Obesity

Obesity as a Potential Predictor of Disease Severity in Young COVID-19 Patients: A Retrospective Study

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Objective: This study aims to explore the indicators for severity of coronavirus disease 2019 (COVID-19) in young patients between the ages of 18 and 40 years.

Methods: This retrospective cohort study included 65 consecutively admitted patients with COVID-19 who were between 18 and 40 years old in Zhongnan Hospital of Wuhan University in Wuhan, China. Among them, 53 were moderate cases, and 12 were severe or critical cases. Epidemiological, clinical, and laboratory characteristics and treatment data were collected. A multivariate logistic regression analysis was implemented to explore risk factors.

Results: The patients with severe/critical cases had obviously higher BMI (average 29.23 vs. 22.79 kg/m^2) and lower liver computed tomography value (average 50.00 vs. 65.00 mU) than the group of moderate cases. The patients with severe/critical cases had higher fasting glucose, alanine aminotransferase, aspartate aminotransferase, and creatinine compared with patients with moderate cases (all $P < 0.01$). More severe/critical cases (58.33% vs. 1.92%) had positive urine protein levels. The severe/critical cases also experienced a significant process of serum albumin decline. Logistic regression analysis showed that male sex, high BMI (especially obesity), elevated fasting blood glucose, and urinary protein positivity were all risk factors for young patients with severe COVID-19.

Conclusions: Obesity is an important predictor of COVID-19 severity in young patients. The main mechanism is related to damage of the liver and kidney.

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Study Importance

What is already known?

- Severe coronavirus disease 2019 (COVID-19) occurs mostly in the elderly. But the risk factors for young patients with severe COVID-19 are not yet clear.
- How obesity affects the occurrence and development of severe COVID-19 is still not clear.

What does this study add?

- Obesity is an important predictor of severe COVID-19 among young patients. The main mechanism is related to the ectopic deposition of fat in the liver and kidneys.
- Young patients with severe COVID-19 can experience rapid changes after admission. An important feature is the rapid decline in albumin level. During the course of the disease, the decrease in albumin is accompanied by an increase in D-dimer, which is an indicator of hypercoagulation. Disseminated intravascular coagulation is possible in critically ill patients.

How might these results change the direction of research or the focus of clinical practice?

- We need to pay more attention to those young patients with obesity, especially those with fatty liver hepatitis and those who are urine protein positive. Albumin and D-dimer must be monitored after admission to provide early warning of rapid changes in condition and to improve patient outcomes.

Introduction

According to a report by the World Health Organization, as of April 30, 2020, coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has infected more than 3 million people in more than 52 countries and has led to more than 200,000 deaths (1). At present, our knowledge of COVID-19 remains limited. Pathological studies following the autopsies of patients who had COVID-19 have shown that the virus mainly invades the lungs. However, the virus can

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also invade other organs, including immune organs, heart, liver, kidneys, etc (2-4). Current research has shown that in addition to the respiratory system, COVID-19 can affect multiple organs throughout the body, including the cardiovascular system (5,6), liver (7), kidneys (8), and coagulation system (9). These findings emphasize the extensive nature of the effects of COVID-19 and the complexity of its pathological mechanisms.

According to current evidence, the patient group at greatest risk for severe COVID-19 are the elderly, especially those with underlying diseases such as diabetes, hypertension, cardiovascular disease, etc. (10,11). The prevalence and mortality rate of COVID-19 among young people are much lower than those among the elderly (12). However, given the large number of patients with COVID-19, the absolute number of critically ill cases of young adults with COVID-19 is still large. At present, there remains a major lack of information about the characteristics and risk factors associated with severe disease among young adult patients with COVID-19. Because the young population has far fewer underlying diseases than the elderly, they may have different characteristics compared with older patients with COVID-19. The ability to recognize any factors that may contribute to disease severity in young adult patients without known underlying conditions would certainly be useful for the managements of these cases. In a recent study of the characteristics of COVID-19 cases among medical staff, for which the average age was 35 years, patients with severe cases were found to have a significantly elevated BMI (13). The present aimed to identify potential predictive factors for severe COVID-19 among young patients, with particular attention given to the evaluation of obesity-related indicators.

Methods

Study patients and data collection

Before March 13, 2020, Zhongnan Hospital of Wuhan University received patients with COVID-19 from the community, other hospitals, and isolation points. After this date, all hospitalized patients with COVID-19 were transferred to Leishenshan Hospital for further medical treatment, according to the unified deployment strategy. Patients treated in Zhongnan Hospital of Wuhan University were included in the present retrospective study according to the following criteria: (1) confirmed COVID-19 based on a positive RNA test for SARS-CoV-2 in a respiratory sample, (2) age between 18 and 40 years, (3) chest computed tomography (CT) scan data were available, and (4) weight and height had been recorded. In consideration of the complex factors affecting pregnant women, they were excluded from our study population. This case series was approved by the Institutional Ethics Board of Zhongnan Hospital of Wuhan University (No. 2020011). A total of 65 patients were included in the analysis. All cases were classified as moderate, severe, or critical according to the Guidance for Corona Virus Disease 2019 (6th edition) released by the National Health Commission of China (14). Moderate cases have fever and respiratory tract–related symptoms as well as visible signs of pneumonia on imaging. Cases were classified as severe if they met any of the following criteria: (1) shortness of breath, according to a respiratory rate (RR) ≥ 30 times/min; (2) an oxygen saturation ≤ 93% in the resting state; and (3) arterial blood oxygen partial pressure (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mm Hg. Critical cases had to meet any of the following criteria: (1) occurrence of respiratory failure and mechanical ventilation, (2) shock, and (3) organ failure in addition to respiratory distress that required intensive care unit monitoring and treatment. The need for written informed consent was waived owing to the rapid emergence of this infectious disease.

Clinical data were collected up to March 13, 2020, and data were collected for one critically ill patient until April 12, 2020, after transfer to Leishenshan Hospital. We used a standard case report form for data collection. Past medical history, family history, anthropometric data, laboratory test results, treatment details, and oxygen support data during hospital admission were collected from the patients' medical records by two independent researchers. If any key data were missing, we contacted the physician in charge of the patient's care to request further information.

Laboratory measurements

Data for metabolic indexes (i.e., fasting blood glucose [FBG] and triglyceride, high-density lipoprotein cholesterol, and lipoprotein(a) levels), white blood cell counts (i.e., neutrophil and lymphocyte counts), coagulation indexes (i.e., D-dimer level and activated partial thromboplastin time), cardiac disease indexes (i.e., creatine kinase myocardial band, troponin I [TnI], and brain natriuretic peptide [BNP] levels), liver function indexes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, direct bilirubin, indirect bilirubin, and albumin levels), kidney function indexes (creatinine, cystatin C, and uric acid levels in addition to urine protein positivity), as well as C-reactive protein and lactate dehydrogenase (LDH) levels were collected. Respiratory samples and blood samples were taken, and immunoglobulin G/M testing of blood samples was performed to exclude infection by other types of viruses.

SARS-CoV-2 testing

The presence of the SARS-CoV-2 virus in respiratory samples was confirmed with real-time reverse transcription polymerase chain reaction using a nucleic acid detection kit developed by DAAN Gene Co., Ltd., of Sun-Yatsen University (Guangzhou, China). This kit is designed to qualitatively detect the ORF1ab and N genes of the SARS-CoV-2 virus.

Lung lesion volume, liver CT value, subcutaneous fat, epicardial fat, and visceral fat measurements

In this study, the Intelligent Evaluation System (Hangzhou YITU Healthcare Technology Co., Ltd., Hangzhou, China) was employed as the CT image analysis tool for the detection of COVID-19–related pneumonia. The system was used for segmentation of the left and right lungs and detection of patchy shadows, and from the collected images, quantitative parameters, including the inflammatory volume and proportion of the inflammatory volume among the total lung volume, were computed.

Axial CT images were reconstructed with slice thicknesses of 5 and 1 mm. The thickness of subcutaneous fat was measured on the axial images under the midline of the anterior abdominal wall, and the thickness in the largest transverse view was taken as the final measurement.

The CT value of the liver was determined by selecting the left lateral lobe, the left medial lobe, and the right hepatic lobe on the transverse images of the 12th thoracic vertebra using a Digital Imaging and Communications in Medicine (DICOM) viewer. During the measurement, the area of interest is positioned as far away from the blood vessels as possible. The average of the three measurements was used as the CT value of the liver. In addition, the evaluation criteria for fatty liver

was a liver density lower than that of the spleen (<60 Hounsfield units) (15). CT density of epicardial fat and visceral fat were measured by standard methods.

We assessed the volume of epicardial fat volume using the original chest CT data as the basic data. The pixel from the upper edge of the outer pericardium to the heart fat was extracted layer by layer, and the volume of the fat was accumulated according to the chest CT image thickness (Supporting Information Figure S1).

Statistical analysis

This small-sample study had unbalanced numbers of patients in the moderate and severe/critical groups (severe and critical cases were combined in one group for analysis). For descriptive statistical analysis, categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as medians with quartiles (Q1, Q3). Continuous variables were also transformed into categorical variables for further analysis. Differences in categorical variables between the moderate and severe/critical groups were assessed by Fisher's exact test, and differences in continuous variables between the two groups were tested using the Wilcoxon rank-sum test (nonparametric test).

Many factors presented statistical significance in the initial difference analysis. However, the sample sizes for the different conditions limited their simultaneous inclusion in multiple logistical regression. To maintain the interpretability of the multiple regression, variable selection was performed for a set of binary predictors using Lasso logistic regression. Multivariable logistical regression was performed by Exact logistic regression and Firth's logistical regression, which are standard approaches for the analysis of binary outcomes with a small sample size. Exact logistic regression was selected to explore the effect of the selected variables. Sex and BMI were considered as forced-in covariates, and selected variables from Lasso regression were included in turn. To assess the robustness of the results, these binary predictors were replaced by their continuous types, and Firth's logistical regression was performed instead of exact logistical regression.

The data were analyzed using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina) and R software version 3.4.2 (The R Foundation for Statistical Computing, Vienna, Austria) with the glmnet package. Two-sided $P<0.05$ was considered statistically significant.

Results

Baseline information for young adult patients with COVID-19

A total of 65 COVID-19 cases among young adults were included in the analysis, of which 53 were moderate cases and 12 were severe or critical cases. Because only three cases were classified as critical, we combined the severe cases ($n=9$) and critical cases ($n=3$) for comparison with moderate cases (Table 1). Notable findings included the fact that all severe/critical cases were male, making the proportion of male patients in this group significantly higher than that in the moderate group (100.00% vs. 45.28%). The age distribution and proportions of patients who reported cigarette smoking and alcohol drinking were similar between the two groups. Few patients in either group had a history of chronic disease or a related family history before admission. The systolic pressure and diastolic pressure were comparable between the moderate cases (average 122/77 mm Hg) and severe/critical cases (average 120/77 mm Hg). Before hospital admission, moderate cases and severe/critical cases experienced a similar duration of symptoms. More severe/critical cases had diarrhea (2%), but the frequencies of other symptoms were similar between the two groups.

Evaluation of metabolic and inflammatory indicators showed that the severe/critical group had higher levels of FBG (6.77 vs. 5.15 mmol/L), lipoprotein(a) (147.85 vs. 74.80 mg/L), C-reactive protein (80.04 vs. 13.72 mg/L), and LDH (364.50 vs. 163.00 U/L) and a lower level of high-density lipoprotein cholesterol (0.84 vs. 1.09 mmol/L) compared with moderate cases (Table 1). The neutrophil count also was higher in the severe/critical group than in the moderate group (4.10×10^9 vs. 2.71×10^9/L). Coagulation indexes including D-dimer and activated partial thromboplastin time were comparable between the two groups at admission (Table 1).

Indexes for dysfunction of different organs also were measured and compared between the two groups. Regarding cardiovascular functioning, the creatine kinase myocardial band levels of the moderate and severe/critical groups were similar (9.40 vs. 12.40 ng/mL). Because cardiac TnI and BNP data were available for only a few patients, these two indicators could not be included in the analysis. Among the cases with test results, all had a normal BNP level, and only one critically ill patient who experienced cardiac arrest before hospitalization had an elevated TnI concentration (108 pg/mL). We also found from CT imaging that all patients had good coronary vascular conditions. From the CT images, we observed that even the patient with the highest BMI had no coronary calcification similar to the normal-weight patient (Supporting Information Figure S1). Regarding liver function, the severe/critical group had higher levels of ALT (42.50 vs. 20.50 U/L) and AST (46.00 vs. 20.00 U/L) than did the moderate group. Because the increases in ALT and AST levels were nearly parallel ($r=0.83$), we considered that the elevated ALT and AST levels were caused by impaired liver function. Regarding renal function, the severe/critical group had higher levels of creatinine (84.40 vs. 60.90 μmol/L), uric acid (398.75 vs. 293.35 μmol/L), and cystatin C (1.17 vs. 0.79 mg/L) compared with the moderate group. In addition, the frequency of urine protein positivity was greater among severe/critical cases than among moderate cases (58.33% vs. 1.92%). Because immune cell counts after admission were available for only a few moderate cases and less than half of severe/critical cases, we did not include this indicator in the analysis. However, among those patients, we observed a decreased trend in T cell counts in severe/critical cases (Supporting Information Table S1).

From the evaluation of obesity among the study population, the severe/critical group had an obviously higher mean BMI than the moderate group (average 29.23 vs. 22.79; Table 1). In addition, the liver CT value was less for the severe/critical group compared with the moderate group (50.00 vs. 65.00 mU), which indicates more fat deposition in the liver (Table 2). The epicardial fat volume is significantly higher in severe/critical group (207,469 vs. 112,861 mm^3). The subcutaneous fat thicknesses were similar between the two groups. CT density of epicardial fat and viseral fat were similar between the two groups. According to CT examination, severe/critical cases had a larger intrapulmonary lesion volume compared with moderate cases (5.76% vs. 0.72%) (Table 2).

TABLE 1 Basic characteristics of young adult patients with COVID-19 included in study[a]

	Moderate group ($n=53$)	Severe/critical group ($n=12$)	*P* value
Sex, male	24 (45.28%)	12 (100.00%)	0.001
Age (y)	35.00 (29.00, 37.00)	32.50 (30.50, 37.50)	0.973
BMI (kg/m^2)	22.79 (19.53, 24.61)	29.23 (27.46, 31.08)	<0.001
≤24	34 (68.00%)	0 (0.00%)	<0.001
24-28	14 (28.00%)	4 (33.33%)	
≥28	2 (4.00%)	8 (66.67%)	
Systolic pressure (mm Hg)	122 (111, 133)	120 (105, 135)	0.61
Diastolic pressure (mm Hg)	77 (68, 86)	77 (66, 88)	0.92
Cigarette smoking	0 (0.00%)	1 (8.33%)	0.185
Alcohol consumption	1 (1.89%)	2 (16.67%)	0.085
Past medical history			
Diabetes	1 (1.9%)	1 (8.3%)	0.809
Hypertension	3 (5.66%)	0 (0.00%)	1.000
Heart disease	0 (0.00%)	0 (0.00%)	—
Cancer	0 (0.00%)	1 (8.33%)	0.185
Family history			
Diabetes	0 (0.00%)	0 (0.00%)	—
Hypertension	1 (1.88%)	0 (0.00%)	1.000
Heart disease	0 (0.00%)	0 (0.00%)	—
Cancer	0 (0.00%)	0 (0.00%)	—
Symptoms			
Fever	45 (84.9%)	11 (91.7%)	0.881
Fatigue	14 (26.4%)	4 (33.3%)	0.899
Cough	29 (54.7%)	9 (75.0%)	0.335
Muscle pain	14 (26.4%)	3 (25.0%)	1.000
Headache	5 (9.4%)	1 (8.3%)	1.000
Diarrhea	0 (0%)	2 (16.7%)	0.032
Shortness of breath	5 (9.4%)	2 (16.7%)	0.830
Chest tightness	4 (7.5%)	0 (0%)	1.000
Anorexia	2 (3.8%)	1 (8.3%)	1.000
Days of symptom before admission	6.43 (3.42, 9.44)	7.00 (4.00, 10.00)	0.758
FBG (mmol/L)	5.15 (4.66, 5.63)	6.77 (5.86, 8.92)	<0.001
<6.1	44 (86.27%)	4 (33.33%)	<0.001
≥6.1	7 (13.73%)	8 (66.67%)	
TG (mmol/L)	0.99 (0.88, 1.33)	1.29 (0.95, 1.93)	0.424
<1.7	21 (84.00%)	4 (66.67%)	0.70
≥1.7	4 (16.00%)	2 (33.33%)	
HDL-C (mmol/L)	1.09 (0.80, 1.38)	0.84 (0.65, 1.01)	0.043
<0.9	8 (32.00%)	3 (50.00%)	
≥0.9	17 (68.00%)	3 (50.00%)	
Lp(a) (mg/L)	74.80 (44.90, 130.60)	147.85 (126.20, 178.50)	0.018
<300	24 (96.00%)	6 (100.00%)	
≥300	1 (4.00%)	0 (0.00%)	
NEU (×10^9/L)	2.71 (1.92, 3.29)	4.10 (2.72, 4.88)	0.016
<6.3	52 (100.00%)	10 (83.33%)	0.033
≥6.3	0 (0.00%)	2 (16.67%)	
LYMP (×10^9/L)	1.28 (0.98, 1.76)	1.21 (1.06, 1.66)	0.850
<1.1	21 (40.38%)	3 (25.00%)	0.508
≥1.1	31 (59.62%)	9 (75.00%)	
D-dimer (ng/mL)	126.00 (78.50, 167.00)	151.50 (83.00, 270.50)	0.355
<500	47 (97.92%)	11 (91.67%)	0.363
≥500	1 (2.08%)	1 (8.33%)	

TABLE 1 (continued).

	Moderate group ($n=53$)	Severe/critical group ($n=12$)	*P* value
APTT (s)	32.40 (30.70, 33.80)	31.95 (30.70, 34.20)	0.835
<31.1	14 (28.57%)	4 (33.33%)	0.848
31.1~33	17 (34.69%)	3 (25.00%)	
≥33	18 (36.73%)	5 (41.67%)	
ALT (U/L)	20.50 (12.00, 38.50)	42.50 (21.00, 95.00)	0.006
<50	47 (90.38%)	7 (58.33%)	0.021
≥50	5 (9.62%)	5 (41.67%)	
AST (U/L)	20.00 (18.00, 28.50)	46.00 (32.00, 81.00)	<0.001
<40	47 (90.38%)	5 (41.67%)	<0.001
≥40	5 (9.62%)	7 (58.33%)	
TB (μmol/L)	9.80 (8.20, 12.15)	9.90 (9.20, 15.90)	0.476
<21	49 (94.23%)	9 (100.00%)	1.00
≥21	3 (5.77%)	0 (0.00%)	
DB (μmol/L)	2.10 (1.70, 3.00)	4.20 (2.30, 6.90)	0.006
<7	50 (96.15%)	7 (77.78%)	0.100
≥7	2 (3.85%)	2 (22.22%)	
IDB (μmol/L)	7.60 (5.80, 9.95)	7.60 (5.00, 9.10)	0.684
<18	49 (94.23%)	9 (100.00%)	1.00
≥18	3 (5.77%)	0 (0.00%)	
Albumin (g/L)	42.05 (39.90, 44.05)	41.20 (38.60, 42.90)	0.185
<40	13 (25.00%)	4 (33.33%)	0.821
≥40	39 (75.00%)	8 (66.67%)	
LDH (U/L)	163.00 (132.00, 190.00)	364.50 (277.00, 539.00)	<0.001
<243	43 (91.49%)	0 (0.00%)	<0.001
≥243	4 (8.51%)	6 (100.00%)	
Cr (μmol/L)	60.90 (50.05, 75.05)	84.40 (80.25, 100.55)	<0.001
<104	52 (100.00%)	9 (75.00%)	0.005
≥104	0 (0.00%)	3 (25.00%)	
UA (μmol/L)	293.35 (229.95, 355.45)	398.75 (332.25, 439.20)	0.002
<428	48 (92.31%)	8 (66.67%)	0.053
≥428	4 (7.69%)	4 (33.33%)	
Urine protein positive	1 (1.92%)	7 (58.33%)	<0.001
Cystatin C (mg/L)	0.79 (0.70, 0.87)	1.17 (0.91, 1.23)	<0.001
<1.1	47 (92.16%)	5 (41.67%)	<0.001
≥1.1	4 (7.84%)	7 (58.33%)	
CK-MB (U/L)	9.50 (6.50, 13.00)	10.00 (0.90, 19.00)	0.82
<25	48 (100.00%)	9 (81.82%)	0.03
≥25	0 (0.00%)	2 (18.18%)	<0.001
CRP (mg/L)	5.05 (1.40, 21.59)	95.45 (25.90, 119.76)	0.004
<10	24 (57.14%)	0 (0.00%)	
≥10	18 (42.86%)	10 (100.00%)	

[a]Data presented as *n* (%) or median (Q1, Q3).
ALT, alanine aminotransferase; aPPT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK-MB, creatine kinase myocardial band; COVID-19, coronavirus disease 2019; Cr, creatinine; CRP, C-reactive protein; DB, direct bilirubin; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; IDB, indirect bilirubin; LDH, lactate dehydrogenase; Lp(a), lipoprotein(a); LYMP, lymphocyte count; NEU, neutrophil count; TB, total bilirubin; TG, triglycerides; UA, uric acid.

Treatments administered according to severity of COVID-19 in young patients

As treatments for COVID-19, more cases in the severe/critical group received glucocorticoids (83.33% vs. 24.52%) and albumin supplementation (25% vs. 0.00%). More cases in the severe/critical group required oxygen support, and accordingly, the frequency of nasal catheter use (83.33% vs. 24.52%) and extracorporeal membrane oxygenation (25% vs. 0.00%) was higher in the severe/critical group than in the moderate group (Table 3).

TABLE 2 CT image measurements for young adult patients with COVID-19 included in study[a]

Characteristic	Moderate ($n=53$)	Severe/critical ($n=12$)	*P* value
Liver CT value (mU)	65.00 (57.00, 73.00)	50.00 (40.00, 60.50)	0.002
<60	16 (30.19%)	9 (75.00%)	0.011
≥60	37 (69.81%)	3 (25.00%)	
Subcutaneous fat thickness (mm)	11.00 (9.70, 13.00)	12.00 (9.50, 20.00)	0.28
<10	19 (35.85%)	4 (33.33%)	1.00
≧10	34 (64.15%)	8 (66.67%)	
Intrapulmonary lesion volume (%)	0.72 (0.16, 2.74)	5.76 (3.73, 12.96)	<0.001
<0.31	20 (37.74%)	1 (8.33%)	0.001
0.31~3.13	20 (37.74%)	1 (8.33%)	
≥3.13	13 (24.53%)	10 (83.33%)	
Epicardial fat volume (mm^3)	112,861.0 (80,749.00, 167,030.0)	207,469.0 (172,881.0, 213,101.0)	0.004
<104,916	13 (39.39%)	0 (0.00%)	0.01
104,916~171,990	12 (36.36%)	1 (14.29%)	
≥171,990	8 (24.24%)	6 (85.71%)	
Epicardial fat CT density (HU)	−76.30 (−60.88, −91.72)	−80.17 (−57.27, −103.07)	0.05
<−83.22	15 (28.3%)	6 (50%)	0.104
−69.44 to about −83.22	21 (39.7%)	1 (8.3%)	
≥−69.44	17 (32.0%)	5 (41.7%)	
Visceral fat CT density (HU)	−101.81 (−90.72, −112.9)	−103.83 (−95.32, −112.34)	0.25
<−107.00	15 (28.3%)	4 (33.3%)	0.706
−97.00 to about −107.00	18 (34.0%)	5 (41.7%)	
≥−97.00	20 (37.7%)	3 (25.0%)	

[a]Data presented as *n* (%) or median (Q1, Q3).
COVID-19, coronavirus disease 2019; CT, computed tomography; HU, Hounsfield units.

TABLE 3 Treatments and oxygen support administered to young adult patients with COVID-19 included in study[a]

	Moderate ($n=53$)	Severe/critical ($n=12$)	*P* value
Treatments			
Antiviral	53 (100%)	12 (100%)	—
Antibacterial	40 (75.47%)	12 (100%)	0.104
Glucocorticoid	13 (24.52%)	10 (83.33%)	<0.001
Immunoglobulin	8 (15.09%)	4 (33.33%)	0.290
Albumin	0 (0.00%)	3 (25.0%)	0.005
Oxygen support			
Nasal catheter	11 (20.8%)	8 (66.7%)	0.005
High flow oxygen	0 (0%)	1 (8.3%)	0.185
Ventilator	0 (0%)	1 (8.3%)	0.185
ECMO	0 (0%)	2 (16.7%)	0.032

[a]Data presented as *n* (%) or median (Q1, Q3).
COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.

Relationship between different obesity evaluation indexes and severity of COVID-19 in young patients

We observed the distribution of different indicators of obesity among young adult patients with COVID-19 according to the difference in disease severity (Figure 1). According to BMI measurements, both severely and critically ill patients were distributed in the overweight/obesity interval. Among them, all three critically ill patients had obesity. According to the liver CT value, all the severely and critically ill cases were in the fatty liver interval. Consistent with the results of the comparative analysis, subcutaneous fat thickness did not have a detectable effect on the severity of disease.

Decreased albumin levels in severely and critically ill patients

The serum albumin level was examined twice during hospitalization for four patients with severe disease, and in these patients, the serum albumin level dropped rapidly in a short period of time (Figure 2). In addition to changes in serum albumin, the D-dimer level in critically ill patients also changed significantly. Interestingly, the decline in the serum albumin level in critically ill patients and the rise in the D-dimer level showed an essentially parallel inverse relationship, even when anticoagulant drugs were used (Figure 3). From the detailed data for the three critically ill patients (Supporting Information Tables S2-S4), we observed that the changes in serum albumin levels were also parallel to the changes in the lung lesions. Notably, all three of the critically ill patients experienced acute respiratory distress syndrome. However, cardiovascular, liver, and kidney function did not show significant changes during the course of the disease. In critical patient 2, the elevated levels of TnI and renal and liver function indexes at the time of admission may have been related to the occurrence of cardiac arrest before admission, and these indexes quickly recovered and stabilized after treatment. Obvious changes in

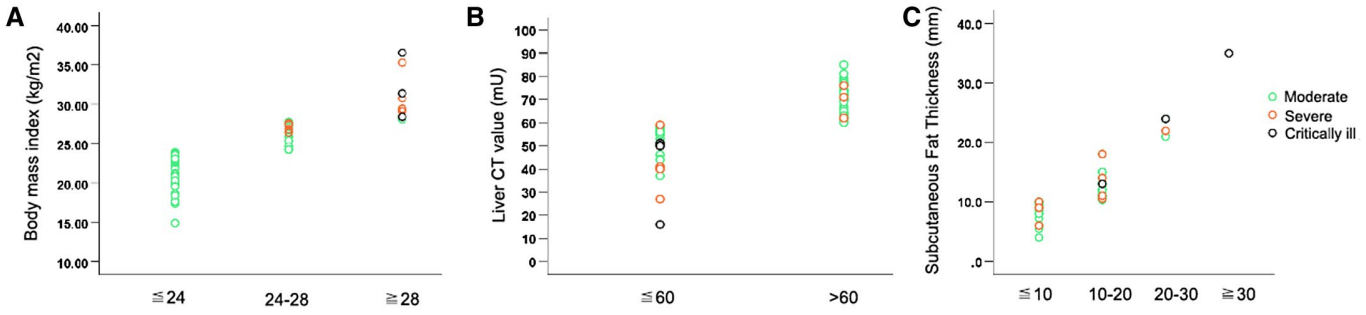

Figure 1 Distribution of moderate, severe, and critically ill patients with coronavirus disease 2019 in (**A**) different BMI categories, (**B**) liver CT value, and (**C**) subcutaneous fat thickness. [Color figure can be viewed at wileyonlinelibrary.com]

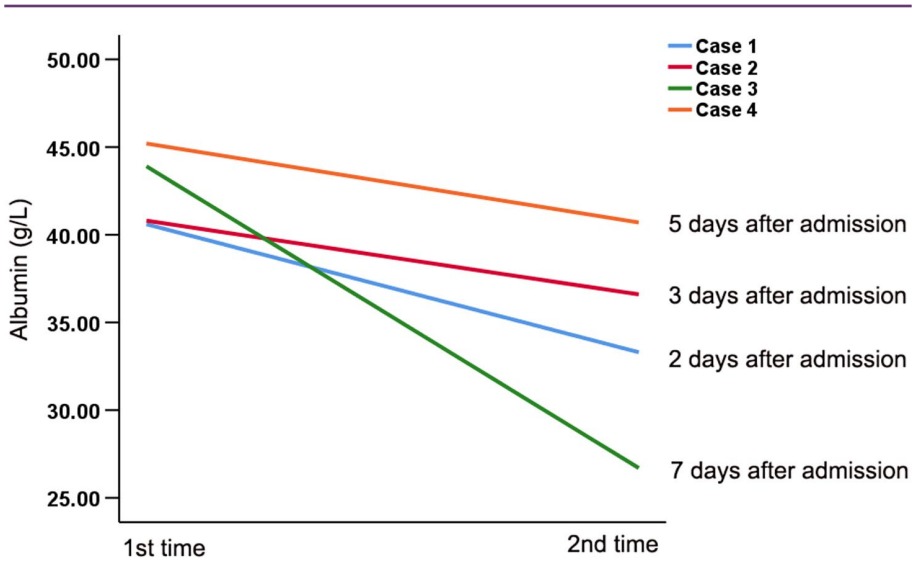

Figure 2 Changes of albumin levels in four patients with severe cases of coronavirus disease 2019. [Color figure can be viewed at wileyonlinelibrary.com]

coagulation indexes were observed in all of the critically ill patients during the disease process. Critically ill patient 1 eventually experienced disseminated intravascular coagulation (DIC).

Predictors of severity in young adult patients with COVID-19

Logistic regression analysis was applied to assess the potential risk factors for the severity of COVID-19 in young patients (Tables 4-5). The analysis showed that a high BMI (especially obesity), an elevated FBG level, an elevated LDH level, and urinary protein positivity were all risk factors for severe COVID-19 in these young patients. In particular, urinary protein positivity could increase the risk of severe disease by more than 20-fold.

Discussion

In the analysis of relevant risk factors for severe COVID-19 published in China before April, little was mentioned about the correlation between obesity and severe illness in patients with COVID-19 (16). However, more and more updated research indicates that the role of obesity is very important (17-20). A study from New York University School of Medicine showed that in the population under 60 years old, the proportion of people with a BMI over 30 who were hospitalized and admitted to the ICU was more than double that among patients with a lower BMI (20). A recently published study from China also showed that in patients with metabolic-associated fatty liver disease, obesity can increase the risk for severe COVID-19 by about sixfold (21). The present study provides more detailed information about the role of obesity in the severity of young patients with COVID-19. Our findings show that obesity is an important predictor of severe COVID-19 among young patients. Further analysis found that obesity mainly affects the severity of COVID-19 through the deposition of ectopic fat in multiple organs, which in turn damages the organ function. According to our data, in young patients with severe COVID-19, the organs most likely to be affected were the liver and kidneys. In our study, the liver CT values in people with overweight and obesity (average 53 mU) is similar to those in a previous study (22). Only one critically ill patient in this study had myocardial

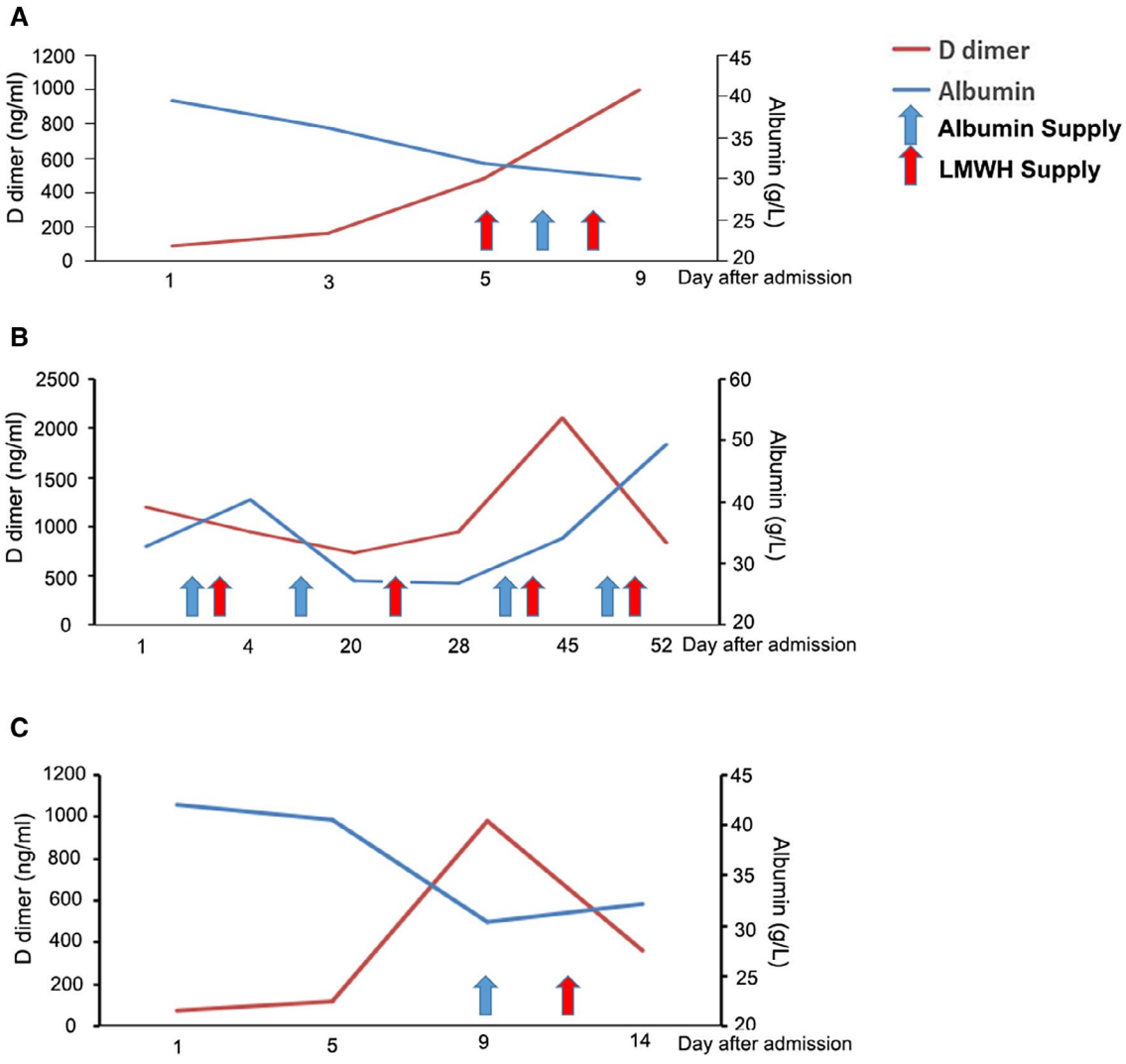

Figure 3 Changes of albumin and D-dimer levels in critically ill patients: (**A**) case 1, (**B**) case 2, and (**C**) case 3. LMWH, low-molecular-weight heparin. [Color figure can be viewed at wileyonlinelibrary.com]

damage, and it was most likely caused by cardiac arrest. Notably, in the present study, all of the severely or critically ill patients with COVID-19 were males, an observation which may also be related to the distribution of obesity in China. Among people under the age of 40 years, the number of men with obesity is three times greater than the number of women (23).

Although all patients in the current study had comparable albumin levels on admission, we observed a rapid decline in albumin concentration in severely and critically ill patients after admission. Because the albumin level was not tested a second time in moderate cases during hospitalization, we cannot be sure that the moderate patients did not also experience a decline in albumin concentration. A study evaluating patients with COVID-19 after 2 weeks of hospitalization found that patients with aggravated conditions had significantly reduced albumin levels, whereas those with stable or improved conditions had an average albumin level of 41.27 g/L (24), suggesting that moderate cases are less likely to experience a significant decrease in albumin. Additional studies have suggested that hypoalbuminemia on admission can help predict the progression of COVID-19 cases to severe or critical condtiion (25-27). Chronic liver disease due to synthesis disorders and chronic kidney disease due to glomerular leakage are common causes of hypoalbuminemia. Even without liver and kidney dysfunction, obesity itself will be accompanied by hypoalbuminemia (28). However, abnormal albumin function is more commonly reported in fatty liver disease (29). This study suggests that young patients with proteinuria at admission are more than 20 times more likely to develop severe and critical illness. A renal histopathological analysis of deceased patients with COVID-19 showed that SARS-CoV-2 can directly infect and damage proximal tubular epithelial cells and podocytes (30). Podocyte damage is usually associated with the formation of proteinuria (31). Hypoproteinemia may be very obvious in some critically ill patients. We observed that in one critically ill patient who continued to be

TABLE 4 Exact logistical regression to explore potential effects of selected covariates on type of COVID-19

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
Potential factor	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
BMI												
24~28	**11.73 (1.89, +∞)**	**0.01**	**7.63 (1.14, +∞)**	**0.04**	**8.31 (1.21, +∞)**	**0.03**	6.89 (0.80, +∞)	0.07	**8.56 (1.25, +∞)**	**0.03**	6.55 (0.77, +∞)	0.07
≥28	**115.89 (18.96, +∞)**	**0.001**	**73.77 (11.79, +∞)**	**<0.001**	**88.76 (13.31, +∞)**	**<0.001**	6.46 (0.58, +∞)	0.10	**86.00 (13.56, +∞)**	**<0.001**	**90.03 (12.71**, +∞)	**<0.001**
≤24	reference		reference		reference		reference		reference			
Liver CT value, ≥60 vs. <60	—	—	0.43 (0.03-3.98)	0.67	—	—	—	—	—	—		
FBS, ≥6.1 vs. <6.1	—	—	—	—	**16.48 (1.28, +∞)**	**0.03**	—	—	—	—		
LDH, ≥243 vs. <243	—	—	—	—	—	—	**35.16 (5.45, +∞)**	**<0.001**	—	—		
Cr, ≥104 vs. <104	—	—	—	—	—	—	—	—	4.53 (0.47, +∞)	0.14		
Urine protein, yes vs. no	—	—	—	—	—	—	—	—			**25.68 (3.66, +∞)**	**0.002**

+∞, positive infinity; Cr, creatinine; COVID-19, coronavirus disease 2019; FBS, fast blood sugar; LDH, lactate dehydrogenase; NE, not estimated; OR, odds ratio.
All the bold values were significant covariates for the type of COVID-19.

TABLE 5 Sensitivity analysis for Firth's logistical regression to explore potential effects of selected covariates on type of COVID-19

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
Potential factor	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
BMI	**2.34 (1.37-3.98)**	**0.002**	**2.26 (1.33-3.83)**	**0.003**	**2.63 (1.29-5.40)**	**0.008**	1.33 (0.90-1.98)	0.15	**2.26 (1.26-4.07)**	**0.007**	**2.31 (1.29-4.15)**	**0.005**
Liver CT value	—	—	0.99 (0.92-1.06)	0.74	—	—	—	—	—	—		
FBS	—	—	—	—	2.66 (0.89-7.99)	0.08	—	—	—	—		
LDH	—	—	—	—	—	—	**1.02 (1.00-1.03)**	**0.03**	—	—		
Cr	—	—	—	—	—	—	—	—	1.05 (0.99-1.13)	0.12		
Urine protein, yes vs. no											**43.24 (1.80-+∞)**	**0.02**

+∞, positive infinity; COVID-19, coronavirus disease 2019; Cr, creatinine; CT, computed tomography; FBS, fast blood sugar; LDH, lactate dehydrogenase; OR, odds ratio.
All the bold values were significant covariates for the type of COVID-19.

treated with endotracheal intubation and mechanical ventilation at the time of this reporting, normal albumin levels could only be maintained by continuous large infusions of albumin. Our understanding of the functions of albumin continues to increase. Albumin can not only effectively maintain plasma osmotic pressure but also has functions in transport, antithrombosis, immune regulation, and endothelial stability (32). In patients with severe and critical COVID-19 illness, low albumin levels may also be accompanied by impaired organ function. In this study, it was considered that the rapid onset of hypoalbuminemia may be related to the attack of the virus on the organs because almost all young patients with COVID-19 had normal serum albumin levels at admission. Preexisting damage to liver and kidney function may cause further damage to organ functions under the attack of SARS-CoV-2 infection.

In the present study, we also observed that although the difference in D-dimer between moderate and severe/critical COVID-19 cases was not significant at admission, the level of D-dimer continued to increase in critically ill cases. Some studies have suggested that D-dimer may be a risk factor for severe COVID-19 (33,34), and the risk of thrombosis is high for patients with severe COVID-19 (9,35). Our follow-up of three critically ill patients showed that even when anticoagulant drugs were administered, the decrease in albumin and increase in D-dimer were nearly parallel. In a critically ill patient who later died, DIC eventually appeared. Hypoalbuminemia has been considered a high risk factor for thrombosis (36,37), and albumin itself also has antithrombotic effects because of its capacity to bind nitric oxide and prolong its biologic activity (32). Of course, the increased D-dimer level in critically ill COVID-19 patients in this study could also be related to other factors, including the hypercoagulable state combined with obesity, viral infection and later combined bacterial infections, and multiple organ dysfunction.

Consistent with previous studies (38), this study also suggests that elevated FBG levels at admission are also risk factors for critical illness in young patients with COVID-19, although most people have no previous history of diabetes. Considering that previous studies have suggested the role of inflammation in severe COVID-19 cases (39) and that fat density in people with obesity may be related to inflammation of adipose tissue (40,41), we evaluated epicardial fat and visceral fat CT density in the study population but found that the difference between moderate and severe/critical group was not significant.

This study had limitations. The sample size of this study was small and the distribution of the two groups was uneven, which has been considered as much as possible in this analysis. Two methods were used in the logistic analysis for identification of risk factors. In moderate COVID-19 cases, the absence of multiple albumin test results during hospitalization made it impossible to accurately determine the changes in albumin levels among moderate cases. In addition, immune cell numbers were not tested for many cases, making it impossible for us to thoroughly assess the role of the immune response in young patients with COVID-19. In addition, we need to note that the Chinese definition of overweight and obesity is different from that used in the United States and Europe (42). Therefore, when applying the conclusions of this study, it is necessary to consider the possible impact of this difference. Our research suggests that the liver CT value is helpful for predicting severe cases of COVID-19 in young patients. However, we should note that liver CT value is an imaging index, which cannot reflect pathophysiological changes. Therefore, we also need further research to help clarify low liver CT values associated with severe COVID-19 cases.

Conclusion

The present study investigated predictive factors for severe COVID-19 among young patients, which resulted in several major findings: (1) Obesity is an important predictor of severe COVID-19 among young patients. The main mechanism is related to the ectopic deposition of fat in organs and damage to organ function. The main participating organs are the liver and kidneys. (2) Young patients with severe/critical COVID-19 illness often have no underlying disease before admission, and vital signs are often stable at the time of admission. However, they can experience rapid changes after admission. An important feature is the rapid decline in albumin level. During the course of the disease, the decrease in albumin is accompanied by an increase in D-dimer, which is an indicator of hypercoagulation. DIC is possible in critically ill patients. (3) In the management of young adult patients with COVID-19, particularly those who obviously have obesity and especially those with fatty liver hepatitis and urine protein positive, albumin and D-dimer should be routinely monitored after admission. Changes in D-dimer provide an early warning for rapid decline in condition, and relevant interventions can help to improve patient outcomes. O

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Author contributions: MD, YQ, LD, and HW contributed equally to this paper, as did YX, ZL, ZM and JT. ZD designed the study, had full access to all data in the study, and takes responsibility for the integrity and accuracy of the data analysis. MD, YQ, LD, HW, and JT contributed to patient recruitment, data collection, data analysis, data interpretation, literature searching, and writing of the manuscript. Particularly, MD made a great contribution to the CT image data collection and analysis. YX, ZL, YQ, and ZM had roles in patient recruitment, data collection, and clinical management. MD, YQ, LD, JT, and YX had roles in patient management. All authors contributed to data acquisition, data analysis, or data interpretation and were involved in writing the paper. All authors reviewed and approved the final version of the manuscript. ZD is the guarantor.

Supporting information: Additional Supporting Information may be found in the online version of this article.

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