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Estimating the Case Fatality Risk of COVID-19 among Mechanically Ventilated Patients

The current coronavirus disease (COVID-19) pandemic has exerted significant strain on the delivery of critical care worldwide (1, 2). Published reports describing the characteristics and outcomes of critically ill patients with COVID-19 have shown they have similar features to patients with non–COVID-19–related acute respiratory distress syndrome (3, 4). The reported all-cause in-hospital mortality for those patients with COVID-19 requiring intensive care and invasive mechanical ventilation is very high but also varies across countries and regions (5–7). More precise estimation of the case fatality risk in patients with severe COVID-19 would help to provide a better understanding of the overall burden of the pandemic and to identify the subgroups who are at greatest risk of dying (8).

The case fatality risk of an infection is represented by the proportion of patients who die among all infected cases in a population over a period of time (9). The estimation of case fatality risks during an ongoing pandemic—especially during periods marked by exponential increases in number of cases—is not without challenges (9, 10). Major pitfalls include overestimating the case fatality risk if less severe (or asymptomatic) cases are not identified or included in the denominator or underestimating the risk if follow up is too short, leading patients who are still alive but who ultimately die to be missed in the numerator (9, 11).

In this issue of the *Journal*, Lim and colleagues (pp. 54–66) present a rigorous and comprehensive systematic review and meta-analysis of 69 studies involving 57,420 adult patients with severe COVID-19 (12). Their main objective was to estimate the overall global case fatality risk among the sickest subgroup of infected patients—those receiving invasive mechanical ventilation. The review included patients from 23 countries, and these tended to be mostly from North America, Europe, or Asia. The authors used appropriate methods to pool estimates in the presence of high heterogeneity, and their results were robust to a variety of sensitivity analyses and under a diverse set of assumptions (13). The overall case fatality risk for these ventilated patients was approximately 45%, or about one death for every two patients. The case fatality risk ranged from 0 to 100% across all studies, owing to significant variability across included reports, including clinical, methodological, and statistical heterogeneity. The latter was most notably associated with the quality of individual studies and those arising from so-called early epicenter locations. This case fatality risk consistently increased with older age, reaching 84% overall among patients older than 80 years.

These findings have important clinical and epidemiological implications. First, the estimated case fatality risk among patients receiving mechanical ventilation is high and similar to that of other patients with severe acute respiratory distress syndrome (14). This information may, in turn, aid in ongoing pandemic planning, resource allocation, and the estimation of both the health-related and socioeconomic impact of COVID-19 (8). It should help inform the design of future studies of critically ill patients with COVID-19 by providing a more precise estimate of mortality risk. Furthermore, it may also help to motivate the development of strategies to reduce the occurrence of COVID-19–related critical illness or the need for invasive mechanical ventilation (15). Finally, the very high case fatality risk among older patients highlights the importance of preventing further outbreaks among this extremely vulnerable group (16).

The results reported by Lim and colleagues showcase useful methods for estimating risk across multiple studies during an evolving pandemic and also their inherent limitations. First, the authors did not provide an estimate of the overall case fatality risk but rather only the risk for a highly selected group of critically ill patients who received invasive mechanical ventilation. This approach helped to avoid the major challenge of identifying all asymptomatic or mildly symptomatic patients for inclusion in the denominator, but it also limits generalizability to a broader spectrum of critically ill patients or to the entire population. This approach also assumes that the

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determinants that lead to decisions to provide invasive mechanical ventilation are relatively consistent across studies, but, in fact, these may be influenced by patient factors, treatment preferences, and resource availability, which, in turn, may lead to variation in the estimated case fatality risk across studies. Other sources of heterogeneity across studies could have included variations in case mix across cohorts, ICU triage and admission criteria across regions, maximum time of outcome recording, and whether complete follow up was available. Notably, Lim and colleagues addressed the possibility of incomplete mortality data by applying best- and worst-case scenarios for patients who remained in hospital at the end of follow up. Even across these sensitivity analyses, the case fatality risk of patients with severe COVID-19 remained invariably high.

It is often tempting to use case fatality risks to compare outcomes among populations with or without a specific characteristic or treatment. For example, if the data presented from the study by Lim and colleagues were used to compare the outcomes of patients with severe COVID-19 to other distinct populations (e.g., patients with influenza pneumonia), then the usual caveats apply about the limitations of deriving causal inferences from observational data (17). Specifically, differences in case fatality risks between different patient cohorts may indeed be explained by causal mechanisms but could alternatively arise because of differences in case definitions (e.g., only mechanically ventilated versus all cases), confounding by differences in disease susceptibility, selection bias created by decisions to provide or withhold intensive care treatments, and potential for survivor treatment bias (9). For the specific case of COVID-19, differences in case fatality risk across regions may also arise if the virus prevalence varies across groups of different age, sex, or comorbid conditions. Standardized case fatality risks adjusting for such potential confounders would provide more reliable comparisons across populations, but the individual patient data required to calculate these are seldom available (9).

Overall, the systematic review and meta-analysis from Lim and colleagues reinforces that patients with COVID-19 who receive invasive mechanical ventilation have a very high case fatality risk, which increases dramatically among older groups. Even though this information does not apply to a broader population of critically ill patients (or the entire spectrum of patients with COVID-19), it helps improve our understanding of prognosis among these important subgroups. These sobering results highlight the urgent need to identify new treatment options to reduce this case fatality risk—or to prevent the disease from spreading altogether. ■

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