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

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Subtitle: A retrospective review of the VIRUS registry.

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On Behalf of the *Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group*
A complete list of study group members is included in the Appendix. These investigators served as collaborators and site investigators and should be indexed in PubMed as collaborative co-authors on this manuscript.

Short Title: Obesity and COVID-19 in children

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Access to de-identified patient data is 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.

Abbreviations

ICU Intensive Care Unit, NIH National Institute of Health, CDC Centers for Disease Control, WHO World Health Organization, SCCM Society of Critical Care Medicine, VIRUS Viral Infection and Respiratory Illness Universal Study, MIS-C Multisystem Inflammatory Syndrome in Children, PRISM Pediatric Risk of Mortality, BMI Body Mass Index

Author Contributions

Dr. Tripathi designed the study. He designed the data collection instruments, obtained data from the VIRUS registry, and carried out the initial analysis and interpretation. He supervised the literature search and drafted the initial manuscript and the final manuscript. Dr. Arteaga conceptualized the study. She assisted in the literature search and drafting of the initial manuscript. She 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. They 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. They conceptualized and designed the data collection instruments (REDCap) for the registry. They reviewed and provided critical input for intellectual content. Dr. Bansal assisted in data collection and extraction for this manuscript from the VIRUS registry. He reviewed the final manuscript and provided necessary inputs in design and analysis.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Article summary

This study leverages data from the SCCM VIRUS registry on 795 patients from 45 sites to describe the impact of obesity on disease severity with COVID-19 in children.

What is known about the subject?

Obesity is associated with worse outcomes among adults with COVID-19. The overall prognosis of children with COVID-19 is favorable; however, a small proportion of children get acutely sick with COVID-19 and require invasive respiratory and hemodynamic support.

What this study adds to the subject

This study shows that 31.5% of all hospitalized children with COVID-19 in the VIRUS registry had obesity. Children with obesity had higher rates of critical illness (aOR 3.11, p<0.01) and had longer adjusted hospital length of stay (30% longer, p<0.01) compared to children without obesity. However, rates of mortality due to COVID-19 were similar between these groups, p=0.38.

Abstract

Objective: To describe the impact of obesity on disease severity and outcomes of COVID-19 among hospitalized children.

Methods: This retrospective cohort study from the SCCM VIRUS registry included all children hospitalized with COVID-19 from 3/2020 to 01/2021. Obesity was defined by CDC Body Mass Index or WHO weight for length criteria. Critical Illness definition adapted from NIH criteria of critical COVID. Multivariate mixed logistic and linear regression was performed to calculate the adjusted odds ratio (aOR) of critical illness and the adjusted impact of obesity on hospital length of stay (LOS).

Results: Data from 795 patients (96.4% U.S.) 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 MIS-C (35.7% vs. 28.1%, p= 0.04) and had higher ICU admission rates (57% vs. 44%, p<0.01) with more critical illness (30.3% vs. 18.3%, p<0.01). Obesity had more impact on acute COVID-19 severity than on MIS-C presentation. The aOR for critical illness with obesity was 3.11 (95% CI 1.8, 5.3). Patients with obesity had longer adjusted LOS (exp parameter estimate 1.3 (95% CI 1.1, 1.5) compared to patients without obesity but did not have increased mortality risk due to COVID-19 (2.4% vs. 1.5%, p=0.38).

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

Introduction

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.[3,4-6, 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% CI 1.1, 7.0) in children with obesity. However, this analysis was performed on a small subset of

studies, including fewer than 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 under five years of age are estimated to be affected by obesity or

overweight, according to the World Health Organization (WHO).[12] The United States (U.S.) is

particularly affected by this epidemic, with 18% of U.S. children diagnosed with obesity and 6%

with severe obesity.[13,14] Elucidating to what degree obesity affects COVID-19 severity in a

larger, multi-center cohort of children can help guide prevention, prognostication, and clinical

care.

This study's primary objective 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 (SCCM) 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-CO-V-2 infection from 03/20 to 01/21. 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 body mass index (BMI) and weight for height percentiles were also excluded. There is possibility of significant overlap between the patients included in this manuscript and those already reported in the literature. Therefore, in keeping with current reporting recommendations, [17] we have provided details of manuscripts that may contain overlapping patients. (SDC A)

Measurements

Demographic (age, gender, race/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 due to their complex relationship with social-economic disparities in healthcare access.[19] Age was stratified into discrete categories; neonate ($\leq$28 days), infant (28 days to <2 years), child (2 to <12 years), and adolescent ($\geq$12 years).[20] BMI percentiles for children $\geq$ 2 years of age were calculated based on Centers for Disease Control (CDC) SAS codes[21]; while the weight for length percentiles for children <2 years of age were calculated based on WHO SAS codes.[22] Categorization of underweight, normal, overweight, and obese were defined by CDC criteria for $\geq$ 2 years (< 5th, 5th to <85th, 85th to <95th and $\geq$95th BMI percentiles respectively),[23] and WHO weight for length percentile criteria of

+2 and +3 standard deviations 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 co-infection." Patients with concurrent blood, urine, and bacterial respiratory infections were combined into categories of "bacterial co-infection". Diagnosis of Multisystem Inflammatory Syndrome in Children (MIS-C) was made by the individual sites based on the CDC definition[25] and was not further adjudicated for this analysis.

Outcomes

The outcome measures of hospital length of stay (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 one or more of the following: 1) positive pressure ventilation (invasive or non-invasive), 2) vasoactive – inotropic support, 3) pulmonary vasodilator therapy (inhaled nitric oxide, epoprostenol), 4) extracorporeal life support (ACLS) and/or 5) new renal replacement therapy (Acute Dialysis or Continuous Renal Replacement Therapy [CVVH]). This classification was modified from the National Institute 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 Inter Quartile Range (IQR) and number with percentages. The nonparametric Wilcoxon rank-sum test and Chi-square/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% confidence interval (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 based on the theoretical understanding of their impact on critical illness and hospital length of stay and their interaction with obesity. A Directed Acyclic Graph (DAG) was created to represent the causal relationships using standard terminology and rules as described before. [27,28] (SDC B) Age (adolescent and non-adolescent), race (Black, White and others/unknown), ethnicity (Hispanic, non-Hispanic, other/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). Due to non-normal distribution, LOS was log-transformed, and parameter estimates and confidence intervals 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 due to their potential impact on the length of stay. Mediator analysis as described by Baron and Kenny[29] indicated at least partial mediation of the impact of obesity on length of stay by these variables. These variables were thus excluded from the linear regression model presented. Complete mediator analysis for the length

of stay model is provided in SDC C. 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 using JMP (v 16.0) SAS Institute, Cary, NC, and an open-source statistical program *R* (V 4.0.0). P-value <0.05 was considered statistically significant. This study reporting conforms to the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) statement [30] (SDC D).

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 pre-specified 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 (Figure 1). Only 11.2% (24/213) of children <2 years met the criteria for obesity as compared to 39% (227/582) of children between 2-18 years. The proportion of patients within the four weight categories by age (< 2 and ≥ 2 years) is provided in SDC E.

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<0.01) with more adolescents comprising the group with obesity compared to the group without (57.4% [144/251] vs 30.5% [166/544], p<0.01. There was no difference in the sex or race distribution among the two groups; however, there was a much higher proportion of patients of Hispanic ethnicity in patients with obesity (47.8% [108/251] vs. 32.9% [158/544], p<0.01. Patients from the U.S.

comprised 96.4% (767/795) of the total cohort, with a higher proportion of patients from the U.S. in the obese category (99.2% [249/251] vs. 95.2% [518/544]. Patients with obesity were more likely to have a diagnosis of MIS-C as opposed to acute COVID-19 (35.7% [85/251] vs. 28.1% [147/544], p=0.04) and were more likely to have ≥3 organ system involvement at presentation (61.4% [154/251] vs. 47.8% [260/544], p<0.01). Among the five most common signs and symptoms, fever was more common in patients without obesity, while patients with obesity were more likely to present with dyspnea/shortness of breath and cough. Presence of any other comorbidity was more likely in patients with obesity (48.6% [122/251] vs 40.0% [218/544], p= 0.02). Among the five most common comorbidities, asthma was significantly more common in children with obesity (18.3% [46/251] vs. 9.0% [49/544], p<0.01). (Table 1). Comparison of all signs and symptoms and comorbidities included in the VIRUS registry between patients with and without obesity is provided in SDC F&G.

Disease course and Outcomes

A total of 14 patients died during their hospitalization (14/795, 1.7% mortality). There was no difference in mortality rate due to COVID-19 between those with obesity (2.4% [6/251]) and those without (1.5% [8/544], p=0.38). A higher proportion of patients with obesity were admitted to the ICU (56.9% [143/251] versus 43.9% [239/544], p<0.01) and had critical illness related to COVID-19 (30.3% [76/251] versus 18.3% [100/544], p<0.01). There was a greater need for various organ support interventions, including mechanical ventilation, inotropes, and ECLS, in patients with obesity. Among the five most prominent complications recorded in the registry, only acute kidney injury was significantly more common in those with obesity (12.7% [32/251 vs. 6.8% [37/544], p<0.01). Comparative rates of all complications in the VIRUS registry are provided in SDC H. 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<0.01). There was no difference in ICU length of stay or the duration of the ventilator and other modes of oxygen therapy between the two groups. (Table 2)

Risk Factors for Critical Illness and Hospital Length of stay.

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 (aOR 3.11 [95% CI 1.84, 5.27], p<0.01). 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 to 17% for patients ≥12 years (Figure 2). Separate analysis for factors associated with critical illness among the cohort with obesity (n=251) demonstrated that the presence of ≥2 comorbidities was marginally associated with the critical illness (aOR 1.90 (95% CI 1.01, 3.58), p=0.05). (SDC I) 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 length of stay (exponentiated parameter estimate 1.3 (95% CI 1.1, 1.5), p<0.01. (SDC J)

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% (153/528) had obesity. Patients with obesity in this cohort were older (median age 13.2 years vs. 4 years, p<0.001), more likely to be Hispanic, and had more comorbidities. A higher proportion of those with obesity and acute

COVID-19 had critical illness (22% versus 11%, p= 0.001), required ICU admission (50% versus 33%, p<0.001), mechanical ventilation (13% versus 6.7%, p= 0.01) and had longer hospital length of stay (3.8 [IQR 2.0, 7.3] days vs 2.8 [1.5, 5.9] days, p=0.004). (SDC K) In contrast, even though a higher proportion of MIS-C patients had obesity (36.6%, 85/232), there was no significant difference in critical illness, ICU admission, or mechanical ventilation rate in MIS-C patients with obesity and compared to those without obesity. However, a similar increased length of stay occurred among the MIS-C cohort with obesity as for those with acute COVID-19 (8.0 [IQR 4.7, 10.4] days vs. 5.7 [3.1, 9.4] days, p=0.01). (SDC L)

Comparison of Disease Severity among Children and Adolescents in Different Weight Categories (≥2 years)

Comparative analysis across five different weight categories (underweight to severe obesity) showed that the median age was higher with increasing weight categories. Adolescents comprised 71% of the patients with severe obesity compared to 28.8% of underweight patients. There was no difference in race or sex distribution across the groups; however, Hispanics comprised 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 to those in underweight (33%) and normal weight (53%) categories. Even though notable differences were observed in the rates of MIS-C, critical illness, and ICU admission across the five weight categories, they did not reach statistical significance. Both patients with underweight and obesity/severe obesity significantly longer hospital and ICU length of stay than those with normal weight (p=0.04). Although, a significant difference on multiple group comparison with Bonferroni adjustment was only observed for obese vs. 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 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. Since this cohort's mortality was relatively low (1.8%), our study may be underpowered to detect such a difference; the post hoc power calculation showed 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.

The percentage of children with obesity in our cohort was higher than the average percentage of children with obesity in the general U. S. population (31.5% vs. 17.8% [1221/6863],[13] p<0.01), and in typically hospitalized children (31.5% vs. 17.0% [14,137/83,329],[33] p<0.01). Thus, while obesity, in general, has been associated with increased ICU mortality in 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 length of stay 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/death due to COVID-19 among adult patients in a large population-based study from the UK,[35] suggesting a role of nutritional status on disease course and outcome. While studies on the impact of underweight/severe obesity on COVID-19 in children are lacking, adult studies have shown 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 (ACE 2) receptors on the cell surface. The ACE2 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 immunological response to obesity has been characterized by a chronic pro-inflammatory state, including endoplasmic reticulum stress and localized hypoxia[39] and elevated levels of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF 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 two 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" post-infectious hyper-inflammatory 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 showed 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 demonstrated a similar BMI and age interaction, with the association of BMI with death or mechanical ventilation being most substantial in younger adults compared to 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 is Missing Completely at Random (MCAR). 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. Due to the limitation of the de-identified data set, further source verification could not be conducted for this analysis. A high proportion of hospitalized children have incidental positive PCR 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. Due to 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 which 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 (e.g., mortality and non-invasive 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.

In conclusion, 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. Though adolescents comprised of 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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Figure Legends

Figure 1: Patient selection flow diagram

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% C.I 0.18, 0.82), p=0.01. Using a predicted probability threshold of 0.19, using 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.

SDC B (Figure): Directed Acyclic Graph (DAG) elucidating the conceptual framework on the causal effect of obesity [A] on critical illness from COVID-19 (Y).

Confounders/common causes include Age [B], Sex [C], race and ethnicity [L], and other comorbidities [D], that may cause an association between obesity [A] and critical illness [Y], which is not due to an effect of A on Y. Box represent blocked 'back door path' by the inclusion of the factors in the regression model. Socio-economic disparities [U] is a confounder; however, it is not measured in the study. Race and ethnicity [L] is used as a surrogate/proxy confounder. It will not eliminate all confounding, so the possibility of bias remains. E represents selection bias (patients with critical illness more likely to be entered in the registry, and bias may occur if obese patients are also more likely to be hospitalized for reasons unrelated to COVID-19.
A* represent measurement error in obesity (missing/erroneous data), and Y* represents measurement error in diagnosing critical COVID-19 (not all patients with critical COVID-19 with be captured by our definition). U_A and U_Y represent unmeasured causes of errors (partially dependent if the same person is entering data on obesity and outcomes), but non-differential (outcome of critical illness is not expected to impact error in entering BMI data.

Table 1: Demographics of the study population

Category	Subcategory	Total cohort (n=795)	Non-obese (n= 544)	Obese (n= 251)	*P* value
Age		8.0 (1.6, 14.0)	5.31 (0.83, 13.0)	13.0 (7.0, 16.0)	<0.01
Age category	Neonate	31 (3.8%)	28 (5.1%)	3 (1.2%)	<0.01
	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	% Males	433 (54.4%)	293 (53.8%)	140 (50.8%)	0.64
Race	Black	186 (23.3%)	125 (22.9%)	61 (24.3%)	0.72
	White	349 (43.8%)	244 (44.8%)	105 (41.8%)	
	Others	260 (32.7%)	175 (32.2%)	85 (33.9%)	
Ethnicity[1]	Hispanic	266 (37.6%)	158 (32.9%)	108 (47.8%)	<0.01
	Non-Hispanic	440 (62.3%)	322 (67.1%)	118 (52.2%)	
Country[3]	United States	767 (96.4%)	518 (95.2%)	249 (99.2%)	<0.01
Coinfection	Viral	34 (4.2%)	28 (5.2%)	6 (2.4%)	0.08
	Bacterial	102 (12.8%)	73 (13.4%)	29 (11.6%)	0.49
MIS-C[2]	Yes	232 (30.5%)	147 (28.1%)	85 (35.7%)	0.04
≥3 organ system involvement	Yes	414 (52.0%)	260 (47.8%)	154 (61.4%)	<0.01
Signs and symptoms	Fever	534 (67.1%)	379 (69.7%)	155 (61.8%)	0.02
	Nausea vomiting	276 (34.7%)	177 (32.5%)	99 (39.4%)	0.06
	Cough	238 (29.9%)	149 (27.4%)	89 (35.5%)	0.02
	Abdominal pain	201 (25.3%)	128 (23.5%)	73 (29.1%)	0.09
	Dyspnea	175 (22.0%)	91 (16.7%)	84 (33.5%)	<0.01
Comorbidity	Yes	340 (42.7%)	218 (40.0%)	122 (48.6%)	0.02
≥2 comorbidities		179 (22.5%)	114 (20.9%)	65 (25.9%)	0.12
Comorbidity types	Asthma	95 (11.9%)	49 (9.0%)	46 (18.3%)	<0.01
	Seizures	62 (7.7%)	40 (7.4%)	22 (8.8%)	0.48
	Developmental delay	54 (6.7%)	34 (6.3%)	20 (7.9%)	0.36
	Diabetes	23 (2.8%)	12 (2.2%)	11 (4.4%)	0.11
	CLD/BPD	19 (2.3%)	13 (2.4%)	6 (2.4%)	1.0

[1]Ethnicity missing in 89 patients (11.2%). [2] MIS-C missing 4.4% (35/795), [4.0% in nonobese (22/544) and 5.2% in obese (13/251)]. Values represent proportion out of 760, 522 and 238 respectively. [3]Pakistan 13 (1.6%), India 7 (0.8%), Croatia 6 (0.7%), Saudi Arabia 2 (0.2%). CLD chronic lung disease. BPD Bronco Pulmonary dysplasia. p values represent comparison of cohort with and without obesity. Values represent Median (IQR) or number (percentage) as applicable.

Table 2: Hospital Course and Outcomes

Category	Subcategory	Total cohort (n=795)	Non obese (n= 544)	Obese (n= 251)	P value
Categorical variables					
Hospital Mortality		14 (1.7%)	8 (1.5%)	6 (2.4%)	0.38
ICU admission		382 (48.0%)	239 (43.9%)	143 (56.9%)	<0.01
Critical illness		176 (22.1%)	100 (18.3%)	76 (30.3%)	<0.01
Organ support	Invasive ventilator	90 (11.3%)	53 (9.7%)	37 (14.7%)	0.04
	NIV[1]	52 (6.5%)	25 (4.6%)	27 (10.7%)	<0.01
	HFNC[2]	58 (7.2%)	26 (10.3%)	32 (5.8%)	0.03
	Inotropes	94 (11.8%)	55 (10.1%)	39 (15.5%)	0.03
	ECLS	9 (1.1%)	3 (0.5%)	6 (2.4%)	0.03
Complication	BNP/pro BNP[3] ↑	74 (9.3%)	48 (8.8%)	26 (10.4%)	0.51
	Acute kidney injury[4]	69 (8.6%)	37 (6.8%)	32 (12.7%)	<0.01
	Septic shock	43 (5.4%)	28 (5.2%)	15 (6.0%)	0.61
	Myocarditis	40 (5.0%)	23 (4.2%)	17 (6.8%)	0.16
	Seizures	14 (1.8%)	12 (2.2%)	2 (0.8%)	0.25
Continuous variables[5&6]					
Hospital length of stay		4.0 (1.9, 7.6)	3.5 (1.8, 6.9)	4.8 (2.5, 8.9)	<0.01
ICU length of stay		3.9 (2.0, 7.6)	3.7 (1.8, 7.4)	4.0 (2.5, 8.0)	0.17
Ventilator duration		4.7 (1.5, 7.5)	4.8 (1.5, 7.5)	4.6 (1.6, 8.8)	0.57
NIV duration		2.0 (0.9, 4.4)	2.0 (0.6, 6.0)	2.1 (1.0, 3.2)	0.69
HFNC duration		2.2 (0.8, 3.8)	2.0 (0.7, 3.7)	2.7 (1.2, 4.4)	0.24

[1&2]Maximum degree of respiratory support. Total number of patients with NIV 82 (10.3%), of which 30 (36.5%) required invasive ventilation. Total number of patients who required HFNC 113 (14.2%), of which 38 (33.6%) required NIV and 32 (28.3%) required invasive ventilation.[3]Reported as discrete yes/no variable in the data collection forms in the registry for hospital complications (not analyzed based on laboratory values in this study). [4]Definition of acute kidney injury was not standardized in the registry and may have varied between sites. [5] Among survivors, ICU length of stay missing 2.7% (10/368), ventilator duration missing 9.0% (7/77), NIV duration missing 3.7% (3/79), HFNC duration missing 18.5% (20/108). [6] Survived patients only.
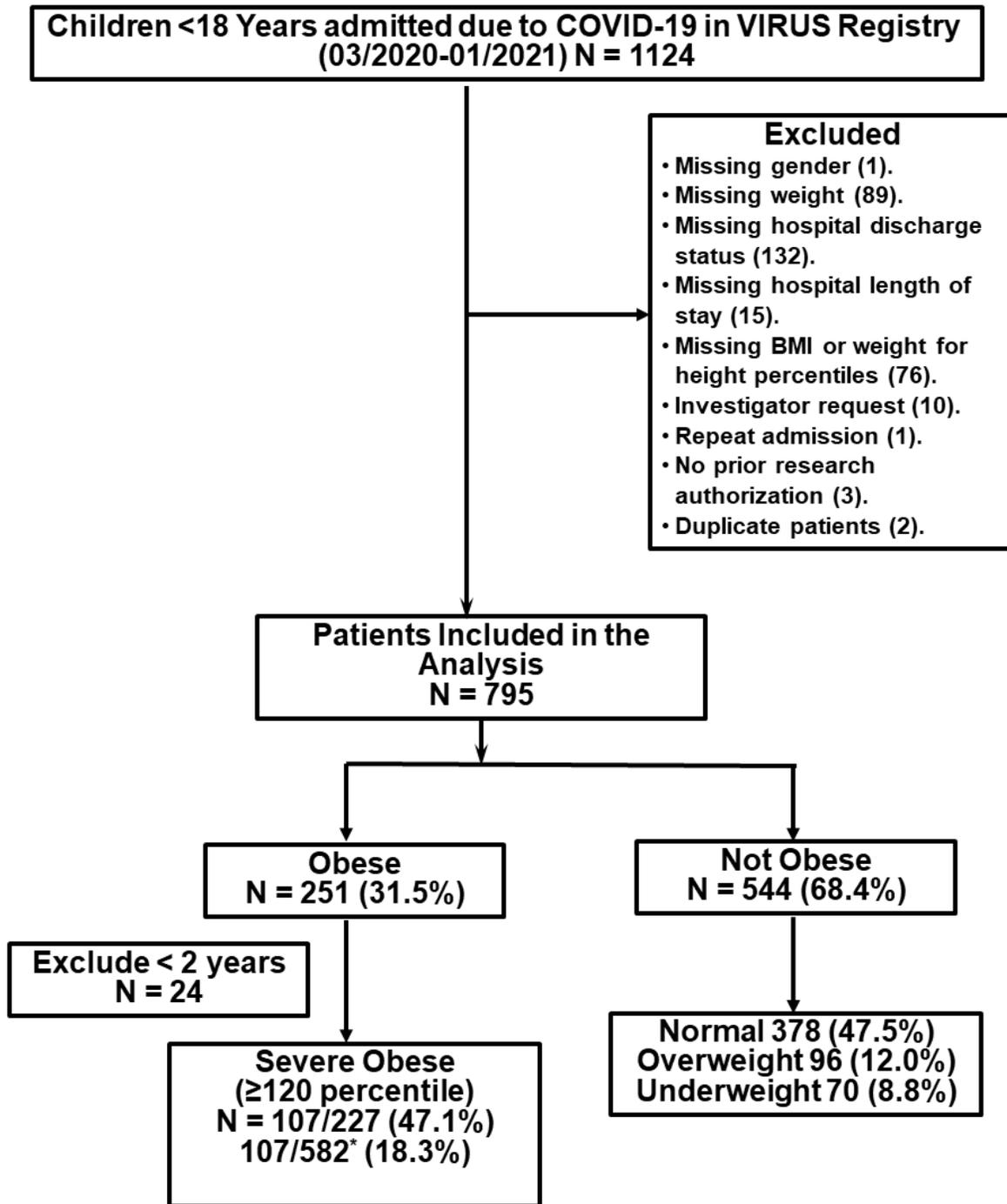
Values represent median (IQR) or frequency (percentage) as applicable.

NIV Non-Invasive Ventilation, HFNC High Flow Nasal Cannula, ECLS Extracorporeal Life Support, BNP Brain Natriuretic Peptide,
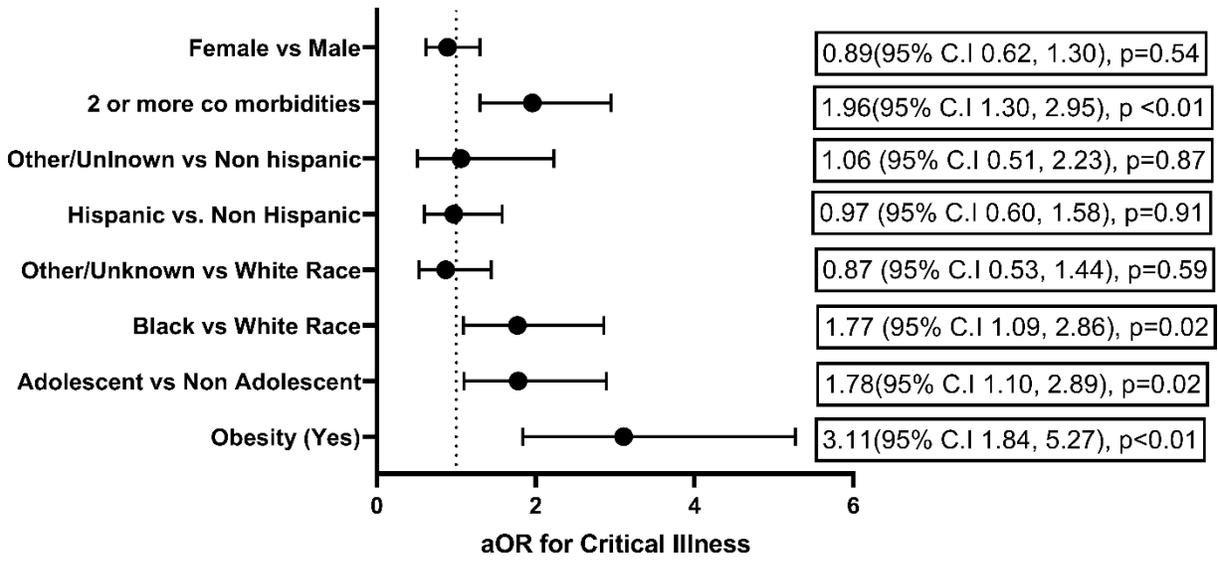
Table 3: Comparison of demographics, comorbidities and outcomes in different BMI categories (children≥2 years only)

Category	Subcategory	Underweight (n= 45)	Normal (n= 231)	Overweight (n= 79)	Obese (n= 120)	Severely obese (n= 107)	P value#
Age		7 (4, 12.5)	11 (5.4, 15)	11.5 (8, 15)	12.9 (7.8, 16)	14 (10.9, 16)	<0.001
Age category	% Adolescent	13 (28.8%)	114 (49.3%)	39 (49.4%)	68 (56.7%)	76 (71.0%)	<0.001
Sex	Males	25 (55.5%)	126 (54.6%)	42 (53.2%)	68 (56.7%)	58 (54.2%)	0.99
Race	Black	12 (26.7%)	61 (26.4%)	17 (21.5%)	30 (25.0%)	30 (28.0%)	0.23
	White	15 (33.3%)	109 (47.2%)	35 (44.3%)	56 (46.7%)	36 (33.6%)	
	Other/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%)	<0.001
Country	United States	34 (75.5%)	221 (95.7%)	79 (100%)	119 (99.2%)	107 (100%)	<0.001
MIS-C	Yes	10 (25.0%)	72 (32.9%)	28 (36.4%)	44 (39.3%)	37 (35.9%)	0.52
≥3 organ system	Yes	15 (33.3%)	123 (53.3%)	44 (55.7%)	66 (55.0%)	76 (71.0%)	<0.001
Coinfection	Viral	1 (2.2%)	10 (4.3%)	3 (3.8%)	5 (4.2%)	0 (0.0%)	0.29
	Bacterial	10 (22.2%)	28 (12.1%)	5 (6.3%)	17 (14.2%)	9 (8.4%)	0.07
Comorbidity	Yes	23 (51.1%)	108 (46.7%)	40 (50.6%)	58 (48.3%)	60 (56.0%)	0.61
≥2 comorbidity	Yes	12 (26.7%)	57 (24.7%)	19 (24.1%)	30 (25.0%)	32 (29.9%)	0.86
Critical illness	Yes	10 (22.2%)	55 (23.8%)	20 (25.3%)	45 (37.5%)	30 (28.0%)	0.07
ICU admission	Yes	23 (51.1%)	117 (50.6%)	36 (45.6%)	72 (60.0%)	65 (60.7%)	0.13
Mortality	Yes	1 (2.2%)	5 (2.2%)	1 (1.3%)	3 (2.5%)	3 (2.9%)	0.96
Mechanical ventilation	Yes	4 (8.9%)	28 (12.1%)	11 (13.9%)	21 (17.5%)	15 (14.0%)	0.58
Hospital length of stay*		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)	0.04
ICU length of stay*		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)	0.04
Ventilator duration*		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)	0.23

*Survived patients only. #P value of categorical variable by chi-square test, and for continuous variables by nonparametric Wilcoxon/Kruskal Wallis test. Nonparametric Dunn test with Bonferroni adjustment for multiple comparisons using patients with normal weight as control, showed significant difference in hospital LOS only with obese patients (p=0.043). No significant difference was observed in ICU length of stay between any weight category in comparison to normal weight patients on multiple comparisons.

Children <18 Years admitted due to COVID-19 in VIRUS Registry
(03/2020-01/2021) N = 1124

Excluded
• Missing gender (1).
• Missing weight (89).
• Missing hospital discharge
  status (132).
• Missing hospital length of
  stay (15).
• Missing BMI or weight for
  height percentiles (76).
• Investigator request (10).
• Repeat admission (1).
• No prior research
  authorization (3).
• Duplicate patients (2).

Patients Included in the
Analysis
N = 795

Obese
N = 251 (31.5%)

Not Obese
N = 544 (68.4%)

Exclude < 2 years
N = 24

Severe Obese
(≥120 percentile)
N = 107/227 (47.1%)
107/582* (18.3%)

Normal 378 (47.5%)
Overweight 96 (12.0%)
Underweight 70 (8.8%)

Female vs Male — 0.89(95% C.I 0.62, 1.30), p=0.54

2 or more co morbidities — 1.96(95% C.I 1.30, 2.95), p <0.01

Other/Uninown vs Non hispanic — 1.06 (95% C.I 0.51, 2.23), p=0.87

Hispanic vs. Non Hispanic — 0.97 (95% C.I 0.60, 1.58), p=0.91

Other/Unknown vs White Race — 0.87 (95% C.I 0.53, 1.44), p=0.59

Black vs White Race — 1.77 (95% C.I 1.09, 2.86), p=0.02

Adolescent vs Non Adolescent — 1.78(95% C.I 1.10, 2.89), p=0.02

Obesity (Yes) — 3.11(95% C.I 1.84, 5.27), p<0.01

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

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