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ORIGINAL ARTICLE

Safety of the pulmonary embolism rule-out criteria rule: Findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry

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Abstract

Background: The diagnostic strategy for pulmonary embolism (PE) includes a D-dimer test when PE probability is low or intermediate, but false-positive D-dimer results are frequent and can result in an unnecessary computed tomography pulmonary angiogram. The PE rule-out criteria (PERC) rule excludes PE without D-dimer testing when pretest probability is <15%. The aim of this study was to assess the safety of the PERC rule strategy in patients included in the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry.

Methods: This retrospective cohort study used data from the RIETE registry, an ongoing, international prospective registry of patients with objectively confirmed venous thromboembolism. The primary outcome was the failure rate of the PERC strategy, represented by the proportion of PERC-negative (PERC-N) patients with a PE included in the registry. Secondary outcomes were a comparison of the clinical characteristics, treatment strategy, and outcome of PERC-N versus PERC-positive (PERC-P) patients at 3 months.

Results: From 2001 to 2021, a total of 49,793 patients with acute PE were enrolled in the RIETE registry. We included 48,903 in the final analysis after exclusion of 890 patients with an undetermined PERC status. Only 346 patients were PERC-N with a failure rate of 0.7% (95% confidence interval 0.6%–0.8%). PERC-N patients presented more frequently with chest pain but less often with dyspnea, syncope, or hypotension. They also had subsegmental or segmental PE more frequently, were more often treated with direct oral anticoagulants, and received mechanical or pharmacological thrombolysis less often. In addition, PERC-N patients had a lower incidence of recurrent deep vein thrombosis, major bleeding, and death attributed to PE during the 3-month follow-up.

[†]A full list of RIETE investigators is given in Appendix A.

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Conclusions: A low failure rate of the PERC rule was observed in the RIETE registry, thus supporting its use to safely identify patients with an unlikely probability of PE.

KEYWORDS
diagnostic algorithm, PERC, pretest probability, pulmonary embolism, pulmonary embolism rule-out criteria rule, RIETE

INTRODUCTION

Pulmonary embolism (PE) is a common and potentially fatal disease. The validated diagnostic strategy to identify PE in hemodynamically stable patients combines the assessment of the pretest probability of PE derived from the revised Geneva score, Wells' criteria,[1–4] or from the unstructured clinician's gestalt.[1,5] When PE probability is low or intermediate, D-dimers are measured.[1] If they are above the predefined cutoff, pulmonary vascular imaging, mainly pulmonary computed tomography angiography (CTPA), rules in or out PE. However, D-dimer results are false positive in >50% of cases,[6] resulting in unnecessary CTPAs. Fear of missing PE, combined with the ubiquitous availability of D-dimers and CTPA, has led to more frequent testing, thus leading to an increasing number of CTPAs performed over the past decades[7] but a decreasing diagnostic yield.[8]

To reduce the proportion of false-positive D-dimer results, the positivity threshold has been increased, based on older age or a lower clinical probability.[9–11] In a more radical approach, the PE rule-out criteria (PERC) rule, an eight-item set of clinical criteria (Table 1), proposes to rule out PE without D-dimer testing when no criteria are met (PERC-negative [PERC-N]) in patients with a pretest PE probability of <15%.[12,13] The risk–benefit ratio of further testing is unfavorable as PE probability is lower than the test threshold for PE, estimated at 1.8%.[12,14,15] The safety of a PERC rule diagnostic strategy is critical. In 2012, a meta-analysis based on 12 studies including 14,844 patients from six countries supported PERC rule use when pretest PE probability was low (pooled specificity and negative likelihood ratios of 97% and 0.17, respectively).[13] Nevertheless, its external validity and transportability have been questioned as six of the 12 studies, which represented 74% of all patients, were authored by at least one of the original authors of the rule.[16]

A recent meta-analysis with over 35,000 patients showed that the PERC rule was safe to use in emergency care centers when patients presented without referral by a general physician or specialist. In this setting with a PE prevalence of 7%, the PERC rule had a failure rate of 1.12% when combined with Wells' criteria or 0.90% with clinical gestalt.[17] However, with a PE prevalence of 20% in referred secondary care, the failure rate was 6.01%, with the upper bound of the 95% confidence interval (CI) reaching 8.8%, thus indicating an insufficient safety profile when used in a population with a higher PE prevalence.[17–20] Of note, this point remains controversial as some studies showed that the PERC rule was safe when PE prevalence was <15% or even close to 30% when combined with a low probability assessed by gestalt.[21] The safety of the PERC was also confirmed in a randomized noninferiority study,[22] but the number of nonenrolled eligible patients was not reported and the proportion of low-probability patients in the PERC arm was higher, which was suggestive of an inclusion bias.[23] Finally, a large European prospective observational study found that the PERC failure rate was only 1.2%, with a PE prevalence of 11.4%.[24] Although the UK National Institute for Health and Care Excellence (NICE) guidelines encourage clinicians to consider using the PERC rule if clinical suspicion of PE is <15% based on their gestalt,[23] it is not yet recommended in the latest European guidelines.[1]

Evidence regarding the PERC rule is based on publications from clinical trials, but their generalizability to the real-life clinical setting may be limited.[25] The Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry provides data on the management of venous thromboembolism (VTE) in such a setting with an unselected patient population.[26] Notably, the registry offers a unique opportunity to assess the performance of the PERC rule by using its large international database of VTE patients enrolled in diverse types of hospitals over the past 20 years. The purpose of this study was to assess the safety of the PERC rule in patients included in the RIETE registry.

TABLE 1 The PERC rule.

Age < 50 years
Pulse < 100 beats/min
Pulse oximetry > 94%
No unilateral leg swelling
No hemoptysis
No surgery or trauma within 4 weeks
No prior DVT or PE
No oral hormone use

Note: Patients who meet all eight criteria are considered to be at a very low risk for pulmonary embolism.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; PERC, PE rule-out criteria.

METHODS

Study design

This retrospective cohort study used data from the RIETE registry from March 1, 2001, through December 31, 2021. The methodology of the RIETE registry has been described elsewhere.[27] Briefly, this ongoing, international prospective registry has enrolled consecutive patients with objectively confirmed VTE since 2001. At each

participating site, consecutive patients are screened by the site investigators and checked for eligibility. Regular audits are conducted to check for the sequential inclusion of patients, data completeness, and accuracy. Patients are excluded if they are currently participating in a therapeutic clinical trial involving blinding of their medication or if they are unavailable for a 3-month follow-up. The ethics committees at all participating sites approved the protocol for enrollment and all patients or their health care proxies provided informed consent. As of January 2022, the registry contained data from over 101,000 patients from 210 hospitals in 26 countries, followed up for at least 3 months.

Measures

The primary outcome of our study was the overall percentage of PE patients included in the RIETE registry who were PERC-N and therefore represented the failure rate of the PERC rule. The registry does not provide all the items required to estimate the pretest probability of PE as clinicians' gestalt, "PE as the most likely diagnosis" in the Wells' score, and "unilateral lower leg pain" in the revised Geneva score are not recorded. Therefore, we draw a parallel with the two-tier Wells' score: given the shared criteria between the Wells' score and the PERC rule, PERC-N could have a maximum of 4 points (Appendix S1), i.e., PE unlikely using the two-tier rule with a prevalence of <15%.[28]

Secondary outcomes were: (1) to identify if specific characteristics suggested by others,[12,24] such as chest pain, pregnancy, or postpartum status, were associated with PERC-N cases; (2) to compare the localization of PE, a mandatory item since 2012 in the database, its hemodynamic repercussion on the right ventricle, treatment strategies, and outcome at 3 months of PERC-N versus PERC-positive (PERC-P) patients, with the aim to determine the clinical significance of missed PE in both patient groups[12]; and (3) to assess if the proportion of PERC-N patients had decreased over the years in the registry, a potential indicator that more PEs had been left undiagnosed as the PERC rule has been more widely applied.

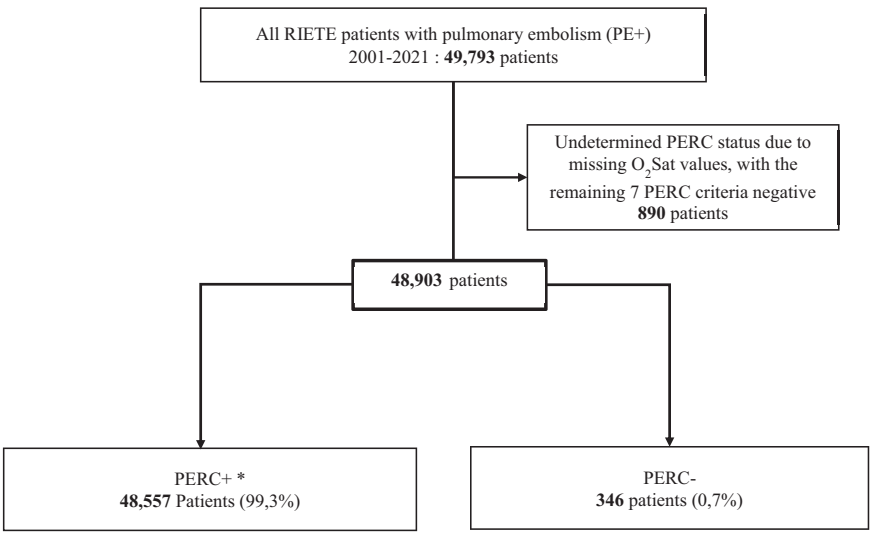
Data analysis

Descriptive statistics are presented as the mean and standard deviation for continuous variables or as proportions for categorical variables. Baseline characteristics between groups were compared using the chi-square test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. We excluded multiple patient visits and verified the normal distribution of continuous variables. We used a chi-square test to compare the burden of the index PE (the proportion of patients with PEs in subsegmental only, segmental, more proximal arteries, or not provided) and also the proportion of patients in each of the four categories. For clinical outcomes, odds ratios and corresponding 95% CIs were calculated. Incidence rates were calculated as the cumulative incidence (events per 100 patient-years of follow-up) and compared between PERC-N and PERC-P patients. Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0. We defined a bilateral *p*-value of <0.05 to be statistically significant in all analyses, with no adjustment for multiple comparisons.

RESULTS

Characteristics of study subjects

From March 1, 2001, to December 31, 2021, a total of 49,793 patients with objectively confirmed acute, symptomatic PE were enrolled in the RIETE registry (Figure 1). Of these, 20,438 (41%) had missing oxygen saturation (O_2Sat) values, but as 19,548 (96%) had at least one other positive PERC criteria, they were considered to be PERC-P. PERC status could not be determined



*≥1 positive PERC criteria, with and without missing blood gas values.

FIGURE 1 Study flow diagram. O_2Sat, oxygen saturation; PE, pulmonary embolism; PERC, PE rule-out criteria; PERC-N (PERC–), PERC negative; PERC-P (PERC+), PERC positive; RIETE registry, Registro Informatizado de la Enfermedad TromboEmbolica venosa registry.

in 890 (4.3%) patients despite all PERC criteria being negative, except for a missing O_2Sat, and they were excluded from our analyses.

PERC-P patients were similar in age to PERC-N patients, with similar VTE risk factors, apart from less frequent immobilization (Appendix S1). They had similar underlying diseases but presented less frequently with dyspnea and had a lower respiratory rate, while their heart rate was similar. PERC-P patients also had similar rates of measured and positive troponins, as well as echocardiogram results, with similar pulmonary pressures or signs of right ventricular dysfunction, and the same proportion was classified at low risk of a poor outcome. By contrast, PERC-P patients had a few more severe characteristics than PERC-N patients, such as a higher proportion of active cancer and more frequent syncope, hypotension, and PE located in the lobar and pulmonary arteries (Appendices S1 and S1).

Primary and secondary outcomes

A total of 48,903 patients were included in the final analysis. Among these, 48,557 (99.3%) had at least one positive PERC item. The three most frequently positive criteria were age ≥ 50 years, O_2Sat ≤ 94%, and a heart rate of ≥100 beats/min. Only 346 patients were PERC-N, representing a failure rate of 0.7% (95% CI 0.6%–0.8%). These patients were predominantly male and younger and females were more likely to be pregnant or postpartum, but they were less likely to have an active cancer, leg varicosities, chronic heart failure or chronic pulmonary disease, anemia, or renal failure (Table 2).

In terms of clinical presentation, PERC-N patients had chest pain and a lower respiratory rate more often but dyspnea, syncope, or hypotension less often (Table 2). Regarding diagnostic tests, they received the same percentage of CTPAs, a lower percentage of compression ultrasonography that was more frequently negative, and more pulmonary arteriographies. Diagnosed PEs were more likely to be subsegmental or segmental and associated with lower pulmonary artery pressure and a lower proportion of right ventricle hypokinesis. They had a similar frequency of D-dimer and troponin measurements, with less likelihood of positive results. A higher proportion of PERC-N patients were classified at low risk of 30-day mortality or of bleeding during anticoagulation.

For their initial anticoagulation, PERC-N patients were treated more often with direct oral anticoagulants (Table 3). They less often received mechanical or pharmacological thrombolysis. Long-term anticoagulation relied more frequently on direct oral anticoagulants and less often on vitamin K antagonists (VKA) or low-molecular-weight heparin (LMWH). Patients in all groups were anticoagulated for slightly more than 6 months on average. PERC-N patients had a lower incidence of recurrent deep vein thrombosis (DVT), a 10-fold lower incidence of major bleeding, and a sevenfold lower incidence of death attributed to PE (Table 4). After discontinuation of

TABLE 2 Patients' clinical and paraclinical characteristics, according to the PERC rule.

	PERC-negative ($n = 346$)	PERC-positive ($n = 48,557$)
Clinical characteristics		
Male	208 (60)	22,856 (47)***
Age (years)	39.0 (±7.8)	67.7 (±16.4)***
Body weight (kg)	79.6 (±17.8)	76.6 (±16.6)**
PERC items		
Age ≥ 50 years	—	41,433 (85)
O_2Sat ≤ 94%, $n = 29,365$	—	19,638 (68)
Pulse ≥ 100 beats/min	—	17,888 (37)
Unilateral leg swelling	—	12,550 (26)
Prior VTE	—	7003 (14)
Recent surgery	—	5436 (11)
Estrogen therapy	—	2655 (5.5)
Hemoptysis	—	2576 (5.3)
Recent trauma	—	1862 (3.8)
Other VTE risk factors		
Immobility for other reasons	78 (23)	9662 (20)
Pregnancy or postpartum	22 (6.4)	342 (0.70)***
Active cancer	20 (5.8)	8304 (17)***
Leg varicosities	13 (3.8)	8036 (17)***
Recent travel	13 (3.8)	1248 (2.6)
Underlying diseases		
Chronic heart failure	8 (2.3)	4283 (8.8)***
Chronic lung disease	14 (4.0)	6899 (14)***
Recent major bleeding	5 (1.4)	1188 (2.4)
Anemia	76 (22)	15,779 (32)***
CrCl levels < 60 mL/min	3 (0.9)	18,141 (37)***
Signs and symptoms,		
Dyspnea	257 (74)	39,244 (81)**
Chest pain	242 (70)	21,470 (44)***
Syncope	19 (5.5)	6929 (14)***
O_2Sat (%)	97.0 (±3.7)	90.2 (±9.4)***
SBP levels < 90 mm Hg	2 (0.6)	1625 (3.3)**
SBP levels < 100 mm Hg	16 (4.6)	3856 (7.9)*
Heart rate (beats/min)	81 (±11)	93 (±20)***
Respiratory rate (breaths/min), $n = 19,753$	19.0 (±4.7)	21.0 (±6.6)***
Diagnostic tests		
Positive chest CTA	295 (85)	40,429 (83)
High-probability V/Q lung scintigraphy	36 (10)	6806 (14)
Pulmonary arteriography	15 (4.3)	1171 (2.4)*
Compression ultrasonography	173 (61)	29,645 (74)***

TABLE 2 (Continued)

	PERC-negative ($n=346$)	PERC-positive ($n=48,557$)
Positive	35 (20)	18,023 (37)***
Pulmonary vascular location on CT scan		
Subsegmental arteries only	33 (11)	1446 (3.0)***
Segmental arteries	73 (25)	6534 (13)***
Lobar arteries	52 (18)	8018 (17)
Pulmonary arteries	32 (11)	10,779 (22)***
Data not available	114 (39)	22,126 (46)*
Echocardiogram	139 (40.2)	21,883 (45.1)*
PAP levels (mm Hg)	37.6 (±19.9)	45.3 (±16.7)***
Right ventricle hypokinesis	16 (13)	4222 (23)*
Blood tests		
Measured troponin levels	118 (34)	15,059 (31)
Increased troponin levels, $n=15,152$	19 (16)	9623 (64)***
Measured D-dimer levels	264 (76)	36,264 (75)
Positive D-dimer levels	215 (81)	35,532 (98)***
Prognostic scores		
PESI ≤ 65 points	298 (86)	7739 (16)***
sPESI 0 point	292 (84)	16,598 (34)***
RIETE score low risk 0 point	229 (66)	12,509 (26)***

Note: Data are reported as *n* (%) or mean (±SD). Differences between PERC-positive patients vs. PERC-negative patients.

Abbreviations: CrCl, creatinine clearance; CTA, CT-angiography; DVT, deep vein thrombosis; O_2Sat, oxygen saturation; PAP, pulmonary artery pressure; PERC, pulmonary embolism rule-out criteria; PESI, pulmonary embolism severity index; sPESI, simplified PESI; SBP, systolic blood pressure; RIETE, Registro Informatizado de la Enfermedad TromboEmbolica venosa registry; VTE, venous thromboembolism.

*$p<0.05$; **$p<0.01$; ***$p<0.001$.

TABLE 3 Initial and long-term therapeutic strategies.

	PERC-negative ($n=346$)	PERC-positive ($n=48,557$)
Initial therapy[a]		
LMWH	267 (77)	40,313 (83)**
LMWH dose (IU/kg/day)	177 (±41)	177 (±41)
Unfractionated heparin	21 (6.1)	4020 (8.3)
Fondaparinux	7 (2.0)	679 (1.4)
DOACS	32 (9.3)	1344 (2.8)***
Thrombolytics	1 (0.3)	1197 (2.5)**
Inferior vena cava filter	5 (1.4)	1377 (2.8)
ECMO	0	12 (1.0)
Embolectomy	0	382 (0.9)
Long-term therapy		
VKA	174 (50)	27,811 (57)*
LMWH	67 (19)	12,068 (25)*
LMWH dose (IU/kg/day)	157 (±51)	152 (±45)
DOACS	99 (29)	6162 (13)***

Note: Differences between patients with positive vs. negative PERC.

[a]Eighty-nine patients undergoing embolectomy received LMWH. Three patients had ECMO and LMWH. Of these, 647 patients with inferior vena cava filter received LMWH and 220 patients with thrombolytic drugs also received LMWH.

Abbreviations: DOACS, direct-acting oral anticoagulants; ECMO, extracorporeal membrane oxygenation; LMWH, low-molecular-weight heparin; PERC, pulmonary embolism rule-out criteria; VKA, vitamin K antagonists.

*$p<0.05$; **$p<0.01$; ***$p<0.001$.

anticoagulation, PERC-N patients continued to have a lower incidence of recurrent DVT.

The absolute number of PERC-N patients increased over the years in the RIETE registry with 55 patients during the 2001–2005 period (16%; 95% CI 12%–20%) and 135 during the 2016–2021 period (39%; 95% CI 34%–44%). However, given the concomitant absolute increase of PERC-P patients, the relative proportion of PERC-N did not change between 2001 and 2015 and only increased significantly after 2015 ($p<0.05$; Figure 2A; Appendix S1). In the 2016–2021 period, PERC-N patients had less hypotension than during the precedent periods, less positive D-dimer levels and more were at low risk of 30-day mortality (Table 5). Since 2012, more PEs were located distally in the pulmonary arteries. Finally, PE in PERC-N patients was diagnosed progressively more often in larger hospitals.

DISCUSSION

In this retrospective cohort study based on the RIETE registry that included the highest number of PERC-N patients to date, we found that the PERC rule had a low failure rate when used in a large group of patients diagnosed with PE in diverse emergency department (ED) settings and mostly located in Europe. In addition, PERC-N patients had low 3-month rates of hemorrhagic complications or recurrence of VTE, but similar rates of PE recurrence once anticoagulation was discontinued.

Among 48,903 PE patients, 346 were retrospectively PERC-N, representing a failure rate of 0.7% in unlikely PE patients based on the two-tier Wells' score. This remained unchanged between 2001 and 2021. Compared to all PERC-P patients, PERC-N patients were predominantly male and younger, with fewer VTE risk factors and comorbidities and less cardiopulmonary repercussions from PE than PERC-P patients. These findings are consistent with a more distal PE, as found on CTPAs in the registry (Figure 2B). Although based on a small number of cases, others have also suggested that the PERC rule may miss low-risk events, such as small subsegmental PE.[22] This smaller clot burden is consistent with physicians' initial treatment that included invasive or thrombolytic treatments less frequently and direct oral anticoagulants more often and by patients' lower 30-day mortality risk scores and lower mortality during follow-up.

TABLE 4 Clinical outcomes during and after the course of anticoagulant therapy.

	During anticoagulation				After anticoagulation discontinuation			
	PERC-negative ($n=346$)		PERC-positive ($n=48,557$)		PERC-negative ($n=346$)		PERC-positive ($n=48,557$)	
	N	*N* per 100 patient-years	*N*	*N* per 100 patient-years	*N*	*N* per 100 patient-years	*N*	*N* per 100 patient-years
Patients	346 (100)		48,557 (100)		145 (42)		14,482 (30)	
Duration of therapy								
Days	190 (124–330)		190 (104–362)			182 (94–357)		180 (52–503)
<190 days	176 (0.51)		24,404 (0.50)			75 (52)		7461 (52)
Outcomes								
Recurrent PE	4	1.5 (0.5–3.5)	721	1.7 (1.6–1.8)	7	5.1 (2.2–10.0)	974	5.9 (5.6–6.3)
Recurrent DVT	0	—	467	1.1 (1.0–1.2)*	0	—	385	2.3 (2.1–2.6)*
Major bleeding	1	0.4 (0.0–1.8)	1692	4.0 (3.9–4.2)***	0	—	135	0.8 (0.7–1.0)
Sites of bleeding								
Gastrointestinal	1	0.4 (0.0–1.8)	541	1.3 (1.2–1.4)	0	—	54	0.3 (0.2–0.4)
Cerebral	0	—	343	0.8 (0.7–0.9)	0	—	43	0.3 (0.2–0.3)
Death	5	1.8 (0.7–4.0)	5705	13.4 (13.0–13.7)***	1	0.7 (0.0–3.6)	1614	9.7 (9.3–10.2)***
Causes of death								
PE	0	—	709	1.7 (1.5–1.8)*	0	—	34	0.2 (0.1–0.3)
Initial PE	0	—	591	1.4 (1.3–1.5)*	0	—	2	0.0 (0.0–0.0)
Recurrent PE	0	—	118	0.3 (0.2–0.3)	0	—	32	0.2 (0.1–0.3)
Bleeding	0	—	299	0.7 (0.6–0.8)	0	—	93	0.6 (0.5–0.7)
Gastrointestinal	0	—	84	0.2 (0.2–0.2)	0	—	27	0.2 (0.1–0.2)
Cerebral	0	—	123	0.3 (0.2–0.3)	0	—	46	0.3 (0.2–0.4)

Note: Data are reported as *n* (%) or median (IQR). Differences between patients with positive vs. negative PERC.

Abbreviations: DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; PERC, pulmonary embolism rule-out criteria.

*$p<0.05$; ***$p<0.001$.

The 0.7% false-negative PERC rate, with an upper 95% CI of 0.8%, lies largely under the 1.8% pretest probability threshold, below which the risks of investigation and associated complications outweigh the risks of a missed PE.[12] It also lies under the 1.7% false-negative rate of CT scans in the PE diagnosis.[29] Our study results therefore support the use of the PERC rule. However, this 0.7% rate may be spuriously low for several reasons. First, 890 of the 49,793 patients (1.8%) were excluded due to an undetermined PERC status owing to a missing O_2Sat value. Missing O_2Sat values are frequent among patients in the RIETE registry as it was not a mandatory variable during the first years of the registry (2001–2008). Since 2009, it is recorded only if the O_2Sat level is measured on room air. Levels in patients arriving to the ED receiving supplemental oxygen are not collected. If these 890 patients with missing O_2Sat were PERC-N, the failure rate would increase to 2.5% (95% CI 2.4%–2.7%). Second, only patients with diagnosed PE are enrolled in the RIETE registry, but up to 27.5% of PE patients may be initially misdiagnosed in the ED.[30] As PERC-N patients have slightly different PE symptoms and less severe cardiopulmonary PE repercussions, their PE diagnosis may be more likely to be missed. Interestingly, the proportion of PERC-N significantly increased in the 2016–2021 period, during which the results of the pivotal PERCEPIC and PROPER trials were published, supporting the use of the PERC rule.[22,24] However, the failure rate remained <1% and this higher proportion may be related to many other factors than the dissemination of the rule, such as the more widespread investigation of PE in the ED.[8]

Importantly, the PERC rule should only be applied to patients with a low pretest probability based either on clinician's gestalt or on a clinical prediction rule.[14] Although the pretest PE probability is not formally known here, the maximal Wells' score of PERC-N patients could have reached 4 points if they had cancer (Appendix S1), which affected only a small fraction of our patient population. As a result, 95% of PERC-N patients had a score of 3 points, associated with a <15% PE prevalence, which is the probability range below which the PERC rule can be safely used.[28] Thus, our results are in line with small studies that found a false-negative rate ranging from 0% to 1.39% when applying the PERC rule alone in an ED with a prevalence of PE between 5.3% and 11.8%.[16,31–35] The subjective question in the Wells score (an alternative diagnosis is less likely than PE) was not collected in the RIETE registry, but carries the greatest weight among all the score items to predict PE. However, in populations with a PE prevalence of between 4.5% and 10%, PE prevalence was

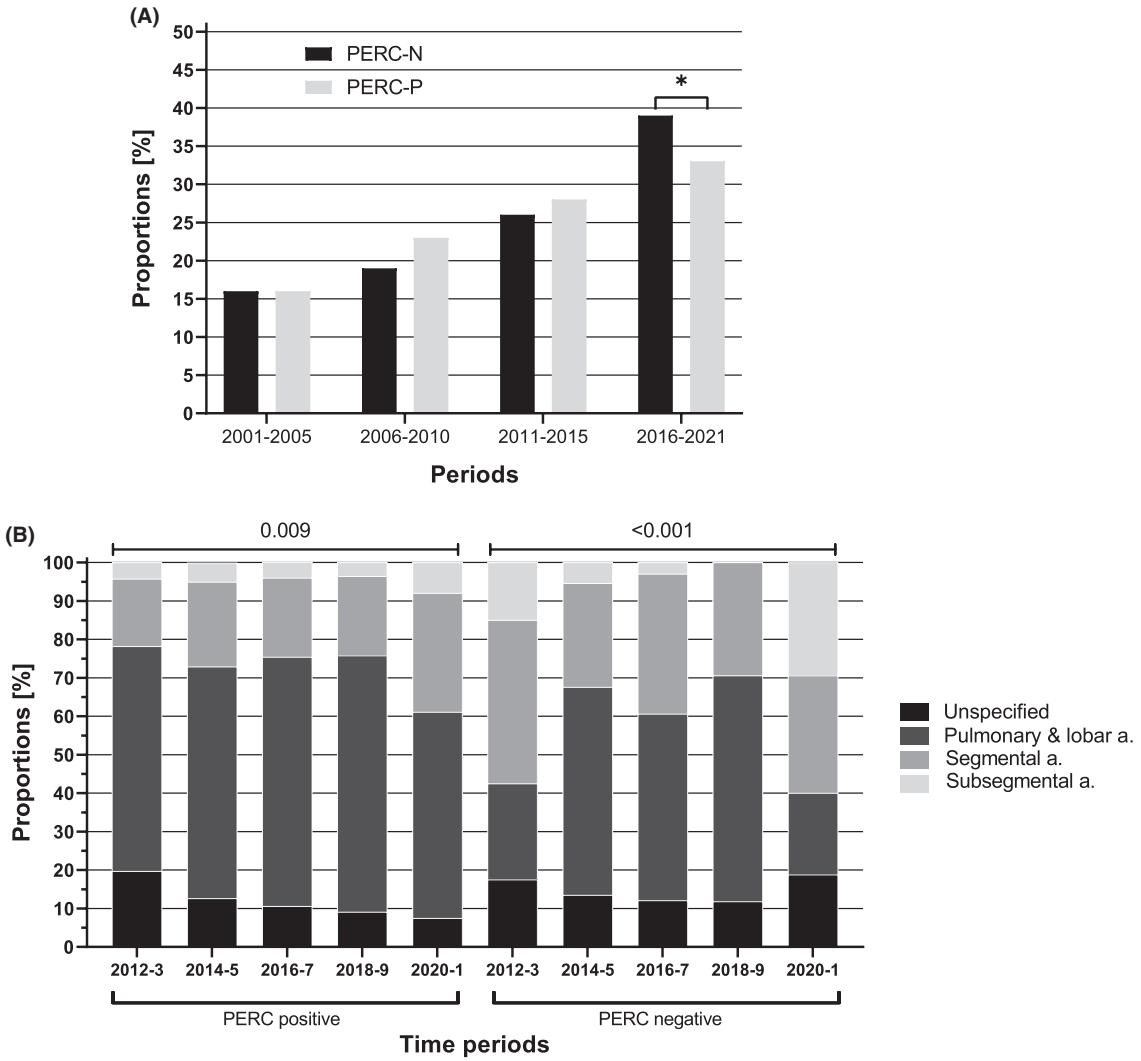


FIGURE 2 (A) Distribution of PERC-N and PERC-P patients by time periods. (B) Localization of PE in PERC-N and PERC-P in the RIETE registry by 2-year period since 2012. PERC, PE rule-out criteria; PERC-N (PERC–), PERC negative; PERC-P (PERC+), PERC positive.

between 0.5% and 6.5% if only the subjective question was positive, which is well below 15%.[35,36] Nevertheless, PE can be missed in up to 8.8% of patients if the PERC rule is used without a preliminary assessment of probability in patient populations with a PE prevalence of >15%.[17]

To the best of our knowledge, our study included the highest number of PERC-N patients to date. It also confirms findings from smaller earlier studies,[37] which found a higher proportion of chest pain (+26%) and a lower proportion of dyspnea (−7%) and right ventricular dysfunction (−10%) in PERC-N patients. The most common VTE risk factors in PERC-N patients was immobilization for reasons other than surgery or trauma, followed by pregnancy/postpartum status and active cancer. Including these three risk factors in the PERC rule would have reduced our number of PERC-N patients from 346 (0.7%) to 226 (0.5%), a 29% relative reduction.[24] Interestingly, a recently validated 4-level clinical PE probability score (4PEPS) included immobilization in the previous 4 weeks as a scoring item, but not cancer or pregnancy/postpartum status.[38] However, failure to include pregnancy in clinical prediction rules may result from the low inclusion rate of pregnant women in clinical trials, e.g., <3% in the 4PEPS study.[38] Furthermore, 18 PERC-N patients had a systolic blood pressure < 100 mm Hg. As systolic blood pressure is not a criterion used in the Wells or revised Geneva scores, its impact on the pretest probability of EP is uncertain. If considered as indicative of PE based on physician's gestalt, these patients would be excluded from the PERC-N patient group, leading to a further reduction of the PERC-N patients to 208 and a failure rate of 0.4%.

D-dimers were not measured in all PERC-N patients, despite having an unlikely probability of PE according to Wells score, but this proportion was higher than in recent publications.[8,39] D-dimers were not measured for reasons that were not documented, but it may reflect physicians' nonadherence with published PE guidelines.[40,41] Of note, when measured, D-dimers were positive only in 81% of PERC-N patients (Table 2) compared to 98% of PERC-P patients. This likely reflects the more distal PE location in PERC-N patients, associated with a significantly reduced D-dimer sensitivity.[42]

PERC-N patients were at low risk of complications from the VTE according to validated prognostic scores and no patient died of the

TABLE 5 PE presentation in patients with negative PERC.

	2001–2005 (*n* = 55)	2006–2010 (*n* = 65)	2011–2015 (*n* = 91)	2016–2021 (*n* = 135)
Proportion (%)	16	19	26	39
Initial presentation				
SBP levels < 90 mm Hg	1 (1.8)	1 (1.5)	0	0
SBP levels < 100 mm Hg	7 (13)	4 (6.2)	4 (4.4)	1 (0.7)***
Measured troponin levels	18 (33)	19 (29)	37 (41)	44 (33)
Increased troponin levels	0	2 (9.5)	6 (14)	11 (20)
Measured D-dimer levels	39 (71)	59 (91)**	64(70)	102(76)
Positive D-dimer levels	33 (85)	55 (93)	60 (94)	67 (66)*
DVT in lower limbs	9 (16)	4 (6.2)	9 (9.9)	10 (7.4)
Prognostic scores				
PESI ≤ 65 points	41 (75)	52 (80)	78 (86)	127 (94)***
sPESI 0 point	37 (67)	50 (77)	79 (87)**	126 (93)***
RIETE score 0 point	36 (65)	45 (69)	66 (73)	82 (61)
PE location on CT scan				
Subsegmental arteries	NA	NA	7 (7.7)*	26 (19)***
Segmental arteries	NA	NA	27 (30)***	43 (32)***
Lobar arteries	NA	NA	25 (27)***	24 (18)**
Pulmonary arteries	NA	NA	11 (12)**	20 (15)**
Unspecified	NA	NA	21 (23)*	22 (16)***
Countries				
Spain	55 (100)	51 (78)***	47 (52; 41–62)***	108 (80; 73–87)***
Rest of Europe	0	11 (17)***	41 (45; 35–55)***	26 (19; 13–26)***
United States	0	0	2 (2.2; 0–5.3)	0
Other	0	3 (4.6)	1 (1.1; 0–3.3)	1 (0.74; 0–2.2)
Hospital size[a]				
Small	20 (36)	24 (37)	30 (33)	29 (21)*
Intermediate	16 (29)	28 (43)	28 (31)	19 (14)*
Large	19 (35)	13 (20)	33 (36)	87 (64)***

Note: Data are reported as *n* (%) or *n* (%; 95% CI). Comparisons between patients.

Abbreviations: DVT, deep vein thrombosis; NA, not available; PERC, pulmonary embolism rule-out criteria; PESI, pulmonary embolism severity index; sPESI, simplified PESI.

[a]Small = less than 500 beds; intermediate = 500–1000 beds; large = over 1000 beds.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

index or recurrent PE during follow-up. They had a low risk of bleeding during anticoagulation, concordant with a low RIETE score, and none had a major bleeding event during follow-up. In addition, the overall mortality rate was much lower than for PERC-P patients. The rate of nonfatal VTE during the first 3 months of anticoagulation was usually around 3.8%, while the rate of fatal PE was 0.5%, both higher than observed in PERC-N patients.[43] During and after being anticoagulated, PERC-N patients had a similarly low rate of PE recurrence but a lower recurrence of DVT. These differences reflect the PERC-N patients' younger age, fewer comorbidities, and lower proportion of anticoagulation with LMWH and VKA.[44–47]

According to published clinical studies, PERC-N patients have a very low risk of recurrent PE or death at 3 months without anticoagulation.[22,24] However, the prevalence of PE was <5% in these studies and they had probably very few PERC-N patients. Our study showed that PERC-N patients had nonnull rates of recurrent PE or death, albeit much lower than in PERC-P patients during anticoagulation, but the rates of recurrent PE were similar after discontinuation of anticoagulation. Our data indicate that missed PEs are consequential in PERC-N patients.

PERC-N patients remained a stable proportion of PE patients during the first periods of the registry, but increased between 2016 and 2021 (Figure 2A). During this latter period, patients were diagnosed more frequently with more distal PE, lesser hemodynamic instability, and improved 30-day prognostic scores. An increasing use of the PERC rule in this period would have probably led to a decreasing

proportion of PERC-N patients in the RIETE registry as some PE patients would have remained undiagnosed. However, our results show the opposite. It is probable that clinicians have a lower threshold to test for PE due to a fear of missing this diagnosis and that improvements in CTPA performance over the past few years have led to the diagnosis of smaller PE, as reported in other settings.[48–50] An increased proportion of large hospitals participated in the RIETE database during this period and were probably associated with a higher proportion of PERC-N patients. A higher adherence to guidelines may have played a role in this increase, such as the use of the PERC rule.[51]

STRENGTHS AND LIMITATIONS

The strength of our study lies in the use of the RIETE registry, a large-scale, multinational, observational study that has been ongoing for the past 20 years, with the inclusion of PE patients covering the whole spectrum of PE severity managed in various international settings, all of which provide a good external validity to our results.

However, our study has several limitations. First, the number of PERC-N patients was relatively small, with additional loss-to-follow-up or missing data. Nevertheless, to the best of our knowledge, this study has included the largest number of PERC-N patients to date. Second, the RIETE registry is an ongoing observational registry with data collected from multiple international hospitals on a voluntary basis, which may differ from nonparticipating ones. For example, most patients were included in Spanish hospitals whose PE investigation and management may differ from those in other countries. Third, the registry does not control the accuracy of all data entry, so errors may be possible. Fourth, PE diagnosis, bleeding, or VTE recurrence were not adjudicated and could be subject to misclassification. Fifth, our failure rate is to be understood in the context of our study, where all patients benefitted from an angio-CT, and no PE was missed. Failure would only happen in the real clinical setting if PERC-N patients would not benefit from any additional investigation. Finally, patient management, including anticoagulation, was not standardized and was likely to vary according to local practice. However, this variability reflects real-life practice and contributes to the validity of our results.

CONCLUSIONS

A low failure rate of the pulmonary embolism rule-out criteria rule was observed in the Registro Informatizado de la Enfermedad TromboEmbolica venosa registry, thus supporting its use to safely identify patients with an unlikely probability of pulmonary embolism according to a Wells' score of 4 points or less. However, our study was observational and the proportion of missing data is a source of uncertainty around the pulmonary embolism rule-out criteria rule true failure rate. Prospective and interventional studies are still needed before the use of the pulmonary embolism rule-out criteria rule can be universally recommended.

AUTHOR CONTRIBUTIONS

Perrine Truong, Olivier Hugli, and Manuel Monreal conceived the study. Iñigo Cabriada Saez and Manuel Monreal conducted the analyses. Perrine Truong, Olivier Hugli, and Manuel Monreal drafted the manuscript, and all authors contributed to the critical revision of the manuscript for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

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Penn State Health Emergency Medicine

About Us:

Penn State Health is a multi-hospital health system serving patients and communities across central Pennsylvania. We are the only medical facility in Pennsylvania to be accredited as a Level I pediatric trauma center and Level I adult trauma center. The system includes Penn State Health Milton S. Hershey Medical Center, Penn State Health Children's Hospital and Penn State Cancer Institute based in Hershey, Pa.; Penn State Health Hampden Medical Center in Enola, Pa.; Penn State Health Holy Spirit Medical Center in Camp Hill, Pa.; Penn State Health Lancaster Medical Center in Lancaster, Pa.; Penn State Health St. Joseph Medical Center in Reading, Pa.; Pennsylvania Psychiatric Institute, a specialty provider of inpatient and outpatient behavioral health services, in Harrisburg, Pa.; and 2,450+ physicians and direct care providers at 225 outpatient practices. Additionally, the system jointly operates various healthcare providers, including Penn State Health Rehabilitation Hospital, Hershey Outpatient Surgery Center and Hershey Endoscopy Center.

We foster a collaborative environment rich with diversity, share a passion for patient care, and have a space for those who share our spark of innovative research interests. Our health system is expanding and we have opportunities in both academic hospital as well community hospital settings.

Benefit highlights include:

- Competitive salary with sign-on bonus
- Comprehensive benefits and retirement package
- Relocation assistance & CME allowance
- Attractive neighborhoods in scenic central Pa.

PennState Health

FOR MORE INFORMATION PLEASE CONTACT:

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