ORIGINAL RESEARCH

Pediatric OBESITY WILEY

Outcomes and risk factors of death among hospitalized children and adolescents with obesity and COVID-19 in Brazil: An analysis of a nationwide database

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Summary

Background: Obesity is a well-recognized risk factor for critical illness and death among adult patients with SARS-CoV-2 infection.

Objective: This study aimed to characterize the clinical outcomes and risk factors of death related to obesity in a cohort of hospitalized paediatric patients with COVID-19.

Methods: We performed an analysis of all paediatric patients with obesity and COVID-19 registered in SIVEP-Gripe, a Brazilian nationwide surveillance database, between February 2020 and May 2021. The primary outcome was time to death, which was evaluated by using cumulative incidence function.

Results: Among 21 591 hospitalized paediatric patients with COVID-19, 477 cases (2.2%) had obesity. Of them, 71 (14.9%) had a fatal outcome as compared with 7.5% for patients without obesity (hazard ratio [HR] = 2.0, 95% confidence interval [CI] 1.59–2.53, $p < 0.001$). After adjustment, the factors associated with death among patients with obesity were female gender (HR = 2.8, 95% CI 1.70–4.61), oxygen saturation < 95% (HR = 2.58, 95% CI 1.38–4.79), presence of one (HR = 1.91, 95% CI 1.11–3.26), and two or more comorbidities (HR = 4.0, 95% CI 2.21–7.56).

Conclusions: Children and adolescents with obesity had higher risk of death compared with those without obesity. The higher risk of death was associated with female gender, low oxygen saturation at admission, and presence of other comorbidities.

KEYWORDS
children, COVID-19, obesity, outcome, risk factors, SARS-CoV-2

1 | INTRODUCTION

Obesity has been well established as an independent risk factor for adverse COVID-19 outcomes in adults.[1–3] Some studies suggests that obesity predisposes children to SARS-CoV-2 infection.[4] Accordingly, nationwide data from paediatric cases in Mexico reported that

SARS-CoV-2 infection seems to be significantly more frequent among children with obesity.[5] Concomitantly, essential non-pharmacological measures to control the COVID-19 pandemic are worsening the childhood overweight and obesity epidemic globally.[6,7] Consequently, the disruption in the diet and activities of children and adolescents due to lockdown policies may place paediatric

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patients at greater risk for SARS-CoV-2 infection and maybe severe forms of COVID-19.[8]

Severe SARS-CoV-2 illness is less common in the paediatric population compared with that in adults.[9,10] However, hospitalization, intensive care admission and even death have occurred in children and adolescents.[11–13] It is therefore crucial to identify risk factors associated with clinical outcomes of COVID-19 in paediatric patients. It has been previously reported that childhood obesity may also increase the risk of severe COVID-19.[14] However, few paediatric studies have addressed the association of obesity with COVID-19 severity in children and adolescents. In addition, the paediatric studies conducted have several limitations, including small sample sizes, precluding a comprehensive investigation of risk factors, and confounding covariates.[12] In a review article, Nogueira de Almeida et al.[8] commented that additional studies with large cohorts of paediatric patients are still necessary to investigate the role of obesity as a risk factor for morbidity and mortality related to COVID-19.

We previously characterized the first 11 613 children and adolescents hospitalized for COVID-19 in Brazil in 2020[15] and, in a subsequent study, we compared the first wave and the second wave of COVID-19 in a total of 21 591 paediatric patients hospitalized.[16] In both studies, we found a similar mortality rate (7.6% of hospitalized paediatric patients) and the same risk factors for death, including residing in the poorest regions of the country (North and Northeast), being of indigenous ethnicity, age younger than 2 years or adolescents and an additive effect according to the number of comorbidities. However, in both studies we did not address the issue of the impact of specific comorbidities on clinical outcomes. Therefore, in the present study, we focused our analysis on children and adolescents with obesity among 21 591 hospitalized paediatric patients with COVID-19 by using the same database Influenza Epidemiological Surveillance Information System (SIVEP-Gripe), a Brazilian nationwide registry.[17] Using this dataset, we aimed to describe the features and outcomes of paediatric patients with obesity and to evaluate the risk factors for COVID-19 related-death in this population.

2 | METHODS

2.1 | Study design

We performed a retrospective cohort study including all hospitalized paediatric cases recorded in the SIVEP-Gripe. Detailed information regarding this database, including reporting form and data dictionary, codes, and all de-identified data, are publicly available at https://opendatasus.saude.gov.br/dataset.

2.2 | Participants and case-defining

We included all consecutively registered patients, aged less than 20 years, with a positive quantitative reverse transcription polymerase chain reaction (RT-qPCR) test result for SARS-CoV-2 infection, which had been admitted to the hospital. For the present study, we integrated two datasets. We downloaded the first database on 10 January 2021 and the second database on 29 May 2021. For the purpose of analysis, we merged both datasets into a unique database and the cases were divided into two groups: (1) Wave 1 (44 epidemiological weeks from 16 February 2020 to 31 December 2020) and (2) Wave 2 (19 epidemiological weeks from 1 January 2021 to 29 May 2021). In addition, we updated on 29 May 2021, the outcomes of interest for paediatric patients admitted at Wave 1.

We identified cases with obesity by revising the close-end fields regarding comorbidities in the SIVEP-Gripe database. The detailed information about included and excluded cases was displayed in the flowchart (Figure 1).

2.3 | Covariates and definitions

Clinical, demographic, and epidemiological data recorded in SIVEP-Gripe are described elsewhere.[15] For analysis purpose, we created a categorical covariate to include all other comorbidities. This variable considered the sum of the other comorbidities included in the SIVEP-gripe. Beyond obesity, the other comorbidities including in the SIVEP-gripe were heart disease, pulmonary disease, asthma, renal diseases, hepatic disease, autoimmune disease, neurologic disease, hematologic disease, and diabetes. The variable was categorized into four groups (none, 1, 2, and 3 or more comorbidities).

The clinical course of the disease was reported in terms of respiratory support (none, non-invasive oxygen support, and mechanical ventilation), admission to intensive care unit (ICU), discharge, death, and ongoing clinical situation.

2.4 | Outcome

The primary outcome was time until death (in-hospital-mortality). The survival time was defined from the day of admission until the event of interest (death or discharge).

2.5 | Statistical analysis

Median and interquartile range or mean and standard deviation summarized continuous variables, and calculated frequencies and proportions were used for categorical variables. We used the chi-square test to compare the proportions between the groups. For comparison of means, the independent samples t-test for two groups was used (equal variance not assumed). Mortality was evaluated by competing risks analysis, with discharge as competitive event, using cumulative incidence function (CIF)[18] and the Fine and Gray model.[19] The covariates used for multivariate analyses were chosen based on their significance in the univariate analysis ($p < 0.20$). Then, using a backward elimination strategy, those variables that retained an independently significant association with the outcome were included in the final model. Proportionality assumption for the competing risks model was graphically checked by using the plot of log[-log(1-CIF)] against log (time).[20] The assumption of proportionality

FIGURE 1   Flow diagram of cohort selection. RT-qPCR, quantitative reverse transcription polymerase chain reaction
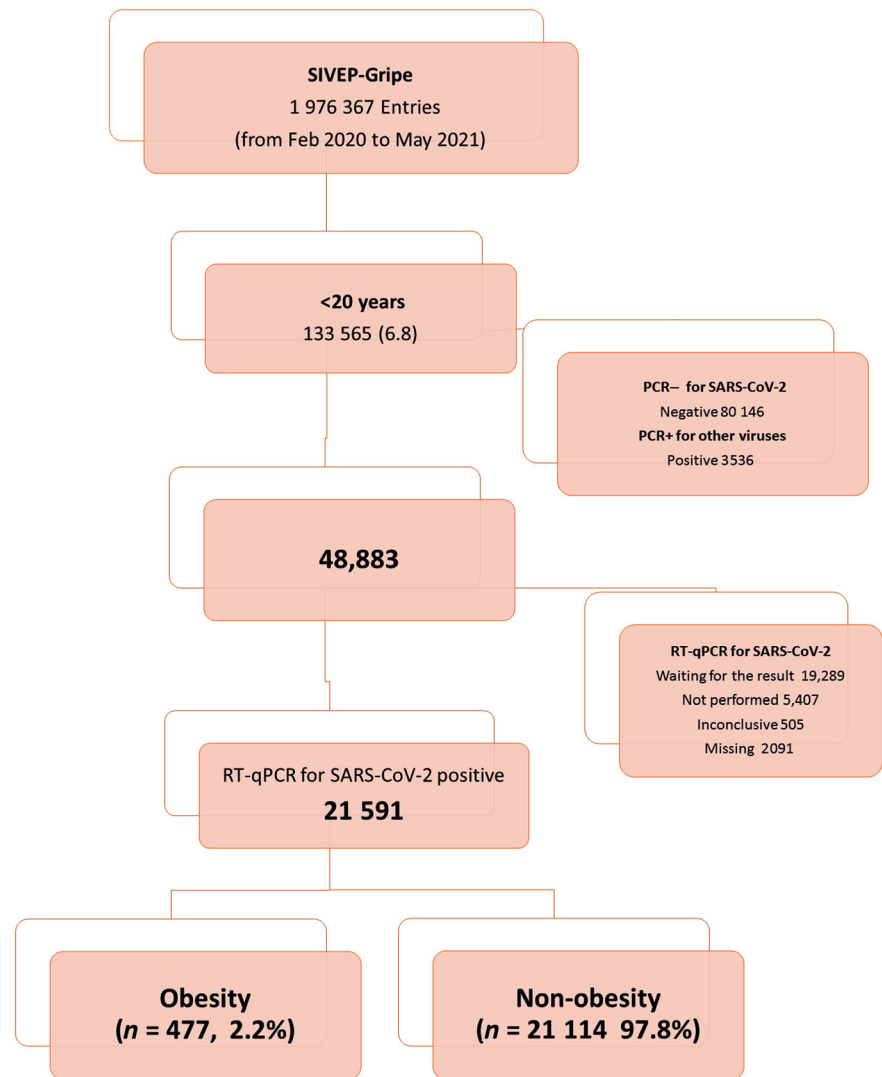
was met for all covariates included in the model (Graphs are available as Supporting information). All statistical tests were two tailed, and statistical significance was defined as $p < 0.05$.

Data were not available for all variables, especially ethnicity and oxygen saturation. We carried out multiple imputations using all predictors plus the CIF for the primary outcome. This procedure creates multiple copies of the data and allows imputations of the missing values for each dataset with sensible values randomly selected from their predicted distribution. Ten imputed values were generated using the multiple imputation chain equations package of the software R. We combined the results from analyses on each of the imputed values using Rubin's rules to produce estimates and confidence intervals that incorporate the uncertainty of imputed values.[21,22] For comorbidities, we assumed missing values as the absence of the clinical condition.

2.6 | Ethical aspects

We accessed data in SIVEP-Gripe, which are already de-identified and publicly available. Following ethically agreed principles on open data,

this analysis did not require ethical approval in Brazil. We reported our findings following the guideline STROBE for observational cohort studies.[23]

3 | RESULTS

3.1 | Baseline demographic, clinical characteristics, and outcomes

The demographic and clinical characteristics of the cohort according to presence of obesity are shown in Table 1. The cohort comprised 21 519 cases. Children with obesity were significantly older at presentation and were admitted more frequently in the second wave. Proportionally, children with obesity were more frequently from the richest regions (South and Southeast) of the country and of white ethnicity compared with non-obese children. These patients also presented at baseline greater proportion of respiratory symptoms and oxygen saturation < 95%. Children with obesity also had more associated comorbidities than the non-obese patients. Among 477 children

TABLE 1 Demographic, clinical characteristics, and outcomes of children and adolescents with laboratory-confirmed COVID-19 according to presence of obesity (n = 21 591)

	Overall (%) 21 591 (100)	Non-obesity (%) 21 114 (97.8)	Obesity (%) 477 (2.2)	p-Value
Age (years)				
Median (interquartile range)	4.7 (0.8–14.6)	4.4 (0.8–14.2)	17.0 (13.0–18.8)	<0.001
Mean (SD)	7.4 (7.0)	7.3 (7.0)	15.0 (5.2)	<0.001
Age group (years)				
0.0–9.9	13 856 (64.2)	13 781 (65.3)	75 (15.7)	<0.001
10–19.9	7735 (35.8)	7333 (35.7)	402 (84.3)	
Gender (n = 21 573)				
Female	10 411 (48.3)	10 189 (48.2)	222 (46.5)	0.46
Male	11 162 (51.7)	10 907 (51.7)	255 (53.5)	
Wave				
First	11 574 (53.6)	11 413 (54.1)	161 (33.8)	<0.001
Second	10 017 (46.4)	9701 (45.9)	316 (66.2)	
Region				
Southeast	8075 (37.4)	7859 (37.2)	216 (45.3)	<0.001
South	2204 (10.2)	2079 (9.8)	125 (26.2)	
Central-West	2293 (10.6)	2257 (10.7)	36 (7.5)	
Northeast	5748 (26.6)	5667 (26.8)	81 (17.0)	
North	3271 (15.1)	3252 (15.4)	19 (4.0)	
Ethinicity				
White	8047 (37.2)	7772 (36.8)	275 (57.7)	<0.001
Black/Brown	13 107 (60.7)	12 911 (61.1)	196 (41.0)	
Asian	181 (0.84)	176 (0.8)	5 (1.0)	
Indigenous	256 (1.2)	255 (1.2)	1 (0.2)	
Signs and symptoms at baseline				
Fever	14 140 (65.5)	13 805 (65.4)	335 (70.2)	0.03
Cough	12 971 (60.1)	12 167 (59.8)	354 (74.2)	<0.001
Respiratory distress	9733 (45.1)	9463 (44.8)	270 (56.6)	<0.001
Oxygen saturation < 95%	9580 (44.4)	9253 (43.8)	327 (68.6)	<0.001
Dyspnoea	10 470 (48.5)	10 127 (48.0)	343 (71.9)	<0.001
Odynophagia	3476 (16.5)	2859 (17.4)	114 (23.9)	<0.001
Diarrhoea	3094 (14.7)	2524 (15.4)	93 (19.5)	0.004
Vomit	3629 (16.8)	3549 (16.8)	80 (16.8)	0.99
Abdominal pain	1454 (6.7)	1415 (6.7)	39 (8.2)	0.19
Number of associated comorbidities				
None	16 574 (76.8)	16 255 (77.0)	319 (66.9)	<0.001
1	4282 (19.8)	4169 (19.7)	113 (23.7)	
2	735 (3.4)	690 (3.3)	45 (9.4)	
ICU admission (n = 19 867)				
Yes	5243 (26.4)	5059 (26.1)	184 (40.6)	<0.001
No	14 624 (73.6)	14 355 (73.9)	269 (59.4)	
Ventilatory support (n = 20.396)				
None	11 272 (55.3)	11 159 (56.0)	113 (24.3)	<0.001
Non-invasive	6994 (34.3)	6737 (33.8)	257 (55.3)	
Invasive	2130 (10.4)	2035 (10.2)	95 (20.4)	

TABLE 1 (Continued)

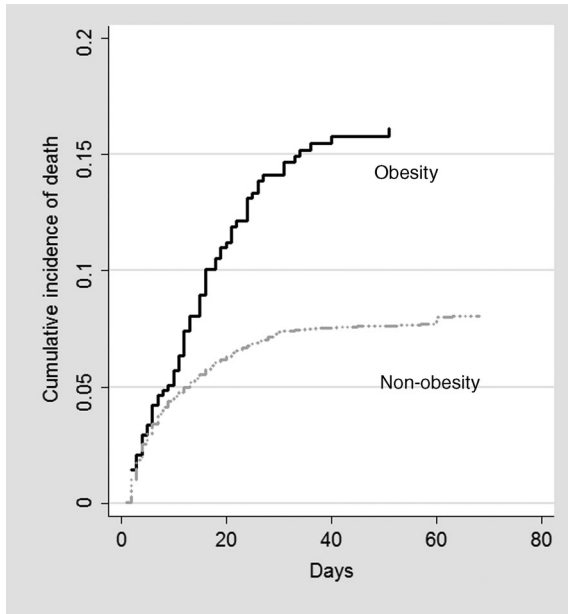|	Overall (%) 21 591 (100)	Non-obesity (%) 21 114 (97.8)	Obesity (%) 477 (2.2)	p-Value
Death				
No	19 930 (92.3)	19 524 (92.5)	406 (85.1)	<0.001
Yes	1661 (7.7)	1590 (7.5)	71 (14.9)	

Abbreviation: ICU, intensive care unit.

FIGURE 2 Cumulative incidence functions of death for patients with proven COVID-19 according to presence of obesity (n = 21 591)

with obesity, 162 (34%) had one or more associated pre-existing chronic condition compared with 5098 (24%) of the non-obese cohort. Among patients with obesity, the most frequent comorbidities were asthma (12.4%), heart disorders (7.1%), diabetes mellitus (6.5%), neurologic diseases (5.5%), and chromosomal abnormalities or syndrome (5.5%).

The clinical outcomes are also shown in Table 1. Overall, children with obesity had higher prevalence of the severe spectrum of COVID-19, considering ICU admission, invasive ventilation, and death. Regarding the need of critical care support, about 41% of children with obesity were admitted to ICU compared with 26% of non-obese ($p < 0.001$). Of 477 children and adolescents with obesity, 95 (20.4%) required invasive ventilation as opposed of about 10% of other cases ($p < 0.001$). In relation to the primary outcome (death or discharge), 71 patients with obesity (14%) had a fatal outcome as compared with 7.5% of the non-obese cases ($p < 0.001$).

The CIF of death for children with obesity and non-obese groups is shown in Figure 2. The estimated probability of fatal outcome for the first 10, 30, and 50 days of hospitalization for paediatric patients without obesity was respectively 4.5%, 6.3%, 7.3%, and 7.6%. For children with obesity, the respective figures were about 5.7%, 11.2%,

TABLE 3 Multivariate survival analysis competing-risk of children and adolescents with obesity and positive quantitative reverse transcription polymerase chain reaction COVID-19

	HR	95% CI	p-Value
Gender			
Male	Reference		
Female	2.80	1.70–4.61	<0.001
Signs and symptoms			
O₂ saturation > 95%	Reference		
O₂ saturation < 95%	2.58	1.39–4.79	0.002
Number of associated comorbidities			
0	Reference		
1	1.91	1.11–3.26	0.018
>2	4.01	2.21–7.56	<0.001

Abbreviation: CI, confidence interval; HR, hazard ratio.

14.7%, and 16.1%. According to the Fine-Gray model, children and adolescents with obesity had twice hazard of death compared with paediatric patients without obesity (hazard ratio [HR] = 2.0, 95% confidence interval [CI] 1.59–2.53, $p < 0.001$). In the competing-risk multivariate survival analysis, adjusted by age, gender, region, ethnicity, respiratory symptoms, and comorbidities, children and adolescents with obesity remained at higher risk of death compared with paediatric patients without obesity (HR = 1.42, 95% CI 1.11–1.79, $p = 0.004$).

3.2 | Risk factors of fatal outcome

Table 3 shows the competing-risk univariate analysis for the risk of death regarding the demographic characteristics and clinical features among the 477 children and adolescents with obesity. Using the Fine and Gray model-to-model mortality, female gender, occurrence of respiratory symptoms at baseline, oxygen saturation < 95%, and presence of other associated comorbidities were significantly associated with higher hazard of death (Table 2).

Associations between risk factors and the hazard of COVID-19 related death after adjustment by the competing-risk multivariate regression analysis are shown in Table 3. In multivariable analysis, the factors associated with the primary outcome were female gender (HR = 2.8, 95% CI 1.7–4.6, $p < 0.001$), oxygen saturation < 95%

TABLE 2 Univariate survival analysis competing-risk of children and adolescents with obesity diseases and positive quantitative reverse transcription polymerase chain reaction COVID-19 ($n = 477$)

	Discharged (%) 358 (75.0)	Death (%) 71 (15.0)	Censored (%) 48 (10.0)	HR (95% CI)[a]	p-Value
Age (years)					
0.0–9.9	57 (76.0)	10 (10.7)	10 (13.3)	1.0	
10–19.9	301 (74.9)	30 (15.7)	38 (9.5)	1.52 (0.73; 3.16)	0.26
Gender					
Male	201 (78.8)	22 (8.6)	32 (12.5)	1.0	
Female	157 (70.7)	49 (22.1)	16 (7.2)	2.73 (1.66; 4.50)	<0.001
Wave					
First	132 (82.0)	23 (14.3)	6 (3.7)	1.0	
Second	226 (71.5)	48 (15.2)	42 (13.3)	1.06 (0.65; 1.75)	0.79
Region					
Southeast	165 (76.4)	32 (14.8)	19 (8.8)	1.0	
South	97 (77.6)	15 (12.0)	13 (10.4)	0.79 (0.43; 1.45)	0.45
Central-West	24 (66.7)	7 (19.4)	5 (13.9)	1.38 (0.60; 3.16)	0.44
Northeast	55 (67.9)	15 (18.5)	11 (13.6)	1.31 (0.71; 2.40)	0.38
North	17 (89.5)	2 (10.5)	0 (0.0)	0.68 (0.16; 2.89)	0.60
Race					
White	206 (74.9)	40 (14.5)	29 (10.5)	1.0	
Non-white	152 (75.2)	31 (15.3)	19 (9.4)	1.04 (0.65; 1.66)	0.85
Signs and symptoms					
Fever	259 (77.3)	46 (13.7)	30 (9.0)	0.75 (0.46, 1.22)	0.25
Cough	277 (70.8)	48 (13.6)	28 (8.2)	0.70 (0.43, 1.15)	0.16
Odynophagia	93 (81.6)	9 (7.9)	12 (10.5)	0.43 (0.21, 0.87)	0.02
Respiratory distress	188 (69.6)	51 (18.9)	31 (11.5)	2.08 (1.24, 3.48)	0.005
Dyspnoea	250 (72.9)	56 (16.3)	37 (10.8)	1.51 (0.85, 2.65)	0.15
O_2 saturation < 95%	234 (71.6)	59 (18.0)	34 (10.4)	2.37 (1.28, 4.40)	0.006
Diarrhoea	77 (82.8)	10 (10.8)	6 (6.5)	0.64 (0.33, 1.27)	0.21
Vomit	70 (87.5)	6 (7.5)	4 (5.0)	0.42 (0.18, 0.97)	0.04
Abdominal pain	29 (74.4)	4 (10.3)	6 (15.4)	0.65 (0.24, 1.78)	0.40
Number of associated comorbidities					
0	255 (79.7)	34 (10.7)	30 (9.4)	1.0	
1	79 (69.9)	22 (19.5)	12 (10.6)	1.86 (1.09, 3.18)	0.022
≥2	24 (53.3)	15 (33.3)	6 (13.3)	3.60 (1.97, 6.55)	<0.001

[a]HR, subdistribution hazard ratio for death from the competing risks model.
Abbreviation: CI, confidence interval.

(HR = 2.6, 95% CI 1.4–4.8, $p = 0.002$), and presence of one (HR = 1.9, 95% CI 1.1–3.3, $p = 0.018$), two or more of comorbidities (HR = 4.0, 95% CI 2.2–7.6, $p < 0.001$). Figure 3 illustrates the CIFs for mortality of these risk factors.

4 | DISCUSSION

We describe the outcomes of SARS-CoV-2 infection in 477 paediatric patients with obesity included in a large cohort of hospitalized children and adolescents with laboratory-confirmed diagnosis of COVID-

19 in Brazil. Our findings have shown that, in general, children and adolescents with obesity had a higher risk of severe COVID-19 and a significantly increased hazard of death compared with cases without obesity. In our analysis, children and adolescents with obesity had an approximately 40% higher risk of fatal outcome compared with the general paediatric population, even after adjusting by clinical and demographic characteristics. Among paediatric patients with obesity, after adjustment by the competing risk survival analysis, the risk factors significantly associated with a higher hazard of death including female gender, oxygen saturation < 95% at entry, and presence and number of associated other comorbidities.

FIGURE 3 Obesity cohort. Cumulative incidence functions of death according to the (A) gender, (B) oxygen saturation at admission, and (C) presence of comorbidities
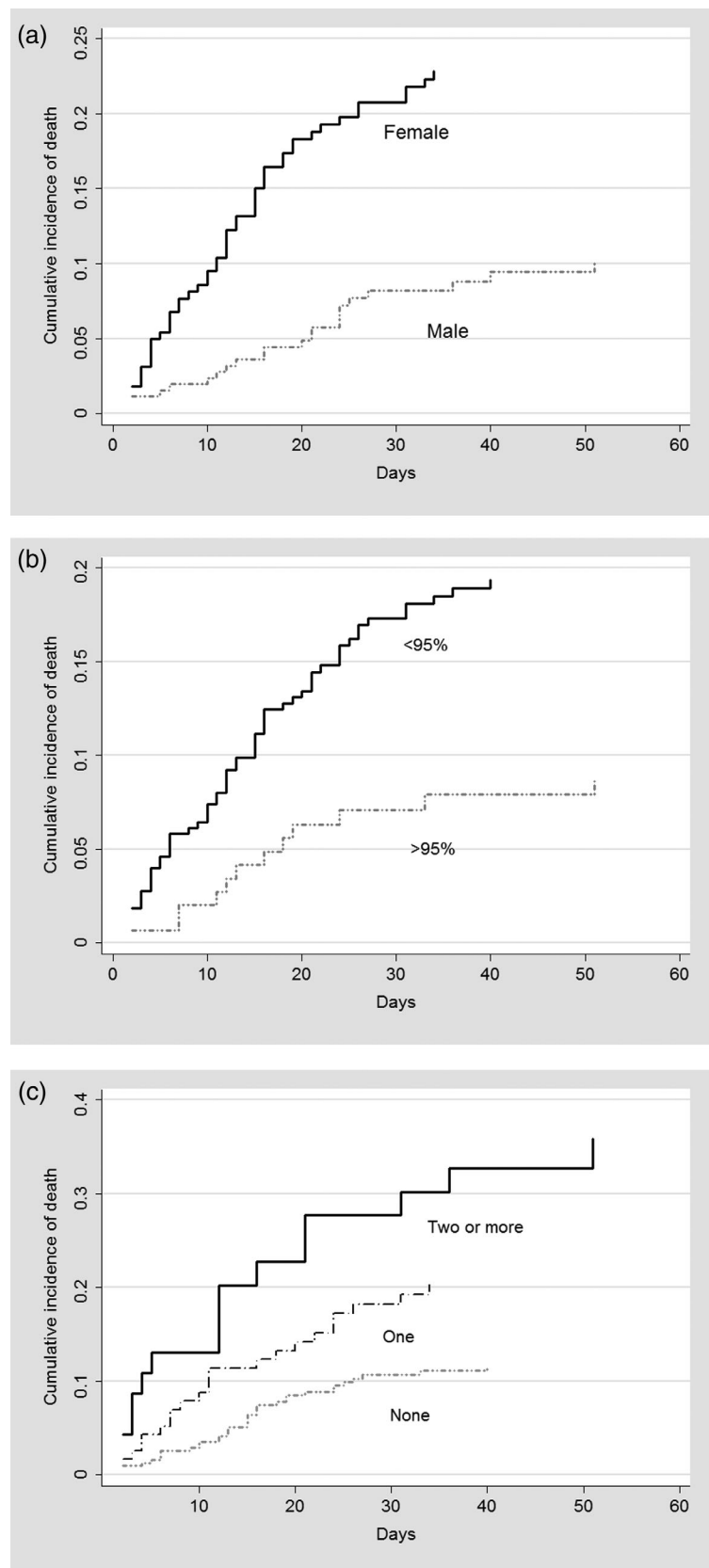
Previous studies of hospitalized children with COVID-19 have shown that obesity was the most prevalent underlying medical condition.[4,24] Few paediatric studies have suggested that obesity is associated with increased COVID-19 severity. For instance, in a case series of 50 children and adolescents hospitalized with COVID-19 at the New York-Presbyterian Morgan Stanley Children's Hospital,

Zachariah et al.[14] found that obesity was the most common comorbidity, the requirement for mechanical ventilation was significantly associated with obesity and children with obesity above 2 years old were more likely to require mechanical ventilation. Guzman et al.[25] reported that, among a cohort of 494 paediatric patients, obesity was an independent risk factor for critical illness (adjusted risk ratio 2.02, 95% CI 1.17–3.48). Of note, this association was modified by age, with obesity related to a greater risk for critical illness in adolescents but not in children. Our findings are in agreement with these studies. Overall, in our cohort, patients with obesity had higher prevalence of the severe spectrum of COVID-19, considering ICU admission and need of invasive ventilation. In addition, according to the survival analysis the presence of obesity doubled the hazard of death compared with paediatric patients without obesity (HR = 2.0, 95% CI 1.59–2.53). However, our analysis did not confirm the findings of Guzman et al.[25] regarding the effect of age. Although in the univariate analysis adolescents had a higher risk of death, the difference was not significative (HR = 1.52, 95% CI 0.73–3.16).

The reasons for more frequent fatal outcome of SARS-CoV-2 infection among children with obesity seem to be multifactorial.[25] Several factors directly related to obesity, including excessive adipose tissue, lean mass deficit, insulin resistance, dyslipidaemia, hypertension, high levels of proinflammatory cytokines, and low intake of essential nutrients, have been previously associated with worse outcome in SARS-CoV-2 infection.[8,26] The state of chronic inflammation characteristic of obesity shifts the immune response towards a reduced functionality and overexpression of inflammatory cytokines by macrophages and T cells, characteristics also commonly associated with COVID-19.[27] Such mechanisms suffer a significant influence from the release of inflammatory adipokines by adipocytes. 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.[28] All these factors may also impair the cardiovascular, respiratory, and urinary systems as well as modify the intestinal microbiota, thus contributing to the severity of COVID-19.[8]

Our study adds to the literature by showing some possible risk factors of a fatal outcome among paediatric population with obesity. An intriguing result of our analysis is the worse outcome associated with female gender. In contrast, several studies of general adult population agreed that case-fatality rate is higher for male individuals than females, even though contamination rates do not appear to be significantly different between sexes.[29] For instance, in a systematic review of 42 studies and 423 117 patients with COVID-19, Dessie and Zewotir[30] have shown that male gender had a significantly higher risk of death compared with female patients (HR = 1.24, 95% CI 1.07–1.41). Several hypotheses have been formulated as attempts to explain this gender disparity, including sex differences in the ACE2 and TMPRSS2 receptors in which SARS-CoV-2 binds to enter to the cells,[31] different profiles of antibody expression,[32] contrasting patterns of stress-related disorders,[33] and higher prevalence of comorbidities in men.[34] However, the studies published so far that analysed gender differences in COVID-19 included only adult patients. Interestingly, in our previous analysis of risk factors of death

in the paediatric Brazilian cohort, we did not find any difference regarding the sexes.[15] The oxygen saturation lower than 95% at hospital admission was another independent predictive factor of mortality in our cohort of paediatric patients with obesity. The association of obesity with the need of mechanical ventilation in paediatric age was previously reported.[14] Normal respiratory function is usually impaired in children and adolescents with obesity.[35] The lung is one of the main target organs for SARS-CoV-2 infection and its damage results in greater risk of death for patients with COVID-19.[36] Therefore, early signs of lung involvement as reduced oxygen saturation at admission probably indicate higher disease severity. In fact, haematosis is impaired in obesity, which becomes even more relevant when the exchange areas are reduced due to SARS-CoV-2 infection.[37] In addition, abdominal adiposity exerts an exaggerate pressure on the lungs, through the diaphragm, and by doing so limits respiratory muscles movements, leading to less oxygen saturation and lower lung volume in patients with obesity.[38]

The coexistence of comorbidities has been previously associated with mortality in paediatric cohorts of COVID-19. Accordingly, a European multicentre study with 582 children and adolescents showed that the presence of comorbidities was significantly associated with ICU admission.[11] Additionally, pre-existing medical conditions were found in 40 (83%) of 48 paediatric patients admitted to United States and Canadian paediatric ICUs.[39] In this regard, in our previous analysis of Brazilian cohort, we found that the presence and the number of associated pre-existing medical conditions had a step gradient effect on the in-hospital risk of death for paediatric patients.[39] In the present study, we shown a similar effect of the presence of comorbidities on risk of death among children and adolescents with obesity.

The strength of this study relies on the size of the cohort, allowing the analysis of clinical characteristics, risk factors, and outcomes of hospitalized children and adolescents with obesity and laboratory confirmed COVID-19. On the other hand, this study has several limitations. In our view, a major limitation of the study is the absence of a better characterization of the obesity features in the SIVEP-gripe database. Although the database included a specific field for body mass index, this relevant information was missing for most of cases. Thus, we were not enabled to classify the cases according to the severity of obesity. In this sense, we must point out that it is certainly more difficult to assess the issue of obesity in young children compared with older children in an epidemiological database such as SIVEP-Gripe. For example, in our cohort, the prevalence of obesity among adolescents was 5.2%, a value comparable to that found in a recent systematic review performed to investigate the prevalence of paediatric obesity in Brazil.[40] On the other hand, the prevalence of around 0.5% for children younger than 10 years is much lower than the prevalence of around 3% found in this systematic review.[40] Therefore, although age was not a risk factor for death among children with obesity in our model, we cannot rule out some impact on this finding due to the underestimation of obesity in young children in our cohort. Another relevant limitation is that the risk factors included in the SIVEP-gripe are self-reported (provided by the patients themselves or their families). Therefore, the analysis could be biased due to the

restricted knowledge of the patient regarding their medical condition.[41] Moreover, we had no access to hospital record data to include laboratory results or detailed clinical course of the patients. Therefore, important information, including data regarding the in-hospital management of the patients, was not possible to consider in the analysis. Another relevant limitation is that the sample is comprised only for hospitalized patients with certainly a more severe spectrum of the disease. Missing data is another inherent issue due to the nature of a registry based on point-of-care case report forms. In this regard, the covariable 'ethnicity' had overall 20% of missing information. To try to overcome the limitations of missing variables, we used multiple imputation technique for relevant predictors.

In this analysis of a large nationwide database of hospitalized patients with laboratory-confirmed COVID-19, we found that children and adolescents with obesity had more severe spectrum of the disease and higher risk of death than patients without this condition. The higher hazard of death was associated with female gender, low oxygen saturation at admission, and the presence of other associated comorbidities. Our findings support the need of specific preventive measures for paediatric patients with obesity, considering the high risk for severe COVID-19.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

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