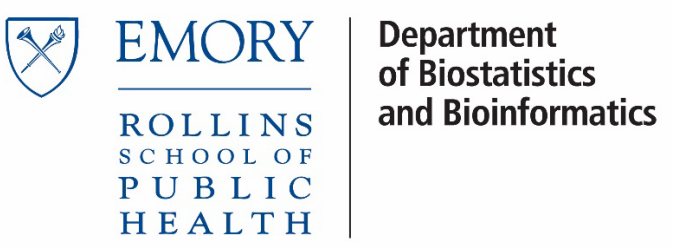


BIOS 522: Survival Analysis Methods

Reading 12:

Competing risks

This week, we will define the concept of competing risks in time-to-event data. We will introduce analytical approaches for estimating cause-specific hazard functions.

Part 1. Competing risks overview

Motivation

Throughout this course we have assumed that there is only one survival endpoint of interest and that the censoring time is independent of the survival time (non-informative censoring). However, there may be settings where our event of primary interest is censored because another event occurs first, and there may be dependence between these events. This other event is known as a **competing risk**.

For example, consider a study of surgical interventions on breast cancer. We are interested in the time from surgery to tumor progression, i.e., worsening of disease. When a patient dies due to other non-cancer causes, their time to tumor progression is censored. Death due to other non-cancer causes is a competing risk.

Examples of competing risks in health studies

Type of study	**Endpoint of primary interest**	**Competing risk(s)**
Cardiovascular study	Cardiovascular death (e.g. fatal myocardial infarction, stroke)	Non-cardiovascular death
Nephrology study	Death on dialysis	Kidney transplant

Intrauterine device (IUD) study	Accidental pregnancy	Expulsion of the device, removal for medical reasons, removal for personal reasons

Where it is reasonable to assume that a competing risk is independent from our endpoint of interest, we can use right censoring to censor observations at the time when the competing risk event occurs. Then we are able to use all of the standard methods available to us. For example, death due to traffic accident may be considered independent from tumor progression.

Often, though, this assumption is not reasonable. Individuals at highest risk of tumor progression may also be at increased risk for death due to other causes because of their overall poor health. If death due to other causes is treated as a censoring event, censoring is informative/correlated with the primary endpoint.

Informative censoring can lead to a lot of bias. It is even possible for this type of censoring to make a covariate that actually increases risk *appear* to be protective, fully reversing the direction of the effect. This could occur in extreme settings where the competing risk event results in heavy censoring in the high-risk population early on.

A simple strategy for handling competing risks is to define a single primary endpoint that includes all types of events (composite endpoint). **All-cause mortality (overall survival)**, for example, is time to either cardiovascular or non-cardiovascular death. **Progression-free survival** includes both disease progression and death due to any cause, whichever comes first. By redefining our endpoint to include the competing risks (making them no longer competing risks, but rather part of the primary endpoint), we can use standard methods to analyze our data.

This strategy comes with some costs, though. In evaluating the efficacy of a blood pressure drug, deaths due to non-cardiovascular causes are of lesser interest than deaths due to cardiovascular causes. The blood pressure drug may also have no impact on non-cardiovascular deaths, and combining them may dilute the effect on cardiovascular deaths. Thus, we want to model the effect of the drug on cardiovascular deaths only.

Alternatively, we may be interested in simultaneously studying multiple events, without specifying one as the primary endpoint of interest. We want to model both the *time until failure* and the *type of failure*. For example, a new blood pressure drug could reduce time until stroke but increase death due to other complications (e.g. kidney failure).

In these types of settings, it is useful to analyze the data using a competing risks framework.

Part 2. Analysis of competing risks data

Notation

Suppose we have m different types of failures, the respective times to failure are:

$$T_1, T_2, \dots, T_m$$

For example, let T_1 be time until cardiovascular death, and let T_2 be time until non-cardiovascular death.

With competing risks, an individual only fails once, so we observe only the earliest failure time:

$$T = \min(T_1, T_2, \dots, T_m)$$

We also observe the failure type j $(= 1,2, \dots, m)$. For example, we know that a person failed due to cardiovascular death $(j = 1)$.

There might also be independent censoring C, in which case we observe:

$$T^* = \min(T, C)$$

Competing risk data are often presented in the form (T_i^*, δ_i) for $i = 1, \dots, n$ where $\delta_i = j$ if the individual failed due to cause j and $\delta_i = 0$ if the individual was censored.

Example with cardiovascular and non-cardiovascular deaths:

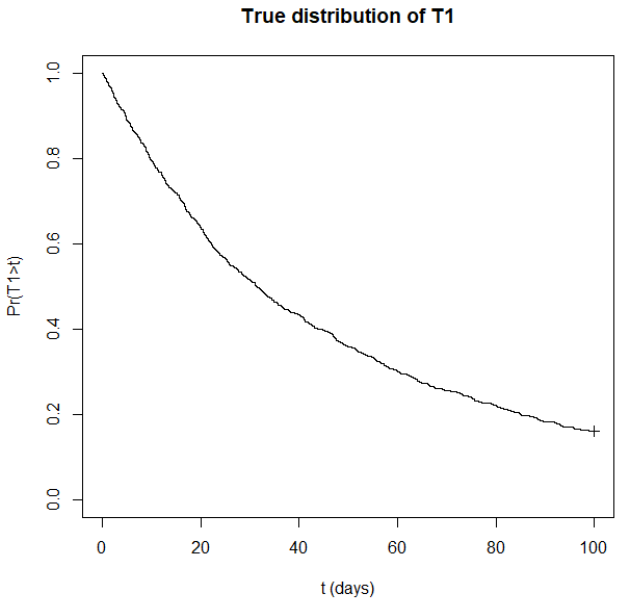
T_i^*	δ_i	**Description**
5 years	1	Cardiovascular death at 5 years
6 years	2	Non-cardiovascular death at 6 years
7 years	0	Censored at 7 years

As mentioned previously, a major challenge is that the event types may be correlated. Individuals at elevated risk of cardiovascular death may also be at elevated risk of non-cardiovascular death. Our analytical methods like Kaplan-Meier estimation rely on independent (non-informative) censoring.

Worked example

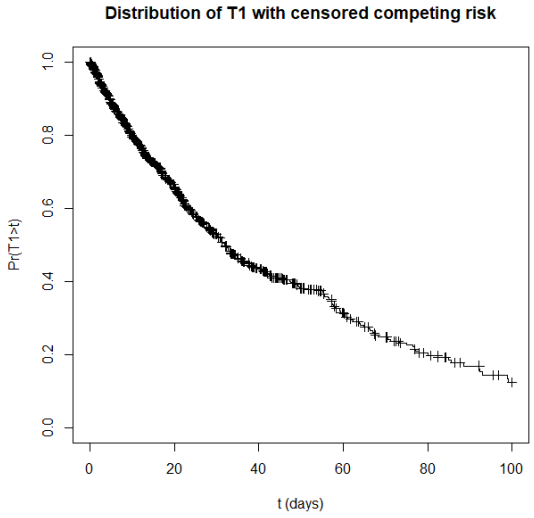
We are interested in studying time until cardiovascular death T_1. Time until non-cardiovascular death T_2 is a competing risk. There is also administrative censoring C in our study that occurs at the end of follow-up (100 days).

If we were able to directly observe the distribution of T_1, imagine that it would have the following shape. This is known as our cause-specific survival function $S_1(t) = \Pr(T_1 > t)$, and it is an estimand of interest.



Yet we are not able to directly observe the distribution of T_1 because there exists a competing risk T_2, that also has some distribution.

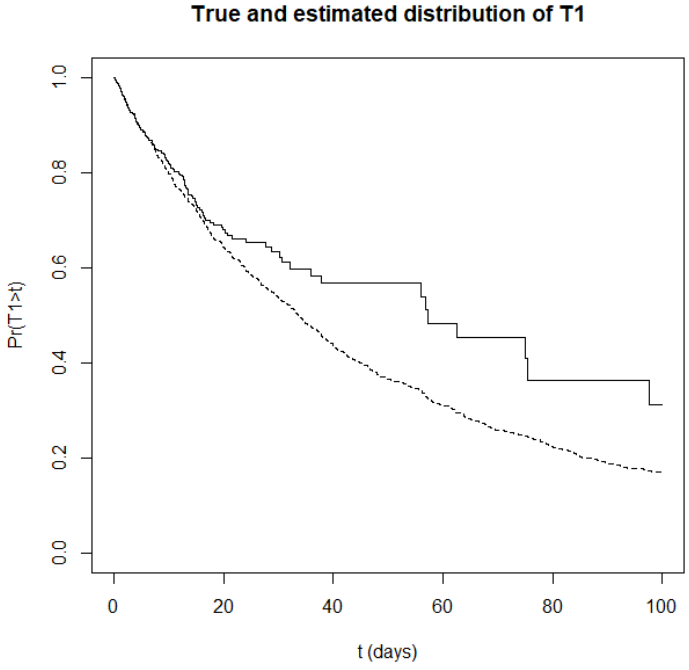
Consider first the setting where T_1 and T_2 are uncorrelated. There is no association between risk of cardiovascular and non-cardiovascular death. When T_2 occurs before T_1, thereby preventing the direct observation of T_1, it is reasonable then to treat T_2 as a censoring time because it is independent.



This figure shows a Kaplan-Meier plot of the times until cardiovascular death T_1, treating non-cardiovascular deaths T_2 as a type of independent censoring.

Note that many observations are censored because non-cardiovascular deaths frequently occur before cardiovascular deaths in this population, yet the estimated survival function faithfully captures the true shape.

Now consider the setting where T_1 and T_2 are positively correlated. A latent variable of underlying health status affects the timing to both events. If we naively treated T_2 as a type of independent censoring, this is what our distribution of T_1 would look like:



The dotted line is the true distribution, and the solid line is the KM estimate of the cause-specific survival function for T_1, treating T_2 as an independent censoring time.

Note that the distribution of T_1 is *over-estimated* in this example because the people who are censored are those who died of non-cardiovascular causes; yet these censored individuals were themselves at high risk of cardiovascular death.

The magnitude of this over-estimation (or under-estimation) depends on the strength of correlation between the outcomes, as well as the frequency of the competing risk. If the competing risk is common, there will be heavy censoring, exacerbating the bias.

Thus, we cannot simply fit a Kaplan-Meier curve for each event type, treating participants with the other event types as censored when there is correlation.

The cause-specific hazard function

Recall that we consider j event types, where $T = \min(T_1, T_2, \dots, T_m)$ is δ specifies the event type.

We can define the **cause-specific hazard function** for failure type j as:

$$h_j(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \Pr(t \leq T < t + \Delta t, \delta = j | T \geq t)$$

This characterizes the hazard of event type j for an individual who has not yet experienced *any* event.

This is not a hazard function for any random variable, but rather is a new concept specific to competing risks.

The **overall hazard of failure** is the sum over the cause-specific hazard functions:

$$h(t) = \sum_{j=1}^{m} h_j(t)$$

The overall hazard of failure is a proper hazard function. It is the hazard function for the composite variable of failure by any type.

The cause-specific hazard function is distinct from the **marginal hazard function**, which characterizes the hazard of event type j for an individual who has not experienced event type j:

$$\tilde{h}_j(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \Pr\left(t \leq T_j < t + \Delta t \middle| T_j \geq t\right)$$

The main challenge in competing risks is that we cannot estimate the marginal hazard function when the risks are dependent. Thus, we cannot estimate the cause-specific survival function $S_j(t) = \Pr(T_j \geq t)$.

While we would like to know the cause-specific for each cause, we cannot estimate this from the data without assuming independent censoring.

Estimable quantities

Instead of estimating the cause-specific survival function, a popular approach to analyze competing risks data is to estimate the **cumulative incidence function (CIF)** for each failure type. It is sometimes also called the **subdistribution function**. The CIF is the probability that failure type j occurs before time t.

$$F_j(t) = \Pr(T \leq t, \delta = j)$$

The type-specific cumulative incidence functions sum up to equal the distribution function for the combined event T:

$$F(t) = \sum_{j=1}^{m} F_j(t)$$

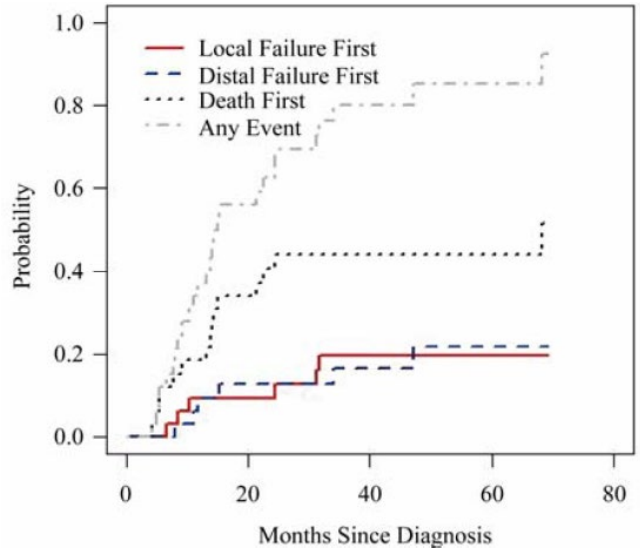
The distribution function for the combined event T is a true CDF, whereas the cumulative incidence functions don't have the same properties. For example, it is likely that $F_j(\infty) < 1$ because there are other causes of failure that will prevent the occurrence of failure type j. In contrast, $\sum_{j=1}^{m} F_j(\infty) = 1$.

The cumulative incidence function is estimated by multiplying an estimate of the combined survival distribution $\hat{S}(t-)$ leading up to the time, times an estimate of the cause specific hazard function, summed over all times:

$$\hat{F}_j(t) = \sum_{t_k : t_k \leq t} \hat{S}(t_{k-1})\, \hat{h}(t_k)$$

Cumulative incidence functions reflect what proportion of the total study population has the particular event by time t. In practice, the type-specific sub-distribution function is presented along with the CIF for each other failure type, and together they provide a complete picture of the results.

For example, consider the following plot from Sandhu et al. (2011). The study included patients aged 75 years and older who received radiotherapy for stage I non-small cell carcinoma. Researchers considered three types of events: (1) local failure first, (2) distal failure first, and (3) death before local or distal failure. These events were analyzed in a competing risks framework.



Time since diagnosis in months is plotted on the x-axis, and the cumulative incidence function for each failure type is plotted on the y-axis. We see that 20 months after diagnosis, approximately 10% of patients had experienced local failure, 12% had experienced distal failure, and 34% had died.

The cumulative incidence functions for each failure type can be added together to estimate the cumulative distribution function (CDF) for T, i.e., $\hat{F}(t)$. The overall survival function is $\hat{S}(t) = 1 - \hat{F}(t)$. This is equal to the survival function that we would calculate if we defined a single primary endpoint that included all types of events (local failure, distal failure, or death).

In the plot above, the gray curve summarizes the cumulative incidence of any event $\hat{F}(t)$. It is the sum of the three type-specific cumulative incidence functions. It is also what we would estimate if we fit a composite endpoint of time to any event. Thus, 20 months after diagnosis, approximately 56% of participants had experienced one of the events. Approximately 44% of participants had not experienced any event.

Part 3. Looking ahead

We are reaching the end of BIOS 522: Survival Analysis Methods. It has been a pleasure having you in the course. Please be sure to complete your evaluations as your feedback is important and highly valued!