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A brief introduction on competing risks in the context of kidney disease epidemiology

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Competing risk analysis remains underappreciated in applied survival analysis of both observational studies and randomized trials, in part because statistical software enshrined Kaplan-Meier (KM) estimation and Cox regression long before widespread awareness of competing risks existed. However, competing risks are omnipresent, particularly in populations characterized by older age and chronic diseases. Chronic kidney disease (CKD) is the basis of one such population. Throughout both CKD and end-stage kidney disease (ESKD), follow-up of patients for clinical events of interest is complicated by the possibility that an entirely different event may occur first, thereby preventing the occurrence of the event of interest. People with CKD may die before progressing to ESKD. Home dialysis patients may receive a kidney transplant before converting to in-facility hemodialysis. Transplant recipients may experience cardiovascular death before experiencing graft failure. In each case, eventual occurrence of the event of the interest—ESKD onset, home dialysis technique failure, or graft failure—is precluded by occurrence of another event, which is often fatal in nature. When competing events are ignored during the course of analysis, researchers may reach misleading conclusions about absolute risk. However, also inappropriate is the simplistic rubric that automatically applies Fine-Gray regression to settings with competing risks; rather, the specific context of the study should dictate the particular analytic approach. In this article, we review what a competing risk is, the challenge of estimating absolute risk in the presence of competing risks, and regression modeling techniques for survival analysis with competing risks.

In the canonical survival analysis, patients are followed from a well-defined baseline (e.g., the date of diabetes diagnosis) to the date of an event of interest (e.g., the admission date of a hospitalization for myocardial infarction). Of course, some people may not experience the event of interest during the study period and consequently will be censored at the end of their
observed follow-up. Conventional survival analysis methods, such as KM estimation and Cox regression, assume that censoring is non-informative, meaning that the risk of the event of interest is the same, on average, for those who remain in the study and those who exit. For example, administrative end of follow-up, such as the date on which study data were extracted from electronic health records, is typically considered to be a type of non-informative censoring, because if people were followed for another one or two years, more events would surely occur.

However, some reasons for the end of follow-up are informative. One such example is death, which for obvious reasons precludes the occurrence of experiencing any future event. Thus, when estimating absolute risk, it is usually inappropriate to treat death as a censoring event. This is a particularly common feature in studies of CKD progression that specify ESKD onset (i.e., either dialysis initiation or kidney transplantation) as the event of interest. It is well-known that among people with late stage CKD, far more will die than will progress to ESKD. In this context, death is a competing risk. In fact, the word “competing” can be interpreted quite literally if one imagines each person having a theoretical number of years from diagnosis of CKD to ESKD onset and another theoretical number of years from diagnosis of CKD to death. If the former length of time is shorter than the latter, then ESKD “wins” the race and the event of interest is observed. On the other hand, if the latter length of time is shorter than the former, then death “wins” the race and follow-up necessarily ends.

The application of KM estimation to a scenario in which the event of interest faces competition from death can be very problematic. To understand why this is so requires some unpacking of the logic of KM estimation. Suppose we are interested in estimating event-free survival of a nonfatal outcome in a study of 25 patients. Assume that the first two events occur at 6 and 12 months, respectively, and that 4 deaths unrelated to the study outcome occur between 6
and 12 months. Consider the graphical display of a KM survival curve, with its classical “stairstep” pattern starting from 1 (or 100%) at time zero. The building blocks of that display are times at which events occur. In general, KM event-free survival for longer than time $t$ is the product of event-free survival up to time $t$ and 1 minus the proportion of at-risk patients who experience the event at time $t$. Thus, when the first event occurs at 6 months, KM event-free survival is estimated as

$$1 \times \left(1 - \frac{1}{25}\right) = 0.96,$$

or 96%. At the time of the second event, at 12 months, there are only 20 patients at risk since 1 patient already experienced the event and 4 others were censored upon dying. So, the 12-month KM estimate is

$$0.96 \times \left(1 - \frac{1}{20}\right) = 0.912,$$

or 91.2% event-free survival. The cumulative incidence at time $t$, or the probability that an event occurs before time $t$, can be naively estimated as “one minus the KM survival,” which is 4% at 6 months and 8.8% at 12 months.

But are these estimates correct? The KM estimate implicitly assumes that the 20 at-risk people at 12 months are perfectly representative of the 24 people who were under follow-up at the time of the 6-month event, and if only we could have followed further the four people who died between 6 and 12 months, we might have observed additional events. However, this is absurd! These people died. They certainly did not experience nonfatal events after death. Instead, the cumulative incidence function (CIF) can be used to properly account for death as a competing event [1]. The CIF estimate at time $t$ is calculated as the sum of the cumulative incidence up to time $t$ and the product of the KM survival estimate for any event (either the event
of interest or death) up to time $t$ and the proportion of at-risk patients who experience the event at time $t$. Thus, the CIF estimate at 6 months is

$$0 + 1 \times \frac{1}{25} = 0.04,$$

or 4%, and the CIF estimate at 12 months is

$$0.04 + \left[ 0.96 \times \left( 1 - \frac{4}{24} \right) \right] \times \frac{1}{20} = 0.08,$$

or 8%. Thus, prior to the occurrence of any competing events, we see that the KM and CIF methods produce the same estimate of cumulative incidence (4% at 6 months). But after a competing event has occurred, the cumulative incidence is overestimated when using the KM method (8.8%) compared to the CIF method (8%). For this reason, in the presence of competing risks, the CIF method is generally preferred for estimating absolute risk.

As a more concrete illustration, we also show an example of absolute risk estimation with administrative claims data. Using a point prevalent cohort of Medicare fee-for-service enrollees aged 66 and older and with stage 4-5 CKD on January 1, 2015, we estimated the cumulative incidence of progression to ESKD as the event of interest, in the presence of death as a competing risk, over five years of follow-up. Dying before progression to ESKD was the most common event, with a five-year cumulative incidence of 54.9% (Figure). By contrast, the cumulative incidence of ESKD was much lower, reaching only 17.3% by five years using the CIF estimate, which accounts for the competing risk of death. The KM method, which does not account for competing risks, consistently overestimated the cumulative incidence of ESKD. At one year, the KM estimate (7.0%) was modestly larger than the CIF estimate (6.2%) (percentage relative difference, 12.1%), but by five years, the difference (25.6% vs 17.3%) was more substantial (percentage relative difference, 48.1%). Thus, concern over the proper handling of
competing risks may be of particular importance in studies with longer follow-up and common competing events.

Nevertheless, there may be an interest in examining the risk of an outcome in a hypothetical world in which a competing event can be prevented from occurring. For instance, perhaps we want to know the risk of a patient dying while receiving dialysis under the scenario that the patient never goes on to receive a kidney transplant (as elucidated by van Geloven et al [2]). In this specific context, using the KM method (i.e., treating transplant as a censoring event as opposed to a competing risk) would actually be preferred, although the analysis would rely on the untestable assumption of non-informative censoring—namely that transplanted patients have the same underlying risk of death as patients remaining on dialysis. This assumption may or may not be plausible and will heavily depend on the research question at hand.

Consideration of competing events also extends to comparison of CIFs (e.g., using Gray’s test [3]) and the context of regression modeling. In our example, perhaps we are aware that the incidence of ESKD and death vary by the characteristics of the patients in our cohort, and we want to know the impact of these covariates on the CIF estimates. A regression analysis of subdistribution hazards, proposed by Fine and Gray [4], can be used to build a model that uses individual patient characteristics to predict, say, five-year risk estimates for experiencing the various competing events of interest; namely (i) progression to ESKD, (ii) death, and (iii) remaining alive and not having reached ESKD. On the other hand, an analysis of cause-specific hazards using the standard Cox proportional hazards model would, in the presence of competing events, produce biased estimates of predicted risk, since competing events are handled as censored observations in the model. Thus, when there is an interest in using covariates to predict absolute risk, the Fine-Gray model is generally preferred.
However, regression modeling of survival outcomes is not always used for prediction. In the context of causal inference, there remains debate about whether cause-specific or subdistribution estimates should be preferred [5], which sometimes leads to the suggestion to present information from both methods [6]. However, as a word of caution, we would emphasize that each type of model should be viewed as answering a different research question, as opposed to one serving as a type of “sensitivity” analysis for the other. It is also worth noting that other model assumptions (in particular, the proportionality assumption) should be verified when using either type of model.

Regarding the types of questions that can be answered using each regression model, the Medicare claims example is illustrative. Perhaps we are interested in estimating the 5-year relative risk of progression to ESKD for men compared to women. In models adjusted for age and race/ethnicity, the hazard ratio is 1.57 in the Cox model and 1.50 in the Fine-Gray model. While these estimates are numerically similar and demonstrate a higher risk of ESKD among men than women, each has a unique interpretation. The Cox estimate can be interpreted as the relative risk of ESKD between men and women in a hypothetical world in which deaths are prevented (and with the additional assumption that death can be prevented in a way that does not also affect the risk of ESKD [7]). On the other hand, the Fine-Gray estimate represents the relative risk of progressing to ESKD before dying, and it can be interpreted as such without the need for hypothetical qualifications.

In some situations, as an alternative to accounting for competing risks analytically, it may be appropriate instead to combine the outcome of interest and the competing risks into a single, composite endpoint [8, 9]. An example is the inclusion of all-cause death in the definition of
major adverse cardiac events. Although this approach is convenient for analysis, it may compromise the clinical sensibility of an analysis.

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**Author Contributions**

Nicholas Roetker: Conceptualization; Formal analysis; Methodology; Writing - original draft; Writing - review and editing. David Gilbertson: Conceptualization; Methodology; Supervision; Writing - review and editing. Eric Weinhandl: Conceptualization; Methodology; Writing - original draft; Writing - review and editing.
References


**Figure Legend**

**Figure.** Five-year cumulative incidence of ESKD and death in Medicare fee-for-service enrollees aged 66 and older and with stage 4-5 CKD.
Figure

Cumulative incidence

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<tr>
<td>Death prior to ESKD</td>
<td>7.0%</td>
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<tr>
<td>ESKD (death as censoring event)</td>
<td>6.2%</td>
</tr>
<tr>
<td>ESKD (death as competing event)</td>
<td>12.1%</td>
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</tbody>
</table>

Overestimation

Death prior to ESKD
ESKD (death as censoring event)
ESKD (death as competing event)