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ESTIMATING MEAN QUALITY ADJUSTED LIFETIME WITH CENSORED DATA*

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SUMMARY. Quality of life is an important component in the evaluation of clinical trials. A measure called quality adjusted lifetime has received great interest recently. In this paper, we consider the problem of estimating mean quality adjusted lifetime with censored data. Using the general representation theorem for missing data processes, we are able to define a class of estimators which are asymptotically equivalent to all possible consistent asymptotically normal estimators of mean quality adjusted lifetime, as well as deriving the semiparametric efficiency bound. Simulation experiments are conducted to evaluate our theoretical results. In addition, data from a breast cancer clinical trial are analyzed to illustrate our method.

1. **Introduction**

In the clinical trials of chronic diseases such as cancer or AIDS, it has been increasingly recognized that it is not enough just to consider simple time to event end points. For example, a new experimental drug may prolong overall survival time of patients, but in the meantime, it can be toxic for a longer period of time. Therefore, the trade-off between the quality and quantity of life of patients needs to be considered. The concept of quality adjusted survival analysis arises from situations like this.

Quality adjusted survival analysis is a method that puts patients' health status on a utility scale, with coefficients ranging from 0 to 1, where 1 represents a state of perfect health, and 0 a state equivalent to death. Quality adjusted lifetime (QAL) is simply the linear combination of time spent at each health state weighted by

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the utility coefficient. A special example of QAL is Q-TWiST, which stands for Quality-Adjusted Time Without Symptoms and Toxicity (Glasziou, Simes and Gelber 1990, Gelber *et al.*, 1995). In a clinical trial setting, due to the loss to follow-ups and study termination, we cannot always observe the quality adjusted lifetime for each patient. Therefore, our goal is to make treatment comparisons using censored quality adjusted lifetime data.

If we are interested in comparing two treatments in terms of their survival distributions of QAL, we can use the consistent estimator for the survival distribution of QAL that was proposed by Zhao and Tsiatis (1997). This paper deals with the problem of estimating the mean QAL, which is often of interest in its own right. Because of the presence of the censoring, it is impossible to obtain a consistent nonparametric estimate for mean QAL over the entire health history. Therefore, one has to consider mean QAL restricted to a certain time, which is usually determined by the follow-up time of clinical trials.

A naive method for estimating the survival distribution of QAL is by using the Kaplan-Meier estimator with the censored QAL data. The estimator for the mean QAL can then be obtained by integrating the survival curve of QAL. However, as shown by Gelber, Gelman and Goldhirsch (1989), this leads to a biased estimator due to the induced informative censoring. A consistent estimator for mean QAL was proposed by Glasziou *et al.* (1990) for progressive state models. In a progressive state model, patients move from one state of health to another in a fixed sequential manner. Using the so-called partitioned survival analysis method, one first computes separate Kaplan-Meier estimates for the survival distributions of the transitions times to different states of health. Since the area under the survival curve for any transition time is a consistent estimator for the mean transition time, weighted areas under the curves of different transition times give us a consistent estimator for the mean quality adjusted lifetime. This method is good for progressive state models, which are common in many problems where patients usually go through periods of toxicity, good health and disease relapse sequentially. However, a consistent estimator for the variance was not provided, and was instead obtained through bootstrapping. There was also no study of the efficiency of their estimator.

Using the general representation theorem for missing data processes developed by Robins and Rotnitzky (1992), and Robins, Rotnitzky and Zhao (1994), we can identify all influence functions for estimating mean QAL with right censored data in a more general setting. Consequently, we can derive a class of estimators of mean QAL that are asymptotically equivalent to all possible consistent asymptotically normal estimators, and derive consistent estimators for their asymptotic variance. We can further find the form of the most efficient estimator, and the semiparametric efficiency bound for this problem. Since the partitioned survival analysis estimator fits into the general class of estimators, its variance can be derived accordingly. With these tools, we can carry out the treatment comparison of mean QAL easily. We conduct simulation experiments to evaluate our theory. An example from a breast cancer trial is used to demonstrate our method.

2. Method

2.1 *Notation.* We first introduce some notation. For n individuals under study, let the ith individual's health history be described by a discrete-state continuous time stochastic process, $\{V_i(t), t \geq 0\}$, where $V_i(t)$ maps to the state space $S = \{0, 1, \ldots, k\}$; that is, at any time t, the health status $V_i(t)$ can take on any of $k+1$ values corresponding to different states of health. We shall assume that states $1, \ldots, k$ are transient, whereas state "0" is absorbing. In a progressive state model states $1, \cdots, k$ have to be experienced in order. Let T_i denote the time it takes the ith individual to move into the absorbing state "0": that is $T_i = \inf\{t : V_i(t) = 0\}$; T_i can be considered as the overall survival time. Define $V_i^H(t)$ as the i-th individual's health history up to time t, i.e. $V_i^H(t) = \{V_i(u) : u \leq t\}$. This notation is needed later when efficiency is studied. Let Q stand for a quality of life function mapping the state space S to the interval $[0, 1]$. It can be interpreted as the relative quality of life as compared to perfect health, which has a value of one. For each health state, Q can be different for each individual according to his or her own perception of quality of life for that state. It can also vary with time to reflect the patient's change of perception. In this paper, the functional form of Q is assumed to be known or can be specified. With this notation, the i-th individual's quality adjusted lifetime is

$$U_i = \int_0^\infty Q_i\{t, V_i(t)\}dt.$$

The i-th individual also has a potential time to censoring denoted by $C_i > 0$. The survival distribution function for C is given by $K(u) = \text{pr}(C > u)$. It is assumed in this paper that censoring is independent of the health status process $V_i(\cdot)$. This assumption is reasonable in many clinical trials where censoring occurs primarily by end of study or administrative censoring. The assumption of independence may be weakened somewhat to accommodate situations where we believe censoring may be related to an individual's health history. A short discussion of this is given in the Conclusion section. Due to the existence of the censoring, we need to consider the quality adjusted lifetime up to a limit denoted by L. The value L corresponds to a time where at least some reasonable proportion of our sample have been followed. Therefore, the survival time for i-th individual should be $T_i^* = \min(T_i, L)$. For ease of notation, we still use T_i instead of T_i^* in this paper.

In a typical clinical trial, we observe for the ith individual the random vectors

$$\left\{X_i = \min(T_i, C_i), \Delta_i = I(T_i \leq C_i), V_i^H(u) : 0 \leq u \leq X_i, i = 1, \ldots, n\right\}.$$

Our aim is to make inference about the mean quality adjusted lifetime, $\mu = E(U)$, from such a sample.

Another major goal of this paper is to develop the variance formula for the partitioned survival analysis estimator of μ, which is denoted as $\widehat{\mu}_{PSA}$. The partitioned survival analysis method works when each individual's health history can be viewed as a series of progressive health states $1, \cdots, k, 0$. For the ith individual in the group, let T_{1i} denote time from the beginning of the study to the end of health state 1,

and T_{ki} time to the end of state k. T_{ki} is also denoted by T_i, the overall survival time. The QAL under this situation can be expressed as $U_i = \sum w_j T_{ji}$, where by a simple algebraic identity the weights $w_j = Q(j) - Q(j+1),\ j = 1, \ldots, k-1$ and $w_k = Q(k)$. We use $j = 1, \cdots, k$ to index different health states, and $i = 1, \cdots, n$ to index individuals. The partitioned survival analysis estimator is obtained by

$$\widehat{\mu}_{PSA} = \sum_{j=1}^{k} w_j \widehat{E}(T_j),$$

where $\widehat{E}(T_j) = \int_0^L \widehat{S}_j(u)du$ is the area under the Kaplan-Meier curve $\widehat{S}_j(u)$ for survival time T_j.

2.2 *A simple weighted estimator for mean QAL.* The building block for the class of estimators we will define is the weighted estimator given by

$$\widehat{\mu}_{WT} = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i U_i}{\widehat{K}(T_i)}, \tag{1}$$

where $\Delta_i = I(T_i \leq C_i)$, $\widehat{K}(T_i)$ is the Kaplan-Meier estimator for the censoring random variable C (Kaplan and Meier, 1958). That is, with data $\{X_i = \min(T_i, C_i), \Delta_i, i = 1, \ldots, n\}$,

$$\widehat{K}(t) = \prod_{u \leq t} \left\{ 1 - \frac{dN^c(u)}{Y(u)} \right\},$$

where $N^c(u) = \sum I(X_i \leq u, \Delta_i = 0)$, and $Y(u) = \sum I(X_i \geq u)$. Since $\widehat{K}(T_i)$ is a consistent estimator for the true probability $K(T_i)$, and

$$\begin{aligned} E\{\frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i U_i}{K(T_i)}\} &= E[E\{\frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i U_i}{K(T_i)} | T_i, V_i(\cdot)\}] \\ &= E[\frac{1}{n}\sum_{i=1}^{n} \frac{U_i}{K(T_i)} E\{I(C_i \geq T_i) | T_i, V_i(\cdot)\}] = E(\frac{1}{n}\sum_{i=1}^{n} U_i) = \mu, \end{aligned}$$

this simple weighted estimator is indeed a consistent estimator for estimating μ.

Using the theory of counting processes (Fleming and Harrington, 1991), we can derive the asymptotic variance for this simple weighted estimator. Letting $\lambda^c(u)$ denote the hazard function for the censoring distribution, we define a filtration $\mathcal{F}(u)$ as the increasing sequence of σ-algebras generated by

$$\sigma\{I(C_i \leq x), x \leq u; V_i(s), 0 \leq s < \infty, i = 1, \ldots, n\}.$$

That is, $\mathcal{F}(u)$ defines all the health status information for all time and the information for the censoring variables that is observed within time unit u. The corresponding martingale process $M_i^c(u)$ can be expressed as $M_i^c(u) = N_i^c(u) - \int_0^u \lambda^c(t) Y_i(t) dt$, where $N_i^c(u) = I(X_i \leq u, \Delta_i = 0), Y_i(u) = I(X_i \geq u)$. Let

$M^c(u) = \sum M_i^c(u), N^c(u) = \sum N_i^c(u)$, and $Y(u) = \sum Y_i(u)$. Using similar techniques as appeared in Zhao and Tsiatis (1997, eqs. A.4-A.7), we can expand the simple weighted estimator as

$$\begin{aligned} & n^{\frac{1}{2}}(\widehat{\mu}_{WT} - \mu) \\ &= n^{-\frac{1}{2}} \sum_{i=1}^{n} (U_i - \mu) - n^{-\frac{1}{2}} \sum_{i=1}^{n} \int_0^\infty \frac{dM_i^c(u)}{K(u)} \{U_i - \widehat{G}(U,u)\} \\ &\approx n^{-\frac{1}{2}} \sum_{i=1}^{n} (U_i - \mu) - n^{-\frac{1}{2}} \sum_{i=1}^{n} \int_0^\infty \frac{dM_i^c(u)}{K(u)} \{U_i - G(U,u)\}, \end{aligned} \tag{2}$$

where

$$\begin{aligned} \widehat{G}(U,u) &= \frac{1}{n} \frac{1}{\widehat{S}(u)} \sum_{i=1}^{n} \frac{\Delta_i U_i I(T_i \geq u)}{\widehat{K}(T_i)}, \\ G(U,u) &= \frac{1}{S(u)} E\{U_i I(T_i \geq u)\}. \end{aligned}$$

Such a form is used later in developing the general class of estimators for μ.

Since U_i is $\mathcal{F}(0)$ measurable, the two terms in (2) are uncorrelated. Using the martingale central limit theorem (Fleming and Harrington 1991), the variance for $n^{\frac{1}{2}}(\widehat{\mu}_{WT} - \mu)$ is

$$\mathrm{var}(U_i - \mu) + \mathrm{E} \int_0^\infty [\{U_i - G(U,u)\}^2 I(T_i \geq u)] \frac{\lambda^c(u)}{K(u)} du.$$

This variance can be estimated consistently by

$$n^{-1} \sum_{i=1}^{n} \frac{\Delta_i \{U_i - \widehat{\mu}_{WT}\}^2}{\widehat{K}(T_i)} + n^{-1} \int_0^\infty \frac{dN^c(u)}{\widehat{K}(u)^2} \{\widehat{G}(U^2,u) - \widehat{G}(U,u)^2\}, \tag{3}$$

where $\widehat{G}(U^2,u)$ is defined analogously as $\widehat{G}(U,u)$.

2.3 *Efficiency study.* In developing the general class of estimators of mean quality adjusted lifetime, we shall rely heavily on the notion of influence functions and the theory of semi-parametric efficiency. Interested readers can refer to Newey (1990) for a good review on this subject. Since most estimators are asymptotically linear, that is, the estimator minus the estimand can be approximated by the sum of independently identically distributed mean zero random variables called influence functions, the asymptotic properties for the estimators can be obtained via the asymptotic properties of influence functions. We shall derive the general class of influence functions for estimating mean QAL, from which we can later obtain the estimators.

We first need the influence function in the case when we can observe complete health history for each individual. As pointed out by Newey (1990), the influence function for estimating mean QAL in the complete data case is simply $U_i - \mu$, where $\mu = E(U_i)$.

Using the general representation theory for missing data processes that was developed by Robins, Rotnitzky and Zhao (1994, Proposition 8.1), the general class of influence functions for the mean QAL is of the form

$$U_i - \mu - \int_0^\infty \frac{dM_i^c(u)}{K(u)}\{U_i - G(U,u)\} + \int_0^\infty \frac{dM_i^c(u)}{K(u)}[e\{V_i^H(u)\} - \overline{e}(u)], \qquad (4)$$

where $e\{V_i^H(u)\}$ is any functional of the health history $V_i^H(u)$, $\overline{e}(u) = \mathrm{E}[e\{V_i^H(u)\} I(T_i \geq u)]/S(u)$, $G(U,u)$ and $M_i^c(u)$ are defined in §2.2.

Examining the influence function (4), we note that the first two terms in (4) constitute the influence function for the simple weighted estimator (2). Therefore, we can improve efficiency over the simple weighted estimator by multiplying the last term of (4) by a constant C, where

$$\begin{aligned} C &= \frac{\mathrm{cov}\left[\int_0^\infty \frac{dM_i^c(u)}{K(u)}\{U_i - G(U,u)\}, \int_0^\infty \frac{dM_i^c(u)}{K(u)}[e\{V_i^H(u)\} - \overline{e}(u)]\right]}{\mathrm{var}\left[\int_0^\infty \frac{dM_i^c(u)}{K(u)}[e\{V_i^H(u)\} - \overline{e}(u)]\right]} \\ &= \frac{\mathrm{E}\int_0^\infty \{U_i - G(U,u)\}[e\{V_i^H(u)\} - \overline{e}(u)] I(T_i \geq u)\frac{\lambda^c(u)}{K(u)}du}{\mathrm{E}\int_0^\infty [e\{V_i^H(u)\} - \overline{e}(u)]^2 Y_i(u)\frac{\lambda^c(u)}{K(u)^2}du}. \end{aligned}$$

The improved influence function now becomes

$$U_i - \mu - \int_0^\infty \frac{dM_i^c(u)}{K(u)}\{U_i - G(U,u)\} + C\int_0^\infty \frac{dM_i^c(u)}{K(u)}[e\{V_i^H(u)\} - \overline{e}(u)].$$

Its variance is

$$\begin{aligned} &\mathrm{var}(U_i - \mu) + \mathrm{E}\int_0^\infty [\{U_i - G(U,u)\}^2 I(T_i \geq u)]\frac{\lambda^c(u)}{K(u)}du \\ &- \frac{\left[\mathrm{E}\int_0^\infty \{U_i - G(U,u)\}[e\{V_i^H(u)\} - \overline{e}(u)] I(T_i \geq u)\frac{\lambda^c(u)}{K(u)}du\right]^2}{\mathrm{E}\int_0^\infty [e\{V_i^H(u)\} - \overline{e}(u)]^2 Y_i(u)\frac{\lambda^c(u)}{K(u)^2}du}. \end{aligned} \qquad (5)$$

Using the expansion for the the simple weighted estimator, a class of improved estimators is given by

$$\widehat{\mu}_{imp} = n^{-1}\sum_{i=1}^n \frac{\Delta_i U_i}{\widehat{K}(T_i)} + n^{-1}\widehat{C}\sum_{i=1}^n \int_0^\infty \frac{dN_i^c(u)}{\widehat{K}(u)}[e\{V_i^H(u)\} - \widehat{\overline{e}}(u)], \qquad (6)$$

where

$$\widehat{C} = \frac{\int_0^\infty \sum_{i=1}^n \frac{\Delta_i U_i}{\widehat{K}(T_i)}\left[e\{V_i^H(u)\} - \widehat{\overline{e}}(u)\right] I(T_i \geq u)\frac{dN^c(u)}{Y(u)\widehat{K}(u)}}{\int_0^\infty \sum_{i=1}^n [e\{V_i^H(u)\} - \widehat{\overline{e}}(u)]^2 Y_i(u)\frac{dN^c(u)}{Y(u)\widehat{K}(u)^2}}$$

and

$$\widehat{\overline{e}}(u) = \frac{\sum_{i=1}^{n} e\{V_i^H(u)\} Y_i(u)}{Y(u)}$$

are consistent estimators of C and $\overline{e}(u)$.

The variance of the improved estimator $\widehat{\mu}_{imp}$ can now be estimated by substituting empirical estimates for the nonstochastic quantities in (5); that is,

$$n^{-1} \sum_{i=1}^{n} \frac{\Delta_i \{U_i - \widehat{\mu}_{imp}\}^2}{\widehat{K}(T_i)} + n^{-1} \int_0^\infty \frac{dN^c(u)}{\widehat{K}(u)^2} \{\widehat{G}(U^2, u) - \widehat{G}(U, u)^2\}$$

$$-n^{-1} \frac{\left[\int_0^\infty \sum_{i=1}^{n} \frac{\Delta_i U_i}{\widehat{K}(T_i)} [e\{V_i^H(u)\} - \widehat{\overline{e}}(u)] I(T_i \geq u) \frac{dN^c(u)}{Y(u)\widehat{K}(u)}\right]^2}{\int_0^\infty \sum_{i=1}^{n} [e\{V_i^H(u)\} - \widehat{\overline{e}}(u)]^2 Y_i(u) \frac{dN^c(u)}{Y(u)\widehat{K}(u)^2}}. \tag{7}$$

The class of improved estimators is generated through the functional of health history $e\{V_i^H(u)\}$. In practice, we can obtain an improved estimator by choosing any form of $e\{V_i^H(u)\}$. We find that a computationally simple form of $e\{V_i^H(u)\}$, which often gives us a very efficient estimator as well, is the accumulated quality adjusted lifetime up to time u,

$$e\{V_i^H(u)\} = \int_0^u Q_i\{t, V_i(t)\} dt. \tag{8}$$

Using the Cauchy-Schwarz inequality, the most efficient estimator is obtained by choosing

$$e_{eff}\{V_i^H(u)\} = \mathrm{E}\{U_i | V_i^H(u)\}. \tag{9}$$

Its asymptotic variance is equal to (5), evaluated using the functional $e_{eff}\{V_i^H(u)\}$ given above, which corresponds to the semiparametric efficiency bound.

Although the efficient estimator is known to us conceptually, the functional $e_{eff}\{V_i^H(u)\}$ is a complicated function of the population parameters which are virtually impossible to estimate nonparametrically.

2.4 *Variance formula for* $\widehat{\mu}_{PSA}$. When the progressive health state model applies, we can use the partitioned survival analysis estimator to estimate the mean QAL. Using the notation developed in §2.1, this estimator is

$$\widehat{\mu}_{PSA} = \sum_{j=1}^{k} w_j \widehat{E}(T_j), \tag{10}$$

where $\widehat{E}(T_j) = \int_0^L \widehat{S}_j(u) du$ is the area under the Kaplan-Meier curve $\widehat{S}_j(u)$ for survival time T_j. We first express $\widehat{E}(T_j)$ as the general form of influence functions

developed earlier, then we can show that $\widehat{\mu}_{PSA}$ is just one member of the improved estimators.

Subject to the last event being uncensored, and from a result by Zhao and Tsiatis (1997, p.342, remark 1), the Kaplan-Meier estimator for the time to jth events, $\widehat{S}_j(u)$, can be written as

$$\widehat{S}_j(u) = n^{-1} \sum_{i=1}^{n} \frac{\Delta_{ji} I(T_{ji} \geq u)}{\widehat{K}_j(T_{ji})},$$

where $\Delta_{ji} = I(T_{ji} < C_i)$, $\widehat{K}_j(T_{ji})$ is the Kaplan-Meier estimator for censoring based on using the pairs $\{X_{ji} = \min(T_{ji}, C_i), \Delta_{ji}\}$. Note we get different Kaplan-Meier estimators for censoring depending on j, even though each of these is an estimate of $K(u) = \text{pr}(C > u)$.

The area under the curve can be expressed as

$$\widehat{E}(T_j) = \int_0^L \widehat{S}_j(u) du = n^{-1} \sum_{i=1}^{n} \frac{\Delta_{ji} T_{ji}}{\widehat{K}_j(T_{ji})}.$$

Similar methods to those in (2) can be used to derive

$$\begin{aligned} \widehat{E}(T_j) &= n^{-1} \sum_{i=1}^{n} T_{ji} - n^{-1} \sum_{i=1}^{n} \int_0^{\infty} \frac{dM_{ji}^c(u)}{K(u)} \{T_{ji} - \widehat{G}_j(T_j, u)\} \\ &\approx n^{-1} \sum_{i=1}^{n} T_{ji} - n^{-1} \sum_{i=1}^{n} \int_0^{\infty} \frac{dM_{ji}^c(u)}{K(u)} \{T_{ji} - G_j(T_j, u)\}, \end{aligned}$$

where

$$dM_{ji}^c(u) = dN_{ji}^c(u) - \lambda^c(u) I(X_{ji} \geq u), \quad N_{ji}^c(u) = I(X_{ji} \leq u, \Delta_{ji} = 0),$$

$$\widehat{G}_j(T_j, u) = \frac{1}{n \widehat{S}_j(u)} \sum_{i=1}^{n} \frac{\Delta_{ji} T_{ji} I(T_{ji} \geq u)}{\widehat{K}_j(T_{ji})},$$

$$G_j(T_j, u) = \frac{E\{T_j I(T_j \geq u)\}}{S_j(u)}.$$

It is convenient to introduce a new martingale representation for the censoring process; namely, $dM_i^{c*}(u) = dN_i^{c*}(u) - \lambda^c(u) I(C_i \geq u)$, where $N_i^{c*}(u) = I(C_i \leq u)$. It can be shown that the following relationship holds for this martingale: $dM_{ji}^c(u) = dM_i^{c*}(u) I(T_{ji} \geq u)$. Therefore, we can express $\widehat{E}(T_j)$ with respect to this new martingale process as

$$\widehat{E}(T_j) = n^{-1} \sum_{i=1}^{n} T_{ji} - n^{-1} \sum_{i=1}^{n} \int_0^{\infty} \frac{dM_i^{c*}(u)}{K(u)} I(T_{ji} \geq u) \{T_{ji} - G_j(T_j, u)\}$$

$$= n^{-1}\sum_{i=1}^{n} T_{ji} - n^{-1}\sum_{i=1}^{n}\int_0^\infty \frac{dM_i^{c*}(u)}{K(u)} I(T_i \geq u)\{T_{ji} - G(T_j,u)\}$$

$$+n^{-1}\sum_{i=1}^{n}\int_0^\infty \frac{dM_i^{c*}(u)}{K(u)} I(T_i \geq u)\{e_j\{V_i^H(u)\} - \overline{e}_j(u)\}, \tag{11}$$

where

$$G(T_j,u) = \frac{E\{T_j I(T \geq u)\}}{S(u)},$$

$$e_j\{V_i^H(u)\} = T_{ji}I(T_{ji} < u) + I(T_{ji} \geq u)G_j(T_j,u) = E\{T_j|\mathcal{F}_{ji}(u)\},$$

$$\overline{e}_j(u) = \frac{E[e_j\{V_i^H(u)\}I(T \geq u)]}{S(u)} = \frac{E\{T_j I(T \geq u)\}}{S(u)} = G(T_j,u),$$

$\mathcal{F}_{ji}(u)$ is the filtration corresponding to all the information up to time u for individual i involving only events of the j-th type.

Substituting (11) into the formula for the partitioned survival analysis estimator (10), interchanging summations, and noting that $\sum w_j T_{ji} = U_i$, we obtain

$$\widehat{\mu}_{PSA} = n^{-1}\sum_{i=1}^{n} U_i - n^{-1}\sum_{i=1}^{n}\int_0^\infty \frac{dM_i^{c}(u)}{K(u)}\{U_i - G(U,u)\}$$

$$+n^{-1}\sum_{i=1}^{n}\int_0^\infty \frac{dM_i^{c}(u)}{K(u)}[h\{V_i^H(u)\} - \overline{h}(u)],$$

where

$$G(U,u) = \frac{E\{U I(T \geq u)\}}{S(u)},$$

$$h\{V_i^H(u)\} = \sum_{j=1}^{k} w_j e_j\{V_i^H(u)\} = \sum_{j=1}^{k} w_j E\{T_j|\mathcal{F}_{ji}(u)\},$$

$$\overline{h}(u) = \sum_{j=1}^{k} w_j \overline{e}_j(u) = \frac{E[h\{V_i^H(u)\}I(T \geq u)]}{S(u)} = G(U,u).$$

Therefore, it is clear that the partitioned survival analysis estimator belongs to the general class of estimators we identified earlier. Since we can show that the covariance of the last two terms in the above equation is equal to the variance of the last term, the partitioned survival analysis estimator is in fact an improved estimator. Hence, it is always more efficient than the simple weighted estimator.

Using standard results for the variance of stochastic integrals of martingale processes and noting that U is $\mathcal{F}(0)$ predictable, therefore uncorrelated with the martingales processes above, we obtain that the asymptotic variance is equal to

$$\mathrm{var}\{\widehat{\mu}_{PSA}\} = n^{-1}\mathrm{var}(U_i) + n^{-1}\mathrm{E}\int_0^\infty [\{U_i - G(U,u)\}^2 I(T_i \geq u)]\frac{\lambda^c(u)}{K(u)}du$$

$$-n^{-1}\mathrm{E}\int_0^\infty [h\{V_i^H(u)\} - \overline{h}(u)]^2 Y_i(u)\frac{\lambda^c(u)}{K(u)^2}du.$$

This can be estimated consistently by

$$n^{-2}\sum_{i=1}^{n}\frac{\Delta_i\{U_i-\widehat{\mu}_{PSA}\}^2}{\widehat{K}(T_i)}+n^{-2}\int_0^\infty\frac{dN^c(u)}{\widehat{K}(u)^2}\{\widehat{G}(U^2,u)-\widehat{G}(U,u)^2\}$$

$$-n^{-2}\int_0^\infty\frac{dN^c(u)}{Y(u)\widehat{K}(u)^2}\sum_{i=1}^{n}[\widehat{h}\{V_i^H(u)\}-\widehat{G}(U,u)]^2Y_i(u), \tag{12}$$

where

$$\widehat{h}\{V_i^H(u)\}=\sum_{j=1}^{k}w_j\{T_{ji}I(T_{ji}<u)+\widehat{G}_j(T_j,u)I(T_{ji}\geq u)\},$$

$$\widehat{G}_j(T_j,u)=n^{-1}\frac{1}{\widehat{S}_j(u)}\sum_{i=1}^{n}\frac{\Delta_{ji}}{\widehat{K}_j(T_{ji})}T_{ji}I(T_{ji}\geq u).$$

2.5 *Two–sample problem.* In clinical trials, we are often interested in comparing two treatments in order to find the more effective therapy. If we want to take the quality of life of patients into accounts, then we might be interested in comparing mean QAL from two treatments. For each treatment group, we can use methods outlined in the previous section to find the mean and variance estimate of QAL, denoted here as $\widehat{\mu}_1$, $\widehat{\mu}_2$, $\widehat{var}(\widehat{\mu}_1)$, and $\widehat{var}(\widehat{\mu}_2)$. Supposing that patients from two treatment groups are independent of each other, then the estimate for the difference in mean QAL is $\widehat{\mu}_1-\widehat{\mu}_2$, and its variance is $\widehat{var}(\widehat{\mu}_1)+\widehat{var}(\widehat{\mu}_2)$. The test statistics for testing whether the mean QALs are the same from two treatments can be formed by

$$Z=\frac{\widehat{\mu}_1-\widehat{\mu}_2}{\sqrt{\widehat{var}(\widehat{\mu}_1)+\widehat{var}(\widehat{\mu}_2)}}.$$

Alternatively, we can find the 95% confidence interval of the treatment difference in mean QAL: $[\widehat{\mu}_1-\widehat{\mu}_2-1.96\sqrt{\widehat{var}(\widehat{\mu}_1)+\widehat{var}(\widehat{\mu}_2)},\widehat{\mu}_1-\widehat{\mu}_2+1.96\sqrt{\widehat{var}(\widehat{\mu}_1)+\widehat{var}(\widehat{\mu}_2)}]$.

3. **Simulation Study**

In this simulation study, we examine the performance of the estimators we have discussed and their variance estimate for mean QAL. We use an example where the progressive state model applies so the partitioned survival analysis estimator can be obtained. We assume patients entering the study first experience some toxicity, "TOX", and then they have some period of good quality time until their disease relapse. We use "TR" to represent the time from treatment initiation to disease relapse. Each patient also has a follow-up time "FU". The utility coefficient for TOX is denoted as Q_{TOX}. The utility coefficient is assumed to be 1 for the period of good health, and 0 for the state after disease relapse. The quality adjusted lifetime is therefore $U=TR-(1-Q_{TOX})*TOX$.

We conduct 2000 simulations. For each simulation, TOX is uniformly distributed on [0,TOX2] ([0,60]), TR is exponentially distributed with a hazard $\lambda = \frac{1}{120}$, and truncated at L. If TOX is greater than TR, than it will be assigned the same value as TR. The follow-up time FU is uniform on [48,96]. Q_{TOX} is fixed at 0.5. The true mean QAL is therefore

$$\mu = \frac{1}{\lambda}(1 - e^{-\lambda L}) - (1 - Q_{TOX})\{\frac{1}{\lambda} - \frac{1}{\lambda^2 TOX2}(1 - e^{-\lambda TOX2})\}. \qquad (13)$$

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 THE TRUE MEAN BY THE 95% CONFIDENCE INTERVAL FOR DIFFERENT ESTIMATORS, AMOUNT OF CENSORING, AND SAMPLE SIZES.

Censor	μ	Sample Size	Estimator	Bias	SSE	ESE	CP
light	37.40	200	$\widehat{\mu}_{PSA}$	-0.04	1.343	1.345	0.951
			$\widehat{\mu}_{WT}$	-0.04	1.392	1.390	0.945
			$\widehat{\mu}_{imp}$	-0.11	1.347	1.341	0.950
			$\widehat{\mu}_{eff}$	-0.11	1.348	1.341	0.949
		400	$\widehat{\mu}_{PSA}$	0.01	0.944	0.952	0.952
			$\widehat{\mu}_{WT}$	0.02	0.971	0.983	0.955
			$\widehat{\mu}_{imp}$	-0.03	0.946	0.949	0.950
			$\widehat{\mu}_{eff}$	-0.03	0.946	0.949	0.950
		800	$\widehat{\mu}_{PSA}$	0.00	0.666	0.673	0.955
			$\widehat{\mu}_{WT}$	-0.01	0.691	0.695	0.954
			$\widehat{\mu}_{imp}$	-0.01	0.667	0.672	0.955
			$\widehat{\mu}_{eff}$	-0.01	0.667	0.672	0.955
heavy	46.12	200	$\widehat{\mu}_{PSA}$	0.03	1.825	1.799	0.948
			$\widehat{\mu}_{WT}$	-0.01	1.934	1.926	0.948
			$\widehat{\mu}_{imp}$	-0.32	1.897	1.759	0.917
			$\widehat{\mu}_{eff}$	-0.32	1.897	1.759	0.916
		400	$\widehat{\mu}_{PSA}$	-0.02	1.288	1.277	0.950
			$\widehat{\mu}_{WT}$	-0.01	1.368	1.365	0.953
			$\widehat{\mu}_{imp}$	-0.18	1.304	1.261	0.938
			$\widehat{\mu}_{eff}$	-0.19	1.305	1.261	0.938
		800	$\widehat{\mu}_{PSA}$	0.01	0.902	0.904	0.949
			$\widehat{\mu}_{WT}$	0.01	0.963	0.965	0.948
			$\widehat{\mu}_{imp}$	-0.07	0.909	0.898	0.944
			$\widehat{\mu}_{eff}$	-0.07	0.909	0.898	0.943

Our program is written in C, and run on Sun Workstation. Estimators are calculated for L=65, 81; sample size n=200, 400, 800, respectively. The amount of censoring is about 20% and 40% for these two different choices of L. We calculated true mean QAL (13), the partitioned survival estimator $\widehat{\mu}_{PSA}$ (10), the simple weighted estimator $\widehat{\mu}_{WT}$ (1), the improved estimator $\widehat{\mu}_{imp}$ and the efficient estimator $\widehat{\mu}_{eff}$ (6), using $e\{V_i^H(u)\}$ from (8) and (9) respectively. We also calculate the sample standard error (SSE) for these estimators. The sample average of the estimated standard errors (ESE) are obtained from the variance formulae (12) for

$\widehat{\mu}_{PSA}$, (3) for $\widehat{\mu}_{WT}$, (7) using $e\{V_i^H(u)\}$ from (8) and (9) for $\widehat{\mu}_{imp}$ and $\widehat{\mu}_{eff}$ respectively. Here we are able to evaluate $e_{eff}\{V_i^H(u)\}$ because we know the population distribution, but in general this quantity is not computable. Also calculated is the average of the sample coverage probability (CP) of the true parameter by the 95% confidence interval of these estimators.

The results are shown in Table 1. It is clear that when the censoring is light (20% censored), all the estimators for mean QAL have small bias. They all have the correct sample coverage probability of true mean, 0.95. The sample average of estimated standard errors are very close to the sample standard errors for all the estimators. The partitioned survival estimator and the improved estimator are both very efficient. When heavy censoring is present, all estimated standard errors are still close to the sample standard errors. However, the bias for the improved estimator is a little bigger for small sample size. Again, both the partitioned survival estimator and the improved estimator are very efficient. The coverage probabilities for the simple weighted estimator and the partitioned estimator are very close to 0.95 for all sample sizes, and for the improved estimator when the sample size is large. When the sample size is 200, the coverage probability for the improved estimator is not as accurate due to the small sample bias.

In summary, the partitioned survival analysis estimator is very efficient. This is true even for heavy censoring and small sample size. Its variance formula works well. The simple weighted estimator has a small bias and a good variance estimate, but it is not very efficient. The improved estimator is very efficient. But when censoring is heavy, we must be cautious of the bias which may result from smaller sample sizes.

4. **A Real Example**

We now illustrate our method using the breast cancer example from Gelber *et. al.* (1995). This was a randomized clinical trial of adjuvant chemotherapy for breast cancer. Trial V of the International Breast Cancer Study Groups (IBCSG) investigated the short duration (One month) treatment compared with long duration treatment (six or seven months). A total of 1,229 patients were recruited in the study. Among them 413 patients were randomized to the short duration arm, and the other 816 patients were randomized to the long duration treatment. The median follow up for this analysis was 7 years.

The health history for each patient was partitioned progressively into three health states, TOX (toxicity period), TWiST (perfect health) and REL (disease relapse). The method is illustrated with the quality of life coefficients $Q_{TOX} = Q_{REL} = 0.5$, and the time limit L=84 (months). About 30% of the data are censored in each group as a result.

We calculate the partitioned survival analysis estimator $\widehat{\mu}_{PSA}$, the simple weighted estimator $\widehat{\mu}_{WT}$, and the improved estimator $\widehat{\mu}_{imp}$ using formulae as indicated in the previous section. Their standard error estimates are also obtained. For the purpose

of comparison, we also list the results from Gelber's paper. The partitioned survival analysis method was used in that paper (also called Q-TWiST method there, so we denote it as $\widehat{\mu}_{Q-TWiST}$). Their variance is obtained with bootstrapping method. (In their paper, only 95% confidence interval for the difference was given, the standard error estimate listed here was obtained by contacting the authors.)

The results are shown in Table 2. As expected, the simple weighted estimator gives a larger standard error estimate. The improved estimator and the partitioned survival analysis estimator are very close. The standard error estimate from our method agrees well with the one obtained by bootstrapping method.

TABLE 2: ESTIMATES OF MEAN QAL AND THEIR STANDARD ERRORS FOR IBCSG BREAST CANCER TRIAL V

	Chemotherapy treatment						
	Long duration		Short duration		Difference		
Estimator	Mean	S.E.	Mean	S.E.	Mean	S.E.	95% C.I.
$\widehat{\mu}_{Q-TWiST}$	61.03	0.906	55.63	1.287	5.40	1.574	2.3-8.5
$\widehat{\mu}_{PSA}$	61.03	0.901	55.63	1.312	5.40	1.592	2.3-8.5
$\widehat{\mu}_{WT}$	60.97	0.929	55.38	1.380	5.59	1.664	2.3-8.9
$\widehat{\mu}_{imp}$	61.07	0.906	55.56	1.323	5.51	1.603	2.4-8.7

5. Conclusion and Discussion

Both simulation results and the real example show that our variance formula for the partitioned survival analysis estimator is correct. The simulation study also shows that the partitioned survival analysis estimator is very efficient. Therefore, in the situation where progressive health state models apply, such as in AIDS and cancer studies, the partitioned survival analysis estimator is recommended.

In a more general setting where patients can change health states in an arbitrary manner, we have given the formula for calculating the most efficient estimator of mean QAL. In order to use this formula, we need to know the optimal functional $e_{eff}\{V_i^H(u)\}$ which depends on the underlying distribution for the health states. In actuality, we don't know $e_{eff}\{V_i^H(u)\}$ and it is impossible to estimate it non-parametrically. Instead, we recommend using a simple choice of $e\{V_i^H(u)\}$, the accumulated quality adjusted lifetime, to get the improved estimator. Our simulation studies show that this estimator has a greater efficiency than the simple weighted estimator, although we must be careful of the increased small sample bias which may result from heavy censoring.

The consistency of our estimator depends on the assumption of independence between the censoring time and the health history. In situations where we believe that censoring depends on the health history, the weighted estimator proposed will be biased. In theory, we can model the censoring distribution on the health history, say with a proportional hazards model, then substitute this estimated censoring

distribution in the denominator of our weighted estimator to obtain consistent estimates. The study of this method will be a subject of future research.

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