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Analysing and interpreting competing risk data

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SUMMARY

When competing risks are present, two types of analysis can be performed: modelling the cause specific hazard and modelling the hazard of the subdistribution. This paper contrasts these two methods and presents the benefits of each. The interpretation is specific to the analysis performed. When modelling the cause specific hazard, one performs the analysis under the assumption that the competing risks do not exist. This could be beneficial when, for example, the main interest is whether the treatment works in general. In modelling the hazard of the subdistribution, one incorporates the competing risks in the analysis. This analysis compares the observed incidence of the event of interest between groups. The latter analysis is specific to the structure of the observed data and it can be generalized only to another population with similar competing risks. Copyright 2006 John Wiley & Sons, Ltd.

KEY WORDS: cause specific hazard; competing risk; hazard of the subdistribution; modelling; interpretation

1. BACKGROUND

When analysing the time to event data, there is the possibility that more than one type of event can be observed. For example, if the interest lies in analysing the time to death due to heart disease, it is obvious that some individuals could die of other causes. This situation is usually termed as *competing risk* (CR). Gooley *et al*. [1] gave a more formal definition: a CR is an event, which either hinders the observation of the event of interest or alters its probability of occurrence. Thus, in the above example the death of other causes than heart disease needs to be considered a CR event. Another example can be given from the cancer area. Suppose that a cohort of patients diagnosed with breast cancer is followed up. A local recurrence is a return of the cancer in the same

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breast. However, other types of events can occur. For example, the cancer can recur at other sites (regional or distant recurrences). Technically, if the first event is a regional or distant recurrence, one could still observe a subsequent local recurrence. However, a patient with a regional or distant recurrence would be treated, very likely in a systemic way. The treatment would fundamentally alter the probability of observing the local recurrence. Therefore, if the event of interest is local recurrence, all the other recurrences are CR type of events.

In analysing CR data one has the choice of taking into account the CR or ignoring it. Statisticians are uneasy with the latter choice, their training teaches them to consider all possible situations and not to ignore anything. In this paper it is argued that in the presence of CRs sometimes ignoring the CRs could be beneficial, as long as the interpretation of the results is correct. Accounting for CR could also be advantageous since it answers the direct question whether one group has more events of interest than the other. Ultimately, the type of analysis depends on the clinical question.

In this paper only two types of events are considered: the event of interest (using ev as subscript) and the CR type of event (using cr as subscript). In general, when there are more types of events that are competing with the event of interest, they can all be grouped under one type of CR event. The situation of multiple events per patient is not discussed here.

In Section 2 an example of a hypothetical study is given. Its two main goals reflect the two methods of analysing the CR situation. General theoretical details on the cause specific hazard (CSH) and the hazard of subdistribution (HoS) will be given in Section 3. Section 4 presents details on proportional hazards models for each of these two hazards. Two examples are considered in Sections 5 and 6, followed by conclusions in Section 7.

2. HYPOTHETICAL EXAMPLE

Suppose that A, a relatively new industrial town, is situated very close to a hydro power plant. The mean age for this population is 45 years. On the other hand, B is an old town of equal size with A but with no hydro plant close by. The average age for B population is 65. The object of the study is to test whether:

(1) The incidence of cancer is larger in one of the two towns. This objective will help to properly distribute funding to create the necessary infra-structure (hospitals, doctors, nurses, schools for nursing).
(2) Rates of cancer are different between the two towns. The implication for this objective is whether the existence of a hydro power plant adversely affects people's health, specifically with respect to cancer rates.

The endpoint is the time from birth to incidence of cancer. Thus, the time scale is age. Obviously, the death without cancer is a CR event. Since the mean age for town B is higher, it is possible that the risks for both the event of interest (incidence of cancer) and the CR event (death without cancer) is higher than in town A. It is assumed that the observations are independent. This could be achieved, for example, by choosing only one individual per family. For simplicity's sake, only the incidence of the first cancer is considered.

For objective 1, it is of interest to estimate how many more (or less) cancer cases are seen in town A *versus* town B. The presence of CRs influences this number of cancer cases seen, since a person who dies of heart disease will never have the chance of having cancer. Thus, the statistical

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analysis for the first objective needs to take into consideration the CRs. Gray [2] and Fine and Gray [3] devised tests for this type of situation. In this paper this type of analysis is called: *Analysis of the hazard of subdistribution* (*HoS*).

In contrast, the goal of objective 2 is to test whether the cancer incidence rates are different between the two towns. The possibility that CR event rates are different between the two towns is an undesirable phenomenon. We want to compare the cancer event rates in the virtual situation when the CR did not exist. The *analysis of the cause specific hazard* (*CSH*) models the event of interest in the absence of CR events and thus is the appropriate method.

3. TWO TYPES OF HAZARD

Suppose T is a random variable with the density function $f(t)$ and survivor function $S(t)$. In the absence of CR the hazard is defined as

$$h(t) = \lim_{\delta t \to 0} \frac{P(t < T \leqslant t + \delta t \mid T > t)}{\delta t} = \frac{f(t)}{S(t)}$$

In this paper the mathematic definition of the CR is based on the latent failure time approach. Within this framework both HoS and CSH can be defined.

Let T_{ev} and T_{cr} be two random variables representing the time to event of interest and CR event, respectively. The joint distribution function is denoted by $F(t_{\text{ev}}, t_{\text{cr}})$ and the joint density function by $f(t_{\text{ev}}, t_{\text{cr}})$. We observe T, the time to first failure, $T = \min\{T_{\text{ev}}, T_{\text{cr}}\}$.

The subdistribution function is defined as

$$\tilde{F}_{\text{ev}}(t) = P(T \leqslant t, C = \text{ev}) = P(T_{\text{ev}} \leqslant t, T_{\text{cr}} > T_{\text{ev}})$$

where C is the type of event observed at time t: event of interest (ev) or CRs type of event (cr). If no event is observed at time t, the observation is censored with $C = 0$.

An example of a subdistribution function is

$$\tilde{F}_{\text{ev}}(t) = \frac{\lambda_{\text{ev}}}{\lambda_{\text{ev}} + \lambda_{\text{cr}}}(1 - \mathrm{e}^{-(\lambda_{\text{ev}} + \lambda_{\text{cr}})t}) \tag{1}$$

It is clear that this function is not a proper distribution function since it takes values in an interval $[0, p]$, with $p = [\lambda_{\text{ev}}/(\lambda_{\text{ev}} + \lambda_{\text{cr}})] < 1$.

The subdensity is defined as the derivative of the subdistribution function:

$$\tilde{f}_{\text{ev}}(t) = \frac{\mathrm{d}\tilde{F}_{\text{ev}}(t)}{\mathrm{d}t}$$

The marginal distribution and density functions are:

$$F_{\text{ev}}(t) = F(t_{\text{ev}} = t, t_{\text{cr}} = \infty) \quad \text{and} \quad f_{\text{ev}}(t) = \frac{\mathrm{d}F_{\text{ev}}(t)}{\mathrm{d}t}$$

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The HoS is defined [4] as

$$\gamma_{\mathrm{ev}}(t) = \lim_{\delta t \to 0} \frac{P(T \leqslant t + \delta t, C = \mathrm{ev} \mid \{T > t \text{ or } (T \leqslant t \text{ and } C \neq \mathrm{ev})\})}{\delta t}$$

$$= \frac{\tilde{f}_{\mathrm{ev}}(t)}{1 - \tilde{F}_{\mathrm{ev}}(t)}$$

The condition in the curled brackets expresses the fact that the event of interest did not happen until t, but it is possible that the observation for a subject has stopped because a competing event was observed.

CSH is the hazard of the marginal distribution:

$$h_{\mathrm{ev}}(t) = \frac{f_{\mathrm{ev}}(t)}{1 - F_{\mathrm{ev}}(t)}$$

To facilitate the understanding of these two types of hazard, they are calculated for the subdistribution function in formula (1). Thus, the subdensity is:

$$\tilde{f}_{\mathrm{ev}}(t) = \frac{\mathrm{d}\tilde{F}_{\mathrm{ev}}(t)}{\mathrm{d}t} = \lambda_{\mathrm{ev}} \mathrm{e}^{-(\lambda_{\mathrm{ev}} + \lambda_{\mathrm{cr}})t}$$

and the HoS is

$$\gamma_{\mathrm{ev}}(t) = \frac{\tilde{f}_{\mathrm{ev}}(t)}{1 - \tilde{F}_{\mathrm{ev}}(t)} = \frac{\lambda_{\mathrm{ev}} \mathrm{e}^{-(\lambda_{\mathrm{ev}} + \lambda_{\mathrm{cr}})t}}{1 - [\lambda_{\mathrm{ev}}/(\lambda_{\mathrm{ev}} + \lambda_{\mathrm{cr}})](1 - \mathrm{e}^{-(\lambda_{\mathrm{ev}} + \lambda_{\mathrm{cr}})t})}$$

The CSH is given by

$$h_{\mathrm{ev}}(t) = \frac{f_{\mathrm{ev}}(t)}{1 - F_{\mathrm{ev}}(t)} = \frac{\lambda_{\mathrm{ev}} \mathrm{e}^{-\lambda_{\mathrm{ev}} t}}{1 - (1 - \mathrm{e}^{-\lambda_{\mathrm{ev}} t})} = \lambda_{\mathrm{ev}}$$

4. ANALYSING HoS AND CSH

To analyse CSH one can employ the usual techniques for the time to event analysis. Thus the observed time is the time to the first event and the censored variable takes the value of 1 when an event of interest occurred and 0 when either the observation is censored or a CR event occurred. Cox proportional hazards model can be employed in the usual manner.

$$h_{\mathrm{ev}}(t|x) = h_{\mathrm{ev0}}(t) \mathrm{e}^{\sum_{l=1}^{k} \beta_l x_l}$$

where h_{ev0} is the baseline CSH, β_l is the coefficient obtained from the model for the covariate x_l. For simplicity's sake, in the rest of the manuscript only one covariate x is considered. The concepts presented can easily be generalized to more than one covariate.

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If there are r failures at the time points $t_1 < t_2 < \cdots < t_{r-1} < t_r$ and R_j is the risk set at time t_j then the partial likelihood to be maximized is

$$L(\beta) = \prod_{j=1}^{r} \left(\frac{\exp(\beta x_j)}{\sum_{i \in R_j} \exp(\beta x_i)} \right)$$

Note that the risk set is: $R_j = \{i; t_i \geqslant t_j\}$. The quantity $\exp(\beta)$ is called the CSH ratio and represents the increase of the CSH due to one unit increase of the covariate x.

HoS can be modelled in a similar fashion [3]:

$$\gamma_{\text{ev}}(t|x) = \gamma_{\text{ev0}}(t) e^{\beta x}$$

where γ_{ev0} is the baseline hazard of the subdistribution. Fine and Gray [3] constructed the partial likelihood as

$$\tilde{L}(\beta) = \prod_{j=1}^{r} \left(\frac{\exp(\beta x_j)}{\sum_{i \in \tilde{R}_j} w_{ji} \exp(\beta x_i)} \right) \tag{2}$$

There are two major formal alterations for the partial likelihood for the HoS: the inclusion of weights at the denominator and the risk set is defined differently. The observation for which the CR event is observed is in the risk set at all times.

$$\tilde{R}_j = \{i; t_i \geqslant t_j \text{ or } t_i \leqslant t_j \text{ and the subject had a CR event}\}$$

The observations in the risk set which satisfy the first condition ($t_i \geqslant t_j$) participate fully in the partial likelihood with the weight $w_{ji} = 1$. The observations for which the second condition is met ($t_i \leqslant t_j$ and the subject had a CR event) have a weight $w_{ji} \leqslant 1$: the further t_i is from t_j, the smaller the weight. These weights are given by the formula:

$w_{ji} = \hat{G}(t_j)/\hat{G}(\min(t_j, t_i))$, where $\hat{G}(.)$ is the survivor function for the censoring distribution.

More details on this topic can be found in Fine and Gray's original paper [3]. The interpretation for $\exp(\beta)$ in this framework is similar: it represents the increase of the hazard of the subdistribution due to one unit increase of x.

5. EXAMPLE FOR HoS ANALYSIS

Hodgkin's Lymphoma (HL) is a type of cancer which is diagnosed mostly in young adults (median age is 30 years). The early stage of this disease is highly curable with the survival at 10 years being approximately 80 per cent or better. Studying this group of patients can give some insight into the long-term toxicity of the treatment. The main concern is the possibility of developing a second malignancy. The treatment for HL consists of either radiation (RT) or chemotherapy, or a combination of both, referred to as combined modality therapy (CMT). The knowledge that a specific group of patients has a higher rate of developing a second cancer could influence the frequency and type of follow-up planned.

As an example, a group of 1546 HL patients diagnosed, treated and followed in Princess Margaret Hospital (PMH), a tertiary cancer centre, is analysed. The patients had been diagnosed between 1968 and 2003. All were early stage disease (stage I or II) and had been treated with either RT or CMT. The time to second malignancy was calculated between diagnosis and the date

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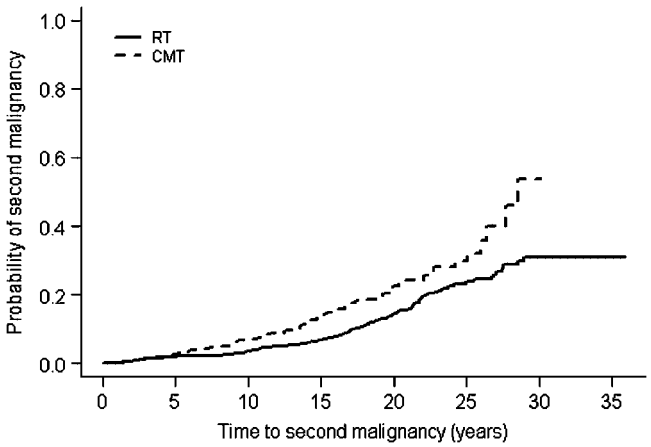

Figure 1. Probability of second malignancy by treatment.

Table I. The results of the HoS analysis on second malignancy.

	HoS ratio	95% CI	*p*-value
Treatment	1.5	1.1–2.1	0.0058
Age	1.01	1.007–1.02	0.0004
Gender	0.82	0.62–1.1	0.17

of first malignancy after HL. A CR event is when a death occurred without a preceding second malignancy.

The ***R*** software, which can be downloaded from the CRAN site, has the package *cmprsk* which can analyse the CR data. This package contains functions which calculate the probability of the event of interest (*cuminc*) and can model HoS (*crr*) with the possibility of including a time dependent covariate. The *cuminc* function uses the cumulative incidence approach introduced by Kalbfleisch and Prentice [5] to calculate the probability of event of interest and the comparison is performed based on Gray's test [2]. Thus, the incidence of second malignancy at 10 years for the RT group and CMT group (Figure 1) are calculated to be 3.5 and 6.6 per cent, respectively. The *crr* function maximizes the partial likelihood (2). The results for the model where the treatment effect was adjusted for age and gender are in Table I. The significance does not change much when the other two factors are added to the model. It can be concluded that the CMT group has a higher probability of second malignancy, even when the CR events are taken into account. Thus, this information can be potentially used by the clinicians in the process of follow-up of these patients in terms of surveillance for second primary cancer, and development of preventative strategies.

A CSH analysis is not useful for this group of patients. The CMT group is really a mixture of different types of regimens as they changed over years. The goal of the study was not to find whether chemotherapy causes the second malignancy and the cohort was not selected with this purpose in mind. Had it had this goal then the cohort would have been more carefully selected for a specific chemotherapy regimen.

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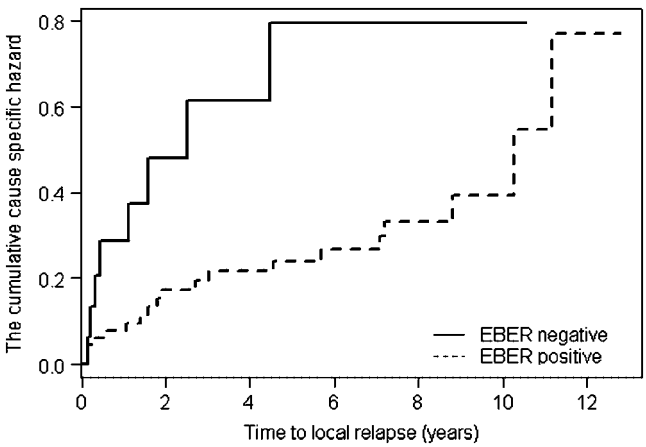

Figure 2. The cumulative CSH for EBER negative and EBER positive.

6. EXAMPLE FOR CSH ANALYSIS

This study cohort consists of a group of 83 patients diagnosed with cancer of the nasopharynx between 1985 and 1992. All patients were treated in PMH and the presence of the Epstein-Barr virus (EBER) was assessed using in situ hybridization for EBV encoded RNA. (More details can be found in References [6, 7]). For this paper the goal is to assess whether EBER status has a prognostic value for local recurrence. Amongst the 83 patients, 67 had EBER positive, 27 failed locally and 14 either died or experienced another type of recurrence before local failure. The latter 14 are patients for whom a CR event was observed. The data presented in this paper is slightly modified from the original.

To test whether EBER is associated with the risk for local recurrence, regardless of the possible CR events observed in this data set, we need to perform a CSH analysis. For this purpose, the time to first event since diagnosis is calculated first. When the first event is local recurrence, the censoring variable takes the value 1, for observed event. For all the other situations: censored observations or other types of events, the censoring variable takes the value 0. The usual techniques for time to event analysis can be applied, for example logrank test or Wald test within the Cox proportional hazards model. Based on Wald test the CSH ratio is 0.4 with 95 per cent confidence interval 0.2–0.9 and p-value $= 0.037$. Figure 2 exhibits the plot of the cumulative CSH for the two groups suggesting that patients with EBER negative tumours had a poorer prognosis than the patients with EBER positive tumour.

7. CONCLUSION

When there is more than one type of event that can be observed, all the events other than the event of interest may be CR events. If the occurrence of an event changes the risk of observing the event of interest then this event is of CR type. The data set, which contains CR events, can be analysed in two different ways.

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When HoS is analysed, the goal is to compare the probability of the event of interest and thus, the CR events are included in the analysis. The generality of this analysis is limited to populations with similar characteristics and similar CR rate.

The results of the CSH analysis apply in a virtual world where the CR events do not exist. This type of analysis is beneficial when the goal is to test whether a specific factor (a treatment, a marker) has biological relevance. The results are valid for any population with similar characteristics regardless of the rate of CR events.

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