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STUDY PROTOCOL

Bedside exclusion of pulmonary embolism in children without radiation (BEEPER): a national study of the Pediatric Emergency Care Applied Research Network—Study protocol

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Abstract

Background: The Pulmonary Embolism Rule Out Criteria (PERC) Peds rule, derived from the PERC rule, was derived to estimate a low pretest probability for pulmonary embolism (PE) in children but has not been prospectively validated.

Objective: The objective of this study was to present a protocol for an ongoing multicenter prospective observational study that evaluates the diagnostic accuracy of the PERC-Peds rule.

Methods: This protocol is identified by the acronym, BEdside Exclusion of Pulmonary Embolism without Radiation in children. The study aims were designed to prospectively validate, or if necessary, refine, the accuracy of PERC-Peds and D-dimer in excluding PE among children with clinical suspicion or testing for PE. Multiple ancillary studies will examine clinical characteristics and epidemiology of the participants. Children aged 4 through 17 years were being enrolled at 21 sites through the Pediatric Emergency Care Applied Research Network (PECARN). Patients taking anticoagulant therapy are excluded. PERC-Peds criteria data, clinical gestalt, and demographic information are collected in real time. The criterion standard outcome is image-confirmed venous thromboembolism within 45 days, determined from independent expert adjudication. We assessed interrater reliability of the PERC-Peds, frequency of PERC-Peds use in routine clinical care, and descriptive characteristics of missed eligible and missed patients with PE.

Results: Enrollment is currently 60% complete with an anticipated data lock in 2025.

Conclusions: This prospective multicenter observational study will not only test whether a set of simple criteria can safely exclude PE without need for imaging but also provide a resource to fill a critical knowledge gap about clinical characteristics of children with suspected and diagnosed PE.

KEYWORDS
children, clinical decision support systems, diagnosis, pulmonary embolism, research design, venous thromboembolism

Essentials

- No study has prospectively evaluated how to rule out blood clots in the lungs of children.
- Methods of ruling out lung blood clots in adults have not been validated in children.
- This study tested whether Pulmonary Embolism Rule Out Criteria-Peds can rule out blood clots in children.
- The criteria will be successful if it predicts <2% chance of clots.

1 | INTRODUCTION

Emergency department (ED) providers lack high-quality evidence to guide decisions around diagnostic testing for suspected pulmonary embolism (PE) in children. National databases indicate that PE occurs in approximately 1 in 20,000 children in the community [1,2]. Several pediatric studies have suggested a bimodal prevalence among infants and adolescents, with a pooled mean and median age of 15 years at diagnosis based on 10 retrospective studies [3–6]. Although some symptoms are similar to those of PE in adults—tachycardia, hemoptysis, hypoxemia, and limb swelling [3,4,7]—a comprehensive review of published literature of PE diagnosis and exclusion in children reveals the absence of any prospective trial evaluating clinical criteria that can distinguish the presence or absence of PE [3]. Pooled data from 9 studies in this review demonstrated that a PE diagnosis was first made on autopsy in 87% of children with PE, suggesting a high rate of missed diagnosis. Children often require multiple ED visits and experience ≥7 days of symptoms, before receiving a PE diagnosis [8]. This high frequency of failure to diagnose may contribute to the 1 in 10 mortality rate for children with PE (range of 6%-18% in reporting studies) [7,8].

Meanwhile, the diagnostic approach to PE in children remains highly variable and provider-specific with unknown accuracy. In the ED setting, the rate of computed tomography pulmonary angiography (CTPA) in the United States is increasing by 30% per year in both adult and pediatric populations [9]. Approximately one-third of children who undergo CTPA have had a negative CTPA performed within the previous year [4,10], whereas epidemiologic studies have linked CT scanning with an increased lifetime risk of lethal cancer, with a greater risk when CT is performed during childhood [9,11–15].

The use of structured criteria to guide PE screening and evaluation in the adult population in ED has been associated with improvements in testing frequency and an increase in the yield of PE per CTPA *without* reduction in the rate of PE diagnosis [16–19]. The use of the Pulmonary Embolism Rule-Out Criteria (PERC) rule has decreased the proportion and number of negative CTPAs performed in adults [18–20]. Designed and derived to decrease over-testing in adults at risk of PE, the PERC rule combines a low clinical gestalt (implicit belief of <15% probability a PE) and 8 objective criteria: age of <50 years, heart rate of <100 beats/min, pulse oximetry reading of >94%, no estrogen use, no recent surgery, no previous venous thromboembolism (VTE), no hemoptysis, and no unilateral limb swelling. Using a retrospective database of children tested for PE, the PERC rule exhibited 100% sensitivity and 34% specificity for identifying children with PE in the ED setting [21]. A subsequent modification of the PERC rule for children, the PERC-Peds, was proposed that allows a heart rate of <120 beats/min for children aged <12 years and maintained high sensitivity with improved specificity in PE diagnosis [22]. Although clinical practice guidelines recommend use of the D-dimer to screen for PE in adults, the diagnostic sensitivity and specificity of the D-dimer as a screening test for PE in children remains uncertain and controversial, again owing to the lack of any prospective study of any diagnostic test or clinical criteria for PE in children [23,24]

1.1 | Objectives

The aims of this project were as follows: (1) to determine whether the PERC-Peds rule can exclude PE in children with an upper limit of the 95% CI for the point estimate of the false negative rate <1.5% and (2) to test the diagnostic accuracy of the D-dimer ordered as part of usual care for children with symptoms of PE in the ED setting. Exploratory aims include the assessment of provider diagnostic accuracy in their gestalt estimation of the probability of PE and to better understand which clinical and diagnostic criteria predict the presence or absence of PE in childhood [22]. The criterion standard outcome is the diagnosis of PE or deep vein thrombosis (DVT) within 45 days of ED presentation.

In this study, we hypothesized that a clinical prediction rule can produce a diagnostic sensitivity of >95% and specificity of at least 45% in children aged 4 through 17 years with clinically suspected PE, leading to <1.5% rate of missed PE among children with a negative PERC-Peds. We further hypothesize that a D-dimer threshold value, ordered as part of usual care for children with symptoms of PE, can produce a diagnostic sensitivity of >95%, with a specificity >40%—similar to what has been observed in adults with suspected PE. Finally, we posit that refinement of the rule may further increase test accuracy.

2 | METHODS

2.1 | Study overview

This report describes the protocol for a prospective, observational cohort study of children aged 4 through 17 years with sufficiently high probability of PE to warrant consideration of diagnostic testing with a D-dimer or pulmonary vascular imaging. The goal was to measure the

diagnostic accuracy of a clinical prediction rule for exclusion of PE (the PERC-Peds rule) among children, and an optimal D-dimer threshold for this population. This study will enroll up to 4030 eligible children aged >4 years up until their 18th birthday. All participants will be followed for 45 days after enrollment (primary), and 90 days for those diagnosed with isolated VTE.

2.2 | Setting

The study is being conducted at 21 academic EDs in the United States specializing in the care of children (19 PECARN centers plus 2 others). The data coordinating center (DCC) is located at the University of Utah in Salt Lake City, Utah. For all PECARN projects, the DCC also functions largely as the clinical coordinating center, working in coordination with the principal investigators to perform the ancillary studies to examine for bias and the adjudication processes.

2.3 | Study population

2.3.1 | Inclusion criteria

Participants aged 4 through 17 years must meet one of the following criteria: a diagnostic test ordered for suspected PE, including: D-dimer, CT scan, ventilation perfusion (VQ) scan, magnetic resonance angiography, or other pulmonary vascular imaging study. Patients in whom the evaluating clinician strongly suspects a PE may also be included, even if no imaging is performed or imaging is ordered and then canceled.

All evidence in children is derivative from studies in adults for all methods of diagnosis, including CTPA and VQ. Given that the American Society of Hematology's clinical practice guidelines from 2018 asserted the level of evidence for VQ as a diagnostic and exclusionary modality to be at least equal to CTPA in adults and that VQ scanning may stress the kidneys less, this test was included as a criterion standard in children [24]. In our study, only approximately 1 in 500 children enrolled have received VQ scanning.

2.3.2 | Exclusion criteria

Potential study participants will be excluded if they report any of the following: (1) known pregnancy (stated verbally by patient or a documented pregnancy test), (2) current anticoagulant medication for VTE diagnosis, (3) drug or alcohol intoxication, or (4) incarceration. Children will also be excluded if the participant is unable to provide waiver of documentation of informed consent because of the lack of caregiver presence or if the subject's caregiver is unable to be contacted by text, email, or telephone in 45 days. Patients are limited to a total of 3 enrollments throughout the study period. Participants will be excluded if they have a known previous enrollment in the past 45 days.

2.4 | Study procedures

2.4.1 | Participant screening and consent

Potential participants will be screened by trained research personnel at each site. Under a waiver of authorization for recruitment, research personnel will screen electronic health records for patients tested for PE with D-dimer or pulmonary vascular imaging. Electronic order systems will be screened for orders of qualifying tests (D-dimer, CT scanning of the pulmonary arteries with intravenous contrast, or pulmonary vascular imaging). Research personnel will also remind providers to notify them of patients that prompted a consideration of PE testing even when no test is performed.

Once eligibility is confirmed, research personnel will contact patients (either in-person or remotely) to obtain verbal consent (under waiver of written documentation) for receiving a text, email, or telephone call 45 days after the initial ED visit and to access the medical record to determine the health status. Qualified translators or bilingual study personnel will be used to enroll Spanish-speaking patients. At enrollment, each participant will be assigned a unique study identity number. No portion of this study will alter usual patient care.

2.5 | Data collection and assessment for expected biases

Research personnel will record baseline data for all enrolled participants, including contact information, PERC-Peds predictor variables, variables corresponding to other pretest probability rules [25–27], and other plausible clinical factors currently not a part of other prediction rules. They will also collect provider demographics, qualifying reason for patient enrollment, and patient-level data observed during treatment. Finally, ordering clinicians will be asked provide their gestalt pretest probability of PE from 0% to 100% using a visual analog scale before any definitive testing, if obtained.

To assess for potential biases, we will collect 4 other data components designed to assess potential sources of bias. First, we will assess interrater reliability for gestalt assessment and the 8 objective components of PERC-Peds from 2 independent clinicians in real time on a convenience sample of 400 children. These clinicians must either be board-certified in Pediatrics, General Emergency Medicine, Pediatric Emergency Medicine, and/or a PEM fellow. Second, we will survey clinicians at the beginning of the study and at the end of year 3 to determine their age, gender, training level, frequency of PERC, or PERC-Peds use in their practice. Third, sites will review participants tested for PE but who were missed for enrollment. A table will compare the demographic and PE diagnosis rate for these patients vs those enrolled. This will determine if children recruited into this study are representative of the overall population of children at risk for PE. Demographic information will be collected on these "missed eligible" patients, along with whether they were ultimately diagnosed with VTE. Finally, sites will conduct a retrospective query of the electronic medical record to determine whether the enrollment process missed

any children diagnosed with VTE. Missed patients with VTE will be identified by the International Classification of Diseases 10 code; recent work indicates a reasonable sensitivity for this identification method of 91.1% (95% CI, 89.4-92.6) and a specificity of 99.9% (95% CI, 99.9-99.9) [28].This query will search for all diagnoses of VTE made during the enrollment period and identify those patients with a documented health care visit in the 2 weeks before diagnosis. These patient encounters will be reviewed and select data collected, including: the verbatim chief complaint, vital signs, physical findings, test results, and diagnosis. These data will be adjudicated by the same panel responsible for deciding the criterion standard to determine whether the visit represented a missed opportunity to diagnose PE (see section on case adjudication).

2.6 | Participant follow-up

The criterion standard for PE will require outcome assessment at 45 days, which can be evaluated either by text, telephone, or email contact with the patient or parent/caregiver, supplemented by examination of the medical record [29]. Follow-up contact will occur starting 45 days after the index ED visit using a centralized texting service from the DCC. If no response, patients will be contacted by phone, then email. Research staff will indicate which patients had PE or DVT diagnosed during their index visit. Those patients will receive a separate medical record review at the site 90 days after enrollment to determine their outcome. The focus of this assessment will be on medication adherence, bleeding, and VTE recurrence (for ancillary work).

Despite the assiduousness, these measures to establish text, telephone, and email contact may fail in up to 10% of cases. All participants will have medical record review to determine outcome. For participants with no text, email, or telephone contact, the medical history, and physical examination documented in the electronic medical record after 45 days, without any mention of VTE recurrence, will serve as the surrogate to patient-reported outcome. If no medical record can be located, then the master death index and local medical examiners databases will be searched for vital status. This methodology allows the adjudication panel to decide the criterion standard even without text, email, or telephone follow-up, as opposed to declaring the patient lost to follow-up or deeming the subject as VTE+ by default. Dedicated sensitivity analysis will then be performed including only those patients who could be reached.

2.7 | Potential predictor variables

No prospective study to date has allowed a direct comparison of the frequency of suspected risk factors for PE in children using a case-control approach, in which cases are patients with the criterion standard for PE and controls have clinically suspected PE that meets the inclusion criteria but have no PE at 45 days. The case report form (Supplementary Data 1), includes symptoms, vital signs, medical history, physical examination, laboratory, and chest radiography findings. For each of these variables, we will report descriptive bivariable frequency analysis, with associated risk data (eg, odds ratios and 95% CIs). These variables will also be examined for strength of association with PE/VTE using a traditional multivariable approach and machine-learning techniques. The study is collecting criteria required for the Well's score [26], including the subjective question about alternative diagnosis more likely than PE.

We will also use multivariable approaches to derive new rules/criteria and determine whether this can improve the test characteristics over the PERC-Peds rule.

2.8 | Criterion standard for PE definition

The primary outcome is the occurrence of one or more episodes of new or recurrent VTE diagnosis including either PE or DVT discovered within 45 days of enrollment. A new VTE in a patient with no history is defined as either (1) a filling defect on CT pulmonary angiography or a perfusion defect on VQ scan or other pulmonary vascular imaging (including echocardiography) that leads to the diagnosis of PE, as documented in the medical record, regardless of treatment or (2) a new, noncompressible vein including the following: calf veins, saphenous vein, popliteal vein, femoral vein, axillary, or jugular vein leading to the diagnosis of DVT, regardless of treatment or superficial thrombophlebitis that leads to a decision to administer >7 days of full-dose anticoagulation therapy.

Recurrent VTE refers to evidence of a new VTE in patients with previous VTE. Patients will receive a PE diagnosis if they have the following: (1) a new intraluminal filling defect in segmental or more proximal branches on CT, (2) a new intraluminal filling defect or an extension of an existing defect or a new sudden cutoff of vessels >2.5 mm in diameter on the pulmonary angiogram, (3) a new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy, or (4) an inconclusive CT, pulmonary angiography, or lung ventilation/perfusion scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography (CT or ventilation/perfusion scans showing unchanged filling defects compared with the study qualifying images do not qualify as recurrent PE).

Patients will be categorized as having a suspected recurrent DVT with one of the following findings, if there were no previous DVT investigations: (1) abnormal compression of a deep vein, including calf, gastrocnemius, saphenous vein, femoral, brachial, axillary, or jugular veins on ultrasound or (2) an intraluminal filling defect on venography performed by any technique (eg, magnetic resonance imaging or planar venography).

Patients will be categorized as having a suspected recurrent DVT with one of the following findings if there *was* a DVT investigation at screening: (1) abnormal compression ultrasound in which compression had been normal or if noncompressible during screening, a substantial increase (≥4 mm) in diameter of the thrombus during full compression or (2) proximal extension of an intraluminal filling defect, or a new intraluminal filling defect or proximal extension of nonvisualization of veins in the presence of a sudden cutoff on venography.

2.9 | Case adjudication

Three physicians who are site investigators volunteered to serve as adjudicators and determine the criterion standard outcome of each study case which could have the following 4 possibilities: (1) PE only, (2) DVT only, (3) both DVT and PE, or (4) No PE or DVT. These individuals are board-certified in PEM and hold academic appointments at their home institutions. These investigators make decisions independently of the research team and are blinded to the form that clinicians complete that have the criteria for the PERC-Peds rule but otherwise have access to the case report form and the ability to ask for additional information from the medical record or person who contacted the patient or family. Based on review of the initial 1000 cases, structured query language computer program was used to formulate automated adjudication for the criterion standard. This algorithm resulted in a clear criterion standard in approximately 90% of the initial 1000 cases. This algorithm is described in tabular format in Supplementary Data 2. Ten percent of these automatically categorized outcomes were hand-reviewed to ensure accuracy of the structured query language algorithm. Cases that the algorithm cannot determine a clear criterion standard will undergo case-by-case review by the 3 adjudicators via teleconference. The outcome of each case was determined by each adjudicator, and the ultimate categorization was determined by consensus of at least 2 of the 3 adjudicators, with an associated scale of certainty, including: very low, low, moderate, high, and very high. Those cases found to have missing or unclear information prompted additional review from the originating institution and repeat evaluation by the adjudication committee.

2.10 | Sample size and power

The sample size of approximately 4030 children is predicated on an expected 4.5% prevalence of PE. This prevalence estimate was based on the PECARN registry and reports by the study sites drawing from the diagnosis rate in children who either had a D-dimer and/or CT scan ordered. The sample size is also based on the 95% sensitivity and 45% specificity of the PERC-Peds rule, and 90% power to demonstrate that the upper limit of the 95% CI for the false negative rate is <1.5%. A false negative rate refers to those children negative for all components of the PERC-Peds rule, but criterion standard positive, of all PERC-Peds-negative children. The test threshold method was used to determine 1.5% as the worst tolerable upper limit of the 95% CI [30]. In comparison, a threshold of 1.8% was used for derivation and validation of the PERC rule for adults [31].

2.11 | Statistical analysis plan

For each predictor variable, we will report descriptive bivariable frequency analysis, with associated risk data (eg, odds ratios and 95% CI). The primary outcome is the adjudicated PE status within 45 days. The primary analysis will originate from the standard 2 × 2 contingency table to produce the point estimates with 95% CIs of the diagnostic sensitivity, specificity, and exclusionary rates for the dichotomized PERC-Peds rule. A successful validation will consist of an upper limit <1.5% for the 95% CI of the false negative rate, of those predicted negative (1 minus the negative predictive value). CIs will be computed from the exact binomial distribution. We will also assign one point to each variable present from the PERC-Peds rule and use this as a diagnostic score to construct receiver operating characteristic curves and compute areas under the curves using the Wilcoxon method with 95% CIs.

We will analyze D-dimer by using the following 3 approaches: (1) the site-specific cutoff/determination of positive, (2) the cutoff recommended by the designer of the assay, and (3) a receiver operating characteristics analysis to determine optimal cutoffs for this population. We also recognize that comorbidities may affect the overall diagnostic accuracy of D-dimer in the subset of children with no comorbidities [32].

We will use multivariable approaches to derive new rules/criteria and determine whether this can improve the test characteristics over the PERC-Peds rule. Approaches will include multivariable logistic regression, classification and regression trees, and random forests. Performance of these rules and existing rules (eg, Wells) will be compared with the PERC-Peds by using the McNemar's test and exact binomial tests. Specifically, a 2 × 2 table will be constructed with rows corresponding to correct and incorrect classification by PERC-Peds and columns corresponding to correct and incorrect classification by the new rule. This table will be the basis for the McNemar's chi-squared test. Exact binomial tests will compare the number classified correctly out of the patients with and without PE separately

2.12 | Ethics

This study poses minimal risk to participating children and their families. The University of Utah institutional review board is serving as the single IRB for all sites. Patients will receive the standard of care. Participation in this study will not negatively impact or restrict care provided to enrolled patients. All patients and families will provide written or verbal informed consent/assent and have the ability to withdraw at any time without explanation. Ethics approval has been obtained at all participating sites.

2.13 | Impact of the COVID-19 pandemic

The application that led to funding from the National Heart, Lung, and Blood Institute (NHLBI) was written before the COVID-19 pandemic, and the funding decision was made in October, 2019. The protocol was revised in early 2020 in recognition of the possibility that COVID-19 represented a risk factor for PE and also that many D-dimer tests were being ordered in children to assess for the multiple inflammatory syndrome in children [32]. To decide how to handle potential

enrollment of children with known or suspected COVID-19 and a D-dimer ordered, investigators met several times and included site investigators in a consensus process. The final decision was to include these patients but only if the ordering physician could verify that they suspected PE as a diagnosis. This group will be analyzed both together with the rest of the population and separately.

2.14 | Data sharing

After publication of the primary and planned secondary manuscripts, at approximately 1 year after data lock, the data will be deposited in the Biologic Specimen and Data Repository Information Coordinating Center in accordance with NHLBI Policy for Data Sharing from Clinical Trials and Epidemiological Studies.

3 | RESULTS TO DATE

The first patient was enrolled in July 2020, and as of June 2022, approximately 2000 patients have been enrolled. Approximately 20% of study participants were known or suspected to have COVID-19. The adjudication process has been completed on 1000 patients.

4 | DISCUSSION

This article describes the methods for a large, multicenter, prospective diagnostic study of the PERC-Peds rule and its potential to safely exclude acute PE without diagnostic testing in children in emergency care. The second aim will for the first time, prospectively test the diagnostic accuracy of the D-dimer for exclusion of PE in children. The database derived from this work will provide a large resource for testing many ancillary questions and generating new hypotheses about the clinical characteristics, risk factors, and epidemiology of acute PE in children seeking unscheduled care. The database will be made freely available to the public in accordance with NHLBI policy for data sharing.

4.1 | Limitations

We anticipate several limitations of this study. First, enrollment is limited by provider clinical experience. Patients will be selected based on clinical suspicion by providers, and this suspicion is largely derived from studies in adults. Previous work has shown that younger adults with VTE/PE present with different symptom patterns than older adults [20]. This implies the possibility of spectrum bias in as much as BEdside Exclusion of Pulmonary Embolism without Radiation may miss children with minimally symptomatic VTE/PE, or those with symptoms not associated with PE in adults. We also recognize that comorbidities may affect the overall diagnostic accuracy of D-dimer in the subset of children with no comorbidities.

The study's approach to case follow-up by using medical record review and family contact may miss those patients with asymptomatic PE/VTE. In addition, the selected 45-day follow-up period may be too short to catch some delayed events or be far enough from the sentinel examination that a PE/VTE event is missed. Given the study population includes children between the ages of 4 and 18 years, this trial may miss an important subgroup of patients with their own unique risks and presentation of VTE and PE. Finally, the study does not control for the diagnostic testing choices of clinicians; PE/VTE events may be missed, given the individual clinician practice patterns based on their background and clinical suspicion.

5 | CONCLUSIONS

PE in children is a rare but potentially lethal condition, often presenting as a delayed or missed diagnosis. This project aimed to identify which factors increase or decrease the probability of VTE among those children arousing clinical suspicion of this diagnosis. If PERC-Peds, or a further refined new rule, is found to meet the objective with acceptable interrater reliability, then, this decision rule could constitute a reasonable method to exclude PE by using readily available clinical data without the need for phlebotomy or radiation. In addition, to our knowledge, this study will be the first to test the diagnostic accuracy of the D-dimer among those children who do not qualify exclusion by using the PERC-Peds rule, which may further decrease reliance ionizing radiation. Exploratory analyses will help define currently unrecognized risk factors that could increase PE understanding and detection.

5.1 | Patient and public involvement

This study was designed and implemented without patient nor public involvement. Patients were not invited to provide feedback on study design. Collaborating clinicians were involved in the adjudication process; no patients were involved in either reviewing data or determining outcomes. They were also not invited to contribute to the composition or editing of this manuscript. We anticipate that clinicians will play a key role in implementing the decision rules developed in this study.

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AUTHOR CONTRIBUTIONS

A.M.E., J.A.K., and N.K. were involved in the original conception, funding, data collection, analysis, manuscript preparation, and revisions. D.C., L.M., R.K., and T.C.C. were involved in data collection, analysis, manuscript preparation, and revisions. All authors read and approved the final paper.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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REFERENCES

[1] Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. *J Pediatr*. 2004;145:563–5.
[2] Rajpurkar M, Biss TT, Amankwah EK, Martinez D, Williams S, Van Ommen CH, et al. Pulmonary embolism and in situ pulmonary artery thrombosis in paediatrics. A systematic review. *Thromb Haemost*. 2017;117:1199–207.
[3] Kanis J, Pike J, Hall CL, Kline JA. Clinical characteristics of children evaluated for suspected pulmonary embolism with D-dimer testing. *Arch Dis Child*. 2018;103:835–40.
[4] Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in Children's Hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124:1001–8.
[5] Byard RW. Fatal embolic events in childhood. *J Forensic Leg Med*. 2013;20:1–5.
[6] Carpenter SL, Richardson T, Hall M. Increasing rate of pulmonary embolism diagnosed in hospitalized children in the United States from 2001 to 2014. *Blood Adv*. 2018;2:1403–8.
[7] Rajpurkar M, Warrier I, Chitlur M, Sabo C, Frey MJ, Hollon W, et al. Pulmonary embolism—experience at a single children's hospital. *Thromb Res*. 2007;119:699–703.
[8] Feng LB, Pines JM, Yusuf HR, Grosse SDUS. trends in computed tomography use and diagnoses in Emergency Department visits by patients with symptoms suggestive of pulmonary embolism, 2001-2009. *Acad Emerg Med*. 2013;20:1033–40.
[9] Kline JA, Courtney DM, Beam DM, King MC, Steuerwald M. Incidence and predictors of repeated computed tomographic pulmonary angiography in emergency department patients. *Ann Emerg Med*. 2009;54:41–8.
[10] Reiter M, Wen LS, Allen BW. The emergency medicine workforce: profile and projections. *J Emerg Med*. 2016;50:690–3.
[11] Hoffman JR, Cooper RJ. Overdiagnosis of disease: a modern epidemic. *Arch Intern Med*. 2012;172:1123–4.
[12] Crichlow A, Cuker A, Mills AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. *Acad Emerg Med*. 2012;19:1219–26.
[13] Miglioretti DL, Johnson E, Williams A, Greenlee RT, Weinmann S, Solberg LI, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. *JAMA Pediatr*. 2013;167:700–7.
[14] Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet*. 2012;380:499–505.
[15] Mills AM, Ip IK, Langlotz CP, Raja AS, Zafar HM, Khorasani R. Clinical decision support increases diagnostic yield of computed tomography for suspected pulmonary embolism. *Am J Emerg Med*. 2018;36:540–4.
[16] Jiménez D, Resano S, Otero R, Jurkojc C, Portillo AK, Ruiz-Artacho P, et al. Computerised clinical decision support for suspected PE. *Thorax*. 2015;70:909–11.
[17] Drescher MJ, Fried J, Brass R, Medoro A, Murphy T, Delgado J. Knowledge translation of the PERC rule for suspected pulmonary embolism: a blueprint for reducing the number of CT pulmonary angiograms. *West J Emerg Med*. 2017;18:1091–7.
[18] Kline JA, Jones AE, Shapiro NI, Hernandez J, Hogg MM, Troyer J, et al. Multicenter, randomized trial of quantitative pretest probability to reduce unnecessary medical radiation exposure in emergency department patients with chest pain and dyspnea. *Circ Cardiovasc Imaging*. 2014;7:66–73.
[19] Freund Y, Cachanado M, Aubry A, Orsini C, Raynal PA, Féral-Pierssens AL, et al. Effect of the pulmonary embolism rule-out criteria on subsequent thromboembolic events among low-risk emergency department patients: The PROPER randomized clinical trial. *JAMA*. 2018;319:559–66.
[20] Kline JA, Ellison AM, Kanis J, Pike JW, Hall CL. Evaluation of the pulmonary embolism rule out criteria (PERC rule) in children evaluated for suspected pulmonary embolism. *Thromb Res*. 2018;168:1–4.
[21] Hennelly KE, Ellison AM, Neuman MI, Kline JA. Clinical variables that increase the probability of pulmonary embolism diagnosis in symptomatic children. *Res Pract Thromb Haemost*. 2020;4:124–30.
[22] Kanis J, Hall CL, Pike J, Kline JA. Diagnostic accuracy of the D-dimer in children. *Arch Dis Child*. 2018;103:832–4.
[23] Biss TT, Brandao LR, Kahr WHA, Chan AKC, Williams S. Clinical probability score and D-dimer estimation lack utility in the diagnosis of childhood pulmonary embolism. *J Thromb Haemost*. 2009;7:1633–8.

[24] Lim W, le Gal G, Bates SM, Righini M, Haramati LB, Lang E, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2:3226–56.

[25] Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med*. 2001;135:98–107.

[26] Klok FA, Kruisman E, Spaan J, Nijkeuter M, Righini M, Aujesky D, et al. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. *J Thromb Haemost*. 2008;6:40–4.

[27] Burles K, Innes G, Senior K, Lang E, McRae A. Limitations of pulmonary embolism ICD-10 codes in emergency department administrative data: let the buyer beware. *BMC Med Res Methodol*. 2017;17:89.

[28] Kline JA, Mitchell AM, Runyon MS, Jones AE, Webb WB. Electronic medical record review as a surrogate to telephone follow-up to establish outcome for diagnostic research studies in the emergency department. *Acad Emerg Med*. 2005;12:1127–33.

[29] Lessler AL, Isserman JA, Agarwal R, Palevsky HI, Pines JM. Testing low-risk patients for suspected pulmonary embolism: a decision analysis. *Ann Emerg Med*. 2010;55:316–26.e1.

[30] Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *J Thromb Haemost*. 2004;2:1247–55.

[31] Avila L, Amiri N, Pullenayegum E, Sealey VA, De R, Williams S, et al. Diagnostic value of D-dimers for limb deep vein thrombosis in children: a prospective study Funding information. Published online 2021.

[32] Lee KH, Li H, Lee MH, Park SJ, Kim JS, Han YJ, et al. Clinical characteristics and treatments of multi-system inflammatory syndrome in children: a systematic review. *Eur Rev Med Pharmacol Sci*. 2022;26:3342–50.

SUPPLEMENTARY MATERIAL

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