Pinpointing the Cause of Variation in Mortality in COVID-19

Improving outcomes such as mortality for patients who are critically ill involves identifying the root causes, developing options for improvement, and then implementing changes in either preventive measures or treatments. Although this sounds easy when written, it includes a myriad of complex steps, the first of which is identifying drivers of mortality for a given condition. One way this is often approached is through the identification of variation in outcomes across ICUs, hospitals, regions, or countries. However, stopping at the point of describing variation, which is almost always present (1), leaves unanswered the next key question, which is whether variation in outcomes is due to factors inherent to individuals (e.g., age, comorbidities) or systems (e.g., specific aspects of care delivery) or remains due to unidentified causes. The first may be improved by identifying preventive strategies for individuals or groups or implementing new drugs or interventions, the second offers opportunities for quality improvement in delivery of care, and the third requires searching for those unidentified causes.

Published mortality rates for patients who are critically ill with coronavirus disease (COVID-19) have ranged from as low as 29.1% to as high as 89.9% (2, 3), raising the urgent question of whether this variability is due to underlying differences among patients or whether some hospitals were able to provide "better" care. As we try to move the needle on outcomes for patients with COVID-19, answering this question is important for understanding where to focus our efforts. In this issue of the *Journal*, Churpek and colleagues (pp. 403–411) seek to answer this question by examining variation in mortality for adults with COVID-19 hospitalized in ICUs at 70 U.S. hospitals between March and June 2020 (4). The reported mortality for patients with COVID-19 in these U.S. hospitals ranged from 0 to 82%, similar to the variability seen across studies globally (5). The study linked several sources that provided rich data on patient comorbidities, hospital strain, hospital capacity, hospital quality ratings, socioeconomic status, and local rates of new COVID-19 cases for the counties where each hospital was located. By sequentially adjusting for variables, moving from patient-level to hospital-level variables, the authors estimated contributions from each variable to interhospital variation in mortality. They found that acute physiology (49%), demographics and comorbidities (20%), and socioeconomic status (12%) were the largest contributors to observed variation in mortality, with strain (9%), hospital quality (8%), and treatments (3%) contributing a total of approximately 20% to variation in mortality.

The authors also calculated the adjusted median odds ratio (AMOR), which measures unexplained variation in outcomes between institutions. An AMOR of 2 would indicate that for two patients who are otherwise identical except that one was admitted to a "high-mortality hospital" and the other was admitted to a "low-mortality hospital," the odds of 28-day mortality would be twofold higher in the high-mortality hospital. Churpek and colleagues found that the median odds ratio decreased from 2.06 in the unadjusted model to 1.22 in the fully adjusted model. This is an encouraging finding, indicating that there is relatively little variability in COVID-19 mortality among patients in the ICU that is due to the hospital they were admitted to, and there is lower unexplained variability than in many other studies of different aspects of ICU care. For example, a study of arterial catheter use among mechanically ventilated patients in U.S. centers found an AMOR of 2.56 (6), and a study examining rates of administration of hydrocortisone, ascorbic acid, and thiamine among patients with septic shock at U.S. centers found an AMOR of 12.05 (7). The findings for variation in COVID-19 mortality and contributions from unmeasured hospital factors are similar to those observed for in-hospital mortality in acute myocardial infarction (8), trauma (9), and burns (10).

Studies like the one by Churpek and colleagues demonstrate how important it is to have high-quality measures of illness severity. In this case, the authors obtained detailed patient information, including vital signs, laboratory values, respiratory parameters, number of vasopressors required each day, presence of altered mental status, and preexisting comorbidities, among others. Without these detailed data, one might conclude that variation in mortality across centers was much higher. The true variability, in fact, is probably even less than the study's estimate, as there is usually residual confounding owing to severity of illness, something that may be especially true during pandemic conditions when precise and accurate data collection can be more difficult.

Another concern in studying variability in care across hospitals is ensuring that each hospital has a high enough patient volume for analysis. One needs an adequate number of patients at each site to obtain estimates with reasonable confidence intervals (11). At the same time, part of what drives variation in practice and outcomes can be the volume of patients treated (12), and excluding hospitals with few patients may lead to exclusion of precisely those centers that struggle to provide high-quality care. Churpek and colleagues chose a cutoff of 10 patients per site for inclusion, with a median number of patients per hospital of 34. Although this may make it difficult to be confident in mortality estimates at some sites, the low cutoff allows for a more representative sample of hospitals with the volumes of patients seen in many centers early in the COVID-19 pandemic.

Another important consideration, particularly for studies of patients with COVID-19, is the choice of mortality time point. Relative to many groups of patients in the ICU, patients with

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COVID-19 have a long length of stay (13). The 28-day mortality is a measurement that is more easily obtainable than longer-term measurements. However, one study of 4,244 patients with COVID-19 in the ICU found that although 26% of patients had died at Day 28, an additional 5% died by Day 90 (14). Moreover, practices around end-of-life care and time to a decision to withdraw life-sustaining therapies may be altered by unusual circumstances such as lack of visitation by families (15). We can only speculate that using a longer-term measure such as 60- or 90-day mortality, although more difficult to measure, may reveal even less variation between hospitals.

It is reassuring that variability in mortality for patients with COVID-19 in these centers, which seems alarmingly high at first glance, was mostly explained by patient factors, as it suggests that patients were not subject to uneven care across U.S. hospitals. As next steps, these findings suggest that prevention measures for high-risk individuals and novel therapeutic interventions remain key targets. However, this work also should be repeated in other healthcare settings, as standards of care and access to resources likely vary much more across hospitals in many less resourced countries and may very well remain the leading cause of variability in outcomes across much of the world. ■

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