Osteoporosis International (2019) 30:2073–2078
https://doi.org/10.1007/s00198-019-05048-w

ORIGINAL ARTICLE

Assessing risk factors of non-fatal outcomes amid a competing risk of mortality: the example of hip fracture

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Received: 18 September 2018 / Accepted: 4 June 2019 / Published online: 29 June 2019

Abstract

Summary The Fine-Gray method is often used instead of Cox regression to account for competing risks of death in time-to-event analyses for non-fatal outcomes. A series of examples using well-known risk factors of hip fracture in an older cohort with substantial competing mortality demonstrates that the Fine-Gray approach can yield estimates that implausibly contradict long-established associations, while Cox regression preserves them. Cox regression is generally preferred for risk factor-outcome associations even in the presence of competing risk of death.

Introduction Factors like age, sex, and race are associated not only with risk of hip fracture but also with mortality. Substantial misunderstanding remains regarding the appropriate statistical approach to account for the competing risk of mortality.

Methods In the Cardiovascular Health Study, an ongoing cohort study of 5888 older adults, we followed participants for incident hip fracture from their 1992–1993 visit through June 2014. We contrasted the conventional cause-specific Cox analysis, which censors individuals at the time of death, with the Fine-Gray (FG) approach, which extends participant follow-up even after death, to estimate the association of well-established demographic and clinical factors with incident hip fracture.

Results For age, current smoking and sex, Cox and FG methods yielded directionally concordant but quantitatively different strengths of association. For example, the Cox hazard ratio (HR) for a 5-year increment in age was 1.74 (95% CI, 1.61–1.87), while the corresponding FG HR was 1.16 (1.09–1.24). In contrast, the FG approach estimated a stronger association of hip fracture with sex. The two approaches yielded nearly identical results for race. For diabetes and kidney function, the estimates were discordant in direction, and the FG HRs suggested effects that were in the opposite direction of well-understood and widely accepted associations.

Conclusions Cause-specific Cox models provide appropriate estimates of hazard for non-fatal outcomes like hip fracture even in the presence of competing risk of mortality. The Cox approach estimates hazard in the population of individuals who have not yet had an incident hip fracture and remain alive, which is typically the group of clinical interest. The Fine-Gray method estimates hazard in a hypothetical population that can yield misleading inferences about risk factors in populations of clinical interest.

Keywords Competing risk · Cox regression · Fine-Gray approach · Hip fracture · Mortality

Introduction and Methodology

In geriatric research, mortality often precludes individuals from reaching the end of clinical follow-up. Death makes it impossible to experience and observe the primary event of interest. Other common occurrences in geriatric populations, such as institutionalization, may also limit observation of the primary event. Many statisticians and non-statisticians believe that accounting for death by censoring future follow-up years results in biased findings [1]. Perhaps the most widely used alternative method to conventional regression censoring of individuals at the time of death is the Fine-Gray (FG) approach [2]. Substantial confusion exists about this methodology [3–5]. A systematic review of the

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use and interpretation of the FG methodology in 2015 found that only 9% of papers in which the method was used interpreted FG estimates correctly [3]. Nonetheless, researchers continue to use the FG methodology for studies of risk factors in the geriatric literature in general and for hip fracture in particular [6–9].

To understand the difference between these methods, a brief review of survival analysis is useful. In time-to-event data, the outcome of interest is not only whether or not an event occurred but also the time at which the event occurred. Censoring occurs when an individual is lost to follow-up before experiencing the event and before or at the end of the study. In that situation, inferences from the observed, partially censored population can only be generalized in an unbiased manner to the entire population if censoring is non-informative [10]. That is, individuals who remain under follow-up must be similar to those who were censored, and individuals cannot be censored because they are at an unusually high or low risk of the primary event. Competing risk is a form of censoring, when we observe only the first of the primary or a competing event. Death is a model example of competing risk, for it necessarily precludes observation of any subsequent events.

Two populations can be conceived in the presence of competing risk of death. In one, a largely hypothetical population, death does not preclude an individual from experiencing the primary event but merely precludes its observation. In other words, one wishes to know when a primary event would have happened had the person not died. The FG approach operates in this population, wherein individuals with competing events (including death) remain in the population at risk until the end of study despite having no risk of hip fracture. In essence, the competing event (death) protects them from ever sustaining a hip fracture, not only from observing it. The subdistribution hazard from FG [5] therefore estimates the instantaneous rate of incident hip fracture among individuals who are currently alive and free of incident hip fracture as well as those who have died but remain "observable" until the end of the study. Those subjects who have died prior to sustaining a hip fracture are artificially retained in the risk set. The FG approach estimates a hazard in the entire population regardless of whether an individual is truly at risk of incident hip fracture or is not.

In contrast, the second and more commonly conceived, and more intuitively useful population, is comprised of all individuals alive up to any given point during follow-up, for whom one is interested in their subsequent risk. This approach is called cause-specific (CS); CS Cox regression is the most common form [11]. This approach does not exclude individuals who die during follow-up but merely censors them at the time of their death, i.e., it incorporates all of their observable person-time while alive. In the conventional CS Cox regression [11], the instantaneous rate of incident hip fracture among individuals who are still alive is modeled—a useful clinical parameter. Even though CS Cox regression is often not considered a "competing risk" approach, it is nonetheless a valid approach contrasting individuals who are truly at risk across different levels of risk factors even in the presence of competing risk.

As previously noted, the FG approach assumes that hip fractures can, but do not, occur after the competing event; that is, once the competing event occurs, subjects become "immune" to the primary event. An intuitively opposite approach would be to treat each competing event as a primary event. Thus, one could model a "composite event" of hip fracture and death. This approach has a ready interpretation, for it models the instantaneous rate of a single event among everyone at risk. However, drawing clinical inferences from a composite outcome model is challenging due to heterogeneity of its components [12, 13]. Importantly, the FG approach and the composite outcome approach represent lower and upper boundaries to the true rate of events, respectively (i.e., because follow-up continues after the competing event with no new primary events in FG, while follow-up ceases with the maximum number of primary events with the composite event approach).

Analytically, the FG approach uses the same underlying model and statistical equations for estimating hazard ratios as does the traditional CS Cox approach [5]. By redefining the population at risk, FG redefines the hazard function, known as a subdistribution hazard. For ease of communication, we use the term FG when referring to estimating the subdistribution hazard using Cox statistical methodology, and we reserve the term Cox approach for estimating the CS hazard with Cox regression.

In the following sections, we contrast the conventional CS Cox approach, the Fine-Gray approach and the composite event approach. We demonstrate their impact using data from the Cardiovascular Health Study (CHS), examining hip fracture as the primary outcome and mortality as the competing event. We use a selected series of well-understood risk factors to illustrate how these approaches differ. Our results highlight how the two approaches come to different conclusions and emphasize the credibility of the Cox approach even in the presence of competing risk.

Methods

Participants

The CHS is a prospective, population-based cohort study of 5888 Medicare-eligible adults of at least 65 years of age in four US communities [14]. In the original cohort, 5201 men and women were enrolled during 1989–1990. In the second recruitment, during 1992–1993, an additional 687 predominantly black men and women were enrolled. All participants signed informed consent upon study entry. CHS prospectively gathers all hospitalization data, including discharge summaries, from participants every 6 months.

Outcome

Incident hip fracture was identified using International Classification of Diseases, Ninth Revision (ICD-9) codes from hospitalization records from the time of the 1992–1993 visit through June 30, 2014. Hip fracture was defined as any ICD-9 code of 820.xx. Admissions for pathological fractures (ICD-9 code 773.1x) and motor vehicle accidents (E810.xx–E825.xx) were not considered as hip fractures.

Risk factors

For this illustrative example, we used six common risk factors for hip fracture—age, sex, race, smoking, kidney function, and diabetes. All have been associated with risk of hip fracture in younger populations in which the competing risk of mortality is far less substantial [15–20]. Smoking history was obtained by participant self-report. Renal function was assessed by cystatin C-based estimated glomerular filtration rate (eGFR). Diabetes was defined as use of insulin or oral hypoglycemic agents or a fasting glucose level ≥ 126 mg/dL.

Statistical methods

In all models, we used Cox regression to estimate hazard ratios. The only difference between the cause-specific approach and the Fine-Gray methodology in complete data is the manner in which individuals who died are coded at the time of death and thereafter. With the CS approach, we modeled the hazard among individuals alive up to the point of death. With FG, we modeled the subdistribution hazard [2], a hazard in the entire population where a participant who dies is immune to hip fracture until the end of the study, regardless of risk factor profile. We additionally checked these estimates with a built-in function for the Fine-Gray subdistribution hazard.

We first created a model with age, gender and race (model 1). We then added the three other risk factors (current smoking, cystatin C-based eGFR [per 15 mL/min/1.73 m^2], and diabetes status) into model 1 and ran separate regressions for each risk factor.

All statistical analysis was conducted in R [21].

Results

Among 5265 participants followed for a median of 11 years (inter-quartile range 6–17, maximum 22), 688 incident hip fractures occurred. During this time, 3979 individuals (76%) died prior to an incident hip fracture, representing the competing risk. Another 601 participants died following hip fracture, leaving 598 individuals who reached the end of follow-up without any event. Table 1 presents selected baseline characteristics of the study population. The average age at baseline was 75 years, 59% were women, 17% were black, and 10% were current smokers. The prevalence of diabetes was 17%, and the average eGFR was 73 ml/min/1.73 m^2.

Table 2 presents results of models that include standard demographic factors of age, gender, and race. The Cox HR for incident hip fracture associated with a 5-year higher age was 1.74 (95% CI 1.61, 1.87). The corresponding FG subdistribution hazard ratio estimate was 1.16 (95% CI 1.09, 1.24). This estimate implies an effect of age that is almost five times lower than the Cox estimate, which assesses hazard only among participants alive at any given point. This is so because death is positively associated with age. By setting the risk for hip fracture to zero among those who died, the FG approach lowers the apparent importance of age for the risk of hip fracture. This attenuation is particularly dramatic because the proportion of individuals who died during follow-up is large and the association of death with age is strong. The age hazard ratio for a composite endpoint of hip fracture and death was similar to the hazard ratio for mortality alone because the composite event is dominated by mortality. This is the case for hazard ratios of all risk factors.

The association of incident hip fracture with sex demonstrates that the FG approach can also yield estimates further from the null than are estimated from the Cox approach. The Cox HR estimate for male versus female sex is 0.62 (95% CI 0.53, 0.74), while the FG subdistribution hazard ratio estimate is 0.49 (95% CI 0.41, 0.58). In this case, the explanation is the opposite direction of the association between male sex and death (positive) and that of male sex and hip fracture (inverse). Since mortality is similar among whites and blacks, the HRs for race estimated by the two methods did not differ.

The two regression approaches can sometimes lead to qualitative differences as well, as demonstrated in Table 3. The Cox method suggests the expected association between incident hip fracture and current smoking (HR 1.66, 95% CI 1.28, 2.14). In contrast, the FG approach suggests no statistically significant association. Because current smoking is associated with mortality, the FG approach tends to dilute the hip fracture hazard ratio for current smoking.

Last, the Cox and FG approaches may come to opposite conclusions. For example, while we do not find a statistically significant association between higher cystatin C-based eGFR and hip fracture (HR 0.95, 95% CI 0.89, 1.02) using the Cox approach, the association was inverse, as expected. In contrast, the FG approach attributes an implausibly harmful association to higher eGFR (HR 1.09, 95% CI 1.02, 1.17).

A similarly implausible outcome with the FG approach is found for the association of diabetes with hip fracture risk. In Cox analyses, there is a non-significant association toward higher hazard associated with diabetes (HR 1.19, 95% CI 0.94, 1.52), but the FG approach suggests a protective trend (HR 0.79, 95% CI 0.62, 1.01). This is because diabetes is strongly positively associated with mortality, and individuals

Table 1 Descriptive characteristics of the CHS population at the 1992/93 visit. We provide mean ± standard deviation for continuous variables and percentages for categorical variables

	Total	Women	Men
	5265	3099	2166
Age (years)	75.13 ± 5.51	74.84 ± 5.39	75.55 ± 5.67
Black race	16.8%	18%	15.1%
Good health	77.4%	76.2%	79.2%
Education (≥ 12 g)	44.8%	41.4%	49.7%
Diabetes	16.5%	14.6%	19.3%
ADL difficulty	11.8%	14%	8.6%
Fall	16.2%	19.6%	11.3%
Systolic BP (mmHg)	136.6 ± 21.66	137.46 ± 21.92	135.38 ± 21.24
Diastolic BP (mmHg)	71.28 ± 11.59	70.38 ± 11.57	72.56 ± 11.49
Glucose (mg/dL)	108.47 ± 35.61	106.9 ± 35.6	110.64 ± 35.52
Insulin (mIU/L)	14.29 ± 24.12	14.05 ± 23.56	14.61 ± 24.88
Current smoking	9.8%	10.1%	9.5%
Cystatin C eGFR (mL/min/1.73 m^2)	72.53 ± 19.03	74.83 ± 19.19	69.31 ± 18.32

in this cohort who died prior to hip fracture were protected from future hip fracture risk.

Discussion

CHS not only has proven to be a rich source of information on risk factors for hip fracture but also illustrates the differences in methods addressing competing risk extremely well owing to its prolonged follow-up and the large proportion of the cohort that is now deceased. In this setting, we demonstrate sharp differences between traditional Cox and FG methods that highlight the value of standard methodology even in the presence of extreme degrees of competing risk. As noted below, the FG method may have utility in absolute risk prediction, but its approach to follow-up time yields risk factor-outcome associations that do not apply to the most common clinical population of interest—individuals still alive at any moment in time.

Table 2 Age-, sex-, and race-adjusted hazard ratio estimates for incident hip fracture, mortality, and the composite event. For hip fracture, the cause-specific (CS) Cox approach is contrasted with the Fine-Gray (FG) approach

	HR	95% CI	*p* value
5 years of increased age			
Hip fracture, CS	1.74	(1.61, 1.87)	< 0.01
Hip fracture, FG	1.16	(1.09, 1.24)	< 0.01
Composite event	1.70	(1.66, 1.75)	< 0.01
Mortality	1.72	(1.67, 1.77)	< 0.01
Male			
Hip fracture, CS	0.62	(0.53, 0.74)	< 0.01
Hip fracture, FG	0.49	(0.41, 0.58)	< 0.01
Composite event	1.31	(1.23, 1.38)	< 0.01
Mortality	1.41	(1.33, 1.49)	< 0.01
Black			
Hip fracture, CS	0.39	(0.29, 0.52)	< 0.01
Hip fracture, FG	0.38	(0.29, 0.51)	< 0.01
Composite event	0.99	(0.92, 1.07)	0.82
Mortality	1.05	(0.97, 1.14)	0.21

The traditional Cox regression association contrasting current smoking with non-smoking on risk of hip fracture that we estimated here is consistent with a substantial external body of evidence. For example, a recent meta-analysis of 14 prospective cohort studies in men estimated this association with a relative risk (RR) of 1.47 (95% CI 1.28, 1.66) [15]. In women, a meta-analysis of 10 prospective cohort studies estimated the contrast between current smokers and current non-smokers to be RR of 1.54 (95% CI 1.20, 1.87) [16]. Another meta-analysis in both men and women, adjusting for race, age, and gender, found an even higher RR of 1.84 (95% CI 1.52, 2.22) [17]. While these analyses used traditional Cox or Poisson regression methods, the FG approach provides asymptotically identical estimates to traditional estimates in situations where competing risk is rare, such as in younger cohorts with less mortality. Our results in a cohort with an extensive degree of competing risk using traditional Cox regression matches these results extremely well, but the FG approach provides estimates that, for smoking, imply no biological association whatsoever. Thus, the Cox approach, even in the face of substantial competing risk, yields estimates that match what appears to happen in the absence of competing risk, while the FG does not.

Much like smoking, our results for kidney function and diabetes with standard Cox models match established estimates far more believably than the FG approach does. In the Atherosclerosis Risk in Communities (ARIC) study of middle-aged individuals, where the competing risk of death was smaller than in our cohort of older adults, a negative association was

Table 3 Hazard ratio estimates for incident hip fracture, mortality, and the composite event. For hip fracture, the cause-specific (CS) Cox approach is contrasted with the Fine-Gray (FG) approach. Separate models are presented for each risk factor, adjusted for age, race, and gender

	HR	95% CI	*p* value
Current smoking			
Hip fracture, CS	1.66	(1.28, 2.14)	< 0.01
Hip fracture, FG	1.17	(0.90, 1.51)	0.24
Composite event	1.59	(1.44, 1.76)	< 0.01
Mortality	1.58	(1.44, 1.75)	< 0.01
Diabetes			
Hip fracture, CS	1.19	(0.94, 1.52)	0.15
Hip fracture, FG	0.79	(0.62, 1.01)	0.06
Composite event	1.66	(1.53, 1.8)	< 0.01
Mortality	1.69	(1.56, 1.84)	< 0.01
Cystatin C-based eGFR (per 15 ml/min/1.73m^2)			
Hip fracture, CS	0.95	(0.89, 1.02)	0.19
Hip fracture, FG	1.09	(1.02, 1.17)	< 0.01
Composite event	0.81	(0.79, 0.83)	< 0.01
Mortality	0.79	(0.77, 0.81)	< 0.01

found between higher cysGFR and hip fracture that had a similar magnitude to the estimated HR found in CHS data with traditional Cox [18]. We found an opposite direction of association with the FG approach in which better kidney function paradoxically increased the risk of hip fracture. The frank implausibility of such a finding highlights the problem of using FG to estimate risk factor-outcome associations.

Likewise, and contrary to the FG approach finding in CHS regarding diabetes, ARIC investigators found diabetes to increase the hazard of fracture-related hospitalization [19], a result that matches a recent analysis of this topic [20]. Their sensitivity analysis using the FG approach found the positive association attenuated by half, but still significant, consistent with the lesser degree of competing risk in a younger cohort. In CHS, where the majority of the population died before experiencing a hip fracture or reaching the end of the study (76%), the protective effect of death in the FG approach not only attenuated the risk but paradoxically also reversed the association, making diabetes protective against hip fracture.

Finally, we note that the composite event approach in all risk factors provided estimates similar to the mortality estimates, simply because over 85% of the composite events were deaths.

In general, the FG methodology was not intended for etiologic questions [4, 12]. The FG approach was not specifically designed to solve problems with competing risk, but rather to estimate subdistribution hazard ratios that would more closely correspond to cumulative incidence ratios from the entire population than do standard hazard ratios among individuals at risk. However, this correspondence does nothing to improve the ability of its method to answer questions about risk factors, and several of the examples here illustrate why.

In spite of the popular belief that the FG approach answers the question about what would have happened had the competing event not occurred, which is clearly a question of great interest, it in fact does not accomplish that. The FG approach adds more time at risk—following death, in the case described here—but *not* more events. Thus, the competing event, death in our scenario, protects individuals from the occurrence of the primary event until the end of the study. The question of what would have happened had the competing event not occurred naturally presumes that some cases would have accrued had participants not been censored, but the FG approach unrealistically presumes the opposite.

Although etiologic questions relating risk factors to outcomes are best examined with traditional Cox models, the FG estimates may be more useful in specific, typically less common settings. Specifically, when the adjusted cumulative incidence of a primary event according to levels of a specific risk factor is needed, then the FG estimate may be of use. For example, as the kidney function example makes clear, the Cox estimate appropriately suggests that better kidney function is associated with a lower subsequent hazard of hip fracture. However, the FG estimate suggests that the adjusted cumulative incidence of hip fracture will be lower among those with worse kidney function because their underlying mortality rate removes them from the Cox risk pool at an even faster rate. This observation may be useful for those assigning limited resources for hip fracture prevention or in tailoring prevention strategies for patients with chronic kidney disease. Nonetheless, we note that the FG hazard ratio magnitudes are not directly linked to the effects of a covariate on cumulative incidence, as the magnitudes are only relative [3].

One area of confusion with the FG approach relates to its use of weighting. Participants who sustain competing events continue to contribute person-time until the end of the study, but they do so with a weight (ranging from 0 to 1) that is determined by the probability of censoring for reasons other than primary or competing events (e.g., loss-to-follow-up). In cohorts like CHS where follow-up is complete, these weights do not decline [2, Sec 3.1], and deceased participants fully contribute person-time throughout follow-up. When follow-up is incomplete, deceased participants contribute person-time until the end of the study but with progressively smaller weights over time, based on the probability of censoring for the full study population over time [2, Sec 4].

When estimating hazard ratios for association of an event and a predictor, the conventional Cox approach estimates the hazard of the event in individuals who are event-free and alive—the group of individuals a clinician faces when implementing its results. The FG approach dilutes that association, attenuating the magnitude of HRs, if the predictor influences hazard of both the primary and competing outcomes in

the same direction. Similarly, the FG approach overestimates the magnitude of the association in individuals at risk if the effect is opposite for the two types of events. In neither case, however, does the FG approach necessarily better estimate what would have happened in the absence of competing risk.

Although the FG approach was introduced almost 20 years ago, and its developers have themselves cautioned about its misuse, clinical researchers continue to misinterpret its output, particularly in fields such as geriatrics where competing events are common. In our view, recognition of how individuals who experience the competing event are accommodated in the two approaches clarifies the problems that can accompany the use and interpretation of the FG. As the examples here illustrate, the FG approach can yield estimates close to or far from those of traditional CS Cox analysis and that are closer to or further from the null. They can also produce results that contradict well-established, biologically plausible associations observed in cohorts much less susceptible to competing risk. In our view, FG should be used for its original intention—namely to yield adjusted estimates of hazard ratios that are indirectly related to the cumulative incidence ratios in entire samples or in specific subgroups—but traditional CS Cox analysis, which has served survival analyses for decades, should continue to be used when questions about association of outcomes in clinical subsets at risk are addressed, even in the presence of competing risk of death.

Acknowledgments A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

Funding information This research was supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, and N01HC85086 and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA).

Compliance with ethical standards

Conflicts of interest None.

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