, PE is associated with increased mortality as compared to the general population.[6, 7] Importantly, AE-COPD and PE share signs and symptoms, which may lead to error and delay in diagnosis and subsequently, worse prognosis.[8-10]

The Wells and simplified Geneva scores are clinical decision rules widely used for early stratification of PE risk.[11-14] However, these rules were developed on unselected populations without COPD or where its prevalence was low.[15] Given that the key signs and symptoms collected by these predictive tools might also be present in patients with AE-COPD triggered by other causes, these might not be useful in patients with COPD. To our knowledge, there is a paucity of data assessing the diagnostic performance of these scores in this population.[7, 16]

The aim of this study was to evaluate the diagnostic performance of the Wells and Geneva Scores for the diagnosis of PE in patients with COPD. Furthermore, given that the cardinal symptoms of AE-COPD include the triad of worsening dyspnea, increased cough and sputum, we hypothesized that the presence of isolated worsening dyspnea without the other two aforementioned symptoms could be associated with a higher likelihood of PE in this population.[17]

MATERIALS AND METHODS

We conducted a cross-sectional study at a tertiary care teaching facility in the city of Buenos Aires, Argentina, between December 2009 and March 2014. Patients were included if they suspected PE in the presence of a background diagnosis of COPD. The information was extracted from an institutional registry of thromboembolic disease with a validated quality data control process that served for extensive previous research.[18-22] This registry systematically

collects information on all patients with suspected PE who underwent Computed Tomography Angiography (CT-A) for diagnosis. The decision to perform a CT-A was at the discretion of the treating physician in each individual case. Patients' baseline characteristics, including Wells and Geneva Scores, and other respiratory symptoms (i.e.: dyspnea, cough, sputum) were recorded by a research assistant who was blinded to the status of PE. The Hospital Italiano de Buenos Aires Institutional Review Board gave ethical approval to perform this study (N°2314).

Patients' baseline characteristics were summarized using proportions for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, as appropriate. Initially, we compared the baseline characteristics of patients with confirmed PE versus those without PE. Normally distributed continuous variables were compared using Student's t-test. Non-normally distributed variables were compared using the Wilcoxon Rank Sum test. Categorical variables were compared using the chi-square test.

In order to assess the diagnostic performance of the Wells and Geneva score, we estimated the sensitivity, specificity and likelihood ratios with their corresponding 95% confidence intervals for different cut-off points of these scores. As a global parameter of discrimination, we also plotted the receiver operating characteristic (ROC) curve and estimated the area under the curve (AU-ROC) with the corresponding 95% confidence interval. A positive CT-A was considered the reference standard for PE. We performed a subgroup analysis comparing the diagnostic performance of these scores depending if patients were assessed in the emergency department versus as inpatients. Furthermore, we calculated the sensitivity and specificity for the presence of isolated worsening dyspnea (without the presence of cough or sputum). All analyses were performed with the Stata v. 13 software.

RESULTS

During the study period, 168 patients with a diagnosis of COPD underwent a CT-A to rule out PE. Baseline characteristics of study participants are summarized in Table 1. Briefly, median age was 74 years (IQR 66-81 years) and 37% (n=62) were female. Most of the patients presented at the Emergency Department, representing 82% (n=137) of the entire population. A diagnosis of PE was confirmed in 22% (n=37) of this cohort. Table 1 also summarizes the Wells and Geneva

scores for the overall population and for patients with versus those without PE. As depicted from this table, the median Wells score was higher in patients with confirmed PE compared to those without (3 versus 1.5, p=0.0022) whereas the Geneva score was similar between both groups (3 versus 3, p=0.23). Furthermore, patients with confirmed PE were more likely to present as outpatients (95% versus 78%, p=0.021) and to present with isolated dyspnea (92% versus 63%, p=0.001).

Table 2 summarizes the diagnostic performance for the Wells and Geneva scores in patients with COPD and suspected PE. When considering the most widely used cut-off value for the Wells score (higher than four), sensitivity and specificity were 24% and 90%, respectively. Conversely, the most widely used cut-off point for the simplified Geneva Score (3 points or higher) held a sensitivity and specificity of 59% and 43%, respectively. The AU-ROC was 0.66 (95% CI 0.56-0.76) for the Wells score and 0.54 (95% CI 0.45-0.67) for the Geneva score. The diagnostic performance of these scores did not change significantly depending where the patients were assessed (emergency department versus inpatient).[13, 23]

Interestingly, the presence of isolated dyspnea (without increased cough or sputum) had a sensitivity and specificity of 91.9% and 37.4%, respectively.

DISCUSSION

We present the results of a study assessing the diagnostic performance of traditional risk stratifying scores for PE in the specific population of patients with COPD. The most significant findings of our study are (1) In patients with COPD and suspected PE, the overall prevalence of PE was 22% (2) Both Wells and Geneva score perform poorly in patients with COPD and (2) The presence of isolated dyspnea without the other classic cardinal symptoms of AE-COPD has a high sensitivity for the diagnosis on PE in patients with COPD.

The diagnosis of PE in patients with COPD has unique challenges with relevant clinical implications. PE presents more frequently in patients with COPD than in the general population and is associated with poor prognosis.[5-7] Furthermore, PE can be the underlying trigger of an acute exacerbation of COPD, which is frequently treated empirically without considering a PE

work-up. Therefore, it becomes paramount to assess which clinical tools can help identify those patients with a higher risk of PE among those presenting with AE-COPD.

In the current study, we demonstrate that the usual risk scoring systems (Wells and Geneva) hold poor diagnostic performance in this population. The low performance of the Wells score in our population contrasts with the higher sensitivity and specificity in general population.[11] "Alternative diagnosis less likely than PE" is one of the items that assigns more points to the final Wells' score. This criterion can be particularly misleading in patients with COPD, given that considering AE-COPD as an alternative diagnosis can frequently lead to failure of this item. As a result, the false negative rate would increase, explaining the overall low sensitivity that the Wells score had in our population. Furthermore, both the Wells and Geneva include the presence of tachycardia and cancer as criteria. Patients with COPD frequently present with increased heart rate secondary to hypoxemia and inhaled beta agonists use.[24] Primary lung cancer and other malignancies are also more frequent in patients with COPD compared to the general population.[25-27] Furthermore, hemoptysis is also present in COPD patients which can be secondary associated to bronchitis, bronchiectasis o malignancy.[28-30] The Geneva Score has been previously studied in patients with COPD by Tillie-Leblond et al., but the diagnostic performance was not described.[16] In agreement to our study, the performance of the Wells score was superior to the Geneva score in the study by Gunan et al., although their performance was lower in our findings. In agreement to our study, the performance of the Wells score was superior to the Geneva score in the study by Gunan et al., although their performance was lower in our findings.[7] These results could be related to the systematic use of CT-A and the employment of previous (non-simplified) versions of the scores in this study

Perhaps one of the most interesting findings of our study is that the presence of isolated dyspnea had a high sensitivity for the diagnosis of PE in patients with COPD. This is a simple and easy to identify criteria that holds high face validity and could be used as an initial screening tool to identify which patients with AE-COPD could be at risk of PE. Symptom based analysis as a tool has been evaluated in other studies with different results [16] Our findings are consistent with previous studies conducted in COPD patients.[7, 31, 32]

This study has several limitations that merit consideration. First, it describes a population of patients with a diagnosis COPD and suspected PE rather than a systematic assessment of PE diagnosis in all patients with AE-COPD. The decisions to perform a CT-A were done individually by the treating physicians. This could naturally select a spectrum of the population with a higher risk of PE, although it could also represent more accurately a real-life scenario where clinical uncertainty is present. In any case, even if the spectrum of the patient population represents a group of patients with a higher likelihood of PE, we would expect the Wells and Geneva score to perform better, which was not the case in this study. Second, the findings represent the experience of a single center, which could not be extrapolated to different populations. However, the population included in the institutional registry represent a huge range of socioeconomic status and clinical backgrounds.[20] Third, although we report an overall poor performance of both Wells and Geneva scores, we did not compare these scores in a more general population to show they are actually different. However, previous research using the same registry demonstrated a much better performance of the Wells score in a broader population. [19]

CONCLUSIONS

In summary, we present the results of a study evidencing that the classic scores for PE risk stratification don't perform well in patients with COPD. Importantly, the presence of isolated dyspnea could serve as an easy to collect criteria for the initial triage of patients who require further investigation. The results of this study need to be prospectively and externally validated to be incorporated into clinical practice.

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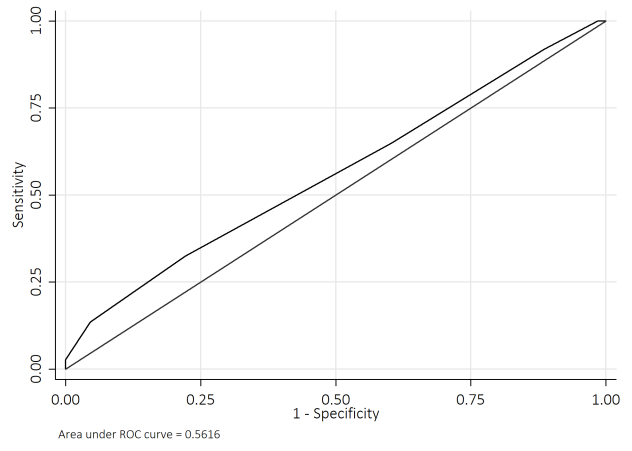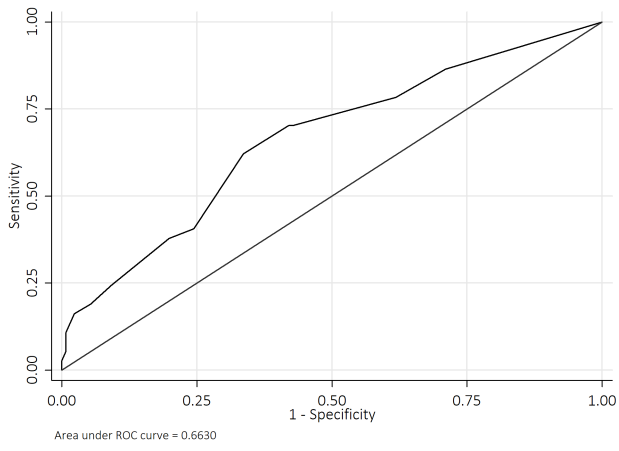
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Table 1. Population characteristics

	All Patients	Confirmed Pulmonary Embolism	No Pulmonary Embolism	p value†
	n=168	n=37	n=131	
Demographics				
Age in years, median (IQR)	74 (66-81)	75 (70-84)	73 (66-80)	0.09
Female sex, n (%)	62 (36.9)	16 (43.2)	46 (35.1)	0.37
BMI in kg/m^2, mean (SD)	26.3 (4.9)	26.8 (4.0)	26.2 (5.2)	0.48
Comorbidities				
Charlson Comorbidity Score, median (IQR)	3 (2-5)	4 (2-5)	3 (2-5)	0.63
Active Cancer, n (%)	49 (29.2)	13 (35.1)	36 (27.5)	0.37
COPD characteristics				
Pack/years, median (IQR)	50 (40-63)	50 (40-90)	50 (35-60)	0.4
FEV1 in %, median (IQR)	46 (34-68)	50 (41.5-76)	44 (31-65)	0.053
Home Oxygen, n (%)	37 (22)	10 (27)	27 (20.6)	0.4
Corticosteroid use, n (%)	25 (14.9)	5 (13.5)	20 (15.3)	0.79
PaCO2 as outpatient in mmHg, median (IQR)	48 (40-58)	46.5 (38-59)	49 (41-57)	0.98
Emphysema on CT, n (%)	132 (78.6)	28 (75.7)	104 (79.4)	0.63
Presentation Characteristics				
Outpatient status, n (%)	137 (81.6)	35 (94.5)	102 (77.9)	0.021
Isolated dyspnea, n (%)	116 (69.1)	34 (91.9)	82 (62.6)	0.001
Wells score, median (IQR)	1.5 (0-4)	3 (1.5-4.5)	1.5 (0-3)	0.0022
Geneva score, median (IQR)	3 (2-3)	3 (2-4)	3 (2-3)	0.23

IQR: Interquartile Range; SD: Standard Deviation; BMI: Body Mass Index; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in one second; PaCO2: Arterial Pressure of Carbon Dioxide; CT: Computed Tomography

†Comparison of confirmed pulmonary embolism to no pulmonary embolism

Table 2. Diagnostic performance for Wells and Geneva Scores using different cut-off points.

	Sensitivity (95%CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
Wells Score				
>=8	5.41% (0.66-18.2)	99.2% (95.8-100)	7.08 (0.66-75.9)	0.95 (0.88-1.03)
>=7	16.2% (6.19-32)	97.7% (93.5-99.5)	7.08 (1.86-27)	0.86 (0.74-0.99)
>=6	18.9% (7.96-35.2)	94.% (89.3-97.8)	3.54 (1.33-9.45)	0.86 (0.73-1.01)
>=5	24.3% (11.8-41.2)	90.8% (84.5-95.2)	2.66 (1.21-5.81)	0.83 (0.69-1.01)
>= 4	37.9% (22.5-55.2)	80.2% (72.3-86.6)	1.91 (1.11-3.26)	0.78 (0.60-1.01)
>= 3	62.2% (44.8-77.5)	66.4% (57.6-74.4)	1.85 (1.31-2.62)	0.56 (0.37-0.88)
>=2	70.3% (53-84.1)	57.3% (48.3-65.9)	1.64 (1.23-2.19)	0.5 (0.31-0.87)
>=1	86.5% (71.2-95.5)	29% (21.4-37.6)	1.22 (1.03-1.44)	0.47 (0.20-1.1)
Simplified Geneva Score				
>=6	2.7% (0.07-14.2)	100% (97.2-100)	0 (-)	0.97 (0.92-1.03)
>=5	13.5% (4.54-28.8)	95.4% (90.3-98.3)	2.95 (0.95-9.13)	0.91 (0.79-1.04)
>=4	32.4% (18-49.8)	77.9% (69.8-84.6)	1.47 (0.83-2.58)	0.87 (0.68-1.10)
>=3	64.9% (47.5-79.8)	39.7% (31.3-48.6)	1.08 (0.82-1.42)	0.89 (0.54-1.44)
>=2	91.9% (78.1-98.3)	11.5% (6.55-18.2)	1.04 (0.93-1.16)	0.71 (0.22-2.32)
>=1	100% (90.5-100)	1.53% (0.19-5.41)	1.02 (0.99-1.04)	0 (-)

Area under ROC curve = 0.6630

Area under ROC curve = 0.5616

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