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Research Letter

The role of obesity in inflammatory markers in COVID-19 patients



ARTICLE INFO

Keywords:

Obesity
COVID-19
Inflammation
CRP
ESR
D-dimer

ABSTRACT

Obesity has emerged as a significant risk factor for severe COVID-19 worldwide. Given both COVID-19 infection and obesity have been associated with increased systemic inflammation, we evaluated inflammatory markers in obese and non-obese individuals hospitalized for COVID-19 at Massachusetts General Hospital. We hypothesized that obese patients would have a more exuberant inflammatory response as evidenced by higher initial and peak inflammatory markers along with worse clinical outcomes. Of the 781 patients, 349 were obese (45%). Obese individuals had higher initial and peak levels of CRP and ESR as well as higher peak D-dimer ($P < 0.01$ for all) in comparison to non-obese individuals, while, IL-6 and ferritin were similar. In addition, obese individuals had a higher odds of requiring vasopressor use (OR 1.54, 95% CI 1.00–2.38, $P = 0.05$), developing hypoxemic respiratory failure (OR 1.58, 95% CI 1.04–2.40, $P = 0.03$) and death (OR 2.20, 95% CI 1.31–3.70, $P = 0.003$) within 28 days of presentation to care. Finally, higher baseline levels of CRP and D-dimer were associated with worse clinical outcomes even after adjustment for BMI. Our findings suggest greater disease severity in obese individuals is characterized by more exuberant inflammation.

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Introduction

Obesity has emerged as a significant risk factor for severe COVID-19 worldwide [1–3]. Greater disease severity in obesity remains poorly understood, but may be due to reduced lung compliance, maladaptive effects on ventilation and perfusion, and a heightened state of inflammation [2,4,5]. We sought to examine differences in systemic inflammation among obese and non-obese individuals hospitalized for COVID-19. We hypothesized that obese patients would have a more exuberant inflammatory response, including higher initial and peak markers of inflammation along with worse clinical outcomes.

Methods

Seven hundred and eighty one hospitalized patients with PCR-confirmed COVID-19 admitted to Massachusetts General Hospital from February 28 to April 27, 2020 were included in the study. We excluded patients with active cancer except non-melanoma skin cancers ($n = 35$), current pregnancy ($n = 19$), age < 18 years ($n = 7$), and those with missing lab values or covariates ($n = 22$).

C-reactive Protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), D-dimer, and ferritin were abstracted with ini-

tial and peak (highest value recorded) values within 14 days of hospitalization. Clinical history was abstracted using chart review. Outcomes were ascertained up to 28 days after presentation to care (defined as first encounter with the health system) until discharge or death.

We examined the association of obesity status ($\text{BMI} \geq 30 \text{ kg/m}^2$) and BMI with natural log-transformed inflammatory markers using multivariable linear regression. Models were adjusted for age, sex, hypertension, diabetes mellitus, liver disease, kidney disease, smoking history and pulmonary disease. In addition, we examined the association of obesity and inflammatory markers with clinical outcomes using multivariable logistic regression.

Results

Of the 781 patients (mean age 61 and 42% women), 349 were obese (45%) (Table 1).

Obese individuals had higher initial levels of CRP and ESR after accounting for potential confounders in multivariable analyses ($P < 0.01$ for both) (Table 1). Peak CRP and ESR remained higher in the obese, in addition to peak D-dimer (Fig. 1).

Obese individuals had a higher odds of requiring vasopressor use (multivariable OR 1.54, 95% CI 1.00–2.38, $P = 0.05$), developing hypoxemic respiratory failure (OR 1.58, 95% CI 1.04–2.40, $P = 0.03$) and death (OR 2.20, 95% CI 1.31–3.70, $P = 0.003$) within 28 days of presentation to care (Fig. 1).

Given CRP, ESR and D-dimer demonstrated an association with obesity, we examined the association of the baseline markers with

Abbreviations: COVID-19, coronavirus disease 2019; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; ICU, intensive care unit; ARDS, Acute Respiratory Distress Syndrome.

Table 1

Baseline demographic, comorbidities, medications, inflammatory markers and outcomes in obese and non-obese with COVID-19 infection.

	Total N = 781	Obese N = 349	Non-obese N = 432	P-value*
Baseline demographics				
Age, years	61 (17)	57 (16)	65 (17)	<0.001
Women, n (%)	328 (42%)	161 (46%)	167 (39%)	0.04
Race, n (%)				0.04
White	315 (41%)	124 (37%)	191 (45%)	
Hispanic	279 (37%)	145 (43%)	134 (32%)	
Black	87 (11%)	36 (11%)	51 (12%)	
BMI, kg/m ²	30.7 (9.7)	37.0 (11.3)	25.5 (2.9)	<0.001
Comorbidities				
Cardiovascular disease, n (%)	185 (24%)	69 (20%)	116 (27%)	0.02
Diabetes mellitus, n (%)	283 (36%)	145 (42%)	138 (32%)	0.01
Hypertension, n (%)	416 (53%)	180 (52%)	236 (55%)	0.40
Pulmonary disease, n (%)	245 (31%)	124 (36%)	121 (28%)	0.02
COPD, n (%)	90 (11%)	30 (9%)	60 (14%)	0.02
Asthma, n (%)	106 (14%)	61 (18%)	45 (10%)	0.004
Obstructive sleep apnea, n (%)	51 (6%)	38 (11%)	13 (3%)	<0.001
Kidney disease, n (%)	137 (18%)	48 (14%)	89 (21%)	0.01
Liver disease, n (%)	72 (9%)	31 (9%)	41 (9%)	0.77
Current cigarette smoker, n (%)	60 (8%)	18 (5%)	42 (10%)	
Former cigarette smoker, n (%)	257 (33%)	99 (28%)	158 (37%)	<0.001
Baseline medications				
NSAIDs, n (%)	173 (22%)	76 (22%)	97 (22%)	0.82
Statins, n (%)	344 (44%)	150 (43%)	194 (45%)	0.60
Inflammatory markers, median (inter-quartile range)				
Initial CRP, mg/L (n = 770)	71 (34–142)	76 (40–145)	67 (28–137)	<0.001
Peak CRP, mg/L (n = 770)	137 (51–245)	147 (71–264)	127 (60–230)	<0.001
Initial ESR, mm/h (n = 718)	37 (22–57)	38 (26–61)	35 (21–56)	0.007
Peak ESR, mm/h (n = 718)	56 (34–103)	62 (36–110)	52 (29–91)	0.002
Initial D-dimer, ng/mL (n = 760)	987 (633–1729)	931 (613–1615)	1061 (673–1817)	0.55
Peak D-dimer, ng/mL (n = 760)	1655 (868–3663)	1785 (877–4313)	1570 (862–3186)	0.004
Initial IL-6, pg/mL (n = 271)	31 (14–73)	32 (15–70)	31 (14–74)	0.24
Peak IL-6, pg/mL (n = 271)	32 (15–79)	35 (16–104)	31 (14–76)	0.10
Initial Ferritin, ug/L (n = 773)	518 (267–990)	548 (291–952)	505 (256–1027)	0.62
Peak Ferritin, ug/L (n = 773)	775 (399–1587)	807 (426–1614)	767 (372–1555)	0.26
Outcomes				
ICU admission, n (%)	242 (31%)	129 (37%)	113 (26%)	0.11
Death, n (%)	116 (15%)	49 (14%)	67 (16%)	0.003
ARDS, n (%)	188 (24%)	99 (28%)	89 (21%)	0.15
Hypoxemic respiratory failure, n (%)	207 (27%)	116 (33%)	91 (21%)	0.03
Intubated, n (%)	204 (26%)	109 (31%)	95 (22%)	0.16
Vasopressor/inotrope use, n (%)	200 (26%)	109 (31%)	91 (21%)	0.05

Values are means (standard deviations) or medians (inter-quartile ranges) unless otherwise noted. Abbreviations: BMI = body mass index, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, IL-6 = interleukin-6, ARDS = Acute Respiratory Distress Syndrome.

* P-values represent unadjusted comparison (obese vs non-obese individuals) for baseline demographic and clinical variables, and multivariable-adjusted linear or logistic regression models for inflammatory markers and outcomes. Multivariable models are adjusted for age, sex, hypertension, diabetes mellitus, liver disease, kidney disease, smoking history, and pulmonary disease.

clinical outcomes. For each 1-SD higher CRP, patients had greater than two-fold odds of ICU admission (OR 2.21, 95% CI 1.71–2.86), hypoxemic respiratory failure (OR 2.49, 95% CI 1.86–3.33) and death (OR 2.23, 95% CI 1.63–3.05) and near three-fold odds of intubation (OR 2.79, 95% CI 2.03–3.82) and vasopressor use (OR 2.74, 95% CI 2.00–3.75) ($P < 0.001$ for all). In addition, for each 1-SD higher D-dimer, patients had nearly 1.5 greater odds for ICU admission, hypoxemic respiratory failure, intubation, vasopressor use and death ($P < 0.01$ for all).

Discussion

Among 781 hospitalized COVID-19 PCR-confirmed positive patients at MGH, we examined the association of obesity with markers of inflammation and clinical outcomes. Our principal findings are: a) obesity is associated with greater inflammation as evidenced by higher initial and peak CRP and ESR and peak D-dimer; b) obesity is associated with greater COVID-19 disease severity, including higher likelihood of vasopressor use, hypoxemic respiratory failure and death; c) higher baseline levels of CRP and D-dimer are associated with worse clinical outcomes even after adjustment for BMI. Our findings suggest that greater disease severity among

obese individuals is characterized by more exuberant inflammation.

Our results demonstrate higher initial and peak levels of CRP and ESR and peak D-dimer among obese vs non-obese individuals. Similar to other studies, we also demonstrate that CRP and D-dimer in turn have been linked to disease severity and death in COVID-19 [6,7]. Although prior data have demonstrated that obesity is associated with T cell depletion and low T cell levels have been negatively correlated with IL-6 levels, we did not find an association between obesity and IL-6 levels [8]. Given recent data suggesting that CRP levels may predict response to glucocorticoid therapy, our results further highlight the role of CRP in the obese population when considering potential therapeutic options [9].

Our study has limitations. This study was an observational study and is subject to potential ascertainment bias as inflammatory markers were not obtained at set intervals, limiting causal inferences. We acknowledge that mechanistic studies are needed to better understand the role of inflammation in obesity as it pertains to COVID-19 disease severity. Finally, this is a single center study and generalizability to other samples may be limited.

In sum, among individuals hospitalized for COVID-19, obesity is associated with greater inflammation including initial and peak

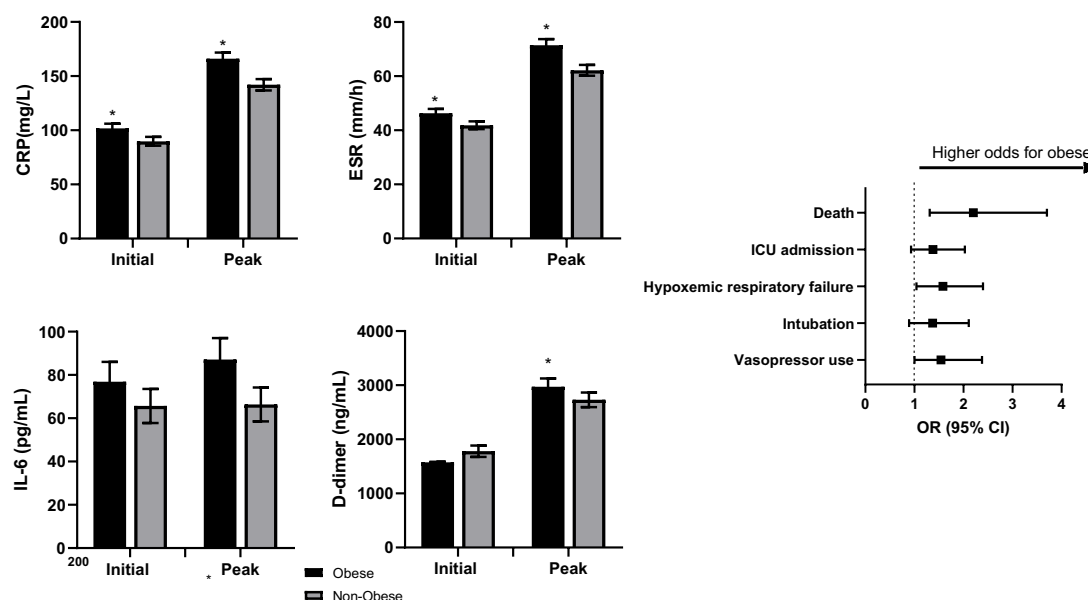


Fig. 1. Obesity status is associated with inflammatory markers and clinical outcomes among hospitalized COVID-19 patients. Obese patients had higher initial and peak CRP and ESR as well as higher peak D-dimer in comparison to non-obese patients (mean and s.e.; *denotes $P < 0.05$ using multi-variable linear regression). Obese patients demonstrated greater odds for death, hypoxemic respiratory failure and vasopressor use.

ESR and CRP and peak D-dimer levels, as well as worse clinical outcomes. Specifically, obesity and inflammation were associated with higher odds of vasopressor use, hypoxemic respiratory failure and death. Further studies are needed to examine how inflammation may render obese individuals more susceptible to severe COVID-19.

Author contributions

Conception and design: J.N.M., E.S.L., S.M.P., I.V.B., A.S.F., J.E.H. Collection, analysis and interpretation of data: J.N.M., E.S.L., S.M.P., E. E. L., J.K.W., C.A.S., I.V.B., S.A.L., A.S.F., J.E.H. Drafting of the manuscript: J.N.M., E.S.L., S.M.P., C.A.S., I.V.B., S.A.L., A.S.F., J.E.H. Guarantor of paper: J.N.M., E.S.L., J.E.H.

Funding

This work was funded by the MGH Division of Clinical Research (A.S.F.), Weissman Family MGH Research Scholar Award (I.V.B); NIH grants:5T32HL094301-07 (E.S.L.),1R01HL139731 (S.A.L.),K24AI141036 (I.V.B), R01HL134893 (J.E.H.);R01 HL140224 (J.E.H.);K24 HL153669(J.E.H.) American Heart Association 18SFRN34250007 (S.A.L.).

Ethical statement

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There were no experiments performed as a part of this study. There were no animals involved in this study. The Partners Institute Review Board (Protocol #2020P00829) approved the study.

Disclosures

Dr. Lubitz receives sponsored research support from Bristol Myers Squibb/Pfizer, Bayer AG, Boehringer Ingelheim, and Fitbit, and has consulted for Bristol Myers Squibb/Pfizer and Bayer AG, and participates in a research collaboration with IBM. Dr. Ho has

received research support from Gilead Sciences and Bayer AG, and research supplies from EcoNugenics.

Competing interests

The authors have no competing interests to report.

Acknowledgements

The authors would like to acknowledge the patients who were included in this study.

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8 November 2020