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Failure rate of the pulmonary embolism rule-out criteria rule for adults 35 years or younger: Findings from the RIETE Registry

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Abstract

Background: The use of a computed tomography pulmonary angiogram to diagnose pulmonary embolism (PE) has increased, leading not only to higher PE diagnoses but also to overdiagnosis and unnecessary radiation exposure, even in young patients despite a lower PE incidence. The aim of this study was to assess the failure rate of the pulmonary embolism rule-out criteria 35 (PERC-35) rule developed to reduce unnecessary testing in individuals aged ≤35 years among 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 missed PE rate using PERC-35 criteria. Secondary outcomes included the comparison of demographic and clinical characteristics, PE localization, treatment strategies, and outcomes between PERC-negative (PERC-35N) versus PERC-positive (PERC-35P) patients.

Results: Of 58,918 adult patients with acute PE, the PERC-35 rule demonstrated a low missed PE rate of 0.35% ($n = 204$), with an upper 95% confidence interval [CI] of 0.40%. The missed rate was 7.0% (95% CI 6.0%–7.9%) in the 18- to 35-year subgroup. Compared to PERC-35P patients, PERC-35N patients were younger (mean age 28.4 years), with a lower body mass index, and included a higher proportion of pregnant/postpartum women. PERC-35N patients had a significantly lower rate of chronic diseases and presented less frequently with dyspnea or syncope but more often with chest pain. They showed lower rates of positive D-dimer and troponin levels. PERC-35N patients experienced fewer major bleeding episodes, similar recurrence rates of PE/deep vein thrombosis, and no deaths during anticoagulation.

A full list of RIETE investigators is given in Appendix S1.

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Conclusions: The PERC-35 rule demonstrated a low failure rate to exclude PE in patients aged 18–35 years and could reduce imaging and radiation exposure in young patients with a low PE pretest probability if confirmed prospectively.

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

INTRODUCTION

Pulmonary embolism (PE) is a significant concern in the emergency department (ED) and associated with high mortality if untreated. Although PE mortality is higher in older patients, it also significantly affects younger patients, particularly young women.[1,2] Studies show that in nearly 400,000 autopsy cases, critical PE was found in 2.3% of the 20- to 39-year age group. The combination of nonspecific PE presentation, a poor outcome of missed PE, and the widespread availability of computed tomography pulmonary angiogram (CTPA) in most EDs has led to an increased imaging rate.[3] Consequently, more PEs are diagnosed, especially subsegmental PEs whose clinical significance remains a subject of debate.[4] However, this rise in CTPA use leads to prolonged ED stays,[5] increased radiation exposure, and higher health care costs.

To address the potential overuse of CTPA and the subsequent overdiagnosis of PE, particularly in younger patients, a clinical decision rule, the pulmonary embolism rule-out criteria (PERC) rule has been developed to help rule out PE without additional testing in patients <50 years with a low PE pretest probability by clinical gestalt or Wells score.[6] This approach avoids unnecessary D-dimer testing and pulmonary imaging. Our recent study using data from the Registro Informatizado de la Enfermedad Tromboembólica (RIETE) Registry demonstrated that the PERC rule had a low missed PE rate of 0.7%.[7]

Age is a crucial risk factor for PE, with an incidence 10 times lower in adults aged 18–35 years than in those over 65 years.[8] Despite these differences, CTPA rates are similar between younger and older patients, resulting in a diagnostic yield 5.6 and 7.6 times lower in younger male and female patients, respectively.[9] According to a recent study in the United States, 21% of CTPAs were performed on women under 45 years.[10] Young women are at higher risk of overtesting due to their greater lifetime risk of radiation-induced breast cancer, estimated at 0.4% for 20-year-old female patients.[11] Given the lower PE prevalence and increased radiation risk in young patients,[12] the PERC-35 rule, a modification of the original PERC rule,[9] was specifically developed for patients aged 35 years and younger (Appendix S2). This modification of the original PERC rule substitutes fever for heart rate as tachycardia failed to meet the thresholds required by the creators of the rule to be retained as a final PE predictor in the 18- to 35-year age group. On the other hand, fever was a significant predictor in this younger age group, thus justifying the switch.[9] In the PRINCEPS study, applying the PERC-35 rule to the 1839 patients aged 18–35 years in the PERC data set would have reduced testing by 62% and increased the PE diagnostic yield from 4.0% to 9.2%.[9] Moreover, a recent retrospective study using three European cohorts totaling 1235 patients aged 18–35 years found the PERC-35 failure rate to be 0.9%, similar to the PERC rule.[13] However, the 95% confidence interval (CI) was above 2%, higher than the threshold of 1.85% considered as the maximal false-negative rate to safely exclude a PE in the ED.[14] This encouraging low failure rate of the PERC-35 rule suggested that it could be a valuable tool if validated externally as both accurate and safe. Therefore, the main goal of this study was to assess the missed PE rate of the PERC-35 rule in a larger cohort of PE adult patients enrolled in the RIETE Registry.

METHODS

Study design

This retrospective cohort study is based on data of patients ≥18 years included in the RIETE Registry from its initiation on March 1, 2001, through July 30, 2023. The methodology of the RIETE Registry has been described previously.[15] Briefly, this ongoing international prospective registry has enrolled consecutive patients of any age with objectively confirmed venous thromboembolism (VTE) since 2001. At each participating site, local investigators enroll consecutive patients. Auditors regularly check for the sequential inclusion of patients, data completeness, and accuracy. Exclusion criteria include participation in another clinical trial involving the blinding of a patient's medication or unavailability 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 October 2023, over 101,000 patients had been included and followed-up for at least 3 months in 210 hospitals from 26 countries.

Measures

The primary outcome of our study was the overall percentage of PE patients included in the RIETE registry with all eight negative PERC-35 criteria (PERC-35N), representing the missed PE rate of the rule. Secondary outcomes included: (1) identifying specific characteristics associated with PERC-35N patients; (2) comparing

the localization of PE, documented since 2006 and mandatory since 2012 in the database, cardiopulmonary repercussions, treatment strategies, and outcomes between PERC-35N patients and those positive for at least one PERC-35 criterion (PERC-35P); (3) assessing changes in the proportion of PERC-35N patients over the years; and (4) comparing the missed PE rates of the PERC-35 rule overall and by gender to that of the PERC rule when applied to the age-matched 18- to 35-year subgroup of the RIETE population. The overall missed PE rate was assessed using the complete RIETE population, while all secondary outcomes were limited to the 18- to 35-year subgroup.

Data analysis

Descriptive statistics are presented as mean and standard deviation (SD) for continuous variables or as counts, proportions, and their 95% CIs for categorical variables. Baseline characteristics between groups were compared using the Student's *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Incidence rates were calculated as the cumulative incidence (events per 100 patient-years of follow-up) and compared between PERC-35N and PERC-35P patients in the overall RIETE population and the 18- to 35-year subgroup. Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 22. A bilateral *p*-value of <0.05 indicated statistically significant differences in all analyses.

RESULTS

Primary outcome

Between 2001 and 2023, a total of 58,918 adult patients with objectively confirmed acute, symptomatic PE were enrolled in the RIETE Registry (Figure 1). Of these, 373 patients had seven PERC-35N criteria, but were excluded from our analyses because the eighth criterion (oxygen saturation) was missing, thus preventing the classification of the PERC-35 status. Thus, 58,341 patients (99.65%) had at least one PERC-35P criterion, while 204 (0.35%; 95% CI 0.30%–0.40%) met none (PERC-35N). In the age-matched 18- to 35-year subgroup of 2935 patients, there were 2731 PERC-35P patients, with a proportion of PERC-35N of 7.0% (95% CI 6.0%–7.9%).

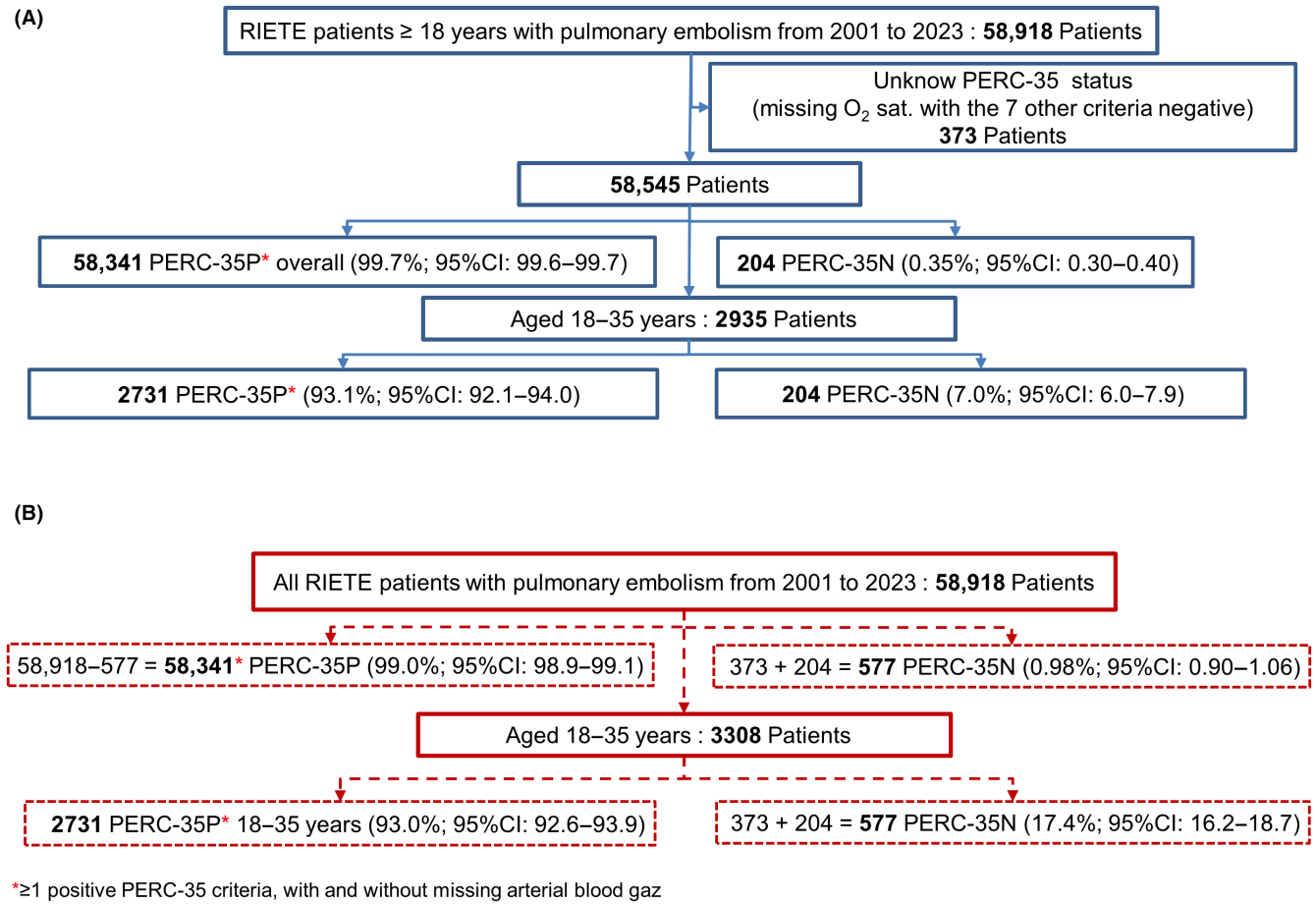

FIGURE 1 Study flow chart. (A) With patients with unknown PERC-35 status removed. (B) With patients with unknown PERC-35 status considered PERC-35N (worst-case scenario). PERC-35, pulmonary embolism rule-out criteria rule for adults 35 years or younger; PERC-35N, PERC-35 negative; PERC-35P, PERC-35 positive.

Comparisons with the overall PERC-35 group

More than one-half of the PERC-35N patients were males, with a mean age of 28.4 years and a mean body mass index (BMI) of 26.9 kg/m^2; 35% were tachycardic (Table 1). Compared to PERC-35P patients, PERC-35 N patients were significantly younger, had a lower BMI, included a higher proportion of pregnant or postpartum women, and had much lower proportions of chronic diseases. The three most frequent positive items of the PERC-35 rule were age (95%), oxygen saturation≤94% (63%), and unilateral leg swelling (25%). Regarding symptoms and signs, PERC-35N patients presented less frequently with dyspnea or syncope, but more often with chest pain. Their vital signs were less altered, with a mean oxygen saturation in the normal range and a lower respiratory rate; systolic blood pressure was also less frequently ≤90 mm Hg.

In terms of diagnostic tests, PE was mostly diagnosed with CTPA, but pulmonary arteriography was used twice as often in PERC-35N patients. Ultrasonography for deep vein thrombosis (DVT) was performed in a similar proportion in both groups, but was positive twice as often in PERC-35P patients. Subsegmental PE represented 9.3% of PE location in PERC-35N patients versus 3.5% in the PERC-35P group ($p < 0.001$), with over 90% of PEs in the PERC-35N group being more proximal. Troponin levels were measured in a similar proportion in both groups, but were twice less likely to be elevated in PERC-35N patients. D-dimers were positive in 93% of PERC-35N versus 98% of PERC-35P patients ($p < 0.001$). Finally, the PERC-35N group had more often low-risk prognostic scores, defined as a PESI score of ≤65 points or a sPESI score of 0 points.

Regarding management, PERC-35N patients were more frequently treated with direct oral anticoagulants as an initial or long-term treatment (Table 2). They had a slightly shorter duration of anticoagulation and fewer major bleedings but a similar recurrence of PE or DVT (Table 3). No death occurred in the PERC-35N patients during anticoagulation and only one death after anticoagulation discontinuation. Recurrence of PE or DVT was similar once anticoagulation was discontinued.

Comparisons with age-matched PERC-35P group

Compared to PERC-35N patients, age-matched PERC-35P patients were slightly younger with a lower proportion of males. The three most frequent positive items of the PERC-35 rule in this group were estrogen therapy, oxygen saturation ≤94%, and unilateral leg swelling. Additionally, 45% of PERC-35P patients had a pulse ≥100 beats/min, 10% more than in PERC-35N patients, and 16% had a temperature≥38°C.

In terms of VTE risk factors, PERC-35N patients were more likely to have a recent immobilization or to be pregnant or postpartum. No significant difference was found in other VTE risk factors or comorbidities. PE signs and symptoms were similar, with dyspnea and chest pain being the most common reported symptoms. PERC-35N patients had a higher mean oxygen saturation and less hypotension.

Diagnostic testing rates were similar for CTPA, the main diagnostic procedure. However, in age-matched PERC-35P patients, compression ultrasonography was more frequently performed with a higher proportion of diagnosed DVT. PERC-35N patients had more distal PE, although PE locations were less frequently documented. Echocardiography and troponin measurements were equally performed, with mean pulmonary pressures and troponin levels similar between the two groups. D-dimers were more frequently measured in PERC-35N patients, with a slightly lower rate of positive results. Finally, PERC-35N patients had more favorable prognostic scores.

PERC-35N patients were more often anticoagulated with direct oral anticoagulants as initial and long-term treatment and with similar rates for other initial therapeutic options, except for thrombolytics, which were more often administered in the age-matched PERC-35P group (Table 2). PERC-35N patients had a slightly shorter duration of anticoagulation, fewer major bleedings, but a similar recurrence of PE or DVT. Recurrence rates during and after anticoagulation were similar.

PERC-35N patient characteristics from 2001 to 2023 (Table 4)

The proportion of PERC-35N patients significantly increased over time, quadrupling between the first (2001–2005) and the last period of recruitment (2022–2023), with an increasing proportion of men in both groups (Figure 2A). Systolic blood pressure and troponin levels were similar across the years. The rate of ultrasonography significantly decreased from 75% in the 2001–2005 period to 42% in 2016–2021. PE location on CTPA, increasingly documented over time, was primarily lobar, followed by in the pulmonary, segmental, and subsegmental arteries (Figure 2B). The RIETE Registry began with Spain and progressively included other European countries, now accounting for 63% of all sites in the past year. Hospital size remained similar throughout the study period.

Performance of PERC-35 versus the original PERC rule in patients aged 18–35 years (Appendix S3)

The missed PE rate of the PERC-35 was higher (7.0%) compared to that of the PERC rule (5.5%), although this difference was not statistically significant. No difference was observed in terms of clinical characteristics, additional VTE risk factors, underlying diseases, initial PE presentations, or prognostic scores between the two groups. In the PERC-35N group, one-third had a pulse of ≥100 beats/min, and 16% of PERC-N had a temperature of >38°C. Adding the item "pulse ≥100" to the PERC-35 rule would lower its failure rate to 0.28% overall and to 5.9% in the 18- to 35-year-old group.

TABLE 1 Clinical characteristics and treatment according to the PERC-35 rule in the global RIETE population and the age-matched group.

		PERC-35P	
	PERC-35N	All	18 to 35 years
	(*n* = 204)	(*n* = 58,341)	(*n* = 2731)
Clinical characteristics			
Male	110 (54)	27,946 (48)	959 (35)‡
Age (years)	28.4 ± 4.2	67.1 ± 16.4‡	27.5 ± 4.7*
BMI (kg/m^2)	26.9 ± 7.0	28.4 ± 5.9†	26.9 ± 6.6
PERC items			
Age≥35 years	0	55,610 (95)‡	0
O_2Sat≤94%, *n* = 34,085	0	21,404 (63)‡	575 (41)‡
Temperature>38°C	0	5529 (9.9)‡	419 (16)‡
Pulse ≥100 beats/min	68 (35)	19,945 (35)	1171 (45)‡
Unilateral leg swelling	0	14,200 (25)‡	825 (31)‡
Prior VTE	0	8226 (14)‡	271 (9.9)‡
Surgery in the past 4 weeks	0	6333 (11)‡	441 (16)‡
Estrogen therapy	0	3253 (5.8)‡	1294 (48)‡
Hemoptysis	0	2975 (5.3)‡	412 (16)‡
Trauma in the past 4 weeks	0	2106 (3.6)†	238 (8.7)‡
Other VTE risk factors			
Immobility for other reasons	35 (17)	10,960 (19)	199 (7.3)‡
Pregnancy or postpartum	42 (21)	390 (0.67)‡	178 (6.5)‡
Active cancer	4 (2.0)	9815 (17)‡	67 (2.5)
Leg varicosities	5 (2.8)	8847 (17)‡	161 (6.4)
Recent travel	10 (5.2)	1502 (2.7)*	132 (4.9)
Underlying diseases			
Chronic heart failure	1 (0.49)	4834 (8.3)‡	14 (0.5)
Chronic lung disease	5 (2.5)	7909 (14)‡	82 (3.0)
Recent major bleeding	5 (2.5)	1440 (2.5)	67 (2.5)
Anemia	41 (20)	18,935 (32)‡	709 (26)
CrCl levels <60 mL/min	1 (0.49)	20,546 (35)‡	26 (1.0)
Signs and symptoms			
Dyspnea	131 (68)	46,383 (81)‡	1953 (73)
Chest pain	149 (76)	25,406 (45)‡	1926 (72)
Syncope	16 (8.8)	7996 (14)*	302 (12)
O_2Sat	97.2 ± 1.5	91.5 ± 6.8‡	93.8 ± 6.2‡
SBP levels <90 mm Hg	1 (0.49)	1886 (3.2)*	86 (3.2)*
SBP levels <100 mm Hg	11 (5.4)	4477 (7.7)	253 (9.3)
Heart rate (beats/min)	91.4 ± 20.5	92.1 ± 20.0	96.7 ± 20.8
Respiratory rate (breaths/min), *n* = 23,107	19.1 ± 5.8	20.6 ± 6.4*	20.0 ± 6.4
Diagnostic tests			
Positive chest CTA	176 (86)	49,197 (84)	2312 (85)
High-probability V/Q lung scintigraphy	15 (7.4)	5383 (9.2)	205 (7.5)
Pulmonary arteriography	12 (5.9)	1548 (2.7)*	120 (4.4)
Compression ultrasonography	112 (55)	34,340 (59)	1821 (67)†
Positive ultrasonography for DVT	32 (29)	20,883 (61)‡	1031 (57)‡
Pulmonary vascular location on CT scan			
Subsegmental arteries only	19 (9.3)	2017 (3.5)‡	82 (3.0)‡
Segmental arteries	36 (18)	8927 (15)	427 (16)
Lobar arteries	40 (20)	10,455 (18)	483 (18)

(Continues)

TABLE 1 (Continued)

	PERC-35N	PERC-35P	
		All	18 to 35 years
	(*n* = 204)	(*n* = 58,341)	(*n* = 2731)
Pulmonary arteries	34 (17)	13,315 (23)*	521 (19)
Data not available	47 (27)	14,483 (29)	799 (35)*
Echocardiogram	89 (53)	26,154 (52)	1351 (58)
PAP levels (mm Hg)	42.4 ± 19.9	44.8 ± 16.7	39.3 ± 16.8
Blood tests			
Measured troponin levels	99 (49)	29,913 (51)	1266 (46)
Increased troponin levels (*n* = 30,012)	19 (19)	11,781 (39)‡	300 (24)
Measured D-dimer levels	168 (82)	43,102 (74)†	2060 (75)*
Positive D-dimer levels	156 (93)	42,168 (98)‡	1991 (97)*
Median D-dimer concentration (ng/mL)	1831 (1000–4000)	3359 (1539–6670)‡	2410 (1156–4790)*
Prognostic scores			
PESI ≤65 points	191 (94)	10,356 (18)‡	2405 (88)*
sPESI 0 point	136 (72)	10,058 (31)‡	716 (53)‡
RIETE score low-risk 0 point	126 (63)	8001 (16)‡	643 (35)‡

Note: Data are reported as *n* (%) or mean ± SD. Differences between patients with PERC-35N and those with PERC-35P: *p <0.05; †p⟨0.01; ‡p <0.001.

Abbreviations: CrCl, creatinine clearance; CTA, computed tomography angiography; DVT, deep vein thromboembolism; PESI, Pulmonary Embolism Severity Index; PERC-35, pulmonary embolism rule-out criteria rule for adults 35 years or younger; PERC-35N, PERC-35 negative; PERC-35P, PERC-35 positive; sPESI, simplified PESI; VTE, venous thromboembolism.

TABLE 2 Therapeutic strategies in the 18- to 35-year subgroup of the RIETE Registry.

	PERC-35N	PERC-35P	PERC-35P in 18- to 35-year subgroup
	(*n* = 204)	(*n* = 58,341)	(*n* = 2731)
Initial therapy			
LMWH	157 (77)	48,663 (83)*	2082 (76)
LMWH dose (IU/kg/day)	180 ± 51	175 ± 43	180 ± 40
Unfractionated heparin	15 (7.4)	4598 (7.9)	250 (9.2)
Fondaparinux	4 (2.0)	835 (1.4)	58 (2.1)
DOACS	25 (12)	2301 (4.0)‡	192 (7.0)*
Thrombolytics	3 (1.5)	1406 (2.4)	132 (4.8)*
Inferior vena cava filter	6 (2.9)	1648 (2.8)	78 (2.9)
ECMO	1/66 (1.5)	61/11,568 (0.5)	8/474 (1.7)
Embolectomy	0	300 (0.6)	14 (0.56)
Long-term therapy			
VKA	87 (43)	30,790 (53)†	1649 (60)‡
LMWH	49 (24)	14,616 (25)	404 (15)‡
LMWH dose (IU/kg/day)	174 ± 78	151 ± 45	159 ± 46
DOACS	67 (33)	10,167 (18)‡	629 (23)†

Note: Data are reported as *n* (%) or mean ± SD. Differences between patients with PERC-35N and those with PERC-35P: *p <0.05; †p <0.01; ‡p <0.001.

Abbreviations: DOACS, direct oral anticoagulants; ECMO, extracorporeal membrane oxygenation; LMWH, low-molecular-weight heparin; PERC-35, pulmonary embolism rule-out criteria rule for adults 35 years or younger; PERC-35N, PERC-35 negative; PERC-35P, PERC-35 positive; VKA, vitamin K antagonists.

TABLE 3 Clinical outcome during the course of anticoagulant therapy in the overall and age-matched 18- to 35-year-old subgroups of the RIETE Registry.

	During anticoagulation						After anticoagulation discontinuation					
			PERC-35P						PERC-35P			
	PERC-35N		All		18–35 years		PERC-35N		All		18–35 years	
	N	*N*/100 patient-years	*N*	*N*/100 patient-years	*N*	*N*/100 patient-years	*N*	*N*/100 patient-years	*N*	*N*/100 patient-years	*N*	*N*/100 patient-years
Patients	204		58,251		2731		89		17,544		1096	
Duration of follow-up												
Days	185 (112–309)		190 (105–366)		191 (115–327)		290 (152–565)		258 (84–641)		271 (93–724)	
Less than 190 days	108 (53%)		28,959 (50%)		1342 (49%)		27 (30%)		7435 (42%)*		439 (40%)	
Outcomes												
Recurrent PE	1	0.55 (0.03–2.74)	846	1.64 (1.53–1.75)	31	1.30 (0.90–1.83)	4	3.26 (1.04–7.87)	1238	5.20 (4.91–5.49)	38	2.08 (1.49–2.83)
Recurrent DVT	3	1.73 (0.44–4.71)	543	1.05 (0.96–1.14)	40	1.71 (1.24–2.31)	2	1.84 (0.31–6.09)	515	2.06 (1.89–2.24)	31	1.69 (1.17–2.36)
Major bleeding	1	0.55 (0.03–2.73)	1794	3.48 (3.32–3.64)*	34	1.43 (1.01–1.98)	0	—	219	0.86 (0.75–0.98)	1	0.05 (0.00–0.26)
Sites of bleeding												
Gastrointestinal	0	—	602	1.15 (1.06–1.25)	2	0.08 (0.01–0.28)	0	—	87	0.34 (0.27–0.42)	1	0.05 (0.00–0.26)
Cerebral	0	—	333	0.64 (0.57–0.71)	2	0.08 (0.01–0.28)	0	—	61	0.24 (0.18–0.30)	0	—
Death	0	—	6722	12.8 (12.5–13.1)‡	37	1.54 (1.10–2.11)	1	0.78 (0.04–3.83)	2414	9.40 (9.03–9.78)‡	16	0.85 (0.50–1.35)
Causes of death												
PE	0	—	769	1.47 (1.37–1.57)	6	0.25 (0.10–0.52)	0	—	48	0.19 (0.14–0.25)	1	0.05 (0.00–0.26)
Initial PE	0	—	636	1.21 (1.12–1.31)	5	0.21 (0.08–0.46)	0	—	7	0.03 (0.01–0.05)	1	0.05 (0.00–0.26)
Recurrent PE	0	—	133	0.25 (0.21–0.30)	1	0.04 (0.00–0.21)	0	—	41	0.16 (0.12–0.21)	0	—
Bleeding	0	—	340	0.65 (0.58–0.72)	1	0.04 (0.00–0.21)	0	—	64	0.25 (0.19–0.32)	0	–
Gastrointestinal	0	—	94	0.18 (0.15–0.22)	0	—	0	—	18	0.07 (0.04–0.11)	0	–
Cerebral	0	—	149	0.28 (0.24–0.33)	0	—	0	—	29	0.11 (0.08–0.16)	0	–

Note: Data are reported as median (IQR) or *n* (%). Differences between patients with PERC-35N and those with PERC-35P: *p <0.05; †p <0.01; ‡p <0.001. Ninety patients not included because they did not receive anticoagulant therapy (all were PERC-35P).

Abbreviations: DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; PERC-35, pulmonary embolism rule-out criteria rule for adults 35 years or younger; PERC-35N, PERC-35 negative; PERC-35P, PERC-35 positive; VTE, venous thromboembolism.

TABLE 4 PE presentation in PERC-35N from 2001 to 2023 of the RIETE Registry.

	2001–2005 (*n* = 16)	2006–2010 (*n* = 40)	2011–2015 (*n* = 38)	2016–202 (*n* = 87)	2022–2023 (*n* = 23)	*p*-trends
Proportion	0.2%	0.3%	0.3%	0.4%	0.8%	<0.001
Initial presentation						
SBP levels <90 mm Hg	1 (6.3)	0	0	0	0	0.203
SBP levels <100 mm Hg	3 (19)	2 (5.0)	1 (2.6)	4 (4.6)	1 (4.3)	0.230
Measured troponin levels	3	19	17	46	14	0.020
Increased troponin levels	0	4 (21)	3 (18)	11 (24)	1 (7.1)	0.674
Measured D-dimer levels	13	38	29	72	16	0.112
Positive D-dimer levels	12 (92)	35 (92)	29 (100)	64 (89)	16 (100)	0.593
Ultrasonography performed	12 (75)	26 (65)	28 (74)	36 (41)	10 (43)	<0.001
DVT by ultrasonography	2 (17)	6 (23)	12 (43)	11 (31)	1 (10)	0.424
Prognostic scores						
PESI ≤65 points	15 (94)	38 (95)	36 (95)	81 (93)	21 (91)	0.599
sPESI 0 point	10 (63)	24 (63)	28 (78)	61 (79)	13 (62)	0.294
RIETE score 0 point	11 (69)	26 (67)	23 (64)	54 (64)	12 (52)	0.341
PE location on CT scan						
Subsegmental arteries	N/A	0	5 (13)	12 (14)	2 (8.7)	0.008
Segmental arteries	N/A	1 (2.5)	8 (21)	22 (25)	5 (22)	0.002
Lobar arteries	N/A	1 (2.5)	8 (21)	21 (24)	10 (43)	<0.001
Pulmonary arteries	N/A	2 (5.0)	7 (18)	19 (22)	6 (26)	0.003
Unspecified	7 (100)	29 (88)	6 (18)	5 (6.3)	0	<0.001
Countries						
Spain	16 (100)	27 (68)	18 (47)	43 (49)	4 (17)	<0.001
Rest of Europe	0	13 (33)	18 (47)	38 (44)	15 (65)	0.001
Other	0	0	2 (5.3)	6 (6.9)	4 (17)	0.069
Hospital size[b]						
Small	5 (31)	9 (23)	13 (34)	25 (29)	10 (43)	0.310
Intermediate	4 (25)	19 (48)	11 (29)	27 (31)	8 (35)	0.260
Large	7 (44)	12 (30)	14 (37)	35 (40)	5 (22)	0.890

Note: Data are reported as *n* (%).

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; PERC-35, pulmonary embolism rule-out criteria rule for adults 35 years or younger; PERC-35N, PERC-35 negative; PESI, Pulmonary Embolism Severity Index; sPESI, simplified PESI; VTE, venous thromboembolism.

b stands for: Small = less than 500 beds; intermediate = 500-1000 beds; large = over 1000 beds

Gender and PERC-35 (Table 5)

The missed PE rate was higher in males (11.5%) than females (5.3%), although not a statistically significant difference. Almost one-half of female patients were pregnant or postpartum (45%). Male patients were more than twice as likely to have been immobilized or to have a proven DVT on ultrasonography than female patients. A higher proportion of male patients had increased troponin levels, although this difference just failed to reach statistical significance ($p = 0.059$). Prognostic scores were similar between genders.

DISCUSSION

In this retrospective cohort study based on a large group of PE patients in the RIETE registry, we found that the PERC-35 rule had a 0.35% false-negative rate, with an upper 95% CI of 0.40%. In a sensitivity analysis considering those with unknown PERC-35 status as PERC-35N, the upper 95% CI would have been 1.06%. These figures are well below the false-negative rate of 1.85% considered as the maximum missed PE rate for a clinical decision rule in the ED, without adjustment for PE prevalence.[14] Our study confirms the low failure rate of the PERC-35 rule and extends the findings of the only other smaller cohort that recently attempted to validate it.[13] During the 2001–2023 period, the proportion of PERC-35N patients significantly rose, possibly reflecting the increasing use of multidetector CTPA in young patients whose improved diagnostic performance allows for the diagnosis of smaller PE.[16–18]

Compared to the overall RIETE population, the 204 PERC-35N patients were younger and mostly male. Age was by far the most discriminant criterion of the PERC-35 rule for the whole RIETE population, reflecting the increasing incidence of PE with age. The reliance on age as a criterion may limit the external validity of the rule if applied to ED populations with very different age distributions. In a recent

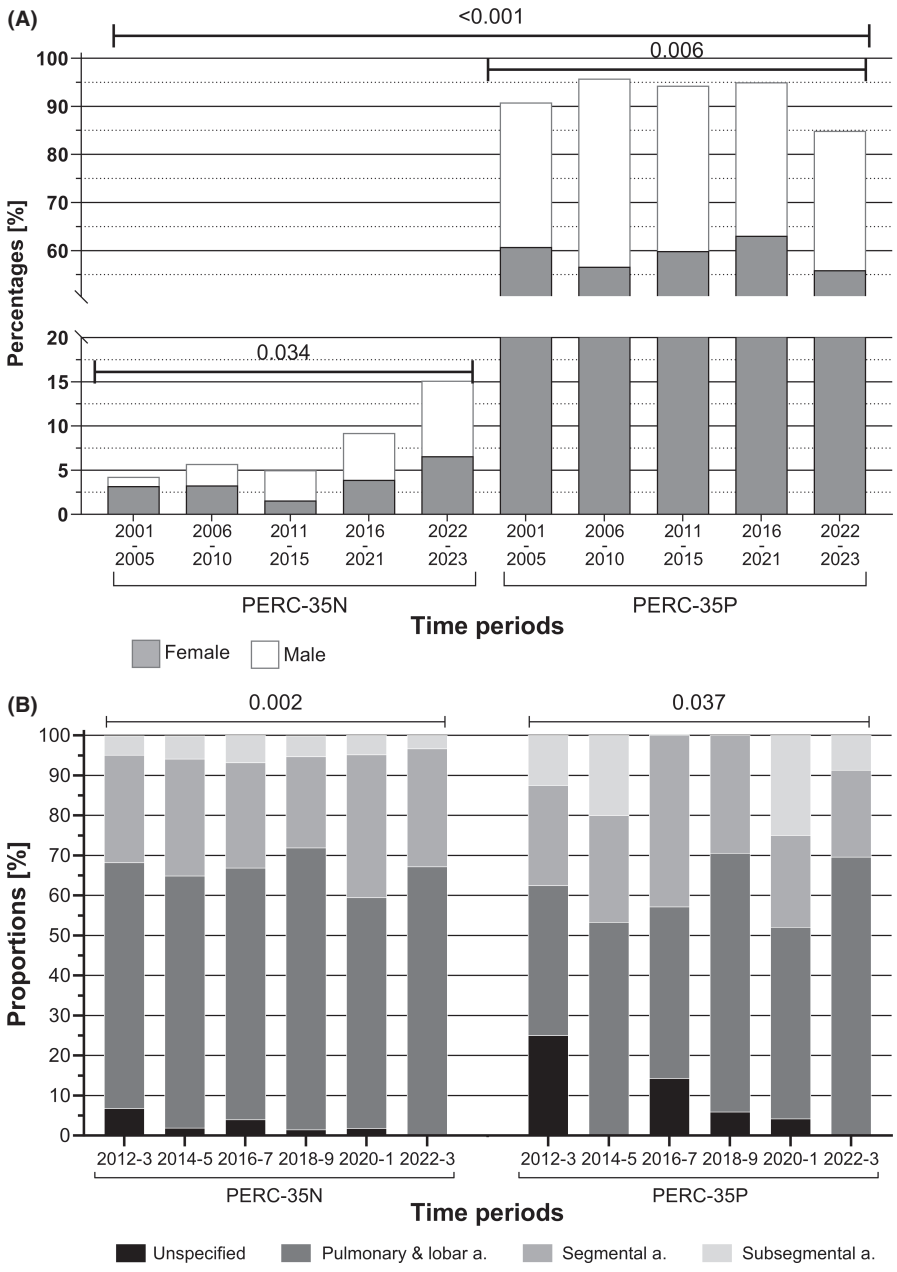

FIGURE 2 Proportions of PERC-35N and PERC-35P in the subgroup of patients aged 18–35 years. (A) PERC-35N et PERC-35P over time. (B) PE location over time in PERC-35N and PERC-35P groups. PERC-35, pulmonary embolism rule-out criteria rule for adults 35 years or younger; PERC-35N, PERC-35 negative; PERC-35P, PERC-35 positive.

systematic review conducted in 59 low-/middle-income countries, the median patient age was 35 years,[19] with the 25- to 35-year-old age group accounting for one-quarter of patients in a Pakistani ED.[20] In these much younger settings, the failure rate of the PERC-35 could be closer to the 7.0% found in our 18- to 35-year subgroup.

PERC-35N patients were more likely to have a transient major VTE risk factor, such as immobility, and one-half of female patients were pregnant, as observed by others.[21] D-dimers were more frequently measured, but with a lower positivity rate, accounting for 93% of PERC-35N patients compared to 98% of PERC-35P patients. D-dimer positivity and concentration reflect the clot burden, with lower levels associated with a more distal PE location, less cardiac repercussions, and a better prognosis. This is confirmed in our study where PERC-35N patients presented lower risk PEs, better prognostic scores, more initial anticoagulation by direct oral anticoagulants, shorter duration of anticoagulation, less major bleeding, and no deaths during treatment.

Compared to the age-matched PERC-35P group, PERC-35N patients presented the same rate of underlying diseases, but had less severe clinical presentations, with higher oxygen saturation and less hypotension. Estrogen use was the most frequent VTE risk factor, as in other young populations.[22] D-dimers were less frequently measured in this group, which had higher rates of ultrasonography and DVT. This may hint at an "ultrasound-first" strategy as an initial diagnostic test, given that one-third had signs of DVT. PERC-35P patients presented fewer subsegmental PEs and had worse prognostic or bleeding scores, which translated into different treatment decisions with less direct oral anticoagulants and more thrombolytic use. These findings suggest that identified PERC-35N patients had a less clinically significant PE with a better prognosis.

TABLE 5 Characteristics of PERC-35N by gender.

	PERC-35N ($n=204$)	
	Female	Male
Patients	94 (46)	110 (54)
Missed PE rate	5.3 (4.2–6.4)‡	11.5 (9.2–13.8)
Pulse ≥100 beats/min	34 (37)	34 (32)
Clinical characteristics		
Age (years)	28.2 ± 4.2	28.6 ± 4.3
Body weight (kg)	70.9 ± 17.3	87.5 ± 24.2
BMI (kg/m^2)	25.8 ± 6.5	27.9 ± 7.2
Additional risk factors for VTE		
Immobility for other reasons	10 (11)*	25 (23)
Pregnancy or puerperium	42 (45)	0
Cancer	0	4 (3.6)
Underlying diseases		
Chronic heart failure	1 (1.1)	0
Chronic lung disease	2 (2.1)	3 (2.7)
CrCl levels <60 mL/min	0	1 (0.91)
Recent major bleeding	2 (2.1)	3 (2.7)
Initial PE presentation		
SBP levels <90 mm Hg	1 (1.1)	0
SBP levels <100 mm Hg	8 (8.5)	3 (2.7)
Increased troponin levels ($n=99$)	5 (12)	14 (25)
Positive D-dimer levels	73 (90)	83 (95)
Proven DVT in ultrasonography	9 (19)*	23 (36)
Prognostic scores		
PESI <65 points	89 (95)	102 (93)
sPESI <1 point	62 (69)	74 (76)
RIETE score low-risk <1 point	60 (65)	66 (62)

Note: Data are reported as *n* (%), % (95% CI), or mean ± SD. Differences between female and male patients: *$p<0.05$; †$p<0.01$; ‡$p<0.001$.
Abbreviations: DVT, deep vein thrombosis; CrCl, creatinine clearance rate; PERC-35, pulmonary embolism rule-out criteria rule for adults 35 years or younger; PERC-35N, PERC-35 negative; PESI, Pulmonary Embolism Severity Index; sPESI, simplified PESI; VTE, venous thromboembolism.

In terms of gender, male patients constituted the majority of the PERC-35N group. Although the original PERC-35 derivation cohorts were approximately two-thirds female, gender was not a significant predictor.[9] We found that the proportion of male PERC-35N patients was twice that of females and increased over time, although our small sample size precludes definitive conclusions regarding the significance of this difference. Male patients were more likely to have recent immobilization, while nearly one-half of the PERC-35N female patients were pregnant or postpartum. Compared to age-matched nonpregnant women, VTE is three to 10 times and 12 to 35 times more frequent during pregnancy and postpartum, respectively.[23,24] The exclusion of pregnancy/postpartum from the clinical decision rule is related on one hand to the exclusion or low inclusion rates of pregnant women in clinical trials and, on the other hand, to their threefold lower incidence of PE compared to older patients.[25] Clinical decision rules adapted to pregnancy have been validated to reduce CTPA by including lower-extremities ultrasound and an adapted D-dimer positivity threshold to the PE probability.[26,27] However, they all include D-dimer measurement whose false-positive results lead to unnecessary CTPA, maternal and fetal exposure to iodinated contrast media, and radiation.[28] Adding "pregnancy or postpartum status" to the PERC-35 rule could improve its performance and avoid imaging in young women.

When applied to the age-matched PE group, the original PERC rule had a nonsignificant, lower false-negative rate. The addition of the item "pulse ≥100" to the PERC-35 would lower its failure rate to 0.23% overall and to 4.6% in the 18- to 35-year-old age group. Fever in PE, present in one in six PERC-35P patients, is typically low grade and may be secondary to pulmonary infarction, infection, or malignancy. Important temperature variations can be caused by the place of measurement, circadian variations, or antipyretics administration; thus its utility as a prognostic factor should be carefully reassessed.

STRENGTHS AND LIMITATIONS

The strength of our study lies in the use of the RIETE Registry, a large-scale, multinational, observational database. To our knowledge, our subgroup comprising patients aged 18–35 years is the largest sample used to validate the PERC-35 rule. The RIETE Registry covers a broad spectrum of PE severity managed in diverse international health care settings, thus providing good external validity. Our study has also some limitations. The number of PERC-35N patients was relatively small, with some loss to follow-up and missing data. The failure rate of the PERC-35 rule had sufficient precision to confirm its safety, but errors in data accuracy are possible. Additionally, the registry does not document the number of CT detectors, making the hypothesis of improved CT sensitivity speculative. The PERC-35 rule should only be applied to patients with a low pretest PE probability by clinician's gestalt or Wells score, which were not formally recorded in this study. With the two-tier Wells score, PE is unlikely if the score is ≤4 points. However, given the partial overlap between the PERC-35 and Wells items (Appendix S4), some of our patients could have a score>4 points (PE likely) if PE was the most likely diagnosis and patients had a heart rate of >100 beats/min. The PERC-35 rule should not be used in these potentially "PE likely" patients as they require additional investigations. Based on our data, this constellation could have been present in a maximum of 19,945 patients (68 PERC-35N and 19,877 PERC-35P patients). However, if all those patients were excluded based on a PE likely probability, the PERC-35 failure rate would still be 0.35% (95% CI 0.30–0.42 [136

PERC-35N; 38,396 PERC-35P]), still below the maximal acceptable failure rate of 1.85%. Our study period included the COVID-19 pandemic time frame, but the proportion of PERC-35N did not vary significantly during that period. Finally, patient management, including anticoagulation, was not standardized and may have varied according to local practice. However, this variability reflects real-life practice and contributes to the external validity of our results.

CONCLUSIONS

In conclusion, the pulmonary embolism rule-out criteria rule for adults 35 years or younger (PERC-35 rule) demonstrated a low failure rate in the RIETE Registry, supporting its potential use to rule out pulmonary embolism in patients aged 18–35 years with an unlikely pretest probability. Specifically tailored to this young age group, the PERC-35 rule could reduce unnecessary imaging, while increasing the diagnostic yield. However, it should not be used currently to rule out PE in pregnant or peripartum women. The addition of a "pregnancy or peripartum status" item to the rule could avoid unnecessary imaging in young women. In addition, the PERC-35 rule should not be used in settings with much younger patient populations, given that older age was the most frequent positive criterion of the rule. Base on the limitations associated with our retrospective design, prospective implementation studies are needed prior to the clinical application of the PERC-35 rule.

AUTHOR CONTRIBUTIONS

Thibaut Jossein, Olivier Hugli, and Manuel Monreal conceived the study. Irene González Recio, and Manuel Monreal conducted the analyses. Thibaut Jossein, Olivier Hugli, and Manuel Monreal drafted the manuscript, and all authors critically revised the manuscript for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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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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