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Quality-Adjusted Survival Estimation with Periodic Observations

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SUMMARY. Quality-adjusted survival is a measure that integrates both longevity and quality-of-life information. The analysis of quality-adjusted survival in a clinical study with data collected at periodic intervals encounters difficulties due to incomplete information. Based on observed time points, the time axis is partitioned into a set of disjoint time intervals, and under a Markovian assumption on patient's health status, the expected quality-adjusted survival is estimated as the summed product of the quality of life and its mean sojourn time of each health state within partitioned intervals. It is shown that the estimator is asymptotically normal with a simple variance calculation. A simulation study is conducted to investigate the behavior of the estimator, and a stroke study illustrates the use of the estimator.

KEY WORDS: Interval censoring; Kaplan Meier estimator; Markov process; Quality of life; Right censoring; Survival analysis.

1. Introduction

In clinical trials, often the change of a patient's health, which is a composite of related outcomes that reflect physical and emotional well-being as well as survival, is measured over time under the influence of one or more treatments. A clinical endpoint that can integrate both longevity and quality-of-life (QOL) information in trials is preferable. Quality-adjusted survival (QAS) is a measure proposed to incorporate health-related QOL and survival time. For example, a QAS can be expressed as a summary statistic that presents the area under the curve of QOL scores (or utility coefficients) plotted against time or as a function the QOL scores and the times spent in each health state (Gelber, Gelman, and Goldhirsch, 1989; Glasziou, Simes, and Gelber, 1990; Cox et al., 1992; Zhao and Tsiatis, 1999). In general, the QAS is a time-dependent function reflecting an individual's experiences and perceptions over life history.

Many QAS studies rest on the assumption that the transition information of a patient's health status is available or that the health status follows a consecutive process. However, due to the nature of disease and practical constraints, the health status may not be a consecutive process and the transition of a patient's health status is not always observable. For example, in a spontaneous intracerebral hemorrhage (SICH) clinical study (Bernard, 1994), investigators are typically interested in a patient's morbidity and mortality. In this study,

the clinical observations are made monthly after a patient is discharged from a hospital, and the patient's QOL or health status is recorded into five categories of the Glasgow Outcome Score. However, due to loss to follow-up or missing visits, patients may experience more than one type of health status between two clinic visits, and information about transitions and the duration of health status between these discrete time points may not be available. Since the QOL for a patient with SICH behaves as a process with reversible health status, the problems of incomplete patient health information can complicate the estimation of QAS. Zhao and Tsiatis (2000) proposed a method using a general representation theorem for missing data processes in adjusting for informative censoring to estimate the distribution and mean of the QAS. Nevertheless, when an individual's QAS may be unobservable due to missing health status transition information, their method as well as other existing methods of estimating mean QAS, like the partitioned survival method (Glasziou et al., 1990) and the time-marginal method (Huang and Louis, 1999), may not be applicable without a further assumption about the distribution of health status. Glasziou et al. (1998) used an interpolation method to measure the QOL with missing observations or nonresponses. However, for subjects who are lost to follow-up, are censored, or die, the interpolations are based on the previous QOL history rather than the current QOL information in-study, and hence, their estimates can be biased.

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Because of the difficulty of specifying the life history through periodic observation, it is necessary to postulate some underlying statistical model for the QOL process. Multistate models (Chiang, 1980) and compartmental models (Faddy, 1976) under Markovian assumptions have been proven to be useful tools for understanding health transitions and have been proposed for comparable situations (Olschewski and Schumacher, 1990). In this study, we derive an estimator of mean QAS based on the assumption that the QOL process is Markovian; this in turn allows the estimator to accommodate a QOL process with periodic observations. There is no requirement of continuous observation of patients' QOL or exact transition times, which may not be feasible in clinical trial settings. Using Slutsky's Theorem, we show that the estimator is asymptotically normal.

Section 2 presents a decomposition of mean QAS based on observed time points. The decomposed mean QAS involves two unknown components: weights of health status and expected survival times for given time intervals. In Section 3, we propose an estimation procedure for the unknown components with right-censored and interval-censored data. Section 4 describes treatment comparison with estimated QAS. Sections 5 and 6 contain a simulation study and a stroke study illustrating the proposed estimation, and we conclude with a discussion in Section 7.

2. Decomposition of QAS

Suppose that there are n individuals under study and each individual may experience $k + 1$ events $\{0, 1, \dots, k\}$, where state 0 denotes an absorbing state while states $1, 2, \dots, k$ are transient. We further assume that the h th individual's health history can be described by a continuous-time multistate process, $\{X_h(t)\}$, where $X_h(t)$ maps to the state space $\Gamma = \{0, 1, \dots, k\}$; i.e., at any time t , the health status $X_h(t)$ can take on any of $k + 1$ values corresponding to different states of health. Let $T_h = \inf\{t : X_h(t) = 0\}$ be the time that it takes the h th individual to move into the absorbing state 0, i.e., T_h is the survival time for the h th individual. In addition, we define a QOL function Q mapping the state space to a prespecified set of real numbers. For reference and convenience, the value of QOL is set to zero for the absorbing state, i.e., $Q(0) \equiv 0$. With this notation, the h th individual's quality-adjusted survival is

$$U_h = \int_0^{T_h} Q\{X_h(t)\}dt.$$

To evaluate U_h in a study with a periodic observational scheme, we first partition the time axis into a set of disjoint intervals based on the observed times. Suppose that t_0, t_1, \dots, t_m correspond to the times of scheduled follow-up of a study and let $X_h(t_{h,0}), X_h(t_{h,1}), \dots, X_h(t_{h,m_h})$ be the observation of the sequence of health states $\{0, 1, \dots, k\}$ for a given individual h at times $t_{h,0}, t_{h,1}, \dots, t_{h,m_h}$ in which $\{t_{h,0}, t_{h,1}, \dots, t_{h,m_h}\}$ is a subset of $\{t_0, t_1, \dots, t_m\}$. Using the set of times $0 = t_0 \leq t_1 \leq \dots \leq t_m < \infty$, one can partition the time axis into a set of disjoint intervals such that the following two conditions are satisfied:

- (a) $\{t_{h,0}, t_{h,1}, \dots, t_{h,m_h}\} \subseteq \{t_0, t_1, \dots, t_m\}$ for all h ;
- (b) $\cup_{1 \leq h \leq n} \{t_{h,0}, t_{h,1}, \dots, t_{h,m_h}\} = \{t_0, t_1, \dots, t_m\}$.

Under the partition, any intervals of successive observed

time points $O_{h,r} = \{t_{h,r-1}, t_{h,r}\}$, $1 \leq r \leq m_h$, can be expressed as a finite union of the disjoint intervals, i.e., $O_{h,r} = \cup_{s=1}^m E^s$ with $E^s = \{t_{s-1}, t_s\} I(\{t_{s-1}, t_s\} \subseteq O_{h,r})$.

In connection with the partition, we further assume that individuals with the same health status within the same interval $[t_{s-1}, t_s]$ will have the same QOL, q_{is} , $i = 1, \dots, k$, i.e., $Q\{X_h(t)\} = q_{is}$ if $X_h(t) = i, t \in [t_{s-1}, t_s]$. By this setting, the QAS for subject h can be represented as the sum of the quality of life multiplied by its sojourn time

$$\begin{aligned} U_h &= \sum_{s=1}^m \int_{t_{s-1}}^{t_s} Q\{X_h(t)\}dt \\ &= \sum_{s=1}^m \sum_{i=1}^k \int_{\mathcal{I}_{his}} Q\{X_h(t)\}dt \\ &= \sum_{s=1}^m \sum_{i=1}^k q_{is} l_{his}, \end{aligned} \tag{1}$$

where \mathcal{I}_{his} is the time interval for an individual h with health state i within $[t_{s-1}, t_s]$ and $l_{his} = \|\mathcal{I}_{his}\|$ is the norm of \mathcal{I}_{his} . Note that $l_{his} = 0$ for an individual either in the absorbing state or censored by time t_{s-1} . Therefore, the expected QAS for an individual is found to be

$$\mu_{QAS} = \sum_{s=1}^m \sum_{i=1}^k q_{is} l_{is},$$

where l_{is} is the mean sojourn time of an individual with health state i in $[t_{s-1}, t_s]$. Since the mean sojourn time, l_{is} , is still a measure involving survival time and health status, for estimation, we further decompose l_{is} such that the survival time and the duration of health status can be separated. Let L_s be a random variable representing the length of survival within the time interval $[t_{s-1}, t_s]$ and let w_{is} be the weight as a chance that a subject would stay at state i in the time interval $[t_{s-1}, t_s]$. If $S(t)$ is the survival distribution, the mean sojourn time for an individual staying at state i in the time interval $[t_{s-1}, t_s]$ is

$$l_{is} = w_{is} \times E(L_s) = w_{is} \times \int_{t_{s-1}}^{t_s} S(t)dt = w_{is} \times g_s(S).$$

Under this representation of sojourn time, the μ_{QAS} can be displayed as

$$\mu_{QAS} = \sum_{s=1}^m \sum_{i=1}^k q_{is} w_{is} g_s(S) = \mathbf{q}' \times \mathbf{W} \times \mathbf{H} \times \mathbf{G}(S), \tag{2}$$

where $\mathbf{q} = (q_{is})_{mk \times 1}$, $\mathbf{W} = \text{diag}(w_{11}, w_{12}, \dots, w_{1m}, \dots, w_{k1}, \dots, w_{km})_{mk \times mk}$, $\mathbf{G}(S)' = (g_1(S), \dots, g_m(S))$, and $\mathbf{H} = \mathbf{I}_{m \times m} \otimes \mathbf{J}_{k \times 1}$ is the Kronecker product of an identity matrix $\mathbf{I}_{m \times m}$ and a vector $\mathbf{J}_{k \times 1}$ with all elements equal to one.

3. Estimation of the Mean QAS

Based on the decomposition, the μ_{QAS} can be estimated by the estimation of weight \mathbf{W} and the expected survival time $\mathbf{G}(S)$. We next estimate \mathbf{W} and $\mathbf{G}(S)$ under the assumption that the observed health history $\{X(t)\}$ follows a $(k+1)$ -state Markov process. Let $P_{ij}(t_{s-1}, t_s)$ be the transition probability

for a subject from health state i at time t_{s-1} to health state j at time t_s . Under the first-order Markov assumption,

$$\begin{aligned} \Pr\{X(t_s) = j \mid X(t_{s-1}) = i, X(t_r), 0 \leq r < s-1\} \\ = \Pr\{X(t_s) = j \mid X(t_{s-1}) = i\} = P_{ij}(t_{s-1}, t_s) \end{aligned}$$

and the transition probability matrix for the interval $[t_{s-1}, t_s)$ can be expressed as

$$P(\theta_s) = \begin{pmatrix} 1 & 0 & \dots & 0 \\ \theta_{10s} & \theta_{11s} & \dots & \theta_{1ks} \\ \theta_{20s} & \theta_{21s} & \dots & \theta_{2ks} \\ \vdots & \vdots & \ddots & \vdots \\ \theta_{k0s} & \theta_{k1s} & \dots & \theta_{kks} \end{pmatrix},$$

with $\theta_{ijs} = p_{ij}(t_{s-1}, t_s)$ and $\theta_{iis} = 1 - \sum_{j \neq i} \theta_{ijs}$. We note that a greater value of θ_{iis} indicates a smaller chance of transition from state i to other states, i.e., the longer is the time period individuals will stay at the same state. Moreover, a greater value of θ_{lis} ($l \neq i$) indicates a greater chance of transition from other states to state i . Therefore, the weight of the mean sojourn time at state i for individuals in $[t_{s-1}, t_s)$ can be considered as an increasing function of $(\theta_{lis})_{l=1, \dots, k}$ and it can be viewed as the chance of the health status that individuals might experience during interval $[t_{s-1}, t_s)$. In this study, an intuitive weight is chosen as

$$w_{is}(\theta) = \frac{\sum_{l=1}^k \theta_{lis}}{\sum_{j=1}^k \sum_{l=1}^k \theta_{ljs}} \quad i = 1, 2, \dots, k.$$

By the choosing of this weight, we can estimate W by estimating θ . Suppose that $\{P(\theta_s)\}_{ij} = \theta_{ijs}$ is the (i, j) element of $P(\theta_s)$. By the Chapman-Kolmogorov equation, the observed transition probability for subject h , $p_{ij}(t_{h,r-1}, t_{h,r})$, can be represented by

$$p_{ij}(t_{h,r-1}, t_{h,r}) = \left[\prod_{s=1}^m P(\theta_s)^{\Delta_{h,r}(s)} \right]_{ij}$$

where $\Delta_{h,r}(s) = 1$ if $[t_{s-1}, t_s) \subset [t_{h,r-1}, t_{h,r})$ and is zero otherwise and $P(\theta_s)^0$ is defined as an identity matrix. Since $m_h \leq m$ for all h , we further define a $1 \times mk(k+1)$ random vector $Y_h = (y_{h,r,ij})$ of binary random variables such that $y_{h,r,ij} = 1$ if subject h is in state j at time $t_{h,r}$ and in state i at time $t_{h,r-1}$; otherwise, it is zero. By definition, Y_1, Y_2, \dots, Y_n are distributed independently and identically. Then the likelihood function based on n individuals can be displayed as

$$L(\theta) = \prod_{h=1}^n \prod_{r=1}^{m_h} \prod_{i,j} \left[\prod_{s=1}^m P(\theta_s)^{\Delta_{h,r}(s)} \right]^{y_{h,r,ij}}$$

where $\theta = \{\theta_1, \dots, \theta_m\}'$. The maximum likelihood estimate, $\hat{\theta}_n$, of θ can be obtained using the Fisher scoring procedure. Note that, under some regularity conditions, $\hat{\theta}_n$ is strongly consistent with θ (Sen and Singer, 1993). It can also be shown that $w_{is}(\hat{\theta}_n)$ and $W(\hat{\theta}_n)$ are strongly consistent estimates of $w_{is}(\theta)$ and $W(\theta)$, respectively.

When T is determined exactly or T is right censored, the Kaplan-Meier estimator (Kaplan and Meier, 1958), $\hat{S}_n(t)$, can be used to estimate the survival function $S(t)$. Under certain conditions, it has been shown that

$$\sqrt{n}\{\hat{S}_n(t) - S(t)\} \xrightarrow{D} -S(t) \cdot U(t) \quad \text{as } n \rightarrow \infty$$

on $t \in [0, t_m]$, where $U(t)$ is a Gaussian martingale with $U(0) = 0$ and $\text{cov}\{U(t'), U(t'')\} = \sigma^2(t' \wedge t'')$ (Andersen et al., 1993). It has been shown that, given t_0, t_1, \dots, t_m , $n^{1/2}\{G(\hat{S}_n) - G(S)\}$ is asymptotically multivariate normal with mean 0 and asymptotic covariance matrix $\Psi = (\psi_{s_1, s_2})$, where

$$\begin{aligned} \psi_{s_1, s_2} &= (t_{s_1+1} - t_{s_1}) \times (t_{s_2+1} - t_{s_2}) \times S(t_{s_1}) \times S(t_{s_2}) \\ &\quad \times \sigma^2(t_{s_1} \wedge t_{s_2}), \end{aligned}$$

and $\sigma^2(t_{s_1} \wedge t_{s_2})$ can be estimated consistently by

$$\hat{\sigma}^2(t_{s_1} \wedge t_{s_2}) = \int_0^{t_{s_1} \wedge t_{s_2}} J(s)\{Y(s)\}^{-2} dN(s),$$

where $Y(s)$ is the number at risk just before time s , $N(s)$ is the number of the observed failures, and $J(s)$ is an indicator function that equals one if $Y(s) > 0$ and that is zero otherwise. Hence, the mean sojourn time for subjects with state i within $[t_{s-1}, t_s)$ is estimated as

$$\hat{i}_{is,n} = w_{is}(\hat{\theta}_n) \times g_s(\hat{S}_n)$$

and the estimated μ_{QAS} is

$$\hat{\mu}_{QAS}(\hat{\theta}_n, \hat{S}_n) = \sum_{s=1}^m \sum_{i=1}^k q_s \hat{i}_{is,n} = q' \times W(\hat{\theta}_n) \times H \times G(\hat{S}_n). \tag{3}$$

By the Slutsky Theorem, it can be shown that

$$\sqrt{n}\{\hat{\mu}_{QAS}(\hat{\theta}_n, \hat{S}_n) - \mu_{QAS}(\theta, S)\} \xrightarrow{D} N(0, \gamma^2) \quad \text{as } n \rightarrow \infty. \tag{4}$$

where

$$\gamma^2 = \{q' \times W(\theta) \times H\} \Psi \{q' \times W(\theta) \times H\}',$$

which can be estimated consistently by substituting the consistent estimators $\hat{\theta}_n$ and $\hat{\Psi}$ for the unknown parameters. As one referee points out, this method allows for simpler variance calculations using Slutsky's Theorem than those within the similar context of Huang and Louis (1999) and Murray and Cole (2000).

We next consider the interval-censoring case for QAS analysis. Even though the survival endpoint death is rarely interval censored in many trials, the idea of QAS analysis can be extended to studies with QOL and nonfatal endpoints like HIV studies with AIDS occurrence as the endpoint. Interval-censored endpoints for such studies are not uncommon. In the case of T being interval censored, there are many methods in the literature proposed for survival function estimation with interval-censored data (e.g., Whittemore and Keller, 1986; Lindsey and Ryan, 1998). One can obtain the estimated μ_{QAS} using those methods if the survival function and its variance can be well estimated. For example, if a piecewise exponential model is imposed on a set of interval-censored data with J intervals $D_v = [\tau_{v-1}, \tau_v)$ for $v = 1, 2, \dots, J$ and assuming

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Table 1

The bias, sample standard error (SSE), sample average of the estimated standard error (ESE), and the sample average of the coverage probability (CP) of $\mu_{QAS} = 5.421$ by the 95% confidence interval based on different sample sizes, censoring rates, and nonresponse rates

Censoring rate (%)	Sample size	Nonresponse rate							
		20%				40%			
		Bias	SSE	ESE	CP	Bias	SSE	ESE	CP
20	20	0.242	1.372	1.235	0.840	0.305	1.402	1.415	0.828
	40	0.194	1.034	1.042	0.938	0.248	1.092	1.100	0.920
	80	-0.058	0.719	0.723	0.943	0.159	0.736	0.730	0.947
	200	0.034	0.466	0.460	0.955	0.120	0.474	0.476	0.949
	400	0.019	0.302	0.308	0.951	0.087	0.380	0.369	0.953
	800	0.017	0.225	0.223	0.954	0.054	0.279	0.283	0.952
40	20	-0.309	1.462	1.379	0.810	-0.343	1.620	1.611	0.763
	40	-0.147	1.171	1.192	0.903	0.231	1.193	1.184	0.893
	80	-0.094	0.782	0.768	0.924	0.161	0.787	0.791	0.919
	200	-0.067	0.600	0.609	0.951	0.130	0.656	0.648	0.949
	400	0.046	0.408	0.417	0.950	0.096	0.421	0.426	0.947
	800	0.041	0.301	0.295	0.953	0.091	0.316	0.310	0.951

a constant hazard λ_n within each interval D_n and some regularity conditions, it can be shown that $\hat{\lambda}_n$ is consistent for λ and $n^{1/2}(\hat{\lambda}_n - \lambda)$ is asymptotically multivariate normal with mean vector $\mathbf{0}$ and asymptotic covariance matrix $\{I(\lambda)\}^{-1}$, which can be estimated consistently by $\{I(\hat{\lambda}_n)\}^{-1}$. By the Slutsky Theorem and the delta method, it can be shown that

$$\sqrt{n}\{\hat{\mu}_{QAS}(\hat{\theta}_n, \hat{\lambda}_n) - \mu_{QAS}(\theta, \lambda)\} \xrightarrow{D} N(0, \mathcal{V}(\theta, \lambda))$$

as $n \rightarrow \infty$,

where

$$\begin{aligned} \mathcal{V}(\theta, \lambda) = & \{q' \times W(\theta) \times H\} \\ & \times \left[\frac{\partial}{\partial \lambda} G(\lambda) \times \{I(\lambda)\}^{-1} \times \frac{\partial}{\partial \lambda} G(\lambda)' \right] \\ & \times \{q' \times W(\theta) \times H\}', \end{aligned}$$

and this can be estimated consistently by $\mathcal{V}(\hat{\theta}_n, \hat{\lambda}_n)$.

4. Treatment Comparison

The main purpose of the clinical trial is often to investigate therapeutic efficacy. For example, in cancer trials, cancer treatments often offer a cure that would interfere with the patient's bodily integrity. The purposes of the treatments are not only to prolong the total or disease-free lifetime but also to prevent the adverse events due to the introduction of the treatments. The quality-adjusted survival would be an appropriate measure for treatment comparison. Suppose the treatment-equivalent efficacies of two treatments are examined by their quality-adjusted survivals. Based on the estimation of mean sojourn time l_{is} , an individual's QAS, U_h , can be obtained from (1). With two independent QAS samples, one can use nonparametric methods, like the Mann-Whitney-Wilcoxon test, to compare treatment-equivalent efficacy. This is possible by noting that the ranks are invariant under monotone transformations, and this is preserved by using pooled estimates of the θ 's. For large sample sizes, one can also use an approximation test to examine the treatment-equivalent

efficacy. Under the equivalent efficacy assumption, the test statistic $(\hat{\mu}_{QAS, n_1} - \hat{\mu}_{QAS, n_2})$ has an asymptotically normal distribution with mean zero and with an appropriate asymptotic variance where n_1 and n_2 are the sample sizes for the two treatment groups. The main problem in analyzing QOL is the lack of a gold standard to evaluate the QOL score, q , for diseases. The assessment of a QOL is difficult and is often criticized because QOLs are obtained with biased measurement (Smith, 1987). However, as Olschewski and Schumacher (1990) pointed out, in a randomized clinical trial, nonparametric test statistics or the test based on asymptotic results may still be valid for the treatment comparison even if one assumes that a QOL assessment is systematically biased.

5. Simulation Study

In this section, we conduct a simulation study to evaluate the performance of the proposed estimator. We first consider a study that is designed to follow patients' QOLs monthly for 12 months and where patients' survival times, T , are exponentially distributed with hazard $\lambda = 1/15$. Suppose that a patient's QOL follows a three-state time-homogeneous Markov process with death as state 0, poor QOL as state 1, and good QOL as state 2, and the QOL scores, q_s , for these states are 0, 0.5, and 1, respectively. The transition probabilities between 2 months are assumed to be $(\theta_{10}, \theta_{12}, \theta_{20}, \theta_{21}) = (0.4, 0.2, 0.1, 0.3)$, i.e., the probability that a patient with a poor QOL in the previous month could die during the current month is 0.4, etc. In this simulation, we consider data with average 20 and 40% censoring rates and with the same percentages of nonresponse rates at each monthly visit. We assume that each subject would have a 50% chance of having a poor QOL or a good QOL health status at the initial visit. Table 1 shows the estimation results based on 2000 simulations for each scenario.

It is clear that, when the censoring and the nonresponse rates are light (20%), the estimators of μ_{QAS} have smaller biases with smaller sample standard errors compared with

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Table 2
 Transition probabilities, hazards, expected survival, and mean sojourn time estimates (SE) within intervals for the SICH study

	Time interval s		
	1	2	3
Transition probability			
θ_{10s}	0.154 (0.071)	0.056 (0.012)	0.042 (0.055)
θ_{12s}	0.115 (0.063)	0.167 (0.085)	0.176 (0.096)
θ_{20s}	0.056 (0.054)	0 ^a	0.008 (0.018)
θ_{21s}	0 ^a	0.050 (0.049)	0.008 (0.018)
Hazard			
λ_s	0.121 (0.051)	0.046 (0.061)	0.004 (0.060)
Weight			
w_{1s}	0.408	0.410	0.443
w_{2s}	0.592	0.590	0.557
Expected survival			
g_s	0.942 (0.248)	0.864 (0.369)	0.841 (0.486)
Mean sojourn			
l_{1s}	0.384 (0.092)	0.354 (0.118)	0.373 (0.149)
l_{2s}	0.558 (0.124)	0.510 (0.169)	0.468 (0.171)

^a Since there is no observation with this outcome, the transition probability among these data is restricted to zero.

those estimators that have the heavy censoring rate and/or the nonresponse rate (40%). The sample averages of the estimated standard errors are very close to the sample standard errors for all scenarios. The correct sample coverage probabilities are lower when sample sizes are less than 80 but are increasing in sample size and are close to 0.95 when sample sizes are greater than 80. In general, the proposed estimator provides an accurate estimate with a sample of moderate size.

6. SICH Study

A clinical observation study is used to illustrate the proposed estimators for assessing the μ_{QAS} . There were 65 consecutive patients with deep (epicenter in basal ganglia or thalamus) supratentorial SICH admitted to the Neurosurgical Service of the University of North Carolina Hospitals between March 1985 and June 1994. After discharge, the clinical courses for only 44 patients were available through four monthly follow-up visits; the rest were either lost to follow-up or missing at least one monthly follow-up. The Glasgow Outcome Score (GOS) is used to describe patient morbidity and mortality as an outcome measure for patients who survived beyond 30 days at 1, 2, 3, and 4 months, respectively. The components of the GOS include the rating one for dead, two for persistent vegetative state (no cortical function), three for moderate disability (conscious but disabled), four for moderate disability (disabled but independent), and five for good recovery (resuming normal activities).

A multistate Markov process can be used to describe the change of the clinical course of SICH. For illustration purposes, we redefine a patient's health status as being state 0, representing death; as state 1, representing GOS = 2 and 3 as unfavorable outcomes; or as state 2, representing GOS = 4 and 5 as favorable outcomes. Since the data are collected

monthly, we consider the survival outcome to be interval censored. Suppose that θ_{ijs} ($i = 1, 2$, $j = 0, 1, 2$, and $s = 1, 2, 3$) is the transition probability from state i to state j at the time interval between month s and month $s + 1$. Based on the estimation procedure described in the previous sections, one can estimate the transition probabilities, the weights, and the mean sojourn time for each monthly interval. Table 2 contains the estimates. From Table 2, we note that the transition probabilities from state 2 to other states are smaller than the transition probabilities from state 1 to other states across time. This implies that patients with favorable outcomes at any time interval are stable and shall have a longer mean sojourn time at the favorable health status than the patients with unfavorable outcomes. The estimated weights, w_{1s} , and mean sojourn times, l_{1s} , are consistent with this conclusion. For example, patients in this study will survive an expected 0.942 months (g_1) at the first monthly interval, while there will be a 0.408 chance (w_{11}), or 0.384 months (l_{11}), with the unfavorable health state and a 0.592 chance (w_{21}), or 0.558 months (l_{11}), with the favorable health state. The consistency of the results indicates the proposed weight function is a reasonable choice.

For illustration purposes, we choose a set of hypothetical QOL scores $q_1 = 0.5$ and $q_2 = 1$ to calculate the expected QAS and its variance. The chosen QOL scores indicate that the QAS for a patient with 1 month of favorable health outcome is equivalent to the QAS for a patient with 2 months of unfavorable health outcome. Given the estimators in the above, the estimated mean quality-adjusted survival time for the 3-month interval of this study is 2.091 with variance 0.684. In case that one chooses alternative QOL scores $(q_1, q_2) = (0.25, 0.75)$, the estimated mean quality-adjusted survival time for this study is 1.430 with a variance of 0.257.

The difference between these two estimated quality-adjusted survival times indicates the impact of choosing QOL scores.

7. Discussion

An estimator of the mean quality-adjusted survival time is investigated under the Markov assumption that tries to avoid the estimation problems due to periodic observation. The proposed estimator allows the QOL score to be dependent on both health status and survival time and can be applied to right-censored and interval-censored observations. It is also possible to incorporate covariate effects into the estimation of the weight or the expected survival time. For example, the transition probability or the hazard rate can be a function of covariates. The estimation of covariate effects can be implemented using the same estimation procedures for the weight and survival time.

Note that the proposed estimator has its own limitations. First, the assumption that the disease process is Markovian is difficult to verify with periodic nonpanel observations. When the Markov assumption is violated, the proposed estimator can be significantly biased. For example, suppose that a disease process follows a three-state semi-Markov process with constant latent risks (hazards) $(\gamma_{10}, \gamma_{12}, \gamma_{20}, \gamma_{21}) = (0.25, 0.25, 0.13, 0.20)$. By a similar simulation study as in Section 5, the proposed estimator of mean QAS is biased about 20-70% in various censoring and nonresponse rates. Therefore, using the proposed estimator for a semi-Markov model should be appraised properly. Second, in this context, the maximum number of observation times, m , is prespecified by the study. This limitation can be relieved as long as the sampling scheme is noninformative (Grüger, Kay, and Schumacher, 1991) and $m \leq n^5$, $\xi < 1/2$ such that the convergence properties that have been discussed in the context still hold. However, large m in a study will introduce a large number of parameters and therefore will increase the complexity of the estimation. For a small sample size study, the estimates are problematic. For example, there are 48 transition probabilities that need to be estimated in each of our simulation scenarios. With only 20 subjects, the bias estimates would have a large estimated standard error and the coverage probabilities are less than 85% for any scenario. To resolve the problem, certain intervals can be grouped based on biological judgment or on practical reasons such that the number of parameters is reduced to a manageable level.

We note that it may be possible to apply a full likelihood approach to estimate the transition probabilities and the survival distribution simultaneously. For example, Huang and Louis (1998) use a nonparametric maximum likelihood approach to estimate the joint distribution of survival time and mark variables. A similar approach can be used if one can replace mark variables as functions of QOL appropriately. However, to thoroughly address these issues with the nonresponses and loss to follow-up due to a periodic observation scheme, additional investigation is needed.

In conclusion, the estimator developed here did provide a flexible framework for the quality-of-life adjusted survival study with periodic observations. Important study insights, which may have been overlooked by merely considering complete observations, might be gained from the use of such a method.

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RÉSUMÉ

La survie ajustée sur la qualité est une mesure qui intègre à la fois des informations concernant la longévité et la qualité de vie. L'analyse de la survie ajustée sur la qualité pose des problèmes dans les études cliniques avec données recueillies à intervalles réguliers à cause des données manquantes. En se basant sur les dates de recueil observées, on peut découper l'axe des temps en intervalles de temps disjoints. Sous une hypothèse markovienne sur l'état de santé d'un patient, la survie ajustée sur la qualité attendue est estimée comme étant le produit cumulé de la qualité de vie et de la durée moyenne de séjour dans chaque état de santé au sein de chaque intervalle de temps. On montre que l'estimateur est asymptotiquement normal avec un calcul de variance simple. Une étude de simulation est réalisée pour examiner le comportement de l'estimateur et une étude sur les accidents vasculaires cérébraux illustre l'utilisation de cet estimateur.

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