Competing risk analyses: how are they different and why should you care?

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Running title: A competing risks primer

Summary/Abstract

Competing risks are events in which at least one precludes the observation of the other, such as toxicity and death. This Commentary discusses and distinguishes between the two common types of competing risk analyses, the Kaplan-Meier and Cumulative Incidence curves.

In this issue of *Clinical Cancer Research*, Dignam et al. [1] discussed how to choose competing risks regression models to evaluate the association between predictors and cause-specific failures of interest. They differentiate the situations in which this choice is important from those where it makes little difference using an RTOG trial of prostate cancer as a nice example. The point of this commentary is to present some background to the issue and, as its title implies, to show how the two principle types of competing risks analysis' interpretations differ from each other. I restrict myself to the one-sample case, and conclude that though each analysis can be the right thing to do, they answer different questions. This conclusion also extends to the multivariable models which are the subject of Dignam, et al.'s investigations.

Consider a treatment failure associated with a time such as late toxicity due to radiation or death in remission after bone marrow transplant in acute lymphoblastic leukemia (ALL) patients, both discussed below. Each failure is subject to a so-called competing risk, or censoring, meaning that some other event interferes with our observation of it. The competing risk may be the happy circumstance of the study ending with a patient lacking evidence of toxicity or death, or it may a different failure such as death in the first case or recurrence in the second. Regardless, it must be accounted for in estimating failure rates. The first way of doing so, in terms of priority and popularity, is the traditional Kaplan-Meier
(KM) estimate [2]. It estimates the probability of a failure in the absence of the competing risk - it mathematically factors it out. The second and increasingly common method of assessing failure rates is by using the cumulative incidence (CI) curve to estimate the probability of failures actually observed in patients who are subject to censoring by the competing risk [3]. The crux of the distinction between the italicized phrases lies in the effect of the competing risk on the estimates: it doesn’t change the Kaplan-Meier curve (besides reducing the effective sample size); but by removing patients from being subject to failure, it will lower the cumulative incidence. Two examples should render this point intelligible.

The first example consists of what academics prefer to call a “spirited discussion” in the pages of the Red Journal. In 1994 Caplan, et al. [4] launched a firm critique of the Kaplan-Meier (KM) curve for estimating rates of cause-specific failures such as late complications of radiation. They point out that the KM estimates of component causes of failure would sum to more than the KM estimate of any cause. This is correct: to take an extreme example, with sufficient follow-up the KM estimate of cause of death due to heart disease would eventually equal one, or nearly so, as would the estimates of death due to cancer, kidney disease, etc. These clearly sum to more than unity, the all cause long-term probability of death [5]. This is because the KM curve estimates probabilities of one failure in the absence of any others. On the other hand, the CI curves of each of these causes of death will sum to the CI of any death. Caplan, et al. concluded that KM analysis of cause-specific failure “should be avoided ... in favor of appropriate methods [CI curves]." Bentzen, et al. [6] and Denham, et al. [7] equally strongly endorsed KM in their rebuttal. Their logic, summarized by Bentzen et al., was that “The reason is that this type of estimate [the CI function] is not specific for the endpoint of interest but is affected by the risk of the competing events as well.” That is, if a late complication is uncommon because most patients die of their disease then the cumulative incidence will be low while the KM could be high: remember, KM estimates late complication rates only among survivors. (The only point which all authors held in common was their dislike of giving crude proportions, that is the total fraction of patients who had late toxicities. These figures are not adjusted for follow-up in any way; thus shorter studies have lower rates.)

Which method is preferable? It depends on the use to which the results are to be put. Chappell [8], in an attempt to get in the last word, asked readers to consider a nonce example in which a population of patients has an 80% mortality rate during the first year of disease with no subsequent events. Suppose also that all survivors exhibit complications by three years. Then CI would give a 20% estimate of gross toxicity at three years along with an 80% estimate of death. That is, only 20% of patients will have toxicities because the rest died too soon. KM, on the other hand, would estimate a 100% toxicity rate among patients who survive three years as well as the 80% mortality. This is no contradiction – the choice depends on the status of the competing risk, death. To a radiation biologist or other theorist seeking to characterize the toxicity process (perhaps out of interest in applying the same regimen to a different group of patients with better prognoses), death is a nuisance
to be factored out and KM would be the right method. But to a patient or physician, death is a quite relevant event and the low chance of toxicity as estimated by CI might be worth possibly extending quality or quantity of life.

I end with a numerical example taken from Klein & Moeschberger [9], to whom I recommend the reader who wants a more thorough explanation of the data and calculations. They consider outcomes among 38 patients who received bone marrow transplant for ALL. The time scale is days after transplant, and one quantity of interest is the chance of a patient dying in remission. The opportunity for this failure to occur is clearly obviated by recurrence as a competing risk. The KM and CI estimates are plotted in the Figure (because KM curves traditionally start at one and decrease to zero, one minus KM is shown here for comparability). We see that, as is generally the case, KM exceeds CI. This is because KM estimates the probability of death in remission assuming no relapse occurs, and CI estimates the probability of death in remission among all patients whose pattern of relapses is similar to that observed in our data. The CI curve is naturally lower because relapsed patients count as a "success" (in terms of death in relapse), while for the KM curve they are eliminated from consideration. The preference again depends upon the question which is being asked and the purposes to which the answer will be put. CI gives the "real-world" chances of an event and KM is more informative about the medical processes involved in treatment-related mortality.

Dignam, et al. extend the KM and CI methods to include covariates with what they label the “Cox CHR” and “Fine-Gray SHR” models, respectively. I hope that the reader has survived this commentary with some intuition about the Kaplan-Meier and cumulative incidence forms of survival curve estimation and, thus enlightened, proceeds to read Dignam et al.’s important work on the topic.


Caption to Figure

Figure 1. Estimated probability of death in remission via CI and KM method. ALL transplant data of Klein and Moeschberger. Cumulative incidence (dashed) and one minus Kaplan-Meier (solid) curves for the probability of death in remission using the bone marrow transplant in acute lymphoblastic leukemia data of Klein and Moeschberger [9].
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