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Age-dependent association of obesity with COVID-19 severity in paediatric patients

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Summary

Background: Limited research has addressed the obesity–COVID-19 severity association in paediatric patients.

Objective: To determine whether obesity is an independent risk factor for COVID-19 severity in paediatric patients and whether age modifies this association.

Methods: SARS-CoV-2-positive patients at NYU Langone Health from 1 March 2020 to 3 January 2021 aged 0–21 years with available anthropometric measurements: weight, length/height and/or body mass index (BMI). Modified log-Poisson models were utilized for the analysis. Main outcomes were 1) hospitalization and 2) critical illness (intensive care unit [ICU] admission).

Results: One hundred and fifteen of four hundred and ninety-four (23.3%) patients had obesity. Obesity was an independent risk factor for critical illness (adjusted risk ratio [ARR] 2.02, 95% CI 1.17 to 3.48). This association was modified by age, with obesity related to a greater risk for critical illness in adolescents (13–21 years) [ARR 3.09, 95% CI 1.48 to 6.47], but not in children (0–12 years). Obesity was not an independent risk factor for hospitalization for any age.

Conclusion: Obesity was an independent risk factor for critical illness in paediatric patients, and this association was modified by age, with obesity related to a greater risk for critical illness in adolescents, but not in children. These findings are crucial for patient risk stratification and care.

KEYWORDS
adolescent health/medicine, COVID-19, obesity, paediatric obesity, paediatrics

1 | INTRODUCTION

As cases of the coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), continue to increase across the globe, more than 136.1 million infections have been reported as of 12 April 2021.[1] Of these, more than 31.2 million are in the United States, with the vast majority of the cases being reported in adults.[2,3] Over 3.54 million infection cases have been reported within the paediatric population since the onset of the pandemic.[4] While severe SARS-CoV-2 illness is less common in the paediatric population than that in adults, hospitalization, intensive care admission and even death have occurred in children and adolescents.[5–7] It is therefore crucial to identify risk factors that may influence the severity of COVID-19 in paediatric patients.

In addition to age, sex, hypercholesterolemia and diabetes,[8,9] obesity has been well established as an independent risk factor for adverse COVID-19 outcomes in adults.[10,11] However, limited research has addressed the association of obesity with COVID-19 severity in

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children and adolescents.[12] The few paediatric studies conducted thus far have several limitations, such as utilizing small sample sizes,[5,7] and examining this association without controlling for other confounding variables, such as age and sex.[5,7,13] Age-related differences in infection susceptibility,[14] transmission[15] and incidence[16] have been previously noted. However, no study thus far has explored possible age-related differences in the association of obesity with COVID-19 severity in paediatric patients. Because obesity affects nearly 20% of the paediatric population in the United States,[17] a deeper understanding of the association between obesity and COVID-19 severity is crucial. Moreover, it is important to know whether the possible associated risk within the paediatric population is age-dependent, to support paediatric risk stratification of developing increased COVID-19 severity and decision-making regarding patient care.

Our work aims to address these gaps in the literature and establish whether obesity is an independent risk factor for COVID-19 severity in children and adolescents by 1) analysing a relatively large paediatric cohort, 2) conducting multivariable analyses and 3) stratifying our cohort by age to explore if age is an effect modifier of the association between obesity and COVID-19 severity.

2 | METHODS

2.1 | Data source and inclusion criteria

The study site was NYU Langone Health (NYULH), a network including 260 outpatient and 6 inpatient sites located in Manhattan, Brooklyn and Long Island, New York. We identified all patients with a positive result for the SARS-CoV-2 virus polymerase chain reaction (PCR) test from the assay of sputum, nasopharyngeal swab or oropharyngeal swab specimens between 1 March 2020 and 3 January 2021. Electronic medical records of these patients, including data from previous inpatient and outpatient encounters in the health system, were retrieved from our integrated electronic health records (EHR) system (Epic Systems, Verona, WI). The inclusion criteria for the final cohort were 1) positive SARS-CoV-2 PCR test, 2) age between 0 and 21 years, and 3) anthropometric measurements (weight, length/height and/or body mass index [BMI]) availability in the EHR. This study was approved by the NYU Institutional Review Board.

2.2 | Study outcomes

For this study, COVID-19 illness outcomes were defined as 1) hospitalization and 2) critical illness, defined as requiring admission to an intensive care unit (ICU), due to COVID-19. Hospitalization and critical illness were defined as due to COVID-19 if the patient had 1) a positive SARS-CoV-2 PCR test and 2) COVID-19-related symptoms and/or complications described in the literature,[3,6] such as fever, shortness of breath, cough, acute respiratory distress syndrome (ARDS), pneumonia and acute respiratory failure, as recorded in the medical history, problem list, hospital problem or diagnosis fields in the EHR.

2.3 | Exposure variables

All variables were selected based on published literature[3,6,18] and clinical knowledge. The following were extracted for each patient: 1) age at the time of COVID-19 testing, categorized as children (0–12 years old) and adolescents (13–21 years old) (13 years was used as the starting age cutoff for the adolescent group because it is the mean age when menarche, which is the most definitive sign of puberty in females,[19] occurs in the United States [i.e., 12.5 years in 2013–2017][20]; given the scarcity of studies regarding pubertal onset in males due to the absence of an easily identifiable marker such as menarche,[21] we also designated 13 years as the starting age cutoff for males in our study.); 2) race/ethnicity, recorded as non-Hispanic white, non-Hispanic black, Asian, Hispanic, other race or unknown; 3) male and female sex; 4) anthropometric measures: weight, length or height and/or BMI (weight in kilograms divided by height in meters squared); 5) presence of comorbidities, defined as history of asthma, any malignancy or metastatic solid tumour, congenital malformations, deformations, and chromosomal abnormalities (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]: Q00-Q99), and/or diabetes, as noted in the medical history, problem list, hospital problem or diagnosis fields in the EHR; 6) initial vital signs taken in the emergency department (ED) or during hospital admission, including oxygen saturation and temperature; 7) initial laboratory results taken in the ED or during hospital admission, including C-reactive protein (CRP), creatinine, d-dimer, ferritin, lymphocyte count, procalcitonin and troponin; 8) hospitalization and ICU length of stay in days; 9) COVID-19-related symptoms, including fever, shortness of breath, cough, nausea/vomiting, diarrhoea and abdominal pain; 10) COVID-19-related complications, including ARDS, pneumonia, acute respiratory failure, myocarditis, multisystem inflammatory syndrome in children (MIS-C) and acute kidney injury; and 11) oxygen delivery device required during hospitalization and/or ICU admission, including high flow nasal cannula, bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP), and/or invasive mechanical ventilation (IMV).

Obesity status was determined for each patient using the US Centers for Disease Control and Prevention (CDC) growth charts.[22] Sex-specific weight-for-length (WFL) for children <24 months (2 years) or BMI (for children and adolescents 24 months [2 years]–240.99 months [20.08 years]) z-scores were calculated for all patients with available length or height in the medical record; weight-for-age (WFA) z-scores were utilized for those with missing length or height measurements. BMI ≥95th percentile was designated as obese. Similarly, the 95th percentile cutoff point was also utilized for 1) WFL, as it was found to be that CDC WFL ≥95th percentile, World Health Organization (WHO) WFL 97.7th percentile, and WHO BMI 97.7th percentile provided similar prevalence of overweight,[23,24] and for 2) WFA, as it was found to be that the 95th percentile is a viable cutoff point if the goal is to identify children and adolescents with an overweight status with high certainty (i.e., high positive predictive value [PPV]), as well as with reasonable sensitivity.[25] For adolescents aged >240.99 months (20.08 years), CDC adult BMI categories were used to define obesity status, with ≥30.0 kg/m^2 designated as obese.[26]

2.4 | Statistical analysis

Continuous variables were compared in patients with any of our COVID-19 study outcomes (hospitalization and critical illness) versus patients without those outcomes using t test or Mann–Whitney U test, depending on data distribution. χ^2 test or Fisher's exact test was utilized for comparisons involving categorical variables. In addition, COVID-19-related clinical presentations were compared between paediatric patients with obesity versus without obesity using the same descriptive statistics methods.

Generalized estimated equation with a log-link function and a Poisson distribution was used to quantify the association between obesity and hospitalization and critical illness due to COVID-19. Risk ratios and 95% confidence intervals (CIs) for obesity were adjusted for age (dichotomized as 0–12 group and 13–21 group), sex and presence of comorbidity; other variables listed above were excluded to prevent model saturation and multicollinearity (i.e., variables with variance inflation factor [VIF] > 2 were excluded from our models). For the critical illness multivariable model, one hospitalized patient, whose final outcome has not yet been determined (i.e., hospital discharge, critical illness or mortality), was excluded. We set a two-tailed α of 0.05 to be statistically significant. To formally test whether the association of obesity and COVID-19 severity is modified by age, an interaction term between obesity and age (obesity*age) was included in our modified log-Poisson models. Given that homogeneity tests (e.g., regression-based test of interaction) generally have very low statistical power, which may lead to undetected cases of true heterogeneity, the significance level for the interaction term was increased to 0.10.[27–29]

We also conducted five sensitivity analyses: model 1) given the limitations in the predictive value of WFA in categorizing weight status,[25] we excluded 74 patients with missing length or height measurements in the EHR; model 2) given the limitations of WFL in assessing adiposity,[30] we excluded 67 patients aged <24 months (2 years) with length measurement available in the EHR (the remaining 27 patients aged <24 months [2 years] had missing length measurement in the EHR, and therefore, WFA was utilized for categorizing their weight status); model 3) given that adult BMI categories do not account for age or sex, we excluded 90 patients aged >240.99 months (20.08 years); model 4) given the limitations of using WFA, WFL and adult BMI, we excluded 231 patients whose obesity status was determined using WFA, WFL or adult BMI categories, thereby limiting the cohort to 263 patients whose obesity status was determined using sex-specific BMI-for-age; model 5) given that anthropometric measures are not routinely taken during all COVID-19 testing encounters, we excluded 97 patients whose only available anthropometric measurements in the EHR were from inpatient or outpatient encounters in the health system >30 days pre- or post-COVID-19 testing encounter; model 6) given that the US CDC and US Department of Health and the Food and Drug Administration define the starting age for adolescence as 12 years,[16,31] we utilized 12 as the starting age cutoff for the adolescent group, thereby redefining our age groups as children (0–11 years) and adolescents (12–21 years).

All data extraction and data processing were performed with *pandas* modules in Python, version 3.7.3; descriptive statistics were performed using the library *gtsummary*, and multivariable analyses were performed using the geeglm function within the library *geepack*[32] in R, version 3.6.1.

3 | RESULTS

3.1 | Overall cohort characteristics

Of 12 998 patients with positive SARS-CoV-2 PCR test identified in our health system during the study period, 565 were paediatric patients aged 0–21 years; among these, 71 did not have anthropometric measurements available in the EHR, resulting in a final cohort of 494 paediatric patients (Figure S1). Of this population, 280 (56.7%) were adolescents; 236 (47.8%) were male; 129 (26.1%) were non-Hispanic white; 40 (8.1%) were non-Hispanic black; and 214 (43.3%) were Hispanic; 115 (23.3%) had obesity; and 168 (34.0%) had pre-existing comorbidities other than obesity (asthma, any malignancy or metastatic solid tumour, congenital malformations, deformations, and chromosomal abnormalities, and/or diabetes). Hospitalization was required for 130/494 (26.3%) and critical illness, requiring admission to the ICU, occurred for 48/494 (9.7%). At the time of analysis, there had been two reported fatalities and five patients had not yet been discharged from the hospital.

3.2 | Factors associated with hospitalization and critical illness: unadjusted analyses

Among the full cohort, hospitalized patients were more likely to be younger (median 12.0 years vs. 15.0 years; $p = 0.006$) and to have comorbidities of asthma (37/130 [28.5%] vs. 64/364 [17.6%]; $p = 0.008$), any malignancy or metastatic solid tumour (12/130 [9.2%] vs. 9/364 [2.5%]; $p = 0.001$) and diabetes (5/130 [3.8%] vs. 2/364 [0.5%]; $p = 0.016$), than non-hospitalized patients. At presentation, hospitalized patients also had lower oxygen saturation (mean 96.8% vs. 97.9%; $p \leq 0.001$) and higher temperature (mean 37.7°C vs. 37.4°C; $p = 0.001$) (Table 1). Patients with critical illness were more likely to have asthma (17/48 [35.4%] vs. 84/445 [18.9%]; $p = 0.007$), any malignancy or metastatic solid tumour (8/48 [16.7%] vs. 13/445 [2.9%]; $p = <0.001$), diabetes (4/48 [8.3%] vs. 3/445 [0.7%]; $p = 0.002$) and to be male (33/48 [68.8%] vs. 203/445 [45.6%]; $p = 0.002$). These patients also had, at presentation, lower oxygen and elevated inflammatory markers, such as creatinine (median 0.7 mg/dL vs. 0.6 mg/dL; $p = 0.005$), than patients who were not critically ill (Table 2). Non-Hispanic white (34/130 [26.2%] vs. 95/364 [26.1%]), non-Hispanic black (15/130 [11.5%] vs. 25/364 [6.9%]), Asian (6/130 [4.6%] vs. 5/364 [1.4%]) and Hispanic (59/130 [45.4%] vs. 155/364 [42.6%]) race/ethnicity were associated with hospitalization ($p = 0.014$), but not with critical illness. Congenital malformations, deformations and chromosomal abnormalities were not associated with hospitalization nor critical illness.

TABLE 1 Characteristics of the cohort by age group and hospitalization status

Characteristics[a]	Full cohort (Total = 494)			0–12 Age group (Total = 214)			13–21 Age group (Total = 280)		
	Non-hospitalized *N* = 364	Hospitalized *N* = 130	*p*-value	Non-hospitalized *N* = 146	Hospitalized *N* = 68	*p*-value	Non-hospitalized *N* = 218	Hospitalized *N* = 62	*p*-value
Age (years), median (IQR)	15.0 (6.0–19.0)	12.0 (0.2–18.0)	0.006	3.0 (0.0–8.0)	1.0 (0.0–7.0)	0.016	19.0 (17.0–20.0)	18.0 (17.0–20.0)	0.96
Age grouping			0.016			—			—
0–12	146 (40.1)	68 (52.3)		—	—	—	—	—	—
13–21	218 (59.9)	62 (47.7)		—	—	—	—	—	—
Race/Ethnicity			0.014			0.056			0.18
Non-hispanic white	95 (26.1)	34 (26.2)		29 (19.9)	17 (25.0)		66 (30.3)	17 (27.4)	
Non-hispanic black	25 (6.9)	15 (11.5)		9 (6.2)	6 (8.8)		16 (7.3)	9 (14.5)	
Asian	5 (1.4)	6 (4.6)		1 (0.7)	4 (5.9)		4 (1.8)	2 (3.2)	
Hispanic	155 (42.6)	59 (45.4)		70 (47.9)	32 (47.1)		85 (39.0)	27 (43.5)	
Other race	26 (7.1)	8 (6.2)		9 (6.2)	4 (5.9)		17 (7.8)	4 (6.5)	
Unknown	58 (15.9)	8 (6.2)		28 (19.2)	5 (7.4)		30 (13.8)	3 (4.8)	
Sex			0.069			0.21			0.42
Female	199 (54.7)	59 (45.4)		67 (45.9)	25 (36.8)		132 (60.6)	34 (54.8)	
Male	165 (45.3)	71 (54.6)		79 (54.1)	43 (63.2)		86 (39.4)	28 (45.2)	
WFL/WFA/ BMI z-score[b], median (IQR)	0.7 (−0.2–1.5)	0.5 (−0.8–1.7)	0.13	0.5 (−0.6–1.4)	0.1 (−1.3–1.2)	0.075	0.8 (0.1–1.5)	1.1 (0.3–2.0)	0.65
Obesity status[c]			0.17			0.98			0.025
Non-obese	285 (78.3)	94 (72.3)		120 (82.2)	56 (82.4)		165 (75.7)	38 (61.3)	
Obese	79 (21.7)	36 (27.7)		26 (17.8)	12 (17.6)		53 (24.3)	24 (38.7)	
Any comorbidity[d]			0.001			0.57			<0.001
Absent	255 (70.1)	71 (54.6)		96 (65.8)	42 (61.8)		159 (72.9)	29 (46.8)	
Present	109 (29.9)	59 (45.4)		50 (34.2)	26 (38.2)		59 (27.1)	33 (53.2)	
Asthma			0.008			0.15			0.008
Absent	300 (82.4)	93 (71.5)		127 (87.0)	54 (79.4)		173 (79.4)	39 (62.9)	
Present	64 (17.6)	37 (28.5)		19 (13.0)	14 (20.6)		45 (20.6)	23 (37.1)	
Any malignancy or metastatic solid tumour			0.001			0.67			<0.001
Absent	355 (97.5)	118 (90.8)		141 (96.6)	67 (98.5)		214 (98.2)	51 (82.3)	
Present	9 (2.5)	12 (9.2)		5 (3.4)	1 (1.5)		4 (1.8)	11 (17.7)	

TABLE 1 (Continued)

Characteristics[a]	Full cohort (Total = 494)			0–12 Age group (Total = 214)			13–21 Age group (Total = 280)		
	Non-hospitalized *N* = 364	Hospitalized *N* = 130	*p*-value	Non-hospitalized *N* = 146	Hospitalized *N* = 68	*p*-value	Non-hospitalized *N* = 218	Hospitalized *N* = 62	*p*-value
Congenital malformations, deformations and chromosomal abnormalities			0.33			0.93			0.32
Absent	315 (86.5)	108 (83.1)		113 (77.4)	53 (77.9)		202 (92.7)	55 (88.7)	
Present	49 (13.5)	22 (16.9)		33 (22.6)	15 (22.1)		16 (7.3)	7 (11.3)	
Diabetes			0.016			–			0.007
Absent	362 (99.5)	125 (96.2)		146 (100.0)	68 (100.0)		216 (99.1)	57 (91.9)	
Present	2 (0.5)	5 (3.8)		0 (0)	0 (0)		2 (0.9)	5 (8.1)	
SpO2[e], mean (SD)	97.9 (1.3)	96.8 (3.4)	<0.001	98.0 (1.2)	96.8 (3.8)	0.014	97.9 (1.4)	96.8 (2.9)	0.010
Temperature (°C)[e], mean (SD)	37.4 (0.9)	37.7 (1.1)	0.001	37.9 (1.1)	37.9 (1.1)	0.96	37.1 (0.6)	37.6 (1.1)	0.002

Abbreviations: BMI, body mass index; ICD-10-CM, international classification of diseases, tenth revision, clinical modification; IQR, interquartile range; SD, standard deviation; WFA, weight-for-age; WFL, weight-for-length.

[a]Presented as N (%), unless otherwise specified.

[b]Calculated for children and adolescents up to 240.99 months (20.08 years) old.

[c]Non-obese: WFL/WFA percentile <95th percentile (< 24.0 months [2 years]), BMI/WFA < 95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI < 30 (> 240.99 months [20.08 years]); obese: WFL/WFA percentile ≥95th percentile (< 24.0 months [2 years]), BMI/WFA ≥95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI ≥30 (> 240.99 months [20.08 years]).

[d]Asthma, any malignancy or metastatic solid tumour, congenital malformations, deformations, and chromosomal abnormalities (ICD-10-CM codes Q00-Q99), and/or diabetes.

[e]SpO2 measured for 70.6% of the patients in the full cohort; temperature measured for 70.9% of the patients in the full cohort..

TABLE 2 Characteristics of the cohort by age group critical illness status

Characteristics[b]	Full cohort (Total = 493)[a]			0–12 Age group (Total = 213)			13–21 Age group (Total = 280)		
	Non-Critical *N* = 445	Critical *N* = 48	*p*-value	Non-critical *N* = 193	Critical *N* = 20	*p*-value	Non-critical *N* = 252	Critical *N* = 28	*p*-value
Age (years), median (IQR)	15.0 (4.0–19.0)	15.0 (6.0–17.2)	0.48	2.0 (0.0–8.0)	3.0 (0.0–7.0)	0.73	19.0 (17.0–20.0)	17.0 (16.8–19.0)	0.061
Age grouping			0.82			–			–
0–12 Age group	193 (43.4)	20 (41.7)		–	–	–	–	–	–
13–21 Age group	252 (56.6)	28 (58.3)		–	–	–	–	–	–
Race/Ethnicity[c]			0.11			–			–
Non-hispanic white	118 (26.5)	11 (22.9)		42 (21.8)	4 (20.0)		76 (30.2)	7 (25.0)	
Non-hispanic black	33 (7.4)	7 (14.6)		11 (5.7)	4 (20.0)		22 (8.7)	3 (10.7)	
Asian	8 (1.8)	2 (4.2)		3 (1.6)	1 (5.0)		5 (2.0)	1 (3.6)	
Hispanic	191 (42.9)	23 (47.9)		91 (47.2)	11 (55.0)		100 (39.7)	12 (42.9)	
Other race	31 (7.0)	3 (6.2)		13 (6.7)	0 (0.0)		18 (7.1)	3 (10.7)	
Unknown	64 (14.4)	2 (4.2)		33 (17.1)	0 (0.0)		31 (12.3)	2 (7.1)	
Sex			0.002			0.092			0.007
Female	242 (54.4)	15 (31.2)		86 (44.6)	5 (25.0)		156 (61.9)	10 (35.7)	
Male	203 (45.6)	33 (68.8)		107 (55.4)	15 (75.0)		96 (38.1)	18 (64.3)	
WFL/WFA/ BMI z-score[d], median (IQR)	0.6 (−0.3–1.4)	1.3 (−0.1–1.9)	0.19	0.5 (−0.8–1.4)	0.8 (−1.1–1.5)	0.88	0.8 (0.1–1.5)	1.8 (0.6–2.3)	0.002
Obesity status[e]			0.002			0.76			<0.001
Non-obese	350 (78.7)	28 (58.3)		159 (82.4)	16 (80.0)		191 (75.8)	12 (42.9)	
Obese	95 (21.3)	20 (41.7)		34 (17.6)	4 (20.0)		61 (24.2)	16 (57.1)	
Any comorbidity[f]			<0.001			0.058			0.004
Absent	304 (68.3)	21 (43.8)		128 (66.3)	9 (45.0)		176 (69.8)	12 (42.9)	
Present	141 (31.7)	27 (56.2)		65 (33.7)	11 (55.0)		76 (30.2)	16 (57.1)	
Asthma			0.007			0.10			0.051
Absent	361 (81.1)	31 (64.6)		166 (86.0)	14 (70.0)		195 (77.4)	17 (60.7)	
Present	84 (18.9)	17 (35.4)		27 (14.0)	6 (30.0)		57 (22.6)	11 (39.3)	
Any malignancy or metastatic solid tumour			<0.001			0.45			<0.001
Absent	432 (97.1)	40 (83.3)		188 (97.4)	19 (95.0)		244 (96.8)	21 (75.0)	
Present	13 (2.9)	8 (16.7)		5 (2.6)	1 (5.0)		8 (3.2)	7 (25.0)	
Congenital malformations, deformations and chromosomal abnormalities			0.97			0.40			0.49
Absent	381 (85.6)	41 (85.4)		151 (78.2)	14 (70.0)		230 (91.3)	27 (96.4)	
Present	64 (14.4)	7 (14.6)		42 (21.8)	6 (30.0)		22 (8.7)	1 (3.6)	

TABLE 2 (Continued)

Characteristics[b]	Full cohort (Total = 493)[a]			0–12 Age group (Total = 213)			13–21 Age group (Total = 280)		
	Non-Critical *N* = 445	Critical *N* = 48	*p*-value	Non-critical *N* = 193	Critical *N* = 20	*p*-value	Non-critical *N* = 252	Critical *N* = 28	*p*-value
Diabetes			0.002			—			0.002
Absent	442 (99.3)	44 (91.7)		193 (100.0)	20 (100.0)		249 (98.8)	24 (85.7)	
Present	3 (0.7)	4 (8.3)		0 (0)	0 (0)		3 (1.2)	4 (14.3)	
SpO2[g], mean (SD)	97.7 (1.8)	96.2 (4.3)	0.020	97.7 (1.9)	96.2 (5.8)	0.26	97.8 (1.7)	96.2 (3.0)	0.013
Temperature[g] (°C), mean (SD)	37.5 (1.0)	37.7 (1.2)	0.30	37.9 (1.0)	37.5 (1.1)	0.15	37.1 (0.7)	37.7 (1.2)	0.015
C-Reactive protein[h,i] (mg/L), median (IQR)	13.2 (3.4–55.3)	44.7 (14.5–129.5)	0.058	7.6 (1.1–67.1)	37.0 (17.2–83.1)	0.47	23.3 (4.1–53.8)	57.4 (15.9–129.5)	0.076
Creatinine[h,i] (mg/dL), median (IQR)	0.6 (0.5–0.7)	0.7 (0.5–0.9)	0.005	0.5 (0.4–0.5)	0.5 (0.4–0.7)	0.14	0.7 (0.6–0.8)	0.9 (0.7–1.0)	0.012

Abbreviations: BMI, body mass index; ICD-10-CM, international classification of diseases, tenth revision, clinical modification; IQR, interquartile range; SD, standard deviation; WFA, weight-for-age; WFL, weight-for-length.

[a]1 hospitalized patient, whose final outcome has not yet been determined (hospital discharge, critical illness or mortality), was excluded for this part of the analysis.

[b]Presented as N (%), unless otherwise specified.

[c]χ^2 test not performed in age-stratified groups due to violation of the test's assumptions.

[d]Calculated for children and adolescents up to 240.99 months (20.08 years) old.

[e]Non-obese: WFL/WFA percentile <95th percentile (< 24.0 months [2 years]), BMI/WFA < 95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI < 30 (> 240.99 months [20.08 years]); obese: WFL/WFA percentile ≥95th percentile (< 24.0 months [2 years]), BMI/WFA ≥95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI ≥30 (> 240.99 months [20.08 years]).

[f]Asthma, any malignancy or metastatic solid tumour, congenital malformations, deformations and chromosomal abnormalities (ICD-10-CM codes Q00-Q99), and/or diabetes.

[g]SpO2 measured for 70.6% of the patients in the full cohort; temperature measured for 70.8% of the patients in the full cohort.

[h]SI conversion factors: to convert c-reactive protein to nmol/L, multiply by 9.5238; to convert creatinine to SI unit μmol/L, multiply by 88.42.

[i]Percentage of patients with available laboratory results in the full cohort: C-reactive protein, 25.6%; creatinine, 36.1%.

TABLE 3 COVID-19 clinical presentations by age group and obesity status[a]

Clinical Presentations[b]	Full cohort (Total = 494)			0–12 Age group (Total = 214)			13–21 Age group (Total = 280)		
	Non-obese *N* = 379	Obese *N* = 115	*p*-value	Non-obese *N* = 176	Obese *N* = 38	*p*-value	Non-obese *N* = 203	Obese *N* = 77	*p*-value
Hospitalization Length of stay (Days), median (IQR)	2.0 (1.5–7.0)	6.0 (4.0–12.5)	0.20	2.0 (1.0–3.8)	3.0 (2.8–4.2)	0.49	6.0 (3.0–11.0)	8.0 (5.5–16.5)	0.16
Signs/Symptoms[c]									
Symptomatic[d]	133 (35.1)	44 (38.3)	0.53	83 (47.2)	16 (42.1)	0.57	50 (24.6)	28 (36.4)	0.051
Fever	82 (21.6)	25 (21.7)	0.98	64 (36.4)	12 (31.6)	0.58	18 (8.9)	13 (16.9)	0.056
Shortness of breath	14 (3.7)	11 (9.6)	0.012	3 (1.7)	2 (5.3)	0.22	11 (5.4)	9 (11.7)	0.069
Cough	32 (8.4)	15 (13.0)	0.14	18 (10.2)	6 (15.8)	0.39	14 (6.9)	9 (11.7)	0.19
Nausea/Vomiting	35 (9.2)	10 (8.7)	0.86	18 (10.2)	2 (5.3)	0.54	17 (8.4)	8 (10.4)	0.60
Diarrhoea	17 (4.5)	7 (6.1)	0.48	13 (7.4)	1 (2.6)	0.47	4 (2.0)	6 (7.8)	0.029
Abdominal pain	27 (7.1)	8 (7.0)	0.95	8 (4.5)	4 (10.5)	0.23	19 (9.4)	4 (5.2)	0.26
ICU Length of stay (Days), median (IQR)	5.0 (2.4–10.8)	5.0 (3.5–11.5)	0.59	3.5 (1.8–13.2)	3.0 (3.0–3.0)	0.19	6.5 (5.0–10.8)	6.5 (4.0–15.2)	0.70
Complications[e]									
ARDS	16 (4.2)	15 (13.0)	<0.001	6 (3.4)	1 (2.6)	>0.99	10 (4.9)	14 (18.2)	<0.001
Pneumonia	23 (6.1)	18 (15.7)	0.001	6 (3.4)	1 (2.6)	>0.99	17 (8.4)	17 (22.1)	0.002
Acute respiratory failure	19 (5.0)	14 (12.2)	0.007	8 (4.5)	0 (0.0)	0.36	11 (5.4)	14 (18.2)	<0.001
Myocarditis	5 (1.3)	4 (3.5)	0.22	1 (0.6)	2 (5.3)	0.082	4 (2.0)	2 (2.6)	0.67
MIS-C	6 (1.6)	3 (2.6)	0.44	5 (2.8)	2 (5.3)	0.61	1 (0.5)	1 (1.3)	0.48
Acute kidney injury	7 (1.8)	6 (5.2)	0.087	2 (1.1)	2 (5.3)	0.15	5 (2.5)	4 (5.2)	0.26
Oxygen delivery device									
High flow nasal cannula	12 (3.2)	8 (7.0)	0.10	4 (2.3)	0 (0.0)	>0.99	8 (3.9)	8 (10.4)	0.047
BiPAP/CPAP	7 (1.8)	6 (5.2)	0.087	3 (1.7)	0 (0.0)	>0.99	4 (2.0)	6 (7.8)	0.029
IMV	6 (1.6)	8 (7.0)	0.006	3 (1.7)	1 (2.6)	0.55	3 (1.5)	7 (9.1)	0.005
Mortality	1 (0.3)	1 (0.9)	0.41	0 (0.0)	1 (2.6)	0.18	1 (0.5)	0 (0.0)	>0.99

Abbreviations: ARDS, acute respiratory distress syndrome; BiPAP, bilevel positive airway pressure; BMI, body mass index; CPAP, continuous positive airway pressure; ICD-10-CM, international classification of diseases, tenth revision, clinical modification; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; SD, standard deviation; WFA, weight-for-age.

[a]Non-obese: WFL/WFA percentile <95th percentile (< 24.0 months [2 years]), BMI/WFA < 95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI < 30 (> 240.99 months [20.08 years]); obese: WFL/WFA percentile ≥95th percentile (< 24.0 months [2 years]), BMI/WFA ≥95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI ≥30 (> 240.99 months [20.08 years]).

[b]Presented as *N* (%), unless otherwise specified.

[c]ICD-10-CM codes: Fever (R50.9); shortness of breath (R06.02); cough (R05); nausea/vomiting (R11.2, R11.10, R11.15, P92.09, R11.0, R11.11); diarrhoea (R19.7, R11.10); abdominal pain (R10.84, R10.9, R10.31, R10.32, R10.813, R10.30, R10.13, R10.10).

[d]Presenting with fever, shortness of breath, cough, nausea/vomiting, diarrhoea and/or abdominal pain.

[e]ICD-10-CM codes: ARDS (U07.1, J80, B97.29); pneumonia (U07.1, B97.29, J12.89); acute respiratory failure (J96.01, J96.02, J96.91, J96.00, U07.1); myocarditis (I40.0, I40.8, I51.4, U07.1, I40.9); MIS-C (M30.3); acute kidney injury (N17.9, U07.1).

Among adolescents, patients with higher WFA/BMI z-score (median 1.8 vs. 0.8; $p = 0.002$) were more likely to experience critical illness, and obesity was associated with both hospitalization (24/62 [38.7%] vs. 53/218 [24.3%]; $p = 0.025$) and critical illness (16/28 [57.1%] vs. 61/252 [24.2%] $p = <0.001$). Compared to adolescents without obesity, adolescents with obesity were more likely to present with severe respiratory complications, such as ARDS (14/77 [18.2%] vs. 10/203 [4.9%]; $p = <0.001$), pneumonia (17/77 [22.1%] vs. 17/203 [8.4%]; $p = 0.002$) and acute respiratory failure (14/77 [18.2%] vs. 11/203 [5.4%]; $p = <0.001$), requiring high flow nasal cannula (8/77 [10.4%] vs. 8/203 [3.9%]; $p = 0.047$), BiPAP/CPAP (6/77 [7.8%] vs. 4/203 [2.0%]; $p = 0.029$) and/or IMV (7/77 [9.1%] vs. 3/203[1.5%]; $p = 0.005$) (Table 3). For children, such differences in clinical presentations between those with obesity and those without obesity, were not observed in our cohort. Obesity was not associated with the length of hospitalization and ICU admission stay, myocarditis, MIS-C, acute kidney injury, nor mortality for any age.

TABLE 4 Multivariable analysis of risk factors for COVID-19-related hospitalization and critical illness

				CRR		ARR	
Variable	**Total *N***	***N* Events**	**CRR**	**95% CI**	**ARR**	**95% CI**	***p*-value**
Hospitalization outcome							
Age grouping							
0–12	214	68	—	—	—	—	
13–21	280	62	0.70	0.52, 0.94	0.71	0.52, 0.95	0.023
Sex							
Female	258	59	—	—	—	—	
Male	236	71	1.32	0.98, 1.77	1.17	0.87, 1.59	0.30
Any comorbidity[a]							
Absent	326	71	—	—	—	—	
Present	168	59	1.61	1.21, 2.16	1.51	1.12, 2.04	0.007
Obesity status[b]							
Non-obese	379	94	—	—	—	—	
Obese	115	36	1.26	0.91, 1.74	1.22	0.88, 1.69	0.24
Critical illness outcome[c]							
Age grouping							
0–12	213	20	—	—	—	—	
13–21	280	28	1.06	0.62, 1.84	1.14	0.67, 1.96	0.63
Sex							
Female	257	15	—	—	—	—	
Male	236	33	2.40	1.34, 4.30	2.27	1.24, 4.16	0.008
Any comorbidity[a]							
Absent	325	21	—	—	—	—	
Present	168	27	2.49	1.45, 4.26	1.98	1.12, 3.50	0.019
Obesity status[b]							
Non-obese	378	28	—	—	—	—	
Obese	115	20	2.35	1.38, 4.01	2.02	1.17, 3.48	0.011

Abbreviations: ARR, adjusted risk ratio; BMI, body mass index; CI, confidence interval; CRR, crude risk ratio; ICD-10-CM, international classification of diseases, tenth revision, clinical modification; WFA, weight-for-age; WFL, weight-for-length.

[a]Asthma, any malignancy or metastatic solid tumour, congenital malformations, deformations and chromosomal abnormalities (ICD-10-CM codes Q00-Q99) and/or diabetes.

[b]Non-obese: WFL/WFA percentile <95th percentile (< 24.0 months [2 years]), BMI/WFA < 95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI < 30 (> 240.99 months [20.08 years]); obese: WFL/WFA percentile ≥95th percentile (< 24.0 months [2 years]), BMI/WFA ≥95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI ≥30 (> 240.99 months [20.08 years]).

[c]1 hospitalized patient, whose final outcome has not yet been determined (hospital discharge, critical illness or mortality), was excluded for this part of the analysis.

TABLE 5 Multivariable analysis of risk factors for COVID-19-related hospitalization and critical illness, stratified by age

	0–12 Age group							13–21 Age group						
Variable	**Total *N***	***N* Events**	**CRR**	**CRR 95% CI**	**ARR**	**ARR 95% CI**	***p*-value**	**Total *N***	***N* Events**	**CRR**	**CRR 95% CI**	**ARR**	**ARR 95% CI**	***p*-value**
Hospitalization outcome Measure of effect modification *p*-value: 0.19[a]														
Sex														
Female	92	25	—	—	—	—		166	34	—	—	—	—	
Male	122	43	1.30	0.86, 1.96	1.29	0.84, 1.96	0.24	114	28	1.20	0.77, 1.86	1.13	0.73, 1.74	0.59
Any comorbidity[b]														
Absent	138	42	—	—	—	—		188	29	—	—	—	—	
Present	76	26	1.12	0.75, 1.68	1.08	0.72, 1.62	0.71	92	33	2.33	1.51, 3.58	2.12	1.34, 3.35	0.001
Obesity status[c]														
Non-obese	176	56	—	—	—	—		203	38	—	—	—	—	
Obese	38	12	0.99	0.59, 1.66	0.95	0.56, 1.61	0.86	77	24	1.67	1.07, 2.58	1.33	0.85, 2.08	0.22
Critical illness outcome[d] Measure of effect modification *p* value: 0.08[a]														
Sex														
Female	91	5	—	—	—	—		166	10	—	—	—	—	
Male	122	15	2.24	0.84, 5.93	1.99	0.74, 5.36	0.18	114	18	2.62	1.26, 5.47	2.62	1.26, 5.46	0.010
Any comorbidity[b]														
Absent	137	9	—	—	—	—		188	12	—	—	—	—	
Present	76	11	2.20	0.96, 5.08	1.98	0.82, 4.78	0.13	92	16	2.72	1.35, 5.52	1.79	0.85, 3.76	0.12
Obesity status[c]														
Non-obese	175	16	—	—	—	—		203	12	—	—	—	—	
Obese	38	4	1.15	0.41, 3.25	1.01	0.36, 2.87	0.99	77	16	3.52	1.74, 7.09	3.09	1.48, 6.47	0.003

Abbreviations: ARR, adjusted risk ratio; BMI, body mass index; CI, confidence interval; CRR, crude risk ratio; ICD-10-CM, international classification of diseases, tenth revision, clinical modification; WFA, weight-for-age; WFL, weight-for-length.

[a]*p* values derived from interaction models as test of homogeneity for effect modification.

[b]Asthma, any malignancy or metastatic solid tumour, congenital malformations, deformations and chromosomal abnormalities (ICD-10-CM codes Q00-Q99), and/or diabetes.

[c]Non-obese: WFL/WFA percentile <95th percentile (< 24.0 months [2 years]), BMI/WFA < 95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI < 30 (> 240.99 months [20.08 years]); obese: WFL/WFA percentile ≥95th percentile (< 24.0 months [2 years]), BMI/WFA ≥95th percentile (24.0 months [2 years]–240.99 months [20.08 years]), BMI ≥30 (> 240.99 months [20.08 years]).

[d]1 hospitalized patient, whose final outcome has not yet been determined (hospital discharge, critical illness or mortality), was excluded for this part of the analysis.

TABLE 6 Sensitivity analysis of the association of obesity with COVID-19-related hospitalization and critical illness

Sensitivity analysis[a]	Total *N* w/ obesity	*N* Events w/ obesity	Obesity CRR	Obesity CRR 95% CI	Obesity ARR[b]	Obesity ARR 95% CI	*p*-value
Hospitalization outcome							
Model 1							
Full cohort	106	36	1.20	0.87, 1.65	1.17	0.85, 1.62	0.33
0–12 Age group	32	12	0.93	0.56, 1.52	0.90	0.54, 1.48	0.67
13–21 Age group	74	24	1.60	1.04, 2.48	1.32	0.84, 2.05	0.23
Model 2							
Full cohort	106	32	1.59	1.10, 2.29	1.36	0.93, 2.00	0.12
0–12 Age group	29	8	1.42	0.71, 2.83	1.33	0.64, 2.78	0.44
13–21 Age group	–	–	–	–	–	–	–
Model 3							
Full cohort	88	29	1.27	0.89, 1.80	1.26	0.88, 1.81	0.20
0–12 Age group	–	–	–	–	–	–	–
13–21 Age group	50	17	1.83	1.09, 3.08	1.61	0.94, 2.75	0.081
Model 4							
Full cohort	70	25	1.57	1.04, 2.35	1.46	0.95, 2.22	0.081
0–12 Age group	23	8	1.31	0.66, 2.61	1.24	0.60, 2.57	0.56
13–21 Age group	47	17	1.74	1.04, 2.90	1.58	0.93, 2.66	0.089
Model 5							
Full cohort	87	34	1.38	1.00, 1.89	1.36	0.99, 1.86	0.057
0–12 Age group	28	12	1.19	0.73, 1.92	1.16	0.72, 1.89	0.54
13–21 Age group	59	22	1.72	1.11, 2.67	1.44	0.92, 2.23	0.11
Model 6							
Full cohort	115	36	1.26	0.91, 1.74	1.24	0.89, 1.72	0.21
0–11 Age group	34	11	1.01	0.59, 1.73	0.98	0.57, 1.68	0.94
12–21 Age group	81	25	1.60	1.05, 2.46	1.29	0.83, 2.01	0.26
Critical illness outcome							
Model 1							
Full cohort	106	20	2.19	1.28, 3.73	1.96	1.14, 3.38	0.015
0–12 Age group	32	4	1.04	0.37, 2.92	0.95	0.34, 2.66	0.92
13–21 Age group	74	16	3.39	1.68, 6.81	3.07	1.47, 6.40	0.003
Model 2							
Full cohort	106	19	2.88	1.60, 5.18	2.46	1.33, 4.55	0.004
0–12 Age group	29	3	1.53	0.43, 5.40	1.32	0.36, 4.80	0.68
13–21 Age group	–	–	–	–	–	–	–

(Continues)

TABLE 6 (Continued)

Sensitivity analysis[a]	Total *N* w/ obesity	*N* Events w/ obesity	Obesity CRR	Obesity CRR 95% CI	Obesity ARR[b]	Obesity ARR 95% CI	*p*-value
Model 3							
Full cohort	88	18	2.68	1.53, 4.72	2.23	1.26, 3.94	0.006
0–12 Age group	–	–	–	–	–	–	–
13–21 Age group	50	14	4.90	2.19, 11.0	4.05	1.72, 9.58	0.001
Model 4							
Full cohort	70	17	3.12	1.65, 5.92	2.77	1.41, 5.41	0.003
0–12 Age group	23	3	1.27	0.36, 4.50	1.15	0.32, 4.09	0.83
13–21 Age group	47	14	4.65	2.09, 10.4	3.98	1.70, 9.33	0.001
Model 5							
Full cohort	87	18	2.56	1.46, 4.46	2.25	1.29, 3.93	0.004
0–12 Age group	28	4	1.57	0.55, 4.47	1.52	0.55, 4.18	0.42
13–21 Age group	59	14	3.28	1.61, 6.69	2.88	1.37, 6.06	0.005
Model 6							
Full cohort	115	20	2.35	1.38, 4.01	2.03	1.17, 3.51	0.012
0–11 Age group	34	4	1.29	0.46, 3.66	1.20	0.43, 3.38	0.73
12–21 Age group	81	16	3.24	1.63, 6.42	2.84	1.38, 5.87	0.005

Abbreviations: ARR, adjusted risk ratio; BMI, body mass index; CI, confidence interval; CRR, crude risk ratio; EHR, electronic health records; WFA, weight-for-age; WFL, weight-for-length.

[a]Model 1 excludes all 74 paediatric patients without a length/height measurement in the EHR; model 2 excludes 67 patients aged <24 months (2 years) with length measurement available in the EHR; model 3 excludes 90 patients aged >240.99 months (20.08 years); model 4 excludes all 231 patients whose obesity status was determined via WFL, WFA or adult BMI categories, thereby limiting the cohort to 263 patients whose obesity status was determined using sex-specific BMI-for-age; model 5 excludes all 97 patients whose only available anthropometric measurements in the EHR were from inpatient or outpatient encounters in the health system >30 days pre- or post-COVID-19 testing encounter; model 6 utilizes 12 as the starting age cutoff for the adolescent group, thereby redefining the age groups as children (0–11 years) and adolescents (12–21 years).

[b]Full cohort models were adjusted for age, sex and other comorbidities; age-stratified models were adjusted for sex and other comorbidities.

3.3 | Factors associated with hospitalization and critical illness: multivariable analyses, effect modification and sensitivity analysis

In the full cohort multivariable analyses, with adjustment for age, sex and presence of comorbidities (asthma, any malignancy or metastatic solid tumour, congenital malformations, deformations, and chromosomal abnormalities, and/or diabetes), obesity was not independently associated with hospitalization (adjusted risk ratio [ARR] 1.22, 95% CI 0.88 to 1.69; $p = 0.24$), but was an independent risk factor for critical illness (ARR 2.02, 95% CI 1.17 to 3.48; $p = 0.011$) (Table 4). Factors associated with increased risk for hospitalization included the presence of comorbidities (ARR 1.51, 95% CI 1.12 to 2.04; $p = 0.007$). In addition to obesity, factors associated with increased risk for critical illness were male sex (ARR 2.27, 95% CI 1.24 to 4.16; $p = 0.008$) and presence of comorbidities (ARR 1.98, 95% CI 1.12 to 3.50; $p = 0.019$).

When separate models were created for each age group (children aged 0–12 years and adolescents aged 13–21 years) and outcome, the interaction term was not statistically significant for hospitalization ($p_{interaction} = 0.19$), but was for critical illness ($p_{interaction} = 0.08$) (Table 5). In adolescents, obesity was not an independent risk factor for hospitalization (ARR 1.33, 95% CI 0.85 to 2.08; $p = 0.22$), but was substantially associated with 3.09-fold risk for critical illness (ARR 3.09, 95% CI 1.48 to 6.47; $p = 0.003$). In children, obesity was not associated with hospitalization (ARR 0.95, 95% CI 0.56 to 1.61; $p = 0.86$), nor with critical illness (ARR 1.01, 95% CI 0.36 to 2.87; $p = 0.99$).

For sensitivity analysis models 1 to 5, obesity remained an independent risk factor for critical illness for the full paediatric cohort and for adolescents despite exclusion of the following: 1) 74 paediatric patients without a length/height measurement (full paediatric cohort: ARR 1.96, 95% CI 1.14 to 3.38; $p = 0.015$, adolescents: ARR 3.07, 95% CI 1.47 to 6.40; $p = 0.003$); 2) 67 patients aged <24 months

[2 years] with length measurement (full paediatric cohort only: ARR 2.46, 95% CI 1.33 to 4.55; $p = 0.004$); 3) 90 patients aged >240.99 months [20.08 years] (full paediatric cohort: ARR 2.23, 95% CI 1.26 to 3.94; $p = 0.006$, adolescents: ARR 4.05, 95% CI 1.72 to 9.58; $p = 0.001$); 4), 231 patients whose obesity status was determined via WFL, WFA or adult BMI categories (full paediatric cohort: ARR 2.77, 95% CI 1.41 to 5.41; $p = 0.003$, adolescents: ARR 3.98, 95% CI 1.70 to 9.33; $p = 0.001$); 5) and 97 patients whose only available anthropometric measurements in the EHR were from inpatient or outpatient encounters in the health system >30 days pre- or post-COVID-19 testing encounter (full paediatric cohort: ARR 2.25, 95% CI 1.29 to 3.93; $p = 0.004$, adolescents: ARR 2.88, 95% CI 1.37 to 6.06; $p = 0.005$). Furthermore, despite redefining the age groups as 0–11 years for children and 12–21 years for adolescents in model 6, obesity still remained an independent risk factor for critical illness for the full paediatric cohort (ARR 2.03, 95% CI 1.17 to 3.51; $p = 0.012$) and for the adolescent group (ARR 2.84, 95% CI 1.38 to 5.87; $p = 0.005$). In all of the sensitivity analyses we performed, obesity remained not an independent risk factor for hospitalization for any age, nor for critical illness in children (Table 6).

4 | DISCUSSION

In this cohort study of 494 SARS-CoV-2-positive paediatric patients, though not independently associated with hospitalization, obesity was found to be an independent risk factor for COVID-19-related critical illness, and this association was modified by age. Obesity was independently related to greater risk for critical illness in adolescents, but not in children. These findings suggest that age-related differences in COVID-19 between children and adolescents exist for the association between obesity and COVID-19 severity, in addition to SARS-CoV-2 infection susceptibility,[14] transmission[15] and incidence.[16]

Existing paediatric studies have suggested that obesity is associated with increased COVID-19 severity.[5,7,13] Our study adds to the literature by showing that within the paediatric population, the association of obesity and COVID-19 severity is age-dependent and that obesity substantially increases the risk for COVID-19-related critical illness in adolescents, but not in children. The risk of critical illness for adolescents with obesity is similar to that found in adults.[33] In our cohort, compared to adolescents without obesity, adolescents with obesity are more likely to present with severe respiratory complications (i.e., ARDS, pneumonia and acute respiratory failure), requiring high flow nasal cannula, BiPAP/CPAP and/or IMV even though some of these clinical presentations were observed in a limited number of patients. Such differences in COVID-19 clinical presentations are not observed between children with obesity and children without obesity. These findings are crucial for medical practitioners in stratifying paediatric risk of developing COVID-19 severity and in decision-making regarding patient care.

The underlying mechanism of obesity-driven COVID-19 severity in older paediatric patients is likely multifactorial. First, adipose tissue expansion related to obesity induces a systemic pro-inflammatory state, as characterized by an increased expression of cytokines.[34] In our study and others,[5,18] paediatric patients who experienced critical illness–regardless of obesity status–presented with a hyper-inflammatory state, as evident in elevated inflammatory biomarkers such as creatinine. The chronically elevated basal inflammatory biomarker levels in patients with obesity may also contribute to the exacerbation of COVID-19 course in these patients.[35,36] Moreover, among other organs, angiotensin-converting enzyme 2 (ACE2)–which has high affinity for SARS-CoV-2 spike proteins–is also expressed in adipose tissue.[37] The observed age-related differences in the association of obesity and COVID-19 severity may be explained in part by hormonal changes, which occur during puberty, such as the progressive decline in adiponectin, particularly in males.[38] Adiponectin has been noted as an anti-inflammatory agent,[39] and in individuals with obesity, circulating levels of adiponectin are decreased, which potentiates the exaggerated inflammatory response on pulmonary capillaries[40] and lung injury[41] due to COVID-19. Further studies are needed to better understand what factors lead to the increased risk of critical COVID-19 illness in adolescents with obesity during adolescence.

Other than obesity, the presence of comorbidities was identified in our multivariable analyses as a major risk factor for increased COVID-19 severity within the paediatric population. This result parallels with the US CDC COVID-19 Response Team paediatric report, which showed 28/37 (77%) of hospitalized patients, including those who were admitted to the ICU, as having at least one comorbidity such as 'chronic lung disease (including asthma)'.[3] Our analysis shows that asthma is associated with hospitalization and critical illness. Further studies must be performed to further ascertain this association. Any malignancy or metastatic solid tumour appears to be related to COVID-19 severity in our full cohort, but it must be noted that this association was apparent in adolescents only and that 11/15 (73.3%) of the SARS-CoV-2-positive patients with this comorbidity in this age group had obesity and 6/15 (40.0%) were 20–21 years old. Therefore, this association in our study may be confounded by age and obesity. Other data regarding the prognosis of SARS-CoV-2-positive children and adolescents with cancer have been limited, with few studies suggesting that paediatric patients with cancer are not more vulnerable to increased COVID-19 severity than other children.[42,43] Although diabetes has been shown to be another comorbidity linked with COVID-19-related hospitalization and critical illness in our cohort, this result must be interpreted with caution given that the number of patients with diabetes in our cohort was limited, and all of these patients were adolescents. Paediatric patients with congenital malformations, deformations and chromosomal abnormalities in our cohort, including those with congenital heart disease, were not more likely to experience COVID-19-related hospitalization and critical illness, as was reported previously by an academic centre in New York City.[44] Younger age was associated with hospitalization, but not with critical illness in our cohort, which is aligned with results reported by the CDC COVID-NET report.[13] Similarly, several studies have reported that a majority of COVID-19 cases within the paediatric population are males,[3,45] and in our study, male sex was identified as an independent risk factor for critical illness. Reasons for this sex predisposition for increased COVID-19 severity still need to be elucidated.

4.1 | Limitations

Our study is not without limitations. First, our cohort size, though larger than other COVID-19 paediatric studies, was still limited. As a result, it was necessary to collapse some variables into one category (e.g., presence of comorbidities) due to insufficient exposed patients for each individual disease (e.g., any malignancy or metastatic solid tumour, diabetes), and obesity status was dichotomized as obese and non-obese, with patients with underweight, normal weight and overweight status grouped in the non-obese category. Consequently, we might have missed important associations, and CIs may have been narrower if we had a larger cohort. Second, although we found no association between obesity and MIS-C, the true cases of MIS-C in our cohort may have been undercounted given that we only considered patients to experience MIS-C if ICD-10-CM diagnosis code M30.3 was recorded in the medical history, problem list, hospital problem or diagnosis fields in the EHR. Further studies are warranted to ascertain the association between obesity and MIS-C. Third, given that we focused on a single healthcare system in one geographic location and more than 43% of our cohort were Hispanics, it is possible that there may be differences in risk factors for different paediatric settings.

5 | CONCLUSION

Our study shows that obesity is an independent risk factor for COVID-19-related critical illness and that this association is modified by age, with obesity related to a greater risk for critical illness in adolescents, but not in children. These findings suggest that age-related differences in COVID-19 between children and adolescents are not only limited to aspects such as SARS-CoV-2 infection susceptibility, transmission and incidence, but are also apparent in the obesity-COVID-19 severity association. A better understanding of the association between obesity and COVID-19 severity is crucial for medical practitioners in stratifying paediatric risk of developing COVID-19 severity and in decision-making regarding patient care.

CONFLICT OF INTEREST

No conflict of interest was declared.

AUTHOR CONTRIBUTIONS

Mr Guzman substantially contributed to the conception and design of the study, performed acquisition of data, analysed the data, reviewed the analysis, drafted the initial manuscript, and reviewed and revised the manuscript. Drs Elbel and Jay substantially contributed to the analysis and interpretation of data, and reviewed and revised the manuscript for important intellectual content. Dr Messito substantially contributed to the conception and design of the study, and to the analysis and interpretation of data, and reviewed and revised the manuscript for important intellectual content. Dr Curado substantially contributed to the conception and design of the study, and to the analysis and interpretation of data, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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