Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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

We applaud the recent Article in *The Lancet Respiratory Medicine* by Jean-Pierre Gangneux and colleagues regarding the prevalence of fungal infections in critically ill patients with COVID-19.[1] The inclusion of consecutive patients in a multicentre study with repeated sampling and comprehensive fungal analyses can provide an accurate estimate of the incidence of COVID-19-associated pulmonary aspergillosis (CAPA). However, the omission of the factor time and competing risks in studying the relation between CAPA and outcome raises serious concerns.

Let us examine the complex relation between CAPA and outcomes (figure). All patients enrolling in the study started with a state we refer to as intubated, without CAPA, and were only sampled when they remained intubated. Some patients develop CAPA during mechanical ventilation whereas others do not. Development of CAPA is, of course, a time-dependent phenomenon. The absorbing (final), and competing, states are extubated or death. In the study by Gangneux and colleagues, competing risks were ignored, and the Article focused on mortality alone. This narrow focus might have given a biased estimate of the association of interest.[2]

More importantly, patients who developed CAPA at any timepoint during their stay in the intensive care unit were classified as having CAPA at the start of invasive ventilation in the survival model used by the authors. When unexposed person-time is misclassified as exposed time because of an exposure in the future, "time-dependent bias" or "immortal time bias" occurs.[3]

Based on a dataset of 177 consecutive patients with prolonged invasive ventilation due to acute respiratory distress syndrome related to COVID-19 who underwent weekly bronchoscopy for fungal diagnostics to identify probable or proven CAPA (as defined by 2020 consensus criteria[4]) in our hospital, we illustrate that the estimated hazard ratio (HR) of mortality associated with CAPA depends on whether this time-dependent bias is taken into account. In our cohort, the subdistribution HR for death was 1·2 (95% CI 0·8–1·8; figure A) in the competing risk model that does not account for this bias. When modelling CAPA as a time-dependent covariate, the cause-specific HR for death was 1·8 (1·2–2·7), with a subdistribution HR of 2·6 (1·7–3·9). This association cannot be plotted because models with time-dependent covariates do not have a meaningful probability interpretation. We found similar probabilities using multistate modelling[5] (ratio transition intensities 1·3, 1·2–1·7; figure B), an alternative method to account for this bias, with age and gender as covariates. Our analyses show that without taking the time-dependent bias into account, the cause-specific HR for death was underestimated within our cohort.

Admittedly, an effort was made to adjust for time-dependent bias by landmark analysis at day 11 by Gangneux and colleagues, but this timepoint was selected post hoc on the basis of the mean day of CAPA development, and it is unclear how unexposed person-time was handled. In this case, therefore, this adjustment does not sufficiently address immortal time bias.[6] Furthermore, the identification of the duration of mechanical ventilation of more than 14 days as a risk factor for CAPA suggests that it indeed is a time-dependent phenomenon. We

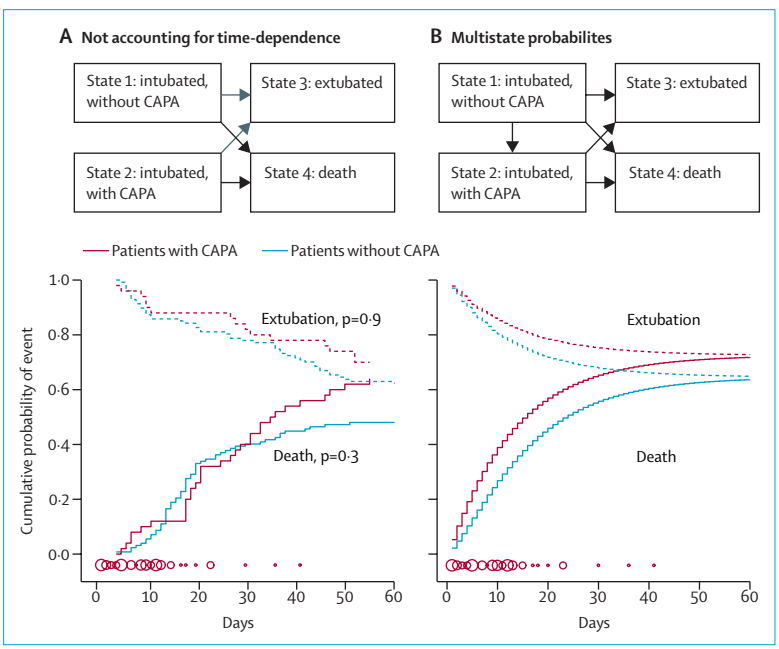

Figure: **Comparison of statistical techniques.**
Gangneux and colleagues[1] assumed that state 1 (intubated, without CAPA) and state 2 (intubated, with CAPA) occur independently (A), and assume that death is the only absorbing state—ignoring that patients can be extubated and are no longer at risk for CAPA, or for CAPA-related mortality in the analysis. An illness-death model without recovery and two competing endpoints is more appropriate to model the association between CAPA and outcomes (B). In this model, a patient always starts from state and can move directly or via state to two absorbing states: state 3: (extubated) and state four (death). The graphs show the estimated probability of events not accounting for time dependence (A), and accounting for time dependence (B). Solid lines show mortality and dashed lines show extubation events. The circles indicate the number of patients developing CAPA on each day (smallest circle: one patient, largest circle: five patients). CAPA=COVID-19-associated pulmonary aspergillosis.

Published **Online**
February 2, 2022
https://doi.org/10.1016/S2213-2600(21)00582-8

welcome a response on how additional accounting for immortal time bias would influence the association between development of CAPA and mortality within the MYCOVID cohort.

We declare no competing interests.

*Justin de Brabander, Leonoor S Boers, Robert F J Kullberg, Jan W Duitman, *Lieuwe D J Bos, on behalf of the ArtDeco consortium*
l.d.bos@amsterdamumc.nl

Center of Experimental Molecular Medicine (JdB, RFJK), Intensive Care (LSB, LDJB), Department of Experimental Immunology (JWD), and Department of Respiratory Medicine (JWD, LDJB), Amsterdam UMC, University of Amsterdam, Amsterdam, 1105Az, Netherlands

1 Gangneux J, 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* 2022; **10:** 180–90.
2 Beyersmann J, Allignol A, Schumacher M. Competing risks and multistate models with R. New York, NY: Springer, 2012.
3 Chubak J, Boudreau DM, Wirtz HS, McKnight B, Weiss NS. Threats to validity of nonrandomized studies of postdiagnosis exposures on cancer recurrence and survival. *J Natl Cancer Inst* 2013; **105:** 1456–62.
4 Koehler P, Bassetti M, Chakrabarti A, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis* 2021; **21:** e149–62.
5 Jackson CH. Multi-state models for panel data: the msm package for R. *J Stat Softw* 2011; **38:** 1–28.
6 Morgan CJ. Landmark analysis: a primer. *J Nucl Cardiol* 2019; **26**: 391–93.