STIMA DELL'HAZARD RATIO IN PRESENZA DI RISCHI COMPETITIVI: UN'ANALISI TRAMITE SIMULAZIONI

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Introduction

In traditional survival analysis each subject has a single, possibly censored, failure time, but more complex situations may arise. Competing risks analysis extends this classical framework, since a finite number of different event types are assumed to be possible and the interest lies not only in the time to the first event occurring, but also in the event cause ([1],[2]). The main problem in estimating survival models in such cases is that failures for any cause should account for the withdrawal of subjects for failures due to other possible causes since outcomes can occur that may alter the probability of experiencing the main outcome. Suitable methods have been introduced for survival analysis in the presence of competing risks, that differ in how they contrast the structure of the risk sets and hence in the interpretation of the parameters obtained ([3],[4]).

Aims

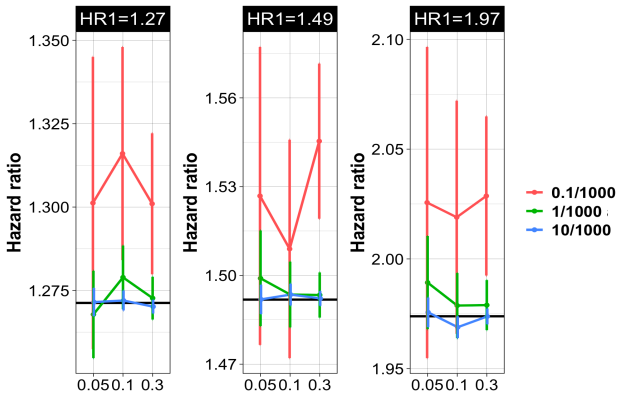
One of the most widely employed methods for this kind of data analysis is Cox regression model built on the cause-specific hazards. Its estimation is obtained by removing all subjects failed for other competing causes from the risk set, that is from the group of individuals that have not experienced the outcome of interest and therefore are at risk at a given time t ([5]). We study here the main features of the performance of cause-specific model in some meaningful frameworks by means of simulations ([6]). The aim is to underlay possible settings in which computing cause-specific hazard ratios (HR's) can be misleading in quantifying the risk in a hypothetical population where competing events are eliminated.

Methods

To perform simulations for analyzing synthetic data that can mimic real applications a suitable algorithm to study different scenarios in the framework of cause-specific hazard estimation is needed. We employed the method described in [7]. It was necessary to make some preliminary adjustments to the source code to correctly simulate the event distributions and to get survivors alive at the end of the follow up period ([8]). Each of the cause-specific hazards is first specified independently of the rest of the competing events. Event times are simulated through an inversion method starting from all-cause hazard. Given a failure at timeT=t, the probability that the individual fails from a specific cause is computed through a multinomial experiment. We simulated cohort of up to $n = 10^5$ subjects in a framework with two competing causes. We did not add censoring since it was not relevant in this context, while we chose one Bernoulli exposition variable and two different Weibull distributions for times to event due to the main and to the competing cause. The parameters were modulated to get time to event distributions and survival curves in the range of what might be found in an epidemiological study considering for example a cardiovascular disease as event of interest and all-cause death as competing event. Different follow-up times were considered up to 20 years. For comparison purposes in some cases two different cohorts were simulated, one of individuals potentially subject to both failures and another one of individuals possibly experiencing only the event of interest.

Results

Simulations conducted under a series of different scenarios made it possible to ascertain that the estimation of HR in the presence of competing risks using cause-specific regression that censors subjects failing for other causes is not free from bias. The most frequent type of bias is the overestimation of the HR value when the distribution of the competing events overwhelms that of the event of interest. This happens when the HR for the exposure or the incidence density for the event of interest in the exposed is markedly higher for events due to the competing cause than for those due to the cause of interest. The same bias can be observed also if the density distribution for the events of the two types are not very overlapping over time, in favor of the one corresponding to the competing cause. These results were confirmed by comparing the HR's estimated under the competing risk scenario with those obtained through the simulation of similar populations where the competing event could not occur. In the figure below the mean HR's obtained from 10^5 simulations for each scenario are shown together with their confidence interval under conditions similar to those described above for different incidence densities (colors) and exposition prevalence 5, 20 and 30 per cent respectively.



Mean and confidence interval for the estimated HR's in a scenario where the event incidence density in the exposed is markedly higher for the competing cause; true values in the black strip

A wider variance in the HR distribution was observed in the competing risk setting with respect to the case of single failure cause in all the scenario considered. Moreover, the estimated HR's reached statistical significance in fewer cases in the first setting than in the second. Finally, the bias in the estimate was greater if the follow-up period was reduced.

Conclusions

Estimation of HR in the presence of competing risks is often done in clinical and epidemiological studies. However, not much attention is paid to the problems that can arise in using cause specific HR's obtained through Cox regression by censoring all events due to competing causes. In cases where exposure significantly affects survival for competitive events, the estimate of HR may be biased due to the reduction of the set at risk. Furthermore, it can be more difficult to detect a significant effect of the exposure on the outcome of interest. It may therefore be useful to precisely identify the situations in which it is necessary to give particular attention to these aspects.

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