RT-MAE 2005-14

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by

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- Abril de 2005 -

Estimation of the Mean Quality Adjusted Survival using a Multistate Model for the Sojourn Times

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Abstract

In clinical trials, it may be of interest to take into account physical and emotional well-being of patients in addition to survival when comparing treatments. Quality-adjusted survival time has the advantage of incorporating information about both survival time and quality-of-life. In this paper, we discuss the estimation of the expected value of the quality adjusted survival, based on multi-state models for the sojourn times in health states. A semi parametric and a parametric (exponential distribution) approaches are considered. A simulation study is presented to evaluate the performance of the proposed estimator and the Jackknife resampling method is used to compute bias and variance of the estimator.

Keywords: Quality of life; survival analysis; multi state models; exponential distribution; semi parametric proportional hazards.
AMS Classification: 62N01; 62N02; 62F10; 62F40; 62G05; 62G09.

1 Introduction

Clinical trials based on survival analysis usually consider the comparison of treatments with respect to the survival time of patients. As drugs are improved, such comparisons tend to result in similarity between treatments (usually the primary endpoints), so that comparisons related to secondary endpoints become more important. In this setting, the quality of life of patients is important when one wants to evaluate clinical therapies or compare different treatments. Because conventional models consider only the time until death or other event of interest, they become inappropriate in this setting.

The quality adjusted survival is a natural extension of the Q-TWiST ("Quality adjusted Time Without Symptoms of Disease and Toxicity of Treatment") methodology, developed by Gelber et al. (1989).

The estimation of some quantities of interest has been already considered. Zhao and Tsiatis (1997) obtained an estimator of the survival distribution of quality adjusted lifetime, assuming independent censoring and using weighted estimating equations. They also showed that the estimator is asymptotically consistent and normally distributed, using the martingale theory. Later, Zhao and Tsiatis (1999) derived an estimator which is more efficient than the one proposed by Zhao and Tsiatis (1997).

Zhao and Tsiatis (2001) proposed a method for comparing survival functions of quality-adjusted lifetime for two different treatments when there is right-censoring. Their test reduces to the usual log-rank test when there are only two states (perfect health and death) and the quality adjusted lifetime is the same as the survival time. They discussed an extension for the case when there are G groups, but the properties of the estimator are still to be developed.

Inferences about the mean quality adjusted lifetime $\mu = E(U)$ was discussed by Zhao and Tsiatis (2000). They constructed a class of estimators asymptotically equivalent to consistent asymptotically normal estimators for the mean quality adjusted lifetime, based on the theory of influence functions Robins et al. (1994). When the data from a clinical study is collected at periodic intervals, the information is usually incomplete, which is a problem for the analysis.

Chen and Sen (2001) proposed an estimator of the expected quality adjusted survival which can be applied to right and interval censored data. They showed the estimator is asymptotically normal and considered cases

in which the transition of a patient's health status is not always observable. This is common when the clinical observations are made on a periodic basis (e.g., monthly) and patients may experience more than one type of health status between two visits.

In this paper we propose an estimator of the mean quality adjusted survival time using a multistate model (parametric and semi-parametric) for the sojourn times. In Section 2 we present the definition of the quality adjusted survival time and an expression for its expected value is obtained. In section 3 it is described the parametric and semi-parametric model for the sojourn times. In section a simulation study is presented.

2 Quality adjusted survival time

We assume that there is an appropriate instrument to measure the quality of life and these measurements are available. The intuitive idea of quality adjusted survival time is very simple. We consider first that there is a finite number of health states and, at any instant of time, patients can be classified into one of these states. A coefficient, known as utility coefficient, is associated to each health state and, hopefully, it should reflect the quality of life of a given patient at each state. The coefficients must be in the interval $[0, 1]$, where 1 is associated to perfect health and zero is associated with death. Values of the utility coefficient close to zero should be associated with poor health states and values close to 1 should be associated with better health states.

It is not an easy job to define the health states and the utility coefficients. Usually, the states and values of utility coefficients should be chosen by specialized researchers based on the instruments used to measure the quality of life and prior experience.

Once the states and utility coefficients are defined, the idea is to sum up the sojourn times spent by the patient in the health states multiplied by their respective utility coefficients, i.e.,

$$U = \sum_{j=1}^{K} q_j T_j,$$

where $q_1, \ldots, q_K$ are the utility coefficients corresponding to the health states, K is the total number of states (excluding death) and T_j is the sojourn time

in the state j. If there are only two states, one corresponding to perfect health and the other corresponding to death, and their utility coefficients are 1 and 0, respectively, then the quality adjusted survival time reduces to the usual survival time.

Formally, assume that there are n individuals under study and consider that the health history of the i-th patient can be described by a process $\{V_i(t), t \geq 0\}$, where $V_i(t)$ assume any of the $K+1$ states belonging to the space state $\Gamma = \{0, 1, \ldots, K\}$. Suppose that the states $1, 2, \ldots, K$ are transient and the state 0 is absorbing, corresponding death, i.e., $V_i(t) = 0$ implies $V_i(s) = 0 \; \forall s \geq t$. The usual survival time of the i-th individual is given by $T_i(t) = \inf\{t : V_i(t) = 0\}$. Define also the function Q that maps the state space to a prespecified set of real numbers (the utility coefficients). Using this notation, the quality adjusted survival time is given by

$$U_i = \int_0^{T_i} Q\{V_i(t)\}dt = \int_0^{\infty} Q\{V_i(t)\}dt, i = 1, \ldots, n. \qquad (1)$$

Note that this definition is more general than the intuitive sketch initially presented. The definition (1) allows, for example, that $Q\{\cdot\}$ be a continuous function of the health state and the quality adjusted survival time would be the area of the curve of the quality of life. One may also define the function Q as a function of both health state and time, i.e., consider the function $Q\{V_i(t), t\}$, meaning that the quality of life associated to each state may change with time. However, this situation will be not considered in this paper.

As it is usual in survival data, observations are subject to censoring. If one is working with quality adjusted survival time, the censoring adds a serious issue to the analysis. Usually, patients with poor quality of life tend to *accumulate* the quality adjusted survival time slowly and, because of that, they have smaller censoring times corresponding to the quality adjusted survival time. Therefore, as pointed out by Glasziou et al. (1990), small censoring times can be associated to poor quality of life, implying that the censoring has an informative pattern. Because of this, it is not possible to apply directly usual survival methodologies to analyze data related to quality adjusted survival time and it is necessary to develop new methodologies to estimate quantities of interest (mean, survival function, etc.) for the quality adjusted survival time.

We assume there are $K+1$ health states and it is known the instants when there is a change in the health state of each patient until he/she dies

or is censored. We also assume that a transient state can be visited more than once and denote by $T_j^{(k)}$ the sojourn time in the j-th visit to state k. Using this notation and considering that the quality of life is constant when patients are in each health state, the quality adjusted survival time can be written in the form

$$\begin{aligned} U &= \int_0^\infty Q\{V(t)\}dt \\ &= q_1 \sum_{j=1}^{N_1} T_j^{(1)} + q_2 \sum_{j=1}^{N_2} T_j^{(2)} + \ldots + q_K \sum_{j=1}^{N_K} T_j^{(K)}, \end{aligned}$$

where q_k is the coefficient associated with the k-th health state and where N_k is the number of entrances in state k, $k = 1, 2, \ldots, K$.

It is usually of interest to estimate the mean quality-adjusted lifetime, which we denote by μ_Q, usually for a given vector of covariates $\mathbf{Z}$:

$$\mu_Q = \mathrm{E}(U|\mathbf{Z}) = \mathrm{E}\left(\int_0^\infty Q\{V(t)\}dt \mid \mathbf{Z}\right),$$

which can be expressed as follows

$$\begin{aligned} \mu_Q &= \mathrm{E}(U \mid \mathbf{Z}) \\ &= q_1 \mathrm{E}\left[\sum_{j=1}^{N_1} T_j^{(1)} \mid \mathbf{Z}\right] + q_2 \mathrm{E}\left[\sum_{j=1}^{N_2} T_j^{(2)} \mid \mathbf{Z}\right] + \cdots + q_K \mathrm{E}\left[\sum_{j=1}^{N_K} T_j^{(K)} \mid \mathbf{Z}\right] \\ &= q_1 \mathrm{E}\left[\mathrm{E}\left(\sum_{j=1}^{N_1} T_j^{(1)} | N_1, \mathbf{Z}\right) \mid \mathbf{Z}\right] + \cdots + q_K \mathrm{E}\left[\mathrm{E}\left(\sum_{j=1}^{N_K} T_j^{(K)} | N_K, \mathbf{Z}\right) \mid \mathbf{Z}\right]. \end{aligned} \tag{2}$$

Expression (2) is general and can be applied in different situations. In this paper we are concerned with the estimation of μ_Q when the sojourn times in each state are random variables assumed independent and identically distributed for a given vector of covariates $\mathbf{Z}$. We also consider a competitive risk structure for the sojourn times in states, i.e., the observed sojourn time in state k is

$$T_j^{*(k)} = \min_{l \in B_{(k)}} \{T_j^{(k)\to(l)}\},$$

where $T_j^{(k)\to(l)}$ is the time spent in state k until a transition to state l (which may not be observable) and $B_{(k)}$ is the set of all states that can be reached from k.

In order to simplify expression (2), note that it is necessary to compute the conditional expectation of $T_j^{*(k)}$ given N_k, the number of entrances in the state. For the states from which the absorbing state can be reached, for $j = 1, \ldots, N_k - 1$, it is known that, given N_k, the next state visited after $T_j^{*(k)}$ is not the absorbing one. Therefore, the distribution of $T_j^{*(k)}$ given N_k is the distribution of the minimum of all latent times $T_j^{(k)\to(l)}$ given that the time $T_j^{(k)\to(0)}$ is greater than the minimum of the others. In others words, we have that $T_j^{*(k)}$ given N_k has the distribution of $\min_{l\in B_{(k)}}\{T_j^{(k)\to(l)}\}$ given that $T_j^{(k)\to(0)} > \min_{l\in B_{(k)}^*}\{T_j^{(k)\to(l)}\}$, where $B_{(k)}^* = B_{(k)} \setminus \{0\}$. In order to simplify the notation, we will denote by $T_j^{(k)}$ the random variable with the same distribution of $\min_{l\in B_{(k)}}\{T_j^{(k)\to(l)}\}$ given $T_j^{(k)\to(0)} > \min_{l\in B_{(k)}^*}\{T_j^{(k)\to(l)}\}$.

For the last time the state is visited, the distribution of $T_{N_k}^{*(k)}$ given N_k is givev by the distribution of $\min_{l\in B_{(k)}}\{T_j^{(k)\to(l)}\}$ given that $T_j^{(k)\to(m)} > \min_{l\in B_{(k)}^{**}}\{T_j^{(k)\to(l)}\}$ for $m \in B_{(k)} \setminus B_{(k)}^{**}$, where $B_{(k)}^{**}$ is the set of all states that can be visited when it is known that state k was visited for the last time. We will denote by $T_{N_k}^{\dagger(k)}$ the random variable with this distribution. The set of states in $B_{(k)}^{**}$ depends on the process considered, i.e., on both number of states and number of possible transitions in the process. If one consider, for example, a illness-death process, with three states, in which the death state can only be reached from the ill state, then $B_{(k)}^{**}$ contains only the absorbing state.

With the assumption of identically distributed sojourn times in each state, (2) can be further simplified to

$$\begin{aligned}\mu_Q = {} & q_1\left[\mathrm{E}(N_1 \mid \mathbf{Z}) - 1\right]\mathrm{E}\left(T_1^{(1)} \mid \mathbf{Z}\right) + q_2\left[\mathrm{E}(N_2 \mid \mathbf{Z}) - 1\right]\mathrm{E}\left(T_1^{(2)} \mid \mathbf{Z}\right) \\ & + \cdots + q_K\left[\mathrm{E}(N_K \mid \mathbf{Z}) - 1\right]\mathrm{E}\left(T_1^{K} \mid \mathbf{Z}\right) \\ & + \mathrm{E}\left(T_{N_1}^{\dagger 1} \mid \mathbf{Z}\right) + \cdots + \mathrm{E}\left(T_{N_K}^{\dagger K} \mid \mathbf{Z}\right). \end{aligned} \tag{3}$$

An estimator for μ_Q can be obtained by specifying a model for the sojourn times and substituting the unknown quantities in (3) by their estimators obtained. It will be shown later that all unknown quantities in (3) can be estimated based on the model for the sojourn times.

Expression (3) can be further simplified with additional assumptions on the model for the sojourn times. In order to simplify (3), suppose that the latent random variables $T_j^{(k)\to(l)}$ for $l \in B_{(k)}$ have proportional hazards, i.e., the hazard function associated to $T_j^{(k)\to(l)}$ is given by

$$\alpha_{k,l}(t) = \alpha_{0_k}(t)e^{\beta_{kl}^T Z},$$

$l \in B_{(k)}$, where $\alpha_{0_k}(t)$ is the baseline hazard function.

When this assumption is valid, it can be that $T_j^{(k)}$ and $T_{N_k}^{\dagger(k)}$ are identically distributed. Therefore, the mean quality adjusted survival can be expressed as

$$\begin{aligned}\mu_Q =& q_1 \left[\mathrm{E}(N_1 \mid \mathbf{Z})\right] \mathrm{E}\left(T_1^{(1)} \mid \mathbf{Z}\right) + q_1 \left[\mathrm{E}(N_2 \mid \mathbf{Z})\right] \mathrm{E}\left(T_1^{(2)} \mid \mathbf{Z}\right) + \\ & \cdots + q_K \left[\mathrm{E}(N_K \mid \mathbf{Z})\right] \mathrm{E}\left(T_1^{(K)} \mid \mathbf{Z}\right).\end{aligned}$$

Two different approaches are considered for the model of the sojourn times: parametric and semi parametric models.

3 Model for the sojourn times

Usual survival models can be applied and all the results concerning the asymptotic distribution of estimators can also be used. Time independent covariates can be included easily and the mean quality adjusted survival time is obtained for fixed values of the covariates. In the following we consider a semi parametric approach, based on Dabrowska et al. (1994) and Cox (1972), and also a parametric approach, based on the exponential distribution. In the two approaches, we assume data is subject to right censoring, with non-informative censorship in the chronological time scale.

3.1 Semi-parametric Model

The semi-parametric model developed by Dabrowska et al. (1994) can be directly applied here. Details of this model can be found in the paper by Dabrowska et al. (1994).

Denote by $0 = \tau_0 < \tau_1 < \tau_2 < \tau_3 < \cdots$ the instants of entrance in states $V_0, V_1, V_2, V_3, \ldots$, respectively. It is assumed that the process is a Markov

renewal process, i.e.,

$$P(\tau_{n+1} - \tau_n \leq x, V_{n+1} = j | V_0, \tau_0, V_1, \tau_1, \ldots, \tau_n, \tau_n) \\ = P(\tau_{n+1} - \tau_n \leq x, V_{n+1} = j | V_n).$$

In terms of counting processes, define

$$\tilde{N}_{jk}(t) = \sum_{N \geq 1} I(\tau_n \leq t, V_{n-1} = j, V_n = k)$$

and

$$\tilde{N}(t) = \sum_{j,k} \tilde{N}_{jk}(t),$$

$j, k = 1, \ldots, K$.

Note that $\tilde{N}_{jk}(t)$ is counting the number of transitions from states j to k and $\tilde{N}(t)$ is the observed total number of transitions. Define also the so called backwards recurrence time, given by $L(t) = t - \tau_{\tilde{N}(t^-)}$. It is assumed that the intensities are calculated with respect to the history or filtration $\mathcal{F}_t$ generated by the counting processes $\tilde{N}_{jk}(t)$ and the information available at $t = 0$.

Under the Cox proportional hazards assumption, the process $\{\tilde{N}_{jk}(t) : t \in [0, \tau], j, k \leq K\}$ is determined by the intensity

$$\begin{aligned} \Lambda_{jk}(dt) =& I\left[V(t^-) = j\right] \alpha_{jk}\left(L(t); \mathbf{Z}_{jk}\right) \\ =& I\left[V(t^-) = j\right] \alpha_{0,j}\left(L(t)\right) e^{\beta^T \mathbf{Z}_{jk}(L(t))} dt, \end{aligned}$$

where $\mathbf{Z}_{jk}(L(t))$ is a vector of covariates, $V(t^-)$ denotes the state of the observation at t^- and $\alpha_{0,j}$ is the baseline hazard function corresponding to the state j. Notice we are assuming that the intensities associated with the processes $\tilde{N}_{jk}(t)$ have proportional hazards.

The partial likelihood and score vector can be written in terms of the counting process associated to the sojourn times. In order to define the modified counting processes, it is necessary to create stopping times variables U_n, $n \geq 1$ given by

- $U_n = \tau_{n+1}$ if τ_n, τ_{n+1}, V_n and V_{n+1} are known;
- $\tau_n < U_n < \tau_{n+1}$ if V_n is known, V_{n+1} is unknown and $\tau_{n+1} - \tau_n > U_n - \tau_n$;
- $U_n = \tau_n$ if no information is available on $\tau_{n+1} - \tau_n$, V_n and V_{n+1}.

The counting processes associated with the sojourn times are then given by

$$N_{jk}(x) = \sum_{n\geq 0} I\left(\tau_{n+1} - \tau_n \leq x, V_n = j, V_{n+1} = k, U_n = \tau_{n+1}\right),$$

which counts the number of observed transitions from state j to state k with a sojourn time in state j less or equal to x, and

$$Y_j(x) = \sum_{n\geq 0} I\left(\tau_{n+1} - \tau_n \geq x, V_n = j, U_n - \tau_n \geq x\right),$$

which counts the number of times the patient was in state j for a sojourn time greater than x.

The partial log-likelihood can be written as

$$l(\boldsymbol{\beta}) = \log L(\boldsymbol{\beta}) = \sum_{i=1}^{m} \sum_{jk} \int_0^\tau \left[\boldsymbol{\beta}^T \mathbf{Z}_{jk,i}(x) - \log\left(m S_j^{(0)}(x,\boldsymbol{\beta})\right)\right] dN_{jk,i}(x),$$

where

$$S_j^{(0)}(x,\boldsymbol{\beta}) = \sum_k S_{jk}^{(0)}(x,\boldsymbol{\beta}),$$

$N_{jk,i}(x)$ and $Y_{j,i}(x)$ are replications of $N_{jk}(x)$ and $Y_j(x)$ for the i-th subject. The partial likelihood estimator $\hat{\boldsymbol{\beta}}$ is the solution of $U(\boldsymbol{\beta},\tau) = 0$, where $U(\boldsymbol{\beta},\tau)$ is the usual score vector. Dabrowska et al. (1994) shows that the usual normal asymptotic approximation for the distribution of $\hat{\boldsymbol{\beta}}$ holds.

The baseline cumulative hazard can be estimated by

$$\hat{A}_{0,j}(y,\boldsymbol{\beta}) = \sum_{i=1}^{m} \sum_k \int_0^y \frac{dN_{jk,i}(u)}{m S_j^{(0)}(u,\boldsymbol{\beta})}$$

and, given the proportional hazards assumption, the survival function of $T^{(j)\to(k)}$ is

$$\hat{S}_{jk}(x|\mathbf{Z}) = \left[e^{-\hat{A}_{0,jk}(x)}\right]^{e^{\hat{\boldsymbol{\beta}}^T \mathbf{Z}}}.$$

Recall that it is needed to estimate $\mathrm{E}(T^{(j)}|\mathbf{Z})$ in expression (3). Using the independence assumption among the latent times, the estimated survival function of $T^{(j)} = \min_{k\in B_{(j)}}\{T^{(j)\to(k)}\}$ is given by

$$\hat{S}_j(x|\mathbf{Z}) = \prod_{k\in B_{(j)}} \hat{S}_{jk}(x|\mathbf{Z})$$

and, finally,

$$\widehat{\mathrm{E}(T^{(j)}|\mathbf{Z})} = \int_0^\infty \hat{S}_j(x|\mathbf{Z})dx.$$

3.2 Parametric Model

Let us now consider that he sojourn times are independent random variables and identically distributed for a given vector of covariates with a known proportional hazards distribution (Weibull or exponential), in a competing risks framework. For the i-th realization of the process, denote by $0 = \tau_{i0} < \tau_{i1} < \tau_{i2} < \tau_{i3} < \ldots$ the instants of entrance in states $V_{i0}, V_{i1}, V_{i2}, V_{i3}, \ldots$, respectively. Also let $\mathbf{Z}_i$ be a vector of time independent covariates associated with the i-th observation.

Using arguments similar to those presented by Kalbfleisch and Prentice (2002), one can conclude that the contribution of an observation (patient) to the likelihood function is given by

$$L_i(\beta) = \prod_n \left\{ \left[\prod_{k \in B_j^*} \left(\alpha_{jk}(\tau_{i,n+1} - \tau_{i,n}; \mathbf{Z}_i)\right)^{\delta_{in}^{(k)}} \right] \times \right.$$
$$\left. \exp\left[-\int_0^{(C_i \wedge \tau_{i,n+1}) - \tau_{i,n}} \sum_{l \in B_j^*} \alpha_{jk}(u; \mathbf{Z}_i) du \right] \right\}^{I(V_{in}=j)},$$

where

$$\delta_{in}^{(k)} = \begin{cases} 1, & \text{if } V_{i(n+1)} = k \text{ and } \delta_i = 1 \\ 0, & \text{otherwise,} \end{cases}$$

δ_i is an indicator variable and equals 1 if the absorbing state is reached by the patient and 0 if the observation is censored before reaching the absorbing state and C_i is the censoring time ($C_i = \infty$ if $\delta_i = 1$).

Consider an exponential model with hazards

$$\alpha_{jk}(u; \mathbf{Z}_i) = \exp\left\{\beta^T \mathbf{Z}_{i,jk}\right\},$$

where $\mathbf{Z}_{i,jk}$ is the vector $\mathbf{Z}_i$ properly rearranged so that the vector of parameters β contains all parameters of each specific transition. The log-likelihood under this model is

$$\ell(\beta) = \sum_i \sum_{k,l} \left[\int_0^\tau \left(\beta^T \mathbf{Z}_{i,jk} dN_{i,jk}(u)\right) - e^{\beta^T \mathbf{Z}_{i,jk}} \int_0^\tau Y_{i,j}(u) du \right].$$

Maximum likelihood estimators are obtained by maximizing this log-likelihood and asymptotic results for parametric models are valid in this situation:

$$n_T^{1/2}(\hat{\beta} - \beta_0) \xrightarrow{\mathcal{D}} N\left(\mathbf{0}, \Sigma(\beta_0)^{-1}\right),$$

and $\Sigma(\beta_0)$ can be consistently estimated by $n_T^{-1} I(\hat{\beta})$, where $I(\beta) = -\frac{\partial^2 \ell(\beta)}{\partial \beta \partial \beta^T}$ is the observed information matrix.

4 Expected Number of Entrances in Each State

In order to compute (3), we also need the estimation of $\mathrm{E}(N_k)$, based on the model for the sojourn times. Consider initially the situation with 3 states, as illustrated in Figure 1.

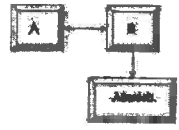

Figure 1: Three state process

Define the binary variables

$$M_{A,m} = \begin{cases} 1, & \text{if state A was visited at least } m \text{ times;} \\ 0, & \text{if the absorbing state was reached before,} \end{cases}$$

$m \geq 1$. In this case, $N_A = \sum_m M_{A,m}$. If $P(M_{A,1} = 1) = 1$, then $N_B = N_A$ and

$$\begin{aligned} P(M_{A,2} = 1) =& P(A \to B \to A) = \int_0^\infty \alpha_{BA}(u) \left(S_{BA}(u) S_{B0}(u)\right) du = p \\ & \vdots \\ P(M_{A,m} = 1) =& P(A \to B \to A \to B \to A \cdots \to A) \\ =& \int_0^\infty \alpha_{BA}(u) \left(S_{BA}(u) S_{B0}(u)\right) du \times \cdots \\ & \times \int_0^\infty \alpha_{BA}(u) \left(S_{BA}(u) S_{B0}(u)\right) du = p^{m-1}, \end{aligned}$$

where $\alpha_{BA}(u)$ is the hazard function of the transition $B \rightarrow A$, $S_{BA}(u)$ and $S_{B0}(u)$ are the corresponding survival functions. It follows that

$$\mathrm{E}(N_A) = \sum_m \mathrm{E}(M_{Am}) = 1 + \sum_{m=2}^{\infty} p^{m-1} = \frac{1}{1-p},$$

where $p = \int_0^\infty \alpha_{BA}(u) S_{BA}(u) S_{B0}(u) du$.

More generally, consider the situation with K transient states. Analogous to the easier case already presented, define

$$M_{k,m} = \begin{cases} 1, & \text{if state k was visited at least} m \text{ times;} \\ 0, & \text{if the absorbing state was reached before.} \end{cases}$$

As before, we have that $N_k = \sum_m M_{k,m}$, $\mathrm{E}(N_k) = \sum_m \mathrm{E}(M_{k,m}) = \sum_m P(M_{km} = 1)$ and the probability that a transition from k to k' occurs is

$$p_{kk'} = \int_0^\infty \alpha_{kk'}(u) \left(\prod_{l \in B_k^*} S_{kl}(u) \right) du.$$

Based on these probabilities, a transition matrix $\mathbf{P}$ with elements $p_{kk'}$ can be constructed. Assuming that all patients enter in the study in the same health state, it is possible to compute the probability f_{1k} of reaching k for the first time, given by the sum of the probabilities of reaching k in one, two, three, ...steps. Denote by $f_{kk}^{(n)}$ the probability of going from k to k in n steps, which can also be computed based on the transition matrix $\mathbf{P}$, and let

$$f_{kk} = \sum_{n=0}^{\infty} f_{kk}^{(n)}$$

be the probability of returning to k from k.

We have that $P(M_{k1} = 1) = f_{1k}$ and $P(M_{km} = 1) = f_{1k} (f_{kk})^{m-1}$, $m = 1, 2, \ldots$. Therefore,

$$\mathrm{E}(N_k) = f_{1k} \sum_{m=0}^{\infty} (f_{kk})^m = \frac{f_{1k}}{1 - f_{kk}}.$$

If it is not easy to compute f_{kk} for some reason, there is another way of computing the expected number of entrances in each state. For a single

realization of the processes, define the variables $W_n = 1, 2, \ldots, K$ indicating the state after the n-th transition. Note that $N_k = \sum_{n=1}^{\infty} I(W_n = k)$, $k = 1, \ldots, K$ and, assuming that all patients enter the study in the same health state,

$$E(N_k) = \sum_{n=1}^{\infty} p^{(n)}(E_0, k),$$

$k = 1, \ldots, K$, where $p^{(n)}(E_0, k)$ is the probability of being in state k after n steps from the initial state E_0 Hoel et al. (1972). This probability can be computed using the transition probability matrix $\mathbf{P}$.

The easiest way of computing the expected number of entrances in each state depends on the process considered. Consider the case in which the absorbing state can be reached from all transient states, i.e, $p_{j0} > 0 \; \forall j$. In this situation, it can be obtained easily based on the eigenvalues ad eigenvectors of the matrix $\mathbf{P}$. Since $\mathbf{P}$ is a stochastic matrix, it is clear that $\lambda = 1$ is an eigenvalue of $\mathbf{P}$. Define the matrix $\mathbf{Q}$ given by the matrix $\mathbf{P}$ with the first row and column deleted. If there are k transient states, then P is a $(k+1) \times (k+1)$ matrix and $\mathbf{Q}$ has dimensions $k \times k$. Also, the sum of row elements of $\mathbf{Q}$ is less than 1 because we are assuming that $p_{j0} > 0$, $\forall j$. In this situation, it can be shown that all eigenvalues of $\mathbf{Q}$ are less than unity in absolute value.

It is also important to verify that the probabilities $p^{(n)}(i, i)$, $i = 1, \ldots, k$ can be obtained based on the reduced matrix $\mathbf{Q}$ for the matrix $\mathbf{P}$ considered here. This is true because the first row of $\mathbf{P}$ has the first element equal to 1 and all others equal to zero. The two step probability transition matrix is

$$\mathbf{P} \times \mathbf{P} = \begin{pmatrix} 1 & 0 & \cdots & 0 \\ q_{10}^* & & & \\ \vdots & \mathbf{Q} \times \mathbf{Q} & & \\ q_{k0}^* & & & \end{pmatrix}.$$

By the spectral decomposition of $\mathbf{Q}$, we have

$$\mathbf{Q} = \mathbf{U}\mathbf{D}\mathbf{U}^{-1},$$

where $\mathbf{D} = \text{diag}\{\lambda_1, \ldots, \lambda_k\}$ and $\mathbf{U}$ is the matrix formed by the eigenvectors of $\mathbf{Q}$. The n-th step transition probability matrix is

$$\mathbf{Q}^{(n)} = \underbrace{\mathbf{Q} \times \mathbf{Q} \ldots \times \mathbf{Q}}_{n \text{ times}} = \mathbf{U}\mathbf{D}^{(n)}\mathbf{U}^{-1},$$

since $\mathbf{U}^{-1}\mathbf{U} = \mathbf{I}$. Therefore,

$$\sum_{n=1}^{\infty} \mathbf{Q}^{(n)} = \sum_{n=1}^{\infty} \mathbf{U}\mathbf{D}^{(n)}\mathbf{U}^{-1} = \mathbf{U}\left(\sum_{n=1}^{\infty} \mathbf{D}^{(n)}\right)\mathbf{U}^{-1}.$$

If all eigenvalues of $\mathbf{Q}$ are less than 1, then

$$\sum_{n=1}^{\infty} \mathbf{D}^{(n)} = (\mathbf{I} - \mathbf{D})^{-1} - \mathbf{I}$$

and

$$\sum_{n=1}^{\infty} \mathbf{Q}^{(n)} = \mathbf{U}\left((\mathbf{I} - \mathbf{D})^{-1} - \mathbf{I}\right)\mathbf{U}^{-1}.$$

The expected number of entrances in a state is the corresponding element of the diagonal of the above matrix.

It is clear that the expected number of entrances in each state can be expressed in terms of quantities of the model for the sojourn times. The quantities f_{kk} and f_{1k} depend on the baseline hazard functions of the model for the sojourn times.

5 Three state process

We present here, in details, the estimator of the mean quality adjusted survival time in the situation in Figure 1, with only three states (two transient and one absorbing). The mean quality adjusted survival time (2) in these situations, given a vector of covariates $\mathbf{Z}$, is

$$\begin{aligned}\mu_Q &= q_A \mathrm{E}\left[\sum_{j=1}^{N_A} T_j^{(A)} \mid \mathbf{Z}\right] + q_B \mathrm{E}\left[\sum_{j=1}^{N_B} T_j^{(B)} \mid \mathbf{Z}\right] \\ &= q_A \mathrm{E}\left[\mathrm{E}\left(\sum_{j=1}^{N_A} T_j^{(A)} | N_A, \mathbf{Z}\right)\middle| \mathbf{Z}\right] + q_B \mathrm{E}\left[\mathrm{E}\left(\sum_{j=1}^{N_B} T_j^{(B)} | N_B, \mathbf{Z}\right)\middle| \mathbf{Z}\right] \quad (4)\end{aligned}$$

By the competitive risk structure for the sojourn times in state B, we have

$$T_j^{*(B)} = \min\{T_j^{(B)\to(A)}, T_j^{(B)\to(O)}\},$$

where O denotes the absorbing state. It is not necessary to assume a competitive risk structure for the sojourn time in state A because from this state it is not possible to reach the absorbing state from A.

We now assume that $T_j^{(A)}, T_j^{(B)\to(A)}$ and $T_j^{(B)\to(O)}$ are independent random variables for all j. According to Section 2, it is needed to compute the conditional expectation of $T_j^{*(B)}$, given the number of entrances in state B, that is the distribution of

$$\min\{T_j^{(B)\to(A)}, T_j^{(B)\to(O)}\} | T_j^{(B)\to(0)} > T_j^{(B)\to(A)}$$

for $j = 1, \ldots, N_B - 1$ and of

$$\min\{T_{N_B}^{(B)\to(A)}, T_{N_B}^{(B)\to(O)}\} | T_j^{(B)\to(0)} < T_j^{(B)\to(A)}.$$

Recall that we denote by $T_j^{(B)}$ the random variable with same distribution as $\min\{T_j^{(B)\to(A)}, T_j^{(B)\to(O)}\} | T_j^{(B)\to(0)} > T_j^{(B)\to(A)}$ and by $T_{N_B}^{\dagger(B)}$ the random variable distributed as $\min\{T_{N_B}^{(B)\to(A)}, T_{N_B}^{(B)\to(O)}\} | T_j^{(B)\to(0)} < T_j^{(B)\to(A)}$. We consider two different situations: assuming that the sojourn times are exponentially distributed and assuming a semi parametric proportional hazards model for the sojourn times. In both situations, it is assumed tha the latent times in each health state have proportional hazards, so that the mean quality-adjusted survival (4) can be expressed as

$$\mu_Q = q_A \left[\mathrm{E}(N_A|\mathbf{Z})\right] \mathrm{E}(T^{(A)}|\mathbf{Z}) + q_B \left[\mathrm{E}(N_B|\mathbf{Z})\right] \mathrm{E}(T^{(B)}|\mathbf{Z}).$$

Consider now the exponential assumption, i.e., assume that $T_j^{(B)\to(A)}$ and $T_j^{(B)\to(O)}$ are exponentially distributed with hazards respectively given by λ_{BA} and λ_{BO}.

It can be shown that $T_j^{(B)}$ and $T_{N_B}^{\dagger(B)}$ are both exponentially distributed with hazard given by $\lambda_{\min|\mathbf{Z}} = \lambda_{BA|\mathbf{Z}} + \lambda_{BO|\mathbf{Z}}$. Denoting by $\lambda_{A|\mathbf{Z}}$ the hazard associated with the sojourn times $T_j^{(A)}$, the mean quality adjusted survival time is

$$\mu_Q = q_A \left[\mathrm{E}(N_A|\mathbf{Z})\right] \frac{1}{\lambda_{A|\mathbf{Z}}} + q_B \left[\mathrm{E}(N_B|\mathbf{Z})\right] \frac{1}{\lambda_{BA|\mathbf{Z}} + \lambda_{BO|\mathbf{Z}}}.$$

In order to compute $\mathrm{E}(N_A|\mathbf{Z})$ and $\mathrm{E}(N_B|\mathbf{Z})$, notice that $N_A = N_B$ in the situation considered here. Using the results in Section 3, we have that

$\mathrm{E}(N_A|\mathbf{Z}) = \frac{1}{1-p_\mathbf{Z}}$, where

$$p_\mathbf{Z} = \int_0^\infty \lambda_{BA|\mathbf{Z}}(u) S_{BA|\mathbf{Z}}(u) S_{BO|\mathbf{Z}}(u) du = \frac{\lambda_{BA|\mathbf{Z}}}{\lambda_{BA|\mathbf{Z}} + \lambda_{BO|\mathbf{Z}}}.$$

Finally, the expression for the mean quality adjusted survival for this situation is

$$\mu_Q = q_A \frac{1}{\lambda_{A|\mathbf{Z}}} \frac{\lambda_{BA|\mathbf{Z}} + \lambda_{BO|\mathbf{Z}}}{\lambda_{BO|\mathbf{Z}}} + q_B \frac{1}{\lambda_{BO|\mathbf{Z}}}. \tag{5}$$

The estimation of $\lambda_{A|\mathbf{Z}}$, $\lambda_{BA|\mathbf{Z}}$ and $\lambda_{BO|\mathbf{Z}}$ can be done in the usual way. Assuming that for a single observation the sojourn times in each state are independent, the likelihood function for right censored data can be easily constructed as in Section 3.2 and maximum likelihood estimators can be obtained by maximizing the log-likelihood. An estimator of (5) is computed replacing the unknown quantities by its estimators.

Consider the semi parametric approach, i.e., assume that $T_j^{(B)\to(A)}$ and $T_j^{(B)\to(O)}$ are have hazard functions given by $\lambda_{BA|\mathbf{Z}}(t) = \lambda_0(t) e^{\mathbf{Z}^T \beta_{BA}}$, and $\lambda_{BO|\mathbf{Z}}(t) = \lambda_0(t) e^{\mathbf{Z}^T \beta_{BO}}$, respectively, where λ_0 is a baseline hazard function. It is important to notice tha we are assuming that $T_j^{(B)\to(A)}$ and $T_j^{(B)\to(O)}$ have proportional hazards. With this assumption, it can be shown that $T_j^{(B)} = \min\{T_j^{(B)\to(A)}, T_j^{(B)\to(O)}\} | T_j^{(B)\to(0)} > T_j^{(B)\to(A)}$ is distributed with hazard given by $\lambda_{\min|\mathbf{Z}}(t) = \lambda_{BA|\mathbf{Z}}(t) + \lambda_{BO|\mathbf{Z}}(t)$. Similarly, it can also be shown that $T_{N_B}^{\dagger(B)}$ is also distributed with hazard $\lambda_{\min|\mathbf{Z}}(t) = \lambda_{BA|\mathbf{Z}}(t) + \lambda_{BO|\mathbf{Z}}(t)$. Denoting by $\lambda_{A|\mathbf{Z}}(t)$ the hazard associated with the sojourn times $T_j^{(A)}$, the mean quality adjusted survival time is

$$\mu_Q = q_A \left[\mathrm{E}(N_A|\mathbf{Z})\right] \mathrm{E}(T^{(A)}|\mathbf{Z}) + q_B \left[\mathrm{E}(N_B|\mathbf{Z})\right] \mathrm{E}(T^{(B)}|\mathbf{Z}).$$

In order to compute $\mathrm{E}(N_A|\mathbf{Z})$ and $\mathrm{E}(N_B|\mathbf{Z})$, notice that $N_A = N_B$ in the situation considered here. Using the results in section 4, we have that $\mathrm{E}(N_A|\mathbf{Z}) = \frac{1}{1-p_{|\mathbf{Z}}}$, where

$$p_\mathbf{Z} = \int_0^\infty \lambda_{BA|\mathbf{Z}}(u) S_{BA|\mathbf{Z}}(u) S_{BO}(u) du = \frac{e^{\mathbf{Z}^T \beta_{BA}}}{e^{\mathbf{Z}^T \beta_{BA}} + e^{\mathbf{Z}^T \beta_{BO}}}.$$

Finally, the expression for the mean quality adjusted survival for this situation is

$$\mu_Q = \frac{e^{\mathbf{Z}^T \beta_{BA}} + e^{\mathbf{Z}^T \beta_{BO}}}{e^{\mathbf{Z}^T \beta_{BO}}} \left(q_A \mathrm{E}(T^{(A)}|\mathbf{Z}) + q_B \mathrm{E}(T^{(B)}|\mathbf{Z})\right). \tag{6}$$

Estimators for β_{BA} and β_{BO} are obtained by fitting a semi parametric model, as described in Section 3.1. Assuming that for a single observation the sojourn times in each state are independent, the partial likelihood function for right censored data can be constructed as shown in Section 3.1 and estimators can be obtained by maximizing the partial log-likelihood. An estimator of (6) is obtained substituting the unknown quantities by its estimators.

6 Simulation Study

In this section, we conduct a simulation study in order to evaluate the performance of the proposed estimator. We applied the Jackknife in order to compute the estimated variance and also the estimated bias of the proposed estimator. We consider the model shown in Figure 1, with two transient states and one absorbing state, and one binary covariate was included in the model. In the simulation, we assigned the value 1 for the covariate for half of the observations, so that each observation have a 50% chance of being assigned the value 1 for the covariate. We assume that all observations are in the good health state in the beginning of the study. The sojourn times in state A are exponentially distributed with hazards equal to $\lambda_{A|x} = \exp(2 + \beta_A x)$, where x is the binary covariate, and the sojourn times in state B is the minimum of the time until a a transition to A, $T_j^{(B)\to(A)}$, and the time until a transition to the absorbing state, $T_j^{(B)\to(O)}$. $T_j^{(B)\to(A)}$ and $T_j^{(B)\to(O)}$ are exponentially distributed with equal hazards, given by $\lambda_{B|x} = \exp(1 + \beta_B x)$. In the results shown here, we also assumed that $\beta_A = \beta_B$.

We consider data with 0%, 30% and 50% of censoring. An observation is considered censored if it is not known the instant in which it reaches the absorbing state; it is only known that the observation reaches the absorbing state after the censoring time. We consider a random censoring and the censoring times are random variables exponentially distributed. The hazard of the censoring variable was computed so that the probability of an observation being censored equals the desired proportion of censoring. In order to do so, first notice that from (5) it is possible to obtain an expression for the expected survival time:

$$\mu_x = \frac{1}{\lambda_{A|x}} \frac{\lambda_{BA|x} + \lambda_{BO|x}}{\lambda_{BO|x}} + \frac{1}{\lambda_{BO|x}}.$$

Since the probability of $x = 1$ is $1/2$, it is possible to compute the mean

survival time:

$$\mu = (1/2)\mu_1 + (1/2)\mu_0.$$

For T and C independent exponentially distributed random variables, it is known that $P(C > T) = \frac{\lambda_T}{\lambda_C + \lambda_T}$ and $\lambda_T = \frac{1}{\mu_T}$. Motivated by this results, the hazard of the censoring variable was considered to be

$$\lambda_C = \frac{p_c}{(1 - p_c)\mu},$$

where p_c is the desired proportion of censored observations. The simulated data showed that these approximations worked very well and the proportions of censored observations were very close to the desired ones.

If no transition between two states is observed in a particular sample or data, it is not possible to estimate the parameters associated to that transition. In our simulation, it happened for heavy censoring rates and small sample size and we took those samples off and generated another sample, so that all parameters could be estimated in all samples used to compute the results. Actually, we considered samples with at least two observed transitions from state A to B, B to A and B to 0, so that the Jackknife could be applied. In this simulation, the Jackknife was done removing all sojourn times observed in a patient, i.e., removing one patient at each jackknife sample. This can be viewed as a grouped Jackknife with different group sizes.

We applied the parametric model with exponential distribution and also the semi parametric approach. Tables 1 and 2 show the simulations results for the parametric model and sample sizes $n = 30$ and $n = 200$, respectively, based on 1000 simulations for each scenario. Tables 3 and 4 refer to simulations results for the semi parametric model and sample sizes $n = 30$ and $n = 200$, also based on 1000 simulations. We assumed that the QOL scores for states A and B are 1 and 0.3, respectively.

In general, the proposed estimator provides accurate estimates with light and moderate censoring rates, even with small sample sizes. It is clear that for light censoring our proposed estimator have small bias, but the bias increases when there is heavy censoring rate. The results for the parametric approach were in general better than the semi parametric, but it was expected since the data was simulated with exponential distribution. The Jackknifed estimator has smaller bias, but it is still biased when the rate of censoring is heavy. The Jackknife estimator for the variance of $\hat{\mu}_Q$ provides in general a very

Table 1. Simulation results for sample size $n = 30$ for the parametric model with exponential distribution: sample average of $\hat{\mu}_Q$. sample average of the Jackknife estimator $\hat{\mu}_{Q,J}$, sample average of the estimated bias using Jackknife, sample variance of μ_Q (SV) and sample average of the estimated variance using Jackknife (EVJ).

Censoring rate (%)	β	Covariate value	μ_Q	$\hat{\mu}_Q$	$\hat{\mu}_{Q,J}$	Bias	SV	EVJ
0	0.5	0	15.59	15.67	15.67	0.0000	2.30	2.36
0	0.5	1	25.71	25.72	25.72	0.0000	6.47	6.38
0	2	0	15.59	15.67	15.67	0.0000	2.30	2.35
0	2	1	115.22	115.28	115.28	0.0000	129.98	127.51
0	1	0	15.59	15.67	15.67	0.0000	2.30	2.36
0	1	1	42.39	42.41	42.41	0.0000	17.59	17.34
30	0.5	0	15.59	16.83	16.77	0.0639	3.99	3.73
30	0.5	1	25.71	29.22	29.03	0.1847	14.28	13.29
30	2	0	15.59	15.97	15.95	0.0188	2.78	2.68
30	2	1	115.22	139.21	137.95	1.2562	371.14	362.78
30	1	0	15.59	16.47	16.43	0.0441	3.37	3.26
30	1	1	42.39	49.82	49.45	0.3730	38.59	42.18
50	0.5	0	15.59	18.73	18.56	0.1693	6.49	6.54
50	0.5	1	25.71	35.33	34.79	0.5414	31.13	32.77
50	2	0	15.59	16.52	16.47	0.0463	3.24	3.31
50	2	1	115.22	179.24	175.27	3.9627	1009.80	1115.50
50	1	0	15.59	17.90	17.78	0.1142	4.56	5.02
50	1	1	42.39	61.31	60.20	1.1108	109.90	112.26

Table 2. Simulation results for sample size $n = 200$ for the parametric model with exponential distribution: sample average of $\hat{\mu}_Q$, sample average of the Jackknife estimator $\hat{\mu}_{Q,J}$, sample average of the estimated bias using Jackknife, sample variance of μ_Q (SV), sample average of the estimated variance using Jackknife (EVJ) and sample average of estimated variance using Delta method (EVD).

Censoring rate (%)	β	Covariate value	μ_Q	$\hat{\mu}_Q$	$\hat{\mu}_{Q,J}$	Bias	SV	EVJ
0	0.5	0	15.59	15.67	15.67	0.0000	2.30	2.36
0	0.5	1	25.71	25.72	25.72	0.0000	6.47	6.38
0	2	0	15.59	15.67	15.67	0.0000	2.30	2.35
0	2	1	115.22	115.28	115.28	0.0000	129.98	127.51
0	1	0	15.59	15.67	15.67		2.30	2.36
0	1	1	42.39	42.41	42.41		17.59	17.34
30	0.5	0	15.59	16.83	16.77	0.0639	3.99	3.73
30	0.5	1	25.71	29.22	29.03	0.1847	14.28	13.29
30	2	0	15.59	15.97	15.95	0.0188	2.78	2.68
30	2	1	115.22	139.21	137.95	1.2562	371.14	362.78
30	1	0	15.59	16.47	16.43	0.0441	3.37	3.26
30	1	1	42.39	49.82	49.45	0.3730	38.59	42.18
50	0.5	0	15.59	18.73	18.56	0.1693	6.49	6.54
50	0.5	1	25.71	35.33	34.79	0.5414	31.13	32.77
50	2	0	15.59	16.52	16.47	0.0463	3.24	3.31
50	2	1	115.22	179.24	175.27	3.9627	1009.80	1115.50
50	1	0	15.59	17.90	17.78	0.1142	4.56	5.02
50	1	1	42.39	61.31	60.20	1.1108	109.90	112.26

Table 3. Simulation results for sample size $n = 30$ for the semiparametric model: sample average of $\hat{\mu}_Q$. sample average of the Jackknife estimator $\hat{\mu}_{Q,J}$, sample average of the estimated bias using Jackknife, sample variance of μ_Q (SV) and sample average of the estimated variance using Jackknife (EVJ).

Censoring rate (%)	β	Covariate value	μ_Q	$\hat{\mu}_Q$	$\hat{\mu}_{Q,J}$	Bias	SV	EVJ
0	0.5	0	15.59	16.34	15.84	0.4950	16.80	17.45
0	0.5	1	25.71	26.55	26.08	0.4706	44.64	47.42
0	2	0	15.59	16.44	15.70	0.7347	16.62	17.41
0	2	1	115.22	120.46	117.43	3.0360	905.15	959.57
0	1	0	15.59	16.35	15.74	0.6168	17.05	17.63
0	1	1	42.39	44.02	43.17	0.8488	123.02	129.88
30	0.5	0	15.59	18.22	17.24	0.9760	33.60	36.69
30	0.5	1	25.71	30.51	29.70	0.8151	111.49	133.03
30	2	0	15.59	16.93	15.57	1.3552	19.75	22.97
30	2	1	115.22	149.14	145.85	3.2828	3925.47	5479.13
30	1	0	15.59	18.01	16.69	1.3126	29.09	32.59
30	1	1	42.39	51.73	50.68	1.0569	357.38	448.87
50	0.5	0	15.59	22.40	21.21	1.1856	77.34	112.58
50	0.5	1	25.71	37.13	35.44	1.6837	308.47	601.12
50	2	0	15.59	18.82	16.03	2.7855	37.86	51.94
50	2	1	115.22	189.98	179.27	10.7036	9812.50	25142.07
50	1	0	15.59	21.76	19.98	1.7816	77.24	99.05
50	1	1	42.39	65.97	62.70	3.2612	1018.02	2308.04

Table 4. Simulation results for sample size $n = 200$ for the semiparametric model: sample average of $\hat{\mu}_Q$, sample average of the Jackknife estimator $\hat{\mu}_{Q,J}$, sample average of the estimated bias using Jackknife, sample variance of μ_Q (SV) and sample average of the estimated variance using Jackknife (EVJ).

Censoring rate (%)	β	Covariate value	μ_Q	$\hat{\mu}_Q$	$\hat{\mu}_{Q,J}$	Bias	SV	EVJ
0	0.5	0	15.59	15.68	15.59	0.0953	2.14	2.38
0	0.5	1	25.71	25.88	25.72	0.1647	6.81	6.43
0	2	0	15.59	15.68	15.58	0.0982	2.13	2.36
0	2	1	115.22	116.32	115.28	1.0455	136.31	128.61
0	1	0	15.59	15.66	15.58	0.0852	2.13	2.36
0	1	1	42.39	42.75	42.41	0.3358	18.46	17.43
30	0.5	0	15.59	17.42	17.22	0.1940	4.26	4.32
30	0.5	1	25.71	30.24	30.36	-0.1169	16.53	17.75
30	2	0	15.59	16.12	15.97	0.1543	2.63	2.76
30	2	1	115.22	148.81	150.96	-2.1422	593.76	621.39
30	1	0	15.59	16.79	16.57	0.2205	3.26	3.59
30	1	1	42.39	51.87	52.38	-0.5141	66.20	65.52
50	0.5	0	15.59	21.95	22.16	-0.2069	16.06	15.96
50	0.5	1	25.71	39.49	41.39	-1.9058	60.17	69.62
50	2	0	15.59	16.86	16.56	0.2967	3.78	3.77
50	2	1	115.22	214.63	232.61	-17.9789	2690.86	3093.24
50	1	0	15.59	20.06	19.74	0.3211	9.60	10.68
50	1	1	42.39	71.17	75.78	-4.6126	261.80	273.50

good approximations and also the delta method for the parametric situation provided good results. For small samples sizes and heavy censoring rates, however, the Jackknife estimator of variance may overestimate the variance due to the fact that some jackknife samples (the original data with an observation deleted) do not have enough observed data on some transitions. Although all samples used had at least two observed transitions between states, some Jackknife samples had only one observed transition.

7 Discussion

In this paper, an estimator of the mean quality-adjusted survival time is proposed, based on multi state models. It is especially useful when one wants to compare treatments or drugs using both quality-of-life and survival. The estimator allows the incorporation of covariates and it is very flexible since it can be obtained based on parametric and semi parametric models.Although only right censoring was considered, the extension for interval and left censored observations is straightforward.

We assumed independence among sojourn times for a given patient. This assumption may not be appropriate and, although it may be reasonable as a first approximation, extension to a more general framework should be considered. A possible solution could be to consider multi state models with frailty terms associated to the dependence among the sojourn times. The identically distributed assumption of sojourn times given a vector of covariates also may not be an appropriate assumption. For example, it may be reasonable to assume that the mean sojourn time spent in a state of good health decreases with chronological time and this trend should be included in the model. These issues are still to be developed.

In conclusion, the proposed estimator allows the incorporation of quality-of-life in addition to survival time in the analysis of data. Despite the assumptions made, simulations results show that the estimator behaves properly and may be a very helpful tool for comparisons of treatments or drugs.

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