Pulmonary Embolism in Childhood: A Multicenter Experience from Turkey

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Background: Pulmonary embolism is a clinical condition caused by the obstruction of the pulmonary artery and its branches with endogenous, exogenous embolism, or local thrombus formation. It is a rare but potentially life-threatening event in the pediatric population. Pediatric pulmonary embolism has many unknown characteristics.

Aims: To evaluate clinical features, genetic and acquired risk factors, diagnostic imaging, and treatment strategies with long-term results in children with pulmonary embolism.

Study Design: A retrospective multicenter clinical trial

Methods: Patients aged 0-18 years who were diagnosed with pulmonary embolism with computed tomography pulmonary angiography (CTPA) findings (intraluminal filling defect in the lobar or main pulmonary artery) in 3 university hospitals between 2006 and 2021 were included in the study. A form was created for data standardization, and variables were collected retrospectively through medical record review. In addition to the features given above, we also evaluated in situ pulmonary artery thrombosis (ISPAT) and patients’ Wells scores. Follow-up CTPA results were evaluated for patient response to treatment. Complete recovery means that there were no lesions, incomplete recovery if there was still embolism, and no response if there was no change.

Results: Twenty-four patients (female:13, male:11) were included in the study. The mean age was 13.5 years. All patients but one had at least one or more genetic or acquired risk factors. Factor V Leiden mutation (16.6%) was the most common genetic risk factor. Six of 16 patients with Doppler ultrasonography were diagnosed with ISPAT because there was no sign of thromboembolic thrombosis. Nine (41.6%) patients had a Wells score of >4 (pulmonary embolism clinically strong), and 15 (58.4%) patients scored <4 (pulmonary embolism clinically likely weak), indicating that an alternative diagnosis was more likely than pulmonary embolism (sensitivity 37.5%). The mean follow-up period was 23 (±17) months. Complete and incomplete recovery was observed in 15 (62.5%) and 7 (29.1%) patients, respectively, among the patients who underwent follow-up evaluation. No response was obtained in 2 patients (8.3%) who died.

Conclusion: The Wells scoring system seems insufficient to diagnose pulmonary embolism in children and should be improved by adding new parameters. ISPAT may be more common in children with congenital heart disease and systemic disease.
INTRODUCTION

Pulmonary embolism (PE) is a clinical condition caused by the obstruction of the pulmonary artery and its branches with endogenous, exogenous embolism, or local thrombus formation. PE is a rare but potentially life-threatening event in the pediatric population. The accurate diagnosis of PE in children is often difficult because clinical findings are nonspecific, and the clinical presentation can be confused with diseases such as pneumonia and asthma. Suspicion requires early and accurate diagnosis in the pediatric population. Pediatric PE is very rare. Therefore, the risks associated with pediatric PE, diagnostic imaging, PE risk score, duration of anticoagulant therapy, role of thrombolytics, and many other critical factors are not well defined.

This retrospective study aimed to evaluate the clinical features, acquired and congenital risk factors, diagnostic imaging, treatment strategies, and long-term outcomes of PE. There are only a limited number of studies on in situ pulmonary artery thrombosis (ISPAT) or PE scoring in children. Unlike other studies, we assessed them from this perspective in our study.

MATERIALS AND METHODS

In this retrospective multicenter study, we evaluated 24 patients aged 0-18 years with PE who were diagnosed between January 2006 and December 2021 based on computed tomography pulmonary angiography (CTPA) findings (intraluminal filling defect in the lobar or main pulmonary artery) at Erciyes University, School of Medicine, Meram University, School of Medicine, and Gazi University, School of Medicine. A form was created for data standardization, and variables were collected retrospectively through medical record review.

The study was conducted according to the ethical norms and standards of the Declaration of Helsinki, and ethical approval was obtained from the local ethics committee.

Demographic data, symptoms at diagnosis, and physical examination findings were evaluated. D-dimer levels (average values, 0-550 µg/l) and genetic and acquired risk factors were evaluated at the time of diagnosis. Chest X-ray, Doppler ultrasonography, echocardiography, and CTPA were evaluated. Follow-up CTPA results were evaluated for patient response to treatment. Complete recovery means that there were no lesions, incomplete recovery if there was still embolism, and no response if there was no change. Patients were classified as having thromboembolic PE and ISPAT, which is thrombosis of the pulmonary artery due to local causes. When assessing patients with ISPAT, patients with no thrombosis in the Doppler ultrasonography were included. Patients without detailed imaging were not included in this group.

The Wells scores of the patients were evaluated retrospectively. The Wells criteria were as follows: [1] clinical signs or symptoms of DVT, [2] heart rate (HR) of >100 beats per minute (children were evaluated for tachycardia according to the HR appropriate for their age range), [3] immobilization or surgery in the past 4 weeks, [4] previous DVT or PE, [5] hemoptysis, [6] malignancy, and [7] alternative diagnosis is less likely than PE. As this study was retrospective, it was difficult to tell from the medical records whether an alternative diagnosis was less likely than PE. Therefore, we assessed the Wells criteria by assigning three points to all patients separately (meaning that an alternative diagnosis was less likely than PE).

RESULTS

Demographic Data

Within the 12-year period, we registered 24 patients, averaging two pulmonary emboli cases annually. The mean age of the patients was 11.58 (± 5.23). PE was most frequently observed in adolescence. Seventeen patients (70%) were adolescents, and 11 (45.9%) patients were male (Table 1).

Clinical Characteristics

All patients had respiratory symptoms at the time of diagnosis. The most common symptom was dyspnea (75%) or chest pain (58.3%), palpitations (37.5%), cough (37.5%), lower extremity pain, and swelling (33.3%), and hemoptysis (4.5%). The most common finding on physical examination was tachypnea (79.1%), followed by tachycardia (54.1%), decrease in breath sounds (39.1%), redness and swelling of the extremities (33.3%), and cyanosis (17.4%). All clinical and laboratory data of patients with PE are listed in Table 1.

Genetic and Acquired Risk Factors

Except for one patient, all other patients had at least one or more genetic or acquired risk factors (mean, 2.2). The 18 patients were screened for genetic risk factors. The most common genetic risk factors for PE were factor V Leiden mutation (16.6%), antithrombin deficiency III (5.5%), PAI-1 mutation (5.5%), and elevated factor (VIII) (Table 2).

The most common acquired risk factors were previous deep vein thrombosis (DVT) 37.4%, central venous line (CVL; 25%), immobility (25%), major surgery (20.8%), trauma (20.8%), malignancy (16.6%), and obesity (body mass index >30) (8.3%), chemotherapy (8.3%), congestive heart failure (8.3%), congenital heart disease (8.3%), and nephrotic syndrome (4.1%) (Table 2).

Diagnostic Examinations

Computed tomography and pulmonary angiography were performed to diagnose all patients. On thoracic tomography, the thrombi were located on the right side in 13 patients, on the left side in 4 patients, and bilaterally in 6 patients. One patient had a thrombus on the right side because of a foreign body (Table 3).

All patients underwent chest X-ray imaging because of respiratory distress at the time of initial application. Seventeen patients had chest X-ray findings of infiltration (66.6%), pleural effusion (37.5%), pulmonary artery dilation (29.1%), and atelectasis (12.5%), whereas 29.2% of the patients had normal X-ray results (Table 1). Sixteen patients were evaluated with Doppler ultrasonography: 56.3% of
the patients had DVT; 25% had thrombus in the popliteal vein, 25% had thrombus in the femoral vein, and 6.25% had it in the iliac vein. Moreover, 43.7% of the patients did not have DVT. Three patients with DVT were asymptomatic. One patient had a cardiac thrombus. One patient had a thrombus due to a foreign body (devices used to close ventricular septal defects). Eight patients had no Doppler ultrasonography information available, so no definite information about ISPAT or thromboembolic embolism could be obtained. Six patients were found to have ISPAT, since there was no evidence of thromboembolic thrombosis. Patients with ISPAT had Behcet’s disease, congenital heart disease, lupus anticoagulant, complicated pneumonia, family history, and genetic risk factors (factor V Leiden and factor VIII elevation) (Table 3).

Echocardiography was performed on 19 patients. Echocardiographic results of 57.8% of the patients were normal, and no signs of thrombosis were found. The other 42.2% of the patients had echocardiography findings, namely, tricuspid failure, pulmonary hypertension, congenital heart disease, congestive heart failure, and cardiac thrombus (Table 1). D-dimer levels at the time of diagnosis with PE were available for 21 children, whereas those of three patients were not available. The D-dimer values of the children were high at the time of diagnosis. The median value was 2,503 (minimum, 822; maximum, 10,000) µg/l (Table 1).

Wells scoring was performed. As this was a retrospective study, it is difficult to determine if an alternative diagnosis is less likely than PE from medical records. Therefore, we scored the Wells criteria individually twice; a score of 3 points indicated that an alternative diagnosis was less likely than PE and a score of 0 indicated that an alternative diagnosis was more likely than PE. Firstly, patients were given a score of 0
TABLE 2. Genetic Risk Factors and Acquired Risk Factors of the Patients

| Genetic risk factors | Acquired risk factors | Observed/examined | Observed/examined |
|----------------------|-----------------------|-------------------|-------------------|
| Factor V Leiden mutation | Het: 1/12, homo: 2/12 (16.6%) | Previous DVT | 9/24 (37.4%) |
| Protein C deficiency | 0/18 (0.0%) | Central venous line | 6/24 (25%) |
| Protein S deficiency | 1/18 (5.5%) | Immobility | 6/24 (25%) |
| Prothrombin G20210A | 0/12 (0.0%) | Major surgery | 5/24 (20.8%) |
| Antithrombin III deficiency | 1/18 (5.5%) | Trauma | 5/24 (20.8%) |
| Elevated factor VIII | 2/18 (11%) | Malignancy | 4/24 (16.6%) |
| Elevated factor IX | 0/18 (0.0%) | None | 3/24 (12.5%) |
| Anticardiolipin | 2/18 (11%) | Obesity | 2/24 (8.3%) |
| Hyperhomocysteinemia | 2/18 (11%) | Chemotherapy | 2/24 (8.3%) |
| PAI-1 polymorphism | Het: 1/8 (5.5%) | Congestive heart failure | 2/24 (8.3%) |
|                      |                       | Congenital heart disease | 2/24 (8.3%) |
|                      |                       | Nephrotic syndrome | 1/24 (4.1%) |
|                      |                       | Polistemi vera | 0/24 (0.0%) |
|                      |                       | Oral contraceptive | 0/24 (0.0%) |

if the probability of an alternative diagnosis was higher than PE. According to this result, nine (41.6%) patients had a Wells score of >4 (PE clinically strong), and 15 (58.4%) patients scored <4 (PE clinically weak). The sensitivity of Wells scoring for PE was 37.5%. Secondly, patients were given a score of 3 if the probability of an alternative diagnosis was lower than that of PE. According to this result, in 17 (70.8%) patients, the Wells score was >4 (PE clinically strong), and in 7 (29.1%) patients, it was <4 (PE clinically likely weak). The sensitivity of Wells scoring for PE was 70%. None (0.0%) patients had a Wells score of >4 (PE clinically strong), and 9 (37.5%) patients scored <4 (PE clinically likely weak), which means that an alternative diagnosis was less likely than PE. The sensitivity of Wells scoring for PE was 70%.

Treatment and Outcome

All children received anticoagulant therapy (low-molecular-weight heparin [LMWH], warfarin, heparin, and thrombolytic therapy [tissue plasminogen activator]. However, there was no standardized treatment regimen among the three centers (Table 3). The foreign body that caused the embolism was surgically removed in one patient. The mean follow-up time of the patients was 23 (±17) months. Two patients died. No adverse event was observed during anticoagulant therapy. Control CTPA performed during patient follow-up resulted in complete recovery in 15 patients but incomplete recovery in 7 patients (Table 3).

DISCUSSION

To our knowledge, this is one of the Turkish studies with the highest number of children with PE, one of the few European studies of pediatric PE, and one of the largest in terms of the number of patients, time period, and data analyzed. In contrast to previous studies,4 we found that women were 1.18 times more likely than men to develop an embolism. This could be because the patients in this study were mostly adolescents. Carpenter et al.5 found that PE was more common in adolescent girls, similar to our study patients. In the study by Carpenter et al.5 and some studies,6,7 PE predominantly occur in female patients who used oral contraceptives. In a previous study, women were found to have a higher risk for PE because of oral contraceptives. Despite no oral contraceptive usage in our study, oral contraceptives should be considered for adolescent girls with PE.

Childhood PE has been reported to have two distinct peaks in adolescence and infancy.3 In this study, PE peaked in adolescent patients, but not in infants. PE is likely underdiagnosed in early childhood because of its nonspecific clinical presentation. The mean age of our patients was 13.5 years, which is roughly in line with the literature.5,8 Studies examining the incidence of PE in children report an incidence of 8.6-57 per 100,000 hospitalized children and 0.14-0.9 per 100,000 in non-hospitalized children.3-7,10 We did not report the incidence of PE in our study because we lacked reliable data on hospital admissions. However, on average, two patients per year were diagnosed with PE in our centers. Given that these are the three most important centers in Turkey, we assume that the number of diagnoses is insufficient. This might be because PE is frequently clinically silent or misdiagnosed. The nonspecific and quiet symptoms of PE can be confused with other respiratory diseases. In our clinical series, dyspnea, chest pain, palpitations, cough, redness, swelling of the extremities, and hemoptysis were common. These findings are consistent with the literature.3 With these symptoms, DVT in patients with respiratory symptoms should alert us to PE. In the literature, most PE cases have been associated with DVT. This rate varies in different studies; DVT and PE occur simultaneously in 54%-72% of patients.3,9,10
| Age/sex | Acquired risk factors | Genetic risk factors | Wells score | Elevated D-dimer | Imaging | D-USG | PTE | DVT | Treatment | Radiological resolution |
|---------|-----------------------|----------------------|------------|------------------|--------|------|-----|-----|-----------|------------------------|
| 4/F     | Trauma family history | Antithrombin III deficiency, Protein S deficiency | 6 | Yes | CTPA | Yes | Bilateral | Yes | UH + LMWH coumadin | Complete recovery |
| 16/M    | Trauma                | No                   | 7.5        | Yes | CTPA | Yes | Bilateral (saddle) | Yes | TPA + UH + LMWH | Complete recovery |
| 18/M    | Trauma (fracture on the right leg) | Anticardiolipin antibodies | 7.5        | Yes | CTPA | Yes | Bilateral | Yes | UH + LMWH | Complete recovery |
| 5/F     | Congenital heart disease | No                   | 6 | YES | CTPA | Yes | Right | Yes | LMWH | Complete recovery |
| 14/M*   | Behcet diseases Steroid treatment | No                   | 2 | Yes | CTPA | Yes | Right | No | TPA + UH + LMWH + coumadin | Incomplete recovery |
| 11/F    | Obesity congestive heart failure | Not examined | 1 | N/A | CTPA | No | Left | N/A | LMWH + coumadin | Complete recovery |
| 17/M    | Nephrotic syndrome | Not examined | 1 | N/A | CTPA | No | Right | N/A | LMWH + coumadin | Complete recovery |
| 15/M    | -                     | Not examined | 1 | N/A | CTPA | No | Left | N/A | LMWH | Complete recovery |
| 1/M     | Cancer (neuroblastoma) Central venous line | Elevated level of homocysteine, PAI mutation | 2.5        | Yes | CTPA | Yes | Right | No | LMWH | Complete recovery |
| 16/F*   | Family history | LA                   | 1 | Yes | CTPA | Yes | Right | No | UH + coumadin | Complete recovery |
| 12/F*   | Congenital heart disease (VSD) | Not examined | 1 | Yes | CTPA | Yes | Right | N/A | LMWH | Complete recovery |
| 15/M    | Trauma (fracture on the right leg) Obesity | Elevated levels of F8 | 9 | Yes | CTPA | Yes | Right | Yes | TPA + UH + LMWH + coumadin | Incomplete recovery |
| 11/F    | Congestive heart failure Central venous line | No                   | 1 | Yes | CTPA | Yes | Right | No | LMWH + coumadin | EX |
| 8/M     | Central venous line Family history | No                   | 1 | Yes | CTPA | No | Bilateral | N/A | UH + coumadin | Complete recovery |
| 15/M    | Trauma Immobilization Major surgery | Elevated level of homocysteine | 3 | Yes | CTPA | No | Left | N/A | LMWH + coumadin | Complete recovery |
| 3/F     | Major surgery, Wilms Tm Central venous line | Factor V Leiden mutation | 4 | Yes | CTPA | No | Right | N/A | LMWH + coumadin | Incomplete recovery |
| 17/M*   | Appendectomy Immobilization | Factor V Leiden mutation Elevated levels of F8 | 3 | Yes | CTPA | Yes | Right | No | LMWH + coumadin | Incomplete recovery |
| 14/F*   | Immobilization Complicated pneumonia | No                   | 2.5        | Yes | CTPA | Yes | Bilateral | No | LMWH + coumadin | Incomplete recovery |
| 3/M     | Cancer (ALL) Central venous line Family history | Not examined | 2.5        | Yes | CTPA | No | Right | N/A | LMWH | Complete recovery |
In this study, 54.2% of the patients with PE had DVT. One patient had a cardiac thrombus. Eight patients did not have Doppler ultrasonography data. These patients had no symptoms or signs of DVT, so Doppler ultrasonography may not have been performed. If these patients had been included, the DVT rate might have been higher. Three patients were asymptomatic or had no signs of DVT, but Doppler ultrasonography findings were positive. Children with PE should be screened with Doppler ultrasonography to determine the focus of the embolism. In a report from the Canadian Pediatric Thrombophilia Registry, emboli were more common in the upper venous system. However, in this study, emboli were more likely to be associated with lower limb thrombosis, as in the study by Rajpurkar et al.11

It seems difficult to diagnose PE in children with these signs and symptoms. Despite improved scores (Well's and Perc, etc.) in adult patients that aid in diagnosis, no such system exists for children. Hennelly et al.12 found that the Wells criteria have a sensitivity of 86% (an alternative diagnosis is less likely PE) and specificity of 16.7% (an alternative diagnosis is more likely PE). In our study, the sensitivity of Wells scoring for PE was 70% (an alternative diagnosis is less likely PE) and the sensitivity for PE is 37.5% (an alternative diagnosis is more likely PE). In this study, the sensitivity of the Wells score was approximately similar to other studies.12,13 Patients with DVT symptoms have a high risk score. In patients without DVT, the sensitivity of the scoring system is much lower. Most patients in our study had no DVT signs. Generally, clinicians have low suspicion of PE in children, and if the patient does not have DVT, Wells scoring is inadequate in the absence of clinical suspicion.13 Therefore, risk factors for PE in children should be identified, and new scoring systems for PE should be introduced. According to our study, the inclusion of tachypnea, the most common finding in children and CVL as an acquired risk factor, in the scoring system may increase diagnostic sensitivity.

This study found high D-dimer levels in patients with PE. However, these levels alone were not conclusive for diagnosing PE, as D-dimer levels can be elevated in pneumonia, sepsis, malignancies, and inflammatory processes. Patients should be examined with accompanying clinical findings. High D-dimer levels and pulmonary symptoms, which are positive in adults, indicate that the patient may have PE.14 However, this situation is not observed in children. In contrast to this study, not all patients with PE may have high D-dimer levels. PE has been found even in children with normal D-dimer levels.15,16,17 Negative D-dimer levels can be used to exclude PE in adults, but this is non-discriminatory for diagnosing PE in children. Late diagnosis of PE in children may result from having normal D-dimer levels in these children.18,19

On chest X-ray imaging, some patients had findings of atelectasis, pleural effusion, pulmonary infiltration, etc. However, these findings are not specific to PE. Some patients with PE also had normal chest X-ray findings. It can help rule out other conditions such as pneumonia or pneumothorax. However, a chest X-ray cannot reliably confirm or rule out the diagnosis of PE.1 The diagnosis of PE should be made with CTPA, which is the gold standard.

Echocardiography can show whether a thrombus originates in the heart and pulmonary artery or support the diagnosis with indirect findings, such as right ventricular dysfunction or dilatation, tricuspid regurgitation, and PHT.2 In addition, echocardiography can help hemodynamically unstable patients when CTPA cannot be performed to differentiate between PE and cardiac pathology in the emergency department.10 In this study, 11 patients had normal echocardiography, and eight had pathological findings. Normal echocardiography does not rule out disease; while its effectiveness in distal embolism is low, it may be of greater use in central embolism.1 It can also be used to determine prognosis in adult patients. However, its usefulness in children is unknown. Echocardiography, a non-invasive method, may be evaluated in future studies.

Childhood thrombosis is very rare in children without triggering factors. The pathogenesis of PE in children has several risk factors.
Acquired risk factors are an important risk factor predisposing to venous thromboembolic events in childhood. In this study, acquired risk factors were more common than inherited risk factors as in other studies.\textsuperscript{7,11} In this study, DVT was the most common risk factor for PE. In addition, CVL was the next most common concomitant acquired factor. In the most recent systematic review, CVL was the most common factor.\textsuperscript{4} In addition, immobilization, major surgery, trauma, cancer, obesity, congenital heart disease, nephrotic syndrome, and sepsis increase the risk of PE. In any child with thrombosis, the possible triggering acquired factors should be carefully investigated before hereditary factors are considered. In the absence of precipitating factors or others with thrombosis in the family, these children should be screened for hereditary thrombophilia. Children with risk factors are at high risk of embolism and should be monitored more closely.\textsuperscript{2,6,18} In this study, one or more risk factors were found in 66% of the patients, and 24% had no risk factors. The most common genetic risk factors for PE were factor V Leiden mutation.

Two types of emboli have been described in children, i.e., classic thromboembolism PE and ISPAT.\textsuperscript{9} In this study, six patients with isolated pulmonary artery embolism were examined, and in one of them, the embolism was caused by a foreign body. There are insufficient studies in the literature on this topic. In this study, these patients had risk factors such as Behcet’s disease, cancer, congenital heart disease, and complicated pneumonia. In a study conducted on adults, patients with ISPAT had underlying conditions such as congenital heart disease, sickle cell anemia, and a destroyed lung (destruction of a large portion of a lung induced by chronic or recurrent lung infections).\textsuperscript{19} These risk factors were comparable with those in our study. ISPAT should also be considered in unexplained tachypnea and hypoxemia, especially in children with congenital heart disease or additional disease. However, the literature does not include sufficient information regarding ISPAT. To distinguish patients with ISPAT from other patients, more clinical research is necessary.

Antithrombotic therapy in pediatric patients is challenging because of the rapidly developing hemostatic system of children and the age-related variation in the pharmacokinetics of antithrombotic drugs, including distribution, binding, and clearance.\textsuperscript{13,20,21} In our study, no standard treatment approach was presented. In this multicenter study, each center had different treatment approaches depending on the age, clinical condition, and treatment adherence of the patient. There is no consensus on treatment in the literature for children.

In conclusion, given the rarity of PE, this study has one of the highest numbers of children with PE in the literature. If PE is not considered in the differential diagnosis, its diagnosis is challenging. PE should be considered in the differential diagnosis if there is a risk factor for PE in children with unexplained respiratory symptoms. The pulmonary emboli scoring system is still insufficient for children. Unexplained tachypnea and CVL could be added to the pulmonary emboli scoring systems as risk factors for children. Moreover, ISPAT may be present in children with congenital heart disease and systemic disease. Childhood PE is still an area with many controversial issues. Multicenter studies is children are needed to evaluate clinical characteristics, acquired risk factors, prothrombotic risk factors, diagnostic tests (D-dimer), scoring systems, optimal duration of anticoagulant therapy, and role of thrombolysis, long-term outcomes, and effects of PE.

**Ethics Committee Approval:** Ethics committee approval was obtained from Gaziantep University (no: 2021/223 date: 01/03/2022).

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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