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Journal of Statistical Planning and Inference 129 (2005) 253–262
journal of statistical planning and inference
www.elsevier.com/locate/jspi

A proportional hazards model for informatively censored survival times

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Available online 13 October 2004

Abstract

The models in Demasi et al. (1997) are adapted for informatively censored failure times to a primary event and times to followup events. The proposed model treats informative censoring as a type of risk in a competing risks setup. Inferences about the parameters in the model can be based on standard partial-likelihood theory. A simulation study shows that likelihood inference works well in practice. Use of the model is demonstrated by analyzing some data on waiting time to bone marrow transplantation (primary event) and time to relapse or death after transplantation (followup event) for leukemia patients. Residual inspection was performed to check the adequacy of the model.

Keywords: Informative censoring; MPLE; Semi-parametric models; Partial likelihood; Counting process

1. Introduction

Right censored observations of survival times of study subjects are common in longitudinal studies and clinical trials, where some individuals may be lost to followup for various reasons. Depending upon the reason for loss to followup, censoring of an individual's failure time may be informative or non-informative. In this paper, we follow Demasi et al. (1997) to develop a hazard model for survival times in which randomly or informatively censored followup times are available for two types of events.

As an example of possible applications of the proposed model, we cite a Pediatric Oncology Group (POG) study of leukemia to evaluate waiting time to BMT of children with AML

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0378-3758/$ - see front matter
doi:10.1016/j.jspi.2004.06.051

(acute myelocytic leukemia) who receive chemotherapy and bone marrow transplantation (BMT). A hazard model for time to BMT should account for the fact that (1) the waiting time for BMT is subject to time to relapse or death since it censors the time to BMT, and (2) a patient will be followed after BMT and a patient's survival time may be affected by his or her waiting time for BMT. One can consider BMT and relapse or death as two types of events in the competing risks setting. When the outcome of interest is BMT, time to relapse or death (if it occurs before BMT) may provide the information for the failure rate of BMT as high-risk patients may relapse or die prior to BMT. The proposed model will incorporate such information as well as followup time after BMT.

In an attempt to account for informative censoring, Fisher and Kanarek (1974) introduced a survival model in which the effect of informative censoring is determined by a scale parameter that stretches or contracts the survival time. Peterson (1976) derived bounds for survival function under the competing risks model when the risks may not be independent. Slud and Rubinstein (1983) and Klein and Moeschberger (1988) strengthened the Peterson bounds. Link (1989) modified the product limit estimator by assuming that censoring occurs in a high-risk or low-risk subpopulation. One can consider frailty models proposed by Clayton (1978) and Clayton and Cuzick (1985) to adapt informative censoring. Xue and Brookmeyer (1996) extended the univariate fraility model to the bivariate case by proposing a bivariate log-normal frailty model. One can also consider multistate models to incorporate informative censoring as one state. Several multistate models were studied by Kay (1986), Andersen (1998), Andersen et al. (2000), Hsieh et al. (1983), and Andersen et al. (1991). Under a setting where the study subjects are followed after the first failure, Lin et al. (1996) proposed a semi-parametric approach by assuming the bivariate location shift model to adjust for informative censoring when comparing failure time distributions in two groups. Closely related to the present work is the work of Demasi et al. (1997), wherein models for randomly censored times to two types of events were modeled using a conditional hazard function at the followup event time by assuming that the primary event affects the followup event.

The proposed model and the appropriate partial likelihood is described in Section 2. Also, asymptotic properties of the partial-likelihood estimators are described in this section. In Section 3, the performance characteristics of the maximum partial-likelihood estimators are evaluated using a simulation study. In Section 4, the use of the proposed model is illustrated with BMT data. Finally, in Section 5, martingale residuals were examined for the model checking from the BMT data.

2. Model

Let T_v be the time at which the subject experiences two types of mutually exclusive events E_v, $(v=1,2)$, and let $S=\min\{T_1,T_2\}$ and $T=\max\{T_1,T_2\}$ be the times of the first and second events, respectively. Let $\mathbf{Z}$ denote a vector of covariates and define the hazard functions as

$$\lambda_v(s|\mathbf{z}) = \lim_{\Delta s\to 0+} \frac{P\{s \leqslant S < s+\Delta s,\, S=T_v \mid S \geqslant s, \mathbf{z}\}}{\Delta s},$$
$$\lambda_{w|v}(t|s,\mathbf{z}) = \lim_{\Delta t\to 0+} \frac{P\{t \leqslant T < t+\Delta t,\, T=T_w \mid T \geqslant t,\, S=T_v=s, \mathbf{z}\}}{\Delta t},$$