Competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions Web Appendix

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1 Proportional hazards models for Competing Risks

We will consider that 2 competing events act on the patients, namely *Interest* and *Other*. The failure type, ε, is 1 for *Interest* and 2 for *Other*. If patients can experience more than 2 events, we will consider *Interest vs* a single endpoint after the competing causes of failure are *aggregated* together.

Let Z be a binary covariate that could denote a treatment arm or a dichotomized continuous covariate and T be the time to failure. The Cox model assumes that the CSH for a given patient can be factored into a baseline hazard that is common to all patients and a parametric function of the covariates that describes the patients' characteristics [1]. The CSH for the event of interest may be expressed as

$$\alpha_{01}(t; Z = 1) = \alpha_{01}(t; Z = 0) \exp \gamma^{\text{Interest}}. \tag{1}$$

The CSH for the competing event satisfies the following model:

$$\alpha_{02}(t; Z = 1) = \alpha_{02}(t; Z = 0) \exp \gamma^{\text{Other}} \tag{2}$$

with $\exp(\gamma^\star)$ being the cause-specific hazard ratio (CSHR) for event of type $\star$. The all-causes hazard, which is the sum of the 2 CSHs, completely determines the survival function $S(t) = P(T > t)$ as: $S(t) = \exp(-\int_0^t \alpha_{01}(u) + \alpha_{02}(u)du)$. This relation clearly exemplifies why we have to consider the 2 competing CSH for a probability interpretation [2]. Note that, neither $\exp(-\int_0^t \alpha_{01}(u)du)$ nor $\exp(-\int_0^t \alpha_{02}(u)du)$ have probabilistic interpretations, although they do in terms of overall survival function S.

The CIF of *Interest*, CIF_1, is defined as $P(T \leq t, \varepsilon = 1)$. Note that the relation between the CIF of *Interest* involves the CSH of *Interest* as well as the CSH of *Other*. Thus, for interpreting the CIF of *Interest*, both CSH are required.

The subdistribution hazard (SH) is the hazard attached to CIF, *i.e.* the SH of *Interest* is directly related to the CIF of *Interest*. Indeed, the CIF of *Interest* is determined by $\text{CIF}_1(t) = \int_0^t P(T > u-)\, \alpha_{01}(u)\, \mathrm{d}u$. We define the SH, $\lambda_{01}(t)$, by requiring that

$$\text{CIF}_1(t) = 1 - \exp\{-\int_0^t \lambda_{01}(u)du\}$$

The Fine–Gray model for the event of interest

$$\lambda_{01}(t; Z = 1) = \lambda_{01}(t; Z = 0) \exp \beta^{\text{Interest}} \tag{3}$$

with $\exp \beta^{\text{Interest}}$ being the subdistribution hazard ratio (SHR).

We stress on that there is no reason why β^{Interest} should equal γ^{Interest}, although in practice close estimates (of CSHR and SHR) can be found [3, 4].

Of note, fitting a Fine–Gray model for the competing risk endpoint *Other* implicitly constrains that the SHR for the competing event *Other* depend on the SHR of *Interest* and the baseline SH. As

a result, an increase in the CIF of Interest may be due to either a physiological effect of the exposure or to a decrease in the competing CIF.

Unadjusted analyses are performed using log–rank test for comparing the CSHs across groups or by a Gray's test for comparing CIFs across groups [5, 6, 7, 8]. The 2–sample test and unadjusted analysis in the presence of competing risks are discussed extensively in [9, 10].

2 Goodness of fit

Cox model

Univariate GoF test results are in agreement with the multivariate tests used in the article: the PH assumption of the CSH of relapse is met for treatment (p=0.386) and for status at transplantation (p=0.2) while the PH assumption of the CSH of TRM is met neither for the treatment (p= 0.0235) nor for the status at transplant (p=0.0121).

The Schoenfeld's residuals for each endpoint are displayed in Figure (1) and Figure (2).

Fine–Gray

The proportionality assumption was first investigated by testing for *time by covariate interaction* in a multivariate analysis using the `crr` function of the `cmprsk` `R`-package. When a significant interaction was found, we provide a graphical procedure (often refer to as H-H plot) that plots the cumulative subdistribution hazard of one cumulative SH stratified on $Z = 0$ against the other cumulative SH stratified on $Z = 1$. Under a proportional hazards, such an H-H plot should approximate a straight line with slope $\exp(\beta)$ using the same notation as in equation (3). This is illustrated with the covariate "status at transplantation" in Figure (3) and Figure (4).

For sake of completeness, we should mention that the Schoenfeld residuals can also be use for the PSH model. We provide plots for the each endpoint in Figure (5) and Figure (6).

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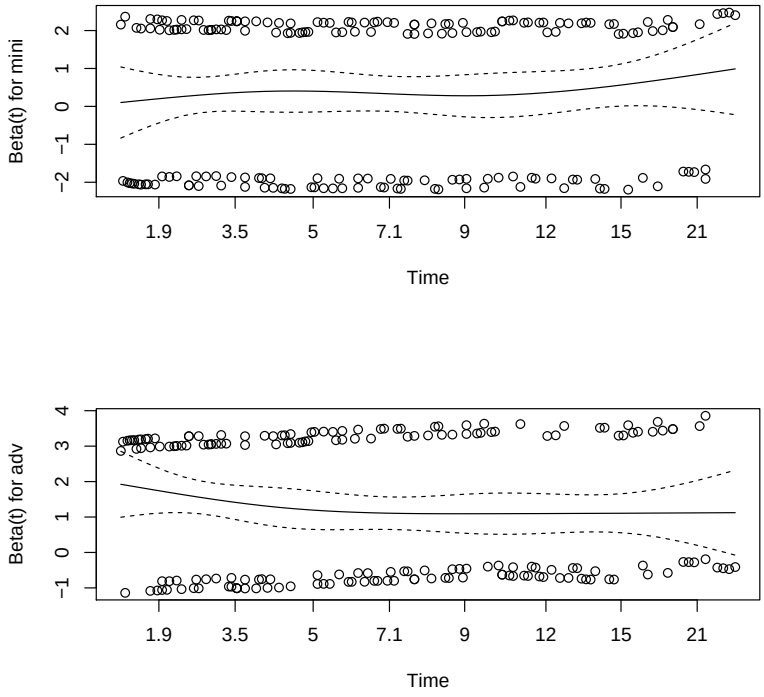

Figure 1: Schoenfeld residuals for the CSH of Relapse from multivariate model for covariate treatment (up) and disease status (bottom)

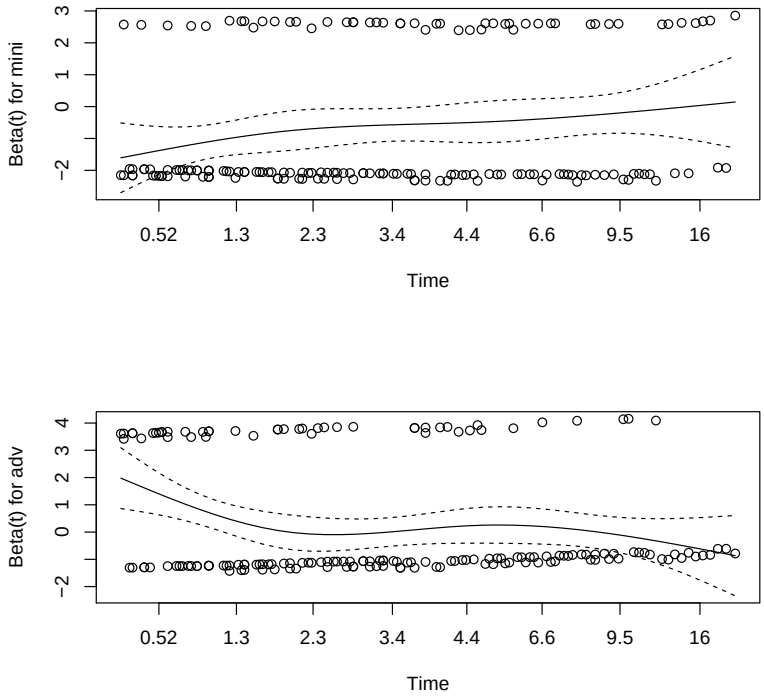

Figure 2: Schoenfeld residuals for the CSH of TRM from multivariate model for covariate treatment (up) and disease status (bottom)

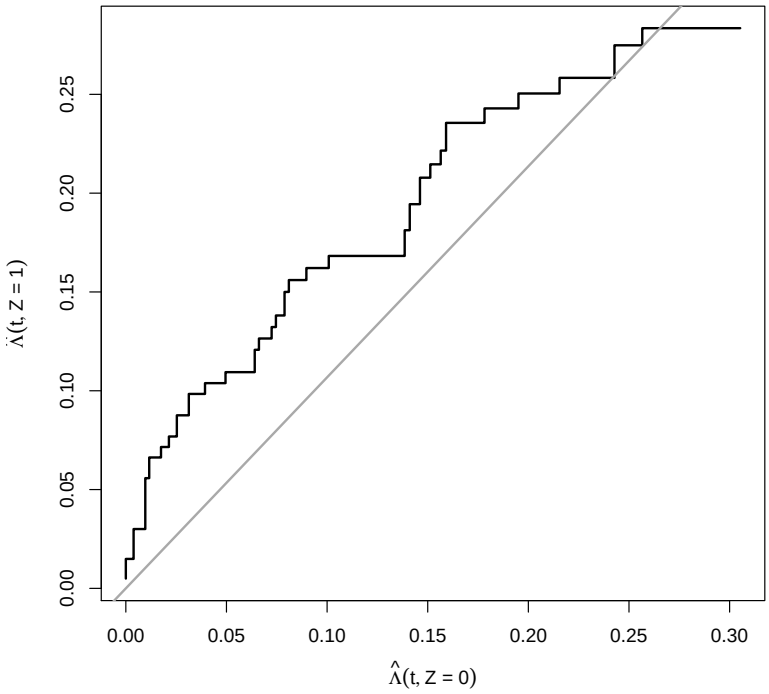

Figure 3: H-H plot: Cumulative subdistribution plots of TRM according to status at transplantation

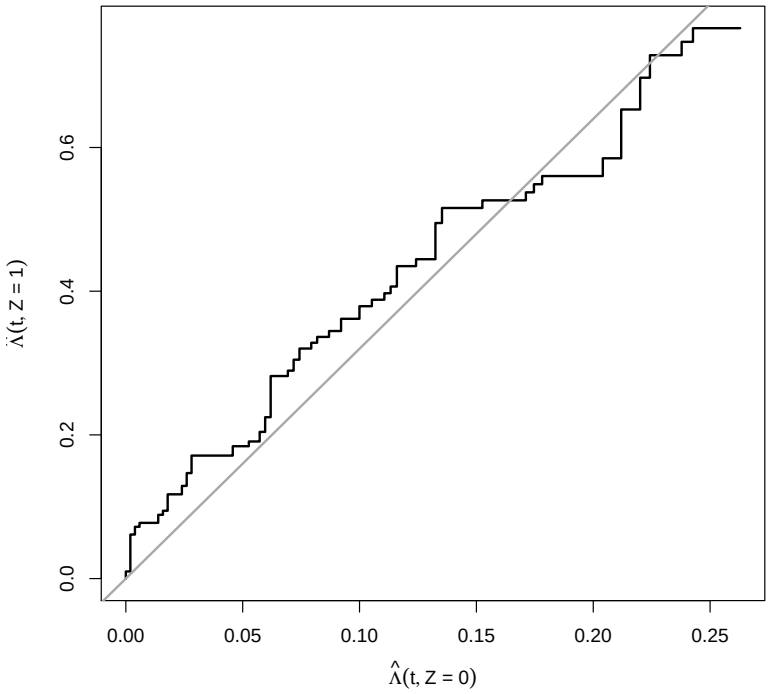

Figure 4: H-H plot: Cumulative subdistribution plots of relapse according to status at transplantation

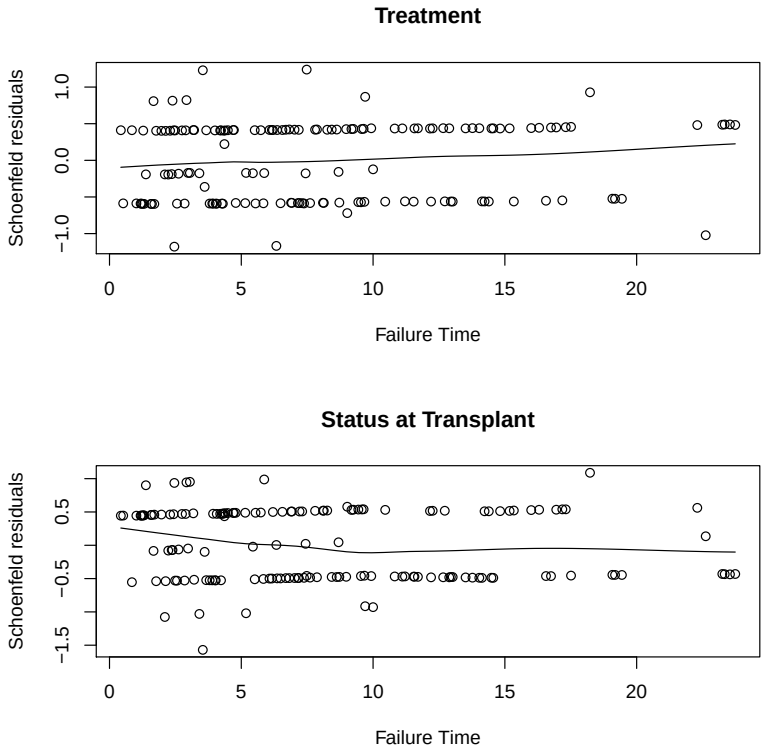

Figure 5: Schoenfeld residuals for the subdistribution hazard of relapse (multivariate model) for covariate treatment (up) and disease status (bottom)

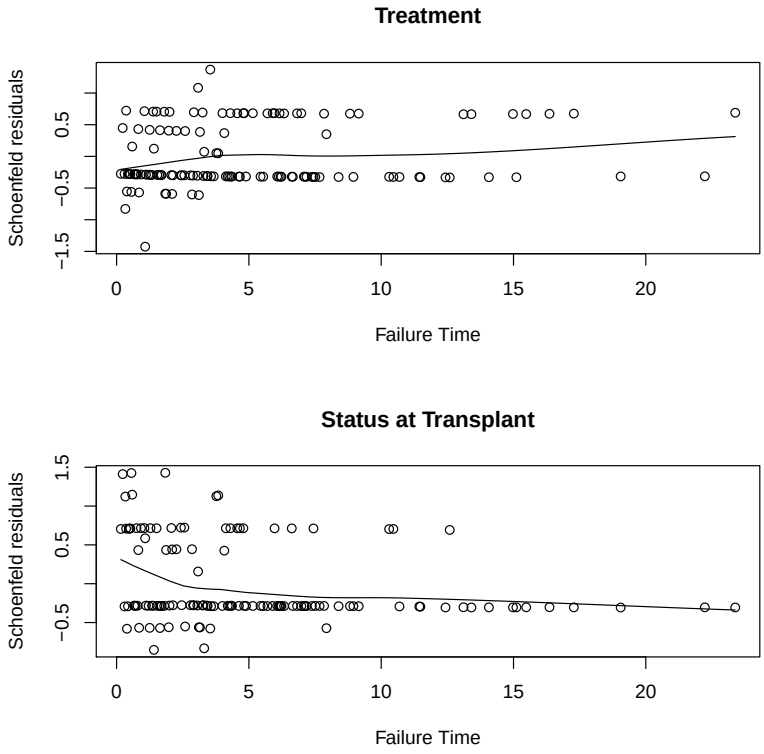

Figure 6: Schoenfeld residuals for the subdistribution hazard of TRM (multivariate model) for covariate treatment (up) and disease status (bottom)

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