

Treatment of Death in the Analysis of Longitudinal Studies of Gerontological Outcomes

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Background. Longitudinal studies in gerontology are characterized by termination of measurement from death. Death is related to many important gerontological outcomes, such as functional disability, and may, over time, change the composition of an older study population. For these reasons, treating death as noninformative censoring of a longitudinal outcome may result in biased estimates of regression coefficients related to that outcome.

Methods. In a longitudinal study of community-living older persons, we analytically and graphically illustrate the dependence between death and functional disability. Relative to survivors, decedents display a rapid decline of functional ability in the months preceding death. Death's strong relationship with functional disability demonstrates that death is not independent of this outcome and, hence, leads to informative censoring. We also demonstrate the "healthy survivor effect" that results from death's selection effect, with respect to functional disability, on the longitudinal makeup of an older study population.

Results. We briefly survey commonly used approaches for longitudinal modeling of gerontological outcomes, with special emphasis on their treatment of death. Most common methods treat death as noninformative censoring. However, joint modeling methods are described that take into account any dependency between death and a longitudinal outcome.

Conclusions. In longitudinal studies of older persons, death is often related to gerontological outcomes and, therefore, cannot be safely assumed to represent noninformative censoring. Such analyses must account for the dependence between outcomes and death as well as the changing nature of the cohort.

Key Words: Informative censoring—Joint analysis—Longitudinal study—Healthy survivor effect—Functional disability.

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AGING, especially later in life, is characterized by the progressive failure of the body's homeostatic mechanisms resulting in multiple comorbidities. In this article, we will refer to this phenomenon as the "aging process," which reaches its physiological conclusion with the person's death, and restrict our discussion to outcomes exclusive of death. The aging process is commonly evaluated through longitudinal studies of disability, falls, and cognitive function, and assessments of potential interventions (1–4). These studies typically proceed for a predetermined follow-up period at which time data collection ceases. Data from people with incomplete follow-up (eg, deaths and dropouts) are termed censored data. This type of censoring is technically known as "right censoring," and in this article, we use the term "censoring" to refer only to this most common type. Although the treatment of censoring because of dropout has been widely addressed in the statistical literature, the treatment of censoring because of death requires special consideration and is the focus of this article.

It is often tacitly assumed that the event (or mechanism) leading to censoring, such as death or dropout, is not associated

with the outcome of interest. When the data comply with this assumption, the mechanism results in noninformative censoring. For example, stopping data collection because the predefined length of the study has been reached is a mechanism that is not related to the outcome and thereby represents noninformative censoring. In contrast, informative censoring occurs when the mechanism causing the cessation of data collection is related to the outcome. With few exceptions (see Donaldson and colleagues (5)), the assumption of noninformative censoring is not explicitly stated in most published reports.

A second way in which death can affect a longitudinal analysis is the selection effect it exerts on the cohort over time. In gerontological studies, a significant proportion of participants may die, with survivors contributing disproportionately larger amounts of data than decedents. The tendency for healthier persons to live longer and contribute more data may lead to a "healthy survivor" effect in estimates obtained from a longitudinal analysis.

The objective of this article is to make gerontological researchers aware of the need to properly adjust for the

occurrence of death in longitudinal studies of older persons. To illustrate the concepts, we use data from the Precipitating Events Project (PEP) (2). We then briefly summarize the most commonly used longitudinal modeling techniques with emphasis on their treatment of death. We conclude with some observations on some features needed in longitudinal modeling techniques to better address this challenge.

DATA FROM THE PEP ARE USED TO ILLUSTRATE HOW DEATH CAN RESULT IN INFORMATIVE CENSORING AND CREATE A HEALTHY SURVIVOR EFFECT

The Precipitating Events Project

The PEP is an ongoing longitudinal study of 754 community-living persons, aged 70 or older, who were initially non-disabled in four basic activities of daily living (ADLs)—bathing, dressing, walking, and transferring. The assembly of this cohort has been described in detail elsewhere (2,6). Potential participants were members of a large health plan and were excluded for significant cognitive impairment with no available proxy (7), life expectancy less than 12 months, plans to move out of the area, or inability to speak English. Only 4.6% of persons contacted refused screening, and 75.2% of those eligible agreed to participate and were enrolled from March 1998 to October 1999.

Comprehensive home-based assessments were completed at baseline and subsequently at 18-month intervals for 108 months, whereas telephone interviews, to assess disability, were completed monthly through December 2008. Complete details regarding the assessment of disability are provided elsewhere (6,7). Deaths were ascertained by review of the local obituaries and/or from an informant during a subsequent telephone interview. This article uses data collected up to 108 months after each participant's baseline interview. Over this 108-month follow-up period, 330 (43.8%) participants died with median follow-up of 56.5 months, whereas 34 (4.5%) dropped out with median follow-up of 23.5 months. Data were otherwise available for 99.4% of the 61,589 monthly telephone interviews.

At baseline, the cohort had a mean age of 78.4 years, with 13.5% being 85 years or older. About two third of the cohort were female (65%), and the vast majority were non-Hispanic White (90.5%). A minority lived alone (39.5%), and the median educational level was 12 years. As indicated by a score less than 24 on the Folstein Mini-Mental State Examination (8), 86 persons (11.4%) had cognitive impairment. As defined by a score of 16 or less on the Center for Epidemiological Studies-Depression scale (9), 156 persons (20.7%) exhibited depressive symptoms. Nine chronic conditions were prevalent in the following proportions: hypertension (55.2%), arthritis (30.1%), myocardial infarction (18%), cancer (16.4%), chronic lung disease (10.2%), stroke (8.6%), diabetes mellitus (8.2%), congestive heart failure (6.5%), and hip fracture (4.5%).

Analysis of Number of ADL Disabilities Over 9 Years of Follow-Up

We first illustrate how death serves as a mechanism of informative censoring with respect to the number of four basic ADLs (bathing, dressing, walking, and transferring) for which PEP participants were disabled in any given month over a 9-year follow-up period. We fit a repeated measures Poisson regression model to the number of ADL disabilities over time as a function of both fixed and time-varying predictors. In this model, robust sandwich estimators (10) were used to account for the correlation of observations within individuals. We regressed the number of ADL disabilities on binary (0/1) indicators of advanced age (greater than or equal to 85 = 1), gender (female = 1), gait speed (slow gait = 1), race (non-White = 1), and history of recovery from disability (recovery = 1). Advanced age and gait speed were included in the model as time-varying covariates. As a simple sensitivity analysis, we estimated models with and without a binary (0/1) indicator term that takes the value 1 during the last 6 months of life.

For illustrative purposes, we focus on the coefficient for advanced age. In the model without the indicator term representing the last 6 months of life, the risk ratio (95% confidence interval) is 1.71 (1.46–2.02). In contrast, adjusting for the last 6 months of life yields a risk ratio of 1.61 (1.38–1.89), a reduction of 12.5% in the effect of advanced age. This reduction provides some evidence that death, with regards to the estimated association between advanced age and number of ADL disabilities, is acting as a mechanism of informative censoring.

Analysis of Decedents in Year of Death: Graphical Illustration of Informative Censoring

Informative censoring because of death can also be graphically illustrated using data on PEP participants in their last year of life. Prior research (11,12) has shown that the majority of older persons are disabled in the last year of life, and more recently, five clinically distinct trajectories of disability in the terminal year were identified (13). For purposes of illustration, we divided the decedents into two age subgroups, those who were 85 years or older at time of death and those who died at a younger age. For each subgroup of decedents, we plotted the average number of ADL disabilities for each month during the 12 months preceding death. As reference, we created corresponding subgroups of survivors, those aged 85 years or older and those of age less than 85 years, and plotted their average number of ADL disabilities in each month during the last 12 months of follow-up. Figure 1 depicts the average number of ADL disabilities for these younger (age less than 85 years in panel A) and older participants (aged 85 years or older in panel B).

Among the survivors in both panels of Figure 1, the 12-month trend in ADL disability is reasonably linear with a slight negative slope. In contrast, the trend for decedents is

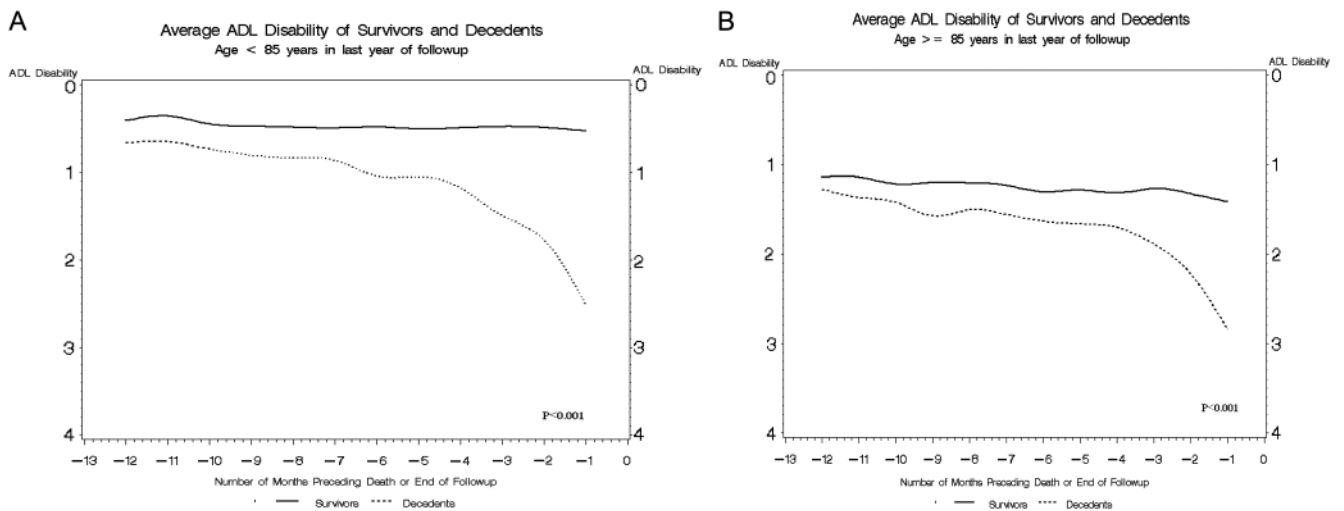


Figure 1. (A) Average activities of daily living (ADLs) disability in those younger than 85 years. (B) Average ADL disability in those aged 85 years or older. The p values in each panel correspond to the overall death effect over time from general estimating equation (GEE) Poisson models of number of ADL disabilities.

curvilinear with a sharp decline in the months just preceding death. By providing graphical evidence of the informative nature of death, these data complement the analysis reported in the previous section.

Although simple modeling strategies show how death leads to informative censoring of functional disability, there are additional tools that are useful once informative censoring has been established. For example, Siannis and colleagues (14) have proposed a sensitivity analysis for informative censoring in time-to-event models that provides the level of bias induced on a particular covariate effect in situations characterized by small values of dependence between the lifetime and censoring mechanisms.

Death Changes the Composition of a Longitudinal Cohort: The Healthy Survivor Effect

We next use the PEP data to illustrate how the cumulative effect of death can result in a population of healthier survivors.

A Cox analysis of time to death with the same covariates discussed earlier shows that number of ADL disabilities exhibits a positive association with time to death (hazard ratio = 2.72, $p < .001$). These results confirm our clinical observation that older persons with more severe ADL disability are likely to die sooner than those with less severe disability, leaving groups of survivors with less ADL disability, that is, healthier.

As in our earlier demonstration, we augment these model results with a tabular presentation that provides a more tangible view of the healthy survivor effect. For this illustration, we define a dichotomous state of functional disability based on whether a person requires assistance with any of the four ADLs. Those who require any assistance are classified as disabled; otherwise, they are classified as independent. Table 1 displays the distribution of disability and independence among survivors and decedents in three follow-up time-periods: those with 1–3, 4–6, and 7–9 years of follow-up, respectively.

Table 1. ADL Disability State by Interval of Follow-up and Death Status over 9 Years

ADL Disability State in Last Assessment Within Each 3-y Interval of Follow-Up							
N at Risk	Interval of Follow-up	Death Status	Independent (no. items disabled)		Disabled (disabled ≥1 item)		Interval-Specific Mortality n (%)
			n	% of row	n	% of row	
754	Years 1–3	Decedents	31	33.3	62	66.7	93 (12.3)
		Survivors	553	83.7	108	16.3	
		Subtotal*	584		170		
661	Years 4–6	Decedents	20	16.7	100	83.3	120 (18.2)
		Survivors	384	74.7	130	25.3	
		Subtotal*	404		230		
544	Years 7–9	Decedents	16	13.7	101	86.3	117 (21.5)
		Survivors	253	64.2	141	33.8	
		Subtotal*	269		242		

Notes: ADLs = activities of daily living.

*Subtotal denotes the number of participants with ADLs scores at the last available monthly assessment within each specific follow-up interval.

Table 2. Longitudinal Modeling Techniques and Treatment of Death

Longitudinal Modeling Technique	Treatment of Death	Salient Features
Cox proportional hazards model (outcomes other than time to death)	Death is not modeled Death treated as noninformative censoring	Handles continuous outcome (time to event) Population level inference only Does not provide trajectories
Generalized estimating equations	Death is not modeled Death treated as noninformative censoring	Handles binary, ordinal, and continuous outcome types Population level inference only Provides population level trajectories
Generalized linear mixed models	Death is not modeled Death treated as noninformative censoring Missing values, including before and after death, are extrapolated Outcome trajectory does not account for the healthy survivor effect	Handles binary, ordinal, and continuous outcome types Individual level random effects Both population and individual level inference Provides population and individual level trajectories
Extended Cox multistate transition models (special case of competing risks model)	Death is modeled as an absorbing state that competes with other recurring outcomes Outcomes comprise times to discrete competing events	Limited to modeling occurrence of discrete longitudinal outcomes No random effects included Population level inference only Does not provide trajectories
Joint modeling methods	Death jointly modeled in parallel with the trajectory of the longitudinal outcome Missing values prior to death are properly calculated Less vulnerable to biased estimates of regression coefficients and standard errors from healthy survivor effect	Theoretically capable of handling binary, ordinal, and continuous outcome types, several in active development Random effects shared between models for time to death and longitudinal outcome Population and individual level inference Provides population and individual level trajectories

Within each time period, the disability state is based on the last recorded measure of ADL disability. Relative to decedents, a higher percentage of survivors were independent and a lower percentage were disabled in each follow-up time interval. These trends provide evidence for the existence of a healthy survivor effect in the PEP data.

Although some may argue that informative censoring and the healthy survivor effect are one and the same, we prefer to view their relationship as that of cause and effect. Although Figure 1 and the corresponding model results have shown that death leads to informative censoring, Table 1 illustrates how the healthy survivor effect has resulted in a qualitatively different sample.

BRIEF REVIEW OF COMMON LONGITUDINAL MODELING TECHNIQUES AND THEIR TREATMENT OF DEATH

In this section, we briefly compare the most commonly used longitudinal modeling techniques and describe newer joint modeling approaches with special emphasis on their treatment of death. Table 2 summarizes the key features of these methods in order of increasing complexity.

Longitudinal Modeling Techniques that Treat Death as Noninformative Censoring

Most existing models for longitudinal outcome in gerontological research censor individuals at their time of death and assume that death and the outcome of interest are not

associated, that is, that death represents noninformative censoring (15).

Generalized estimating equations (GEE) are often used to analyze data from longitudinal studies with repeated correlated outcomes (eg, number of ADL disabilities). They can accommodate a wide range of outcome scales, including continuous, binary, and ordinal, and provide standard errors that properly account for the correlation among repeated observations on the same participant (16). GEE also assumes that censoring is noninformative.

Generalized linear mixed models or “mixed models” provide greater flexibility than GEE for accommodating repeated observations on the same participant (17,18), yet also assume censoring to be noninformative. Mixed models permit random effects, which can be used to estimate a trajectory for each individual, enabling inference at the individual level. Models that do not employ random effects, such as GEE, can only provide inference at the population level, that is, averaged over all individuals. In further contrast with GEE, mixed models extrapolate missing values after cessation of measurement, such as from death. Although mathematically plausible, values extrapolated after death are difficult to justify to a clinical audience.

Because Cox, GEE, and generalized linear mixed models all treat death as non-informative censoring, they neither adjust for the dependence between outcome and death nor account for the healthy survivor effect.

Techniques that Model Death Simultaneously With Gerontological Outcomes

We next discuss techniques that evaluate death in parallel with the longitudinal outcome of interest.

Competing risk models.—The most common form of competing risk analysis is formally known as cause-specific analysis (19), in which Cox regression is applied to several discrete outcome events for which participants are simultaneously at risk. These models are suitable when participants are followed until whichever of these events, from among the group of events competing to occur, first takes place. The defining characteristic of competing risk models is that the occurrence of any particular event censors the other competing events. In this context, the occurrence of functional disability among PEP participants effectively censors the occurrence of death and vice versa. Although there is abundant literature on competing risk models, the seminal paper by Prentice and colleagues (19) laid the foundation for the cause-specific approach in which each competing risk can be characterized by its own cause-specific hazard function, that is, the hazard function among the subpopulations not having experienced any competing event by each given time and related subdistribution. Standard Cox regression analysis treating competing events as censoring accurately characterizes relative cause-specific hazards provided that the usual model assumptions for that analysis are met. Gray (1988) builds on this framework to develop a class of tests for comparing the cumulative incidence of a particular outcome type among different groups. The utility of Gray's contribution is manifest when testing for equal association between several candidate drugs and one specific outcome, for instance, death from a particular type of cancer, in the presence of competing risks (20). A helpful non technical overview of competing risks is provided in Chapter 6 of Allison (21). Our brief introduction serves as background for the multistate transition models next discussed.

Extending the Cox model: Multistate transition models.—We restrict our discussion to a multistate transition model, which is a special case of the cause-specific competing risk model that can accommodate recurrent events, for example, independence and disability. Extensions of this method for recurrent events have been previously discussed and illustrated with the PEP cohort (22). In these models, because there are always at least two possible destination states, transition from one state to another is a competing risk process. This extension of the Cox proportional hazards model evaluates the times to event of each of the competing outcomes during each of the recurring periods of time in which a transition can occur. These models are more complex than simple Cox models and are discussed in Hougaard (2000) and Therneau and Grambsch (2000) (23,24). Hidden Markov models constitute an alternative approach that estimates the transition probabilities between several candidate states. Recently Keeler and colleagues (2010) used this approach

to model transition probabilities between states of functional ability and death (25).

In the multistate transition models we are describing, the association between a covariate of interest (eg, advanced age) and outcome is expressed as a hazard ratio based on time spent in a given state prior to the transition out of that state. A multistate transition model is a suitable analytic strategy in PEP because participants are simultaneously at risk for recurrent transitions between states of disability and independence as well as death (26,27). Death is defined as an absorbing state, meaning that individuals are no longer at risk for additional transitions. These multistate transition models are characterized by two important limitations. First, because their main purpose is to capture the transitions of a discrete longitudinal outcome from one state to another, they do not account for the healthy survivor effect. Second, these models are not suitable for continuous longitudinal outcomes, such as values of cognitive status as assessed by the Folstein Mini-Mental State Examination (8).

Joint models.—When, as in our PEP example, death is informative with respect to the longitudinal outcome, all previously discussed models may produce biased estimates of regression coefficients and standard errors (28–30) from not having adequately accounted for the healthy survivor effect. However, a joint model that simultaneously models the longitudinal outcome of interest and risk of death is able to appropriately account for the healthy survivor effect by adjusting for participants who die earlier in the study.

The joint model actually comprises two separate submodels, one for the longitudinal outcome and the other for time to death, with the submodels usually linked by a shared individual level random effect. The joint model is able to more rigorously account for the healthy survivor effect by exploiting these random effects, which account for the dispersion among individual times to death (31,32).

The major limitation of the joint model is the computational complexity of fitting the survival submodel for which no existing commercial software currently exists. To date, joint models have been mainly developed in the context of longitudinal outcomes with dropout (33,34). Although some freeware is available to fit these models, this code is suitable only for the particular case for which it was developed and not applicable to ordinal outcomes, such as the number of ADL disabilities in the PEP data. The development of joint models that accommodate ordinal outcomes in combination with Cox analysis of time to death will greatly expand the utility of these methods.

CONCLUSIONS

Researchers possess an ever-growing array of statistical techniques with which to longitudinally evaluate gerontological outcomes. The appropriate use of these techniques depends on whether the censoring mechanism is informative

or noninformative. Using data from the longitudinal PEP Study, we have demonstrated, with respect to number of ADL disabilities, how death not only results in informative censoring but also creates a healthy survivor effect.

Analytical approaches such as GEE, generalized linear mixed models, and Cox models are regularly used in gerontological research and available in most statistical software packages. Their assumption of death as a form of noninformative censoring requires verification. Although the multistate extended Cox models are being increasingly used for their ability to simultaneously model time to death in a competing risk framework, they do not account for the healthy survivor effect induced by informative censoring.

By combining the attractive properties of generalized linear mixed models and multistate transition models, joint models provide a comprehensive approach for properly addressing censoring by death. However, the lack of commercially available software and previous application to a limited range of outcome types continue to pose substantive obstacles to their widespread use.

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