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ORIGINAL ARTICLE

The pulmonary embolism rule-out criteria (PERC) rule does not safely exclude pulmonary embolism

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Summary. *Background:* The Pulmonary Embolism Rule-out Criteria (PERC) rule is a clinical diagnostic rule designed to exclude pulmonary embolism (PE) without further testing. We sought to externally validate the diagnostic performance of the PERC rule alone and combined with clinical probability assessment based on the revised Geneva score. *Methods:* The PERC rule was applied retrospectively to consecutive patients who presented with a clinical suspicion of PE to six emergency departments, and who were enrolled in a randomized trial of PE diagnosis. Patients who met all eight PERC criteria [$PERC_{(-)}$] were considered to be at a very low risk for PE. We calculated the prevalence of PE among $PERC_{(-)}$ patients according to their clinical pretest probability of PE. We estimated the negative likelihood ratio of the PERC rule to predict PE. *Results:* Among 1675 patients, the prevalence of PE was 21.3%. Overall, 13.2% of patients were $PERC_{(-)}$. The prevalence of PE was 5.4% [95% confidence interval (CI): 3.1–9.3%] among $PERC_{(-)}$ patients overall and 6.4% (95% CI: 3.7–10.8%) among those $PERC_{(-)}$ patients with a low clinical pretest probability of PE. The PERC rule had a negative likelihood ratio of 0.70 (95% CI: 0.67–0.73) for predicting PE overall, and 0.63 (95% CI: 0.38–1.06) in low-risk patients. *Conclusions:* Our results suggest that the PERC rule alone or even when combined with the revised Geneva score cannot safely identify very low risk patients in whom PE can be ruled out without additional testing, at least in populations with a relatively high prevalence of PE.

Keywords: D-dimer, decision-making, decision rule, diagnosis, pulmonary embolism, venous thromboembolism.

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Introduction

Because the symptoms and signs of pulmonary embolism (PE) are common and nonspecific, the definitive diagnosis or exclusion of PE is generally based on validated diagnostic strategies combined with clinical probability assessment, D-dimer (DD) testing and imaging, such as helical multidetector computed tomography (MDCT). Evidence from recent studies suggests that the prevalence of PE among patients who undergo diagnostic work-up has decreased from 30% to below 10% [1], possibly as a consequence of the wide availability of DD testing that may lower physicians' threshold of clinical suspicion and lead to overtesting. While a negative, highly sensitive DD test reliably excludes venous thromboembolism (VTE) in patients with a non-high clinical pretest probability, DD tests have a low specificity, leading to false-positive result rates of 50% or more [2]. Because positive D-dimer results are usually followed by costly additional tests (usually MDCT), the high false-positive test rate exposes many patients to unnecessary risks, such as contrast-induced allergic reactions and nephropathy, or the delayed occurrence of radiation-induced solid tumors [3–5].

The Pulmonary Embolism Rule-out Criteria (PERC) rule was developed to identify patients at such a low pre-test risk for PE that PE can safely be excluded without the need for DD testing, thus avoiding false-positive DD results [6] and the risks of unnecessary testing. The rule is based on eight clinical criteria (Table 1A). Patients who meet these eight criteria are identified as PERC-negative [$PERC_{(-)}$] and appear to have a

Table 1 The Pulmonary Embolism Rule-out Criteria (PERC) rule (A) and the revised Geneva score (B)

(A) The Pulmonary Embolism Rule-out Criteria (PERC) rule [9]*
Age < 50 years
Pulse < 100 bpm
Pulse oxymetry > 94%
No unilateral leg swelling
No hemoptysis
No surgery or trauma within 4 weeks
No prior deep vein thrombosis or pulmonary embolism
No oral hormone use

(B) The revised Geneva score [24]	
Risk factors	Points
Age > 65 years	1
Previous deep vein thrombosis or pulmonary embolism	3
Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month	2
Active malignant condition (solid or hematologic malignant condition, currently active or considered cured < 1 year)	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate	
75–94 beats min^{-1}	3
≥ 95 beats min^{-1}	5
Pain on lower-limb deep venous palpation and unilateral edema	4
Clinical probability	
Low	0–3
Intermediate	4–10
High	≥ 11

*Patients who meet all of these eight criteria are considered to be at a very low risk for pulmonary embolism.

very low pretest probability of PE, with a residual risk of PE similar to the risk after a normal pulmonary angiogram [7].

A series of retrospective and prospective validation studies demonstrated that $PERC_{(-)}$ patients have a risk of PE varying between 0% and 1.4% [8–11]. However, these validation studies included selected patients who were at low risk for PE (e.g. patients with a low probability of PE based on physician assessment or with pleuritic chest pain only) or were limited by a small sample size [8–11]. More importantly, the prevalence of PE only varied between 5.3% and 12% in these studies [8–12]. When applied to a sample of unselected patients with an overall PE prevalence of 26%, 6.7% of $PERC_{(-)}$ patients had PE, a proportion that is unacceptably high [13]. It has therefore been suggested that the PERC rule should be applied only to patients at a very low risk for PE, which requires the application of another PE clinical decision rule [14].

The goal of the present study was to assess the diagnostic performance of the PERC rule alone and in combination with clinical probability assessment based on the revised Geneva score in a large sample of patients with suspected PE.

Methods

We tested the PERC rule using prospectively collected data from a clinical trial that evaluated a diagnostic algorithm for PE based on MDCT [15]. The trial enrolled patients with suspected PE from emergency departments at six university hospitals in Switzerland, France and Belgium between 1 January 2005 and 30 August 2006. Consecutive adult outpatients who were treated in the emergency department (ED) with a clinical suspicion of PE were potentially eligible. Patients were excluded from the present study if they had a contraindication to MDCT (i.e. allergy to iodine contrast agents, creatinine clearance < 30 mL min^{-1} or pregnancy), a terminal illness with an expected survival of < 3 months, a previous documented diagnosis of PE or were receiving anticoagulant therapy at presentation. The criteria used to establish the diagnosis of PE were a positive MDCT or pulmonary angiography, a high-probability ventilation/perfusion lung scan or a proximal deep vein thrombosis (DVT) documented by compression ultrasonography. PE was considered ruled out if patients had (i) a low or intermediate probability of PE and an ELISA DD < 500 ng mL^{-1} or an ELISA DD ≥ 500 ng mL^{-1} and a negative MDCT or (ii) a high clinical probability of PE, a negative MDCT plus a normal ventilation-perfusion lung scan and/or a negative pulmonary angiography. The pretest clinical probability of PE was determined using the revised Geneva score (Table 1B). Plasma DD was assayed using an automated quantitative analyzer (rapid ELISA assay, Vidas DD; BioMérieux, Marcy-l'Etoile, France) [16]. Compression ultrasonography and MDCT followed standard protocols which have been described elsewhere [17–19]. Variables comprised in the PERC rule were part of the routine prospective data collection within the trial. The PERC rule results did not influence the management of patients in the initial study. The trial was approved by the ethics committees of all participating study sites.

All patients included in the study underwent a 3-month follow-up, at the end of which all patients and/or their family physician were interviewed by telephone to disclose all health-related events since their hospital discharge. Charts were reviewed only in those cases where there was a hospital readmission for any cause or death during the follow-up period. The proportion of venous thromboembolic events in the 3-month follow-up period was assessed in all patients in whom PE was considered ruled out based on the initial assessment and who did not receive anticoagulants. Diagnoses of venous thromboembolic events during follow-up were established on the basis of abnormal results on ultrasonography for DVT, a ventilation-perfusion lung scan showing a high-probability pattern or CT or angiography showing intraluminal defects. Deaths were adjudicated as related, possibly related or unrelated to PE by three blinded, independent experts. We used a combination of index visit testing and follow-up information as a reference standard for the final diagnosis.

Statistical analyzes

Baseline characteristics between PERC-positive and -negative patients were compared using the χ^2-test for categorical variables or the Mann–Whitney *U*-test for continuous variables. We calculated the PERC rule's sensitivity, specificity and positive and negative predictive values and likelihood ratios for predicting PE. For all analyzes, a bilateral $P < 0.05$ was indicative of statistical significance. All analyzes were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Overall, 1693 patients were included in the per-protocol analysis of the clinical trial [15]. We excluded 17 patients in whom the PERC rule could not be assessed and one patient who was lost to follow-up, leading to a final study sample of 1675 patients. Overall, 221 patients [13.2%, 95% confidence interval (CI): 11.6–14.9%] met all the criteria of the PERC rule [$PERC_{(-)}$]. Compared with patients who did not meet at least one criterion of the PERC rule [$PERC_{(+)}$], $PERC_{(-)}$ patients were younger and were less likely to have active malignancy, dyspnea, varicose veins and elevated DD values (Table 2). $PERC_{(-)}$ patients were more likely to have chest pain and had better arterial oxygen saturation values, and a lower heart and respiratory rate. Among the 221 $PERC_{(-)}$ patients, 188 (85.1%, 95% CI: 79.7–89.5%) had a low clinical pretest probability and 33 (14.9%, 95% CI: 10.5–20.3%) had an intermediate clinical pretest probability according to the revised Geneva score. No $PERC_{(-)}$ patient had a high clinical pretest probability.

Overall, 357 patients (21.3%, 95% CI: 19.4–23.4%) were diagnosed with PE based on the initial assessment and during the 3-month follow-up. Among the 221 $PERC_{(-)}$ patients, 5.4% (95% CI: 3.1–9.3%) had PE. When stratified by the clinical pretest probability based on the revised Geneva score, the prevalence of PE was 6.4% (95% CI: 3.7–10.8%) among low-risk and 0% (95% CI: 0.0–10.4%) among intermediate-risk $PERC_{(-)}$ patients (Table 3).

Overall, the PERC rule had a negative predictive value and negative likelihood ratio for PE of 94.6% (95% CI: 90.8–96.9%) and 0.70 (95% CI: 0.67–0.73), respectively (Table 4). Among low-risk patients based on the revised Geneva rule, the PERC rule had a negative predictive value of 93.6% (95%CI: 89.2–96.3%) and a negative likelihood ratio of 0.63 (95%CI: 0.38–1.06).

Discussion

We found that the PERC rule identified only a modest proportion of patients with suspected PE as a very low risk (13.2%) and that the prevalence of PE among these patients was 5.4%. When combined with the revised Geneva score, the diagnostic performance of the PERC rule did not improve. $PERC_{(-)}$ patients with a low probability of PE based on the revised Geneva score had a 6.4% probability of PE, a risk that is unacceptably high. Thus, the PERC rule, alone or combined

Table 2 Patient baseline characteristics

	N (%) or median (IQR)			
	All (n = 1675)	$PERC_{(-)}$ (n = 221)	$PERC_{(+)}$ (n = 1454)	P-value
Male gender	758 (45.3)	109 (49.5)	649 (44.7)	0.18
Age, years	61 (45–76)	40 (33–45)	65 (51–77)	< 0.001
Prior history of VTE	300 (17.9)	0 (0.0)	300 (20.6)	< 0.001
Active malignancy	126 (7.5)	5 (2.3)	121 (8.3)	0.001
Surgery, trauma or fracture within 1 month	134 (8.0)	0 (0.0)	134 (9.2)	< 0.001
Oral hormone use	147 (8.8)	0 (0.0)	147 (10.1)	< 0.001
Chest pain	1150 (68.7)	192 (86.9)	958 (66.0)	< 0.001
Dyspnea	1206 (72.0)	120 (54.3)	1086 (74.7)	< 0.001
Syncope	353 (21.1)	44 (19.9)	309 (21.3)	0.64
Hemoptysis	83 (5.0)	0 (0)	83 (5.7)	< 0.001
Heart rate, bpm	84 (76–99)	77 (70–86)	87 (74–100)	< 0.001
Respiratory rate, rpm	20 (16–28)	16 (14–20)	20 (16–24)	< 0.001
O_2 saturation, %	96 (93–98)	98 (97–99)	96 (93–98)	< 0.001
Symptoms of DVT	200 (11.9)	22 (10.0)	178 (12.2)	0.33
Clinical signs of DVT	153 (9.1)	6 (2.7)	147 (10.1)	< 0.001
Unilateral leg swelling	121 (7.2)	0 (0)	121 (8.3)	< 0.001
Varicose veins	350 (20.9)	16 (7.3)	334 (23.1)	< 0.001
D-dimer < 500 ng mL^{-1}	547 (32.7)	149 (67.4)	398 (28.3)	< 0.001
Clinical pretest probability of PE*				
Low	587 (35.0)	188 (85.1)	399 (27.4)	< 0.001
Intermediate	1038 (62.0)	33 (14.9)	1005 (69.1)	
High	50 (3.0)	0 (0)	50 (3.5)	

PERC, pulmonary embolism rule-out criteria; IQR, interquartile range; VTE, venous thromboembolism; bpm, beats per minute; rpm, respirations per minute; DVT, deep vein thrombosis; PE, pulmonary embolism. *Based on the revised Geneva score.

Table 3 Prevalence of pulmonary embolism by PERC rule and clinical pretest probability based on the revised Geneva score

	Percent (95% Confidence Interval)			
	All (n = 1675)	Low pretest probability (n = 587)	Intermediate pretest probability (n = 1038)	High pretest probability (n = 50)
$PERC_{(+)}$	23.7 (21.6–26.0)	11.3 (8.5–14.8)	25.7 (23.1–28.5)	84.0 (71.5–91.7)
$PERC_{(-)}$	5.4 (3.1–9.3)	6.4 (3.7–10.8)	0.0 (0.0–10.4)	–

Table 4 Diagnostic performance of the PERC rule according to clinical pretest probability of pulmonary embolism based on the revised Geneva score (n = 1675)

	Parameter (95% confidence interval)			
	All	Low pretest probability	Intermediate pretest probability	High pretest probability
Sensitivity (%)	96.6 (94.2–98.1)	79.0 (66.7–87.5)	100.0 (98.5–100)	100 (91.6–100)
Specificity (%)	16.0 (14.0–17.9)	33.2 (29.3–37.3)	4.2 (3.0–5.9)	0
PPV (%)	23.7 (21.6–26.0)	11.3 (8.5–14.8)	25.7 (23.1–28.5)	84.0 (71.5–91.7)
NPV (%)	94.6 (90.8–96.9)	93.6 (89.2–96.3)	100 (89.6–100)	
LR+	1.15 (1.11–1.18)	1.18 (1.02–1.37)	1.04 (1.03–1.06)	1.00
LR−	0.70 (0.67–0.73)	0.63 (0.38–1.06)	0	

PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio.

with another clinical decision rule, cannot be used to safely rule out PE without additional tests, at least not in populations with a relatively high prevalence of PE.

Our findings are consistent with the results from a previous retrospective analysis conducted in an European cohort of 965 consecutive ED patients, with an overall PE prevalence of 26% [13]. In that study, the prevalence of PE was 6.7% (95%CI: 3–14%) among $PERC_{(-)}$ patients.

In contrast, the prevalence of PE was substantially lower in previous studies validating the PERC rule (5.3–12.0%), resulting in a much lower false-negative rate (0–1.4%) among $PERC_{(-)}$ patients [8–11]. We have several potential explanations for the lower PE prevalence in these studies. First, several studies applied the PERC rule to patients with a low clinical probability of PE (e.g. based on clinical gestalt), which may have resulted in a low overall PE prevalence [6,8,9]. Second, the majority of studies validating the PERC rule were conducted in the USA where the prevalence of PE among patients with a clinical suspicion of PE may be lower than in Europe [13]. This phenomenon has been attributed to a lower test threshold in the USA, where the fear of lawsuits may promote a more 'defensive' medicine [20–22]. Although the LR(−) in the present study was somewhat higher than in previously published studies [9,13], the LR(−) was still within the upper 95% confidence limit of these studies.

What other options do clinicians have to avoid false-positive DD results? Preliminary evidence suggests that the threshold for defining an abnormal DD result can be increased in elderly patients, without compromising patient safety. In a retrospective analysis, a DD cut-off of 10 × age in patients over 50 years safely reduced the number of false-positive DD results by up to 18% [23]. However, the safety of age-adjusted DD cut-offs needs to be prospectively validated before age adjustment of DD results can be generally recommended.

Our study has several limitations. First, the present study was performed within a clinical trial to compare two diagnostic strategies for PE, and was not originally designed to validate the PERC rule. Although our validation of the PERC rule is retrospective, the data used to assess the PERC rule were collected prospectively, minimizing the risk of information bias. Second, because the clinical trial excluded 32% of patients, mostly because of severe renal failure and the inability to give informed consent, we cannot entirely rule out the possibility of a selection bias. However, because excluded patients were more likely to be older and sicker and probably had an even higher prevalence of PE, it is very unlikely that the PERC rule would have had a better diagnostic performance in this patient group. Third, our study excluded patients with severe renal failure (creatinine clearance < 30 mL min^{-1}) and terminally ill patients. Thus, it is possible that our results are not applicable to those patient subgroups. Finally, because all participating hospitals were tertiary care centers, the risk of referral bias cannot be entirely excluded. However, because several centers also served as primary care centers for their local populations, the risk of such a bias seems low.

In conclusion, our results indicate that the PERC rule, even when combined with the revised Geneva score, cannot safely rule out PE without additional testing, at least not in populations with a relatively high prevalence of PE.

Addendum

O. Hugli designed the study, participated in the statistical analysis of the data and drafted the manuscript. M. Righini collected the data of the initial study, participated in the design

of the protocol, helped to analyze the data and to write the manuscript. G. Le Gal participated in the design of the protocol, was responsible for the statistical analysis and helped to write the manuscript. P.-M. Roy, O. Sanchez, F. Verschuren, G. Meyer and H. Bounameaux collected the data of the initial study, participated in the analysis of the data and critically reviewed the manuscript. D. Aujesky collected the data of the initial study, participated in the conception of the study and the statistical analysis of the data, drafted and revised the manuscript.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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