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On concerns with cause-specific incidence and subdistribution hazard

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Abstract

An event that hinders or changes the possibility of observing the event of interest is called a competing risk. For instance, clinical studies for those with multimorbidity or critically severe illnesses often require consideration of competing risks, as the occurrence of other events may preclude the primary event of interest. Since the one-to-one correspondence between the cause-specific hazard and the cause-specific incidence is lost in the classical competing risk model (Andersen et al., International Journal of Epidemiology 41:861–870, 2012), the Fine-Gray hazard was developed. The cause-specific incidence and the Fine-Gray hazard have been widely used and have become the default methods in competing risk analysis. The cause-specific incidence, however, often fails to represent treatment effects properly due to failures of the competing causes, particularly when the hazards of the competing causes are considerably different between the control and treatment arms. This study introduces a new incidence termed, *cause-distinct incidence*, which has a one-to-one correspondence with the cause-specific hazard and is less affected by competing causes than the cause-specific incidence. Whilst, recent studies have found unexpected effects of censors on the Fine-Gray hazard analysis. For instance, the estimation of the censoring distribution can affect the accuracy or censoring can complicate the estimation. The root cause of these unexpected phenomena has been uninvestigated. The basic requirement for the hazard is that it be independent of the distribution of independent censoring. Nevertheless, this study verifies mathematically and also numerically that the Fine-Gray hazard depends on the distribution of independent censoring.

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1 Introduction

An event that hinders or changes the possibility of observing the event of interest is called a competing risk (Li et al., 2022). Competing risk analysis refers to time-to-event analysis, or survival analysis, which aims to correctly estimate the possibility of an event of interest in the presence of competing events. Populations susceptible to competing risks include those with multimorbidity or critically severe illnesses such as cancer, cardiovascular diseases, stroke, diabetes, nephrology, and chronic obstructive pulmonary disease (COPD). Drug efficacy research needs to assess the effects of exposure on the disease-specific failure endpoint of interest rather than on the composite endpoint that combines all-cause mortality. Ignoring competing risks in time-to-event analyses can lead to biased risk estimates (Tullio et al., 2019). However, the decision to conduct competing risk analysis is not always straightforward, and even when deemed necessary, misconceptions exist about the appropriate choice of analytical methods (Li et al., 2022).

Gray (1988) demonstrated that the cause-specific hazard does not correspond one-to-one with the cause-specific incidence. This finding eventually led him to develop the Fine-Gray, or subdistribution, hazard (Fine & Gray, 1999), which has the property of one-to-one correspondence with the cause-specific incidence. The cause-specific incidence and the Fine-Gray subdistribution hazard have become the default methods for estimating the incidence of outcomes over time in the presence of competing risks (Austin et al., 2021; Kremers et al., 2021; Macek et al., 2020; Pintilie, 2011; Rehman et al., 2022). This remark prompted us to perform a literature search for papers published between 2020 and 2023. A search using Scopus with key words "competing risk" hit 5691 papers, "cause-specific" 3902, and "Fine-Gray" or "subdistribution hazard" 1712.

Nevertheless, some clinicians seem to be unable to correctly interpret the results obtained from the Fine-Gray hazard. Koller et al., (2012) surveyed major biostatistics and clinical journals to find that the competing risk issues were often ignored and that the application of inappropriate statistical methods was a frequent problem. Noordzij et al. (2013) suggest that the Fine-Gray hazard is suitable for the prediction of survival probability, while for etiological studies, when hazard ratios need to be derived, the cause-specific hazard is appropriate. Abdel-Qadir et al. (2018) warn that the cause-specific hazard ratio is not directly comparable to the magnitude of the effect of the covariate on the risk of stroke derived from the Fine-Gray model. Li et al. (2022) warn that a lower cause-specific hazard and a lower cumulative incidence are distinct and may result in analytical contrasts with different, even opposing, conclusions depending on the nature and extent of the competing risks. Macek et al. (2020) warn that the Fine-Gray hazard ratio should not be interpreted in the same way as the cause-specific hazard ratio which is by far the most suited method for prognostic studies.

Several commentaries have been written regarding proper usage and sound interpretation in the practice of competing risk analysis (Austin et al., 2016, 2021; Austin

& Fine, 2017) and some statisticians have warned against using the Fine-Gray hazard (e.g., Andersen et al., 2012; Putter et al., 2020; Troendle et al., 2018). These suggestions and warnings derive primarily from two facts. First, recent studies have found unexpected effects of censors on Fine-Gray model analysis. Donoghoe and Gebski (2017) observe that the estimation of the censoring distribution can affect the accuracy of an analysis using the Fine-Gray hazard. Putter et al. (2020) observe that censoring complicates estimation in the Fine-Gray regression model. Poguntke et al. (2018) conclude that cause-specific hazard analysis is the method of choice for general right-censored data. These warnings concerning the Fine-Gray hazard were based on observed phenomena, but the root cause of these phenomena has not yet been clarified. The most basic requirement for hazards is that they should be independent of the distribution of independent censoring. Nevertheless, this study finds through mathematical considerations that the Fine-Gray hazard depends on the distribution of independent censoring, which is also confirmed numerically.

Second, and more fundamentally, there is *no* one-to-one correspondence between the cause-specific hazard and the cause-specific incidence. Andersen et al. (2012) emphasize that "The key feature of competing risks is that the one-to-one correspondence between cause-specific hazard and cumulative incidence, between rate and risk, is lost." Then, they warn that "The loss of one-to-one correspondence should be kept in mind when deciding on how to make inferences." To resolve this situation, this study proposes an incidence termed, *"cause-distinct incidence"*. The cause-distinct incidence (CD-incidence) is less susceptible to the failure times of competing causes and corresponds one-to-one with the cause-specific hazard.

Section 2 describes the notation and symbols, Sect. 3 addresses the dependency of Fine-Gray hazard on independent censoring, Sect. 4 defines and studies the cause-distinct incidence in the presence of competing causes, and Sect. 5 summarizes the findings and results.

2 Notation and symbols

We first consider a homogeneous (no covariates) competing risk model. Let T and J be random variables to denote the failure time and the failure type, respectively. C denotes random censoring time independent of T. We observe $\min(T, C)$ and $\delta = I(T \leq C)$, where $I(\cdot)$ is the indicator function. $F(t) = P(T < t)$ is the *cumulative incidence*, $S(t) = P(T \geq t) = 1 - F(t)$ the *survivor function*, $f(t) = dF(t)/dt$ the *incidence*, $\lambda(t) = f(t)/S(t)$ the *hazard* and $\Lambda(t) = \int_0^t \lambda(u)du$ the *cumulative hazard*. Then it follows that $\lambda(t) = -d \log S(t)/dt$ and $S(t) = \exp\{-\Lambda(t)\}$.

For notational simplicity, we assume two types of failure, namely $J = 1$ or 2. $J = 1$ denotes the primary cause and $J = 2$ the competing cause. Failure due to $J = i$ is termed Type-i failure ($i = 1, 2$). We define a cause-specific incidence (CS-incidence), cause-specific hazard (CS-hazard) and cumulative cause-specific incidence (CCS-incidence) in the presence of the other type of failure to be $f_i(t) = \lim_{\Delta \to 0} P(t \leq T < t + \Delta, J = i)/\Delta$, $\lambda_i(t) = \lim_{\Delta \to 0} P(t \leq T < t + \Delta, J = i | t \leq T)/\Delta$ and

$F_i(t) = P(T < t,\ J = i) = \int_0^t f_i(u)du$, respectively, $(i = 1, 2)$. It holds that $\lambda_i(t) = f_i(t)/S(t)$, $\lambda(t) = \lambda_1(t) + \lambda_2(t)$ and $f(t) = f_1(t) + f_2(t)$.

The Fine-Gray, or subdistribution, hazard is defined as

$$\lambda^{\phi}(t) = \lim_{\Delta \to 0} P\{(t \le T < t + \Delta,\ J = 1) | (t \le T) \cup (T \le t,\ J = 2)\}/\Delta \qquad (1)$$

Since $P(t \le T) + P(T \le t,\ J = 2) = 1 - P(T < t,\ J = 1) = 1 - F_1(t)$, we have

$$\lambda^{\phi}(t) = \lim_{\Delta \to 0} \frac{P\{(t \le T < t + \Delta,\ J = 1)\}}{\Delta P\{(t \le T) \cup (T \le t,\ J = 2)\}} = \frac{f_1(t)}{1 - F_1(t)} = \frac{-d \log\{1 - F_1(t)\}}{dt}.$$

3 Dependency of Fine-Gray hazard on censoring

3.1 Hazard formula explicitly including censoring

The hazard $\lambda(t) = \lim_{\Delta \to 0} P(t \le T < t + \Delta | t \le T)/\Delta$ is defined without considering C, although T is observed only if $T \le C$. To consider whether $\lambda(t)$ is independent of C, C is explicitly included in $t \le T$ and $t \le T < t + \Delta$ in the definition of $\lambda(t)$. First, $t \le T$ means that T is under observation at t. Hence, we have $(t \le T) \cap (t \le C)$, as described in Fine and Gray (1999). Second, $t \le T < t + \Delta$ implies that T is observed to fail in $(t,\ t + \Delta)$ and hence $(t \le T < t + \Delta) \cap (T \le C)$ holds. Consequently, if C is explicitly included in the definition of $\lambda(t)$, it is written as

$$\begin{aligned} \lambda_C(t) &= \lim_{\Delta \to 0} \frac{P((t \le T < t + \Delta) \cap (T \le C) | (t \le T) \cap (t \le C))}{\Delta} \\ &= \lim_{\Delta \to 0} \frac{P((t \le T < t + \Delta) \cap (T \le C))}{\Delta P((t \le T) \cap (t \le C))}. \end{aligned} \qquad (2)$$

For the Fine-Gray hazard (1), the explicit inclusion of C needs further attention since *at risk* at t in (1) includes those who have been observed to fail by$t$. That is, the *at risk* at t in $\lambda^{\phi}(t)$ consists of not only $(t \le T)$ but also $(T \le t,\ J = 2)$. As previously described, $(t \le T)$ consists of subjects such that $t \le T$ and $t \le C$. Whilst, $(T \le t,\ J = 2)$ means that T is observed to fail of $J = 2$ at or before t, hence it holds that $(T \le t,\ J = 2) \cap (T \le C)$. Thus, we have

$$\lambda_C^{\phi}(t) = \lim_{\Delta \to 0} \frac{1}{\Delta} \frac{P\{(t \le T < t + \Delta,\ J = 1) \cap (T \le C)\}}{P[\{(t \le T) \cap (t \le C)\} \cup \{(T \le t,\ J = 2) \cap (T \le C)\}]}.$$

3.2 Independence of the hazard from censoring

The following theorem is the most fundamental in the failure time analysis. A detailed proof is described, since the proof technique is essential for examining the effect of censoring on the Fine-Gray hazard.

Theorem If C is independent of T, then $\lambda_C(t) = \lambda(t)$holds.

Proof A point to consider in the proof is that, $(t \le T)$ and $(t \le C)$ are mutually independent given t, but $(t \le T)$ and $(T \le C)$ are not necessarily. Thus, we first show

$$\lim_{\Delta\to 0} \frac{P((t \le T < t+\Delta) \cap (T \le C))}{\Delta} = \lim_{\Delta\to 0} \frac{P((t \le T < t+\Delta) \cap (t \le C))}{\Delta} \quad (3)$$

That is, $(T \le C)$ in the numerator may be replaced by $(t \le C)$.

Since $(t \le T < t+\Delta) \cap (T \le C)$ implies $(t \le T \le C)$, we have $(t \le T < t+\Delta) \cap (t \le C) \supset (t \le T < t+\Delta) \cap (T \le C)$. For notational simplicity, put $\alpha = (t \le T < t+\Delta)$ and define $\delta = P\{\alpha \cap (t \le C)\} - P\{\alpha \cap (T \le C)\}$. If $\lim_{\Delta\to 0} \delta/\Delta = 0$, then (3) holds.

Since $(t \le C) - (T \le C) = (t \le C) \cap (T \le C)^c = (t \le C) \cap (C < T) = (t \le C < T)$, we have $P\{\alpha \cap (t \le C < T)\} = P\{\alpha \cap (t \le C)\} - P\{\alpha \cap (T \le C)\}$. Thus, $\delta = P\{\alpha \cap (t \le C < T)\}$. Since $T < t+\Delta$ in α and T and C are mutually independent, $\delta \le P\{\alpha \cap (t \le C \le t+\Delta)\} = P(\alpha)P(t \le C < t+\Delta)$. It follows from $\lim_{\Delta\to 0} P(\alpha)/\Delta = f(t)$ and $\lim_{\Delta\to 0} P(t < C < t+\Delta) = 0$ that $\lim_{\Delta\to 0} \delta/\Delta = 0$. Since T and C are mutually independent, it follows from (2) that

$$\begin{aligned}\lambda_C(t) &= \lim_{\Delta\to 0} \frac{P((t \le T < t+\Delta) \cap (T \le C))}{\Delta P((t \le T) \cap (t \le C))} = \lim_{\Delta\to 0} \frac{P((t \le T < t+\Delta) \cap (t \le C))}{\Delta P((t \le T) \cap (t \le C))} \\ &= \lim_{\Delta\to 0} \frac{P(t \le T < t+\Delta)P(t \le C)}{\Delta P(t \le T)P(t \le C)} = \lim_{\Delta\to 0} \frac{P(t \le T < t+\Delta)}{\Delta P(t \le T)}.\end{aligned}$$

Thus, $\lambda_C(t) = \lambda(t)$ is obtained. □

The theorem indicates that $\lambda(t)$ is well defined. Similarly, $\lambda_1(t)$ is verified to be well defined. On the other hand, the Fine-Gray hazard $\lambda^{\phi}(t)$ is not necessarily independent of independent censoring. This is verified as follows.

First, it follows from (3) that

$$\lambda_C^{\phi}(t) = \lim_{\Delta\to 0} \frac{1}{\Delta} \frac{P\{(t \le T < t+\Delta,\ J=1) \cap (t \le C)\}}{P[\{(t \le T) \cap (t \le C)\} \cup \{(T \le t,\ J=2) \cap (T \le C)\}]}$$

Since T and C are mutually independent and $(t \le T)$ and $(T \le t)$ are mutually disjoint, or more precisely $P(T = t) = 0$, we have

$$\lambda_C^{\phi}(t) = \lim_{\Delta\to 0} \frac{1}{\Delta} \frac{P(t \le T < t+\Delta,\ J=1)P(t \le C)}{P(t \le T)P(t \le C) + P\{\{(T \le t,\ J=2) \cap (T \le C)\}}$$

First, $(T \leq C)$ in the denominator may not be replaced by $(t \leq C)$, since, as previously noted, $(T \leq t,\ J = 2) \cap (t \leq C)$ does not include $(T \leq t,\ J = 2) \cap (T \leq C \leq t)$, a subset of $(T \leq t,\ J = 2) \cap (T \leq C)$. Furthermore, $(T \leq t,\ J = 2)$ and $(T \leq C)$ are not necessarily mutually independent. Thus, $P(t \leq C)$ is not cancelled out and remains in the equation.

However, Fine and Gray (1999) replaced $(T \leq C)$ by $(t \leq C)$ in their proof (line 4 in the right column, p. 499) to obtain a modified hazard

$$\lambda_C^{\gamma}(t) = \lim_{\Delta \to 0} \frac{1}{\Delta} \frac{P(t \leq T < t + \Delta,\ J = 1) P(t \leq C)}{P(t \leq T) P(t \leq C) + P\{(T \leq t,\ J = 2) \cap (t \leq C)\}}.$$

Then $P(t \leq C)$ is canceled out since C is independent of $(T,\ J)$. Thus, it follows

$$\lambda_C^{\gamma}(t) = \lim_{\Delta \to 0} \frac{1}{\Delta} \frac{P(t \leq T < t + \Delta,\ J = 1)}{\{P(t \leq T) + P(T < t,\ J = 2)\}} = \lambda^{\phi}(t).$$

Therefore, $\lambda_C^{\gamma}(t)$ is independent of C.

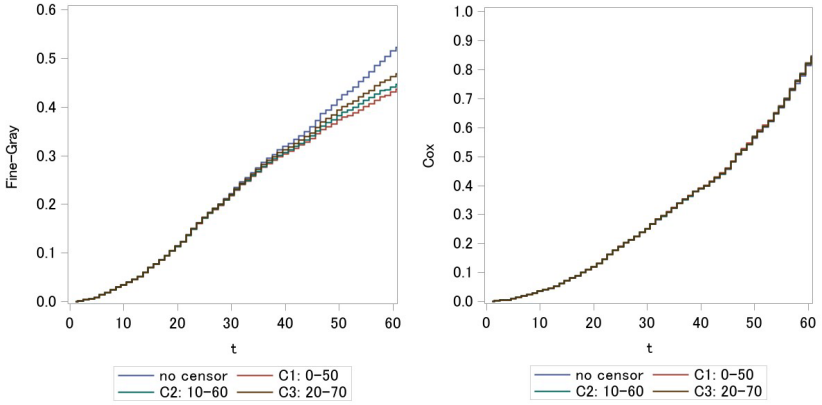
Consider cases such that $(T, J = 2)$ with $T < C < t$. Those cases are included in $(T \leq t,\ J = 2) \cap (T < C)$ but not in $(T \leq t,\ J = 2) \cap (t < C)$; therefore, those cases cause $\lambda_C^{\gamma}(t) \neq \lambda_C^{\phi}(t)$. These facts indicate that $\lambda^{\phi}(t)$ is *not* necessarily independent of C. Fine and Gray (1999) introduced "*censoring complete*", or "*administrative censoring*" (Joffle, 2001), which means censoring times are known at the baseline; however, that does not allow $(T \leq C)$ to be replaced by $(t \leq C)$ in $\lambda_C^{\phi}(t)$.

3.3 Numerical study

A numerical study is performed to examine the degree of dependency on censoring of the Fine-Gray hazard. For comparison, the cause-specific hazard is also examined.

Let X, Y and Z independently follow *Unif* (0, 1). Type-1 and Type-2 failure times are defined as $T_1 = 80X + 20Y$ and $T_2 = 20X + 80Y$, respectively. The correlation coefficient *Corr* (T_1, T_2) is approximately 0.5. A total of 1000 cases of (T_1, T_2) are generated and the Fine-Gray hazard $\lambda^{\phi}(t)$ and cause-specific hazard $\lambda_1(t)$ are obtained. The cumulative hazard with no censoring is regarded as "*true*" and the effects of censoring on them are examined by simulations using three censoring patterns. The censoring pattern is $C_1 = 50Z$, $C_2 = 10 + 50Z$, or $C_3 = 20 + 50Z$; the supports of C_1,C_2 and C_3 are (0, 50), (10, 60) and (20, 70), respectively.

In each iteration of the simulation, 750 cases out of the 1000 (T_1, T_2) were randomly selected and assigned censoring times C_1,C_2 and C_3 and the remaining 250 cases were assigned no censoring time, or $C_1 = C_2 = C_3 = \infty$. Thus, three samples $\{(T_1, T_2, C_1)\}$, $\{(T_1, T_2, C_2)\}$ and $\{(T_1, T_2, C_3)\}$ of size 1000 were obtained for each iterration. In each iteration $\lambda^{\phi}(t)$ and $\lambda_1(t)$ were obtained for each of C_1,C_2 and C_3, that produced cumulative hazards $\Lambda^{\phi}(t)$ and $\Lambda_1(t)$ for $0 < t < 100$. We performed 1,000 iterations and obtained 1000 of $\Lambda^{\phi}(t)$ and $\Lambda_1(t)$ for each of C_1,C_2 and C_3. We obtained the average of them for$t$ such that $n < t < n + 1$ for each of $\Lambda^{\phi}(t)$ and $\Lambda_1(t)$. The frequencies of $\lambda^{\phi}(t)$ and $\lambda_1(t)$ considerably decreased for $t > 60$.



(a) Fine-Gray hazard $\lambda^{\phi}(t)$ (b) Cause-specific hazard $\lambda\ (t)$

Fig. 1 The cumulative hazards according to the censoring pattern. No censoring (blue), $C_1 = 50Z$ (red), $C_2 = 10 + 50Z$(green) and $C_3 = 20 + 50Z$ (yellow)

Given t, $\lambda_C^{\gamma}(t) \neq \lambda_C^{\phi}(t)$ can be caused by cases such that $C < t$; therefore, the smaller C, the more such cases should be. Accordingly, the influence of censoring on the Fine-Gray hazard should be greatest for C_1, and decrease in order of C_2 and C_3. Figure 1 demonstrates the cumulative hazards by the censoring pattern for (a) the Fine-Gray hazard $\lambda^{\phi}(t)$ and (b) the cause-specific hazard $\lambda_1(t)$, labeled Cox. As expected, $\Lambda^{\phi}(t)$ depends on censoring, with C_3 being closest to the no-censoring, followed by C_2 and then C_1. In contrast, $\Lambda_1(t)$ does not depend on censoring, also as expected.

To examine the effect of the random numbers used in the SAS simulation, the same simulation with different seeds for random number generations was performed, and the result are shown in the Appendix.

4 Cause-distinct incidence in the presence of competing causes

4.1 Definition

In the competing risk analysis, it is customary to consider Type-2 failures as censors to obtain the maximum likelihood estimate of the type-1 specific hazard λ_1(t). We will briefly review the rationale following Kalbfleisch and Prentice (2002). For notational simplicity, we assume there are two types of failures, namely Type-1 and Type-2, and no censored subjects. Let $\{t^1{}_i\}$and $\{t^2{}_j\}$ denote the failure times for Type-1 and Type-2 failures, respectively. Let $\lambda_i(t)$ denote a Type-i specific hazard, $\Lambda_i(t) = \int_0^t \lambda_i(s)ds$ and $S_i(t) = \exp\{-\Lambda_i(t)\}$ for $i = 1, 2$. Since $S_i(t)$ accounts only $\lambda_i(t)$, $S_i(t)$ is Type i-specific survivor function obtained by regarding other types of failures as censored. $S(t) = S_1(t)S_2(t)$ is

the survivor function, and $f_i(t) = \lambda_i(t)S(t)$ is the CS-incidence. Then, the likelihood $L(\lambda_1, \lambda_2) = \prod_i f_1(t_i^1) \prod_j f_2(t_j^2)$ factorizes as $L(\lambda_1, \lambda_2) = L_1(\lambda_1)L_2(\lambda_2)$ where $L_1(\lambda_1) = \prod_i \lambda_1(t_i^1)S_1(t_i^1)\prod_j S_1(t_j^2)$ and$L_2(\lambda_2) = \prod_j \lambda_2(t_j^2)S_2(t_j^2)\prod_i S_2(t_i^1)$. Since λ_1 is included only in $L_1(\lambda_1)$, the λ_1 that maximizes $L_1(\lambda_1)$ is the maximum likelihood estimate (MLE) of λ_1 (8.2.3, Kalbfleisch & Prentice, 2002). The critical point is that $S_1(t) = \exp\{-\Lambda_1(t)\}$ is the Type-1 survivor function in the presence of Type-2 failure, not the survivor function $S(t)$.

This consideration led us to propose $f_1^*(t) = \lambda_1(t)S_1(t)$, termed the "*cause-distinct incidence* in the presence of Type-2 failure (CD-incidence)". $F_1^*(t) = \int_0^t f_1^*(s)ds$ is termed the cumulative cause-distinct incidence (CCD-incidence). It follows that $f_1(t) = \lambda_1(t)S(t) = \lambda_1(t)S_1(t)S_2(t) = f_1^*(t)S_2(t)$. Table 1 shows the notations and

Table 1 Notation and symbols in Kalbfleisch and Prentice (2002), SAS and this study

Kalbfleisch and Prentice	SAS	This study
(Overall) Hazard $\lambda(t)$	$h(t)$	(Overall) Hazard $\lambda(t)$
Type-i Cause-specific hazard $\lambda_i(t)$	$\lambda_i(t)$	Type-i Cause-specific hazard $\lambda_i(t)$
(Overall) Survivor function $F(t)$	$S(t)$	Survivor function $S(t)$
Type-i (sub) density function $f_i(t) = \lambda_i(t)F(t)$	No name	Type-i specific incidence $f_i(t) = \lambda_i(t)S(t)$
See footnote[a] No name	No name	Type-i survivor function $S_i(t) = exp\left\{-\int_0^t \lambda_i(s)ds\right\}$
Type-i cumulative hazard $-\log F_i(t)$	$\Lambda_i(t) = \int_0^t \lambda_i(s)ds$	Type-i cumulative hazard $\Lambda_i(t) = \int_0^t \lambda_i(s)ds$
Type-i cumulative incidence[b] $\overline{F}_i(t) = \int_0^t f_i(s)ds$	No name	Type-i cumulative incidence $F_i(t) = \int_0^t f_i(s)ds$
		Type-i distinct incidence $f_i^*(t) = \lambda_i(t)S_i(t)$
		Type-i cumulative distinct incidence $F_i^*(t) = \int_0^t f_i^*(s)ds$

[a]Kalbfleisch and Prentice (2002) define $F_i(t) = exp\left\{-\int_0^t \lambda_i(s)ds\right\}$ with the remark "these functions *will not, in general, have any survivor function interpretation*" and assign no name to it

[b]Kalbfleisch and Prentice (First edition, 1980) defined Type-i cumulative incidence as $I_i(t) = \int_0^t f_i(s)ds$

symbols in Kalbfleisch and Prentice (2002), SAS (PHREG or LIFETEST) and this study.

4.2 One-to-one correspondence between hazard and incidence

The following theorem assures that there is a one-to-one correspondence between $\lambda_1(t)$, $S_1(t)$ and $f_1^*(t)$ when $S_1(t) \to 0$, as $t \to \infty$.

Theorem When $S_1(t) \to 0$, as $t \to \infty$, each of the three functions $\lambda_1(t)$ $S_1(t)$ and $f_1^*(t)$ determines the other two. It also holds that $F_1^*(t) + S_1(t) = 1$ for $t \geq 0$.

Proof First, $\lambda_1(t)$ determines $S_1(t) = \exp\{-\Lambda_1(t)\}$, and therefore also $f_1^*(t) = \lambda_1(t)S_1(t)$. Conversely, $f_1^*(t)$ determines $S_1(t)$ and $\lambda_1(t)$ as follows. Since $dS_1(t)/dt = -\lambda_1(t)S_1(t) = -f_1^*(t)$ and $S_1(t) \to 0$ as $t \to \infty$, we have $\int_t^\infty f_1^*(s)ds = -[S_1(s)]_t^\infty = S_1(t)$. Then $\lambda_1(t)$ is obtained by $\lambda_1(t) = f_1^*(t)/S_1(t)$. Finally, $S_1(t)$ determines $\lambda_1(t) = d\{-\log S_1(t)\}/dt$ and therefore $f_1^*(t) = \lambda_1(t)S_1(t)$.

The last equality follows from $F_1^*(t) + S_1(t) = \int_0^\infty f_1^*(s)ds = -[S_1(s)]_0^\infty = 1$ when $S_1(t) \to 0$ as $t \to \infty$. □

Since $S_1(t)$ is a survivor function for Type-1 failures that regards Type-2 failures as censoring at the individual's failure time, $S_1(t)$ is an ordinary survivor function with one failure type. Therefore, $S_1(t) \to 0$ as $t \to \infty$ is generally assumed in most applications. The last equality $F_1^*(t) + S_1(t) = 1(t \geq 0)$ is useful in application.

On the other hand, $\lambda_1(t)$ is not obtained from $f_1(t)$ without additional information on Type-2 failure. Andersen et al. (2012) describe the property as "no one-to-one correspondence between $\lambda_1(t)$ and $f_1(t)$". There is another inconvenience with $f_1(t)$. Since $f_1(t) = f_1^*(t)S_2(t)$, $f_1(t)$ is more severely influenced by Type-2 failures than $f_1^*(t)$, particularly when $\lambda_2(t) > \lambda_1(t)$ as in Gray's example (4.3.1) or when $\lambda_2(t)$ is considerably different between the groups.

4.3 Comparison between CD-incidence and CS-incidence

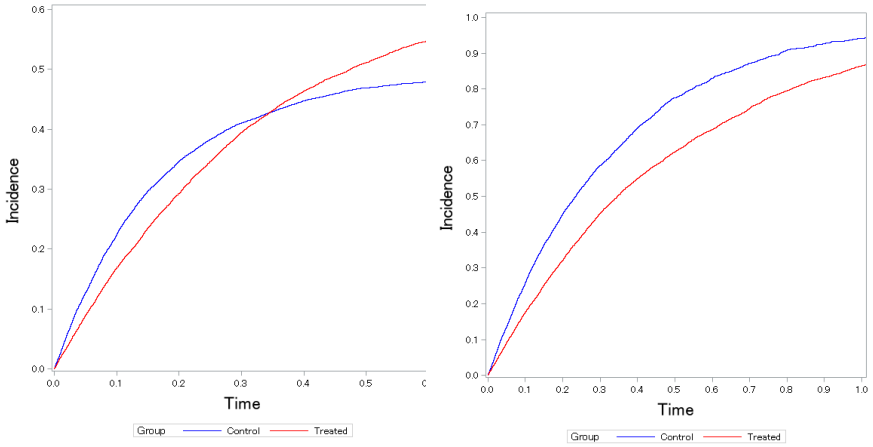
4.3.1 Gray's example: when the competing cause is high hazard

In the introduction of Gray (1988), a paradoxical relationship between CS-incidence and CS-hazard was described using two groups and two types of failure. Gray assigned $\lambda(1)_1 = \lambda(1)_2 = 3$, $\lambda(2)_1 = 2$ and $\lambda(2)_2 = 1$, where $\lambda(k)_i$ denotes the Type-i specific hazard for Group k. We consider groups 1 and 2 as the control and treatment groups and types 1 and 2 as the primary and competing causes, respectively. According to our interpretation, this treatment reduces the hazard from 3 to 2 for the primary cause and 3 to 1 for the competing cause, making it highly effective. Some related functions are presented in Table 2. Since the failure types are mutually independent, the competing failures are treated as independent censoring in calculating the CD-incidence.

Figure 2a shows Type-1 CCS-incidences for the groups. Since they cross each, they fail to represent the treatment effect properly. This paradoxical phenomenon is caused by the impact of competing failures on Type-1 CS-incidence, as explained in Sect.

Table 2 Functions determined from the hazards specified by Gray (1988)

	Group 1: Control	Group 2: Treatment arm
Type-l Hazard	$\lambda(1)_1 = 3$	$\lambda(2)_1 = 2$
Type-2 Hazard	$\lambda(1)_2 = 3$	$\lambda(2)_2 = 1$
Total Hazard	$\lambda(1) = 6$	$\lambda(2) = 3$
Survivor function	$S^C(t) = \mathrm{e}^{-6t}$	$S^T(t) = \mathrm{e}^{-3t}$
Cumulative incidence	$F^C(t) = 1\text{- } \mathrm{e}^{-6t}$	$F^T(t) = 1\text{-}\mathrm{e}^{-3t}$
Type-1 Survivor function	$S^C{}_1(t) = \mathrm{e}^{-3t}$	$S^T{}_1(t) = \mathrm{e}^{-2t}$
Type-1 CCS-incidence	$F^C{}_1(t) = (1\text{-}\mathrm{e}^{-6t})/2$	$F^T{}_1(t) = 2(1\text{-}\mathrm{e}^{-3t})/3$
Type-1 CS-incidence	$f^C{}_1(t) = 3\mathrm{e}^{-6t}$	$f^T{}_1(t) = 2\mathrm{e}^{-3t}$
Type-1 CD-incidence	$f^{*C}{}_1(t) = 3\mathrm{e}^{-3t}$	$f^{*T}{}_1(t) = 2\mathrm{e}^{-2t}$
Type-l cumulative hazard	$\Lambda^{\mathrm{C}}{}_1(t) = 3t$	$\Lambda^{\mathrm{T}}{}_1(t) = 2t$



(a) CCS-incidence

(b) CCD-incidence

Fig. 2 The horizontal lines denote time, while the vertical lines denote **a** CCS-incidence and **b** CCD-incidence. The control and treatment arms are denoted by blue and red lines, respectively. They cross in (**a**) but not in (**b**)

4.2. On the other hand, Fig. 2b shows that Type-1 CCD-incidence for the treatment arm is consistently lower than that for the control arm, which presents the treatment effect properly. Gray's example, in effect, demonstrates that the CD-incidence is more reliable than the CS-incidence.

Figure 2 can be directly obtained from the Type-1 CS incidence and Type-1 CD-incidence functions in Table 2. However, to clarify the difference between the CS-

and CD- incidences in the calculations, we present a SAS-code that calculates the incidences: https://www.med.osaka-u.ac.jp/pub/dmi/opendata/files/yamada/CS_CD_incidence.zip.

It first generates competing failure times (T, J) for the control and treatment arms based on the hazards specified in Table 2. Then, it calculates the CCS- and CCD-incidences from the data. The sample size is set 10,000 for each arm.

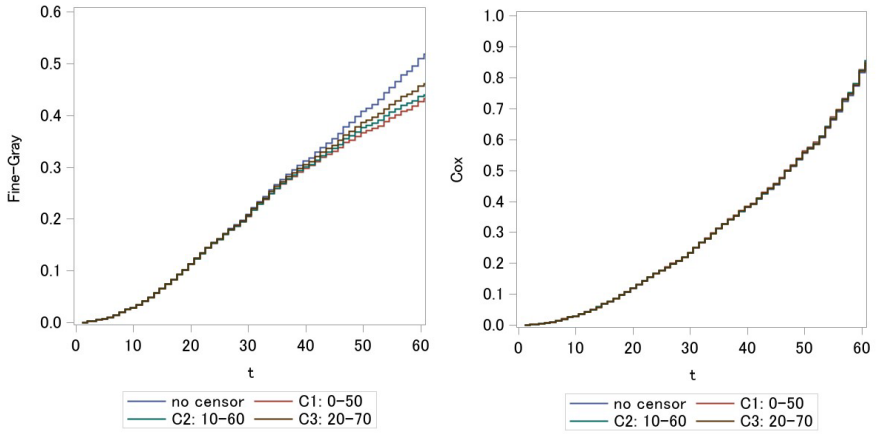
5 Conclusion

This study shows that a one-to-one correspondence, the key feature of competing risk analysis (Andersen et al., 2012), holds between the CD-incidence $f_i^*(t)$ and CS-hazard $\lambda_i(t)$. The fact that the key feature holds for CD-incidence but not for CS-incidence is based on the following fact. Let $\{t^1{}_i\}$and $\{t^2{}_j\}$ denote the failure times for Type-1 and Type-2 failures, respectively, and assume no censoring. Then, the likelihood $L(\lambda_1, \lambda_2) = \prod_i f_1(t_i^1) \prod_j f_2(t_j^2)$ is obtained using the CS-incidences $f_1(t)$ and $f_2(t)$, however, the maximum likelihood estimate of λ_1 is obtained by maximizing $L_1(\lambda_1) = \prod_i f_1^*(t_i^1) \prod_j S_1(t_j^2)$, which uses the CD-incidence $f_1^*(t)$. Since $f_1^*(t) = \lambda_1(t)S_1(t)$, $L_1(\lambda_1)$ coincides with the likelihood that is obtained by regarding $\{t^1{}_i\}$ as failures and $\{t^2{}_j\}$ as censoring. This fact has been overlooked, and the feature of CD-incidence $f_i^*(t)$ has not been well investigated. This study also verifies that CD-incidence is less susceptible to competing causes than CS-incidence, and consequently CD-incidence is more appropriate than CS-incidence in drug efficacy comparisons.

The Fine-Gray hazard is not well defined; that is, it depends on independent censoring. This is caused by an error when random censoring is explicitly includied in the hazard formula (Fine-Gray, 1999). The Fine-Gray hazard is well defined when censoring occurs only at the termination of the study, or no loss to follow.

Appendix

See Fig. 3.



(a) Fine-Gray hazard $\lambda^{\Phi}(t)$

(b) Cause-specific hazard $\lambda_1(t)$

Fig. 3 To examine the effect of the random numbers used in the SAS simulation on Fig. 1, the same simulation with different seeds for the random numbers was performed. The result is these figures that are nearly the same as those in Fig. 1. * SAS code for the simulation is obtained from the following site: https://www.med.osaka-u.ac.jp/pub/dmi/opendata/files/yamada/FineGray_Cox_Simulation.zip

Line 12 in the SAS code: "local seed = 579384925" specifies the random seed when generating (T_1, T_2). The number of iterations is specified by "for k = 1, 1000 do" on Line 31. The number of iterations is modified by modifying only 1000.

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Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

References

Abdel-Qadir, H., Fang, J., Lee, D. S., Tu, J. T., Amir, E., Austin, P. C., & Anderson, G. M. (2018). Importance of considering competing risks in time-to-event analyses. Application to stroke risk in a retrospective cohort study of elderly patients with atrial fibrillation. *Circ: Cardiovascular Quality and Outcomes, 11*, e004580. https://doi.org/10.1161/CIRCOUTCOMES.118.004580

Andersen, P. K., Geskus, R. B., de Witte, T., & Putter, H. (2012). Competing risks in epidemiology: possibilities and pitfalls. *International Journal of Epidemiology, 41*, 861–870. https://doi.org/10.1093/ije/dyr213

Austin, P. C., & Fine, J. P. (2017). Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Statistics in Medicine, 36*, 4391–4400. https://doi.org/10.1002/sim.7501

Austin, P. C., Latouche, A., & Fine, J. P. (2019). A review of the use of time-varying covariates in the Fine-Gray subdistribution hazard competing risk regression model. *Statistics in Medicine, 39*, 103–113. https://doi.org/10.1002/sim.8399

Austin, P. C., Lee, D. S., & Fine, J. P. (2016). Introduction to the analysis of survival data in the presence of competing risks. *Circulation, 133*, 601–609. https://doi.org/10.1161/CIRCULATIONAHA.115.017719

Austin, P. C., Steyerberg, E. W., & Putter, H. (2021). Fine-Gray subdistribution hazard models to simultaneously estimate the absolute risk of different event types: Cumulative total failure probability may exceed 1. *Statistics in Medicine, 40*, 4200–4212. https://doi.org/10.1002/sim.9023

Berger, M., Schmid, M., & Welchowski, T. (2020). Subdistribution hazard models for competing risks in discrete time. *Biostatistics, 21*, 449–466. https://doi.org/10.1093/biostatistics/kxy069

Donoghoe, M. W., & Gebski, V. (2017). The importance of censoring in competing risks analysis of the subdistribution hazard. *BMC Medical Research Methodology, 17*, 52. https://doi.org/10.1186/s12874-017-0327-3

Fine, J. P., & Gray, R. J. (1999). A proportional hazards model for the subdistribution of a competing risk. *Journal of American Statistical Association, 94*, 496–509. https://doi.org/10.1080/01621459.1999.10474144

Gray, R. J. (1988). A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Annals of Statistics, 16*, 1141–1154. https://doi.org/10.1214/aos/1176350951

Huebner, M., Wolkewitz, M., Enriquez-Sarano, M., & Schumacher, M. (2017). Competing risks need to be considered in survival analysis models for cardiovascular outcomes. *Journal of Thoracic and Cardiovascular Surgery, 153*, 1427–1431. https://doi.org/10.1016/j.jtcvs.2016.12.039

Joffle, M. M. (2001). Administrative and artificial censoring in censored regression models. *Statistics in Medicine, 20*, 2287–2304. https://doi.org/10.1002/sim.850

Kalbfleisch, J. D., & Prentice, R. L. (2002). *The statistical analysis of failure time data* (2nd ed.). Wiley-Interscience.

Klein, J. P., & Moeschberger, M. L. (1997). *Survival analysis: Techniques for censored and truncated data*. Springer-Verlag.

Koller, M. T., Raatz, H., Steyerberg, E. W., & Wolbers, M. (2012). Competing risks and the clinical community: Irrelevance or ignorance? *Statistics in Medicine, 31*(11–12), 1089–1097. https://doi.org/10.1002/sim.4384

Kremers, H. M., Devick, K. L., Larson, D. R., Lewallen, D. G., Berry, D. J., & Crowson, C. S. (2021). Competing risk analysis: What does it mean and when do we need it in orthopedics research? *Journal of Arthroplasty, 36*(10), 3362–3366. https://doi.org/10.1016/j.arth.2021.04.015

Li, Y., Sun, L., Burstein, D. S., & Getz, K. D. (2022). Considerations of competing risks analysis in cardio-oncology studies. *JACC: Cardio-Oncology, 4*(3), 287–301. https://doi.org/10.1016/j.jaccao.2022.08.002

Macek, P., Biskup, M., Terek-Derszniak, M., Manczuk, M., Krol, H., Naszydlowska, E., Smok-Kalwat, J., Gozdz, S., & Zak, M. (2020). Competing risks of cancer and non-cancer mortality when accompanied by lifestyle-related factors—A prospective cohort study in middle-aged and older adults. *Frontiers in Oncology, 10*, 545078. https://doi.org/10.3389/fonc.2020.545078

Noordzij, M., Leffondré, K., van Stralen, K. J., Zoccali, C., Dekker, F. W., Kitty, J., & Jager, K. J. (2013). When do we need competing risks methods for survival analysis in nephrology? *Nephrology, Dialysis, Transplantation, 28*, 2670–2677. https://doi.org/10.1093/ndt/gft355

Pintilie, M. (2011). An introduction to competing risks analysis. *Revista Espanola De Cardiologia, 64*(7), 599–605. https://doi.org/10.1016/j.rec.2011.03.016

Poguntke, I., Schumacher, M., Beyersmann, J., & Wolkewitz, M. (2018). Simulation shows undesirable results for competing risks analysis with time-dependent covariates for clinical outcomes. *BMC Medical Research Methodology, 18*, 79. https://doi.org/10.1186/s12874-018-0535-5

Putter, H., Schumacher, M., & van Houwelingen, H. C. (2020). On the relation between the cause-specific hazard and the subdistribution rate for competing risks data: The Fine-Gray model revisited. *Biometrical Journal, 62*, 790–807. https://doi.org/10.1002/bimj.201800274

Rehman, H., & Chandra, N. (2022). Inferences on cumulative incidence function for middle censored survival data with Weibull regression. *Japanese Journal of Statistics and Data Science, 5*, 65–86. https://doi.org/10.1007/s42081-021-00142-y

Troendle, J. F., Leifer, E. S., & Kunz, L. (2018). Dealing with competing risks in clinical trials: How to choose the primary efficacy analysis? *Statistics in Medicine, 37*, 2787–2796. https://doi.org/10.1002/sim.7800

Tullio, A., Magli, A., Moretti, E., & Valenta, F. (2019). Why we should take care of the competing risk bias in survival analysis: A phase II trial on the toxicity profile of radiotherapy for prostate cancer. *Reports of Practical Oncology and Radiotherapy, 24*, 511–519. https://doi.org/10.1016/j.rpor.2019.08.001