Competing Risk of Death With End-Stage Renal Disease in Diabetic Kidney Disease

Yue Jiang, Jason P. Fine, and Amy K. Mottl

The concept of competing risks is particularly relevant to survival analyses of diabetic ESRD given the high likelihood of death prior to ESRD. Approaches such as Kaplan-Meier curves and Cox regression models operate on the assumption that there are no competing risks for the event of interest, yielding uninterpretable and generally biased estimates in the presence of competing risks. The cumulative incidence function and Fine-Gray regression are more appropriate methodologies for survival analysis when competing risks are present. We present an example taken from the Action to Control Cardiovascular Risk in Diabetes, a randomized trial of people with type 2 diabetes at high risk for cardiovascular disease. Participants were stratified according to baseline markers of kidney disease: (1) no kidney disease; (2) low estimated glomerular filtration rate; (3) microalbuminuria alone; and (4) macroalbuminuria. The macroalbuminuria group had the highest risk for ESRD and demonstrated the most marked difference between the Kaplan-Meier and cumulative incidence estimator. Cox and Fine-Gray regression models yielded similar risk estimates for baseline characteristics, with the exception of diabetes duration, which was significant in the Cox but not Fine-Gray model. We underscore the importance of competing risk methods, particularly when the competing risk is common, as is the case in diabetic kidney disease.

Key Words: Survival analysis, Competing risk, Diabetic kidney disease, ESRD, Death

INTRODUCTION

Diabetic kidney disease (DKD) is a major public health problem; however, it is the minority of people with diabetes who ultimately experience ESRD, as most will die prior to requiring kidney replacement therapy. Although diabetes alone carries an independent risk for mortality,[1] several large epidemiologic studies have identified that the increased risk for death is predominantly carried by the increased prevalence of kidney disease.[1-3] The increased risk of death from kidney disease is often thought to be due to the increased burden of macrovascular complications accompanying kidney disease; however, there is an increased risk of both cardiovascular and noncardiovascular deaths.[2,3] The severity of albuminuria and low estimated glomerular filtration rate (eGFR) are each independently associated with mortality in both type 1 and 2 diabetes.[1,2,4] ESRD risk also increases with worsening albuminuria and eGFR.[5,6] Absolute and relative risks for ESRD vs death evolve over the natural history of DKD. Although the risk of both outcomes increase with worsening degrees of both albuminuria and eGFR, the risk of ESRD does not rise above the risk for death until late stage disease.[2,7,8]

The relationship between the risks of ESRD and death leads to discussion of a critical methodologic issue in clinical studies of DKD progression: the competing risk of death for diabetic ESRD.[9-11] Most clinical trials for DKD design their primary outcome as a composite of kidney outcomes and death, removing the issue of competing risk. Drugs and therapeutic approaches designed to target cardiovascular outcomes often include kidney outcomes as prespecified, secondary outcomes or are studied in post hoc analyses. This is also often the case for clinical and translational studies aimed at identification of risk factors and biomarkers of DKD progression.[6,7,12] Such studies have often disregarded the competing risk of death, despite the availability of statistical methods designed to deal with this important issue.

Our aim is to call attention to the relevance of competing risks in kidney outcomes, with a goal of permeating this issue into the design of future clinical studies in DKD. We begin by introducing the concept of competing risks in survival contexts and discuss the importance of accounting for it in studies of DKD outcomes. Next, we introduce approaches that extend standard descriptive and inferential methods in survival analysis to the competing risks setting. We provide a real-world application of a competing risk analysis by examining DKD outcomes in the Action to Control Cardiovascular Risk in Diabetes trial. Finally, we summarize the results of the analysis and provide suggestions and implications for future clinical investigators.

IMPORTANCE OF COMPETING RISKS IN DIABETIC KIDNEY DISEASE

In the standard survival analysis context, individuals are observed through a period of time until an event of interest ("failure") occurs. The outcome of interest is the time to that event, or the time to censoring, whereby the patient survives follow-up without experiencing the event of interest, with investigators observing only the maximum failure-free time. Investigators often assume noninformative censoring, meaning that individuals who are censored have the same probability of experiencing the event of interest as noncensored individuals.

From the Department of Biostatistics, University of North Carolina School of Public Health, Chapel Hill, NC; and University of North Carolina Kidney Center, UNC School of Medicine, Chapel Hill, NC.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Amy K. Mottl, MD, MPH, UNC Kidney Center, 7024 Burnett Womack; CB#7155, Chapel Hill, NC 27599-7155. E-mail: amy_mottl@med.unc.edu

1548-5595/$36.00

https://doi.org/10.1053/j.ackd.2018.01.008

The literature for standard survival analysis is well established and widely used by clinicians. Investigators often use the nonparametric Kaplan-Meier (K–M) estimator to estimate survival functions, the log-rank test to test differences in estimated survival functions, and the Cox proportional hazards model to estimate covariate effects on the event hazard.[8,13] Such analyses do correctly account for censoring due to noninformative loss to follow-up or dropout. However, it is often the case that individuals may experience more than a single type of event: the "event of interest" (ie, the outcome being studied) and one or more events other than the one of interest. When such alternate events preclude the occurrence of the event of interest, we say that these events are competing risks; once the alternate event occurs, it becomes impossible for the event of interest to happen. This differs conceptually from the standard concept of censoring, wherein the event of interest could potentially occur after censoring. The presence of competing risks complicates the analysis of time to event outcomes.[14,15]

In many published analyses, investigators treat competing risks as independent censoring, using for instance K-M estimates or the Cox proportional hazards model. Treating death as censoring as opposed to a competing event leads to either biased estimates of measures of interest or results that must be viewed in artificial contexts that may have little clinical relevance. The K-M estimate is biased in competing risk scenarios because individuals are treated as being at risk for a specific event (ESRD) after having already failed from a competing event (death). By decreasing the number of individuals in the risk set via censoring, we overestimate the probability of experiencing the event of interest.[16] Furthermore, even if the competing risk and the event of interest are independent, the K-M estimates the ESRD event probability in a world where nobody is at risk of death before ESRD, a situation with little practical relevance for patient populations with a substantial risk of death.[17]

In DKD, competing risks are a particular concern, since diabetes, worsening eGFR, and albuminuria all increase the risk of cardiovascular events and all-cause mortality. As will be shown in the case study, the magnitude of the bias from using noncompeting risks methods when a competing risk approach is warranted depends on the absolute and relative risks for the primary outcome vs the competing outcomes. In many nephrology contexts, the risk of death is high, and so, the use of noncompeting risk approaches will lead to noticeably biased estimates of event incidence, covariate effects, or other measures of interest.

CLINICAL SUMMARY

- In survival analysis, a competing risk is an event which precludes the possibility of experiencing the event of interest, such as the case of death as a competing risk for ESRD.
- The cumulative incidence function is the appropriate for quantifying event-specific probabilities in the presence of competing risks (eg, death prior to ESRD), yielding results which are more easily interpreted in clinical settings, as compared with noncompeting risk approaches such as Kaplan-Meier, which is interpreted in hypothetical populations where death is not a possibility.
- Kaplan-Meier is generally upwardly biased in estimation of the cumulative incidence function and as the incidence of a competing risk rises (as does death in progressive diabetic kidney disease), Kaplan-Meier will yield more upwardly biased results, highlighting the importance of competing risk approaches in analyses of diabetic ESRD.
- In evaluating risk factors on the cumulative incidence of ESRD mortality, the subdistribution hazard regression model should be used which correctly accounts for the competing risk of non-ESRD mortality and not standard proportional hazards regression.

INTRODUCTION TO COMPETING RISKS

Let us assume that our population is followed from some baseline, with the time to an event denoted by T. The survival function ($S(t)$) gives the probability that an event has not yet occurred by some time t and is commonly estimated by the K-M estimator. In survival analysis, T is often equivalently characterized by its hazard function, which describes the instantaneous rate of event occurrence at time t given that it has not yet occurred. Let us also assume that there are multiple competing event causes, described by a variable J taking values 1, 2, … to the number of distinct event causes. Suppose we are interested in the hazard of event type j. In the presence of competing events, there are 2 hazard functions of potential interest, each with different interpretations and uses:

- The cause-specific hazard (noncompeting risk approach), the instantaneous rate of failing from cause j, given that no events of any cause have yet occurred.
- The subdistribution hazard (competing risk approach), the instantaneous rate of failing from cause j, given that no events of cause j have yet occurred.

The 2 hazards differ in the set of patients at risk. In the former, everyone who has not yet failed at time t is considered to be in the risk set, implicitly censoring subjects who have experienced a competing event by time t. With the subdistribution hazard, we additionally include those who have failed of a competing cause, noting that such individuals remain in the risk set after their failure time for the competing risk forevermore.

Cumulative Incidence Function Estimation

Though the complement of the K-M estimate of the survival function, $1 - \widehat{S}(t)$, is often used to estimate the total incidence of events by time t, it is problematic to use this estimator to provide cause-specific estimates in the competing risks setting, since the sum of cause-specific K-M estimates is larger than the estimate of incidence of all-cause failure. To address this limitation, one may instead use the cumulative incidence function (CIF) (also known as the subdistribution function, as it has a direct