

# Regression Models for the Mean of the Quality-of-Life-Adjusted Restricted Survival Time Using Pseudo-Observations

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**SUMMARY.** In this research we develop generalized linear regression models for the mean of a quality-of-life-adjusted restricted survival time. Parameter and standard error estimates could be obtained from generalized estimating equations applied to pseudo-observations. Simulation studies with moderate sample sizes are conducted and an example from the International Breast Cancer Study Group Ludwig Trial V is used to illustrate the newly developed methodology.

**KEY WORDS:** Gap time; Inverse weighting; Nonparametric; Quality-of-life; Successive events.

## 1. Introduction

In clinical trials, the length of specific disease or treatment stages and the quality-of-life (QOL) are of high interest to the practitioner. For instance, in the initial phase (TOX) of the International Breast Cancer Study Group (IBCSG) Ludwig Trial V (see Gelber et al., 1992), patients experience moderate or increased toxicity, according to treatment arm assignment (short- versus long-duration chemotherapy). Unless precluded by death, TOX is followed by a disease-free period known as time without symptoms or toxicity (TWiST), and then by a period of cancer relapse (REL). The amount of chemotherapy received during TOX impacts patient well-being thereafter; hence, the need for tools summarizing the quantitative and qualitative health aspects in a unitary and meaningful way.

When data are not censored, the quality-adjusted-life-year (QALY) method is one such simple and easily interpretable measure (see Torrance and Feeny, 1989). Essentially, the patient's well-being is classified into a discrete number of health states, each having a utility value. QALY is the sum of the utility-weighted time periods spent in each health state. As mentioned in Glasziou et al. (1998), sensitivity analyses of the utility weights in QALY provide insight into the nature of the quantity versus QOL tradeoff. Examples and practical considerations involving QALY are presented, for instance, in Goldhirsch et al. (1989), Glasziou, Simes, and Gelber (1990), or Gelber et al. (1995).

When censoring is present, QALY may only be identifiable in restricted or truncated form and quality-of-life-adjusted lifetime (QAL) tests, which are based on integrated weighted

areas under the survival curve, could be used instead. This class of tests has been studied by Gelber, Gelman, and Goldhirsch (1989) and Huang and Louis (1999), among others. A particular QAL test, attractive in its simplicity, Q-TWiST has been introduced by Glasziou et al. (1990) and successfully used as an inferential tool in various AIDS or cancer clinical trials, as presented in Gelber et al. (1992), Cole et al. (1996), and Gelber et al. (1996). Its closed-form asymptotic variance has been given by Murray and Cole (2000). The survival distribution of QAL is also of clinical interest. Gelber et al. (1989) pointed out that, in this case, the Kaplan-Meier estimator is biased due to the induced dependent censoring. To correct for the bias, Zhao and Tsiatis (1997, 1999) have proposed estimators involving inverse probability-of-censoring weighting techniques, as in Robins and Rotnitzky (1992). Zhao and Tsiatis (2001) have developed testing methods for detecting differences between survival functions of QALs.

As a way to incorporate prognostic covariates, Cole, Gelber, and Goldhirsch (1993) have proposed and studied Cox regression models for the QOL-adjusted survival analysis. Another regression method involving Cox models has been proposed by van der Laan and Hubbard (1999). However, because these methods usually model the QALs indirectly via their hazard functions, the coefficient estimates thus obtained lack a clinically meaningful interpretation. Although meritorious, this approach to modeling has moved away from the simple and intuitive characteristics of mean QAL.

Alternatively, we propose a much simplified approach to multiple regression of QALs, by using the so-called

pseudo-observations (see, e.g., Wu, 1986). In connection to Wu (1986), and building from Andersen, Klein, and Rosthøj (2003), generalized regression models for mean restricted survival time analysis were developed by Andersen, Hansen, and Klein (2004). We extend this methodology to the multiple regression analysis of mean QOL-adjusted restricted lifetimes. This approach has a few important advantages. First, we model the mean QALs directly, rather than via QOL-adjusted hazard functions, thus maintaining the interpretability of the regression coefficients. While remaining in the realm of linear regression, this approach is very appealing to the practitioner, because it makes it easier to understand the clinical significance of the results obtained. Second, minimal assumptions are needed and the inferential procedures, generalized estimating equation (GEE) in this case, are very well understood and developed. Third, standard software is implemented in most statistical packages, hence parameter and variance estimates are available with no additional effort.

The rest of this article is structured as follows: in Section 2, the new regression methodologies for the mean of the QOL-adjusted restricted survival time are introduced and studied. In Section 3, extensive simulations studies are presented, followed by an example from the IBCSG Ludwig Trial V in Section 4. Several remarks and related future research directions conclude this article.

## 2. Pseudo-Observations-Based Regression for Mean of QOL-Adjusted Restricted Survival Times

To begin, a general introduction to pseudo-observations is given, followed by a brief description of their use in generalized regression models. Next, the concept of QOL-adjusted lifetime is described, along the lines of Zhao and Tsiatis (1997). In the last part, regression methods for analyzing means of QOL-adjusted restricted survival times are proposed.

### 2.1 Pseudo-Observations: An Introduction

In general, the so-called pseudo-observations are obtained as a result of using the jackknife, which is a resampling technique preceding the bootstrap. The initial purpose of the pseudo-observations was to study the estimators' bias and standard errors. Devised for balanced data situations, the original "leave-one-out" or "delete-one" jackknife has been found to be a useful tool in situations where one is presented with unbalanced data, such as linear or nonlinear regression models.

The idea behind the original jackknife is very easy to convey. Suppose that an estimator  $\hat{\theta}$  of a quantity of interest  $\theta$  is available based on a size  $n$  random sample. Then,  $n$  estimates  $\hat{\theta}^{(-i)}$  of  $\theta$  become available based on the "leave-one-out" samples obtained by successively dropping the  $i$ th observation from the original sample, where  $i = 1, \dots, n$ . The  $i$ th pseudo-observation is defined as  $n\hat{\theta} - (n-1)\hat{\theta}^{(-i)}$ .

### 2.2 Pseudo-Observations in the Context of Regression Models

There are multiple versions of the jackknife applied to regression settings, and they involve various weighting schemes in the way the pseudo-observations are defined. The specifics are discussed at length by Fox, Hinkley, and Larntz (1980), Hinkley (1977), Simonoff and Tsai (1986), among others. A detailed review of the existing methods, including jackknifing for regression M-estimators, nonlinear regression, and generalized regression models, is part of the innovative paper of Wu

(1986). Andersen et al. (2003, 2004) propose using pseudo-observations based on generalized linear models with a robust variance estimator, in the context of multi-state models and restricted mean survival time regression, thus opening up possibilities for employing these techniques in survival analysis problems. Following Andersen et al. (2003), the main ideas will be presented subsequently and then extended for use with models of restricted means of QOL-adjusted survival times.

The data consist of  $\{(X_i, Z_i), i = 1, \dots, n\}$  assumed to be i.i.d. random vectors and one would like to estimate  $\theta_i(Z_i) = E\{f(X_i) | Z_i\}$ , for some function  $f$ , possibly multivariate. The random variable  $X_i$  can be thought of as an outcome of interest, while  $Z_i$  may represent a vector of covariates for the  $i$ th individual. Unbiased (or nearly unbiased) nonparametric estimators of  $\theta = E\{f(X_i)\}$  tend to be either explicit or implicit mixtures of the parameters of interest because  $E\{\theta_i(Z_i)\} = E[E\{f(X_i) | Z_i\}] = E\{f(X_i)\} = \theta$ . For instance, averaging over the empirical distribution for  $Z$  gives

$$\tilde{\theta} = \frac{1}{n} \sum_{i=1}^n \theta_i(Z_i),$$

and

$$\tilde{\theta}^{(-i)} = \frac{1}{n-1} \sum_{j \neq i}^n \theta_j(Z_j),$$

both unbiased estimators of  $\theta$ . Estimators resembling  $\tilde{\theta}$  in a restricted mean context have been studied by Chen and Tsiatis (2001) and Zucker (1998).

The definition of the  $i$ th pseudo-observation  $\nu_i = n\tilde{\theta} - (n-1)\tilde{\theta}^{(-i)} = \theta_i(Z_i)$ ,  $i = 1, \dots, n$ , suggests an indirect method for obtaining inference on  $\theta_i(Z_i)$  when the functional form of  $\theta_i(Z_i)$  is unknown or when the investigators are unwilling to make strong parametric assumptions. Namely, one may construct any unbiased estimates  $\hat{\theta}$  and  $\hat{\theta}^{(-i)}$ ,  $i = 1, \dots, n$ , (nonparametric or otherwise) of  $\theta$ , construct the corresponding pseudo-observations  $\nu_i$  and regress  $\nu_i$  on the covariate  $Z_i$  instead of regressing  $\theta_i(Z)$  on  $Z_i$ . This is justified because the pseudo-observation  $\nu_i$  is equal to  $\theta_i(Z_i)$  in expectation, with respect to the joint distribution of  $(X, Z)$ . In particular, one can perform regression analysis of  $\nu_i$  on  $Z_i$  by means of generalized linear models, assuming that there exists a link function  $g(\cdot)$  such that

$$g(\nu_i) = \beta^T Z_i,$$

where  $\beta$  is the vector of regression parameters. Due to the fact that the pseudo-observations might be correlated,  $\beta$  may be estimated using GEE methods as in Liang and Zeger (1986) and Zeger and Liang (1986). A consistent estimator  $\hat{\beta}$  of  $\beta$  is obtained from the GEE

$$U(\beta) = \sum_{i=1}^n U_i(\beta) = \sum_{i=1}^n \left\{ \frac{\partial}{\partial \beta} g^{-1}(\beta^T Z_i) \right\} V_i^{-1} \\ \times \{ \nu_i - g^{-1}(\beta^T Z_i) \} = 0,$$

and the variance of  $\hat{\beta}$  is estimated using the classical "sandwich" estimator,

$$\widehat{\text{var}}(\hat{\beta}) = I(\hat{\beta})^{-1} \widehat{\text{var}}\{U(\hat{\beta})\} I(\hat{\beta})^{-1},$$

where

$$I(\beta) = \sum_{i=1}^n \left\{ \frac{\partial}{\partial \beta} g^{-1}(\beta^T Z_i) \right\}^T V_i^{-1} \left\{ \frac{\partial}{\partial \beta} g^{-1}(\beta^T Z_i) \right\},$$

$$\widehat{\text{var}}\{U(\hat{\beta})\} = \sum_{i=1}^n U_i(\hat{\beta})U_i(\hat{\beta})^T,$$

and  $V_i$  is the working covariance matrix for  $Z_i$ .

To extend this approach for our purposes, we need to define appropriate pseudo-observations for mean of QOL-adjusted restricted survival times.

### 2.3 Extension to Mean of QOL-Adjusted Restricted Survival Time Estimation

First, the mean of QOL-adjusted  $L$ -restricted survival times  $\mu_Q(L)$  is reviewed. In line with the early parts of this section, we obtain estimators  $\hat{\mu}_Q(L)$  of  $\mu_Q(L)$  based on the methods of Zhao and Tsiatis (1997), create the corresponding pseudo-observations, and analyze them using generalized linear regression models.

With individual lifetime  $Y$  being subject to independent right censoring at time  $C$ , one observes  $\{\tilde{Y} = Y \wedge C, \Delta = I(Y \leq C)\}$ , where  $a \wedge b = \min(a, b)$ . For technical reasons, described in detail by Zhao and Tsiatis (1997), assume the existence of a constant  $L > 0$  such that  $P(Y \leq L) = 1$  and  $P(C > L) > 0$ . Individual health history is described by a continuous time stochastic process  $V(\cdot)$  with disease severity ordered states  $\{0, 1, \dots, S\}$ , where state “0” represents death and state “ $S$ ” means perfect health. A deterministic, non-decreasing, and known utility function  $Q(\cdot)$  assigns to each health state a value between 0 (state “0”) and 1 (state “ $S$ ”). Even though  $V(\cdot)$  and  $C$  are assumed to be independent,  $V(\cdot)$  and  $Y$  are likely to be dependent. The QOL-adjusted lifetime is defined as

$$QY = \int_0^Y Q\{V(t)\} dt.$$

Subject to censoring, its observed version is

$$\widetilde{QY} = \int_0^{\tilde{Y}} Q\{V(t)\} dt.$$

Subscript  $i$  attached to a previously defined quantity indicates that the respective quantity is computed based on the  $i$ th individual’s data.

Let  $D_i(q) = \inf\{s \geq 0; \int_0^s Q\{V_i(t)\} dt \geq q\} \wedge Y_i$  be the first time when the  $i$ th individual has accumulated at least the amount  $q$  of QOL-adjusted lifetime. Should this happen past  $Y_i$ , the expression  $D_i(q)$  is set to be equal to  $Y_i$ . As described by Zhao and Tsiatis (1997), a consistent estimator of the survival function  $H_Q(q) = P(QY > q)$  is

$$\hat{H}_Q(q) = n^{-1} \sum_{i=1}^n \frac{I\{\widetilde{QY}_i > q\}}{\hat{G}\{D_i(q)\}},$$

where  $\hat{G}(\cdot)$  is the Kaplan–Meier estimator of the censoring time  $C$  survival function  $G(\cdot)$  obtained based on  $\{(\tilde{Y}_i, \Delta_i), i = 1, \dots, n\}$ .

The mean of the QOL-adjusted  $L$ -restricted survival time is defined as  $\mu_Q(L) = \int_0^L H_Q(q) dq = \int_0^L P(QY > q) dq$  and can be estimated by  $\hat{\mu}_Q(L) = \int_0^L \hat{H}_Q(q) dq$ . Then, the  $n$  jackknife

versions of this estimator are constructed, according to the definition, as  $\hat{\mu}_Q^{(-i)}(L)$ , where superscript  $(-i)$  indicates that the  $i$ th observation in the original sample is being left out. Thus, the pseudo-observations for the mean of the QOL-adjusted  $L$ -restricted survival times are

$$\nu_i(L) = n\hat{\mu}_Q(L) - (n - 1)\hat{\mu}_Q^{(-i)}(L), \quad i = 1, \dots, n.$$

As described earlier in the section, generalized linear regression models based on  $\{\nu_i(L), Z_i\}$  can be constructed in order to assess the covariate effect(s). This approach is very appealing because it reduces a potentially complicated regression problem with censored survival data to a more straightforward linear regression problem with parameters that are easy to interpret.

### 3. Simulation Studies

Four simulation scenarios have been devised in order to assess the moderate sample size properties of the estimates of the regression coefficients. The results are presented in Tables 1 and 2. The utility function  $Q(s) = s/100$ , where  $s \in S = \{0, 1, \dots, 100\}$ , has been employed throughout. Independent Uniform (0, 2) censoring has been generated, resulting in censoring percentages ranging from 10% to 50%. Under each scenario random samples of size  $n = 50$  were replicated 1000 times, with  $L$  chosen to be equal to 2. Throughout, the identity matrix was used to model the working correlation matrix.

In the first simulation scenario, the health process was  $V(s) = 100$ , for all  $s \in S$ , so the mean of the QOL-adjusted survival time was equal to its unadjusted counterpart. A multistep general algorithm, described subsequently, has been used to generate the individual survival times  $T_1, \dots, T_n$ :

*Step 1:* Generate individual covariates  $Z_1, \dots, Z_n$  from either a discrete (Bernoulli) or continuous (Uniform) distribution.

*Step 2:* Given  $\beta$ , find  $\lambda_i = \lambda_i(Z_i)$  that solves the equation  $\int_0^L e^{-\lambda_i t} dt = e^{\beta Z_i}, i = 1, \dots, n$ .

**Table 1**

*Simulation scenarios (SS) 1 and 2 results:  $\beta = \text{true}$  parameter value,  $\hat{\beta} = \text{empirical mean of estimated } \beta \text{ values}$ ,  $\text{ESE}(\hat{\beta}) = \text{empirical standard error of estimated } \beta \text{ values}$ ,  $\text{MSE}(\hat{\beta}) = \text{mean of estimated standard errors of } \beta \text{ values}$ ,  $\text{CP}(\hat{\beta}) = \text{coverage probability of true } \beta \text{ by the 95\% confidence intervals}$ .*

	$Z$	$\beta$	$\hat{\beta}$	$\text{ESE}(\hat{\beta})$	$\text{MSE}(\hat{\beta})$	$\text{CP}(\hat{\beta})$
SS 1	Bernoulli(0.5)	0	0.01	0.41	0.41	0.95
		−0.25	−0.29	0.38	0.39	0.94
		−0.50	−0.53	0.36	0.37	0.95
	Uniform(0,1)	0	0.00	0.68	0.67	0.95
		−0.25	−0.31	0.67	0.67	0.94
		−0.50	−0.60	0.67	0.67	0.95
SS 2	Bernoulli(0.5)	0	0.11	0.38	0.39	0.93
		−0.25	−0.22	0.37	0.37	0.95
		−0.50	−0.48	0.37	0.38	0.94
	Uniform(0,1)	0	0.14	0.65	0.68	0.95
		−0.25	−0.20	0.65	0.65	0.94
		−0.50	−0.47	0.64	0.66	0.93

**Table 2**

Simulation scenarios (SS) 3 and 4 results in correctly (C) or incorrectly (I) specified models, with covariates correlated at approximately 0.3 level:  $\beta_i$  is the true parameter value,  $\hat{\beta}_i$  = empirical mean of estimated  $\beta_i$  values,  $ESE(\hat{\beta}_i)$  = empirical standard error of estimated  $\beta_i$  values,  $MSE(\hat{\beta}_i)$  = mean of estimated standard errors of  $\beta_i$  values,  $CP(\hat{\beta}_i)$  = coverage probability of true  $\beta_i$  by the 95% confidence intervals,  $i = 1, 2$ .

	Model	$\beta_1$	$\hat{\beta}_1$	$ESE(\hat{\beta}_1)$	$MSE(\hat{\beta}_1)$	$CP(\hat{\beta}_1)$	$\beta_2$	$\hat{\beta}_2$	$ESE(\hat{\beta}_2)$	$MSE(\hat{\beta}_2)$	$CP(\hat{\beta}_2)$
SS 3	C	0	0.00	0.73	0.73	0.94	-1.00	-1.22	0.89	0.88	0.95
		-0.25	-0.30	0.71	0.75	0.91	-1.00	-1.16	0.86	0.92	0.93
		-0.50	-0.53	0.68	0.67	0.86	-1.00	-1.06	0.82	0.85	0.93
	I	0	-0.27	0.71	0.72	0.92	-1.00	-	-	-	-
		-0.25	-0.50	0.68	0.73	0.85	-1.00	-	-	-	-
		-0.50	-0.77	0.66	0.66	0.77	-1.00	-	-	-	-
SS 4	C	0	-0.04	0.65	0.63	0.96	-1.00	-0.89	0.20	0.21	0.86
		-0.25	-0.26	0.64	0.62	0.95	-1.00	-0.87	0.19	0.19	0.86
		-0.50	-0.50	0.63	0.66	0.93	-1.00	-0.87	0.19	0.21	0.82
	I	0	-0.85	0.75	0.74	0.80	-1.00	-	-	-	-
		-0.25	-1.03	0.73	0.73	0.80	-1.00	-	-	-	-
		-0.50	-1.29	0.72	0.75	0.79	-1.00	-	-	-	-

*Step 3:* Generate survival time  $T_i$  from an exponential distribution with rate  $\lambda_i$ ,  $i = 1, \dots, n$ . This way, the means  $\mu_Q(Z) = e^{\beta Z}$  of the QOL-adjusted survival times are guaranteed to follow the log-linear regression model  $\log\{\mu_Q(Z)\} = \beta Z$ . Based on the observed data  $[\tilde{T}_i = T_i \wedge C_i, \Delta_i = I(T_i \leq C_i), \tilde{V}_i = \{V_i(t), t \leq \tilde{T}_i\}, Z_i, i = 1, \dots, n]$ , one computes the pseudo-observations  $\{\nu_{Q,i}(Z_i), i = 1, \dots, n\}$ . Then, one obtains an estimate  $\hat{\beta}$  of  $\beta$ , using the generalized regression model,  $\log\{\nu_Q(Z)\} = \beta Z$ . Table 1 contains simulation results when this scenario is replicated for  $\beta \in \{0, -0.25, -0.5\}$ , with covariate  $Z$  being distributed Bernoulli (0.5) or Uniform (0, 1).

The major change in the second simulation scenario lies in the choice of the health process  $V_i(t)$  described in step 4 below. With some minor alterations, the algorithm described earlier can again generate QOL-adjusted times  $QT_1, \dots, QT_n$  with means following  $\mu_Q(Z) = e^{\beta Z}$ :

*Step 1:* Generate sample of individual covariates  $Z_1, \dots, Z_n$ .

*Step 2:* Given  $\beta$ , find  $\lambda_i = \lambda_i(Z_i)$  that solves the equation  $\int_0^L e^{-\frac{\lambda_i}{\xi_i} t} dt = e^{\beta Z_i}$ , where  $\xi_i = I(Z_i > 0.5) + 0.85I(Z_i \leq 0.5)$  for  $i = 1, \dots, n$ .

*Step 3:* Generate survival time  $T_i$  from an exponential distribution with rate  $\lambda_i$ ,  $i = 1, \dots, n$ .

*Step 4:* Given  $Z_i$ , define the health process

$$V_i(t) = \begin{cases} 100, & \text{if } 0 \leq t \leq T_i \text{ and } Z_i > 0.5 \\ 90, & \text{if } t \leq \frac{T_i}{2} \text{ and } Z_i \leq 0.5 \\ 80, & \text{if } \frac{T_i}{2} \leq t \leq T_i \text{ and } Z_i \leq 0.5, \end{cases}$$

and let  $QT_i = \int_0^{T_i} Q\{V_i(t)\} dt = I(Z_i > 0.5)T_i + 0.9I(Z_i \leq 0.5)T_i/2 + 0.8I(Z_i \leq 0.5)T_i/2 = \xi_i T_i$ .

Then, the means  $\mu_Q(Z) = e^{\beta Z}$  of the QOL-adjusted survival times follow the log-linear regression model  $\log\{\mu_Q(Z)\} = \beta Z$ . Simulation results are shown in Table 1, with  $\beta \in \{0, -0.25, -0.5\}$  and covariate  $Z$  distributed Bernoulli (0.5) or Uniform (0, 1).

The third simulation scenario employs the same health process  $V(s) = 100$ , for all  $s \in S$ , but a covariate vector  $(Z, W)$  is used instead, with  $Z$  and  $W$  correlated at approximately 0.3 level. The data-generating algorithm is as follows:

*Step 1:* Generate covariate vectors  $(Z_1, W_1) \dots, (Z_n, W_n)$ , with  $Z$  distributed as Uniform (0, 1),  $W$  as Exponential (4) and  $Z$  and  $W$  are correlated at approximately 0.3 level.

*Step 2:* Given  $\beta_1$  and  $\beta_2$ , find  $\lambda_i = \lambda_i(Z_i, W_i)$  that solves the equation  $\int_0^L e^{-\lambda_i t} dt = e^{\beta_1 Z_i + \beta_2 W_i}$ ,  $i = 1, \dots, n$ .

*Step 3:* Generate survival time  $T_i$  from an exponential distribution with rate  $\lambda_i$ ,  $i = 1, \dots, n$ .

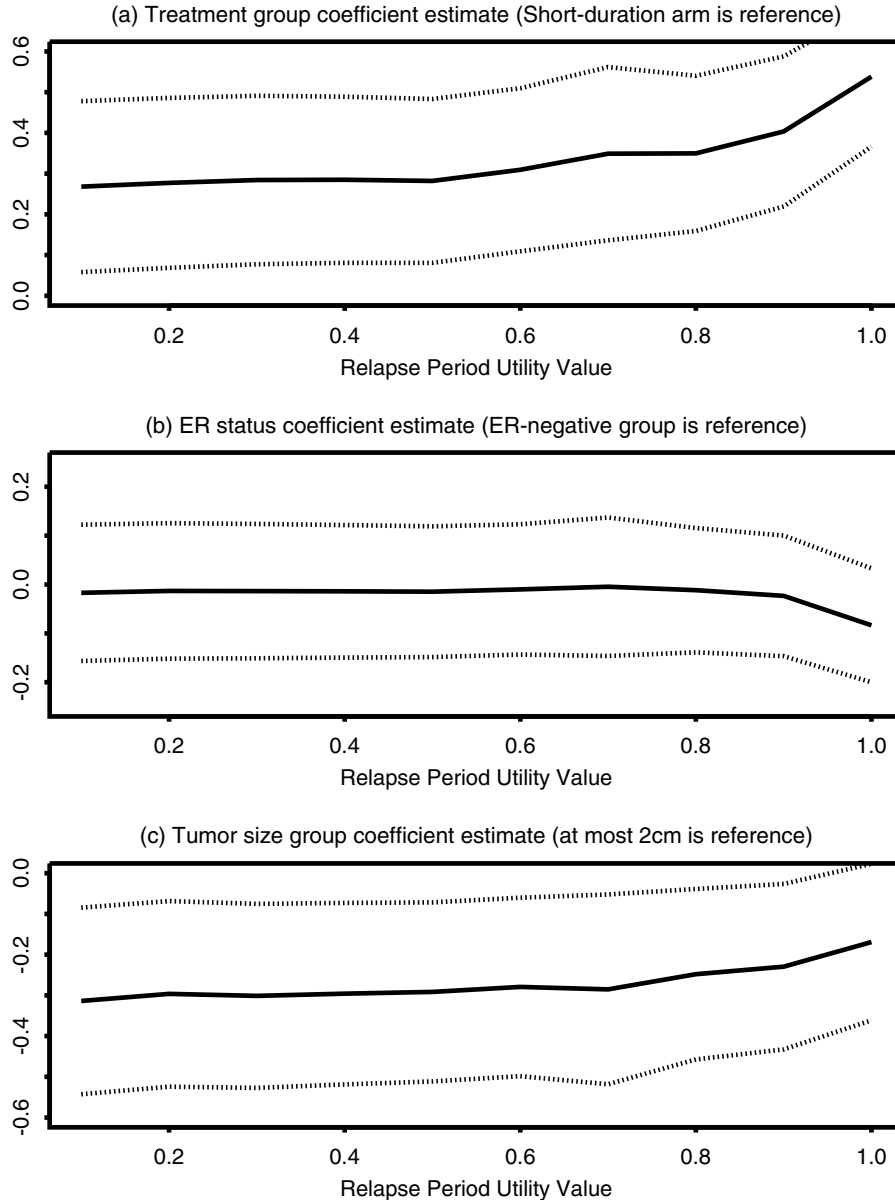
The mean  $\mu_Q(Z, W) = e^{\beta_1 Z + \beta_2 W}$  of the QOL-adjusted survival times follow the log-linear regression model  $\log\{\mu_Q(Z, W)\} = \beta_1 Z + \beta_2 W$ . The pseudo-observations  $\{\nu_{Q,i}(Z_i, W_i), i = 1, \dots, n\}$  are computed and two log-linear regression models are fitted. In the first one, the functional forms of both  $Z$  and  $W$  are correctly specified. To explore the parameter estimates behavior under model misspecifications, in the second model the functional form of  $Z$  only is correctly specified, while  $W$  is entirely left out of the model. Simulations are carried on for  $\beta_1 \in \{0, -0.25, -0.5\}$ ,  $\beta_2 = -1$  and the results are shown in Table 2.

Finally, the fourth scenario bears similarity to the previous one, except for the choice of the health process:

*Step 1:* Generate covariate vectors  $(Z_1, W_1) \dots, (Z_n, W_n)$ , with  $Z$  and  $W$  distributed as Uniform (0,1) and Exponential (1) random variables, respectively, and  $Z$  and  $W$  correlated at approximately 0.3 level.

*Step 2:* Given  $\beta_1$  and  $\beta_2$ , find  $\lambda_i = \lambda_i(Z_i, W_i)$  that solves the equation  $\int_0^L e^{-\frac{\lambda_i}{\xi_i} t} dt = e^{\beta_1 Z_i + \beta_2 W_i}$ , where  $\xi_i = I(Z_i > 0.5, W_i > 1) + 0.975I(Z_i > 0.5, W_i \leq 1) + 0.95I(Z_i \leq 0.5, W_i > 1) + 0.90I(Z_i \leq 0.5, W_i \leq 1)$ ,  $i = 1, \dots, n$ .

*Step 3:* Generate survival time  $T_i$  from an exponential distribution with rate  $\lambda_i$ ,  $i = 1, \dots, n$ .



**Figure 1.** IBCSG Ludwig trial V example results for the premenopausal women group: coefficient estimates (—) and 95% pointwise confidence intervals (...) in univariate regression models for  $\log\{Q - TWiST(60)\}$  when toxicity period utility value  $\mu_{TOX} = 0.5$  and relapse period utility value  $\mu_{REL}$  is between 0 and 1.

Step 4: Given  $(Z_i, W_i)$ , define the health process

$$V_i(t) = \begin{cases} 100, & \text{if } Z_i > 0.5 \text{ and } W_i > 1 \\ 97.5, & \text{if } Z_i > 0.5 \text{ and } W_i \leq 1 \\ 95, & \text{if } Z_i \leq 0.5 \text{ and } W_i > 1 \\ 90, & \text{if } Z_i \leq 0.5 \text{ and } W_i \leq 1, \end{cases}$$

so that  $QT_i = \int_0^{T_i} Q\{V_i(t)\} dt = \xi_i T_i$ . Simulations are conducted for values of  $\beta_1 \in \{0, -0.25, -0.5\}$  and  $\beta_2 = -1$  and results are presented in Table 2.

Overall, the results confirm that when the regression models are correctly specified, the estimators show very little or no bias. Furthermore, the sample average coverage probabilities

of the 95% confidence intervals tend to be near the nominal level in most simulation scenarios. Coverage probabilities somewhat below the nominal level are observed under scenario 4, likely due to the correlation of the covariates present in the respective model.

The empirical standard deviations of the estimated parameters agree very closely with the empirical means of the estimated parameters' standard errors. Model misspecification leads to biased estimates and reduced coverage probabilities.

#### 4. IBCSG Ludwig Trial V Example

Recall the IBCSG Ludwig Trial V mentioned in the introduction, where adjuvant chemotherapy was aimed towards

eliminating undetected tumor sites after surgical removal of the primary tumor.

Of the 1229 patients in the study, we focus on the subgroup of 715 premenopausal women, age range 24 to 60 years, and mean age at enrollment of 44 years (SD = 42). Of them, 240 were in the short-duration (SD) treatment arm, while 475 were in the long-duration (LD) treatment arm. With toxicity period (TOX), cancer relapse period (REL) and truncation time measured in months, the mean of the QOL-adjusted 60-month-restricted survival time QTWiST (60) is the version of  $QTWiST = \mu_{TOX}TOX + TWiST + \mu_{REL}REL$  based on 60-month-restricted overall survival data, where  $\mu_{TOX}, \mu_{REL} \in (0, 1]$  are utility scores assigned to the toxicity and the relapse periods, respectively. Throughout this example, we employ  $\mu_{TOX} = 0.5$ , as was used in the analyses by the original authors.

Investigators were interested in learning how the mean of the QOL-adjusted 60-month-restricted survival time QTWiST (60) is related to several factors of high clinical importance such as treatment group (SD vs. LD), estrogen-receptor ER status (positive or negative/unknown) and tumor size measured in centimeters (greater than 2 cm or not). The results are presented in Figure 1 depicting a three-panel plot containing coefficient estimates for the variable of interest in univariate regression models, when  $\mu_{REL} \in (0, 1]$  and  $\mu_{TOX} = 0.5$ . Throughout, the identity matrix was used to model the working correlation matrix.

For clarification purposes, let us describe the findings in detail. Figure 1a presents a sensitivity analysis of the estimated treatment effect when the outcome is QTWiST(60) on the log scale. Treatment arm coefficients are positive throughout, indicating that the LD treatment arm patients have significantly higher QTWiST(60) values than those in the SD treatment (reference group), even increasingly more so for higher  $\mu_{REL}$  utility values. Figure 1b shows that there is no significant ER status effect on QTWiST(60) for the entire range of  $\mu_{REL}$  utility scores. Results involving the tumor size effect are shown in panel (c). When patients with tumors of at most 2 cm form the reference group, the coefficient estimates are negative throughout, indicating that a greater tumor size is associated with a lower QTWiST(60) value. Giving higher utility values to the REL period leads to a slight attenuation of the tumor size effect, but the significant advantage of having smaller tumors is still preserved. These sensitivity analyses can be used by the investigators as a starting point in understanding the complex relationships between QOL and quantity-of-life in breast cancer patients.

## 5. Discussion

The methods developed in this article provide useful tools that allow an investigator to assess, in a direct way, the effects of prognostic covariates on the mean of a QOL-adjusted restricted survival time. Although Cox model-based regression methods are also available, they are not as user friendly because they model the QOL-adjusted hazard function, an object lacking a direct practical interpretation.

Since nonparametric methods are used, very few assumptions are being made in the process of obtaining pseudo-observations. There is the added advantage that the Zhao and Tsiatis-based components of the pseudo-observations have

been demonstrated to be asymptotically normal, further validating the generalized linear regression approach to analysis of the pseudo-observations. Translating a survival analysis problem into a well-understood generalized linear regression is beneficial on multiple levels. Computational simplicity is gained because regression methods and techniques are implemented in many statistical packages. Model-checking techniques for generalized regression models are plentiful and arguably easier to apply and interpret than those for censored survival data.

Due to its simplicity, the pseudo-observation approach has wide appeal to complex survival analysis problems. One possible future application of the current method is to incorporate covariates in the context described in Andrei and Murray (2006), where the QOL-adjusted gap time distribution of successive events is estimated. With covariate adjustments, one could examine, in even greater detail, the complex relationships among successive landmark events, gap time joint or conditional distributions, and QOL scores.

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