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Association between Obesity and Length of COVID-19 Hospitalization: Unexpected Insights from the American Heart Association National COVID-19 Registry

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Background: The mechanism for possible association between obesity and poor clinical outcomes from Coronavirus Disease 2019 (COVID-19) remains unclear.
Methods: We analyzed 22,915 adult COVID-19 patients hospitalized from March 2020 to April 2021 to non-intensive care using the American Heart Association National COVID Registry. A multivariable Poisson model adjusted for age, sex, medical history, admission respiratory status, hospitalization characteristics, and laboratory findings was used to calculate length of stay (LOS) as a function of body mass index (BMI). We similarly analyzed 5,327 patients admitted to intensive care for comparison.
Results: Relative to normal BMI subjects, overweight, class I obese, and class II obese patients had approximately half-day reductions in LOS (–0.469 days, $P<0.01$; –0.480 days, $P<0.01$; –0.578 days, $P<0.01$, respectively).
Conclusion: The model identified a dose-dependent, inverse relationship between BMI category and LOS for COVID-19, which was not seen when the model was applied to critically ill patients.

Key words: Obesity, Hospitalization, Length of stay, COVID-19

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INTRODUCTION

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, obesity has been linked to poor clinical outcomes from the disease.[1] Despite conflicting conclusions regarding mortality, several analyses have suggested that higher body mass index (BMI) may increase risk of hospitalization, supplemental oxygen requirement, and intensive care unit (ICU) admission.[1-3] Obesity coincides with many comorbidities independently associated with worse health outcomes in acute illness, yet the physiological mechanisms making obese patients more susceptible to COVID-19 remain uncertain. Adiposity-derived immunosuppression, increased thrombogenicity, and inflammatory hyperreactivity have all been postulated mediators of this phenomenon.[4,5] However, the most immediate explanation is that obese patients have reduced respiratory reserve from lower diaphragmatic contractility, smaller airways (making intubation more challenging), and stiffer pulmonary compliance from greater thoracic wall mass, predisposing them to increased hypoxia and mechanical ventilation requirement.[4,6]

Given the extreme stress placed upon inpatient resources during COVID-19 surges, hospital length of stay (LOS) is a metric of great interest to both acute care clinicians and hospital administrators.[7,8]

Furthermore, as newer variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been associated with lower virulence and mortality than those in earlier phases of the COVID-19 pandemic, alternate markers of disease severity such as LOS are becoming increasingly meaningful as clinical endpoints. Thus, to explore the contribution of non-respiratory effects of obesity on hospitalization-based outcomes, we assessed the association of BMI with LOS in patients admitted to non-ICU care with lower initial respiratory distress.

METHODS

The American Heart Association (AHA) National COVID-19 Registry, a retrospective cohort of adults admitted with COVID-19 to any of over 130 participating U.S. hospitals across 30 states, was used to query index admissions between March 2020 and April 2021 for patients aged ≥ 18 years initially hospitalized to non-intensive care to address confounding from immediate respiratory compromise.[9] A total of 22,915 patients met these criteria and were included in the analysis, and 5,327 patients initially admitted to the ICU were additionally analyzed as a comparison group for the regression model. We described patient and hospital characteristics by BMI group (classified as a categorical variable with levels of underweight [BMI < 18.5 kg/m^2], normal [BMI 18.5 to < 25 kg/m^2], overweight [25 to < 30 kg/m^2], class I obesity [30 to < 35 kg/m^2], class II obesity [35 to < 40 kg/m^2], and class III obesity [≥ 40 kg/m^2]). To quantify the association between LOS and BMI category, we applied a multivariable Poisson regression model with identity link and reported ß coefficients for difference in LOS with 95% confidence intervals (CIs). Model covariates were chosen a priori based on clinical relevance and > 80% completeness to reflect patient-, hospital-, and physician-level characteristics. Patient characteristics included age, sex, medical insurance source, medical history (preexisting malignancy, diabetes, cerebrovascular, respiratory, and cardiac comorbidities), admission respiratory rate, oxygenation status, admission month, thromboembolic event complication, hemodialysis requirement, intubation requirement, and baseline serum laboratory results (hemoglobin, white blood cell count, absolute lymphocyte count, platelet count, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine, and interleukin-6). Hospital characteristics included transfer from another hospital, hospital size, and region. As physician caseloads have been shown to affect LOS, we also included a measure of hospital COVID-19 burden (if ≥ 20% of beds were occupied by COVID-19 patients on day of admission).[7] Multiple imputation was performed for missing data. Analyses were performed using R v3.6.2 (R Foundation, Vienna, Austria) and the AHA Precision Medicine Platform (https://precision.heart.org). Enrollment in the registry was approved or review waived by the Institutional Review Board at each participating site, including Stanford Health Care, where it was exempted as quality improvement.

RESULTS

In univariable analysis, higher BMI class was associated with younger age and greater hypoxia on admission. Elevated BMI category patients had lower prevalence of cancer and cerebrovascular disease, higher prevalence of diabetes and respiratory disorders, and no difference in cardiac diseases. There were no differences in incident thrombotic events or hemodialysis. Increasing BMI category was associated with increased intubation requirement but greater disposition alive (Table 1).

In multivariable regression, overweight and obese patients showed a statistically significant dose-dependent relationship between increasing BMI category and decreasing LOS (overweight: –0.469 days [95% CI, –0.708 to –0.231; $P < 0.01$]; class I obesity: –0.480 days [95% CI, –0.733 to –0.226, $P < 0.01$]; class II obesity: –0.578 days [95% CI, –0.852 to –0.304; $P < 0.01$]) (Table 2). Only class III obesity did not follow this trend (–0.320 days; 95% CI, –0.615 to –0.024; $P = 0.034$) but still represented a shorter LOS relative to the normal weight category. The same analysis was applied to patients initially admitted to the ICU, which showed no significant association between BMI and LOS (Table 2).

DISCUSSION

Our analysis revealed a counterintuitive inverse trend between BMI and COVID-19 LOS when controlling for respiratory compromise via restriction to non-ICU-level patients and adjusting for respiratory rate, oxygenation status, and mechanical ventilation re-

Table 1. Patient characteristics by BMI category in non-ICU-level patients

Characteristic	Overall (n=22,915)	Underweight (n=400)	Normal (n=4,980)	Overweight (n=6,681)	Class I obesity (n=5,121)	Class II obesity (n=2,910)	Class III obesity (n=2,823)	*P*	SMD*
Age (yr)	63.00 (49.00–76.00)	76.00 (59.75–85.25)	72.00 (58.00–83.00)	65.00 (52.00–77.00)	61.00 (48.00–72.00)	58.00 (46.00–69.00)	54.00 (42.00–65.00)	<0.001	0.472
Sex								<0.001	0.183
Woman	10,977 (48)	211 (53)	2,297 (46)	2,722 (41)	2,418 (47)	1,591 (55)	1,738 (62)		
Unknown	5	0	1	2	1	0	1		
Medical history									
Cancer	2,719 (12)	71 (18)	771 (15)	842 (13)	555 (11)	263 (9.0)	217 (7.7)	<0.001	0.145
Diabetes mellitus	8,081 (35)	91 (23)	1,472 (30)	2,222 (33)	1,901 (37)	1,196 (41)	1,199 (42)	<0.001	0.197
Cerebrovascular disease	2,143 (9.4)	68 (17)	607 (12)	654 (9.8)	420 (8.2)	209 (7.2)	185 (6.6)	<0.001	0.148
Respiratory disease	4,577 (20)	108 (27)	921 (18)	1,157 (17)	956 (19)	638 (22)	797 (28)	<0.001	0.134
Cardiac disease	14,767 (64)	270 (68)	3,206 (64)	4,158 (62)	3,276 (64)	1,941 (67)	1,916 (68)	<0.001	0.058
Respiratory rate at admission (breaths/min)								<0.001	0.081
Mean±SD	20.66±4.93	20.63±5.25	20.19±4.87	20.63±4.92	20.71±4.79	20.90±5.07	21.22 ±5.04		
Unknown	234	4	45	72	51	32	30		
Oxygen level at admission								<0.001	0.227
SpO_2 ≥95% on room air	8,702 (42)	177 (51)	2,199 (49)	2,571 (43)	1,861 (41)	999 (38)	895 (35)		
SpO_2 <95% on room air	6,391 (31)	56 (16)	1,123 (25)	1,882 (31)	1,551 (34)	910 (35)	869 (34)		
On supplementary oxygen	5,452 (27)	112 (32)	1,150 (26)	1,550 (26)	1,145 (25)	706 (27)	789 (31)		
Unknown	2,370	55	508	678	564	295	270		
New thrombotic event								0.011	0.031
Yes	686 (3.0)	11 (2.8)	110 (2.2)	217 (3.3)	157 (3.1)	99 (3.4)	92 (3.3)		
Unknown	132	1	18	48	32	22	11		
New hemodialysis or CRRT								0.001	0.073
Yes	458 (2.0)	2 (0.5)	72 (1.5)	126 (1.9)	116 (2.3)	72 (2.5)	70 (2.5)		
Unknown	131	1	18	46	31	23	12		
Level of care during stay								<0.001	0.085
Stayed on floor	19,301 (84)	349 (87)	4,336 (87)	5,625 (84)	4,266 (83)	2,392 (82)	2,333 (83)		
Transfer to ICU without intubation	1,428 (6.2)	24 (6.0)	291 (5.8)	392 (5.9)	330 (6.4)	193 (6.6)	198 (7.0)		
Intubated	2,186 (9.5)	27 (6.8)	353 (7.1)	664 (9.9)	525 (10)	325 (11)	292 (10)		
Disposition								<0.001	0.123
Discharged alive	20,852 (91)	341 (85)	4,404 (88)	6,042 (90)	4,737 (93)	2,687 (92)	2,641 (94)		
Length of stay (day)									
Mean±SD	8.51±10.31	9.02±8.25	9.05±11.42	8.48±9.82	8.39±10.17	8.11±9.64	8.22±10.52	0.001	0.048
Median (IQR)	5.44 (3.30–9.86)	6.41 (3.50–11.84)	5.65 (3.34–10.64)	5.45 (3.30–10.22)	5.41 (3.29–9.49)	5.34 (3.26–9.41)	5.36 (3.32–9.33)	<0.001	0.048
Range	0.01–237.22	0.16–72.60	0.02–233.20	0.08–161.24	0.01–135.42	0.19–200.36	0.07–237.22		

Values are presented as median (IQR) or number (%) unless otherwise indicated.
*SMD is a measure of effect size. Magnitude of effect is small if SMD=0.2, medium if SMD=0.5, and large if SMD=0.8.
BMI, body mass index; ICU, intensive care unit; SMD, standardized mean difference; SD, standard deviation; CRRT, continuous renal replacement therapy; IQR, interquartile range.

Table 2. Association between BMI category and LOS in non-ICU-admitted and ICU-admitted patients

Multivariable model	Overall	Underweight	Normal	Overweight	Class I obesity	Class II obesity	Class III obesity
Non-ICU admitted							
Number	22,915	400	4,980	6,681	5,121	2,910	2,823
Difference - ß in LOS (day)		0.368	Ref	–0.469	–0.480	–0.578	–0.320
95% CI (day)		–0.311 to 1.047	Ref	–0.708 to –0.231	–0.733 to –0.226	–0.852 to –0.304	–0.615 to –0.024
P		0.253	Ref	<0.01	<0.01	<0.01	0.034
ICU-admitted							
Number	5,327	92	1,011	1,497	1,196	707	824
Difference - ß in LOS (day)		–0.868	Ref	0.199	0.328	0.235	0.072
95% CI (day)		–2.355 to 0.620	Ref	–0.463 to 0.862	–0.397 to 1.053	–0.651 to 1.122	–0.760 to –0.904
P		0.253	Ref	0.555	0.375	0.601	0.865

Table 2 presents the results of the Poisson regression model of the relationship between BMI category and length of hospital stay (ß coefficient in days) for patients initially admitted to a non-intensive care setting alongside those initially admitted to an ICU, with normal weight as the reference. The model was adjusted for age, sex, medical insurance source, medical history (pre-existing malignancy, diabetes, cerebrovascular, respiratory, and cardiac comorbidities), admission respiratory rate, oxygenation status, admission month, transfer from another hospital, hospital size, hospital region, hospital COVID-19 burden (if ≥20% of beds were occupied by COVID-19 patients on admission day), thromboembolic event complication, hemodialysis requirement, intubation requirement, and baseline serum laboratory results (hemoglobin, white blood cell count, absolute lymphocyte count, platelet count, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine, and interleukin-6).
BMI, body mass index; LOS, length of stay; ICU, intensive care unit; CI, confidence interval; COVID-19, coronavirus disease 2019.

quirement. This suggests the most potent drivers of increased length of hospitalization and intensive care use associated with obesity may involve ventilatory compromise, rather than other proposed mechanisms such as the inflammatory or thrombotic sequelae of increased adiposity. Furthermore, these findings support the "obesity paradox" of non-critical COVID-19, a phenomenon positing that higher BMI may correlate with improved outcomes.[2,10,11] Though this paradox is often described for critical illness, it has been observed in non-critical illness such as pulmonary embolism and pneumonia as well as multiple chronic illnesses.[12-14] In COVID-19, it is possible that obesity provides a metabolic reserve that may benefit less ill hospitalized patients but is overwhelmed by poor respiratory mechanics in sicker patients.[2,15] Interestingly, the trend in LOS did not remain linear at the highest obesity category, suggesting that negative effects of more extreme obesity may counteract possible benefits of metabolic reserve. Notably, an analysis of the AHA registry early in the pandemic found an association between BMI category and mortality and mechanical ventilation, but not LOS.[16] Our study, which was restricted to patients who did not initially require ICU care or ventilation, adds insight into a possible mechanism for these findings.

A limitation of our analysis is the use of a registry, which may select for higher disease severity. Future prospective analyses of obese individuals with COVID-19 should examine pulmonary function testing and serum inflammatory markers to further elucidate the mechanisms of this phenomenon.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study concept and design: WJC and AYC; acquisition of data: WJC, CGO, FR, and NR; analysis and interpretation of data: WJC, AYC, and YW; drafting of the manuscript: WJC and AYC; critical

revision of the manuscript: all authors; statistical analysis: YW; obtained funding: FR; administrative, technical, or material support: WJC, AYC, CGO, NA, FR, and NR; and study supervision: WJC, AYC, and NR.

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