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A note on statistical association and causality derived from epidemiological ICU data

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Bekaert and colleagues, in their commentary on our review recently published in *Intensive Care Medicine* [1], raise the issue of detecting a causal effect of a time-dependent exposure such as nosocomial infection on subsequent hospital death. In this letter, we clarify and discuss the challenges in the interpretation of statistical measures.

The survival models presented in our review are correct in the sense that the statistical association between a nosocomial infection and hospital death is adequately investigated. A key aim of our paper was to explain the special role of time, which is often neglected not just in hospital epidemiology. Another key characteristic of intensive care data are competing events: A patient is either discharged alive or dies in the hospital. Thus, the other aim of our paper was to explain that any analysis ignoring this competing events setting has the potential to be misleading.

However, reality is usually even more complex: Further time-dependent risk factors might be present and require consideration. In our review, we refer to multivariate survival regression models to study the statistical association with further time-dependent risk factors. To explore risk factors on the occurrence of nosocomial infection, one may additionally study this relationship analogous to a propensity score analysis. An example is given in [2]. This approach is also correct in terms of studying the statistical association since the chronological order of time-dependent factors is adequately accounted for.

It is getting philosophical to consider how statistical association is linked to causality (see the excellent review paper by Aalen and Frigessi [3]). We believe that time is also crucial to the notion of causality: The cause has to precede the effect. This is the reason for highlighting the importance of time in our review.

Bekaert and colleagues claim to infer causal inference using specific techniques [4]. These techniques might be helpful for a more sophisticated analysis. We wish to emphasize our agreement on the importance of both time and causality. But one has to keep in mind: Causal inference cannot be received from statistical models applied to data from observational studies (i.e., no experiment, no randomized controlled trial) without additional assumptions. In the hospital setting, one assumption is, for example, that discharge as the competing event for death is 'sequentially ignorable' [4]. As demonstrated in our review, this assumption is not reliable. It is absolutely essential that all these

assumptions have to be made transparent and understandable for hospital epidemiologists and clinicians so that they can correctly interpret the results. Further, a thorough discussion is needed about whether these assumptions are reasonable in the specific setting of a particular study.

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