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

Sarah D. Berry, MD, MPH,† Long Ngo, PhD,‡ Elizabeth J. Samelson, PhD,*† and Douglas P. Kiel, MD, MPH*†*

Clinical studies often face 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, but these methods can overestimate risk of disease by failing to account for the competing risk of death. This report discusses traditional survival analysis and competing risk analysis as used to estimate risk of disease in geriatric studies. Furthermore, it illustrates a competing risk approach to estimate risk of second hip fracture in the Framingham Osteoporosis Study and compares the results with traditional survival analysis. In this example, survival analysis overestimated the 5-year risk of second hip fracture by 37% and the 10-year risk by 75% compared with competing risk estimates. In studies of older individuals in which a substantial number of participants die during a long follow-up, the cumulative incidence competing risk estimate and competing risk regression should be used to determine incidence and effect estimates. Use of a competing risk approach is critical to accurately determining disease risk for elderly individuals and therefore best inform clinical decision-making. **J Am Geriatr Soc 58:783–787, 2010.**

Key words: competing risk; competing risk regression

In prospective studies of disease outcomes, statistical approaches such as Kaplan-Meier (KM) 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 before study completion. These survival analysis methods were originally developed to describe all-cause mortality (rather than incident disease) in the presence of loss to follow-up independent of the study outcome.[1] When KM estimates and Cox proportional 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 in which the competing risk of death is high because of the older age and comorbidities of older participants. Table 1 lists examples of geriatric studies in which a significant competing risk is present and indicates 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 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, the objective of the current study was to highlight for clinical researchers and healthcare 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 comorbidities without the opportunity for gain?" Despite the clinical importance of this question,

*Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts; †Divisions of Gerontology and ‡General Internal Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

Address correspondence to Sarah D. Berry, Hebrew SeniorLife, Institute for Aging Research, 1200 Centre Street, Boston, MA 02131. E-mail: sarahberry@hrca.harvard.edu

DOI: 10.1111/j.1532-5415.2010.02767.x

© 2010, Copyright the Authors
Journal compilation © 2010, The American Geriatrics Society
0002-8614/10/$15.00

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 after the first hip fracture	Overestimate incidence of second hip fracture
Cancer-related mortality after treatment for breast cancer in postmenopausal women	Mortality from treatment toxicity; non-cancer-related mortality	Overestimate breast cancer–related mortality
Time to CABG in older adults with cardiac disease	Percutaneous intervention	Overestimate time to CABG
Effect of delirium on hospitalization in frail nursing home residents	Mortality within nursing home	Biased effect estimate of delirium on risk of hospitalization
Effect of age on macular degeneration	Mortality	Biased effect estimate of age on risk of macular degeneration

CABG = coronary artery bypass surgery.

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 affect treatment decisions. As an illustration, consider a retrospective cohort study in men aged 70 and older with clinically localized prostate cancer.[8] Over 20 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 outcome other than death. For instance, in a study of time to coronary artery bypass grafting (CABG) in individuals with coronary artery disease, percutaneous coronary intervention may be considered a competing risk to CABG.[3] 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 uses a KM estimate. This statistical method was originally developed to describe mortality in the presence of incomplete follow-up from unrelated causes (study dropout).[1] Economists, engineers, and scientists have since widely adopted it 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.

Although 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 in 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, the residents who 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 dead 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 in nursing home residents. In 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, all residents who were censored because of the competing risk of death could be excluded. This approach has its drawbacks. By removing all residents who died, the sample size will be decreased and survivor bias introduced because 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 after chemotherapy, the CICR estimate describes the probability of cancer-free survival adjusting for the associated risk of dying from infection, bleeding, or other causes.

Although the CICR method has been in existence for some time, it remains surprisingly 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). One study provides detailed instructions on how to download, use, and interpret the *cmprsk* package using software R.[10] Appendix S1 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 in which follow-up time varies, KM and CICR estimates describe univariate or bivariate associations. In contrast, Cox proportional hazards regression uses multivariable risk ratios (hazards ratios) 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.

Checking the proportional hazards assumption does not remove the possibility of bias that a competing risk introduces. 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 in smokers versus nonsmokers 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 (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), which 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 allows 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). Appendix S1 provides a numerical example comparing the differences in effect estimates calculated using Cox regression with CRR based on the Fine and Gray approach.

Klein and Anderson developed an alternative approach to determine effect estimates in the presence of a competing risk.[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 using 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, although 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, but 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 submodel 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] Because 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 Using Standard Survival Analysis and Competing Risk Analysis

A simulation study was performed to compare standard survival analysis with a competing risk approach in a study of second hip fracture in older adults with a prior hip fracture. The incidence of second hip fracture and relative risk of second hip fracture associated with age at the time of the first hip fracture was calculated 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]

Incidence of second hip fracture was estimated at 1, 3, 5, and 10 years using survival and competing risk analysis. For survival analysis, time to event (1–KM) estimate of incidence was calculated, and for competing risk approach, a CICR estimate was used. Competing risks (e.g., mortality) do not affect traditional survival analysis, whereas competing risk estimates are conditional on mortality. Thus, mortality was varied between 10% and 85% in these analyses to illustrate the difference in estimates obtained when using survival analysis versus a competing risk approach.

Next the unadjusted risk of second hip fracture associated with age (per 5 years) at the time of the first hip fracture was examined. Hazard ratios (and 95% confidence intervals) were calculated using Cox proportional hazards regression and compared with hazards ratios using CRR. Again, to demonstrate the significance of competing risks, the competing risk mortality was varied from 10% to 85%.

RESULTS

In this 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. The magnitude of the difference between incidence of second hip fracture as calculated using 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 using traditional survival analysis versus competing risk approach increases with increasing mortality.

The hazard ratio for older age (per 5 years) and risk of second hip fracture as calculated using Cox regression was 1.3 (95% CI = 1.1–1.5), indicating that older age is associated with greater risk of second hip fracture. In contrast, the hazard ratio calculated using CRR was 0.9 (95% CI = 0.8–1.0), suggesting that older age is associated with less 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%, older age was associated with a 20% greater risk of second hip fracture (95% CI = 1.0–1.3), but when mortality was 85%, older age was associated with a 10% lower risk of second hip fracture (95% CI = 0.8–1.0). Varying mortality made no difference

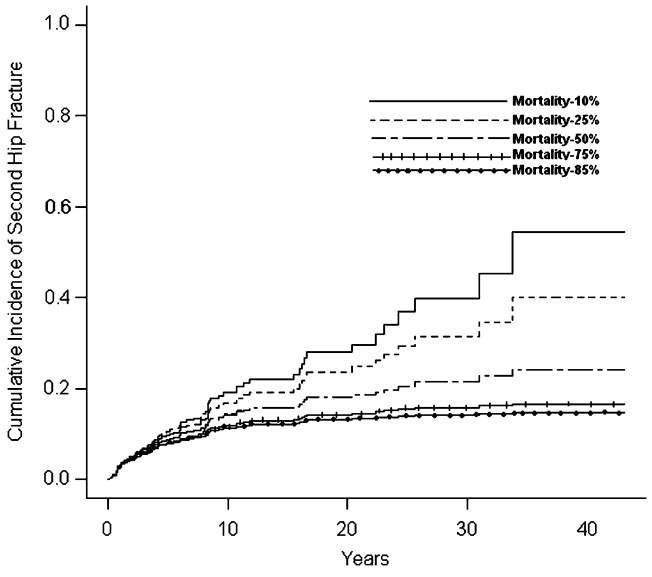

Figure 1. Simulated estimates of incidence of second hip fracture according to varying mortality as calculated using cumulative incidence competing risk estimates.

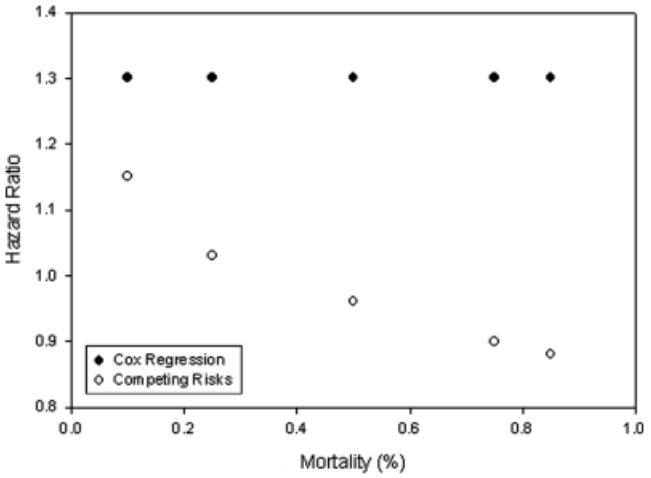

Figure 2. Difference in Cox regression and competing risk regression results when calculating the effect estimate of age on the risk of second hip fracture in a simulation study with varying mortality.

in the effect estimate of age on risk of second hip fracture as calculated using Cox regression; thus, the difference between effect estimates as calculated using these two methods increased as mortality increased (Figure 2).

These 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 using traditional survival analysis and competing risk approach, but the 5-year incidence of second hip fracture was estimated as 37% greater and 10-year incidence was 75% greater using survival analysis than with a competing risk approach. The results also showed that, as mortality (competing risk) increased, the bias introduced by calculating incidence and effect estimates using standard survival analysis increased.

These results indicate 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, the median time to second hip fracture was found to be 26 years. This statistic in itself is misleading because 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. To do this, it is necessary to consider 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.

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 risk 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 to demonstrate that results are not biased.

In conclusion, a competing risk approach to estimating incidence and effect estimates in geriatric studies with long follow-up in which mortality unrelated to the study itself may be substantial is recommended. 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 for clinical decision-making for geriatricians and their patients.

ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

This work was supported by Grant T32 AG023480-03 to Beth Israel Deaconess Medical Center and the Hartford Geriatrics Health Outcomes Research Scholars Awards Program.

Author Contributions: Kiel and Berry: concept and design. Kiel: acquisition of data. Berry, Ngo, and Samelson: the analysis and interpretation. All authors: preparation and critical revisions of the manuscript.

Sponsor's Role: None.

REFERENCES

1. Kaplan ELMP. Nonparametric observation from incomplete data. J Am Stat Assoc 1958;53:457–481.
2. Gooley TA, Leisenring W, Crowley J et al. Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 1999;18:695–706.
3. Southern DA, Faris PD, Brant R et al. Kaplan-Meier methods yielded misleading results in competing risk scenarios. J Clin Epidemiol 2006;59:1110–1114.
4. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. Clin Cancer Res 2007;13(2 Pt 1):559–565.
5. Satagopan JM, Ben-Porat L, Berwick M et al. A note on competing risks in survival data analysis. Br J Cancer 2004;91:1229–1235.
6. Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? Stat Med 1993;12:737–751.
7. Kalbfleisch JDPR. Estimation of the average hazard ratio. Biometrika 1980;68:105–112.
8. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095–2101.
9. Bergstralh E.comprisk. 2008 [on-line]. Available at http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm Accessed December 9, 2008.
10. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: An easy guide for clinicians. Bone Marrow Transplant 2007;40:381–387.
11. Fine JP, Gary RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
12. Klein JP, Andersen PK. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. Biometrics 2005;61:223–229.
13. Klein JP, Gerster M, Andersen PK et al. SAS and R functions to compute pseudo-values for censored data regression. Comput Methods Programs Biomed 2008;89:289–300.
14. Li N, Elashoff RM, Li G. Robust joint modeling of longitudinal measurements and competing risks failure time data. Biom J 2009;51:19–30.
15. Williamson PR, Kolamunnage-Dona R, Philipson P et al. Joint modelling of longitudinal and competing risks data. Stat Med 2008;27:6426–6438.
16. Xue QL, Fried LP, Glass TA et al. Life-space constriction, development of frailty, and the competing risk of mortality: The Women's Health and Aging Study I. Am J Epidemiol 2008;167:240–248.
17. Klein R, Klein BE, Knudtson MD et al. Fifteen-year cumulative incidence of age-related macular degeneration: The Beaver Dam Eye Study. Ophthalmology 2007;114:253–262.
18. Berry SD, Samelson EJ, Hannan MT et al. Second hip fracture in older men and women: The Framingham Study. Arch Intern Med 2007;167:1971–1976.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

APPENDIX S1

Table S1. Numerical computation of the incidence of second hip fracture as determined using a Kaplan-Meier (KM) estimate.

Table S2. Numerical computation of the incidence of second hip fracture as determined using a cumulative incidence competing risk (CICR) estimate.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.