Risk Factors for Severe COVID-19 in Children

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Background: There are limited pediatric data regarding severe COVID-19 disease. Our study aims to describe the epidemiology and identify risk factors for severe COVID-19 disease in children.

Methods: This is a retrospective cohort study among children with positive SARS-CoV-2 PCR from March to July 2020 at Children's Hospital Colorado. Risk factors for severe disease were analyzed as defined by hospital admission, respiratory support, or critical care. Univariable and multivariable analyses were conducted.

Results: Among 454 patients identified with SARS-CoV-2, 191 (42.1%) were females, median age 11 years. Fifty-five percent of all patients identified as Hispanic compared with 29% among all hospital visits in 2019 ($P<0.0001$). In multivariable analyses, age 0–3 months or >20 years [adjusted odds ratio (aOR), 7.85; $P<0.0001$ and aOR, 5.1; $P=0.03$, respectively], preterm birth history (aOR, 3.7; $P=0.03$), comorbidities [including immunocompromise (aOR, 3.5; $P=0.004$), gastrointestinal condition (aOR, 2.7; $P=0.009$), diabetes (aOR, 6.6; $P=0.04$), asthma (aOR, 2.2; $P=0.04$)], and specific symptoms at presentation were predictors for admission. Age 0–3 months or >20 years, asthma, gastrointestinal condition, and similar symptoms at presentation were also predictors for respiratory support. Elevated C-reactive protein was associated with the need for critical care with median of 17.7 mg/dL (IQR, 5.3–22.9) versus 1.95 mg/dL (IQR, 0.7–5.5) among patients requiring critical versus no critical care (OR, 1.2; $P=0.02$).

Conclusions: Extremes of age, comorbid conditions, and elevated CRP are predictors of severe disease in children. Findings from this study can inform pediatric providers and public health officials to tailor clinical management, pandemic planning, and resource allocation.

Key Words: SARS-CoV-2, pediatrics, C-reactive protein, health disparities

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More than 1.3 million (12%) COVID-19 cases have been reported in children in the United States as of late November 2020.[1] Several case series have described the clinical characteristics of COVID-19 in pediatric patients [2–8] and suggest milder illness severity in children compared with adults.[4,5,7–11] However, children can present with a wide spectrum of disease ranging from asymptomatic infection to severe respiratory disease and diverse inflammatory complications.[12–14]

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Severe or life-threatening disease occurs in about 10%–20% of adults with COVID-19.[15,16] Increasing age, male sex, and certain comorbid conditions are risk factors for severe COVID-19 in adults.[17–20] Medically complex children may be more likely to require critical care, but most early pediatric studies have not evaluated specific risk factors in further detail.[4,5,7,8,11,21] Much remains to be learned regarding the epidemiologic, demographic, and clinical risk factors for severe COVID-19 illness in children.

Colorado has reported over 36,000 pediatric cases of SARS-CoV-2 as of early December 2020, representing 14% of all cases in the state.[22] Children's Hospital Colorado (CHCO) has established one of the largest single-institution cohorts of pediatric patients with COVID-19 disease in the United States. In this study, we evaluated risk factors for severe disease among children with SARS-CoV-2 infection. Our findings can help pediatric providers and public health stakeholders to tailor clinical management and enhance pandemic planning and resource allocation.

MATERIALS AND METHODS

Study Design and Setting

In this retrospective cohort study, we captured clinical and epidemiologic data from every pediatric patient with SARS-CoV-2 infection at CHCO between March 15 and July 8, 2020. CHCO is the largest pediatric referral center for children in a 7-state region and includes a 434-bed acute care hospital in Aurora, Colorado, a 111-bed acute care hospital in Colorado Springs, Colorado, and 13 additional network locations offering outpatient, specialty, and urgent care. All sites use a common electronic health record (EHR; Epic systems, Verona, WI).

SARS-CoV-2 Testing

SARS-CoV-2 molecular testing was performed on nasopharyngeal swabs, nasopharyngeal washes/aspirates, tracheal aspirates, and bronchoalveolar lavage specimens using 1 of 4 qualitative real-time reverse transcription PCR assays for molecular detection of SARS-CoV-2, all of which have been granted Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA): CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel (CDC, Atlanta, GA), Simplexa COVID-19 Direct assay (DiaSorin Molecular LLC, Cypress, CA), Abbott RealTime SARS-CoV-2 assay (Abbott Molecular Inc., Des Plaines, IL), and Xpert Xpress SARS-CoV-2 test (Cepheid, Sunnyvale, CA). These 4 assays had 100% positive and negative agreement in preclinical studies, demonstrated no cross-reactivity to other human coronaviruses nor to a diverse panel of other common respiratory pathogens.

Study Population

All patients <21 years of age with a positive SARS-CoV-2 molecular test performed at CHCO were included. Patients ≥21 years were included only if they were followed by CHCO for a chronic medical condition. SARS-CoV-2 molecular testing first became available on March 16, 2020, with the first positive patient identified on March 19. During the first 4 weeks, testing was limited to admitted patients with fever and respiratory symptoms who

tested negative for other respiratory viruses on a multiplex panel and symptomatic immunocompromised outpatients. On April 10, 2020, CHCO began testing all patients for SARS-CoV-2 on admission. On April 18, a drive-through test site opened for preprocedural and ambulatory patients. We excluded patients tested outside of the state of Colorado, parents/caregivers of pediatric patients, pregnant women, and health care workers.

Data Collection and Management

We received a daily report from the EHR for every patient with a positive SARS-CoV-2 PCR result in the CHCO system. Demographic and clinical data were abstracted from the EHR in real time and entered into standardized data collection forms developed in REDCap, hosted by the University of Colorado, Denver. EHR data included all available emergency department/urgent care encounters, primary care or specialty provider encounters, in-patient notes and diagnostic test results as available. Race and ethnicity were recorded as documented in the EHR. Body mass index (BMI) was calculated from the most recent height and weight documented in the EHR (measured within the last month for infants <12 months of age, within the last 6 months for those 1–5 years, and within the last year for children >5 years). Those with BMI in the 85th percentile to <95th percentile for age were considered overweight, those ≥the 95th percentile were considered obese, and those ≥120% of the 95th percentile for age were considered severely obese.[23,24] Active comorbid conditions were recorded as documented in the EHR and categorized according to body system. Exposure history, social history, and other risk factors for SARS-CoV-2 acquisition were recorded if documented in the EHR. Results of diagnostic testing were recorded for all inpatients during the period of admission or through symptom resolution, for outpatients from symptom onset through symptom resolution, and for asymptomatic patients if any laboratory testing or imaging was performed on the same day as SARS-CoV-2 PCR testing. Chest radiographs were considered abnormal if the impression included airspace opacity, consolidation, or peribronchial thickening.[25,26] We categorized patients as requiring critical care if they either (1) were admitted to the pediatric intensive care unit (ICU) for symptomatic COVID-19, or (2) were admitted to the neonatal ICU for symptomatic COVID-19 and required a higher level of respiratory support than low-flow nasal cannula. This study was approved by the Colorado Multiple Institutional Review Board with a waiver of informed consent.

Statistical Analysis

We described demographic characteristics using summary statistics. Descriptive data include all eligible patients with positive SARS-CoV-2 testing and are presented as means and standard deviations; medians and interquartile ranges; or counts and proportions. Among all patients with symptomatic SARS-CoV-2 infection, we analyzed the odds of severe outcomes, defined as either (1) hospital admission; (2) need for critical care; or (3) need for respiratory support. Asymptomatic inpatients who were incidentally identified with SARS-CoV-2 were excluded from these analyses. Simple logistic regression was performed for admission, respiratory support, and critical care. Multivariable regression grouped variables to identify demographic predictors, comorbidity predictors, and symptom predictors of the outcomes. Each variable within a group was tested using the following criteria: $P < 0.10$ for entry and $P < 0.05$ to remain. Those variables with >20% of missing data were excluded from the multivariable analyses; these included BMI, laboratory values, baseline oxygen use, and exposure history; all other variables had zero missing values, so no imputation was required. All analyses were 2-tailed and P values <0.05 were considered significant. Multivariable analysis was not done for the outcome of critical care due to small numbers in this category. All analyses were performed in SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Study Population

A total of 454 children and youth median age 11 years (upper limit 23 years), 42.1% female were identified with SARS-CoV-2 infection during the study period (Fig. 1 and Table 1). The vast majority (N = 427, 94%) were identified during expanded testing access in which asymptomatic and symptomatic children could be tested. The number of cases per week during the study period steadily rose and peaked in the second week of July (Fig. 2A). Patients identifying as Latino or Hispanic contributed 54.6% of cases followed by White non-Hispanic (22.9%), and Black non-Hispanic (5.1%) (Table 1). The proportion of patients with SARS-CoV-2 infection with Hispanic ethnicity was significantly higher than the patient population seen at CHCO in 2019 (29%, $P < 0.0001$) (Fig. 2B,C).

Clinical Presentation

Among all SARS-CoV-2 PCR positive patients, 315 (69%) were symptomatic and 80 (18%) were asymptomatic (Fig. 1). The most common symptom at time of positive SARS-CoV-2 PCR result was fever (>100.4 F) (27%), followed by cough (23%), and congestion or rhinorrhea (18%) (Table 1).

The most frequently documented risk factor for COVID-19 exposure was a family member testing positive for SARS-CoV-2 (N = 114, 25%) followed by social gatherings of more than 10 people (N = 85, 19%). Symptomatic cases more commonly reported these risk factors with 98 (31%) reporting a family member with COVID-19 versus 16 (12%) of asymptomatic cases, and 79 (25%) of symptomatic cases reporting a social gathering compared with 6 (4%) of asymptomatic cases. Over a third of symptomatic cases (N = 115, 37%) had no exposure documented, while over two-thirds (N = 98, 71%) of asymptomatic cases had no documented risk factor.

Nearly half (45%) of children with SARS-CoV-2 had at least 1 comorbid condition. The most common types of comorbid conditions identified were pulmonary (16.7%), gastrointestinal (10.8%), and neurologic disease (10.6%) (specific diagnoses in Table, Supplemental Digital Content 1, http://links.lww.com/INF/E299). Of the 211 children with BMI data available, nearly half (45%) were overweight. Of these, 30% were categorized as obese and 11% were considered severely obese.

A total of 85 children (19%) were admitted of whom 66 (78%) were symptomatic. The remaining 19 patients (22%) were admitted for other reasons and were never symptomatic with COVID-19. Among the 66 symptomatic admitted children, 55% required respiratory support and 17% required critical care (Fig. 1). A total of 40 admitted patients had chest radiographs performed on admission, of which 25 (63%) had abnormal findings. Five of 39 (13%) admitted patients tested with a respiratory pathogen panel had coinfection with an additional respiratory tract virus.

Treatment and Outcomes

Of the patients admitted for symptomatic COVID-19, median length of stay was 3.0 days (IQR, 1–6). Among the 36 children requiring respiratory support, 26 (72%) received low-flow oxygen via nasal cannula, 2 (6%) high-flow oxygen via nasal cannula, 5 (14%) noninvasive positive pressure ventilation, 2 (6%) intubation/ventilation, and 1 (3%) ECMO. Eight patients (12%) received COVID-directed antiviral therapy and 10 (15%) received

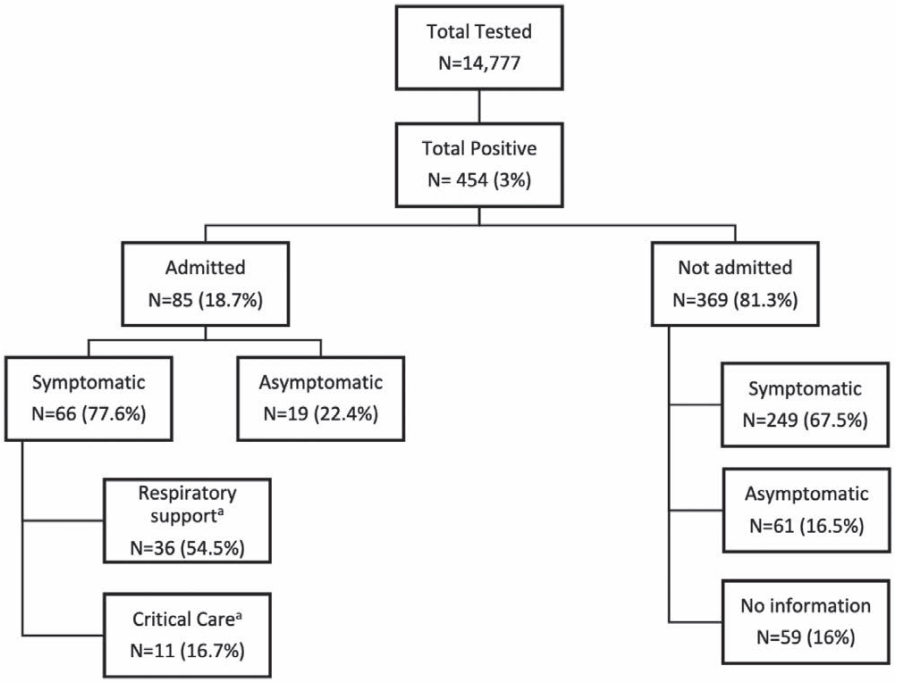

FIGURE 1. Summary of patients with SARS-CoV-2 at Children's Hospital Colorado (March 19–July 8, 2020). *Patients with respiratory support and critical care may overlap; percentages are of symptomatic admitted patients.

COVID-19-directed immunomodulatory therapy (Table, Supplemental Digital Content 2, http://links.lww.com/INF/E299). Five patients required readmission for COVID-19–related disease, 1 of whom was readmitted twice. Three patients (4.5%) had complications of venous thromboembolism. One medically complex patient with multiple preexisting comorbidities died due to complications of ECMO.[27] All other patients were discharged from the hospital.

Risk Factors for Severe COVID-19

Risk factors associated with symptomatic hospital admission were evaluated (Table 2). There were no sex or race/ethnicity differences associated with need for admission. As compared with children age 11–15 years, infants 0–3 months [odds ratio (OR), 7.86; $P<0.001$] and young adults >20 years (OR, 5.09; $P=0.03$) were more likely to require admission. Comorbid conditions emerged as significant predictors of admission. The presence of any comorbid condition increased the odds of admission (OR, 2.73; $P=0.0003$), and the odds increased with each additional comorbidity (OR, 1.36; $P<0.0001$). Several categories of comorbidities increased the risk of admission including pulmonary, gastrointestinal, endocrine, neurologic, and psychiatric disease; immunocompromising conditions; and history of preterm birth (Table 2). Specific diagnoses including asthma, obstructive sleep apnea, baseline oxygen requirement, and diabetes or prediabetes were all significantly associated with admission. Obesity resulted in more than twice the odds of admission and severe obesity almost 5 times the odds. Symptoms of respiratory infection (including fever, cough, shortness of breath) were predictive of admission as were diarrhea, abdominal pain, and fatigue.

Many of the same risk factors were associated with need for respiratory support and critical care (Tables 2 and 3). Demographic risk factors associated with the need for respiratory support included Hispanic ethnicity, age 0–3 months or >20 years. Comorbid conditions including obesity and asthma were associated with the need for respiratory support, as were several symptoms of respiratory infection at the time of SARS-CoV-2 testing. The need for critical care was associated with comorbid obstructive sleep apnea (OR, 4.7; $P=0.04$) as well as elevated C-reactive protein (CRP) at time of admission (Table 3). Median CRP among patients requiring critical care was 17.7 mg/dL (IQR, 5.3–22.9) compared with those not requiring critical care (1.95 mg/dL; IQR, 0.7–5.5). For every 1-unit increase in CRP at admission, the odds of requiring critical care increased by 1.2 ($P=0.02$). Other laboratory values at admission were not associated with the need for critical care, including white blood cell count, absolute neutrophil count, platelet count, procalcitonin, ferritin, D-dimer, and lactate.

In multivariable analyses (Table 2), age 0–3 months or >20 years remained significant demographic predictors of need for admission and respiratory support. Comorbid conditions that remained significantly associated with admission included immunocompromising conditions, gastrointestinal disease, history of preterm birth, asthma, and diabetes/prediabetes, while only gastrointestinal disease and asthma remained significantly associated with respiratory support. Fever, shortness of breath, and vomiting at presentation remained significantly associated with admission and respiratory support.

DISCUSSION

In this large pediatric cohort identified at a tertiary referral hospital network, we identify important factors associated with severe COVID-19 in children. Importantly, we focused on symptomatic children who were admitted, required respiratory support or received critical care to better inform health care providers of the population at risk for severe COVID-19. In our cohort, 1 in 5 symptomatic children with SARS-CoV-2 infection required

TABLE 1. Characteristics of Children and Youth Positive for SARS-CoV-2 by Admission Status

	Critical Care		Hospital Admission		
	Symptomatic Only		Symptomatic Only		Total
	Yes	No	Yes	No	All
	(n = 11)	(n = 55)	(n = 66)*	(n = 369)	(n = 454)†
	n (%)	n (%)	n (%)	n (%)	n (%)
Child's age (yrs), median (IQR)	16.0 (12–17)	9.0 (0.2–16)	12 (1.7–17)	10 (3–16)	11 (3–11)
Age category					
0–3 mo	1 (9.1)	14 (25.4)	15 (22.7)	14 (3.8)	30 (6.6)
4–12 mo	0 (0)	0 (0)	0 (0)	21 (5.7)	22 (4.8)
1–5 yrs	0 (0)	10 (18.2)	10 (15.1)	93 (25.2)	107 (23.6)
6–10 yrs	1 (9.1)	6 (10.9)	7 (10.6)	57 (15.4)	65 (14.3)
11–15 yrs	1 (9.1)	10 (18.2)	11 (16.7)	84 (22.8)	101 (22.2)
16–20 yrs	6 (54.5)	13 (23.6)	19 (28.8)	94 (25.5)	119 (26.2)
>20 yrs	2 (18.2)	2 (3.6)	4 (6.1)	6 (1.6)	10 (2.2)
Gender					
Male	6 (54.5)	32 (59.3)	39 (59.1)	211 (57.2)	262 (57.7)
Female	5 (45.5)	22 (40.7)	27 (40.9)	157 (42.5)	191 (42.1)
Other	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Race/ethnicity					
White—not Hispanic/Latino	1 (9.1)	12 (21.8)	13 (19.7)	87 (23.6)	104 (22.9)
Black/African American—not Hispanic/Latino	1 (9.1)	2 (3.6)	3 (4.5)	18 (4.9)	23 (5.1)
Hispanic/Latino	8 (72.7)	32 (58.2)	40 (60.6)	196 (53.1)	248 (54.6)
Other	1 (9.1)	9 (16.4)	10 (15.1)	68 (18.4)	79 (17.4)
Body mass index‡					
Normal weight	3 (37.5)	15 (46.9)	19 (46.3)	90 (58.1)	116 (55.0)
Overweight	5 (62.5)	17 (53.1)	22 (53.7)	65 (41.9)	95 (45.0)
Obese	4 (50.0)	15 (46.9)	19 (46.3)	40 (25.8)	63 (30.1)
Severely Obese	0 (0)	11 (34.4)	11 (26.8)	11 (7.1)	24 (11.4)
Symptomatic COVID-19					
Yes	11 (100.0)	55 (100.0)	66 (100.0)	249 (67.5)	315 (69.4)
No	0 (0)	0 (0)	0 (0)	62 (16.8)	80 (17.6)
Unknown	0 (0)	0 (0)	0 (0)	58 (15.7)	59 (13.0)
Specific symptoms					
Fever (>100.4 F)	9 (81.2)	34 (61.8)	43 (65.1)	81 (21.9)	124 (27.3)
Chills	1 (9.1)	5 (9.1)	6 (9.1)	11 (3.0)	17 (3.7)
Cough (new or above baseline)	7 (63.6)	23 (41.8)	30 (45.5)	72 (19.5)	102 (22.5)
Congestion/runny nose	1 (9.1)	16 (29.1)	17 (25.8)	65 (17.6)	82 (18.1)
Shortness of breath	7 (63.6)	12 (21.8)	19 (28.8)	18 (14.9)	37 (8.1)
Chest pain/tightness	2 (18.2)	7 (12.7)	9 (13.6)	12 (3.2)	21 (4.6)
Loss of taste/smell	0 (0)	5 (9.1)	5 (7.6)	18 (4.9)	23 (5.1)
Headache	0 (0)	12 (21.8)	12 (18.2)	38 (10.3)	50 (11.0)
Myalgia	3 (27.3)	7 (12.7)	10 (15.1)	32 (8.7)	42 (9.2)
Joint pain	0 (0)	2 (3.6)	2 (3.0)	1 (0.3)	3 (0.7)
Sore throat	2 (18.2)	6 (10.9)	8 (12.0)	37 (10.0)	45 (9.9)
Wheezing	0 (0)	4 (7.3)	4 (6.1)	1 (0.3)	5 (1.1)
Hypoxia	4 (36.4)	10 (18.2)	14 (21.2)	0 (0)	14 (3.1)
Diarrhea	0 (0)	7 (12.7)	7 (10.6)	13 (3.5)	20 (4.4)
Abdominal pain	1 (9.1)	12 (21.8)	13 (19.7)	10 (2.7)	23 (5.1)
Vomiting	3 (27.3)	12 (21.8)	15 (22.7)	12 (3.2)	27 (5.9)
Seizure	0 (0)	2 (3.6)	2 (3.0)	2 (0.5)	4 (0.9)
Rash	1 (9.1)	1 (1.8)	2 (3.0)	9 (2.4)	11 (2.4)
Conjunctivitis	0 (0)	1 (1.8)	1 (1.5)	2 (0.5)	3 (0.7)
Altered mental status	0 (0)	2 (3.6)	2 (3.0)	0 (0)	2 (0.4)
Fatigue	2 (18.2)	15 (27.3)	17 (25.8)	24 (6.5)	41 (9.0)
Other	7 (63.6)	27 (47.3)	33 (50.0)	33 (8.9)	66 (14.5)
Respiratory support					
Yes	10 (90.9)	26 (47.3)	36 (54.5)	0 (0)	43 (9.5)
No	1 (9.1)	29 (52.7)	30 (45.5)	350 (94.8)	392 (86.3)
Unknown	–	–	–	19 (5.2)	19 (5.2)

*Includes only symptomatic children, including critical care admissions.
†Includes 19 admitted patients who were asymptomatic.
‡Categories may overlap, for example, overweight (BMI >85th %ile) includes obese (>95th %ile) and severely obese (>120% of 95th %ile).

hospital admission. Clear risk factors for admission or need for respiratory support emerged, including extremes of age, obesity, and other underlying comorbidities. Elevated CRP was predictive of the need for critical care.

Our findings support demographic trends identified in literature from the United States and elsewhere.[3–5] Similar to other studies, we found a bimodal age distribution among those requiring admission with young infants and young adults most likely to be

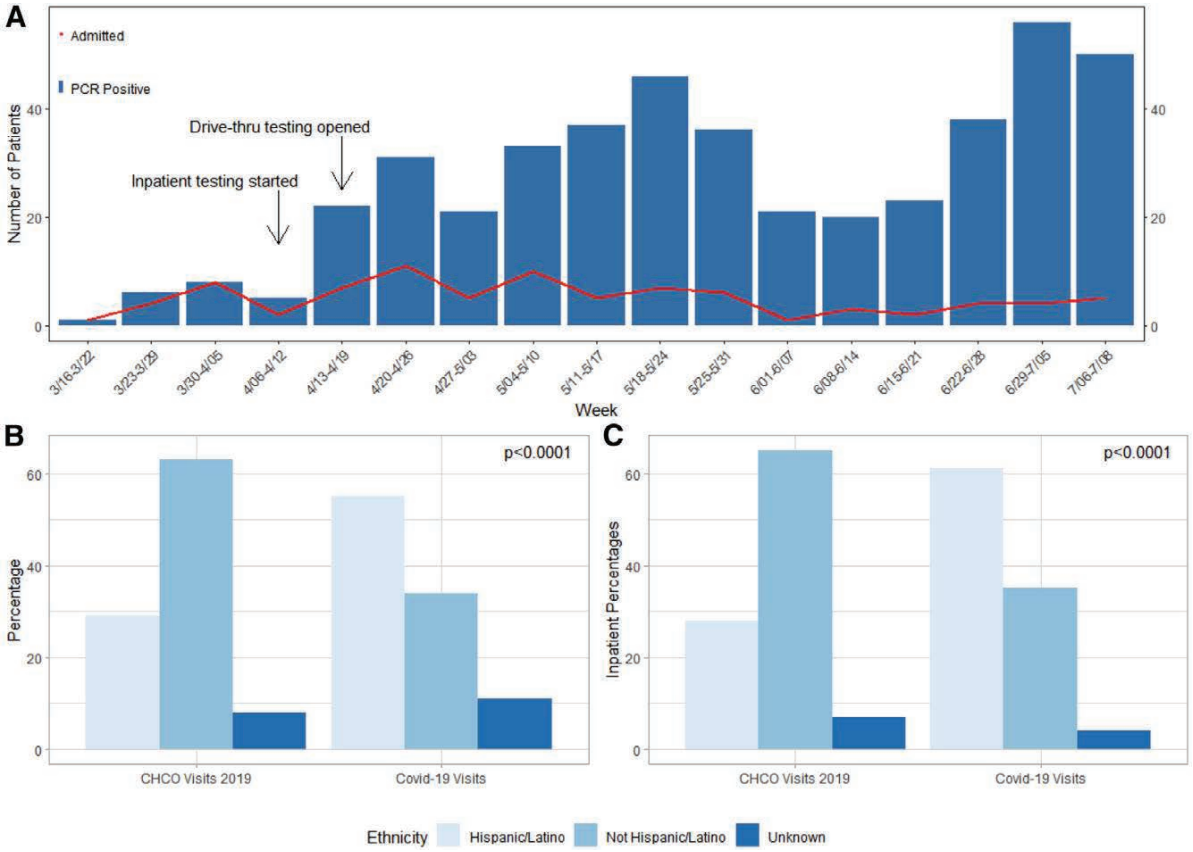

FIGURE 2. A, Number of SARS-CoV-2 positive children and youth by week. Red line indicates number admitted. B, Comparison of ethnicity of patients with COVID-19 versus usual patient visits at Children's Hospital Colorado in 2019. C, Comparison of ethnicity of patients admitted with COVID-19 versus patients admitted to Children's Hospital Colorado in 2019.

admitted.[5,11,28] We detected a male predominance among children and youth testing positive, but sex was not predictive of severe COVID-19. Nearly 70% of the children in our cohort with positive SARS-CoV-2 PCR were symptomatic, with 21% requiring hospital admission and 3.5% critical care, similar to other pediatric reports.[4,5] Encouragingly, lengths of stay were relatively short and the need for intubation/mechanical ventilation or ECMO remained rare, consistent with the published literature on children with COVID-19.[4,29,30]

We identified an ethnic disparity with overrepresentation of children identifying as Hispanic as compared with the usual population served by CHCO and the general population of Colorado.[11,31] Racial and ethnic disparities have emerged as a key predictor of COVID-19 in adults and children throughout the United States.[9,32–37] In Colorado, while Hispanic and Latino populations make up 21.7% of Colorado's residents, they have represented 36.9% of COVID-19 cases.[22] Our study demonstrates an even larger disparity among Hispanic children and youth in Colorado. Additionally, Hispanic ethnicity was associated with higher odds of respiratory support in univariable analysis but not in multivariable analyses, indicating that some other factor among Hispanic children may have been confounding this association. Several factors may be contributing to these ethnic and racial disparities, which deserve further exploration, including increased prevalence of medical comorbidities, high-density housing, stigma, and barriers to accessing medical care.[38–41]

Our study investigated risk factors for severe COVID-19 defined as need for admission, respiratory support, or critical care. We identified particular comorbid conditions, including asthma, diabetes and obesity, to be predictive of more severe pediatric COVID-19. There is growing evidence that children with comorbidities (in particular medically complex patients) may be at higher risk of hospitalization and critical care.[3,5,42] One-third of children in our study who were categorized as having a gastrointestinal comorbidity required a gastrostomy or jejunostomy tube, which supports the association of severe COVID-19 with medical complexity. Among children with endocrine disease, one-third had diabetes mellitus or prediabetes, which are related to COVID-19 outcomes in adult studies.[43,44] Obesity has emerged as an independent risk factor for severe COVID-19 in adults, with increasing evidence of the same trend in children.[11,17–20,45,46] Several factors may be contributing to this association, including increased prevalence of other medical comorbidities, obesity-related complications, race/ethnicity, and socioeconomic or behavioral factors.[46,47] Thirty percent of patients in our cohort with BMI data were obese, which is alarming as the obesity rate reported in children with 10–17 years of age in Colorado is only 10.7%.[48] Obesity and severe obesity in our cohort were significantly associated with admission and respiratory

TABLE 2. Univariable and Multivariable Predictors of Admission and Respiratory Support in Children With COVID-19

	Admitted						Respiratory Support					
			Univariable		Multivariable				Univariable		Multivariable	
Demographic Predictors	Yes n=66(%)	No n=369(%)	OR (95% CI) Yes vs. No	*P*	OR‡ (95% CI)	*P*	Yes n=36(%)	No n=399(%)	OR (95% CI) Yes vs. No	*P*	OR‡ (95% CI)	*P*
Age												
0–3 mo	15 (23)	14 (4)	7.86 (3.0–20.4)	<.0001	7.86 (3.0–20.4)	<.0001	7 (19)	22 (6)	4.59 (1.4–14.6)	0.01	4.59 (1.4–14.6)	0.01
4–12 mo	0 (0)	21 (6)	0.17 (0.01–3.2)	0.24			0 (0)	21 (5)	0.32 (0.02–6.3)	0.45		
1–5 yrs	10 (15)	93 (25)	0.83 (0.3–2.0)	0.67			4 (11)	99 (25)	0.62 (0.2–2.2)	0.45		
6–10 yrs	7 (11)	57 (15)	0.96 (0.4–2.6)	0.93			3 (8)	61 (15)	0.78 (0.2–3.0)	0.72		
16–20 yrs	19 (29)	94 (25)	1.52 (0.7–3.3)	0.30			13 (36)	100 (25)	1.85 (0.7–4.9)	0.22		
> 20 yrs	4 (6)	6 (2)	5.1 (1.2–20.7)	0.03	5.1 (1.2–20.7)	0.03	3 (8)	7 (2)	6.43 (1.4–30.4)	0.02	6.43 (1.4–30.4)	0.02
11–15 yrs	11 (16)	84 (23)	Reference		Reference		6 (17)	89 (22)	Reference		Reference	
Age (continuous)	–	–	1.00 (1.0–1.0)	0.99			–	–	1.03 (0.9–1.1)	0.26		
Gender												
Male vs. female	39 (59)	211 (57)	1.07 (0.6–1.8)	0.83			19 (8)	231 (92)	0.81 (0.4–1.6)	0.99		
Race/ethnicity												
African Am./Black	3 (4)	19 (5)	1.12 (0.3–4.3)	0.87			1 (5)	20 (95)	2.45 (0.2–28.3)	0.47		
Hispanic	40 (61)	196 (53)	1.37 (0.7–2.7)	0.37			28 (12)	208 (88)	6.60 (1.5–28.2)	0.01		
Other	10 (15)	68 (18)	0.98 (0.4–2.4)	0.97			5 (6)	73 (94)	3.36 (0.6–17.8)	0.15		
White (non-Hispanic)	13 (20)	87 (24)	Reference	–			2 (2)	98 (98)	Reference	–		
Household size (continuous)	–	–	1.12 (0.9–1.3)	0.22			–	–	1.23 (0.9–1.5)	0.06		
Baseline Oxygen*												
Yes vs. No	9 (14)	3 (1)	13.03 (3.3–50.9)	0.0002			–	–	–	–		
Body mass index*†												
BMI (continuous)	–	–	1.02 (1.01–1.04)	0.0016			–	–	1.02 (1.0–1.03)	0.03		
Overweight	22 (25)	65 (75)	1.60 (0.8–3.2)	0.18			13 (15)	74 (85)	1.57 (0.7–3.7)	0.31		
Obese	19 (32)	44 (68)	2.48 (1.2–5.1)	0.01			12 (20)	47 (80)	2.66 (1.1–6.3)	0.03		
Severely obese	11 (50)	11 (50)	4.8 (1.9–12.1)	0.0009			6 (22)	16 (78)	3.25 (1.1–9.4)	0.03		
Any comorbidities	23 (35)	219 (59)	2.73 (1.6–4.7)	0.0033			12 (33)	169 (42)	2.72 (1.3–5.6)	0.01		
Type Comorbidities												
Pulmonary disease	21 (32)	52 (14)	2.85 (1.6–5.2)	0.0006			14 (39)	59 (15)	3.67 (1.8–7.6)	0.0004		
Asthma	16 (24)	37 (10)	2.87 (1.5–5.5)	0.0017	2.17 (1.1–4.5)	0.04	11 (31)	42 (11)	3.74 (1.7–8.1)	0.0009	3.1 (1.4–6.9)	0.007
Sleep Apnea	10 (15)	19 (5)	3.29 (1.5–7.4)	0.0042			5 (14)	24 (6)	2.52 (0.9–7.1)	0.08		
Gastrointestinal disease	17 (26)	28 (8)	4.22 (2.2–8.3)	<0.0001	2.71 (1.3–5.7)	0.0087	11 (31)	34 (9)	4.72 (2.1–10.4)	0.0001	3.96 (1.7–9.0)	0.001
Endocrine disease	13 (20)	10 (3)	8.81 (3.7–21.1)	<0.0001			7 (19)	16 (4)	5.78 (2.2–15.2)	0.0004		
Diabetes/prediabetes	5 (8)	2 (.5)	15.03 (2.9–79.2)	0.0014	6.6 (1.1–39.8)	0.04	2 (6)	5 (1)	4.6 (0.9–24.8)	0.07		
Cardiac disease	3 (5)	12 (3)	1.42 (0.4–4.2)	0.60			2 (6)	13 (3)	1.75 (0.4–8.1)	0.47		
Neurologic disease	11 (17)	31 (8)	2.18 (1.0–4.6)	0.04		0.004	7 (19)	35 (9)	2.51 (1.0–6.1)	0.04		
Immunocompromising	13 (20)	18 (5)	4.78 (2.2–10.3)	<0.0001	3.47 (1.5–8.1)		4 (11)	27 (7)	1.72 (0.6–5.2)	0.34		
Psychiatric disease	7 (11)	15 (4)	2.80 (1.1–7.2)	0.03			4 (11)	18 (5)	2.65 (0.8–8.3)	0.09		
Develop/Behavioral	9 (14)	29 (8)	1.85 (0.8–4.1)	0.13			6 (17)	32 (8)	2.29 (0.9–5.9)	0.09		
Otolaryngolic disease	2 (3)	25 (7)	0.43 (0.1–1.9)	0.26			1 (3)	26 (7)	0.41 (0.05–3.1)	0.39		
Preterm birth	5 (8)	8 (2)	3.70 (1.2–11.7)	0.03	3.48 (1.1–11.4)	0.04	2 (6)	11 (3)	2.10 (0.4–9.7)	0.36		
Symptom Predictors												
Fever (>100.4F)	43 (65)	81 (22)	6.65 (3.8–11.7)	<.0001	3.82 (2.0–7.4)	<.0001	25 (69)	99 (25)	6.89 (3.3–14.5)	<.0001	5.26 (2.2–12.5)	0.0002
Chills	6 (9)	11 (3)	3.26 (1.2–9.1)	0.02			5 (14)	12 (3)	5.20 (1.7–15.7)	0.0035		
Cough	30 (45)	72 (20)	3.44 (2.0–6.0)	<.0001			21 (58)	81 (20)	5.50 (2.7–11.1)	<.0001		
Congestion/runny nose	17 (26)	65 (18)	1.62 (0.9–3.0)	0.12			11 (31)	71 (18)	2.03 (0.9–4.3)	0.07		
Shortness of breath	19 (29)	18 (5)	7.88 (3.9–16.1)	<.0001	6.32 (2.8–14.3)	<.0001	17 (47)	20 (5)	16.96 (7.7–37.5)	<.0001	15.71 (6.4–38.5)	<.0001
Chest pain/tightness	9 (14)	12 (3)	4.70 (1.9–11.7)	0.0008			9 (25)	12 (3)	10.75 (4.2–27.7)	<.0001		
Loss of taste/smell	5 (8)	18 (5)	1.60 (0.6–4.5)	0.37			3 (8)	20 (5)	1.72 (0.5–6.1)	0.40		
Headache	12 (18)	38 (10)	1.94 (1.0–3.9)	0.07			7 (19)	43 (11)	2.00 (0.8–4.8)	0.12		
Myalgia	10 (15)	32 (9)	1.88 (0.9–4.0)	0.11			7 (19)	35 (9)	2.51 (1.0–6.1)	0.04		
Sore throat	8 (12)	37 (10)	1.24 (0.5–2.8)	0.61			5 (14)	40 (10)	1.45 (0.5–3.9)	0.47		
Diarrhea	7 (11)	13 (4)	3.25 (1.2–8.5)	0.02			3 (8)	17 (4)	2.04 (0.6–7.3)	0.27		
Abdominal pain	13 (20)	10 (2)	8.81 (3.7–21.1)	<.0001	3.01 (1.1–8.5)	0.04	7 (19)	16 (4)	5.78 (2.2–15.2)	0.0004	3.88 (1.4–11.1)	0.01
Vomiting	15 (23)	12 (3)	8.75 (3.9–19.7)	<.0001	3.89 (1.5–10.2)	0.0059	9 (25)	18 (5)	7.06 (2.9–17.2)	<.0001		
Fatigue	17 (26)	24 (5)	4.99 (2.5–9.9)	<.0001			11 (31)	30 (8)	3.78 (1.04–13.7)	0.04		
Other	33 (50)	33 (9)	10.18 (5.6–18.6)	<.0001	5.17 (2.6–10.2)	<.0001	16 (44)	50 (13)	5.58 (2.7–11.5)	<.0001	2.63 (1.1–6.1)	0.02

*Variable excluded from multivariate analysis due to missing data.

†Body mass index categorized as overweight (>85%ile), obese (>95%ile), and severely obese (120% of the 95%ile). Categories may overlap (e.g., overweight includes obese and severely obese).

‡For variables with more than 2 categories only significant Wald statistics are shown in multivariate analysis.

TABLE 3. Association of Demographic, Clinical, and Laboratory Predictors With Symptomatic Critical Care Compared With Noncritical Care Admissions in Children With COVID-19

	Yes	No	Odds ratio	
	N = 11	N = 55		
	N (%)	N (%)	(95% confidence interval)	*P*
Age				
0–3 mo	1 (9)	14 (25)	0.7 (0.06–8.7)	0.80
4–12 mo	0 (0)	0 (0)	–	–
1–5 yrs	0 (0)	10 (18)	0.3 (0.01–10.7)	0.53
6–10 yrs	1 (9)	6 (11)	1.6 (0.1–21.9)	0.72
16–20 yrs	6 (55)	13 (24)	3.4 (0.4–25.6)	0.24
>20 yrs	2 (18)	2 (4)	7.0 (0.5–99.3)	0.15
11–15 yrs	1 (9)	10 (18)	reference	
Age (continuous)			1.12 (1.01–1.25)	0.03
Gender				
Male vs. female	6 (55)	32 (58)	0.83 (0.2–3.0)	0.77
Race/Ethnicity				
Black non-Hispanic	1 (9)	2 (4)	6.0 (0.3–140.0)	0.26
Hispanic	8 (73)	32 (58)	3.0 (0.3–26.6)	0.32
Other	1 (9)	9 (16)	1.3 (0.07–24.3)	0.85
White non-Hispanic	1 (9)	12 (22)	reference	
Household size			1.2 (1.0–1.3)	0.03
Comorbidities				
Pulmonary	6 (29)	15 (71)	3.2 (0.8–12.1)	0.09
Asthma	4 (25)	12 (75)	2.0 (0.5–8.2)	0.31
Sleep Apnea	4 (40)	6 (60)	4.7 (1.0–20.8)	0.04
GI	4 (24)	13 (76)	1.8 (0.5–7.3)	0.38
Endocrine	4 (31)	9 (69)	2.9 (0.7–12.1)	0.14
Diabetes or prediabetes	1 (20)	4 (80)	1.3 (.1–12.6)	0.84
Neurology	3 (28)	8 (73)	2.2 (0.5–10.1)	0.31
Immunocompromising	1 (8)	12 (92)	0.4 (0.04–3.1)	0.35
Prematurity	1 (20)	4 (80)	1.3 (0.1–12.6)	0.84
Number of comorbidities			1.19 (0.9–1.6)	0.21
Symptoms				
Fever (>100.4 F)	9 (81.2)	34 (61.8)	2.78 (0.5–14.1)	0.22
Cough	7 (63.6)	23 (41.8)	2.44 (0.6–9.3)	0.19
Congestion/runny nose	1 (9.1)	16 (29.1)	0.24 (0.3–2.1)	0.20
Shortness of breath	7 (63.6)	12 (21.8)	6.27 (1.6–25.0)	0.01
Chest pain/tightness	2 (18.2)	7 (12.7)	1.52 (0.3–8.5)	0.63
Diarrhea	0 (0)	7 (12.7)	———	———
Abdominal pain	1 (9.1)	12 (21.8)	0.36 (0.04–3.1)	0.35
Vomiting	3 (27.3)	12 (21.8)	1.34 (0.31–5.9)	0.69
Fatigue	2 (18)	15 (27)	0.60 (0.1–3.1)	0.53
Baseline oxygen use	2 (18)	7 (13)	11.24 (0.2–7.5)	0.82
Body mass index*				
Overweight	5 (45)	17 (31)	1.57 (0.3–7.7)	0.58
Obese	4 (36)	15 (27)	1.20 (0.3–5.6)	0.82
Severely obese	0 (0)	11 (20)	———	———
Laboratory values	Median (IQR)	Median (IQR)		
C-reactive protein	17.7 (5.3–22.9)	1.95 (0.7–5.5)	1.22 (1.03–1.43)	0.02
White blood cell	6.1 (4.0–8.1)	7.3 (5.5–12.8)	0.91 (0.78–1.06)	0.23
Absolute neutrophil count	4.1 (2.7–6.3)	3.4 (2.4–6.1)	0.98 (0.79–1.21)	0.83
Platelet count	169.5 (102–265)	232 (216–325)	0.99 (0.99–1.00)	0.09
Procalcitonin	0.3 (0.2–3.1)	0.1 (0.1–0.5)	1.15 (0.55–2.37)	0.71
Ferritin	315 (309–453)	86 (58–673)	1.00 (1.00–1.00)	0.98
D-dimer	2.85 (1.5–6.8)	0.8 (0.5–1.0)	7.17 (0.69–74.89)	0.1
Lactate	4.8 (1.8–6.1)	1.25 (1.1–2.2)	1.06 (0.85–1.33)	0.61

*Body mass index categorized as overweight (>85%ile), obese (>95%ile), and severely obese (120% of the 95%ile). Categories may overlap (e.g., overweight includes obese and severely obese).

support; however, due to missing data, we were not able to include this variable in the multivariable analyses.

Importantly, elevated CRP emerged as a clear risk factor for children requiring critical care, consistent with 2 other US studies in children.[3,49,50] A history of sleep apnea also emerged as a risk factor for critical care in our cohort. However, we did not identify any other demographic or clinical factors associated with the need for critical care, possibly due to inadequate power to detect these associations given the small number of symptomatic critical care admissions in our cohort.

This is one of the largest pediatric cohorts reported with over 400 children and youth. We performed a comprehensive analysis of factors associated with more severe COVID-19 in children, including demographics, comorbid conditions, and symptoms at

presentation. We focused on symptomatic children to ensure that children admitted for other reasons did not bias findings. Further, we performed a multivariable analysis to address potential confounders. Our data were limited to those available in the EHR; while sufficient data were available for most participants, limited information was available for some outpatient cases. Changing recommendations on whom to test may also have impacted our findings; the early focus on testing only symptomatic admitted children may have skewed our cohort toward the inclusion of more ill children, but only 6.9% of our cohort were diagnosed while testing was restricted, so we do not anticipate this created significant bias.

In conclusion, we found that age, comorbid conditions, and elevated CRP are risk factors for severe COVID-19 in children. Findings from this study can inform pediatric providers and public health officials to tailor clinical management, pandemic planning, and resource allocation. Counseling of families with children with comorbid medical conditions should include a discussion of increased risk of severe illness. Health care providers may consider screening for CRP at admission to inform the need for critical care. Additional research should evaluate approaches to mitigate these risk factors and explore associations of ethnicity and COVID-19 in children.

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