Maarten Bekaert
Dominique Benoit
Johan Decruyenaere
Stijn Vansteelandt

Reply to Wolkewitz et al.

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Dear Sir: In a recent issue of the journal, Wolkewitz and colleagues reviewed several statistical survival methods and clarified their differences in a typical intensive care unit (ICU) setting with time-varying exposures (e.g. nosocomial infection, NI) and competing events (e.g. ICU discharge and mortality) [1]. We join the authors and believe that ignoring the time-dependent nature of exposures is a root cause of important biases in the analysis of ICU data, and would like to thank the authors for providing valuable insights. In this letter, we provide additional considerations which we believe are of key importance to take into account as well.

The necessity to respect the time-dependent nature of exposures calls for specialized methods for confounder control, which pertinently acknowledge that patients who do and do not develop a NI at a given time during ICU admission may not be comparable in terms of severity of illness. Contrary to the suggestion of Wolkewitz and colleagues [1], this is not possible by merely including time-dependent risk factors in the considered time-dynamic models.

The reason for this is that, when assessing the impact of NI on the risk of death on a given day during ICU admission, adjustment is required for the history of time-varying confounders (e.g. disease severity) before that day. Since the history of disease severity is itself affected by the earlier infection status, standard regression adjustment for time-varying exposures and confounders no longer obeys the key statistical principle that it is not appropriate to adjust for consequences of an exposure [2]. When ignoring this, the analysis is subject to two potentially major biases. First, the adjustment removes the indirect effects of early infection on the risk of death that are mediated through the considered confounders (e.g. the patients' health status). These indirect effects can be substantial, consequently inducing an underestimation of the overall infection effect. Second, these techniques also induce a so-called collider-stratification bias [3] by which a spurious association between infection and mortality arises, even in the absence of an infection effect. Noteworthy is that analyses that adjust for length of ICU stay are subject to similar biases, because length of stay is affected by earlier infection status.

The above-mentioned issues can be mitigated by using so-called causal inference techniques [4], designed to compare the risk of death in the observed population (with infected patients) versus that in case infection would have been avoided. Provided that all confounders have been measured, potential differences in mortality can then be attributed to a real infection effect. Such techniques have proven to be very successful in epidemiology [4] and have been adopted in ICU settings with time-varying exposures [5] and, more recently, with competing events [6].

We close by joining Wolkewitz and colleagues in supporting that

statistical analyses should respect the time-dependent nature of exposures, such as infection [1]. We hope that this letter will help clarify that the analysis of time-varying exposures also calls for specialized methods of confounder control [4–6].

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M. Bekaert (✉) · S. Vansteelandt
Department of Applied Mathematics and
Computer Sciences, Ghent University,
Krijgslaan 281, S9, 9000 Ghent, Belgium
e-mail: maarten.bekaert@ugent.be
Tel.: +32-9-2644881
Fax: +32-9-2644995

D. Benoit · J. Decruyenaere
Department of Intensive Care Medicine,
Ghent University Hospital, De Pintelaan
185, 9000 Ghent, Belgium