Obesity

Obesity is Associated with Increased Risk for Mortality Among Hospitalized Patients with COVID-19

Natasha N. Pettit [1], *Erica L. MacKenzie*[2], *Jessica P. Ridgway*[3], *Kenneth Pursell*[3], *Daniel Ash*[4], *Bhakti Patel*[2], *and Mai T. Pho*[3]

Objective: Obesity has been identified as a risk factor for severe coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 virus. This study sought to determine whether obesity is a risk factor for mortality among patients with COVID-19.
Methods: The study was a retrospective cohort that included patients with COVID-19 between March 1 and April 18, 2020.
Results: A total of 238 patients were included; 218 patients (91.6%) were African American, 113 (47.5%) were male, and the mean age was 58.5 years. Of the included patients, 146 (61.3%) had obesity (BMI > 30 kg/m^2), of which 63 (26.5%), 29 (12.2%), and 54 (22.7%) had class 1, 2, and 3 obesity, respectively. Obesity was identified as a predictor for mortality (odds ratio [OR] 1.7 [1.1-2.8], $P = 0.016$), as was male gender (OR 5.2 [1.6-16.5], $P = 0.01$) and older age (OR 3.6 [2.0-6.3], $P < 0.0005$). Obesity (OR 1.7 [1.3-2.1], $P < 0.0005$) and older age (OR 1.3 [1.0-1.6], $P = 0.03$) were also risk factors for hypoxemia.
Conclusions: Obesity was found to be a significant predictor for mortality among inpatients with COVID-19 after adjusting for age, gender, and other comorbidities. Patients with obesity were also more likely to present with hypoxemia.

Obesity (2020) **28**, 1806-1810.

Study Importance

What is already known?

- Obesity has been found to be associated with hospital admission and increased need for mechanical ventilation among patients with COVID-19.

What does this study add?

- We found that obesity is associated with increased risk of mortality among patients admitted to the hospital with COVID-19. For every increase from one BMI category to the next, there was a 70% increased risk of mortality.

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

- Studies evaluating outcomes among patients with COVID-19 should factor in the potential contribution of obesity to untoward clinical outcomes. In clinical practice, it should be recognized that obesity is a risk factor for poor outcomes, and management of patients should take into consideration this information with respect to prioritization for higher level care or drug resources.

Introduction

Several risk factors for severe disease and poor outcomes in coronavirus disease 2019 (COVID-19) have been identified (1-7). Early reports from a Chinese series identified hypertension, diabetes, chronic pulmonary disease, and cardiovascular disease as the comorbidities most consistently associated with hospitalization, respiratory support, intensive care unit (ICU) admission, and death in patients with COVID-19. Subsequent reports from the United States and Europe suggested that patients with a higher BMI are at greater risk for hospital admission and severe disease requiring respiratory support (8,9).

Based on these reports outlining that many patients hospitalized for COVID-19 had BMI greater than 30 kg/m^2, we sought to evaluate whether obesity was associated with all-cause mortality in hospitalized patients with confirmed COVID-19 at a single academic medical center. We also examined the association between obesity and secondary outcomes including hypoxemia on hospital admission, ICU admission at any point, mechanical ventilation at any point, and hospital length of stay.

[1] Department of Pharmacy, University of Chicago Medicine, Chicago, Illinois, USA. Correspondence: Natasha N. Pettit (natasha.pettit@uchospitals.edu) [2] Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago Medicine, Chicago, Illinois, USA [3] Department of Medicine, Section of Infectious Diseases and Global Health, University of Chicago Medicine, Chicago, Illinois, USA. Correspondence: Mai T. Pho (mpho@bsd.uchicago.edu) [4] Department of Medicine, Section of Hospital Medicine, University of Chicago Medicine, Chicago, Illinois, USA.

 Received: 12 May 2020; **Accepted:** 21 June 2020; **Published online 25 August 2020. doi:10.1002/oby.22941**

TABLE 1 Baseline characteristics based on BMI category

	All patients, $N = 238$	Normal weight (BMI < 25), $n = 43$	Overweight (BMI: 25 to < 30), $n = 49$	Class 1 (BMI: 30 to < 35), $n = 63$	Class 2 (BMI: 35 to < 40), $n = 29$	Class 3 (BMI: ≥40), $n = 54$	*P* value
Age, mean (SD)	58.5 (17)	65.4 (19)	63.4 (18)	57.1 (13)	56.9 (14)	51.1 (17)	< 0.0001*
Male sex, *n* (%)	113 (47.5)	21 (48.8)	32 (65.3)	31 (49.2)	12 (41.4)	17 (31.5)	0.01
Race/ethnicity, *n* (%)							
African American	218 (91.6)	40 (93)	43 (87.8)	61 (96.8)	26 (89.7)	48 (88.9)	0.05
Caucasian	11 (4.6)	3 (7)	5 (10.2)	0 (0)	1 (3.5)	2 (3.7)	
Asian	3 (1.3)	0 (0)	1 (2)	1 (1.6)	1 (3.5)	0 (0)	
Multiple/unknown	6 (2.5)	0 (0)	0 (0)	1 (1.6)	1 (3.5)	4 (7.4)	
Hispanic	2 (0.8)	0 (0)	0 (0)	2 (3.2)	0 (0)	0 (0)	
Comorbidities, *n* (%)							
Hypertension	126 (52.9)	20 (46.5)	27 (55.1)	34 (54)	21 (72.4)	24 (44.4)	0.15
Diabetes	68 (28.6)	7 (16.3)	7 (14.3)	26 (41.3)	14 (48.3)	14 (25.9)	0.001*
Pulmonary disease[a]	63 (26.5)	9 (20.9)	12 (24.5)	9 (14.3)	11 (37.9)	22 (40.7)	0.01
Cardiovascular disease[b]	51 (21.4)	12 (27.9)	18 (36.7)	8 (12.7)	4 (13.8)	9 (16.7)	0.02
Kidney disease	17 (7.1)	7 (16.3)	3 (6.1)	3 (4.8)	2 (6.9)	2 (3.7)	0.19
Cancer	27 (11.3)	11 (25.6)	8 (16.3)	4 (6.4)	3 (10.3)	1 (1.9)	0.002*
HIV	5 (2.1)	2 (4.7)	1 (2)	0 (0)	1 (3.5)	1 (1.9)	0.56
Stroke	12 (5)	8 (18.6)	2 (4.1)	1 (1.6)	1 (3.5)	0 (0)	0.001*
Hyperlipidemia	21 (8.8)	3 (7)	6 (12.2)	1 (1.6)	7 (24.1)	4 (7.4)	0.01
VTE	10 (4.2)	3 (7)	2 (4.1)	0 (0)	0 (0)	5 (9.3)	0.08

[a]Asthma, chronic obstructive pulmonary disease, bronchitis, sarcoidosis, obstructive sleep apnea.
[b]Coronary artery disease, heart failure, valvular heart disease, arrhythmia.
*Significant after Bonferroni correction for multiple comparisons ($P < 0.0038$).
HIV, human immunodeficiency virus; VTE, venous thromboembolism.

Methods

All severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive patients admitted to the University of Chicago Medical Center, an 811-bed academic medical center on the south side of Chicago, between March 1, 2020, and April 18, 2020, who had completed their hospital course (including deceased patients) were included in the analysis. A diagnosis of COVID-19 required a positive SARS-CoV-2 test using the Roche Cobas SARS-CoV-2 reverse transcription-polymerase chain reaction high-throughput assay (Roche Diagnostics, Basel, Switzerland) or Xpert Xpress SARS-CoV-2 assay (Cepheid, Sunnydale, California) (10). BMI was analyzed as a categorical variable with values of BMI < 25 (normal weight), 25 to < 30 (overweight), 30 to < 35 (obesity, class 1), 35 to < 40 (obesity, class 2), or ≥ 40 (obesity, class 3) (11). Information was recorded on patient age, race/ethnicity, BMI, comorbidities, COVID-19–directed therapies (antivirals, interleukin-6 cytokine inhibitor therapy), admission oxygen requirement, and survival-to-discharge. Admission to the ICU, need for mechanical ventilation, and hospital length of stay were also documented. The primary analysis was the relationship between the primary endpoint of all-cause mortality and BMI group after multivariable adjustment for demographics and comorbidities. Secondary analyses included assessing the association of BMI group with oxygen requirement on hospital admission, length of stay, ICU admission at any point, and mechanical ventilation at any point.

Data are reported as median (interquartile range) or mean (SD) for continuous variables and as frequency (percentage) for categorical variables. Tests of significance for differences between obesity groups were performed using the Kruskal–Wallis test for continuous variables, and the Fisher's exact test for categorical variables. Effects of obesity on mortality and admission hypoxemia were assessed using a multivariable logistic regression with an additive effects model to adjust for comorbidity. A value of $P < 0.05$ was considered significant for covariates in the multivariable analysis, and bivariate analyses were also done for all covariates in the multivariable model. Bonferroni correction was applied to all univariate and bivariate P values to control the familywise error rate at 0.05. All statistical analyses were performed with Stata Software version 15.0 (StataCorp LLC, College Station, Texas). This project received a formal Determination of Quality Improvement status according to University of Chicago Medicine institutional policy. As such, this initiative was deemed to not involve human subjects research and was therefore not reviewed by the Institutional Review Board.

Results

A total of 238 patients with COVID-19 were included. Baseline characteristics, length of stay, and mortality rates for each of the five BMI categories are shown in Tables 1 and 2. The mean age was 58.5 years, with patients with class 3 obesity being significantly younger than patients with normal weight and with overweight (mean age for normal weight vs. overweight vs. class 3 obesity: 65.4 vs. 63.4 vs. 51.1; Kruskal–Wallis $P < 0.0001$; Dunn's pairwise test, $P = 0.0001$, or $P = 0.0003$ after Bonferroni correction). The majority of patients were African American (91.6%). The most common comorbidities were hypertension (52.9%), diabetes (28.6%), pulmonary disease (26.5%), and cardiovascular disease (21.4%). More patients in the higher obesity groups had diabetes.

TABLE 2 COVID-19 hospital course and outcomes

	All patients, $N = 238$	Normal weight (BMI< 25), $n = 43$	Overweight (BMI 25 to < 30), $n = 49$	Class 1 (BMI 30 to < 35), $n = 63$	Class 2 (BMI 35 to < 40), $n = 29$	Class 3 (BMI ≥ 40), $n = 54$	P value
Oxygen requirement on admission, *n* (%)							< 0.001*
RA	98 (41.2)	29 (67.4)	20 (40.8)	26 (41.3)	11 (37.9)	12 (22.2)	
1-5 L NC	120 (50.4)	13 (30.2)	22 (44.9)	33 (52.4)	13 (44.8)	39 (72.2)	
6 L + NC	12 (5)	0 (0)	4 (8.2)	1 (1.6)	4 (13.8)	3 (5.6)	
HFNC	4 (1.7)	0 (0)	3 (6.1)	1 (1.6)	0 (0)	0 (0)	
Intubated	4 (1.7)	1 (2.3)	0 (0)	2 (3.2)	1 (3.5)	0 (0)	
Receipt of any COVID-19–directed therapy, *n* (%)	166 (69.8)	24 (55.8)	34 (69.4)	48 (76.2)	21 (72.4)	39 (72.2)	0.26
ICU admission at any point, *n* (%)	65 (27.3)	10 (23.3)	17 (34.7)	16 (25.4)	8 (27.6)	14 (25.9)	0.77
Intubated at any point, *n* (%)	35 (14.7)	5 (11.6)	7 (14.3)	9 (14.3)	6 (20.7)	8 (14.8)	0.88
Length of stay, d, median (IQR)	5 (3-8)	6 (3-9)	5 (3-8)	5 (3-8)	4 (3-7)	5 (3-8)	0.84
Mortality, *n* (%)	24 (10.1)	3 (7)	7 (14.3)	5 (7.9)	4 (13.8)	5 (9.3)	0.70

*Significance after Bonferroni correction ($P < 0.0083$).
P values reported for Fisher exact or Kruskal–Wallis (length of stay only).
COVID-19, coronavirus disease 2019; HFNC, high-flow nasal cannula; ICU, intensive care unit; IQR, interquartile range; NC, nasal cannula; RA, room air.

TABLE 3 Bivariate and multivariable analysis for mortality and admission hypoxemia

	Bivariate analysis		Multivariable analysis	
Mortality variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Obesity	1.0 (0.8-1.4)	0.90	1.7 (1.1-2.8)	0.016
Age	2.4 (1.5-3.8)	<0.0005*	3.6 (2.0-6.3)	<0.0005
Gender	2.4 (1.0-5.9)	0.05	5.2 (1.6-16.5)	0.01
Hypertension	0.7 (0.3-1.7)	0.46	0.3 (0.1-0.9)	0.03
Diabetes	0.8 (0.3-2.2)	0.68	0.5 (0.2-1.7)	0.29
Pulmonary disease[a]	1.2 (0.5-2.9)	0.75	1.4 (0.4-4.6)	0.56
Cardiovascular disease[b]	1.3 (0.5-3.3)	0.65	0.7 (0.2-2.3)	0.53
Kidney disease	0.5 (0.1-4.2)	0.56	0.3 (0.03-2.9)	0.30
Cancer	2.3 (0.8-6.8)	0.13	2.7 (0.7-10.9)	0.17
Stroke	1.9 (0.4-9.0)	0.44	0.9 (0.1-6.5)	0.93
Hyperlipidemia	2.3 (0.7-7.6)	0.16	1.7 (0.4-7.0)	0.43
VTE	2.3 (0.5-11.7)	0.30	6.0 (0.6-61.0)	0.13
	Bivariate analysis		**Multivariable analysis**	
Admission hypoxemia variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Obesity	1.5 (1.2-1.8)	<0.0005*	1.7 (1.3-2.1)	<0.0005
Age	1.0 (0.9-1.3)	0.62	1.3 (1.0-1.6)	0.03
Gender	0.8 (0.5-1.3)	0.36	1.0 (0.6-1.8)	1.0
Hypertension	1.1 (0.7-1.9)	0.62	0.9 (0.5-1.7)	0.87
Diabetes	0.8 (0.5-1.5)	0.56	0.6 (0.3-1.2)	0.13
Pulmonary disease[a]	1.4 (0.8-2.6)	0.24	1.1 (0.6-2.2)	0.72
Cardiovascular disease[b]	1 (0.5-1.9)	1.0	1.0 (0.5-2.1)	1.0
Kidney disease	0.5 (0.2-1.3)	0.13	0.5 (0.2-1.5)	0.23
Cancer	0.6 (0.3-1.4)	0.23	0.9 (0.4-2.2)	0.80
Stroke	0.7 (0.2-2.2)	0.52	1.1 (0.3-4.0)	0.94
Hyperlipidemia	0.8 (0.3-1.8)	0.53	0.7 (0.3-1.8)	0.42
VTE	2.9 (0.6-14.0)	0.18	3.1 (0.6-17.3)	0.20

[a]Asthma, chronic obstructive pulmonary disease, bronchitis, sarcoidosis, obstructive sleep apnea.
[b]Coronary artery disease, heart failure, valvular heart disease, arrhythmia.
*Bivariate analysis significant after Bonferroni correction for multiple comparisons ($P<0.0042$).
OR, odds ratio; VTE, venous thromboembolism.

On hospital admission, 98 (41.2%) patients were on room air, 120 (50.4%) required 1 to 5 L of supplemental oxygen via nasal cannula, and 12 (5%) required oxygen supplementation of 6 L via nasal cannula or more. Four patients (1.7%) required high-flow nasal cannula, and an additional four patients (1.7%) were intubated on presentation. Patients with obesity were more likely to require supplemental oxygen on presentation compared with normal weight patients (32.6% of normal weight patients required supplemental oxygen vs. 58.7% in class 1 obesity, 62.1% in class 2 obesity, and 77.8% in class 3 obesity; Fisher's exact test, $P<0.001$).

Approximately 70% of patients received COVID-19–directed therapy (antivirals and/or immune modulators). About one-quarter of patients (27.3%) eventually required ICU admission, and 14.7% were intubated during their hospital course. The overall median length of stay was 5 days (interquartile range: 3-8), and the overall mortality rate was 10.1%. There were no significant differences between groups with respect to these outcomes.

Table 3 summarizes the results of the regression analyses for mortality and hypoxemia on admission. Obesity, male gender, and older age were associated with increased mortality. Significant predictors for hypoxemia on admission included obesity and age as well. Older age was the only variable associated with ICU admission after multivariable adjustment for other covariates (odds ratio [OR]: 1.4; 95% CI: 1.1-1.8; $P=0.01$, data not shown). Older age (OR: 1.6; 95% CI: 1.2-2.2; $P=0.01$) was associated with requirement for mechanical ventilation (data not shown). None of the variables assessed were significantly associated with length of stay after multivariable adjustment (data not shown).

Discussion

Our study shows that among hospitalized patients with COVID-19 infection, obesity was significantly associated with mortality after adjusting for age, gender, and other comorbidities. For every increase from one BMI category to the next, there was a 70% increased odds of mortality in the multivariable model. This finding provides further evidence that obesity is a key comorbidity in COVID-19 that may not

only predict severe disease requiring hospital admission, oxygen supplementation, or mechanical ventilation but may also predict increased mortality (8,9).

We also found that older age and male gender was significantly associated with mortality, as has elsewhere been reported (1-7). Although patients with obesity in our study were more likely to require supplemental oxygen on admission, there was no significant association between obesity and the need for ICU admission or mechanical ventilation throughout the hospital stay. This may reflect our small sample size or our institution's practice of using high-flow nasal cannula or helmet ventilation rather than intubation for respiratory support, when possible.

Our finding of an association between obesity and severe COVID-19 with poor clinical outcomes is congruent with what has been observed with other severe viral infections, including H1N1. Obesity was found to be associated with an increased risk of severe disease, hospitalization, and death during the 2009 H1N1 influenza pandemic (12,13). There is evidence that impaired lung mechanics and higher concentrations of proinflammatory molecules may both contribute to the propensity in patients with obesity to develop more severe complications from respiratory viral infections. Abdominal obesity restricts the movement of the diaphragm and chest wall, resulting in a reduction in functional residual capacity making mechanical ventilation more challenging (14,15). Patients with obesity are also known to have higher concentrations of proinflammatory cytokines and adipokines (e.g., leptin, tumor necrosis factor-alpha, monocyte chemoattractant protein-1, and interleukin-6) and lower anti-inflammatory adipokine concentrations (e.g., adiponectin), which can result in a dysregulated immune response (16).

Our study has several limitations, including small sample size and use of retrospective observational analysis. Additionally, >90% of the patients in our study population were African American, potentially limiting applicability of our results to other populations and limiting our ability to examine the relationship between race, obesity, and severe illness. As we did not evaluate cause of death, we were unable to assess whether there is a common pathway to mortality in patients with COVID-19 who have obesity.

Our findings add further weight to the evidence that patients with obesity are at greater risk for severe disease and mortality in COVID-19. Future studies reporting on the COVID-19 patient population should include obesity as a comorbidity to validate and account for these findings. Additional studies are also needed to further explore the relationship between race and obesity in severe disease.

Disclosure: The authors declared no conflict of interest.

References

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054-1062.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.
3. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically Ill patients with SARS-CoV2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475-481.
4. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA* 2020;323:1488-1494.
5. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020;323:1574-1581.
6. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020;323:1612-1614.
7. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle Region – case series. *N Eng J Med* 2020;382:2012-2022.
8. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. *Clin Infect Dis* 2020;71:896-897.
9. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring)* 2020;28:1195-1199.
10. Moran A, Beavis KG, Matushek SM, et al. The detection of SARS-CoV-2 using the Cepheid Xpert Xpress SARS-CoV-2 and Roche Cobas SARS-CoV-2 assays *J Clin Microbiol*. 2020;58:e00772-20. doi:10.1128/JCM.00772-20
11. Centers for Disease Control and Prevention. Defining adult overweight and obesity. https://www.cdc.gov/obesity/adult/defining.html. Accessed April 12, 2020 Updated June 30, 2020.
12. Morgan OW, Bramley A, Fowlkes A, et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A (H1N1) disease. *PLoS One* 2010;5:e9694. doi:10.1371/journal.pone.0009694
13. Van Kerhove MD, Vandemaele KA, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. *PLoS One* 2011;8:e1001053. doi:10.1371/journal.pmed.1001053
14. Peters U, Dixon AE. The effect of obesity on lung function. *Expert Rev Respir Med* 2018;12:755-767.
15. De Jong A, Verzilli D, Jaber S. ARDS in obese patients: specificities and management. *Crit Care* 2019;23:74. doi:10.1186/s13054-019-2374-0
16. Luzzi L, Radaelli MG. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. *Acta Diabetol* 2020;57:759-764.