Journal of Clinical Epidemiology 122 (2020) 42−48

ORIGINAL ARTICLE

Ignoring competing events in the analysis of survival data may lead to biased results: a nonmathematical illustration of competing risk analysis

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Accepted 5 March 2020; Published online 9 March 2020

Abstract

Objective: Competing events are often ignored in epidemiological studies. Conventional methods for the analysis of survival data assume independent or noninformative censoring, which is violated when subjects that experience a competing event are censored. Because many survival studies do not apply competing risk analysis, we explain and illustrate in a nonmathematical way how to analyze and interpret survival data in the presence of competing events.

Study Design and Setting: Using data from the Longitudinal Aging Study Amsterdam, both marginal analyses (Kaplan−Meier method and Cox proportional-hazards regression) and competing risk analyses (cumulative incidence function [CIF], cause-specific and subdistribution hazard regression) were performed. We analyzed the association between sex and depressive symptoms, in which death before the onset of depression was a competing event.

Results: The Kaplan−Meier method overestimated the cumulative incidence of depressive symptoms. Instead, the CIF should be used. As the subdistribution hazard model has a one-to-one relation with the CIF, it is recommended for prediction research, whereas the cause-specific hazard model is recommended for etiologic research.

Conclusion: When competing risks are present, the type of research question guides the choice of the analytical model to be used. In any case, results should be presented for all event types.

Keywords: Competing risk analysis; Survival analysis; Epidemiological methods; Censoring; Hazard; Cumulative incidence

1. Introduction

Survival data are often encountered in epidemiologic studies. In this kind of data, the outcome of interest is time to the occurrence of a certain event. An important feature of survival data is censoring, which occurs when the exact survival time is unknown. This is the case, for example, when a subject is lost to follow-up, withdraws from the study, or does not experience the event of interest before the end of the study. Conventional methods used in the analysis of survival data like the Kaplan−Meier method and Cox proportional-hazards regression make the assumption of independent or noninformative censoring. This means that individuals who are censored have the same future risk of the event of interest as subjects under observation [1,2]. In other words, this kind of censoring does not change study outcome on disease prognosis or risk factor detection.

Funding: E.H. is supported by an NWO/ZonMw Veni fellowship (grant number 91618067). The Longitudinal Aging Study Amsterdam is supported by a grant from the Netherlands Ministry of Health, Welfare and Sport, Directorate of Long-Term Care. The study sponsors had no role in the design of the study; the collection, analysis, or interpretation of data; the writing of the report; or the decision to submit the article for publication.

Conflict of interest: None.

Authors' contributions: N.S. and E.H. designed the study. N.S. performed the statistical analyses and drafted the manuscript. All authors contributed to data interpretation, critically revised the manuscript, and approved the final version of the manuscript.

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https://doi.org/10.1016/j.jclinepi.2020.03.004

What is new?

Key findings

- Ignoring competing risks may lead to an overestimation of the cumulative incidence. Depending on the research question, in the presence of competing events, survival data should be analyzed using either a cause-specific hazard model or a subdistribution hazard model. Instead of the Kaplan−Meier method, the cumulative incidence function should be used to estimate the cumulative incidence.

What this adds to what was known?

- Despite the fact that competing risks are often present in epidemiological studies, specific competing risk methodology is rarely applied. In addition, most articles on this topic are highly theoretical. This paper explains how to analyze survival data in the presence of competing risks in a nonmathematical way and subsequently illustrates this using real-life epidemiological data.

What is the implication and what should change now?

- Before analysis, the research question, that is, etiologic or predictive, should be formulated carefully and the appropriate model to analyze the data should be selected (ie, a cause-specific hazard model for etiologic research and a subdistribution hazard model for prediction research). Results should be presented for all event types (both the event of interest and the competing event(s)) and extra attention should be paid to the interpretation of the results.

Another important but less well-known feature of survival data are competing risks. A competing risk is an event that prevents the event of interest from happening [3]. Suppose we are interested in the onset of depression, then death before the onset of depression is a competing event. Censoring these subjects is problematic in two ways. First, the assumption of independence or noninformative censoring is violated, as a subject that experiences a competing event (death) is censored in an informative manner [4,5]. Second, the probability of experiencing the event of interest is estimated in a hypothetical setting in which the competing event cannot occur, which has very little clinical relevance [1,2].

In epidemiological and medical research, competing risks are often ignored in the analysis of survival data. However, failing to account for competing risks generally leads to an overestimation of the cumulative incidence of the event of interest [1,4,6−8]. In 2012, Koller et al. critically appraised 50 recently published articles in which competing risks were present from different biostatistical, clinical, and high-impact medical journals [9]. In 70% of the included articles, they observed at least one competing risks issue. However, in only 20% of the studies, specific competing risks methodology was applied.

Although there is extensive literature on competing risks [1,3,7,10,11], articles that explain how to analyze survival data in the presence of competing risks in a nonmathematical way are scarce [5]. In addition, there is a lack of articles that focus on the application of different methods in real-life data and subsequently on the interpretation of the results. Therefore, the aim of this study was to explain and illustrate how to analyze and interpret survival data in the presence of a competing event. We will compare conventional methods of survival analysis with competing risk methods in the analysis of real-life data from an observational cohort study.

2. Description of the data

The application of methods is illustrated using data from the Longitudinal Aging Study Amsterdam (LASA), a prospective cohort study among older adults in the Netherlands [12,13]. In the present study, we included respondents that participated in the second measurement wave of LASA (1995−1996). Data on various domains of function were collected approximately every 3 years. More information on LASA and the measurements included in this study can be found elsewhere [12,13].

The outcome of interest was incident depression, approximated by a score of $\geq$16 on the Center for Epidemiologic Studies Depression (CES-D) scale [14]. Individuals who already suffered from depression at the start of the study were excluded, leaving a sample of 1,187 subjects.

Subjects that were not contacted for a new round of interviews, that were ineligible, or that refused were censored on the date of their last completed interview. Subjects that were still event free at the end of the study (01-07-2015) were also censored.

3. Statistical analyses

We analyzed the association between sex and the onset of depression. Because a comprehensive assessment of predictors of depression incidence was beyond the aim of this study, we limited our model to the inclusion of sex, baseline age, number of chronic diseases, and smoking. We performed both crude and adjusted analyses. Age was categorized into quartiles due to nonlinearity.

3.1. Marginal analyses

In a classic survival setting, the survivor function is estimated using the Kaplan−Meier (KM) method [15]. The complement of the Kaplan−Meier estimate denotes the

probability of experiencing the event of interest before a specified time. As this method can only handle one outcome and thus assumes independent or noninformative censoring, the cumulative incidence derived from this method is interpreted as the probability of depression in a world in which subjects cannot die before developing depressive symptoms [16,17]. Using the Kaplan−Meier method, censoring subjects at the time they experience a competing event has no influence on the cumulative survival probability [18], which generally leads to an overestimation of the cumulative incidence [2,4,7].

Marginal multivariable survival analysis is performed using Cox PH regression. The marginal hazard derived from a Cox model denotes the instantaneous rate of occurrence of the event of interest in a setting in which subjects cannot experience the competing event. Just like the Kaplan−Meier method, Cox PH regression assumes independent or noninformative censoring. In the absence of competing risks, the hazard and cumulative incidence are directly related in such a way that an increased hazard has a one-to-one association with a shorter survival time [2,3,9,19,20]. Then, by fitting a Cox PH regression model in our example dataset, inference can be made about the effect sex has on both the hazard function and on the prognosis or survival.

3.2. Competing risk analyses

The competing risk equivalent of the Kaplan−Meier method is the cumulative incidence function (CIF). The CIF denotes the probability of experiencing the event of interest before a specific time and before the occurrence of any other type of event [2], meaning that subjects experiencing the competing event are considered no longer to be at risk of developing the event of interest [16−18]. As a result of this, the cumulative survival probability is lowered by the occurrence of a competing event because the number of persons at risk decreases more quickly over time [18]. Thus, the CIF estimates the probability of depression in a clinically relevant setting in which subjects may also die [2,21]. In a scenario in which there are no competing events, the CIF yields the same cumulative incidence as the KM method.

The one-to-one relation between the hazard and cumulative incidence that is present in the multivariable marginal analysis does not automatically translate to a competing risk framework [22]. Therefore, in the presence of competing risks, the hazard and cumulative incidence cannot be estimated from one single model and different models need to be applied to answer etiologic and prognostic epidemiologic research questions: the cause-specific hazard model (etiologic) or the subdistribution hazard model (prognostic) [3,7,9,10,23].

3.2.1. Cause-specific hazard regression

The cause-specific hazard denotes the instantaneous rate of occurrence of the event of interest in a setting in which subjects can also experience the competing event [1,3]. This hazard is estimated by removing individuals from the risk set the moment they experience the competing event, meaning that competing events are treated as censored observations [3,21]. Thus, the estimation procedure is the same as the procedure for marginal survival analysis and the cause-specific hazard can be estimated by fitting a standard Cox PH model in which all events other than the event of interest are treated as censoring. Consequently, when censoring is noninformative, we quantify the effects on the marginal hazard, whereas in the case of informative censoring, we quantify the effects on the cause-specific hazard [1,3,23]. Thus, hazard ratios derived from a cause-specific hazard model should be interpreted among subjects who did not (yet) experience the event of interest or a competing event [16]. As the cause-specific hazard is directly quantified among subjects that are actually at risk of developing the event of interest, the cause-specific hazard model is considered more appropriate for etiologic research [16].

Whereas in the marginal analysis a model is fitted for the event of interest only, for the cause-specific hazard model, separate models are fitted for each type of event in which individuals that experience the competing event are censored [1,3]. Thus, in our study, we will fit two models: one for depression in which subjects that die are censored and one for death in which subjects that are diagnosed with depression are censored, and we interpret both hazard ratios at the same time.

3.2.2. Subdistribution hazard regression

The subdistribution hazard denotes the instantaneous risk of the event of interest in subjects that have not (yet) experienced the event of interest. This means that subjects who experience the competing event remain in the risk set [3,10,20]. Thus, the risk set for the subdistribution hazard model contains not only subjects that are currently free of the event of interest but also subjects that have previously experienced the competing event. In our example, this means that the risk set consists of both individuals that have not (yet) developed depressive symptoms and individuals that died before the onset of depression. Although this feels unnatural—as subjects who have died are naturally no longer at risk of developing depressive symptoms—this is necessary to establish the one-to-one relation with the CIF. Because of the direct relation between the covariates and the CIF, the subdistribution hazard model is considered the right model for prediction research.

Because in the subdistribution hazard model individuals that experienced the competing event remain in the risk set, the hazard ratios derived from a subdistribution hazard model are not straightforward to interpret [7,23]. As a result of this, the subdistribution hazard model is not considered appropriate for etiologic research. However, in prediction research, the hazard ratios are used to calculate individual risks. Thus, the regression coefficients derived from the subdistribution hazard model can be used to compute the

cumulative incidence of depression, taking competing risks into account [8,20].

Like for the Cox model, both the cause-specific hazards and the subdistribution hazards are assumed to be proportional over time. This can be checked using Schoenfeld residuals [24].

3.3. Notation and reporting

In a classic survival setting, researchers often simply address the risk of an event without specifying whether risk denotes the hazard or the cumulative incidence of the event [2]. In a competing risk framework, the use of clear terminology is required to avoid the misconception that the cause-specific and subdistribution hazard are essentially the same. Therefore, the cause-specific hazard and subdistribution hazard ratios will be reported as HR_{cs} and HR_{sd}, respectively. In addition, Latouche et al. have suggested to use both models and present the results for all causes for complete understanding [5,21]. Therefore, in competing risk analysis, in the example, both the hazard for depression and the hazard for death will be reported.

3.4. Software

All analyses were conducted using the R (version 3.5.3) statistical programming language [25] and the ''cmprsk'' package (version 2.2-7) for the competing risk analyses [26]. Detailed information on how to perform competing risk analyses in R using the ''cmprsk'' package can be found elsewhere [2,3,27,28].

4. Results

4.1. Descriptive statistical analyses

The population consisted of 625 males and 562 females (Table 1). Of all males, 16% developed clinically relevant depressive symptoms, whereas for women, this was 27%. Just over half of all women died without having had clinically relevant depressive symptoms during the study (50.36%), whereas for males, this percentage was much higher (66.08%). Median follow-up was longer for females (3,320 days) than for males (2,241 days).

4.2. Cumulative incidence

Figure 1 shows the cumulative incidence of depression (panel a) and both depression and death (panel b) for both males and females derived from the Kaplan−Meier method and the CIF, respectively. As anticipated, the Kaplan−Meier estimate of the incidence of clinically relevant depressive symptoms is larger than the corresponding estimate derived from the CIF. For instance, at 4,000 days, the cumulative incidence of clinically relevant depressive symptoms derived from the Kaplan−Meier method is 20.61% for males and 28.96% for females, whereas the cumulative incidence of depressive symptoms derived from the CIF is 14.55% for males and 24.21% for females. At 6,000 days, the difference in probabilities is even larger.

4.3. Modeling covariate effects

Table 2 shows the cause-specific and subdistribution hazard ratios for depression and death. The hazard ratio for depression derived from the Cox PH model is not included in Table 2 as this is equal to the cause-specific hazard ratio for depression.

4.3.1. Cause-specific hazard model

Female sex is associated with an increase in the rate of the development of clinically relevant depressive symptoms among those who are still alive and do not yet suffer from depressive symptoms (adjusted HR_{cs} 1.537, 95% CI 1.193−1.982), whereas it significantly decreases the rate of death before the onset of depression in the same group (adjusted HR_{cs} 0.684, 95% CI 0.586−0.797).

4.3.2. Subdistribution hazard model

As expected with a higher rate of depression for females associated with a reduced rate of death, we observe more females than males diagnosed with depression at any point during the study. Being female increases the probability of depression, resulting in an 84% higher relative incidence of clinically relevant depressive symptoms for females than for males (adjusted HR_{sd} 1.842, 95% CI 1.430−2.370), whereas it decreases the probability of dying before the onset of depression. The relative incidence of death was more than 35% lower for females than for males (adjusted HR_{sd} 0.639, 95% CI 0.547−0.746). Survival probabilities can be calculated for each individual by combining the subdistribution hazard ratios with their baseline hazard, just like one would do with the hazard ratios derived from a Cox model in a situation in which no competing risks are present.

In conclusion, sex has a more pronounced effect on the incidence of depression than on the cause-specific hazard of depression, as evidenced by the finding that the HR_{sd} (1.842) was larger than the HR_{cs} (1.537). The apparent increase in the absolute risk of depression for females might

Table 1. Characteristics of study population

	Males n = 625	Females n = 562
Status, n (%)		
Censored	109 (17.44)	125 (22.24)
Developed clinically relevant depressive symptoms	103 (16.48)	154 (27.40)
Deceased	413 (66.08)	283 (50.36)
Follow-up in days, median (IQR)	2,441 (3,621)	3,220 (4,159.25)

Abbreviations: n = number; IQR = interquartile range.

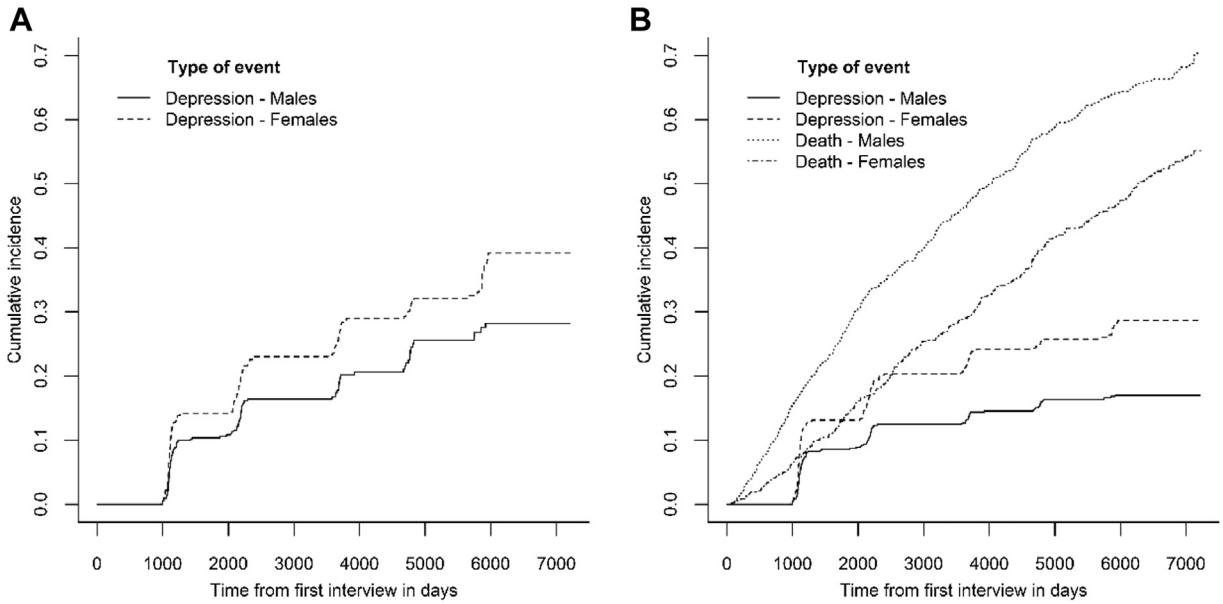

Fig. 1. Cumulative incidence of depression derived from the Kaplan–Meier method (panel a) and the cumulative incidence function (panel b).

be explained via the effect sex has on death before the onset of depression.

5. Discussion

In epidemiologic research, competing risks are generally not considered in the analysis of survival data. In the presence of competing risks, cumulative incidence should be estimated using the cumulative incidence function instead of the Kaplan–Meier method. Our illustration showed that failing to account for death before the onset of depression as a competing risk resulted in an overestimation of the cumulative incidence of clinically relevant depressive symptoms by 6.06 percentage point for males and 4.75 percentage point for females. For prediction research, the subdistribution hazard model should be used. In our illustration, the adjusted subdistribution hazard ratio for depression in females was greater than in the marginal analysis (HR_{sd} 1.842 [1.430–2.370] vs. HR 1.537 [1.193–1.982]), whereas the adjusted subdistribution hazard ratio for death in females was lesser (HR_{sd} 0.639 [0.547–0.746] vs. HR 0.684 [0.586–0.797]).

The extent to which the cumulative incidence is overestimated is related to the proportion of subjects experiencing the event of interest and the competing event. It is discussed in literature that specific competing risk analysis should be considered when the proportion of subjects that experience the competing event is equal to or greater than the proportion of subjects that experience the outcome of interest [6] or when the absolute percentage of competing events is greater than 10% [2]. In our data example, the incidence of clinically relevant depressive symptoms is relatively low, whereas mortality is high. As a result, the cumulative incidence is greatly overestimated using marginal analysis methods, illustrating the importance of applying specific competing risk analysis [5]. In a younger population in which the incidence of depression is higher [29,30] and mortality naturally is lower, the estimates derived from marginal analyses and competing risk analyses will not differ to the same extent as what we found in our older study population.

Table 2. Cause-specific and subdistribution hazards for depression and death

	Cause-specific hazard model		Subdistribution hazard model	
	Depression	**Death**	**Depression**	**Death**
Crude				
Sex—female	1.453 (1.132–1.865)	0.664 (0.571–0.722)	1.780 (1.390–2.290)	0.618 (0.534–0.718)
Adjusted				
Sex—female	1.537 (1.193–1.982)	0.684 (0.586–0.797)	1.842 (1.430–2.370)	0.639 (0.547–0.746)

Death represents ''death before the onset of depression.'' The cause-specific and subdistribution hazard model return the cause-specific (HR_{cs}) and subdistribution hazard (HR_{sd}) and their corresponding 95% confidence intervals, respectively. In the adjusted analyses, we correct for age, number of chronic diseases, and smoking.

Overestimation of the cumulative incidence of the outcome of interest has both practical and public health implications. An example of these implications is that treatment decisions by clinicians are often guided by risk prediction models. Ignoring competing risks in the development of these models could, among other things, lead to possible overtreatment in future patients.

5.1. Limitations

A limitation of the real-life data example is that in LASA, as in many cohort studies, disease information is collected at discrete follow-up visits, whereas the exact date of death is retrieved from municipality registers. It is therefore possible that we have missed some cases of incident depression [31]. Another limitation is that we could not distinguish between first-onset and recurrent depression. Because incidence of depression was based on a screening instrument [14], this does not necessarily indicate a clinical diagnosis, and there was no information on previous episodes. It is therefore possible that a part of the observed incidence of depression in our study represents recurrent episodes.

5.2. Prediction model performance in the presence of competing risks

The process of developing a prediction model in a competing risks framework is essentially the same as for other regression models, except that the subdistribution hazard model should be applied instead of regular Cox PH regression. The performance of a prediction model is usually assessed using the calibration and discrimination. A detailed proposal of how to assess calibration and discriminative capacity of a prediction model in a competing risks setting is described by Wolbers et al. [8].

5.3. Competing risks in randomized controlled trials

Whereas our paper focusses on competing risks in observational studies, competing risks also appear in the setting of randomized controlled trials (RCTs). A recent review of randomized controlled trials with survival outcomes that were published in four high-impact general medical journals showed that most of the studies were potentially susceptible to competing risks, but that this was not accounted for in the statistical analyses [32].

In RCTs with time-to-event outcomes, often additional effect measures that are derived from the KM survival curves, like the number needed to treat (NNT), are reported. Because the KM method overestimates the cumulative incidence in the presence of competing risks, the estimated NNT may also be biased. Therefore, to correctly estimate the NNT in the presence of competing risks, it is recommended to use a method based on the CIF [33]. For multivariable analysis, the same applies for RCTs as for observational studies: the cause-specific hazard model should be used when one is interested in the effect of the intervention on the instantaneous rate of occurrence of the event of interest in subjects that are currently event free, whereas the subdistribution hazard model should be used when one is interested in the relative effect of the intervention on the cumulative incidence function [32].

5.4. Software

The cause-specific hazard model can be fitted with any software that can perform a Cox PH model. However, this is not the case for the CIF and the subdistribution hazard model. How to estimate the CIF in SPSS with the use of a macro is described elsewhere [18]. In STATA, the subdistribution hazard model can be fitted using the *stcrreg* package [10]. For SAS, macros for both the estimation of the CIF and the subdistribution hazard model are available [34,35].

6. Conclusion

In conclusion, competing risks form an important issue in the analysis of survival data. Researchers should be aware of the potential problems associated with censoring subjects when they experience a competing event. Dealing with competing risks requires careful formulation of the research question, selection of the appropriate method for data analysis, and interpretation of the results.

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