Evaluation of the pulmonary embolism rule out criteria (PERC rule) in children evaluated for suspected pulmonary embolism

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ABSTRACT

BACKGROUND: The pulmonary embolism rule out criteria (PERC) reliably predicts a low probability of PE in adults. We examine the diagnostic accuracy of the objective components of the PERC rule in children previously tested for PE.

METHODS: Children aged 5-17 who had a D-dimer or pulmonary vascular imaging ordered from 2004-2014 in a large multicenter hospital network were identified by query of administrative databases. Using explicit, predefined methods, trained abstractors selected charts of children clearly tested for PE, collected the 8 objective variables for PERC, and determined PE criterion standard status (image or autopsy confirmed PE or deep vein thrombosis within 30 days by query of the Indiana Network for Patient Care (INPC).

RESULTS: We identified 543 patients, including 56 (10.3%, 95% CI: 7.8-13.1%) who were PE+, with a mean and median age of 15 years. All 8 objective criteria from PERC were negative in 170 patients (31%), including one with PE (false negative rate 0.6%, 0-3.2%). Diagnostic sensitivity and specificity were 98.2% (90.5-100%), and 34.7 (30.5-39.1%), respectively, leading to a likelihood ratio negative 0.05 (0.1-0.27). When treated as a diagnostic test based upon sum of criteria positive, PERC had good discrimination between PE+ vs PE- with an area under receiver operating characteristic curve 0.81 (0.75-0.86).

CONCLUSIONS

In this sample of children and teenagers with suspected PE, the PERC rule was negative in 31%, and demonstrated good overall diagnostic accuracy, including a low false negative rate. These data support the need for a large, prospective diagnostic validation study of PERC in children.

Introduction:

The diagnostic approach to children and teenagers with signs or symptoms of pulmonary embolism (PE) is hampered by a dearth of evidence specific to pediatric populations.[1-7] Literature-based reviews have suggested that PE occurs in about 0.5 per 10,000 children per year; but the case fatality rate for PE is about 10%, and some evidence has suggested that clinicians miss the majority of fatal PE in children.[2,8-10] Current literature also lacks any real world data to describe how frequently clinicians evaluate PE in children. Work by the authors has suggested that clinicians order a D-dimer or pulmonary vascular imaging study for PE in approximately 1 in 400 children over age 4 in pediatric emergency departments.[11] It is clear that current clinical decision-making of children with suspected PE is occurring in the absence of any age-specific, validated pretest probability strategy, or any clinical prediction rule to prevent formal diagnostic testing. This raises the question of whether current usual practice might expose children and teenagers to unnecessary medical radiation.

The PE rule out criteria (PERC rule) was derived and validated to exclude PE in adults without need for formal diagnostic testing.[12] The PERC rule requires that clinicians express an overall low gestalt clinical suspicion for PE (defined as implicit belief that the patient has <15% probability of PE), and the patient has the following eight objective criteria (age< 50 years, heart rate <100 beats/minute, oxygen saturation >94%, no unilateral leg swelling, no hemoptysis, no use of exogenous estrogen, no prior venous thromboembolism (VTE), no recent surgery or trauma requiring endotracheal intubation or epidural anesthesia). In adults, a systematic review found the pooled diagnostic sensitivity and specificity of PERC to be 97%

(95% CI 96-98%) and specificity of 22% (95% CI 22-23%).[12] The diagnostic accuracy of the PERC rule in children has been examined in two retrospective studies, which found a diagnostic sensitivity of 84% and 100%.[3,5] In this work, we examine the diagnostic accuracy of the eight objective criteria PERC rule in a cohort of children who were selected by usual care processes for evaluation of PE.

Methods:

This study was approved by the Indiana University School of Medicine Institutional Review Board (February 18, 2016, protocol # 1502856953). The description of patients and data collection were published previously.[6] Patients in this study were aged 5 to 17 years, and who underwent testing for PE with either a D-dimer, computed tomography pulmonary angiography (CTPA), scintillation lung scan, or formal pulmonary angiography between 2004 and 2014 in the Indiana University Health hospital system. This system includes a pediatric tertiary care center (Riley Hospital) and 8 community hospitals. Patients were identified by query of two separate administrative databases for D-dimer and pulmonary vascular imaging orders. Patients could be located in an emergency department (ED), observation unit, hospital ward or intensive care unit. Chart abstracters had a minimum education of three years of medical school and underwent rigorous, structured training with one of the PIs, together with a research coordinator. Eligibility required the patient to either undergo a pulmonary vascular imaging study (computerized tomographic pulmonary angiography, ventilation perfusion lung scanning, or formal pulmonary angiography), or a D-dimer for suspected PE. The training focused on using written, explicit methods to review each chart for written evidence by care providers that the

D-dimer was performed for suspected PE. The hypothesis of the study was not disclosed to abstractors. Abstracters used a written protocol in the process of case selection and data selection. Suspicion for PE was determined if written words indicated that PE or a synonym, such as thromboembolism, was on the differential diagnosis, clinical impression, indication for imaging, or medical decision-making. Patients were excluded if D-dimer was performed in the evaluation of another process, such as cancer surveillance or suspected disseminated intravascular coagulation, or the reason was undetermined. For eligibility to be recorded, clinical data had to be documented within 48 hours of the time of PE diagnosis. If a variable was not written anywhere in the medical record as either present or absent (e.g., recent surgery), the variable was assumed to be absent. One author (JK) performed regular random audits of approximately 10% of all charts to test for agreement with abstracters and provided real-time feedback as needed to facilitate exclusion of cases. Abstracters used a paper data collection template, printed from REDCap electronic data archiving system to record demographic, clinical and comorbidity data, including the objective criteria for the PERC rule. As a retrospective analysis, we had no way of determining the clinicians' gestalt pretest probability. Data were then transferred to the actual REDCap electronic form.

Outcomes included a search of any visits by the same patient to hospitals contained within the Indiana Network for Patient Care (INPC) up to 30 days from the initial evaluation for PE. We retrieved and analyzed any documented return visit for any reason, but we planned in advance to report only deaths or the diagnosis of DVT or PE. The INPC, is part of the Indiana Health Information Exchange project (http://www.ihie.org/about-us/) and includes records from over

90% of healthcare facilities in Indiana, including admission and discharge diagnoses from 25,000 physician's offices, 117 hospitals, 110 clinics and surgery centers in Indiana.

Criterion standard for PE

Outcome of PE+ vs. PE- status was determined by adjudication (2 of 3 reviewers) using imaging data and available outcome records. The definition of PE+ followed guidelines that were used to derive and test the PERC rule in adults, and required a filling defect on CTPA interpreted as positive for PE or a ventilation-perfusion scintillation lung scan interpreted as high probability for PE.[13] We included any patient with PE or DVT diagnosed within 30 days after the D-dimer as PE+. Patients with a negative D-dimer and no PE or DVT within 30 days were considered PE-.

Quality assurance of chart reviews

We held regular meetings with abstracters to gauge progress and review problems, (e.g., vague charting, multiple D-dimer results, differing D-dimer tests and units). The senior investigators and an experienced research coordinator performed periodic random audits of charts to examine for discordance or missing results. Study investigators did not disclose any hypotheses to the abstracters (e.g., a desire for the D-dimer to have good accuracy or not). Lastly, two abstracters coded a random sample of 10% of all charts to compute a kappa for agreement on whether the patient was positive for PE.

Analysis

The primary analysis was done with 95% confidence intervals for the diagnostic accuracy data of the PERC rule, including sensitivity, specificity, likelihood ratio negative and false negative rate and receiver operating characteristic curve analysis, with area under the curve estimated using the method of Hanley and McNeil.[14] Analyses were done using StatsDirect software, Cheshire, England, v3.0.187.

Results

From 13,792 orders for D-dimer testing and 997 orders for pulmonary vascular imaging, abstracters identified 3,404 children between ages of 5 and 17 which was reduced to 543 charts of unique children tested for PE with either a D-dimer alone (n=210) or pulmonary vascular imaging with or without D-dimer (n=333). A random sample of 100 charts reviewed independently by two abstracters revealed agreement in this designation in 99/100 cases (kappa = 0.95, 95% CI 0.85-1.0). Of the 543 cases, 56 (10.3%, 95% CI 7.8 to 13.1%) had the criterion standard for PE+ including 51 with imaging evidence of PE and five with isolated deep vein thrombosis (DVT). No patient in the study died within 30 days.

Table 1 presents demographic and clinical of the population, including the objective components of the PERC rule. The mean and median age was 15 years for children with and without PE (1st-3rd quartiles: 14-17), although among patients with PE+, 14/56 (25%) were age <13 years. Most children (432/543, 80%) were evaluated for PE in the ED or ED observation unit setting. Being tested in the ED appeared to significantly lower the probability of a PE+ outcome: 24/432 or 5.5% (95% CI 3.5 to 8.1%) for ED patients versus 22/101 or 21.7% (14.1 to

31.1%) in inpatients. The remaining patients were diagnosed in a clinic (n=5), or at an outside hospital (n=5).

Table 2 shows the number of PERC criteria positive, stratified by PE status. Most importantly, 1/56 children with PE+ were "PERC negative," meaning that patient could have been missed by the PERC rule. That patient was a teenager evaluated in an emergency department, aged 17, with pulse rate 86 beats/min, respiratory rate 20 breaths/min, pulse oximetry reading of 95%, and blood pressure 161/101 mm Hg, weight of 107 Kg (body mass index 42 kg/m^2), with chest pain and dyspnea and no comorbid conditions. A screening D-dimer was positive (1672 ng/mL) and a CTPA was positive for bilateral PE. Another relevant point from Table 2 is that 70% of PE+ patients had >1 PERC criteria, compared with 25% of PE- patients. When the number of PERC criteria were treated as a diagnostic test result, and examined by receiver operating characteristic curve analysis, the area under the curve was 0.81, (0.75-0.86).

Table 3 shows the diagnostic indexes of the PERC rule negative in the entire population and for patients evaluated in the ED. The sensitivity was good at 98.3% (95% CI 90.5-100%) in the overall population, but when the population was restricted to patients evaluated in the ED, sensitivity was 95.8%, with wider confidence intervals (79-99%) as a result of the smaller denominator. Specificity was moderate at 35 to 39%. The false negative rate was 0.6% with upper limit 95% confidence intervals of 3.2% and 3.4% for all patients and ED patients, respectively. Had the objective criteria of the PERC rule been applied and followed in the entire population, 170/543 patients, or 31% would have been PERC negative, including 44 (25% of

PERC negative patients, and 8% of the total sample) who underwent CTPA scanning. The sensitivity of the PERC rule in children <13 years of age was 14/14 (sensitivity 100%, 95% CI 78%-100).

Discussion

This is the first examination of the diagnostic sensitivity and specificity of the PERC rule in a population of children and teenagers under age 18 years. We found an excellent sensitivity (98.2%, 95% CI 90.5-100%) and modest specificity (34.5%), leading to a false negative rate (0.6%, 95% CI 0-3.2%) that is similar to the false negative rate of accepted methods of excluding PE with formal diagnostic testing in adults.[15] Two prior studies examined the PERC rule in children, but data presented by Agha et al, did not allow calculation of specificity, and Hennelly et al included patients up to 21 years of age.[3,5] The specificity in the present data set was 35% (95% CI: 31-39%), which was slightly higher than the 24% (95% CI: 21-28%) Hennelly et al found. We do not have a clear explanation for this difference. In the present study, the objective criteria of the PERC rule were negative in 31% of all patients, and 25% of these patients underwent CTPA scanning with usual care. Hypothetical use of the PERC rule would have reduced CTPA scanning by an absolute 8% rate in the entire group. Interestingly, two recent validation studies of the PERC rule demonstrated similar numbers in adults. First in a non-interventional study, Penaloza et al found a 32% PERC negative rate among 1,052 adults with a low pretest probability for PE. As part of usual care, 13% of these PERC negative patients underwent CTPA scanning. The false negative rate of the PERC rule was 1.2% (95% CI, 0.5 to

2.8%).[16] Second, in a multicenter cluster randomized trial, Freund et al found that the PERC rule was negative in 459/962 (48%) of gestalt low probability ED adult patients, and use of the PERC rule led to an absolute 8% reduction in CTPA scanning with a 0.1% failure rate.[17]} Thus, the present work adds significantly to existing literature by demonstrating promise for the PERC rule to safely exclude PE in a clinically important fraction of children and teenagers without the use of any formal diagnostic testing.

The present work does not use the PERC rule as it was originally designed, because we did not have the required gestalt component of an overall low (<15%) clinical probability of PE. We have no method to estimate the proportion of the population that would have been deemed low risk by gestalt, but it is probable that it would shrink the eligible sample. In adult populations, about 2/3 of all patients tested for PE have a low gestalt pretest probability.[13,16] A relevant observation in the present data is that overall prevalence of PE was 10.3%, which is similar to--or slightly higher than--the prevalence of PE in many diagnostic studies of adults conducted in the US.[13,18,19] When the population was restricted to the ED, the prevalence decreased to 5.5%, and without any gestalt prescreening, the false negative rate of the objective criteria alone was 0.6% (5% CI 0-3.4%).

This study is limited by the retrospective nature of data collection. While it is possible that a child could have migrated out of Indiana to another state, we submit that it is exceedingly unlikely that a child who was within Indiana and had follow-up care for any venous thromboembolism would have been missed by our search. We can make only a highly limited

inference about the safety of the PERC rule in children under age 13. Only 14 patients with PE+, were under age 13, leading to a very wide confidence interval around the sensitivity estimate. Another aspect of the present data is the lack of clinician gestalt low risk, which is a requirement before the objective criteria of the PERC rule can be applied in adults. The diagnostic accuracy of gestalt pretest probability for PE has never been examined in children. Moreover, the current specificity datum (35%) suggest that about 1/3 of patients under 18 without PE in this retrospective dataset might have avoided any diagnostic testing. However, this also means that 2/3 of PE- patients were PERC+, and needed some type of objective test. The present data offer no inference into whether real-world use of the PERC rule would increase or decrease the net radiation exposure of children without PE. Future studies should aim to validate the PERC rule in a large prospective study.

In conclusion, in this retrospective sample of children and teenagers tested for PE, the objective criteria of the PERC rule demonstrated good overall diagnostic accuracy.

What is already known on this topic:

In adults, the pulmonary embolism rule out criteria (PERC) rule can exclude PE with reasonable certainty.

What this study adds:

The PERC rule demonstrated good sensitivity and moderate specificity in children tested for PE.

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Table 1. Clinical characteristics of the study population (n=543)		
Demographics		
Female gender	360	66%
Non-Caucasian race	132	24%
Hispanic/Latino ethnicity	9	2%
Symptoms		
Chest pain	275	51%
Dyspnea	354	65%
Cough	91	17%
Syncope or seizure	42	8%
Comorbidities		
Active cancer	24	4%
Congenital heart disease	16	3%
Connective tissue disease	33	6%
Nephrotic syndrome	7	1%
Asthma	120	22%
PERC criteria		
Age<50 years	543	100%
Heart rate > 100 beats/min	207	38%
Pulse oximetry <95%	43	8%
Exogenous estrogen use	86	16%
Unilateral leg swelling	25	5%
Hemoptysis	6	1%
Prior venous thromboembolism	138	25%
Recent surgery or trauma	79	15%

Table 2. Distribution of the number of PERC criteria positive by diagnosis				
	PE+ (n=56)		PE- (n=487)	
Number of PERC criteria positive	n	% of 56	n	% of 487
0	1	2%	169	35%
1	16	29%	197	40%
2	16	29%	102	21%
3	18	32%	18	4%
4	5	9%	1	0%
subtotals	56	100%	487	100%

Abbreviations-PE, pulmonary embolism; PERC, pulmonary embolism rule out criteria

Table 3. Diagnostic accuracy of the PERC rule				
	Total population		ED population	
	Value	95% CI	Value	95% CI
Sensitivity	55/56= 98.2%	90.5-100%	23/24=95.8	78.9-99.8%
Specificity	169/487=34.7%	30.5-39.1%	160/409=39.1%	34.4-44.0%
False negative rate	1/170= 0.6%	0-3.2%	1/161=0.6%	0-3.4%
Likelihood ratio negative	0.05	0.01-0.27	0.1	0.02-0.52