Title

The effect of obesity on in-hospital mortality among patients with COVID-19 receiving corticosteroids

Journal

Diabetes & Metabolic Syndrome Clinical Research & Reviews, 16(1)

ISSN

1871-4021

Authors

So, Matsuo
Takahashi, Mai
Miyamoto, Yoshihisa
et al.

Publication Date

2022

DOI

10.1016/j.dsx.2021.102373

Peer reviewed

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 16 (2022) 102373

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

The effect of obesity on in-hospital mortality among patients with COVID-19 receiving corticosteroids

Matsuo So [a], Mai Takahashi [a], Yoshihisa Miyamoto [b], Yoshiko Ishisaka [a], Masao Iwagami [c], Yusuke Tsugawa [d, e], Natalia N. Egorova [f], Toshiki Kuno [a, g, *]

[a] Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, USA
[b] Division of Nephrology and Endocrinology, The University of Tokyo, Tokyo, Japan
[c] Department of Health Services Research, University of Tsukuba, Tsukuba, Japan
[d] Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine at UCLA, University of California, Los Angeles, USA
[e] Department of Health Policy and Management, UCLA Fielding School of Public Health, University of California, Los Angeles, USA
[f] Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, USA
[g] Division of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, New York, USA

ARTICLE INFO

Article history:
Received 7 December 2021
Received in revised form
15 December 2021
Accepted 16 December 2021

Keywords:
COVID-19
Obesity
Mortality
Acute kidney injury

ABSTRACT

Background and aims: Obesity has been reported to be one of the most frequent comorbidities in COVID-19 patients and associated with higher rates of in-hospital mortality compared to non-obese patients. Acute kidney injury (AKI) is also known to be a complication associated with obesity in critically-ill COVID-19 patients. We aimed to investigate whether obesity was associated with increased risk of in-hospital mortality and AKI among patients with COVID-19 treated with corticosteroids.

Methods: We utilized 9965 hospitalized COVID-19 patient data and divided patients who were treated with corticosteroids into 6 groups by body mass index (BMI) (less than 18.5, 18.5−25, 25−30, 30−35, 35−40, 40 kg/m^2 or greater). The association between BMI and in-hospital mortality and between BMI and incidence rate of AKI during admission among COVID-19 patients receiving corticosteroids were retrospectively investigated.

Results: There were 4587 study participants receiving corticosteroids (mean age 66.5 ± 15.5 years, men 56.6%, mean BMI 29.0 ± 7.2 kg/m^2). The smooth spline curve suggested a J-shape association between BMI and in-hospital mortality. Patients with BMI above 40 kg/m^2 exhibited a higher in-hospital mortality and higher incidence rate of AKI during admission compared to patients with BMI between 25 and 30 kg/m^2. The differences in in-hospital mortality and the rate of AKI were larger among patients with severe COVID-19.

Conclusions: Class III obesity was associated with high in-hospital mortality and AKI in patients with COVID-19 treated by corticosteroids. Clinicians must stay vigilant on the impact of class III obesity and development of AKI to disease trajectory of COVID-19 patients.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has resulted in 245,373,039 cases and 4,979,421 deaths worldwide as of October 29, 2021 [1]. Obesity has been reported to be one of the most frequent comorbidities in COVID-19 patients [2,3] and known to be associated with multiple cardiovascular comorbidities, acute kidney injury (AKI) in non-COVID-19 patients in intensive care unit (ICU), respiratory dysfunction, as well as impaired immune responses and hyper-inflammatory state [4–7]. The prevalence of obesity among COVID-19 patients requiring mechanical ventilation was higher than among patients with non-COVID-19 acute pulmonary diseases [8], and the mortality was significantly higher in obese patients compared to patients with normal weight

*Corresponding author. Division of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210th St, Bronx, NY, 10467−2401, USA.
E-mail addresses: so.matuo@gmail.com (M. So), mai.takahashi@mountsinai.org (M. Takahashi), ymiyamoto70@gmail.com (Y. Miyamoto), Ishisakayoshiko@gmail.com (Y. Ishisaka), iwa1983@gmail.com (M. Iwagami), ytsugawa@mednet.ucla.edu (Y. Tsugawa), Natalia.egorova@mountsinai.org (N.N. Egorova), tkuno@montefiore.org (T. Kuno).

https://doi.org/10.1016/j.dsx.2021.102373
1871-4021/

among COVID-19 patients [9].

A recent meta-analysis has shown that the proportion of obese people being hospitalized with COVID-19 was almost double compared to non-obese people, and mortality was approximately 50% higher [10]. Another meta-analysis showed that obesity was associated with an increased likelihood of presenting with more severe COVID-19 symptoms, developing acute respiratory distress syndrome, requiring hospitalization and ICU admission [11]. A study from a registry including 88 US hospitals showed that obese patients with BMI above 30 kg/m^2 had a higher risk of in-hospital death and mechanical ventilation and that class III obesity with BMI above 40 kg/m^2 was associated with an even higher risk of in-hospital mortality [12]. However, the proportion of patients who were receiving corticosteroids and interleukin-6 inhibitors, which are currently the mainstay treatment for moderate to severe COVID-19 patients [13], was underreported since these studies were conducted in the first wave of the pandemic. Therefore, it remains a concern whether patients' BMI is associated with in-hospital mortality among patients who were treated with corticosteroids.

In addition, development of AKI has been demonstrated to be one of the complications associated with obesity in critically ill patients without COVID-19 [14–16] and commonly observed in COVID-19 patients [17,18]. Several studies have shown that development of AKI during hospital stay is significantly associated with higher in-hospital mortality in COVID-19 patients [19,20]. However, the association between the degree of obesity and AKI in COVID-19 patients has not been reported.

In this context, we examined the association of in-hospital mortality and obesity in COVID-19 patients who were treated with corticosteroids and also examined the association between BMI and AKI to test the possibility of whether a higher incidence of AKI is a causal mechanism that is linking a high BMI with high in-hospital mortality.

2. Materials and methods

2.1. Subjects

In this retrospective study, we first identified 9965 hospitalized patients with laboratory-confirmed COVID-19 infection by using medical records at the Mount Sinai Health System in New York, USA, between March 1, 2020, and March 30, 2021 [21–24]. Confirmation of COVID-19 infection was based on a nasopharyngeal swab, which was tested using a reverse transcription polymerase chain reaction. We excluded 51 patients who were younger than 18 years old and 349 patients who were transferred to another facility. Then, we limited the patient population to those who received corticosteroids during admission (N = 4751). Finally, we excluded 125 patients who did not have information of BMI and 39 patients who had extreme BMI (<10 kg/m^2 or >60 kg/m^2), resulting in 4587 patients in the final cohort.

2.2. Baseline characteristics and treatments during admission

Comorbidities were characterized based on the International Classification of Disease (ICD) 10 codes. All vital signs and blood tests were recorded at the time of admission. The estimated glomerular filtration rate (eGFR) was reported by laboratory department in basic metabolic panel which was calculated by using The Modification of Diet in Renal Disease equation [25]. Continuous variables are presented as mean ± standard deviation or median [interquartile range] depending on the data distribution, and categorical variables were expressed as percentages. We also identified treatments that were provided during admission, including convalescent plasma, remdesivir, tocilizumab, therapeutic anticoagulation, and prophylactic anticoagulation.

2.3. The definition of obesity and categorization

The exposure of interest in this study was BMI. BMI was studied as a continuous variable in our first analysis using a smooth spline curve. We also divided the patients into 6 groups: BMI≤18.5 kg/m^2 (underweight), 18.5 < BMI≤25 kg/m^2 (normal weight), 25 < BMI≤30 kg/m^2 (overweight), 30 < BMI≤35 kg/m^2 (class I obesity), 35 < BMI≤40 kg/m^2 (class II obesity), BMI>40 kg/m^2 (class III obesity) [26].

2.4. Outcomes definition

The primary outcome of interest was in-hospital mortality, and the secondary outcome was the incidence of AKI observed during admission. AKI was defined according to kidney disease improving global outcomes (KDIGO) criteria stratified by the difference of creatinine level; stage 1: 1.5–1.9 times baseline or ≥0.3 mg/dL increase; stage 2: 2.0–2.9 times baseline; stage 3: 3 times or creatinine >4.0 mg/dL compared to baseline creatinine that was obtained on admission [25].

2.5. Statistical analysis

Differences in baseline characteristics between groups were evaluated, using the χ^2 test for categorical variables and *t*-test or Wilcoxon test for continuous variables depending on the distribution. A multivariate logistic regression model with a spline curve function was created to estimate the association between BMI and in-hospital mortality as well as association between BMI and incidence of AKI during admission. The following variables were included: age, sex, race, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension, diabetes mellitus, human immunodeficiency virus, cancer, atrial fibrillation, coronary artery disease, heart failure, peripheral artery disease, chronic viral hepatitis, alcoholic/non-alcoholic liver disease, estimated glomerular filtration rate (eGFR), blood urea nitrogen, white blood cell count, hemoglobin, d-dimer, vital signs, therapeutic anticoagulation, prophylactic anticoagulation, remdesivir, tocilizumab, and treatment with convalescent plasma, admission to intensive care unit, endotracheal intubation [27,28]. We also analyzed the association between the aforementioned six categories of BMI (the overweight category was used as a reference group) and in-hospital mortality as well as the association between BMI and the incidence of AKI during admission by adjusting covariates listed above. Finally, we investigated the association of BMI and in-hospital mortality in a subgroup of patients with severe COVID-19 infection, which was defined by the presence of ICU admission and/or endotracheal intubation.

All statistical analyses were performed using R (version 3.6.2, R). P-values <0.05 considered statistically significant.

This study was approved by the institutional review boards of Icahn School of Medicine at Mount Sinai (#2000495) and conducted in accordance with the principles of the Declaration of Helsinki. The waiver of patients' informed consent was also approved by the institutional review boards.

3. Results

Among 4587 study participants, patients with higher BMI were younger, had more comorbidities, including asthma, obstructive sleep apnea, and diabetes mellitus, higher serum lactate dehydrogenase, lower serum urea nitrogen, and received more treatments

Table 1
Baseline characteristics and treatments stratified by obesity category.

	Underweight (BMI<18.5) N = 170	Normal weight (18.5≦BMI<25) N = 1231	Overweight (25≦BMI<30) N = 1460	Class I obesity (30≦BMI<35) N = 932	Class II obesity (35≦BMI<40) N = 436	Class III obesity (BMI≧40) N = 358	p
Baseline Characteristics							
Age, year (mean, SD)	73.05 (16.37)	71.45 (14.76)	66.68 (14.67)	64.50 (14.57)	61.44 (15.38)	57.01 (15.26)	<0.001
Male, n (%)	100 (58.8)	753 (61.2)	903 (61.8)	480 (51.5)	209 (47.9)	147 (41.1)	<0.001
Race, n (%)							<0.001
WHITE	46 (27.1)	387 (31.4)	435 (29.8)	271 (29.1)	139 (31.9)	94 (26.3)	
BLACK	42 (24.7)	199 (16.2)	255 (17.5)	198 (21.2)	104 (23.9)	110 (30.7)	
HISPANIC	34 (20.0)	270 (21.9)	385 (26.4)	260 (27.9)	107 (24.5)	87 (24.3)	
ASIAN	25 (14.7)	146 (11.9)	97 (6.6)	34 (3.6)	8 (1.8)	7 (2.0)	
OTHERS	23 (13.5)	229 (18.6)	288 (19.7)	169 (18.1)	78 (17.9)	60 (16.8)	
Comorbidity, n (%)							
Asthma	5 (2.9)	50 (4.1)	100 (6.8)	67 (7.2)	38 (8.7)	49 (13.7)	<0.001
COPD	16 (9.4)	83 (6.7)	68 (4.7)	61 (6.5)	24 (5.5)	27 (7.5)	0.045
Hypertension,	59 (34.7)	484 (39.3)	526 (36.0)	341 (36.6)	161 (36.9)	141 (39.4)	0.48
Diabetes mellitus	22 (12.9)	288 (23.4)	332 (22.7)	220 (23.6)	120 (27.5)	100 (27.9)	0.002
Chronic Kidney Disease	20 (11.8)	170 (13.8)	153 (10.5)	92 (9.9)	53 (12.2)	35 (9.8)	0.040
Obstructive Sleep Apnea	2 (1.2)	7 (0.6)	18 (1.2)	36 (3.9)	28 (6.4)	30 (8.4)	<0.001
Obesity	0 (0.0)	11 (0.9)	59 (4.0)	115 (12.3)	112 (25.7)	126 (35.2)	<0.001
HIV	59 (34.7)	484 (39.3)	526 (36.0)	341 (36.6)	161 (36.9)	141 (39.4)	0.48
Cancer	25 (14.7)	132 (10.7)	134 (9.2)	79 (8.5)	32 (7.3)	21 (5.9)	0.005
Atrial Fibrillation	15 (8.8)	127 (10.3)	102 (7.0)	75 (8.0)	31 (7.1)	31 (8.7)	0.054
Heart Failure	17 (10.0)	128 (10.4)	115 (7.9)	63 (6.8)	45 (10.3)	32 (8.9)	0.036
Coronary Artery Disease	19 (11.2)	221 (18.0)	213 (14.6)	132 (14.2)	52 (11.9)	35 (9.8)	0.001
Peripheral Vascular Disease	6 (3.5)	84 (6.8)	66 (4.5)	32 (3.4)	14 (3.2)	14 (3.9)	0.002
Chronic Viral Hepatitis	3 (1.8)	15 (1.2)	17 (1.2)	8 (0.9)	3 (0.7)	2 (0.6)	0.69
Alcoholic, non-Alcoholic Liver Disease	1 (0.6)	33 (2.7)	44 (3.0)	26 (2.8)	19 (4.4)	10 (2.8)	0.23
Admission vital signs (median, IQR)							
Temperature max, °C	37.8 [37.4, 38.6]	38.0 [37.4, 38.8]	38.1 [37.4, 38.9]	38.0 [37.4, 38.9]	38.1 [37.5, 39.1]	38.2 [37.4, 39.1]	0.008
Heart Rate, beats/min	88.5 [78.0, 102.0]	94.0 [80.0, 106.0]	95.0 [82.0, 108.0]	95.0 [83.0, 108.0]	95.0 [86.0, 108.0]	99.0 [87.0, 112.0]	<0.001
Respiratory Rate, breaths/min	18.0 [18.0, 20.0]	20.0 [18.0, 22.0]	20.0 [18.0, 22.0]	20.0 [18.0, 22.0]	20.0 [18.0, 24.0]	20.0 [18.0, 23.8]	<0.001
Systolic Blood Pressure, mmHg	125 [113, 140]	129 [115, 145]	129 [116, 145]	132 [119, 147]	132 [119, 148]	130 [116, 146]	<0.001
Diastolic Blood Pressure, mmHg	72.0 [65.0, 83.0]	73.0 [65.0, 82.0]	75.0 [67.0, 84.0]	77.0 [68.0, 85.0]	77.0 [68.0, 86.0]	74.0 [65.0, 85.8]	<0.001
Oxygen Saturation, %	88.0 [76.3, 92.0]	88.0 [78.0, 91.5]	88.0 [78.0, 91.0]	88.0 [80.0, 91.0]	88.0 [79.0, 91.0]	88.0 [71.0, 91.0]	0.42
Admission laboratory tests (median, IQR)							
White Blood Cell, 10^3/μL	7.0 [5.0, 10.8]	7.3 [5.2, 10.5]	7.1 [5.3, 10.2]	7.1 [5.1, 10.0]	7.0 [5.3, 9.7]	6.8 [5.2, 9.8]	0.68
Hemoglobin, g/dL	12.3 [10.5, 13.8]	13.0 [11.2, 14.2]	13.4 [11.9, 14.5]	13.3 [11.9, 14.7]	13.2 [11.9, 14.6]	13.3 [11.9, 14.6]	<0.001
BUN, mg/dL	23.0 [15.3, 39.8]	21.0 [14.0, 36.0]	19.0 [13.0, 29.0]	17.0 [12.0, 28.0]	18.0 [11.5, 29.5]	15.0 [11.0, 25.0]	<0.001
Creatinine, mg/dL	0.93 [0.73, 1.40]	1.04 [0.77, 1.55]	1.00 [0.79, 1.45]	0.97 [0.76, 1.44]	1.00 [0.80, 1.57]	0.97 [0.76, 1.40]	0.066
eGFR, mL/min/1.73m2	71.9 [49.5, 101.6]	64.9 [41.7, 92.0]	70.5 [46.0, 92.3]	71.8 [45.4, 92.7]	67.4 [42.0, 93.4]	72.2 [46.4, 94.8]	0.011
AST, U/L	37.0 [25.0, 64.0]	41.0 [28.0, 63.0]	44.0 [29.0, 71.0]	42.0 [28.0, 64.5]	43.0 [28.0, 65.0]	40.0 [28.0, 63.0]	0.025
ALT, U/L	23.0 [15.0, 40.3]	28.0 [18.0, 44.0]	32.0 [20.0, 55.0]	30.0 [20.0, 54.0]	34.0 [21.0, 56.0]	31.0 [20.0, 49.0]	<0.001
CRP, mg/L	71.9 [28.8, 156.0]	94.1 [44.5, 172.4]	100.7 [45.6, 177.2]	95.8 [47.3, 172.8]	85.7 [47.1, 156.4]	107.7 [52.2, 168.6]	0.028
LDH, U/L	349.0 [251.0, 478.0]	386.0 [291.0, 3.0]	410.0 [305.0, 562.3]	414.0 [312.0, 523.0]	400.0 [312.0, 556.0]	427.0 [312.0, 587.0]	<0.001
Procalcitonin, ng/mL	2.05 (7.49)	1.39 (7.19)	1.92 (13.51)	1.11 (8.53)	0.45 (1.37)	1.40 (11.18)	0.150
D-dimer, μg/mL	1.77 [1.02, 3.05]	1.56 [0.84, 2.82]	1.25 [0.76, 2.29]	1.12 [0.65, 2.14]	1.16 [0.63, 2.01]	1.10 [0.62, 2.03]	<0.001
INR	1.1 [1.0, 1.3]	1.1 [1.0, 1.3]	1.1 [1.0, 1.2]	1.1 [1.0, 1.2]	1.1 [1.0, 1.2]	1.1 [1.0, 1.2]	<0.001
PTT, sec	34.2 [30.4, 38.7]	33.8 [30.0, 38.2]	32.9 [29.6, 37.1]	32.5 [29.5, 36.6]	32.4 [29.2, 35.5]	31.5 [28.7, 35.2]	<0.001
Treatments during admission, n (%)							
Therapeutic Anticoagulation, n (%)	67 (39.4)	528 (42.9)	646 (44.2)	431 (46.2)	216 (49.5)	155 (43.3)	0.111
Prophylactic Anticoagulation, n (%)	90 (52.9)	647 (52.6)	745 (51.0)	472 (50.6)	206 (47.2)	189 (52.8)	0.50
Remdesivir, n (%)	44 (25.9)	399 (32.4)	484 (33.2)	346 (37.1)	150 (34.4)	120 (33.5)	0.056
Tocilizumab, n (%)	6 (3.5)	48 (3.9)	74 (5.1)	43 (4.6)	35 (8.0)	32 (8.9)	<0.001
Convalescent plasma, n (%)	29 (17.1)	222 (18.0)	307 (21.0)	202 (21.7)	101 (23.2)	73 (20.4)	0.12

Abbreviations: SD = standard deviation, IQR = interquartile range, BMI = body mass index, COPD = chronic obstructive pulmonary disease, HIV = human immunodeficiency virus, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, AST = asparate aminotransferase, ALT = alanine aminotransferase, CRP = c reactive protein, LDH = lactate dehydrogenase, INR = international normalized ratio, PTT = partial thromboplastin time.

Table 2
In-hospital events and outcomes by BMI category.

	Underweight (BMI<18.5) N = 170	Normal weight (18.5≦BMI<25) N = 1231	Overweight (25≦BMI<30) N = 1460	Class I obesity (30≦BMI<35) N = 932	Class II obesity (35≦BMI<40) N = 436	Class III obesity (BMI≧40) N = 358	p
AKI, n (%)	52 (30.6)	407 (33.1)	435 (29.8)	257 (27.6)	136 (31.3)	124 (34.6)	0.061
Acute VTE, n (%)	3 (1.8)	12 (1.0)	16 (1.1)	11 (1.2)	4 (0.9)	3 (0.8)	0.94
Cerebral Infarction, n (%)	1 (0.6)	14 (1.1)	9 (0.6)	3 (0.3)	1 (0.2)	2 (0.6)	0.20
Intracerebral Hemorrhage, n (%)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0.73
ICU admission, n (%)	37 (21.8)	324 (26.3)	435 (29.8)	272 (29.2)	150 (34.4)	130 (36.3)	<0.001
Endotracheal Intubation, n (%)	22 (12.9)	210 (17.1)	290 (19.9)	178 (19.1)	95 (21.8)	90 (25.1)	0.003
Death, n (%)	57 (33.5)	359 (29.2)	399 (27.3)	220 (23.6)	108 (24.8)	105 (29.3)	0.015

Abbreviations: BMI = body mass index, AKI = acute kidney injury, VTE = venous thromboembolism, ICU = intensive care unit.

with tocilizumab. ICU admission rate and endotracheal intubation rate were highest among the BMI≥40 kg/m^2 group (Tables 1 and 2).

The smooth spline curve suggested a J curve association in BMI and in-hospital mortality, and the inflection point was located within the overweight category group (i.e., BMI between 25 and 30 kg/m^2) (Fig. 1). Compared to overweight patients with BMI between 25 and 30 kg/m^2, class III obesity patients with BMI>40 kg/m^2 had significantly higher adjusted in-hospital mortality. Underweight patients with BMI≤18.5 kg/m^2, normal-weight patients with 18.5 < BMI≤25 kg/m^2, class I obesity patients with 30 < BMI≤35 kg/m^2, class II obesity patients with 35 < BMI≤40 kg/m^2 showed no significant difference in in-hospital mortality compared to overweight patients with BMI between 25 and 30 kg/m^2 (Table 3).

As to the secondary outcome, a smooth spline curve also suggested a J curve association in BMI and the in-hospital incidence of AKI (Fig. 2). Class III obesity patients with BMI above 40 kg/m^2 had a significantly higher risk of in-hospital AKI compared to overweight patients with BMI between 25 and 30 kg/m^2 (OR [95% CI]: 1.52 [1.06−2.18], P = 0.024) (Table 3). Notably, patients with AKI (N = 1,411, 30.8%) had significantly higher mortality compared to those without (60.1% versus 12.6%, P < 0.001).

In a subgroup analysis among severe COVID-19 patients who required ICU admission and/or endotracheal intubation, class III obesity patients with BMI above 40 kg/m^2 had significantly higher in-hospital mortality compared to overweight patients with BMI between 25 and 30 kg/m^2 (Supplemental Table 1).

4. Discussion

Using large data of hospitalized COVID-19 patients receiving corticosteroids, we found that patients with class III obesity (BMI≥40 kg/m^2) had significantly higher in-hospital mortality, as well as a higher incidence of in-hospital AKI, compared to overweight (25≤BMI<30 kg/m^2) patients. These findings were consistent with most of the previous reports, which reportedly included fewer patients who were treated with corticosteroids, the current standard treatment for COVID-19. Our findings highlight the importance of obesity as a meaningful risk factor of in-hospital mortality and development of AKI even among the COVID-19

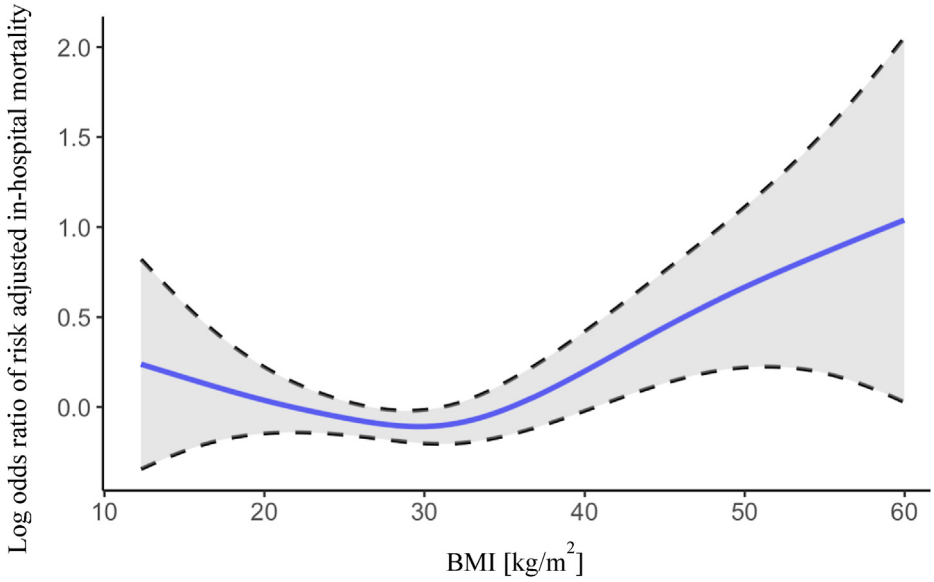

Fig. 1. The association of BMI with in-hospital mortality in COVID-19 patients with corticosteroids treatment. Adjusted for age, sex, race, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension, diabetes mellitus, human immunodeficiency virus, cancer, atrial fibrillation, coronary artery disease, heart failure, peripheral artery disease, chronic viral hepatitis, alcoholic/non-alcoholic liver disease, estimated glomerular filtration rate (eGFR), blood urea nitrogen, white blood cell count, hemoglobin, d-dimer, vital signs, therapeutic anticoagulation, prophylactic anticoagulation, remdesivir, tocilizumab, and treatment with convalescent plasma, admission to intensive care unit, endotracheal intubation.

Table 3
The adjusted odds ratio for in-hospital mortality and incidence of acute kidney injury by body mass index category in COVID-19 patients with corticosteroids treatment.

	Adjusted* OR of in-hospital mortality[95%CI]	P value	Adjusted* OR of AKI [95%CI]	P value
Reference; Overweight (25≤BMI<30, kg/m^2)	1		1	
Underweight (BMI <18.5)	1.37 [0.83−2.24]	0.22	1.16 [0.70−1.89]	0.57
Normal weight (18.5≤BMI<25)	1.03 [0.80−1.32]	0.83	1.19 [0.94−1.51]	0.15
Class I obesity (30≤BMI<35)	0.92 [0.69−1.24]	0.60	0.96 [0.74−1.26]	0.79
Class II obesity (35≤BMI<40)	1.16 [0.78−1.71]	0.47	0.99 [0.69−1.40]	0.95
Class III obesity (BMI≥40)	1.90 [1.26−2.86]	<0.001	1.52 [1.06−2.18]	0.024

Abbreviations: OR = odds ratio, CI = confidence interval, BMI = body mass index.
*Adjusted for age, sex, race, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension, diabetes mellitus, human immunodeficiency virus, cancer, atrial fibrillation, coronary artery disease, heart failure, peripheral artery disease, chronic viral hepatitis, alcoholic/non-alcoholic liver disease, estimated glomerular filtration rate (eGFR), blood urea nitrogen, white blood cell count, hemoglobin, d-dimer, vital signs, therapeutic anticoagulation, prophylactic anticoagulation, remdesivir, tocilizumab, and treatment with convalescent plasma, admission to intensive care unit, endotracheal intubation.

patients treated by corticosteroids.

The higher mortality observed in COVID-19 patients with obesity has been well-documented in multiple observational studies; however, the proportion of corticosteroids use among these patients was underreported. Despite under treatment with corticosteroids which was expected to counteract and suppress the immune reaction, class III obesity (BMI≥40 kg/m^2) was associated with higher mortality in our study. This was also observed in a subgroup analysis among patients with severe COVID-19 infection requiring ICU admission and/or endotracheal intubation and the effect was much larger. There are several possible explanations for these findings. It is known that adipose tissue, especially visceral fat, is associated with chronic inflammation resulting from immune cell activity in dysfunctional visceral adipose tissue. Multiple proinflammatory adipokines such as tumor necrosis factor-α and interleukin (IL)-6 are known to be produced by visceral adipose tissue [29]. COVID-19 infection-induced hyper-inflammatory state can be more prominent in obese patients due to their predisposition to hyper-ferritinemia as well [30], thus obesity with higher BMI level is supposedly related to a higher level of cytokine release to the extent that corticosteroids or other anti-inflammatory agents are not sufficient to suppress the response. This also leads to a question if the fixed dose of corticosteroids are equally effective in patients with higher body weight. Obesity is also related to immobility and dyspnea at baseline, which tends to mask the worsening course of respiratory status leading to late presentation to the hospital when the inflammatory response is already too severe to control with immunosuppressants. Another consideration is that other factors related to obesity can play more roles leading to higher mortality, such as dysfunctional lung mechanics due to reduction in lung volume, increased airway resistance and impaired diaphragmatic mobility, which may be considered to be an explanation for larger effect of class III obesity to COVID-19 patients who required ICU admission and/or endotracheal intubation and ventilator management.

We used overweight group as a reference to compare the outcomes of other groups because the inflection point was located within the range of overweight group. While this finding leads to a question whether or not overweight is protective, none of the previous studies have reported the protective effect of being overweight compared to normal weight or obesity groups. A recent retrospective study showed both underweight and obesity are associated with increased risk of developing acute lung injury and secondary infection compared to normal weight [31]. This study also demonstrated that low serum albumin or low serum prealbumin level were more common in underweight and obesity

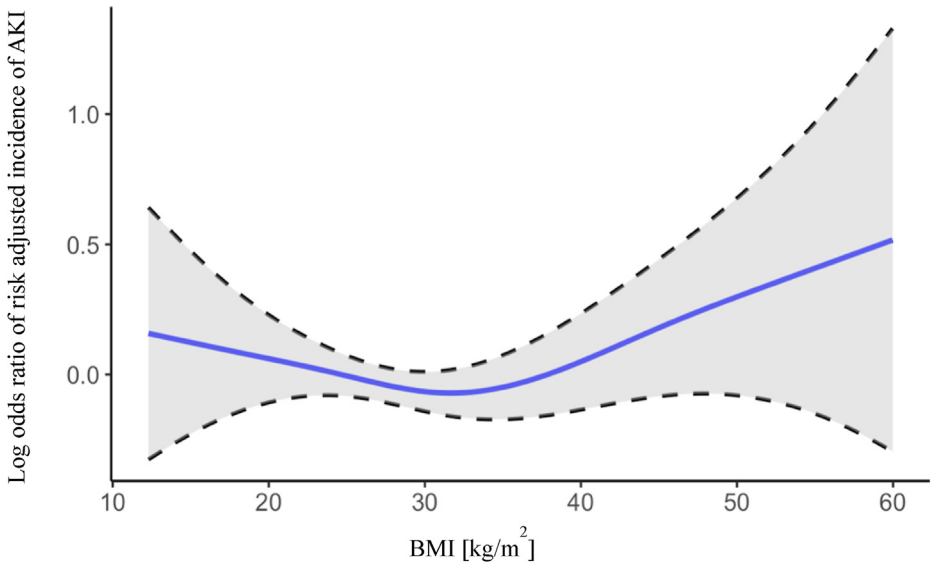

Fig. 2. The association of BMI with the incidence of acute kidney injury in patients with corticosteroids treatment. Adjusted for age, sex, race, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension, diabetes mellitus, human immunodeficiency virus, cancer, atrial fibrillation, coronary artery disease, heart failure, peripheral artery disease, chronic viral hepatitis, alcoholic/non-alcoholic liver disease, estimated glomerular filtration rate (eGFR), blood urea nitrogen, white blood cell count, hemoglobin, d-dimer, vital signs, therapeutic anticoagulation, prophylactic anticoagulation, remdesivir, tocilizumab, and treatment with convalescent plasma, admission to intensive care unit, endotracheal intubation.

group. Our study results showed J-curve association between BMI and in-hospital mortality. Although the adjusted in-hospital mortality did not show significant difference between underweight patients and other BMI groups, only a small portion of patients were categorized in underweight (170/4587) group and they were older, had higher rate of cancer and received less treatments. This result suggests that underweight patients were more malnourished and leading to numerically higher in-hospital mortality.

The risk of developing AKI during COVID-19 admission was higher in class III obesity compared to overweight patients in our study. Several mechanisms of developing AKI in patients with obesity have been reported. Obese patients often suffer from obesity-related hypoventilation and sleep apnea, leading to corpulmonale and subsequent venous congestion [32]. Further, venous congestion is experimentally related to increased renal venous pressure and decreased urine formation [33]. The pathophysiology of COVID-19-associated AKI is reported to include acute tubular injury, collapsing glomerulopathy, and endothelial injury or thrombotic microangiopathy in studies of renal histology [34]. A significantly higher incidence of AKI in class III obesity was presumably mediating the association between the higher BMI and higher in-hospital mortality. Clinicians should be aware of the significance of class III obesity in paitents' COVID-19 disease course and stay vigilant on kidney function and use of nephrotoxic agents.

Our study has limitations. First, this is a retrospective analysis, and unmeasured confounders such as baseline mobility and respiratory functions, patients' vaccination status, doses of glucocorticoid therapy and others are potentially present and unadjusted which resides in the study design itself. In addition, the timing of symptom onset in COVID-19 was not taken into account and patients with severe obesity may present later to hospitals. Finally, this is a large but single-center study in New York City, and therefore, the generalizability of the study findings to other states in the US and other countries should be examined in future studies.

5. Conclusions

Among patients who received corticosteroids for COVID-19, class III obesity was associated with higher in-hospital mortality and a higher incidence rate of AKI during admission compared to overweight patients. This implicates that clinicians should keep in mind class III obesity patients with COVID-19 has a higher risk of death and AKI during hospital stay and be more cautious about using nephrotoxins or contrast imaging studies. The pathophysiology behind the relation between obesity and mortality among COVID-19 patients is multifactorial and warrants further studies.

Author contributions

TK, MT, NE, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: TK. Data Curation: TK, MT, NE. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: SM. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: TK, MT. Administrative, technical, or material support: NE. Study supervision: NE.

Ethical approval and consent to participate

This study was approved by the institutional review boards of Icahn School of Medicine at Mount Sinai (#2000495) and conducted in accordance with the principles of the Declaration of Helsinki. The waiver of patients' informed consent was also approved by the institutional review boards.

Declaration of competing interest

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2021.102373.

References

[1] World Health Organization. COVID-19 dashboard. Accessed October 29th, 2021. Available from https://covid19.who.int/.
[2] Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, Liu XQ, Chen RC, Tang CL, Wang T, Ou CQ, Li L, Chen PY, Sang L, Wang W, Li JF, Li CC, Ou LM, Cheng B, Xiong S, Ni ZY, Xiang J, Hu Y, Liu L, Shan H, Lei CL, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Cheng LL, Ye F, Li SY, Zheng JP, Zhang NF, Zhong NS, He JX. China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020 May 14;55(5):2000547.
[3] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, , the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA 2020 May 26;323(20):2052–9.
[4] Falagas ME, Athanasoulia AP, Peppas G, Karageorgopoulos DE. Effect of body mass index on the outcome of infections: a systematic review. May Obes Rev 2009;10(3):280–9.
[5] Carbone F, La Rocca C, De Candia P, Procaccini C, Colamatteo A, Micillo T, De Rosa V, Matarese G. Metabolic control of immune tolerance in health and autoimmunity. Semin Immunol 2016 Oct;28(5):491–504.
[6] Lecube A, Hernández C, Pelegrí D, Simó R. Factors accounting for high ferritin levels in obesity. Nov Int J Obes 2008;32(11):1665–9.
[7] Druml W, Metnitz B, Schaden E, Bauer P, Metnitz PG. Impact of body mass on incidence and prognosis of acute kidney injury requiring renal replacement therapy. Intensive Care Med 2010 Jul;36(7):1221–8.
[8] Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M. LICORN and the Lille COVID-19 and obesity study group. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity 2020 Jul;28(7):1195–9.
[9] Hussain A, Mahawar K, Xia Z, Yang W, El-Hasani S. Obesity and mortality of COVID-19. Meta-analysis. Obes Res Clin Pract 2020 Jul-Aug;14(4):295–300.
[10] Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, Alsukait RF, Alluhidan M, Alazemi N, Shekar M. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. Obes Rev 2020 Nov;21(11):e13128.
[11] Zhang X, Lewis AM, Moley JR, Brestoff JR. A systematic review and meta-analysis of obesity and COVID-19 outcomes. Sci Rep 2021 March 30;11(1):7193.
[12] Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, Rosenblatt A, Walchok J, Omar W, Khera R, Hegde AA, Drazner MH, Neeland IJ, Grodin JL. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: results from the American heart association COVID-19 cardiovascular disease registry. Circulation 2021 January 12;143(2):135–44.
[13] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, Cavalcanti AB, Dequin PF, Du B, Emberson J, Fisher D, Giraudeau B, Gordon AC, Granholm A, Green C, Haynes R, Heming N, Higgins JPT, Horby P, Jüni P, Landray MJ, Le Gouge A, Leclerc M, Lim WS, Machado FR, McArthur C, Meziani F, Møller MH, Perner A, Petersen MW, Savovic J, Tomazini B, Veiga VC, Webb S, Marshall JC. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 2020 Oct 6;324(13):1330–41.
[14] Danziger J, Chen KP, Lee J, Feng M, Mark RG, Celi LA, Mukamal KJ. Obesity, acute kidney injury, and mortality in critical illness. Crit Care Med 2016 Feb;44(2):328–34.
[15] Soto GJ, Frank AJ, Christiani DC, Gong MN. Body mass index and acute kidney injury in the acute respiratory distress syndrome. Crit Care Med 2012 Sep;40(9):2601–8.
[16] Wang B, Li D, Gong Y, Ying B, Cheng B, Sun L. Body mass index is associated with the severity and all-cause mortality of acute kidney injury in critically ill patients: an analysis of a large critical care database. BioMed Res Int 2021 June 28:6616120. 2021.
[17] Gutiérrez-Abejón E, Martín-García D, Tamayo E, Álvarez FJ, Herrera-Gómez F. Clinical profile, pharmacological treatment, and predictors of death among

hospitalized COVID-19 patients with acute kidney injury: a population-based registry analysis. Front Med 2021 Jun 15;8:657977.
[18] Sullivan MK, Lees JS, Drake TM, Docherty AB, Oates G, Hardwick HE, Russell CD, Merson L, Dunning J, Nguyen-Van-Tam JS, Openshaw P, Harrison EM, Baillie JK. ISARIC4C Investigators. Acute kidney injury in patients hospitalised with COVID-19 from the ISARIC WHO CCP-UK Study: a prospective, multicentre cohort study. Nephrol Dial Transplant 2021 Oct 18. gfab303.
[19] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020 May;97(5):829–38.
[20] Ng JH, Hirsch JS, Hazzan A, Wanchoo R, Shah HH, Malieckal DA, Ross DW, Sharma P, Sakhiya V, Fishbane S, Jhaveri KD, Northwell Nephrology COVID-19 Research Consortium. Outcomes among patients hospitalized with COVID-19 and acute kidney injury. Am J Kidney Dis 2021 Feb;77(2). 204-215.e1.
[21] Kuno T, Takahashi M, Egorova NN. The association between convalescent plasma treatment and survival of patients with COVID-19. J Gen Intern Med 2021 May 13:1–4.
[22] So M, Steiger DJ, Takahashi M, Egorova NN, Kuno T. The characteristics and outcomes of critically Ill patients with COVID-19 who received systemic thrombolysis for presumed pulmonary embolism: an observational study. J Thromb Thrombolysis 2021 May 8:1–7.
[23] Kuno T, So M, Takahashi M, Egorova NN. U shape association of hemoglobin level with in-hospital mortality for COVID-19 patients. J Thromb Thrombolysis 2021 Jul 2:1–5.
[24] So M, Kabata H, Takahashi M, Egorova NN, Kuno T. The association of inhaled corticosteroid before admission and survival of patients with COVID-19. J Aerosol Med Pulm Drug Deliv 2021 Aug;34(4):265–7.
[25] Acosta-Ochoa I, Bustamante-Munguira J, Mendiluce-Herrero A, Bustamante-Bustamante J, Coca-Rojo A. Impact on outcomes across KDIGO-2012 AKI criteria according to baseline renal function. J Clin Med 2019 Aug 28;8(9):1323.
[26] Kuno T, Tanimoto E, Morita S, Shimada YJ. Effects of bariatric surgery on cardiovascular disease: a concise update of recent advances. Front Cardiovasc Med 2019 July 10;6:94.
[27] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020 May 22;369:m1966.
[28] Mehta RM, Bansal S, Bysani S, Kalpakam H. A shorter symptom onset to remdesivir treatment (SORT) interval is associated with a lower mortality in moderate-to-severe COVID-.
[29] Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006 Oct;6(10):772–83.
[30] Demeulemeester F, de Punder K, van Heijningen M, van Doesburg F. Obesity as a risk factor for severe COVID-19 and complications: a review. Cells 2021 Apr 17;10(4):933.
[31] Ye P, Pang R, Li L, Li HR, Liu SL, Zhao L. Both underweight and obesity are associated with an increased risk of coronavirus disease 2019 (COVID-19) severity. Front Nutr 2021 Oct 8;8:649422.
[32] Marik PE, Desai H. The emergent malignant obesity hypoventilation syndrome: a new critical care syndrome. Author reply. J Intensive Care Med. 2013 May-Jun;28(3):200.
[33] Winton FR. The influence of venous pressure on the isolated mammalian kidney. J Physiol 1931 June 6;72(1):49–61.
[34] Akilesh S, Nast CC, Yamashita M, Henriksen K, Charu V, Troxell ML, Kambham N, Bracamonte E, Houghton D, Ahmed NI, Chong CC, Thajudeen B, Rehman S, Khoury F, Zuckerman JE, Gitomer J, Raguram PC, Mujeeb S, Schwarze U, Shannon MB, De Castro I, Alpers CE, Najafian B, Nicosia RF, Andeen NK, Smith KD. Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. Am J Kidney Dis 2021 Jan;77(1):82–93. e1.