Obesity

Obesity is Associated with Worse Outcomes in COVID-19: Analysis of Early Data from New York City

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Objective: The 2019 novel coronavirus disease (COVID-19) has triggered a rapidly expanding global pandemic in which patients exhibit a wide spectrum of disease severity. Given the high prevalence of obesity in the United States, we hypothesized that the presence of obesity may play a role in the clinical course of patients with COVID-19.

Methods: This is a retrospective review of adult patients admitted with confirmed severe acute respiratory syndrome coronavirus 2. Demographics, clinical characteristics, laboratory data, and clinical outcomes were abstracted. BMI (kilograms per meter squared) was analyzed with regard to a composite outcome of intensive care unit (ICU) admission or death and intubation rate.

Results: About 770 patients were included (61% male, mean age 63.5 years). Patients with obesity were more likely to present with fever, cough, and shortness of breath. Obesity was also associated with a significantly higher rate of ICU admission or death (RR = 1.58, $P = 0.002$) even after adjusting for age, race, and troponin level.

Conclusions: Patients with obesity had an increased risk for critical illness leading to ICU admission or death compared with normal weight individuals. This study confirms that obesity is a major risk factor for COVID-19 disease severity, significantly impacting disease presentation and critical care requirements.

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Study Importance

What is already known?

- The 2019 novel coronavirus disease (COVID-19) has triggered a rapidly expanding global pandemic in which patients exhibit wide spectrums of disease severity.
- Patient comorbidities such as diabetes and hypertension appear to influence clinical outcomes.
- Obesity influences immune function and inflammatory response, and early data from China suggested that BMI and critical illness in COVID-19 may be related.

What does this study add?

- Patients admitted with COVID-19 and obesity were more likely to present with features of fever, cough, and dyspnea and be younger than normal weight patients. Obesity was associated with a significantly higher rate of ICU admission or death independent of age, race, and troponin I level.

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

- Obesity is an independent risk factor for disease severity in COVID-19.This observation will permit improved risk stratification of patients upon presentation and lead to improved clinical care and distribution of crucial resources including ICU admission.
- These findings can help guide future research and improve our understanding of the pathophysiology by which obesity determines outcomes in patients with COVID-19.

Introduction

The 2019 novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), triggered a global pandemic (1). The large number of people infected with the virus combined with the wide spectrum of disease severity and clinical outcomes have led scientists and clinicians to investigate whether various phenotypes and baseline biomarkers are associated with a higher risk for infection and critical illness. Initial data on COVID-19 has implicated several factors associated with worse disease severity, including older age and comorbidities such as diabetes and hypertension (2,3). Considering the close relationship between these conditions and metabolic syndrome, characterized by insulin resistance and excess adiposity, obesity may also be a risk factor for worse clinical outcomes.

Although early descriptive COVID-19 studies did not report on the direct association of obesity with disease severity, BMI is higher in those with critical illness in COVID-19 (4,5). There are also emerging data that obesity is an independent predictor of intensive care unit (ICU)

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admission, mechanical ventilation, and death (5-7), and in a recent report from a large cohort of COVID-19 patients in New York, obesity was found to be one of the most common associated comorbidities in hospitalized patients (8). The underlying impairments in the cardiovascular, respiratory, metabolic, and thrombotic pathways that characterize COVID-19, combined with the immune dysregulation and systemic inflammation seen in obesity, may potentiate critical illness (9-11). Often the inflammatory response to SARS-CoV-2 causes more clinical complications than the direct viral cytopathic injury alone, with development of acute respiratory distress syndrome, cardiac injury, thromboembolic disease, and disseminated intravascular coagulation (12-17).

Some estimates have suggested that almost 50% of adults in the United States are at increased risk for complications from COVID-19 because of chronic health conditions, even without considering the role of obesity (18). Given the high prevalence of obesity in Western countries, whether obesity confers an additional risk to patients with COVID-19 must be delineated. Although there is a suggestion that obesity may be associated with worse outcomes, much of the data has originated from China, where obesity rates are much lower than the United States (19). We hypothesized that the presence of obesity would significantly influence the clinical features and spectrum of illness in a large cohort of patients with COVID-19 within New York City.

Methods

Patients and exposure variables

This is a retrospective review of adult patients (age ≥ 18) with a positive real-time reverse-transcription polymerase chain reaction from a respiratory sample (naso- or oropharyngeal or bronchial/sputum samples) for SARS-CoV-2 recorded between March 4 and April 9, 2020 at one of two hospitals in New York City (an academic tertiary care referral center and a smaller community hospital). Patients who were admitted (including those in temporary observation defined as admission to the emergency department and discharge within 24 hours) were included in the final analysis. The study was reviewed and approved by the institutional review board at our medical center (1804019146).

The epidemiological history, demographics (age, gender, race/ethnicity), clinical characteristics, laboratory data, treatment plans, and outcome measures were obtained from patients' medical records. Clinical outcomes were followed up to April 16, 2020. The following was recorded for each patient with COVID-19 diagnosis: date of presentation (defined as the time when the polymerase chain reaction test for COVID-19 was performed), initial vital signs (respiratory rate, heart rate, blood pressure, and temperature, with fever defined as ≥ 37.8°C), presence of comorbidities (including cancer, chronic kidney disease, chronic obstructive pulmonary disease, asthma, cardiovascular disease, history of venous thromboembolism, diabetes, hypertension, inflammatory bowel disease, chronic liver disease, or solid organ transplantation), medications of interest (anticoagulants, steroids, statins, nonsteroidal anti-inflammatory drugs, and nonsteroidal immunosuppressive medications), laboratory and imaging results (including inflammatory markers such as C-reactive protein, D-dimer, albumin, and ferritin, as well as complete blood count, procalcitonin, troponin I, creatine kinase, interleukin [IL]-6, total bilirubin, and liver enzymes), and outcome measures. Patient's degree of hypoxemia on presentation was categorized as the following: (1) not hypoxemic (defined as an oxygen saturation of ≥ 95% on ambient room air), (2) moderate hypoxemia (defined as maintaining an oxygen saturation of 90%-95% on room air or ≥ 90% with 4 L or less supplemental oxygen through a nasal cannula), or (3) severe hypoxemia (defined as needing more than 4 L of supplemental oxygen, nonrebreather mask, or noninvasive (e.g., bilevel positive airway pressure) or invasive ventilation to maintain an oxygen saturation of ≥ 90%, or failure to maintain an oxygen saturation of ≥ 90%). Patients were considered to have acute liver injury at presentation if they had alanine aminotransferase or aspartate aminotransferase > 40 U/L, total bilirubin > 1.2 mg/dL, or alkaline phosphatase > 150 U/L (upper limits of normal at our laboratory).

The exposure of interest was BMI (kilograms per meter squared). Because of the known J-shaped association of BMI and clinical outcomes (i.e., both underweight and patients with obesity can have higher risk of adverse outcomes), BMI was analyzed as a categorical variable. Given available evidence from COVID-19 literature suggesting an association between BMI and outcomes, BMI categories were defined as normal (including overweight), BMI ≥ 18.5 and < 30 (reference category); underweight, BMI < 18.5; and obesity, BMI ≥30. Secondary analysis was done on the standard BMI categories, which were defined as normal weight, BMI ≥ 18.5 and < 25 (reference category); underweight, BMI < 18.5; overweight, BMI ≥ 25 and BMI < 30; obesity, BMI ≥ 30 and BMI < 40; and severe obesity, BMI ≥ 40. Finally, sensitivity analysis was performed using race specific cutoff points for the Asian patients as suggested by the World Health Organization defining normal and overweight, BMI ≥ 18.5 and < 27.5 (reference category); underweight, BMI < 18.5; and obesity, BMI ≥ 27.5 (20).

Outcomes

For admitted patients, data were extracted regarding their clinical course, including need for supplementary oxygen, noninvasive positive pressure ventilation, or invasive ventilatory support with mechanical ventilation, ICU admission, and death.

The main outcome of interest in this study was the composite of ICU admission (with or without invasive mechanical ventilation) or death. Patients were considered to have the outcome if they were admitted to ICU at any time during their admission regardless of need for invasive ventilation or if they died before or after being transferred to the ICU. Secondary outcomes included ICU admission and death separately as well as need for intubation for invasive mechanical ventilation (regardless of indication).

Statistical analysis

Descriptive statistics were reported as means (SD) or counts and proportions. Variables were compared using ANOVA and χ^2 tests in unadjusted analysis. Logistic regressions were used for univariable comparison of outcomes across BMI categories. Generalized linear models (with maximum likelihood optimization and robust standard error estimation) with a Poisson distribution for the dependent variable and a logarithmic link function were used to estimate risk ratios and their CIs. All analyses were based on nonmissing data, and missing data were not imputed. All tests were two tailed with a significance level of alpha = 0.05, except when adjusted for multiple comparisons as described above. All analyses were performed with Stata 13.0 for Windows (StataCorp LLC, College Station, Texas).

TABLE 1 Demographic, laboratory, and clinical findings of patients with COVID-19 at presentation

Variable	Total	BMI			*P* value
		<18.5, *n* = 28	18.5-30, *n* = 465	≥30, *n* = 277	
Age, y	64 ± 16.7	74 ± 17.7	66 ± 16.7	59 ± 15.2	< 0.001
BMI, kg/m^2	29 ± 7.9	17 ± 1.2	25 ± 2.9	36 ± 8.1	NA
Gender					0.135
Male	468 (60.8)	13 (46.4)	293 (63)	162 (58.5)	
Female	302 (39.2)	15 (53.6)	172 (37)	115 (41.5)	
Race/ethnicity					< 0.001
White/Caucasian	229 (41.1)	10 (43.5)	139 (40.9)	80 (41.2)	
Black/African American	79 (14.2)	3 (13.0)	43 (12.7)	33 (17.0)	
Asian	88 (15.8)	8 (34.8)	68 (20.0)	12 (6.2)	
Other	161 (28.9)	2 (8.7)	90 (26.5)	69 (35.6)	
Pre-existing comorbidities					
Hypertension	432 (56.1)	20 (71.4)	251 (54)	161 (58.1)	0.137
Diabetes	238 (30.9)	8 (28.6)	133 (28.6)	97 (35)	0.181
Chronic kidney disease	100 (13.0)	7 (25.0)	66 (14.2)	27 (9.7)	0.064
Cardiovascular disease	162 (21.0)	8 (28.6)	95 (20.4)	59 (21.3)	0.585
COPD/asthma	98 (12.7)	2 (7.1)	47 (10.1)	49 (17.7)	0.007
Obstructive sleep apnea	36 (4.7)	0 (0)	7 (1.5)	29 (10.5)	< 0.001
VTE	65 (8.4)	4 (14.3)	33 (7.1)	28 (10.1)	0.190
Cancer	98 (12.7)	6 (21.4)	64 (13.8)	28 (10.1)	0.131
IBD	9 (1.2)	0 (0)	7 (1.5)	2 (0.7)	0.531
Chronic liver disease	22 (2.9)	1 (3.6)	14 (3.0)	7 (2.5)	0.905
Solid organ transplantation	17 (2.2)	1 (3.6)	11 (2.4)	5 (1.8)	0.778
Fever	140 (23.3)	4 (17.4)	77 (20.6)	59 (28.9)	0.031
Respiratory rate	21 ± 5.5	20 ± 4.2	21 ± 5.8	21 ± 5	0.616
Heart rate	93 ± 18.5	91 ± 18.5	91 ± 18.4	96 ± 18.3	0.001
Mean arterial pressure, mmHg	93 ± 13.4	90 ± 16.9	92 ± 12.9	94 ± 13.7	0.209
Hypoxia on presentation					0.071
No	205 (34.8)	12 (54.6)	131 (35.9)	62 (30.5)	
Moderate	208 (35.3)	4 (18.6)	120 (32.9)	84 (41.4)	
Severe	176 (29.9)	6 (27.3)	113 (31.2)	57 (28.1)	
Symptoms					
Fever	558 (72.5)	14 (50.0)	329 (70.8)	215 (77.6)	0.003
Cough	539 (70.0)	13 (46.4)	325 (69.9)	201 (72.6)	0.016
Shortness of breath	535 (69.5)	14 (50.0)	304 (65.4)	217 (78.3)	< 0.001
Myalgia/fatigue	233 (30.3)	8 (28.6)	138 (29.7)	87 (31.4)	0.867
Anorexia	226 (29.4)	10 (35.7)	139 (29.9)	77 (27.8)	0.627
Altered mental status	110 (14.3)	7 (25.0)	82 (17.6)	21 (7.6)	< 0.001
Anticoagulant	148 (19.2)	10 (35.7)	79 (17.0)	59 (21.3)	0.028
Aspirin	101 (13.1)	4 (14.3)	61 (13.1)	36 (13.0)	0.982
NSAIDs	106 (13.8)	4 (14.3)	58 (12.5)	44 (15.9)	0.426
Chronic steroids	39 (5.1)	3 (10.7)	21 (4.5)	15 (5.4)	0.329
Immunosuppressant	39 (5.1)	0 (0)	26 (5.6)	13 (4.7)	0.398
Statin	262 (34.0)	8 (28.6)	148 (31.8)	106 (38.3)	0.166
Laboratory findings					
White blood cell count, × 10^3	8 ± 6.3	8 ± 4.9	8 ± 7.6	7 ± 3.6	0.419
Absolute lymphocyte count, × 10^3	1 ± 1.8	1 ± 0.6	1 ± 2.1	1 ± 1.4	0.873
Absolute neutrophil count, × 10^3	7 ± 8.5	6 ± 2.5	7 ± 8.6	7 ± 8.6	0.782
Platelet count, × 10^3	214 ± 94.2	215 ± 87.9	213 ± 96.5	216 ± 91.0	0.939
Procalcitonin, ng/mL	1 ± 9.3	1 ± 6.3	1 ± 4.2	1 ± 5.8	0.715

TABLE 1 (continued).

Variable	Total	BMI			*P* value
		<18.5, *n* = 28	18.5-30, *n* = 465	≥30, *n* = 277	
D-dimer, ng/mL	1,761 ± 4,857	8,052 ± 17,857	1,977 ± 4,886	1,118 ± 2,858	0.002
C-reactive protein, mg/dL	15 ± 15.8	11 ± 8.6	15 ± 16.2	16 ± 15.5	0.389
Ferritin, ng/mL	1,215 ± 1,572	1,071 ± 1,068	1,312 ± 1,510	1,061 ± 1,694	0.219
Troponin I, ng/mL	0.2 ± 0.9	0.8 ± 2.8	0.2 ± 0.9	0.1 ± 0.3	0.004
Creatine kinase, U/L	386 ± 876	587 ± 941	361 ± 763	410 ± 1043	0.632
IL-6, pg/mL	92 ± 160	na	118 ± 190	62 ± 116	0.358
Albumin, g/dL	3.1 ± 0.6	3.1 ± 0.7	3.1 ± 0.6	3.2 ± 0.6	0.606
Total bilirubin, mg/dL	1.1 ± 0.5	1.2 ± 0.5	1.1 ± 0.6	1.1 ± 0.4	0.474
ALT, U/L	51 ± 65	37 ± 45	53 ± 76	48 ± 44	0.361
AST, U/L	61 ± 80	49 ± 35	64 ± 77	58 ± 88	0.516
Alkaline phosphatase, U/L	85 ± 55	97 ± 99	88 ± 57	80 ± 43	0.119
INR	1.1 ± 0.9	1.1 ± 0.2	1.1 ± 0.8	1.0 ± 1.2	0.776
aPTT, seconds	30 ± 13	29 ± 8	30 ± 16	29 ± 7	0.781

Data are mean ± SD or *n* (%). *P* values are calculated using ANOVA and χ^2 tests.
VTE, venous thromboembolism; IBD, inflammatory bowel disease; NSAID, nonsteroidal anti-inflammatory drug; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

Results

Patients and baseline characteristics

Of the 975 patients with COVID-19 admitted to either the Emergency Department or inpatient wards, 770 patients had complete BMI data and were included in the final analysis. Patients had a mean age of 63.5 (SD = 17) years and mean BMI of 29 (SD = 8), and 61% were male (Table 1). Patient baseline characteristics were compared in univariable analysis according to their weight group (Table 1). There was an inverse association between age and BMI, as patients with obesity tended to be younger, and patients with underweight tended to be older on average ($P < 0.001$). Distribution of race and ethnicity was not homogenous across BMI categories as patients with underweight and normal weight were more likely to be Asian, while patients with obesity were more likely to be white/Caucasian or black/African American ($P < 0.001$). Asian patients were likely to present to the hospital on average 1.7 days later after their first symptom compared with white/Caucasian patients (8.5 vs. 6.8 days, respectively, $P = 0.009$). Patients with obesity were more likely to have a prior diagnosis of asthma/chronic obstructive pulmonary disease or obstructive sleep apnea ($P = 0.007$ and $P < 0.001$, respectively). However, the prevalence of hypertension, diabetes, cardiovascular disease, chronic kidney disease, chronic liver disease, or cancer was not statistically different among weight groups (Table 1). Furthermore, patients with underweight had a significantly higher level of D-dimer ($P = 0.002$) and troponin I (p = 0.004) at presentation compared with patients with normal weight or obesity.

Presenting symptoms among weight categories

Patients with underweight were less likely to present with a history of fever (50%) compared with patients with normal weight (71%, $P < 0.003$). In contrast, patients with obesity were more likely to present with a history of fever (78%, $P < 0.003$). Similarly, patients with obesity were more likely to present with cough (73%) compared with patients with normal weight (70%, $P = 0.016$). They were also significantly more likely to present with dyspnea (78%, $P < 0.001$). Patients with underweight had the lowest rate of cough and shortness of breath at presentation, but they presented more commonly with altered mental status compared with patients with normal weight or obesity ($P < 0.001$). Patients with obesity were more likely to have tachycardia at presentation (mean heart rate of 96 bpm) compared with patients with underweight (mean heart rate of 91 bpm, $P < 0.001$). Although patients with normal weight showed a trend toward lower prevalence of hypoxemia compared with patients with obesity, this difference did not reach statistical significance. There was a trend, albeit not significant, for patients with obesity (41%) to have more moderate hypoxemia at presentation compared with patients with underweight (19%; $P = 0.071$).

Weight and risk of adverse clinical outcomes

Univariable analysis. Table 2 details the unadjusted rate of outcomes among different weight groups. Both patients with obesity (35%) and those with underweight (43%) appeared to have a higher risk for composite outcome of ICU admission or death compared with patients with normal weight (28%, $P = 0.032$). Patients with obesity had a higher risk for ICU admission and intubation (33%) compared with patients with underweight (18% and 11%, respectively) and normal weight (21%, $P = 0.001$), while underweight patients showed a higher risk for death ($P < 0.001$; Table 2).

Multivariable analysis. Although distribution of obstructive sleep apnea, respiratory disease, and D-dimer levels were different across weight categories, the multivariable analysis was not adjusted for these variables, as they can represent downstream effects of obesity on respiratory physiology as well as inflammatory and prothrombotic states (i.e., mediators of the effect of obesity). Therefore, the multivariable analysis was adjusted for age, race/ethnicity, and troponin I levels.

Obesity (BMI ≥ 30) was associated with increased risk for ICU admission or death (RR = 1.58, $P = 0.002$), whereas underweight was not (RR = 1.04, $P = 0.892$; see Table 3). Older age, increased troponin I, and Asian race were other significant predictors of ICU admission and death (Table 3). The same analysis was repeated in the subset of patients who were 60 years

TABLE 2 Distribution of outcomes according to weight categories in study population

Variable	BMI			*P* value
	<18.5, *n* = 28	18.5-30, *n* = 465	≥30, *n* = 277	
ICU admission	5 (18)	99 (21)	92 (33)	0.001
Intubation	3 (11)	99 (21)	91 (33)	<0.001
Death	9 (32)	57 (12)	22 (8)	<0.001
Composite outcome of ICU admission or death	12 (43)	131 (28)	98 (35)	0.032

Data presented are risk of outcome in each category of BMI as number of event (%). *P* values are from univariable χ^2 test.

TABLE 3 Multivariable analysis of effect of weight on composite outcome of ICU admission or death, with sensitivity analysis of weight categories, adjusted for age, race/ethnicity, and troponin I level

Main analysis				Sensitivity analysis with 5 categories of weight			
	RR	95% CI	*P*		RR	95% CI	*P*
BMI, kg/m^2				BMI, kg/m^2			
18.5-30	Ref.			18.5-25	Ref.		
<18.5	1.04	0.59-1.84	0.892	<18.5	1.04	0.58-1.89	0.885
≥30	1.58	1.18-2.13	0.002	25-30	1.01	0.70-1.47	0.942
				30-40	1.57	1.11-2.23	0.012
				≥40	1.75	0.97-3.18	0.065
Age, y	1.02	1.01-1.03	<0.001	Age, y	1.02	1.01-1.03	<0.001
Race/ethnicity				Race/ethnicity			
White/Caucasian	Ref.			White/Caucasian	Ref.		
Black/African American	1.06	0.67-1.66	0.808	Black/African American	1.06	0.68-1.67	0.786
Asian	1.53	1.08-2.17	0.017	Asian	1.54	1.08-2.19	0.016
Other	0.99	0.69-1.43	0.975	Other	1.00	0.69-1.44	0.996
Troponin I	1.10	1.02-1.18	0.012	Troponin I	1.1	1.02-1.18	0.012

of age or more. Obesity remained an independent predictor of ICU admission or death in this age group (RR = 1.48, *P* = 0.020) even after adjusting for race and troponin I levels. As expected, obesity remained associated with significantly increased risk for ICU admission (RR = 1.76, *P* = 0.001) and intubation (RR = 1.72, *P* = 0.002) even after adjusting for age, race, and troponin levels in multivariable analysis of secondary outcomes (Table 4).

Sensitivity analysis. The above analysis was repeated using race-specific BMI categories as described in the Methods. Obesity (BMI ≥ 30 or ≥ 27.5 for Asian patients) remained associated with increased risk for ICU admission or death (RR = 1.61, *P* = 0.001), whereas underweight was not (RR = 1.30, *P* = 0.332). Older age, elevated troponin I, and Asian race remained other significant predictors of ICU admission and death similar to the main analysis. The same analysis in the subset of patients who were 60 years of age or older showed that obesity remained an independent predictor of ICU admission or death in this age group (RR = 1.53, *P* = 0.0008) after adjusting for race and troponin I levels. Similar to the main analysis, obesity remained associated with significantly increased risk for ICU admission (RR = 1.79, *P* = 0.001) and intubation (RR = 1.79, *P* = 0.001).

Finally, the association between BMI and the composite outcome of ICU admission or death was evaluated using five categories of BMI (Table 3). Obesity, defined as BMI ≥ 30 and BMI < 40, was associated with a significantly higher rate of ICU admission or death compared with normal weight in multivariable analysis (RR = 1.57, *P* = 0.012). Severe obesity (i.e., BMI ≥ 40) showed a trend toward increasing risk but did not reach statistical significance (RR = 1.75, *P* = 0.065).

Discussion

Utilizing a large cohort of patients with COVID-19 in New York City, we found that patients with obesity were more likely to present with overt symptoms including fever, cough, and dyspnea and had about a doubling in risk of critical illness requiring ICU admission or leading to death when compared with individuals with normal weight. Although another study only found an increased risk for ICU admission in patients with obesity younger than 60 years of age, our study found this association to hold true across all age groups as well as in the subset of patients older than 60 years specifically (9). Additionally, in multivariable analysis, we saw an increased need for mechanical ventilation in patients with BMI ≥ 30, corroborating findings that were seen by others who found that those with a BMI > 35 had a higher risk for need for mechanical ventilation compared with those with BMI < 25 (6,7).

TABLE 4 Multivariable analysis of effect of weight on outcomes of ICU admission, intubation, and death adjusted for age, race/ethnicity, and troponin I level

	ICU admission			Intubation			Death		
Variable	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
BMI, kg/m^2									
18.5-30	Ref.			Ref.			Ref.		
<18.5	0.68	0.21-2.17	0.519	0.48	0.11-2.12	0.333	1.64	0.84-3.19	0.145
≥30	1.76	1.24-2.48	0.001	1.72	1.22-2.44	0.002	1.15	0.62-2.14	0.663
Age, y	1.01	1.01-1.02	0.123	1.01	0.99-1.01	0.430	1.06	1.04-1.08	<0.001
Race/ethnicity									
White/Caucasian	Ref.			Ref.			Ref.		
Black/African American	1.16	0.70-1.94	0.558	1.23	0.74-2.06	0.420	1.49	0.67-3.29	0.328
Asian	1.65	1.05-2.60	0.031	1.68	1.06-2.66	0.027	1.47	0.85-2.55	0.168
Other	1.17	0.77-1.77	0.457	1.22	0.8-1.84	0.357	0.57	0.24-1.37	0.206
Troponin I	1.07	0.96-1.20	0.201	1.08	0.96-1.21	0.183	1.12	1.05-1.19	0.001

Ref., reference.

The COVID-19 pandemic has resulted in significant global morbidity and mortality with almost 3 million confirmed cases at the time this manuscript was prepared (21). The disease itself has a wide spectrum of clinical symptoms and trajectory of outcomes, with some patients recovering without any complications, whereas others were afflicted by critical illness requiring ICU admission, prolonged hospitalization, and death (8). Previous studies have attempted to identify characteristics associated with a higher risk for complications in order to appropriately risk stratify patients. Reported data have shown that age and comorbidities such as diabetes, cardiovascular disease, and hypertension are associated with worse outcomes (2,3). As these conditions are associated with metabolic syndrome, it is possible that obesity is one of the underlying reasons for clinical deterioration among these patients.

It is not surprising that obesity is associated with worse outcomes in patients with COVID-19. Similar findings are described in patients with obesity infected with H1N1, the novel influenza A that emerged in 2009, for whom weight impacted risk for hospitalization, mechanical ventilation, and death, independent of other comorbidities (15,22,23). The adverse respiratory outcomes seen in COVID-19 and other respiratory infections are thought to be a result of a systemic inflammatory response, which is initiated by activation of CD4+ T lymphocytes into T-helper 1 cells that generate cytokines. These cytokines then induce CD14+ and CD16+ inflammatory monocytes to produce IL-6, IL-10, tumor necrosis factor alpha, and other proinflammatory factors, triggering a cytokine storm (24,25). The consequences of the aforementioned syndrome include apoptosis, vascular leakage, impaired viral clearance, altered tissue homeostasis, acute lung injury, cardiac dysfunction, and ultimately acute respiratory distress syndrome (26). As a result, elevated biomarkers of inflammation such as ferritin, lactate dehydrogenase, D-dimer, and C-reactive protein have been seen in severe COVID-19 (27,28). One link to obesity's impact on COVID-19 disease severity could be the underlying low-grade chronic inflammatory state that includes elevation of the same key inflammatory markers that are implicated in the cytokine storm. Although these inflammatory markers are typically elevated among all weight groups as seen in our study, the already existing chronic subclinical inflammatory state in patients with obesity may further exacerbate COVID-19 severity (29,30).

Additional possible explanations for a worse disease course in patients with obesity include altered immune function, including complement activation, risk of thrombosis, and changes in inherent lung function. Studies have also shown that patients with obesity have altered immune cell function compared with those with normal weight (9). This known disruption of host defense in obesity may further increase the risk for complications from COVID-19. The inflammation, platelet activation, and endothelial dysfunction seen in COVID-19 also predispose patients to thrombotic disease, both in the venous and arterial circulation (31). Although not evaluated directly in our study, thrombotic disease such as pulmonary embolism is thought to be another manifestation of severe disease and contributes to the need for ICU admission and increase in mortality. In obesity, enhanced rates of thrombosis secondary to elevated expression of prothrombotic molecules and increased platelet activation are commonly reported (32). This prothrombotic state may predispose patients with obesity with COVID-19 to experience thrombotic events associated with increased severity of disease and poor prognosis (10). Finally, elevated BMI has damaging effects on lung function, diminishing forced expiratory volume, and forced vital capacity (9). The change in respiratory mechanics directly affects a patient's ability to maintain adequate oxygenation. Importantly, our study supports this hypothesis with higher rates of obstructive sleep apnea and chronic pulmonary disease in patients with obesity and higher rates of cough and dyspnea as presenting symptoms compared with those without obesity as probable mediators of the adverse effects of obesity on outcomes.

In contrast to the biomechanical complications of obesity, the frequency of cardiometabolic diseases, such as hypertension, diabetes, and caridiovascular disease, did not increase with the progressive rise in BMI. This suggests that these diseases could be conferring risk for poor outcomes independent of BMI per se. These findings regarding the association of obesity with worse respiratory mechanics and chronic respiratory diseases in addition to elevated inflammatory markers regardless of BMI category in our study are interesting. Although the aforementioned important association of obesity with an inflammatory state, especially in presence of insulin resistance, should be considered, our results suggest that it might be the obesity itself and its effect on lung function, and not the associated insulin resistance and inflammation, that are the main drivers of poor outcomes in patients

with COVID-19. This is a potentially important distinction that merits further studies. Unfortunately, the lack of availability of data on hemoglobin A1C levels prevents us from further evaluation of these associations in the present study.

The observed adverse effect of Asian race on outcomes in our study does not necessarily suggest a genetic predisposition or a significant difference in COVID-19 pathophysiology based on race or ethnicity. As mentioned in the results, Asian patients were likely to present later after their first symptom compared with white/Caucasian patients, likely leading to worse outcomes. Furthermore, Asians were more likely to be older and underweight in our patient population. Although the multivariable analyses are adjusted for these variables, there is still a potential for residual confounding. Additionally, these results should be interpreted cautiously given the heterogeneity within the broad racial/ethnic categories used in this study. Before further studies are conducted on a representative sample of COVID-19 patients with careful adjustment for socioeconomic factors, the observed effect of race in this study could be considered a potential artifact of our specific patient population in New York.

Using a large cohort of hospitalized patients afflicted with COVID-19 at two hospitals located in New York City, the epicenter of the United States during the COVID-19 pandemic, we have demonstrated that obesity is strongly associated with ICU admission and death. The study's strengths lie in the large number of consecutively admitted patients and the depth of analyses that included information regarding clinical presentation and associated outcome metrics. The study also featured multivariable analysis that corrected for common confounding factors of disease severity among patients with obesity, including age and ethnicity. Limitations of this study include its retrospective design. Because the study lacked a control group and included only two hospitals, our findings will require further external validation in order to ensure generalizability to other populations. In addition, lack of power (type II error) when analyzing the BMI extremes (i.e., underweight and severe obesity) may have prevented us from accurately detecting differences in clinical outcomes among these specific patient groups.

Nevertheless, it is becoming increasingly apparent that obesity is a major risk factor for COVID-19 disease severity and that it clearly impacts disease presentation and critical care requirements. Continued prospective multicenter registries are warranted to further refine the relationship between weight and clinical outcomes, including focus on factors such as body composition or presence of frailty. Indeed, further assessment of these factors may enhance the ability to risk stratify this vulnerable population and thereby elucidate patients' prognoses and need for health care resources, providing benefit to providers and patients alike.**O**

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