On Quality-Adjusted Lifetime Analysis

Hongkun Wang
hongkun.wang@georgetown.edu

Department of Biostatistics, Bioinformatics, & Biomathematics
Georgetown University
Washington, DC 20057
Why QAL?

- In clinical research, improving patients’ quality of life has become increasingly important, especially in patients with chronic disease such as cancer, AIDS, or cardiovascular diseases.
- Quality-adjusted lifetime (QAL) is a measure which combines patients’ quality and quantity of life together.
- It provides a useful summary for evaluating the treatment effect.
QAL with censored data

- In most clinical trials, patients enter the study over a period of time, and we cannot always observe the QAL for every patient due to loss to follow-up and study termination. Thus inference on the mean QAL has to be drawn based on censored data.
- Censoring poses a unique problem for making inference on QAL. Even though we can assume that censoring is independent of the health history process, the censored QAL is often correlated with the potential uncensored QAL due to the induced informative censoring problem.
The IBCSG trial V

The International Breast Cancer Study Group (IBCSG).

- The IBCSG Trial V: a randomized clinical trial investigating two treatments for the node-positive breast cancer: short duration chemotherapy (one month) and long duration chemotherapy (six or seven months).

- 1229 patients were enrolled in the study with 413 patients randomized to the short term chemotherapy and 816 patients randomized to the long term chemotherapy. The median follow-up for the study was seven years.
• Six covariates were recorded from each patient upon enrollment in the trial, which included age, treatment (short duration or long duration), tumor size (less than 2 cm or at least 2 cm), tumor grades (medium or high), and number of nodes (fewer than 4 or at least 4) involved.

• Each patient’s health history was partitioned progressively into three health states: toxicity period (TOX), time without symptoms and toxicity (TWiST), and disease relapse (REL).

• It was of interest to estimate patients mean QAL, and learn how it might depend on these prognostic factors.
Outline

Analysis of Quality-Adjusted-Lifetime (QAL) with censored data

- Estimating the mean QAL
- Confidence Intervals for the mean QAL
- Regression of the mean QAL
- Empirical likelihood inference for confidence regions in the regression of mean QAL
Estimating mean QAL with censored data

- Glasziou *et al.* (1990) proposed the partitioned survival analysis estimator to estimate the mean QAL for progressive state models.

- Zhao and Tsiatis (2000) proposed two estimators based on the inverse probability weighting.
Estimating mean QAL: Notations

\( Q_i \): the \( i \)th subject’s quality-adjusted lifetime,
\( \{V_i(t), t \geq 0, i = 1, \ldots, n\} \) health history process,
\( T_i \) the survival time,
\( q \) a known utility function mapping \( V_i(t) \) to the interval \([0, 1]\).
\( C_i \): the \( i \)th individual’s censoring time, assumed to be independent of \( V_i(.) \). The distribution of \( C \) is assumed to be continuous.
Because of censoring, we only consider the QAL accumulated within a time limit $L$. Consequently, the survival time of an individual will be truncated at $L$, $T^L = \min(T, L)$.

$$Q_i = \int_0^{T_i^L} q_i \{V_i(t)\} dt.$$
Estimating mean QAL

The simple weighted (WT) estimator and the improved (IMP) estimator by Zhao and Tsiatis (2000)

\[
\hat{\mu}_{WT} = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i Q_i}{\hat{K}(T_i)},
\]

where \(\Delta_i = I(T_i \leq C_i)\), \(\hat{K}(T_i)\) is the Kaplan-Meier estimator for \(C\). Variance formula for the WT estimator was derived using the theory of counting processes (Fleming and Harrington, 1991).
Denote \( e\{V^H_i(u)\} \) any functional of the health history \( V^H_i(u) \),
\[
\bar{e}(u) = \frac{E[e\{V^H_i(u)\}I(T_i \geq u)]}{S(u)}
\]
\( M^c_i(u) = N^c_i(u) - \int_0^u \lambda^c(t)Y_i(t)\,dt \) a martingale,
\( N^c_i(u) = I(X_i \leq u, \Delta_i = 0) \) a counting process,
\( X_i = \min(T_i, C_i), \ Y_i(t) = I(X_i \geq t), \)
\( \lambda^C(u) = \lim_{h \to 0} 1/h \Pr(t < C < t + h \mid C \geq t, T \geq t) \) the hazard function for \( C \).
Using the general theory by Robins et al. (1994) for missing data process, the general class of influence functions (IF) for the mean QAL is of the form

\[
Q_i - \mu - \int_0^{\infty} \frac{dM_i^c(u)}{K(u)} \{Q_i - G(T, u)\} \\
+ \int_0^{\infty} \frac{dM_i^c(u)}{K(u)} [e\{V_i^H(u)\} - \bar{e}(u)],
\]
Estimating mean QAL

The improved method (IMP) \( \hat{\mu}_{IMP} \)

\[
\frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i Q_i}{\hat{K}(T_i)} + \frac{1}{n} \hat{C} \sum_{i=1}^{n} \int_{0}^{\infty} \frac{dN_i^c(u)}{\hat{K}(u)} \left[ e\{V_i^H(u)\} - \hat{e}(u) \right],
\]

where \( \hat{C} \) is a consistent estimator of the covariance between the third and last terms, divided by the variance of the last term in the IF, and \( \hat{e}(u) \) is a consistent estimator of \( \bar{e}(u) \).
The partitioned survival analysis method (PSA) by Glasziou et al. (1990)

If each individual’s health history can be viewed as a series of progressive health states 1, · · · , k, 0, then

\[
\hat{\mu}_{PSA} = \sum_{j=1}^{k} w_j \hat{E}(T_j),
\]

where \( \hat{E}(T_j) = \int_0^L \hat{S}_j(u) \) is the area under the Kaplan-Meier curve \( \hat{S}_j(u) \) for the survival time \( T_j \), and \( w_j \) the weight assigned to each health state \( j \).
Constructing the CI for mean QAL

- A confidence interval can be constructed using the estimator’s variance formula.
- If there is no existing explicit formula, we can construct a CI using the bootstrapping method.
- Particularly consider:
  - Bootstrap percentile method ($B_p$)
  - Bootstrap bias-corrected and accelerated percentile method ($B_{bca}$)
  - Bootstrap-t method ($B_t$)
Similar to the IBCSG Trial V, we assume patients entering the study first experience toxicity, then a period of good health, then their disease relapse. 

TOX: the time from the treatment initiation to the end of toxicity 
TR: the time from treatment initiation to disease relapse 
FU: the follow-up time. 
The QAL is defined as:

\[ Q = TR - (1 - q_{TOX}) \times TOX \]

\( q_{TOX} \): the utility coefficient for TOX.
We generate 2000 simulations. For each simulation, TOX is unif [0, 60], TR is exp with $\lambda = 120$ truncated at L. FU is unif [48, 96] independent of TOX and TR. Estimators are calculated at 2 different value of L, which results in the censoring rate to be about 20% and 40%, respectively. The sample sizes vary from 20 to 200.
Results

- Simulation studies show that when sample size is below 100, the $B_{bca}$ has the best coverage probability among all the methods discussed here.
- When sample size is above 100, the WT performs well under different censoring rates.
- When patients’ health states follow a progressive state model, the PSA provides CIs with coverage probabilities close to the nominal value and the shortest length when sample size is above 100.
- The IBCSG Trial V data was re-analyzed using $q_{TOX} = q_{REL} = 0.5$, $L = 84$ months. The results agree with that from simulation studies.
Regression of the mean QAL with censored data

Assume that the mean QAL depends on the covariates in a very general form

\[ E(Q_i|Z_i) = g(\beta, Z_i), \quad (0.1) \]

\(Z_i\): the \((p + 1) \times 1\) vector of covariates with the first covariate being the constant 1,
\(\beta\): a \((p + 1) \times 1\) unknown vector of parameters.

In the linear regression model: \(g(\beta, Z_i) = \beta' Z_i\)
In the generalized linear regression model: \(g(\beta, Z_i) = g(\beta' Z_i).\)
Regression of the mean QAL with censored data

If complete data are observed, a consistent estimator $\hat{\beta}$ for $\beta$ can be obtained from:

$$S^F_n(\beta) = \sum_{i=1}^{n} h(Z_i)\{Q_i - g(\beta, Z_i)\} = 0,$$

(0.2)

where $h(Z_i)$ is $(p + 1)$-dimensional vector of functions of $Z_i$. 
Regression of the mean QAL with censored data

The most efficient estimating equation for complete data case is

$$h_{eff}^F(Z_i) = \operatorname{Var}(Q_i|Z_i)^{-1} \frac{\partial g(\beta, Z_i)}{\partial \beta} |_{\beta_0},$$

where $\beta_0$ is the true value of the parameters.
In the linear model case $g(\beta, Z_i) = \beta' Z_i$ and $\text{Var}(Q_i | Z_i)$ is assumed to be a constant, the most efficient estimating equation is obtained by setting $h_{eff}^F(Z_i) = Z_i$, and hence

$$S_{n,eff}^F(\beta) = \sum_{i=1}^{n} Z_i(Q_i - \beta' Z_i) = 0.$$  

This equation is the same as the ordinary least squares estimating equation for the linear regression models.
Regression of the mean QAL with censored data

When censoring is present, a simple weighted estimating equation for $\beta$:

$$S_n^{WT}(\beta) = \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} h(Z_i) \{Q_i - g(\beta, Z_i)\} = 0. \quad (0.3)$$

where $\Delta_i = I(T_i \leq C_i)$, $\hat{K}(T_i)$ is the K-M estimates for $C_i$ survival probability at time $T_i$. 

On Quality-Adjusted Lifetime Analysis
In the special case when $g(\beta, Z_i) = \beta' Z_i$ and $h(Z_i) = Z_i$, the estimating equation (0.3) has a closed-form solution for $\beta$ given by

$$\hat{\beta}^{WT} = \left\{ \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} Z_i \otimes^2 \right\}^{-1} \left\{ \sum_{i=1}^{n} \frac{\Delta_i}{\hat{K}(T_i)} Q_i Z_i \right\},$$

where $a \otimes^2 = aa'$, $a \otimes b = ab'$, for vectors $a$ and $b$. 

---

On Quality-Adjusted Lifetime Analysis
Regression of the mean QAL with censored data: Efficiency Study

From the semi-parametric theory for missing data processes developed by Robins and Rotnitzky (1992) and Robins et al. (1994), the influence function for the estimating equation for any regular asymptotic linear estimators of $\beta_0$ can be written as

\[
D_i^h - \int_0^\infty \left\{ D_i^h - G(D^h, u) \right\} \frac{dM_i^C(u)}{K(u)}
\]

\[
+ \int_0^\infty \left[ e\{V_i^H(u)\} - G[e\{V^H(u)\}, u] \right] \frac{dM_i^C(u)}{K(u)}
\]
Regression of the mean QAL with censored data: Efficiency Study

where $D^h_i \equiv h(Z_i)\{Q_i - g(\beta, Z_i)\}$ is the influence function for the complete data,

$G(W, u) = E\{W_i I(T_i \geq u)\}/S(u)$ for any random variable or functional $W$, $S(u) = \Pr(T > u)$,

$e\{V^H_i(u)\}$ is any $(p + 1)$-dimensional vector of functionals of the health history $V^H_i(u)$.

As before, we have $M^C_i(u) = N^C_i(u) - \int_0^u \lambda^C(t)Y_i(t)dt$,

where $N^C_i(u) = I(X_i \leq u, \Delta_i = 0)$, $Y_i(t) = I(X_i \geq t)$,

$\lambda^C(t) = \lim_{h \to 0} \frac{1}{h} \Pr(t < C < t + h|C \geq t, T \geq t)$ the hazard function for the censoring distribution $C'$. 

On Quality-Adjusted Lifetime Analysis
Regression of the mean QAL with censored data: Efficiency Study

The most efficient estimating equation is obtained by choosing

\[ e_{eff} \{ V_i^H(u) \} = \mathbb{E}\{ D_i^{heff} \mid V_i^H(u) \} = h_{eff}(Z_i) \mathbb{E}\{ D_i \mid V_i^H(u) \}, \]

where \( D_i \equiv Q_i - g(\beta, Z_i) \), and

\[ h_{eff}(Z_i) = \{ \text{Var}(Q_i \mid Z_i) + P(Z_i) \}^{-1} \frac{\partial}{\partial \beta} g(\beta, Z_i) \bigg|_{\beta_0}, \]

with

\[ P(Z_i) = \mathbb{E} \left[ \int_0^\infty \frac{dN_i^C(u)}{K(u)} \text{Var}\{ D_i \mid V_i^H(u), Y_i(u) = 1, Z_i \} \bigg|_{Z_i} \right] \]
The most efficient estimating equation can be formed by

\[
S_{n, eff}(\beta) = \sum_{i=1}^{n} \frac{\Delta_i D_i h_{eff}(Z_i)}{\hat{K}(T_i)}
\]

\[\quad + \sum_{i=1}^{n} \int_{0}^{\infty} \left\{ e_{eff} - \hat{G}^*(e_{eff}, u) \right\} \frac{dN_i^C(u)}{\hat{K}(u)} = 0, \]

where \( \hat{G}^*(W, u) = \sum_{i=1}^{n} W_i Y_i(u)/Y(u) \) is a consistent estimator for \( G(W, u) \), for any functional \( W \).
Regression of the mean QAL with censored data

- In theory, the asymptotic variance of $\hat{\beta}$ from solving the most efficient estimating equation should achieve the semi-parametric efficiency bound, which means that $\hat{\beta}$ has the smallest variance among the class of all regular asymptotically linear estimators.

- However, it is not useful to use it for data analysis, since $e_{eff}$ and $h_{eff}$ depend on the unknown true population parameters which are difficult to estimate non-parametrically.
Regression of the mean QAL with censored data

We proposed 3 different approaches to improve the efficiency of the estimating equation based on observed data, which can be more efficient than the WT equation for any choice of $h(Z)$.

- The best-coefficient approach
- The Improved Estimating Equation with $\Gamma = 1$ and $Q_i(u)$ in Place of $E\{Q_i|V_i^H(u)\}$
- The Estimating Equation Using Regression Approach
Similar to the IBCSG Trial V, we consider patients entering the study first experiencing toxicity for a certain time, then a period of good health (TWiST), then their disease relapse followed by death. The QAL is defined as:

\[ Q = q_{TOX} \times TOX + TWiST + q_{REL} \times REL \]
Simulations

We generate 5000 simulations, each consisting of two groups of censored health status data with sample sizes varying from 100 to 400 for each group.

Two scenarios:

1) group 1 (G1) and group 2 (G2) are different
   - TOX is uniform \([0, T1]\) for G1, is uniform \([0, T2]\) for G2;
   - TR is exp with \(\lambda_1\) for G1, \(\lambda_2\) for G2, truncated at \(L1\)
   - OS is exp with \(\lambda_3\), truncated at \(L2\)
   - The censoring variables is unif and independent of TOX, TR, and OS, censoring rate is about 35% for G1 and 36% for G2.

2) group 1 and group 2 are the same
Results

- Simulation studies showed that the best performing estimator is the IMP estimator with \( \Gamma = 1 \) and \( Q_i(u) \) in Place of \( \mathbb{E}\{Q_i|V_i^H(u)\} \).

- The estimators using regression method (linear regression, or additive models) do not perform well.

- The BC estimator should always have smaller variance than the WT estimator from the large sample theory, however, the improvement is not very big from our simulation studies.
Results

- The IBCSG Trial V data was re-analyzed and results agree with that from simulation studies.
- A subject who is older, who has smaller tumor size, smaller number of nodes involved, lower tumor grade, and who is on the long duration arm, has a longer expected quality-adjusted lifetime.
- This finding also agrees with the description provided in Cole et al. (1993).
Empirical likelihood method in constructing confidence regions

- Our interest here is in the interval estimation of the parameter vector $\beta$.
- Applying the asymptotic normality of the estimator discussed before, we could obtain the asymptotic $100(1 - \alpha)\%$ confidence regions for $\beta$.
- The normal approximation based confidence regions are easy to construct. However, they are symmetric which is not always a desirable property (the distribution of the parameter estimator may be skewed); their coverage probabilities very often fall far short of the nominal level $(1 - \alpha)$.
Empirical likelihood method in constructing confidence regions

- To overcome the limitation of the normal approximation based confidence regions, we investigated the empirical likelihood (EL) method in constructing confidence regions for the parameter vector $\beta$.
- After deriving the limiting distribution of the empirical likelihood ratio, we propose the unadjusted and the adjusted empirical likelihood (AEL) confidence regions for the unknown regression parameters $R_1, \ldots, R_6$. 

On Quality-Adjusted Lifetime Analysis
Empirical likelihood method in constructing confidence regions

$\mathcal{R}_1$: asymptotic $100(1 - \alpha)\%$ confidence region for $\beta$ using the WT estimating equation

$$\mathcal{R}_1 = \{ \beta : n(\hat{\beta} - \beta)^T \hat{V}_0(\hat{V}_{WT})^{-1} \hat{V}_0(\hat{\beta} - \beta) \leq \chi^2_{p+1}(\alpha) \}$$

$\mathcal{R}_2$: asymptotic $100(1 - \alpha)\%$ confidence region for $\beta$ using the IMP estimating equation

$$\mathcal{R}_2 = \{ \beta : n(\hat{\beta} - \beta)^T \hat{V}_0(\hat{V}_{IMP})^{-1} \hat{V}_0(\hat{\beta} - \beta) \leq \chi^2_{p+1}(\alpha) \}$$
Empirical likelihood method in constructing confidence regions

\( R_3 \): asymptotic \( 100(1 - \alpha)\% \) empirical likelihood confidence region for \( \beta \) based on the IMP estimating equation

\[
R_3 = \{ \beta : \hat{l}^{IMP}(\beta) \leq c_1(\alpha) \}
\]

\( R_4 \): asymptotic \( 100(1 - \alpha)\% \) adjusted empirical likelihood confidence region for \( \beta \) based on the IMP estimating equation

\[
R_4 = \{ \beta : \hat{l}_{ad}^{IMP}(\beta) \leq \chi^2_{p+1}(\alpha) \}
\]
Empirical likelihood method in constructing confidence regions

$\mathcal{R}_5$: asymptotic $100(1 - \alpha)\%$ empirical likelihood confidence region for $\beta$ based on the WT estimating equation

$$\mathcal{R}_5 = \{\beta : \hat{l}^{WT}(\beta) \leq c_1(\alpha)\}$$

$\mathcal{R}_6$: asymptotic $100(1 - \alpha)\%$ adjusted empirical likelihood confidence region for $\beta$ based on the WT estimating equation

$$\mathcal{R}_6 = \{\beta : \hat{l}^{WT}_{ad}(\beta) \leq \chi^2_{p+1}(\alpha)\}$$
Simulations

Similar to the IBCSG Trial V, we consider patients entering the study first experiencing toxicity for a certain time, then a period of good health (TWiST), then their disease relapse followed by death. The QAL is defined as:

\[ Q = q_{TOX} \times TOX + TWiST + q_{REL} \times REL \]
We generate 5000 simulations, each consisting of two groups of censored health status data with sample sizes varying from 100 to 400 for each group. Two scenarios:

1) group 1 (G1) and group 2 (G2) are different
   TOX is uniform $[0, T1]$ for G1, is uniform $[0, T2]$ for G2; TR is exp with $\lambda_1$ for G1, $\lambda_2$ for G2, truncated at $L1$
   OS is exp with $\lambda_3$, truncated at $L2$
   The censoring variables is unif and independent of TOX, TR, and OS, censoring rate is about 35% for G1 and 36% for G2.

2) group 1 and group 2 are the same
Results

- A linear model with treatment as a covariate was considered in simulation studies.

- The coverage probabilities for the normal approximation methods and the AEL are consistently lower than the nominal level for small samples ($n = 50, 100$). The coverage probabilities for the $R_3$ and $R_5$ are larger than the nominal level for small samples in most cases.

- The $R_4$ outperforms the normal approximation method. Particularly, under heavy censoring rate (CR=47%), it has more accurate coverage probabilities than other confidence regions.
Contour plot for the confidence regions for the IBCSG Trial V data.
Contour plot for the confidence regions for the IBCSG Trial V data.
Some reference


Some reference


THANK YOU!