Obesity and COVID-19 in Adult Patients With Diabetes

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Obesity has caused wide concerns due to its high prevalence in patients with severe coronavirus disease 2019 (COVID-19). Coexistence of diabetes and obesity could cause an even higher risk of severe outcomes due to immunity dysfunction. We conducted a retrospective study in 1,637 adult patients who were admitted into an acute hospital in Wuhan, China. Propensity score–matched logistic regression was used to estimate the risks of severe pneumonia and requiring in-hospital oxygen therapy associated with obesity. After adjustment for age, sex, and comorbidities, obesity was significantly associated with higher odds of severe pneumonia (odds ratio [OR] 1.47 [95% CI 1.15–1.88]; $P = 0.002$) and oxygen therapy (OR 1.40 [95% CI 1.10–1.79]; $P = 0.007$). Higher ORs of severe pneumonia due to obesity were observed in men, older adults, and those with diabetes. Among patients with diabetes, overweight increased the odds of requiring in-hospital oxygen therapy by 0.68 times ($P = 0.014$) and obesity increased the odds by 1.06 times ($P = 0.028$). A linear dose-response curve between BMI and severe outcomes was observed in all patients, whereas a U-shaped curve was observed in those with diabetes. Our findings provide important evidence to support obesity as an independent risk factor for severe outcomes of COVID-19 infection in the early phase of the ongoing pandemic.

The ongoing coronavirus disease 2019 (COVID-19) pandemic first emerged in Wuhan, China in December 2020 and has infected >113 million people in >200 countries as of 26 February 2021, of whom 2.5 million died (1). Clinical investigations have identified that the elderly and people with comorbidities such as hypertension and diabetes were at high risks of severe complications, intensive care unit (ICU) admissions, and mortality (2–4). For example, Zhou et al. (2) reported that 31% of nonsurvivors of COVID-19 had diabetes in China. Another risk factor that caused wide concerns is obesity, due to its high prevalence in patients with severe COVID-19 (5). Obesity has been regarded as an independent risk factor for mortality and morbidity of the 2009 pandemic and seasonal influenza (6,7). It has been hypothesized that a similar positive association could also occur between obesity and COVID-19 (8). But the evidence is still sparse in the literature. Recent studies in two cities in China reported a higher incidence rate of severe pneumonia in patients with COVID-19 with overweight and obesity compared with those with normal weight (9,10). One study in the U.S. found that in populations with a high prevalence of obesity, there were more young people infected by COVID-19 (11). However, to date, few studies have investigated the association between obesity and adverse

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outcomes of COVID-19 with adequate adjustment for confounding factors. Recent studies have shown that diabetes is one of the leading comorbidities in patients with COVID-19 (4). In a retrospective cohort study, Zhou et al. (2) reported that 31% of nonsurvivors of COVID-19 had diabetes. This echoes the previous findings that coexistence of obesity and diabetes could remarkably increase the infection risks and disease severity, due to damaged T-cell response and immunity dysfunction (12,13). However, to the best of our knowledge, no studies have so far explored the interaction between obesity and diabetes on severe outcomes of patients with COVID-19.

The pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was similar to SARS-CoV, with the primary target of ACE2 receptors, which are abundant in adipocytes, arterial endothelial cells, and smooth muscle cells, as part of the renin-angiotensin system (14–16). Ryan and Caplice (17) hypothesized that SARS-CoV-2 virus might directly attack adipose tissue via ACE2 receptors or spread to adipose tissue adjacent to infected organs to result in longer viral shedding in patients with obesity. Moreover, elevated interleukin-6 (IL-6) levels in patients with obesity could also trigger the cytokine storm, leading to severe damage to infected organs. Therefore, we speculated that drugs targeting ACE2 and IL-6 might modify the effects of obesity on COVID-19.

In this study, we collected the demographic and clinical data of 1,637 adult patients in Wuhan, China, with the aim of estimating the risks of severe outcomes of COVID-19 associated with obesity, overweight, and underweight compared with normal weights. The risk estimates were also calculated for the subgroups by age, sex, diabetes, and receiving angiotensin II receptor blockers (ARB) or IL-6 inhibitor drugs in hospitalization.

RESEARCH DESIGN AND METHODS

Patients

The anonymized data of patients aged >18 years on admission were obtained from the electronic medical records in Huoshenshan Hospital, which was an acute field hospital built in response to the COVID-19 outbreak in Wuhan, China. The clinical data and laboratory test results of inpatients admitted from 4 February to 23 March 2020 and followed up until 31 March 2020 were obtained. We retrieved the data of 2,977 adult patients who tested positive for SARS-CoV-2 in RT-PCR of throat swabs or negative in RT-PCR but positive for both IgM and IgG in serum SARS-CoV-2 antibody tests, prior to admission or in hospitalization (18). According to the guideline by the National Health Commission of the People's Republic of China, these patients were classified into four groups: *1*) mild cases with mild respiratory symptoms but no signs of pneumonia in chest X-ray or computed tomography (CT) imaging; *2*) moderate cases with respiratory symptoms and typical signs of pneumonia in chest X-ray or CT imaging; *3*) severe cases that met one of the following criteria during hospitalization: respiratory rate ≥30/min, percent saturation of oxygen ≤93%, or ratio of arterial oxygen partial pressure to fractional inspired oxygen ≤300 mmHg; and *4*) critical cases that met one of the four following criteria: having respiratory failure, requiring mechanical ventilation, having symptoms of shock, or ICU admission. Clinical data and laboratory investigations were retrieved from the electronic medical records for individual patients.

BMI Categories

Individual BMI data were calculated from the weight (in kilograms) and height (in meters squared) measured on admission. The cutoff points of four BMI groups followed the criteria for Chinese populations: underweight, BMI <18.5 kg/m^2; normal weight, 18.5–23.9 kg/m^2; overweight, 24.0–27.9 kg/m^2; and obesity, ≥28 kg/m^2 (19).

Outcome Measurements

Severe pneumonia and requiring oxygen therapy were defined a priori as the key end points in our study. Due to a small number of patients with severe clinical outcomes, we defined the primary outcome as severe pneumonia, combining patients of the severe and critical cases, similar to the previous studies (9,10). The secondary outcome was the requirement of oxygen therapy in hospitalization, including high-flow nasal cannula oxygen therapy, noninvasive mechanical ventilation, invasive mechanical ventilation, endotracheal intubation, and extracorporeal membrane oxygenation (ECMO).

Statistical Analysis

As BMI data were only available in 1,637 out of 2,977 patients, we compared the clinical characteristics between those with and without BMI data (Supplementary Table 1). We also used the inverse probability of the treatment weighting (IPTW) method to reduce potential selection bias due to missing data (20). A propensity score was calculated for individual patients from the logistic regression models, including covariates of age, sex, and comorbidity score (0 = no comorbidity, 1 = one comorbidity, and 2 = more than one comorbidity). Coexisting comorbidities included in the comorbidity score were malignancy, hypertension, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, and diabetes. The diagnosis of comorbidities was made by doctors based on their medical history and assessment on admission. Univariate and multivariate logistic regression models were fitted to the selected severe outcomes and the latter adjusted for confounding factors of age, sex, and comorbidity score. Patients with the events were weighted by the inverse of the propensity score, while each patient without events by the inverse of (1 − propensity score). The crude and adjusted odds ratios (ORs) associated with BMI categories were derived from univariable and multivariable regression models, respectively. We further explored the dose-response relationships of BMI with severe outcomes using the natural

spline regression with three df that yielded a minimal Akaike information criterion in model selection.

Effect modification of age was assessed by an interaction model that added a productive term of age binary variables (<65 years and ≥65 years old) and BMI categories into the multivariable model. The significance of interaction terms was evaluated by the likelihood ratio test. Stratified analyses were subsequently conducted to fit multivariable regression models to the age groups (<65 years and ≥65 years old), sex, diabetes, and in-hospital use of ARB (or IL-6 inhibitors), respectively.

Furthermore, as smoking status was only available in 1,331 out of 1,637 patients, to make the best use of the data, we did not include smoking in the main analyses, but conducted a sensitivity analysis by adding smoking (yes = current smoker or no = ever/never smoker) into the multivariable regression models. Another sensitivity analysis was conducted by fitting the above models to the unweighted raw data. The third sensitivity analysis was to fill in missing BMI data with multiple imputation. We used the multivariate imputation by chained equations method, which has been widely used to deal with missing data (21–23). Height and other covariates, such as age, sex, weight, and severe outcomes, were selected for the imputation model to generate five complete data sets. We then recalculated the propensity score and IPTW and repeated the analysis. The separate estimates from five imputed data sets were pooled together. The statistical analysis of data was performed using R 3.6.2 software, and statistical significance was set to 0.05.

Ethical Approval

The ethical approval was obtained from the No. 923 Hospital of Joint Service Supporting Force in China, which led the military medical team in Huoshenshen Hospital and officially kept the database of electronic medical records after this hospital was closed on 15 April 2020. Signed consent forms were waived since all of the data were anonymized and all personal identifications were removed from the database.

Data and Resource Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

RESULTS

We compared the clinical characteristics between those with (n = 1,637) and without BMI data (n = 1,340) and found that most demographic data and clinical investigations were similar, except that the patients without BMI data were more likely to have symptoms of dry cough, fatigue, and dyspnea on admission, as well as coexisting congestive heart failure (Supplementary Table 1).

Of 1,637 patients, 75 (4.6%), 845 (51.6%), 572 (34.9%), and 145 (8.9%) were classified into underweight, normal, overweight, and obesity groups, respectively. Compared with normal and underweight groups, patients in overweight and obesity groups were younger, were more often male, and had more comorbidities, especially hypertension (Table 1). On admission, the presenting symptoms and the percentage of abnormal chest CT image were similar among these BMI groups, except for higher systolic/diastolic blood pressure and fasting plasma glucose in patients with overweight and obesity.

Clinical characteristics and outcomes of patients with COVID-19 by BMI groups are summarized in Table 2. There were 518 patients (31.6%) who developed severe pneumonia (both severe and critical COVID-19 groups). The proportion of severe pneumonia was slightly higher in the obesity group (36.6%), but the difference was not statistically significant. Forty-two patients were admitted into the ICU, with the underweight group having a slightly higher rate. Eight patients died of COVID-19 infection. A total of 404 patients required oxygen therapy, of whom most received high-flow nasal cannula oxygen therapy, and 211 (52.2%) were classified as severe pneumonia. There were 211 out of 518 patients (40.7%) with severe pneumonia also requiring oxygen therapy. Only three patients received ECMO and two renal replacement therapy. The median length of hospital stay ranged 11–12 days across BMI groups. No significant difference of these outcomes was observed among the BMI groups, except that normal-weight patients tended to have a longer ICU stay than the other groups. The duration from first admission to death appeared to be shorter in the obesity and underweight groups, although this difference did not reach statistical significance.

The most common complications were septic shock in these patients, followed by hypoproteinemia and secondary infection (Table 2). All three occurred most often in the underweight group than the remaining three groups. Drug prescriptions of antivirals, corticosteroids, IL-6 receptor blocker, convalescence serum, and Chinese medicine were not significantly different among the BMI groups. The only exception was that underweight patients prescribed with more intravenous immunoglobin injection than other groups, which was probably due to a higher rate of septic shock.

After the propensity score matching by age, sex, and comorbidities using the IPTW method, crude OR was estimated from the univariate logistic regression models for two outcome measures: incidence of severe pneumonia and requiring oxygen therapy in hospitalization. In all patients, obesity was significantly associated with higher odds of severe pneumonia and oxygen therapy (Table 3). After adjustment for age, sex, and comorbidity score, obesity remained significant, showing 1.47-fold (95% CI 1.15–1.88; P = 0.002) and 1.40-fold (95% CI 1.10–1.79; P = 0.007) odds of severe pneumonia and oxygen therapy compared with normal weight.

Interaction terms in most models were statistically significant (P < 0.05 in likelihood ratio tests), with the only exceptions being BMI * age and BMI * ARB in the models of oxygen therapy (Supplementary Table 2).

Table 1—Demographic characteristics of patients with COVID-19 by BMI groups

Characteristic	BMI groups^ Normal (*n* = 845)	Underweight (*n* = 75)	Overweight (*n* = 572)	Obesity (*n* = 145)	*P*#
Age, years, median (IQR)	61.00 (51.00, 67.00)	66.00 (53.50, 75.50)	58.00 (50.00, 67.00)	58.00 (49.75, 66.00)	0.001
Male, *n* (%)	369 (43.9)	36 (48.0)	335 (58.6)	74 (51.0)	<0.001
Smoking status, *n* (%)					0.063
Never/unknown	643 (94.1)	52 (86.7)	412 (90.9)	107 (93.0)	
Former/current	40 (5.9)	8 (13.3)	41 (9.1)	8 (7.0)	
Comorbidities, *n* (%)					
Any	296 (35.0)	31 (41.3)	247 (43.2)	68 (46.9)	0.003
None	549 (65.0)	44 (58.7)	325 (56.8)	77 (53.1)	0.004
1	201 (23.8)	22 (29.3)	154 (26.9)	38 (26.2)	
>1	95 (11.2)	9 (12.0)	93 (16.3)	30 (20.7)	
Malignancy	11 (1.3)	5 (6.7)	13 (2.3)	0 (0.0)	0.002
Hypertension	205 (24.3)	14 (18.7)	196 (34.3)	58 (40.0)	<0.001
Coronary artery disease	38 (4.5)	6 (8.0)	37 (6.5)	9 (6.2)	0.294
Congestive heart failure	8 (0.9)	1 (1.3)	7 (1.2)	0 (0.0)	0.594
COPD	18 (2.1)	6 (8.0)	19 (3.3)	3 (2.1)	0.022
Chronic kidney disease	6 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.130
Chronic liver disease	13 (1.5)	2 (2.7)	11 (1.9)	6 (4.1)	0.206
Diabetes	110 (13.0)	10 (13.3)	86 (15.0)	25 (17.2)	0.485
Symptoms on admission, *n* (%)					
Fever	451 (53.4)	33 (44.0)	289 (50.5)	81 (55.9)	0.271
Chills	43 (5.1)	1 (1.3)	23 (4.0)	2 (1.4)	0.108
Dry cough	408 (48.3)	27 (36.0)	258 (45.1)	67 (46.2)	0.183
Sore throat	37 (4.4)	5 (6.7)	21 (3.7)	6 (4.1)	0.661
Myalgia	233 (27.6)	19 (25.3)	171 (29.9)	39 (26.9)	0.705
Fatigue	254 (30.1)	18 (24.0)	154 (26.9)	45 (31.0)	0.418
Headache	21 (2.5)	5 (6.7)	18 (3.1)	10 (6.9)	0.016
Diarrhea	62 (7.3)	4 (5.3)	49 (8.6)	12 (8.3)	0.705
Dyspnea	189 (22.4)	14 (18.7)	120 (21.0)	32 (22.1)	0.846
RR, median (IQR)	20.00 (19.00, 22.00)	20.00 (20.00, 22.00)	20.00 (19.00, 22.00)	20.00 (19.75, 21.00)	0.435
SBP, mmHg, median (IQR)	128.00 (118.00, 137.00)	130.00 (117.50, 138.00)	131.00 (120.00, 142.00)	132.00 (120.00, 141.00)	<0.001
DBP, mmHg, median (IQR)	80.00 (73.00, 87.00)	76.50 (70.00, 85.75)	83.00 (76.00, 90.00)	80.00 (76.00, 90.00)	<0.001
FPG, mmol/L, median (IQR)	4.90 (4.50, 5.67)	4.76 (4.38, 5.41)	5.00 (4.66, 5.88)	5.19 (4.72, 6.55)	<0.001
CT image, *n* (%)					
Ground-glass opacity	247 (29.2)	18 (24.0)	157 (27.4)	37 (25.5)	0.624
Bilateral pulmonary infiltration	13 (1.5)	1 (1.3)	9 (1.6)	2 (1.4)	0.997
Consolidation					0.758
Left lung	26 (3.1)	4 (5.3)	11 (1.9)	5 (3.4)	
Right lung	35 (4.1)	3 (4.0)	22 (3.8)	4 (2.8)	
Both lungs	347 (41.1)	33 (44.0)	249 (43.5)	57 (39.3)	

COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; IQR, interquartile range; RR, respiratory rate; SBP, systolic blood pressure. ^BMI categories: underweight, BMI <18.5 kg/m^2; normal weight, 18.5–23.9 kg/m^2; overweight, 24.0–27.9 kg/m^2; and obesity, ≥28 kg/m^2. #*P* value was calculated from Kruskal-Wallis test for nonnormally distributed continuous variables or from χ^2 test or Fisher exact test for categorical variables.

Among 231 patients with diabetes, significant associations with overweight and obesity were found in oxygen therapy, but not in severe pneumonia (Table 3). Compared with normal weight, overweight increased the odds of requiring in-hospital oxygen therapy by 0.68 times ($P = 0.014$) and obesity increased the odds by 1.06 times ($P = 0.028$).

Stratified analysis by age shows that in patients aged ≥65 years, obesity was independently associated with significantly higher odds of severe pneumonia (adjusted OR 2.21 [95% CI 1.37–3.57]; $P = 0.001$) and oxygen therapy (adjusted OR 1.88 [95% CI 1.19–2.97]; $P = 0.007$), respectively (Table 3). In those aged <65 years, obesity was associated with higher odds of these outcomes, but none reached statistical significance. By contrast, underweight patients had lower odds (adjusted OR 0.54 [95% CI 0.30–0.97]; $P = 0.037$), while overweight increased the odds of severe pneumonia (adjusted OR 1.28 [95% CI 1.06–1.55]; $P = 0.010$).

The association between obesity and severe pneumonia was more pronounced in men than in women (adjusted OR 1.85 [95% CI 1.31–2.61], $P < 0.001$; vs. OR 1.14 [95% CI 0.80–1.64], $P = 0.472$). The effect estimates of obesity on oxygen therapy were comparable between men and women

Table 2—Clinical characteristics and outcomes of patients with COVID-19 by BMI groups

Characteristic	BMI groups^ Normal (*n* = 845)	Underweight (*n* = 75)	Overweight (*n* = 572)	Obesity (*n* = 145)	*P*#
COVID-19 severity, *n* (%)					0.577
Mild	7 (0.8)	2 (2.7)	4 (0.7)	1 (0.7)	
Moderate	581 (68.8)	48 (64.0)	385 (67.3)	91 (62.8)	
Severe	243 (28.8)	25 (33.3)	176 (30.8)	50 (34.5)	
Critical	14 (1.7)	0 (0.0)	7 (1.2)	3 (2.1)	
Outcomes					
Death	3 (0.4)	1 (1.3)	2 (0.3)	2 (1.4)	0.261
Discharge	764 (90.4)	68 (90.7)	509 (89.0)	133 (91.7)	0.721
Transfer	1 (0.1)	2 (2.7)	1 (0.2)	0 (0.0)	<0.001
Length of hospital stays, median (IQR)	12.00 (7.00, 19.00)	11.00 (7.00, 16.50)	12.00 (7.00, 17.00)	11.00 (7.00, 18.50)	0.548
ICU admission	20 (2.4)	3 (4.0)	15 (2.6)	4 (2.8)	0.854
Length of ICU stay, median (IQR)	9.00 (8.00, 14.25)	3.00 (2.00, 5.00)	5.00 (3.00, 9.00)	6.00 (3.50, 9.00)	0.039
Days from first admission to death, median (IQR)	19.00 (18.00, 34.00)	12.00 (12.00, 12.00)	20.50 (13.75, 27.25)	9.00 (6.00, 12.00)	0.335
Oxygen therapy	209 (24.7)	17 (22.7)	134 (23.4)	44 (30.3)	0.369
High-flow nasal cannula oxygen therapy	200 (23.7)	15 (20.0)	128 (22.4)	42 (29.0)	0.343
Noninvasive mechanical ventilation	21 (2.5)	0 (0.0)	17 (3.0)	5 (3.4)	0.434
Invasive mechanical ventilation	16 (1.9)	3 (4.0)	9 (1.6)	4 (2.8)	0.462
Endotracheal intubation	9 (1.1)	2 (2.7)	5 (0.9)	3 (2.1)	0.391
ECMO	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0.910
Renal replacement therapy	1 (0.1)	1 (1.3)	0 (0.0)	0 (0.0)	0.019
Complications, *n* (%)					
Sepsis	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.7)	0.202
Respiratory failure	6 (0.7)	0 (0.0)	7 (1.2)	1 (0.7)	0.611
Heart failure	8 (0.9)	1 (1.3)	7 (1.2)	0 (0.0)	0.594
Septic shock	42 (5.0)	9 (12.0)	23 (4.0)	10 (6.9)	0.021
Coagulopathy	5 (0.6)	2 (2.7)	2 (0.3)	0 (0.0)	0.060
Acute cardiac injury	4 (0.5)	0 (0.0)	3 (0.5)	0 (0.0)	0.774
Acute kidney injury	1 (0.1)	1 (1.3)	1 (0.2)	0 (0.0)	0.117
Secondary infection	22 (2.6)	8 (10.7)	12 (2.1)	6 (4.1)	<0.001
Hypoproteinemia	23 (2.7)	9 (12.0)	16 (2.8)	5 (3.4)	<0.001
Acidosis	7 (0.8)	0 (0.0)	3 (0.5)	2 (1.4)	0.608
Medication, *n* (%)					
Antiviral	376 (44.5)	35 (46.7)	251 (43.9)	65 (44.8)	0.972
Chloroquine	43 (5.1)	4 (5.3)	29 (5.1)	3 (2.1)	0.450
Oseltamivir	83 (9.8)	4 (5.3)	51 (8.9)	13 (9.0)	0.616
Arbidol	347 (41.1)	32 (42.7)	236 (41.3)	63 (43.4)	0.952
Ribavirin	15 (1.8)	1 (1.3)	13 (2.3)	4 (2.8)	0.796
Two of the above	68 (8.0)	4 (5.3)	43 (7.5)	12 (8.3)	0.846
Corticosteroids	98 (11.6)	12 (16.0)	68 (11.9)	19 (13.1)	0.697
Intravenous Ig	198 (23.4)	31 (41.3)	108 (18.9)	31 (21.4)	<0.001
IL-6 inhibitors	26 (3.1)	2 (2.7)	12 (2.1)	3 (2.1)	0.689
Convalescence serum	59 (7.0)	4 (5.3)	47 (8.2)	11 (7.6)	0.742
Chinese medicine (any)	618 (73.1)	55 (73.3)	406 (71.0)	93 (64.1)	0.160

IQR, interquartile range. ^BMI categories: underweight, BMI <18.5 kg/m^2; normal weight, 18.5–23.9 kg/m^2; overweight, 24.0–27.9 kg/m^2; and obesity, ≥28 kg/m^2. #*P* value was calculated from Kruskal-Wallis test for nonnormally distributed continuous variables or from χ^2 test or Fisher exact test for categorical variables.

(adjusted OR 1.33 [95% CI 0.94–1.87], $P = 0.105$; vs. OR 1.40 [95% CI 0.98–1.99]; $P = 0.062$).

There were only 43 and 135 patients prescribed with IL-6 inhibitors and ARB drugs, respectively. Due to small sample sizes, fewer OR estimates in the drug-user subgroups remain significant after adjustment (Supplementary Table 3). The ORs for severe pneumonia and oxygen therapy in the subgroup without IL-6 inhibitor prescription were 1.54 (95% CI 1.20–1.98) and 1.67 (95% CI 1.28–2.16), respectively, slightly higher than the corresponding estimates in all patients.

Sensitivity analysis with additional adjustment for smoking status yielded generally similar results to those of main analysis (Supplementary Table 4), except for

Table 3—Crude and adjusted OR of severe outcomes of COVID-19 of underweight, overweight, and obese patients, with reference to normal-weight patients from propensity score–matched data using the IPTW method

	Severe pneumonia				Oxygen therapy			
	Crude OR	*P*	Adjusted OR	*P*	Crude OR	*P*	Adjusted OR	*P*
All patients								
Underweight	0.95 (0.68, 1.33)	0.762	0.95 (0.67, 1.33)	0.759	0.84 (0.60, 1.18)	0.304	0.84 (0.60, 1.18)	0.307
Overweight	1.13 (0.97, 1.32)	0.105	1.14 (0.98, 1.32)	0.099	0.95 (0.82, 1.10)	0.495	0.95 (0.81, 1.10)	0.488
Obesity	1.46 (1.14, 1.86)	0.002	1.47 (1.15, 1.88)	0.002	1.40 (1.10, 1.79)	0.006	1.40 (1.10, 1.79)	0.007
Aged <65 years								
Underweight	0.54 (0.30, 0.97)	0.040	0.54 (0.30, 0.97)	0.037	0.73 (0.43, 1.23)	0.238	0.71 (0.42, 1.21)	0.211
Overweight	1.26 (1.05, 1.52)	0.014	1.28 (1.06, 1.55)	0.010	0.96 (0.80, 1.15)	0.637	0.97 (0.80, 1.17)	0.754
Obesity	1.26 (0.95, 1.69)	0.113	1.28 (0.95, 1.71)	0.100	1.23 (0.92, 1.64)	0.157	1.25 (0.93, 1.67)	0.138
Aged ≥65 years								
Underweight	1.23 (0.79, 1.92)	0.353	1.28 (0.82, 2.00)	0.275	0.93 (0.59, 1.46)	0.756	0.94 (0.59, 1.48)	0.773
Overweight	0.92 (0.71, 1.19)	0.516	0.90 (0.69, 1.17)	0.414	0.93 (0.72, 1.21)	0.578	0.93 (0.71, 1.21)	0.589
Obesity	2.28 (1.41, 3.67)	0.001	2.21 (1.37, 3.57)	0.001	1.93 (1.22, 3.04)	0.005	1.88 (1.19, 2.97)	0.007
Men								
Underweight	1.40 (0.88, 2.24)	0.157	1.43 (0.89, 2.29)	0.137	0.99 (0.62, 1.60)	0.981	1.03 (0.64, 1.68)	0.886
Overweight	1.22 (0.98, 1.50)	0.072	1.23 (0.99, 1.52)	0.062	0.84 (0.68, 1.04)	0.110	0.85 (0.68, 1.05)	0.124
Obesity	1.84 (1.31, 2.58)	<0.001	1.85 (1.31, 2.61)	<0.001	1.36 (0.97, 1.90)	0.077	1.33 (0.94, 1.87)	0.105
Women								
Underweight	0.62 (0.37, 1.03)	0.062	0.62 (0.37, 1.03)	0.064	0.69 (0.42, 1.12)	0.134	0.69 (0.42, 1.13)	0.141
Overweight	1.08 (0.87, 1.34)	0.496	1.08 (0.86, 1.34)	0.514	1.08 (0.87, 1.35)	0.482	1.07 (0.86, 1.33)	0.564
Obesity	1.14 (0.80, 1.63)	0.466	1.14 (0.80, 1.64)	0.472	1.43 (1.01, 2.02)	0.045	1.40 (0.98, 1.99)	0.062
Diabetes								
Underweight	1.46 (0.60, 3.55)	0.400	1.50 (0.61, 3.65)	0.378	1.20 (0.48, 2.96)	0.700	1.22 (0.49, 3.05)	0.673
Overweight	0.90 (0.60, 1.35)	0.608	0.88 (0.58, 1.34)	0.553	1.64 (1.10, 2.44)	0.016	1.68 (1.11, 2.54)	0.014
Obesity	1.03 (0.56, 1.89)	0.937	1.01 (0.54, 1.89)	0.972	1.95 (1.04, 3.64)	0.037	2.06 (1.08, 3.92)	0.028

The results of age, sex, and diabetes subgroups are also shown. Models were adjusted for age, sex, and comorbidity score.

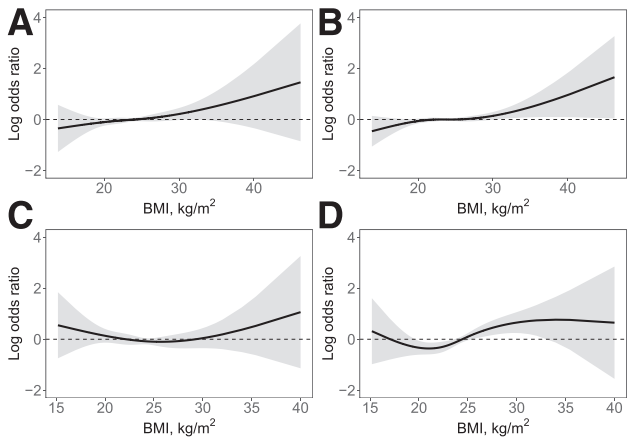

Figure 1—Dose-response relationships of BMI with severe outcomes of COVID-19 in all patients and the subgroup with diabetes. *A*: Association of BMI with severe pneumonia in all patients. *B*: Association of BMI with oxygen therapy in all patients. *C*: Association of BMI with severe pneumonia in patients with diabetes. *D*: Association of BMI with oxygen therapy in patients with diabetes.

a significant inverse association of overweight with severe pneumonia in older adults (adjusted OR 0.72 [95% CI 0.53–0.98]; $P = 0.034$). The adjusted OR became significant for severe pneumonia in the older age group and for oxygen therapy in the younger age group, but the associations between obesity and oxygen therapy were no longer significant in the older age and diabetes groups. The sensitivity analyses using unweighted raw data gave similar estimates, but none of adjusted ORs reached statistical significance, with the only exception being observed in the ≥65 years of age group (Supplementary Table 4).

DISCUSSION

In this study, we investigated the association of obesity with COVID-19 clinical characteristics and outcomes in a large sample of 1,637 adult inpatients in the first epicenter in Wuhan, China. Compared with normal weight, obesity was significantly and independently associated with increased risks of severe pneumonia and requiring in-hospital oxygen therapy, with the adjusted OR estimates of 1.47 and 1.40, respectively. Our estimates are slightly lower but more precise than those reported in two recent studies in other cities in China (9,10). One study in a sample of 383 inpatients in Shenzhen reported an adjusted OR of 3.40 (95% CI 1.40–2.86) for severe pneumonia in patients with obesity (BMI ≥28 kg/m^2), compared with those of normal weight (9). Another study in Wenzhou estimated an adjusted OR of 3.00 (95% CI 1.22–7.38) for severe pneumonia in 75 pairs of inpatients with COVID-19 with (BMI ≥25 kg/m^2) and without obesity, who were matched by age and sex (10). It is of note that 31.6% of the patients in our study were classified as severe pneumonia, slightly higher than 23.8% in Shenzhen, which was probably due to the overwhelmed health care system in Wuhan during the early phase of the COVID-19 pandemic.

To the best of our knowledge, our study is the first to demonstrate that obesity was an independent risk factor for COVID-19 severity in the elderly and patients with diabetes. It is not surprising to observe higher effect estimates in these high-risk populations than in the general population (Table 2). Our results echo the expert calls on enhancement of anthropometric and metabolic data collection in routine care of patients with COVID-19 in order to fully understand the pathogenicity of adverse cardiovascular and respiratory events in these high-risk populations (8,24).

There were only 8.9% of patients in our study classified as obesity, slightly lower than the national rate in Chinese adults (14% in men and 14.1% in women) (25) and the COVID-19 study in Shenzhen (10.7%) (9). It is of note that the prevalence of obesity was much lower in China than in western countries, and only two patients in our study had severe obesity (BMI >40 kg/m^2). People with severe obesity are classified as high-risk populations for COVID-19 by the Centers for Disease Control and Prevention in the U.S. (26). However, our findings observed a significant detrimental effect of obesity even in a population with relatively low prevalence and low BMI cutoff points in the early phase of the pandemic. Studies in France reported that BMI ≥35 kg/m^2 was associated with a higher risk of invasive mechanical ventilation in patients with COVID-19 (5,27). Further investigations are warranted on the BMI cutoff point for the increased severity of COVID-19 infection in different populations.

The detrimental effects of obesity on respiratory infections caused by influenza and adenovirus have been well documented in the literature (12). But the mechanism of SARS-CoV-2 pathogenesis in patients with obesity remains unclear. Misumi et al. (28) used a mouse model to demonstrate overexpression of virus-specific memory T cells in adipose tissue and spleen, resulting in severe damage to adipocytes, spleen, and pancreas. A hypothesis has been raised by Ryan and Caplice (17) to suggest that abundant ACE2 receptors in adipocytes and high levels of IL-6 could be involved in increased severity of COVID-19 in obese people. If this is true, we would expect the use of ARB (in hypertensive patients only) or IL-6 inhibitor could modify the risk in patients with obesity. We found significant interactions between these two types of drugs and BMI groups, but unfortunately, due to a relatively small sample size in this study, the effect estimates in the subgroups were unstable with wide CIs. Nevertheless, we found higher risk estimates in patients without IL-6 inhibitor prescriptions than in all patients, suggesting a potential benefit of IL-6 inhibitor on COVID-19 severity. More evidence is still needed to elucidate the roles of ACE2 receptors and IL-6 in pathogenesis of COVID-19 in patients with obesity.

It is not surprising to observe higher risks of severe outcomes associated with obesity in the elderly and patients

with diabetes. Patients with diabetes have relatively comprised immunity, rendering higher susceptibility to respiratory pathogens (29). A study by Zhu et al. (30) analyzed a large sample of patients with COVID-19 and found that diabetes significantly increased the mortality risk (adjusted hazard ratio 1.49 compared with patients without diabetes). It has been speculated that overexpressed ACE2 in patients with diabetes could facilitate virus entry to host cells and thereby increase susceptibility and disease severity (31,32). Hence, shared regulatory pathways could cause a synergist effect of obesity and diabetes on COVID-19 severity. Interestingly, we found a U-shaped dose-response curve between BMI and severe outcomes in the subgroup with diabetes, but in all patients, underweight was found to be a protective factor (Fig. 1). Both malnutrition and obesity have been found to have similar effects on regulation of renin-angiotensin system pathways and inflammatory response in animal experiments (33). To our surprise, underweight patients had low odds of severe outcomes of COVID-19, whereas high odds were found in overweight and obesity in adults <65 years old. A study in New York City found that obesity significantly increased the risk of hospital admission for COVID-19 due to respiratory distress in adults aged <60 years (34). The lack of significant effects of obesity in younger patients could be due to a relatively low prevalence of comorbidities. In our data, 38% of patients aged <65 years with obesity had one or more comorbidities, comparable to 36% in overweight, slightly >28% in underweight, and 24% in normal weight. The vulnerability of underweight and obese young adults to COVID-19 still needs further investigations.

There are several limitations in our study. First, all patients were from one single acute hospital in Wuhan, and the incidence rate of deaths was relatively low. As a result, we were only able to assess the risks of severe pneumonia and requiring oxygen therapy. We did not use the outcomes that were likely affected by the availability of health care resources in the pandemic, such as the delay from symptom onset to hospital admission and the length of hospital stay, although such variables might also reflect the severity of infections. Future studies with a large sample from different ethnicities and regions are needed to demonstrate the generalization of our findings. Nevertheless, our study provides a protocol for comprehensive evaluation of obesity effects on COVID-19. Second, nearly half of the patients in this hospital had missing BMI data; therefore, a selection bias might have existed. Nevertheless, we addressed the issue by adopting a matching method based on a propensity score. We also showed there was no dramatic difference between patients with and without missing BMI data, suggesting that the missing information might have been caused by negligence in collecting anthropometric data in clinical practice. Sensitivity analysis using the data with multiple imputation showed similar estimates to main analysis without imputation, but fewer remained significant due to reduced data variations (Supplementary Table 5). Third, our study had a relatively small number of patients with COVID-19 with diabetes. Future studies with larger sample sizes of patients from different countries are warranted to demonstrate the modifying effects of diabetes.

In summary, our study provides important evidence to support obesity as an independent risk factor for severe COVID-19 infection in the early stage of the ongoing pandemic. Patients with COVID-19 with obesity require more medical attention and active management, especially in the elderly, men, and people with diabetes. The risks of severe outcomes associated with underweight in patients with diabetes require further investigations.

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