

An Introduction to Competing Risks

Beenish S. Manzoor, MPH¹, Sruthi Adimadhyam, MS¹, Surrey M. Walton, PhD^{1,2}, ¹Department of Pharmacy, Systems Outcomes and Policy; ²Center for Pharmacoepidemiology and Pharmacoeconomic Research, University of Illinois at Chicago, College of Pharmacy, Chicago, IL, USA



Beenish S. Manzoor, MPH

KEY POINTS . . .

Competing risks are events which prevent the occurrence or modify the risk of the primary event or outcome of interest.

Cumulative incidence function should be used in the presence of competing risks to avoid overestimation and bias that occurs using the traditional Kaplan-Meier method.

In the presence of competing risks, the analyst may determine cause-specific or subdistribution hazards based on their research question.



Survival analysis, or time-to-event analysis, is a cornerstone of health outcomes research. Common examples include studies of treatment related effects related to progression-free survival in cancer patients, time to stroke in patients with atrial fibrillation, or time to receiving a transplant in dialysis patients. Almost always, data sets used for conducting survival analyses include censored observations where patients are lost to follow up or the study period ends before the event of interest has occurred. Conventional methodology used in survival analysis, based on the standard Kaplan-Meier method, typically relies on the assumption of non-informative censoring which asserts that censoring occurs independently of the risk for the outcome of interest [1,2]. Violation of this assumption introduces bias in the analysis. In a cohort of patients where the main outcome is cardiovascular death, patients surviving to the end of the study are censored and this censoring is typically assumed to be non-informative.

Of note, however, is that if a patient is deemed to have died from a non-cardiovascular event during the study period, then the patient is also considered censored when using the Kaplan Meier survival function to evaluate the incidence of cardiovascular death. This latter case of censoring is called a competing risk and often results in informative censoring. The use of a Kaplan-Meier survival function in presence of competing events violate the assumption of independent censoring whenever the competing event results in informative censoring.

This article will provide a brief introduction to methods for describing competing risks, methods to account for competing risks in survival analysis, and practical considerations when using a competing risks framework.

Methods for Competing Risks

Competing risks (CR) are events which prevent the occurrence or modify the risk of the primary event or outcome of interest [2]. In the absence of CR, estimating cumulative incidence of events over time via the

complement of the Kaplan-Meier function (1 minus Kaplan-Meier function) is appropriate. However, in the presence of competing risks, the Kaplan-Meier estimate upward biases the estimation of incidence [2-6] by treating competing events as censored and removing censored observations from the risk sets in subsequent time points. In contrast, the Cumulative Incidence Function (CIF) uses the censored competing event to inform event-free survival probability and consequently, overall survival probability. As such, the incidence derived from CIF is interpreted as the probability of experiencing the primary event conditioned upon not experiencing either event (primary or competing) until that time. Given this, the CIF appropriately calculates incidence by correctly handling competing events, instead of just censoring them.

In traditional survival analysis, the overall survival function (and its complement, cumulative incidence) describes the data. One way to determine the effect of covariates on the survival function is using a Cox proportional hazards model (CPH) which assumes that hazard functions are proportional over time. In a CR framework, data is described using CIF; and the effect of covariates is determined by using either of two different hazard functions: cause-specific or Fine and Gray/ subdistribution. The cause-specific hazard function represents the instantaneous rate of occurrence of the kth event in patients that have not experienced any event and the Fine and Gray subdistribution hazard function represents the instantaneous rate of failure from the kth event in patients that have not experienced any event, plus patients that have experienced a competing event [2]. Given our previous example above, the cause-specific hazard of cardiovascular death describes the instantaneous rate of cardiovascular death in patients that have not experienced any event. Similarly, the subdistribution hazard function describes the instantaneous rate of cardiovascular death in patients that have not experienced any event and those who have experienced death due to non-cardiovascular events. Both of these hazard functions can be employed in hazard regression models,

Table 1: Recommendations for Analyzing Competing Risks [2]

- A cumulative incidence function (CIF) should be used in the presence of competing risks to avoid overestimation and bias using the Kaplan-Meier method in traditional survival analysis
- Depending on the objective of the study, analysts should decide which of the two competing risk hazard functions to use.
- The Cause-specific hazard function is more appropriate for etiologic research objectives.
- The Subdistribution hazard function is more appropriate for prognostic research objectives.

Adapted from Austin et al.[2]

and practical considerations of their use are centered on the objective of the research being conducted. Regression using a cause-specific hazard function will render a coefficient that describes the relative effect of a covariate on the relative increase in the rate of the primary event in observations that are event-free, leading to the examination of the casual relationship between risk factors and an event, and therefore more appropriate for etiologic research objectives including treatment effects [2-3,8]. Whereas regression using the subdistribution hazard function describes the effect of covariates on the incidence and this may be more in-line with predicting the rate of occurrence of events [2,7]. Of course, it may be best to utilize both methods for a full understanding of the impact of particular covariates and/or treatments.

“The use of a Kaplan-Meier survival function in presence of competing events violates the assumption of independent censoring.”

Conclusion

Datasets used in survival analysis may often lend themselves to CR. When informative censoring is related to the treatment or underlying risk factors, then it becomes problematic in measuring treatment effects. CR can also be issue in accurately forecasting events in a decision or markov model. The CIF, accounting for censored observations in its risk set, avoids overestimation compared to the traditional Kaplan-Meier estimate, and is the preferred method of measuring incidence in the

presence of CR. Furthermore, two CR related hazard functions may be employed in hazard regression analysis and should be chosen given the research question. These CR analysis options are available in statistical software packages including SAS, STAT and R, and recommendations for analysis of CR appear in Table 1.

References

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