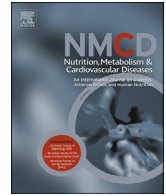




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## LETTER TO THE EDITOR

## Leptin as a potential prognostic marker of the severity of COVID-19 infection in obese patients



Dear Editor,

We read with great interest the article “Obesity as a risk factor for unfavorable outcomes in critically ill patients affected by COVID-19” [1], and we believe this is an important contribution toward understanding the relationship between the severity of the disease COVID-19 and obesity. Although we agree on the apparent role of adipokines, we believe that there is evidence suggesting that leptin may have a significant role in the underlying mechanisms of severe COVID-19 in obese patients due to its important immunological function [1].

Since the onset of the COVID-19 pandemic, obesity has been associated with poorer outcomes of COVID-19 infections. A study by Biscarini et al. [2] identified this association in the earlier times of the pandemic (February–March 2020) by analyzing the data from 427 COVID-19 patients referred to a hospital in Italy and the results showed that 33% of obese patients required admission to ICU compared to 19% of nonobese patients. Later on, Bellini et al. [3] analyzed a large population registered in the Tuscany regional database and concluded that there was an association between obesity and the risk of hospitalization (RR 1.74, 95% CI: [1.56–1.97]). Furthermore, Zeng et al. [4] retrospective study of the Wuhan’s inpatients’ data, revealed that an increased BMI positively correlated with the severity of many symptoms such as fever, dyspnea, and ground-glass opacity CT scan ( $p < 0.05$ ) with a hazard ratio (HR) of 2.54 for mortality with COVID-19 in obese patients. Thus, the association between obesity and unfavorable outcomes for COVID-19 patients appears to be robust across geography and it stands even after adjusting the confounding variables such as age, sex, and comorbidities.

Multiple other studies have further supported the association between obesity and severity of COVID-19 infection but some studies suggest the role of adipokines in this mechanism. Cai et al. [5] published a meta-analysis including 46 articles where obesity was associated with a

high risk of mortality (OR 1.61, 95% CI: [1.29–2.01]), hospitalization (OR 1.72, 95% CI: [1.55–1.92]), and clinically severe disease (OR 3.81, 95% CI: [1.97–7.35]) and suggested that adipokines may have a role in this association as the imbalance caused by the inflammatory status observed in obese individuals may dysregulate the immune response resulting in increased susceptibility to viral infections like COVID-19. Particularly, leptin’s pro-inflammatory functions, such as activation of M1 monocytes, may play an important role in the cytokine storm related to COVID-19 aggravation, acute respiratory distress syndrome, and multiple organ failure; especially in obese patients, whose fat mass excess produce more leptin upon infection [6].

Hyperleptinemia is one of the clinical characteristics associated with SARS-CoV-2 ventilated patients admitted to ICU [7]. Van de Voort et al. [7] found that SARS-CoV-2 ventilated patients had higher levels of serum leptin ( $p = 0.0007$ ). Similarly, Wang et al. [8] reported increased leptin levels, in patients with BMI  $>24$ , in both mild and severe COVID-19 patients with the later group exhibiting significantly higher levels. Notably, leptin levels are associated with the immunologic abnormalities and systemic pro-inflammatory state seen in COVID-19 patients [8]. The finding of an increase in visceral fat in severe patients compared to mild ones also suggests that the use of leptin as a biomarker of inflammation could be useful to determine the risk of COVID-19 and its possible complications even in patients with central obesity [9].

All these studies support the association of leptin and severe COVID-19 in obese patients. However, many of them have limitations such as limited medical resources and sample sizes. Therefore, more research should be conducted to further understand leptin’s role in severe COVID-19 patients and maybe, in the future, use leptin as a therapeutic target. Also, it is important to evaluate its potential as a prognostic marker to anticipate complications of its release in obese patients. Finally, we emphasize the importance of leptin as a molecule with diverse immunological functions that can not only help address

COVID-19 disease's progression but also in ensuring the development of effective vaccines for obese patients whose elevated serum leptin levels could downregulate antibody production and class switching [10].

### Conflicts of interest

The authors declare no conflicts of interest.

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