Obesity

Overweight and Obesity are Risk Factors of Severe Illness in Patients with COVID-19

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Objective: This study aimed to observe the clinical characteristics of patients with coronavirus disease 2019 (COVID-19) with overweight and obesity.
Methods: Consecutive patients with COVID-19 from 10 hospitals of Jiangsu province, China, were enrolled.
Results: A total of 297 patients with COVID-19 were included, and 39.39% and 13.47% of patients had overweight and obesity, respectively. The proportions of bilateral pneumonia (92.50% vs. 73.57%, $P=0.033$) and type 2 diabetes (17.50% vs. 3.57%, $P=0.006$) were higher in patients with obesity than lean patients. The proportions of severe illness in patients with overweight (12.82% vs. 2.86%, $P=0.006$) and obesity (25.00% vs. 2.86%, $P<0.001$) were significantly higher than lean patients. More patients with obesity developed respiratory failure (20.00% vs. 2.86%, $P<0.001$) and acute respiratory distress syndrome (5.00% vs. 0%, $P=0.024$) than lean patients. The median days of hospitalization were longer in patients with obesity than lean patients (17.00 days vs. 14.00 days, $P=0.029$). Overweight (OR, 4.222; 95% CI: 1.322-13.476; $P=0.015$) and obesity (OR, 9.216; 95% CI: 2.581-32.903; $P=0.001$) were independent risk factors of severe illness. Obesity (HR, 6.607; 95% CI: 1.955-22.329; $P=0.002$) was an independent risk factor of respiratory failure.
Conclusions: Overweight and obesity were independent risk factors of severe illness in COVID-19 patients. More attention should be paid to these patients.

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (1). Although most of the SARS-CoV-2 infection typically leads to relatively mild symptoms, 287,399 patients still died globally up to May 13, 2020 (2). Old age and comorbidities, such as hypertension, diabetes, and chronic respiratory disease, were identified as risk factors of poor outcomes for patients with COVID-19 according to previous studies (3,4). Obesity was regarded as a common risk factor to aggravate the severity of respiratory diseases, which was associated with poor prognosis in influenza A pulmonary infection (5,6). Animal experiments have found that obesity alters inflammatory and pathological responses in the lung during influenza (7-9). Excessive adipose accumulation could result in insulin resistance, oxidative stress, chronic inflammation, and circulating nutrients abnormality (10,11). However, few studies have focused on the impacts of obesity on COVID-19.

A retrospective study that enrolled 124 patients with COVID-19 who were admitted to intensive care unit (ICU) showed more patients required invasive mechanical ventilation (IMV) therapy with increased BMI (12). Another study found that patients with COVID-19 who were aged<60 years with a BMI between 30 and 34 kg/m^2 had 2.0 and 1.8 times the

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risk for admission to acute and critical care as compared with individuals with a BMI <30 kg/m^2, respectively (13). These studies suggested that obesity may be associated with the severity of COVID-19. However, for several confounders such as age, the presence of comorbidities were not adjusted, which might have impacted the results. Whether overweight and obesity are independent risk factors of severe COVID-19 requires further research. In addition, the sample sizes are relatively small in the previous studies (12,13). This study aimed to investigate the clinical features of patients with COVID-19 with overweight and obesity in a multicenter cohort of COVID-19 in Jiangsu province, China.

Methods

Study population

Between January 18, 2020, and February 26, 2020, 342 consecutive patients with COVID-19 from 10 medical centers in 10 cities of Jiangsu, China, were enrolled. All patients with COVID-19 were diagnosed by clinical manifestations, chest computed tomography, and real-time polymerase chain reaction according to World Health Organization interim guidance and the Guidelines for the Diagnosis and Treatment of Novel Coronavirus Infection by the National Health Commission (Trial Version 5) (14,15). All patients with COVID-19 were tested positive for SARS-CoV-2 by real-time polymerase chain reaction in throat swab specimens. The last followed-up date was February 29, 2020. The study was approved by the ethics review boards of these medical centers.

Data collection and study definitions

We retrospectively recorded the clinical characteristics, complications, and outcomes of patients by electronic medical record system. The computational formula of BMI was weight (kilograms) divided by height (meters) squared. According to criterion of guidelines for prevention and control of overweight and obesity in Chinese adults, 24 ≤ BMI < 28 and BMI ≥ 28 was defined as overweight and obesity, respectively (16,17). Severe COVID-19 was defined according to the current guideline as follows: (1) respiratory frequency ≥ 30/min, (2) pulse oximeter oxygen saturation ≤ 93% at rest, and (3) oxygenation index ≤ 300 mmHg (15). Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition (18).

Statistical analysis

Continuous variables were described as medians (interquartile range [IQR]), and categorical variables were presented as the counts and percentages. The independent group *t* tests (normal distribution) and Mann-Whitney U (non-normal distribution) were used to compared continuous variables between groups. Chi-square or Fisher exact test was used to compare the categorical variables. Multivariate logistic and cox regression analysis was used to adjust for confounding factors, including age, gender, and comorbidities. $P < 0.05$ was considered to be statistically significant. SPSS version 22.0 software (SPSS Inc., Chicago, Illinois) was used for the analysis.

Results

Clinical characteristics of patients with overweight and obesity on admission

Thirty-four patients were excluded because of the lack of BMI data, and 11 patients under 12 years old were also excluded. Eventually, 297 patients were enrolled in this study. The clinical characteristics were presented in Table 1. Of the 297 patients with COVID-19, 117 (39.39%) and 40 (13.47%) had overweight (24 ≤ BMI < 28) and obesity (BMI ≥ 28), respectively. The median age was 38.00 (IQR, 31.25-54.00) years, 48.00 (IQR, 36.50-57.00) years, and 47.00 (IQR, 34.25-57.75) years in patients with lean (BMI < 24), overweight, and obesity, respectively. Patients with overweight and obesity were older, and the proportion of male gender was higher in patients with overweight and obesity than lean patients. The median BMI was 22.17 (IQR, 20.55-23.12), 25.71 (IQR, 24.87-26.61), and 29.75 (IQR, 29.18-30.81) in these three groups, respectively. The proportions of a medical history of type 2 diabetes were significantly different in these three groups ($P = 0.008$). More patients had a history of type 2 diabetes in the obesity group than the lean group (17.50% vs. 3.57%, $P = 0.006$), whereas the proportion was comparable between the overweight group and lean group (11.11% vs. 3.57%, $P = 0.054$). The clinical symptoms on admission were similar among the three groups. The median levels of fasting blood glucose (FBG) presented an increasing trend in patients who were lean and with overweight and obesity ($P < 0.001$). Patients with obesity presented higher FBG levels than lean patients (6.48 mmol/L vs. 5.47 mmol/L, $P < 0.001$), whereas patients with overweight had similar FBG levels with lean patients (5.69 mmol/L vs. 5.47 mmol/L, $P = 0.119$). However, there were no significant differences in triglycerides and total cholesterol among the three groups. The proportion of bilateral pneumonia presented an increasing trend in patients who were lean and with overweight and obesity ($P = 0.018$). More patients with obesity had bilateral pneumonia on admission than lean patients (92.50% vs. 73.57%, $P = 0.033$), while there was no difference between patients with overweight and lean patients (82.91% vs. 73.57%, $P = 0.219$).

Treatment and clinical outcomes of patients with overweight and obesity

The proportions of patients who used atomized inhalation of interferon α-2b (60.00%, 56.41%, and 57.50%, $P = 0.84$), lopinavir-ritonavir (70.01%, 75.21%, and 80.00%, $P = 0.383$), and arbidol (52.86%, 47.86%, and 52.50%, $P = 0.709$) were comparable among the three groups (Table 2). The proportions of oxygen therapy ($P = 0.009$) and non-IMV therapy ($P = 0.003$) were significantly different in these three groups. More patients with overweight received oxygen therapy compared with lean patients (66.67% vs. 48.57%, $P = 0.012$) during hospitalization, while the proportion of oxygen therapy was comparable between patients with obesity and lean patients (65.00% vs. 48.57%, $P = 0.201$). Moreover, more patients with overweight (6.84% vs. 0.71, $P = 0.024$) and obesity (12.50% vs. 0.71, $P < 0.001$) received non-IMV therapy than lean patients. No patient received IMV treatment in our study. The proportions of patients who developed respiratory failure ($P = 0.001$) and ARDS ($P = 0.049$) were significantly different in these three groups. In total, 20% of patients with obesity developed respiratory failure, which was significantly higher than in lean patients (2.86%, $P < 0.001$), while the proportion of respiratory failure was comparable between patients with overweight and lean patients (8.55% vs. 2.86%, $P = 0.135$). Similarly, the proportions of patients developing ARDS were higher in patients with obesity than lean patients (5.00% vs. 0%, $P = 0.024$), while the proportion of ARDS was comparable between patients with overweight and lean patients (1.71% vs. 0%, $P = 0.360$). The proportions of severe illness were different in the three groups ($P < 0.001$). More patients with overweight (12.82% vs. 2.86%, $P = 0.006$) and obesity (25.00% vs. 2.86%, $P < 0.001$) had severe illness than lean patients. However, the proportions of patients admitted to ICU were comparable among the three groups ($P = 0.087$). The median days of hospitalization were different among the three groups ($P = 0.025$). Patients

TABLE 1 Demographic and clinical features of patients with COVID-19

Variables (*n* [%] or median [IQR])	Lean (*n* = 140)	Overweight (*n* = 117)	Obesity (*n* = 40)	*P* value
Age (y)	38.00 (31.25-54.00)	48.00 (36.50-57.00)	47.00 (34.25-57.75)	0.024
Male	68 (48.57)	72 (61.54)	24 (60.00)	0.092
BMI (kg/m^2)	22.17 (20.55-23.12)	25.71 (24.87-26.61)	29.75 (29.18-30.81)	< 0.001
Comorbidities				
Hypertension	15 (10.71)	24 (20.51)	9 (22.50)	0.053
Diabetes	5 (3.57)	13 (11.11)	7 (17.50)	0.008
Chronic lung diseases	4 (2.86)	6 (5.13)	2 (5.00)	0.620
Cardiovascular diseases	0	5 (4.27)	1 (2.50)	0.051
Malignant tumors	1 (0.71)	1 (0.85)	2 (5.00)	0.098
Onset symptoms				
Fever	89 (63.57)	84 (71.79)	32 (80.00)	0.099
Cough	75 (53.57)	70 (59.83)	23 (57.50)	0.597
Fatigue	24 (17.14)	24 (20.51)	13 (32.50)	0.106
Sore throat	16 (11.43)	12 (10.26)	5 (12.50)	0.914
Muscle ache	19 (13.57)	9 (7.69)	1 (2.50)	0.072
Headache	11 (7.86)	7 (5.98)	1 (2.50)	0.462
Laboratory and imaging findings				
WBC (×10^9/L)	4.46 (3.39-5.57)	5.10 (4.01-6.23)	5.23 (4.04-6.36)	0.006
Lymphocytes (×10^9/L)	1.18 (0.89-1.62)	1.23 (0.87-1.61)	1.11 (0.88-1.60)	0.879
ALT (U/L)	23.00 (15.00-30.00)	29.00 (22.00-40.00)	31.00 (23.00-48.50)	< 0.001
Cr (μmol/L)	63.00 (52.50-77.15)	70.00 (57.90-82.00)	66.20 (59.05-82.55)	0.048
INR	1.05 (1.00-1.12)	1.04 (1.00-1.11)	1.02 (0.99-1.06)	0.284
UA (mmol/L)	263.75 (210.75-309.75)	272.20 (197.03-331.75)	295.90 (216.35-383.75)	0.482
FBG (mmol/L)	5.47 (4.90-6.11)	5.69 (5.08-6.50)	6.48 (5.45-7.89)	< 0.001
TG (mmol/L)	1.09 (0.76-1.61)	1.27 (0.90-1.72)	1.37 (1.03-1.55)	0.063
TC (mmol/L)	3.75 (3.21-4.52)	3.83 (3.25-4.47)	3.80 (3.18-4.30)	0.968
Chest CT				
No pneumonia	14 (10.00)	5 (4.27)	2 (5.00)	0.175
Unilateral pneumonia	23 (16.43)	15 (12.82)	1 (2.50)	0.07
Bilateral pneumonia	103 (73.57)	97 (82.91)	37 (92.50)	0.018
Days from symptom onset to admission	5.00 (2.00-8.00)	6.00 (3.00-8.75)	4.50 (2.00-7.25)	0.069

ALT, alanine transaminase; Cr, creatinine; FBG, fasting blood glucose; INR, international normalized ratio; IQR, interquartile range; TC, total cholesterol; TG, triglyceride; UA, uric acid; WBC, white blood cells.

with obesity stayed longer in hospital than lean patients (17.00 days vs. 14.00 days, $P = 0.029$), while there was no significant difference of hospital stays between patients with overweight and lean patients (16.00 days vs. 14.00 days, $P = 0.421$).

The distributions of BMI categories were significantly different between patients with severe illness and nonsevere illness ($P < 0.001$), respiratory failure and nonrespiratory failure ($P = 0.001$), noninvasive mechanical ventilation and without noninvasive mechanical ventilation ($P = 0.003$) (Figure 1). However, although the proportions of patients with overweight and obesity had a higher rate of ICU admission, the difference was not statistically significant ($P = 0.087$).

Associations of overweight and obesity with severe illness

Logistic regression analysis was performed to identify the association between obesity and severe illness (Table 3). Univariate analysis presented that overweight (odds ratio [OR], 5.000; 95% CI: 1.611-15.516; $P = 0.005$), obesity (OR, 11.333; 95% CI: 3.329-38.583; $P < 0.001$), and type 2 diabetes (OR, 7.087; 95% CI: 2.782-18.053; $P < 0.001$) were associated with severe illness. In the multivariate analysis, overweight (OR, 4.222; 95% CI: 1.322-13.476; $P = 0.015$) and obesity (OR, 9.216; 95% CI: 2.581-32.903; $P = 0.001$) were independent risk factors of severe COVID-19 after adjusted age, sex, the presence of hypertension, and type 2 diabetes.

Associations of overweight and obesity with respiratory failure

The associated factors of respiratory failure in patients with COVID-19 were analyzed by cox regression analysis (Table 4). The univariate analysis showed that the factors for respiratory failure were obesity (HR, 7.542; 95% CI: 2.270-25.055; $P = 0.001$) and type 2 diabetes (HR, 4.986; 95% CI: 1.949-12.756; $P = 0.001$). On multivariate analysis,

TABLE 2 Treatment, complications, and clinical outcome of patients with COVID-19

Variables (*n* [%] or median [IQR])	Lean (*n* = 140)	Overweight (*n* = 117)	Obesity (*n* = 40)	*P* value
Treatment				
Atomized inhalation of interferon α-2b	84 (60.00)	66 (56.41)	23 (57.50)	0.84
Lopinavir-ritonavir	98 (70.00)	88 (75.21)	32 (80.00)	0.383
Arbidol	74 (52.86)	56 (47.86)	21 (52.50)	0.709
Oxygen therapy	68 (48.57)	78 (66.67)	26 (65.00)	0.009
Noninvasive mechanical ventilation	1 (0.71)	8 (6.84)	5 (12.50)	0.003
Complications				
Respiratory failure	4 (2.86)	10 (8.55)	8 (20.00)	0.001
ARDS	0	2 (1.71)	2 (5.00)	0.049
Outcomes				
Severe illness	4 (2.86)	15 (12.82)	10 (25.00)	< 0.001
Admission to ICU	4 (2.86)	10 (8.55)	4 (10.00)	0.087
Days of Hospitalization	14.00 (12.00-19.00)	16.00 (12.00-20.00)	17.00 (14.00-22.50)	0.025

ARDS, acute respiratory distress syndrome; ICU, intensive care unit; IQR, interquartile range.

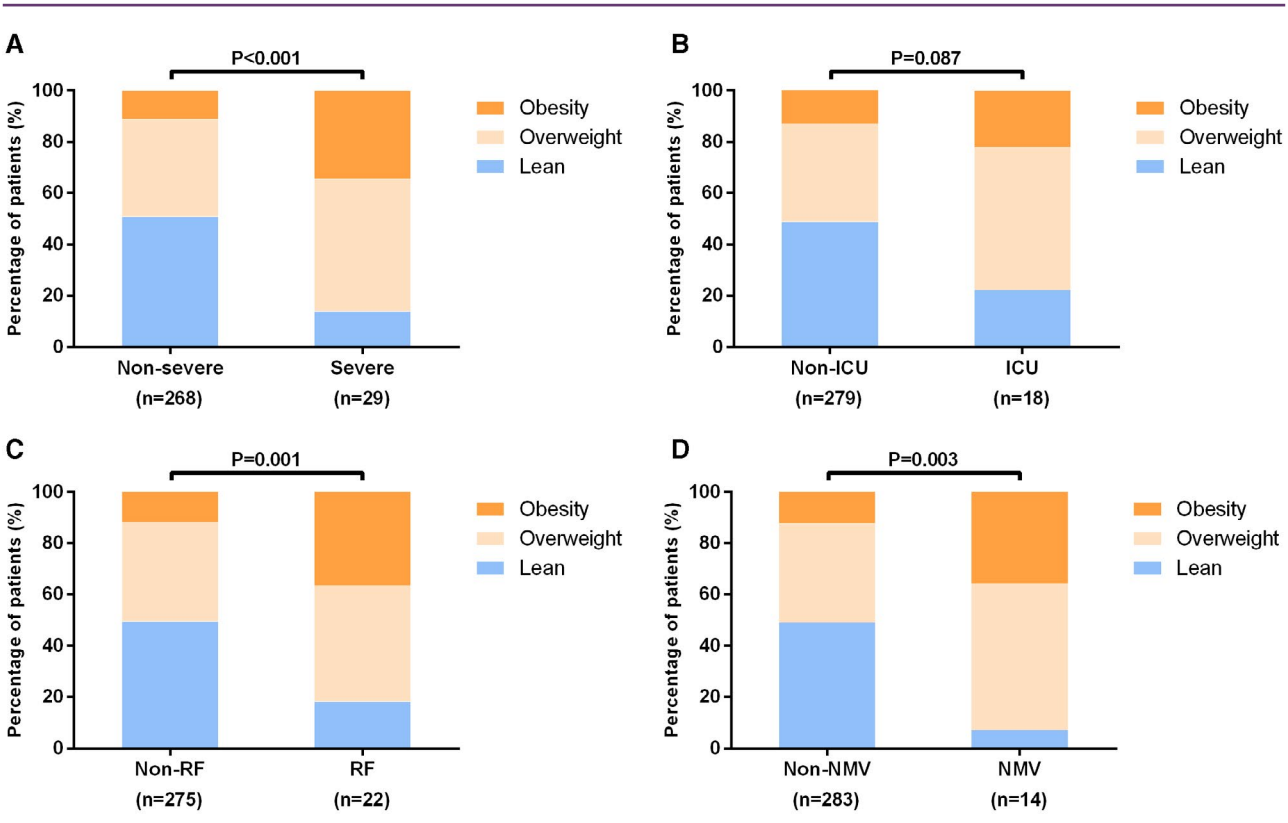

Figure 1 Distributions of lean, overweight, and obesity of patients with COVID-19 with different conditions. ICU, intensive care unit; RF, respiratory failure; NMV: noninvasive mechanical ventilation.

obesity (HR, 6.607; 95% CI: 1.955-22.329; $P=0.002$), type 2 diabetes (HR, 5.197; 95% CI: 1.837-14.699; $P=0.002$), and age > 60 years (HR, 2.766; 95% CI: 1.018-7.514; $P=0.046$) were associated with an increased risk of respiratory failure.

Discussion

Overweight and obesity are serious global health problems (19,20). The global prevalence ratios of overweight and obesity are 38.5% to

39.4% and 10.1% to 14.8%, respectively, in the general population (21). In our study, 39.39% and 13.47% of the patients with COVID-19 had overweight and obesity, respectively, suggesting that overweight and obesity may be not susceptible factors of COVID-19.

In our study, the most common symptoms were fever and cough, which were similar with previous studies (22,23). However, there were no significant differences in clinical symptoms among patients with different BMI. Patients with obesity had higher FBG levels and higher proportion of type 2 diabetes, indicating that obesity was associated with an increased risk for type 2 diabetes. Several studies have demonstrated that the presence of type 2 diabetes was a significant risk factor for severe illness and fatal outcome of COVID-19 (24-26). Thus, the association between the obesity-related comorbidities and severe COVID-19 deserves further investigation.

In our study, more patients with obesity had bilateral pneumonia compared with lean patients. In the report by Cai et al. (27), among 383 patients with COVID-19 from Shenzhen, China, obesity was also associated with a higher risk for severe pneumonia compared with lean patients. More patients with overweight and obesity received oxygen therapy and non-IMV in the present study. Our results revealed that overweight and obesity were risk factors of severe illness and more likely to develop complications such as respiratory failure and ARDS. After adjusting the confounding factors such as age and sex, overweight and obesity were still independent risk factors of severe illness of COVID-19. Taken together, these results suggested that overweight and obesity were independently associated with the severity of COVID-19.

However, the mechanisms of overweight and obesity contributing to severe COVID-19 are not yet defined. Obesity has been regarded as a risk factor of severe illness and poor prognosis in many infectious diseases (28). Obesity induces systematically chronic inflammation by increasing the secretion of cytokines such as interleukin 6, interleukin 8, and tumor necrosis factor-α, which may aggravate the injury of lung parenchyma and bronchi (29-31). A previous study has also found that obesity might impair adaptive immune responses in influenza virus infection (32). A similar mechanism might exist in patients with COVID-19. In addition, obesity causes a decrease in protective cardiorespiratory reserve and immune dysfunction (33). Sattar et al. (33) also reported obesity could increase the risk of thrombosis, which is an unignorable risk factor of severe COVID-19. With regard to lung function, obesity reduces expiratory volume and forced vital capacity (33-35). In addition, animal models demonstrated that obesity leads to decreased natural killer cell cytotoxicity and increased mortality in influenza infection (36). However, the mechanisms of overweight and obesity in the severity of COVID-19 deserve further investigation.

TABLE 3 Logistic regression analysis of risk factors for patients with severe COVID-19

	Univariate		Multivariate	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
Age				
≤60	Reference			
>60	1.577 (0.635-3.913)	0.326	1.410 (0.469-4.244)	0.541
Sites	1.023 (0.897-1.190)	0.770		
Sex				
Female	Reference			
Male	2.295 (0.982-5.363)	0.055	1.925 (0.729-5.088)	0.186
BMI (kg/m^2)				
<24	Reference			
24-28	5.000 (1.611-15.516)	0.005	4.167 (1.296-13.402)	0.017
≥28	11.333 (3.329-38.583)	<0.001	9.028 (2.523-32.299)	0.001
Hypertension				
No	Reference			
Yes	1.090 (0.394-3.015)	0.868	0.435 (0.124-1.528)	0.194
Type 2 diabetes				
No	Reference			
Yes	7.087 (2.782-18.053)	<0.001	5.333 (1.800-15.800)	0.003
Chronic lung diseases				
No	Reference			
Yes	1.911 (0.398-9.178)	0.418	1.751 (0.322-9.511)	0.517
Cardiovascular diseases				
No	Reference			
Yes	1.879 (0.212-16.653)	0.571	0.968 (0.066-14.280)	0.981
Malignant tumors				
No	Reference			
Yes	3.155 (0.317-31.354)	0.327	1.768 (0.150-20.879)	0.651

OR, odds ratio.

TABLE 4 Cox regression analysis of risk factors for respiratory failure

	Univariate		Multivariate	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Age				
≤60	Reference			
>60	1.927 (0.754-4.926)	0.170	2.766 (1.018-7.514)	0.046
Sex				
Female	Reference			
Male	1.808 (0.737-4.434)	0.196	1.432 (0.537-3.824)	0.473
BMI (kg/m^2)				
<24	Reference			
24-28	2.969 (0.931-9.467)	0.066	2.349 (0.708-7.798)	0.163
≥28	7.542 (2.270-25.055)	0.001	6.607 (1.955-22.329)	0.002
Hypertension				
No	Reference			
Yes	0.803 (0.238-2.713)	0.724	0.359 (0.092-1.400)	0.140
Type 2 diabetes				
No	Reference			
Yes	4.986 (1.949-12.756)	0.001	5.197 (1.837-14.699)	0.002
Chronic lung diseases				
No	Reference			
Yes	2.446 (0.572-10.467)	0.228	2.233 (0.489-10.198)	0.300
Cardiovascular diseases				
No	Reference			
Yes	0.048 (0.000-15003.613)	0.638		0.981
Malignant tumors				
No	Reference			
Yes	3.741 (0.503-27.835)	0.198	2.319 (0.285-18.878)	0.432

OR, odds ratio.

There were several limitations in our study. First, the outcomes of patients with COVID-19 had relatively favorable outcomes with no deaths. Thus, we could not analyze the association of overweight/obesity and fatal outcome in patients with COVID-19. Second, the associations of overweight/obesity with IMV could not be analyzed either. However, Kalligeros et al. (37) reported the potential association of obesity with severe outcomes in 102 patients hospitalized with COVID-19. They found that obesity was independently associated with the use of IMV (37). Third, many of the treatments and outcomes (oxygen therapy, non-IMV, admission to ICU, days of hospitalization) are subject to bias from clinicians who were in charge for the management of patients. Fourth, our study was conducted later in the pandemic, and by this point, people had suspicions and some studies were already conducted on the topic that overweight and obesity were risk factors for more severe COVID-19 outcomes. Thus, the clinicians in charge of care might have just been overly cautious, which might have biased our results. Furthermore, we could not include all the patients in our province. Thus, there is a potential selection bias in our study. However, nearly half of the confirmed cases in our province were included in our present study. We consider that our study is representative. Finally, the impacts of overweight and obesity on the long-term outcomes of patients with COVID-19 remain unclear.

In conclusion, patients with COVID-19 with overweight and obesity had higher risks for severe illness. Therefore, more attention should be paid to patients with COVID-19 with overweight or obesity. However, more studies are needed to confirm our findings and to reveal the underlying mechanisms of overweight and obesity associated with higher risks for severe illness in COVID-19.O

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