BRIEF REPORT

Pediatric Massive and Submassive Pulmonary Embolism: A Single-Center Experience

Catherine E. Ross, MD,a,c,d Jenny A. Shih, MD,c,f Monica E. Kleinman, MD,b,c Michael W. Donnino, MDc,d,e,g

OBJECTIVES: To describe and compare patient and event characteristics and outcomes in pediatric massive pulmonary embolism (MPE) and submassive pulmonary embolism (SMPE).

METHODS: A retrospective cohort study at a quaternary-care pediatric hospital was conducted. Patients age <19 years with MPE (acute pulmonary embolism [PE] with cardiac arrest, hypotension, or compensated shock due to PE) or SMPE (right ventricular strain due to acute PE) between January 1997 and June 2019 were included.

RESULTS: Thirty-three patients were identified, including 9 (27%) patients with MPE and 24 (73%) patients with SMPE. The most commonly identified risk factor was use of oral contraceptive pills in 16 (49%) patients. Six (18%) patients died, 3 (9%) of which were PE-related deaths. Before PE, patients with MPE were more likely to be hospitalized (89% vs 13%, P < .001), have major comorbidities (89% vs 25%, P = .002), central venous catheters (67% vs 17%, P = .01), critical illness (56% vs 8%, P = .009), immobility (67% vs 13%, P = .005), and be postoperative (44% vs 4%, P = .01). MPE patients were also more likely to die before discharge (56% vs 4%, P = .003). Both groups were equally likely to have primary reperfusion attempts (78% of MPE versus 67% of SMPE, P = .69).

CONCLUSIONS: Pediatric MPE and SMPE differed in presentation, comorbidities, and risk factors, many of which were associated with hospitalization status. Pediatric-specific studies are warranted to determine risk assessment and management strategies, which may differ from adult guidelines.
The incidence of pediatric pulmonary embolism (PE) is estimated at 0.9 per 100,000 children in the United States, and massive pulmonary embolism (MPE) and submassive pulmonary embolism (SMPE) are far less common. MPE may represent a more-common cause of pediatric in-hospital cardiac arrest than previously reported and is often only identified postmortem. Given the rarity and emergent nature of these diseases, understanding the associated characteristics and outcomes in children is essential in guiding management. In the current study, we describe characteristics associated with these diseases and explore possible differences between the 2 forms of severe PE in children.

METHODS

We performed a retrospective review at a quaternary-care academic children’s hospital with approval by our institutional review board.

Patients

Patients <19 years old with MPE or SMPE acutely managed at our institution were included. Patients with Glenn or Fontan procedures were excluded because the physiology, diagnosis, and management of PE in these patients greatly differ from the general population. All PEs were confirmed by computed tomography angiogram, fluoroscopic pulmonary angiogram, ventilation and/or perfusion scan, or autopsy. Cases were identified from the electronic medical record and autopsy reports by key word searches between January 1, 1997, and June 30, 2019.

Definitions

Because pediatric PE classifications have not been established, we adapted adult definitions from the European Society of Cardiology.

MPE: Acute PE with cardiopulmonary arrest, sustained hypotension, or normotension with signs of shock. Criteria for MPE were an acute PE with (1) cardiac arrest, (2) hypotension requiring vasopressor infusion, or (3) compensated shock with severe tachycardia, tachypnea, relative hypotension, and poor perfusion on examination (adapted definition from the Pediatric Advanced Life Support Guidelines).

SMPE: Acute PE without hypotension or shock but with evidence of right ventricular (RV) strain or injury. Criteria for SMPE included acute PE with presence of RV dilation and/or dysfunction on echocardiogram absent hypotension or shock.

Primary reperfusion: Removal or disintegration of PE resulting in restored pulmonary blood flow.

Data Collection and Outcomes

Chart reviews were performed to determine case details. Risk factors according to the Caprini Score were collected. All patients admitted to the ICU before PE were considered immobile. All other patients were considered mobile unless otherwise stated in clinical documentation. Prothrombotic disorders were reported only in patients who received full hypercoagulable workup at our institution. We additionally screened for cardiac disease, critical illness (defined as admission to an ICU receiving critical care interventions), use of psychotropic medications, vascular malformations, and genetic syndromes. Comorbidities included chronic conditions present before PE. Comorbidities were categorized as "major" if they were generally considered life-threatening, life-limiting, or caused major disability. Patient outcomes included in-hospital mortality, PE-related in-hospital mortality, defined as cardiac death, severe neurologic injury contributing to death, or death as a result of complications from PE-specific therapies; and development of chronic thromboembolic pulmonary hypertension (CTEPH), defined as pulmonary hypertension on echocardiogram at least 6 months after PE without other known cause.

Statistical Analysis

Descriptive statistics are presented as counts with relative frequencies or medians with interquartile ranges (IQRs). Tests of comparison between the MPE and SMPE groups included Wilcoxon rank-sum tests for continuous variables and Fisher’s exact tests for categorical variables. P values <.05 were considered significant.

RESULTS

Thirty-three patients met inclusion criteria (Supplemental Fig 2). Nine (27%) patients initially presented with MPE, and 24 (73%) presented with SMPE, including 2 patients who progressed from SMPE to MPE during the hospitalization. Patient and event characteristics are presented in Table 1. Underlying disorders and case details are presented in Supplemental Tables 3 and 4.

In the overall cohort, the median age was 15 years (IQR: 14–16, Fig 1), and 22 (67%) patients were female. The most commonly identified risk factor was use of oral contraceptive pills in 16 (49%) patients (73% of female patients). One (3%) patient was found to have Ewing sarcoma massive tumor embolus on surgical pathology. Six (18%) patients died during the hospitalization, 3 (9%) of which were PE-related deaths. One (4%) of the 25 survivors who had follow-up developed CTEPH and later died of related complications. The remaining 24 survivors with follow-up, including 2 patients who had suffered cardiac arrest, had excellent outcomes with no sequel from PE nor recurrence of PE (median time to follow-up: 16 months; IQR: 6–41).

In the MPE group, 4 (44%) patients presented with sudden cardiac arrest. Initial management consisted of surgical embolectomy in 3 (33%) patients, catheter-based therapy in 3 (33%) patients, and systemic thrombolysis in 1 (11%) patient. Only 2 (22%) patients with MPE did not receive primary reperfusion attempts: 1 because of a lack of recognition antemortem, and 1 because of a concomitant paradoxical emboli with massive cerebral infarction leading to redirection of care. Two additional patients developed MPE after initially presenting with SMPE and received thrombolysis and catheter-based therapy as the initial therapy for the MPE, respectively. Three (27%) of 11 patients who ultimately had MPE required a second attempt at reperfusion therapy after initial attempts (Table 2).

Of the 24 patients with SMPE, initial management consisted of systemic thrombolysis in 13 (54%) patients and surgical embolectomy in 1 (4%) patient.
TABLE 1  Patient and Event Characteristics and Outcomes

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All Cases (n = 33)</th>
<th>Initial MPE (n = 9)</th>
<th>Initial SMPE (n = 24)</th>
<th>P</th>
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<tr>
<td><strong>Demographics</strong></td>
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<td>Age in y, median (IQR)</td>
<td>15 (14–16)</td>
<td>16 (10–16)</td>
<td>15 (15–16)</td>
<td>.77</td>
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<td>Female, n (%)</td>
<td>22 (67)</td>
<td>5 (56)</td>
<td>17 (71)</td>
<td>.44</td>
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<td><strong>Comorbidities, n (%)</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Major</td>
<td>14 (42)</td>
<td>8 (89)</td>
<td>6 (25)</td>
<td>.002</td>
</tr>
<tr>
<td><strong>Risk factors, n (%)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Cardiac disease</td>
<td>2 (6)</td>
<td>2 (22)</td>
<td>0 (0)</td>
<td>.07</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>10 (30)</td>
<td>6 (67)</td>
<td>4 (17)</td>
<td>.01</td>
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<tr>
<td>Critical illness</td>
<td>7 (21)</td>
<td>5 (56)</td>
<td>2 (8)</td>
<td>.009</td>
</tr>
<tr>
<td>Family history of VTE&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 out of 30 (27)</td>
<td>0 out of 8 (0)</td>
<td>8 out of 22 (36)</td>
<td>.07</td>
</tr>
<tr>
<td>History of VTE</td>
<td>2 (6)</td>
<td>2 (22)</td>
<td>0 (0)</td>
<td>.07</td>
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<tr>
<td>Immobility</td>
<td>9 (27)</td>
<td>6 (67)</td>
<td>3 (13)</td>
<td>.005</td>
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<td>Malignancy</td>
<td>5 (15)</td>
<td>2 (22)</td>
<td>1 (4)</td>
<td>.17</td>
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<td>Obesity</td>
<td>11 (33)</td>
<td>2 (22)</td>
<td>9 (38)</td>
<td>.68</td>
</tr>
<tr>
<td>Oral contraceptives&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16 out of 22 (73)</td>
<td>1 out of 5 (20)</td>
<td>15 out of 17 (88)</td>
<td>.009</td>
</tr>
<tr>
<td>Postoperative</td>
<td>5 (15)</td>
<td>4 (44)</td>
<td>1 (4)</td>
<td>.01</td>
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<td>Prothrombotic disorder&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8 out of 19 (42)</td>
<td>1 out of 1 (100)</td>
<td>7 out of 11 (39)</td>
<td>.42</td>
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<td>Psychiatric medications</td>
<td>8 (24)</td>
<td>1 (11)</td>
<td>7 (29)</td>
<td>.39</td>
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<td>Pulmonary disease</td>
<td>3 (9)</td>
<td>2 (22)</td>
<td>1 (4)</td>
<td>.17</td>
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<tr>
<td>Vascular malformation</td>
<td>4 (12)</td>
<td>2 (22)</td>
<td>2 (8)</td>
<td>.3</td>
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<td><strong>Presentation, n (%)</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
<td></td>
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<tr>
<td>In hospital</td>
<td>11 (33)</td>
<td>8 (89)</td>
<td>3 (13)</td>
<td>&lt;.001</td>
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<td>Emergency department</td>
<td>1 out of 11 (9)</td>
<td>1 out of 8 (13)</td>
<td>0 out of 3 (0)</td>
<td>3.99</td>
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<td>General care ward</td>
<td>2 out of 11 (18)</td>
<td>1 out of 8 (13)</td>
<td>1 out of 3 (33)</td>
<td>3.001</td>
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<tr>
<td>ICU</td>
<td>6 out of 11 (55)</td>
<td>4 out of 8 (50)</td>
<td>2 out of 3 (67)</td>
<td>3.001</td>
</tr>
<tr>
<td>Operating room</td>
<td>2 out of 11 (18)</td>
<td>2 out of 8 (25)</td>
<td>0 out of 3 (0)</td>
<td>3.001</td>
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<td><strong>Diagnostic method</strong></td>
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<tr>
<td>Computed tomography</td>
<td>25 (76)</td>
<td>2 (22)</td>
<td>23 (96)</td>
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<td>Angiography</td>
<td>5 (15)</td>
<td>5 (56)</td>
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<td>Ventilation or perfusion scan</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (4)</td>
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<td>Autopsy</td>
<td>2 (6)</td>
<td>2 (22)</td>
<td>0 (0)</td>
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<tr>
<td>MPE presentation&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>Sudden cardiac arrest</td>
<td>4 (12)</td>
<td>4 (44)</td>
<td>0 (0)</td>
<td>.29</td>
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<td>Vasopressor requirement</td>
<td>6 (18)</td>
<td>5 (56)</td>
<td>1 out of 2 (50)</td>
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<td>Compensated shock</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 out of 2 (50)</td>
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<td><strong>Final PE-specific therapies, n (%)</strong>&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Anticoagulation</td>
<td>31 (94)</td>
<td>7 (78)</td>
<td>24 (100)</td>
<td>.07</td>
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<tr>
<td>Any primary reperfusion</td>
<td>23 (70)</td>
<td>7 (78)</td>
<td>16 (67)</td>
<td>.89</td>
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<tr>
<td><strong>Type of primary reperfusion</strong></td>
<td></td>
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<tr>
<td>Surgical embolectomy</td>
<td>5 out of 23 (22)</td>
<td>3 out of 7 (43)</td>
<td>2 out of 18 (13)</td>
<td>.009</td>
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<td>Catheter-directed therapy</td>
<td>4 out of 23 (17)</td>
<td>3 out of 7 (43)</td>
<td>1 out of 18 (6)</td>
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<td>Systemic thrombolysis</td>
<td>14 out of 23 (61)</td>
<td>1 out of 7 (14)</td>
<td>13 out of 18 (81)</td>
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<td><strong>Outcomes, n (%)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>6 (18)</td>
<td>5 (56)</td>
<td>1 (4)</td>
<td>.003</td>
</tr>
<tr>
<td>PE-related in-hospital mortality</td>
<td>5 (0)</td>
<td>3 (53)</td>
<td>0 (0)</td>
<td>.015</td>
</tr>
<tr>
<td>CTEPH&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1 out of 25 (4)</td>
<td>0 out of 4 (0)</td>
<td>1 out of 21 (5)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

<sup>a</sup>Column totals may exceed the number of patients because of multiple counts for some patients.

<sup>b</sup>Includes patients with missing information.

<sup>c</sup>Includes only female patients.

<sup>d</sup>Includes 2 patients with initial SMPE who progressed to MPE during the hospitalization.

<sup>e</sup>Includes only patients who survived to hospital discharge and had follow-up at our institution.

<sup>f</sup>Includes only patients who survived to hospital discharge and had follow-up at our institution.

<sup>g</sup>CTEPH includes 2 patients with initial SMPE who progressed to MPE during the hospitalization.

<sup>h</sup>SMPE, systemic thromboembolism; VTE, venous thromboembolism.

In this study, we report our single-center experience with 33 cases of pediatric MPE and SMPE. We found that MPE and SMPE appeared to differ in comorbidities, risk factors, and presentation, many of which were associated with hospitalization status. Both groups were equally likely to receive primary reperfusion. As expected, the MPE group had higher in-hospital and PE-related mortality. Additionally, 1 patient was found to have massive tumor embolism, which, to our knowledge, has only been reported in case reports.<sup>10–11</sup>

In a recent study from Pelland-Marccotte et al, researchers compared 49 pediatric patients with MPE and SMPE combined versus patients with low-risk PE at 2 centers in Canada over a similar time period. Compared with this study, our cohort appeared to have lower proportions of infants <1 year, cardiac disease, and presence of central venous catheters.

Pelland-Marccotte et al showed that the adult PE severity index and simplified PE severity index were challenging to interpret in the pediatric population because of younger age and lower prevalence of comorbidities. They suggest that variables...
such as age <1 year and presence of a central venous catheter should be considered for a pediatric predictive tool. Our lack of similar findings in age distribution and prevalence of heart disease suggests that presence of cardiac disease combined with young age may be a more-specific predictor than either one alone. We did observe higher prevalence of central venous catheter in patients with MPE, which supports use of this variable as a predictor of severity. However, our concurrent findings of more hospitalized patients, critical illness, immobility, and postoperative status in MPE suggest that presence of a central line could be a surrogate marker for acute illness leading to more-severe forms of PE. Further studies are warranted to determine which factors are the strongest predictors for severity of PE in children.

Patient outcomes appeared similar between the 2 studies; however, PE-specific therapeutic strategies appeared to differ. Management in both studies also appeared to differ from the current adult guidelines, which include thrombolysis as first line for MPE and anticoagulation only for SMPE. Intra- and interhospital heterogeneity in the management of pediatric MPE and SMPE is not surprising given the extreme rarity of these diseases and lack of pediatric data. This highlights the need for dedicated pediatric studies to provide insight on optimal management in children, which may differ from adult guidelines.

There were several limitations in our study. First, normotensive shock was difficult to identify retrospectively, and some MPE cases may have been miscategorized as SMPE. Second, some cases of MPE and SMPE could not be captured because of a paucity of electronic documentation in the early years of this study or in the event of death due to an unrecognized MPE without autopsy. This may have led to an underestimation in the frequency of MPE and SMPE at our institution. Finally, given our small cohort, multivariate analysis was not performed, and conclusions based on statistical comparisons are limited.

**CONCLUSIONS**

Pediatric MPE and SMPE differed in presentation, comorbidities, and risk factors, many of which were associated with hospitalization status. These differences should be considered when investigating pediatric-specific risk assessment and management strategies.

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REFERENCES


Pediatric Massive and Submassive Pulmonary Embolism: A Single-Center Experience
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