Annals of Clinical Epidemiology 2021;3(4):97–100

Annals of Clinical Epidemiology

SEMINAR

Introduction to Survival Analysis in the Presence of Competing Risks

Kojiro Morita

Global Nursing Research Center, Graduate School of Medicine, The University of Tokyo

ABSTRACT

Survival analysis is often used in studies of clinical epidemiology, but the existence of competing risks has not been adequately considered. Competing risks may hinder observation of the outcome of interest or modify the occurrence of the outcome. In the presence of competing risks, conventional survival analysis leads to biased results. To conduct a survival analysis in the presence of competing risks, researchers should select an appropriate method from the following two options: cause-specific hazard model and subdistribution hazard model. This article explains the issues raised by the presence of competing risks and describes methods to account for competing risks in survival analysis.

KEY WORDS

censoring, competing risks, epidemiological method, hazard, survival analysis, survival time

1. INTRODUCTION

In many clinical studies, the outcome of interest includes not only the occurrence of an outcome but also the time to its occurrence. For example, the clinical significance for cancer recurrence would differ between recurrence after 1 year and recurrence after 5 years.

"Survival time" is defined as the time from starting an observation to the occurrence of an outcome of interest. However, the terminology can sometimes be misleading because survival time analysis is also applied to favorable outcomes, such as "time from surgery to hospital discharge" and "time from starting rehabilitation to functional recovery".

One of the important features of survival data is that some individuals do not encounter the outcome of interest before the end of the study period or are lost to follow-up. These individuals are treated as censored. Censored individuals should not be excluded from the analysis because they impart important information by not experiencing the outcome before they were censored. Conventional methods for survival analysis (Kaplan–Meier method and Cox regression method) rely on the assumption of non-informative censoring. This assumption means that censoring occurs independently of the outcome of interest, and that individuals censored at a given point in time have the same risk of the outcome as those who remain under follow-up at the same time point, even though they cannot be observed after being censored.

However, in survival analysis, the presence of competing risks is generally important. When an individual can experience multiple possible outcomes, the occurrence of one outcome prevents the occurrence of other outcomes [1]. In other words, the competing risks prevent the individual from experiencing the outcome of interest or modify the likelihood of the occurrence of the outcome.

The present article explains the issues raised by competing risks and describes methods to account for competing risks in survival analysis.

2. WHAT IS A COMPETING RISK?

During the follow-up period in clinical studies, several types of outcomes may occur. When competing risks exist, the occurrence of any outcome other than the primary outcome causes a situation in which the occurrence of the primary outcome is unobservable [1].

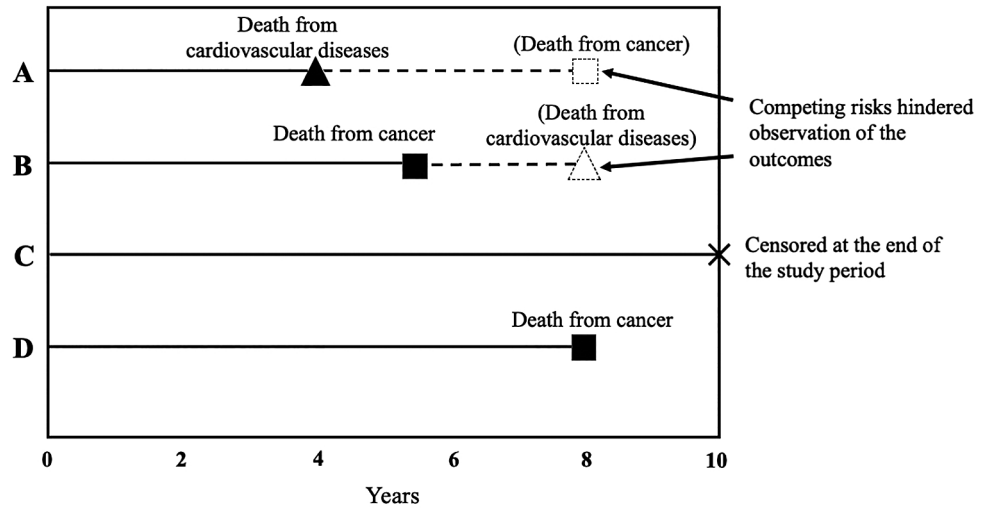

Fig. 1 Example of competing risks

For example, when the primary outcome is time to death from cardiovascular diseases, death from cancer is regarded as a competing risk against the primary outcome. Conversely, when the primary outcome is time to death from cancer, death from cardiovascular diseases is a competing risk (**Fig. 1**).

Although the conventional methods for survival analysis are based on the assumption of non-informative censoring, censoring caused by competing events prevents the occurrence of the primary outcome and alters the probability of the occurrence of the primary outcome [2]. Therefore, censoring due to the occurrence of competing events may violate the assumption of non-informative censoring.

3. SURVIVAL ANALYSIS IN THE PRESENCE OF COMPETING RISKS

A feasible option to deal with competing risks is the creation of a composite outcome (combination of multiple outcomes). For example, the composite outcome of major adverse cardiovascular events (MACE) combines cardiovascular death, myocardial infarction, unstable angina, heart failure, and stroke, and is frequently used in cardiovascular research. Although the use of a composite outcome is often criticized [3], it can increase statistical power and avoid the issue of competing risks [4].

There are two statistical approaches for survival analysis in the presence of competing risks: cause-specific hazard model and subdistribution hazard model.

The cause-specific hazard model is generally suitable for examining the etiology of a disease including treatment effects (etiologic research objectives), while the subdistribution hazard model is suitable for examining a prognosis or predicting an individual's risk (prognostic research objectives) [2, 5, 6].

Table 1 summarizes the methods for conventional survival analysis in the absence of competing risks and survival analysis in the presence of competing risks.

3.1 Cause-Specific Hazard Model

The cause-specific hazard model treats competing events other than the outcome of interest as censored, and a Cox regression analysis is applied for the specific outcome.

For a simple comparison of survival probabilities between two groups, the cumulative incidence in each group (1 – Kaplan–Meier estimate) is estimated and compared by the log-rank test. In a multivariate regression analysis, the cause-specific Cox regression model is used to estimate cause-specific hazard ratios. Cumulative incidence and cause-specific hazard ratio findings in the presence of competing risks should be interpreted with caution. The cumulative incidence is the probability of the outcome of interest occurring at a given time in a hypothetical world where competing risks do not exist [7].

Non-existence of competing risks means that no outcome will occur that would prevent observation of the outcome based on the assumption that the competing risks are independent of one another. Therefore, using

Table 1 Statistical methods for survival analysis in the absence or presence of competing risks

	Conventional methods for survival analysis	Survival analysis in the presence of competing risks	
		Etiological research objectives	Prognostic research objectives
Estimation of survival probability	Survival probability or cumulative incidence estimated by the Kaplan–Meier survival function	Cumulative incidence (1 – Kaplan–Meier estimate)	Cumulative incidence function
Simple comparison of survival probability in two groups	Log rank test	Log rank test	Gray's test
Regression model	Cox proportional hazard model	Cause-specific hazard model	Subdistribution hazard model (Fine–Gray model)

the Kaplan–Meier estimate in the presence of competing risks overestimates the cumulative incidence [2, 8].

The cause-specific hazard function reflects an instantaneous proportion of the primary outcome in individuals who have not experienced any events, including the outcome of interest and competing risks at a given time. The cause-specific hazard ratio is the ratio between the hazard of the outcome in the exposed group and the hazard of the outcome in the unexposed group. The cause-specific hazard model can be fitted to a conventional Cox hazard model with competing events.

3.2 Fine–Gray Subdistribution Hazard Model

The subdistribution hazard model treats individuals who experienced competing risks as remaining in the observational population rather than being censored [5, 7]. For a simple comparison of survival probabilities between two groups, the cumulative incidence function is estimated and compared by the Gray test. The cumulative incidence function is interpreted as the probability of occurrence of the outcome among the population that has not experienced any type of event, including the outcome and competing risks at a given time.

As a multivariate regression analysis, the subdistribution hazard regression model proposed by Fine and Gray can be used to estimate subdistribution hazard ratios [9]. This model allows estimation of the effects of covariates on the cumulative incidence function for the outcome. As mentioned above, in the subdistribution hazard model, subdistribution hazard ratios cannot be interpreted as conventional hazard ratios because those who experienced competing risks are also included in the number at risk of experiencing the outcome of interest.

4. STUDIES USING SURVIVAL ANALYSIS IN THE PRESENCE OF COMPETING RISKS

This section presents examples of studies that performed a survival analysis in the presence of competing risks.

4.1 Investigation of Factors Associated with a Lower Likelihood of Discharge to Home from Geriatric Intermediate Care Facilities [10]

The authors investigated factors associated with a lower likelihood of discharge to home among 342,758 people admitted to geriatric intermediate care facilities between April 2012 and March 2014, using data from a nationwide long-term care insurance claims database. The outcome of interest was defined as returning home from geriatric care facilities. Death, hospitalization, and transfer to other care facilities were regarded as competing risks. The study aimed to investigate risk factors associated with a lower likelihood of discharge to home, and the authors estimated cause-specific hazard ratios using the cause-specific hazard model.

The median follow-up time was 137 days, and 19% of the residents returned to home during the observation period. The cause-specific Cox regression analysis showed that several factors were significantly associated with a lower likelihood of discharge to home, including older age, higher level of care need, having several medical conditions, private ownership of the facility, more beds in the facility, and more long-term care facility beds per 1,000 adults aged ≥65 years in the region.

4.2 Effect of Surgical Left Atrial Appendage Occlusion on Thromboembolism Among Older Patients Undergoing Cardiac Surgery [11]

Using US Medicare claims data and the Society of Thoracic Surgeons Adult Cardiac Surgery Database, the

authors evaluated whether surgical left atrial appendage occlusion (S-LAAO) was associated with a lower risk of readmission for thromboembolism among 10,524 elderly patients with atrial fibrillation who underwent cardiac surgery between January 2011 and June 2012.

The study compared the incidence of hospitalization for thromboembolism (stroke, transient ischemic attack, systemic embolism) between the groups with and without S-LAAO. Death was considered a competing risk because the outcome of interest was defined as hospitalization for thromboembolism. The subdistribution hazard regression model proposed by Fine and Gray was used to compare the prognosis (readmissions for thromboembolism) between the S-LAAO group and the control group without S-LAAO.

Overall, during the mean follow-up period of 2.6 years, readmission for thromboembolism occurred in 5.4% of the patients (4.2% in the S-LAAO group versus 6.2% in the control group). The subdistribution hazard model produced an adjusted subdistribution hazard ratio of 0.67 (95% confidence interval, 0.56–0.81), suggesting that S-LAAO was associated with a lower risk of readmission for thromboembolism.

CONCLUSIONS

For survival analysis in the presence of competing risks, it is necessary to select an appropriate approach according to the research objectives and to correctly interpret the results of the analysis. In general, there are two approaches to survival analysis that can address the presence of competing risks. The cause-specific hazard model is suitable for etiologic research objectives, while the subdistribution hazard model is suitable for prognostic research objectives.

ACKNOWLEDGMENTS

Not applicable.

CONFLICTS OF INTEREST

None.

REFERENCES

1. Pintilie M. Competing Risks: A Practical Perspective. 2007. John Wiley & Sons, Chichester, UK.
2. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation* 2016;133:601–9.
3. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, et al. Problems With Use of Composite End Points in Cardiovascular Trials: Systematic Review of Randomised Controlled Trials. *BMJ* 2007;334:786.
4. Manja V, AlBashir S, Guyatt G. Criteria for Use of Composite End Points for Competing Risks–A Systematic Survey of the Literature With Recommendations. *J Clin Epidemiol* 2017;82:4–11.
5. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol* 2009;170:244–56.
6. Austin PC, Fine JP. Practical Recommendations for Reporting Fine-Gray Model Analyses for Competing Risk Data. *Stat Med* 2017;36:4391–400.
7. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When Do We Need Competing Risks Methods for Survival Analysis in Nephrology? *Nephrol Dial Transplant* 2013;28:2670–7.
8. Andersen PK, Geskus RB, de Witte T, Putter H. Competing Risks in Epidemiology: Possibilities and Pitfalls. *Int J Epidemiol* 2012;41:861–70.
9. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* 1999;94:496–509.
10. Morita K, Ono S, Ishimaru M, Matsui H, Naruse T, Yasunaga H. Factors Affecting Discharge to Home of Geriatric Intermediate Care Facility Residents in Japan. *J Am Geriatr Soc* 2018;66:728–34.
11. Friedman DJ, Piccini JP, Wang T, Zheng J, Malaisrie SC, Holmes DR, et al. Association Between Left Atrial Appendage Occlusion and Readmission for Thromboembolism Among Patients With Atrial Fibrillation Undergoing Concomitant Cardiac Surgery. *JAMA* 2018;319:365–74.