Competing risks regression on time-dependent covariates for finding optimal chemotherapy dosages

Giuliana Cortese[1], Per K. Andersen[2], Marianne Ryberg[3] and Dorte Nielsen[3]

[1] Department of Statistics, University of Padova, Italy
[2] Department of Biostatistics, Institute of Public Health, University of Copenhagen, Denmark
[3] Department of Oncology, Herlev Hospital, University of Copenhagen, Denmark

Competing risks arise often in biostatistics, especially in cancer studies. Chemotherapy treatments can have serious side effects. In studying concurrent events due to side effects, competing risks models are a very useful approach. Finding recommended dosages, which controls the risk of side effect events, is an important medical aim, which can be obtained by competing risks regression on treatment dose as a time-dependent covariate.
We illustrate the statistical methods and the medical problem by an application to advanced breast cancer, where cardiotoxicity is a very serious side effect of anthracyclin-based chemotherapy. A competing risks regression model with two causes is performed. Cardiotoxicity is the event of primary interest and mortality from breast cancer is the competing event. Regression is on the time-dependent cumulative dose administrated during the treatment period and on other predictors.
The optimal dose is defined as the maximal total dose, below which the risk of cardiotoxicity is lower than 5%. In order to predict this optimal dose, the estimated cumulative incidence probability for cardiotoxicity, in a certain given time interval, is considered as a function of the cumulative dose. Predictors in the model allow discriminating between optimal total dose for different typologies of patients.
We find new optimal levels for the total dose, which are lower than the one recommended in the literature. Moreover, while the existing literature suggests a single level for all types of patient, we demonstrate that the optimal recommended dosage varies substantially between patients with different characteristics and predictors.
The application reveals that particular care needs to be taken in handling and interpreting time-dependent covariates in a competing risks analysis. An important aspect to emphasize is that a time-dependent covariate, such as the cumulative dose in the application, can be considered deterministic when it is varied in a predetermined way over time, for instance controlled by the clinician according to a treatment schedule. In this case, the covariate can be incorporated into the general framework of inference for competing risks models without complications.
In addition, problems about goodness-of-fit when a time-dependent covariate is included in the regression model, are studied. Graphical diagnostics based on martingale residuals might fail in investigating the functional form of such a covariate. We discuss the need of cumulative martingale residuals in model diagnostics as they overcome problems related to time-dependency of covariates.
The approach taken here should be of general interest in medical statistics, where competing risks are present, and an optimal total dose is desired.