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Original article

COVID-19 patients with obesity at risk for worse outcomes despite younger age and fewer inflammatory derangements

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a viral pulmonary infection that can progress to cytokine storm syndrome because of widespread dysregulated inflammatory response. Many patients at risk for severe COVID-19 manifestation have been identified as those with preexisting conditions of pulmonary origin, as well as conditions that impair appropriate immune response, such as obesity.

Objectives: The aim of this study is to describe the manifestation, clinical course, and inflammatory biomarker milieu of COVID-19 in patients with obesity.

Setting: University Hospital Philadelphia, Pennsylvania.

Methods: In this retrospective cohort study, 600 patients who were positive for COVID-19 were stratified by World Health Organization (WHO) obesity class and their presenting symptoms, disease biomarkers, demographics, and outcomes (intubation rate, intensive care unit [ICU] admission, length of stay [LOS], and mortality) were investigated.

Results: Age was inversely related to obesity class; patients of obesity class III presented 12.9 years younger than patients of normal weight ($P < .0001$). Initial ferritin lab values were negatively correlated with increasing obesity class ($P = .0192$). Normal or near-normal lymphocyte profile was noted in patients with obesity compared with patients without obesity ($P = .0017$). Patients with obesity had an increased rate of ICU admission ($P = .0215$) and increased length of stay ($P = .0004$), but no differences in intubation rate ($P = .3705$) or mortality ($P = .2486$).

Conclusion: Patients with obesity were more likely to present to the hospital at a younger age, with reduced levels of COVID-19 related biomarker disturbances, and increased LOS and ICU admission rates, although were not at increased risk for mortality. (Surg Obes Relat Dis 2021;17:1722–1730.)

Key words: COVID-19; SARS-CoV-2; Obesity; Body mass index; Inflammation; Ferritin; D-dimer; Lymphopenia

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Coronavirus disease 2019 (COVID–19) is caused by the coronavirus SARS-CoV-2 virus and was classified as a global pandemic on March 11, 2020. At the time of writing, the number of cases has skyrocketed, with the World Health Organization (WHO) reporting over 21 million cases and more than 761,000 deaths globally. As of September 2020, the United States bears the greatest burden of the disease with over 5.2 million cases and more than 167,000 deaths [1].

The presentation of COVID-19 can vary widely among patients. While a significant number of patients infected with SARS-CoV-2 are asymptomatic or minimally symptomatic with cold-like complaints, others progress to hypoxemic respiratory failure, cytokine storm syndrome, and multi-organ system failure [2]. Evidence of hyperinflammatory states and resulting cell injury can be observed via elevations of ferritin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Derangements in these markers of inflammation, as well as with presence of lymphopenia, are indicators of severe COVID-19 disease [3]. D-dimer, a fibrin degradation product signaling prothrombotic states, has also been shown to correlate with disease severity [4]. Measuring these biomarkers in patients with COVID-19 has become more common in clinical practice with the aim of identifying those at greatest risk for severe disease.

The manifestation of COVID-19 in patients with obesity has been of particular interest in the United States, where the prevalence of obesity – defined as body mass index (BMI) $\geq$30 kg/m^2 – is 42.4%, and the prevalence of class III obesity (BMI $\geq$40 kg/m^2) is reported at 9.2% [5]. Multiple early reports have described increasing trends of younger patients with obesity requiring hospitalization, and in some cases, increased risk of mortality [6,7]. However, little has been described in terms of the clinical course of these patients as they present for hospitalization for COVID-19. This is an important area of investigation, as patients with obesity are a prevalent subgroup of the US population. People with obesity represent a demographic that is younger in age and with more disease burden compared with age-matched peers without obesity [8]. In the United States, the obesity rates are highest among people aged 20–39 (40.0%) and 40–59 (44.8%) [5]. People with obesity also often have baseline underlying respiratory deficits, such as asthma, obesity hypoventilation syndrome, obstructive sleep apnea, and pulmonary hypertension, in addition to the diseases which constitute metabolic syndrome, such as type 2 diabetes (T2D), hypertension, and hyperlipidemia [9,10]. Patients with obesity also exhibit basal levels of chronic inflammation, altered immune response, increased inflammatory response, and abnormal T-cell response, which further increases their risk profile [11]. With a respiratory disease such as COVID-19, which has been shown to negatively affect people with underlying lung problems as well as those with hypertension and diabetes, it is important to characterize how this disease presents and manifests in people with obesity, who are often affected by several of these high-risk co-morbidities.

The objective of this study was to characterize the clinical presentation of COVID-19 in patients with obesity, investigate their outcomes, and describe their early presenting symptoms and inflammatory biomarker trends during their clinical course.

Methods

Study design and patient population

This retrospective, observational, cohort study was performed at 2 hospitals within a North Philadelphia academic medical institution. Shortly after the WHO declared COVID-19 a global pandemic, the infrastructure at this institution was reorganized to separately house patients admitted from emergency departments identified as "high risk" for COVID-19 as well as those confirmed COVID-19 positive by nasopharyngeal swab testing. Patients identified as being admitted to these designated COVID-19 wards from March 15 through May 6, 2020, and diagnosed with laboratory confirmed COVID-19 by reverse transcriptase polymerase chain reaction (RT-PCR) testing were included. We excluded 6 patients for whom BMI data were not available in their electronic medical record (EMR). At the time of analysis, the cohort of 600 included patients had a disposition of either discharge from inpatient hospitalization or inpatient death. This study was approved by our institutional review board (protocol 27050).

Data extraction

We reviewed EMR and laboratory results for patients who had been admitted to COVID-19–designated wards with COVID-19 positive test results. We extracted data on demographics, co-morbidities, presenting symptoms, initial vital measurements, initial oxygen requirement in the emergency department (ED), maximum oxygen requirement during hospitalization, initial laboratory data, length of stay, need for intubation due to hypoxemic respiratory failure or an inability to protect airway (e.g, altered mental status secondary to hypercarbia or hypoxia), intensive care unit (ICU) admission, ICU hours, need for initiation of renal replacement therapy, thromboembolic events, vasopressor requirement, and death. The data obtained from the electronic medical records were independently validated by a secondary chart review by institutional review board–approved physicians and researchers.

Outcomes

The primary clinical outcome was in-hospital mortality. Secondary clinical outcomes included ICU admission, incidence of invasive mechanical ventilation, and length of stay (LOS). Inflammatory biomarkers were analyzed as additional variables of interest. Patients were classified into 5

groups based on BMI: normal weight BMI<25 kg/m^2, overweight BMI 25–30 kg/m^2, class I obesity BMI 30–35 kg/m^2, class II obesity BMI 35–40 kg/m^2, class III obesity BMI ≥40 kg/m^2.

Statistical analysis

Continuous data were expressed with means (standard deviation [SD]) or medians (interquartile range). Categorical data were expressed as absolute and relative frequency. Normally distributed continuous variables were compared with the use of two-sample *t*-test or analysis of variance. Non-normally distributed lab parameters were compared using Wilcoxon rank-sum test or Kruskal-Wallis test. Categorical variables were compared with the use of the Pearson chi-square test. Clinical outcomes and inflammatory markers of clinical interest underwent secondary multivariate analysis. Multivariable linear regression for inflammatory markers and multivariable logistic regression for binary outcomes were used to analyze the relationship to BMI after adjusting for age, gender, and race. A second model was developed adjusting for ICU admission status as an indicator of disease severity. In all multivariate analysis models, BMI and age were treated as continuous variables, and gender, race, and ICU admission status were treated as categorical variables. All statistical tests were two-tailed, and $P < .05$ were considered to indicate statistical significance. All statistical analyses were performed with the use of SAS 9.4 (SAS Institute, Cary, NC).

Results

Between March 15 and May 6, 2020, 600 patients with laboratory-confirmed COVID-19 and subsequent immediate admission to inpatient COVID-19 designated wards were included in the study. The mean BMI was 31.5 kg/m^2 (SD 7.8) with 301 (50.2%) classified with obesity. Our cohort represented a wide BMI range spanning from 15.1 kg/m^2–62 kg/m^2. The mean age of the cohort was 58.9 (SD 15.2) years with significant differences between the BMI groups (BMI <25 kg/m^2: 63.9; BMI 25–30 kg/m^2: 61.5; BMI 30–35 kg/m^2: 58.7; BMI 35–40 kg/m^2: 54.4; BMI ≥40 kg/m^2: 51.0; $P < .0001$) (Fig. 1). Women comprised 45.4% (273) of our cohort and had a higher rate of obesity than men. The racial/ethnic composition of the cohort was 56.8% (341) Black, non-Hispanic, 30.7% (184) Hispanic, and 8.2% (49) White, Non-Hispanic. Coronary artery disease, congestive heart failure, and hypertension were present in 14.2%, 18.5%, and 67.0% of the cohort, respectively. Chronic obstructive pulmonary disease (COPD) was present in 10.2% of patients and 14.7% had asthma. With regard to renal disease, 18.5% had a history of chronic kidney disease and 9% had end-stage renal disease (ESRD). T2D was present in 42.4% of our patients. Lastly, 21.9% had a psychiatric diagnosis, 14.0% had a history of substance abuse, and 6% had a history of malignancy. Detailed baseline demographic and comorbidity characteristics are presented in Table 1.

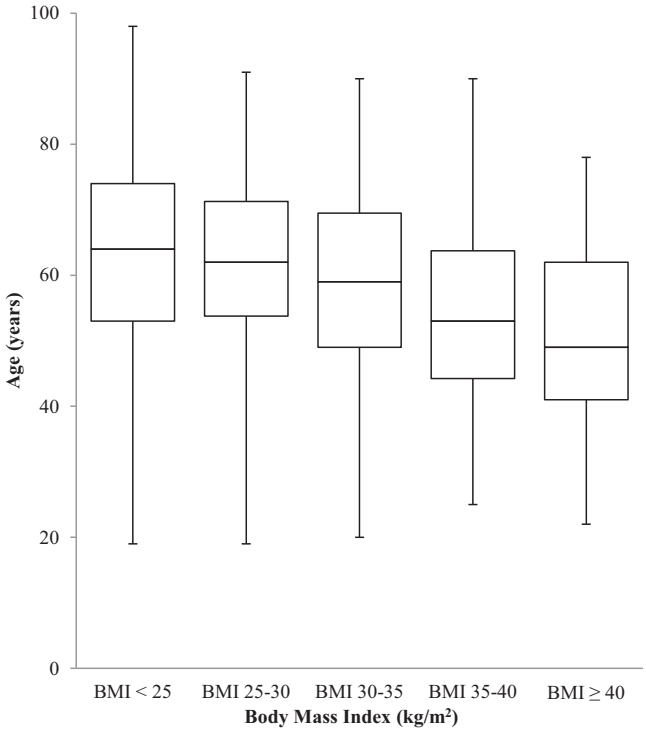

Figure 1. Age distribution by body mass index

The most common presenting symptoms were fever (55.8%), cough (57.7%), and dyspnea (60.2%). Upon presentation to the ED, 31.7% required supplemental oxygen via nasal cannula, 10.0% required high flow nasal therapy (HFNT), 2.2% required non-invasive mechanical ventilation (NIMV), 3.0% required intubation and mechanical ventilation, and 53.2% were maintained on room air. Detailed symptoms and signs data are presented in Table 2.

Lymphopenia was common with 55.5% of patients presenting with an absolute lymphocyte count <1.0 K/mm^3, and a median lymphocyte relative frequency of 16.2%. D-dimer was elevated in our cohort, with a median of 840.0 ng/mL. A negative correlation was identified between ferritin and BMI (Fig. 2). Detailed laboratory findings are presented in Table 3. Absolute lymphocyte count and percent lymphocyte were significantly positively correlated with BMI ($P = .0032$, $P = .0017$) in multivariate analysis with adjustment for age, sex, and race. Ferritin was significantly negatively correlated with BMI ($P = .0192$). D-dimer was not significantly associated with BMI ($P = .5225$), and trends seen in univariate analysis were driven by age ($P < .001$) (Model 1, Supplementary Table 1).

Analysis was performed examining the relationship between admission inflammatory biomarker levels, BMI, and ICU admission as an indicator of disease severity (Model 2, Supplementary Table 2). Lower lymphocyte percent and higher ferritin and D-dimer levels were significantly

Table 1
Demographics and co-morbidities

	All patients	BMI group					*P**
	n = 600	BMI <25	BMI 25–30	BMI 30–35	BMI 35–40	BMI ≥40	
		(n = 115)	(n = 184)	(n = 138)	(n = 80)	(n = 83)	
Sex, n (%)							<.001
Women	273 (45.5)	41 (35.7)	66 (35.9)	70 (50.7)	47 (58.8)	49 (59.0)	
Men	327 (54.5)	74 (64.3)	118 (64.1)	68 (49.3)	33 (41.3)	34 (41.0)	
Age, y							<.001
Mean (SD)	58.9 (15.2)	63.9 (16.0)	61.5 (14.3)	58.7 (14.7)	54.5 (14.0)	51.0 (13.9)	
Distribution, mean (SD)							
<50	164 (27.3)	19 (16.5)	32 (17.4)	36 (26.1)	34 (42.5)	43 (51.8)	
50–59	134 (22.3)	20 (17.4)	43 (23.4)	36 (26.1)	20 (25.0)	15 (18.1)	
60–69	149 (24.8)	35 (30.4)	54 (29.3)	32 (23.2)	12 (15.0)	16 (19.3)	
≥70	153 (25.5)	41 (35.7)	55 (29.9)	34 (24.6)	14 (17.5)	9 (10.8)	
Race, n (%)							.021
Black, non-Hispanic	341 (56.8)	63 (54.8)	95 (51.6)	71 (51.4)	51 (63.8)	61 (73.5)	
Hispanic	184 (30.7)	34 (29.6)	60 (32.6)	50 (36.2)	20 (25.0)	20 (24.1)	
White, non-Hispanic	49 (8.2)	16 (13.9)	15 (8.2)	11 (8.0)	5 (6.3)	2 (2.4)	
Asian, Non-Hispanic	8 (1.3)	1 (.9)	5 (2.7)	1 (.7)	1 (1.3)	0 (.0)	
Other	18 (3.0)	1 (.9)	9 (4.9)	5 (3.6)	3 (3.8)	0 (.0)	
Comorbidities, n (%)							
COPD	61 (10.2)	16 (13.9)	22 (12.0)	11 (8.0)	5 (6.3)	7 (8.4)	.313
Asthma	88 (14.7)	12 (10.4)	21 (11.4)	23 (16.7)	18 (22.5)	14 (16.9)	.096
Hypertension	402 (67.0)	76 (66.1)	112 (60.9)	96 (69.6)	59 (73.8)	59 (71.1)	.210
Coronary artery disease	85 (14.2)	20 (17.4)	26 (14.1)	24 (17.4)	7 (8.8)	8 (9.8)	.249
Congestive heart failure	111 (18.5)	20 (17.4)	37 (20.1)	28 (20.3)	12 (15.0)	14 (16.9)	.827
Stroke	60 (10.0)	11 (9.6)	24 (13.0)	11 (8.0)	7 (8.8)	7 (8.4)	.572
Diabetes	253 (42.2)	38 (33.0)	81 (44.0)	62 (44.9)	40 (50.0)	32 (38.6)	.132
Chronic kidney disease	111 (18.5)	26 (22.6)	30 (16.3)	30 (21.7)	16 (20.0)	9 (10.8)	.186
End-stage renal disease	48 (8.0)	15 (13.0)	16 (8.7)	8 (5.8)	5 (6.3)	4 (4.8)	.166
Psychiatric diagnosis	131 (21.9)	22 (19.3)	40 (21.7)	34 (24.6)	13 (16.3)	22 (26.5)	.465
Substance abuse	84 (14.0)	14 (12.2)	29 (15.8)	19 (13.8)	8 (10.0)	14 (16.9)	.657
Malignancy	36 (6.0)	7 (6.1)	10 (5.4)	12 (8.7)	6 (7.5)	1 (1.2)	.232
Smoking status							.002
Active smoker	89 (14.8)	25 (21.7)	28 (15.2)	18 (13.0)	7 (8.8)	11 (13.3)	
Former smoker	196 (32.7)	42 (36.5)	71 (38.6)	42 (30.4)	27 (33.8)	14 (16.9)	
Non-smoker	315 (52.5)	48 (41.7)	85 (46.2)	78 (56.5)	46 (57.5)	58 (69.9)	

BMI = body mass index; COPD = chronic obstructive pulmonary disease; SD = standard deviation.
Data are represented as no. (%) unless otherwise specified.
* *P* values represent unadjusted comparison between obesity classes.

associated with ICU admission. This analysis was repeated looking exclusively at patients with BMI ≥30 kg/m^2, and the same statistically significant trends were identified. Of patients who required ICU admission, those with higher BMI had lower admission lymphocyte percent, ferritin, and D-dimer compared with those with lower BMI. Detailed multivariable regression analysis results are presented in Supplementary Tables 1 and 2.

At maximum respiratory support, 12.8% required mechanical ventilation, 2.5% required NIMV, 15.7% required HFNT, 38.2% required nasal cannula, and 30.8% did not have a supplemental oxygen requirement. There were no statistical differences in maximum respiratory support level among the different BMI groups. During hospitalization, 26.5% required ICU level care, 9.5% required vasopressor or ionotropic support, and 3.3% required newly initiated renal replacement therapy. Thromboembolic events occurred in 4% of our cohort. The mortality rate was 10%. Primary and secondary outcome results are presented in Table 4. In multivariate analysis, adjusting for age, sex, and race, BMI was positively correlated with need for ICU admission (OR 1.031, 95% CI 1.004–1.058, P = .0215), as well as in-hospital LOS (β = .187, 95% CI .0834–.291, P = .0004). For every 5 kg/m^2 increase in BMI, risk for ICU admission increased by 16.5% and inpatient hospital duration increased by .93 days. In multivariate analysis, there were no statistically significant associations with BMI and need for vasopressor support (OR 1.031, 95% CI .995–1.069, P = .092), need for renal replacement therapy (OR 0.957, 95% CI .894–1.024, P = .957), thromboembolic events (OR 1.001, 95% CI 0.947–1.057, P = .981), incidence of intubation (OR 1.077, 95% CI .915–1.268, P = .371), ICU LOS (β = 4.573, 95% CI -.103–9.249, P = .055), or mortality (OR 1.125, 95% CI .921–1.375, P = .249).

Table 2
Symptoms and signs on presentation

	All patients	BMI group					*P*
	N = 600	BMI <25	BMI 25–30	BMI 30–35	BMI 35–40	BMI ≥40	
		(n = 115)	(n = 184)	(n = 138)	(n = 80)	(n = 83)	
Symptoms, n (%)							
Fever	335 (55.8)	60 (52.2)	104 (56.5)	80 (58.0)	48 (60.0)	43 (51.8)	.731
Dyspnea	361 (60.2)	60 (52.2)	100 (54.3)	89 (64.5)	52 (65.0)	60 (72.3)	.013
Fatigue	210 (35.0)	48 (41.7)	63 (34.2)	42 (30.4)	27 (33.8)	30 (36.1)	.447
Cough	346 (57.7)	65 (56.5)	94 (51.1)	76 (55.1)	54 (67.5)	57 (68.7)	.027
Diarrhea	126 (21.0)	17 (14.8)	43 (23.4)	35 (25.4)	19 (23.8)	12 (14.5)	.117
Nausea or vomiting	121 (20.2)	27 (23.5)	38 (20.7)	25 (18.1)	12 (15.0)	19 (22.9)	.578
Temperature (°F), mean (SD)	99.6 (1.9)	99.4 (1.7)	99.7 (2.2)	99.6 (1.6)	99.5 (1.9)	99.9 (1.7)	.347
Heart rate, mean (SD)	98.7 (18.5)	96.0 (19.6)	98.1 (17.5)	96.6 (18.6)	103.0 (17.2)	103.1 (18.8)	.009
Systolic blood pressure, mean (SD)	137.1 (25.5)	136.6 (28.2)	137.5 (24.8)	133.9 (24.6)	140.8 (24.7)	138.9 (25.4)	.352
Respiratory rate, mean (SD)	20.6 (5.2)	21.1 (6.6)	20.6 (5.3)	19.9 (4.0)	21.2 (5.4)	20.5 (4.6)	.368
Oxygen saturation, mean (SD)	93.3 (7.7)	92.4 (7.2)	93.3 (9.1)	93.4 (7.7)	94.0 (7.1)	93.5 (5.4)	.670
Initial oxygen requirement, n (%)							.495
Room air	319 (53.2)	62 (53.9)	98 (53.3)	79 (57.2)	41 (51.3)	39 (47.0)	
Nasal cannula	190 (31.7)	31 (27.0)	57 (31.0)	46 (33.3)	25 (31.3)	31 (37.3)	
High flow nasal therapy	60 (10.0)	15 (13.0)	17 (9.2)	11 (8.0)	8 (10.0)	9 (10.8)	
Non-invasive mechanical ventilation	13 (2.2)	1 (.9)	5 (2.7)	2 (1.4)	2 (2.5)	3 (3.6)	
Mechanical ventilation	18 (3.0)	6 (5.2)	7 (3.8)	0 (.0)	4 (5.0)	1 (1.2)	

BMI = body mass index; SD = standard deviation.
Data are represented as no. (%) or mean (SD)

Discussion

This study describes the demographic information, clinical presentation, and clinical laboratory features of 600 patients who were hospitalized for COVID-19 at a North Philadelphia academic medical center. The institution serves a predominately Black and Hispanic, medically underserved population and is representative of many urban centers found throughout the United States [12]. The aim of this study was to provide further insight into the disease presentation and course in patients with varying classes of obesity. Although our study validated the findings of other institutions conferring higher risk of COVID-19 in patients with obesity and younger age at presentation for patients with obesity, we also identified a novel association between ferritin, a marker of inflammation, and lymphocyte profile, a marker of disease severity, with obesity [6,13].

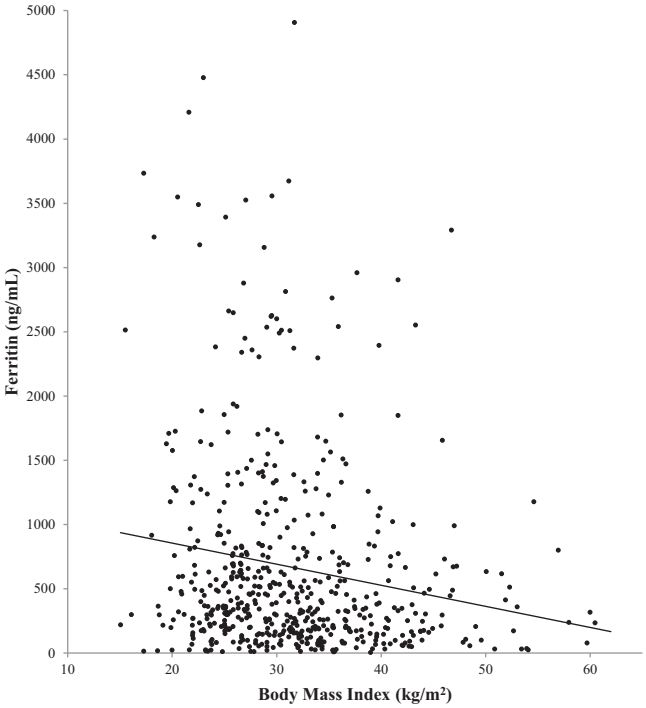

Figure 2. Scatterplot showing the relationship between initial ferritin levels obtained and body mass index.

In the zip codes directly served by this institution, obesity rates range from 32.3%– 39.5% [14]. The rate of obesity in our hospitalized COVID-19 cohort was over 50%. Similar hospitalization rates of COVID-19 patients with obesity have been reported by multiple institutions throughout the United States, including aggregate data collected by the Centers for Disease Control COVID-NET surveillance network [15,16].

The risk of hospitalization with obesity is likely multifaceted. Patients with obesity experience altered respiratory physiology, which results in diminished total respiratory compliance, respiratory muscle dysfunction and inefficiency, decreased functional reserve capacity, and increased oxygen consumption dedicated to respiratory work. This places them at risk for respiratory distress and subsequent failure with any pulmonary insult [9,17,18]. Patients with obesity are at high risk for pulmonary, cardiovascular, and metabolic co-morbidities [8,19]. Hypertension, T2D, cardiovascular disease, and lung disease have been identified

Table 3
Laboratory findings on presentation

	All patients	BMI group					Univariate analysis P*	Multivariate analysis P†
	N = 600	BMI <25	BMI 25–30	BMI 30–35	BMI 35–40	BMI ≥40		
		(n = 115)	(n = 184)	(n = 138)	(n = 80)	(n = 83)		
Lymphocyte %	16.2 (10.6–24.1)	15.1 (9.0–24.1)	14.8 (9.4–23.0)	16.6 (12.4–24.3)	17.0 (11.7–24.8)	19.5 (13.3–26.7)	.003	.0017
Absolute lymphocyte count (K/mm^3)	1.0 (.8–1.4)	1.0 (.7–1.4)	1.0 (.7–1.3)	1.0 (.8–1.4)	1.1 (.8–1.5)	1.1 (.9–1.6)	.080	.0032
D-dimer (ng/mL)	840.0 (482.0-1554.0), 583	1055.0 (549.0-1913.0), 114	915.0 (506.0-1984.0), 175	715.0 (469.0-1238.0), 133	754.0 (426.0-1196.0), 79	695.0 (442.0–1212.0), 82	.017	.5225
Ferritin (ng/mL)	392.0 (184.0-836.0), 571	484.0 (232.0-1178.0), 110	533.5 (271.5-1044.5), 172	314.5 (156.0-746.0), 132	340.0 (154.0-743.0), 79	263.0 (108.0–618.0), 78	<.001	.0192
White blood cell count (K/uL)	6.4 (4.9–8.5)	6.5 (4.8–9.5)	6.5 (5.0–8.5)	6.4 (4.9–8.2)	5.9 (4.9–9.5)	6.4 (4.8–7.7)	.124	
Platelet count (K/uL)	200.0 (156.0-258.0)	182.0 (149.0-262.0)	191.0 (148.0-255.5)	205.0 (159.0-256.0)	215.5 (165.0-265.0)	208.0 (180.0–258.0)	.532	
Alanine transaminase (U/L)	31.0 (21.0–48.0), 591	30.0 (19.0–47.0), 115	31.0 (21.0–50.5), 180	29.0 (21.0–40.0), 136	31.0 (21.0–45.0), 79	33.0 (22.0–52.0), 81	.441	
Aspartate transaminase (U/L)	36.0 (24.0–57.0), 551	38.0 (24.5–62.5), 108	36.5 (25.0–59.0), 164	32.5 (22.0–46.0), 130	31.0 (21.0–53.0), 76	39.0 (25.0–68.0), 73	.046	
Total bilirubin (mg/dL)	.5 (.4–.7), 593	.6 (.4–.9), 115	.5 (.4–.8), 180	.5 (.4–.7), 136	.5 (.4–.6), 80	.5 (.4–.7), 82	.123	
Lactate dehydrogenase (U/L)	269.5 (208.0-380.0), 542	258.0 (203.0-376.0), 107	270.0 (210.0-389.0), 163	261.0 (204.0-354.0), 125	272.0 (220.0-408.0), 74	307.0 (219.0–408.0), 73	.637	
Blood urea nitrogen (mg/dL)	17.0 (11.0–30.0)	21.0 (13.0–36.0)	17.0 (13.0–32.0)	16.0 (11.0–31.0)	15.5 (10.0–26.0)	13.0 (10.0–17.0)	.020	
Creatinine (mg/dL)	1.1 (.9–1.7)	1.1 (.9–1.9)	1.1 (.9–1.8)	1.1 (.9–1.8)	1.0 (.8–1.6)	1.00.9–1.3)	.187	
C-reactive protein (mg/L)	6.2 (2.2–11.4), 569	6.4 (2.2–12.4), 114	6.6 (2.6–11.8), 169	4.7 (1.9–9.1), 127	4.9 (1.8–12.4), 79	7.2 (1.8–11.6), 80	.368	

BMI = body mass index.

Data are represented as median (interquarile range) or number if fewer patients were assessed for those laboratory studies than the total number of patients in the study.

* P values represent unadjusted comparison between obesity classes.

† P values represent multivariable linear regression with log transformation of inflammatory marker, with adjustment for age, gender, and race performed for secondary analysis.

Table 4
Primary and secondary clinical outcomes

	All patients	BMI group					*P**
	N = 600	BMI <25	BMI 25–30	BMI 30–35	BMI 35–40	BMI ≥40	
		(n = 115)	(n = 184)	(n = 138)	(n = 80)	(n = 83)	
Mortality, n (%)	60 (10.0)	16 (13.9)	18 (9.8)	9 (6.5)	10 (12.5)	7 (8.4)	.2486
Intubation, n (%)	77 (12.8)	17 (14.8)	19 (10.3)	18 (13.0)	9 (11.3)	14 (16.9)	.3705
Intensive care unit care, n (%)	159 (26.5)	34 (29.6)	47 (25.5)	31 (22.5)	21 (26.3)	26 (31.3)	.0215
ICU hours - mean (SD)	65.5 (161.7)	51.4 (123.2)	58.3 (138.9)	65.0 (172.3)	73.0 (195.0)	93.6 (196.5)	.0552
Length of stay (d) - mean (SD)	9.2 (9.6)	8.4 (6.7)	9.0 (7.8)	8.9 (10.0)	9.3 (8.5)	11.6 (14.9)	.0004

BMI = body mass index; ICU = intensive care unit; SD = standard deviation.
Data are represented as no. (%) unless otherwise specified.
* *P* values represent multivariable logistic regression, with adjustment for age, sex, and race, performed for secondary analysis.

as independent risk factors for COVID-19 disease severity and mortality [15,16,20,21]. Therefore, obesity confers a higher risk of severe COVID-19 due to this constellation of altered respiratory physiology and high-risk co-morbidities.

We identified an inverse relationship between age and obesity class with regard to hospitalization rates. For every 5 kg/m^2 increase in BMI, the age of patients decreased 2.9 years. This trend was first identified by Klang et al. (2020) in a cohort of 265 patients, and has since been corroborated in larger observational studies [6,13]. While younger patients have a tendency for decreased severity of COVID-19 disease compared with older counterparts, obesity mitigates this benefit and skews admission rates to younger age groups. Obesity as a risk factor for COVID-19 severity and the high preponderance of the disease in the United States has created a significant need to understand the mechanisms by which this occurs.

It is known that obesity is associated with chronic low-grade inflammation and immune dysregulation, resulting in baseline elevation of pro-inflammatory cytokines such as TNF-α, MCP-1, IL-6, and leptin [22]. TNF-α subsequently activates ferritin transcription, causing elevation of ferritin as an acute phase reactant, with chronic elevations in patients with obesity [23]. Ferritin levels can also be increased in obesity due to concomitant liver injury, that is, non-alcoholic steatohepatitis, with damaged hepatic cells releasing ferritin to the systemic circulation [24]. It has been hypothesized that this chronic inflammatory state pre-disposes patients with obesity to severe disease manifestation as COVID-19 severity is largely driven by the dysregulated inflammatory host response and subsequent damage. Our analysis identified a paradoxic association of lower ferritin levels on admission as BMI increased. Though the overall relationship between high ferritin levels and ICU admission was maintained, those with higher BMI who were admitted to the ICU had comparatively lower ferritin levels than those with a lower BMI who were admitted to the ICU.

In general, patients with obesity have also been recognized to be at higher risk for thrombotic events due to procoagulant imbalance and platelet hyperactivity [25]. Despite the demonstrated risk of thrombogenicity in obesity, the relationship between D-dimer and elevated BMI has yielded inconsistent results in literature. Variations in D-dimer levels have been proposed to be a result of decreased fibrinolysis capacity in patients with obesity, yielding counteracting effects [26]. With COVID-19, a clearer relationship exists between elevated D-dimer levels and disease severity. Increased macro and micro-thrombotic events have been observed in patients with severe illness, and as such, D-dimer levels have been correlated with increasing severity of disease [27]. In our analysis, we did note a decreasing trend in admission D-dimer levels with increasing BMI, however, after adjustment in multivariate analysis, this relationship was not statistically significant. The trend appeared to be largely driven by age, with increasing age and elevated D-dimer having an established relationship [28]. However, patients with severe illness requiring ICU admission did demonstrate overall elevated admission D-dimer levels compared with those with milder disease who did not require ICU admission.

Lymphopenia in COVID-19 occurs early in the disease process and the degree of lymphopenia is prognostic for disease severity [29]. Patients in our obesity cohorts presented with normal or near-normal lymphocyte relative frequency and absolute lymphocyte count compared with patients without obesity. Increased adiposity has been linked to an increased number of lymphocytes, which may contribute to this finding [30]. This overall picture of decreased ferritin and decreased lymphopenia in patients with increasing BMI portrays, at face value, a less severe presentation of COVID-19. However, there were significant differences in need for ICU admission and total in-hospital LOS, though no differences in outcomes related to need for advanced respiratory support or mortality were identified in our cohort.

Patients with obesity manifest significant respiratory symptoms necessitating hospitalization at a higher rate than their age matched peers. This may be because patients with obesity operate at a reduced respiratory functional state at baseline and the respiratory insult of an early or even mild SARS-CoV-2 infection manifestation is not well tolerated, resulting in respiratory distress and hypoxemia. Additionally, it has been proposed that patients with obesity have a

blunted pro-inflammatory response to viral infections, such as influenza, which may provide some insight into the reduced initial inflammatory response [22]. Despite having lower levels of biochemical and hematologic marker derangements upon admission, patients with obesity remain at elevated risk for ICU admission and increased hospital LOS. As inflammatory markers are trended to direct therapy, understanding these mechanisms can be key to improving survival.

As we have gained a greater understanding of the mechanisms underlying SARS-CoV-2 infection, treatment of the disease has evolved. Currently, supportive care, anti-retrovirals, immunomodulatory agents, corticosteroids, convalescent plasma, and anticoagulation therapy comprise the tools in the treatment arsenal against COVID-19. The decision of which treatment modalities to pursue is guided by clinical assessment, radiologic findings, and laboratory findings, with particular focus on inflammatory and hematologic biomarkers. Recognition that patients with obesity present initially with a different inflammatory profile may affect the choice of treatments utilized. Further investigation is needed to see how these markers evolve in this population and the subsequent impact on therapeutic decisions. Additionally, pharmacokinetic data are lacking with regard to optimal medication dosing of these agents and their efficacy in COVID-19 patients with obesity. A combination of these factors may be contributory to the poorer outcomes that have been seen.

This study has several limitations. The study population included patients within the Philadelphia metropolitan area and as such, the results may not be generalizable. It is also important to note that the laboratory values presented in this study are those obtained on admission labs to the COVID-19 designated wards and do not characterize the trends throughout hospitalization as it relates to clinical course. The sample size of this study was limited to 600 patients. Larger studies have examined outcomes of mortality, ICU admission, and intubation rates in people with obesity; however, they do not address trends in inflammatory biomarkers as analyzed here [31]. Our study took place in the early stages of the COVID-19 outbreak in the United States, and our outcomes may be influenced by the treatment at this time in an evolving global pandemic. Further studies with newer treatment strategies are needed to validate these findings.

Conclusion

Patients with obesity present with fewer derangements in admission inflammatory labs, specifically ferritin, absolute lymphocyte count, and lymphocyte percent, however, tended to have increased hospital LOS and increased need for ICU admission. Because these markers are frequently used to stratify patients by severity and guide treatment choice, it is important to recognize that these trends are manifest in patients with obesity and may subsequently have implications in their treatment course. A more complete understanding of the biochemical and inflammatory response to COVID-19 is needed to improve outcomes in patients with obesity.

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Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.soard.2021.06.006.

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Editorial comment

Comment on: COVID-19 patients with obesity at risk for worse outcomes despite younger age and fewer inflammatory derangements

At the time this editorial was written COVID-19 cases in the United States totaled above 33.4 million. The disease has accounted for 600,000 deaths in this country. Globally the number has reached counts above 18,000 per 100,000 individuals in parts of the world. The staggering impact of this pandemic makes understanding every facet of the disease of great importance. Currently, 151.6 million people in the US are now fully vaccinated and this rising number represents hope for the future in the face of newly emerging variants of concern [1].

Due to nonspecific symptomatology associated with COVID-19, early in the pandemic pro-inflammatory markers were helpful for providers to stratify patients who were at higher risk of a positive COVID-19 diagnosis. This was of particular importance when molecular testing had a long turnaround time. Now that molecular testing can be done rapidly, these markers have less diagnostic utility but may now serve as predictors of disease severity. Early identification of patients who are at high risk for a worse clinical course will allow for appropriate resource utilization and hopefully improved clinical outcomes. It may even help to increase survival and decrease length of stay for these patients.

An increased focus on predicting disease severity associated with COVID-19 based on biochemical markers has become evident in the literature. A recent review showed predictive factors of severe disease from COVID-19 to include older age, male sex, and presence of 1 or more pre-existing co-morbidities. In terms of biochemical markers, lymphopenia was found to be inversely related with disease prognosis and serum lactate dehydrogenase was found to correlate with disease severity [2]. A group from Wuhan, China, recently identified that the neutrophil-to-lymphocyte ratio was a strong predictor of disease severity [3].

Research looking at ways to improve outcomes in patients with obesity who develop COVID-19 is of great importance. Data from studies like this especially in areas of particularly high obesity rates amongst patients hospitalized with COVID-19 is a great place to identify trends. It was quite notable that this study showed blunting of the inflammatory marker response in patients with COVID-19 and