

# COVID-19–Associated Pulmonary Embolism in Pediatric Patients

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## ABSTRACT

**BACKGROUND AND 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 determine the prevalence of pulmonary embolism in pediatric subjects with COVID-19, evaluate patient characteristics, and describe treatments applied.

**METHODS:** We performed a retrospective cohort study using TriNetX electronic health record data of subjects aged <18 years who were diagnosed with COVID-19 infection (*International Classification of Diseases, 10th Revision*, code U07.1). Pulmonary embolism was identified by using *International Classification of Diseases, 10th Revision*, 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 among 41 health care organizations, of which 693 (2.8%) were hospitalized. Eight subjects (0.03% overall and 1.2% of hospitalized patients) were diagnosed with pulmonary embolism. The median age (25th to 75th percentile) of patients diagnosed with pulmonary embolism was 16.5 years, and median (25th to 75th percentile) BMI was 22.1 (19.6–47.9). Three (37.5%) received critical care services, and 1 (12.5%) underwent mechanical ventilation. Five (62.5%) subjects had potentially significant risk factors (obesity, malignancy, recent surgery, and oral contraceptive use). All patients received anticoagulation, but none underwent thrombolysis. There were no reported deaths.

**CONCLUSIONS:** Although 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 with previous reports in hospitalized children in general. All patients survived, with only 1 requiring mechanical ventilation.

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In 2020, the United States was impacted by the coronavirus disease 2019 (COVID-19) pandemic.<sup>1,2</sup> Because of 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 multisystem inflammatory syndrome in children.<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 may be unrecognized because of 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 are not completely known. Using retrospective electronic health record (EHR) data sets 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 determine the prevalence of pulmonary embolism in pediatric subjects (aged <18 years) with COVID-19<sup>2</sup>, evaluate patient characteristics, and<sup>3</sup> 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 conducted by using the TriNetX EHR data of pediatric patients aged <18 years with a pulmonary embolism (*International Classification of Diseases, 10th Revision* [ICD-10], code I26) and COVID-19 infection (ICD-10 code U07.1). TriNetX is a global, federated research network that provides access to EHR data elements (eg, diagnoses, procedures, and laboratory values) from 41 participating health care organizations (HCOs) predominately in the United States in this current data set query.<sup>10</sup> For this study, TriNetX was used to provide a deidentified data set 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 are deidentified on the basis of the standard defined in section §164.514(a) of the Health Insurance Portability and Accountability Act Privacy Rule. The process by which data sets are deidentified is attested to through a formal determination by a qualified expert, as defined in section §164.514(b)<sup>1</sup> of the Health Insurance Portability and Accountability Act Privacy Rule. Protected health information or personal data are made available to the users of the platform. As a federated network, and because no protected health information is received by the user, use of the TriNetX database has an institutional review board 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). Using ICD-10 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 on the basis of 2 time frames<sup>1</sup>: (1) age, sex, BMI, race, ethnicity, and laboratory results on the reported day of acute pulmonary embolism and COVID-19 diagnosis and<sup>2</sup> (2) medications, nonpulmonary embolism and non-COVID-19

diagnostic codes, procedures, comorbidities, and outcomes 30 days before and after the reported day of acute pulmonary embolism and COVID-19 diagnosis. Because of database limitations, radiologic 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 Supplemental Table 3. To also gain current understanding of the reported frequency of venous thromboembolism (ICD-10 diagnostic code I82) and use of computed tomographic (CT) angiography of the chest with contrast in COVID-19 patients, on March 1, 2021, we used TriNetX browser-based real-time analytical features to evaluate these 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 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 query to understand the overall frequency of venous thromboembolism and use of CT 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%) reported to have undergone CT angiography of the chest with contrast.

The cohort of patients with pulmonary embolisms was predominantly girls (6 [75%]). The median (25th to 75th percentile) age of subjects was 16.5<sup>11,12</sup> years and BMI (median [25th to 75th percentile]) was 22.1 (19.6–47.9). Age, sex, race, and ethnicity are summarized in Table 1.

**TABLE 1** Patient Characteristics

Characteristic	Pediatric Subjects Diagnosed With Pulmonary Embolism (ICD-10 Code I26) and COVID-19 (ICD-10 Code U07.1)
No. of subjects	8
Median age, y	16.5 (15–18)
Sex, <i>n</i> (%)	
Male	2 (25)
Female	6 (75)
Median BMI, <i>n</i> = 39 156-5	22.1 (19.6–47.9) <sup>a</sup>
Race, <i>n</i> (%)	
White	5 (62.5)
Black or African American	2 (25.0)
Unknown	1 (12.5)
Ethnicity, <i>n</i> (%)	
Hispanic	2 (25.0)
Not Hispanic	6 (75.0)
No. of deaths	0 (0.0)
Presence of venous thromboembolism	3 (37.5)

<sup>a</sup> Five subjects.

Six subjects (75%) were diagnosed with a pulmonary embolism on the same day as the COVID-19 infection; 1 received a diagnosis 21 days after the COVID-19 diagnosis; and 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 an erythrocyte sedimentation rate (ESR), a 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 are 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. Because of database restrictions, the severity of illness was not obtained. No deaths were reported.

**TABLE 2** Other Diagnoses and Medications Administered for Each Subject on the First Day of Pulmonary Embolism Presentation

Subject	Other Diagnoses and/or Recent Procedures Noted	Medications Administered	ESR Level, <sup>a</sup> mm/h	CRP Level, <sup>b</sup> mg/dL	D-Dimer Level, <sup>c</sup> ng/mL
1	Other venous embolism and thrombosis	Heparin	—	—	—
2	Overweight and obesity (BMI >40); asthma	Enoxaparin	61	2.7	1.3
3	None noted	Apixaban	—	—	0.94
4	Adverse effect of other estrogens and progestogens, initial encounter	Heparin and enoxaparin	—	—	—
5	Type 2 diabetes mellitus; overweight and obesity (BMI >40); and obstructive sleep apnea	Enoxaparin and hydrocortisone	—	—	—
6	Essential hypertension; other venous embolism and thrombosis; Wegener's granulomatosis with renal involvement; and acute kidney failure; renal biopsy	Heparin	—	—	—
7	Elevated ESR; severe sepsis with shock; and encephalopathy, unspecified	Immunoglobulin G, methylprednisolone, and enoxaparin	37	281	—
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; and laparoscopy	Enoxaparin and aspirin <sup>d</sup>	—	—	—

CRP, C-reactive protein; —, not applicable.

<sup>a</sup> ESR reference range, 0 to 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 d after a pulmonary embolism diagnosis was 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 low. A majority of pediatric patients with COVID-19–related pulmonary embolism were girls, of adolescent age, hemodynamically stable on presentation, and all survived. These findings may inform clinical decision-making in this patient population.

On the basis of 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. Although the COVID-19 subjects in this study cohort were reported to have a pulmonary embolism, other subjects may not have been identified because of a low index of suspicion and, thereby, lack of testing. The estimated COVID-19 mortality rate is reported to be low in children,<sup>13</sup> but it is unknown whether a subset of subjects with COVID-19–associated pulmonary embolism presented with sudden death and were unable to be identified because of the resuscitation effort. Adult patients may be more at risk from thromboembolic complications when compared with 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>14,15</sup> In addition, this intense inflammation may be focused within the lungs, resulting in local thrombosis (versus embolization from the lower extremities).<sup>16</sup> Further study and data are needed to discern if there are differences in how acute thrombosis presents between adults 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 with younger patients. It is unknown whether the subjects included in this study presented first in an emergency department setting, in which it is possible that an adult-trained provider (vigilant to COVID-19 thromboembolic complications) may have had a higher index

of suspicion compared with pediatric providers. Finally, some subjects did have predisposing 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 >40. In adult COVID-19–positive patients, an elevated BMI is associated with not only severe disease but death.<sup>11</sup> It is thought that obesity contributes to more severe disease because of the proinflammatory state and other associated vascular comorbidities (ie, coronary artery disease).<sup>11</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>17</sup> The data in COVID-19–positive children, however, are limited. It is known that the most common underlying condition in children who require hospitalization because of COVID-19 is obesity.<sup>18</sup> But case-fatality rates in general remain low, even in children with more severe disease.<sup>18</sup> It is unclear why, but children may have a different immune response and infectivity (ie, lower viral load), when compared with adults, which may limit the severity of disease in this population.<sup>15,12</sup> Nevertheless, despite this possibility, caution must be taken because thromboembolic complications typically seen in adult patients with COVID-19 can occur in children.

Before 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 a pulmonary embolism out of 693 who were hospitalized with COVID-19. 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 HCOs that participate in the database retrieval system. Because of database limitations, it is possible not all EHR data were reported (including vital

signs data). We were unable to confirm the diagnosis of pulmonary embolism with imaging data because these reports are not currently reported in the system. Because of a lack of documentation, we were unable to confirm whether 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. Although 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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