The authors reported no conflicts of interest.

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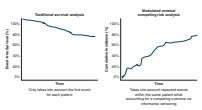

RETHINKING TRADITIONAL SURVIVAL ANALYSIS: MODULATED RENEWAL ANALYSIS WITH COMPETING RISKS REGRESSION

To the Editor:

We read with interest the article by Guariento and colleagues[1] regarding long-term outcomes of truncus arteriosus repair. In their study, the authors applied an innovative statistical methodology that they call "modulated renewal analysis with competing risks regression." In contrast to traditional survival analysis, this methodology allows one to perform time-to-event analysis of repeated events within the same patient while accounting for mortality as a competing outcome via informative censoring.

The methodology addresses an important statistical issue that is in fact common to various pathologies, ranging from tetralogy of Fallot[2] to aortic valve degeneration.[3] Patients suffering from these pathologies often undergo a series of reoperations and adverse events, while traditional Kaplan–Meier curves only take into account the first event for each patient. Furthermore, patients who died early might carry an elevated risk had they continued to be followed.

For instance, we encountered a similar issue when studying the literature about coronary artery disease in patients with HIV.[4] These patients often experience recurrent major adverse cardiovascular events following revascularization. Nonetheless, various studies failed to show any difference with regard to major adverse cardiovascular event–free survival between HIV-positive versus HIV-negative patients. In contrast, cumulative hazard estimates for recurrent acute coronary syndrome did show a significantly greater incidence in HIV-positive patients.[5]

From the perspective of therapy, 2 goals can be pursued in these populations: (1) reducing the number of patients experiencing any events, and (2) reducing the number of recurrent events in patients who have already experienced an event. It seems that traditional Kaplan–Meier curves are restricting us from observing effects of the latter type. This is alarming, because one would be discouraged to find out that a certain therapy does not reduce the overall event rate in a population, while failing to recognize that this therapy in fact protects a subset of patients from an avalanche of events.

Returning to Guariento and colleagues,[1] the use of cumulative hazard estimates rather than traditional event-free survival estimates is important to predict the risk of recurrent events in patients who already had one or more preceding events. As demonstrated by the authors, a shorter duration of the interval from previous reoperation was associated with increased hazard risk of subsequent reoperations. In other words, there might exist a subset of patients who are at elevated risk of being caught up in a series of events. Being able to timely identify these would allow for better prognostication, closer follow-up, and/or adjustment of therapy.

In conclusion, developments in the statistical methodology urge to rethink survival analysis. While the Kaplan–Meier curve remains one of the most frequently used methods, blind worship should be discouraged, and other tools, including those that take repeated events into account, should always be considered when appropriate. Guariento and colleagues[1] are thus to be congratulated on their important contribution.

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https://doi.org/10.1016/j.xjon.2021.09.020