Sankhya B (May 2011) 73:81–104
DOI 10.1007/s13571-011-0020-1

Semiparametric estimation of quality adjusted lifetime distribution in semi-Markov illness–death model

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Received: 9 September 2010 / Revised: 9 February 2011 / Accepted: 23 February 2011 /
Published online: 29 June 2011
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Abstract In this work, we consider semiparametric estimation of quality adjusted lifetime (QAL) distribution using Cox proportional hazards model for the sojourn time in each health state. The regression coefficients are estimated by maximizing the corresponding partial likelihood and the baseline cumulative hazards are estimated by using the method of Breslow (Biometrics 30:89–99, 1974). The estimate of QAL distribution is obtained by using these estimates in the theoretical expression of QAL distribution. The asymptotic normality of the proposed estimator is established. The performance of the proposed estimator is studied using Monte Carlo simulation. A real data example of the Stanford Heart Transplant Program is used to illustrate the proposed method. Extension to a general model is also discussed and illustrated with an analysis of International Breast Cancer Study Group (IBCSG) Trial V data.

Keywords Breslow estimator · Gaussian process · Quality adjusted lifetime · Proportional hazard model · Weak convergence

AMS 2000 Subject Classifications 62N02 · 62F12

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1 Introduction

Quality adjusted lifetime is a composite measure, which incorporates both quality and duration of life. This composite measure introduced by Goldhirsch et al. (1989), is used as an end point in many clinical trials when a patient passes through different health states, each of which is associated with a utility coefficient ranging from zero to one. The utility coefficient corresponding to a state reflects the quality of life in this state, which assumes the value 1 in the perfectly healthy state while taking value 0 in the absorbing state death. This leads to a utility function over time which takes the value of the utility coefficient of the state occupied at that time. Then, quality adjusted lifetime (QAL) is defined as the integration of the utility function over the survival duration. The number of health state is usually finite. Then, the QAL reduces to a weighted sum of the time spent in each health state.

There have been a number of works developing methods for estimating either mean QAL (Hwang et al. 1996; Huang and Louis 1999; Zhao and Tsiatis 2000) or the distribution of QAL (Korn 1993; Zhao and Tsiatis 1997, 1999; Huang and Louis 1998; van der Laan and Hubbard 1999; Pradhan et al. 2010; Pradhan and Dewanji 2009a, b, 2010). In contrast, regression analysis of QAL data has not received much attention. Cole et al. (1993) have considered a Cox-type parametric regression model to estimate mean QAL using the bootstrap method to obtain the variance estimate. Wang and Zhao (2007) have considered the problem of estimating the mean QAL in the presence of covariates. They have considered a regression model for the mean QAL and used the idea of inverse probability weighting to construct a simple weighted estimating equation for the regression parameters of the model. These parameter estimates are then used to estimate the mean QAL. See also Tunes-da-Silva et al. (2009) for a similar regression analysis to estimate mean QAL for semi-Markov multistate non-progressive processes. Pradhan et al. (2010) have considered parametric regression analysis to estimate the QAL distribution for a given covariate value. In this work, we propose a semi-parametric approach to estimate the QAL distribution using proportional hazards model under semi-Markov assumption. Although we develop the methodology for a simple three-state illness–death model, this can be generalized to other progressive illness–death models. In addition to estimating the QAL distributions, an additional objective is to assess the covariate effects.

In our approach, we write down the theoretical expression for the QAL distribution in terms of the sojourn time distributions in each health state. Hazard rates for these sojourn times are modeled using Cox's proportional hazards regression (Cox 1972). The semi-Markov assumption leading to independence between different sojourn times allows construction of partial likelihood for each transition type. This gives maximum partial likelihood estimates of the regression parameters and, then, the baseline cumulative hazards are estimated using the method of Breslow (1974). Therefore, as in Pradhan et al. (2010) and Pradhan and Dewanji (2010), the baseline sojourn time distributions in different states and the regression parameters are estimated by using the standard techniques of survival analysis. These estimates are then substituted in the theoretical expression for the QAL distribution, for a given covariate value, to obtain the corresponding estimate. By construction, this method gives a monotonic estimate of the QAL distribution. Since this method explicitly uses the information on the interrelationship between the different health states, the corresponding estimates are efficient, but less robust against misspecification of such information.

The simple three-state illness–death model is discussed in Section 2. Estimation of the regression parameters and the QAL distribution for a given covariate value is considered in Section 3 and the asymptotic properties are also discussed. A simulation study is carried out in Section 4. We illustrate the methodology by means of an example of heart transplant data in Section 5. Extension to more general model is considered in Section 6 and the method is illustrated by means of an example of IBCSG Trial V data. Section 7 ends with some concluding remarks.

2 The model

In the simple three-state illness–death model, as shown in Fig. 1, one starts in a normal healthy state 0 from which the possible transitions are to the illness state 1 followed by transition to death (state 2), the absorbing state, or directly from state 0 to state 2. Let T_0 be the sojourn time in state 0, that is the time to illness (transition to state 1) or death without illness (transition to state 2), whichever occurs first. Also, let δ_0 be the failure type indicator, which takes the values 1 and 2 for illness and death without illness, respectively. Also, let T_{12} denote the sojourn time in state 1 before moving to state 2. Then, the QAL is defined by

$$Q = \begin{cases} w_0 T_0 + w_1 T_{12} & \text{if } \delta_0 = 1 \\ w_0 T_0 & \text{if } \delta_0 = 2, \end{cases}$$

where w_0 and w_1 are the utility coefficients in state 0 and 1, respectively.

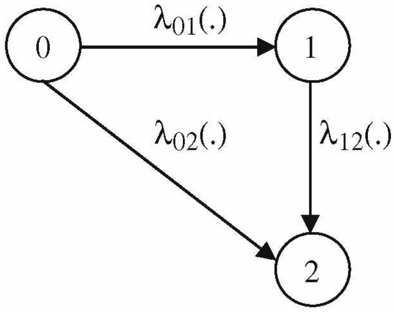

Fig. 1 Three-state illness–death model

Let $\lambda_{hj}(\cdot;\cdot)$ be the rate of the $h \to j$ transition. We assume that the transition rates depend only on the sojourn time in the current state (a semi-Markov model) which implies that T_0 and T_{12} are independent. The dependence of the transition rates on the covariates are specified via Cox's proportional hazards regression model (Cox 1972), as given by

$$\lambda_{hj}(t; \mathbf{Z}_i) = \lambda_{hj0}(t) \exp\left(\beta^T \mathbf{Z}_{hji}\right), \text{for } hj = 01, 02, 12, \text{and } i = 1, \ldots, n, \quad (1)$$

where $\lambda_{hj0}(t)$ is the arbitrary baseline rate for the $h \to j$ transition, $\beta = (\beta_1, \ldots, \beta_p)$ is the vector of regression coefficients and $\mathbf{Z}_{hji}$ is the vector of state-specific covariates for individual i obtained from the basic covariates $\mathbf{Z}_i$. It may be noted that β contains all the parameters corresponding to different transitions, therefore, not depending on the specific transition hj (see Andersen et al. 1993, p. 478). In the heart transplant data (see Section 4), for example, let $\mathbf{Z}_i = (Z_i^{(1)}, Z_i^{(2)}, Z_i^{(3)})^T$, where $Z_i^{(1)}$ = an indicator for previous history of surgery, $Z_i^{(2)}$ = age at acceptance into the program and $Z_i^{(3)}$ = mismatch score. Note that the mismatch score is available after heart transplantation. Hence, it has possible effect on T_{12} only. The state-specific covariate vector $\mathbf{Z}_{hji}$ for individual i is, therefore, formed to be a 7-variate vector by including the extra components equal to zero . We have $\mathbf{Z}_{01i} = (Z_i^{(1)}, Z_i^{(2)}, 0, 0, 0, 0, 0)$, $\mathbf{Z}_{02i} = (0, 0, Z_i^{(1)}, Z_i^{(2)}, 0, 0, 0)$ and $\mathbf{Z}_{12i} = (0, 0, 0, 0, Z_i^{(1)}, Z_i^{(2)}, Z_i^{(3)})$.

The survival function for a given covariate $\mathbf{Z}_0$, with state-specific covariate $\mathbf{Z}_{hj0}$, is given by (Pradhan and Dewanji 2010)

$$S_Q(q; \mathbf{Z}_0) = S_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right) + P_{12}\left(\frac{q}{w_0}; \mathbf{Z}_0\right), \quad (2)$$

where $S_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right) = \exp\left[-\Lambda_{01}\left(\frac{q}{w_0}; \mathbf{Z}_0\right) - \Lambda_{02}\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\right]$, the survival function of T_0 for given $\mathbf{Z}_0$, and $P_{12}\left(\frac{q}{w_0}; \mathbf{Z}_0\right) = \int_0^{q/w_0} S_{12}\left(\frac{q - w_0 x}{w_1}; \mathbf{Z}_0\right) S_0(x; \mathbf{Z}_0) d\Lambda_{01}(x; \mathbf{Z}_0)$ with $\Lambda_{hj}(x; \mathbf{Z}_0) = \int_0^x \lambda_{hj}(u; \mathbf{Z}_0) du$, for $hj = 01$, 02 and 12, and $S_{12}(\cdot, \mathbf{Z}_0) = \exp[-\Lambda_{12}(\cdot; \mathbf{Z}_0)]$ being the survival function of T_{12} for given $\mathbf{Z}_0$.

It may be noted that the semi-Markov model does not fit readily into the multiplicative intensity framework because of its renewal nature (see Voelkel and Crowley 1984; Shu et al. 2007). This can be dealt with by introducing time-shifted multivariate counting process over a fixed interval, say $[0, \tau]$, given by

$$\mathbf{N}(x) = \left\{N_{hji}(x), hj = 01, 02, 12;\ i = 1, \ldots, n, x \in [0, \tau]\right\},$$

where $N_{hji}(x)$ counts the number of $h \to j$ transitions for individual i whose transition time from state h to state j is less than or equal to x, for $hj = 01, 02$ and 12. Note that such formulated counting process $N_{hji}(x)$ have the intensity processes $\alpha_{hji}(x; \mathbf{Z}_i)$ in the form of a multiplicative intensity model given by

$$\alpha_{hji}(x; \mathbf{Z}_i) = Y_{hi}(x)\lambda_{hj}(x; \mathbf{Z}_i), \quad (3)$$

with $\lambda_{hj}(x; \mathbf{Z}_i)$ given by Eq. 1, where $Y_{hi}(x)$ is the indicator for individual i being at risk just before sojourn time x in the state h, for $h = 0, 1$. That is, $Y_{hi}(x) = 1$ if the sojourn time of the ith individual in state h is larger than or equal to x, and 0 otherwise. Under independent censoring, $N_{hji}(x)$ can be uniquely decomposed as

$$N_{hji}(x) = \int_0^x Y_{hi}(u) \exp\left(\beta^T \mathbf{Z}_{hji}\right) \lambda_{hj0}(u) du + M_{hji}(x),$$

where $M_{hji}(x)$ are orthogonal local square-integrable martingales with predictable variation process given by $\langle M_{hji}(x) \rangle = \int_0^x Y_{hi}(u) \exp\left(\beta^T \mathbf{Z}_{hji}\right) \lambda_{hj0}(u) du$. For convenience, we use the following notation (Shu et al. 2007):

$$S_{hj}^{(m)}(\beta, x) = \sum_{i=1}^n Y_{hi}(x) \mathbf{Z}_{hji}^{\otimes m} \exp\left(\beta^T \mathbf{Z}_{hji}\right) \text{ and } E_{hj}(\beta, x) = \frac{S_{hj}^{(1)}(\beta, x)}{S_{hj}^{(0)}(\beta, x)},$$

for $m = 0, 1, 2$ and $hj = 01, 02, 12$, where for a column vector a, $a^{\otimes 0} = 1$, $a^{\otimes 1} = a$ and $a^{\otimes 2} = aa^T$.

3 Estimation and asymptotic theory

In this section, we consider the estimation of β, the cumulative baseline hazards and the survival function $S_Q(\cdot, \mathbf{Z}_0)$. Let C be the censoring random variable. Define $X_0 = \min(T_0, C)$ and let $\delta_0 = 0$ indicate censoring (i.e., $T_0 > C$). When $\delta_0 = 1$, let $X_1' = \min(T_0 + T_{12}, C)$ and $\delta_1 = I(T_0 + T_{12} < C)$. Define $X_1 = X_1' - X_0$, when $\delta_0 = 1$. It is clear that if $\delta_0 = 0$ or 2, then X_1' (and hence X_1) and δ_1 are not defined. For n individuals, we have the data set $\{(x_{0i}, \delta_{0i}, x_{1i}, \delta_{1i}, \mathbf{Z}_{01i}, \mathbf{Z}_{02i}, \mathbf{Z}_{12i}); i = 1, \ldots, n\}$, where $x_{1i} = \delta_{1i} = -1$, whenever $\delta_{0i} = 0$ or 2, to represent their non-existence. The partial likelihood (see Andersen et al. 1993, pp. 481–482) to estimate β is given by

$$L(\beta) = \prod_{hj} \prod_i \left(\frac{\exp(\beta^T Z_{hji})}{S_{hj}^{(0)}(\beta, x_{hi})} \right)^{\eta_{hji}},$$

where $\eta_{01i} = I(\delta_{0i} = 1)$, $\eta_{02i} = I(\delta_{0i} = 2)$ and $\eta_{12i} = I(\delta_{1i} = 1)$. The corresponding information matrix is given by

$$\mathcal{I}(\beta) = \sum_{hj} \int_0^\infty \left\{ \frac{S_{hj}^{(2)}(\beta, x)}{S_{hj}^{(0)}(\beta, x)} - E_{hj}(\beta, x)^{\otimes 2} \right\} dN_{hj}(x).$$

Let $\hat{\beta}$ be the estimate of β obtained by maximizing $L(\beta)$. Then the cumulative hazards $\Lambda_{hj}(t, \mathbf{Z}_0)$ are estimated as $\hat{\Lambda}_{hj}(t, \mathbf{Z}_0) = \hat{\Lambda}_{hj0}(t, \hat{\beta}) \exp(\hat{\beta}^T \mathbf{Z}_{hj0})$, where $\hat{\Lambda}_{hj0}(t, \hat{\beta})$ is the Breslow (1974) estimator of $\Lambda_{hj}(t)$, for $hj = 01, 02$ and 12. Also the survival functions for given $\mathbf{Z}_0$, $S_0(t; \mathbf{Z}_0)$ and $S_{12}(t; \mathbf{Z}_0)$ for T_0 and T_{12}, respectively, are estimated by

$$\hat{S}_0(t; \mathbf{Z}_0) = \prod_{u<t} \left\{1 - d\hat{\Lambda}_{01}(u; \mathbf{Z}_0) - d\hat{\Lambda}_{02}(u; \mathbf{Z}_0)\right\}, \text{ and} \quad (4)$$

$$\hat{S}_{12}(t; \mathbf{Z}_0) = \prod_{u<t} \left\{1 - d\hat{\Lambda}_{12}(u; \mathbf{Z}_0)\right\}. \quad (5)$$

Then, using Eq. 2, an estimate of $S_Q(q; \mathbf{Z}_0)$ is given by

$$\begin{aligned} \hat{S}_Q(q; \mathbf{Z}_0) &= \hat{S}_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right) + \hat{P}_{12}\left(\frac{q}{w_0}; \mathbf{Z}_0\right) \\ &= \hat{S}_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right) \\ &\quad + \int_0^{\frac{q}{w_0}} \hat{S}_{12}\left(\frac{q - w_0 x}{w_1}; \mathbf{Z}_0\right) \hat{S}_0(x; \mathbf{Z}_0) d\hat{\Lambda}_{01}(x; \mathbf{Z}_0). \end{aligned} \quad (6)$$

Note that the two product-limit estimators $\hat{S}_0(u; \mathbf{Z}_0)$ and $\hat{S}_{12}(u; \mathbf{Z}_0)$ are approximately equal to the corresponding ones derived from the Breslow estimators, given by $\exp\left[-\hat{\Lambda}_{01}(u; \mathbf{Z}_0) - \hat{\Lambda}_{02}(u; \mathbf{Z}_0)\right]$ and $\exp\left[-\hat{\Lambda}_{12}(u; \mathbf{Z}_0)\right]$, respectively. For the derivation of asymptotic results, the latter estimators of $S_0(u; \mathbf{Z}_0)$ and $S_{12}(u; \mathbf{Z}_0)$ are considered for some algebraic convenience. Let $\theta \in [0, \tau)$. Following Shu et al. (2007) and under the regularity conditions 1–3 therein, we have the following theorems. The proofs of the theorems are given in the Appendix.

Theorem 1 *The random vector $\sqrt{n}(\hat{\beta} - \beta)$ converges weakly to a multivariate normal with mean zero and a covariance matrix which can be consistently estimated by $n\mathcal{I}(\hat{\beta})^{-1}$.*

Theorem 2 *The process $\sqrt{n}\left[\hat{S}_0(\cdot, \mathbf{Z}_0) - S_0(\cdot, \mathbf{Z}_0)\right]$ converges weakly on $[0, \theta]$ to a zero-mean Gaussian process whose variance at q/w_0 can be estimated uniformly consistently by*

$$\begin{aligned} \hat{\psi}^{(0)}\left(\frac{q}{w_0}; \mathbf{Z}_0\right) &= \widehat{Q}^{(0)}\left(\frac{q}{w_0}, \hat{\beta}\right)^T n\mathcal{I}(\hat{\beta})^{-1} \widehat{Q}^{(0)}\left(\frac{q}{w_0}, \hat{\beta}\right) \\ &\quad + n\left\{\hat{S}_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\right\}^2 \left\{\exp(\hat{\beta}^T \mathbf{Z}_{010})\right\}^2 \int_0^{\frac{q}{w_0}} \frac{d\hat{\Lambda}_{010}(u, \hat{\beta})}{S_{01}^{(0)}(\hat{\beta}, u)} \\ &\quad + n\left\{\hat{S}_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\right\}^2 \left\{\exp(\hat{\beta}^T \mathbf{Z}_{020})\right\}^2 \int_0^{\frac{q}{w_0}} \frac{d\hat{\Lambda}_{020}(u, \hat{\beta})}{S_{02}^{(0)}(\hat{\beta}, u)}, \end{aligned} \quad (7)$$

where

$$\widehat{Q}^{(0)}\left(\frac{q}{w_0},\hat{\beta}\right)=-\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\left[\int_0^{\frac{q}{w_0}}\{\mathbf{Z}_{010}-E_{01}(\hat{\beta},u)\}\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(u,\hat{\beta})\right.$$
$$\left.+\int_0^{\frac{q}{w_0}}\{\mathbf{Z}_{020}-E_{02}(\hat{\beta},u)\}\exp(\hat{\beta}^T\mathbf{Z}_{020})d\hat{\Lambda}_{020}(u,\hat{\beta})\right].$$

Theorem 3 *The process* $\sqrt{n}\left[\hat{P}_{12}(\cdot,\mathbf{Z}_0)-P_{12}(\cdot,\mathbf{Z}_0)\right]$ *converges weakly on* $[0,\theta]$ *to a zero-mean Gaussian process whose variance at* q/w_0 *can be estimated uniformly consistently by* $\hat{\psi}^{(12)}\left(\frac{q}{w_0};\mathbf{Z}_0\right)$

$$=\widehat{Q}^{(12)}\left(\frac{q}{w_0},\hat{\beta}\right)^T n\mathcal{I}(\hat{\beta})^{-1}\widehat{Q}^{(12)}\left(\frac{q}{w_0},\hat{\beta}\right)$$
$$+n\int_0^{\frac{q}{w_0}}\left[\hat{S}_0(u;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right)-\int_u^{\frac{q}{w_0}}\left\{\hat{S}_0(x;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)\right.\right.$$
$$\left.\left.\times\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})\right\}\right]^2\times\left\{\exp\left(\hat{\beta}^T\mathbf{Z}_{010}\right)\right\}^2\frac{d\hat{\Lambda}_{010}(u,\hat{\beta})}{S_{01}^{(0)}(\hat{\beta},u)}$$
$$+n\int_0^{\frac{q}{w_0}}\left\{\int_u^{\frac{q}{w_0}}\hat{S}_0(x;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})\right\}^2$$
$$\times\left\{\exp\left(\hat{\beta}^T\mathbf{Z}_{020}\right)\right\}^2\frac{d\hat{\Lambda}_{020}(u,\hat{\beta})}{S_{02}^{(0)}(\hat{\beta},u)}$$
$$+n\int_0^{\frac{q}{w_1}}\left\{\int_0^{\frac{q-w_1u}{w_0}}\hat{S}_0(x;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})\right\}^2$$
$$\times\left\{\exp\left(\hat{\beta}^T\mathbf{Z}_{120}\right)\right\}^2\frac{d\hat{\Lambda}_{120}(u,\hat{\beta})}{S_{12}^{(0)}(\hat{\beta},u)},\qquad(8)$$

where

$$\widehat{Q}^{(12)}\left(\frac{q}{w_0},\hat{\beta}\right)=\int_0^{\frac{q}{w_0}}\hat{S}_0(u;\mathbf{Z}_0)\hat{S}_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right)$$
$$\times\left[\left\{\mathbf{Z}_{010}-E_{01}(\hat{\beta},u)\right\}-\int_0^u\left\{\mathbf{Z}_{010}-E_{01}(\hat{\beta},x)\right\}\right.$$
$$\times\exp(\hat{\beta}^T\mathbf{Z}_{010})d\hat{\Lambda}_{010}(x,\hat{\beta})$$

$$- \int_0^u \left\{ \mathbf{Z}_{020} - E_{02}(\hat\beta, x) \right\} \exp\left(\hat\beta^T \mathbf{Z}_{020}\right) d\hat\Lambda_{020}(x, \hat\beta)$$

$$\left. - \int_0^{\frac{q - w_0 u}{w_1}} \left\{ \mathbf{Z}_{120} - E_{12}(\hat\beta, x) \right\} \exp\left(\hat\beta^T \mathbf{Z}_{120}\right) d\hat\Lambda_{120}(x, \hat\beta) \right]$$

$$\times \exp\left(\hat\beta^T \mathbf{Z}_{010}\right) d\hat\Lambda_{010}\left(u, \hat\beta\right).$$

Theorem 4 $\sqrt{n}\left[\hat S_Q(q; \mathbf{Z}_0) - S_Q(q; \mathbf{Z}_0)\right]$ *converges weakly to a mean zero Gaussian process in* $[0, \theta_w]$*, where* $\theta_w < \tau w_0$ *is a constant, with a variance at* q *which can be estimated uniformly consistently by*

$$\hat\psi(q, \mathbf{Z}_0) = \hat\psi^{(0)}\left(\frac{q}{w_0}; \mathbf{Z}_0\right) + \hat\psi^{(12)}\left(\frac{q}{w_0}; \mathbf{Z}_0\right)$$
$$+ 2\widehat{\mathrm{cov}}\left\{\sqrt{n}\hat S_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right), \sqrt{n}\hat P_{12}\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\right\}, \qquad (9)$$

where

$$\widehat{\mathrm{cov}}\left\{\sqrt{n}\hat S_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right), \sqrt{n}\hat P_{12}\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\right\}$$

$$= \widehat{Q}^{(0)}\left(\frac{q}{w_0}, \hat\beta\right)^T n\mathcal{I}(\hat\beta)^{-1} \widehat{Q}^{(12)}\left(\frac{q}{w_0}, \hat\beta\right) - n\hat S_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\left\{\exp(\hat\beta^T \mathbf{Z}_{010})\right\}^2$$

$$\times \int_0^{\frac{q}{w_0}} \left\{ \hat S_0(u; \mathbf{Z}_0) \hat S_{12}\left(\frac{q - w_0 u}{w_1} | \mathbf{Z}_0\right) - \int_u^{\frac{q}{w_0}} \hat S_0(x; \mathbf{Z}_0) \hat S_{12}\left(\frac{q - w_0 x}{w_1}; \mathbf{Z}_0\right)\right.$$

$$\left. \times \exp(\hat\beta^T \mathbf{Z}_{010}) d\hat\Lambda_{010}(x, \hat\beta) \right\} \frac{d\hat\Lambda_{010}(u, \hat\beta)}{S_{01}^{(0)}(\hat\beta, u)}$$

$$+ n\hat S_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\left\{\exp\left(\hat\beta^T \mathbf{Z}_{020}\right)\right\}^2$$

$$\times \int_0^{\frac{q}{w_0}} \left\{ \int_u^{\frac{q}{w_0}} \hat S_0(x; \mathbf{Z}_0) \hat S_{12}\left(\frac{q - w_0 x}{w_1}; \mathbf{Z}_0\right) \exp(\hat\beta^T \mathbf{Z}_{010}) d\hat\Lambda_{010}(x, \hat\beta) \right\}$$

$$\times \frac{d\hat\Lambda_{020}(u, \hat\beta)}{S_{02}^{(0)}(\hat\beta, u)}. \qquad (10)$$

4 Simulation study

In this section we investigate finite sample properties of the proposed semi-parametric estimator of the QAL distribution by simulation. In particular, we study the bias and precision of the proposed estimator, given by Eq. 6, for a number of QAL values. In our simulation study, we consider only one covariate effect, say, Z. It is assumed that the sojourn times T_{01}, T_{02} and T_{12} are independent. The hazard rates of the sojourn times are modelled by

$$\lambda_{hj}(t;\, Z_i) = \lambda_{hj} \exp\left(\beta^T Z_{hj}\right), \text{ for } hj = 01, 02, 12 \text{ and } i = 1, \ldots, n,$$

where $\beta = (\beta_{01}, \beta_{02}, \beta_{12})$, $\mathbf{Z}_{01i} = (Z_i, 0, 0)$, $\mathbf{Z}_{02i} = (0, Z_i, 0)$ and $\mathbf{Z}_{12i} = (0, 0, Z_i)$.

The censoring variable C is assumed to be independent of sojourn time variables and follow exponential distribution with parameter λ_c. We consider two sets of parameter values for the simulation study. In parameter set 1, we take $\lambda_{01} = 0.04$, $\lambda_{02} = 0.05$, $\lambda_{12} = 0.08$, $\beta_{01} = 1.5$, $\beta_{02} = 0.5$, $\beta_{12} = 0.8$ and $\lambda_c = 0.035$. Here we generate covariate Z from $N(0, 1)$. The survival probabilities $S_Q(q;\, Z_0)$ are computed for $Z_0 = 0.5$ by taking $w_0 = 1$ and $w_1 = 0.5$ for different q-values. In parameter set 2, we choose $\lambda_{01} = 0.04$, $\lambda_{02} = 0.05$, $\lambda_{12} = 0.06$, $\lambda_c = 0.03$, $\beta_{01} = 1$, $\beta_{02} = 0$, $\beta_{12} = 0.5$. We generate covariate Z from a Bernoulli distribution with probability of success $p = 0.5$. The survival probabilities $S_Q(q;\, Z_0)$ are computed for $Z_0 = 1$ by taking $w_0 = 1$ and $w_1 = 0.6$ for different q-values. The two sets of parameters depict different scenarios with respect to covariates, regression coefficients and censoring percentage. The censoring percentages corresponding to two sets are 56 and 33, respectively.

For each set of simulated data, we generate n observations of the form as in the beginning of Section 3 and calculate the proposed semi-parametric estimate of the QAL distribution using Eq. 6 for some q values. The standard error is calculated using Eq. 9. The simulation is repeated 1,000 times for sample size $n = 100$ and 200. Based on 1,000 estimates of $S_Q(q;\, \mathbf{Z}_0)$, we compute average bias and sample standard error (SSE). The standard errors for the estimated survival probabilities, obtained by using Eq. 9 for the proposed estimator, are averaged over the 1,000 simulations. These are similar to the corresponding SSE values and, hence, not reported. The simulation results are reported in Table 1. As expected, both bias and standard error decrease with sample size.

Table 1 The average bias (*AB*) and sample standard error (*SSE*) in parentheses of the regression coefficients and survival probabilities for two sets of parameter values with sample sizes $n = 100$ and 200

Parameter	n	Regression coefficients		Survival probability			
set		β	AB (SSE)	q	z_0	$S_Q(q;\, Z_0)$	AB (SSE)
1	100	$\beta_{01} = 1.5$	0.038 (0.263)	1.5	0.5	0.895	0.002 (0.032)
	200		0.011 (0.163)				0.000 (0.022)
	100	$\beta_{02} = 0.5$	0.007 (0.216)	7		0.508	0.004 (0.060)
	200		−0.003 (0.158)				0.003 (0.042)
	100	$\beta_{12} = 0.8$	0.031 (0.299)	16		0.159	0.013 (0.050)
	200		0.013 (0.193)				0.008 (0.036)
2	100	$\beta_{01} = 1$	0.024 (0.324)	1.7	1	0.904	0.000 (0.030)
	200		0.022 (0.232)				0.000 (0.021)
	100	$\beta_{02} = 0$	−0.013 (0.371)	8.2		0.509	0.003 (0.062)
	200		0.008 (0.262)				0.001 (0.046)
	100	$\beta_{12} = 0.5$	0.021 (0.413)	19		0.145	0.009 (0.048)
	200		0.011 (0.284)				0.004 (0.036)

The asymptotic normality of the proposed estimators is checked by QQ plot based on 1,000 estimates. The QQ plots, not presented here, gives evidence in favour of asymptotic normality.

5 Analysis of heart transplant data

We use the Stanford Heart Transplant data (Crowley and Hu 1977) to illustrate the proposed estimate of QAL distribution with covariate effect. Patients have been admitted to the heart transplant program, from September 1967 to March 1974. Here we are interested in the quality adjusted life of heart patients. There have been 103 patients altogether. Out of the 103 patients, 69 patients have received heart transplantation, 30 patients have died before getting a suitable heart transplantation and four patients have been lost to follow up before transplantation. Out of the 69 patients with heart transplantation, 24 have been alive when last seen and the remaining 45 have been dead. For each patient, the date of acceptance into the Stanford program and the date seen last are available along with the date of transplantation, if carried out. We view this as an illness–death model by equating the event of heart transplantation with the incidence of illness. Here T_0 is the time, since acceptance into the program, of heart transplantation or death before transplantation, whichever is earlier, and T_{12} is the time till death since heart transplantation. As mentioned in Section 2, the covariates we consider are indicator for previous history of surgery ($Z^{(1)}$), age at acceptance ($Z^{(2)}$) and mismatch score ($Z^{(3)}$). The mismatch score is available after heart transplantation. So $Z^{(3)}$ may have effect on T_{12} only. Let $\beta = (\beta_{011}, \beta_{012}, \beta_{021}, \beta_{022}, \beta_{121}, \beta_{122}, \beta_{123})'$ be the vector of regression coefficients. Out of 103 patients, all the covariate values are available for 99 patients. So the analysis is based on 99 patients. The estimates of the regression coefficients along with standard errors and p-values are presented in Table 2. From Table 2, it is clear that only age at acceptance ($Z^{(2)}$) has significant effect on the hazards of 01 and 12 transitions.

One can easily estimate the survival probabilities for QAL using Eq. 6 and the estimates given in Table 2 for a particular value of **Z**. The standard error is calculated by using Eq. 9. We take the coefficient w_0 for the sojourn time T_0 as 0.3 and, assuming that the heart transplantation improves the quality of

Table 2 Estimates of the regression coefficients for the heart transplant data

Transition	Parameters	Estimate	Standard error	p-value
01	β_{011}	0.1333	0.3224	0.680
	β_{012}	0.0313	0.0142	0.028
02	β_{021}	−0.4784	0.6137	0.440
	β_{022}	0.0149	0.0183	0.410
12	β_{121}	−0.7620	0.4858	0.120
	β_{122}	0.0520	0.0225	0.021
	β_{123}	0.5163	0.2957	0.081

life to some extent, take the coefficient w_1 for the sojourn time T_{12} as 0.8, as in Pradhan et al. (2010). For example, with $Z^{(1)} = 0$, $Z^{(2)} = 45$ and $Z^{(3)} = 1.5$, the survival probability $S_Q(q)$ at $q = 10$ is estimated as 0.7819 with standard error 0.0333.

In order to study the effect of covariate on the QAL distribution, we compare the estimated survival probabilities for different covariate values by graphical method. To show the effect of previous surgery, we plot the estimated survival probabilities for $Z^{(1)} = 0$ and $Z^{(1)} = 1$, keeping $Z^{(2)} = 45$ and $Z^{(3)} = 1.5$ as fixed (see Fig. 2a). To study the effect of age, we plot the estimated survival probabilities for $Z^{(2)} = 30$ and $Z^{(2)} = 45$, keeping $Z^{(1)} = 0$ and $Z^{(3)} = 1.5$ as fixed (see Fig. 2b). Similarly, to study the effect of mismatch score, we plot the estimated survival probabilities for $Z^{(3)} = 0.75$ and $Z^{(3)} = 1.5$, keeping $Z^{(1)} = 0$ and $Z^{(2)} = 45$ as fixed (see Fig. 2c).

Although $Z^{(1)}$ has no effect on the hazards of different transitions, the estimated survival curves indicate some difference. The age at acceptance has significant effect on hazards of different transitions and the two QAL

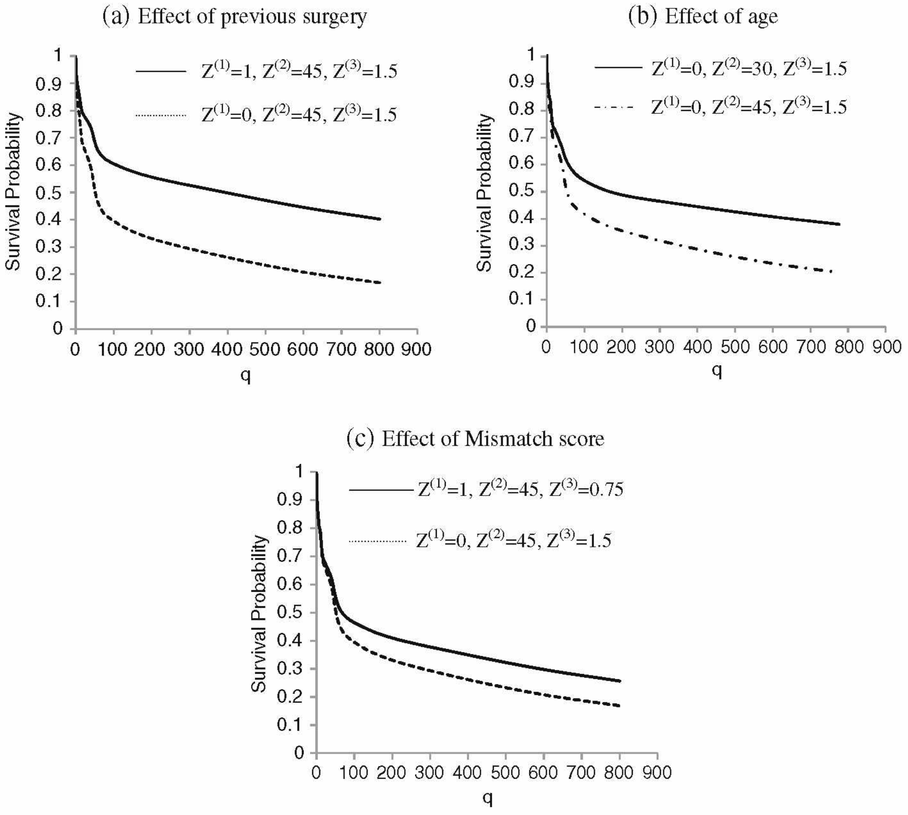

Fig. 2 Effect of covariates on the QAL distribution for the heart transplant data

distributions corresponding to age 30 and 45 also show the difference. The mismatch score has no significant effect on the hazard and the two QAL distributions corresponding to mismatch score 0.75 and 1.50 seem to have no difference. In order to compare two survival curves corresponding to two different values of a particular covariate, we have looked at 95% confidence intervals for the corresponding survival probabilities at several q values. For all the three comparisons, as shown in Fig. 2, all the intervals are found to be overlapping. This indicates that there is no significant difference on the QAL distribution for the choices of covariate values, even though age at acceptance has significant effect on the hazards of 01 and 12 transitions. A more objective test in this regard is necessary.

6 Extension to progressive illness–death model

In this section, we consider estimation of QAL distribution with covariate effect for the progressive illness–death model as described in Fig. 3. Let $T_{h,h+1}$ denote the conceptual sojourn time in state h before moving to the illness state $h+1$ and $T_{h,k+1}$ denote the same before moving directly to the absorbing state $k+1$, for $h = 0, 1, \ldots, k-1$. Also, let $T_{k,k+1}$ denote the sojourn time in the penultimate state k before moving to the next state $k+1$. Then, the QAL is given by $Q = \sum_{h=0}^{m-1} w_h T_{h,h+1} + w_m T_{m,k+1}$, when transition to death $k+1$ occurs from the state m, for $m = 1, \ldots, k$. For m=0, $Q = w_0 T_{0,k+1}$. Note that, with $m(\geq 1)$ fixed, we have $T_{h,h+1} < T_{h,k+1}$, for $h = 0, 1, \ldots, m-1$, and $T_{m,m+1} > T_{m,k+1}$ (except for $m = k$). With $m = 0$, $T_{01} > T_{0,k+1}$.

We estimate the QAL distribution under the assumption that the different sojourn times are independently distributed. It may be noted that the transition from state h to either state $h+1$ or to state $k+1$, for $h = 0, 1, \ldots, k-1$, constitutes a competing risks framework with $T_{h,h+1}$ and $T_{h,k+1}$ denoting the two corresponding conceptual sojourn times. Let $\lambda_{h,h+1}(x_h; \mathbf{Z})$ and $\lambda_{h,k+1}(x_h; \mathbf{Z})$ be

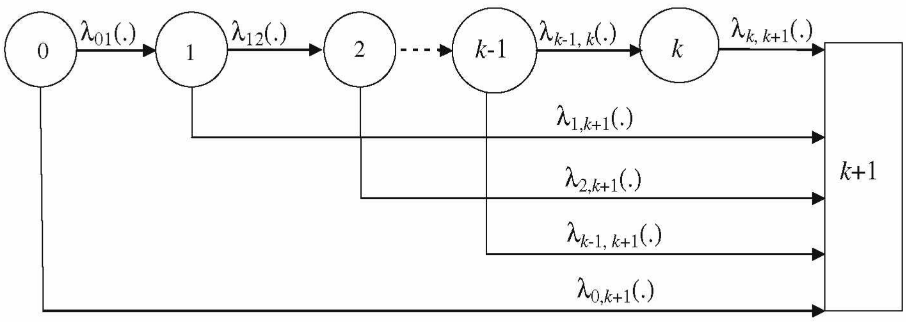

Fig. 3 Progressive illness–death model

the cause specific hazards for the two possible transitions to state $h+1$ or $k+1$, respectively, at time x_h for an individual with covariate vector $\mathbf{Z}$. Note that, for $h=k$, $T_{h,h+1}$ and $T_{h,k+1}$ are the same random variable representing the actual sojourn time in state k before death with ordinary hazard rate $\lambda_{k,k+1}(x_k;\mathbf{Z})$ at time x_k. The distribution of Q, for the given covariate $\mathbf{Z}_0$, is then given by

$$F_Q^{(k)}(q;\mathbf{Z}_0) = P(Q \leq q) = \sum_{m=0}^{k} P_m, \tag{11}$$

where the expressions for P_0, P_m and P_k are as follows (see Pradhan and Dewanji 2009a):

$$\begin{aligned} P_0 &= \int_0^{\frac{q}{w_0}} \lambda_{0,k+1}(x;\mathbf{Z}_0) e^{-(\Lambda_{01}(x;\mathbf{Z}_0)+\Lambda_{0,k+1}(x;\mathbf{Z}_0))} dx \\ &= \int_0^{\frac{q}{w_0}} S_0(x;\mathbf{Z}_0) d\Lambda_{0,k+1}(x;\mathbf{Z}_0), \\ P_m &= \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{i=0}^{m-1} w_i x_i}{w_m}} S_m(x_m;\mathbf{Z}_0) d\Lambda_{m,k+1}(x_m;\mathbf{Z}_0) \\ &\quad \times S_{m-1}(x_{m-1};\mathbf{Z}_0) d\Lambda_{m-1,m}(x_{m-1};\mathbf{Z}_0) \\ &\quad \vdots \\ &\quad \times S_0(x_0;\mathbf{Z}_0) d\Lambda_{01}(x_0;\mathbf{Z}_0), \end{aligned}$$

for $m = 1, \ldots, k-1$, and

$$\begin{aligned} P_k &= \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} \cdots \int_0^{\frac{q-\sum_{i=0}^{k-2} w_i x_i}{w_{k-1}}} F_{k,k+1}\left(\frac{q-\sum_{i=0}^{k-1} w_i x_i}{w_k};\mathbf{Z}_0\right) \\ &\quad \times S_{k-1}(x_{k-1};\mathbf{Z}_0) d\Lambda_{k-1,k}(x_{k-1};\mathbf{Z}_0) \\ &\quad \vdots \\ &\quad \times S_0(x_0;\mathbf{Z}_0) d\Lambda_{01}(x_0;\mathbf{Z}_0), \end{aligned}$$

where $S_h(x;\mathbf{Z}_0) = \exp\left[-\Lambda_{h,h+1}(x;\mathbf{Z}_0) - \Lambda_{h,k+1}(x;\mathbf{Z}_0)\right]$, for $h = 0, 1, \ldots, k-1$, $\Lambda_{i,j}(x) = \int_0^x \lambda_{i,j}(u) du$ and $F_{k,k+1}(\cdot)$ is the distribution function of $T_{k,k+1}$.

6.1 Estimation

The observations for progressive illness–death model are described as follows.

1. For $h = 0, 1, \dots, k$, write

$$\delta_h = \begin{cases} 0, & \text{if censoring takes place in state } h \\ h+1, & \text{if transition takes place from } h \text{ to } h+1 \\ & \quad \text{(that is, } T_{h,h+1} < T_{h,k+1}, C - \sum_{l=0}^{h-1} T_{l,l+1}) \\ k+1, & \text{if transition takes place from } h \text{ to } k+1 \\ & \quad \text{(that is, } T_{h,k+1} < T_{h,h+1}, C - \sum_{l=0}^{h-1} T_{l,l+1}). \end{cases}$$

   Note that for $h = 0$, $\sum_{l=0}^{h-1} T_{l,l+1}$ is treated to be 0.
2. Write $X_0 = \min(T_{01}, T_{0,k+1}, C)$.
3. For $h = 1, \dots, k-1$, if $\delta_{h-1} = h$, write

$$X_h = \min\left(T_{h,h+1}, T_{h,k+1}, C - \sum_{l=0}^{h-1} T_{l,l+1}\right),$$

   and, if $\delta_{k-1} = k$, write

$$X_k = \min\left(T_{k,k+1}, C - \sum_{l=0}^{k-1} T_{l,l+1}\right).$$

4. For $h = 1, \dots, k$, whenever $\delta_{h-1} = 0$ or $k+1$, the hth state and the subsequent states $h+1, \dots, k$ are not attained. We then write $X_l = \delta_l = -1$ for $l = h, h+1, \dots, k$.

For n individuals, the data set is then given by

$$\left\{(x_{hi}, \delta_{hi}, \mathbf{Z}_{hji}), h = 0, 1, \dots, k, i = 1, \dots, n\right\},$$

where (x_{hi}, δ_{hi}) denotes the observed value of (X_h, δ_h) for the ith individual and

$$hj = \begin{cases} (h, h+1), (h, k+1) & \text{for } h = 0, 1, \dots, k-1 \\ (h, h+1) & \text{for } h = k. \end{cases}$$

Define $\eta_{hj} = I(\delta_h = j)$ if $j = h+1$ or $k+1$, for $h = 0, 1, \dots, k-1$ and $\eta_{k,k+1} = I(\delta_k = k+1)$. Also, η_{hji} denotes the value of η_{hj} for the ith individual. The estimate of regression parameters β is obtained by maximizing the partial likelihood (see Andersen et al. 1993, pp. 481–482)

$$L(\beta) = \prod_{hj} \prod_{i} \left(\frac{\exp(\beta^T Z_{hji})}{S_{hj}^{(0)}(\beta, x_{hi})} \right)^{\eta_{hji}},$$

where $S_{hj}^{(0)}(\beta, x)$, for different hj, are defined at the end of Section 2.

Then, the Breslow (1974) estimator for $\Lambda_{hj0}(t) = \int_0^t \lambda_{hj0}(u)$ is given by

$$\hat{\Lambda}_{hj0}(t, \hat{\beta}) = \int_0^t \frac{J_h(x)}{S_{hj}^{(0)}(\hat{\beta}, x)} dN_{hj}(x),$$

where $N_{hj}(t) = \sum_{i=1}^n I(X_{hi} \leq t, \delta_{hi} = j)$, for $j = h+1, k+1$, $Y_h(t) = \sum_{i=1}^n I(X_{hi} \geq t)$ and $J_h(t) = I(Y_h(t) > 0)$, for $h = 0, 1, \ldots, k$. Then, $S_h(t; \mathbf{Z}_0)$ and $F_{k,k+1}(t; \mathbf{Z}_0)$ are estimated by

$$\hat{S}_h(t; \mathbf{Z}_0) = \prod_{u<t} \left\{ 1 - d\hat{\Lambda}_{h,h+1}(u; \mathbf{Z}_0) - d\hat{\Lambda}_{h,k+1}(x; \mathbf{Z}_0) \right\}, \tag{12}$$

for $h = 0, 1, \ldots, k-1$, and

$$\hat{F}_{k,k+1}(t; \mathbf{Z}_0) = 1 - \prod_{u \leq t} \left\{ 1 - d\hat{\Lambda}_{k,k+1}(u; \mathbf{Z}_0) \right\}, \tag{13}$$

respectively. Then, using Eq. 11, an estimate of $F_Q^{(k)}(q; \mathbf{Z}_0)$ is obtained by substituting $S_h(\cdot)$'s, $\Lambda_{h,h+1}(\cdot)$'s, $\Lambda_{h,k+1}(\cdot)$'s and $F_{k,k+1}(\cdot)$ by the corresponding estimates.

Note that $F_Q^{(k)}(q; \mathbf{Z}_0)$ can be written as

$$F_Q^{(k)}(q; \mathbf{Z}_0) = \int_0^{\frac{q}{w_0}} S_0(x; \mathbf{Z}_0) d\Lambda_{0,k+1}(x; \mathbf{Z}_0) + \int_0^{\frac{q}{w_0}} F_{Q^*}^{(k-1)}(q - w_0 x_0; \mathbf{Z}_0) S_0(x) d\Lambda_{01}(x; \mathbf{Z}_0),$$

where Q^* is defined in the same way as Q but starting from state 1 instead of state 0. The corresponding survival function given by

$$S_Q^{(k)}(q; \mathbf{Z}_0) = S_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right) + \int_0^{\frac{q}{w_0}} S_{Q^*}^{(k-1)}(q - w_0 x; \mathbf{Z}_0) S_0(x; \mathbf{Z}_0) d\Lambda_{01}(x; \mathbf{Z}_0),$$

having the similar form as in Eq. 2 with $S_{Q^*}^{(k-1)}(\cdot)$ in place of $S_{12}(\cdot)$. Hence, following the proofs of Theorems 2–4 and using method of induction, one can prove weak convergence of $\sqrt{n}\left[\hat{S}_Q^{(k)}(q; \mathbf{Z}_0) - S_Q^{(k)}(q; \mathbf{Z}_0)\right]$ to a mean zero Gaussian process with a covariance function that can be estimated, where $\hat{S}_Q^{(k)}(q; \mathbf{Z}_0)$ denotes the estimate of $S_Q^{(k)}(q; \mathbf{Z}_0)$, as described above.

6.2 Analysis of IBCSG data

We illustrate our methodology for the progressive illness–death model using data from International Breast Cancer Study Group (IBCSG) Trial V in which 1,229 patients have been randomized to receive either short duration chemotherapy (one month) or long duration chemotherapy (six or seven months) with 413 and 816 patients, respectively. This randomized clinical trial compares two adjuvant chemotherapy schedules for node-positive breast cancer. For each patient, the observation consists of time till (1) the end of treatment toxicity (TOX), (2) relapse (disease-free survival time) (DFS), and (3) death from any cause (overall survival) (OS) along with censoring indicator and covariates. There are 3 health states, namely, (1) toxic side effect of chemotherapy, (2) no symptoms of disease and toxicity of treatments and (3) disease relapsed. The sojourn times in these health states are denoted by TOX (Toxicity period), TWiST (Time without symptoms of disease and toxicity of treatment) = DFS − TOX and REL (Relapsed) = OS − DFS, respectively. In our notation, T_{01} = TOX, T_{12} = TWiST and T_{23} = REL, and they are measured in months. Quality adjusted lifetime (QAL) is then defined by

$$Q = w_0 \times T_{01} + w_1 \times T_{12} + w_2 \times T_{23},$$

where w_i is the utility coefficient corresponding to the ith health state, $i = 0, 1, 2$.

Note that there is no direct death from health states 0 and 1; therefore, the appropriate model for IBCSG data is a special case of the progressive illness–death model of Fig. 3. We consider five covariates recorded from each patient upon enrollment in the clinical trial as given below.

- $Z^{(1)}$ treatment group (0: short duration and 1: long duration),
- $Z^{(2)}$ age in years at the time of enrollment,
- $Z^{(3)}$ menopausal status (0: pre- and 1: post-),
- $Z^{(4)}$ tumor size, and
- $Z^{(5)}$ nodal group (0: 1 to 3 nodes and 1: 4 or more nodes).

The state-specific covariate vectors are

$$\mathbf{Z}_{01} = \left(Z^{(1)}, Z^{(2)}, Z^{(3)}, Z^{(4)}, Z^{(5)}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0\right)'.$$

$$\mathbf{Z}_{12} = \left(0, 0, 0, 0, 0, Z^{(1)}, Z^{(2)}, Z^{(3)}, Z^{(4)}, Z^{(5)}, 0, 0, 0, 0, 0\right)'.$$

$$\mathbf{Z}_{23} = \left(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, Z^{(1)}, Z^{(2)}, Z^{(3)}, Z^{(4)}, Z^{(5)}\right)'.$$

The state-specific hazard rate is modeled as

$$\lambda_{hj}(t; \mathbf{Z}) = \lambda_{hj0}(t) \exp\left(\beta^T \mathbf{Z}_{hj}\right), \text{ for } hj = 01, 12, 23,$$

where $\beta = (\beta_{011}, \beta_{012}, \beta_{013}, \beta_{014}, \beta_{015}, \beta_{121}, \beta_{122}, \beta_{123}, \beta_{124}, \beta_{125}, \beta_{231}, \beta_{232}, \beta_{233}, \beta_{234}, \beta_{235})'$ is the vector of regression coefficients. Then, from Eq. 11, the

Table 3 Estimates of the regression coefficients for the IBCSG data

Transition	Parameters	Estimate	Standard error	p-value
01	β_{011}	−2.7599	0.1043	0.000
	β_{012}	−0.0039	0.0049	0.440
	β_{013}	0.0371	0.0937	0.690
	β_{014}	−0.0009	0.0018	0.620
	β_{015}	0.0739	0.0601	0.220
12	β_{121}	−0.4776	0.0797	0.000
	β_{122}	−0.0281	0.0069	0.000
	β_{123}	0.4281	0.1297	0.001
	β_{124}	0.0066	0.0022	0.003
	β_{125}	0.8523	0.0810	0.000
23	β_{231}	0.3071	0.0929	0.001
	β_{232}	−0.0005	0.0079	0.950
	β_{233}	−0.1725	0.1535	0.260
	β_{234}	0.0040	0.0026	0.130
	β_{235}	0.2099	0.0942	0.026

distribution function of Q for given covariate $\mathbf{Z}_0$ is given by (see also Pradhan and Dewanji 2009a)

$$F_Q(q; \mathbf{Z}_0)) = \int_0^{\frac{q}{w_0}} \int_0^{\frac{q-w_0x_0}{w_1}} F_{23}\left(\frac{q - w_0x_0 - w_1x_1}{w_2}; \mathbf{Z}_0\right) S_1(x_1; \mathbf{Z}_0) d\Lambda_{12}(x_1; \mathbf{Z}_0)$$

$$\times S_0(x_0; \mathbf{Z}_0) d\Lambda_{01}(x_0; \mathbf{Z}_0), \tag{14}$$

where $S_0(t; \mathbf{Z}_0) = \exp\{-\Lambda_{01}(t; \mathbf{Z}_0)\}$, $S_1(t; \mathbf{Z}_0) = \exp\{-\Lambda_{12}(t; \mathbf{Z}_0)\}$ and $F_{23}(\cdot; \mathbf{Z}_0))$ is the distribution function of T_{23}.

Out of 1,229 patients, all the covariate values are available for 1,215 patients. So this analysis is based on 1,215 patients. The estimates of the regression coefficients along with standard errors and p-values are presented in Table 3.

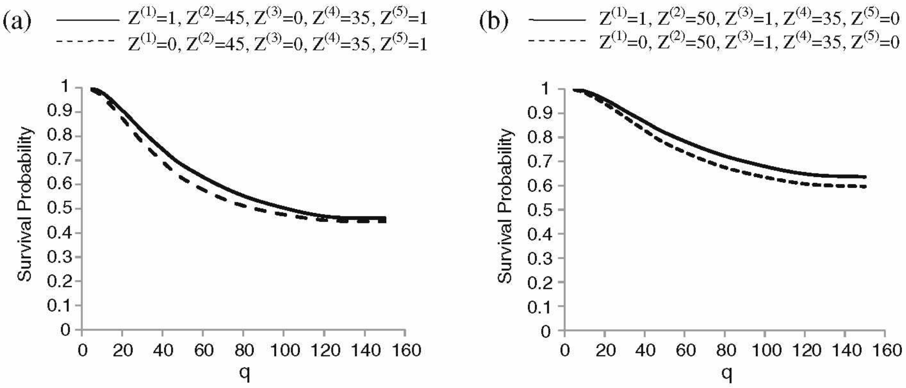

Fig. 4 Effect of covariates on the QAL distribution for the IBCSG data

From the p-values in Table 3, it is clear that the treatment group ($Z^{(1)}$) has significant decreasing effect on the hazards of TOX and TWiST and, increasing effect on the hazard of REL. Age ($Z^{(2)}$), menopausal status ($Z^{(3)}$) and tumor size ($Z^{(4)}$) have significant effect only on the hazard of TWiST. Nodal group ($Z^{(5)}$) has significant effect on both TWiST and REL.

Next, we estimate the survival function for QAL using Eq. 14 and the estimates in Table 3 for a given value of $\mathbf{Z}_0$. Since the algebraic expression for the standard error of this estimate is very complicated and difficult to obtain, it is computed by using a bootstrap method with 500 bootstrap samples, each of size 1,215 drawn with replacement. The utility coefficients are taken as $w_0 = 0.5$, $w_1 = 1$ and $w_2 = 0.5$. The survival probability for $\mathbf{Z}_0 = (1, 50, 0, 35, 1)'$ at $q = 10$ is estimated as 0.9836 with standard error 0.0030. Next we study the effect of treatment ($Z^{(1)}$) on the QAL distribution by graphical method, as in Section 5. We consider two different combinations of other four covariates reflecting two different scenarios. For the first, we plot the estimated survival probabilities for $Z^{(1)} = 0$ and $Z^{(1)} = 1$, keeping $Z^{(2)} = 45$, $Z^{(3)} = 0$, $Z^{(4)} = 35$ and $Z^{(5)} = 1$ as fixed (see Fig. 4a). In the second, we plot the same keeping $Z^{(2)} = 50$, $Z^{(3)} = 1$, $Z^{(4)} = 35$ and $Z^{(5)} = 0$ as fixed (see Fig. 4b). The two survival curves in both the scenarios seem to be close to each other.

7 Concluding remarks

In this work, we have proposed a semi-parametric method for estimating QAL distribution in a three-state illness–death model and a progressive illness–death model. The estimate is easy to obtain and, by construction, monotonic. The closed form expression for the distribution of QAL is available, when the number of states is not too large. Otherwise, this expression involves multiple integration which needs to be evaluated by numerical method. This, however, needs to be done only once when the distribution of QAL is to be estimated by substituting the different sojourn time distributions by the corresponding estimates. Variance estimate has been obtained for three-state model. It is difficult to write the variance expression for the general model in closed form. One can alternatively use some resampling technique (e.g., bootstrap) to estimate the variance of survival estimates. This estimation procedure can be extended to some general models like, for example, the competing illness–death model of Pradhan and Dewanji (2009b).

One can, in principle, use a Markov model in which the different baseline transition rates depend on the time since the beginning instead of the time spent in the current state. This represents a complicated structure of dependence between the different sojourn times. This, however, readily fits into the multiplicative intensity framework. Therefore, the results of Andersen et al. (1993, pp. 481–482) are readily applicable for the estimation of the regression parameters, the baseline cumulative hazards, and, eventually, the QAL distribution. The asymptotic results also follow from those of Andersen et al. (1993, Section VII.2) following similar techniques. In a particular dependence structure, a transition rate may depend on the previous sojourn time(s), say, through a proportional hazards type modelling. The estimation through partial likelihood can be carried out in a similar manner.

Acknowledgements The authors thank the International Breast Cancer Study Group for providing the data used in Section 6. The authors would also like to thank an anonymous referee for helpful comments.

Appendix

Let us assume the regularity conditions 1–3 of Shu et al. (2007). Theorem 1 is Lemma 1(ii) of their work.

Proof of Theorem 2 Using Lemmas 1 and 2 of Shu et al. (2007),

$$\sqrt{n}\left[\hat{S}_0\left(\frac{q}{w_0}, \mathbf{Z}_0\right) - S_0\left(\frac{q}{w_0}, \mathbf{Z}_0\right)\right]$$
$$= n^{-1/2}\sum_{i=1}^{n}\left\{W_{1i}^{(0)}(q) + W_{2i}^{(0)}(q) + W_{3i}^{(0)}(q)\right\} + o_p(1), \tag{15}$$

where

$$W_{1i}^{(0)}(q) = Q^{(0)}\left(\frac{q}{w_0}, \beta\right)^T \Omega^{-1}\sum_{hj}\int_0^\infty \{\mathbf{Z}_{hji} - E_{hji}(\beta, u)\}dM_{hji}(u),$$

$$Q^{(0)}\left(\frac{q}{w_0}, \beta\right) = -S_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\left[\int_0^{\frac{q}{w_0}}\{\mathbf{Z}_{010} - e_{01}(\beta, u)\}d\Lambda_{01}(u; \mathbf{Z}_0)\right.$$
$$\left. + \int_0^{\frac{q}{w_0}}\{\mathbf{Z}_{020} - e_{02}(\beta, u)\}d\Lambda_{02}(u; \mathbf{Z}_0)\right],$$

$$W_{2i}^{(0)}(q) = -nS_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\exp\left(\beta^T\mathbf{Z}_{010}\right)\int_0^{\frac{q}{w_0}}\frac{J_0(u)dM_{01i}(u)}{S_{01}^{(0)}(\beta, u)},$$

$$W_{3i}^{(0)}(q) = -nS_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\exp\left(\beta^T\mathbf{Z}_{020}\right)\int_0^{\frac{q}{w_0}}\frac{J_0(u)dM_{02i}(u)}{S_{02}^{(0)}(\beta, u)}.$$

Note that, for each q, the right hand side of Eq. 15 is essentially a sum of n independent and identically distributed zero-mean random variables. Using the arguments of Shu et al. (2007), we conclude that $\sqrt{n}\big[\hat{S}_0(\cdot; \mathbf{Z}_0) - S_0(\cdot; \mathbf{Z}_0)\big]$

converges weakly to a zero-mean Gaussian process with covariance function at $\left(\frac{q}{w_0}, \frac{q'}{w_0}\right)$ given by

$$\begin{aligned}
&\psi^{(0)}\left(\frac{q}{w_0}, \frac{q'}{w_0}\right) \\
&= \frac{1}{n}\sum_{i=1}^{n} \text{cov}\left\{W_{1i}^{(0)}(q) + W_{2i}^{(0)}(q) + W_{3i}^{(0)}(q), W_{1i}^{(0)}(q') + W_{2i}^{(0)}(q') + W_{3i}^{(0)}(q')\right\} \\
&= Q^{(0)}\left(\frac{q}{w_0}, \beta\right)^T \Omega^{-1}\frac{1}{n}E\left[\sum_{hj}\int_0^{\infty}\left\{\frac{S_{hj}^{(2)}(\beta, u)}{S_{hj}^{(0)}(\beta, u)} - E_{hj}(\beta, u)^{\otimes 2}\right\}\right. \\
&\qquad\qquad \left.\times S_{hj}^{(0)}(\beta, u)d\Lambda_{hj0}(u)\right]\Omega^{-1}Q^{(0)}\left(\frac{q'}{w_0}, \beta\right) \\
&\quad + nS_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)S_0\left(\frac{q'}{w_0}; \mathbf{Z}_0\right)\{\exp\left(\beta^T\mathbf{Z}_{010}\right)\}^2 E\left\{\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}} \frac{J_0(u)d\Lambda_{01}(u)}{S_{01}^{(0)}(\beta, u)}\right\} \\
&\quad + nS_0\left(\frac{q}{w_0}; \mathbf{Z}_0\right)S_0\left(\frac{q'}{w_0}; \mathbf{Z}_0\right)\{\exp\left(\beta^T\mathbf{Z}_{020}\right)\}^2 E\left\{\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}} \frac{J_0(u)d\Lambda_{02}(u)}{S_{02}^{(0)}(\beta, u)}\right\}
\end{aligned}$$

which, for $q = q'$, can be estimated uniformly consistently by Eq. 7 in Section 3. □

Proof of Theorem 3 Following the similar decomposition technique as that used in Voelkel and Crowley (1984) and Shu et al. (2007), we have

$$\begin{aligned}
&\sqrt{n}\left[\hat{P}_{12}\left(\frac{q}{w_0}; \mathbf{Z}_0\right) - P_{12}\left(\frac{q}{w_0}; \mathbf{Z}_0\right)\right] \\
&\quad = n^{-1/2}\sum_{i=1}^{n}\left\{W_{1i}^{(12)}(q) + W_{2i}^{(12)}(q) + W_{3i}^{(12)}(q) + W_{4i}^{(12)}(q)\right\} + o_p(1), \quad (16)
\end{aligned}$$

where

$$W_{1i}^{(12)} = Q^{(12)}\left(\frac{q}{w_0}, \beta\right)^T \Omega^{-1}\sum_{hj}\int_0^{\infty}\{\mathbf{Z}_{hji} - E_{hji}(\beta, u)\}dM_{hji}(u),$$

$$\begin{aligned}
W_{2i}^{(12)}(q) = n\int_0^{\frac{q}{w_0}} &\left\{S_0(u; \mathbf{Z}_0)S_{12}\left(\frac{q - w_0u}{w_1}; \mathbf{Z}_0\right)\right. \\
&\left. - \int_u^{\frac{q}{w_0}} S_0(x; \mathbf{Z}_0)S_{12}\left(\frac{q - w_0x}{w_1}; \mathbf{Z}_0\right)d\Lambda_{01}(x)\right\}, \\
&\times \exp(\beta^T\mathbf{Z}_{010})\frac{J_0(u)dM_{01i}(u)}{S_{01}^{(0)}(\beta, u)},
\end{aligned}$$

$$W_{3i}^{(12)}(q) = -n\int_0^{\frac{q}{w_0}}\left\{\int_u^{\frac{q}{w_0}} S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x)\right\}$$
$$\times\exp\left(\beta^T\mathbf{Z}_{020}\right)\frac{J_0(u)dM_{02i}(u)}{S_{02}^{(0)}(\beta,u)},$$
$$W_{4i}^{(12)}(q) = -n\int_0^{\frac{q}{w_1}}\left\{\int_0^{\frac{q-w_1u}{w_0}} S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{12}(x)\right\}$$
$$\times\exp\left(\beta^T\mathbf{Z}_{120}\right)\frac{J_1(u)dM_{12i}(u)}{S_{12}^{(0)}(\beta,u)},$$
$$Q^{(12)}\left(\frac{q}{w_0},\beta\right) = \int_0^{\frac{q}{w_0}} S_0\left(u;\mathbf{Z}_0\right)S_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right)$$
$$\times\left[\left\{\mathbf{Z}_{010}-e_{01}(\beta,u)\right\}-\int_0^u\left\{\mathbf{Z}_{010}-e_{01}(\beta,x)\right\}d\Lambda_{01}(x;\mathbf{Z}_0)\right.$$
$$-\int_0^u\left\{\mathbf{Z}_{020}-e_{02}(\beta,x)\right\}d\Lambda_{02}(x;\mathbf{Z}_0)$$
$$\left.-\int_0^u\left\{\mathbf{Z}_{120}-e_{12}(\beta,x)\right\}d\Lambda_{12}(x;\mathbf{Z}_0)\right]d\Lambda_{01}(u;\mathbf{Z}_0).$$

Note that, for each q, the right hand side of Eq. 16 is essentially a sum of n independent and identically distributed zero-mean random variables. Using the arguments of Shu et al. (2007), we conclude that $\sqrt{n}\left[\hat{P}_{12}(\cdot)-P_{12}(\cdot)\right]$ converges weakly to a zero-mean Gaussian process with covariance function at $\left(\frac{q}{w_0},\frac{q'}{w_0}\right)$ given by

$$\psi^{(12)}\left(\frac{q}{w_0},\frac{q'}{w_0}\right) = \frac{1}{n}\sum_{i=1}^n \mathrm{cov}\left\{W_{1i}^{(12)}(q)+W_{2i}^{(12)}(q)+W_{3i}^{(12)}(q)+W_{4i}^{(12)}(q),\right.$$
$$\left.W_{1i}^{(12)}(q')+W_{2i}^{(12)}(q')+W_{3}^{(12)}(q')+W_{4i}^{(12)}(q')\right\}$$
$$= Q^{(12)}\left(\frac{q}{w_0},\beta\right)^T\Omega^{-1}$$
$$\times\frac{1}{n}E\left[\sum_{hj}\int_0^\infty\left\{\frac{S_{hj}^{(2)}(\beta,u)}{S_{hj}^{(0)}(\beta,u)}-E_{hj}(\beta,u)^{\otimes 2}\right\}\right.$$
$$\left.\times S_{hj}^{(0)}(\beta,u)d\Lambda_{hj0}(u)\right]\Omega^{-1}Q^{(12)}\left(\frac{q'}{w_0},\beta\right)$$

$$+nE\Bigg[\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}}\Bigg\{S_0(u;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right)-\int_u^{\frac{q}{w_0}}S_0(x;\mathbf{Z}_0)$$

$$\times S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\Bigg\}$$

$$\times\Bigg\{S_0(u;\mathbf{Z}_0)S_{12}\left(\frac{q'-w_0u}{w_1};\mathbf{Z}_0\right)$$

$$-\int_u^{\frac{q'}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q'-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\Bigg\}$$

$$\times\left\{\exp(\beta^T\mathbf{Z}_{010})\right\}^2J_0(u)\frac{d\Lambda_{01}(u)}{S_{01}^{(0)}(\beta,u)}\Bigg]$$

$$+nE\Bigg[\int_0^{\frac{q}{w_0}\wedge\frac{q'}{w_0}}\Bigg\{\int_u^{\frac{q}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}$$

$$\times\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\Bigg\}$$

$$\times\Bigg\{\int_u^{\frac{q'}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q'-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\Bigg\}$$

$$\times\left\{\exp\left(\beta^T\mathbf{Z}_{020}\right)\right\}^2J_0(u)\frac{d\Lambda_{02}(u)}{S_{02}^{(0)}(\beta,u)}\Bigg]$$

$$+nE\Bigg[\int_0^{\frac{q}{w_1}\wedge\frac{q'}{w_1}}\Bigg\{\int_0^{\frac{q-w_1u}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}$$

$$\times\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x;\mathbf{Z}_0)\Bigg\}$$

$$\times\Bigg\{\int_0^{\frac{q'-w_1u}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q'-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x)\Bigg\}$$

$$\times\left\{\exp\left(\beta^T\mathbf{Z}_{120}\right)\right\}^2J_1(u)\frac{d\Lambda_{12}(u)}{S_{12}^{(0)}(\beta,u)}\Bigg]$$

which, for $q=q'$, can be estimated uniformly consistently by Eq. 8 in Section 3.

□

Proof of Theorem 4 Note that

$$\sqrt{n}\left[\hat{S}_Q(q;\mathbf{Z}_0)-S_Q(q;\mathbf{Z}_0)\right]=\sqrt{n}\left[\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)-S_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right]$$
$$+\sqrt{n}\left[\hat{P}_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right)-P_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right].$$

Hence, by some rearrangement of terms and following the techniques used in the proofs of Theorems 2 and 3, $\sqrt{n}\left[\hat{S}_Q(q;\mathbf{Z}_0)-S_Q(q;\mathbf{Z}_0)\right]$ can be written as a sum of n independent and identically distributed zero mean random variables. The weak convergence result follows by using similar arguments. The covariance term in Theorem 4 is given by

$$\text{cov}\left[\sqrt{n}\left\{\hat{S}_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)-S_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right\},\sqrt{n}\left\{\hat{P}_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right)-P_{12}\left(\frac{q}{w_0};\mathbf{Z}_0\right)\right\}\right]$$
$$=\frac{1}{n}\sum_{i=1}^{n}\text{cov}\left\{W_{1i}^{(0)}(q)+W_{2i}^{(0)}(q)+W_{3i}^{(0)}(q),\right.$$
$$\left.W_{1i}^{(12)}(q)+W_{2i}^{(12)}(q)+W_{3i}^{(12)}(q)+W_{4i}^{(12)}(q)\right\}+o_p(1)$$
$$=Q^{(0)}\left(\frac{q}{w_0},\beta\right)^T\Omega^{-1}\frac{1}{n}E\left[\sum_{hj}\int_0^\infty\left\{\frac{S_{hj}^{(2)}(\beta,u)}{S_{hj}^{(0)}(\beta,u)}-E_{hj}(\beta,u)^{\otimes 2}\right\}\right.$$
$$\left.\times S_{hj}^{(0)}(\beta,u)d\Lambda_{hj0}(u)\right]\Omega^{-1}Q^{(12)}\left(\frac{q'}{w_0},\beta\right)$$
$$-nS_0\left(\frac{q}{w_0};\mathbf{Z}_0\right)\left\{\exp(\beta^T\mathbf{Z}_{010})\right\}^2$$
$$\times E\left[\int_0^{\frac{q}{w_0}}\left\{S_0(u;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0u}{w_1};\mathbf{Z}_0\right)\right.\right.$$
$$\left.\left.-\int_u^{\frac{q}{w_0}}S_0(x;\mathbf{Z}_0)S_{12}\left(\frac{q-w_0x}{w_1};\mathbf{Z}_0\right)d\Lambda_{01}(x)\right\}J_0(u)\frac{d\Lambda_{01}(u)}{S_{01}^{(0)}(\beta,u)}\right]$$
$$+nS_0\left(\frac{q}{w_0}\right)\{\exp(\beta^T\mathbf{Z}_{020})\}^2$$
$$\times E\left[\int_0^{\frac{q}{w_0}}\left\{\int_u^{\frac{q}{w_0}}S_0(x)S_{12}\left(\frac{q-w_0x}{w_1}\right)d\Lambda_{01}(x)\right\}J_0(u)\frac{d\Lambda_{02}(u)}{S_{02}^{(0)}(\beta,u)}\right]+o_p(1),$$

which can be estimated uniformly consistently by Eq. 10 in Section 3. □

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