RESEARCH METHODS & REPORTING

Interpreting and comparing risks in the presence of competing events

Competing events are common in medical research. Ignoring them in the statistical analysis can easily lead to flawed results and conclusions. This article uses a real dataset and a simple simulation to show how standard analysis fails and how such data should be analysed

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Introduction

Survival or time-to-event analysis has become a widely used statistical method in medical research.¹ It provides valuable insights into how the risk of the event of interest (such as death or disease) depends on time.² However, the careless application of survival models may easily lead to flawed results when basic assumptions are not fulfilled. For instance, in a recent cluster randomised trial³ not more than 4% of the study patients acquired a primary bloodstream infection in hospital, but the reported cumulative risk of such an infection was up to 25%.⁴ Results from a cohort study of hospitalised children in Kenya reported no association between burns and nosocomial bacteraemia⁵ even though the cumulative risk was three times higher for children with burns.⁶ In a study of intensive care patients⁷ more than 95% were discharged alive, but their survival plots predict a survival probability from the intensive care unit of less than 20%.⁸ Such results are typical when so called competing events prevent us from observing the event of interest (such as primary bloodstream infection, nosocomial bacteraemia, or death in intensive care unit).⁹

Checking model assumptions

In standard survival analysis we are concerned with the time to some event of interest; a patient who has not experienced the event at the end of follow-up is said to be censored. If we want to determine the risk of the event having occurred by a certain time, a fundamental assumption is that such censoring is not associated with an altered chance of the event occurring at any given moment.²

Often, one is interested in specific events such as death due to cancer, but if a patient is censored due to death from another cause the censoring assumption is violated (since the chance of death is now zero). Any such event which causes censoring and which is associated with an altered chance of the event of interest occurring has to be treated as a competing event. Fatal events are quite obvious competing events. For example, death without prior relapse competes with relapse in oncology,^{9 10} and death while waiting for a heart transplant is a competing event for transplantation in cardiovascular research.¹¹

Non-fatal competing events occur if these events change the probability of experiencing the event of interest. If the event of interest is mortality in hospitalised patients and patients are followed up until discharge or death, discharge (alive) is a competing event since discharged patients are usually in better health (with an improved survival) than hospitalised patients.¹² If nosocomial infection is the event of interest, discharge or death without a nosocomial infection are competing events since discharge usually precludes the observation of a nosocomial infection.^{6 13}

Real data example for cumulative risks

We use an example from hospital epidemiology; it is a random sample from a full cohort study that is described in detail elsewhere.¹⁴ In this example, of 1313 patients admitted to hospital, 108 (8.2%) acquired a nosocomial pneumonia (termed "infection" here) and 1189 (90.6%) were discharged (or died) without a nosocomial infection. The remaining 16 (1.2%) patients were administratively censored: they were still

hospitalised at the end of study, and so it is not known which type of event they would experience afterwards. In survival analysis it is important to distinguish between risks (which measure the chance of something happening per individual at risk in a given time period) and hazard rates (which measures risk per unit of time). The daily infection rate is defined as the number of nosocomial infections in a sample divided by the patient-days at risk:

Daily infection rate = (number of patients with a nosocomial infections)/(number of patient-days at risk)

Patient-days at risk is the sum of each patient's length of infection-free hospital stay. In our example, the averaged time at risk (time between admission and nosocomial infection, discharge, or censoring, whichever comes first) was 12.9 days, and there were 1313 patients and 16 953 patient-days at risk. So the daily infection rate is $108/16\ 953 = 0.006$ (0.6%).

During their hospital stay, patients may either acquire a nosocomial infection or they are discharged without a nosocomial infection. That means that discharge without a nosocomial infection is a competing event for a nosocomial infection. We therefore calculate the discharge rate without infection as the number of discharges without infection divided by the number of patient-days at risk:

Daily discharge rate without infection = (number of discharges without infection)/(number of patient-days at risk)

In our example, 1189 patients were discharged without an infection, thus the daily discharge rate is $1189/16\ 953 = 0.07$ (7%).

Relation between overall risks and daily rates

The overall infection risk is related to the infection rate as follows:

Overall infection risk = (daily infection rate)/{(daily infection rate)+(daily discharge rate without infection)}

The number of patient-days at risk cancel out, in our example: $(108/16\ 953)/\{(108/16\ 953)+(1189/16\ 953)\} = 108/(108+1189) = 108/1297 = 0.082$

Thus, the overall infection risk depends on the daily infection but also (and this is crucial) on the competing event, the discharge rate without infection.

Risk accumulates with time

Now, we want to estimate how the risk of a nosocomial infection and the risk to be discharged without a nosocomial infection accumulate with the time from admission. If competing events are accounted for, the cumulative risk (also known as the cumulative incidence function) of nosocomial infection is a product of two probabilities and, therefore, is itself a probability.^{6 15 16} The first term is the probability that an event happens up to time t (either acquiring an infection or to be discharged without an infection), the second term is the probability that this event is an infection. Thus, the cumulative incidence function can be thought of as the probability of observing a specific event up to time t . Separate cumulative risk curves can be calculated for each event, in this case infection and discharge without infection.

Figure 1⇓ shows the cumulative risk of nosocomial infection and of hospital discharge. At every time point, the cumulative probability of nosocomial infection, discharge, and remaining

infection-free in the hospital add up to 100%, the maximal value for a probability (blue and red curves in fig 1⇓). For example, at day 40 after admission, the cumulative risks are 8.2% (nosocomial infection) and 86.1% (discharge), which add up to 94.3%, meaning that the probability to be in hospital without a nosocomial infection is the remaining 5.7%. The other curves in fig 1⇓ show results from a standard survival analysis (as, for example, used in³), ignoring competing events. At day 40 after admission, probabilities are 19.5% (nosocomial infection) and 94.4% (discharge), which add up to 114%, an impossible value for a probability. The bias using the Kaplan-Meier approach is exacerbated if the competing event is relatively common, as in our data example where lots of admissions end in discharge. To overcome this problem we have to account for competing events.

What can happen when comparing risks

Now we consider how competing events affect our ability to compare risks for an exposure of interest. For example, we might be interested to know whether age increases the risk of nosocomial infection, or if a hospital-wide intervention reduced the risk of nosocomial infection. If the exposure is associated with the competing event then this can have surprising effects on our risk estimates. We consider nine hypothetical scenarios (table⇓ and fig 2⇓) and estimate the cumulative incidence function according to a simple formula relating the interplay of risks and rates.^{6 15 16}

In scenarios 1-3, the exposure is not directly associated with the competing event. Hence the daily infection rate ratios are close to the overall infection risk ratios.

In scenario 4, the exposure has no effect on the daily infection risk but decreases the discharge rate—for example, older and younger patients have the same daily infection risk, but older patients stay longer in hospital. This indirectly leads to a increased risk of infection for exposed patients. On the other hand, if exposed patients stay for less time in hospital (increased discharge rate), the overall infection risk would be smaller (scenario 5). Scenarios 4 and 5 show that the exposure can indirectly increase or decrease the overall infection risk, even though the exposure does not directly affect the daily infection risk; it is just the indirect effect of prolonged (or shortened) length of hospital stay that makes exposed patients more (or less) likely to acquire an infection.

In scenario 6, the exposure directly increases the daily infection risk, but exposed patients also have shorter hospital stays, which eventually leads to an equal overall infection risk in both exposure groups. However, the cumulative incidence function differs, and exposed patients have a higher infection risk at earlier times (fig 2⇓). An equal overall infection risk in both exposure groups could also occur if exposed patients have a much smaller daily infection risk but also stay longer in hospital (scenario 7). Scenarios 6 and 7 show that an infection risk ratio of 1 could occur with an infection rate ratio greater or lower than 1 depending on how the exposure decreases or increases the discharge rate.

Infection rate and risk ratios can even differ in sign (scenarios 8 and 9). In these scenarios, the time dependent infection risks are crossing: soon after admission the infection risk for exposed patients is lower than that for the unexposed group, and later it is greater (scenario 8) or vice versa (scenario 9).

Ways of measuring effects

Methods are available to correctly analyse data in the presence of competing risks.^{9 17} These include estimating the risks of

events over time and determining how exposures of interest affect risk.

As a starting point, one should calculate hazard ratios for each event: one daily rate ratio for infection (the event of interest) and one daily rate ratio for discharge without infection (the competing event). These can be obtained from separate Cox proportional hazards regression models or one Cox model using duplicated records.¹⁷ This approach provides an aetiological exploration of risk factors and shows how risk factors are associated with each event; direct and indirect effects can be distinguished.

An additional analysis is necessary to make conclusions on cumulative risks. This is possible with subdistribution hazard ratios, which are interpreted as a comparison of the cumulative incidence functions. As a time-averaged risk comparison, subdistribution hazard ratios extend overall risk ratios. This type of analysis makes use of what is known as a Fine and Gray model.¹⁸

Both approaches are necessary to understand how risk factors are directly and indirectly associated with events of interest when there are competing events.¹⁹ The methods can also account for some important issues which we have neglected in this article, such as time dependent hazard rates, multiple competing events, readmissions and potential confounders. Time dependent hazards and cumulative incidence functions should be estimated using the Nelson-Aalen and Aalen-Johansen estimator¹⁷ to relax our assumption of time constant hazard rate. There are also alternative methods to analyse competing event data.²⁰

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Summary box

In the presence of competing events, classic survival curves (Kaplan-Meier) overestimate cumulative risks and are therefore inadequate

Risk accumulates differently when there are competing events and should be displayed as cumulative incidence functions for each event. Subdistribution hazard ratios measure the effect of exposures in terms of cumulative incidence functions

Reporting one hazard ratio for the event of interest is incomplete, and it does not compare cumulative risks. For an aetiological exploration it is necessary to report hazard ratios also for the competing events

Table

Table 1 | Details of nine possible scenarios for rates of nosocomial pneumonia and of discharge from hospital without infection in a cohort of patients admitted to hospital. Infection and discharge rates are set for an exposed and an unexposed patient group. Then, rate, overall risk ratios and cumulative incidence functions (cumulative infection risks) are calculated based on these values (see fig 2). Note that the overall infection risk ratio compares only the plateau of the curves in the figure. The simulation code is available in the technical appendix of this paper

Scenario	Daily infection rates			Daily discharge rates			Overall infection risk ratio $\{(i_i/(i_i+d_i))/(i_o/(i_o+d_o))\}$
	Exposed (i_i)	Unexposed (i_o)	Infection rate ratio (i_i/i_o)	Exposed (d_i)	Unexposed (d_o)	Discharge rate ratio (d_i/d_o)	
1	0.02	0.02	1	0.15	0.15	1	1
2	0.01	0.03	0.33	0.15	0.15	1	0.375
3	0.03	0.01	3	0.15	0.15	1	2.67
4	0.02	0.02	1	0.1	0.2	0.5	1.83
5	0.02	0.02	1	0.2	0.1	2	0.55
6	0.03	0.01	3	0.3	0.1	3	1
7	0.01	0.03	0.33	0.1	0.3	0.33	1
8	0.01	0.02	0.5	0.1	0.3	0.33	1.45
9	0.02	0.01	2	0.3	0.1	3	0.69

Figures

Fig 1 Cumulative incidence functions of nosocomial pneumonia and discharge from hospital without nosocomial pneumonia in a cohort of 1313 patients admitted to hospital. We use publicly available data from a German cohort study.¹⁴ Data and statistical code are available in the technical appendix of this paper

Fig 2 Cumulative incidence functions of nosocomial pneumonia under nine hypothetical scenarios (see table¹ and text for details of the scenarios)