Pediatric Radiology

A comparison of pulmonary embolism in pediatric and adult patients with acute COVID-19

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A B S T R A C T

Background: COVID-19 is associated with pulmonary embolism (PE) in adults. However, the rate of PE in pediatric patients with acute COVID-19 evaluated by CT pulmonary angiography (CTPA) has not been evaluated.
Objective: Determine PE rate in pediatric patients with acute COVID-19 and compare to adults.
Materials and methods: A retrospective review of CTPA studies, performed between March 2020 and January 2021 on pediatric patients with acute COVID-19, but not MIS-C, was performed. CTPAs performed on an adult cohort of acute COVID-19 patients during April 2020 were reviewed for comparison. Pediatric and chest radiologists independently reviewed CTPAs of pediatric and adult patients, respectively.
Results: Of the 355 acute COVID-19 pediatric patients treated during the study period, 14 (16.6 ± 4.8y, median-18.5y, 64% female) underwent CTPA. Of the 1868 acute COVID-19 adults treated during two weeks in April 2020, 50 (57.2 ± 17.0y, median-57.0y, 42% female) underwent CTPA. The PE rate was 14% in the pediatric group (2 patients) and 18% in the adult group (9 patients) (p = 1.0). Both pediatric patients with PE were obese, over 18y, and had asthma, diabetes mellitus, or hypertension. No child<18y with acute COVID-19 had PE. In the adult cohort, higher alanine-aminotransferase and D-dimer levels were associated with PE (p = 0.04 and p = 0.004, respectively).
Conclusion: Despite similar PE rates in pediatric and adult patients, PE occurred in acute COVID-19 pediatric patients who were >18y, obese, and had at least 1 comorbidity. Children <18y with COVID-19 did not have PE.

1. Introduction

Since March 2020, Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) has become a pandemic with major global impact. Numerous publications have reported an increased incidence of thromboembolic complications in adults with COVID-19, including pulmonary embolism (PE), stroke, and deep vein thrombosis (DVT).[1–5] This may be explained by the underlying endotheliitis, and clot cascade activation associated with COVID-19.[6] The presence of PEs in adults with COVID-19 imparts a higher risk of mortality compared to patients without COVID-19.[1] During the initial wave of COVID-19, there was a heavy burden of adult and pediatric patients with COVID-19 in the New York City region; our hospital system in the Bronx saw many children with COVID-19.[7]

Fortunately, children affected by COVID-19 are more likely to have a milder illness and lower mortality than adults.[8] A small minority may experience a delayed, severe multi-organ illness that requires hospitalization, Multi-System Inflammatory Syndrome in Children (MIS-C).[9,10] We previously reported a 33% incidence of PE in a small series of children with MIS-C, undergoing computed tomographic evaluation for PE.[11] However, the incidence of PE in children with acute COVID-19 infection has not been reported. In this study, we evaluated the rate of PE in children with acute COVID-19 infection and compared to an adult cohort with COVID-19 infection.

2. Materials and methods

This is a retrospective observational cohort study of computed tomographic pulmonary angiograms (CTPAs) performed on pediatric patients, aged 0–21 years, and adult patients, aged >21 years, with acute COVID-19 in a single hospital system. Studies performed in the emergency department or inpatient units were included. The study period for the pediatric patients was from March 1, 2020, to January 10, 2021, and the adult cohort was narrowed to include consecutive patients from April 1, 2020, to April 15, 2020 during the height of the pandemic and after recognition of the risk of PE in COVID-19 patients was established. The Institutional Review Board approved this study and the waiver of informed consent.

Our system consists of a main hospital and includes a children's hospital and several satellite hospitals with emergency departments in which predominantly adult patients and occasional pediatric patients are treated. Pediatric CTPAs were performed either in the Children's Hospital or in two other hospitals that see both pediatric and adult patients. Adult CTPAs were performed in the main hospital or in one of four other satellite hospitals. CTPAs for the pediatric and adult patients were performed on a 64-slice Lightspeed VCT (General Electric, Chicago, IL) or 64-slice iQon Spectral CT (Philips, Cambridge, MA). Adult CTPAs were also performed on a 16-slice Optima CT540 or Optima CT660 scanner (General Electric, Chicago, IL). Intravenous Iopamidol 76% (Isovue-370, Bracco Diagnostics, Monroe Township, NJ) was used in all cases and administered via hand-injection in infants. In children contrast was administered via hand-injection or power-injection (range: 11–70 mL) at a rate of 2.5 mL/s with bolus-tracking in the pulmonary artery. In adolescents and adults, a fixed volume dose (range: 80–100 mL) was administered at a rate 3.5–4 mL/s by power injector. Initiation of scanning was either based on a fixed 24-s delay or by bolus tracking in the main pulmonary artery.

Patients were identified using our reporting database (Montage Analytics, Powerscribe 360, Nuance Communications, Inc., Burlington, MA) for all CTPAs performed on pediatric and adult patients with COVID-19 in the selected time frames. Based on the electronic medical record (EPIC, Verona, WI), only patients with a positive COVID RT-PCR test within 30 days of the CTPA were included in the study group. Those patients with COVID-19 who underwent an outpatient CTPA or those with MIS-C were excluded. Additional exclusion criteria included hypercoagulable state (including treated DVT or PE) before acute COVID-19 diagnosis or admission and patients who were admitted for other indications and who were incidentally found to have COVID-19 during their admission.

Two fellowship-trained pediatric radiologists (J.K. and M.C.L.) with 7 years' experience each reviewed the pediatric CTPAs. A fellowship-trained chest radiologist (M.S.L.) with 2 years' experience and a chest radiology fellow trainee (G.V.) reviewed the adult CTPAs. The CTPAs for each cohort were evaluated for exam quality, and presence, laterality, and most proximal extent of PEs. The reviewers used their standard diagnostic workstations (Centricity PACS, Radiology RA1000 workstation, General Electric Healthcare, Chicago, IL) and monitors (Bracco Diagnostics, Monroe Township, NJ) and were blinded to the initial findings. Any disagreements were resolved by consensus between the two readers in each cohort.

Medical comorbidities, body mass index, serum laboratory results (alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, C-reactive protein (CRP), and fibrin degradation products (D-dimer)), days in the hospital, days requiring intubation, and administration of prophylactic or therapeutic doses of anticoagulants before the performance of the CTPA were recorded. Reports of venous Doppler ultrasound of the extremities performed during the same admission as the CTPA were also reviewed.

The primary outcome was diagnosis of pulmonary emboli, and secondary outcomes were time to discharge, intubation, or death during the same admission as the CTPA or within 30 days of the CTPA or discharge.

Statistical analyses were performed using R package.[12] Interobserver agreement on presence of PE and adequacy of CTPA study was evaluated by Cohen's kappa analysis or, if not possible, by absolute agreement.[13] For binary demographic and clinical factors, Fisher's Exact Test was used to assess their association with the incidence of PE among the adults. For continuous demographic and clinical factors, the Exact Wilcoxon-Mann-Whitney Test was used to assess their association with the incidence of PE among the adults.[14]

3. Results

From March 1, 2020 to January 10, 2021 there were 355 pediatric patients treated for COVID-19. During the limited study period for the adult cohort (April 1–April 15, 2020) 1868 adult patients were treated in our hospital system for COVID-19.

A total of 14 consecutive pediatric patients (16.6 ± 4.8 years, median: 18.5 years, range: 3–20 years, 64% female) and 50 consecutive adult patients (57.2 ± 17.0 years, median: 57.0 years, range: 28–86 years, 42% female) with a diagnosis of acute COVID-19 who underwent CTPA in the inpatient or emergency room setting were identified (Table 1). Most pediatric patients with acute COVID-19 who underwent CTPA were adolescents or young adults (93%). The rate of PE in the pediatric group was 14% (2 out of 14 patients). The rate of PE in the adult group was 18% (9 out of 50 patients). There was no significant difference between the two groups (p = 1.0). One pediatric patient had 2 CTPAs performed on 2 separate inpatient admissions, which were 12 days apart; the initial CTPA was negative, but the second CTPA on the second admission was positive. In the two pediatric patients with PE, the most proximal extent was in the segmental pulmonary artery for both patients; however, one patient had a unilateral embolus while the other had bilateral emboli. Among the nine adults with PE, the most proximal extent was branch pulmonary artery in 11%, segmental pulmonary artery in 67%, and subsegmental in 22%, and the distribution was unilateral in 89% and bilateral in 11%.

3.1. Indications for CTPA

The indications for CTPA included worsening dyspnea, increased oxygen requirement, chest pain, elevated D-dimer, or any combination of these findings, as well as clinical suspicion for PE.

3.2. Interobserver agreement

The absolute agreement on presence of PE in the pediatric cohort was 87% (13/15 CTPAs). The interobserver agreement for detecting the presence of PE in the adult cohort was kappa = 0.85 (95% CI: 0.65–1.00), indicating excellent agreement. Absolute agreement regarding adequacy of the CTPAs was 80% (12/15) in the pediatric cohort and 100% in the adult cohort.

3.3. US for DVT

In the pediatric cohort, five patients underwent ultrasound examination for DVT, and none had DVT. Approximately one third of the adult patients underwent a dedicated ultrasound study for DVT (17/50), of which 4 (1 had PE, 3 did not have PE) were positive for acute DVT.

3.4. Associated risk factors (Table 1)

Due to the small sample size in the pediatric cohort, there were no statistically significant differences in any of the clinical parameters between the pediatric groups with and without PE or between the adult and pediatric cohorts. In the adult cohort, higher ALT (p = 0.04) and higher serum D-dimer levels (p = 0.004) were associated with PE, and higher age (p = 0.07), higher AST (p = 0.09), and lower albumin (p = 0.08) approached statistical significance for being associated with a PE.

Table 1

Demographic, medical history, laboratory values, and outcomes of pediatric and adult patients with acute COVID-19. In cases where the total number of patients with a value for a variable was less than that group's total, then the total number of patients with those values is listed. P-values between those with and those without PE are provided, as applicable, for comparison between the adult groups with and without PE. There were too few pediatric patients to determine statistical significance between those with and those without PE

Cohort	Pediatric			Adult			
	PE positive	PE negative	Total	PE positive	PE negative	p-value	Total
Number	2	12	14	9	41	–	50
Age, years (mean ± SD)	19.5 ± 0.7	16.1 ± 5.0	16.6 ± 4.8	66.7 ± 11.8	55.1 ± 17.4	0.07	57.2 ± 17.0
Female—number (%)	1 (50%)	8 (67%)	9 (64%)	2 (22%)	19 (46%)	0.27	21 (42%)
Obesity—number (%)	2 (100%)	4 (33%)	6 (43%)	2 (22%)	20 (51%) (n = 39)	0.15	22 (46%) (n = 48)
Number hospitalized – number (%)	2 (100%)	6 (50%)	8 (57%)	9 (100%)	36 (88%)	0.57	45 (90%)
Received therapeutic or prophylactic dosage of anticoagulants before CTPA–number (%)	1 (50%)	3 (25%)	4 (29%)	8 (89%)	26 (63%)	0.24	34 (68%)
Past medical history							
Hypertension— number (%)	1 (50%)	0	1 (7%)	7 (78%)	21 (51%)	0.27	28 (56%)
Diabetes Mellitus— number (%)	1 (50%)	0	1 (7%)	5 (56%)	15 (37%)	0.45	20 (40%)
Sickle cell disease— number (%)	0	1 (8%)	1 (7%)	0	0	–	0
Chronic kidney disease— number (%)	0	0	0	0	3 (7%)	1	3 (6%)
Cancer— number (%)	0	1 (8%)	1 (7%)	1 (11%)	6 (15%)	1	7 (14%)
Asthma— number (%)	1 (50%)	4 (33%)	5 (36%)	0	2 (5%)	1	2 (4%)
Lung disease or sleep apnea— number (%)	0	0	0	2 (22%)	6 (15%)	0.62	8 (16%)
Laboratory values (mean ± SD)							
AST (U/L)	29 ± 8	40 ± 31 (n = 11)	38 ± 29 (n = 13)	114 ± 70	97 ± 145 (n = 39)	0.09	100 ± 134 (n = 48)
ALT (U/L)	58 ± 16	54 ± 62	55 ± 58	114 ± 90	76 ± 140 (n = 40)	0.04	83 ± 132 (n = 49)
Albumin (g/dL)	3.1 ± 1.5	4.4 ± 0.8	4.2 ± 1.0	3.2 ± 0.3	3.5 ± 0.6 (n = 40)	0.08	3.5 ± 0.6 (n = 49)
D-dimer (µg/mL)	0.9 ± 0.2	1.0 ± 1.1 (n = 11)	1.0 ± 1.0 (n = 13)	9.4 ± 5.1 (n = 8)	4.4 ± 5.3 (n = 37)	0.004	5.2 ± 5.6 (n = 45)
C-reactive protein (mg/dL)	4.9 ± 5.9	6.3 ± 9.9 (n = 9)	6.0 ± 9.0 (n = 11)	13.9 ± 9.2	16.5 ± 14.1 (n = 36)	0.81	16.0 ± 13.2 (n = 45)
Outcomes							
Length of hospital stay, days (mean ± SD)	5.5 ± 0.7	14.8 ± 19.9 (n = 6)	12.5 ± 17.4 (n = 8)	15.1 ± 7.6	16.4 ± 19.9 (n = 36)	0.12	16.1 ± 18.1 (n = 45)
Intubated while hospitalized—number (%)	0	2/6 (33%)	2/8 (25%)	2 (22%)	5/36 (14%)	0.61	7/45 (16%)
Deceased—number (%)	0	0	0	2/8 (25%)	5/31 (16%)	0.62	7/39 (18%)

Both pediatric patients with PE were >18 years of age, were obese, and had at least one medical comorbidity (asthma, diabetes mellitus, or hypertension). A high percentage of the pediatric patients and adult patients were obese (43% vs 44%). Approximately one third of the pediatric patients had a history of asthma (36%), and only a few had histories of hypertension (5%) or diabetes mellitus (5%). Few adults had asthma (4%); more than half of the adults had hypertension (56%), and 40% had diabetes mellitus.

There was no statistically significant difference in the rate of obesity or histories of chronic kidney disease, cancer, asthma, heart failure, emphysema, or interstitial lung disease between adult patients with PE and those with no PE (p > 0.1). Serum C-reactive protein (p = 0.81) was not statistically significant between the adult patients with and without PE.

3.5. Anticoagulant therapy

One of the pediatric patients who had PE had been given prophylactic and therapeutic anticoagulants before the CTPA. In the PE negative group, 3/12 (25%) pediatric patients received prophylactic or therapeutic anticoagulation before CTPA.

Almost all (89%) adult patients with PE had received prophylactic or therapeutic doses of anticoagulation before CTPA, as compared to 63% (26/41) in the PE negative group. Being given therapeutic anticoagulants before CTPA approached statistical significance between the adult

groups (44% in PE+ group and 15% in PE (−) group, p = 0.07) but not receiving either therapeutic or prophylactic anticoagulants (89% in PE+ group and 63% in PE (−) group, p = 0.24).

3.6. Outcomes

Of the 14 pediatric patients, 8 were hospitalized and 6 were discharged from the emergency department. Both patients with PE and 50% of those without PE were hospitalized, but only 2 (25%) required intubation. Notably, neither had PE. Length of hospital stay (average ± SD) was 5.5 ± 0.7 days in those with PE and 14.8 ± 19.9 days in those without PE. There were no recorded deaths in the pediatric group of patients for 30 days following discharge from the hospital.

Of the 50 adult patients, 45 were hospitalized, and 5 were discharged from the emergency department. All patients with PE and 88% of those without PE were hospitalized, and 2 (22%) of those with PE and 5 (14%) of those without PE required intubation. Length of hospital stay (average ± SD) was 15.1 ± 7.6 days in those with PE and 16.4 ± 19.9 days in those without PE. There were 7 recorded deaths among the 39 adult patients either during admission or in the 30 day follow up period (18%): 2/8 in the PE positive cohort (25%) and 5/31 in the PE negative cohort (16%).

4. Discussion

Our study adds to the growing body of literature specifically evaluating the rate of PE detected by CTPA in a pediatric cohort with acute COVID-19 who were clinically suspected to have PE. The rate of PE in the pediatric cohort was not significantly different than in adults (14% vs 18%, p = 1.0). This rate does not differ much from the PE detected by CTPA in pediatric patients before the COVID-19 era (14–15.5%).[15] A retrospective multi-institutional observational study reported a 1.2% (8/693) prevalence of PE in hospitalized COVID-19 pediatric patients <18 years of age in a similar timeframe as in our study.[16] However, in the study by Chima et al., PE was only identified by the assigned ICD-10 code, not based on review of images or the radiology report, and the modality with which the diagnosis of PE was made is not clear. In our cohort, no patient below 18 years with diagnosis of COVID-19 developed PE, which suggests that PEs may be unlikely to occur in infants and children with acute COVID-19. This differs from patients <18 years of age with MIS-C, some of whom developed PE.[10,11]

The rate of PE in our COVID-19 adult cohort was similar to the rate of 16.5% presented in a meta-analysis of multiple international studies but far from the 37.1% positive rate reported in one New York City hospital system.[2,3]

Laboratory values for distinguishing those with PE and those without PE were only applicable in the adult cohort. D-dimer values were different between adults with PE and those without PE, as has been reported,[17,18] but unlike our adult groups, D-dimer values overlapped in the pediatric groups with and without PE. CRP values were also not helpful in discriminating adult and pediatric patients at risk for PE, which differs from that previously reported.[8] This may reflect our small-sized cohort. Higher ALT levels were associated with PE in the adult cohort only, which has not been previously reported. This is a new finding that should be further evaluated in larger cohorts.

Except for obesity, co-morbidities varied between the adult and pediatric cohorts. Overall, 43% of our pediatric patients were obese, which is representative of our patient population. Both pediatric patients with PE in our cohort were young adults (19 and 20 years), obese, and had at least one comorbidity (hypertension, diabetes mellitus, or asthma). The most common comorbidity among our pediatric patients was asthma, while in adults, the most common comorbidities in those with PE were hypertension and diabetes mellitus, as has been reported.[3]

Outcomes in the pediatric group were better than in the adult group. Despite just more than half of the pediatric patients being hospitalized, only 2 required intubation (those without PE), and there was no mortality. In contrast, there was a considerable mortality rate in adult patients with and without PE (25% and 16%, respectively).

Our study has limitations. First, the rate of PE in both the pediatric and adult cohorts may have been underestimated as imaging was difficult to perform during the period of heavy burden of COVID-19 in our region when our hospital system was overflowing with critically ill adult patients. Furthermore, as more knowledge was gained about the disease, protocols for imaging COVID-19 patients fluctuated.

Additionally, as 25% of the pediatric patients and 63% of the adult patients in the PE negative groups were given anticoagulants before CTPA to prevent or treat subclinical PEs, PE rates may have been underestimated in both cohorts.

Lastly, though a "pediatric patient" typically is less than 18 years of age, we included patients typically treated by pediatricians, which includes late adolescents and young adults up to age 21. The number of patients <18 years old in our pediatric cohort is small. This limits generalizability of statements regarding the PE rate in children and adolescent patients with acute COVID-19.

5. Conclusion

While the rate of PE was similar between the adult and pediatric groups of COVID-19 patients in our institution, PE occurred in older pediatric patients with obesity and comorbidities similar to those in adults. Children younger than 18 years with acute COVID-19 with respiratory symptoms and high levels of D-dimer did not have a PE. In adults with COVID-19, higher ALT levels and high D-dimer levels correlated with the development of PE detected on CTPA. Larger studies may be warranted for further evaluation of the risk of PE in pediatric patients with acute COVID-19.

Ethics declarations

References

1. Liao S, Shao S, Chen Y, et al. Incidence and mortality of pulmonary embolism in COVID-19: a systematic review and meta-analysis. Crit Care 2020;24:464. https://doi.org/10.1186/s13054-020-03175-z.
2. O'Shea A, Parakh A, Hedgire S, Lee SI. Multisystem assessment of the imaging manifestations of coagulopathy in hospitalized patients with COVID-19. AJR 2021; 216:1088–98. https://doi.org/10.2214/ajr.20.24132.
3. Kaminetzky M, Moore W, Fansiwala K, et al. Pulmonary embolism at CT pulmonary angiography in patients with COVID-19. Radiol Cardiothorac Imaging 2020;2: e200308. https://doi.org/10.1148/ryct.2020200308.
4. Suh YJ, Hong H, Ohana M, et al. Pulmonary embolism and deep vein thrombosis in COVID-19: a systematic review and meta-analysis. Radiology 2021;298:E70–80. https://doi.org/10.1148/radiol.2020203557.
5. Kihira S, Schefflein J, Mahmoudi K, Rigney B, Delman BN, Mocco J, et al. Association of coronavirus disease (COVID-19) with large vessel occlusion strokes: a case-control study. AJR 2021;216:150–6. https://doi.org/10.2214/ajr.20.23847.
6. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120–8. https://doi.org/10.1056/nejmoa2015432.
7. Fernandes DM, Oliveira CR, Guerguis, et al. Severe acute respiratory syndrome coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. J Pediatr 2021;230:23–31. https://doi.org/10.1016/j.jpeds.2020.11.016.
8. Pierce CA, Preston-Hulrburt P, Dai Y, et al. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. Sci Transl Med 2020;12: eabd5487. https://doi.org/10.1126/scitranslmed.abd5487.
9. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York state. N Engl J Med 2020;383:347–58. https://doi.org/10.1056/nejmoa2021756.
10. Blumfield E, Levin T. COVID-19 in pediatric patients: a case series from the Bronx, NY. Pediatr Radiol 2020;50:1369–74. https://doi.org/10.1007/s00247-020-04782-2.
11. Blumfield E, Levin TL, Kurian J, Lee EY, Liszewski MC. Imaging findings in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. AJR 2021;216:507–17. https://doi.org/10.2214/ajr.20.24032.
12. Nakazawa Minato. fsmb: Functions for Medical Statistics Book with some Demographic Data. Version 0.7.0, https://CRAN.R-project.org/package=fmsb; 2019.
13. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74. https://doi.org/10.2307/2529310.
14. Hothorn T, Hornik K, van de Wiel MA, Zeileis A. Implementing a class of permutation tests: the coin package. J Stat Softw 2008;28:1–23. https://doi.org/10.18637/jss.v028.i08.
15. Thacker PG, Lee EY. Pulmonary embolism in children. AJR 2015;204:1278–88. https://doi.org/10.2214/ajr.14.13869.
16. Chima M, Williams D, Thomas NJ, Krawiec C. COVID-19-associated pulmonary embolism in pediatric patients. Hosp Pediatr 2021;11:e90–4. https://doi.org/10.1542/hpeds.2021-005866.
17. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York City health system. JAMA 2020;324:799–801. https://doi.org/10.1001/jama.2020.13372.
18. Korevaar DA, Aydemir I, Winnema MW, et al. Routine screening for pulmonary embolism in COVID-19 patients at the emergency department: impact of D-dimer testing followed by CTPA. J Thromb Thrombolysis 2021;52:1068–73. https://doi.org/10.1007/s11239-021-02508-1.