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Statistical methods for evaluating delirium in the ICU

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Wes Ely reported receiving honorariums after giving lectures at CME activities sponsored by Abbot, Orion and Hospira. Ramona Hopkins reported receiving grants for Intermountain Research and Medical Foundation Grants and receiving an honorarium from the Michigan Hospital Association ICU Meeting.

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Recently, several studies have evaluated the effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") and other interventions to reduce delirium in critically ill patients.[1–4] Evaluating the impact of interventions on delirium in the intensive care unit (ICU) setting is challenging for several reasons: (1) delirium is a time-varying process during the ICU stay (i.e., it can change over the course of hours or days); (2) delirium occurs along a continuum of acute brain dysfunction and cannot be assessed when patients are more severely impaired (i.e., during a comatose state); and (3) delirium evaluation is often stopped at ICU discharge inhibiting researchers' ability to know the full duration of delirium. Moreover, death is a common outcome in the critically ill, with deceased patients no longer eligible to experience a delirium outcome. These characteristics of delirium evaluation in the ICU offer important statistical challenges.

In a recent editorial[5], delirium-free days until 28 days post-randomization was suggested as an outcome measure. Delirium-free days until day 28 is similar to another common critical care endpoint, ventilator-free days that was statistically evaluated back in 2002.[6] This endpoint is calculated by counting the days free of delirium up to day 28, with days after ICU discharge typically counted as delirium-free. We recommend *against* the use of this endpoint in favor of a joint modeling approach proposed[7] in 2007 and implemented in the R statistical package *frailtypack* in 2012[8]. Instead of representing delirium over 28 days with a single value, the joint modeling approach combines two survival models: one for the repeated (recurrent) daily indicator of delirium and another for the terminating event (i.e., an event after which patients can no longer be assessed for the outcome) of ICU discharge or death. A random effect (also referred to as a "frailty") is included in the survival model for daily delirium linking the delirium events within a subject, and enters the terminating event model as a main effect linking the delirium events and the terminating event. The effect of the randomized intervention is evaluated by including a main effect of treatment in the survival model for daily delirium. The hazard ratio (HR) for the randomized intervention compares the daily hazard of delirium in the intervention group to that in the control group, with a HR <1 indicating a lower daily hazard of delirium among participants

randomized to the intervention. This finding implies a shorter average duration of delirium among days at risk for delirium (i.e. ICU days in a non-comatose state).

Figure 1 illustrates the differences between delirium-free days and the joint modeling approach by considering 5 hypothetical ICU patients randomized at day 0 and followed until the earliest of discharge from the ICU, death or 28 days. Patient 1 remains alive in the ICU for the entire 28 days and contributes the same information to the joint modeling approach and the analysis of delirium-free days. Patient 2 experiences death at the end of Day 4 after experiencing delirium for 3 days; this patient could be assigned 1 delirium free day. Alternatively, patients who die during follow-up are often assigned 0 delirium-free days (indicating that death is the worst possible outcome), creating a composite endpoint. The interpretability of this composite endpoint that combines mortality and delirium may be questioned when the intervention being evaluated is not expected to affect mortality. In the joint modeling approach, Patient 2 contributes 4 days of exposure and 3 recurrent delirium events.

Patients 3 and 4 are both discharged alive from the ICU after Day 6 with 2 delirium-free days. Patient 4 continues to have delirium until Day 28; however, both patients would be assigned 24 delirium-free days given that they are not followed beyond ICU discharge. As is the case with Patient 4, delirium often continues after ICU discharge (e.g., 16– 49% of patients with acute respiratory distress syndrome had delirium on their final assessment in the ICU[1,9]), creating a problem with either counting zero for days of delirium after discharge or the feasibility of continuing delirium assessments on the ward given the added time and resources required and the low sensitivity of validated ICU-based delirium screening tools in this setting.[10] The joint modeling approach makes no assumption about delirium for patients discharged from the ICU, such that Patients 3 and 4 contribute the same information to the analysis.

Days with coma are common and can further complicate the calculation of delirium-free days. Patient 5 experiences coma (denoted "c" in Figure 1) for the first two days followed by 3 days of delirium and death at the end of Day 5. This patient has 2 delirium-free days. Days with coma may be included in a modified endpoint of delirium- and coma-free days that would yield a value of 0 for Patient 5. In the joint modeling approach, Patient 5 contributes 3 days of exposure and 3 recurrent delirium events to the analysis; this approach only evaluates days when patients are at risk for delirium (i.e. does not include days when the patient is comatose).

Notably, the joint modeling approach has a limitation of incorporating only a single terminating event model. The single terminating event model is flexible to allow for the possible intervention effect to be defined separately for each terminating event type via a statistical interaction term, as was done in our example. However, the correlation between the recurrent event (i.e. delirium) and the hazard of both terminating events is assumed to be the same. In ICU studies, these two terminating events are likely to be correlated with delirium in opposite directions. In our study, 90% of the 256 terminating events were ICU discharge, minimizing the impact that multiple terminating event models would have on our results. Research into expanding the joint modeling approach to accommodate multiple terminating event models is needed.

Given the many problems with delirium-free days as an endpoint and the recent availability of appropriate and flexible statistical methodology and software, we recommend the use of a joint modeling approach to evaluate the impact of interventions on delirium in the ICU.

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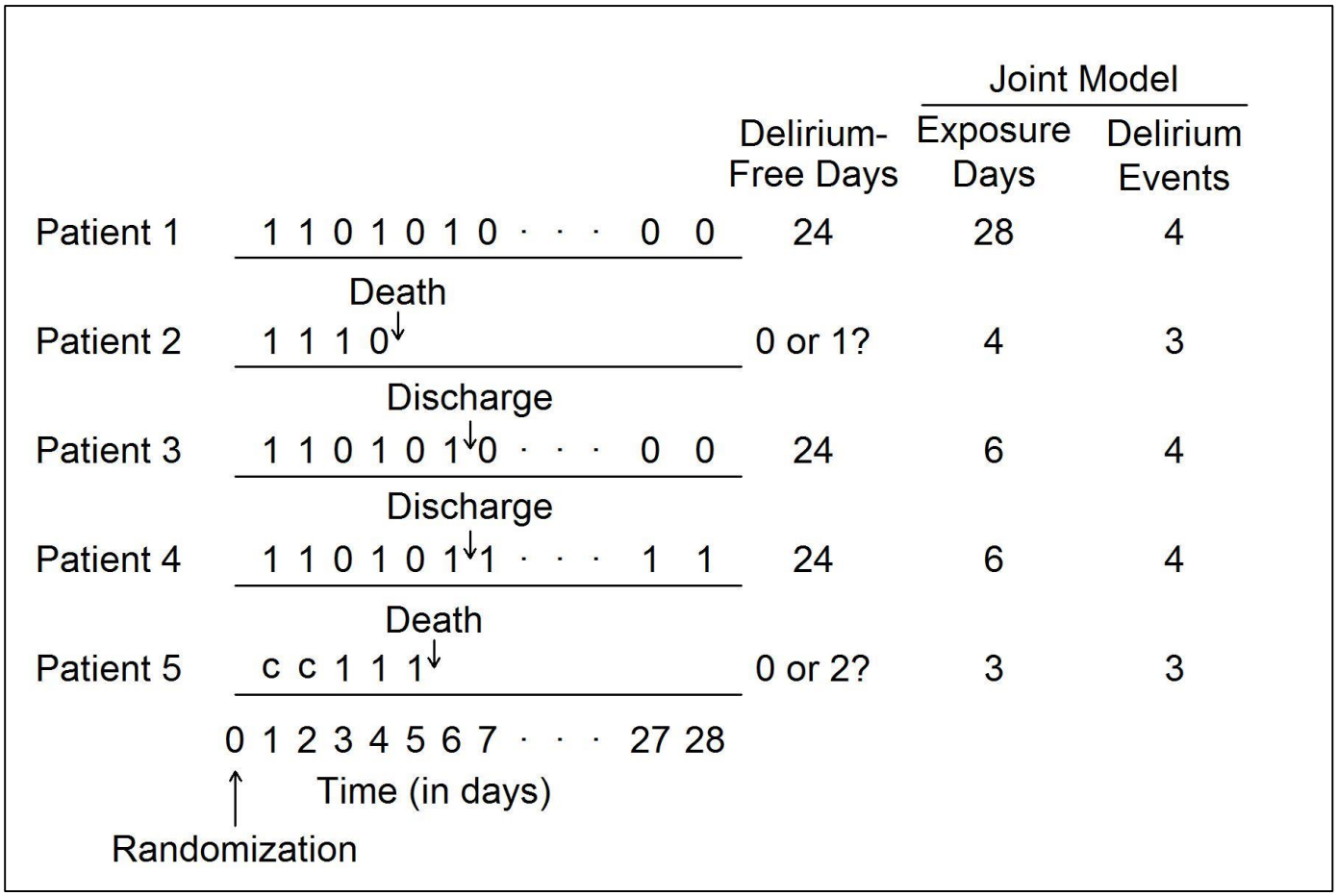
Figure 1: Hypothetical patients from a clinical trial where patients are randomized at day 0 and followed until discharge from the intensive care unit (ICU) or death, up to a maximum of 28 days.



For each patient, delirium-free days to day 28 is calculated along with days of exposure and delirium for the joint modelling approach. 1, 0, and "c" denote a day with delirium, a delirium-free day, and a day in coma, respectively.