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Competing Risk of Death: An Important Consideration in Studies of Older Adults

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Abstract

Clinical studies are often faced with the difficult problem of how to account for participants who die without experiencing the study outcome of interest. In a geriatric population with considerable comorbidities, the competing risk of death is especially high. Traditional approaches to describe risk of disease include Kaplan-Meier survival analysis and Cox proportional hazards regression; however, these methods can overestimate risk of disease by failing to account for the competing risk of death. In this report, we discuss traditional survival analysis and competing risk analysis as used to estimate risk of disease in geriatric studies. Furthermore, we provide an illustration of a competing risk approach to estimate risk of second hip fracture in the Framingham Osteoporosis Study, and we compare the results with traditional survival analysis. In this example, survival analysis overestimated the five-year risk of second hip fracture by 37% and the ten-year risk by 75% compared with competing risk estimates. We conclude, that in studies of older individuals in which a substantial number of participants die during a long follow-up, the Cumulative Incidence Competing Risk (CICR) estimate and Competing Risk Regression (CRR) should be used to determine incidence and effect estimates. Use of a competing risk approach is critical to accurately determine disease risk for elderly individuals, and therefore best inform clinical decision-making.

Keywords

competing risk; competing risk regression

Introduction

In prospective studies of disease outcomes, statistical approaches such as Kaplan-Meier survival analysis and Cox proportional hazards regression are typically used to account for unequal follow-up time, such as when individuals die or drop-out prior to study completion. It is important to note, however, that these survival analysis methods were originally developed to describe all-cause mortality (rather than incident disease) in the presence of a loss to follow-up that is independent of the study outcome (1). When KM estimates and Cox proportional

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hazards models are used to describe outcomes other than all-cause mortality in the presence of a significant and related competing risk, such as death, these methods may lead to biased results (2-6).

Geriatric researchers frequently conduct investigations of disease outcomes where the competing risk of death is high due to the increased age and co-morbidities of older participants. Table 1 lists examples of geriatric studies where a significant competing risk is present, and it describes how traditional survival analysis may result in a biased calculation of disease risk.

Alternative statistical approaches have been developed to account for the presence of competing risks. Given that the success of improving health care in the elderly population is in part dependent on an accurate reporting of the incidence and predictors of disease, it is important that future geriatric studies adequately account for the competing risk of death in their analyses. Therefore, our objective was to highlight for clinical researchers and health care providers the bias that may result when applying standard survival analysis to estimate risk of disease outcomes in elderly populations with high mortality, and to provide alternative statistical approaches to minimize this bias.

Defining Competing Risk

A competing risk is an alternative outcome that is of equal or more significant clinical importance than the primary outcome *and* alters the probability of the outcome of interest (2). Clinically geriatricians often consider competing risks when caring for elderly patients. For example, it is common for a geriatrician to ask, ‘Will my patient benefit from this new medication, or is my patient more likely to die from other co-morbidities without the opportunity for gain?’ Despite the clinical importance of this question, competing risks are less frequently regarded in disease outcomes research.

The concept of competing risks within clinical research was first introduced in the field of Oncology (7). As treatment for cancer produced prolonged survival times, it became important to consider not only the effects of treatment on cancer-free survival, but also how competing risks, such as mortality from unrelated causes, might impact treatment decisions. As an illustration, consider a retrospective cohort study among men over the age of 70 years with clinically localized prostate cancer (8). Over twenty years of follow-up, 66% of men died from causes unrelated to prostate cancer compared with 30% who died from causes related to prostate cancer. Thus, the authors concluded that aggressive treatment for prostate cancer may not be appropriate in all older men with localized disease.

A competing risk may include an alternative outcome other than death. For instance, in a study of time-to-coronary artery bypass grafting (CABG) among individuals with coronary artery disease, percutaneous coronary intervention may be considered a competing risk to CABG (3). It is important to note that in order to control for a competing risk, it should be a discrete, measurable event that influences the occurrence of the primary outcome. For example, in a study of time-to-nursing home placement, recent hospitalization may influence nursing-home placement, but it would be difficult to consider as a competing risk given that the indication for hospitalization often overlaps with the indication for nursing home placement.

Statistical Approaches to Describe Incidence in the Presence of Competing Risks

A traditional approach to describe incidence of disease in the presence of incomplete follow-up utilizes a Kaplan-Meier estimate (KM). This statistical method was originally developed to describe *mortality* in the presence of incomplete follow-up from unrelated causes (i.e. study

drop-out) (1). It has since been widely adopted by economists, engineers, and scientists to describe *event-free survival*, or *time-to-event* (1-KM), for a number of different outcomes. An important assumption of KM survival analysis is that subjects who have not experienced the primary outcome and cannot be followed to study completion *for any reason* are censored. Censored subjects are considered “at risk” for the primary outcome for the duration of the study regardless of the reason why they were censored.

While this assumption works well when the primary outcome of interest is all-cause mortality, it often fails in the presence of competing risks. Consider a hypothetical study of the effect of delirium on hospitalization among nursing home residents. In this study, many nursing home residents will die without being hospitalized, and a few residents may transfer facilities with loss-to-follow-up. Using a KM approach, both the residents that died and the residents with incomplete follow-up will be censored. Censored subjects will be considered “at risk” for hospitalization for the duration of the study, yet deceased residents cannot possibly be at future risk for hospitalization. By failing to account for the competing risk of death, KM estimates will *overestimate* the incidence of hospitalization among nursing home residents. Among delirious nursing home residents with high mortality, this overestimation may be substantial.

To minimize this type of bias, alternative approaches have been suggested to estimate disease incidence in the presence of a competing risk. For instance, in the above example one could exclude all residents who were censored due to the competing risk of death. This approach has its drawbacks. By removing all residents who died, one will decrease the sample size and introduce survivor bias as the remaining population will be healthier than the reference population.

Alternatively, a Cumulative Incidence Competing Risk (CICR) estimate was developed specifically to describe the probability of disease in the presence of a competing risk, such as mortality (2). Unlike KM estimates that describe the probability of disease conditional on *disease-free survival*, CICR estimates describe the probability of disease conditional on *disease-free and competing risk-free survival*. For example, when calculating the time-to-relapse of cancer following chemotherapy, the CICR estimate describes the probability of cancer-free survival adjusting for the associated risk of dying from infection, bleeding, or other causes.

While the Cumulative Incidence Competing Risk method has been in existence for some time, surprisingly it remains infrequently used by clinical geriatric researchers. It is available using statistical software including a SAS macro (9) and through the publicly available software R, *cmprsk* package (version 2.5.1, <http://www.r-project.org>). Scrucca et al. provides detailed instructions on how to download, use, and interpret the *cmprsk* package using the software R (10). Appendix 1 provides a numerical calculation of the difference in estimates obtained when using a KM versus a CICR approach.

Statistical Approaches to Multivariable Regression Modeling in the Presence of Competing Risks

In prospective studies where follow-up time varies, KM and Cumulative Incidence Competing Risk estimates describe univariate or bivariate associations. In contrast, Cox proportional hazards regression uses multivariable risk ratios (hazards ratios) in order to account for confounding. Nonetheless, Cox regression may still lead to biased effect estimates in the presence of competing risks (7).

Let us consider a hypothetical study to determine the effect of smoking on lung cancer in a group of elderly men. In this study, many elderly male smokers will die of heart disease or

stroke before they have the opportunity to be diagnosed with lung cancer. When applying Cox regression, men who die without a diagnosis of lung cancer are censored. If the proportion of smokers who died from cardiovascular disease is much greater than the proportion of smokers who were diagnosed with lung cancer, it may appear that smoking is actually protective of lung cancer.

It is important to note that checking the proportional hazards assumption does not remove the possibility of bias introduced by a competing risk. The purpose of the proportional hazards test is to determine whether the effect of an exposure on the primary outcome is stable over time. In the above example, the proportional hazards assumption may still hold true if the risk of developing lung cancer among smokers versus non-smokers is relatively constant over time.

One solution to modeling effect estimates in the presence of a competing risk is to construct non-cause specific models (i.e. the effect of smoking on lung cancer *and* cardiovascular death combined). This approach has its limitations, primarily that interpretation of the results is difficult.

Consequently, Fine and Gray developed Competing Risk Regression (CRR) that considers the effect of predictors on the subhazard function (cumulative incidence function) *accounting for the presence of competing risks* (11). This method is based on the Cox proportional hazards model, and it does allow for the inclusion of time-varying covariates. Programming for CRR is publicly available using the statistical software R, *cmprsk* package (version 2.5.1, <http://www.r-project.org>). We provide in Appendix 1 a numerical example comparing the differences in effect estimates calculated by Cox regression versus CRR based on the Fine and Gray approach.

An alternative approach to determine effect estimates in the presence of a competing risk was developed by Klein and Anderson (12). This method is based on generalized estimating equations that include pseudovalues derived from a jackknife statistic (difference between the complete sample and the leave-one-out sample constructed from the cumulative incidence curve). SAS macros or the software R (13) can be used to calculate effect estimates with this approach. Effect estimates derived from the Klein and Anderson method yield similar results to those derived from the Fine and Gray method (12).

Alternative Approach to Model Risk of Repeated Disease in the Presence of Competing Risks

The competing risk models that we have described are meant to estimate a unique, time-to-event outcome in the presence of a competing risk. However, it is possible to have a repeated outcome of interest that is affected by a competing risk. For example, in a study of risk factors for injurious falls, investigators may choose to model injurious falls as a repeated outcome, yet they may also want to consider the effect of mortality as a competing risk. Joint modeling allows for the consideration of competing risks that affect a repeated outcome or competing risk of interest (14,15). In this type of modeling, the model for the longitudinal outcome of interest (such as a generalized linear mixed effects model) is linked to a sub-model for competing risks data by latent random effects.

Application of Competing Risk Approach in Aging Research

A competing risk approach has been most commonly used to calculate incidence and progression of cancer when the competing risk of death from treatment toxicities or unrelated causes may be great. Examples from aging research that used a competing risk approach include a 3-year study of the association between constriction of life space and the development of

frailty (16), and a 15-year study of early and late age-related macular degeneration (17). Since a large proportion of subjects died in these studies without developing the outcome of interest, a competing risk approach helped to minimize the bias that would have been introduced had traditional survival analysis been performed.

Simulation Study of Second Hip Fracture According to Varying Mortality as Calculated by Standard Survival Analysis and Competing Risk Analysis

In this section, we performed a simulation study in order to compare standard survival analysis versus a competing risk approach in a study of second hip fracture in older adults with a prior hip fracture. We calculated the incidence of second hip fracture and relative risk of second hip fracture associated with age at the time of the first hip fracture using standard survival and competing risk analysis.

Participants included 481 cohort members of the Framingham Heart Study who experienced an initial hip fracture between 1948 and 2003, and were followed until the occurrence of second hip fracture, death, dropout, or study completion (2003) (18).

We estimated incidence of second hip fracture at 1,3,5, and 10 years using survival and competing risk analysis. For survival analysis, we calculated time-to-event, or (1-KM), estimate of incidence, and for competing risk approach, we used a Cumulative Incidence Competing Risk estimate. Traditional survival analysis is not affected by competing risks (i.e. mortality), whereas competing risk estimates are conditional on mortality. Thus, we varied mortality between 10-85% in these analyses in order to illustrate the difference in estimates obtained when using survival analysis versus a competing risk approach.

Next we examined the *unadjusted* risk of second hip fracture associated with age (per 5 years) at the time of the first hip fracture. We calculated hazard ratios (and 95% confidence intervals) using Cox proportional hazards regression and compared these to hazards ratios using Competing Risk Regression. Again, in order to demonstrate the significance of competing risks, we varied the competing risk mortality from 10-85%.

Results

In our study of second hip fracture, 15% of subjects experienced a second hip fracture (median follow-up = 4.2 years; range 4 days to 43 years). During follow-up, a much greater proportion of subjects died without experiencing a second hip fracture (73%), with most deaths (50%) occurring within 4-years of the first hip fracture.

Using traditional survival analysis, median time to second hip fracture was estimated as 26 years, and the incidence of second hip fracture at 1, 3, 5, and 10 years was 3%, 7%, 11%, and 21%, respectively. A competing risk approach resulted in a lower estimate of incidence: 3%, 6%, 8%, and 12%, respectively. Of note, the magnitude of the difference between incidence of second hip fracture as calculated by these two methods increased with duration of follow-up.

Furthermore, when using a competing risk approach and assuming a low mortality of 10%, the 10-year incidence of second hip fracture was estimated to be as great as 19%. When mortality was increased to 85%, incidence of second hip fracture decreased to 11% (Figure 1). Thus, the difference in incidence of second hip fracture as calculated by traditional survival analysis versus competing risk approach increases with increasing mortality.

The hazard ratio for advancing age (per 5 years) and risk of second hip fracture as calculated by Cox regression was 1.3 (95% CI 1.1, 1.5), indicating that advancing age is associated with

an *increased* risk of second hip fracture. In contrast, the hazard ratio calculated by Competing Risk Regression was 0.9 (95% CI 0.8, 1.0), suggesting that advancing age is associated with a *reduced* risk of second hip fracture.

Using a competing risk approach, as mortality increased the CRR hazard ratio decreased (Figure 2). For example, when mortality was 10%, advancing age was associated with a 20% *increased* risk of second hip fracture (95% CI 1.0, 1.3); however, when mortality was 85%, advancing age was associated with a 10% *reduced* risk of second hip fracture (95% CI 0.8, 1.0). Varying mortality made no difference in the effect estimate of age on risk of second hip fracture as calculated by Cox regression, thus, the difference between effect estimates as calculated by these two methods increased as mortality increased (Figure 2).

Our results demonstrate that traditional survival analysis overestimated the incidence and effect estimates in a study of second hip fracture. When calculating incidence, the magnitude of bias increased as duration of follow-up increased. For example, 1-year incidence of second hip fracture was 3% as calculated by both traditional survival analysis and competing risk approach. However, the 5-year incidence of second hip fracture was estimated as 37% greater and 10-year incidence was 75% greater using survival analysis compared with a competing risk approach. We also showed that as mortality (i.e. competing risk) increased, the bias introduced by calculating incidence and effect estimates using standard survival analysis increases.

Our results point out another limitation of applying a traditional survival analysis in the presence of competing risks: the interpretation of median time-to-events. Using a standard time-to-event approach, we found the median time to second hip fracture was 26 years. This statistic in itself is misleading as far less than 50% of elderly persons with a hip fracture will experience a second hip fracture. In reality, only 15% of subjects experienced a second hip fracture by the end of follow-up, and only 12% were alive at study completion with additional opportunity to experience a second hip fracture.

Summary

It is important to accurately describe the incidence, timing, and risk factors of disease in the geriatric population. In order to do this, it is necessary to consider both the probability of disease and the competing risk of death. Traditional KM estimates and Cox regression are not designed to account for the competing risk of death, and thus, they can overestimate risk of disease in elderly individuals with high mortality.

Of importance, when follow-up time is short or if the competing risk is low, the difference between traditional survival analysis and competing risk approach may not be substantial. Thus, it may not always be necessary to apply a competing risks approach even in the presence of a competing risk. However, when the proportion of subjects experiencing a competing risk is equal or greater to the proportion of subjects experiencing the primary outcome, or when follow-up exceeds 5-years, a failure to consider competing risks can lead to biased results. In these circumstances, researchers should perform additional competing risk analyses in order to demonstrate that results are not biased.

In conclusion, we recommend a competing risk approach to estimating incidence and effect estimates in geriatric studies with long follow-up where mortality unrelated to the study itself may be substantial. A competing risk approach will result in more accurate estimates of disease risk. An accurate determination of an elderly individuals' risk for subsequent disease is likely to have implications on clinical decision-making for geriatricians and their patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Simulated Estimates of Incidence of Second Hip Fracture According to Varying Mortality as Calculated by Cumulative Incidence Competing Risk Estimates

Figure 2. Difference in Cox Regression and Competing Risk Regression Results when Calculating the Effect Estimate of Age on the Risk of Second Hip Fracture in a Simulation Study with Varying Mortality

Table 1

Examples of Geriatric Studies with Competing Risks that Could Affect the Calculation of Risk of Disease

Geriatric Study Example	Competing Risks	Consequence of Ignoring Competing Risks
Incidence of second hip fracture	Mortality following the first hip fracture	Overestimate incidence of second hip fracture
Cancer related mortality following treatment for breast cancer in post-menopausal women	Mortality from treatment toxicity; non-cancer related mortality	Overestimate breast cancer related mortality
Time to coronary artery bypass surgery (CABG) in elders with cardiac disease	Percutaneous intervention (PCI)	Overestimate time to CABG
Impact of delirium on hospitalization among frail nursing home residents	Mortality within nursing home	Biased effect estimate of delirium on risk of hospitalization
Impact of age on macular degeneration	Mortality	Biased effect estimate of age on risk of macular degeneration