ICU outcomes in Covid-19 patients with obesity

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To the Editor:

Obesity is a risk factor for severe pulmonary disease due to viral infections such as H1N1 influenza, but few studies have assessed the impact of obesity in Coronavirus disease 2019 (Covid-19).[1–5] International reports suggest an increased risk of severe Covid-19 disease with poorer outcomes correlating with higher body mass index (BMI).[6,7] The high prevalence of obesity in the United States (US) emphasizes the importance of characterizing this association.[8] This study explores the clinical relationship between obesity and Covid-19 in intensive care unit (ICU) patients admitted to a tertiary hospital.

Methods

Study design, setting, and data collection

We conducted a retrospective cohort study of adult patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who were consecutively admitted to the ICU from 1 March 2020 to 1 May 2020. The study was approved by the Institutional Review Board of Boston Medical Center. Data was extracted manually from electronic medical records by a quality-controlled protocol. Obesity was defined as BMI $\geq$30.

Primary outcomes included in-hospital mortality and need for invasive mechanical ventilation (IMV). Secondary outcomes were length of stay (LOS), ICU LOS, need for continuous renal replacement therapy (CRRT), and advanced acute respiratory distress syndrome (ARDS) therapies, including prone-positioning, neuromuscular blockade, and pulmonary vasodilators. Our institution recommended against the routine use of non-invasive ventilation.

Statistical analysis

We compared characteristics of patients with Covid-19 stratified by BMI into two groups: obese *versus* non-obese. Categorical variables are reported as counts and percentages. Normally distributed continuous variables are reported as mean and standard deviation (SD). Non-normally distributed variables are reported as median and interquartile ranges (IQR).

Logistic regression and Cox proportional-hazards analysis measured outcomes. For both methods, three models were examined: unadjusted, adjusted for demographic imbalances, and adjusted for demographic and comorbidity differences. Variables considered for adjustment were chosen based on clinical relevance and imbalances between groups evaluated at the $p < 0.1$ level.[9,10] Statistical analysis was performed using SAS v9.4 with $p < 0.05$ considered statistically significant, unless otherwise specified.

Results

Characteristics of Covid-19 patients

The demographics, clinical characteristics, therapies, and outcomes of 160 Covid-19 patients admitted to our ICU are summarized in Table 1. Obesity was present in 83 patients (52%) with mean age of 56.5 years and 55.4% (46 patients) male. The differences included older mean age (64.5 years) and higher percentage of men (76.6%) in the non-obese group. The most common comorbidities were hypertension and diabetes mellitus. There was a higher prevalence of asthma (17 patients;20.5%) and obstructive sleep apnea (19 patients;22.9%) within the obese population. At initial admission, higher median values of procalcitonin, ferritin, and D-dimer

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Table 1. Patient characteristics and laboratory values during ICU hospitalization.

	Non-obese (*n* = 77)	Obese (*n* = 83)	*p* value
Demographics			
Age, year, mean (SD)	64.5 (15.4)	56.5 (16.6)	*0.0019*
Male sex, *n* (%)	59 (76.6)	46 (55.4)	*0.0048*
BMI, mean (SD)	25.1 (3.4)	39.2 (10.4)	NA
Ethnicity *n* (%)	0.8855		
African American	38 (49.4)	45 (54.2)	NA
Hispanic	20 (26.0)	19 (22.9)	NA
Caucasian	18 (23.4)	17 (20.5)	NA
Other	1 (1.3)	2 (2.4)	NA
Co-morbidities *n* (%)			
Pulmonary disease	10 (13.0)	23 (27.7)	*0.0215*
Asthma	2 (2.6)	17 (20.5)	*0.0005*
COPD	8 (10.4)	7 (8.4)	0.6715
Hypertension	51 (66.2)	55 (66.3)	0.9967
Cardiac disease (CAD, CHF)	20 (26.0)	19 (22.9)	0.6500
Current or former smoker	32 (41.6)	29 (34.9)	0.3891
OSA on CPAP	5 (6.5)	19 (22.9)	*0.0037*
Diabetes mellitus	33 (42.9)	41 (49.4)	0.4701
Hypothyroidism	2 (2.6)	3 (3.6)	>0.999
Chronic kidney disease	20 (26.0)	19 (22.9)	0.6500
Immunocompromised status	1 (1.3)	5 (6.0)	0.2119
Malignancy	7 (9.1)	11 (13.3)	0.4051
Presenting lab values median (IQR)			
White blood cell count, 1000 per mm^3	8.1 (5.8–11.6)	7.1 (5.8–9.1)	0.1225
Lymphocyte count, 1000 per mm^3	12 (8–21)	17.5 (10–23)	*0.0304*
Ferritin, µg/l	1271 (469–2504)	605 (287–1534)	*0.0189*
D-Dimer, ng/ml	612 (300–1084)	267 (189–648)	*0.0010*
Fibrinogen, mg/dl	653 (448–800)	575 (503–714)	0.2548
LDH, U/l	402 (296–604)	427 (325–565)	0.6339
Procalcitonin, ng/ml	0.35 (0.15–0.91)	0.17 (0.08–0.48)	*0.0055*
Troponin, ng/ml	0.03 (0.01–0.10)	0.02 (0.01–0.05)	0.2624

(Continued)

Table 1. (Continued)

	Non-obese (*n* = 77)	Obese (*n* = 83)	*p* value
Peak lab values during hospitalization median (IQR)			
Creatinine, mg/dl	1.4 (0.8–2.1)	1.1 (0.9–1.7)	0.5395
Lactate, mmol/l	1.85 (1.4–2.9)	1.9 (1.4–2.8)	0.9695
AST, U/l	52 (37–85)	45 (33–64)	0.0830
ALT, U/l	37 (22–62)	30 (22–48)	0.3429
Total bilirubin, mg/dl	0.6 (0.4–0.8)	0.5 (0.4–0.7)	0.1241
Selected inpatient therapy *n* (%)			
Biologic medication	46 (60.5)	42 (51.2)	0.2393
Tocilizumab (IL-6 inhibitor)	23 (30.2)	17 (20.7)	0.1686
Anakinra (IL-1R antagonist)	7 (9.2)	9 (11.0)	0.7133
Sarilumab (IL-6 inhibitor)	16 (21.1)	16 (19.5)	0.8098
Remdesivir	1 (1.3)	1 (1.2)	>0.999
Self-prone (spontaneously breathing)	30 (39.0)	37 (44.6)	0.4718
Vasopressors	33 (42.9)	41 (49.4)	0.4071
Tracheostomy	4 (5.2)	3 (3.6)	0.7117
Outcomes			
In-hospital mortality	28 (36.4)	26 (31.3)	0.5010
IMV	34 (44.2)	52 (61.5)	*0.0285*
IMV Duration, days, median (IQR)	10.3 (5.1–14.3)	9.7 (3.6–15.9)	0.8439
Max PEEP, mmHg median (IQR)	10 (10–15)	14 (10–16)	*0.0223*
Prone-position	14 (18.2)	18 (21.7)	0.5797
Neuromuscular blockade	12 (15.6)	21 (25.3)	0.1291
Pulmonary vasodilator	12 (15.6)	20 (24.1)	0.1787
CRRT	8 (10.4)	11 (13.3)	0.5759
CRRT duration, days, median (IQR)	2.7 (0.85–3.85)	8.8 (1.8–12.4)	0.1071
LOS*	12.1 (6.7–20.8)	13 (7.9–19.6)	0.3917
ICU LOS**	3.0 (1.5–11.8)	5.9 (2.9–13.8)	0.2540

*Time from hospitalization to death (or discharge).
**Time from ICU entry to death (or discharge from the ICU).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRRT, continuous renal replacement therapy; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile ranges; LDH, lactate dehydrogenase; LOS, length of stay; OSA, obstructive sleep apnea; PEEP, positive end expiratory pressure.

Table 2. Odds of outcomes for obese *versus* non-obese hospitalized Covid-19 patients.

Outcome	Unadjusted		Adjusted (age, sex)		Adjusted (age, sex, asthma)	
	OR (95%CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
In-hospital mortality	0.8 (0.4, 1.5)	0.5010	1.1 (0.5, 2.3)	0.8161	1.2 (0.6, 2.6)	0.6374
IMV	2.0 (1.1, 3.8)	*0.0294*	1.9 (1.0, 3.7)	0.0662	1.6 (0.8, 3.1)	0.2107
Prone-position	1.2 (0.6, 2.7)	0.5801	1.3 (0.6, 2.9)	0.5724	1.3 (0.6, 3.1)	0.4951
Neuromuscular blockade	1.8 (0.8, 4.0)	0.1322	1.7 (0.8, 4.0)	0.1956	1.6 (0.7, 3.8)	0.2764
Pulmonary vasodilator	1.7 (0.8, 3.8)	0.1816	1.6 (0.7, 3.8)	0.2779	1.8 (0.8, 4.3)	0.1894
CRRT	1.3 (0.5, 3.5)	0.5767	1.6 (0.6, 4.6)	0.3720	1.4 (0.5, 4.2)	0.5428
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
LOS*	0.8 (0.5, 1.4)	0.3917	0.9 (0.5, 1.7)	0.8292	1.2 (0.7, 2.2)	0.4817
ICU LOS**	0.7 (0.4, 1.3)	0.2540	0.8 (0.4, 1.4)	0.3919	0.9 (0.5, 1.7)	0.8509

*Time from hospitalization to death (or discharge).
**Time from ICU entry to death (or discharge from the ICU).
CI, confidence interval; CRRT, continuous renal replacement therapy; HR, hazard ratio; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; OR, odds ratio; PEEP, positive end expiratory pressure.

and decreased lymphocytes were seen in the non-obese patients compared with obese patients. There were no significant differences between groups in regards to therapies received including immunotherapy, self-proning, and vasopressors.

Outcomes of Covid-19 patients

Table 1 shows the outcomes of in-hospital mortality, LOS, ICU LOS, need for and duration of IMV, positive end expiratory pressure (PEEP), advanced ARDS therapies, and CRRT frequency and duration. The obese and non-obese groups had 61.5% and 44.2% of patients, respectively, on IMV ($p = 0.0285$). Obese patients had a higher median peak PEEP (14 mmHg) compared with non-obese patients (10 mmHg; $p = 0.0223$).

Table 2 shows the unadjusted and adjusted odds for primary and secondary outcomes. In the unadjusted analysis, the obese group had twice the odds for IMV compared with the non-obese group ($p = 0.0285$). In adjusted models, the odds ratio (OR) indicated increased risk of obesity for IMV but was no longer statistically significant. The adjusted OR implied an increased risk within the obese group for developing the other primary and secondary outcomes without statistical significance.

Discussion

This study revealed that obese patients had twice the odds of requiring IMV compared with non-obese individuals infected with SARS-CoV-2. This association was attenuated following adjustment for sociodemographic and comorbid characteristics. There was no significant difference in in-hospital mortality and the secondary outcomes although there was a trend towards increased odds of worse outcomes in the obese population. We found that at baseline, non-obese patients presented with elevated levels of inflammatory markers and decreased lymphocytes.

Our investigation is one of the few studies to focus on obesity outcomes in ICU Covid-19 patients. We examined this population to expand on the established literature linking obesity to SARS-CoV-2.[6,7,11–13] Lighter *et al.*'s analysis of Covid-19 patients found that severe obesity had increased odds for ICU admission.[11] Our findings suggest that, once in the ICU, the clinical trajectory for obese patients continues to differ from the non-obese population. Obese patients more frequently require IMV and a high-PEEP strategy. Optimizing levels of PEEP is a well-documented approach for ARDS especially in obese patients.[14,15] Our findings that obese patients required higher levels of

PEEP is congruent with established evidence that PEEP mitigates the effect of obesity on respiratory mechanics, namely reduced lung compliance and decreased reserve. Advanced ARDS management strategies, however, were not required at a greater frequency in the obese patients.

Based on inflammatory markers alone, non-obese patients may have presented to the hospital with an advanced stage of Covid-19 or at a timepoint later in the disease course compared with the obese population. Alternatively, obese Covid-19 patients requiring ICU admission with a minimal inflammatory response may implicate other etiologies for the decompensation. Elevated levels of ACE2 enzyme expression in adipose tissue, an enzyme for which SARS-CoV-2 has increased affinity, may play a prominent role in the deterioration of obese patients with Covid-19.[16]

This analysis included one healthcare system, therefore limiting the generalizability. The sample size was too small to show a statistically significant impact of obesity in the presence of risk factors such as age and male sex.[9,10] The limited sample size precluded further stratification of patients by obesity class. Laboratory studies and ventilator parameters were not performed or recorded in all of the patients thereby insufficiently representing their clinical role and contributing to residual confounding. However, despite these limitations, our study provides an in-depth evaluation of obesity within Covid-19 disease, focusing on primary and secondary outcomes that characterize severity of illness. The epidemiologic and clinical data included in the investigation assesses multiple confounders while evaluating the study outcomes.

The association between obesity and Covid-19 in ICU patients is an important finding in the US where obesity prevalence is over 40%.[8] In reflecting on this relationship, we emphasize the need for larger-scale investigations that can closely examine the underlying mechanisms behind Covid-19 severity and patients with obesity.

Author contributions

RP was the lead and corresponding author who constructed the study design, coordinated analysis of the data, and was the primary writer of the manuscript.

MAG, IR, SJ, NM assisted RP in his tasks as lead, corresponding author as stated above.

JW analyzed and interpreted the patient data

CCR was a major contributor in regards to providing guidance and advice to the lead author while also helping interpret data and put together the final manuscript.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to personalized/individualized data but are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

This study involved human participants and human data; informed consent was waived as part of the IRB approval for the study

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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