Web-based Supplementary Materials for Semiparametric Models of Time-dependent Predictive Values of Prognostic Biomarkers

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Appendix

Throughout we assume that the joint density of T, C and Y is twice continuously differentiable and $\mathbf{W} = (Y, \mathbf{Z}^{\mathsf{T}})^{\mathsf{T}}$ belongs to a compact set $\Omega_{\mathbf{W}}$. We consider $v \in [p_l, p_u] \subset (0, 1)$ and $t \in [\tau_1, \tau_2]$, where τ_1 and τ_2 are pre-determined constants such that $P(X < \tau_1) > 0$ and $P(X > \tau_2) > 0$. In addition, we assume that $F'_{Y|\mathbf{z}}(y) = \partial F_{Y|\mathbf{z}}(y)/\partial y$, is bounded away from 0 for $y \in [c_{\mathbf{z}}(p_l), c_{\mathbf{z}}(p_u)]$. For $\widehat{F}_{Y|\mathbf{z}}(y)$, without loss of generality, we assume that

$$\sup_y \left| n^{1/2} \left\{ \widehat{F}_{Y|\mathbf{z}}(y) - F_{Y|\mathbf{z}}(y) \right\} - n^{-\frac{1}{2}} \sum_{i=1}^{n} \mathcal{P}_i(y, \mathbf{z}) \right| = o_p(1), \qquad (\text{A}\cdot 1)$$

where $\mathcal{P}_i(y, \mathbf{z}) = \mathcal{P}(y, \mathbf{z}, X_i, \Delta_i, Y_i, \mathbf{Z}_i)$ for some function $\mathcal{P}$ that is bounded for $(y, \mathbf{z}) \in \Omega_{\mathbf{W}}$ with total variation bounded by a constant. The regularity condition on $\mathcal{P}$ ensures the manageability (Pollard, 1990) of $\{\mathcal{P}_i(y, \mathbf{z}), i = 1, ..., n\}$ which leads to the weak convergence of $n^{1/2}\{\widehat{F}_{Y|\mathbf{z}}(y) - F_{Y|\mathbf{z}}(y)\}$ to a zero-mean Gaussian process. Under a semi-parametric location model,

$$\mathcal{P}_i(y, \mathbf{z}) = I(Y_i - \gamma_0^{\mathsf{T}} \mathbf{Z}_i \leqslant y - \gamma_0^{\mathsf{T}} \mathbf{z}) - F_{Y|\mathbf{z}}(y) + F'_{Y|\mathbf{z}}(y) \{E(\mathbf{Z}) - \mathbf{z}\}^{\mathsf{T}} E(\mathbf{Z}^{\otimes 2})^{-1} \mathbf{Z}_i (Y_i - \gamma_0^{\mathsf{T}} \mathbf{Z}_i)$$

which satisfies (A·1).

A. Inference on covariate effects[1]

Consider a general location-scale model for the marker Y:

$$Y_i = \boldsymbol{\gamma}_0^{\mathsf{T}} \mathbf{Z}_i + \exp(\boldsymbol{\kappa}_0^{\mathsf{T}} \mathbf{Z}_i) \epsilon_i. \qquad (\text{A}.2)$$

Claim:

A. Under the model

$$\lambda_{Y_i, \mathbf{Z}_i}(t) = \lambda_0(t) \exp(\alpha_0 Y_i + \boldsymbol{\beta}_0^{\mathsf{T}} \mathbf{Z}_i), \qquad (\text{A}.3)$$

[1]The authors cordially thank Dr. David Zucker for kindly providing help with the proof in this section.

$\mathrm{PPV}_{\mathbf{z}_1}(t,v) = \mathrm{PPV}_{\mathbf{z}_2}(t,v)$ for all $t, v, \mathbf{z}_1$, and $\mathbf{z}_2$ if and only if $\alpha_0\boldsymbol{\kappa}_0 = \mathbf{0}$ and $\boldsymbol{\beta}_0 = -\alpha_0\boldsymbol{\gamma}_0$.

B. Assume the model

$$\lambda_{Y_i,\mathbf{Z}_i}(t) = \lambda_0(t, Y_i)\exp(\boldsymbol{\beta}_0^{\mathsf{T}}\mathbf{Z}_i). \tag{A.4}$$

Write

$$\begin{aligned}\Lambda_0(t,y) &= \int_0^t \lambda_0(u,y)du,\\ \zeta(t,y) &= \frac{\partial}{\partial y}\log\Lambda_0(t,y).\end{aligned}$$

Suppose the following condition:

Non-PH Condition: There exist values y^*, t_1^*, and t_2^* such that $\zeta(t_1^*, y^*) \neq 0$, $\zeta(t_2^*, y^*) \neq 0$, and $\zeta(t_1^*, y^*) \neq \zeta(t_2^*, y^*)$, i.e., $\Lambda_0(t,y)$ does not have the general proportional hazards form $\Lambda_0(t,y) = \Lambda_0(t)\Omega(y)$.

Then $\mathrm{PPV}_{\mathbf{z}_1}(t,v) = \mathrm{PPV}_{\mathbf{z}_2}(t,v)$ for all $t, v, \mathbf{z}_1$, and $\mathbf{z}_2$ if and only if $\boldsymbol{\beta}_0 = \boldsymbol{\gamma}_0 = \boldsymbol{\kappa}_0 = \mathbf{0}$.

Proof:

We note that $\mathrm{PPV}_{\mathbf{z}_1}(t,v) = \mathrm{PPV}_{\mathbf{z}_2}(t,v)$ for all $t, v, \mathbf{z}_1$, and $\mathbf{z}_2$ if and only if

$$\int_{c_{\mathbf{z}_1}(v)}^{\infty} S_{y,\mathbf{z}_1}(t)dF_{Y|\mathbf{z}_1}(y) = \int_{c_{\mathbf{z}_2}(v)}^{\infty} S_{y,\mathbf{z}_2}(t)dF_{Y|\mathbf{z}_2}(y).$$

Taking the derivative with respect to v on both sides and noting that $\partial c_{\mathbf{z}}(v)/\partial v = [f_{Y|\mathbf{z}}(c_{\mathbf{z}}(v))]^{-1}$, we find that the above equality is equivalent to the equality

$$S_{c_{\mathbf{z}_1}(v),\mathbf{z}_1}(t) = S_{c_{\mathbf{z}_2}(v),\mathbf{z}_2}(t) \tag{A.5}$$

for all $t, v, \mathbf{z}_1$, and $\mathbf{z}_2$.

We first consider Claim A. Under Model (A.3), the equality (A.5) is equivalent to the equality

$$\alpha_0 c_{\mathbf{z}_1}(v) + \boldsymbol{\beta}_0^{\mathsf{T}}\mathbf{z}_1 = \alpha_0 c_{\mathbf{z}_2}(v) + \boldsymbol{\beta}_0^{\mathsf{T}}\mathbf{z}_2. \tag{A.6}$$

Under Model (A.2), we have

$$c_{\mathbf{z}}(v) = \boldsymbol{\gamma}_0^{\mathsf{T}}\mathbf{z} + \exp(\boldsymbol{\kappa}_0^{\mathsf{T}}\mathbf{z})G^{-1}(v), \tag{A.7}$$

where G is the distribution function of ϵ_i. It is obvious that the condition $\alpha_0\boldsymbol{\kappa}_0 = \mathbf{0}$ and $\boldsymbol{\beta}_0 = -\alpha_0\boldsymbol{\gamma}_0$ implies (A.7).

We now prove the converse. The condition (A.6) implies that the quantity

$$\alpha_0\{\boldsymbol{\gamma}_0^\mathsf{T}\mathbf{z} + \exp(\boldsymbol{\kappa}_0^\mathsf{T}\mathbf{z})G^{-1}(v)\} + \boldsymbol{\beta}_0^\mathsf{T}\mathbf{z}$$

is constant over $\mathbf{z}$, for all t and v. Taking the derivative with respect to $\mathbf{z}$ yields the equality

$$(\alpha_0\boldsymbol{\gamma}_0 + \boldsymbol{\beta}_0) + \alpha_0\boldsymbol{\kappa}_0\exp(\boldsymbol{\kappa}_0^\mathsf{T}\mathbf{z})G^{-1}(v) = \mathbf{0} \quad \forall v.$$

The above equality implies that, for any given $\mathbf{z}$, there multiple values of v such that $\alpha_0\boldsymbol{\kappa}_0\exp(\boldsymbol{\kappa}_0^\mathsf{T}\mathbf{z})G^{-1}(v) = -(\alpha_0\boldsymbol{\gamma}_0 + \boldsymbol{\beta}_0)$. This, in turn, implies $\alpha_0\boldsymbol{\kappa}_0 = \mathbf{0}$ and $\boldsymbol{\beta}_0 = -\alpha_0\boldsymbol{\gamma}_0$.

Now we consider Claim B. Under Model (A.4), the equality (A.5) is equivalent to

$$\log\Lambda_0\{t, c_{\mathbf{z}_1}(v)\} + \boldsymbol{\beta}_0^\mathsf{T}\mathbf{z}_1 = \log\Lambda_0\{t, c_{\mathbf{z}_2}(v)\} + \boldsymbol{\beta}_0^\mathsf{T}\mathbf{z}_2 \quad \forall t, v, \mathbf{z}_1, \mathbf{z}_2, \tag{A.8}$$

which implies that the function

$$\log\Lambda_0\{t, c_{\mathbf{z}}(v)\} + \boldsymbol{\beta}_0^\mathsf{T}\mathbf{z} \tag{A.9}$$

is constant in $\mathbf{z}$ for all t and v. Under Model (A.2), this obviously holds if $\boldsymbol{\beta}_0 = \boldsymbol{\gamma}_0 = \boldsymbol{\kappa}_0 = \mathbf{0}$. We now show the converse. Taking the derivative of (A.9) with respect to $\mathbf{z}$ yields

$$\zeta\{t, c_{\mathbf{z}}(v)\}\nabla_{\mathbf{z}}c_{\mathbf{z}}(v) + \boldsymbol{\beta}_0 = \mathbf{0} \quad \forall t, v, \mathbf{z},$$

where $\nabla_{\mathbf{z}}c_{\mathbf{z}}(v)$ denotes the gradient of $c_{\mathbf{z}}(v)$. From (A.7) we have

$$\nabla_{\mathbf{z}}c_{\mathbf{z}}(v) = \boldsymbol{\gamma}_0 + \boldsymbol{\kappa}_0\exp(\boldsymbol{\kappa}_0^\mathsf{T}\mathbf{z})G^{-1}(v),$$

so we get

$$\zeta\{t, c_{\mathbf{z}}(v)\}\{\boldsymbol{\gamma}_0 + \boldsymbol{\kappa}_0\exp(\boldsymbol{\kappa}_0^\mathsf{T}\mathbf{z})G^{-1}(v)\} + \boldsymbol{\beta}_0 = \mathbf{0} \quad \forall t, v, \mathbf{z}.$$

Now for all $(\mathbf{z}, v)$ in the set $A = \{(\mathbf{z}, v) : \boldsymbol{\gamma}_0^\mathsf{T}\mathbf{z} + \exp(\boldsymbol{\kappa}_0^\mathsf{T}\mathbf{z})G^{-1}(v) = y^*\}$, we get

$$\zeta(t, y^*)\{\boldsymbol{\gamma}_0 + \boldsymbol{\kappa}_0(y^* - \boldsymbol{\gamma}_0^\mathsf{T}\mathbf{z})\} = -\boldsymbol{\beta}_0 \quad \forall t, \text{ and all } \mathbf{z} \in A_p, \tag{A.10}$$

where A_p is the projection of A onto the first p dimensions. We now argue componentwise. Suppose that $\beta_{0j} = 0$. We then have $\gamma_{0j} + \kappa_{0j}a = 0$ for at least two distinct values of a, which implies that $\gamma_{0j} = \kappa_{0j} = 0$. Next, suppose that $\beta_{0j} \neq 0$ and $\gamma_{0j} = 0$. Then (A.10) gives

$$\kappa_{0j}(y^* - \boldsymbol{\gamma}_0^\top \mathbf{z}) = -\beta_{0j}/\zeta(t, y^*) \quad \forall t, \text{ and all } \mathbf{z} \in A_p.$$

In view of the Non-PH condition, this produces a contradiction. Finally, suppose that $\beta_{0j} \neq 0$ and $\gamma_{0j} \neq 0$. Differentiating (A.10) with respect to z_j leads to $\boldsymbol{\kappa}_0 = \mathbf{0}$. This produces $\gamma_{0j} = -\beta_{0j}/\zeta(t, y^*)$ for all t. Again, in view of the Non-PH condition, this produces a contradiction. We thus conclude that $\beta_{0j} = 0$, and hence $\gamma_{0j} = \kappa_{0j} = 0$.

B. Asymptotic Properties of $\widetilde{\mathbf{PPV}}_{\mathbf{z}}(t, v)$

We let $\widetilde{\boldsymbol{\theta}} = (\widetilde{\alpha}, \widetilde{\boldsymbol{\beta}}^\top)^\top$, $\boldsymbol{\theta}_0 = (\alpha_0, \boldsymbol{\beta}_0^\top)^\top$, and assume that $\boldsymbol{\theta}_0$ is an interior point of a compact parameter space. We also assume the same regularity conditions as in Andersen & Gill (1982). Under such regularity conditions, it was shown in Andersen & Gill (1982) that $n^{\frac{1}{2}}(\widetilde{\boldsymbol{\theta}} - \boldsymbol{\theta}_0)$ is a normal random variate, and $n^{\frac{1}{2}}\{\widetilde{\Lambda}_0(t) - \Lambda_0(t)\}$ converges to a Gaussian process. Furthermore, by a functional delta theorem that

$$\sup_{t,y} \left| n^{\frac{1}{2}}\{\widetilde{S}_{y,\mathbf{z}}(t) - S_{y,\mathbf{z}}(t)\} - n^{-\frac{1}{2}} \sum_{i=1}^{n} \zeta_{i1}(t, y, \mathbf{z}) \right| = o_p(1), \tag{A.11}$$

which converges weakly to a zero-mean Gaussian process, where

$$\zeta_{i1}(t, y, \mathbf{z}) = S_{y,\mathbf{z}}(t) \exp(\alpha_0 y + \boldsymbol{\beta}_0^\top \mathbf{z}) \left[\int_0^t \frac{dM_i(u)}{s_0(u, \boldsymbol{\theta}_0)} + \left\{ \Lambda_0(t) \binom{y}{z} + \mathcal{H}(t, \boldsymbol{\theta}_0) \right\}^\top \mathcal{I}^{-1}(\boldsymbol{\theta}_0) \int_0^\infty \left\{ \mathbf{W}_i - \frac{\mathbb{R}_1(u)}{\mathbb{R}_0(u)} \right\} dM_i(u) \right],$$

$$\mathcal{H}(\boldsymbol{\theta}_0, t) = -\int_0^t \frac{\mathbb{R}_1(u) dE\{N_i(u)\}}{\mathbb{R}_0(u)^2}, \; \mathcal{I}(\boldsymbol{\theta}_0) = \int_0^\infty \frac{\{\mathbb{R}_2(u)\mathbb{R}_0(u) - \mathbb{R}_1(u)^2\} \, dE\{N_i(s)\}}{\mathbb{R}_0(u)^2},$$

$M_i(t) = N_i(t) - \int_0^t I(X_i \geqslant u) \exp(\boldsymbol{\theta}_0^\top \mathbf{W}_i) d\Lambda_0(u)$ and $\mathbb{R}_b(t) = E\{I(X_i \geqslant t)\mathbf{W}_i^{\otimes b} \exp(\boldsymbol{\theta}_0^\top \mathbf{W}_i)\}$, where for any vector $\boldsymbol{a}$, $\boldsymbol{a}^{\otimes 0} = 1$, $\boldsymbol{a}^{\otimes 1} = \boldsymbol{a}$ and $\boldsymbol{a}^{\otimes 2} = \boldsymbol{a}\boldsymbol{a}^\top$.

To establish the uniform consistency of $\widetilde{\mathrm{PPV}}_{\mathbf{z}}(t, v)$, it suffices to show that (i) $\sup_v |\widehat{c}_{\mathbf{z}}(v) - c_{\mathbf{z}}(v)| = o_p(n^{-1/4})$; and (ii) $\sup_{c,t} | \int_c^\infty \{\widetilde{S}_{y,\mathbf{z}}(t) d\widehat{F}_{Y|\mathbf{z}}(y) - S_{y,\mathbf{z}}(t) dF_{Y|\mathbf{z}}(y)\}| = o_p(n^{-1/4})$, where $c_{\mathbf{z}}(v) = F_{Y|\mathbf{z}}^{-1}(v)$. From (A·1), we have $\sup_v |\widehat{F}_{Y|\mathbf{z}}(y) - F_{Y|\mathbf{z}}(y)| = O_p(n^{-1/2})$. This, together with the fact that $F'_{Y|\mathbf{z}}(y)$ is bounded away from 0, we have $\sup_v |\widehat{c}_{\mathbf{z}}(v) - c_{\mathbf{z}}(v)| = o_p(n^{-1/4})$. (ii) follows directly from $\sup_{t,y} |\widetilde{S}_{y,\mathbf{z}}(t) - S_{y,\mathbf{z}}(t)| = O_p(n^{-1/2})$ and Lemma 1 of Bilias, Gu & Ying (1997). This concludes the uniform consistency of $\widetilde{\mathrm{PPV}}_{\mathbf{z}}(t,v)$.

To derive the large sample distribution for $\widetilde{\mathrm{PPV}}_{\mathbf{z}}(t,v)$, we write

$$\widetilde{\mathcal{W}}_{\mathbf{z}}(t,v) = n^{\frac{1}{2}}\{\widetilde{\mathrm{PPV}\mathbf{z}}(t,v) - \mathrm{PPV}\mathbf{z}(t,v)\} = \{\widetilde{\mathcal{W}}_{\mathbf{z}1}(t,v) + \widetilde{\mathcal{W}}_{\mathbf{z}2}(t,v)\}/(1-v),$$

where

$$\widetilde{\mathcal{W}}_{\mathbf{z}1}(t,v) = n^{\frac{1}{2}} \int_{\widehat{c}_{v,\mathbf{z}}}^{\infty} \left\{\widetilde{S}_{y,\mathbf{z}}(t) - S_{y,\mathbf{z}}(t)\right\} d\widehat{F}_{Y|\mathbf{z}}(y),$$
$$\widetilde{\mathcal{W}}_{\mathbf{z}2}(t,v) = n^{\frac{1}{2}} \left\{\int_{\widehat{c}_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) d\widehat{F}_{Y|\mathbf{z}}(y) - \int_{c_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) dF_{Y|\mathbf{z}}(y)\right\}.$$

To approximate the distribution of $\widetilde{\mathcal{W}}_{\mathbf{z}1}(t,v)$, we note that since

$$\sup_y \left|\widehat{F}_{Y|\mathbf{z}}(y) - F_{Y|\mathbf{z}}(y)\right| + \sup_{t,y}\left|\widetilde{S}_{y,\mathbf{z}}(t) - S_{y,\mathbf{z}}(t)\right| + \sup_v |\widehat{c}_{\mathbf{z}}(v) - c_{\mathbf{z}}(v)| = o_p(n^{-\frac{1}{4}}).$$

we have

$$\widetilde{\mathcal{W}}_{\mathbf{z}1}(t,v) = n^{\frac{1}{2}} \int_{c_{\mathbf{z}}(v)}^{\infty} \left\{\widetilde{S}_{y,\mathbf{z}}(t) - S_{y,\mathbf{z}}(t)\right\} dF_{Y|\mathbf{z}}(y).$$

It then follows from (A.11) that

$$\widetilde{\mathcal{W}}_{\mathbf{z}1}(t,v) \simeq n^{\frac{1}{2}} \int_{c_{\mathbf{z}}(v)}^{\infty} \zeta_{i1}(t,y,\mathbf{z}) dF_{Y|\mathbf{z}}(y). \tag{A.12}$$

Now, for $\widetilde{\mathcal{W}}_{\mathbf{z}2}(t,v)$, we note that

$$\begin{aligned}
& n^{\frac{1}{2}} \int_{\widehat{c}_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) d\hat{F}_{Y|z}(y) - \int_{c_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) dF_{Y|\mathbf{z}}(y) \\
\simeq\ & n^{\frac{1}{2}} \int_{c_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) d\left\{\hat{F}_{Y|z}(y) - F_{Y|\mathbf{z}}(y)\right\} + n^{\frac{1}{2}}\left\{\int_{\widehat{c}_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) dF_{Y|\mathbf{z}}(y) - \int_{c_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) dF_{Y|\mathbf{z}}(y)\right\} \\
=\ & n^{\frac{1}{2}} \int_{c_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) d\{\widehat{F}_{Y|\mathbf{z}}(y) - F_{Y|\mathbf{z}}(y)\} - n^{\frac{1}{2}}\left\{\widehat{F}_{Y|\mathbf{z}}(c_{\mathbf{z}}(v)) - v\right\} S_{c_{\mathbf{z}}(v),\mathbf{z}}(t)
\end{aligned}$$

It then follows from (A·1) that

$$\widetilde{\mathcal{W}}_{\mathbf{z}2}(t,v) \simeq n^{-1/2} \sum_{i=1}^{n} \zeta_{i2}(t,v,\mathbf{z}), \tag{A.13}$$

where

$$\zeta_{i2}(t,v,\mathbf{z}) = \int_{c_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) d\mathcal{P}_i(y,\mathbf{z}) - S_{c_{\mathbf{z}}(v),\mathbf{z}}(t)\mathcal{P}_i(c_{\mathbf{z}}(v),\mathbf{z})$$

In a special case when $F_{Y|\mathbf{z}}(\cdot)$ is estimated empirically,

$$\zeta_{i2}(t,v,\mathbf{z}) = \frac{I(\mathbf{Z}_i = \mathbf{z})}{a_z}\left[\left\{S_{Y_i,\mathbf{z}}(t) - S_{c_{\mathbf{z}}(v)}(t)\right\} I\{Y_i > c_{\mathbf{z}}(v)\} + \int_{c_{\mathbf{z}}(v)}^{\infty} \left\{S_{c_{\mathbf{z}}(v)}(t) - S_{y,\mathbf{z}}(t)\right\} dF_{Y|\mathbf{z}}(y)\right],$$

where $a_z = P(Z_i = z)$. Combining (A.12) and (A.13), we have $\widetilde{W}_{\mathbf{z}}(t,v) \simeq n^{-\frac{1}{2}}\sum_{i=1}^n \zeta_i(t,v,\mathbf{z})$, where

$$\zeta_i(t,v,\mathbf{z}) = (1-v)^{-1}\left\{\int_{c_{\mathbf{z}}(v)}^{\infty} \zeta_{i1}(t,y,\mathbf{z}) dF_{Y|\mathbf{z}}(y) + \zeta_{i2}(t,y,\mathbf{z})\right\}. \tag{A.14}$$

With a functional central limit theorem, $\widetilde{W}_{\mathbf{z}}(t,v)$ converges to a zero-mean Gaussian process.

c. Asymptotic Properties of $\widehat{\mathbf{PPV}}_{\mathbf{z}}(t,v)$

For the convergence of $\widehat{\mathrm{PPV}}_{\mathbf{z}}(t,v)$, we require the same conditions as specified in Dabrowska (1997). Briefly, the kernel function $K(\cdot)$ is a symmetric probability density function with bounded support and continuous bounded second derivative. The bandwidth h is chosen such that $nh^2 \to \infty$ and $nh^4 \to 0$ as $n \to \infty$. It follows from Dabrowska (1997) that $\sup_{t,y}\left|\widehat{\Lambda}_{y,\mathbf{z}}(t) - \Lambda_{y,\mathbf{z}}(t)\right| = o_p(n^{-1/4})$ and

$$n^{\frac{1}{2}}(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0) \simeq n^{-\frac{1}{2}}\sum_{i=1}^n \mathcal{A}_i,$$

where

$$\mathcal{A}_i = \mathcal{I}(\boldsymbol{\beta}_0)^{-1}\int\left\{\mathbf{Z}_i - \frac{\mathbb{R}_{Y_i}^{(1)}(u,\boldsymbol{\beta})}{\mathbb{R}_{Y_i}^{(0)}(u,\boldsymbol{\beta})}\right\}\left\{dN_i(u) - I(X_i \geqslant u)\exp(\boldsymbol{\beta}_0^{\intercal}\mathbf{Z}_i)\lambda_{0Y_i}(u)du\right\},$$

$\mathcal{I}(\boldsymbol{\beta})$ is the limit of $\frac{\partial^2 C^*(\beta)}{\partial\boldsymbol{\beta}\partial\boldsymbol{\beta}^{\intercal}}$, and $\mathbb{R}_y^{(l)}(u,\boldsymbol{\beta})$ is the limit of $n^{-1}\sum_{i=1}^n K_h(Y_i - y)I(X_i \geqslant s)\exp(\boldsymbol{\beta}^{\intercal}\mathbf{Z}_i)\mathbf{Z}_i^{\otimes l}$.

The uniform convergence of $\widehat{\Lambda}_{y,\mathbf{z}}(t)$, together with the uniform consistency of $\widehat{F}_{Y|\mathbf{z}}(y)$ and $c_{\mathbf{z}}(v)$, and Lemma A.3 of Bilias et al. (1997), implies the uniform consistency of $\widehat{\mathrm{PPV}}_{\mathbf{z}}(t,v)$.

Now, to derive the large sample distribution for $\widehat{\mathrm{PPV}}\mathbf{z}(t,v)$, we write

$$\widehat{\mathcal{W}}_{\mathbf{z}}(t,v)=n^{\frac{1}{2}}\{\widehat{\mathrm{PPV}}\mathbf{z}(t,v)-\mathrm{PPV}\mathbf{z}(t,v)\}=\{\widehat{\mathcal{W}}_{\mathbf{z}1}(t,v)+\widehat{\mathcal{W}}_{\mathbf{z}2}(t,v)\}/(1-v),$$

where

$$\widehat{\mathcal{W}}_{\mathbf{z}1}(t,v)=n^{\frac{1}{2}}\int_{\widehat{c}_{\mathbf{z}}(v)}^{\infty}\left\{e^{-\widehat{\Lambda}_{y,\mathbf{z}}(t)}-e^{-\Lambda_{y,\mathbf{z}}(t)}\right\}d\hat{F}_{Y|z}(y),$$
$$\widehat{\mathcal{W}}_{\mathbf{z}2}(t,v)=n^{\frac{1}{2}}\left\{\int_{\widehat{c}_{\mathbf{z}}(v)}^{\infty}S_{y,\mathbf{z}}(t)d\hat{F}_{Y|z}(y)-\int_{c_{\mathbf{z}}(v)}^{\infty}S_{y,\mathbf{z}}(t)dF_{Y|\mathbf{z}}(y)\right\}.$$

To approximate the distribution of $\widehat{\mathcal{W}}_{\mathbf{z}1}(t,v)$, we again invoke Lemma A.3 of Bilias et al.(1997) and use the fact that $\sup_{t,y}\left|\widehat{\Lambda}_{y,\mathbf{z}}(t)-\Lambda_{y,\mathbf{z}}(t)\right|+\sup_y|\widehat{F}_{Y|\mathbf{z}}(y)-F_{Y|\mathbf{z}}(y)|+\sup_v|\widehat{c}_{\mathbf{z}}(v)-c_{\mathbf{z}}(v)|=o_p(n^{-1/4})$ to obtain

$$\widehat{\mathcal{W}}_{\mathbf{z}1}(t,v)=-n^{\frac{1}{2}}\int_{c_{\mathbf{z}}(v)}^{\infty}S_{y,\mathbf{z}}(t)\left\{\widehat{\Lambda}_{y,\mathbf{z}}(t)-\Lambda_{y,\mathbf{z}}(t)\right\}dF_{Y|\mathbf{z}}(y)+o_p(1).$$

Now, it follows from the asymptotic expansions for $\widehat{\Lambda}_{y,\mathbf{z}}(t)$ given in Dabrowska (1997) that

$$\widehat{\Lambda}_{y,\mathbf{z}}(t)-\Lambda_{y,\mathbf{z}}(t)=\int_0^t\left\{\frac{d\hat{N}_y(s)}{\widehat{\pi}_y(s,\widehat{\boldsymbol{\beta}})}e^{\widehat{\boldsymbol{\beta}}\mathbf{z}}-\frac{d\hat{N}_y(s)}{\widehat{\pi}_y(s,\boldsymbol{\beta}_0)}e^{\beta_0\mathbf{z}}+\frac{d\hat{N}_y(s)}{\widehat{\pi}_y(s,\boldsymbol{\beta}_0)}e^{\beta_0\mathbf{z}}-\frac{dA_y(s)}{\pi_y(s,\boldsymbol{\beta}_0)}e^{\beta_0\mathbf{z}}\right\}$$
$$=\ \mathcal{B}_{\mathbf{z}}(t,y)(\widehat{\boldsymbol{\beta}}-\boldsymbol{\beta}_0)+e^{\beta_0\mathbf{z}}\int_0^t\left[\frac{d\left\{\hat{N}_y(s)-A_y(s)\right\}}{\pi_y(s)}-\frac{\{\widehat{\pi}_y(s)-\pi_y(s)\}\,dA_y(s)}{\pi_y^2(s)}\right]+o_p(n^{-\frac{1}{2}})$$
$$\simeq\ n^{-1}\sum_{i=1}^n\{\mathcal{B}_{\mathbf{z}}(t,y)\mathcal{A}_i+K_h(Y_i-y)M_{y,\mathbf{z}}(t,X_i,\Delta_i,\mathbf{Z}_i)\}+o_p(n^{-\frac{1}{2}})$$

where $A_y(s)=E\{N_i(s)\mid Y_i=y\}dP(Y_i\leqslant y)/dy$ is the limit of $\widehat{N}_y(s)$, $\widehat{\pi}_y(u)=\widehat{\pi}_y(u,\boldsymbol{\beta}_0)$, $\pi_y(u)=\pi_y(u,\boldsymbol{\beta}_0)$, $\mathcal{B}_{\mathbf{z}}(t,y)$ is $\frac{\partial}{\partial\beta}\int_0^t\frac{e^{\beta\mathbf{z}}dA_y(s)}{\pi_y(s,\beta)}$ evaluated at $\boldsymbol{\beta}=\boldsymbol{\beta}_0$, and

$$M_{y,\mathbf{z}}(t,X_i,\Delta_i,\mathbf{Z}_i)=e^{\beta_0\mathbf{z}}\int_0^t\left\{\frac{dN_i(s)}{\pi_y(s)}-\frac{I(X_i\geqslant s)e^{\beta_0\mathbf{Z}_i}dA_y(s)}{\pi_y^2(s)}\right\}.$$

It follows that

$$\widehat{\mathcal{W}}_{\mathbf{z}1}(t,v)\ \simeq\ -n^{-\frac{1}{2}}\sum_{i=1}^n\int_{c_{\mathbf{z}}(v)}^{\infty}S_{y,\mathbf{z}}(t)\left[K_h(y-Y_i)M_{y,\mathbf{z}}(t;X_i,\Delta_i)+\mathcal{B}_{\mathbf{z}}(t,y)\mathcal{A}_i\right]F'_{Y|\mathbf{z}}(y)dy$$

Now, by a change variable $\psi = \frac{y-Y_i}{h}$ and assuming that $nh^4 = o_p(1)$,

$$
\begin{aligned}
& n^{-\frac{1}{2}} h^{-1} \sum_{i=1}^{n} \int_{c_{\mathbf{z}}(v)}^{\infty} K\left(\frac{y-Y_i}{h}\right) S_{y,\mathbf{z}}(t) F'_{Y|\mathbf{z}}(y) M_{y,\mathbf{z}}(t; X_i, \Delta_i, \mathbf{Z}_i) dy \\
= \;& n^{-\frac{1}{2}} \sum_{i=1}^{n} \int_{-\infty}^{\infty} I\left(Y_i + h\psi \geqslant c_{\mathbf{z}}(v)\right) K(\psi) S_{Y_i+h\psi,\mathbf{z}}(t) F'_{Y|\mathbf{z}}(Y_i + h\psi) M_{Y_i+h\psi,\mathbf{z}}(t; X_i, \Delta_i, \mathbf{Z}_i) d\psi \\
= \;& n^{-\frac{1}{2}} \sum_{i=1}^{n} \int_{-\infty}^{\infty} I\left(Y_i \geqslant c_{\mathbf{z}}(v)\right) K(\psi) S_{Y_i,\mathbf{z}}(t) F'_{Y|\mathbf{z}}(Y_i) M_{Y_i,\mathbf{z}}(t; X_i, \Delta_i, \mathbf{Z}_i) d\psi + o_p(1) \\
= \;& n^{-\frac{1}{2}} \sum_{i=1}^{n} I\left(Y_i \geqslant c_{\mathbf{z}}(v)\right) S_{Y_i,\mathbf{z}}(t) F'_{Y|\mathbf{z}}(Y_i) M_{Y_i,\mathbf{z}}(t; X_i, \Delta_i, \mathbf{Z}_i) + o_p(1)
\end{aligned}
$$

Therefore, $\widehat{\mathcal{W}}_{\mathbf{z}1}(t,v) = -n^{-\frac{1}{2}} \sum_{i=1}^{n} \xi_{i1}(t,v,\mathbf{z}) + o_p(1)$, where

$$\xi_{i1}(t,v,\mathbf{z}) = I(Y_i \geqslant c_{\mathbf{z}}(v)) S_{Y_i,\mathbf{z}}(t) F'_{Y|\mathbf{z}}(Y_i) M_{Y_i,\mathbf{z}}(t; X_i, \Delta_i, \mathbf{Z}_i) + \mathcal{A}_i \int_{c_{\mathbf{z}}(v)}^{\infty} S_{y,\mathbf{z}}(t) \mathcal{B}_{\mathbf{z}}(t,y) F'_{Y|\mathbf{z}}(y) dy.$$

On the other hand, the process $\widehat{\mathcal{W}}_{\mathbf{z}2}(t,v)$ can be approximated by $n^{-\frac{1}{2}} \sum_{i=1}^{n} \zeta_{i2}(t,v,\mathbf{z})$ as for $\widetilde{\mathcal{W}}_{\mathbf{z}2}(t,v)$. Hence,

$$\widehat{\mathcal{W}}_{\mathbf{z}1}(t,v) = n^{-\frac{1}{2}} \sum_{i=1}^{n} \xi_i(t,v,\mathbf{z}) + o_p(1)$$

where $\xi_i(t,v,\mathbf{z}) = \xi_{i1}(t,v,\mathbf{z}) + \zeta_{i2}(t,v,\mathbf{z})$. This, together with a functional central limit theorem, implies that $\widehat{\mathcal{W}}_{\mathbf{z}}(t,v)$ converges weakly to a zero-mean Gaussian process.

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