Diabetes, Obesity, and Risk Prediction of Severe COVID-19

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The global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has unleashed health and economic crises in both the developed and the developing world. Differences in demography, prevalence of comorbidities, health care capacity, and the efficacy of risk mitigation measures affect mortality and complications resulting from COVID-19. Severe COVID-19 disproportionately affects older individuals and patients with comorbidities that include diabetes, obesity, hypertension, cardiovascular disease, chronic kidney disease, and chronic lung disease (1, 2). In the United States, a significant portion of hospitalizations, intensive care unit admissions, and deaths occur in individuals older than age 70 years (1). The presence of comorbidities increases the risk of hospitalizations and deaths. The interplay between age and comorbidities in a given population determines the heterogeneity of risk for severe COVID-19 (3). Indeed, the age-specific prevalence of underlying conditions vary by country. Understanding the interaction between age, comorbidities, and health system capacity is essential for shielding and mitigation strategies (3). Similarly, population-specific models predicting the risk of developing severe COVID-19 that require hospital admission are urgently needed.

COVID-19 is raging across Latin America, and as of June 22, 2020, the region has well over 2 million cases and more than 95,000 deaths, with Brazil, Mexico, Peru, and Chile the most affected countries (4). In this issue of the *Journal*, Bello-Chavolla et al explore the impact of diabetes and obesity on modulating severe COVID-19 in Mexico (5). Consistent with other studies from China, Europe, and the United States, the study reports that obesity and diabetes are important risk factors for poor outcomes of COVID-19 in Mexico (5). Individuals aged 65 years or older have an accentuated risk for hospitalization, intensive care unit admission, and the need for mechanical ventilation, whereas those younger than 40 years have a reduced risk. However, the presence of type 2 diabetes (T2DM) in individuals younger than 40 years (early-onset T2DM) substantially increases the risk of hospitalization and death due to COVID-19. Indeed, early-onset T2DM is common in Mexico and other ethnic groups worldwide (6). In Mexico, nearly 19.6% of patients with diabetes mellitus is younger than 40 years. A recent study estimates that, in Mexico, 16.6% of people at high risk of severe COVID-19 because of underlying health conditions are young individuals (< 40 years). In contrast, that number is 9.6% in the United States and 7.0% in Italy (3). These findings are consistent with the study by Bello-Chavolla et al that suggests that the presence of a comorbidity like diabetes abrogates the protective effect conferred by younger age.

In their modeling, the authors sought to elicit mechanistic insight into how COVID-19's most adverse outcomes are associated with obesity and diabetes. The authors adopt state-of-the-art causal mediation methods. Mediation analyses are helpful to understand causal pathways and their relative contributions to an outcome from an exposure. They

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assume that obesity mediates the negative effects of diabetes on COVID-19 outcomes causally. The authors' claim that 49.5% of diabetes' increase in lethality for COVID-19 is mediated by obesity is not well-founded: their application does not match its method's key assumptions, nor has this point estimate been appropriately couched within a range of values taking uncertainty (including unverifiable assumptions) into account. However, this does not detract from the need to adopt the most appropriate method for their quantification goals; instead, it points to how interdisciplinary teams are needed to consider viable options to pursue such goals. Perhaps there are other ways to cast their mediation quantities of interest into a novel methods application, such as considering obesity as the initial exposure, with diabetes as mediator, itself confounded by an unobserved exposure-induced confounder (e.g., inflammation, cytokines, hypercoagulability) of mediator-outcome relationships (i.e., to account indirectly for inflammation's role in COVID-19 lethality in pathway analyses). There is emerging data on COVID-associated effects on new-onset diabetes as well as severe diabetes-associated complications such as ketoacidosis; goals of the recently formed international COVIDIAB consortium would place metabolic dysfunction at the end of a series of pathophysiologic sequelae to SARS-CoV-2 infection (7).

Bello-Chavolla et al. develop a simple model to predict COVID-19 mortality that can be used for risk stratification within Mexico. The authors explore multiple predictive models to build an easy-to-implement clinical score for prioritizing care for suspected COVID-19 patients. It is a timely publication for populations that exhibit substantial obesity and/or diabetes prevalence. The score holds promise, given the disproportionate burden carried by such communities (i.e., tend toward a greater risk of poor outcomes and SARS-CoV-2 exposure, per increased odds of multigenerational housing and high-contact occupations, among other socioeconomic status-related factors). Ease of calculation is a compelling feature: clinical providers, first responders, and mutual aid community volunteers in even the most resource-poor settings should more easily triage presenting cases. Although a moderately more predictive "black-box" model could be based on these same readily captured predictors, this score has a low barrier to implementation by not requiring algorithmic integration with electronic tools. This simplicity comes without markedly reduced performance: its risk categories appear well-calibrated per stratified survival curves, and the score itself ought to improve clinical discrimination for mortality risk (per its c-statistic of 0.82). For the sake of front-line providers needing to triage presenting cases in resource-poor settings, the team's next steps might include posting web-accessible calculations; this seems a needed supplement. However, it should be noted that this model, like other prognostic models based on suspected-case cohorts (8), suffers from high risk for bias, and its performance needs to be evaluated in real-world conditions in Mexico.

The authors were unable to test the effects of body mass index gradient on hospitalization and death. However, it is important to compare the risk gradients across ethnic groups, sex, and age. Studies exploring the pathophysiological mechanisms that mediate the enhanced risk of severe COVID-19 are needed (2). These studies must include a significant number of individuals from ethnic minorities to help us understand the proximal factors contributing to the disproportionate amount of deaths in these populations (1). Last, prospective studies examining the effects of modifiable factors such as glycemic and blood pressure control on COVID-19 outcomes are warranted.

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