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Melissa Chima, Duane Williams, Neal J. Thomas, Conrad Krawiec

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**COVID-19 Associated Pulmonary Embolism in Pediatric Patients**

Melissa Chima, BS<sup>1</sup>, Duane Williams, MD<sup>2</sup>, Neal J. Thomas, MD<sup>2,3</sup>, Conrad Krawiec, MD<sup>2</sup>

**Authors' Affiliations and Addresses:**

<sup>1</sup>Penn State College of Medicine, 500 University Drive, P.O. Box 850, Hershey, PA, USA 17033-0850, Tel: (717)-531-5337, Fax: (717)-531-8985.

<sup>2</sup>Pediatric Critical Care Medicine, Department of Pediatrics, Penn State Hershey Children's Hospital, 500 University Drive, P.O. Box 850, Hershey, PA, USA 17033-0850, Tel: (717)-531-5337, Fax: (717)-531-8985.

<sup>3</sup>Department of Public Health Sciences, Pennsylvania State University College of Medicine, 500 University Drive, Hershey, Pennsylvania, USA 17033-0850, Tel: (717)-531-8521, Fax: (717)-531-0786.

**Address correspondence to:** Conrad Krawiec, Department of Pediatrics, Penn State Health Children's Hospital, 500 University Drive, P.O. Box 850, Hershey, PA 17033-0850, [[ckrawiec@pennstatehealth.psu.edu](mailto:ckrawiec@pennstatehealth.psu.edu)], Tel: (717) 531-5337, Fax: (717)-531-8985.

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Dr. Krawiec and Ms. Chima conceptualized and designed the study.

Ms. Chima drafted the initial manuscript and approved the final manuscript as written.

Dr. Krawiec and Ms. Chima carried out the initial analyses.

Dr. Thomas and Dr. Williams reviewed the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr. Krawiec, collected and organized the data, reviewed and revised the manuscript, and approved the final manuscript as written.

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**ABSTRACT**

**BACKGROUND/OBJECTIVES:** Coronavirus disease 2019 (COVID-19) is associated with pulmonary embolism in adults, but the clinical circumstances surrounding its presence are unknown in children. The objectives of this study are to (1) determine the prevalence of pulmonary embolism in pediatric subjects with COVID-19; (2) evaluate patient characteristics; and (3) describe treatments applied.

**METHODS:** We performed a retrospective cohort study utilizing TriNetX® electronic health record (EHR) data of subjects aged less than 18 years of age who were diagnosed with COVID-19 infection (International Classification of Diseases-10 [ICD-10] U07.1). Pulmonary embolism was identified using ICD-10 code I26]. We additionally collected data on age, sex, race, ethnicity, all diagnostic codes, medications, procedures, laboratory results, comorbidities, and outcomes.

**RESULTS:** During the study period, 24,723 pediatric subjects were reported to have a COVID-19 infection diagnosis from 41 healthcare organizations, of which 693 (2.8%) were hospitalized. Eight subjects (0.03% overall, 1.2% of hospitalized patients) were diagnosed with pulmonary embolism. The median age median (25<sup>th</sup>, 75<sup>th</sup> percentile) of patients diagnosed with pulmonary embolism was 16.5 (15, 18) years and median (25<sup>th</sup>, 75<sup>th</sup> percentile) body mass index [was 22.1 (19.6, 47.9). Three (37.5%) received critical care services, and one (12.5%) underwent mechanical ventilation. Five (62.5%) subjects had potentially significant risk factors (obesity, malignancy, recent surgery, oral contraceptive use). All patients received anticoagulation but none underwent thrombolysis. There were no reported deaths.

**CONCLUSIONS:** While pulmonary embolism is diagnosed less commonly in children than in adults, its occurrence appears to be more frequent in children hospitalized with COVID-19 as compared to prior reports in hospitalized children in general. All patients survived with only one requiring mechanical ventilation.

### INTRODUCTION

In 2020, the United States was impacted by the coronavirus 2019 (COVID-19) pandemic.<sup>1,2</sup> Due to endothelial dysfunction, an increased proinflammatory cytokine response, abnormal clot formation, and platelet hyperactivity, a hypercoagulable state is one of the prominent clinical features that can occur in individuals who contract COVID-19.<sup>3</sup> This may result in thrombotic manifestations including venous thromboembolism, arterial thrombosis and pulmonary embolism.<sup>4,5</sup>

Pulmonary embolism, in particular, is a potentially life-threatening condition with a reported prevalence of 15.8% in COVID-19 positive adults.<sup>4,5</sup> Currently, to our knowledge, pulmonary embolism has only been reported in the context of multisystemic inflammatory syndrome in children (MIS-C).<sup>6</sup> Overall, pulmonary embolism in children is a rare condition, occurring in 2 to 6 per 10,000 hospital discharges.<sup>7</sup> Its clinical manifestations, however, can be nonspecific, may be associated with unfavorable outcomes, and unrecognized due to a lack of validated clinical decision-making tools.<sup>8</sup>

During this pandemic, our understanding of this novel virus is continuously evolving. Children, however, are currently reported to make up 2% of cases.<sup>9</sup> Thus, the virus' impact on the pediatric population is not completely known. Utilizing retrospective electronic health record (EHR) datasets from multiple centers and compiling demographic and clinical data may assist in evaluating the frequency, presentation, and clinical factors associated with rare but potentially lethal complications of COVID-19, such as pulmonary embolism. It may also inform clinical decision making, potentially raise the index of suspicion in clinicians who manage these patients, and enhance the quality of care provided.

The objectives of this present study are to (1) determine the prevalence of pulmonary embolism in pediatric subjects (less than 18 years) with COVID-19; (2) evaluate patient characteristics; and (3) describe the treatments applied. We hypothesize that COVID-19 associated pulmonary embolism occurs in children, especially those with particular comorbidities.

### METHODS

#### *Study Design:*

This is a retrospective observational cohort study utilizing the TriNetX<sup>®</sup> electronic health record (EHR) data of pediatric patients less than 18 years of age with a pulmonary embolism (I26) and COVID-19 infection U07.1 International Classification of Diseases 10<sup>th</sup> edition diagnostic codes. TriNetX<sup>®</sup> is a global federated research network that provides access to EHR data elements (eg, diagnoses, procedures, laboratory values) from 41 participating health care organizations (HCOs) predominately in the United States in this current dataset query.<sup>10</sup> For this study, TriNetX<sup>®</sup> provided a de-identified dataset of electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information, and settings of care if present) from 8 patients within the United States. The data is de-identified based on standard defined in Section § 164.514(a) of the HIPAA Privacy Rule. The process by which data sets are de-identified is attested to through a formal determination by a qualified expert as defined in Section § 164.514(b)(1) of the HIPAA Privacy Rule. Protected Health Information (PHI) or Personal Data is made available to the users of the platform. As a federated network and no protected health information is received by the user, use of the TriNetX<sup>®</sup> database has an IRB waiver. No protected health information is received by the user. As such, use of the TriNetX database has an IRB waiver.

### *Data Collection:*

On January 15, 2021, we analyzed the EHR data of 8 pediatric subjects who were reported to have a diagnosis of pulmonary embolism and COVID-19 infection (concurrently or within 30 days after COVID-19 diagnosis). Utilizing International Classification of Diseases 10<sup>th</sup> edition diagnostic codes, we included any root code (I26) for pulmonary embolism and the diagnostic code U07.1 for COVID-19 infection. After the query, we collected and evaluated the following data based on two timeframes: (1) on the reported day of acute pulmonary embolism and COVID-19 diagnosis (age, sex, body mass index, race, ethnicity, laboratory results) and (2) 30 days before and after the reported day of acute pulmonary embolism and COVID-19 diagnosis (medications, non-pulmonary embolism and non-COVID-19 diagnostic codes, procedures, comorbidities, and outcomes). Due to database limitations, radiological and ultrasonographic reports were not available for review. For the purposes of this study, we assumed that the day the diagnostic code was entered for billing was the day the diagnosis was made. Diagnostic and procedure codes were summarized in Table Supplementary. In order to also gain current understanding of the reported frequency of venous thromboembolism (ICD-10 diagnostic code I82) and use of computed tomographic angiography of chest with contrast in COVID-19 patients, on March 1, 2021 we utilized TriNetX © browser-based real-time analytical features to evaluate this data.

### *Statistical Analysis:*

Summary statistics using median and interquartile range or proportions were reported for clinical and demographic characteristics of the pediatric patients.

## RESULTS

### *Patient Characteristics:*

During the study period, 24,723 pediatric subjects were reported through the TriNetX® database to have a COVID-19 infection diagnosis from 41 healthcare organizations (HCOs) with 693 (2.8%) requiring hospitalization. Of these, 8 (1.2%) subjects had a diagnosis code for pulmonary embolism, and 3 of those 8 children (37.5%) were also diagnosed with a venous thromboembolism. A real-time re-query to understand the overall frequency of venous thromboembolism and use of computed tomographic angiography of the chest with contrast was performed. That query revealed 37,792 COVID-19 infection diagnoses, with 42 (0.11%) reported to have a venous thromboembolism and 69 (0.18%) that underwent computed tomographic angiography of the chest with contrast.

The cohort of patients with PEs was predominantly female [6 (75%)]. Subject age [median (25<sup>th</sup>, 75<sup>th</sup> percentile)] was 16.5 (15, 18) and BMI [median (25<sup>th</sup>, 75<sup>th</sup> percentile)] was 22.1 (19.6, 47.9). Age, sex, race, and ethnicity are summarized in Table 1.

Six subjects (75%) were diagnosed with pulmonary embolism on the same day as the COVID-19 infection; 1 was diagnosed 21 days after the COVID-19 diagnosis; 1 was diagnosed with a pulmonary embolism before the subject was subsequently diagnosed (24 hours later) with COVID-19. Five (62.5%) subjects had diagnostic codes indicating known risk factors for pulmonary embolism including obesity [2 (25.0%)], oral contraceptive use [1 (12.5%)], recent surgical procedures [2 (25.0%)], and malignancy [1 (12.5%)]. Four subjects had either an erythrocyte sedimentation rate (ESR), C-reactive protein level, and/or D-dimer laboratory results. [Table 2]

### *Treatment and Outcomes*

Five subjects (62.5%) were hospitalized, 1 (12.5%) was seen within the emergency department, and the encounters for 2 (25%) were unknown. With the exception of 1 subject (who received Apixaban), the subjects received either Heparin or Enoxaparin. Other medications administered were summarized in Table 2. Three (37.5%) subjects were reported to have received critical care services on presentation. One (12.5%) received mechanical ventilation. Despite the diagnosis of shock in 1 subject, there was no reported use of inotropes or vasoactive infusions, thrombolysis, or embolectomy. Due to database restrictions, the severity of illness was not obtained. No deaths were reported.

### **DISCUSSION**

We sought to examine the frequency, clinical factors, and outcomes associated with COVID-19 related pulmonary embolism in the pediatric population. Our main findings were that the frequency of occurrence was very low. A majority of pediatric patients with COVID-19 related pulmonary embolism were female, of adolescent age, and hemodynamically stable on presentation, and all survived. These findings may inform clinical decision making in this patient population.

Based on our findings, COVID-19 associated pulmonary embolism appears to be a rare occurrence in children. There are several reasons why this may be the case. Even though the COVID-19 subjects in this study cohort were reported to have pulmonary embolism, other subjects may not have been identified due to a low index of suspicion, and thereby lack of testing. The estimated COVID-19 mortality rate is reported to be low in children,<sup>11</sup> but it is unknown if a subset of COVID-19 associated pulmonary embolism subjects presented with sudden death and were unable to be identified due to the resuscitation effort. Adult patients may

be more at risk from thromboembolic complications when compared to children. It is thought that adult patients may be more likely to be immobilized or have a more severe inflammatory response when they contract COVID-19.<sup>12,13</sup> In addition, this intense inflammation may be focused within the lungs, resulting in local thrombosis (versus embolization from the lower extremities).<sup>14</sup> Further study and data are needed to discern if there are differences in how acute thrombosis presents between adult and children.

A predominance of patients diagnosed with COVID-19 associated pulmonary embolism were of adolescent age. COVID-19 may uniquely impact adolescent patients, resulting in higher complications in this age group when compared to younger patients. It is unknown if the subjects included in this study presented first in an emergency department setting, where it is possible that an adult trained provider (vigilant to COVID-19 thromboembolic complications) may have had a higher index of suspicion compared to pediatric providers. Finally, some subjects did have pre-disposing factors that may have placed them at a higher risk for developing a pulmonary embolism.

In our study, 2 subjects were noted to have a BMI greater than 40. In adult COVID-19 positive patients, an elevated BMI is associated with not only severe disease but death.<sup>15</sup> It is thought that obesity contributes to more severe disease due to the pro-inflammatory state and other associated vascular co-morbidities (eg, coronary artery disease).<sup>15</sup> Because of this and obesity's association with a hypercoagulable state, the risk of pulmonary embolus may also be increased in obese adult patients.<sup>16</sup> The data in COVID-19 positive children, however, is limited. It is known that the most common underlying condition in children who require hospitalization due to COVID-19 is obesity.<sup>17</sup> But, case-fatality rates in general remain low, even in children with more severe disease.<sup>17</sup> It is unclear why, but children may have a different immune response and infectivity

(eg, lower viral load) when compared to adults, which may limit the severity of disease in children.<sup>13,18</sup> Nevertheless, despite this possibility, caution must be taken, as thromboembolic complications typically seen in adult patients with COVID-19 can occur in children.

Prior to the COVID-19 pandemic, pulmonary embolism occurred in 2 to 6 hospitalized children per 10,000 discharges.<sup>7</sup> In our study, 8 COVID-19 positive children were reported to have pulmonary embolism out of 693 hospitalized COVID-19 children. Extrapolating to 10,000 admissions, this could represent a higher prevalence than what a provider may routinely expect. Further study and surveillance are needed as the COVID-19 pandemic continues, especially in the presence of an increase in pediatric admissions.

This study had several limitations. First, it was a retrospective study and was also limited to the United States. The study was restricted to healthcare organizations that participate in the database retrieval system. Due to database limitations, it is possible not all electronic health record data was reported (including vital signs data). We were unable to confirm the diagnosis of pulmonary embolism with imaging data, as these reports are not currently reported in the system. Due to lack of documentation, we were unable to confirm if other subjects required procedures (relying instead on procedural codes entered by clinicians). Finally, some pulmonary emboli may not have been diagnosed and others may have been diagnosed but not coded in the medical record.

### **CONCLUSIONS:**

Pediatric subjects reported to have COVID-19 associated pulmonary embolism survived, with only 1 requiring mechanical ventilation. While pulmonary embolism is diagnosed less commonly in children than in adults, its occurrence appears to be more frequent in children hospitalized with COVID-19.

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Table 1: Patient Characteristics	
Characteristic	Pulmonary Embolism (I26) and COVID-19 (U07.1) Diagnosed Pediatric Subjects
Number of Subjects	8
Median Age	16.5 (15,18)
Sex	25%
Male	2 (25%)
Female	6 (75%)
Median Body Mass Index (kg/m <sup>2</sup> ) [39156-5]	22.1 (19.6,47.9) <sup>a</sup>
Race (n,%)	
<i>White</i>	5 (62.5%)
<i>Black or African American</i>	2 (25.0%)
<i>Unknown</i>	1 (12.5%)
Ethnicity (n,%)	
<i>Hispanic or Latino</i>	2 (25.0%)
<i>Not Hispanic or Latino</i>	6 (75.0%)
Number of Deaths	0 (0.0%)
Presence of Venous Thromboembolism	3 (37.5%)

<sup>a</sup>5 subjects

## Prepublication Release

Table 2: Other Diagnoses and Medications Administered for Each Subject on First Day of Pulmonary Embolism Presentation					
Subject	Other Diagnoses/Recent Procedures Noted	Medications Administered	ESR level <sup>a</sup>	CRP level <sup>b</sup>	D-Dimer level <sup>c</sup>
1	Other venous embolism and thrombosis	Heparin			
2	Overweight and Obesity (BMI>40); Asthma	Enoxaparin	61 mm/h	2.7 mg/dL	1.3 ng/mL
3	None Noted	Apixaban			0.94 ng/mL
4	Adverse effect of other estrogens and progestogens, initial encounter	Heparin and Enoxaparin			
5	Type 2 Diabetes Mellitus; Overweight and Obesity (BMI>40); Obstructive Sleep Apnea	Enoxaparin and Hydrocortisone			
6	Essential Hypertension; Other venous embolism and thrombosis; Wegener's granulomatosis with renal involvement; Acute Kidney Failure; Renal Biopsy	Heparin			
7	Elevated erythrocyte sedimentation rate; Severe Sepsis with Shock; Encephalopathy, unspecified	Immunoglobulin G, Methyprednisolone, Enoxaparin	37 mm/h	281 mg/dL	
8	Malignant neoplasm of long bones of left lower limb; Acute Myocardial Infarction; Cardiomyopathy; Heart Failure; Intracardiac thrombosis, not elsewhere classified; Acquired absence of left leg below knee; Acute Kidney Failure; Ascites; Solitary pulmonary nodule; Laparoscopy	Enoxaparin and Aspirin <sup>d</sup>			

<sup>a</sup>Erythrocyte sedimentation rate, Reference range 0-15 mm/h

<sup>b</sup>C-reactive protein, Reference range <1 mg/dL

<sup>c</sup>D-dimer, Reference range ≤ 0.54 ng/mL

<sup>d</sup>These medications were reported to be administered 14 days after pulmonary embolism diagnosis reported

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