

**SUPPLEMENTARY MATERIALS:**  
**An Estimating Function Approach to the Analysis of**  
**Recurrent and Terminal Events**

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## 1. Deriving Expressions (6), (7) and (8)

Only expression (8) needs derivation, since (6) and (7) are immediate consequences. Note that  $f(\gamma) = f(\gamma|\mathbf{Z})$  by assumption, so that

$$\begin{aligned} E(\gamma|D \geq t, \mathbf{Z}) &= \int_0^\infty \gamma f(\gamma|D \geq t, \mathbf{Z}) d\gamma \\ &= \frac{\int_0^\infty \gamma f(\gamma) P(D \geq t|\gamma, \mathbf{Z}) d\gamma}{\int_0^\infty f(\gamma) P(D \geq t|\gamma, \mathbf{Z}) d\gamma}. \end{aligned}$$

Now, since  $P(D \geq t|\gamma, \mathbf{Z}) = \exp\{-\gamma A(t)\}$ , where  $A(t) = \int_0^t \lambda_0^D(u) \exp\{\boldsymbol{\alpha}^T \mathbf{Z}(u)\} du$ , it is easily seen that

$$\begin{aligned} \int_0^\infty f(\gamma) P(D \geq t|\gamma, \mathbf{Z}) d\gamma &= \int_0^\infty \frac{1}{\theta \Gamma(\frac{1}{\theta})} \left(\frac{\gamma}{\theta}\right)^{\frac{1}{\theta}-1} \exp\left[-\gamma \left\{\frac{1}{\theta} + A(t)\right\}\right] d\gamma \\ &= \{1 + \theta A(t)\}^{-1/\theta}. \end{aligned}$$

Similarly,

$$\int_0^\infty \gamma f(\gamma) P(D \geq t|\gamma, \mathbf{Z}) d\gamma = \{1 + \theta A(t)\}^{-(1+1/\theta)},$$

so that

$$E(\gamma|D \geq t, \mathbf{Z}) = \{1 + \theta A(t)\}^{-1} = w(t),$$

as given in equation (8) of the main paper.

## 2. Estimating function for $\theta$

To show that expression (15) from Section 2 of the main manuscript is an unbiased estimating function, we define

$$dH(t) = \{Y_\ell(t), dN_\ell^D(t), \mathbf{Z}_\ell; \ell = 1, \dots, n\}.$$

Under the assumption of independent censoring, it is easily seen that

$$E[N_i^R(t) dN_i^D(t) | dH(t)] = (\theta + 1) r_{2i}(t) dN_i^D(t).$$

Also, it can be seen that

$$E \left\{ \sum_{j=1}^n \frac{r_{2i}(t)}{r_{2j}(t)} Y_j^*(t) N_j^R(t) | dH(t) \right\} = \sum_{j=1}^n Y_j^*(t) N_i^R(t).$$

Thus, it follows that the quantity

$$E\{N_i^R(t) | D_i > t\} = r_{2i}(t)$$

can be ‘estimated’ with

$$\sum_{j=1}^n \frac{r_{2i}(t)}{r_{2j}(t)} Y_j^*(t) N_j^R(t) \bigg/ \sum_{j=1}^n Y_j^*(t) = r_{2i}(t) \bar{G}(t),$$

where  $\bar{G}(t)$  is defined in equation (16). It follows that

$$E[\{N_i^R(t) - (\theta + 1)r_{2i}(t)\bar{G}(t)\}dN_i^D(t) | dH(t)] = 0$$

Thus, we have

$$E\{N_i^R(t) - (\theta + 1)r_{2i}(t)\bar{G}(t)\}dN_i^D(t) = 0,$$

and the integral of such terms in (15) also has mean 0.

### 3. Extension of proposed methods to competing terminal events

We now complete the description (from Section 4 of the main manuscript) of how the proposed methods can be extended to accommodate terminating events with competing risks.

Picking up where the description at the end of Section 4 left off, we obtain unbiased estimating functions for  $\boldsymbol{\alpha}_1$ ,  $\boldsymbol{\alpha}_2$  and  $\boldsymbol{\beta}$  from the (pseudo) partial likelihood analysis of the rates in (23) and (24) of the main manuscript. Similarly, estimating functions for the cumulative rate and hazard functions are obtained using the Nelson-Aalen estimators. Finally, estimating functions of  $\theta_1$  and  $\theta_2$  are obtained. Specifically, we redefine  $\boldsymbol{\eta} = (\boldsymbol{\beta}^T, \boldsymbol{\alpha}_1^T, \boldsymbol{\alpha}_2^T, \theta_1, \theta_2, [\boldsymbol{\lambda}_{01}^D]^T, [\boldsymbol{\lambda}_{02}^D]^T)^T$ . Here we are considering the time-independent case so that  $\boldsymbol{\lambda}_0^R$  does not need to be estimated simultaneously, which significantly simplifies the computation. Note that the more general

time-dependent case is also feasible, however. Let  $\phi$  represent a parameter (e.g.  $\phi = \alpha$ ) and define

$$\mathbf{S}_{m1}^{(k)}(\phi, t) = n^{-1} \sum_{i=1}^n Y_i(t) w_{mi}(t) \mathbf{Z}_i^{\otimes k} \exp(\phi^T \mathbf{Z}_i),$$

$k = 0, 1, 2$  and  $m = 1, 2, 3$ . Let  $h_{i3}(t) = w_{3i}(t) \exp\{\beta^T \mathbf{Z}_i\}$  and let  $\bar{G}_3(t)$  equal  $\bar{G}(t)$  as defined in (16) of the article, but with  $w_i(t)$  replaced by  $w_{3i}(t)$ . Further, let  $t_{\ell 1}^D, \dots, t_{\ell n_\ell}^D$  be the ordered distinct failure times for type  $\ell$ ,  $\ell = 1, 2$ .

As before, estimates of the intensities are discrete with jumps at the distinct event times. We let  $\boldsymbol{\lambda}_{0\ell}^D = (\lambda_{0\ell 1}^D, \lambda_{0\ell 2}^D, \dots, \lambda_{0\ell n_\ell}^D)^T$ , where  $\lambda_{0\ell j}^D = d\Lambda_{0\ell}^D(t_{\ell j}^D)$ ,  $j = 1, \dots, n_\ell$ , and we define  $d_{\ell j}^D$  as the number of type  $\ell$  terminal event at  $t_{\ell j}^D$ . As above, ties are handled using the Breslow Approximation. The unbiased estimating equations are

$\mathbf{U}_G(\boldsymbol{\eta}) = (\mathbf{U}_{1G}^T, \mathbf{U}_{2G}^T, \mathbf{U}_{3G}^T, U_{4G}, U_{5G}, \mathbf{U}_{6G}^T, \mathbf{U}_{7G}^T)^T = \mathbf{0}$ , where the components of  $\mathbf{U}_G$  correspond to the components in  $\boldsymbol{\eta} = (\beta^T, \alpha_1^T, \alpha_2^T, \theta_1, \theta_2, [\boldsymbol{\lambda}_{01}^D]^T, [\boldsymbol{\lambda}_{02}^D]^T)^T$ . Here, we have

$$\begin{aligned} \mathbf{U}_{1G} &= \sum_{i=1}^n \int_0^\tau \left\{ \mathbf{Z}_i - \frac{\mathbf{S}_{31}^{(1)}(\beta, t)}{S_{31}^{(0)}(\beta, t)} \right\} dN_i^R(t), \\ \mathbf{U}_{2G} &= \sum_{i=1}^n \int_0^\tau \left\{ \mathbf{Z}_i - \frac{\mathbf{S}_{11}^{(1)}(\alpha_1, t)}{S_{11}^{(0)}(\alpha_1, t)} \right\} dN_{i1}^D(t) \\ \mathbf{U}_{3G} &= \sum_{i=1}^n \int_0^\tau \left\{ \mathbf{Z}_i - \frac{\mathbf{S}_{21}^{(1)}(\alpha_2, t)}{S_{21}^{(0)}(\alpha_2, t)} \right\} dN_{i2}^D(t) \\ U_{4G} &= \sum_{i=1}^n \int_0^\tau \{ N_i^R(t) - (\theta_1 + 1) h_{3i}(t) \bar{G}_3(t) \} dN_{i1}^D(t) \\ U_{5G} &= \sum_{i=1}^n \int_0^\tau \{ N_i^R(t) - (\theta_2 + 1) h_{3i}(t) \bar{G}_3(u) \} dN_{i2}^D(t). \end{aligned}$$

Finally the  $j$ th elements of  $\mathbf{U}_{6G}$  and  $\mathbf{U}_{7G}$  are,

$$\begin{aligned} U_{6Gj} &= d_{1j}^D - n S_{11}^{(0)}(\alpha_1, t_{1j}^D) \lambda_{01j}^D, \quad j = 1, \dots, n_{D1}. \\ U_{7Gj} &= d_{2j}^D - n S_{21}^{(0)}(\alpha_2, t_{2j}^D) \lambda_{02j}^D, \quad j = 1, \dots, n_{D2}. \end{aligned}$$

Asymptotic properties are similar to those outlined above, sandwich-type estimators yield-

ing estimates of the asymptotic variance of components of  $\hat{\boldsymbol{\eta}}$ . This method can be generalized to handle any number of competing risks for the terminal event.

#### 4. Extension of the methods to incorporate negative association

Although positive association between the rate of the recurrent events and the terminal event is most common, negative association is also possible. In this section we consider a model that reflects negative association, then develop an approach that incorporates both negative and positive association.

We consider a model in which equation (4) in the main paper is replaced with

$$d\Lambda_R(t|\gamma) = \gamma^{-1} \exp\{\boldsymbol{\beta}^T \mathbf{Z}(t)\} d\Lambda_0^R(t).$$

The equation for the death process is left unchanged as

$$d\Lambda_D(t|\gamma) = \gamma \exp\{\boldsymbol{\alpha}^T \mathbf{Z}(t)\} d\Lambda_0^D(t).$$

As before, we assume that  $\gamma \sim \text{Gamma}(\theta^{-1}, \theta^{-1})$ . In this case, the common frailty reflects a negative association between the event types.

The marginal rate function is given by

$$d\Lambda_R(t) = w^*(t) \exp\{\boldsymbol{\beta}^T \mathbf{Z}(t)\} \lambda_{0R}(t)$$

and the marginal hazard by

$$d\Lambda_D(t) = w(t) \exp\{\boldsymbol{\alpha}^T \mathbf{Z}(t)\} \lambda_{0D}(t),$$

with the weight functions being  $w(t)$  [as defined in (8)] and

$$w^*(t) = E\{\gamma^{-1} | D \geq t\} = \frac{1 + \theta \int_0^t \exp\{\boldsymbol{\alpha}^T \mathbf{Z}(u)\} d\Lambda_0^D(u)}{1 - \theta} = \frac{1}{w(t)(1 - \theta)}.$$

In the equations for  $\boldsymbol{\beta}$  and the increments of  $\Lambda_0^R(t)$ , it is the weight function  $w^*(t)$  that is appropriate. In the equations for  $\boldsymbol{\alpha}$  and  $\Lambda_0^D(t)$ , the weight function  $w(t)$  applies as before. Note that we require  $\theta < 1$  for finite expectation of  $\gamma$  in the negative correlation case.

In this model, it can be seen that equations (12) and (13) are replaced with

$$r_{1i}(t) = w_i^*(t) \int_0^t \exp\{\boldsymbol{\beta}^T \mathbf{Z}_i(u)\} d\Lambda_0^R(u)$$

and

$$r_{2i}(t) = \frac{w_i(t)}{1 - \theta} \int_0^t \exp\{\boldsymbol{\beta}^T \mathbf{Z}_i(u)\} d\Lambda_0^R(u),$$

respectively. Analogous to equation (14), It then follows that

$$\frac{r_{1i}(t)}{r_{2i}(t)} = 1 - \theta.$$

The same estimating equation for  $\theta$  can be used as in (15) except that  $1 + \theta$  is replaced with  $1 - \theta$ .

This can be unified to apply to both positive and negative correlation as follows. We expand the range of  $\theta$  to  $(-1, \infty)$  and use the equation (15) to estimate  $\theta$  on this range. Negative  $\theta$  corresponds to negative correlation. Estimating equations for  $\boldsymbol{\alpha}$  and  $\boldsymbol{\beta}$  are obtained in the same way as before and correspond to weighted estimated equations of the same type as in the main paper. The weights for  $\boldsymbol{\alpha}$  and  $\Lambda_0^D(\cdot)$  are

$$w_i^D(t) = \left[ 1 + |\theta| \int_0^t \exp\{\boldsymbol{\beta}^T \mathbf{Z}(u)\} d\Lambda_0^R(u) \right]^{-1};$$

while for  $\boldsymbol{\beta}$  and  $\Lambda_0^R(\cdot)$ , the weights are

$$\begin{aligned} w_i^R(t) &= w_i^D(t), & \theta > 0 \\ &= \{w_i^D(t)(1 + \theta)\}^{-1}, & \theta < 0. \end{aligned}$$

This combined model allows estimation of  $\theta$  for both positive and negative association. For values of  $\hat{\theta}$  near zero, a confidence interval for  $\theta$  would include both positive and negative values. In most applications, however, positive values of  $\theta$  well removed from 0 will be of most interest. This is the nature of the application in the main paper.

## 5. Further analysis of DOPPS data

In this section we describe additional analyses of the Dialysis Outcomes and Practice Patterns Study (DOPPS) data. In particular, we employ the methods described in Section 3 of this document.

In Table 1, we list results for a model for which deaths are classified as either cardiovascular disease (CVD) or non-CVD. It is revealed that the increased mortality hazard for Italy is much stronger for CVD than non-CVD deaths. On the other hand, the effect of age was much more pronounced for non-CVD than CVD deaths. Although the model from Table 1 indicates that congestive heart failure was not a significant predictor of all-cause mortality, it is shown in Table 1 that CHF significantly increases the CVD mortality hazard. A similar comment applies to CHD/CAD. Somewhat conversely, the PVD increase on mortality appears to be strongest for non-CVD mortality. Results for hospitalization were very similar to those from Table 1, which would be expected. The frailty parameter for the association between CVD death and hospitalization is estimated to be  $\hat{\theta}_1 = 1.30$  with an estimated standard error 0.44 ( $P = 0.003$ ). According to this estimate, a patient who is known to die of CVD at time  $t$  is expected to have 2.3 times more hospitalizations than a patient who has the same covariate values and is alive at time  $t$ . The estimate of  $\theta_2$  is 1.00 with an estimated standard error of 0.30 ( $p < 0.001$ ). Thus, the rate of hospitalization is strongly and positively associated with the hazard of both CVD and non-CVD death.

[Table 1 about here.]

Table 1: Expectation-based analysis of Euro-DOPPS data with two types of terminal events: CVD and non-CVD death

| Covariate            | CVD Death        |                |       | Non CVD Death    |                |         | Hospitalization |                |         |
|----------------------|------------------|----------------|-------|------------------|----------------|---------|-----------------|----------------|---------|
|                      | $\hat{\alpha}_1$ | $\widehat{SE}$ | $p$   | $\hat{\alpha}_2$ | $\widehat{SE}$ | $p$     | $\hat{\beta}$   | $\widehat{SE}$ | $p$     |
| Diabetes             | 0.644            | 0.414          | 0.120 | -0.622           | 0.350          | 0.075   | 0.184           | 0.125          | 0.142   |
| Sex=M                | 0.022            | 0.362          | 0.952 | -0.195           | 0.279          | 0.484   | -0.101          | 0.107          | 0.346   |
| Educ: $\geq$ College | 0.129            | 0.646          | 0.841 | -1.820           | 2.201          | 0.408   | -0.259          | 0.165          | 0.118   |
| Country              |                  |                |       |                  |                |         |                 |                |         |
| France               | 0.901            | 0.608          | 0.138 | 0.322            | 0.074          | < 0.001 | 0.178           | 0.157          | 0.256   |
| Germany              | -0.324           | 0.706          | 0.646 | -0.260           | 0.110          | 0.019   | -0.369          | 0.174          | 0.034   |
| Italy                | 1.122            | 0.599          | 0.061 | 0.493            | 0.098          | < 0.001 | -0.228          | 0.173          | 0.186   |
| Spain                | 0.501            | 0.624          | 0.422 | 0.091            | 0.109          | 0.405   | -0.666          | 0.161          | < 0.001 |
| U.K.                 | 0                | .              | .     | 0                | .              | .       | 0               | .              | .       |
| Age<br>per 5 yrs     | 0.143            | 0.069          | 0.040 | 0.249            | 0.086          | 0.004   | 0.025           | 0.020          | 0.213   |
| Body mass index      |                  |                |       |                  |                |         |                 |                |         |
| $BMI < 20$           | 0.471            | 0.420          | 0.263 | 0.029            | 0.380          | 0.940   | 0.030           | 0.140          | 0.829   |
| $BMI \geq 30$        | -1.088           | 0.726          | 0.134 | -0.057           | 0.381          | 0.881   | 0.045           | 0.160          | 0.779   |
| $BMI \in [20, 30)$   | 0                | .              | .     | 0                | .              | .       | 0               | .              | .       |
| Comorbid conditions  |                  |                |       |                  |                |         |                 |                |         |
| Cer Vas Dis          | 0.973            | 0.407          | 0.017 | 0.679            | 0.261          | 0.009   | 0.147           | 0.126          | 0.241   |
| CHF                  | 0.840            | 0.362          | 0.020 | 0.137            | 0.275          | 0.618   | 0.121           | 0.128          | 0.344   |
| CHD/CAD              | 0.835            | 0.358          | 0.020 | 0.047            | 0.335          | 0.888   | 0.159           | 0.119          | 0.180   |
| Hypertension         | -0.787           | 0.362          | 0.030 | -0.923           | 0.257          | < 0.001 | -0.311          | 0.133          | 0.020   |
| PVD                  | 0.545            | 0.416          | 0.190 | 0.794            | 0.322          | 0.014   | 0.299           | 0.124          | 0.016   |