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EDITORIAL COMMENTARY

# Coronavirus Disease 2019 Severity in Obese Patients May Be Linked to Viral Load and Immune Response

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**(See the Major Article by Epsi et al, on pages 1462–72.)**

There have been intense research efforts worldwide to understand which factors contribute to coronavirus disease 2019 (COVID-19) severity and outcomes. Obesity is one of several independent risk factors for more severe COVID-19 symptoms, need for hospitalization, intensive care unit admission, development of acute respiratory distress syndrome, and need for invasive mechanical ventilation. Several studies have also indicated that obesity is associated with increased mortality from COVID-19, although some meta-analyses and large studies have produced mixed results, making this association less clear [1–3]. However, it has remained unclear why obese patients fare worse with COVID-19.

In this issue of *The Journal of Infectious Diseases*, Epsi and colleagues [4] address this important gap in knowledge, using the Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Disease with Pandemic Potential (EPICC) study dataset (https://epicc.usuhs.edu). EPICC is a prospective cohort study that enrolled individuals eligible for Military Health System care from one of 7 United States military treatment facilities and who had been diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, presented with at least one COVID-like symptom, or had recently been exposed to SARS-CoV-2. Upper respiratory tract specimens and sera were collected at predefined intervals to measure SARS-CoV-2 viral loads and serum anti-Spike protein antibody concentrations, and anthropometric data were obtained to determine body mass index (BMI) and obesity status. There were 511 patients included in the analysis, with 62.0% being 18–44 years old, 26.0% being 45–64 years old, and 11.9% being ≥65 years old. The majority of the participants (51.5%) were active military, with 23.9% being dependents (only adults were included) and 24.7% being retired military service members. Logistic regression models were built for 2 important COVID-19 outcomes, hospitalization and supplemental oxygen therapy, with adjustment for some covariates known to be independently associated with COVID-19 severity, including age, sex, diabetes, and others.

Like several other studies on this subject [3], Epsi et al identified obesity as an independent risk factor for hospitalization (adjusted odds ratio [aOR], 1.91 [95% confidence interval {CI}, 1.15–3.18]) and for requiring supplemental oxygen therapy (aOR, 3.39 [95% CI, 1.61–7.11]) for COVID-19. In addition, the authors measured viral loads and anti-Spike protein immunoglobulin (IgG) antibody concentrations and compared these parameters on the basis of obesity status. In outpatients, severely obese individuals had significantly higher peak viral loads compared to those with normal BMI ($\log_{10}$ 1.89 genome equivalents for the N1 gene and $\log_{10}$ 2.62 for the N2 gene). This association was not observed in patients who required hospitalization. Furthermore, obese patients had significantly increased anti-Spike protein IgG antibody concentrations compared to nonobese patients in both inpatient and outpatient settings. Consistent with this observation, BMI category and anti-Spike IgG concentrations were positively correlated. This latter observation is important because previous studies have documented that anti-Spike protein IgG antibody concentrations are correlated with COVID-19 disease severity [5].

These observations raise interesting questions that deserve further study. First, do these differences in viral load and antibody production reproduce in other populations? If so, this might suggest that host–pathogen interactions are altered in obese patients exposed to SARS-CoV-2. Second, does the higher viral load in obese outpatients have any implications for transmissibility of the virus? If the viral load differences found in this study are also seen for emerging variants with higher transmission rates, such as the Delta variant, the effect could be multiplicative. (Of note, the analysis conducted by Epsi et al was performed before the Delta variant was documented

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to be widespread in the United States.) Third, do the higher anti-Spike protein antibody concentrations result in better or longer lasting SARS-CoV-2 immunity in obese patients? There is an open question about whether the antibodies produced by obese patients are as efficient at neutralizing SARS-CoV-2 compared to antibodies produced by nonobese patients. More does not necessarily mean better antibodies. Finally, are the higher anti-Spike protein IgG concentrations in obesity simply related to higher antigen exposure, or does obesity result in differential immune responses to SARS-CoV-2? These are all important questions that need to continue to be addressed.

It should be acknowledged that there are potential nonimmunologic explanations for why obese patients are more likely to be admitted to the hospital, require oxygen therapy, and experience a more severe disease course. For example, it has been suggested that obesity may result in reduced pulmonary function and hypoventilation [6], and this might contribute to more severe respiratory symptoms and increase the likelihood of requiring supplemental oxygen therapy. Additional studies of nonimmunologic mechanisms that explain more severe COVID-19 in obese patients are warranted.

As pointed out by the authors, a major weakness of the study by Epsi et al is that it defines obesity status using BMI only. Although BMI cutoffs can be useful for defining obesity status in the general population, it may result in higher rates of false positives and false negatives in some populations. For example, in highly muscular groups, such as elite athletes and some members of the military service, BMI can be substantially higher than the obesity cutoff of 30 kg/m$^2$ due to high muscle mass, not high fat mass. This can result in incorrect classification of lean or overweight patients as obese (false-positive classification). In addition, self-reported weight and height, which was one method of anthropometric data acquisition in this study, are frequently misreported by nontrivial amounts that can incorrectly classify patients in a lower BMI category, such as a mildly obese patient being incorrectly classified as overweight (false-negative classification) [7]. The vast majority of reports on COVID-19 outcomes in the context of obesity rely on BMI; however, there are more reliable methods available to define obesity, including skin fold thickness measurements, dual emission x-ray absorbance scans, air volume displacement technologies such as "bod pods," and others. These are more expensive to deploy than determining BMI, can be subject to observer-dependent variations (especially in the case of skin fold thickness), and are not routinely available in most clinical settings. Despite these barriers to use, at least one of these more accurate techniques should be used in future large prospective cohort studies to better understand how obesity status relates to SARS-CoV-2 infection and COVID-19 pathogenesis.

Overall, this study by Epsi et al provides important new data and suggests that host–pathogen interactions might be altered in the setting of SARS-CoV-2 infection in obese patients. Obesity is associated with chronic low-grade inflammation [8], and immune system dysfunction has been linked to more severe infections with influenza and several other pathogens in obese humans [9]. Increasing our understanding of how obesity leads to more severe COVID-19 disease may shed some new light on mechanisms of antiviral immunity, how metabolic diseases such as obesity influence immune system function, and potentially reveal approaches to identify patients most at risk of requiring hospitalization or more advanced care.

## Notes

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***Potential conflicts of interest.*** J. R. B. holds patents 9754220, 8987245, 8809312, and 8598150 that are related or potentially related to obesity, and has pending patent applications that are related or potentially related to obesity or immunoassays. No intellectual property is directly related to SARS-CoV-2 or COVID-19. X. Z. reports no potential conflicts of interest.

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