Visceral Adiposity and High Intramuscular Fat Deposition Independently Predict Critical Illness in Patients with SARS-CoV-2

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Objective: This study aimed to assess the association between adipose tissue distribution and severity of clinical course in patients with severe acute respiratory syndrome coronavirus 2.

Methods: For this retrospective study, 143 hospitalized patients with confirmed coronavirus disease 2019 (COVID-19) who underwent an unenhanced abdominal computed tomography (CT) scan between January 1, 2020, and March 30, 2020, were included. Univariate and multivariate logistic regression analyses were performed to identify the risk factors associated with the severity of COVID-19 infection.

Results: There were 45 patients who were identified as critically ill. High visceral to subcutaneous adipose tissue area ratio (called visceral adiposity) (odds ratio: 2.47; 95% CI: 1.05-5.98, $P = 0.040$) and low mean attenuation of skeletal muscle (called high intramuscular fat [IMF] deposition) (odds ratio: 11.90; 95% CI: 4.50-36.14; $P < 0.001$) were independent risk factors for critical illness. Furthermore, visceral adiposity or high IMF deposition increased the risk of mechanical ventilation ($P = 0.013$, $P < 0.001$, respectively). High IMF deposition increased the risk of death ($P = 0.012$).

Conclusions: COVID-19 patients with visceral adiposity or high IMF deposition have higher risk for critical illness. Therefore, patients with abdominal obesity should be monitored more carefully when hospitalized.

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Study Importance

What is already known?

► Adipose tissue distribution has been considered as an important factor in the body's response to infection.

What does this study add?

► Visceral adiposity and high intramuscular fat deposition were independent risk factors for critical illness of patients with severe acute respiratory syndrome coronavirus 2, and those factors increased the risks of mechanical ventilation and death.

► In the subgroup under 60 years old, patients with visceral adiposity or high intramuscular fat deposition had higher risk for critical illness.

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

► Patients with abdominal obesity should be monitored more carefully when hospitalized.

► Adipose tissue distribution assessed by computed tomography scan could be superior to BMI in risk evaluation of coronavirus disease 2019, as BMI does not provide information on fat distribution.

► Further studies should focus on mechanisms that explain why visceral adiposity and high intramuscular fat deposition are associated with the severity of coronavirus disease 2019.

Introduction

An outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, has rapidly spread throughout China and become a global health threat (1-4). As of May 28, SARS-CoV-2 had affected over 5,593,631 individuals and resulted in more than 353,334 deaths worldwide, and the cases continue to rise (4). The mortality rate of coronavirus disease 2019 (COVID-19) so far is about 2.3% to 7.2%, lower than that of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus diseases (1-3).

In prior studies, approximately 5% to 10% of COVID-19 patients rapidly developed critical illness in the form of acute respiratory distress syndrome (ARDS) or sepsis with acute organ dysfunction (1,5,6). Among those, 71% to 75% of patients required mechanical ventilation, and roughly half ended in death (7,8). Early identification of patients with high risk for critical illness may help prevent worsening at early stage of the disease and may
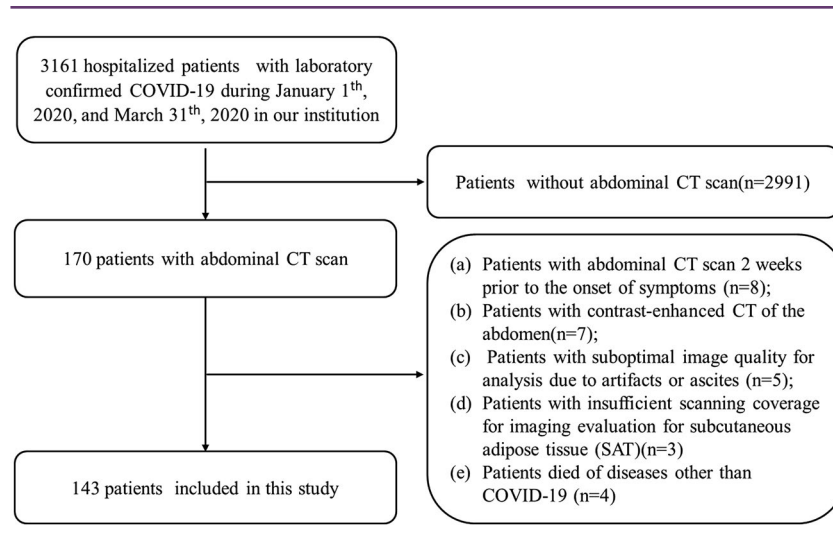
Figure 1 Flowchart for inclusion and exclusion criteria of our cohort.

reduce mortality (9). Advanced age and comorbidity are the most recognized risk factors for adverse outcome of COVID-19 (1,2).

The rising prevalence of obesity has been described as a global pandemic and has become a major public health concern (10). Overnutrition, as well as undernutrition, has been considered an important factor in the body's response to infection for centuries (11). For patients infected with influenza A (H1N1) virus, obesity was identified as a risk factor for hospitalization and mechanical ventilation in several different populations (12,13). The distribution of adipose tissue has a major influence on the body's immune system (14). The elevated inflammatory cytokine levels observed in patients with high visceral fat may be associated with increased obesity-associated morbidity in H1N1 infections (15). Furthermore, lipids can be stored within skeletal muscle when the capacity for fat storage by subcutaneous and visceral tissue are exceeded, known as intramuscular fat (IMF) tissue (14). IMF deposition not only reflects the quality of muscle and poor physical function, it is also an independent risk factor for prognosis after cardiac and oncologic surgery (16-19).

In the present study, we explored the relationship between abdominal adipose tissue distribution, skeletal muscle area (SMA), IMF deposition, and severity of COVID-19 in a retrospective cohort of 143 patients who had an unenhanced abdominal computed tomography (CT).

Methods

The study was approved by the Ethics Commission of our institution, and the requirements for informed consent were waived because of its retrospective nature.

Study population

We consecutively identified 170 hospitalized patients with confirmed COVID-19 who underwent at least one abdominal CT scan (including thoracoabdominal CT) through a review of clinical and imaging databases in Tongji Hospital in Wuhan, China, between January 1, 2020 and March 30, 2020 (Figure 1). The end date for follow-up was April 17, 2020. Exclusion criteria were as follows: (a) patients with abdominal CT scan 2 weeks prior to the onset of symptoms ($n=8$), (b) patients with contrast-enhanced CT of the abdomen ($n=7$), (c) patients with suboptimal image quality for analysis due to artifacts or ascites ($n=5$), (d) patients with insufficient scanning coverage for imaging evaluation for subcutaneous adipose tissue (SAT) ($n=3$), and (e) patients who died of diseases other than COVID-19 ($n=4$). Indication for CT of the abdomen included abdominal symptoms such as abdominal pain, diarrhea, vomiting, and/or abnormal laboratory tests. Finally, a total of 143 patients with unenhanced abdominal CT were included in this study. For patients with multiple abdominal CT examinations, CT scan with the shortest time interval between imaging and the onset of symptom was used for this analysis.

Data collection

Demographic and clinical parameters were obtained from clinical electronic medical records as follows: sex, age, height, weight, underlying comorbidities, history of surgery, treatment measures, and clinical outcome. Results of laboratory examinations that were closest to the abdominal CT scan were also collected. The durations from onset of symptom to requiring mechanical ventilation, death, or discharge were recorded. Critically ill patients are defined as patients with ARDS or sepsis with acute organ dysfunction (6). BMI was calculated as weight in kilograms divided by height in meters squared.

CT examination

All abdominal CT examinations were performed on designated CT scanners for COVID-19 patients (uCT 780 [United Imaging, China] or Somatom Force/Somatom Definition AS+ [Siemens Healthineers, Germany]). After patients were placed in the supine and feetfirst position on the couch, images were acquired at breath-holding following inspiration, using tube voltage 120 kVp, automatic tube current modulation, and slice thickness 10 mm. All images were then reconstructed with a slice thickness of 5 mm.
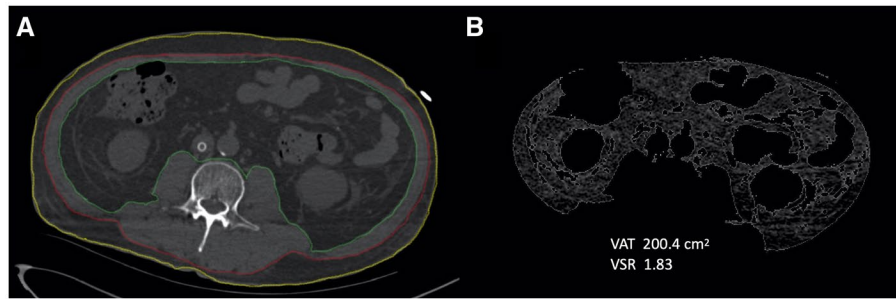
Figure 2 Cross-sectional computed tomography (CT) images of the third lumbar vertebra used to quantify adipose tissue distribution variables. (**A**) Subcutaneous adipose tissue (SAT) area is between the yellow and red lines, and skeletal muscle area is between the red and green lines. (**B**) Visceral adipose tissue (VAT) area is inside the green lines, excluding non-VAT fat within abdominal organs. VSR, VAT to SAT ratio.

CT analyses of adipose tissue and skeletal muscle variables

Detailed spatial maps of attenuation coefficients determined by CT provide a reliable and convenient way to quantify tissue areas and mean attenuation within tissue-specific thresholds of attenuation values. The attenuation values were defined on a Hounsfield unit (HU) scale using calibration points of air ($-1,000$ HU) and water (0 HU) (20,21). Abdominal adipose tissue and skeletal muscle variables were measured on a single 5-mm cross-sectional CT image at the level of the third lumbar vertebra (L3) using Advance workstation (ADW, GE Healthcare, Milwaukee, Wisconsin), software ADW server 4.6 (22). Two radiologists (LD and XLZ, with 7 and 3 years of experience, respectively) independently analyzed adipose tissue and skeletal muscle variables and were blinded to the patient's medical record other than the images belonging to patients with COVID-19 (Figure 2). First, the outer and inner perimeters of SAT were delineated, and only the pixels between the inner and outer perimeters were retained. Then, tissue threshold was set to a minimum value of -190 HU and a maximum value of -30 HU. The applied threshold isolated the area of SAT. The skeletal muscle was obtained using a similar method with tissue-specific thresholds ranging from -29 to 150 HU. SMA and mean attenuation of the entire skeletal muscle (SMD) were measured. Visceral adipose tissue area (VAT) was obtained after hand tracing the outer perimeter of VAT and removing all pixels outside the contoured area as well as the pixels of intestines, kidney, and other organs in the abdominal cavity. Tissue-specific thresholds of -150 to -50 HU were applied and resulted in total VAT area. VAT to SAT ratio (VSR) was calculated to indicate abdominal adipose tissue distributions, and high VSR was termed visceral adiposity (23). Low-density muscle reflects increased muscle lipid content, termed high IMF deposition (22,23).

The cutoff value of 100 cm^2 was used for VAT and SAT, irrespective of sex and age. This value is widely used as a cutoff point to evaluate visceral fat obesity in Asian populations (24). There are no previously recognized threshold values defining abnormal ranges with regard to VSR, SMA, and SMD for healthy individuals or individuals with a viral infection. Therefore, the sex-specific median values were used as cutoff points.

Statistical analysis

The interobserver agreements of SMA, the corresponding muscle mean CT attenuation, and SAT and VAT area of the 143 patients measured by the two radiologists independently were analyzed with intraclass correlation coefficient (ICC). In assessing interobserver reproducibility, ICC<0.2 is considered poor agreement, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, and 0.81-1 excellent (25). The mean value of the aforementioned parameters measured by the two radiologists was calculated for further statistical analysis.

Categorical variables were presented as number (percentage), and continuous variables were presented as median (interquartile range [IQR]). To compare variables between different groups, the χ^2 test or Fisher exact test was used for categorical variables, and the *t* test or Mann-Whitney *U* test was used for continuous variables, when appropriate. Correlations between the continuous adipose tissue and skeletal muscle variables were assessed using Spearman rank correlation analysis. Univariate and multivariate logistic regression analyses were performed to identify the risk factors associated with the severity of COVID-19. Sex, age, and variables with $P<0.05$ at univariate logistic regression analysis were applied to multivariate analysis. The linear relationship between continuous predictor variables and the logit of the outcome was checked. The variance inflation factor was used to check the collinearity of variables included in the multivariate logistic regression equation. No significant interaction was found between variables included in multivariate analyses. Based on the likelihood ratio test, we were allowed to keep sex, age, hypertension, cerebrovascular disease, visceral adiposity, and high IMF deposition in the final model. Cumulative rates of mechanical ventilation and mortality were calculated using Kaplan-Meier methods, and differences between curves were evaluated using the log-rank test. Statistical analysis was done with R software version 3.6.1 (R Project for Statistical Computing; www.r-project.org). A two-tailed $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Critically ill patients were defined as patients with ARDS or sepsis with acute organ dysfunction based on the clinical management of COVID-19 published by the World Health Organization (6). There were 45 patients who met the criteria for critical illness, while the remaining 98 patients did not (Figure 1). The clinical and physical characteristics of the two groups are summarized in Table 1. No significant difference in age or sex was found between the two groups

TABLE 1 Baseline characteristics of hospitalized patients with COVID-19 in Tongji Hospital, Wuhan, China

	Total	Critical illness	Noncritical illness	P value
Age	66 (56-73.5)	67 (60-75)	65 (54-73)	0.105
Sex (male)	70 (49.0%)	27 (60%)	43 (43.9%)	0.107
Height (cm)	165 (160-170)	167.5 (161.8-174)	163 (158-169)	0.034
Weight (kg)	64 (55-70)	68.5 (60-72)	60 (55-66)	0.022
BMI (kg/m^2)	23.4 (21.9-25.3)	24.8 (22.5-26.1)	23.0 (21.4-24.8)	0.148
Comorbidity (yes or no)	84 (58.7%)	31 (68.9%)	53 (54.1%)	0.184
Hypertension	53 (37.1%)	23 (51.1%)	30 (30.6%)	0.03
Diabetes	28 (19.6%)	10 (22.2%)	18 (18.4%)	0.755
Cardiovascular disease	18 (12.6%)	7 (15.6%)	11 (11.2%)	0.65
Other heart diseases	12 (8.4%)	5 (11.1%)	7 (7.1%)	0.518
Cerebrovascular disease	13 (9.0%)	8 (17.8%)	5 (5.1%)	0.025
COPD	10 (7.0%)	3 (6.7%)	7 (7.1%)	1
Chronic liver disease	5 (3.5%)	0	5 (5.1%)	0.326
Chronic kidney disease	5(3.5%)	1 (2.2%)	4 (4.1%)	1
Malignancy	13 (9.1%)	4 (8.9%)	9 (9.2%)	1
History of surgery	23 (16.1%)	8 (17.8%)	15 (15.3%)	0.898
WBC (10^9/L)	6.18 (4.89-9.60)	7.39 (4.78-11.25)	5.92 (5.00-8.23)	<0.001
NBC (10^9/L)	4.43 (2.88-7.67)	5.87 (3.13-9.76)	4.13 (2.79-6.76)	0.021
LBC (10^9/L)	1.12 (0.74-1.61)	0.96 (0.65-1.24)	1.19 (0.79-1.70)	0.031
Hemoglobin (g/L)	111 (92.5-125.5)	103 (88-119)	114 (95.5-128)	0.037
PLT (10^9/L)	185 (151-246.5)	159 (112-203)	200.5 (169.5-259)	0.007
Albumin (g/L)	35.9 (31.9-39.9)	32.6 (29.4-37.1)	37.7 (33.7-41.6)	<0.001
Cholesterol (mmol/L)	3.65 (2.96-4.51)	3.03 (2.34-3.67)	3.93 (3.35-4.71)	<0.001
Glucose (mmol/L)	6.18 (5.18-8.05)	7.07 (6.00-9.23)	5.74 (5.02-7.38)	0.003
Prognosis				<0.001
Death	15 (10.5%)	15 (33.3%)	0	
Discharged	115 (80.4%)	18 (40%)	97 (99.0%)	
Hospitalized	13 (9.1%)	12 (26.7%)	1 (1.0%)	
SAT (cm^2)	108.2 (77.0-156.7)	108.2 (66.0-138.5)	108.8 (83.2-175.2)	0.342
VAT (cm^2)	103.4 (60.3-166.6)	131.9 (79.2-185.7)	90.5 (51.3-156.1)	0.042
VSR	0.94 (0.62-1.40)	1.31 (0.79-1.76)	0.87 (0.57-1.31)	0.003
SMA (cm^2)	96.2 (79.0-118.2)	93.3 (77.0-118.4)	98.5 (81.7-117.2)	0.327
SMD (HU)	32.3 (23.7-39.3)	25.4 (16.3-30.6)	35.7 (28.1-41.3)	<0.001

Categorical variables presented as number (percentage), and continuous variables presented as median (interquartile range). To compare variables between different groups, the χ^2 test or Fisher exact test was used for categorical variables, and the t test or Mann-Whitney U test was used for continuous variables, when appropriate. A two-tailed $P<0.05$ was considered statistically significant.
COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HU, Hounsfield units; LBC, lymphocyte count; NBC, neutrophil count; PLT, platelet count; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area; SMD, the mean attenuation of skeletal muscle; VAT, visceral adipose tissue; VSR, VAT to SAT ratio; WBC, white blood cell.

($P=0.105$; $P=0.107$; respectively). The critical illness group had significantly higher height and body weight ($P=0.034$; $P=0.022$; respectively), but no significant difference was found between the two groups in BMI values ($P=0.148$). Hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and malignancy were the most common comorbidities in patients with COVID-19, and among these comorbidities, hypertension and cerebrovascular disease were significantly more common in the critical illness group ($P=0.03$; $P=0.025$; respectively).

Among the critical illness group, 88.9% (40 out of 45) of the patients required mechanical ventilation, including 34 patients who required invasive ventilation. Median time from onset of symptom to mechanical ventilation was 16 days (IQR, 10-24).

At the end of follow-up, 15 patients died of COVID-19; median time from onset of symptoms to death was 43 days (IQR, 34.5-55.5). A total of 115 patients were discharged from the hospital. Median time from illness onset (i.e., before admission) to discharge was 53 days (IQR, 42-61). Mortality rate among patients with a definite outcome in our cohort was 11.5%. A total of 13 patients were still hospitalized, and most of them were critically ill (92.3%); median time from onset of illness to the end of follow-up was 80 days (IQR, 74-87).

Critically ill patients showed higher VAT and VSR and lower SMD

Interobserver agreement between the two radiologists' measurements of adipose tissue and skeletal muscle variables was excellent (ICC=0.995

TABLE 2 Clinical characteristics of patients with and without visceral adiposity or high intramuscular fat deposition

	Visceral adiposity[1]			High IMF deposition[2]		
	Yes (*n* = 72)	No (*n* = 71)	*P* value	Yes (*n* = 71)	No (*n* = 72)	*P* value
Age (y)	66 (60-75)	65 (51.5-72.5)	0.045	70 (60.5-78.5)	62 (50.5-67)	<0.001
Sex	35 (48.6%)	35 (49.3%)	1	35 (49.3%)	35 (48.6%)	1
Comorbidity (yes or no)	44 (61.1%)	40 (56.3%)	0.682	44 (62.0%)	40 (55.6%)	0.542
Hypertension	28 (38.9%)	25 (35.2%)	0.778	32 (45.1%)	21 (29.2%)	0.073
Diabetes	18 (25%)	10 (14.1%)	0.152	12 (16.9%)	16 (22.2%)	0.555
Cardiovascular disease	9 (12.5%)	9 (12.7%)	1	13 (18.3%)	5 (6.9%)	0.072
Other heart diseases	5 (6.9%)	7 (9.9%)	0.744	7 (9.9%)	5 (6.9%)	0.744
Cerebrovascular disease	9 (12.5%)	4 (5.6%)	0.256	7 (9.9%)	6 (8.3%)	0.979
COPD	8 (11.1%)	2 (2.8%)	0.097	7 (9.9%)	3 (4.2%)	0.208
Chronic liver disease	2 (2.8%)	3 (4.2%)	0.681	1 (1.4%)	4 (5.6%)	0.366
Chronic kidney disease	1 (1.4%)	4 (5.6%)	0.209	3 (4.2%)	2 (2.8%)	0.681
Malignancy	6 (8.3%)	7 (9.9%)	0.979	7 (9.9%)	6 (8.3%)	0.979
History of surgery	11 (15.3%)	12 (16.9%)	0.971	11 (15.5%)	12 (16.7%)	1
Prognosis			<0.001			<0.001
Death	11 (15.3%)	4 (5.6%)		13 (18.3%)	2 (2.8%)	
Discharged	52 (72.2%)	63 (88.7%)		47 (66.2%)	68 (94.4%)	
Hospitalized	9 (12.5%)	4 (5.6%)		11 (15.5%)	2 (2.8%)	
SAT (cm²)	107.5 (69.4-130.9)	111.0 (89.0-171.2)	0.184	126.3 (87.0-171.6)	97.6 (68.8-148.7)	0.087
VAT (cm²)	143.6 (90.6-197.7)	79.1 (45.7-116.8)	<0.001	126.3 (74.0-185.5)	89.6 (49.9-145.3)	0.016
VSR	1.40 (0.93-1.82)	0.61 (0.46-0.92)	<0.001	1.00 (0.65-1.52)	0.89 (0.56-1.36)	0.266
SMA (cm²)	96.4 (78.3-118.5)	95.6 (81.0-115.5)	0.857	91.7 (77.1-108.8)	100.1 (87.3-126.5)	0.006
SMD (HU)	31.8 (20.3-36.8)	33.0 (24.4-41.5)	0.091	23.6 (17.0-28.1)	39.3 (35.9-43.0)	<0.001

Categorical variables presented as number (percentage), and continuous variables presented as median (interquartile range). To compare variables between different groups, the χ^2 test or Fisher exact test was used for categorical variables, and the *t* test or Mann-Whitney *U* test was used for continuous variables, when appropriate. A two-tailed *P* < 0.05 was considered statistically significant.
[1]High VSR was termed visceral adiposity with the cutoff values of 1.33 in male and 0.71 in female.
[2]Low SMD was termed as high IMF deposition with the cutoff values of 32.7 HU in males and 28.9 HU in females.
COPD, chronic obstructive pulmonary disease; CT, computed tomography; HU, Hounsfield units; IMF, intramuscular fat; LBC, lymphocyte count; NBC, neutrophil count; PLT, platelet count; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area; SMD, the mean attenuation of skeletal muscle; VAT, visceral adipose tissue; VSR, VAT to SAT ratio; WBC, white blood cell.

for SAT; ICC = 0.999 for VAT; ICC = 0.909 for SMA; and ICC = 0.993 for SMD).

Critically ill patients had significantly higher VAT and VSR (*P* = 0.003; *P* = 0.042; respectively). Median SMD was 25.4 HU and 35.7 HU in critically ill and noncritically ill groups, respectively, and the difference was statistically significant (*P* < 0.001) (Table 1).

Clinical characteristics among different adipose tissue distribution features

An area of 100 cm² was used as a cutoff point to distinguish high and normal fat areas for VAT and SAT, irrespective of sex. Median VSR (1.33 in male and 0.71 in female) was used to distinguish high from normal VSR. Similarly, the cutoff value for SMA was 115.5 cm² in males and 84.7 cm² in females. The cutoff value for SMD was 32.7 HU in males and 28.9 HU in females.

The clinical characteristics of patients with and without visceral adiposity or high IMF deposition are shown in Table 2. Patients with visceral adiposity or high IMF deposition were significantly older (*P* = 0.045; *P* < 0.001; respectively). A relatively larger area of VAT and

smaller area of SMA were found in patients with high IMF deposition (*P* = 0.016; *P* = 0.006; respectively). There was no difference in sex and complication rate between patients with and without visceral adiposity or high IMF deposition.

Visceral adiposity and high IMF deposition were independent risk factors for critical illness

The overall rate of critical illness in our study was 31.5%. The rates of critical illness in patients with visceral adiposity were almost twice as much as patients with no visceral adiposity (42.3% vs. 22.5%, *P* = 0.035; Table 3). Patients with high IMF deposition showed significantly higher rates of critical illness compared with those without high IMF deposition (52.1% vs. 11.1%, *P* < 0.001; Table 3).

Both univariate and multivariate logistic regression analyses were used to examine the association of adipose tissue and skeletal muscle variables with the risk of critical illness (Table 4). Univariate logistic regression demonstrated that hypertension, cerebrovascular disease, visceral adiposity, and high IMF deposition was significantly associated with the severity of COVID-19 infection. Multivariate logistic regression analysis demonstrated that visceral adiposity (odds ratio [OR]: 2.47,

TABLE 3 Relationship between severity of COVID-19 infection and adipose tissue distribution variables

Group	Critical illness ($n=45$)	Noncritical illness ($n=98$)	P value
SAT			1
High SAT ($n=78$)	25 (32.1%)	53 (67.9%)	
Normal SAT ($n=65$)	20 (30.8%)	45 (69.2%)	
VAT			0.103
High VAT ($n=73$)	28 (38.3%)	45 (61.6%)	
Normal VAT ($n=70$)	17 (24.3%)	53 (75.7%)	
Visceral adiposity			0.035
Visceral adiposity ($n=72$)	29 (42.3%)	43 (59.7%)	
No visceral adiposity ($n=71$)	16 (22.5%)	55 (77.5%)	
SMA			0.134
High SMA ($n=72$)	18 (25%)	54 (75%)	
Low SMA ($n=71$)	27 (38.0%)	44 (62.0%)	
IMF deposition			<0.001
High IMF deposition ($n=71$)	37 (52.1%)	34 (47.9%)	
No high IMF deposition ($n=72$)	8 (11.1%)	64 (88.9%)	

Variables presented as number (percentage); the χ^2 test or Fisher exact test was used to compare variables between different groups. A two-tailed $P<0.05$ was considered statistically significant.
COVID-19, coronavirus disease 2019; IMF, intramuscular fat; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area; VAT, visceral adipose tissue.

95% CI: 1.05-5.98, $P=0.040$) and high IMF deposition (OR: 11.90, 95% CI: 4.50-36.14, $P<0.001$) were independent risk factors for critical illness.

Furthermore, patients with visceral adiposity or high IMF deposition had significantly higher risk of mechanical ventilation compared with patients without those adipose tissue distribution features ($P=0.013$; $P<0.001$; respectively; Figure 3A-3B). No statistical significance was found for visceral adiposity and increased risk of death in patients with COVID-19 ($P=0.056$; Figure 3C). High IMF deposition increased the risk of death ($P=0.012$; Figure 3D).

Patients aged <60 years with visceral adiposity and high IMF deposition had higher risk for critical illness

As adipose tissue distribution is usually associated with age, we studied the relationship between them. Whereas SAT, VAT, and VSR were not correlated with age ($R=-0.162$, $P=0.054$; $R=-0.063$, $P=0.454$; and $R=0.127$, $P=0.130$; respectively), SMA and SMD were moderately correlated with age ($R=-0.333$, $P<0.001$ and $R=-0.459$, $P<0.001$; respectively). Otherwise, SMD was not correlated with VSR ($R=-0.025$, $P=0.760$).

We divided the patients into two subgroups based on age. In the group younger than 60 years old ($n=44$), patients with visceral adiposity (OR: 7.58, 95% CI: 1.7-42.21, $P=0.011$) and high IMF deposition (OR: 18.67, 95% CI: 3.64-147.42, $P=0.001$) had higher risks for critical illness. In the subgroup older than 60 years old ($n=99$), only high IMF deposition (OR: 6.21, 95% CI: 2.39-18.47, $P<0.001$) was significantly associated with the severity of COVID-19 infection.

TABLE 4 Univariate and multivariate analysis of adipose tissue distribution for predicting severity of COVID-19

Characteristic	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age	1.03	1-1.05	0.066	0.98	0.95-1.02	0.270
Sex (male)	1.92	0.94-3.98	0.075	2.11	0.91-5.04	0.086
Comorbidity (yes or no)	1.88	0.9-4.05	0.097			
Hypertension	2.37	1.15-4.93	0.020	1.83	0.75-4.52	0.185
Diabetes	1.27	0.52-2.99	0.59			
Cardiovascular disease	1.46	0.5-3.99	0.47			
Other heart diseases	1.62	0.46-5.4	0.43			
Cerebrovascular disease	4.02	1.26-14.07	0.021	4.4	0.99-21.84	0.057
COPD	0.93	0.19-3.52	0.917			
Chronic liver disease	0	NA	0.988			
Chronic kidney disease	0.53	0.03-3.74	0.58			
Malignancy	0.96	0.25-3.15	0.955			
History of surgery	1.2	0.45-3.01	0.709			
High SAT	1.06	0.52-2.17	0.869			
High VAT	1.94	0.95-4.05	0.072			
Visceral adiposity	2.32	1.13-4.89	0.024	2.47	1.05-5.98	0.040
High SMA	1.84	0.9-3.82	0.095			
High IMF deposition	8.71	3.81-22.07	<0.001	11.90	4.50-36.14	<0.001

Sex, age, and variables with $P<0.05$ at univariate logistic regression analysis were applied to multivariate analysis. A two-tailed $P<0.05$ was considered statistically significant.
COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IMF, intramuscular fat; NA, not available ; OR, odds ratio; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area; VAT, visceral adipose tissue.
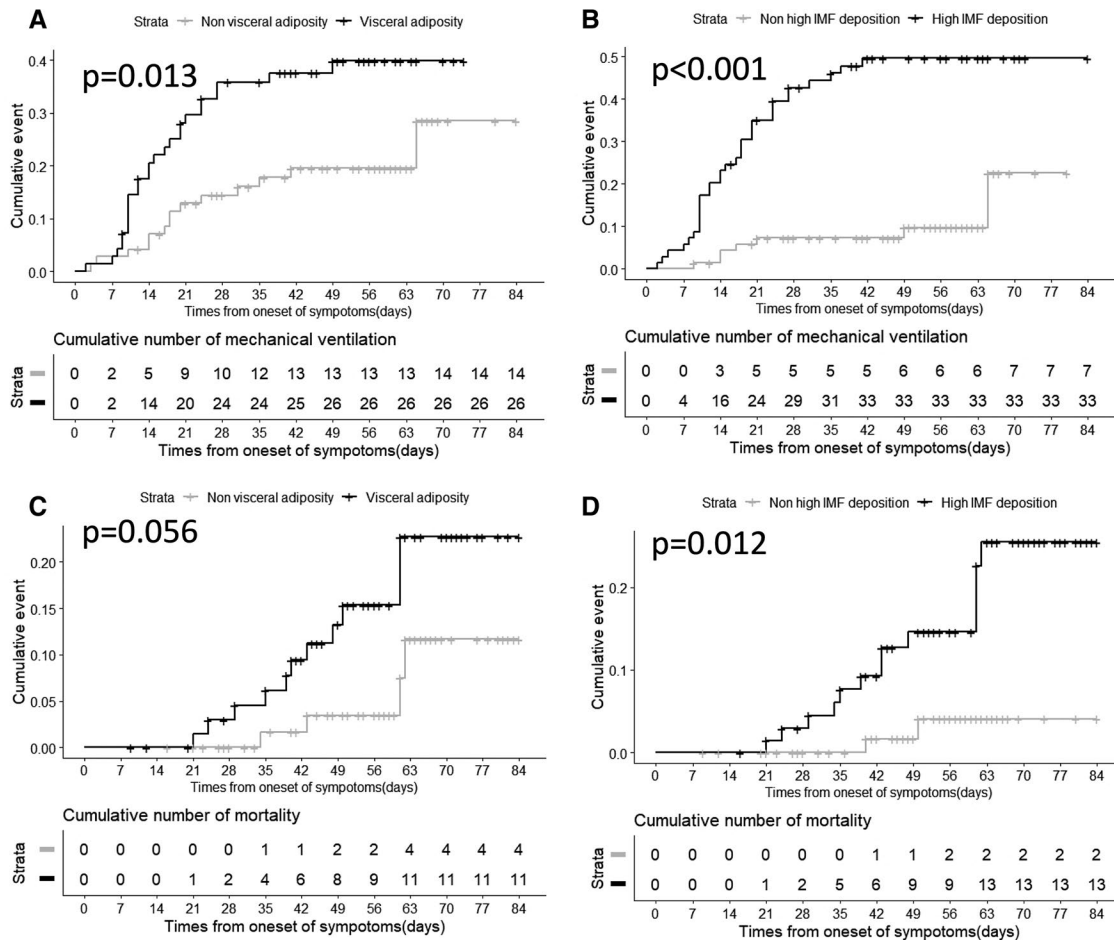
Figure 3 Cumulative rates of mechanical ventilation and mortality were calculated using Kaplan-Meier methods, and differences between curves were evaluated using the log-rank test. (**A**) Time-dependent risk of mechanical ventilation from the time of onset between patients with or without visceral adiposity. (**B**) Time-dependent risk of mechanical ventilation between patients with or without high intramuscular fat (IMF) deposition. (**C**) Time-dependent risk of death from the time of onset between patients with or without visceral adiposity. (**D**) Time-dependent risk of death between patients with or without high IMF deposition. (Two of the enrolled individuals were excluded from analysis because record of time of onset was unavailable.)

Discussion

In this study, we analyzed the impact of adipose tissue distribution on the severity of COVID-19 infection in a hospitalized cohort. Visceral adiposity and high IMF deposition were independent risk factors associated with critical illness, and those factors increased the risks of mechanical ventilation and death. Moreover, in the subgroup younger than 60 years old, patients with visceral adiposity or high IMF deposition had higher risk for critical illness, even though sample size of the subgroup was small.

Body composition not only reflects nutritional status but has significant influence on metabolic activity and inflammatory response (14). Several methods are available for the evaluation of those components, and BMI is the most commonly used one. High BMI was significantly associated with critical illness for patients with COVID-19 in a large prospective cohort study (26). However, no significant difference in BMI value was found between critical illness and noncritical illness groups in our cohort. The inconsistent results may be due to the small sample size of

our cohort. As BMI is an indirect measurement of adipose tissue, it cannot provide information on fat distribution. More recent data have proposed that visceral adiposity and ectopic fat accumulation contribute to various features of metabolic syndrome, over and above the BMI (14). A cross-sectional image of CT scans at the level of the L3 could quantify adipose tissue and skeletal muscle, and currently this is a widely used method to evaluate adipose tissue distribution (23). In this study, visceral adiposity and high IMF deposition were significantly associated with critical illness for patients with COVID-19. This suggested that the fat distribution rather than the total fat may be a better indicator of risk for critical illness of patients with COVID-19.

In this study, we found that VAT rather than SAT deposition was associated with the severity of COVID-19 infection. Previous studies have shown that VAT was different from SAT in pro-inflammatory cytokine production (27). Visceral fat was supposed to be an endocrine organ and had pro-inflammatory characteristics (14). Different studies have demonstrated that people with visceral adiposity have higher concentrations of circulating inflammatory cytokines compared with lean

individuals (14,28). Tumor necrosis factor-α, interleukin (IL)-6, and IL-1b are the main inflammatory cytokines secreted by VAT from adipocytes and resident macrophages, while anti-inflammatory cytokines such as adiponectin are secreted from subcutaneous adipocytes (29). In SARS-CoV-2 infected individuals, studies have reported that IL-6, IL-10, and tumor necrosis factor-α surged during illness and declined during recovery (30,31). And a portion of severe patients with COVID-19 had an elevated cytokine profile resembling cytokine storm in severe acute respiratory syndrome and Middle East respiratory syndrome (32). The dysregulated and exuberant immune responses could exacerbate lung damage as well as lead to other fatal complications (33). Moreover, excessive adipose tissue, especially VAT, can also alter cell-mediated immune responses through the increase in leptin and the decrease in adiponectin (34). The immune dysfunction caused by visceral fat aggravating COVID-19-induced immune damage may be the reason why patients with visceral adiposity were more susceptible to developing a serious illness. In addition, abdominal obesity can profoundly alter pulmonary function by diminishing exercise capacity and augmenting airway resistance, resulting in increased work of breathing (35). For supine patients, ventilation may be more difficult with the decreased diaphragmatic excursion.

The present study showed that high IMF deposition was significantly associated with risk of critical illness and requiring mechanical ventilation in patients with COVID-19. There was a moderate correlation between SMD and age, and high IMF deposition was more common in older patients in our study, but high IMF deposition was still a significant risk factor for critical illness when age was adjusted for statistically. In the subgroup under 60 years old, patients with high IMF deposition had higher risk for critical illness; however, the 95% confidence intervals of the odds ratios were large. This may be due partly to the small sample size of the subgroup. Previous studies have shown that high IMF deposition contributes to muscle weakness independent of the age-associated loss in muscle mass, which is consistent with our findings (19). A previous study reported that IMF deposition delayed and blunted immune responses, especially natural killer lymphocytes involved in innate immunity (14). Montano Loza et al. demonstrated that the presence of skeletal muscle loss and high IMF depositionincreased the risk of sepsis-related death in patients with cirrhosis, probably due to impaired immunity (36). Therefore, high IMF deposition would impair immune function of COVID-19 patients and increase the risk of complications and mortality.

To our knowledge, this is the first study that has investigated the association between adipose tissue distribution and severity of COVID-19 infection. There are several ʟimitations of our study. First, it is a retrospective, single-center study with a small sample of hospitalized patients, therefore larger, multicenter studies are needed to confirm the results of this study. Second, the possibility of selection bias in patient inclusion in the study group must be considered, as abdominal CT scan is not a routine examination for COVID-19 patients. Besides, physical activity levels were not analyzed in our study, although they have been widely associated with adipose tissue distribution in previous studies (16,28). The association between smoking and severity of COVID-19 is controversial; it was not analyzed in our study because electronic medical records for smoking were not complete in our hospital during the outbreak period (37,38). Nevertheless, our study offered the new insight that visceral adiposity and high IMF deposition are significantly associated with the severity of COVID-19 infection. The assessment of adipose distribution and IMF deposition may help with risk stratification of patients with COVID-19 upon hospital admission.

Conclusion

Our findings show that patients with visceral adiposity or high IMF deposition were more likely to develop critical illness when infected with COVID-19. Therefore, patients with abdominal obesity should be monitored more carefully when hospitalized.**O**

Acknowledgments

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