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Rafael Suárez del Villar Carrero [*] , Diego Martínez-Urbistondo , Miguel De la Serna Real de Asua , Alberto Cano Mazarro , María Agud Fernández , Ana Rodriguez Cobo , Paula Villares Fernández

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Rafael Suárez del Villar Carrero [1,*], Diego Martínez-Urbistondo [2],
Miguel De la Serna Real de Asua [3], Alberto Cano Mazarro [3], María Agud Fernández [1],
Ana Rodriguez Cobo [1] and Paula Villares Fernández [1]

[1]   Department of Internal Medicine Hospital HM Sanchinarro. HM Hospitales, Madrid, Spain
[2]   University Clinic of Navarra, Madrid, Spain
[3]   University San Pablo CEU, Madrid, Spain
[*]   Correspondence: Department of Internal Medicine HM Montepríncipe, HM Hospitals, Avenida/Montepríncipe 26, 28260 Madrid, Spain

Abstract: Background: The diagnosis of Pulmonary Embolism (PE) is based on the application of a priori probability scales such as the Wells scale or PERC criteria. However, the clinical heterogeneity of this pathology results in the absence of a target population to apply these algorithms. Moreover, these scales do not consider the possible influence of the presence of an objective alternative diagnosis to PE, complicating its clinical assessment and possibly leading to an increase in unnecessary testing or missed diagnoses. Objective: The aim of this study is to evaluate the discrimination capacity of clinical objective factors with a high negative predictive value for PE, compared to PERC in terms of reducing unnecessary testing across different risk strata of the Wells scale. Materials and Methods: This was a single-center retrospective cohort study, including patients who underwent chest CT angiography to rule out PE at a University Hospital between 2008 and 2017, considering the presence of PE as the study outcome. The study collected demographic data, comorbidities, and clinical presentation data. The presence of objective criteria for pneumonia, heart failure, exacerbation of COPD, or the use of anticoagulation in non-oncological patients was considered a priori criteria with a high negative predictive value. Results: The analyses were performed on a cohort of 399 patients with an average age of 65 years and 53% females. A total of 139 patients were diagnosed with PE by CT angiography. The presence of factors with a high NPV showed a sensitivity and NPV of 100% in low-risk patients according to Wells, with sensitivity dropping below 50% in other populations. The association of these factors in the PERC plus criteria would allow a reduction of up to 34% in CT angiographies in patients with low risk according to the Wells scale. Conclusions: The combination of risk stratification of the Wells scale and PERC plus criteria allows an absolute reduction of 34.3% in the performance of CT angiographies in patients classified as low risk with a sensitivity and a negative predictive value of 100%. The preexistence of an alternative diagnosis does not allow ruling out PE in patients with intermediate or high risk according to the Wells scale.

1. Introduction

Pulmonary Embolism (PE) is a prevalent condition, with an annual incidence ranging from 39 to 115 cases per 100,000 inhabitants [1–4]. It is the third most common cardiovascular disease, following acute myocardial infarction and cerebrovascular accident [5–7], with morbidity and mortality rates reaching up to 30% in some reports [2].

The clinical presentation of PE is highly variable and nonspecific [8–11]. Most commonly, it presents with dyspnea, cough, or chest pain [10,12], symptoms that overlap with other pulmonary

and cardiovascular conditions such as pneumonia, exacerbation of COPD, or decompensated congestive heart failure, among others [9,11,13]. Additionally, the average age of PE presentation is between 60 and 70 years, a period when these other pathologies are also prevalent [1,13–19]. Consequently, establishing a presumptive diagnosis of PE based solely on clinical and epidemiological data can be challenging [8,20,21]. Several risk factors for venous thromboembolic disease (VTE) can modify the probability that a patient's symptoms are due to PE. Notably, cancer, recent surgery, immobility, and estrogen use are associated with an increased risk of PE [22–25].

Clinical prediction scales have been developed to stratify the risk of PE in patients. Among these, the Wells score is widely used and has demonstrated strong external validation, serving as a primary tool for initial PE risk assessment [7,26]. This scale evaluates signs, symptoms, and risk factors, categorizing patients into low, medium, or high risk [7,26]. Based on this assessment, patients are directed through clinical algorithms to undergo further tests for diagnosis or exclusion of PE [21,27–30]. However, the Wells score has limitations, including its exclusion of hospitalized patients, lack of a clearly defined target population, inclusion of subjective elements, and dependence on a hospital setting capable of performing necessary tests and procedures [31].

More recently, alternative approaches to diagnosing VTE have emerged. The Pulmonary Embolism Rule-Out Criteria (PERC) is one such model, including eight factors with a high negative predictive value for PE [32]. This model can rule out PE in patients with very low probability, achieving near 100% sensitivity [33–35]. Despite its usefulness, PERC's representativeness is limited, affecting approximately 13% of the at-risk population and thereby being inadequate for many patients with suspected PE [36].

In summary, the epidemiological, clinical, and analytical heterogeneity of PE patients, combined with the complexity of diagnostic tests, complicates standardized clinical judgment. While it seems reasonable to rule out PE in patients with a clear alternative diagnosis, such as pneumonia, COPD exacerbation, or congestive heart failure, or those on anticoagulant therapy for other reasons [37], definitive evidence supporting this approach is lacking. Therefore, this study aims to evaluate the discrimination capability of clinical factors with a high negative predictive value for PE and compare them to the PERC scale in terms of screening efficacy and reduction in unnecessary testing.

2. Materials and Methods

This observational, retrospective cohort study included all patients who underwent chest Computed Tomography Angiography (CT Angiography) between 2008 and 2017 at HM Sanchinarro Hospital, a 200-bed university hospital. The study was approved by the center's ethics committee, and informed consent was waived (HM Hospitals CEIm Code: 21.03.1792-GHM).

Patients were identified through a review of digitized medical records. Data collection included demographic information, risk factors, comorbidities, clinical variables, vital signs at the time of the test, and analytical and radiographic data. Variables corresponding to the Wells and PERC scales (Tables 1 and 2) [26,32] were recorded. The presence of PE on CT Angiography was considered the outcome variable. Exclusion criteria were being under 18 years of age, undergoing CT Angiography for reasons other than suspected PE, having an acute PE diagnosis at the time of the test, and insufficient data for calculating the Wells or PERC scales. This resulted in a final study cohort of 399 patients.

Table 1. Modified Wells Scale for Pulmonary Thromboembolism.

Characteristics	Value
Clinical Symptoms of Deep Vein Thrombosis	3
Other Diagnoses Less Likely Than PET	3
Heart rate greater than 100 bpm	1.5
Immobilization or surgery within the last 4 weeks	1.5
Deep vein thrombosis or previous pulmonary thromboembolism	1.5

Hemoptysis	1
Cancer	1
PE: Pulmonary thromboembolism; bpm: Beats per minute	

Table 2. PERC Criteria.

Characteristics
-     Under 50 years of age
-     Pulse < 100 lpm (in tachycardia)
-     Absence of hypoxia (SatO$_2$ > 95%)
-     No history of pulmonary embolism or deep vein thrombosis
-     No trauma or recent surgery
-     Absence of hemoptysis
-     Does not use estrogen therapy
-     Absence of swelling in the legs
PERC: Pulmonary Embolism Rule Out Criteria; **SatO$_2$:** Oxygen saturation; **bpm**: Beats per minute

Objective variables with a high negative predictive value were defined based on diagnostic guidelines [38–40]: (i) Pneumonia: fever and radiographic consolidation as assessed by the physician; (ii) COPD Exacerbation: smoking habit, cough, and fever; (iii) Congestive Heart Failure (CHF): radiological pattern consistent with heart failure and dyspnea or orthopnea; (iv) Previous Anticoagulation in Non-Oncological Patients: anticoagulated patients without a prior oncological diagnosis at the time of CT Angiography (Table 3).

Table 3. Definition of objective variables with high negative predictive value.

Pneumonia	**Presence of fever. Radiological pattern compatible with respiratory infection and dyspnea or cough.**
Exacerbation/suspicion of COPD	History of smoking. dyspnea and cough
Heart failure	Presence of radiological pattern compatible with heart failure and dyspnea or orthopnea
Anticoagulation in non-cancer patients	Previous anticoagulation in non-cancer patients
PERC	Those patients who meet the PERC criteria mentioned in Table 2
COPD: Chronic Obstructive Pulmonary Disease; **PERC:** Pulmonary Embolism Rule Out Criteria	

Statistical analysis employed standard methods. Qualitative variables were analyzed using the chi-square test, and quantitative variables were assessed with t-tests and ANOVA. Sensitivity, specificity, and positive and negative predictive values were calculated for each study variable and the PERC scale. A new scale, PERC plus, incorporating all variables with a 100% negative predictive value, was created. The ability of each criterion and the PERC plus set to reduce diagnostic tests was assessed by calculating the incidence of at-risk patients where CT Angiography could have been avoided. Differences with $p < 0.05$ were considered statistically significant. Statistical analysis was performed using SPSS version 27.0 (Armonk, NY, 2020).

3. Results

The study evaluated 399 patients who met the inclusion criteria, with 139 (35%) diagnosed with PE by CT Angiography. The cohort had an average age of 65 ± 16 years, and 53% were female (n=214). The average number of comorbidities per patient was 0.8 ± 0.3, with oncological pathology being the

most common (n=121, 30%). Risk stratification according to the Wells scale showed that 6 patients with PE (4%) were in the low-risk group, 95 patients (68%) were in the moderate-risk group, and 38 patients (27%) were in the high-risk group. CT Angiography was performed after Emergency Department assessment in 81.20% of patients.

The most frequent symptoms were dyspnea (n=269, 67%), pleuritic pain (n=154, 39%), cough (n=115, 29%), fever (n=66, 17%), lower limb pain (n=43, 11%), orthopnea (n=25, 6%), syncope (n=15, 4%), and hemoptysis (n=11, 3%). At diagnosis, 108 patients (27%) had hemodynamic instability, and 185 patients (46%) had acute respiratory failure. PERC criteria were met by 13 patients (3%), pneumonia criteria by 27 patients (7%), COPD exacerbation criteria by 40 patients (10%), CHF criteria by 18 patients (5%), and 29 patients (7%) were anticoagulated without oncological pathology. The distribution of these patients according to Wells scale risk is shown in Table 4.

Table 4. Characteristics of the population.

Variable	Total	Risk According to the Wells Scale			p
	n=399	Low	Intermediate	High	
		n=210	n=150	n=39	
Age, years (SD)	65±16	65±16	65±16	64±16	0.731
Women, %	214 (53.60%)	118 (56.20%)	79 (52.70%)	17 (43.60%)	0.334
Comorbidities					
Patients without comorbidities, %	46 (11.50%)	27 (12.90%)	14 (9.30%)	5 (12.80%)	0.567
Smoking, %	137 (34.30%)	83 (39.50%)	49 (32.70%)	5 (12.80%)	0.005
Ischemic heart disease, %	55 (13.79%)	34 (16.20%)	17 (11.30%)	4 (10.30%)	0.335
COPD, %	48 (12.00%)	34 (16.20%)	14 (9.30%)	0 (0.00%)	0.007
Renal insufficiency, %	17 (4.30%)	9 (4.30%)	8 (5.30%)	0 (0.00%)	0.34
Oncological Pathology, %	121 (30.30%)	48 (22.90%)	56 (37.30%)	17 (43.60%)	0.002
Summa of comorbidities, SD	0.885 ± 0.32	0.871 ± 0.34	0.907 ± 0.29	0.872 ± 0.34	0.569
Symptoms					
Disnea, %	269 (67.40%)	133 (63.30%)	108 (72.00%)	28 (71.80%)	0.186
Hemoptisis, %	11 (2.80%)	5 (2.40%)	5 (3.30%)	1 (2.60%)	0.86
Pleuritic pain, %	154 (38.60%)	84 (40.00%)	57 (38.00%)	13 (33.30%)	0.721
Lower limb pain, %	43 (10.80%)	5 (2.40%)	18 (12.00%)	20 (51.30%)	<0.001
Cough, %	115 (28.80%)	76 (36.20%)	33 (22.00%)	6 (15.40%)	0.002
Faint, %	15 (3.80%)	5 (2.40%)	8 (5.30%)	2 (5.10%)	0.316
Fever, %	66 (16.50%)	39 (18.60%)	23 (15.30%)	4 (10.30%)	0.386
Ortopnea, %	25 (6.30%)	12 (5.70%)	11 (7.30%)	2 (5.10%)	0.784
Vital Signs					
Taquicardia > 100 lpm, %	105 (26.30%)	36 (17.10%)	55 (36.70%)	14 (35.90%)	<0.001
SBP < 90 mmHg, %	21 (5.30%)	9 (4.30%)	8 (5.30%)	4 (10.30%)	0.308
Saturation < 94%, %	185 (46.40%)	95 (45.20%)	71 (47.30%)	19 (48.70%)	0.882
Variables with high a priori negative predictive value for PE					
PERC, %	13 (3.30%)	11 (5.20%)	2 (1.30%)	0 (0.00%)	0.058
Pneumonia, %	27 (6.80%)	18 (8.60%)	9 (6.00%)	0 (0.00%)	0.132
COPD flare-up, %	40 (10.00%)	26 (12.40%)	13 (8.70%)	1 (2.60%)	0.135
Heart failure, %	18 (4.50%)	11 (5.20%)	5 (3.30%)	2 (5.10%)	0.679
Non-oncology patients on anticoagulation, %	29 (7.30%)	18 (8.60%)	11 (7.30%)	0 (0.00%)	0.166
CT angiography result					
Pulmonary thromboembolism, %	139 (34.80%)	6 (2.90%)	95 (63.30%)	38 (97.40%)	<0.001
Patients with CT angiography performed in the Emergency Department, %	324 (81.20%)	166 (79.00%)	121 (80.70%)	37 (94.40%)	0.066

COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; bpm: Beats per minute; PERC: Pulmonary Embolism Rule Out Criteria; PE: pulmonary embolism; CT angiography: Computed Tomography Angiography; SD: standard deviation.

Patients with PE (n=139) had an average age of 66 ± 17 years and 47% were female (n=65), while non-PE patients (n=260) had an average age of 64 ± 16 years and 57% were female (n=149), showing no statistically significant differences. The average number of comorbidities in PE patients was 0.9 ± 0.3, with a predominance of oncological pathology (n=45, 32%), similar to the non-PE group. PE patients were more frequently detected in the Emergency Department (n=124, 89.2%), and were associated with lower limb pain (22.30% vs. 4.60%, p <0.001), heart rate > 100 bpm (33.10% vs. 22.70%, p = 0.025), and oxygen saturation < 94% (56.80% vs. 40.80%, p = 0.002). Cough was associated with negative CT Angiography (15.10% vs. 36.20%, p<0.001). Hemodynamic instability and desaturation were more frequent in PE patients. Both the PERC scale and the presence of COPD exacerbation and anticoagulation in non-oncological patients showed discrimination for PE (p<0.05), while pneumonia criteria approached statistical significance (p=0.06). CHF criteria did not show a significant association with PE (p=0.71) (Table 5).

Table 5. Population characteristics as a function of thoracic CT angiography.

Variable	PE	Not PE	p
Age, years (SD)	66 ± 17	64 ± 16	0.821
Women, %	65 (46.80%)	149 (57.30%)	0.44
Positive CT CT angiography in the Emergency Department, %	124 (89.20%)	200 (76.9%)	0.003
Comorbidities			
Patients without comorbidities, %	16 (11.50%)	30 (11.50%)	0.993
Smoking, %	31 (22.30%)	106 (40.80%)	<0.001
Ischemic heart disease, %	16 (11.50%)	39 (15.00%)	0.335
COPD, %	9 (6.50%)	39 (15.00%)	0.013
Renal insufficiency, %	3 (2.20%)	14 (5.40%)	0.128
Oncological Pathology, %	45 (32.40%)	76 (29.20%)	0.515
Summary of comorbidities (SD)	0.885 ± 0.320	0.885 ± 0.320	0.993
Symptoms			
Disnea, %	101 (72.70%)	168 (64.60%)	0.102
Hemoptisis, %	4 (2.90%)	7 (2.70%)	0.914
Pleuritic pain, %	60 (43.20%)	94 (36.20%)	0.17
Lower limb pain, %	31 (22.30%)	12 (4.60%)	<0.001
Cough, %	21 (15.10%)	94 (36.20%)	<0.001
Faint, %	6 (4.30%)	9 (3.50 %)	0.674
Fever, %	17 (12.20 %)	49 (18.80%)	0.09
Ortopnea, %	6 (4.30%)	19 (7.30%)	0.24
Vital Signs			
Taquicardia > 100 lpm, %	46 (33.10%)	59 (22.70 %)	0.025
SBP < 90 mmHg, %	8 (5.80%)	13 (5.00%)	0.747
$SatO_2$ < 94%, %	79 (56.80%)	106 (40.80%)	0.002
Wells Scale			
Low Risk, %	6 (4.30%)	204 (78.50%)	
Moderate Risk, %	95 (68.30%)	55 (21.20%)	<0.001
High Risk, %	38 (27.30%)	1 (0.40%)	
Variables with high a priori negative predictive value for PE			
PERC, %	0 (0.00%)	13 (5.00%)	0.007

Pneumonia, %	5 (3.60%)	22 (8.50%)	0.065
COPD flare-up, %	6 (4.30%)	34 (13.00%)	0.006
Heart failure, %	7 (5.00%)	11 (4.20%)	0.712
Non-oncology patients on anticoagulation, %	5 (3.60%)	24 (9.20%)	0.039

COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; SatO₂: Oxygen saturation; bpm: Beats per minute; PERC: Pulmonary Embolism Rule Out Criteria; PE: pulmonary embolism; CT angiography: Computed Tomography Angiography; SD: standard deviation.

The sensitivity of the Wells scale for diagnosing PE in the low-risk group was 95%, decreasing to 74.68% in hospitalized patients. Evaluating the sensitivity and specificity of conditions with high negative predictive value revealed 100% sensitivity and NPV for patients meeting criteria for alternative diagnoses in low-risk Wells groups. The PERC plus scale, combining objective clinical criteria with PERC, also achieved 100% NPV and sensitivity in low-risk patients according to the Wells scale but showed an NPV of 46.67% and 0% in medium and high-risk groups, respectively (Table 6).

Table 6. Study of the ability to discriminate factors with high a priori negative predictive value for the diagnosis of pulmonary thromboembolism.

	Risk	Sensitivity	Specificity	VPP	VPN	% CT Angiography Reduction
Pneumonia	Low	100.00%	8.82%	3.13%	100.00%	8.57%
	Middle	94.74%	7.27%	63.83%	44.44%	2.67%
	High	100.00%	0.00%	97.44%	0.00%	0.00%
COPD	Low	100.00%	12.75%%	3.26%	100.00%	12.38%
	Middle	94.74%	14.55%	65.69%	61.54%	5.33%
	High	97.37%	0.00%	97.37%	0.00%	0.00%
Heart failure	Low	100.00%	5.40%	3.02%	100.00%	5.24%
	Middle	94.74%	0.00%	62.07%	0.00%	0.00%
	High	94.74%	0.00%	97.30%	0.00%	0.00%
Non-oncological anticoagulated patients	Low	100.00%	8.82%	3.13%	100.00%	8.57%
	Middle	94.74%	10.90%	64.75%	54.55%	4.00%
	High	100.00%	0.00%	97.44%	0.00%	0.00%
PERC	Low	100.00%	5.39%	3.02%	100.00%	5.24%
	Middle	100.00%	3.64%	64.19%	100.00%	1.33%
	High	100.00%	0.00%	97.44%	0.00%	0.00%
PERC *plus*	**Low**	**100.00%**	**34.31%**	**4.29%**	**100.00%**	**34.30%**
	Middle	83.16%	25.45%	65.83%	46.67%	25.50%
	High	92.11%	0.00%	97.22%	0.00%	0.00%

COPD: Chronic obstructive pulmonary disease; PERC: Pulmonary Embolism Rule-Out Criteria; PPV: Positive predictive value; NPV: Negative Predictive Value; CT angiography: Computed Tomography Angiography

The reduction in CT Angiography use for conditions with high NPV was 9% for pneumonia, 12% for COPD, 5% for CHF, 9% for anticoagulated patients without oncological pathology, and 5% overall (Figure 1).
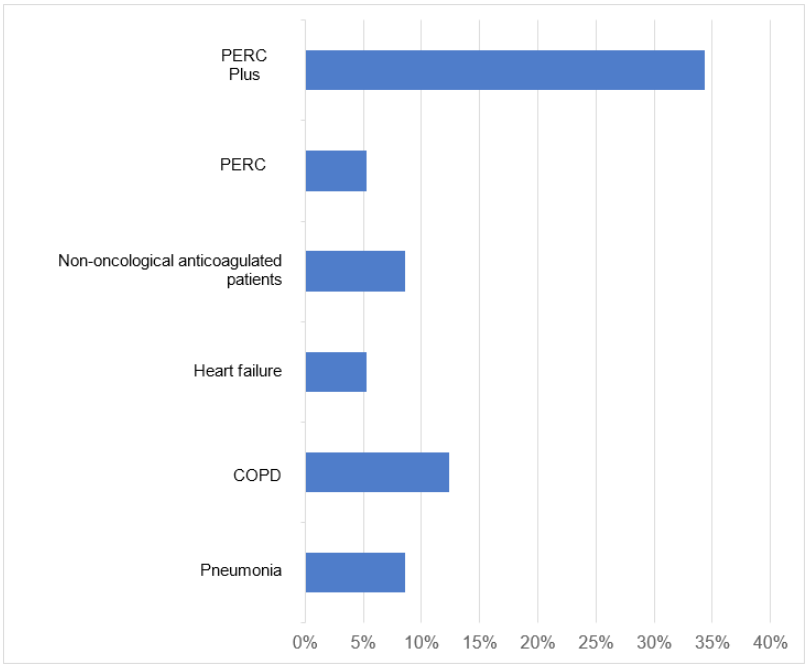
Figure 1. Percentage reduction of CT angiography with features with high negative predictive value and with PERC plus in patients with low Wells risk with a specificity of 100%.

4. Discussion

The findings highlight the importance of a structured approach to diagnosing Pulmonary Embolism (PE) in acute care settings. The 35% prevalence of PE in our cohort underscores the need for effective and efficient diagnostic strategies. The Wells score remains a valuable tool in risk stratification but has limitations, especially when applied to hospitalized patients and subjective factors.

The PERC scale, effective in ruling out PE in very low-risk patients, has limited applicability due to its low representativeness in the broader at-risk population. Our study demonstrates that integrating PERC with additional clinical criteria, such as alternative diagnoses, creates a more robust tool—PERC plus—with a 100% negative predictive value (NPV) and sensitivity in low-risk groups. This combined approach can potentially reduce unnecessary CT Angiography without compromising diagnostic accuracy.

Implementing the PERC plus scale could significantly decrease unnecessary diagnostic tests, optimizing resource allocation while maintaining diagnostic accuracy. This is particularly relevant for enhancing efficiency in emergency settings.

5. Conclusions

The PERC plus scale shows potential in excluding PE in patients classified as low risk by the Wells scale, potentially reducing the need for further tests in both outpatient and inpatient settings. Combining objective clinical criteria with the PERC scale could improve diagnostic accuracy and reduce unnecessary testing, thus enhancing patient management and resource utilization in acute care environments.

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