Pulmonary embolism in pediatric age: a retrospective study from a tertiary Centre

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Abstract

Introduction: Pediatric pulmonary embolism (PE) is rare but associated with adverse outcomes. We aimed to characterize PE cases admitted in a tertiary hospital and to evaluate sensitivity of PE diagnostic prediction tools. Methods: Retrospective, descriptive study of PE cases admitted from 2008 to 2020. Data was collected from hospital records. Patients were grouped according to PE severity and setting (outpatients, inpatients). Associations with demographic characteristics, risk factors, clinical presentation, management and outcomes were analyzed. PE diagnostic prediction tools were applied. Results: 29 PE episodes occurred in 27 patients, 62.9% female, mean age 14.1 years. Most PE were central and massive or submassive. One was diagnosed in autopsy. Outpatients (n=20), admitted for classic PE symptoms, were adolescents; in half the diagnosis had been missed previously. Risk factors included contraceptives (65%), thrombophilia (35%), obesity (20%) and auto-immunity (20%). Inpatients´ PE (n=8), diagnosed during cardiorespiratory deterioration (n=5) or through incidental radiological findings (n=3), were younger and had immobilization (87.5%), complex chronic diseases (75%), infections (75%) and central venous catheter (62.5%) as risk factors. Retrospectively, D-dimer testing and adults' scores performed better than pediatrics' scores (sensitivity 92.9-96% vs 85.7- 92.9%). Both pediatrics' scores missed a case with a positive family history. Discussion: Pediatric PE diagnosis is often delayed or missed. To improve it, the development of pediatric prediction tools as from validated adult scores merits to be explored. We propose that clinical presentation and risk factors may be different in inpatients and outpatients. Family history should be included.

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INTRODUCTION

Pulmonary embolism (PE) is rare in pediatric age, with an estimated incidence inferior to 1:100.000 in general pediatric population[1,2]. In the last decade, incidence increased in both community and hospitalized children[3,5-7], although it is underdiagnosed, as evidenced by autopsy-based studies[3,4]. PE is associated with a high rate of adverse outcomes, with mortality up to 26%[3,6,8]. In pediatric age, almost all the events are associated with at least one risk factor or underlying disorder[9]. Pediatric PE occurs mostly in infants and teenagers[1,2] and in this last group occurs twice as much in females, due to estrogen related risk factors such as pregnancy or combined hormonal contraceptives (CHC)[2].

There is a paucity of data on pediatric PE. Given its rarity, most pediatric studies include venous thrombosis and thromboembolism (VTE), whereas PE only accounts for approximately 15% of VTE episodes[7]. The lack of well-performing pediatric probability models to assist in PE diagnosis is concerning[8,10]. Adult validated diagnostic prediction tools, such as the Wells criteria[11] and the Pulmonary Embolism Rule-out Criteria (PERC) tool[12], are often used[13]. However, they seem to lack sensitivity and specificity in the pediatric population[14,15]. Pediatric models have been proposed[15,16] but were based in a small number of PE patients from single centers. PE management in children and adolescents are also often extrapolated from adult studies[9], a population with different pathophysiology, morbidity and mortality. Thus, pediatric studies are needed to improve diagnostic tools, risk stratification and treatment options.

We intended to characterize patients with PE admitted in a tertiary hospital regarding their clinical presentation, risk factors, severity classification, treatment and outcomes. Secondarily, we intent to investigate the sensitivity of PE diagnostic prediction tools in this population.

METHODS

Population and Setting

We conducted a thirteen-years (January 2008 to December 2020) retrospective study of PE cases admitted in the Pediatric Department or Intensive Care Unit of a tertiary care hospital, in patients up to 18 years old. This is a metropolitan, university-affiliated hospital with a catchment area of approximately 137.000 pediatric patients.

Cases were identified through discharge diagnostic codification, using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), including 415.1 (Pulmonary embolism and infarction) and subsequent codes. Data was extracted from an administrative database, which includes all cases with a length of stay superior to 24 hours. Additionally, an autopsy-diagnosed case that presented as a cardiac arrest was included for outcomes purposes, but no further data was possible to obtain. In the remaining cases, PE diagnosis was confirmed by imagological criteria.

All available electronic medical records were thoroughly reviewed. Follow up was maintained during a variable period from patient to patient. The study was conducted following ethical norms and standards according to Declaration of Helsinki, including Research Ethics Board of the Hospital approval.

Studied variables

We documented temporal data, demographic characteristics (sex, age, race), clinical presentation (signs and symptoms), setting (Emergency Department (ED), outpatient clinic, inpatients) and, when available in electronic medical records, lag time from clinical onset to diagnosis, previous medical observations and complementary investigation. Patients admitted with PE symptoms were classified as outpatients, as opposed to patients who were primarily hospitalized for other reasons, referred to as inpatients. Imagological exams, including Computed Tomography with Pulmonary Angiography (CTPA), ventilation-perfusion (VQ) scan, chest X-ray (CXR), echocardiogram (ECHO), electrocardiogram (ECG)), venous compressive ultrasound (CUS) with Doppler, and laboratory tests (D-dimer, troponin I or B-type natriuretic peptide levels) at diagnosis were registered. Anatomic distribution of the thrombus was classified as central, lobar, segmental or sub-segmental, according to the most central segment of the pulmonary arterial tree affected.

Risk stratification followed the American Heart Association's Scientific Statement, (17) using age-appropriate reference values for heart rate and blood pressure. (18) Massive (high risk) PE was defined by the presence of hypotension, bradycardia or poor peripheral perfusion, whereas sub-massive (intermediate risk) PE was defined by right ventricular strain/injury and/or elevated cardiac biomarkers (troponin I or B-type natriuretic peptide) in non-hypotensive patients. Right ventricular strain/injury was defined by dilation and/or systolic dysfunction on ECHO or CTPA or by ECG changes: new complete or incomplete right bundle – branch block, anteroseptal ST alterations or T wave inversion. The remaining cases were considered non-massive PE (low risk).

Associated deep venous thrombosis (DVT), data on thrombophilia testing and the presence of other underlying risk factors were noted. Obesity was considered when the body mass index was above the 95th percentile for age and sex. Therapeutic and support interventions and secondary prophylaxis were investigated. Outcomes included: PE-related mortality and all-causes mortality during hospitalization and follow up, recurrent VTE, chronic PE (persistence of thrombus in the same territory), chronic thromboembolic pulmonary hypertension (CTPH) and post-thrombotic syndrome (PST).

Finally, we applied PE risk stratification clinical scores, including the Wells criteria, the PERC tool and two pediatric criteria[15,16], to our population and evaluated their sensitivity.

Statistical Analysis

Standard statistical analysis was performed using IBM SPSS(r) Statistics for Windows. Descriptive statistics were used to characterize the sample. We tested the possible associated differences between inpatients/outpatients and demographic characteristics, risk factors, severity and outcomes. Furthermore, we also tested possible associations between PE severity classification and demographic variables, clinical presentation (with or without syncope, tachycardia, hypoxemia), d-dimers levels, management (anticoagulation vs need for thrombectomy, thrombolysis or hemodynamic support), and outcomes, as described. $\chi 2$ -square test was used to assess these associations, considering significance for p-value <0.05.

RESULTS

During the 13-years period, we registered 29 episodes of PE in 27 patients, with an average of 2.2 episodes per year, corresponding to 9.52 per 10.000 admissions. All the patients were Caucasian, with a mean age of 14.1 ± 4.3 years and 17 (62.9%) were female (Table 1). Twenty-four patients (88.9%) were adolescents.

One patient presented as a sudden death and autopsy revealed PE, but no further data was possible to obtain. Twenty episodes occurred in patients admitted for PE symptoms (outpatients), 18 from the ED and two from the outpatient clinic. Thirteen (65%) were female and all were teenagers (mean age 16.0 ± 0,86 years). In this group, the most frequent presentations were thoracalgia (15/20, 75%), dyspnea (14/20, 70%), DVT (8/20, 40%) and syncope (6/20, 30%). Other symptoms included fever (4/20, 20%), anxiety (2/20, 10%), palpitations (1/20, 5%) and hemoptysis (1/20, 5%). Thirteen patients were tachycardic (13/20, 65%) and eight hypoxemic (8/20, 40%). In 10 of these patients, the diagnosis was not established during previous medical examinations that had taken place before admission, and five had been submitted to complementary exams, including CXR, blood analysis and ECG, described as normal. Respiratory infections (2/10, 20%), asthma flare (1/10, (10%)) and anxiety (2/10, 20%) had been the main alternative diagnosis assumed. Mean time lag from presentation to diagnosis was 4.8 days (range 0-42 days). All patients had at least one risk factor (average 1.55) identifiable in clinical history, including oral contraception (13/20, 65%), positive family history (4/20, 20%), obesity (4/20, 20%), immunomediated disorders (4/20, 20%). and thrombophilia history (protein S deficiency) (1/20, 5%). Further investigation revealed seven inherited thrombophilia (7/20, 35%) and two vascular anomalies (May-Turner Syndrome) (2/20, 10%).

In the inpatient group (n=8), mean age was 9.49 ± 6.14 years, and 63% (5/8) were male. Clinical presentation included respiratory failure (4/8, 50%), hemodynamic compromise (2/8, 25%) and hemoptysis (1/8, 12.5%). Three PE (10.7%) were asymptomatic, corresponding to imagological findings discovered during the investigation of underlying pathologies (Table 2). Infections (6/8, 75%), reduced mobility (6/8, 75%), the presence of a central venous catheter (CVC) (5/8, 62.5%) and complex chronic conditions (5/8, 62.5%), such as congenital heart disease, oncologic or neurologic conditions, were the main risk factors for PE in the inpatient group.

Details in complementary exams are displayed in Table 3. The diagnosis was confirmed by CTPA in 82.1% PE (23/28). Nineteen emboli (67.9%) had a central location. D-dimer assays were positive in all acute PE, not being performed in three cases: two asymptomatic PE and in a severely ill patient, in whom CTPA was directly performed. Most PE were non-massive (46.4%, 13/28), 39.3% (11/28) were submassive and 14.3% (4/28) were massive (Table 4). Tachycardia was more prevalent in submassive and massive groups ($p = 0.06$) and didn´t correlate with PE-mortality (p=0.519). There were two intra-cardiac thrombi, in children with complex congenital cardiopathy. Twelve CXR were performed and were normal in 83.3% of the cases (10/12). Pneumomediastinum (n=1) and pleural effusions (n=2) were concomitantly described.

The application of the Wells criteria, assuming that an alternative diagnosis was less likely except in asymptomatic cases, classified 71.4% (20/28) of our PE patients as high risk. The further D-dimer testing recommended to the lower risk patients were positive, and thus, would recommend performing CTPA in all but one (asymptomatic) PE (sensitivity 96%). Application of the PERC criteria correctly classified 26 patients as PE, except two asymptomatic (sensitivity 92.9%). Hennelly's et al. pediatric PE model application misclassified four of our patients as non-risk (sensitivity 85.7%) (two asymptomatic), and Lee´s et al. model missed two PE, one asymptomatic (sensitivity 92.9%).

Two patients with intracardiac thrombi underwent surgical thrombectomy. Fibrinolysis with recombinant tissue plasminogen activator (alteplase) was performed due to significant right ventricular dysfunction in four patients, two with hemodynamic instability (massive PE). Anticoagulation therapy was initiated in all but one patient, due to major simultaneous hemorrhages. Unfractioned Heparin (UFH) (n=8), Low-molecular-weight Heparin (LMWH) (n=13) or both (n=6) were initially used, followed by warfarin. In addition, a patient received an argatroban perfusion due to heparin-induced thrombocytopenia. Support treatment included oxygenotherapy (n=12), aminergic support (n=3) and venoarterial extracorporeal membrane oxygenation (ECMO) in a patient with refractory hemodynamic instability and hypoxia.

During follow up, three patients started non–vitamin K antagonist oral anticoagulants (NOAC) (n=2 apixaban, n=1 rivaroxaban), after a variable period of warfarin. Eight patients were anticoagulated for a defined period (average nine months).

The average length of hospitalization was 22.5 days (range 2-75). Eight patients (8/28, 28.6%) were admitted in the PICU (average 12.1 days). PE-mortality rate was 6.9% (2/29). A further dead occurred during hospitalization in a patient with acute lymphocytic leukemia, due to multisystemic dysfunction with multiple infarcts. During follow up (1 month to 12 years), two patients died from unascertained cause, 3.5 and 6 years after PE event (all-cause mortality 5/29,17.2%). Eighteen patients (64.3%) were submitted to a control CTPA, in average 8.4 months after PE, one presenting a PE recurrence (new territory, symptomatic). There were five recurrences of thrombotic events including two PE recurrences and an ischemic cerebrovascular accident. Furthermore, two patients had PST associated to May-Thurner syndrome and were proposed for vascular surgery. No anticoagulation hemorrhagic complications were registered.

DISCUSSION

To our knowledge, this is the first Portuguese, and one of the few European studies on PE in children, and one of the largest series on number of patients, time period and data analyzed. Furthermore, we describe three incidentally detected PE, a subgroup of patients whose management is particularly unclear, and about whom diagnostic methods, treatment and outcomes details have not been previously reported[8]. We also found a higher sensitivity for diagnosis of PE applying adults' scores, compared to pediatric ones.

The number of PE admissions of 9.19/10.000 is similar to the one reported by Rajpurkar and colleagues (5.12-9.22/10.000 admissions). Although we didn´t observe an increase in the diagnosis rate along the 13 years studied, the incidence during 2020 was one of the highest. All four cases tested negative for SARS-COV-2 PCR at admission and none presented suggestive clinical symptoms, but serological tests were not performed.

We found an overall predominance of female patients, especially in the adolescent group, presumably due to the influence of CHC. The mean age at presentation was similar to that described in other reviews[8], however, as others[7,16], we didn´t find the classical bimodal age distribution described in pediatric PE[4,10]. PE is probably underdiagnosed, especially in infants, whose diagnosis is even more challenging due to the unspecific clinical presentation. The unexpected predominance of central emboli and massive or submassive PE further corroborates the underdiagnosis of less clinically obvious events, missing the opportunity to identify and treat patients with high thromboembolic risk.

The failure to consider PE as part of the differential diagnosis in pediatrics, even in the presence of typical complains, is a major concern[20]. An important clue is the presence of thromboembolic risk factors since it is unlikely for PE to occur in pediatric patients in their absence[16]. We found a higher prevalence of CHC utilization, immunomediated diseases and inherited thrombophilia in PE than previously reported[8]. Risk factors were different in outpatients versus inpatients. In outpatients PE occurred exclusively in adolescents, mainly female, and CHC intake, obesity, immunomediated diseases or a positive family history were the most important risk factors. Remarkably, all the female patients were on CHC, the majority for less than one year, a period in which the risk of VTE is higher[21]. Most, however, had other associated risk factors, and these should be considered when first prescribing CHC in teenagers. Besides the classic prothrombotic conditions, as lupus or antiphospholipid syndrome, recently VTE has been increasingly recognized in patients with several

systemic immunomediated diseases, as found in our series[22-24]. In outpatients there was an important delay in diagnosis, although we found a shorter than the mean lag time described[8]. As reported, other diagnosis had been considered during the previous medical observation, namely infections or psychological distress, emphasizing that the presence of fever or anxiety should not exclude PE.

Inpatients with PE were younger than outpatients, more frequently male, and presented different risk factors, such as CVC, infections and complex chronic diseases. Infections are important triggers and may delay PE diagnosis due to symptoms overlap[25]. As reported, in long-term hospitalizations, especially in critically ill patients, immobilization could have contributed for PE, emphasizing the importance of mechanical methods for DVT prophylaxis in these patients[23]. A worsening of their clinical condition, particularly unexplained cardiorespiratory deterioration, must prompt a PE workout. We found three asymptomatic PE (Table 2) in inpatients that were being studied for other reasons. These patients had multiple risk factors and negative D-dimer testing, possibly corresponding to chronic or subacute PE.

Recently, two distinct patterns of pediatric PE have been acknowledged[8]: classic thromboembolic PE and in situ pulmonary artery thrombosis (ISPAT), which results from local causes, such as congenital heart disease or anomalies of the pulmonary artery[26]. Two patients from our study may fit into this category: an asymptomatic (table 2) and a 13-years old girl, with a Truncus arteriosus type 1, with a right ventricle-pulmonary artery conduct, hospitalized with endocarditis suspicion. Clinically, decrease in pulmonary sounds and worsening of tricuspid regurgitation prompted CTPA with right central PE diagnosis. She was successfully treated with thrombectomy and conduct substitution surgery and maintained anticoagulation for one year. During follow-up a May-Thurner Syndrome was also detected. Several relevant studies[7,10] have included patients with possible septic or tumor thrombus in pediatric PE series, advocating that, in clinical practice, it is often not possible to differentiate septic emboli or tumor thrombus from true thromboembolic PE, as these are independent risk factors for VTE[10]. Furthermore, in the reported case, culture of the conduct and emboli were negative. Hence, we decided to include this patient in the study, even if this cannot be considered a classic thromboembolic PE, but rather an ISPAT.

ECG and CXR are often performed to investigate thoracic pain or dyspnea. However, the normality of these exams may be misleadingly reassuring, as happened in several of our outpatients. In highly suspicious cases, CTPA, the gold standard method to diagnose PE, should be directly performed. In our series, this happened only in one case, revealing the hesitancy to consider this diagnosis in pediatric patients. In lower-risk patients, other first-line exams can be considered. Although not sensitive, ECG may show unspecific alterations suggestive of PE[27], as sinus tachycardia, an alarm sign present in most of our cases. D-dimer testing was reported to lack utility in the diagnosis of childhood PE[14], but in a recent multicentric study[28] revealed a 100% sensitivity. In our data, D-dimer were positive in all acute PE, and negative only in a subacute PE in an anticoagulated patient and an asymptomatic PE, also antiaggregated. As others, we didn´t find an association between the degree of D-dimer increase and PE severity[29].

PE clinical diagnostic prediction models, validated for adult population, have been described as performing poorly in pediatric populations[16]. In a 36 pediatric PE population, Hennelly et al.[15] found Wells criteria to have a sensitivity and specificity of 86% and 58%, and PERC criteria of 100% and a 24%, respectively. Agha et al found the PERC criteria unable to rule out PE in 84% of pediatric emergency room patients[30]. In contrast, in our study these criteria had a high sensitivity and false negatives were only found in asymptomatic PE. Two pediatric models have been proposed, both derived from single-center studies and including a small number of PE[15,16]. Hennelly et al. model[15]performed similarly to Wells criteria in a setting with 36 PE, missing to diagnose four cases of children with clinical findings suggestive of a DVT or a history of malignancy or immobilization. Its application in our PE patients misclassified four patients as non-risk, two of them asymptomatic. A further model developed by Lee et al.[16] missed two of our PE patients, one asymptomatic. Both models misclassified a patient with a protein C deficiency, who had a positive family history. We propose that this should be considered in future pediatric models.

In our series, investigation after PE diagnosis was not uniform. May–Thurner Syndrome was diagnosed in a significant proportion of patients, years after PE, due to PTS. Although rare, this syndrome is likely

underestimated and should be investigated in patients with unexplained left lower extremity thrombosis[31].

A minority of our patients received thrombolysis and two of the massive PE were not eligible due to critical bleeding. Contrastingly, a systematic review[8] reported that a third of pediatric PE patients receive pharmacologic thrombolysis as initial treatment, although recent guidelines reserve it for massive PE[32]. LMWH was used more often to initiate anticoagulation treatment, given its pharmacokinetics profile, while UFH was the first option in high bleeding risk patients[33-34]. Anticoagulant therapy duration in our study was in average longer than described[8,13].

Management of asymptomatic PE lacks evidence, but most physicians claim to treat them similarly to symptomatic PE[26]. In a literature review[8], up to 17% of patients had PE detected incidentally but details on diagnostic methods, treatment and outcomes of this type of PE in pediatric patients had not been reported.

Rajpurkar et al.[8] referred a significant mortality rate in pediatric PE (26%), acknowledging, however, a possible reporting bias and that, in many studies, the cause of death might have been attributable to underlying diseases. Indeed, in our series, PE–related mortality 6.9%, while all causes mortality during follow-up reached 17.3%. Most deaths occurred in inpatients with cardiovascular, oncologic or other complex chronic conditions, as well as younger patients, as described in previous studies[7,8,10].

Follow up practices after a pediatric PE event are highly variable and data on long-term outcomes, including CTPH, pulmonary function or quality of life, and predictors of outcome are sparse[26]. Recurrence of VTE was within the expected reported values (0–18.8%). PTS was an important cause of morbidity for several years after PE. Evaluation of residual thrombosis at the end of anticoagulation therapy is not consensual among experts, 60% admitting they routinely re-image although 35% would not change the duration of anticoagulation therapy based in the results.[13] More than half our patients had a control CTPA, in a variable period after PE, and CTPH was indirectly accessed by ECHO.

Our study has important limitations: it is a single center retrospective study, and it does not necessarily generalize to other settings or communities. Importantly, autopsy-diagnosed PE were not trackable in a database and thus, reported mortality could be underestimated. Data on the autopsy-diagnosed PE case was not possible to analyze. The application of clinical scores retrospectively can be misleading. Also, due to the lack of a control group, we could not compare risk factors to those of the general population. Due to the 13-years span, and the lack of an institutional protocol, clinical management could have changed along the time, although this wasn´t noticed.

Our data emphasizes the need for a high suspicion index for pediatric PE in outpatients with risk factors, as half the cases were initially misdiagnosed. Towards compatible complains, risk factors, including CHC use, obesity, immunomediated diseases and family history should be explored. In inpatients, risk factors are often inherent to underlying diseases, immobilization, co-infections and CVC presence and thus unexplained cardiorespiratory deterioration should prompt PE investigation. May–Thurner Syndrome is likely underestimated and should be considered. The use of validated adult scores merits to be explored and improved in prospective pediatric multicentric studies.

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