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Time-dependent bias when analysing COVID-19-associated pulmonary aspergillosis

Authors' reply

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We thank Justin de Brabander and colleagues for their interest in our findings on COVID-19-associated pulmonary aspergillosis (CAPA) reported from the MYCOVID cohort. They raised a very interesting question on the factor time and competing risks in studying the relation between CAPA and mortality as exemplified by their own cohort.

Initially, we observed a statistically significant association between CAPA occurrence and mortality using a Cox model. Then, we decided to refine the Cox model analysis for mortality estimation with a landmark analysis, considering the mean day of proven or probable CAPA development (11 days in our cohort).¹ But, as suggested by de Brabander and colleagues, we performed a complementary analysis, considering the time-dependent bias due to CAPA occurrence on the estimation of mortality.² Austin and colleagues previously defined a competing risk as an event whose occurrence precludes the occurrence of the primary event of interest.³ Here, the competing states were "time to death" or "discharge", both during intensive care unit (ICU) stay. No follow-up data were collected after ICU discharge as mentioned in the manuscript.² Using this model, the cause-specific hazard ratio (CS-HR) at discharge due to CAPA was 0.57 (95% CI 0.38–0.84) and the CS-HR of death due to CAPA was 2.08 (1.47–2.93), compared to 1.45 (1.03–2.03) found with the initial log-rank analysis.¹

Overall, we provide evidence that the magnitude effect of CAPA on mortality when considering the immortal bias and a cause-specific model increased the strength of the association between development of CAPA and mortality in the MYCOVID cohort.

- 1 Gangneux JP, Dannaoui E, Fekkar A, et al. Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study. *Lancet Respir Med* 2021; **10**: 180–90.
- 2 Bakoyannis G, Touloumi G. Practical methods for competing risks data: a review. *Stat Methods Med Res* 2012; **21**: 257–72.
- 3 Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016; **133**: 601–09.

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