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Coronavirus Pandemic

Effect of obesity on COVID-19 disease severity in children

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Abstract
Introduction: Coronavirus disease 2019 (COVID-19) has caused many injuries and deaths worldwide. Obesity is reported to be an important risk factor for severe COVID-19, although the underlying mechanism is not fully understood. The present study aimed to determine whether obesity or being overweight is associated with the clinical course and severity of COVID-19 in children.
Methodology: In this retrospective study, pediatric patients under the age of 18 years, who applied to our hospital between June 2021 and August 2021, and tested positive with the COVID-19 reverse transcriptase-polymerase chain reaction test were included. Age, gender, symptoms at admission, body weight, height, chest radiographs, hemograms, C-reactive protein and other laboratory findings, and days of hospitalization of the pediatric patients were obtained from the hospital automation system. All data were statistically analyzed and compared between underweight, normal, overweight, and obese groups; categorized according to body mass index (BMI).
Results: The study included 116 patients. The results showed that the incidence of symptoms was higher in overweight and obese children compared to other groups ($p < 0.05$), while the rate of lung involvement was significantly higher in obese patients compared to other groups ($p < 0.05$). The optimum cut-off point for BMI percentile values in terms of lung involvement was determined to be > 91.
Conclusions: The results of this study revealed that obese children show more symptoms of COVID-19 disease than normal-weight children. In addition, these children have more frequent lung involvement and therefore have more severe disease.

Key words: COVID-19; child; obesity, body mass index.

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Introduction

Coronavirus disease 2019 (COVID-19) emerged in Wuhan in early 2020. COVID-19 is caused by severe-acute-respiratory-syndrome-related coronavirus 2 (SARS-CoV-2), which is a new member of the coronavirus family. Since then, the virus spread around the world, and in March 2020, the World Health Organization (WHO) declared the coronavirus outbreak a pandemic. Unfortunately, the virus has since caused many injuries and deaths worldwide. As of April 30, 2023, this pandemic had caused 765 million people to become ill and seven million to die worldwide [1]. It was estimated that 2-5% of all COVID-19 cases worldwide were children under the age of 18 years [2]. Compared to adults, children were often asymptomatic or had mild symptoms. Between 9% and 15% of virologically positive children remained asymptomatic; those primarily symptomatic had mild to moderate symptoms, and about 3% had a severe illness [3,4]. According to the United Nations International Children's Emergency Fund (UNICEF) data, approximately 17,400 children and young people under the age of 20 years died from COVID-19 until March 2023. Of these deaths, 53% were children of age 10-19 years, and 47% were children < 10 years old [5]. The most common symptoms observed in children infected with COVID-19 were fever, cough, runny nose, diarrhea, and nausea or vomiting [6]. However, chronic diseases, including obesity, diabetes, heart disease, chronic lung disease, epilepsy, and immune compromised conditions, were important factors of comorbidity and led to a more severe course of the disease [7].

The worldwide obesity epidemic has become a major public health problem. Obesity is associated with numerous complications, including detrimental impacts on the respiratory system [8]. Studies have shown that basal pulmonary function test parameters are lower in obese children [9]. Obesity has been shown to be a risk factor for hospitalization, need for more intensive care, prolonged hospital stays, and high health care costs in children hospitalized for respiratory tract infections

[10]. Obesity is reported to be an important risk factor for more severe COVID-19, although the underlying mechanism is not fully understood [11]. Studies investigating the relationship between childhood obesity and COVID-19 are limited in literature. The present study aimed to determine whether obesity or being overweight is associated with the clinical course and severity of COVID-19 in children.

Methodology

Study design

Our study included pediatric patients under the age of 18 years who visited our hospital between June 2021 and August 2021 for various medical reasons, were asked to take the COVID-19 test, had their body weight and height measured, and had positive test results. Patients with chronic lung, kidney, heart, nervous system, gastrointestinal and metabolic diseases; patients with suppressed immune systems; and children with type I and type II diabetes mellitus and hypothyroidism were excluded from the study. A total of 116 patients were included in the study. The study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (No. 2021/514/202/38; date 26/05/2021) and was conducted in accordance with the ethical principles of the Helsinki Declaration. The patients' electronic medical data without identification information was retrieved for the study. The Institutional Review Board waived the requirement for written informed parental consent for this retrospective study.

Table 1. Descriptive statistics of patients (*N* = 116).

Variables	Statistics
Age, (month); M (min-max)	140.5 (2–215)
Age, (year); M (min-max)	11.7 (0.17–17.92)
Gender, n (%)	
Female	54 (46.6)
Male	62 (53.4)
BMI percentiles, n (%)	
< 5 (underweight)	8 (6.9)
5–85 (normal weight)	74 (63.8)
85–95 (overweight)	14 (12.1)
> 95 (obesity)	20 (17.2)
Symptom, n (%)	
Yes	82 (70.7)
No	34 (29.3)
Lung involvement, n (%)	
Yes	30 (25.9)
No	86 (74.1)
Hospitalization, n (%)	
Yes	38 (32.8)
No	78 (67.2)
Hospitalization period; M (min-max)	8.0 (3.0–21.0)
WBC; M (min-max)	7440 (3630–41740)
PLT (x 10^3); M (min-max)	275.0 (94.0–616.0)
Euosinophil; M (min-max)	0.50 (0.0–15.30)
CRP; M (min-max)	6.05 (0.10–287.00)
D-Dimer; M (min-max)	730.0 (190.0–8790.0)
Neutrophil lymphocyte ratio; M (min-max)	1.63 (0.25–10.87)

CRP: C-reactive protein; max: maximum; M: median; min: minimum; PLT: platelet; WBC: white blood cell.

Data collection

Age, gender, symptoms at admission, body weight, height, chest radiographs, hemograms, C-reactive protein (CRP) and other laboratory findings, and days of hospitalization of pediatric patients under the age of 18 years and diagnosed with COVID-19 were obtained retrospectively from the hospital automation system. The data obtained were saved in an Excel file. All the data obtained were statistically analyzed and compared between underweight, normal, overweight, and obese groups, categorized according to the body mass index (BMI).

Sample collection and test method

A nasopharyngeal swab was taken from one nostril of the patients for the detection of SARS-CoV-2 infection based on the guidelines of the Ministry of Health of our country [12]. Laboratory confirmation of SARS-CoV-2 was performed using reverse transcriptase-polymerase chain reaction (RT-PCR).

BMI and percentile calculation

BMI was calculated in 116 children as body weight in kilograms divided by height in meters squared and BMI percentile curves were constructed according to gender and age (in months). The national BMI percentile curves were used for reference [13]. Percentile values at < 5, 5 to < 85, 85 to 95, and > 95 were considered to indicate underweight, normal weight, overweight, and obesity, respectively.

Statistical analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) and MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd., Ostend, Belgium). Descriptive statistics were presented as the number of units (n), percentage (%), mean ± standard deviation, median (M), minimum (min), maximum (max), and interquartile range (IQR) values. The normality assumption of numerical variables was evaluated using the Shapiro-Wilk test. The Kruskal-Wallis test was used to compare numerical variables according to BMI percentile groups. Correlations between BMI percentile values and numerical variables were evaluated with Spearman and partial correlation coefficients. BMI percentile groups and categorical variables were compared using the Pearson Chi square and Fisher exact tests. If the Chi square test results were found to be significant, subgroup analyses were performed with the Bonferroni-corrected two-ratio z-test. Finally, the performance of BMI percentile values in predicting lung involvement was evaluated by receiver operating characteristic (ROC) curve analysis. $p < 0.05$ was considered statistically significant.

Results

The study included 116 patients. The age of the patients ranged between 2 and 215 months, with a median age of 140.5 months. Of the patients, 54 (46.6%) were female and 62 (53.4%) were male. According to BMI percentile values, the number of normal-weight patients was 74 (63.8%), and the number of obese patients was 20 (17.2%). Of the patients, 82 (70.7%) had symptoms, 30 (25.9%) had lung involvement, and 38 (32.8%) were hospitalized. The median length of hospitalization was eight days (Table 1).

There was no statistically significant difference between the age and gender distributions of the patients according to BMI percentile groups ($p > 0.05$) (Table 2). The symptom distributions of patients according to BMI percentile groups were significantly different. According to BMI percentile values, 50.0% of underweight, 62.2% of normal-weight, 92.9% of overweight, and 95.0% of obese patients had symptoms. The incidence of symptoms in overweight and obese patients was significantly higher compared to underweight and normal-weight patients ($p < 0.05$) (Table 2). A significant difference was found between BMI percentile groups for lung involvement. According to BMI percentile values, 12.5% of underweight, 20.3% of normal-weight, 28.6% of overweight, and 50.0% of obese patients had lung involvement. The rate of lung involvement was significantly higher in obese patients compared to underweight and normal-weight patients ($p < 0.05$) (Table 2). The differences between BMI percentile groups in terms of hospitalization, length of hospital stay, white blood cell (WBC), platelet (PLT), eosinophil, CRP, D-Dimer, and neutrophils to lymphocytes ratios were not statistically significant ($p > 0.05$) (Table 2).

A statistically significant negative correlation was found between age and BMI percentile values in female patients (rho (r) = -0.269; $p = 0.049$). Although the correlation coefficient between age and BMI percentile was not statistically significant in the entire patient group, it was considered that age could be a confounding factor due to its significance ($p = 0.189$), and the results of the correlation analysis were adjusted for age (Table 3).

There was a statistically significant negative correlation between BMI percentile values and WBC in all groups in age-adjusted comparisons (r = -0.388; *p* =

Table 2. Relationship between patient characteristics and BMI percentile groups.

	BMI percentiles				Test statistics	
Variables	**< 5 (Underweight)**	**5–85 (Normal weight)**	**85–95 (Overweight)**	**> 95 (Obesity)**	**Test value**	***p* value**
Age, (year)	14.0 (8.1)	10.7 (12.9)	10.0 (9.9)	11.8 (6.2)	2.366	0.500†
Gender, n (%)						
Girl	4 (50.0)	37 (50.0)	6 (42.9)	7 (35.0)	1.596	0.683‡
Boy	4 (50.0)	37 (50.0)	8 (57.1)	13 (65.0)		
Symptom, n (%)						
Yes	4 (50.0)[a]	46 (62.2)[a]	13 (92.9)[b]	19 (95.0)[b]	**14.032**	**0.002**‡
No	4 (50.0)	28 (37.8)	1 (7.1)	1 (5.0)		
Lung involvement, n (%)						
Yes	1 (12.5)[a]	15 (20.3)[a]	4 (28.6)[ab]	10 (50.0)[b]	**8.083**	**0.042**‡
No	7 (87.5)	59 (79.7)	10 (71.4)	10 (50.0)		
Hospitalization, n (%)						
Yes	3 (37.5)	22 (29.7)	4 (28.6)	9 (45.0)	1.993	0.653‡
No	5 (62.5)	52 (70.3)	10 (71.4)	11 (55.0)		
Hospitalization period	7.0 (7.0)	8.5 (4.3)	8.0 (0.7)	7.0 (4.0)	3.521	0.318†
WBC (x 10^3)	7.6 (6.1)	8.4 (5.1)	7.6 (10.8)	5.6 (2.2)	7.720	0.052†
PLT (x 10^3)	294.5 (179.5)	287.0 (152.0)	281.0 (143.7)	253.0 (121.0)	0.542	0.910†
Euosinophil	2.70 (3.54)	0.30 (2.1)	0.75 (3.70)	0.50 (3.90)	3.342	0.342†
CRP	0.35 (27.30)	6.20 (25.90)	4.50 (105.27)	11.20 (19.0)	3.373	0.338†
D-Dimer	480.0 (8600.0)	750.0 (720.0)	730.0 (615.0)	590.0 (1180.0)	0.451	0.930†
Neutrophil lymphocyte ratio	1.28 (1.00)	2.71 (3.62)	1.67 (3.16)	1.57 (3.05)	0.407	0.939†

n: Count, %: column percent; numerical data are given as median (interquartile range) values; BMI: body mass index; CRP: C-reactive protein; PLT: platelet; WBC: white blood cell. †: Kruskal-Wallis test; ‡: Chi-square test: a and b superscripts indicate differences between groups in each row. There was no statistical difference between groups with the same superscripts.

Table 3. Correlations between BMI percentile values and numerical variables *

Variables	BMI All patients		BMI Females		BMI Males	
	r	*p*	*r*	*p*	*r*	*p*
Hospitalization Period	-0.302	0.069	-0.327	0.186	-0.294	0.237
WBC (*10^3)	-0.388	0.017	-0.394	0.106	-0.517	0.028
PLT (*10^3)	-0.137	0.420	0.082	0.745	-0.471	0.049
Eosinophil	0.008	0.962	0.205	0.415	-0.284	0.254
CRP	-0.216	0.199	-0.231	0.357	-0.408	0.093
D-Dimer	-0.249	0.137	-0.035	0.890	-0.352	0.153
Neutrophil lymphocyte ratio	-0.008	0.960	0.063	0.805	-0.068	0.788

*: Adjusted for age, *r*: partial correlation coefficient. BMI, body mass index; CRP, C-reactive protein; PLT, platelet; WBC, white blood cell.

0.017) (Table 4). There was no statistically significant relationship between BMI percentile values and other variables in female patients. A statistically significant negative correlation existed between BMI percentile values and WBC and PLT in male patients (r = -0.517; *p* = 0.028 and r = -0.471; *p* = 0.049, respectively). There was a negative correlation, albeit not significant, between BMI percentile values and CRP in male patients (r = -0.408; *p* = 0.093). The other relationship coefficients in Table 3 were not statistically significant.

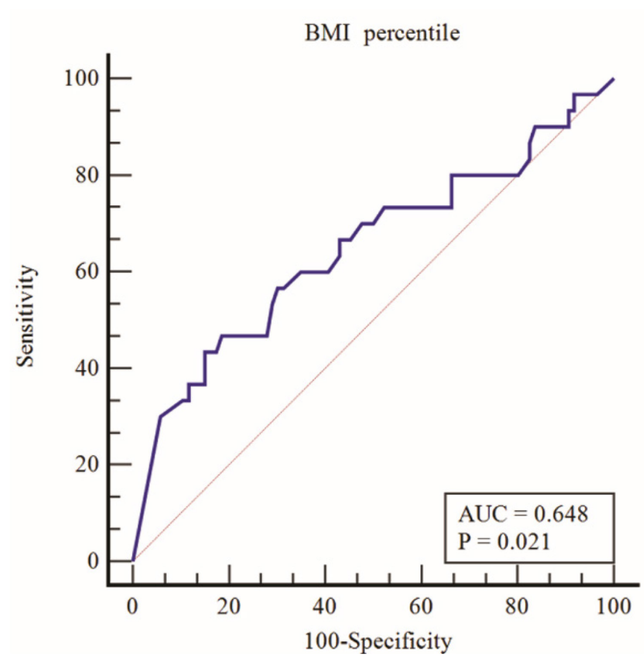
As shown in Table 4, the area under the curve value obtained for the ROC curve plotted for BMI percentile values according to lung involvement was 0.648 and statistically significant (*p* = 0.021). Therefore, the optimum cutoff point for BMI percentile values was determined to be > 91. The sensitivity value for this point was 43.3%, and the specificity value was 84.8%. The ROC curve for BMI percentiles in predicting lung involvement is shown in Figure 1.

Discussion

This study was conducted to investigate the relationship between obesity or being overweight, and the clinical course and severity of COVID-19 in children. The results showed that the incidence of symptoms was higher in overweight and obese children compared to other groups, while the rate of lung involvement was significantly higher in obese patients compared to other groups. On the other hand, the optimum cut-off point for BMI percentile values in terms of lung involvement was determined to be > 91.

Although the relationship between obesity in children and COVID-19 disease is not clear, there are some reasons put forward. To summarize these reasons, it can be said that primarily obese children have impaired immune response to infections, which may be related to increased angiotensin-converting enzyme 2 (ACE-2) expression in the lungs. In addition, the presence of chronic subclinical inflammation and underlying cardiopulmonary diseases, which are the causes mentioned in adults, can also be counted [14-16]. Also, with abdominal adiposity, the pressure exerted on the lungs through the diaphragm will increase, and the physiological movement of the respiratory muscles will become more difficult, and all this can manifest itself with reduced oxygen saturation

Figure 1. ROC curve for BMI percentile values in predicting lung involvement.



ROC: receiver operating characteristic; BMI: body mass index.

Table 4. Evaluation of the performance of BMI percentile values in predicting lung involvement with ROC analysis.

	AUC	p value	Cut-off	Sens	Spec	PPV	NPV
BMI percentile (% 95 CI)	0.648 (0.554–0.734)	0.021	> 91	43.3 (25.5–62.6)	84.8 (75.5–91.7)	50.0 (34.4–65.6)	81.1 (75.6–85.6)

AUC: area under the curve; BMI: body mass index; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; ROC: receiver operating curve; Sens: Sensitivity; Spec: specificity.

and therefore a more serious disease picture [17]. In the study by Kompaniyets *et al.* in which they examined the data of 43,465 children (< 18 years old) who were diagnosed with COVID-19, it was reported that obesity is an important risk factor for hospitalization [18]. In another study conducted in the United States by Campbell *et al.,* 1,877 pediatric patients with the diagnosis of COVID-19 were examined and the hospitalization rate was 15%. In this study, obesity was determined as an independent risk factor for hospitalization [19]. Similarly, risk factors for hospitalization were investigated in a study conducted in Brazil that included data from 964 children diagnosed with COVID-19, and obesity was defined as a risk factor [20]. In our study, obesity was found to be a risk factor for hospitalization, in line with the literature.

Obesity has also been found to be a risk factor in studies examining the risk factors for severe disease in COVID-19. In the study reported by Choi *et al*., 17 systematic reviews and 10 meta-analyses were examined, and it was determined that obesity is a risk factor for serious disease in pediatric patients diagnosed with COVID-19 [21]. A study conducted in the United States reported that obesity is a risk factor for the need for intensive care in hospitalized pediatric patients [22]. In another study by Woodruff *et al.* that included 3,106 hospitalized pediatric patients with COVID-19, risk factors were investigated according to age, and obesity was determined as a risk factor for serious disease in pediatric patients aged 2–17 years, based on multivariate analysis [23]. According to WHO, patients without pneumonia are evaluated as mild, while patients with pneumonia are defined as moderate and severe patients [24]. In our study, we did not classify the disease as mild-moderate-severe, but we interpreted the patients with indications for hospitalization as moderate/serious patients, and we found the rates of hospitalization to be higher in the obese patient group, which we interpreted in accordance with previously published data.

Studies have shown that leukopenia and thrombocytopenia are more common in COVID-19 disease [25,26]. There are hypotheses regarding thrombocytopenia developing during COVID-19 disease. The first symptom of this is the inhibition of platelet synthesis as a result of the virus infecting the bone marrow. Other reasons include platelet destruction by the immune system, and the use of platelets in the lungs during lung infection [27]. On the other hand, in adults, leukopenia is mostly due to lymphopenia. The cause of lymphopenia is interpreted as the direct infection of ACE-2 receptors expressed on lymphocytes by SARS-CoV-2 [28,29]. However, lymphopenia is less expected, especially in young children, due to the low expression of ACE-2 receptors [30]. There are no definite data on the relationship between obesity and hematological parameters in children; however, leukocytosis is a more expected finding in obese patients regardless of COVID-19. There is a chronic mild inflammation associated with obesity, mainly with an increase in cytokines such as IL-6 and IL-8, and adipokines such as leptin, which may cause neutrophil release from the bone marrow and result in leukocytosis [31,32]. In our study, we found a negative correlation between BMI and leukocyte and thrombocyte counts in male children. While leukopenia is expected with COVID-19 disease, leukocytosis is expected with obesity; so, it can be interpreted that the effect of COVID-19 on leukocyte count was more effective than obesity in our study. However, this interpretation should be supported with data and there are not enough studies on the effect of obesity on hematological parameters in children. In our study, a negative correlation was found between BMI and CRP in boys, which can be explained by the hypothesis of chronic mild inflammation of obesity.

The main limitation of this study is that the number of patients was not at the desired level. Despite this, we think that the results of the study will make an extremely important contribution to the literature.

Conclusions

The results of this study revealed that obese children show more signs of COVID-19 disease than normal-weight children; and that these children have more frequent lung involvement and therefore have more severe disease.

Institutional review board approval

The study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital, Health Sciences University (No. 2021/514/202/38; date 26/05/2021).

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and/or ethical restrictions.

Authors' contributions

YÇ, AK, AAÇ, MTK: study conception and design; YÇ, AK, MTK, CÇ: study implementation; YÇ, AK, MTK, CÇ, YA: data analysis and interpretation; YÇ, AK, YA: critical revision of work for intellectual content and final approval for publishing. All authors have reviewed the manuscript and gave consent to publish.

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