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Chest X-ray lung imaging features in pediatric COVID-19 and comparison with viral lower respiratory infections in young children

Gustavo Nino MD, MS[1,2] | Jose Molto MD[3] | Hector Aguilar MD[1,2] | Jonathan Zember MD[3] | Ramon Sanchez-Jacob MD[3] | Carlos T. Diez PhD[4] | Pooneh R. Tabrizi PhD[4] | Bilal Mohammed[4] | Jered Weinstock MD[1,2] | Xilei Xuchen MD[1,2] | Ryan Kahanowitch MD[1,2] | Maria Arroyo MD[1,2] | Marius G. Linguraru PhD[4]

[1]Division of Pediatric Pulmonary and Sleep Medicine, Children's National Hospital, Washington, District Columbia, USA

[2]Department of Pediatrics, George Washington University School of Medicine, Washington, District Columbia, USA

[3]Department of Radiology, George Washington University School of Medicine, Washington, District Columbia, USA

[4]Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Hospital, Washington, District Columbia, USA

Correspondence
Gustavo Nino, MD, MS, Division of Pediatric Pulmonology and Sleep Medicine, Children's National Hospital, 111 Michigan Ave NW, Washington, DC 20010, USA.
Email: gnino@childrensnational.org

Marius G. Linguraru, D.Phil, Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Hospital, 111 Michigan Ave NW, Washington, DC 20010, USA.
Email: MLingura@childrensnational.org

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Abstract

Rationale: Chest radiography (CXR) is a noninvasive imaging approach commonly used to evaluate lower respiratory tract infections (LRTIs) in children. However, the specific imaging patterns of pediatric coronavirus disease 2019 (COVID-19) on CXR, their relationship to clinical outcomes, and the possible differences from LRTIs caused by other viruses in children remain to be defined.

Methods: This is a cross-sectional study of patients seen at a pediatric hospital with polymerase chain reaction (PCR)-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ($n = 95$). Patients were subdivided in infants (0–2 years, $n = 27$), children (3–10 years, $n = 27$), and adolescents (11–19 years, $n = 41$). A sample of young children (0–2 years, $n = 68$) with other viral lower respiratory infections (LRTI) was included to compare their CXR features with the subset of infants (0–2 years) with COVID-19.

Results: Forty-five percent of pediatric patients with COVID-19 were hospitalized and 20% required admission to intensive care unit (ICU). The most common abnormalities identified were ground-glass opacifications (GGO)/consolidations (35%) and increased peribronchial markings/cuffing (33%). GGO/consolidations were more common in older individuals and perihilar markings were more common in younger subjects. Subjects requiring hospitalization or ICU admission had significantly more GGO/consolidations in CXR ($p < .05$). Typical CXR features of pediatric viral LRTI (e.g., hyperinflation) were more common in non-COVID-19 viral LRTI cases than in COVID-19 cases ($p < .05$).

Conclusions: CXR may be a complemental exam in the evaluation of moderate or severe pediatric COVID-19 cases. The severity of GGO/consolidations seen in CXR is predictive of clinically relevant outcomes. Hyperinflation could potentially aid clinical assessment in distinguishing COVID-19 from other types of viral LRTI in young children.

KEYWORDS
COVID-19, CXR, Infections: children, viral infection

1 | INTRODUCTION

A pneumonia of unknown cause detected in the city of Wuhan in Hubei province (China) was first reported to the World health Organization (WHO) office in China on December 31, 2019.[1] The disease was then confirmed to be caused by a novel coronavirus (SARS-CoV-2) and later termed coronavirus disease 2019 (COVID-19). This potentially lethal disease spread quickly in the world and was declared a global pandemic in March 2020. Notably, COVID-19 has become the most lethal pandemic in the modern times with millions of deaths attributed to COVID-19 worldwide.[1] Initially, the risk of serious illness or mortality was thought to be of exclusive concern to adults and the elderly. However, new facts have made clear that children are also at risk for hospitalization and severe health complications.[2–6] According to the American Academy of Pediatrics, children make up to 10% of COVID-19 infections, but less than 2% of the literature on the virus has focused on children.[7] Given the lack of understanding of pediatric COVID-19, and the rising rates of childhood infection and hospitalization,[7] more studies focused on the clinical and imaging features of pediatric COVID-19 are critically needed.

Although children with SARS-CoV-2 infections are often asymptomatic or have minimal clinical or lung imaging manifestations,[8–12] there is no doubt they get infected with this virus and can develop severe COVID-19 complications.[2–6] In a recent meta-analysis (n = 1026 children), we reported that COVID-19 lung disease is present in a significant portion of the pediatric population.[2] We found that 64% of lung CT images in PCR-confirmed pediatric COVID-19 cases had abnormalities, primarily characterized by focal ground-glass opacities (GGO) and consolidations.[2] In adult COVID-19 cases, CT scan-based algorithms have recently been developed for lung disease quantification and prediction of life-threatening complications.[13–16] However, chest CT-based risk prediction approaches cannot be readily applied to infants and children due to concerns about sedation requirements, radiation exposure, and costs.[17,18] An additional complicating factor for the clinical and lung imaging evaluation of pediatric COVID-19 cases is that viral lower respiratory tract infections (LRTI) in young children (often termed viral bronchiolitis) are the top cause of pediatric sick visits affecting more than 800,000 children each year in the United States or 20% of the annual birth cohort.[19] Thus, pediatric clinicians face an enormous challenge differentiating early stages of severe SARS-CoV-2 infection from thousands of common cases of viral LRTIs in infants and young children.

We have previously described predictive algorithms using chest X-ray (CXR) in children as a noninvasive approach of lung disease quantification in viral LRTIs.[19–23] However, the specific CXR abnormalities in pediatric COVID-19 and their relation to clinical outcomes remain to be defined. Addressing this gap is important given the age-related differences in the clinical and imaging features of COVID-19[2] and the challenge of differentiating SARS-CoV-2 infections from other types of viral LRTIs in young children. Accordingly, the goal of this study was to conduct an age-based comparison of CXR lung imaging features in pediatric cases of COVID-19 including infants, children, and adolescents. To define the imaging features that identify severe pediatric COVID-19 cases, we linked the presence of GGO/consolidations and other CXR features with clinical outcomes (e.g., hospitalization and critical care admission). We also performed a subanalysis in infants (0–2 years of age) focused on typical lung imaging findings of viral LRTI (e.g., hyperinflation or increased peribronchial markings/cuffing[19–24]) to examine whether these features could potentially help clinicians distinguish COVID-19 cases from common viral LRTIs caused by other respiratory viruses in infants and young children.

2 | METHODS

2.1 | Study design and population

We conducted a single-center, cross-sectional study that included a retrospective collection of lung images and electronic health records (EHRs) of pediatric patients (range: 0–19 years) with positive COVID-19 polymerase chain reaction (PCR) test from March 2020 to June 2020 at Children's National Hospital (CNH), Washington, DC. We only enrolled patients who underwent a CXR for clinical purposes at the time of the initial diagnosis (PCR testing) and had available EHR data to ascertain variables of interest (e.g., clinical presentation and outcomes). This study was approved by the Institutional Review Board of CNH with a waiver of informed consent as this study involved materials (images and medical records) collected solely for nonresearch purposes (clinical indications).

2.2 | Radiological and clinical variables

CXR images were acquired in the posteroanterior or anteroposterior projection. Images were retrospectively reviewed by three fellowship-trained pediatric radiologists. All three radiologists assessed all CXRs independently and consensus was reached if disagreement. For scoring purposes, radiological features were assessed in terms of the type and the severity of abnormality. We included three main categories: GGOs/consolidations, hyperinflation, and increased peribronchial markings/cuffing using standard definitions for the radiographic findings of viral pneumonia.[25,26] These features were scored as binary variables. To assess the severity of GGO/consolidation, we quantified the number of lung zones compromised from 0 to 4 based on right/left and superior/inferior distribution as

described by our team.[23] We also recorded additional features previously reported as rare in pediatric COVID-19, including airway bronchogram, pleural effusion, pleural thickening, bronchiectasis, and widening of the cardio-mediastinal contour. EHR of patients included were reviewed for the following demographic and clinical information: date of admission, age, sex, self-reported race/ethnicity, hospitalization, need for pediatric critical intensive care unit (PICU), need for supplemental oxygen, maximal temperature, wheezing, subcostal retractions, and the presence of multisystem inflammatory syndrome in children (MIS-C) according to published criteria and definition.[27]

2.3 | Statistical analysis

Differences between groups on continuous variables were analyzed using the unpaired *t* test, the Mann–Whitney *U* test, or one-way analysis of variance for continuous variables, as appropriate. Associations between categorical variables were analyzed using the Fisher exact test or χ^2 test. Multivariate analysis (logistic regression) was used to examine the link between the number of lung areas affected and the respiratory outcomes adjusting by age, sex, and race. The data were analyzed with the Minitab Statistical Package V.19. (Minitab, Inc.).

3 | RESULTS

3.1 | Clinical characteristics

We screened a total of 422 patients who tested positive on PCR for COVID-19 during the study period at CNH. We enrolled all pediatric individuals (range: 0–19 years) with positive PCR test for COVID-19 and available CXR ($n = 95$) independently of clinical presentation or comorbidities. Given that our team and others have reported that pediatric COVID-19 radiological manifestations are affected by age,[2–6] we subdivided our study group according to age groups including infants (0–2 years, $n = 27$), children (3–10 years, $n = 27$), and adolescents (11–19 years, $n = 41$).

The mean age of the enrolled individuals was 9 years, 52% were males, and most were Hispanics or Black/African American (61% and 30%, respectively) (Table 1). Overall, 47% of pediatric patients with COVID-19 were hospitalized and 21% required admission to PICU. A total of 19% of patients with COVID-19 needed supplemental oxygen, 5% had wheezing, 12% had subcostal retractions, and 9% were diagnosed with MIS-C. A comparison of all demographic and clinical characteristics according to the age groups is presented in Table 1.

3.2 | Chest X-ray lung imaging features in pediatric COVID-19

A total of 49 (52%) of pediatric patients with COVID-19 had abnormalities observed in CXR (Table 2). Examples of pulmonary lesions in pediatric COVID-19 cases are shown in Figure 1. The most common pulmonary abnormality identified was the presence of GGO/consolidations (35% of all study subjects, Table 2). The severity of GGO/consolidations was influenced by age as only one infant (3.7%) had GGO/consolidations in multiple lung zones (Table 2). Increased peribronchial markings/cuffing was also common (34% of all study subjects, Table 2). This finding was more common in young and school-age children compared with other age groups (Table 2). All other radiological manifestations were rare in pediatric COVID-19, and we did not identify cases of pleural thickening, bronchiectasis or widening of the cardio-mediastinal contour (Table 2).

The severity of GGO/consolidations in the lungs (number of zones affected) was associated with clinical outcomes. Pediatric patients with COVID-19 had a significantly higher number of zones (0–4) if they required oxygen supplementation (1.1 in cases with oxygen vs. 0.29 in cases without oxygen, $p = .006$), hospitalization (0.65 in hospitalized cases vs. 0.3 in not hospitalized cases, $p = .039$), or PICU care (0.87 in PICU cases vs. 0.36 in PICU cases, $p = .046$). After adjusting by age, sex, and race, the presence of multifocal disease (more than one lung zone with GGO/consolidation) was associated with more than six times increased odds of needing oxygen supplementation (adjOR = 6.6, 95% confidence interval [CI]: 1.7–25, $p = .007$). Children with multifocal disease were also more likely to be hospitalized (adjOR = 3.76, 95% CI: 1.1–14.1, $p = .05$) and trended to have higher probability of PICU admission (adjOR = 3.05, 95% CI: 0.83–11, $p = .09$). We did not find differences in the severity of GGO/consolidation in the CXR of pediatric patients with COVID-19 who were diagnosed with MIS-C (mean lung zones affected in MIS-C group = .73 vs. no MIS-C group = .53, $p = .58$). We also did not identify differences in the presence or absence of increased peribronchial markings/cuffing in CXR among individuals requiring hospitalization (yes = 33% vs. no = 30%, $p = .83$), oxygen supplementation (yes = 48% vs. no = 27%, $p = .07$) or advanced support in PICU (yes = 42% vs. no = 28%, $p = .2$).

3.3 | Chest-X-ray features in infants with COVID-19 compared with other causes of viral LRTI

We next compared the CXR features of SARS-CoV-2 in young children (0–2 years) with the CXR findings of non-COVID-19 viral LRTI in a sample of young children (non-COVID-19 group). Subjects in the non-COVID-19 group were selected from a list of hospitalized children in our institution within the same age range (0–2 years). We screened 100 random hospitalized cases during 2018–2019 and included all with available CXR ($n = 68$). The mean age of the enrolled individuals in the non-COVID-19 group was 1.1 years, 60% were males, and 44% Black/African American. These characteristics were comparable to the group of young children with COVID-19 (Group A, 0–2 years, Table 1). Individuals in the non-COVID-19 group had a positive PCR for any of the viruses included in our panel, including rhinovirus (RV, 53%), respiratory syncytial virus (RSV, 34%), human metapneumovirus (HMPV, 17%), adenovirus (12%), influenza A/B (10%), parainfluenza 1–3 (2%), or mixed viral infections (26%). Of note, for this subanalysis we excluded two individuals from the COVID-19 group who also tested (+) for RV and HMPV (COVID19 group

TABLE 1 Demographics and clinical characteristics according to the age groups

	Total	Group A, 0–2 years	Group B, 3–10 years	Group C, 11–19 years
Number of subjects	95	27	27	41
Age at enrollment, years[a]	9 (6.8)	0.8 (0.9)	6.8 (2.7)	16 (2.6)
Male sex, *n* (%)[a]	49 (52)	18 (67)	13 (48)	18 (44)
Significant between-group difference[b]		–	–	–
White/African American/Hispanic/other (%)[c]	9/30/61	11/26/36	15/41/33	2/46/51
Significant between-group difference[b]		-	-	-
Hospitalized, *n* (%)	45 (47)	11 (41)	18 (67)	16 (39)
Significant between-group difference[b]		B	A,C	B
PICU, *n* (%)	20 (21)	4 (15)	10 (37)	6 (15)
Significant between-group difference[b]		-	C	B
MIS-C, *n* (%)	9 (10)	1 (4)	7 (26)	1 (2)
Significant between-group difference[b]		B	A,C	B
Wheezing, *n* (%)	5 (5)	1 (4)	1 (4)	3 (8)
Significant between-group difference[b]		–	–	–
Subcostal retractions, *n* (%)	12 (13)	9 (33)	2 (7)	1 (3)
Significant between-group difference[b]		B,C	A	A
Need supplemental O2, *n* (%)	19 (21)	5 (19)	8 (30)	7 (18)
Significant between-group difference[b]		–	–	–
O2 Saturation, % (room air at presentation)[a]	97.1 (3)	97.2 (4)	96.9 (3)	97.2 (3)
Significant between-group difference[b]	–	–	–	–
Max temperature at presentation, °C[a]	38 (1)	38.2 (1)	38.2 (1)	37.8 (1)
Significant between-group difference[b]		–	–	–

Abbreviations: MIS-C, multisystem inflammatory syndrome in children; PICU, pediatric critical intensive care unit.

[a]Numeric data expressed as mean and standard deviation (*SD*).

[b]$p < .05$ for each pairwise comparison (vs. the group indicated) by one-way analysis of variance with Bonferroni correction for multiple comparisons across the three groups for continuous variables and by the χ^2 test for categorical variables.

[c]African American is the reference group.

0–2 years, $n = 25$). As shown in Figure 2, we found that hyperinflation, a typical finding of viral bronchiolitis,[19–24] was significantly more common in non-COVID-19 viral LRTI cases than in SARS-CoV-2 infection (SARS-CoV-2 infection = 12% vs. other respiratory viruses = 54%, $p < .01$; Figure 2). Increased peribronchial markings/cuffing also trended to be more common in LRTI caused by other respiratory viruses (SARS-CoV-2 infection = 40% vs. other viruses = 60%, $p = .08$; Figure 2). These findings indicate that SARS-CoV-2 infection is less likely to demonstrate typical pulmonary findings of viral LRTIs caused by other respiratory viruses in infants and young children.

4 | DISCUSSION

Our study provides novel and clinically relevant data regarding the specific imaging patterns of pediatric COVID-19 on CXR, their relationship to clinical outcomes, and the possible differences from LRTIs caused by other respiratory viruses in children. The primary findings of this study are[1]: the most common lung abnormalities in pediatric COVID-19 are GGO/consolidations (36%) and increased peribronchial markings/cuffing (32%).[2] The CXR features of pediatric COVID-19 are influenced by age as GGO/consolidations are more common in older individuals, while peribronchial markings/cuffing are more common in younger subjects.[3] Quantification of GGO/consolidations seen in CXR is linked to higher probability of hospitalization and PICU admission.[4] Typical CXR features of pediatric viral LRTI (e.g., hyperinflation) are less common in COVID-19 cases than in viral LRTIs caused by other respiratory viruses.

Due to the global spread of COVID-19, determining the usefulness of different imaging modalities will improve the ability of clinicians to make decisions considering the confluence of clinical and pulmonary imaging findings. In children with SARS-CoV-2 infections, lung abnormalities have been studied primarily using CT images.[2] However, CT is not routinely performed in children to avoid radiation

TABLE 2 Chest X-ray lung imaging features in pediatric COVID-19 according to the age groups

	Total	Group A, 0–2 years	Group B, 3–10 years	Group C, 11–19 years
Number of subjects	95	27	27	41
Abnormal findings, *n* (%)	49 (52)	17 (63)	16 (59)	16 (39)
Significant between-group difference[a]		–	–	–
GGO/consolidations, *n* (%)	33 (35)	7 (26)	12 (44)	14 (34)
Significant between-group difference[a]		–	–	–
Multifocal GGO/consolidations, *n* (%)[b]	16 (17)	1 (3.7)	7 (26)	8 (20)
Significant between-group difference[a]		B,C	A	A
Lung zones affected (0–4)[c]	0.46 (0.8)	0.15 (0.3)	0.72 (1)	0.51 (0.8)
Significant between-group difference[a]		–	–	–
Hyperinflation, *n* (%)	6 (6)	4 (15)	2 (7)	0
Significant between-group difference[a]		C	–	A
Increased peribronchial markings/cuffing, n (%)	32 (34)	12 (44)	13 (48)	7 (17)
Significant between-group difference[a]		C	C	A,B
Air bronchogram, *n* (%)	1 (1)	0	1 (0.04)	0
Significant between-group difference[a]		–	–	–
Pleural effusion, *n* (%)	4 (4)	0	3 (0.1)	1 (0.02)
Significant between-group difference[a]		–	–	–

Abbreviation: GGO, ground-glass opacity.

[a]$p < .05$ for each pairwise comparison (vs. the group indicated) by one-way analysis of variance with Bonferroni correction for multiple comparisons across the three groups for continuous variables and by the chi-square test for categorical variables.

[b]Multifocal defined as >1 GGO/consolidations.

[c]Numeric data expressed as mean and standard deviation (SD).

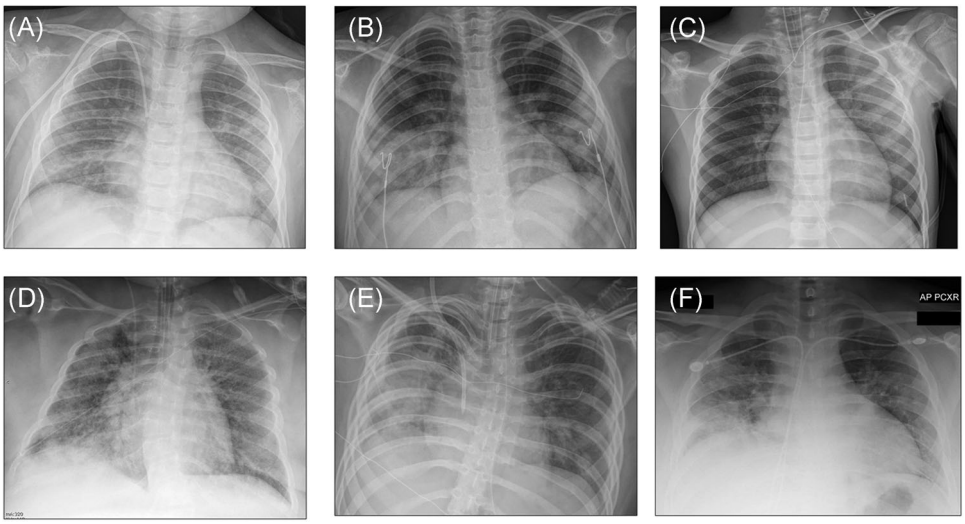

FIGURE 1 Radiological findings in children and adolescents with COVID-19. Images illustrate the presence of GGO/consolidations in different age groups including (A) 5-year-old male, (B) 7-year-old female, (C) 9-year-old male, (D) 17-year-old female, (E) 16-year-old male, and (F) 17-year-old male. COVID-19, coronavirus disease 2019; GGO, ground-glass opacifications

exposure and sedation.[17,18] One of the most clinically used diagnostic modalities to evaluate COVID-19 in the pediatric population is CXR.[26–28] In this study, we found that more than half of all pediatric COVID-19 patients had positive CXR results (Table 2). Other studies including mostly symptomatic patients have reported that CXR abnormalities are found in up to 90% of pediatric COVID-19.[28–30] Despite being quite common, CXR findings in children with COVID-19 have been described in only a few studies.[28–30] Blumfield et al.

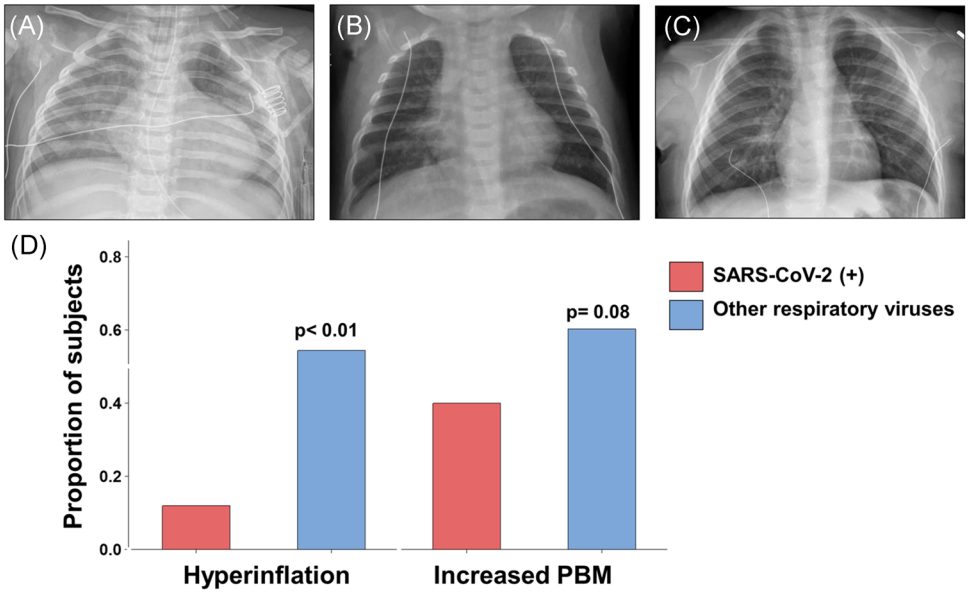

FIGURE 2 Pediatric COVID-19 radiological findings in infants with COVID-19 compared with other causes of viral LRTI. (A) COVID-19 in a 9-month infant demonstrating a GGO/consolidation pattern. (B) RSV bronchiolitis in a 2-month old and (C) in a 17-month old demonstrating typical hyperinflation and increased peribronchial markings (PBM). (C) Comparison of the frequency of hyperinflation and increased PBM in children <2 years of age with COVID-19 ($n = 25$, red bars) versus other viruses ($n = 68$, blue bars). COVID-19, coronavirus disease 2019; GGO, ground-glass opacifications; LRTI, lower respiratory tract infections; RSV, respiratory syncytial virus [Color figure can be viewed at wileyonlinelibrary.com]

reported that children with COVID-19 ($n = 19$) demonstrate parenchymal lung disease with a predominantly perihilar and basilar distribution.[28] Oterino Serrano et al. identified peribronchial cuffing as the most common finding (86.3%) followed by GGOs (50%) among COVID-19 patients aged 0–16 years ($n = 44$).[29] Caro-Dominguez et al. recently published a study of children with COVID-19 ($n = 91$) in which CXRs were primarily characterized by perihilar bronchial wall thickening (58%) and/or airspace consolidation (35%).[30] In our pediatric study ($n = 95$), we also found that GGO/consolidations and peribronchial markings were the most common CXR findings in pediatric COVID-19 (Table 2). Furthermore, we identified age-related differences in lung imaging (Table 2) that are clinically relevant for pediatric COVID-19 and may reflect different pathogenesis of viral LRTI in children compared with older people.

Adults and older children with COVID-19 appear to have alveolar involvement leading to a GGO pattern without bronchial lumen obstruction or air trapping.[2] In contrast, common viral respiratory pathogens in children, such as RSV,[18] are known to cause airway mucosal edema, mucosal plugging, bronchoconstriction, and bronchial lumen obstruction leading to increased perihilar markings and hyperinflation.[18] The latter respiratory syndrome is often referred to as "viral bronchiolitis" and is a leading cause of morbidity and mortality in infants and young children worldwide.[18] The definition of specific characteristics of CXR has become of vital importance in the pediatric population since the symptoms of COVID-19 in children can be confused with viral bronchiolitis. In this study, we found that, unlike viral bronchiolitis, COVID-19 rarely causes lung hyperinflation regardless of the age-group. Furthermore, we found that in young children, pulmonary hyperinflation is much more common in individuals with viral LRTI caused by RSV or other viruses than in cases of SARS-CoV-2 (Figure 2). Although increased peribronchial markings are common in pediatric COVID-19, this feature also appears more frequently in viral bronchiolitis (Figure 2). Taken together, our results indicate that the detection of typical lung imaging patterns of viral bronchiolitis (e.g., hyperinflation) could potentially be used to complement clinical evaluations in pediatric COVID-19 cases.

In studies of adults with COVID-19, lung imaging quantification has been successfully implemented to predict adverse outcomes and severe complications.[13–16] We previously described CXR-based methods to quantify lung disease severity in pediatric viral LRTIs.[19–23] In this study, we examined whether specific CXR abnormalities in pediatric COVID19 are associated with clinical severity. We found that the quantification of GGO/consolidations was predictive of the need for supplemental oxygen during acute infection, the need for hospitalization, and the probability of PICU admission. These data support the notion that CXR analysis can potentially be combined with clinical parameters to indicate whether a child diagnosed with SARS-CoV-2 can be safely discharged or requires further follow-up and treatment. In fact, quantifying CXR abnormalities can help clinicians make critical decisions about the course of therapy and clinical follow-up, which is important for minority and socioeconomically disadvantaged children who carry the highest burden of SARS-CoV-2 infection and complications.[3,5] Indeed, CXRs are readily available in low-income settings and therefore are useful for basic routine evaluations at the initial point of care (e.g., emergency department). CXR-based algorithms could be coupled with additional

clinical information to rapidly assess risk and predict outcomes in children infected with SARS-CoV-2. On the other hand, it is important to emphasize that CXRs should not be overused to search radiological abnormalities in children with suspected SARS-CoV-2 infection without any clinical sign of LRTI. CXR is a complementary exam in the evaluation of moderate or severe COVID-19 and the imaging findings must always be interpreted in combination with clinical signs and symptoms.

The main limitations of the present study are the sample size and the retrospective collection of data. It should be noted that subjects were not systematically evaluated by CXR, and that may have biased results. Furthermore, asymptomatic SARS-CoV-2 infection was not assessed and CXR abnormalities may be present in some of these cases.[31] In addition, it is important to emphasize that our comparison with non-COVID-19 infections only included hospitalized infants (0–2 years old), which represents a subset of severe bronchiolitis cases and not necessarily typical viral LRTIs. Nonetheless, our data provide important evidence that lung imaging may contribute to the clinical evaluations to distinguish SARS-CoV-2 infection from viral bronchiolitis. As schools open, the community-spread of viral infections will be more common, and the rapid differentiation of pediatric COVID-19 from other LRTIs will be more relevant to pediatric clinicians.

In summary, to date, most pediatric studies have focused on lung CT findings, and only a few small studies have reported CXR findings in pediatric COVID-19 cases. Here we provide evidence that CXR abnormalities in pediatric COVID-19 are predictive of clinical outcomes and that in young children they are substantially different from the lung imaging of viral bronchiolitis (e.g., hyperinflation). Future studies are needed to develop robust computational methods to quantify CXR analysis in children, as well as risk predictive models that integrate multidimensional clinical data in pediatric COVID-19 cases. New machine learning technology for the analysis of CXR[32–34] and lung ultrasound, which has become increasingly available to perform bedside monitoring of without radiological risk,[35] can potentially be implemented in children to enable an objective and informed decision on the severity of lung disease and the risk of complications from pediatric COVID-19, resulting in better outcomes and potentially life-saving benefits.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Study design: Gustavo Nino, Marius G. Linguraru, Jose Molto, Jonathan Zember, Ramon Sanchez-Jacob. *Data collection (all) analysis*: Gustavo Nino, Hector Aguilar, Jose Molto, Jonathan Zember, Ramon Sanchez-Jacob, Marius G. Linguraru. *Manuscript drafting, editing, approval*: Gustavo Nino, Jose Molto, Hector Aguilar, Jonathan Zember, Ramon Sanchez-Jacob, Carlos Tor Diez, Pooneh R. Tabrizi, Bilal Mohammed, Jered Weinstock, Xilei Xuchen, Ryan Kahanowitch, Maria Arroyo, and Marius G. Linguraru.

ORCID

Gustavo Nino http://orcid.org/0000-0001-8621-6109

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