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Letters to the Editor

RE: "THE CLINICAL COURSE OF CORONAVIRUS DISEASE 2019 IN A US HOSPITAL SYSTEM: A MULTISTATE ANALYSIS"

We congratulate Mody et al. (1) on their sophisticated multistate analysis of 1,577 hospitalized patients with coronavirus disease 2019 (COVID-19) in a regional US hospital system. Multistate models allow for a detailed investigation of the course of disease while importantly avoiding severe, yet common, types of bias (2).

In previous articles, researchers have characterized the longitudinal trajectory of patients hospitalized with COVID-19 with regard to methodology (3) and outcome classification (4) in multistate settings and applied these methods to German data (5). Our experience enables important additional insights that we would like to contribute here.

First, we stress that recognition of patients being discharged alive as a competing risk in the cause-specific Cox regression is vital for a complete understanding of covariate effects. Patients who are discharged alive are no longer at risk of admission to the intensive care unit (ICU), intubation, or death in the hospital. Effects on the discharge hazard have an indirect effect on the risk of these events. For example, Rieg et al. (5) found that the male sex significantly reduces the discharge hazard. Even though sex was not found to have a significant effect on the death hazard, the absolute risk of death in the hospital was increased for male patients; they stayed longer in the hospital and were consequently longer at risk for ICU admission, intubation and death. Thus, the Cox regression analysis only provides a complete picture of the covariate effects if the effects on the discharge hazard are also presented.

Furthermore, Mody et al. provided detailed stacked probability plots (Figures 1 and 2 in their article (1)) for different levels of care (inpatient floor, intensive care, invasive ventilation and noninvasive ventilation), as well as death and discharge. In addition, the medians and interquartile ranges of the time patients spent in each level of care are given in their Figure 5. We emphasize that the stacked probability plots also impressively combined this information in a single graphic. The mstate R-package that the authors used provides a powerful function that allows for the estimation of the mean time spent in each level of care. Confidence intervals can be obtained via bootstrapping (3, 4, 6). These estimates are directly related to the stacked probability plot as the area between 2 curves (7); readers can discern the different durations spent in each level of care directly from the graphic. In contrast to medians and interquartile ranges, the estimated mean durations provide direct information for the planning of hospital capacities such as ICU beds and ventilators. Of note, the multistate model can be simplified by consolidating states while altering neither these estimates nor the risks of requiring a specific level of care, being discharged alive, or dying. At the same time the simplified model results in higher statistical power, allows a clearer presentation of the results, and facilitates comparison with other studies with lower level of detail.

Finally, we highlight that multistate analyses are also powerful tools to harmonize heterogeneous endpoints in randomized controlled trials (4). For example, all categories of the endpoint scale developed by the World Health Organization for COVID-19 trials can be combined in a single informative stacked probability plot (8). This allows for direct visual comparisons of the course of disease of different treatment groups resulting in fast and easily accessible information.

Mody et al. (1) performed an exemplary analysis and we hope that our insights provide readers with further constructive information on the disease modeling of COVID-19. Researchers are encouraged to also use multistate methodology for the evaluation of emerging threats such as the genetic variants of severe acute respiratory syndrome coronavirus 2. A well-designed study, analyzed with multistate methodology, can provide important insights into the complex disease progression.

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Editor's note: *In accordance with* Journal *policy, Mody et al. were asked if they wished to respond to this letter, but they chose not to do so*.

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