RESEARCH ARTICLE

The Impact of Obesity on Disease Severity and Outcomes Among Hospitalized Children With COVID-19

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ABSTRACT

OBJECTIVE: To describe the impact of obesity on disease severity and outcomes of coronavirus disease 2019 (COVID-19) among hospitalized children.

METHODS: This retrospective cohort study from the Society of Critical Care Medicine Viral Respiratory Illness Universal Study registry included all children hospitalized with COVID-19 from March 2020 to January 2021. Obesity was defined by Centers for Disease Control and Prevention BMI or World Health Organization weight for length criteria. Critical illness definition was adapted from National Institutes of Health criteria of critical COVID. Multivariate mixed logistic and linear regression was performed to calculate the adjusted odds ratio of critical illness and the adjusted impact of obesity on hospital length of stay.

RESULTS: Data from 795 patients (96.4% United States) from 45 sites were analyzed, including 251 (31.5%) with obesity and 544 (68.5%) without. A higher proportion of patients with obesity were adolescents, of Hispanic ethnicity, and had other comorbidities. Those with obesity were also more likely to be diagnosed with multisystem inflammatory syndrome in children (35.7% vs 28.1%, $P = .04$) and had higher ICU admission rates (57% vs 44%, $P < .01$) with more critical illness (30.3% vs 18.3%, $P < .01$). Obesity had more impact on acute COVID-19 severity than on multisystem inflammatory syndrome in children presentation. The adjusted odds ratio for critical illness with obesity was 3.11 (95% confidence interval: 1.8–5.3). Patients with obesity had longer adjusted length of stay (exponentiated parameter estimate 1.3; 95% confidence interval: 1.1–1.5) compared with patients without obesity but did not have increased mortality risk due to COVID-19 (2.4% vs 1.5%, $P = .38$).

CONCLUSION: In a large, multicenter cohort, a high proportion of hospitalized children from COVID-19 had obesity as comorbidity. Furthermore, obesity had a significant independent association with critical illness.

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Coronavirus disease 2019 (COVID-19), the disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affects children and adults of all ages. Although children had generally milder symptoms than adults during the global COVID-19 pandemic, some children developed severe disease requiring hospitalization or critical care.[1,2] Obesity has been highlighted in the adult literature as an independent risk factor for severity of illness, hospital admissions, and mortality.[3–7]

Among children with COVID-19, a recent meta-analysis describing the effects of comorbidities on disease severity estimated the relative risk of more severe disease as 2.8 (95% confidence interval [CI]: 1.1–7.0) in children with obesity. However, this analysis was performed on a small subset of studies, including <64 children with obesity and severe disease.[8] Young adults with obesity have also been shown to have higher mortality from COVID-19.[9] Obesity has been described as a state of chronic inflammation that is often associated with other comorbidities like asthma, diabetes, hypertension, etc.[10] This inflammatory state may also affect the host response to SARS-CoV-2 infection adversely and place them at a higher risk of poor outcomes.[11] Globally, 41 million children <5 years of age are estimated to be affected by obesity or overweight, according to the World Health Organization (WHO).[12] The United States is particularly affected by this epidemic, with 18% of US children diagnosed with obesity and 6% with severe obesity.[13,14] Elucidating to what degree obesity affects COVID-19 severity in a larger, multicenter cohort of children can help guide prevention, prognostication, and clinical care.

Our primary objective with this study was to describe and compare the clinical presentation, disease course, and outcomes in children with and without obesity requiring hospital admission for the treatment of COVID-19. Our secondary objective was to determine the association between obesity and critical illness with COVID-19.

METHODS

Study Design, Population, and Setting

This was a retrospective study of patients enrolled in the Viral Respiratory Illness Universal Study [VIRUS] registry). This international VIRUS registry was established by the Society of Critical Care Medicine at the onset of the COVID-19 pandemic[15] and now includes >60 000 patients (of all ages) from 306 centers in 28 countries.[16] The study protocol was reviewed and approved by the Institutional Review Board at [institution name redacted for review] and all participating centers. The study population included all patients (<18 years) admitted to the participating hospitals (including those admitted and transferred to the ICU) with SARS-CoV-2 infection from March 2020 to January 2021. Patients with incidental COVID-19 diagnoses were excluded from the registry. Incidental diagnosis included patients with positive results for SARS-CoV-2 on routine screening or admission diagnosis not related to SARS-CoV-2, at the discretion of the site investigators. We further excluded patients who had missing essential demographic data (weight, sex) and incomplete outcome variables (hospital discharge status, hospital length of stay [LOS]). Patients with missing BMI and weight for height percentiles were also excluded. There is possibility of significant overlap between the patients included in this article and those already reported in the literature. Therefore, in keeping with current reporting recommendations,[17] we have provided details of articles that may contain overlapping patients. (Supplemental Table 4)

Measurements

Demographic (age, sex, race and ethnicity), clinical characteristics, management, and outcome variables were extracted from the VIRUS REDCap database.[18] Race and ethnicity were included in the analysis as a social construct because of their complex relationship with social-economic disparities in health care access.[19] Age was stratified into discrete categories; neonate (≤28 days), infant (28 days to <2 years), child (2 to <12 years), and adolescent (≥12 years).[20] BMI percentiles for children ≥2 years of age were calculated on the basis of Centers for Disease Control and Prevention (CDC) SAS codes[21] whereas the weight for length percentiles for children <2 years of age were calculated on the basis of WHO SAS codes.[22] Categorization of underweight, normal, overweight, and obese were defined by CDC criteria for ≥2 years (below fifth, fifth to <85th, 85th to <95th and ≥95th BMI percentiles respectively),[23] and WHO weight for length percentile criteria of +2 and +3 SDs above the median.[24] Children, ≥2 years of age, with a BMI ≥120% of the BMI 95th percentile, were classified as having severe obesity.[21]

Presenting signs and symptoms, comorbidities, and COVID-19–related complications were categorized into organ system groups and compared independently and as organ systems. Patients with ≥3 organ system involvement (presenting signs and symptoms in different organ systems) and ≥2 comorbidities were identified. Patients with evidence of other respiratory viral infections were categorized as "viral coinfection." Patients with concurrent blood, urine, and bacterial respiratory infections were combined into categories of "bacterial coinfection." Diagnosis of multisystem inflammatory syndrome in children (MIS-C) was made by the individual sites on the basis of the CDC definition[25] and was not further adjudicated for this analysis.

Outcomes

The outcome measures of hospital LOS and mortality were determined at discharge. Critical illness was defined as a composite index of in-hospital mortality and organ support requirements defined as a need for 1 or more of the following: (1) positive pressure ventilation (invasive or noninvasive), (2) vasoactive–inotropic support, (3) pulmonary vasodilator therapy (inhaled nitric oxide, epoprostenol), (4) extracorporeal life support (ECLS), and/or (5) new renal

replacement therapy (acute dialysis or continuous renal replacement therapy). This classification was modified from the National Institutes of Health (NIH) definition of critical COVID-19[26] and was previously described by our group.[2]

Statistical Analysis

Standard descriptive statistics were performed for continuous and categorical variables and reported as median with interquartile range (IQR) and number with percentages. The nonparametric Wilcoxon rank test and χ^2/Fisher's exact test were used as appropriate. Multivariable logistic regression was performed to assess the risk factors associated with critical illness for the whole cohort and independently for patients with obesity. The odds ratio and 95% CI were calculated. A mixed logistic regression that included a random effect for the site was used to determine potential risk factors associated with an increased likelihood of critical illness after controlling for the impact of other risk factors. The potential confounders with exposure and critical illness were a priori defined for inclusion in the model. These variables were selected on the basis of the theoretical understanding of their impact on critical illness and hospital LOS and their interaction with obesity. A directed acyclic graph was created to represent the causal relationships by using standard terminology and rules as described before.[27,28] (Supplemental Fig 3) Age (adolescent and nonadolescent), race (Black, white, and others or unknown), ethnicity (Hispanic, non-Hispanic, other or unknown), sex, and ≥2 comorbidities were included in the model. Potential interaction between obesity and age (adolescent versus not) was also assessed. Patients with obesity were separately analyzed with a similar model to identify the association with critical illness in that subset of patients.

A multivariable mixed linear regression, with a random intercept for the site, was also performed to assess the association of obesity with hospital LOS after adjusting for confounders (described above with added inclusion of country). Because of nonnormal distribution, LOS was log-transformed, and parameter estimates and CIs were exponentiated. LOS analysis was initially performed after the inclusion of ICU admission status, diagnosis of MIS-C, critical illness, and involvement of multiple organ systems because of their potential impact on the LOS. Mediator analysis as described by Baron and Kenny[29] indicated at least partial mediation of the impact of obesity on LOS by these variables. These variables were thus excluded from the linear regression model presented. Complete mediator analysis for the LOS model is provided in the Supplemental Information. Patients with hospital mortality (n = 14) were excluded from the LOS multivariable analysis. Models' goodness of fit was assessed by evaluating the residual plots. All statistical analysis was conducted by using JMP (v 16.0; SAS Institute, Inc, Cary, NC) and an open-source statistical program R (V 4.0.0). A P value <.05 was considered statistically significant. This study reporting conforms to the Strengthening The Reporting of Observational Studies in Epidemiology statement[30].

RESULTS

Patient Selection

A total of 1124 hospitalized children (<18 years) with COVID-19 were included in the registry during the study period, 329 of which were excluded because of missing essential data elements (n = 313) and other prespecified reasons (n = 16), leaving 795 patients from 45 sites for analysis. Out of these patients, 251 (31.5%) had obesity. Among children ≥2 years of age (n = 582), 107 (18.3%) had severe obesity (Fig 1). Only 11.2% (24 of 213) of children <2 years met the criteria for obesity as compared with 39% (227 of 582) of children between 2 and 18 years. The proportion of patients within the 4 weight categories by age (<2 and ≥2 years) is provided in Supplemental Table 9.

Presenting Characteristics for Those With and Without Obesity

The median age of the total cohort was 8 (IQR: 1.6–14) years. Patients with obesity were significantly older (13 [7.0–16.0] vs 5.3 [0.8–13.0] years, $P < .01$), with more adolescents composing the group with obesity compared with the group without (57.4% [144 of 251] vs 30.5% [166 of 544], $P < .01$). There was no difference in the sex or race distribution among the 2 groups; however, there was a much higher proportion of patients of Hispanic ethnicity in patients with obesity (47.8% [108 of 251] vs 32.9% [158 of 544], $P <$ .01). Patients from the United States made up 96.4% (767 of 795) of the total cohort, with a higher proportion of patients from the United States in the obese category (99.2% [249 of 251] vs 95.2% [518 of 544]). Patients with obesity were more likely to have a diagnosis of MIS-C as opposed to acute COVID-19 (35.7% [85 of 251] vs 28.1% [147 of 544], P = .04) and were more likely to have ≥3 organ system involvement at presentation (61.4% [154 of 251] vs 47.8% [260 of 544], $P < .01$). Among the 5 most common signs and symptoms, fever was more common in patients without obesity, whereas patients with obesity were more likely to present with dyspnea and/or shortness of breath and cough. Presence of any other comorbidity was more likely in patients with obesity (48.6% [122 of 251] vs 40.0% [218 of 544], P = .02). Among the 5 most common comorbidities, asthma was significantly more common in children with obesity (18.3% [46 of 251] vs 9.0% [49 of 544], $P < .01$) (Table 1). Comparison of all signs and symptoms and comorbidities included in the VIRUS registry between patients with and without obesity is provided in Supplemental Tables 10 and 11.

Disease Course and Outcomes

A total of 14 patients died during their hospitalization (14 of 795, 1.7% mortality). There was no difference in mortality rate due to COVID-19 between those with obesity (2.4% [6 of 251]) and those without (1.5% [8 of 544], P = .38). A higher proportion of patients with obesity were admitted to the ICU (56.9% [143 of 251] vs 43.9% [239 of 544], $P < .01$) and had

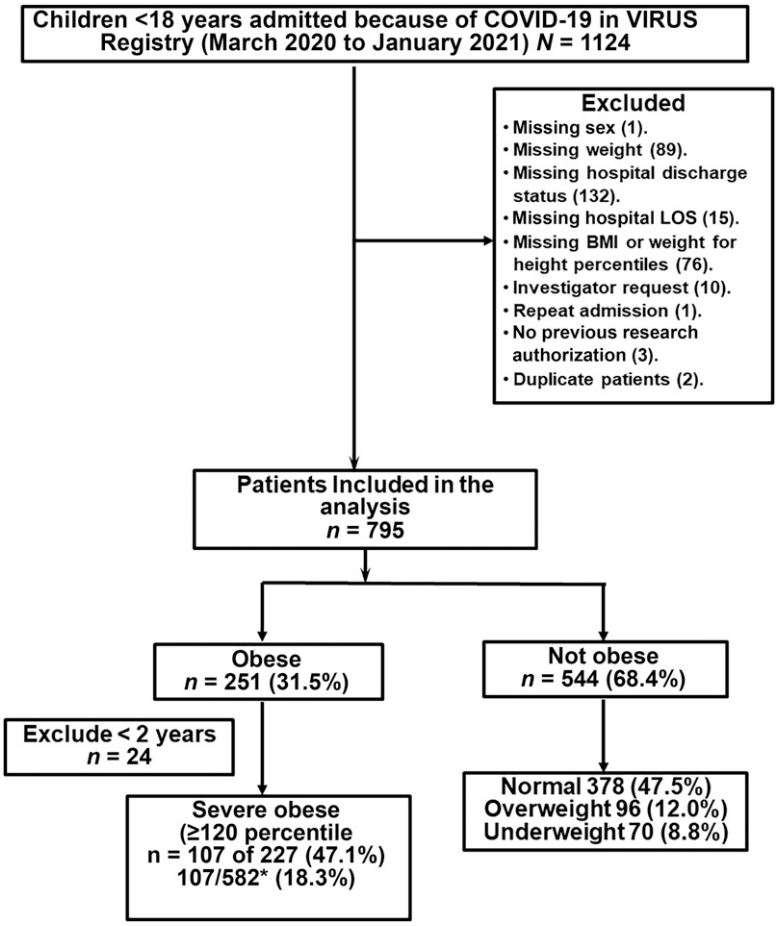

FIGURE 1 Patient selection flow diagram.

critical illness related to COVID-19 (30.3% [76 of 251] vs 18.3% [100 of 544], $P < .01$). There was a greater need for various organ support interventions, including mechanical ventilation, inotropes, and extracorporeal life support (ECLS), in patients with obesity. Among the 5 most prominent complications recorded in the registry, only acute kidney injury was significantly more common in those with obesity (12.7% [32 of 251 vs 6.8% [37 of 544], $P < .01$). Comparative rates of all complications in the VIRUS registry are provided in Supplemental Table 12. The unadjusted median hospital LOS of patients with obesity was longer than those without obesity (4.8 [IQR: 2.5–8.9] vs 3.5 [IQR: 1.8–6.9], $P < .01$). There was no difference in ICU LOS or the duration of the ventilator and other modes of oxygen therapy between the 2 groups. (Table 2)

Risk Factors for Critical Illness and Hospital LOS

By using a multivariate mixed logistic regression analysis adjusting for covariates including age, race, ethnicity, and presence of ≥2 comorbidities, with a random intercept for the site, obesity was independently associated with an increased odds ratio of critical illness (adjusted odds ratio [aOR]: 3.11 [95% CI: 1.84–5.27], $P < .01$). Other factors significantly associated with critical illness included adolescent age, Black race, and ≥2 comorbidities. A significant interaction was found between age group and obesity, with obesity having less impact on the likelihood of critical illness as the patient gets older. The adjusted critical illness rate for patients with obesity was 23% for <12 years of age compared with 17% for patients ≥12 years (Fig 2). Separate analysis for factors associated with critical illness among the cohort with obesity ($n = 251$) revealed that the presence of ≥ 2 comorbidities was marginally associated with the critical illness (aOR: 1.90; 95% CI: 1.01–3.58, $P = .05$) (Supplemental Table 13). On multivariable linear regression including the factors described above (with the addition of country), the presence of obesity was associated with a 30% longer hospital LOS (exponentiated parameter estimate: 1.3; 95% CI: 1.1–1.5), $P < .01$ (Supplemental Table 14).

Disease Course and Outcomes of MIS-C and Acute COVID-19 Among Patients With Obesity

Among the 528 patients with acute COVID-19, 28.9% (153 or 528) had obesity. Patients with obesity in this cohort were older (median age 13.2 vs 4 years, $P < .001$), more likely to be Hispanic, and had more comorbidities. A higher proportion of those with obesity and acute COVID-19 had critical illness (22% vs 11%, $P = .001$), required ICU admission (50% vs 33%, $P < .001$) and/or mechanical ventilation (13% vs 6.7%, $P = .01$) ,and had longer hospital LOS (3.8 [IQR: 2.0–7.3] days versus 2.8 [1.5–5.9] days, $P = .004$) (Supplemental Table 15). In contrast, although a higher proportion of patients with MIS-C had obesity (36.6%, 85/232), there was no significant difference in critical illness, ICU admission, or mechanical ventilation rate in patients with MIS-C with obesity and compared with those without obesity. However, a similar increased LOS occurred among the MIS-C cohort with obesity as for those with acute COVID-19 (8.0 [IQR: 4.7–10.4] days versus 5.7 [3.1–9.4] days, $P = .01$) (Supplemental Table 16).

Comparison of Disease Severity Among Children and Adolescents in Different Weight Categories (≥ 2 Years)

Comparative analysis across 5 different weight categories (underweight to severe obesity) revealed that the median age was

TABLE 1 Demographics of the Study Population

Category	Subcategory	Total Cohort (n = 795)	Nonobese (n = 544)	Obese (n = 251)	P
Age		8.0 (1.6–14.0)	5.31 (0.83–13.0)	13.0 (7.0–16.0)	<.01
Age category	Neonate	31 (3.8)	28 (5.1)	3 (1.2)	<.01
	Infant	182 (22.8)	161 (29.6)	21 (8.4)	—
	Child	272 (34.2)	189 (34.7)	83 (33.0)	—
	Adolescent	310 (38.9)	166 (30.5)	144 (57.4)	—
Sex	% Male	433 (54.4)	293 (53.8)	140 (50.8)	.64
Race	Black	186 (23.3)	125 (22.9)	61 (24.3)	.72
	White	349 (43.8)	244 (44.8)	105 (41.8)	—
	Others	260 (32.7)	175 (32.2)	85 (33.9)	—
Ethnicity[a]	Hispanic	266 (37.6)	158 (32.9)	108 (47.8)	<.01
	Non-Hispanic	440 (62.3)	322 (67.1)	118 (52.2)	—
Country[b]	United States	767 (96.4)	518 (95.2)	249 (99.2)	<.01
Coinfection	Viral	34 (4.2)	28 (5.2)	6 (2.4)	.08
	Bacterial	102 (12.8)	73 (13.4)	29 (11.6)	.49
MIS-C[c]	Yes	232 (30.5)	147 (28.1)	85 (35.7)	.04
≥3 organ system involvement	Yes	414 (52.0)	260 (47.8)	154 (61.4)	<.01
Signs and symptoms	Fever	534 (67.1)	379 (69.7)	155 (61.8)	.02
	Nausea vomiting	276 (34.7)	177 (32.5)	99 (39.4)	.06
	Cough	238 (29.9)	149 (27.4)	89 (35.5)	.02
	Abdominal pain	201 (25.3)	128 (23.5)	73 (29.1)	.09
	Dyspnea	175 (22.0)	91 (16.7)	84 (33.5)	<.01
Comorbidity	Yes	340 (42.7)	218 (40.0)	122 (48.6)	.02
≥2 comorbidities		179 (22.5)	114 (20.9)	65 (25.9)	.12
Comorbidity types	Asthma	95 (11.9)	49 (9.0)	46 (18.3)	<.01
	Seizures	62 (7.7)	40 (7.4)	22 (8.8)	.48
	Developmental delay	54 (6.7)	34 (6.3)	20 (7.9)	.36
	Diabetes	23 (2.8)	12 (2.2)	11 (4.4)	.11
	CLD/BPD	19 (2.3)	13 (2.4)	6 (2.4)	1.0

Values represent median (IQR) or number (percentage) as applicable. P values represent comparison of cohort with and without obesity. BPD broncopulmonary dysplasia; CLD chronic lung disease. —, not applicable.

[a] Ethnicity missing in 89 patients (11.2%).

[b] Pakistan 13 (1.6%), India 7 (0.8%), Croatia 6 (0.7%), Saudi Arabia 2 (0.2%).

[c] MIS-C missing 4.4% (35 of 795) (4.0% in nonobese [22 of 544] and 5.2% in obese [13 of 251]). Values represent proportion out of 760, 522, and 238, respectively.

higher with increasing weight categories. Adolescents composed 71% of the patients with severe obesity compared with 28.8% of underweight patients. There was no difference in race or sex distribution across the groups; however, Hispanic adolescents composed a larger proportion in higher weight categories. A higher proportion of patients with obesity (55%) and severe obesity (71%) had ≥3 organ system involvement compared with those in underweight (33%) and normal-weight (53%) categories. Although notable differences were observed in the rates of MIS-C, critical illness, and ICU admission across the 5 weight categories, they did not reach statistical significance. Both patients with underweight and obesity and/or severe obesity significantly longer hospital and ICU LOS than those with normal weight (P = .04). However, a significant difference on multiple group comparison with Bonferroni adjustment was only observed for obese versus normal-weight patients for hospital LOS. (Table 3).

DISCUSSION

In this large cohort of hospitalized children with SARS-CoV-2–related disease, we report obesity as an independent risk factor for critical illness and hospital LOS. The presence of obesity had a more significant impact on outcomes in children hospitalized with acute COVID-19 patients than in those hospitalized for MIS-C. To the best of our knowledge, this is the largest study describing the impact of obesity on the outcomes of hospitalized pediatric patients with SARS-CoV-2 related disease.

Our findings are similar to the adult studies regarding the severity of illness during acute COVID-19, which have demonstrated that adults with obesity are more likely to require intensive care and

TABLE 2 Hospital Course and Outcomes

Category	Subcategory	Total Cohort (n = 795)	Nonobese (n = 544)	Obese(n = 251)	P
Categorical variables					
Hospital mortality	—	14 (1.7)	8 (1.5)	6 (2.4)	.38
ICU admission	—	382 (48.0)	239 (43.9)	143 (56.9)	<.01
Critical illness	—	176 (22.1)	100 (18.3)	76 (30.3)	<.01
Organ support	Invasive ventilator	90 (11.3)	53 (9.7)	37 (14.7)	.04
	NIV[a]	52 (6.5)	25 (4.6)	27 (10.7)	<.01
	HFNC[b]	58 (7.2)	26 (10.3)	32 (5.8)	.03
	Inotropes	94 (11.8)	55 (10.1)	39 (15.5)	.03
	ECLS	9 (1.1)	3 (0.5)	6 (2.4)	.03
Complication	BNP/pro BNP[c] ↑	74 (9.3)	48 (8.8)	26 (10.4)	.51
	Acute kidney injury[d]	69 (8.6)	37 (6.8)	32 (12.7)	<.01
	Septic shock	43 (5.4)	28 (5.2)	15 (6.0)	.61
	Myocarditis	40 (5.0)	23 (4.2)	17 (6.8)	.16
	Seizures	14 (1.8)	12 (2.2)	2 (0.8)	.25
Continuous variables[e,f]					
Hospital LOS	—	4.0 (1.9–7.6)	3.5 (1.8–6.9)	4.8 (2.5–8.9)	<.01
ICU LOS	—	3.9 (2.0–7.6)	3.7 (1.8–7.4)	4.0 (2.5–8.0)	.17
Ventilator duration	—	4.7 (1.5–7.5)	4.8 (1.5–7.5)	4.6 (1.6–8.8)	.57
NIV duration	—	2.0 (0.9–4.4)	2.0 (0.6–6.0)	2.1 (1.0–3.2)	.69
HFNC duration	—	2.2 (0.8–3.8)	2.0 (0.7–3.7)	2.7 (1.2–4.4)	.24

Values represent median (IQR) or frequency (percentage) as applicable. BNP, brain natriuretic peptide; HFNC, high flow nasal cannula; NIV, noninvasive ventilation.

[a] Maximum degree of respiratory support. Total number of patients with NIV 82 (10.3%), of whom 30 (36.5%) required invasive ventilation.

[b] Maximum degree of respiratory support. Total number of patients who required HFNC 113 (14.2%), of whom 38 (33.6%) required NIV and 32 (28.3%) required invasive ventilation.

[c] Reported as discrete yes or no variable in the data collection forms in the registry for hospital complications (not analyzed based on laboratory values in this study).

[d] Definition of acute kidney injury was not standardized in the registry and may have varied between sites.

[e] Among survivors, ICU LOS missing 2.7% (10 of 368), ventilator duration missing 9.0% (7 of 77), NIV duration missing 3.7% (3/79), HFNC duration missing 18.5% (20 of 108).

f Survived patients only.

intubation and to have more prolonged ICU stays.[3,31] Obesity has also been correlated with mortality in young adult patients[9]; however, we did not find that to be the case in our cohort of hospitalized children. Because this cohort's mortality was relatively low (1.8%), our study may be underpowered to detect such a difference; the post hoc power calculation revealed that this study had a power of 16% to detect the difference observed.[32] The aOR (3.1) of critical COVID-19 in obese patients observed in our study is similar to the relative risk ratio of 2.8 calculated in the recent meta-analysis.[8] However, the variation on the definition of critical illness makes direct comparison difficult.

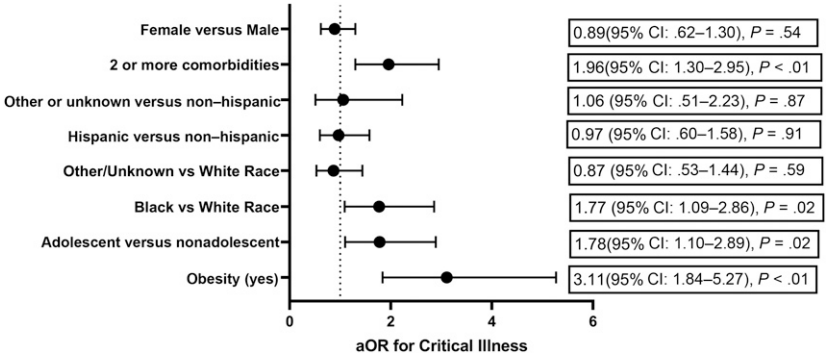

FIGURE 2 Mixed logistic regression model with a random effect for the site for association with critical illness with COVID-19 after controlling for the impact of other risk factors in the model. Interaction effect between adolescent and obesity included in the model and had an adjusted odds ratio of 0.38 (95% CI: 0.18–0.82), P = .01. By using a predicted probability threshold of 0.19, with the R package *cutpoint* to find the optimal threshold, the AUC of the model was 0.77, the sensitivity was 0.78, and the specificity was 0.65.

The percentage of children with obesity in our cohort was higher than the average percentage of children with obesity in the general US population (31.5% vs 17.8% [1221 of 6863],[13] $P < .01$), and in typically hospitalized children (31.5% vs 17.0% [14 137 of 83 329],[33] $P < .01$). Thus, although obesity, in general, has been associated with increased ICU mortality in

TABLE 3 Comparison of Demographics, Comorbidities, and Outcomes in Different BMI Categories (Children ≥2 y Only)

Category	Subcategory	Underweight (*n* = 45)	Normal (*n* = 231)	Overweight(*n* = 79)	Obese (*n* = 120)	Severely Obese (*n* = 107)	*P*[a]
Age		7 (4–12.5)	11 (5.4–15)	11.5 (8–15)	12.9 (7.8–16)	14 (10.9–16)	<.001
Age category	Adolescent, %	13 (28.8)	114 (49.3)	39 (49.4)	68 (56.7)	76 (71.0)	<.001
Sex	Male	25 (55.5)	126 (54.6)	42 (53.2)	68 (56.7)	58 (54.2)	.99
Race	Black	12 (26.7)	61 (26.4)	17 (21.5)	30 (25.0)	30 (28.0)	.23
	White	15 (33.3)	109 (47.2)	35 (44.3)	56 (46.7)	36 (33.6)	
	Other or unknown	18 (40.0)	61 (26.4)	27 (34.2)	34 (28.3)	41 (38.3)	
Ethnicity	Hispanic, %	8 (20.5)	65 (30.8)	26 (37.7)	43 (39.8)	53 (53.0)	<.001
Country	United States	34 (75.5)	221 (95.7)	79 (100)	119 (99.2)	107 (100)	<.001
MIS-C	Yes	10 (25.0)	72 (32.9)	28 (36.4)	44 (39.3)	37 (35.9)	.52
≥3 organ system	Yes	15 (33.3)	123 (53.3)	44 (55.7)	66 (55.0)	76 (71.0)	<.001
Coinfection	Viral	1 (2.2)	10 (4.3)	3 (3.8)	5 (4.2)	0 (0.0)	.29
	Bacterial	10 (22.2)	28 (12.1)	5 (6.3)	17 (14.2)	9 (8.4)	.07
Comorbidity	Yes	23 (51.1)	108 (46.7)	40 (50.6)	58 (48.3)	60 (56.0)	.61
≥2 comorbidity	Yes	12 (26.7)	57 (24.7)	19 (24.1)	30 (25.0)	32 (29.9)	.86
Critical illness	Yes	10 (22.2)	55 (23.8)	20 (25.3)	45 (37.5)	30 (28.0)	.07
ICU admission	Yes	23 (51.1)	117 (50.6)	36 (45.6)	72 (60.0)	65 (60.7)	.13
Mortality	Yes	1 (2.2)	5 (2.2)	1 (1.3)	3 (2.5)	3 (2.9)	.96
Mechanical ventilation	Yes	4 (8.9)	28 (12.1)	11 (13.9)	21 (17.5)	15 (14.0)	.58
Hospital LOS[b]	—	4.9 (3.0–10.9)	4.7 (1.9–7.3)	4.3 (1.9–9.3)	5.5 (2.9–10.5)	5.3 (3.0–8.1)	.04
ICU LOS[b]	—	6.9 (2.0–13.5)	3.5 (1.4–6.1)	4.7 (2.7–8.0)	4.2 (2.9–8.0)	4.0 (2.3–8.6)	.04
Ventilator duration[b]	—	7.6 (5.0–10.1)	4.3 (1.4–6.5)	2.7 (0.3–8.6)	3.0 (1.1–6.1)	6.6 (3.5–15.9)	.23

[a] *P* value of categorical variable by χ^2 test, and for continuous variables by nonparametric Wilcoxon/Kruskal Wallis test. Nonparametric Dunn test with Bonferroni adjustment for multiple comparisons using patients with normal wt as control revealed significant difference in hospital LOS only with obese patients (*P* = .043). No significant difference was observed in ICU LOS between any wt category in comparison with normal wt patients on multiple comparisons.
[b] Survived patients only.

children,[34] our data suggest that the interaction of obesity with COVID-19 predisposes children to higher risk than what is expected from obesity alone.

Our findings of increased hospital and ICU LOS for patients categorized as underweight as well as obese and severely obese aligns with the reports of a J shaped association between BMI and hospital admissions or death due to COVID-19 among adult patients in a large population-based study from the United Kingdom,[35] suggesting a role of nutritional status on disease course and outcome. Although studies on the impact of underweight and severe obesity on COVID-19 in children are lacking, adult studies have revealed that higher BMI has a dose–response relationship with the risk of severe COVID-19.[36]

Multiple mechanisms have been suggested to explain why obesity has a significant impact on the clinical course of acute COVID-19. SARS-CoV-2 penetrates human cells through direct binding with angiotensin-converting enzyme 2 receptors on the cell surface. The angiotensin-converting enzyme 2 expression in adipose tissue has been shown to be higher than that in the lungs.[31] There is also evidence of endothelial dysfunction in obesity[37] and renal disease.[38] The immunologic response to obesity has been characterized by a chronic proinflammatory state, including endoplasmic reticulum stress and localized hypoxia[39] and elevated levels of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6.[40] Our study reported a higher rate of shock requiring inotropes/ECLS and a higher incidence of acute kidney injury in patients with obesity and COVID-19, thus supporting the above hypothesis.

We found that the presence of obesity impacted the outcomes of children with acute COVID-19 more than those with MIS-C. These 2 presentations of SARS-CoV-2–related disease in children have different pathophysiology and clinical manifestations.[2,41] MIS-C is thought to be a "second hit" postinfectious hyperinflammatory condition rather than the result of direct viral-mediated damage.[42] It is possible that the pathophysiological alterations due to obesity amplify the effects of acute COVID infection; however, they may have less impact on the immune dysregulation response theorized to cause MIS-C. These hypotheses need to be further explored in future studies.

Our study revealed a negative correlation of age with disease severity from COVID-19, with obesity having less impact on disease severity in adolescents. Studies in adults have also revealed a similar BMI and age interaction, with the association of BMI with death or mechanical ventilation being most substantial in younger adults compared with older adults.[43] Gao et al[35] demonstrated the highest hazard ratio of

poor prognosis with adult obesity in the youngest age group with progressive decreases in higher age groups. To the best of our knowledge, we are the first to report this interaction in the pediatric population.

This study has limitations inherent to those with other retrospective registry analyses. A complete case analysis such as ours assumes data are missing completely at random. If this assumption is not met, there is potential for bias. The VIRUS registry employs robust data missingness review and cross-validation process with a weekly report to the investigators. However, there is still a possibility of data entry errors. Because of the limitation of the deidentified data set, further source verification could not be conducted for this analysis. A high proportion of hospitalized children have incidental positive polymerase chain reaction of SARS-CoV-2[44,45]; these patients were excluded from the registry. However, the distinction of incidental diagnosis was made by the site investigators. Because of the evolving understanding of the varied COVID-19 presentations, this may have resulted in variability of this characterization leading to a slight over and/or under the inclusion of patients. Variables chosen for the logistic and linear regression models were based on the current theoretical understanding of the risk. There might be other variables associated with critical illness or longer LOS that were not included in our model and could confound the association of obesity. A composite index such as critical illness gives equal weightage to every component of the index, each of which may not be similar from a patient perspective (eg, mortality and noninvasive ventilation are provided the same rank). Although derived from NIH classification, the critical illness definition uses objective parameters to identify patients and may miss some patients who would otherwise qualify for NIH classification of critical illness and vice versa.

CONCLUSIONS

We report obesity as a risk factor for disease severity in pediatric patients hospitalized with acute COVID-19. Hospitalized children with obesity are more likely to have critical illness than hospitalized children without obesity. Although adolescents made up a higher proportion of patients with obesity, adolescent age was itself an independent risk for critical illness, thereby potentially decreasing the impact of obesity on critical illness within this group.

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Access to deidentified patient data are dependent on guidelines of the VIRUS registry. Further information about access to de-identified data from the VIRUS registry can be requested from Dr Vishakha Kumar at vkumar@sccm.org

This trial has been registered at www.clinicaltrials.gov (identifier NCT 04323787).

Dr Tripathi designed the study, designed the data collection instruments, obtained data from the Viral Respiratory Illness Universal Study (VIRUS) registry, conducted the initial analysis and interpretation, and supervised the literature search and drafted the initial manuscript and the final manuscript; Dr Arteaga conceptualized the study, assisted in the literature search and drafting of the initial manuscript, and reviewed the final manuscript and provided critical input for intellectual content; Dr Christison and Dr Levy assisted in the concept and design of the study, literature search, and drafting of the initial manuscript; Mr McGarvey performed statistical analysis and interpretation for the manuscript; Dr Tekin, Ms Bolliger, Dr Chiotos, Dr Gist, Dr Dapul, Dr Bhalala, Dr Gharpure, Dr Heneghan, Dr Gupta, Dr Bjornstad, and Dr Montgomery supervised or performed data collection at their sites and assisted in the review and provided critical input for intellectual content; Dr Kashyap, Dr Walkley, and Dr Kumar are the principal investigators of the VIRUS registry, conceptualized and designed the data collection instruments (REDCap) for the registry, and reviewed and provided critical input for intellectual content; Dr Bansal assisted in data collection and extraction for this manuscript from the VIRUS registry and reviewed the final manuscript and provided necessary inputs in design and analysis; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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In this study, we leverage data from the Society of Critical Care Medicine VIRUS registry on 795 patients from 45 sites to describe the impact of obesity on disease severity with COVID-19 in children.

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