Additional insights on the modelling of the COVID-19 clinical progression using multi-state methodology

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Running head: On the modelling of the COVID-19 clinical progression

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

Previous articles characterize the longitudinal trajectory of COVID-19 hospitalized patients with regard to methodology (3) and outcome classification (4) in multi-state settings, and apply 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 discharge 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 intensive care unit (ICU) admission, intubation and death in the hospital. Effects on the discharge hazard have an indirect effect on the risk of these events. For example in Rieg et al.(5), we 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. provide detailed stacked probability plots (figures 1, 2 (1)) for different levels of care (inpatient floor, intensive-care, invasive and non-invasive ventilation) as well as death and discharge. Separate to the plots, the median and interquartile range (IQR) of the time patients spent in each level of care is given (figure 5). We emphasize that the stacked probability plots also impressively combine this information in one single graphic. The mstate R-package that the authors use 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 two curves (7); readers can discern the different durations spent in each level of care directly from the graphic. In contrast to median and IQR, the estimated mean durations provide direct information for the planning of hospital capacities such as ICU beds and ventilators. Of note, the multi-state model can be simplified by consolidating states while neither altering 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 multi-state analyses are also a powerful tool 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. performed an exemplary analysis and we hope that our insights provide readers with further constructive information on the disease modelling of COVID-19. Researchers are encouraged to also use multi-state methodology for the evaluation of emerging threats such as the genetic variants of SARS-COV-2. A well-designed study, analyzed with multi-state methodology, can provide important insights into the complex disease progression.

Word count: 593 (of 500-600 words)

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