Radiology

Children Suspected of Having Pulmonary Embolism: Multidetector CT Pulmonary Angiography—Thromboembolic Risk Factors and Implications for Appropriate Use[1]

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Purpose: To evaluate thromboembolic risk factors for pulmonary embolism (PE) detected by using computed tomographic (CT) pulmonary angiography in children and to determine whether such information could be used for more appropriate use of CT pulmonary angiography in this patient population.

Materials and Methods: The institutional review board approved this HIPAA-compliant retrospective study and waived the need for patient informed consent. Two hundred twenty-seven consecutive CT pulmonary angiography studies in 227 pediatric patients who underwent CT pulmonary angiography for clinically suspected PE at a single large pediatric referral hospital between July 2004 and March 2011 were evaluated. Age, sex, referral setting, and D-dimer result, as well as seven possible risk factors, were compared between patients with and those without PE. Multiple logistic regression modeling was used to identify the independent risk factors of PE. Receiver operating characteristic curve analysis was applied to determine the optimal cutoff number of risk factors for predicting a positive CT pulmonary angiography result for PE in children.

Results: Thirty-six (16%) of 227 CT pulmonary angiography studies were positive for PE. Five risk factors, including immobilization ($P < .001$), hypercoagulable state ($P = .003$), excess estrogen state ($P = .002$), indwelling central venous line ($P < .001$), and prior PE and/or deep venous thrombosis ($P < .001$), were found to be significant independent risk factors for PE. With use of two or more risk factors as the clinical threshold, the sensitivity of a positive PE result was 89% (32 of 36 patients), and the specificity was 94% (180 of 191 patients).

Conclusion: It is unlikely for CT pulmonary angiography results to be positive for PE in children with no thromboembolic risk factors. The use of risk factor assessment as a first-line triage tool has the potential to guide more appropriate use of CT pulmonary angiography in children, with associated reductions in radiation exposure and costs.

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Pulmonary embolism (PE) is a potentially life-threatening condition that requires accurate diagnosis and timely management (1,2). The incidence of PE ranges from 0.73% to 4.2% in the pediatric population (3,4). Because of the often nonspecific clinical signs and symptoms of PE, imaging studies such as computed tomographic (CT) pulmonary angiography, which can enable direct visualization of PE, currently serve as important diagnostic tools for evaluating PE (1,2,5–8). The sensitivity and specificity ranges for detecting PE by using CT pulmonary angiography in adult patients are 83%–100% and 89%–97%, respectively (8–12). Results of recent studies (13–18) suggest increasing use of CT pulmonary angiography in children suspected of having PE, but the rate of positive studies is relatively low, suggesting potential overutilization of this test.

Thromboembolic risk factor assessment was shown to be useful for directing when to perform CT pulmonary angiography in a recent study in adult patients (19). However, to our knowledge, there is no study published to date in which the potential role of risk factor assessment before CT pulmonary angiography in children clinically suspected of having PE was investigated. If risk factor assessment can be used to guide more appropriate use of CT pulmonary angiography, it would be particularly beneficial for pediatric patients, who are more susceptible than adults to the potential radiation-related adverse effects of CT pulmonary angiography.

Therefore, the purpose of our study was twofold: *(a)* To evaluate thromboembolic risk factors for PE detected by using CT pulmonary angiography in children and *(b)* to determine whether such information may guide more appropriate use of CT pulmonary angiography in this patient population.

Advances in Knowledge

- Immobilization ($P < .001$), hypercoagulable state ($P = .003$), excess estrogen state ($P = .002$), indwelling central venous line ($P < .001$), and prior pulmonary embolism (PE) and/or deep venous thrombosis ($P < .001$) were significant risk factors for a positive CT pulmonary angiography result for PE according to multiple logistic regression analysis.
- The estimated likelihood of PE in pediatric patients with none of the five significant risk factors is 0% (95% confidence interval: 0.1%, 2%).
- D-dimer test results were not correlated with presence of PE detected by using CT pulmonary angiography in children with a high clinical probability of PE ($P = .14$).

Materials and Methods

A subset of patients in this study were also included in several previous investigations aimed at answering uniquely separate research questions, including *(a)* assessing the prevalence and anatomic distribution of PE in CT pulmonary angiography studies that were positive for PE ($n = 84$), *(b)* evaluating the frequency and spectrum of alternative diagnoses in CT pulmonary angiography studies that were negative for PE ($n = 89$), *(c)* comparing the frequencies of parenchymal and pleural abnormalities between children with and those without PE at CT pulmonary angiography ($n = 22$), and *(d)* determining whether the addition of multiplanar reformation multidetector CT images affected reader performance parameters and provided added diagnostic value compared with the use of axial multidetector CT images alone for diagnosing PE in children ($n = 60$) (13,15,16,20).

Implications for Patient Care

- Risk factor assessment should be a primary tool for guiding when to perform CT pulmonary angiography in pediatric patients who are clinically suspected of having PE.
- With the use of risk factor assessment, CT pulmonary angiography can be targeted more appropriately, with the potential to substantially reduce costs and radiation exposure in pediatric patients who are clinically suspected of having PE.
- The D-dimer test has little apparent value in screening for PE among children with a high clinical probability of PE.

Study Patients

The institutional review board of Children's Hospital Boston (Boston, Mass) approved the review of radiologic and clinical data for this retrospective study. The need to obtain patient informed consent was waived, but patient confidentiality was protected in accordance with Health Insurance Portability and Accountability Act guidelines. We used our radiology department's information system to identify consecutive pediatric patients (≤18 years of age) who were clinically suspected of having PE and who underwent CT pulmonary angiography between July 2004 and March 2011 at Children's Hospital Boston, a large pediatric referral hospital.

At our institution, CT pulmonary angiography is currently the imaging modality of choice for clinically suspected

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Abbreviations:
AUC = area under the ROC curve
CI = confidence interval
CVL = central venous line
DVT = deep venous thrombosis
FEU = fibrinogen equivalent units
PE = pulmonary embolism
ROC = receiver operating characteristic
V/Q = ventilation-perfusion

Author contributions:
Guarantors of integrity of entire study, E.Y.L., S.K.S.T.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, E.Y.L., D.Z., N.J.L.; clinical studies, E.Y.L., N.J.L.; experimental studies, S.K.S.T.; statistical analysis, E.Y.L., D.Z., V.M.J.; and manuscript editing, all authors

Potential conflicts of interest are listed at the end of this article.

PE in children. Ventilation-perfusion (V/Q) scanning is performed instead of CT pulmonary angiography in children who are known to have or suspected of having allergy to intravenous contrast media or who are in renal failure. Ten children during the study period underwent V/Q scanning rather than CT pulmonary angiography for suspected PE. Among the 227 patients who underwent CT pulmonary angiography, 153 (67%) also underwent chest radiography within 24 hours before the CT pulmonary angiography examination. The inclusion criterion of this study was all pediatric patients who underwent CT pulmonary angiography at the request of their physicians because of suspicion of PE on the basis of clinical signs and symptoms. The exclusion criterion was suboptimal-quality CT pulmonary angiography data due to insufficient contrast enhancement in the pulmonary arteries and substantial motion and streak artifacts, as detailed in the following discussion of image quality assessment.

The final study cohort consisted of 227 children (105 boys and 122 girls; mean age, 14.1 years ± 4.3; range, 4 months to 18 years). There were 17 patients (7%) who were 5 years of age or younger, 24 patients (11%) who were between 6 and 10 years of age, 89 patients (39%) who were between 11 and 15 years of age, and 97 patients (43%) who were between 16 and 18 years of age. These patients presented with various combinations of clinical signs and symptoms that suggested PE, including tachycardia (n = 122 [54%]), pleuritic chest pain (n = 119 [52%]), shortness of breath (n = 112 [49%]), increased oxygen requirement (n = 57 [25%]), pulmonary hypertension (n = 8 [4%]), and hemoptysis (n = 3 [1%]). Patient referral settings included the inpatient unit for 76 patients (34%), the outpatient clinic for 70 patients (31%), and the Emergency Department for 81 patients (36%).

CT Pulmonary Angiography

All CT pulmonary angiography studies were performed by using one of three available multidetector CT scanners at our institution, including a 16–detector row CT scanner (n = 49 [22%]) (LightSpeed 16; GE Healthcare, Milwaukee, Wis), a 32–detector row CT scanner (n = 60 [26%]) (LightSpeed VCT 32; GE Healthcare), and a 64–detector row CT scanner (n = 118 [52%]) (Sensation 64; Siemens Medical Solutions, Forchheim, Germany).

Nonionic contrast medium (320 milligrams of iodine per milliliter [iopamidol, Isovue-370; Bracco Diagnostics, Milan, Italy]) at a dose of 2 mL per kilogram of body weight (not to exceed 4 mL/kg or 125 mL) was used for all CT pulmonary angiography studies. The contrast material was injected by hand in 12 infants and young children (<5 years of age) with a small-caliber (<22-gauge) catheter. The contrast material was mechanically injected in the remaining 215 children (≥5 years of age) with a power injector at a rate of 1.5–2.0 mL/sec for a 22-gauge catheter and 3 mL/sec for a 20-gauge catheter.

Multidetector CT parameters included 0.75-mm collimation for 16–detector row CT, 0.625-mm collimation for 32–detector row CT, and 0.6-mm collimation for 64–detector row CT, with weight-based kilovoltage, a low-dose tube current, high-speed mode, and a pitch equivalent of 1.0–1.5. The CT data set was reconstructed at a section thickness of 1.5 mm for 16–, 32–, and 64–detector row CT for the review of axial multidetector CT images. Data sets with submillimeter section thickness (0.75 mm for 16–detector row CT, 0.625 mm for 32–detector row CT, and 0.6 mm for 64–detector row CT) were used to create multiplanar reformation images at a section thickness of 1.5 mm in the coronal and sagittal planes by using a standard reconstruction algorithm and a standard window display.

Multidetector CT acquisitions were cranial to caudal from the lung apices to the level of the diaphragm. CT venography was not performed in any patient. The image field of view was from the lateral chest wall skin surface to the opposite lateral chest wall skin surface. The radiologist and/or the CT technologist initiated the CT scanning manually when optimal contrast enhancement (≥150 HU) in the main pulmonary artery was observed on the monitoring scan.

Image Review and Evaluation

Two board-certified faculty pediatric radiologists (E.Y.L. and D.A.T., with 10 and 25 years of experience, respectively) independently reviewed all CT pulmonary angiography studies. Each patient's CT pulmonary angiography study was evaluated for *(a)* the quality of the images (by assessing the degree of contrast enhancement in the pulmonary arteries and the presence of substantial motion and streak artifacts) and *(b)* the presence or absence of PE (as detailed in the following section). To reduce any potential bias, the radiologists were blinded to the original radiology report of the CT pulmonary angiography study, the results of other imaging studies, and clinical and laboratory data. However, they were aware that the CT pulmonary angiography study was performed for clinically suspected PE.

The radiologists evaluated all CT pulmonary angiography images in standard soft-tissue (level, 40–50 HU; width, 400–450 HU) and lung (level, −450 to −550 HU; width, 1600–1800 HU) window settings by using a picture archiving and communication system (PACS). The PACS workstation allowed multiplanar (eg, coronal and sagittal reformation) display, which was used routinely as a complement to the axial images for radiologist evaluation of PE. During the evaluation, the radiologists could also manually alter the window width or level settings and zoom into areas of interest. These factors simulate those involved in the clinical interpretation of CT pulmonary angiography studies in daily practice in our department.

Image quality assessment.—For evaluation of the image quality of the CT pulmonary angiography studies, the contrast enhancement (in Hounsfield units) on the largest image of the main pulmonary artery in a region of interest with a diameter equal to one half the diameter of the main pulmonary artery was measured; this procedure was based on previously published CT pulmonary angiography quality criteria in children

(13,15,16). CT pulmonary angiography studies with suboptimal contrast enhancement (<150 HU) were excluded from our study. In addition, artifacts (eg, motion and streak artifacts) were graded as either absent or present. When artifacts were present, the radiologists were asked to judge whether the artifacts substantially limited their ability to evaluate PE in the pulmonary arteries.

All 227 CT pulmonary angiography studies had diagnostic-quality contrast enhancement in the main pulmonary arteries (mean attenuation, 295 HU ± 96 [standard deviation]; range, 155–565 HU). Studies in three patients (1.3%) had minimal motion and/or respiration artifacts, and studies in six patients (2.6%) had mild streak artifacts from metallic devices such as surgical embolization coils (n = 2) and posterior spinal fusion rods (n = 4); however, these artifacts did not substantially limit evaluation of PE in the pulmonary arteries. Therefore, all 227 CT pulmonary angiography studies were included in the final data analysis. There was no statistically significant difference among the different types of multidetector CT scanners used for patients with PE and those used for patients without PE (P = .457) (Table 1).

Diagnosis of PE.—The radiologists evaluated each diagnostic-quality CT pulmonary angiography study for the presence or absence of PE by using previously published criteria in pediatric patients (13,15,16). The diagnosis of acute PE was made when there was a sharply delineated, complete or partial pulmonary artery filling defect present on at least two consecutive image sections and located centrally in the vessel or with acute angles at its interface with the vessel wall (13,15,16,21). For cases in which there was a discrepancy between the two radiologists' observations, the radiologists reevaluated the cases together and reached a final decision by consensus.

The radiologists' independent interpretations were in agreement with each other in 222 (97.8%) of the 227 CT pulmonary angiography studies. For the remaining five (2.2%) studies for which there was a discrepancy between the two radiologists' initial observations, the radiologists subsequently reevaluated the cases together and were able to reach a final decision by consensus, without the need for a third radiologist to serve as an adjudicator.

Table 1

Comparison of Data in Patients with and Those without PE

Variable	Patients with PE (n = 36)	Patients without PE (n = 191)	P Value*
Age (y)†	13.6 ± 5.4	14.1 ± 4.0	.529
Sex			.623
Male	18 (50)	87 (46)	
Female	18 (50)	104 (54)	
Clinical signs and symptoms			
Tachycardia	22 (61)	101 (53)	.466
Pleuritic chest pain	15 (42)	104 (54)	.203
Shortness of breath	17 (47)	96 (50)	.856
Increased oxygen requirement	9 (25)	48 (25)	.987
Pulmonary hypertension	7 (19)	7 (4)	.999
Hemoptysis	0	3 (2)	.999
Referral setting			
Inpatient	33 (92)	43 (23)	<.0001
Outpatient	2 (06)	68 (36)	
Emergency Department	1 (3)	80 (42)	
Multidetector CT scanner			
16 Detector row	7 (19)	42 (22)	.457
32 Detector row	7 (19)	53 (28)	
64 Detector row	22 (62)	96 (50)	
Risk factors			
Immobilization	27 (75)	10 (5)	<.0001
Indwelling CVL	20 (56)	24 (13)	<.0001
Prior PE and/or DVT	16 (44)	22 (12)	<.0001
Hypercoagulable state	8 (22)	13 (7)	.003
Excess estrogen state	8 (22)	12 (6)	.002
Malignancy	9 (25)	32 (17)	.243
Cardiac disease	3 (8)	18 (9)	.998

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses. Percentages may not add up to 100% owing to rounding. CVL = central venous line, DVT = deep venous thrombosis.

* Calculated with the Fisher exact test (except the P value for age, which was calculated with the Student t test).

† Data are means ± standard deviations.

Thromboembolic Risk Factor Assessment

For evaluation of thromboembolic risk factors in each patient, two authors (S.K.S.T. and N.J.L., with 5 and 12 years of experience, respectively) thoroughly reviewed all available electronic medical records, including history and physical examination results, laboratory results, surgical reports, clinic notes, and discharge summaries from all physicians who took care of each patient during and after hospitalization.

For each patient, an assessment was performed for the presence or absence of the following thromboembolic risk factors: immobilization, malignancy, hypercoagulable state, excess estrogen state, indwelling CVL, underlying cardiac disease, and prior history of PE and/or DVT. The number of risk factors was quantified and recorded for each patient.

The patient was considered to have a risk factor of immobilization if there was either a clinician's documentation that the patient was immobilized or immobilization was assumed on the basis of *(a)* a history of a recent pelvic or lower extremity long bone fracture that required hospitalization, *(b)* postoperative state, *(c)* neurologic episodes,

or *(d)* prolonged travel either by car or plane (which could impair patient mobility) or any combination of these factors (19). A history of primary or metastatic neoplasm was considered to confer the risk factor of malignancy (19,22). A patient was considered to have the risk factor of hypercoagulable state if he or she had either a hereditary condition (eg, factor V Leiden deficiency, protein C or S deficiency) or an underlying systemic medical condition (eg, systemic lupus erythematosus) (19). A patient was considered to have a risk factor of excess estrogen if she was in a peripartum state or used oral contraceptives. The risk factor of an indwelling CVL was denoted by the presence of an indwelling CVL at the time of the CT pulmonary angiography study (19,22). The risk factor of underlying cardiac disease was considered to be present when there was underlying congenital or acquired heart disease and/or a history of cardiac surgery (19). A history of PE and/or DVT was considered to represent a single risk factor because thrombosis rather than the thrombotic location was considered the primary risk factor (19).

D-Dimer Assessment

The two authors (S.K.S.T., N.J.L.) reviewed all patients' electronic medical charts and recorded D-dimer test results. At our institution, the D-dimer test is ordered according to the individual physician's preference. D-dimer testing is typically performed in children with a high clinical probability of PE. Of the 227 patients, 132 (58%) underwent D-dimer testing. These 132 patients were from the inpatient unit (42 patients [31.8%]), the outpatient clinic (31 patients [23.5%]), and the Emergency Department (59 patients [44.7%]).

The D-dimer assay used at our center is an automated latex-enhanced quantitative immunoturbidimetric assay (Advanced D-dimer; Dade Behring, Marburg, Germany), which is performed with a Sysmex CA-1500 instrument (Sysmex America, Mundelein, Ill). At a cutoff value of 1.6 mg/L fibrinogen equivalent units (FEU), this D-dimer assay has sensitivity, specificity, and negative predictive values of 98%, 38%, and 99%, respectively. For the purposes of this study and for daily clinical practice at our institution, 1.6 mg/L FEU is the cutoff value that determines whether a D-dimer result is categorized as positive or negative. D-dimer values greater than 1.6 mg/L FEU are considered positive. Testing was performed in accordance with guidelines set forth by the Department of Pathology and Laboratory Medicine at our institution.

Patient Follow-up Information

For each patient, available follow-up information, including the length of follow-up, any complications related to PE, and mortality from any cause, was investigated by the two authors (S.K.S.T., N.J.L.).

Statistical Analysis

Age, sex, referral setting, and D-dimer result, as well as seven possible risk factors (immobilization, malignancy, hypercoagulable state, excess estrogen state, indwelling CVL, underlying cardiac disease, and a history of prior PE and/or DVT) were compared between patients with and those without PE by using univariate statistics, including the Student *t* test, the Fisher exact test, and the Pearson χ^2 test. Subgroup analysis performed by using the Fisher exact test examined the association between abnormal D-dimer test result and PE within each of the referral settings. Significant associations were then included in a multiple logistic regression model with backward selection to control for confounding. The likelihood ratio test was used to assess the significance of each variable in the model, and the probability of PE based on the number of significant risk factors was derived by using generalized estimating equations with 95% confidence intervals (CIs) (23). The c-index in the multiple logistic regression model was evaluated to assess the quality of the set of risk factors in predicting PE (24,25). Receiver operating characteristic (ROC) curve analysis was applied to evaluate how well the number of multivariate risk factors differentiated patients with from those without PE (ie, sensitivity and specificity), with the area under the ROC curve (AUC) used as the measure of predictive accuracy (26,27). The mean, range, and standard deviation of the length of follow-up were also evaluated. Statistical analysis was performed by using a statistical software package (SPSS, version 19.0; SPSS, Chicago, Ill). A two-tailed *P* value of less than .05 were considered to indicate a statistically significant difference.

Results

Depiction of PE at CT Pulmonary Angiography

On the basis of the final interpretations, a total of 36 (16%) of 227 children were found to have PE at CT pulmonary angiography. CT pulmonary angiography studies were negative for PE in the remaining 191 (84%) children. Of the 36 children with CT pulmonary angiography studies that were positive for PE, 18 (50%) were boys and 18 (50%) were girls (Table 1). The mean age was 13.6 years ± 5.5 for children with CT pulmonary angiography studies that were positive for PE and 14.2 years ± 4.0 for children with CT pulmonary angiography studies that were negative for PE (Table 1). In 36 positive CT pulmonary angiography studies, 87 individual pulmonary emboli were observed at the following levels: segmental (n =32 [37%]), lobar (n = 27 [31%]), subsegmental (n = 20 [23%]), and main or central (n = eight [9%]) (Fig 1).

Relationship of Presence of PE and Age, Sex, and Patient Referral Settings in Patients with and Those without PE

Information regarding age, sex, and referral setting for patients with and those without PE is listed in Table 1. Age (P = .529) and sex (P = .623) were not found to have a significant relationship to the presence of PE detected at CT pulmonary angiography in children who were clinically suspected of having PE. However, inpatient status of the referred patients was found to have a significant relationship to a CT pulmonary angiography study that was positive for PE ($P < .0001$).

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Figure 1

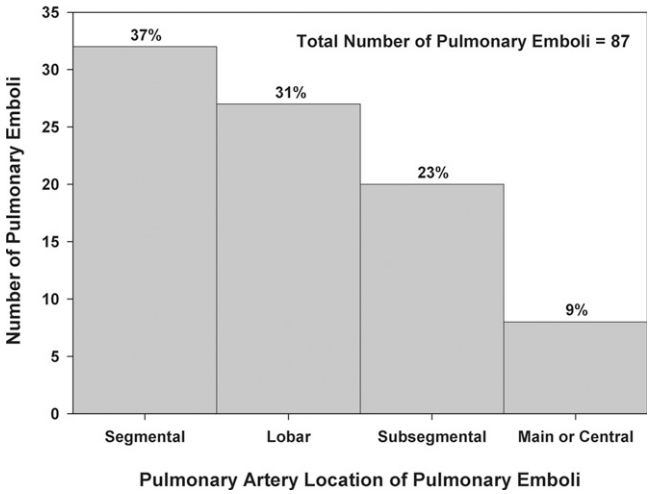

Figure 1: Bar graph shows pulmonary artery location of 87 pulmonary emboli in 36 CT pulmonary angiography studies that were positive for PE.

Figure 2

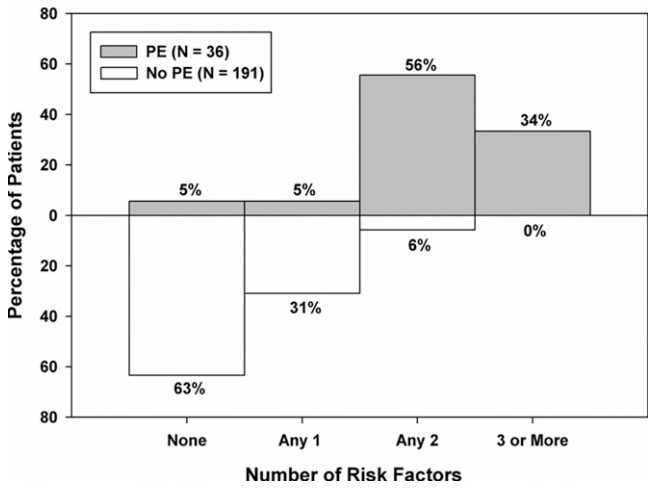

Figure 2: Histogram shows number of risk factors (immobilization, indwelling CVL, prior PE and/or DVT, hypercoagulable state, and excess estrogen state) in patients with PE and those without PE. Among the 36 patients with PE, 34 (94%) had at least two risk factors. Among the 191 patients without PE, 180 (94%) had no or only one risk factor.

Thromboembolic Risk Factors

Number and types of risk factors in children with CT pulmonary angiography studies that were positive for PE.—Of the 36 pediatric patients with CT pulmonary angiography studies that were positive for PE, two (6%) had no identifiable risk factor, two (6%) had one risk factor, 20 (56%) had two risk factors, 11 (31%) had three risk factors, and one (3%) had four risk factors (Fig 2). No patient had more than four risk factors. The frequency of specific risk factors in the 36 pediatric patients with CT pulmonary angiography studies that were positive for PE included immobilization in 27 (75%) patients, indwelling CVL in 20 (56%) patients, prior PE and/or DVT in 16 (44%) patients, hypercoagulable state in eight (22%) patients, and excessive estrogen state in eight (22%) patients (Fig 3).

Number and types of risk factors in children with CT pulmonary angiography studies that were negative for PE.—Of the 191 pediatric patients with CT pulmonary angiography studies that were negative for PE, 121 (63%) had no risk factors, 59 (31%) had one risk factor, and 11 (6%) had two risk factors. None of the patients without PE had more than two risk factors (Fig 2). The specific risk factors in pediatric patients with CT pulmonary angiography studies that were negative for PE included indwelling CVL (n = 24 [13%]), prior PE and/or DVT (n = 22 [12%]), hypercoagulable state (n = 13 [7%]), excessive estrogen state (n = 12 [6%]), and immobilization (n = 10 [5%]) (Fig 3).

Univariate analysis of risk factors for PE.—Seven risk factor variables were assessed with univariate analysis to ascertain whether there were significant differences between the 36 children with PE and the 191 children without PE. Five risk factors, including immobilization (75% vs 5%, $P < .0001$), hypercoagulable state (22% vs 7%, $P = .003$), excess estrogen state (22% vs 6%, $P = .002$), indwelling CVL (56% vs 13%, $P < .0001$), and prior PE and/or DVT (44% vs 12%, $P < .0001$), were found to be present with significantly higher percentages in patients with PE than in those without PE (Table 1).

Multiple logistic regression analysis of risk factors for PE.—Seven risk factors from the univariate analysis were included in a multiple logistic regression model to identify independent risk factors of PE. Of the seven covariates tested, immobilization ($P < .001$), hypercoagulable state ($P = .003$), excess estrogen state ($P = .002$), indwelling CVL ($P < .001$), and prior PE and/or DVT ($P < .001$) remained significant, whereas malignancy ($P = .397$) and underlying cardiac disease ($P = .476$) were not found to be predictive of PE (Table 2).

A summary of the final multiple logistic regression model, with the regression (β) coefficients, odds ratios, 95% CIs, and P values for the five independent risk factors, is presented in Table 2. The final fitted equation used in estimating the probability of PE is given in Appendix E1 (online).

ROC analysis of risk factors for PE.—ROC analysis was performed on the basis of the five significant risk factors to determine the utility in differentiating between a positive CT pulmonary angiography study and a negative CT pulmonary angiography study (Fig 4). The AUC (0.934; $P < .0001$) was excellent, indicating very high predictive utility, and the optimal cutoff for maximizing the area was at least two risk factors (out of five possible). Sensitivity based on a prediction rule that used at least two risk factors was 89%, where PE was correctly identified in 32 of 36 patients (95% CI: 75%, 96%). Conversely, with use of the prediction rule of at least two risk factors out of five as the

Figure 3

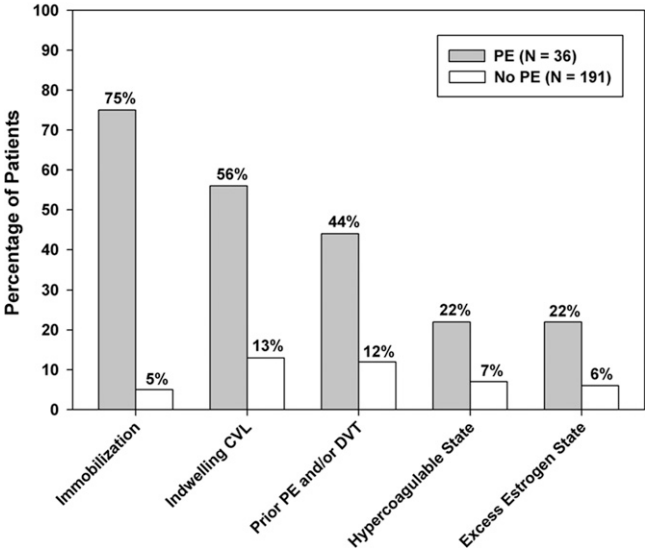

Figure 3: Bar graph shows results of comparison of five statistically significant risk factors (immobilization, indwelling CVL, prior PE and/or DVT, hypercoagulable state, and excess estrogen state) between patients with PE and those without PE. The most common risk factor was immobilization, which was present in 75% (27 of 36) of patients with PE but in only 5% (10 of 191) of patients without PE.

Figure 4

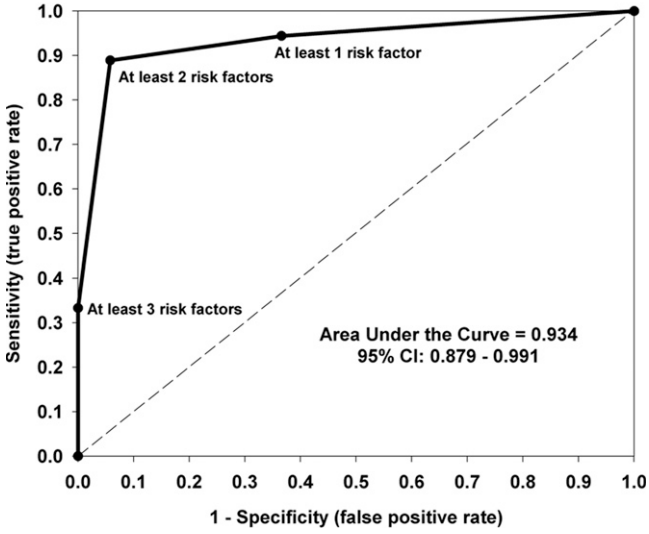

Figure 4: ROC curve for differentiating patients with PE from those without PE on the basis of the total number of risk factors (immobilization, indwelling CVL, prior PE and/or DVT, hypercoagulable state, and excess estrogen state). Dashed line = 45° line of nondiscrimination (equivalent to coin tossing). The AUC of 0.934 indicates excellent discrimination ($P < .0001$).

clinical threshold, specificity was 94%, correctly classifying 180 patients out of 191 without PE (95% CI: 90%, 97%).

Simplified algorithm of number of risk factors and probability of PE.—A look-up table, which provides the predicted probability of PE and the 95% CIs to give clinical assurance regarding the precision of the probability based on the simplified prediction algorithm using the number of risk factors (none, any one risk factor, any two risk factors, or any three or more risk factors), is given in Table 3.

D-Dimer Test Results

D-dimer testing was performed in 132 (58%) of 227 patients. The mean D-dimer value was 5.6 mg/L FEU ± 8.0 (standard deviation) (range, 0–55 mg/L FEU). D-dimer test results were positive in 115 (87%) and negative in 17 (13%) of the 132 patients.

Among 25 patients with both D-dimer test results and CT pulmonary angiography studies that were positive for PE, 22 (88%) had positive D-dimer test results, whereas three (12%) had negative results. The mean D-dimer value was 6.0 mg/L FEU ± 7.1 (range, 1.1–38.1 mg/L FEU) in this group.

Among 107 patients with both D-dimer test results and CT pulmonary angiography studies that were negative for PE, 93 (87%) had positive D-dimer test results, whereas 14 (13%) had negative results. The mean D-dimer value was 5.5 mg/L FEU ± 8.2 (range, 0–55 mg/L FEU) in this group.

A positive D-dimer result was not found to have a significant relationship to the presence of a PE detected by utilizing CT pulmonary angiography in children with a high clinical probability of PE ($P = .14$). A subgroup analysis revealed that D-dimer result was not associated with the presence of PE as detected by utilizing CT pulmonary angiography for any of the three referral settings ($P > .98$ for all).

Patient Follow-up

Follow-up information (mean, 1.8 years ± 1.6; range, 1 week to 6.1 years) was available for all 36 patients with a CT pulmonary angiography study that was positive for PE. At the end of follow-up, 30 (83%) patients were alive, and the remaining six (17%) were deceased. All surviving 30 patients and six deceased patients with available follow-up information did not have evidence of subsequent PE. The cause of death in the six deceased patients included advanced course of underlying neoplasm ($n = 4$), bacterial sepsis ($n = 1$), and human immunodeficiency virus nephropathy ($n = 1$).

Follow-up information (mean, 1.7 years ± 1.6; range, 1 week to 6.2 years) was available for 178 (93%) of 191 patients with a CT pulmonary angiography study that was negative for PE. At the end of follow-up, 162 (91%) patients were alive, and the remaining 16 (9%) were deceased. All surviving 162 patients and 16 deceased patients with available follow-up information did not have evidence of subsequent PE. The cause of death in the 16 deceased patients included advanced course of underlying neoplasm ($n = 7$), vascular malformation ($n = 3$), adenovirus infection ($n = 1$), persistently worsening pulmonary hypertension ($n = 1$), common variable immunodeficiency syndrome ($n = 1$), refractory seizure ($n = 1$),

Table 2

Significant Independent Risk Factors for PE

Risk Factor	β Coefficient	Odds Ratio	95% CI	*P* Value
Immobilization	4.87	130.5	25.0, 681.8	<.001
Hypercoagulable state	3.06	21.4	3.5, 131.5	.003
Excess estrogen state	2.58	13.2	1.5, 123.7	.002
Indwelling CVL	3.28	26.4	5.5, 127.2	<.001
Prior PE and/or DVT	1.96	7.1	2.0, 27.2	<.001

Note.—The risk factors malignancy ($P = .397$) and underlying cardiac disease ($P = .476$) were tested but were not retained in the final multivariable model. The intercept term was –5.89.

Table 3

Simplified Algorithm of Number of Risk Factors and Probability of PE

No. of Risk Factors*	Probability of PE (%)	95% CI (%)
None	0.5	0.1, 2
Any one	8	5, 15
Any two	62	46, 76
Any three or more	89	87, 99

* Risk factors were immobilization, hypercoagulable state, excess estrogen state, indwelling CVL, and prior PE and/or DVT.

cardiomyopathy ($n = 1$), and ruptured hemorrhagic ovarian mass ($n = 1$).

Discussion

Our study results show that it is very unlikely for CT pulmonary angiography results to be positive for PE in children without identifiable thromboembolic risk factors, despite a clinical suspicion of PE. In addition, we also found that there is no significant relationship between a positive D-dimer result and the presence of PE at CT pulmonary angiography in this patient population. Therefore, the results of our study support the use of risk factor assessment as a first-line clinical triage tool to guide when to perform CT pulmonary angiography for PE in pediatric patients.

The two main reasons for optimizing utilization of CT pulmonary angiography are to avoid unnecessary radiation exposure and to reduce health care costs. On the basis of our findings, the use of risk factor assessment has the potential to reduce the utilization of CT pulmonary angiography in children, with associated reduction in radiation exposure and costs.

The results of our study demonstrate that five independent risk factors (immobilization, hypercoagulable state, excess estrogen state, indwelling CVL, and prior PE and/or DVT) are significantly associated with a positive CT pulmonary angiography result for PE in multiple logistic regression analysis. Our findings are in agreement with the results of a recent study in adults (19), which showed a significant association between four independent risk factors (immobilization, hypercoagulable state, excess estrogen state, and prior PE and/or DVT) and the presence of PE at CT pulmonary angiography. However, unlike ourselves, those authors did not specifically attempt to determine whether indwelling CVL is an independent risk factor for a positive CT pulmonary angiography result for PE.

On the basis of these results, CT pulmonary angiography may not be necessary in pediatric patients with no thromboemoblic risk factors. In such cases, investigation for other causes of these patients' symptoms may be more beneficial. Furthermore, we emphasize that investigation with CT pulmonary angiography should be performed promptly in children with more than two risk factors, particularly if they are referred from an inpatient setting.

With regard to the usefulness of D-dimer testing for predicting the presence of PE at CT pulmonary angiography in pediatric patients, our data suggests that this test may have limited apparent value in this setting. The results of our study expand on those recently reported in a small subgroup ($n = 8$) of pediatric patients suspected of having PE (14), in which D-dimer test results did not help statistically distinguish pediatric patients with PE from those without. In contrast, the D-dimer test has been found to be useful as a first-line test in caring for adult patients who are suspected of having PE (19,28). However, we emphasize that D-dimer testing in our study was limited to those children with a high probability of having PE, whereas the previous studies (19,28) involved adult patients in whom D-dimer testing was performed when the clinical probability of PE was low or intermediate. A future study aimed at investigating the efficacy of D-dimer testing in children with low or intermediate probability of PE is thus needed to determine the test's potential role in excluding PE in pediatric patients with low or intermediate clinical probability. We believe that such additional information will be helpful for deciding whether the D-dimer test has a relevant role in the assessment of pediatric patients who are clinically suspected of having PE. Until then, the use of risk factor assessment has great potential as a first-line clinical triage tool to guide when to perform CT pulmonary angiography for PE in pediatric patients.

Recently, there has been rising interest in the importance of limiting ionizing radiation exposure associated with CT imaging, especially among children, who are more vulnerable than adults to potentially harmful ionizing radiation exposure (29–34). Recent studies of CT pulmonary angiography in children (13,14) have reported a wide range of radiation doses (2–26 mSv), which is most likely due to the use of various types of multidetector CT scanners and

differing CT pulmonary angiography protocols at different institutions. Coupled with this finding is the increased awareness of the suboptimal use of radiation dose–reduction techniques for CT pulmonary angiography in children, particularly in the private practice setting (18). Our study results show that 94% (180 of 191) of pediatric patients with fewer than two risk factors and without PE could have potentially avoided CT pulmonary angiography if risk factor assessment had been used before the examination. By bypassing CT pulmonary angiography in this pediatric patient group on the basis of risk factor assessment, potentially unnecessary radiation and costs ($2000–$3000 combined direct and associated costs per examination) could have been avoided (19). However, we emphasize that a detailed cost analysis is beyond the scope of this study. Furthermore, an alternative imaging modality associated with lower radiation dose such as V/Q scanning may be considered for assessment of PE in older pediatric patients (>5 years of age) who can follow the breathing instructions for a V/Q examination. The likelihood of a diagnostic V/Q examination is high in children because most children do not have underlying lung disease, a factor that often limits evaluation of PE with V/Q scanning in adults.

We acknowledge six main potential limitations to our study. First, although the patient population size of our study was relatively large for a study of PE in a pediatric population, only 16% (36 of 227) of patients had CT pulmonary angiography studies that were positive for PE. Considering our relatively small sample of positive studies, a future multicenter study with a larger patient population is necessary to confirm our preliminary recommendation that one can safely withhold imaging evaluation in children with no risk factors for PE. Second, the analysis of immobilization as a risk factor for PE was relatively subjective, particularly for patients without a specifically stated clinician's documentation of immobilization. However, we emphasize that the inclusion of and strict adherence to specific criteria for immobilization minimized potential error in correctly capturing this risk factor in our study. Third, D-dimer testing was not performed for all patients in our study. However, our percentage of available D-dimer test results of 58% (132 of 227 patients) is substantially higher than that (4.9%) reported in a recent study in adults (19). Additionally, we emphasize that this closely reflects the current clinical practice pattern for the use of D-dimer testing in children who are clinically suspected of having PE. In other words, clinicians are not currently required to routinely order D-dimer testing in all pediatric patients who are clinically suspected of having PE. Therefore, the D-dimer assay could be bypassed on the basis of clinical judgment, and patients could proceed directly to CT pulmonary angiography. Fourth, we were not able to retrospectively measure the precise degree of clinical suspicion for PE of the clinicians that prompted them to order D-dimer testing for their patients in our study. Unlike in adults, in pediatric patients, the D-dimer test is usually ordered for patients with a high clinical suspicion for PE but not for those with a low or intermediate level of clinical suspicion. Therefore, we may not have been able to directly determine whether D-dimer testing could have been potentially valuable in the setting of a low or intermediate clinical suspicion of PE. However, we emphasize that such assessments are subjective, and our proposed risk factor assessment is less likely subjective. Fifth, although we made a conscientious effort to reduce potential bias by blinding the radiologists to the results of radiology examinations and clinical and laboratory data, it is possible that some potential recall bias may still have existed in this study because the radiologists for this study also participated in previous studies that included a subset of the same CT pulmonary angiography data used in this study. However, the substantial delay between these investigations and the random, anonymized method of case review likely minimized the possibility of such bias. Last, our study was performed in a large pediatric referral hospital and may not be reflective of findings in pediatric patients in a smaller children's hospital or community setting. Future prospective larger studies aimed at validating our results in a larger and more diverse patient population are necessary.

In conclusion, it is very unlikely for CT pulmonary angiography results to be positive for PE in children with no thromboembolic risk factors. The use of risk factor assessment as a first-line triage tool has the potential to guide more appropriate use of CT pulmonary angiography in children, with associated reductions in radiation exposure and costs.

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