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Short report

Landmark prediction of nosocomial infection risk to disentangle short- and long-stay patients

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SUMMARY

Length of stay is one of the key determinants for the risk of nosocomial infections. The distribution of this at-risk time is heavily skewed and depends on discharge or death. This study applied landmark competing risk prediction models to account for a large proportion of short-stay patients and a small proportion of long-stay patients.

Introduction

The risk of nosocomial infections (NI) depends on the time from hospital or intensive care unit (ICU) admission. This at-risk time for NI ends with the occurrence of NI, discharge or death. Thus, when estimating the cumulative infection risk as a function of time from admission, discharge or death constitute two competing events (as the risk of NI after these events is zero).[1]

For medical decisions, it is of clinical interest to predict the risk of acquiring NI, and this is often done at admission or from 48 h after admission. However, most patients stay in ICUs for fewer than five days, and the heavily skewed distribution of ICU length of stay makes prediction challenging. For instance, in a study of 343,555 admissions to 83 ICUs, patients with an ICU stay of five days or longer accounted for 21% of all admissions but 63% of total ICU-days.[2] Such patients are typically associated with higher severity of illness and higher frequency of invasive devices such as mechanical ventilation.[2,3] Classical prediction models (which make predictions from the time of admission) would use all data from all patients without differentiating between short- and long-stay patients.[1] However, these models may not be

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sufficient for long-stay patients as the large proportion of short-stay patients contributes to their risk calculation.

Thus, in order to provide more accurate predictions for NI and to disentangle short- and long-stay patients, landmark competing risk prediction models are proposed.[4] Such landmark models are basically separate competing risk models that condition on landmark points; for instance, when the landmark equals five days, only those patients who stayed in ICUs for at least five days and are still at risk for NI are considered. Landmark models have been applied previously in other medical disciplines such as transplant research.[5,6] As in a standard competing risk setting, there are basically two methods of analysis: analysis of cumulative risks (which relates to prediction) and analysis of all competing-event-specific hazard rates (which relates to aetiology).[7] This study focused on estimating the cumulative risk of NI depending on preselected landmarks. In order to understand the cumulative risk of NI, this study also explored the shapes of all event-specific hazards, which are actually the elements of cumulative risk.

Methods

Real data

Spanish ICU data were used: two ICUs, 6568 admissions, 432 (6.6%) NI (bacteraemia), 762 (11.7%) deaths in ICUs without NI, 5363 (81.7%) discharges without NI, and 10 administratively censored. The data were collected within the ENVIN-HELICS network and have been used previously for studying nested case–control and case–cohort approaches.[8]

Simulated data

Data with constant hazards 0.015 for NI and death were also simulated; the time-dependent discharge hazard followed a Weibull distribution to mimic a decreasing hazard.[9] Code for simulation and analysis is available upon request.

Analysis of hazards and cumulative risk

For both types of data, the actual event-specific hazard rates for NI, death and discharge without NI were estimated. All hazard rates were estimated in dependency of the time since admission, and were interpreted as the instantaneous (daily) risk of experiencing the corresponding event (NI, death or discharge without NI). In a competing event situation, the cumulative risk (in contrast to the instantaneous risk) of NI depends on all competing hazard rates (i.e. the hazard of NI as well as the hazard of death and discharge without NI). This holds analogously for the other two competing events. In contrast in hazards, cumulative risks are always increasing steadily and converge in the case of uncensored data towards simple proportions (see Table I).

For the time-dynamic prediction of cumulative risk, the landmarks of two, five, 10, 15 and 20 days from admission were chosen after inspection of the risk set (number of patients depending on time from admission) and the maximal at-risk time point as a 'fixed horizon'; alternatively, one could use 'sliding windows' such as five or 10 days.[4] For each landmark, the study conditioned on those patients who are still at risk of NI in ICUs, and made cumulative risk predictions of the competing events (NI, death and discharge without NI) using competing risk methodology (Aalen-Johansen estimator).[9] The 'bshazard' and 'etm' packages from R statistical software[9] were used.

Results

In the real data, the NI hazard is rather low in the first days after admission (approximately 0.5%/day) and increases to a peak at 15–25 days after admission (approximately 2.5%/day) (see upper panels in Figure 1); subsequently, the hazard rate decreases slightly. The hazard of death without NI first increases from 1.5%/day to a plateau of 2.2%/day after 15–20 days after admission. The discharge hazard has a steep peak quite early; the chance of being discharged without NI is approximately 20–30%/day at around five days after admission (it is approximately 5–10%/day shortly before and shortly after five days after admission).

The occurrence of death or discharge precludes the occurrence of NI, determines the at-risk time for NI and decreases the risk of NI. Therefore, both hazards influence the cumulative risk of acquiring NI in addition to the NI hazard; the stronger the competing risk hazard, the stronger the decreasing effect on the risk of NI.

The risk of NI predicted from two days after admission increased up to approximately 6% (lower panels in Figure 1), which corresponds to the crude proportion 423/6568. The risk of death without NI increased up to approximately 12%, which corresponds to the crude proportion 762/6568. The risk of being discharged increased up to 82%, corresponding to the crude proportion 5363/6568 (Table I). Most patients are discharged without NI within five days, but they contribute to the risk sets if prediction is made from two days after admission. These cumulative risks are changing for later landmarks to start prediction (Table I and Figure 1): the cumulative risk of NI (and death without NI) is increasing, whereas the cumulative risk of being discharged is decreasing. For instance, when the

Table I
Frequency and proportions of study population depending on landmark points

Landmark (days after admission)	Patients at risk (hospitalized and without NI)	Remaining at-risk time (ICU-days) after landmark and during stay	Patients who acquire NI after landmark and during stay	Patients who die without NI after landmark and during stay	Patients who are discharged without NI after landmark and during stay
2	6567 (100%)	41,453 (100%)	432 (6.6%)	672 (11.6%)	5363 (81.7%)
5	2292 (34.9%)	15,622 (37.7%)	288 (12.6%)	326 (14.2%)	1671 (72.9%)
10	843 (12.8%)	7962 (19.2%)	150 (17.8%)	160 (19.0%)	529 (62.8%)
15	427 (6.5%)	4705 (11.4%)	78 (18.3%)	85 (19.9%)	260 (60.9%)
20	236 (3.4%)	3004 (7.2%)	41 (17.4%)	50 (21.2%)	143 (60.6%)

NI, nosocomial infection; ICU, intensive care unit.