Modeling relapse-free survival with time-dependent covariate graft-versus-host disease in patients with acute leukemia

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The role of graft-versus-host disease (GVHD) on relapse-free survival (RFS) is being increasingly recognised in clinical studies. In the study reported by Lee and colleagues[1] Kaplan-Meier (KM) RFS estimates of patients stratified according to the occurrence of acute GVHD (aGVHD) have been plotted. A stratification on a variable unknown at baseline is inappropriate for calculation and graphical presentation of KM survivorship estimates. Klein *et al.*[2] discussed this problem four years ago, calling it *a common mistake in transplant studies*, and even providing an example on comparing survival between patients with and without GVHD. An option that accounts for the possibility of occurrence of aGVHD is to use a landmark of 100 days, and plot survival curves for patients who survived at least 100 days stratified by aGVHD given their history and comparing the differences in survival by log-rank test. This option would not work for chronic GVHD (cGVHD) because it can happen anytime after 100 days and use of landmark analysis here does not make sense. A disadvantage of using landmark analysis for aGVHD is that information on patients with follow-up less than 100 days is not used in calculation of survivorship function. According to method suggested by Klein all patients initially are in the non-GVHD group, once they develop GVHD they move into the GVHD group. For more information see paper by Klein *et al.*[2]

aGVHD has been found to protect from relapse, and cGVHD did not affect risk of relapse, p-values 0.042 and 0.776, accordingly. The relevant hazard ratios and their confidence intervals have not been reported. It seems that in these models hazard ratio of GVHD is unadjusted for other variables; we assume it because no details on modeling of Cox regression with GVHD were mentioned. It would have been interesting to know if adjustment on important baseline covariates age at transplant, donor type, type of leukemia etc. changed an effect of GVHD on relapse and if yes to what extent.

A calculation of the cumulative incidence function by Gray has been applied in this study. In modeling this function, stratification on GVHD has been erroneously applied. Test of Gray does not allow for stratification on variable unknown at baseline.[3]

In analyses of independent prognostic factors on survival, the Cox proportional hazards (PH) regression model was applied, and GVHD was tested in this model together with time-fixed covariates. Among appealing features of the Cox PH model are: 1) a possibility of including time-dependent covariates in the model, and 2) the interpretation of a hazard ratio in a relative way.[4] We would like to remind that Cox model does not provide odds ratios as is seen from the table in this publication regarding prognostic factors for overall survival and RFS. The interpretation of ratio for aGVHD adjusted for disease status at transplant and cytogenetic risk group is that patients who do not develop aGVHD are *relapsing* at almost twice the rate of those who develop it. But is this hazard proportional in time? Probably not, but we can not say it for sure because the information to answer that question is missing in the paper.

In summary, one has to be very careful when doing statistical analyses of longitudinal data and especially when time-varying covariates are considered for analysis,

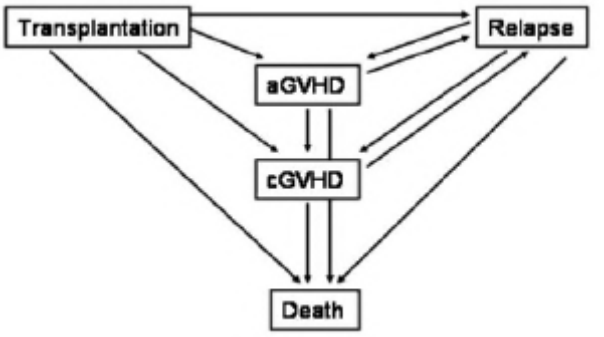

Figure 1. A basic multistate model for patients after the transplantation. Arrows show a possible transition from one state to another, death is an absorbing state.

because otherwise misuse of even such well-known methods like estimation of probability of survival by KM and misinterpretation of findings might result. The assumption of a constant hazard in modeling data of transplanted patients in general may be unrealistic and should be examined carefully. Reporting results on multivariate modeling for covariates which did not change the risk of relapse might be of interest for readers, this will also make data modeling process more transparent and understandable for others. Multistate RFS model with cause-specific transition rates as described elsewhere[5-7] would be perhaps the best method in estimating effects of GVHD on relapse of leukaemia in transplanted patients. A suggestion of a multistate model is shown in Figure 1. Fitting of a Cox regression model with time-dependent covariates can be used to determine which of patients groups (with aGVHD, cGVHD with previous aGVHD, cGVHD without previous aGVHD, and without GVHD) has the highest risk of relapse.[5] This model may be extended to include other possible states on surrogate criteria of cure such as achievement of complete cytogenetic remission, platelet recovery, leukocyte recovery, etc. depending on type of leukaemia.

Commentary on the paper by J-H Lee et al

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