Understanding Dependent Competing Risks: A Simulation Study to Illustrate the Relationship Between Cause-Specific Hazard and Marginal Hazard

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In the analysis of competing risk data, the observed effect of a covariate can be obtained via a Fine and Gray sub-distribution hazard ratio. Sometimes, it is also desirable to obtain the virtual effect of a covariate as if the competing risks were non-existent. Under the latent failure time scenario, when the event of interest and the competing risk event are independent, the cause-specific hazard ratio obtained from the Cox model where the competing events are censored represents the ratio of the marginal hazards and can be interpreted as the virtual effect of the covariate. However, when the two events are not independent, the cause-specific hazard ratio is not the ratio of the marginal hazards as the ratio depends not only on the marginal hazards but also on the correlation between the competing risk and the event of interest. Using simulation, we investigated the degree to which the cause-specific hazard ratio changes relative to the marginal hazard with this correlation. It was found that the discrepancy between the cause-specific hazard ratio and the theoretical marginal hazard ratio increased as the proportion of competing risk events and the correlation between the events increased (>0.2). Depending on the direction of the correlation, the cause-specific hazard ratio can over- or under-estimate the marginal hazard ratio. Using real-life datasets, we show how these results can be used to make inferences on the virtual effects.

Keywords: competing risk; correlated event times; cause-specific hazard ratio; marginal hazard ratio

Introduction

In studies where the focus is on a specific event which occurs over time, the analysis is complicated by the existence of other events, particularly those that may change the probability of occurrence of the event of interest. As an example, let us consider a study on early stage follicular lymphoma, a good prognosis cancer with an 80% probability of survival at five years (Petersen et al., 2004). Suppose that the goal is to study the factors associated with development of a secondary malignancy. As some patients may die before experiencing

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a secondary malignancy, death is considered a competing risk event. As a second illustration, consider the dose escalation study of advanced head and neck cancer (Waldron et al., 2008). In this study, of 171 patients with stage III & IV head and neck cancer, 129 underwent feeding tube insertion prior to or during their treatment. While the focus was on the time to feeding tube removal, patients could develop local or distant relapse prior to the removal of the tube which, will delay or prevent the occurrence of this event of interest. Thus, in this study, any type of relapse would be considered as a competing risk event for the event of interest – removal of the feeding tube. A formal definition of competing risks is given by Gooley (Gooley, Leisenring, Crowley, & Storer, 1999): *a competing risk is an event whose occurrence either precludes the occurrence of another event under examination or fundamentally alters the probability of occurrence of this other event.*

In the competing risks setting, one can model either a) the sub-distribution hazard which is directly linked to the observed probability of event of interest in the presence of competing risks (Beyersmann et al. 2007, Koller et al. 2012; Wolbers et al. 2014), or b) the cause-specific hazard when the competing risks are censored. For the former analysis, Fine and Gray developed a regression model which linearly relates the covariates to the log-log transformation of the cumulative incidence function, yielding sub-distribution hazard ratios (Fine & Gray, 1999). This approach has been widely used in medical research for estimating and predicting individuals' risk for the occurrence of event of interest in the presence of competing risks (Forsblom et al., 2011; Petersen et al., 2004; Waldron et al., 2008).

However, at times it is beneficial to estimate the effects of covariates on the probability of event of interest as if the competing risk events were non-existent. In our first example, researchers may be interested whether a new treatment is associated with development of a secondary malignancy. The new treatment may produce changes at the molecular level which could result in a new malignancy. The analysis on the hazard of sub-distribution may not be able to detect such an effect. Suppose that the new treatment is given preferentially to the patients with more severe disease. These patients would be more likely to die of their primary malignancy for which they are treated and not have a chance to experience a second malignancy. As a result the excess of second malignancies would not be seen when the Fine and Gray model is applied. However, an analysis on marginal hazards, were this possible, would elucidate the very question of interest: does the new treatment promote a second malignancy. In the second example, researchers may be interested whether the treatment will lessen the time to feeding tube removal, when relapses or deaths are non-existent.

However, for the competing risk data where only the first event is observed, the marginal distribution is not identifiable unless one assumes the time to event of interest and competing risks are independent (Prentice et al., 1978; Putter, Fiocco, & Geskus, 2007). Under the independence assumption, the cause-specific hazard provided by the Cox model by censoring the competing risk events coincides with the marginal hazard and thus the hazard ratio of such an analysis can be interpreted as the effect in a virtual world in which competing risk events are no longer operative. However, this assumption can rarely be made and never proven (Tsiatis, 1975).

While the dependence issue has been widely recognized as an impediment to the interpretation (Andersen, Abildstrom, & Rosthøj, 2002; Koller, Raatz, Steyerberg, & Wolbers, 2012; Lau, Cole, & Gange, 2009; Prentice et al., 1978), its mechanism has not been fully addressed and knowledge is limited regarding the relationship between the cause-specific hazard and the marginal hazard under varying degrees of correlation between the time-to-event and time-to-competing risk. In this paper, we focused on latent failure time framework and investigated to what degree the cause-specific hazard ratio approximates the marginal hazard ratio for varying

degree of correlation. In Section 2, general theoretical background of cause-specific hazard and marginal hazard are provided, followed by a simulation study in Section 3. Real-life examples are provided in Section 4 and the discussion and concluding remarks are presented in Section 5.

Background

Cause-specific hazard and Sub-distribution hazard

We define the cause-specific hazard within the latent failure time framework in which one assumes the existence of k potential failure times (Crowder, 2010). In this paper, without losing generality, only two types of events are considered: the event of interest (ev) and the competing risk event (cr, $k = 2$). If there are more types of event competing with the event of interest, they can all be grouped under one type of competing risk event.

Let T_{ev} and T_{cr} be two random variables which denote the time to the event of interest and time to the competing risk, respectively. We observe T , the time to first failure, $T = \min(T_{ev}, T_{cr})$.

In the presence of competing risks, the cause-specific hazard function for failure of type ev in the presence of cr is

$$h_{ev}(t) = \lim_{\Delta t \rightarrow 0} \frac{P(t < T \leq t + \Delta t, E = ev | T > t)}{\Delta t} = \frac{\tilde{f}_{ev}(t)}{S(t)}$$

where $S(t) = P(T > t)$ is the estimate of the overall survivor function when both types of events are considered. The Cox regression applied when the cr events are censored models the cause-specific hazard (h_{ev}).

Lack of Identifiability within the latent failure time framework

Let $S(t_{ev}, t_{cr}) = P(T_{ev} > t_{ev}, T_{cr} > t_{cr})$ denote the joint survivor distribution. Then for $i = ev, cr$, $S_i(t_i) = P(T_i > t_i) = S(t_i, 0)$ represents the marginal survivor function for T_i and

$$\lambda_i = \frac{-d \log(S_i(t_i))}{dt_i}$$

is the corresponding marginal hazard function. Tsiatis (Tsiatis, 1975) showed that, for any joint survivor function with arbitrary dependence between the different failure time distributions, one can find a different joint survivor function with independent failure time distributions, which have the same marginal hazards. It follows that when the marginal distributions are observed it is not possible to know the joint distribution. Thus for the following two joint survivor functions:

$$S(t_{ev}, t_{cr}) = \exp(-\alpha_{ev}t_{ev} - \alpha_{cr}t_{cr} - \tau t_{ev}t_{cr})$$

and

$$S^*(t_{ev}, t_{cr}) = \exp(-\alpha_{ev}t_{ev} - \alpha_{cr}t_{cr})$$

where $\alpha_{ev}, \alpha_{cr} > 0$ and $\tau > -1$, the marginal hazards are the same $h_{ev}^* = \alpha_{ev}$. On the other hand, the cause-specific hazards are different, $h_{ev} = \alpha_{ev} + \tau t_{ev}$. The direct implication is that the hazard ratios obtained when the Cox proportional hazards model is applied (with competing risks events censored) are the cause-specific hazard ratios and are different than the marginal hazard ratios unless $\tau = 0$. It follows that in

spite of the fact that the marginal distributions are the same, the results produced by the Cox regression may be different depending on the correlation between the two types of events.

Simulation

We generated sets of time variables following bivariate exponential distributions when the correlation varies between -0.6 to 0.6 at 0.2 intervals. We believe that the correlation coefficients of -0.6 and 0.6 are extreme enough to reflect real-life situations. The survival times are also associated with a binary covariate coded here as 1 or 0. We created the observed time as the minimum of the two time variables for each observation and the event indicator is either *ev* if the minimum is equal to the first time variable or *cr* if the minimum was equal to the second time variable. We also simulated a censoring variable uniformly distributed between 4 to 8. If the censoring variable was smaller than both time variables then the observed time was equal to this and the event type was coded as 0 representing a censored observation. Cox proportional hazards models were applied for both event of interest and competing risks and the coefficients were kept. This process was repeated 2000 times and the summary statistics of the coefficients were calculated for each situation and scenario. The marginal hazard rates for the event of interest were chosen such that the theoretical marginal hazard ratio for the event of interest was always 2. The marginal hazard rates for the competing risks varied such that the theoretical marginal hazards ratio for the competing risks took the values 0.5, 1, 2, 3. One extra case was added in which both hazard ratios – for the event of interest and the competing risk - are 1. Table 1 summarizes the scenarios generated in this study where the term ‘HR’ refers to the theoretical marginal hazard ratio. In choosing the hazard rates, extra care was applied to allow for the variability in the predominance of the event of interest to competing risk events. Thus, under the ‘Low competing risks’ scenarios the hazard rates for the competing risks are lower or equal to those for the event of interest. The reverse is true for the scenarios under the ‘High competing risks’.

Table 1

Scenarios and parameter settings

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Parameters*	$HR_{ev} = 2$	$HR_{ev} = 2$	$HR_{ev} = 2$	$HR_{ev} = 2$	$HR_{ev} = 1$
	$HR_{cr} = 0.5$	$HR_{cr} = 1$	$HR_{cr} = 2$	$HR_{cr} = 3$	$HR_{cr} = 1$
Low Competing Risks					
$\lambda_{ev,1}$	0.4	0.4	0.4	0.4	0.2
$\lambda_{cr,1}$	0.1	0.2	0.2	0.3	0.2
$\lambda_{ev,0}$	0.2	0.2	0.2	0.2	0.2
$\lambda_{cr,0}$	0.2	0.2	0.1	0.1	0.2
High Competing Risks					
$\lambda_{ev,1}$	0.4	0.4	0.4	0.4	0.2
$\lambda_{cr,1}$	0.3	0.6	0.6	0.9	0.6
$\lambda_{ev,0}$	0.2	0.2	0.2	0.2	0.2
$\lambda_{cr,0}$	0.6	0.6	0.3	0.3	0.6

* ev and cr refer to event of interest and competing risk, 0 and 1 refer to unexposed and exposed group, respectively.

To obtain a bivariate exponential distribution, we first generated a bivariate standard normal distribution with a specific correlation coefficient ρ (Gumbel, 1960). Suppose that (x_{ev}, x_{cr}) is a realization from

$N(0, \Sigma)$, where $\Sigma = \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$. Then t_{ev} and t_{cr} are calculated as

$$t_i = -\frac{\ln(1 - \Phi(x_i))}{\lambda_i}$$

where for $i = ev, cr$, λ_i are the parameters of the marginal distributions in Table 1 and $\Phi(x_i)$ is the cumulative distribution for x_i . Note that the correlation ρ between (x_{ev}, x_{cr}) does not necessarily translate to the same level of correlation between (t_{ev}, t_{cr}) . The average of the empirical correlations r between (t_{ev}, t_{cr}) are reported in the results.

The simulation was performed for a sample size of 300 in each treatment group and repeated 2000 times using R software (<http://cran.r-project.org/>).

In each dataset, the cause-specific hazard ratios (CHR) were obtained by employing the Cox model. The results were summarized by calculating the averages and the variances of the estimated CSH over the 2000 simulations. The deviation of CHR from the HR was calculated as $|\beta - \beta^*|/\beta^*$, where β is the estimate of coefficient and β^* is the theoretical coefficient (the log of the theoretical marginal hazard ratio).

Results of the Simulation

Different patterns emerged depending on the preponderance of the competing risk events in relation to that of the event of interest and the relationship between the distributions of the two types of events. As expected, the deviation of the CHR from the HR was more pronounced when the event times were highly correlated and the theoretical marginal hazard for the competing risk was higher than that for the event of interest. Thus, in each table the lowest deviation is always under the $r = 0$ and it increases as the r departs from 0 on both sides to 0.6 or to -0.6. Note that r represents the average of the empirical correlation between the observed times of event and time for competing risks before applying the censoring distribution. Also, the cases presented in the lower part of the tables, specific to high competing risks, have much higher deviation than in the cases presented in the upper part of table. It is noticeable that for Scenarios 1 ($HR_{ev}=2$ and $HR_{cr}=0.5$) and Scenarios 2 ($HR_{ev}=2$ and $HR_{cr}=1$) the deviation is higher for positive correlations than for negative correlations and the situation is reversed in the Scenarios 3 ($HR_{ev}=2$ and $HR_{cr}=2$) and Scenarios 4 ($HR_{ev}=2$ and $HR_{cr}=3$) (Tables 4 and 5). Thus, one could conclude that when the effect of the covariate is in the same direction for the competing risks as well as for the event of interest a negative correlation will produce a greater departure from the marginal hazards ratio. On the other hand, when the effect is in the opposite direction, the positive correlation creates higher deviation. Scenario 5 ($HR_{ev}=1$ and $HR_{cr}=1$, Table 6) shows that when the effect is null for both the event of interest and the competing risk the cause-specific hazard ratio approximates well the marginal hazard ratio. It is also of interest whether the cause-specific hazard ratio is higher or lower than the theoretical marginal hazard ratio. Figure 1 shows the boxplots of the cause specific hazard ratios for the Scenarios 1-4 for high competing risks. Thus for Scenarios 2 and 3 the CHR is in general larger than 2, while for Scenarios 1 and 4 the CHR can be both higher and lower than 2. Of great importance is that the estimated CHR is, on average, in the direction of the theoretical HR (Tables 2, 4 and 5) except in the cases of the null

effect when it varies around 1. For example, in Scenario 1 the average estimated CHR for the event of interest is >1.5 and for the competing risks is <0.7 . For scenario 2 where the theoretical HR for the competing risks is 1 the average of the estimated CHR for the event of interest is close to 2 but the one for the competing risks varies around 1 depending on the size of the correlation.

Figure 1. Box-plot for cause-specific hazard ratio of event of interest, $HR_{ev}=2$ (dashed green reference line); (A) Scenario 1 ($HR_{cr}=0.5$); (B) Scenario 2 ($HR_{cr}=1$); (C) Scenario 3 ($HR_{cr}=2$); (D) Scenario 4 ($HR_{cr}=3$)

Table 2

The estimated CHR_{ev} , CHR_{cr} , and their percent deviation from the theoretical hazard ratio for Scenario 1 ($HR_{ev}=2$ and $HR_{cr}=0.5$)

r	Unexposed ^a	Exposed ^b	CHR_{ev}	CHR_{cr}	deviation (CHR_{ev} , %)
$\lambda_{ev,1} = 0.4, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.1, \lambda_{cr,0} = 0.2$					
$\lambda_{cr,1} = 0.1, \lambda_{cr,0} = 0.2$					
0.6	0.404	0.818	2.566[2.061,3.195]	0.264[0.171,0.405]	35.95
0.4	0.420	0.788	2.311[1.859,2.873]	0.363[0.252,0.524]	20.86
0.2	0.434	0.767	2.137[1.722,2.653]	0.437[0.312,0.610]	9.58
0.0	0.450	0.753	1.997[1.611,2.474]	0.499[0.365,0.683]	0.25
-0.2	0.465	0.744	1.903[1.538,2.354]	0.550[0.408,0.740]	7.20
-0.4	0.481	0.737	1.820[1.474,2.248]	0.599[0.451,0.797]	13.62
-0.6	0.497	0.729	1.775[1.439,2.19]	0.661[0.503,0.869]	17.21
$\lambda_{ev,1} = 0.4, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.3, \lambda_{cr,0} = 0.6$					
0.6	0.135	0.579	3.593[2.544,5.074]	0.357[0.284,0.448]	84.51
0.4	0.182	0.568	2.678[1.970,3.642]	0.416[0.332,0.520]	42.13
0.2	0.217	0.562	2.262[1.696,3.017]	0.460[0.369,0.574]	17.75
0.0	0.247	0.559	2.000[1.519,2.634]	0.500[0.401,0.623]	0.02
-0.2	0.272	0.559	1.834[1.405,2.394]	0.533[0.428,0.663]	12.50
-0.4	0.294	0.556	1.699[1.310,2.203]	0.561[0.451,0.698]	23.54
-0.6	0.313	0.552	1.573[1.219,2.030]	0.580[0.466,0.722]	34.68

^a proportion of event of interest in the unexposed group(coded as 0)

^b proportion of event of interest in the exposed group (coded as 1)

Table 3

The estimated CHR_{ev} , CHR_{cr} , and their percent deviation from the theoretical hazard ratio for Scenario 2 ($HR_{ev}=2$ and $HR_{cr}=1$)

r	Unexposed ^a	Exposed ^b	CHR_{ev}	CHR_{cr}	deviation (CHR_{ev} , %)
$\lambda_{ev,1} = 0.4, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.2, \lambda_{cr,0} = 0.2$					
0.6	0.404	0.698	2.345[1.871,2.940]	0.730[0.539,0.987]	22.96
0.4	0.420	0.670	2.171[1.734,2.720]	0.846[0.637,1.124]	11.87
0.2	0.434	0.654	2.068[1.653,2.588]	0.927[0.706,1.218]	4.85
0.0	0.450	0.643	1.998[1.599,2.497]	1.003[0.770,1.307]	0.12
-0.2	0.465	0.637	1.978[1.584,2.470]	1.070[0.826,1.386]	1.58
-0.4	0.481	0.631	1.996[1.599,2.492]	1.157[0.897,1.493]	0.28
-0.6	0.497	0.622	2.211[1.761,2.774]	1.365[1.056,1.764]	14.44
$\lambda_{ev,1} = 0.4, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.6, \lambda_{cr,0} = 0.6$					
0.6	0.135	0.329	2.733[1.890,3.953]	0.882[0.731,1.065]	45.06
0.4	0.182	0.362	2.310[1.664,3.208]	0.923[0.762,1.120]	20.82
0.2	0.217	0.383	2.117[1.557,2.879]	0.960[0.789,1.168]	8.22
0.0	0.247	0.397	1.998[1.490,2.680]	1.004[0.823,1.225]	0.11
-0.2	0.272	0.412	1.959[1.475,2.602]	1.043[0.853,1.276]	3.00
-0.4	0.294	0.421	1.965[1.489,2.593]	1.099[0.896,1.347]	2.57
-0.6	0.313	0.429	2.180[1.652,2.878]	1.233[1.001,1.520]	12.44

^a proportion of event of interest in the unexposed group(coded as 0)

^b proportion of event of interest in the exposed group (coded as 1)

Table 4

The estimated CHR_{ev} , CHR_{cr} , and their percent deviation from the theoretical hazard ratio for Scenario 3 ($HR_{ev}=2$ and $HR_{cr}=2$)

r	Unexposed ^a	Exposed ^b	CHR_{ev}	CHR_{cr}	deviation (CHR_{ev} , %)
$\lambda_{ev,1} = 0.4, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.2, \lambda_{cr,0} = 0.1$					
0.6	0.549	0.698	1.991[1.618,2.450]	1.789[1.244,2.573]	0.66
0.4	0.542	0.670	1.976[1.601,2.440]	1.858[1.332,2.592]	1.73
0.2	0.543	0.654	1.978[1.600,2.446]	1.923[1.403,2.635]	1.58
0.0	0.550	0.643	2.000[1.615,2.476]	2.011[1.486,2.722]	0.02
-0.2	0.559	0.637	2.069[1.669,2.565]	2.113[1.575,2.835]	4.91
-0.4	0.574	0.631	2.202[1.771,2.737]	2.314[1.733,3.090]	13.86
-0.6	0.599	0.622	2.655[2.108,3.343]	2.995[2.216,4.049]	40.85
$\lambda_{ev,1} = 0.4, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.6, \lambda_{cr,0} = 0.3$					
0.6	0.297	0.329	1.864[1.388,2.504]	1.964[1.591,2.426]	10.15
0.4	0.330	0.362	1.906[1.438,2.527]	1.955[1.577,2.423]	6.92
0.2	0.355	0.383	1.947[1.480,2.561]	1.965[1.581,2.441]	3.85
0.0	0.377	0.397	1.997[1.526,2.614]	2.014[1.617,2.508]	0.20
-0.2	0.396	0.412	2.108[1.615,2.751]	2.075[1.661,2.592]	7.56
-0.4	0.413	0.421	2.293[1.756,2.995]	2.219[1.769,2.784]	19.74
-0.6	0.428	0.429	2.920[2.202,3.871]	2.713[2.131,3.454]	54.59

^a proportion of event of interest in the unexposed group(coded as 0)

^b proportion of event of interest in the exposed group (coded as 1)

Table 5

The estimated CHR_{ev} , CHR_{cr} , and their percent deviation from the theoretical hazard ratio for Scenario 4 ($HR_{ev}=2$ and $HR_{cr}=3$)

r	Unexposed ^a	Exposed ^b	CHR_{ev}	CHR_{cr}	deviation (CHR_{ev} , %)
$\lambda_{ev,1} = 0.4, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.3, \lambda_{cr,0} = 0.1$					
0.6	0.549	0.579	1.805[1.451,2.245]	3.209[2.303,4.472]	14.81
0.4	0.542	0.568	1.863[1.493,2.323]	3.036[2.225,4.141]	10.27
0.2	0.543	0.562	1.923[1.539,2.402]	2.983[2.213,4.020]	5.68
0.0	0.550	0.559	2.000[1.598,2.502]	3.022[2.260,4.040]	0.01
-0.2	0.559	0.559	2.130[1.699,2.671]	3.122[2.346,4.155]	9.11
-0.4	0.574	0.556	2.344[1.861,2.954]	3.415[2.565,4.546]	22.93
-0.6	0.599	0.552	2.964[2.312,3.800]	4.536[3.330,6.179]	56.75
$\lambda_{ev,1} = 0.4, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.9, \lambda_{cr,0} = 0.3$					
0.6	0.297	0.203	1.469[1.039,2.076]	3.203[2.596,3.951]	44.53
0.4	0.33	0.251	1.691[1.228,2.328]	3.067[2.476,3.799]	24.21
0.2	0.355	0.283	1.851[1.363,2.514]	3.003[2.416,3.731]	11.18
0.0	0.377	0.306	1.998[1.483,2.691]	3.026[2.427,3.773]	0.16
-0.2	0.396	0.329	2.208[1.647,2.960]	3.085[2.464,3.863]	14.28
-0.4	0.413	0.345	2.520[1.878,3.381]	3.306[2.622,4.167]	33.33
-0.6	0.428	0.36	3.417[2.496,4.678]	4.118[3.199,5.300]	77.29

^a proportion of event of interest in the unexposed group(coded as 0)

^b proportion of event of interest in the exposed group (coded as 1)

Table 6

The estimated CHR_{ev} , CHR_{cr} , and their percent deviation from the theoretical hazard ratio for Scenario 5 ($HR_{ev}=1$ and $HR_{cr}=1$)

r	Unexposed ^a	Exposed ^b	CHR_{ev}	CHR_{cr}
$\lambda_{ev,1} = 0.2, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.2, \lambda_{cr,0} = 0.2$				
0.6	0.696	0.698	1.002[0.827,1.214]	0.991[0.704,1.393]
0.4	0.669	0.670	1.001[0.822,1.217]	0.994[0.727,1.358]
0.2	0.654	0.654	1.000[0.820,1.219]	0.996[0.741,1.338]
0.0	0.644	0.643	0.999[0.817,1.220]	1.002[0.755,1.331]
-0.2	0.636	0.637	1.005[0.822,1.230]	1.000[0.760,1.316]
-0.4	0.630	0.631	1.005[0.821,1.230]	1.000[0.766,1.307]
-0.6	0.621	0.622	1.004[0.819,1.231]	1.000[0.770,1.300]
$\lambda_{ev,1} = 0.2, \lambda_{ev,0} = 0.2; \lambda_{cr,1} = 0.6, \lambda_{cr,0} = 0.6$				
0.6	0.329	0.329	1.000[0.756,1.324]	0.997[0.817,1.217]
0.4	0.361	0.362	1.001[0.766,1.308]	0.997[0.814,1.222]
0.2	0.382	0.383	1.000[0.771,1.297]	0.997[0.812,1.225]
0.0	0.399	0.397	0.997[0.772,1.287]	1.004[0.815,1.236]
-0.2	0.411	0.412	1.005[0.782,1.292]	1.001[0.811,1.235]
-0.4	0.420	0.421	1.004[0.783,1.287]	1.000[0.810,1.236]
-0.6	0.428	0.429	1.003[0.784,1.283]	0.999[0.807,1.236]

* The deviation is not provided for this table since the theoretical coefficient in this scenario is zero

^a proportion of event of interest in the unexposed group (coded as 0)

^b proportion of event of interest in the exposed group (coded as 1)

Real-Life Examples

One of the examples is a subset of a large cohort of patients diagnosed with low grade lymphoma between 1967-1987. The analysis presented in this paper is performed on the subset of early stage disease, treated radically. The recorded outcomes included disease failure (relapse, whether local, distant or both), second malignancy and death. Age dichotomized at 60 is the covariate of interest.

We consider relapse to be the event of interest and death without relapse is the competing risk event. In this cohort of 541 patients, 272 relapsed and 76 had died before experiencing a relapse. Thus, the observed number of competing risks is only 22% of all the failures. It is reasonable to assume that if there is any correlation between time to relapse and time to death then it is positive i.e. the patients in this cohort who are likely to relapse are also likely to die of other causes. The effect of age on the cause-specific hazard of relapse is $CHR=1.5$ and for death CHR is 5.4 (Table 7). As the CHR is greater than 1 for both event of interest and the competing risk, this example closely matches Scenario 4 and 5 (Tables 4 and 5) when the competing risks are low and have positive correlation, in which we see that the CHR slightly underestimates the theoretical HR , thus the data suggest that those in the older cohort are more likely to have both relapse and die of other causes.

As a second data analysis example, for the cohort of head and neck patients, the main outcome is the removal of the feeding tube and the competing risk event is defined as any relapse or death. These two types of events are very likely negatively correlated. Of the 129 patients, 100 had their feeding tube removed and 25 had

a relapse/death before the removal of the tube. We are interested in the effect of age (dichotomized at 60) on the chance to remove the feeding tube. Thus, CHR for removal of the feeding tube is 0.48 with the p-value=0.00047 and for relapse/death the CHR is 1.13 with p=0.77 (Table 7). Scenario 1 and 2 may fit in this situation. In Scenario 1, the effects of age for both types of event are shrunk towards the null when the correlation between events is negative. Thus, the effect of age on tube removal may be even larger than estimated and one could be confident that the younger patients have a tendency to have a faster recovery after their cancer treatment. On the other hand, the effect on relapse/death is small and although the simulations suggest that in reality this is larger than estimated the shrinkage is modest and unlikely to hide a real effect. To discuss this example in the context of Scenario 2 we can recode the covariate as 0 for the older patients and 1 for the younger patients in which case the CHR for tube removal is 2.08 and for relapse/death is 0.88. Scenario 2 suggests that if age is not associated with relapse/death then the estimated effect on removal of the feeding tube is approximately correct.

Although these conclusions are not definitive it can help to plan further research. Suppose that in the above example the covariate was a marker, the main outcome was the relapse of the disease and the competing risk was death without relapse. Having some evidence that the presence of a marker has an association with the risk of relapse could be beneficial. The marker can be further studied in the laboratory and new evidence may emerge which could be the basis for a new targeted therapy.

Table 7

The effect of age on the two types of events

Dataset	Main event HR (95% CI)* p-value	Competing risk event HR (95% CI) p-value
Low stage lymphoma	1.5 (1.2-1.9), p=0.0017	5.4 (3.3 – 9.0), p<0.0001
Head and neck cancer	0.48 (0.32-0.72), p=0.0007	1.13 (0.5-2.55) p=0.77

* 95% CI = 95% confidence interval

Discussion

We believe that it would be beneficial to know to what extent and under what conditions the cause-specific hazard ratio can approximate the marginal hazard ratio. To this end, we undertook a simulation study extending the settings investigated by previous authors (Tai, De Stavola, de Gruttola, GebSKI, & Machin, 2008). Our simulation results suggest that the size and the direction of the correlation between event times for the different types of events, and the magnitude of the covariate effects on the event of interest as well as on the competing risk influence the magnitude of the departure of the cause-specific hazard ratio from the marginal hazard ratio. Specifically, deviation increases as the HR of the competing risks increases and with the level of correlation between the two types of events. However, we found that the CHR_{cv} approximates well the HR when i) the degree of correlation between the types of events is low $-0.2 \leq r \leq 0.2$, and ii) the covariate effect is minimal on both the event of interest and the competing risk. Although, the HR and the degrees of correlation between the types of events are not known in practice and independence between event times can hardly be assumed unless detailed knowledge of the biological or physical mechanism regarding the events is possessed, one may be able to use the tables in this paper to surmise whether the effect on the marginal hazards is under- or over-estimated by Cox regression model.

The direction of the correlation coefficient (positive or negative) between the event types may, in certain

instances, be presumed. In the follicular lymphoma study example, it is reasonable to assume that the correlation between relapse and death is positive, in the sense that they likely increase together. In the advanced head and neck cancer study, we may expect the "good" event of tube removal and the "bad" event of relapse to be negatively correlated.

In this paper, we only considered the situation where the marginal hazard ratio for the event of interest was 2 (>1). It is not necessary to consider marginal hazard ratios of <1 since a simple re-coding of the covariate can invert the ratio. We also limited the empirical correlation (r) between event times to range between -0.6 and 0.6 as it is technically difficult to generate correlated exponential distributions higher than 0.6. However, one could deduce the direction of the deviation outside this range based on these simulations. In reality it may also be implausible to have very high correlations between the two events (Iyer, Manjunath, & Manivasakan, 2002).

We are aware that based on these results one can only infer that one possibility is more warranted than the other. While these analyses may be able to spurn new interest and new research they do not constitute a proof. While we only considered the exponential time-to-event distribution, more research is needed to investigate the performance of the cause-specific hazard ratios for other time-to-event distributions and extending the combination of scenarios dealt within this paper.

When the goal is to find the biological mechanism through which a specific characteristic influences the outcome, the modeling of the cause-specific hazard may be beneficial. Although it is difficult to ascertain the true value of the marginal hazard ratio, a suggestion that it is under (or over)-estimated by the cause-specific hazard ratio may be sufficient to design studies in the lab to provide a more definitive answer. As shown in our examples, it is recommended that the analysis for both types of events to be performed.

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