Statistical Methods in Medical Research 2002; **11**: 203–215

Competing risks as a multi-state model

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This paper deals with the competing risks model as a special case of a multi-state model. The properties of the model are reviewed and contrasted to the so-called latent failure time approach. The relation between the competing risks model and right-censoring is discussed and regression analysis of the cumulative incidence function briefly reviewed. Two real data examples are presented and a guide to the practitioner is given.

1 Introduction: the multi-state model

Competing risks is the sub-discipline of survival analysis where, in addition to the survival time X, the 'cause of death' $D \in \{1, \ldots, k\}$ is observed. Interest then focuses on the joint distribution of (X, D). There exists a vast literature on competing risks analysis (see, for example Tsiatis, 1998[1] and the references therein) but the purpose of the present paper is not to review that literature. Rather, we shall discuss competing risks within the framework of multi-state models much in the spirit of Prentice and colleagues.[2]

The structure of the paper is as follows: the remainder of this section deals with the competing risks multi-state model, which is discussed as a special case of the models reviewed by Andersen and Keiding.[3] In particular, models for the transition intensities (cause-specific hazards) and estimation of transition probabilities are discussed. Section 2 deals with the so-called 'latent failure time approach' to competing risks analysis, which is contrasted with the multi-state approach. Also, hypothetical calculations within the competing risks model are discussed. Section 3 deals with the relationship between censoring and competing risks while, in Section 4, regression analysis of competing risks data is discussed. Finally, Section 5 contains a guide to the practitioner.

The competing risks multi-state model (Figure 1) has one transient state '0: alive' and k absorbing states, $h = 1, \ldots, k$ corresponding to 'death from cause h'. The process is Markovian, the transition intensities $\alpha_h(t)$ from state 0 to state $h, h = 1, \ldots, k$ are the cause-specific hazards and have the interpretation:

$$\alpha_h(t)\Delta \approx \text{Prob}(X \leq t + \Delta, D = h \mid X \geq t)$$

These are the basic model parameters from which transition probabilities

$$P_{hj}(s, t) = \text{Prob}(\text{state } j \text{ at } t \mid \text{state } h \text{ at } s), \qquad s < t$$

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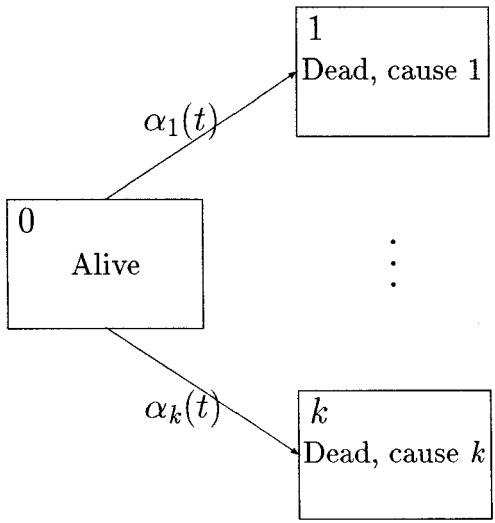

Figure 1 The competing risks multi-state model.

may be derived. Thus,

$$P_{00}(0,t) = \exp\left(-\sum_{h=1}^{k}\int_0^t \alpha_h(u)\,\mathrm{d}u\right) \tag{1}$$

is the marginal survival probability,

$$P_{00}(0,t) = S(t) = \mathrm{Prob}(X > t)$$

and

$$P_{0h}(0,t) = \int_0^t S(u-)\alpha_h(u)\,\mathrm{d}u, \qquad h = 1,\ldots,k \tag{2}$$

are the 'cumulative incidence functions'

$$P_{0h}(0,t) = \mathrm{Prob}(X \le t, D = h)$$

This is, in fact, a rather unfortunate name for this quantity as it may give the incorrect impression that it is a cumulative intensity. Alternative names for $P_{0h}(0,t)$ are marginal or crude failure probabilities. The expression (2) for $P_{0h}(0,t)$ has the interpretation that the probability of the event 'failure from cause h before t' is the sum of the probabilities of the (disjoint) events 'failure from cause h between u and $u+\Delta$' for u between 0 and t. This is the probability of surviving past $u-$, $S(u-)$, times the conditional probability ($\approx \alpha_h(u)\Delta$) of failing from cause h between u and $u+\Delta$ given survival past $u-$. Note that the cumulative incidence for cause h depends (through $S(u-) = \exp(-\sum_{h=1}^{k}\int_0^t \alpha_h(u)\,\mathrm{d}u)$) on the cause-specific hazards for all k causes.

Let $\tilde{X}_i$ be the (possibly right-censored) survival time and D_i the cause of death; $D_i = 0$ if $\tilde{X}_i$ is right-censored, $D_i = h$ if i is observed to die from cause $h = 1, \ldots, k$. The likelihood based on independent observations $(\tilde{X}_i, D_i; i = 1, \ldots, n)$ is:[3]

$$L = \prod_{i=1}^{n} S(\tilde{X}_i) \prod_{h=1}^{k} \alpha_h(\tilde{X}_i)^{I(D_i=h)} \tag{3}$$

It is seen that L is a function of the cause-specific hazards and, thus, models for competing risks data may be specified by these. This means that all the hazard models and estimators reviewed by Andersen and Keiding[3] also apply for the competing risks model including the Nelson–Aalen non-parametric estimator for the cumulative cause-specific hazard $A_h(t) = \int_0^t \alpha_h(u)\,\mathrm{d}u$, the occurrence–exposure rate estimators in models with piecewise constant $\alpha_h(t)$, and estimators from Cox[4] proportional hazards models for the cause-specific hazards. Also tests including the non-parametric log-rank test for comparison of cause-specific hazards are applicable.

From estimates of the cause-specific hazards (or cumulative cause-specific hazards) the transition probabilities $P_{0h}(0, t), h = 0, 1, \ldots, k$, may be estimated as plug-in estimates using equations (1) and (2). Thus, for piecewise constant $\alpha_h(t)$ explicit formulae are available.[5] Using the Nelson–Aalen estimators for $A_h(t)$, the plug-in estimators using equations (1) and (2) are the so-called Aalen–Johansen[6] estimators (for a review, see [7]). Inserting $\hat{A}_h(t)$ in (1) and (2), the exponential function is replaced by the product integral and the estimator for (1) becomes the Kaplan–Meier[8] estimator based on failures from all causes. If the cause-specific hazards are estimated in a Cox regression model[4] then a similar product integral representation of the transition probability estimates is available.[9]

Example 1

To illustrate this, consider the following example concerning mortality after acute myocardial infarction. Such patients may survive or they may die from either cardiovascular causes (CVD) or non-cardiovascular causes (non-CVD). Cardiovascular death can be further divided into sudden cardiovascular death (sudden CVD, occurring within one hour of symptoms and believed to be predominantly caused by arrhythmias) and non-sudden cardiovascular death (non-sudden CVD). We followed 5983 patients who had experienced an acute myocardial infarction and who were discharged from hospital alive. The data were ascertained from 6676 patients screened during the period 1990–1992 at 27 Danish coronary care units for entry into the TRACE trial.[10] Patients were followed for two to four years from infarction. Of the patients, 69% were males and the median age at the time of infarction was 67.7 years. During follow-up a total of 1659 patients died, of which 1261 were cardiovascular deaths and 398 were non-CVD. The CVD was further classified into 536 sudden and 725 non-sudden CVD. In Figure 2 the Aalen–Johansen estimates for the cumulative incidences for each of these three specific causes are shown. The estimates were corrected for delayed entry since only patients discharged alive were included. Increasing age and male gender were associated with an increased all-cause mortality risk. The estimated hazard ratios associated with a ten-year increase in age and male gender for each of the three causes of death are shown in Table 1. These estimates were obtained from separate Cox regression models for the

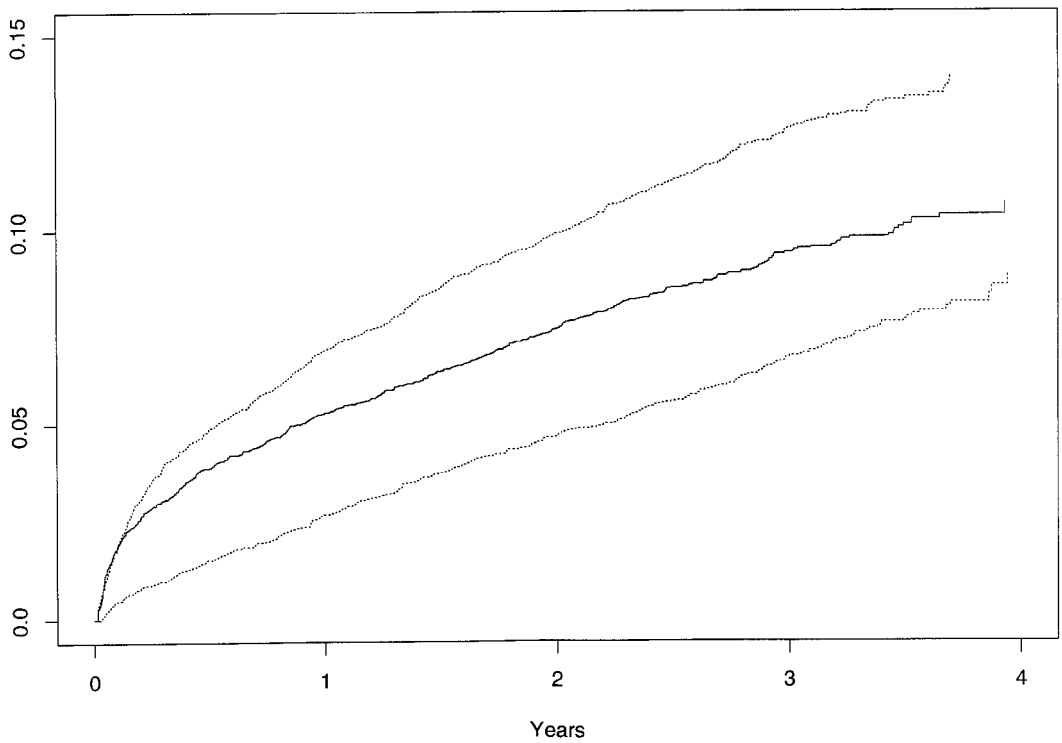

Figure 2 Estimated cumulative incidence functions for three causes of death after acute myocardial infarction. Full line, sudden CVD; upper dashed line, non-sudden CVD; lower dashed line, non CVD.

three cause-specific hazards. Increasing age increased the risk of all three causes of death, but the increase in non-sudden CVD was highest. Male gender was associated with an increased risk of sudden CVD but did not affect the risk of non-sudden CVD independently of age. The increase in non-CVD associated with male gender only reached borderline significance. The table also shows the estimated hazard ratios for age and gender assuming these to be the same for all three causes. However, a likelihood ratio test statistic (based on the Cox,[11] partial likelihood) of 39.2 with 4 degrees of freedom (d.f.) showed that the effects of age and gender on the three causes of death were significantly different ($p < 0.0001$).

Table 1 Estimated hazard ratios (with 95% confidence limits) for age and gender for three causes of death after acute myocardial infarction

	Cause of death			
	Non-CVD	Sudden CVD	Non-sudden CVD	All causes
Age per 10 years	2.06 (1.84, 2.29)	1.56 (1.43, 1.70)	2.13 (1.96, 2.31)	1.90 (1.80, 2.00)
Male gender	1.24 (1.00, 1.53)	1.34 (1.11, 1.63)	1.05 (0.90, 1.23)	1.18 (1.06, 1.31)

2 Latent failure times

In the latent failure time approach to competing risks one imagines the existence of k potential failure times $X_1^{\mathrm{L}}, \ldots, X_k^{\mathrm{L}}$ for each individual and the observations are then, in the uncensored case, the smallest latent failure time (X) and the corresponding 'cause' (D), formally

$$X = \min_{h=1,\ldots,k} X_h^{\mathrm{L}}, \qquad D = \arg \min_{h=1,\ldots,k} X_h^{\mathrm{L}}$$

In the case of a right-censored observation it is only known that all X_h^{L} are larger than the observation time and nothing is known about the cause (for example, one may let $D = 0$ in that case). Interest then focuses on the joint survival distribution

$$Q(t_1, \ldots, t_k) = \mathrm{Prob}(X_1^{\mathrm{L}} > t_1, \ldots, X_k^{\mathrm{L}} > t_k)$$

Thus, the marginal survival distribution of the minimum, X, is

$$S(t) = Q(t, \ldots, t)$$

and the cause-specific hazards are given by

$$\alpha_h(t) = -\frac{\partial \log Q(t_1, \ldots, t_k)}{\partial t_h}\Bigg|_{t_1=\cdots=t_k=t}$$

It turns out, however, that what can be identified from the likelihood (3) based on the observations $(X_i, D_i; i = 1, \ldots, n)$ are the cause-specific hazards $\alpha_h(t)$ whereas the joint distribution $Q(\cdot)$ cannot be identified.[2,12,13] Nor can the marginal survival distributions

$$\mathrm{Prob}(X_h^{\mathrm{L}} > t_h) = Q(0, \ldots, 0, t_h, 0, \ldots, 0) = S_h(t_h)$$

say, and their corresponding hazards

$$\alpha_h^{\mathrm{L}}(t) = -\frac{\partial \log S_h(t)}{\partial t}$$

This has the consequence that the concept of 'independent competing risks' defined by independence of the latent failure times $X_1^{\mathrm{L}}, \ldots, X_k^{\mathrm{L}}$ (i.e., $Q(t_1, \ldots, t_k) = \prod_h S_h(t_h)$) is quite elusive and unverifiable based on the competing risks data $(\tilde{\boldsymbol{x}}_i, D_i; i = 1, \ldots, n)$, as is the weaker condition of equality between the marginal (or 'net') hazards $\alpha_h^{\mathrm{L}}(t)$ and the corresponding cause-specific (or 'crude') hazards $\alpha_h(t)$. In fact, the following 'counter-example'[14] can be given where the likelihood (3) is the same for two different joint distributions $Q(t_1, t_2)$, $Q^*(t_1, t_2)$, one corresponding to independence, the other not.

Thus, we may let

$$Q(t_1, t_2) = \exp(1 - \alpha_1 t_1 - \alpha_2 t_2 - \exp(\alpha_{12}(\alpha_1 t_1 + \alpha_2 t_2)))$$

This distribution has cause-specific hazards:

$$\alpha_h(t) = \alpha_h(1 + \alpha_{12} \exp(\alpha_{12}(\alpha_1 + \alpha_2)t))$$

and if $\alpha_{12} = 0$ the two competing risks 1 and 2 are 'independent'. However, the likelihood would be the same if the model was

$$Q^*(t_1, t_2) = \exp(1 - \alpha_1 t_1 - \alpha_2 t_2) \exp\left(-\frac{\alpha_1 e^{\alpha_{12}(\alpha_1+\alpha_2)t_1} + \alpha_2 e^{\alpha_{12}(\alpha_1+\alpha_2)t_2}}{\alpha_1 + \alpha_2}\right)$$

(because the cause-specific hazards are the same). Here, however, the risks are independent also for $\alpha_{12} \neq 0$, but the marginal hazards are different.

Note that the basic identifiable parameters, the cause-specific hazards $\alpha_h(t)$, refer to the population where all k causes are operating. A question that has been debated in the competing risks literature (ever since Bernoulli in 1760[15]) is what would happen if certain causes of death were 'removed'. This interesting question, however, cannot be assessed from data from a population where all causes are present without making further, unverifiable assumptions.

It also has the consequence that 'probabilities' for certain causes estimated by assuming other cause-specific hazards to be zero have no interpretation within the population from which the observations were taken. Unfortunately, such estimates have been used extensively in the medical literature. In particular, letting $Y(t) = \#\{\tilde{X}_i \geq t\}$ be the observed number at risk at t, the estimator

$$1 - \widehat{S_h}(t) = 1 - \prod_{\tilde{X}_i \leq t} \left(1 - \frac{I(D_i = h)}{Y(\tilde{X}_i)}\right)$$

which is one minus the Kaplan–Meier estimator based only on failures from cause h and treating failures from other causes as censored observations, has been used as an estimate for $P_{0h}(0, t)$. This estimate (sometimes denoted the 'partial' or 'net failure probability for cause h') has, however, no probability interpretation. However, the corresponding Nelson–Aalen estimator

$$\widehat{A_h}(t) = \sum_{\tilde{X}_i \leq t} \frac{I(D_i = h)}{Y(\tilde{X}_i)}$$

is a consistent estimator for the cumulative cause-specific hazard $A_h(t)$, a quantity that is well defined, albeit somewhat more difficult to interpret. This is in spite of the fact that the likelihood (3) splits into a product

$$L = \prod_{h=1}^{k} \prod_{i=1}^{n} \exp(-A_h(\tilde{X}_i))\alpha_h(\tilde{X}_i)^{I(D_i=h)}$$

showing that (unless certain parameters are common in the models for the different $\alpha_h(\cdot)$) each cause-specific hazard may be analysed separately, formally treating deaths from other causes as censorings. Obviously, the degree to which $1 - \widehat{S_h}(t)$ is an inconsistent estimator for the probability of dying from cause h before time t depends

on the magnitude of the other cause-specific hazards $\alpha_j(t)$, $j \neq h$. If these are small, then $1 - \widehat{S_h}(t) \approx \widehat{P_{0h}}(0, t)$.[16] It should be noted that the inequality $1 - \widehat{S_h}(t) \geq \widehat{P_{0h}}(0, t)$ always holds.

What may be of interest as a kind of sensitivity analysis is to study how quantities like the cause h lifetime risk $P_{0h}(0, \infty)$ and the expected life length $\mu(\infty) = \int_0^\infty S(t)\mathrm{d}t$ (or similar quantities where ∞ is replaced by a suitably large value τ) change under different hypothetical scenarios of cause-specific hazards. For example, what would the expected life length be if cardiovascular mortality among individuals aged 40–60 years were halved (and other cause-specific mortalities were the same)? In such hypothetical calculations, various models for the dependence between cause-specific hazards, for example, frailty models,[17] may be useful.

3 Competing risks and right-censoring

There is a close connection between the competing risks model and right-censoring. Thus, in a survival model with failure intensity $\alpha_f(t)$ (Figure 3), one could model right-censoring by a hazard function $\alpha_c(t)$ leading to a competing risks model. Inference on $\alpha_f(t)$ can then be performed in the usual way under the assumption of 'independent censoring', an assumption that is formally identical to the independent competing risks assumption.[7,18] An important difference between the two situations is, however, that for some right-censoring mechanisms, including censoring caused by being alive at the closure of the study or by emigration, the population where the competing risk (censoring) is not operating is not entirely hypothetical; in fact the dynamics in this population is exactly the one shown in Figure 3. Here, the failure probability depends on $\alpha_f(t)$, only, in the usual way $P_{0f}(0, t) = 1 - \exp(-\int_0^t \alpha_f(u)\mathrm{d}u)$. For censoring solely due to survival beyond the closing date of the study, the (potential) censoring time for individuals observed to fail will be known and the independent censoring assumption may actually be tested.

However, if some censoring is due to 'failure from causes other than f' (with hazard $\alpha_o(t)$) then it should be realised that the dynamics in the underlying population is given by a competing risks model where the 'partial cause f probability' $1 - \exp(-\int_0^t \alpha_f(u)\mathrm{d}u)$ has no probability interpretation. In that case a standard analysis of the cause-specific failure rate $\alpha_f(t)$ can be performed, but survival and failure probabilities will also depend on $\alpha_o(t)$. However, when $\alpha_o(t)$ is small the partial cause f probability may provide an acceptable approximation to the cumulative incidence as discussed above.

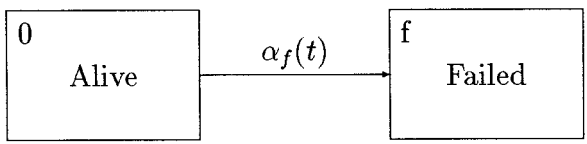

Figure 3 The two-state model for survival data.

4 Regression analysis of competing risks data

As mentioned in Section 1, regression analysis of the cause-specific hazards is straightforward. However, from a simple regression model like the Cox model for the cause-specific hazards, the cumulative incidence functions are fairly complicated non-linear functions of the covariates and, in particular, the effects on the cumulative incidence functions of the covariates are not described by simple parameters. It may still be useful to estimate the cumulative incidence functions for given covariate patterns based on such a model. Confidence intervals may also be obtained as described by Andersen *et al.*[9] or by Cheng *et al.*[19]

Direct regression analysis of the cumulative incidence functions has been discussed.[20–22] Thus, Fine and Gray[20] and Gray[23] defined the 'hazard'.

$$\tilde{\alpha}_h(t) = -\frac{\partial}{\partial t}\log(1 - P_{0h}(0, t))$$

for the defective distribution function $P_{0h}(0, t)$ and studied Cox type models $\tilde{\alpha}_h(t|Z) = \tilde{\alpha}_{h0}(t)\exp(\beta_h^{\mathrm{T}}Z)$ for this. For uncensored competing risks data estimation in this model is straightforward; one simply performs a standard Cox regression analysis of a modified data set where individuals failing from causes other than h are given a censored observation time of $+\infty$ (that is, a censored time larger than the largest observed cause h failure time). For censored competing risks data an inverse probability weighting of the censored observations was used in the estimation procedure. Fine extended this approach to more general transformation models.[21]

Andersen *et al.*[22] on the other hand, used pseudo-observations to obtain a regression model for $P_{0h}(0, t)$. Thus, they defined

$$\hat{P}_{0h}^i(0, t) = n\widehat{P_{0h}}(0, t) - (n-1)\widehat{P_{0h}^{-i}}(0, t)$$

where $\widehat{P_{0h}}(0, t)$ is the Aalen–Johansen estimator[6] based on the entire sample and $\widehat{P_{0h}^{-i}}(0, t)$ is that based on the subsample obtained by deleting observation i. They then studied a generalized linear model

$$g(E\hat{P}_{0h}^i(0, t)) = \alpha_{ht} + \beta_h^{\mathrm{T}}Z_i$$

with a link function g, for example, $g(x) = \mathrm{c}\ \log\ \log(x) = \log(-\log(1-x))$ or $g(x) = \mathrm{logit}(x) = \log(x/(1-x))$, and obtained estimates for (α_{ht}, β_h) using generalized estimating equation techniques.

Example 2

As an example we will study the classical animal carcinogenesis experiment introduced by Hoel and Walburg,[24] see also Andersen *et al.*[9] In brief, 177 mice were given a certain radiation dose at age 5–6 weeks, after which 95 mice were placed in a conventional laboratory environment and 82 in a germ-free environment. The mice were then followed until death from either of the cancer types thymic lymphoma (TL) or reticulum cell sarcoma (RCS) or from other causes (OC). A standard competing risks analysis could include a study of the effect of the covariate 'environment'

Table 2 Estimates of effect of environment (conventional versus germ-free) on cumulative incidence function for each of the three competing causes of death for 177 radiated mice

	Cause of death (h)					
	TL		RCS		OC	
	$\widehat{\beta}_h$	(SE)	$\widehat{\beta}_h$	(SE)	$\widehat{\beta}_h$	(SE)
Fine and Gray	−0.487	(0.283)	0.975	(0.305)	−0.090	(0.236)
Pseudo-observations	−0.401	(0.286)	1.151	(0.321)	0.659	(0.276)

TL, Thymic lymphoma; RCS, reticulum cell sarcoma; OC, other causes.

(conventional versus germ-free) on the cause-specific hazards for the three competing causes of death.

We shall here consider c log log-regression models for the three cumulative incidence functions $P_{0h}(0, t)$, h = TL, RCS, OC. Both an analysis of the kind suggested by Fine and Gray[20] and one based on pseudo-observations are presented. The pseudo-observations were computed at the four time points $t_1 = 200$, $t_2 = 400$, $t_3 = 600$, and $t_4 = 800$ (days). Table 2 shows the estimated values of β_h while Figures 4–6 show the

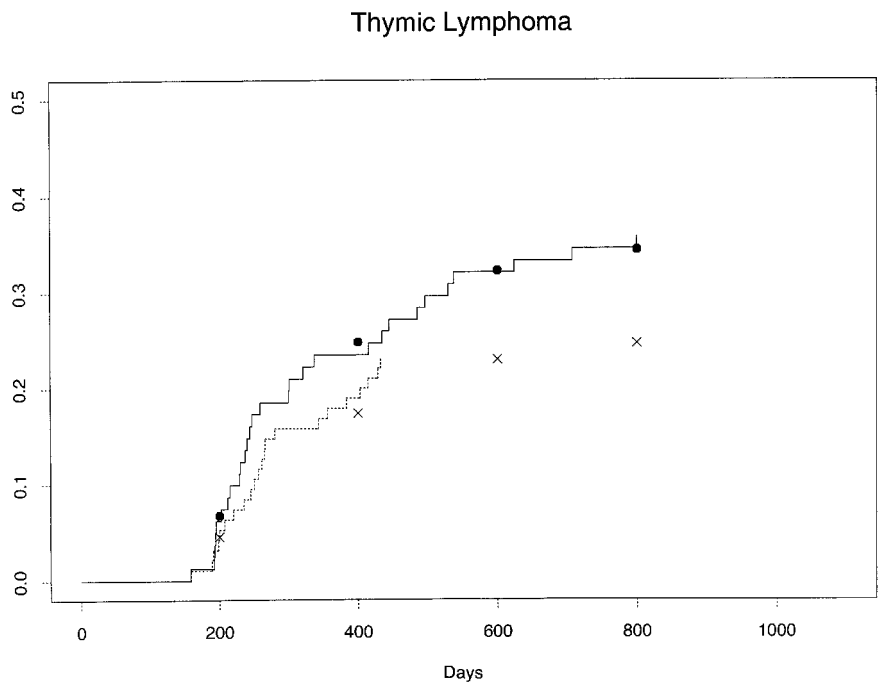

Figure 4 Estimated cumulative incidence functions for the cause of death thymic lymphoma (TL) in the animal carcinogenesis experiment. Full line, Aalen–Johansen estimator for germ-free environment; dashed line, Aalen–Johansen estimator for conventional environment; crosses and dots are estimates based on pseudo-observations for time points 200, 400, 600, and 800 days and for conventional and germ-free environments, respectively.

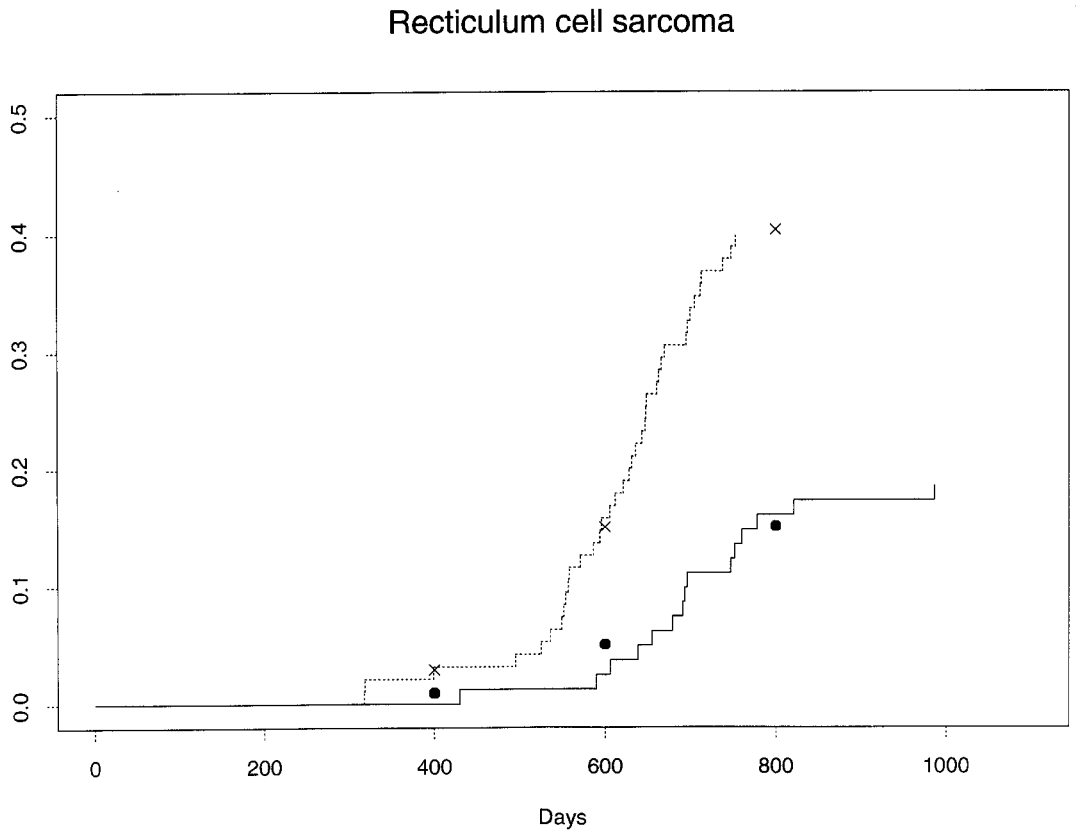

Figure 5 Estimated cumulative incidence functions for the cause of death reticulum cell sarcoma (RCS) in the animal carcinogenesis experiment. Full line, Aalen–Johansen estimator for germ-free environment; dashed line, Aalen–Johansen estimator for conventional environment; crosses and dots are estimates based on pseudo-observations for time points 200, 400, 600, and 800 days and for conventional and germ-free environments, respectively.

Aalen–Johansen estimates $\widehat{P_{0b}}(0, t)$ together with the estimates $\hat{\alpha}_{bt_l} + \hat{\beta}_b Z$, $l = 1, 2, 3, 4$, and $Z = 0, 1$ based on the pseudo-observations.

It is seen from Table 2 that for the two cancer types TL and RCS the estimates based on the method of Fine and Gray[20] and those based on pseudo-observations are quite close, as are their estimated standard errors. For 'other causes', however, the estimated effects from the two methods are rather different. This is probably because the model does not fit very well in this case and, thus, the method based on pseudo-observations may be quite sensitive to the choice of time points. That the model fits badly may be seen on Figure 6, where the estimates assuming a constant difference between the curves on the log minus log scale does not fit very well with the Aalen–Johansen estimates.

It should be noted that the analysis based on pseudo-observations also provides estimates of correlations between the three parameter estimates. These are -0.34, -0.40, and -0.35 for the pairs (TL, RCS), (TL, OC), and (RCS, OC), respectively.

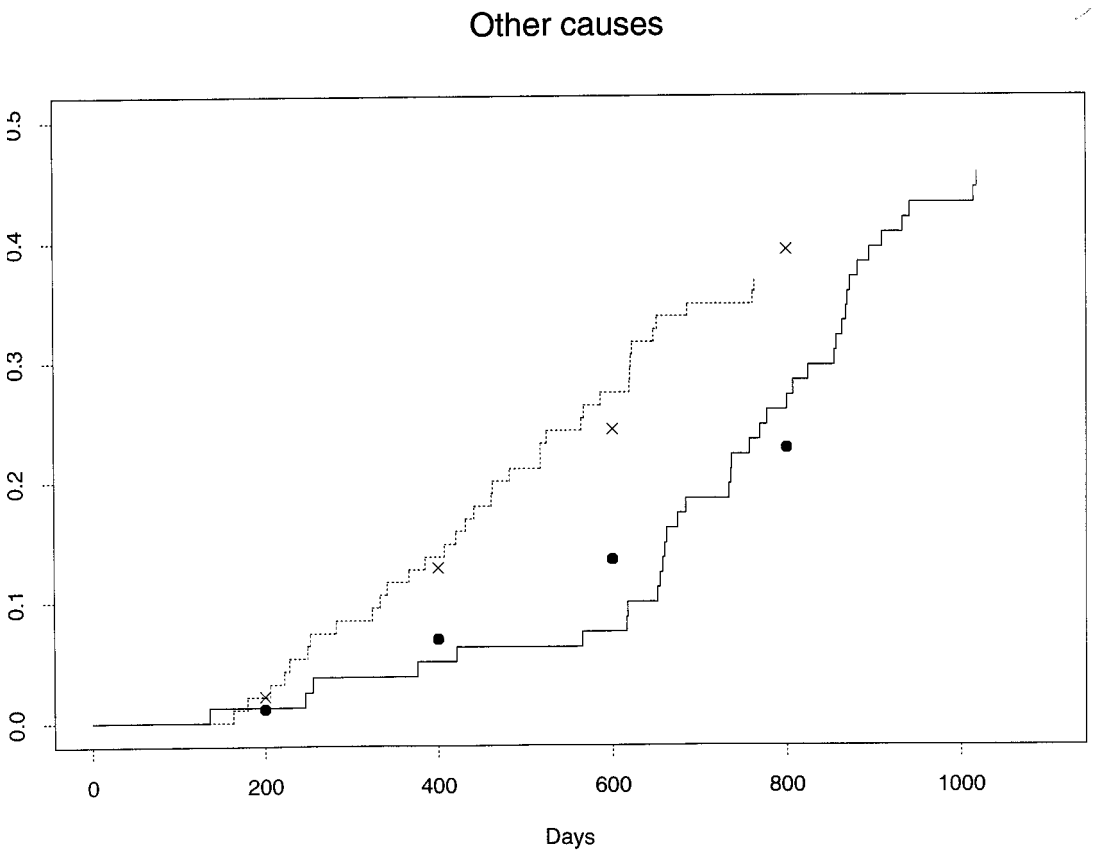

Figure 6 Estimated cumulative incidence functions for the cause of death other causes (OC) in the animal carcinogenesis experiment. Full line, Aalen–Johansen estimator for germ-free environment; dashed line, Aalen–Johansen estimator for conventional environment; crosses and dots are estimates based on pseudo-observations for time points 200, 400, 600, and 800 days and for conventional and germ-free environments, respectively.

5 Guide to the practitioner

Since the basic parameters are the cause-specific hazards, modelling of competing risks data should take these as their starting point. Simple models for cause-specific hazards may be analysed by a series of standard survival analyses, one cause at a time, treating failures from other causes as censored observations. In such an approach, the hazard functions may be compared between groups using standard tests for survival data, and regression models for the hazards may be analysed in the usual way. By simple models we here mean models where no parameters are common for two or more hazard functions, for example, there are no covariates for which the effect is assumed to be the same on several cause-specific hazards. More parsimonious models where some parameters may be common for several causes, for example, Cox regression models

with common regression coefficients, may be analysed using standard software by applying the methods described by Andersen and Keiding.[3] This was, in fact, what was carried out in the example in Section 1 for the model with common age and gender effects on all three causes of death.

The major difference between such an analysis of cause-specific hazards and a standard survival analysis is that the simple relation 'failure probability = 1 − exp(−cumulative hazard)' no longer holds. Thus, presenting results for cause-specific hazards in the failure probability scale '1 − exp(−cumulative hazard)' will be misleading since this transformation of the cause-specific hazard does not have a probability interpretation in the population where both the cause under study and other causes are operating. One may argue that under an assumption of independent competing risks these transformations do posess probability interpretations, but since this assumption is unverifiable from the available data the argument is not very useful. The only situation where such plots are justified is when failures from competing causes are rare, in which case '1 − exp(−cumulative cause − specific hazard)' is close to the cumulative incidence function, which is always interpretable and well defined. But in such a situation, there are few compelling arguments to conduct a competing risks analysis anyway.

So, what will be useful as a way of presenting the results from a competing risks analysis is to compute estimated cumulative incidence functions based on the models for the cause-specific hazards. A SAS MACRO for this purpose (using Cox models for the cause-specific hazards) is available from the authors. A drawback to this approach is that the cumulative incidence functions do not depend on the covariates in a simple way (Section 4) and thus it may be desirable also to analyse models where the cumulative incidences are directly regressed on the covariates. Such models were briefly discussed in Section 4.

Acknowledgements

This research was partially supported by Grant R01-CA54706-09 from the National Cancer Institute and by a grant from the Danish National Research Foundation.

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