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Risk factors for suspected pulmonary embolism in children: Complication of *Mycoplasma pneumoniae* pneumonia

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ABSTRACT

Purpose: Pulmonary embolism (PE) is not a rare complication of *Mycoplasma pneumoniae* pneumonia (MPP) in children. We sought to determine the incidence of PE in children with MPP who underwent clinically indicated CT pulmonary angiography (CTPA) and to evaluate the risk factors for PE.

Methods: All 106 children with MPP who were clinically suspected of having PE and who underwent CTPA were retrospectively enrolled from June 2018 to December 2021. The clinical features, laboratory data, and radiological parameters were recorded (e.g., lung consolidation involved and the Qanadli score). A Cox proportional hazards model and area under the receiver operating characteristic (ROC) curve were used to evaluate the risk factors and prognostic discriminatory capacity for PE.

Results: PE was detected in 26 of 106 (24.5 %) children (mean age, 6.2 years ± 3.3 years; 53 boys). Sixteen of the 26 (61.5 %) children with PE were boys. The mean age of the children with PE was 8.1 ± 2.9 years, and the mean Qanadli score was 15.3 ± 10.2. Children with PE had higher D-dimer levels (9.3 ± 7.1 mg/Lvs. 3.6 ± 3.8 mg/L) and a greater frequency of lung lobe consolidation (25 (96.2 %) vs. 64 (80.0 %)) (all $P < 0.05$). For children with MPP, age (hazard ratio (HR) = 1.96 (95 % CI1.04, 3.71; $P = 0.037$), D-dimer level (HR = 1.52, 95 % CI: 1.03, 2.24; $P = 0.029$), and bilateral lung consolidation (HR = 2.41, 95 % CI: 1.03, 5.58; $P = 0.043$) were found to be independent predictors of PE.

Conclusion: Clinical and CT radiological predictors could be used to predict PE in children with MPP. The use of risk factor assessment as a tool has the potential to guide more appropriate use of CTPA in children.

1. Introduction

Mycoplasma pneumoniae pneumonia (MPP) accounts for a steadily increasing proportion of cases of pneumonia with increasing age[1,2]. In 2011, the incidence of MPP increased steadily and, that winter, the incidence peaked among U.S. children[3]. From 2009 to 2019, MPP was the second leading bacterial pathogen in China, accounting for 29.9 % of the total positive detection of bacteria. In the winter of 2021, we encountered an increase in the incidence of MPP in hospitalized children, which was often accompanied by an elevated D-dimer level in our hospital.

Pulmonary embolism (PE) is rare in children, but its incidence has rapidly increased by 200 % over the past 10 years; moreover, the prevalence of PE is highest in adolescents, and it is increasing more rapidly in these children[4,5]. The majority of disease-associated with PE in children were cardiac disease, central venous catheters, and malignancies. Respiratory tract infection is a rare risk factor for PE[6]. However, PE present in children with *Mycoplasma pneumoniae* has rarely been reported.

According to the 2019 ESC Guidelines, CT pulmonary angiography (CTPA) is the method of choice for imaging the pulmonary vasculature in children with suspected PE[7]. The use of CTPA, which has high sensitivity and specificity and excellent spatial resolution, is optimal for evaluating children with suspected MPP and PE. In recent years, few studies have reported PE in children with MPP[8–10]. However, most of the previous studies were case reports, and few studies have evaluated parameters to predict PE, except for D-dimer level. These prior studies demonstrated that the mechanism of thrombosis after *Mycoplasma pneumoniae* infection is still unknown but is likely related to immune modulation. The purpose of this study was to evaluate the risk factors for pulmonary embolism and demonstrate the diagnostic performance of these factors in children with MPP.

Abbreviations: CTPA, CT pulmonary angiography; MPP, mycoplasma pneumoniae pneumonia; PE, pulmonary embolism; ROC, receiver operating characteristic.

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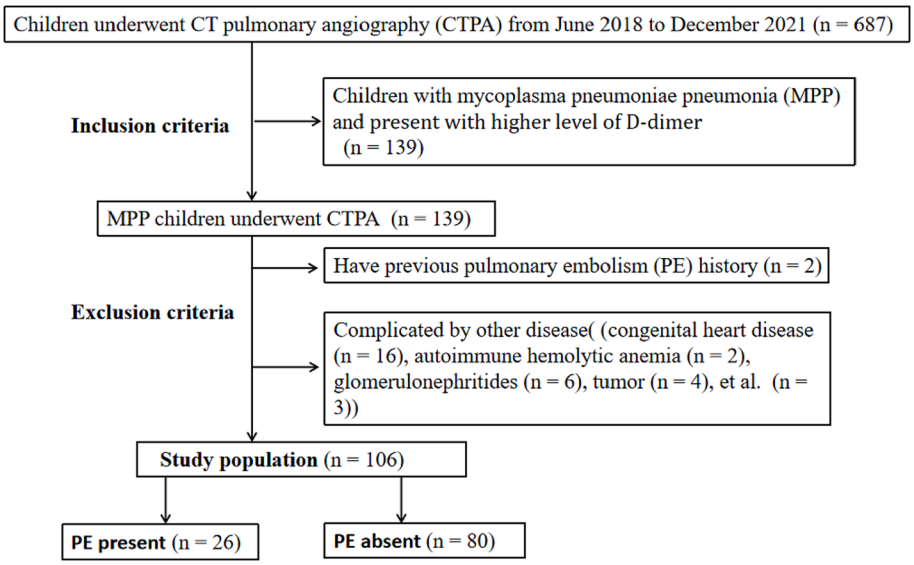

Fig. 1. Flowchart of the study.

Table 1
Patient characteristics laboratory data and radiological features.

	PE present (N = 26)	PE absent (N = 80)	*P* value
Clinical features			
Sex			
Boy	16 (61.5 %)	36 (45.0 %)	**<0.001**
Girl	10 (38.5 %)	44 (55.0 %)	
Age*	8.1 ± 2.9	5.6 ± 3.1	**<0.001**
<2 years	1 (3.8 %)	12 (15.0 %)	
2–4 years	2 (7.7 %)	19 (23.8 %)	
5–9 years	14 (53.8 %)	39 (48.8 %)	
10–13 years	9 (34.6 %)	10 (12.5 %)	
14–18 years	–	–	
Clinical symptoms			
Cough	26 (100 %)	77 (96.3 %)	0.319
Fever	24 (92.3 %)	76 (95.0 %)	0.608
Chest pain	3 (3.8 %)	3 (3.7 %)	0.982
Abdomen pain	2 (7.7 %)	1 (1.3 %)	0.087
Hemoptysis	2 (7.7 %)	5 (6.3 %)	0.724
Interval time from clinical symptom to CTA (days)*	28.8 ± 45.6	25.1 ± 30.7	0.854
Hospitalization Length, days (days) *	15.7 ± 7.6	13.7 ± 6.7	0.362
Laboratory data*			
D-dimer (mg/L)	9.3 ± 7.1	3.6 ± 3.8	**<0.001**
CPR (mg/L)	35.1 ± 55.5	13.1 ± 33.6	**0.010**
WBCC (10^9/L)	11.2 ± 6.0	10.1 ± 3.9	0.724
ESR (mm/H)	47.8 ± 17.6	42.4 ± 25.8	0.405
PCT(ng/mL)	0.7 ± 2.3	4.9 ± 25.5	0.119
SAA (mg/L)	132.5 ± 121.8	110.2 ± 103.3	0.545

Note.– Unless otherwise specified, data are numbers (percentages);
*Data are means standard deviations. The bold figures indicate a $P < 0.05$.
CRP = C-reactive protein, WBCC = white blood cell count, ESR = erythrocyte sedimentation rate, PCT = procalcitonin, PE = pulmonary embolism, SAA = serum amyloid A.

Table 2
Characteristics of radiological features.

	PE present (N = 26)	PE absent (N = 80)	*P* value
No lung consolidation involved	1 (3.8 %)	16 (20.0 %)	**<0.001**
Left or right lung consolidation	25 (96.2 %)	64 (80.0 %)	**<0.001**
Right lung consolidation	16 (61.5 %)	42 (52.5 %)	**0.001**
Upper lobe	3 (11.5 %)	14 (17.5 %)	**0.008**
Middle lobe	3 (11.5 %)	10 (12.5 %)	0.052
Lower lobe	13 (50.0 %)	26 (32.5 %)	**0.037**
Left lung consolidation	15 (57.7 %)	32 (40.0 %)	**0.013**
Upper lobe	5 (19.2 %)	12 (15.0 %)	0.090
Lingula lobe	1 (3.8 %)	10 (12.5 %)	**0.007**
Lower lobe	12 (46.2 %)	22 (28.7 %)	0.086
Bilateral lung consolidation	7 (26.9 %)	10 (12.5 %)	**0.024**
Pleural effusion	15 (57.7 %)	32 (40.0 %)	**0.013**

Note.– Data are numbers (percentages). The bold figures indicate a $P < 0.05$.
PE = pulmonary embolism.

2. Materials and Methods

2.1. Patient population

This retrospective study was approved by our institutional review board, which waived the need for informed consent. All MPP patients who were clinically suspected of having PE underwent CTPA at our hospital. We retrospectively identified 687 children aged ≤ 18 years who underwent CTPA in the Radiology Department from June 2018 to December 2021. The mean time period from the diagnosis of MPP to CT acquisition was 14.7 days. The inclusion criteria were as follows: 1) had been diagnosed with MPP; 2) aged ≤ 18 years; and 3) suspected of having PE (presenting with a higher D-dimer level (>0.5 mg/L) and clinical symptoms of PE). The inclusion and exclusion criteria are shown in Fig. 1. The time interval between the laboratory data and CTPA studies was less than 2 days. The confirmation of MPP infection was made by means of serologic tests (complement fixation tests for the specific antibody to *Mycoplasma pneumoniae*) with elevated single titres ≥ 1:64 or a fourfold increase in titre during the recovery phase compared with those during the acute phase[11]. The exclusion criteria were as follows: 1) had a previous PE history and 2) had MPP complicated by other diseases (congenital heart disease, autoimmune haemolytic anaemia, glomerulonephritides, or tumours). The clinical data, including symptoms, laboratory data, hospitalization length, etc., were collected via the electronic health record system at our institution. All the children were classified into five groups according to age: < 2 years, 2–4 years, 5–9 years, 10–13 years, and 14–18 years. All PE patients were treated with therapeutic anticoagulation agents according to current guidelines [7]. All of these symptoms were relieved or disappeared from the PE clots after treatment.

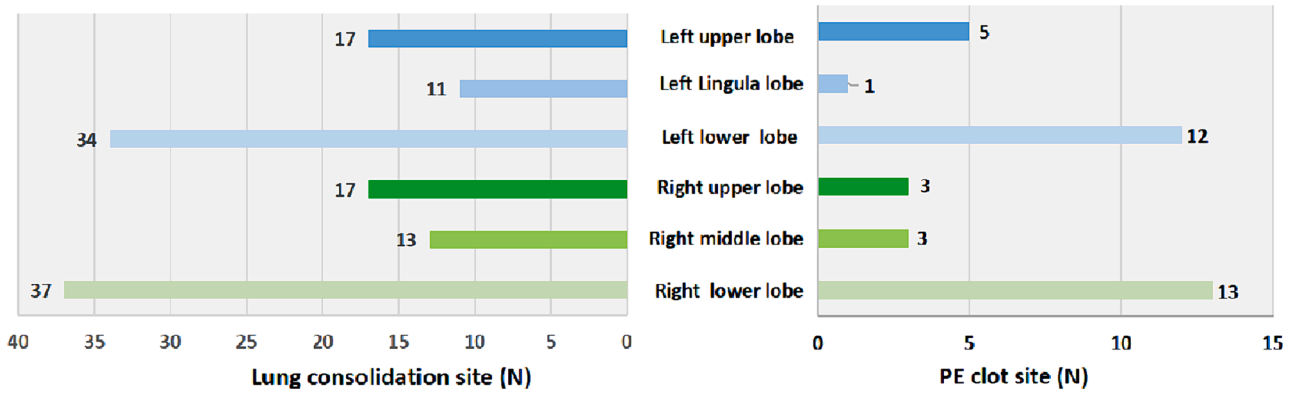

Fig. 2. Location and frequencies of lung consolidation and PE clot occurrence.

Table 3
Association between lung consolidation and Qanadli score.

Characteristic	Qanadli score	*P* value
Frequency of lung lobe consolidation		0.379
1	4.7 ± 9.3	
2	3.5 ± 8.2	
3	2.9 ± 3.7	
4	7.5 ± 8.9	
Lung consolidation pattern		**0.013**
No lung consolidation	1.4 ± 6.1	
Left or right lung consolidation	3.0 ± 7.0	
Bilateral lung consolidation	7.8 ± 12.7	
Right lung consolidation	4.0 ± 8.7	0.656
Upper lobe	1.0 ± 2.4	
Middle lobe	0.8 ± 2.3	
Lower lobe	6.9 ± 7.8	
Left lung consolidation	5.2 ± 9.7	0.328
Upper lobe	0.8 ± 2.0	
Lingula lobe	0.3 ± 1.1	
Lower lobe	3.2 ± 6.3	

Note.– Data are means standard deviations. The bold figures indicate a $P < 0.05$. PE = pulmonary embolism.

2.2. CTA protocol

All CT scans were obtained with a dual-source CT scanner (SOMATOM Force, Siemens Healthcare, Forchheim, Germany) after intravenous injection of iodinated contrast medium (Schering Ultravist, Iopromide, 350 mg I/ml) at a dose of 0.8 mL/kg body weight, followed by a 0.8 mL/kg body weight saline fush. The injection flow rate was 1.0 mL/s. The CT scan parameters were as follows: rotation time, 0.25 s; detector collimation, 2 × 192 × 0.6 mm; tube voltage, 70 kV; and tube current, set by weight (10 mAs/rot/kg up to 6 kg and 5 mAs/rot/kg up to 140 mAs/rot). Images were reconstructed with a slice thickness of 0.70 mm. Patients who could not cooperate during the examination (e.g., lowest age groups) underwent CT under sedation.

2.3. Imaging analysis

CTPA images were analysed by two cardiovascular radiologists (H.G. and Y.C.H., with 8 and 9 years of experience, respectively) on a picture archiving and communication system workstation. We collected lung consolidation, pleural effusion and Qanadli score data[12] from the CTPA images. All patients were assessed via the syngo.via pulmo3D workflow. The frequency of lung lobe consolidation was defined as the number of lung lobe consolidations involving pneumonia. The right lung lobe consolidation was composed of the upper right lung lobe, middle right lung lobe, and lower right lung lobe. The left lung lobe consolidation was composed of the upper left lung lobe, lingula left lung lobe, and lower left lung lobe. Bilateral lung lobe consolidation was defined as one or more lung consolidations in the right lung lobe and as left lung lobe consolidation.

The CT obstruction score determined via PE was based on the Qanadli method[12]. The CT obstruction score can be expressed as $\Sigma (n \cdot d)/40 \times 100$, where n is the value of the proximal thrombus in the pulmonary arterial tree equal to the number of segmental branches arising distally (minimum, 1; maximum, 20) and d is the degree of vascular obstruction (no obstruction, 0; partial obstruction, 1; complete obstruction, 2). The radiologists were blinded to the clinical and laboratory data. A simultaneous reading to reach consensus was achieved when needed.

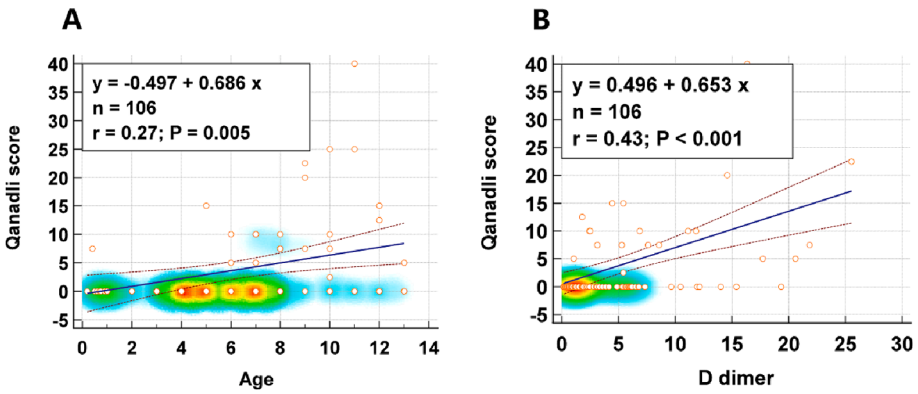

Fig. 3. Scatter plots showing the correlation between age and the Qanadli score (A) and D-dimer level and Qanadli scores (B).

Table 4
Univariate and multivariable association of Clinical and CTPA Characteristics with PE.

	Univariable		Multivariable	
	Hazard ratio (95 % CI)	*P* value	Hazard ratio (95 % CI)	*P* value
Age	2.36 (1.36, 4.11)	**0.002**	1.96 (1.04, 3.71)	**0.037**
Boy	1.53 (1.24, 2.12)	0.129	1.46 (0.60, 3.51)	0.403
D-dimer	2.04 (1.24, 3.34)	**0.005**	1.52 (1.03,,2.24)	**0.029**
Lung consolidation pattern				
No consolidation	1.00			
Unilateral consolidation	1.34 (0.79, 2.67)	0.082		
Bilateral consolidation	3.88 (2.71, 5.54)	**<0.001**	2.41 (1.03, 5.58)	**0.043**
Pleural effusion	1.35 (0.96, 3.06)	0.473		
Hospitalization length	1.01 (0.58, 1.74)	0.989		

Note.– PE = pulmonary embolism. The bold figures indicate a $P < 0.05$.

2.4. Statistical analysis

For descriptive statistics, continuous variables are expressed as medians (interquartile ranges) or means ± standard deviations, and categorical variables are expressed as numbers (percentages). Differences between the groups were assessed using the chi-square test for comparisons of categorical variables. The Mann-Whitney *U* test was used for comparisons of continuous variables. Cumulative event rates of PE were estimated by using the Kaplan-Meier method and log-rank test. The association between MPP and PE was estimated using a Cox proportional hazards model. The area under the receiver operating characteristic (ROC) curve was used to evaluate the prognostic discriminatory capacity of the risk factors and radiological features for predicting PE. A $P < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using the SPSS software package (version 25, IBM SPSS Statistics) and MedCalc, version 12 [MedCalc].

3. Results

3.1. Study population and clinical and radiological characteristics

Of the 106 children diagnosed with MPP and who underwent CTPA, 26 (24.5 %) were confirmed to have PE. Sixteen of these 26 (61.5 %) were boys. The rate of positive PE exams was highest in boys aged 5–9 years, but the highest frequency of positive PE scans was actually in the 10- to 13-year-old age group. The mean age of the children with PE was 8.1 ± 2.9 years, and that of the children without PE was 5.6 ± 3.1 years ($P < 0.001$). Children with PE had higher D-dimer levels than those without PE (9.3 ± 7.1 mg/L vs. 3.6 ± 3.8 mg/L, $P < 0.001$). Patient characteristics are shown in Table 1. The frequency of lung lobe consolidation was higher in children with PE (25 (96.2 %) vs. 64 (80.0 %), $P < 0.001$), and bilateral lung consolidation was more common (7 (26.9 %) vs. 10 (12.5 %), $P = 0.024$) (Table 2). A higher frequency of lung lobe consolidation presented more sites of PE clot occurrence (Fig. 2).

The consolidation pattern was assigned to three groups: bilateral consolidation, unilateral consolidation and no consolidation (Table 3). The presence of bilateral lung consolidation was associated with a higher Qanadli score than the absence of consolidation or unilateral lung consolidation (7.8 ± 12.7 vs. 3.0 ± 7.0 vs. 1.4 ± 6.1, $P = 0.013$). The Qanadli score correlated with age (r = 0.27, $P = 0.005$) and D-dimer level (r = 0.43, $P < 0.001$) (Fig. 3). The mean Qanadli score was 6.9 ± 7.8 for right lower lobe consolidation and 3.2 ± 6.3 for left lower lobe consolidation. The number of PE clots decreased in these children during follow-up.

3.2. Prediction of PE

The results of univariate and multivariate Cox hazard regression analyses for predicting PE are displayed in Table 4. We constructed a multivariate model by including the variables that were significantly associated with PE ($P < 0.05$) via univariate analysis. D-dimer level (HR = 1.52, 95 % CI = 1.03, 2.24, $P = 0.029$) and age (hazard ratio (HR) = 1.96 (95 % CI = 1.04, 3.71, $P = 0.037$) were found to be independent

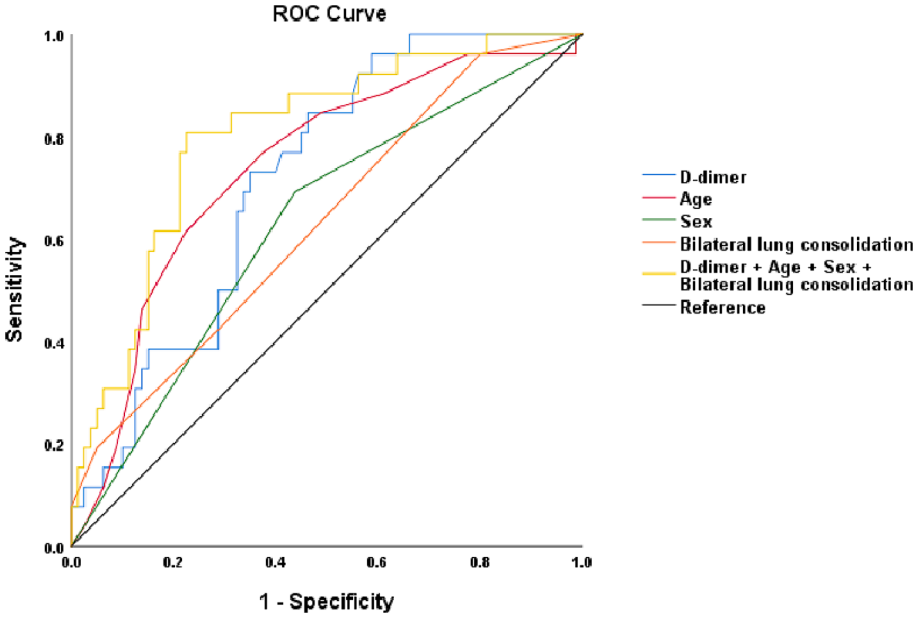

Fig. 4. ROC curve analysis showed the diagnostic performance of the four models for predicting PE incidence: age (AUC = 0.74, $P = 0.001$), sex (AUC = 0.63, $P = 0.052$), D-dimer level (AUC = 0.72, $P = 0.046$), bilateral lung consolidation (AUC = 0.63, $P = 0.062$), and age + sex + D-dimer + bilateral lung consolidation (AUC = 0.81, $P < 0.001$). ROC = receiver operating characteristic, AUC = area under curve.

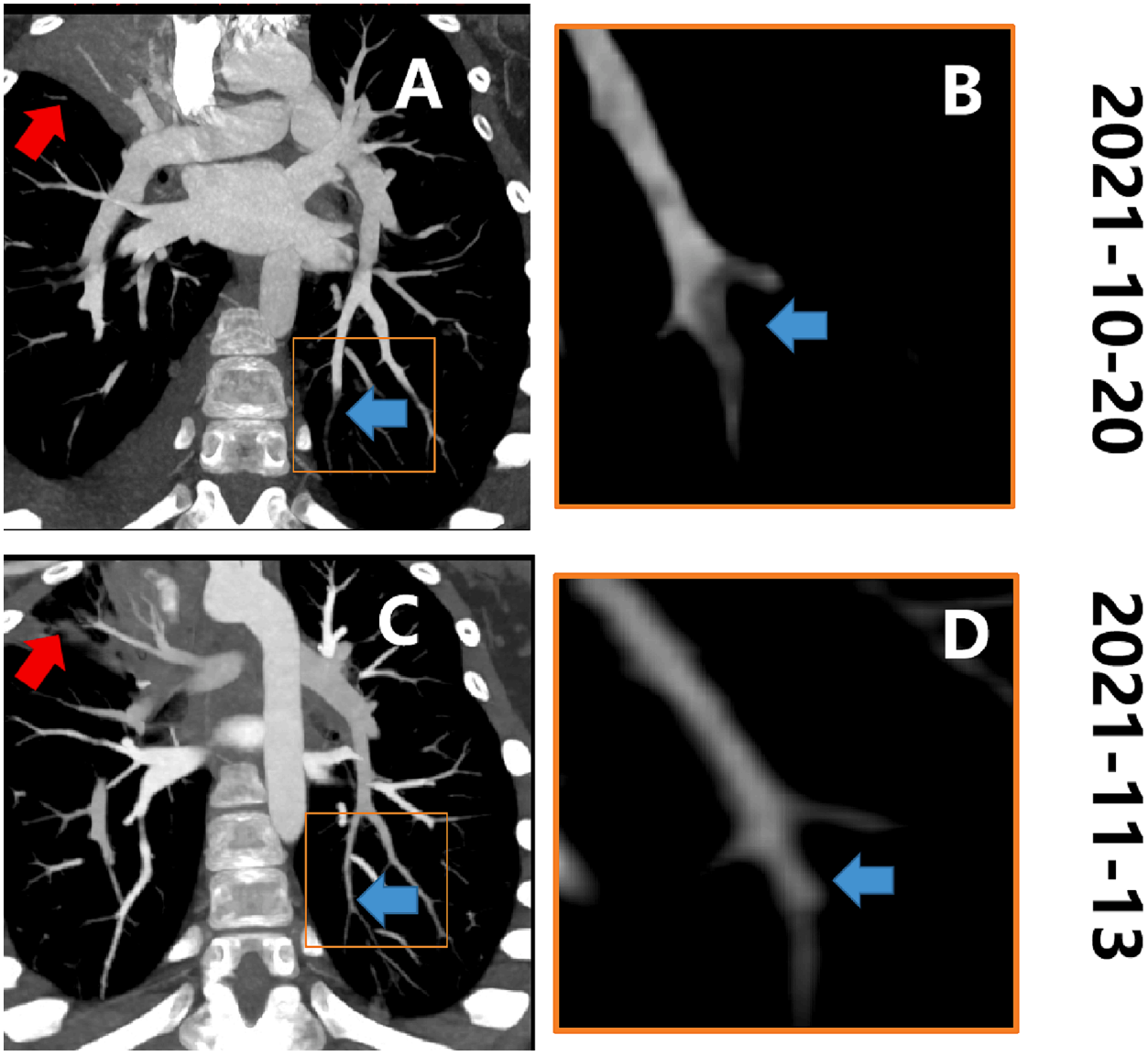

Fig. 5. Images of an 8-year-old boy diagnosed with PE and MPP. Lobar consolidation was detected in the right lung (A, red arrow), and PE was detected in the left lower artery (B, blue arrow) of the reconstructed image on Oct. 20. 2021. This boy was followed up by CTPA on Nov. 13. Lung consolidation improved (C, red arrow), and the PE clot disappeared (D, blue arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

predictors of PE. The presence of bilateral lung consolidation (HR = 2.41, 95 % CI = 1.03, 5.58, $P = 0.043$) was independently predictive of PE compared with the absence of consolidation and unilateral lung consolidation.

3.3. ROC analysis and performance curves

The different parameters of the ROC curves are shown in Fig. 4. The area under the curve (AUC) was 0.74 (95 CI = 0.63, 0.85, $P = 0.001$) for age, 0.63 (95 CI = 0.51, 0.75, $P = 0.052$) for sex, 0.72 (95 CI = 0.62, 0.82, $P = 0.046$) for D-dimer level, 0.63 (95 CI = 0.51, 0.75, $P = 0.062$) for bilateral lung consolidation, and 0.81 (95 CI = 0.71, 0.91, $P < 0.001$) for age + sex + D-dimer level + bilateral lung consolidation. The case of a PE patient complicated with MPP is shown in Fig. 5.

4. Discussion

Our findings demonstrated that 24.5 % of MPP patients who underwent CTPA had PE.

Age, D-dimer level, and bilateral lung consolidation detected by CT were significantly associated with PE.

Up to 16 % of PEs in children can be asymptomatic[13]. The incidence of PE has increased rapidly, possibly due to the increased use of drugs such as hormones or increased obesity, and other lifestyle changes may have contributed to this increase in PE incidence. In addition, the increase in PE may be a result of more sensitive or a more frequent use of imaging techniques (CT), detecting less clinically significant results or due to a higher index of suspicion in paediatric providers[14]. The incidence of PE in children with MPP who underwent CTPA was reported to be 30.1 %[15], which is slightly higher than the 24.5 % in our study. The reason may be related to more physicians paying attention to the complications of MPP, more prompt diagnosis and treatment, or improved supportive care.

There are many risk prediction models for adults with PE[16]: the original Wells, modified Wells, simplified Wells, revised Geneva, and simplified revised Geneva models. However, when these models have been applied to children, they do not perform as well. For instance, the Wells and modified Wells scoring system is based on case history

information: previous deep-vein thrombosis or previous PE (+1.5 point), recent surgery or immobilization, malignancy (+1.0 point), haemoptysis (+1.0 point), tachycardia (≥100 bpm) (+1.5 point), clinical signs of deep vein thrombosis (+3.0 point), high clinical probability (>6 point), etc. Based on the history of deep-vein thrombosis or previous PE, deep vein thrombosis recent surgery or immobilization, and malignancy are slightly more common in children. In addition, tachycardia is probably not a good predictor in children, as heart frequencies are physiologically higher in children than in adults (with a strong age dependence). D-dimer levels were also measured in children in our clinical work.

Our study demonstrated that older children were more likely to have PE (8.1 ± 2.9 vs. 5.6 ± 3.1), and the highest frequency of PE (9/19) was actually in the 10- to 13-year-old age group. However, sex was nonsignificant according to the multivariate Cox hazard regression analyses. Barrera[17] demonstrated that the number of PEs measured was similar between boys and girls. Our result is similar to that of previous studies. The older children were more easily complicated with PE, possibly due to the greater amount of hormone use during MPP treatment. Despite improvements in spatial CT resolution, especially subsegmental PE might be detected more easily in older children (with larger vessel diameters), which may contribute to the higher frequency of PE detection in the older age group. Paparoupa[18] reported that D-dimer performs moderately but significantly better than CRP and leucocyte count for predicting underlying PE in children with pneumonia. Similar to a previous study, D-dimer level had an AUC of 0.716 for predicting PE.

Among participants with suspected pulmonary embolism, a higher D-dimer level was associated with a modest increase in CT angiography yield. In our study, we found that, except for age and D-dimer level, bilateral lung consolidation determined via CTPA was an independent predictor of PE. Despite recent advances in radiological imaging, PE is still a diagnostic challenge for patients, particularly for children[19]. Pneumonia and consolidation are the reasons why PE is most often omitted. Moreover, the concomitant occurrence of pneumonia, consolidation, and PE poses a diagnostic dilemma because pneumonia may occasionally mask PE. The pneumonia patients had higher levels of inflammatory markers, such as C-reactive protein which disappeared after anti-inflammatory treatment. Patients in the PE group had higher D-dimer levels and more chest pain, haemoptysis, and dyspnoea. However, the symptoms of PE were not significant according to our findings, which may be due to the higher level of tolerance and presentation of this disease in children. There are potential pathophysiologic factors between PE and pneumonia and consolidation. This may be because infection can activate the coagulation system, which explains the increased risk for PE in the presence of consolidation of MPP[20]. In addition, inflammation activates the tissue factor pathway in the coagulation cascade by inducing tissue factor production through complement activation, endotoxin production, CRP production and/or inflammatory cytokine production associated with thrombosis[21,22].

This study aimed to stratify patients according to risk prior to performing CTPA. The presence of consolidation is determined when CT has already been performed. For considerable large-area consolidation, conventional X-rays may be used to determine whether CT is necessary based on the consolidation patterns. Thus, further research is needed to assess if X-rays can contribute to risk stratification prior to dose-intensive CT examinations. In this study, we demonstrated that clinical and CT radiological predictors could be used to predict PE in children with MPP and demonstrated that these risk factors in children are important for determining the risk of developing MPP. It is possible that the development of a more accurate prediction tool for children could decrease the likelihood of PE being underdiagnosed.

This study has several limitations. First, the sample from our retrospective study was relatively small because PE is a less common complication than MPP, which is relatively common during the winter season. However, refractory paediatric MPP has often been reported in Eastern Asia in the last 10 years[20–22]. Second, our study was unable to assess long-term outcomes due to the short duration of clinical treatment. However, further follow-up is needed in the future.

5. Conclusion

In our study, we found that age, D-dimer level and bilateral lung consolidation detected by CT were strong predictors of PE and could possibly be used to stratify children prior to performing CTPA. We may be able to reduce unnecessary CTPA by using this stratification of clinical parameters to guide management. However, further research is warranted.

CRediT authorship contribution statement

Hui Gu: Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Bowen Li:** Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Writing – original draft. **Yicheng Han:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Shifeng Yang:** Conceptualization, Data curation, Formal analysis, Investigation, Validation. **Ximing Wang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization, Project administration, Resources, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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