Published in final edited form as:

Stat Med. 2017 December 20; 36(29): 4692–4704. doi:10.1002/sim.7445.

A Semiparametric Joint Model for Terminal Trend of Quality of Life and Survival in Palliative Care Research

Zhigang Li^{a,*,#}, H. R. Frost^{a,#}, Tor D. Tosteson^a, Lihui Zhao^b, Lei Liu^b, Kathleen Lyons^c, Huaihou Chen^d, Bernard Cole^e, David Currow^f, and Marie Bakitas^g

^aDepartment of Biomedical Data Science, Geisel School of Medicine, Dartmouth College, Hanover, NH 03755

^bDepartment of Preventive Medicine, Northwestern University, Chicago, IL 60611

^cDepartment of Psychiatry, Geisel School of Medicine, Dartmouth College, Hanover, NH 03755

^dBiogen, 225 Binney St, Cambridge, MA 02142

^eDepartment of Mathematics and Statistics, University of Vermont, Burlington, VT, 05405

^fDiscipline of Palliative and Supportive Services, Flinders University, Bedford Park SA 5042, Australia

^gSchool of Nursing, The University of Alabama at Birmingham, Birmingham, AL 35233

Abstract

Palliative medicine is an interdisciplinary specialty focusing on improving quality of life (QOL) for patients with serious illness and their families. Palliative care programs are available or under development at over 80% of large US hospitals (300+ beds). Palliative care clinical trials present unique analytic challenges relative to evaluating the palliative care treatment efficacy which is to improve patients' diminishing QOL as disease progresses towards end of life (EOL). A unique feature of palliative care clinical trials is that patients will experience decreasing QOL during the trial despite potentially beneficial treatment. Often longitudinal QOL and survival data are highly correlated which, in the face of censoring, makes it challenging to properly analyze and interpret terminal QOL trend. To address these issues, we propose a novel semiparametric statistical approach to jointly model the terminal trend of QOL and survival data. There are two sub-models in our approach: a semiparametric mixed effects model for longitudinal QOL and a Cox model for survival. We use regression splines method to estimate the nonparametric curves and AIC to select knots. We assess the model performance through simulation to establish a novel modeling approach that could be used in future palliative care research trials. Application of our approach in a recently completed palliative care clinical trial is also presented.

*Correspondence to: Zhigang Li, Department of Biomedical Data Science, Geisel School of Medicine, Dartmouth College, Hanover, NH 03755. Zhigang.Li@dartmouth.edu.

#These authors contributed equally to the paper

Conflict of Interest: None declared

Keywords

Palliative care; End-of-life; Terminal trend; Joint modeling; Semiparametric

1. INTRODUCTION

Palliative care is a relatively new interdisciplinary specialty (medicine, nursing, social work, chaplaincy, and other specialties when appropriate) that focuses on improving quality of life for patients of any age with any serious disease, whether it can be cured or controlled, and for their families [1]. Data from 2010 have shown that palliative care programs were available or under development at more than 80% of large US hospitals (300+ beds) [2]. Understanding of terminal trends or trajectories of QOL through carefully designed palliative care studies is crucial to help practitioners, patients and their care givers gain a better understanding of ill trajectories which may then help them feel in better control and empower them to cope with difficulties [3]. Palliative care clinical trials present unique analytic challenges relative to evaluating the palliative care treatment efficacy in terms of improving patients' diminishing QOL as disease progresses towards EOL. QOL, symptom burden, anxiety, depression, and resource use, rather than survival, are common endpoints chosen to evaluate treatment efficacy of palliative care [4–6]. These measures are captured longitudinally over relatively short time frames prior to death especially in cancer palliative care trials. Additionally, some patients may drop out or live beyond study end, resulting in longitudinal QOL data and survival time being censored. When analyzing palliative care studies, the interplay between longitudinal QOL and survival outcomes should be taken into account because these two outcomes typically strongly related especially during EOL period. Without appropriate modeling of the correlation, estimates could be inefficient and the clinical interpretation could be distorted. Censoring of survival time occurs frequently due to dropout or study end, making it challenging to account for the correlation. To have the most accurate assessment of treatment efficacy (clinical effect) and avoid distorted interpretations and inefficient analyses due to censoring, it is important to thoughtfully consider survival-longitudinal data correlation in data analysis. To address these issues, we propose a novel statistical approach for jointly modeling terminal QOL trend and survival data in palliative care trials.

In the statistical literature, significant effort has been devoted to methods for jointly modeling longitudinal data and time-to-event data such as shared parameter models [7–12], pattern mixture models [13–16] and other types of models [17, 18]. Comprehensive reviews on the differences and connections of these approaches can be found in the literature [19–22]. To the best of our knowledge, only a few methods have been proposed to jointly model terminal trend of longitudinal data and survival data [10, 21, 23–25] by aligning the longitudinal trajectory using death as the time origin on retrospective time scale. Kurland et al. [21] described a terminal trend model for analyzing only the decedents whose survival times are observed. Unfortunately, the decedent analysis can generate substantial loss in efficiency by omitting censored subjects when censoring rate is high (e.g., 47.34% for the motivating example described in Section 2). To alleviate the loss of power due to removing the censored subjects entirely, Li et al. [23] developed a parametric piecewise linear terminal

trend model for cancer palliative care studies by appropriately accounting for censoring. They proposed to model the QOL terminal trend using a piecewise linear trajectory with a breakpoint at 6 months before death. This approach may not be adequate for nonlinear smooth trend as we will see in the simulation study.

There are related methods primarily motivated by jointly analyzing longitudinal cost data and survival. Liu et al. [10] proposed a ‘turn back time’ method to characterize costs on a retrospective time scale. They re-censors the longitudinal outcomes at some fixed time before the actual censoring time, while keeping the actual censoring time for the survival model. Chan and Wang [24] proposed an estimator for mean of backward processes retrospectively from death. They did not consider adjusting for covariates. Under similar assumptions, they [25] also developed a three-level semiparametric joint model for the terminal behavior of marker processes measured at recurrent events before death. Chang and Wang [24, 25] did not consider time-varying covariates or time varying-coefficients. They omitted the longitudinal data from subjects with censored death times when estimating parameters.

In this paper, we will develop a semiparametric terminal trend model with a semiparametric mixed effects sub-model for the longitudinal QOL outcomes and a Cox sub-model for the survival outcome. The nonparametric parts of longitudinal trajectories allow us to build a flexible model that is applicable to disease populations beyond cancer (e.g., heart failure, dementia). Regression spline methods with natural cubic B-splines will be employed to estimate the unspecified nonparametric terminal trend. Quality-adjusted life years (QALY) can be also derived and analyzed using this terminal trend model.

The rest of this paper is organized as follows. Section 2 introduces the palliative care ENABLE III (Educate, Nurture, Advise, Before Life Ends, III) randomized clinical trial (RCT) that motivated this development. Section 3.1 gives notation and specifies the proposed statistical models. Estimation of the model parameters is detailed Section 3.2. A simulation study is described in Section 4. Application of the model to the ENABLE III RCT is provided in Section 5, followed by a discussion in Section 6.

2. MOTIVATING EXAMPLE

ENABLE III [6] was a two-arm palliative care RCT investigating the benefits of palliative care for patients with advanced cancer. The treatment arm received palliative care immediately after enrollment (early treatment arm) and the control arm received standard care for the first 12 weeks and then switched to palliative care (delayed treatment arm). 207 patients were enrolled between October, 2009 and March, 2013 and randomly allocated to either the early arm ($n = 104$) or the delayed arm ($n = 103$) upon enrollment. QOL data were collected at baseline (i.e., enrollment) and at 6, 12, 18, and 24 weeks and every 12 weeks thereafter post enrollment until death or study completion. The primary endpoint QOL was assessed by the 46-item Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-pal).

Higher FACIT-pal scores indicate better QOL. Clinically, QOL is expected to decrease when a patient approaches death [3] as shown in Figure 1B. However, in ENABLE III the overall pattern of observed mean QOL increased overtime (Figure 1A). This paradoxical phenomenon can be explained by the survival distribution and the QOL terminal trend because patients who were very ill, and presumably a lower QOL, died sooner. Thus, the mean QOL increases as the surviving patients were on average healthier. In ENABLE III, the hazard rate was higher in the first 12-month time period (results shown in Section 5), which is consistent with this explanation. When comparing QOL between the two arms in a study such as ENABLE III, it is important to adjust for any survival differences because better QOL in the early treatment group could simply be due to patients' longer survival. Therefore, joint modeling of the terminal decline of QOL and survival data is essential to more accurately interpret the study's results.

3. METHOD

3.1 Notation and Model

Suppose there are N patients in a study. Let D_i denote the survival time for the i th patient calculated as the duration from the date of enrollment to the date of death. Let $Y_i(t^*)$ denote the QOL outcome at time t^* counting backward from the time of death for the i th subject, $i = 1, \dots, N$. Although theoretically t^* is a continuum, QOL data will be collected at discrete time points. Let $Y_i(t_{ij}^*)$ denote the j th QOL measurement at time t_{ij}^* counting backward from the time of death for the i th patient, $j = 1, \dots, n_i$. Since the time scale counts backward, $Y_i(t_{i1}^*)$ is the first measurement counting backward from death. Let A_i denote the binary treatment status with value of 1 being treatment and value of 0 being control for the i th patient. Under a mixed effects model framework for the longitudinal measurements [26], a time-varying treatment effect model adjusting for covariates is given by

$$Y_i(t^*) = \beta_\mu(t^*) + A_i \beta_A(t^*) + X_i^T \psi_X + Z_i^T b_i + \varepsilon_i(t^*), \quad (1)$$

where $\beta_\mu(t^*)$ denotes the mean trajectory in the control group and the $\beta_A(t^*)$ denotes the time-varying treatment effect at time t^* counting backward from the time of death. Both $\beta_\mu(t^*)$ and $\beta_A(t^*)$ are unspecified smooth functions. There is evidence in the literature [4] suggesting that the treatment benefit might vary at different time points. So a time-varying treatment effect is more reasonable than a fixed treatment effect. With the time-varying estimator, we are not only able to provide an overall picture of the treatment effect during the terminal phase of life, but also estimate and test the treatment effect at any specific time point prior to death. Here ψ_X is the P -dimensional vector of fixed effect parameters associated with the baseline covariate vector X_i (the superscript T denotes transpose of a vector or matrix) adjusted in the model and b_i are independent L -dimensional vectors of random effects associated with the baseline covariates Z_i which could be different or the same as X_i . In a randomized trial, covariate adjustment is not necessary for the standard intent-to-treat analysis, but is introduced here to cover observational studies as well. Typical assumptions for mixed effects models are retained as follows: The random effects b_i are

assumed to have a multivariate normal distribution $N(0, \Sigma)$ where Σ is a L by L variance-covariance matrix; The residual error $e_{\lambda}(t^*)$ is assumed to be normally distributed with mean $E[e_{\lambda}(t^*)] = 0$ and $\text{var}[e_{\lambda}(t^*)] = \tau^2$, where $e_{\lambda}(t^*)$ and $e_{\lambda}(s^*)$ are independent for any $t^* \neq s^*$; The random effects b_i and residual error $e_{\lambda}(t^*)$ are assumed independent.

Model (1) naturally allows the longitudinal outcome and survival time dependent on each other by modeling the terminal trend. It is easier to see the dependency if we convert model (1) to its equivalent counterpart on the prospective time scale. Let $Y_i^p(t)$ denote the QOL at time t counting forward since enrollment. The sup script “ p ” is to indicate that it is on the prospective time scale. Let $Y_i^p(t_{ij})$ denote the j th QOL measurement collected at time t_{ij} on the prospective time scale for the i th patient, $j = 1, \dots, n_i$. The equivalent model on the prospective time scale is given by

$$Y_i^p(t) = \beta_{\mu}(D_i - t) + A_i \beta_A(D_i - t) + X_i^T \psi_X + Z_i^T b_i + \varepsilon_i(t).$$

Thus, under model (1), QOL at a specific time t depends on the quantity $D_i - t$, which measures how close a patient is to his death time. For example, if there is a terminal decline trend, which is usually true for cancer patients, the QOL at time t should be lower for patients with shorter life expectancy and higher otherwise. By accounting for the dependency between QOL and survival, it enables our approach to handle informative death events as well. The proposed model is similar to a pattern mixture model where the longitudinal outcome is modeled conditional on survival time. The difference is that our model assumes a terminal decline pattern whereas a pattern mixture model assumes the longitudinal patterns are different for different survival and dropout times.

Remark—In practice, the prospective measurement time points t_{ij} are observed, the time points on retrospective time scale can be calculated as $t_{ij}^* = D_i - t_{i, n_i - j + 1}$. If the survival time D_i are observed for all subjects in the study (ie, there are no censoring), then the retrospective measurement time points t_{ij}^* , $j = 1, \dots, n_i$ can be calculated for all subjects, and the parameters in model (1) can be estimated and tested by treating the model as a regular semiparametric mixed effect model [27]. However, there are often censored subjects whose t_{ij}^* cannot be calculated due to missing death times. This creates difficulty to model terminal trend and also motivates us to jointly model the survival time to tackle this issue.

The survival time D_i may be right censored by another event time denoted by C_i calculated as the duration from the date of enrollment to the date of event such as withdrawal or study end. Time points of longitudinal measurements, t_{ij}^* , on the retrospective time scale are unknown for those subjects whose survival times are censored. A naïve approach to deal with this problem is to omit all those censored patients and model the terminal trend just for the decedents subsample. This will inevitably hurt the efficiency of estimators due to the loss of data from censored subjects. To resolve this issue, we propose to jointly model the survival time with the longitudinal data. With joint modeling, we will be able to construct a likelihood function based on the joint distribution, and thus incorporate information from

censored subjects. We propose to model the survival distribution with Cox model [28] which is on a prospective time scale and can be written as:

$$\lambda_i(t) = \lambda_o(t) \exp(A_i \alpha_A + \tilde{X}_i^T \alpha_X), \quad (2)$$

where t denote the time since enrollment on the prospective time scale and α_X denote the Q -dimensional parameters associated with the Q -dimensional baseline covariates $\tilde{X}_i$. We assume that the censoring time C_i is independent of survival time D_i conditional on covariates in the model which is a typical assumption for Cox model. We also assume that C_i is independent of the longitudinal outcome which is true if there is only administrative censoring.

Models (1) and (2) form the two sub-models of our joint modeling approach for longitudinal and survival outcomes. The joint likelihood function based on the two models will be obtained and maximized to generate maximum likelihood estimators (MLE) of the parameters. Regression splines will be used to handle the unspecified curves as detailed in the next section.

3.2 Estimation

Regression splines approach is proposed to estimate unspecified parameter functions $\beta_\mu(\tilde{t}^*)$ and $\beta_A(\tilde{t}^*)$ in sub-model (1). Natural cubic splines with B-splines basis [27, 29, 30] will be used with the knots at equally spaced sample quantiles of the data. Details for determining the optimal number of knots is given in Section S2 of the supplemental material. For the purpose of illustration, we assume that the natural cubic splines for $\beta_\mu(\tilde{t}^*)$ and $\beta_A(\tilde{t}^*)$ have the same k_1 knots corresponding to k_1 basis functions. The exact same logic can be followed when they have different knots. Let $B_i^1, i = 1, \dots, k_1$ denote the B-spline basis functions. Notice that the basis functions B_i^1 depend on $\tilde{t}^*$ and we suppressed $\tilde{t}^*$ in the notations for simplicity. By approximating the unspecified function with the basis functions:

$\beta_\mu(\tilde{t}^*) = \sum_{k=1}^{k_1} \beta_k B_k^1$ and $\beta_A(\tilde{t}^*) = \sum_{k=1}^{k_1} \beta_{k+k_1} B_k^1$, sub-model (1) can be rewritten as

$$Y_i(\tilde{t}^*) = \mathcal{X}_i(\tilde{t}^*)^T \beta + Z_i^T b_i + \varepsilon_i(\tilde{t}^*) \quad (3)$$

where $\mathcal{X}_i(\tilde{t}^*)^T = (B_1^1, \dots, B_{k_1}^1, A_i B_1^1, \dots, A_i B_{k_1}^1, X_i^T)$, a $(2k_1 + P)$ -dimensional vector of variables and $\beta = (\beta_1, \dots, \beta_{k_1}, \beta_{k_1+1}, \dots, \beta_{2k_1+1}, \psi_X)^T$. The outcome vector

$Y_i = (Y_i(t_{i1}^*), \dots, Y_i(t_{in_i}^*))^T$ has a multivariate normal distribution $N(\mu_i, V_i)$ with mean

vector μ_i having the j th element equal to $\mathcal{X}_i(t_{ij}^*)^T \beta$ and variance matrix

$V_i = \tau^2 I_{n_i} + \mathbf{1}_{n_i} Z_i^T \sum Z_i \mathbf{1}_{n_i}^T$, where I_{n_i} is the n_i by n_i identity matrix and $\mathbf{1}_{n_i}$ is the n_i -dimensional vector of one's. The parameters to be estimated are $(\alpha_A, \alpha_X, \beta, \Sigma, \tau, \Lambda_0(t))$

where the cumulative baseline hazard function $\Lambda_0(t) = \int_0^t \lambda_o(s) ds$.

To calculate the complete log-likelihood function which is the summation of log-likelihood contributions from all subjects, we divide the sample into four groups based on censoring status and availability of follow up longitudinal measurements. The groups are: 1) patients with observed death times and at least one follow-up measurements before death, 2) patients with observed death times, but no follow-up measurements before death, 3) patients with censored death times and at least one follow-up measurements before censoring, and 4) patients with censored death times and no follow-up measurements. We will refer these groups as group 1, 2, 3 and 4 throughout the paper. Assuming the group sizes are r_1 , r_2 , r_3 and r_4 , and let l_1 , l_2 , l_3 and l_4 denote the log-likelihood contributions from the four groups respectively. Explicit expressions for l_3 is given below, and l_1 , l_2 and l_4 can be found in Section S1 of the supplemental material.

$$l_3 = \sum_{i=r_1+r_2+1}^{r_1+r_2+r_3} \log \left(\int_{C_i}^{\infty} f(Y_i|D_i=s) d(1-\exp(-H_i(s))) \right) \\ = \sum_{i=r_1+r_2+1}^{r_1+r_2+r_3} \log \left(\int_{C_i}^{+\infty} f(Y_i|D_i=s) \exp \left(A_i \alpha_A + \tilde{X}_i^T \alpha_X \right) \exp \left[-\exp \left(A_i \alpha_A + \tilde{X}_i^T \alpha_X \right) \Lambda_0(s) \right] d\Lambda_0(s) \right),$$

where $f(Y_i|D_i=s)$ is the conditional multivariate normal density function of the longitudinal outcome given survival time is s .

The baseline hazard $\lambda_0(t)$ and the cumulative baseline hazard $\Lambda_0(t)$ are unspecified nonparametric curves in the log-likelihood functions. We borrow the idea from profile likelihood approach [31] where $\Lambda_0(t)$ is profiled out by a stepwise function, $\tilde{\Lambda}_0(t)$, starting at zero and jumping at uncensored survival times. Let $\tilde{\Lambda}_0\{t\}$ with the curly brackets denote the jump at time t . We substitute $\tilde{\Lambda}_0(t)$ and $\tilde{\Lambda}_0\{t\}$ for $\tilde{\Lambda}_0(t)$ and $\lambda_0(t)$ respectively in l_1 , l_2 , l_3 and l_4 to obtain the profiled log-likelihood functions denoted by l_1^* , l_2^* , l_3^* and l_4^* .

$$l_1^* = -0.5 \sum_{i=1}^{r_1} \left[n_i \log(2\pi) + \log|V_i| + (Y_i - \mu_i)^T V_i^{-1} (Y_i - \mu_i) \right] + \sum_{i=1}^{r_1} \left[\log \left(\tilde{\Lambda}_0\{D_i\} \right) + A_i \alpha_A + \tilde{X}_i^T \alpha_X - \exp \left(A_i \alpha_A + \tilde{X}_i^T \alpha_X \right) \tilde{\Lambda}_0(D_i) \right], \\ l_2^* = \sum_{i=r_1+1}^{r_1+r_2} \left[\log \left(\tilde{\Lambda}_0\{D_i\} \right) + A_i \alpha_A + \tilde{X}_i^T \alpha_X - \exp \left(A_i \alpha_A + \tilde{X}_i^T \alpha_X \right) \tilde{\Lambda}_0(D_i) \right], \\ l_3^* = \sum_{i=r_1+r_2+1}^{r_1+r_2+r_3} \log \left(\sum_{m=1}^M f(Y_i|D_i=d_m) 1(d_m > C_i) P_{im} \right), \\ l_4^* = - \sum_{i=N-r_4+1}^N \exp(A_i \alpha_A + \tilde{X}_i^T \alpha_X) \tilde{\Lambda}_0(C_i),$$

where $d_1, d_2, \dots, d_M$ denote the ascendingly ordered uncensored survival times, $1(d_m > C_i)$ is an indicator function and

$$P_{im} = \exp \left[A_i \alpha_A + \tilde{X}_i^T \alpha_X - \exp \left(A_i \alpha_A + \tilde{X}_i^T \alpha_X \right) \tilde{\Lambda}_0(d_m) \right] \tilde{\Lambda}_0\{d_m\} \text{ in } l_3^*.$$

Group 3 is the troublemaker group. From the expression of l_3 , we can see that the likelihood function for the i th subject in group 3 is $\int_{C_i}^{\infty} f(Y_i|D_i=s) d(1-\exp(-H_i(s)))$ which is essentially a weighted integral of the density function $f(Y_i|D_i=s)$ with the total weight being

$\int_{C_i}^{\infty} d(1 - \exp(-H_i(s))) = \exp(-H_i(C_i))$. This weight is similar to that in Chan and Wang [24] where they call it “a hazard weighted cumulative mean of backward process”. By employing the discretized cumulative hazard function $\tilde{\Lambda}_0(t)$, the total weight in l_3^* becomes $\sum_{m=1}^M 1(d_m > C_i) P_{im}$ which is not equal to $\exp(-H_i(C_i))$ anymore. To correct this distortion, we give a weight W_i to P_{im} so that $\sum_{m=1}^M 1(d_m > C_i) P_{im} W_i = \exp(-H_i(C_i))$. Thus, the re-weighted log-likelihood function in group 3 is given by

$$wl_3^* = \sum_{i=r_1+r_2+1}^{r_1+r_2+r_3} \log \left(\sum_{m=1}^M f(Y_i | D_i = d_m) 1(d_m > C_i) P_{im} W_i \right),$$

where $W_i = \frac{\exp(-\exp(A_i \alpha_A + \tilde{X}_i^T \alpha_X) \tilde{\Lambda}_0(C_i))}{\sum_{m=1}^M 1(d_m > C_i) P_{im}}$. By having the weight W_i in wl_3^* , our approach will generate the same estimates as the partial likelihood approach for α_A and α_X when the longitudinal and survival outcomes are independent. Notice that the weight W_i should converge to 1 in probability because both the numerator and denominator of W_i converges to $\exp(-\exp(A_i \alpha_A + \tilde{X}_i^T \alpha_X) \Lambda_0(t))$ as the Breslow estimator converges to $\Lambda_0(t)$ in probability [32]. This means that the weight W_i does not make a difference when there are enough number of subjects. The complete log-likelihood function can then be calculated as

$$l = l_1^* + l_2^* + wl_3^* + l_4^*.$$

MLEs for all the parameters ($\alpha_A, \alpha_X, \beta, \Sigma, \tau, \tilde{\Lambda}_0\{d_1\}, \dots, \tilde{\Lambda}_0\{d_M\}$) are obtained by maximizing l using quasi-Newton methods [33] in R. There are no closed-form expression for parameter estimators. The nonparametric curves $\beta_{\mu}(t^*)$ and $\beta_A(t^*)$ will be estimated by $\hat{\beta}_{\mu}(t^*) = \sum_{k=1}^{k_1} \hat{\beta}_k B_k^1$ and $\hat{\beta}_A(t^*) = \sum_{k=1}^{k_1} \hat{\beta}_{k+k_1} B_k^1$ where $\hat{\beta}_k$ and $\hat{\beta}_{k+k_1}$, $k = 1, \dots, k_1$, are MLEs. The variance matrix of estimators are calculated from the Fisher information matrix. Since $\hat{\beta}_{\mu}(t^*)$ and $\hat{\beta}_A(t^*)$ are linear combinations of $\hat{\beta}_1, \dots, \hat{\beta}_{k_1}$ and $\hat{\beta}_{k_1+1}, \dots, \hat{\beta}_{2k_1}$ respectively, pointwise variance estimates of $\hat{\beta}_{\mu}(t^*)$ and $\hat{\beta}_A(t^*)$ at any time point t^* can be computed based on the estimated variance matrices of $\hat{\beta}_1, \dots, \hat{\beta}_{k_1}$ and $\hat{\beta}_{k_1+1}, \dots, \hat{\beta}_{2k_1}$.

Similar to Kaplan-Meier estimate, this estimation approach puts survival distribution masses on uncensored survival times. This could induce a potential issue if there are subjects in group 3 with censoring times larger than the longest observed survival time in the entire study. If this happens, the right-hand tail of K-M curve will not reach down to zero and log-likelihood contributions from those subjects in group 3 are not well defined. To resolve this issue, we treat the longest observed censoring time as an uncensored survival time in this case [34]. This corresponds to that the survivor with the longest observed survival duration died immediately after its censoring. By doing this, the K-M curve will reach down to zero at its right-hand end. This approach was studied by Efron [35] who showed that the K-M

estimator remains consistent. We will study the sensitivity of this technique for our joint modeling approach in the simulation study.

Regression splines approach has the advantage of treating the model as if it were a parametric model once the knots were determined, but it requires appropriately selecting the number and position of knots. We place the knots at equally spaced sample quantiles of the data and apply AIC method [36] to select the optimal number of knots. More details can be found in Section S2 of the supplementary material.

4. SIMULATION

Finite sample properties of the estimators were studied through simulations. We randomly generated 1000 datasets with each data set having 500 subjects. All subjects were assumed to enter the study at the same time in the simulation. In each data set, the treatment variable was generated using a Bernoulli distribution with the parameter value $p = 0.5$. Two covariates were also generated: baseline QOL (qol_0) generated from a Uniform distribution on (100, 150) and sex generated using a Bernoulli distribution with the parameter value $p = 0.5$. The models for generating longitudinal QOL and survival outcome were:

$$Y_i(t^*) = \beta_\mu(t^*) + A_i \beta_A(t^*) + \psi_1 qol_0 + \psi_2 sex + b_i + \varepsilon_i(t^*)$$

$$\text{and } \lambda_i(t) = \lambda_0(t) \exp(A_i \alpha_A + \alpha_1 qol_0 + \alpha_2 sex),$$

where b_i is the random intercept with the variance $\sigma^2 = 36$ and the residual $\varepsilon_i(t^*)$ has a variance $\tau^2 = 16$. Here $\beta_\mu(t^*) = 140 - \frac{30}{1+0.2t}$, $\beta_A(t^*) = 30 \exp(-0.23t - 0.92)$, $\psi_1 = 0.3$, $\psi_2 = 1$, $\lambda_0(t) = \exp(-2.5)$ and $\alpha_A = -0.2$, $\alpha_1 = -0.005$ and $\alpha_2 = 0.2$. The trajectory functions $\beta_\mu(t^*)$ and $\beta_A(t^*)$ were chosen to have similar patterns to what was found in the literature for cancer patients [4, 6, 23]. Repeated measurements of QOL were assumed to be taken at every half month until death. Censoring was assumed to be independent of the longitudinal data and survival, and was generated by $G1(G < c) + c1(G \geq c)$ where G follows a Gamma distribution and c is the upper bound of the censoring distribution. In ENABLE III, 36.7% and 10.6% were in groups 3 and 4 respectively. There were also 4.4% whose death times were Censored Beyond the Longest uncensored Survival time (CBLS). To make the censoring rates similar to ENABLE III, we set the shape and scale parameters of G equal to 1.55 and 14.3 respectively, $c = 33.65$, and the first measurement of QOL was set to be collected at $t = 5.5$. We selected the optimal number of knots for each sample within the range $k_1 \in [2, 11]$ using AIC. Results from the simulation showed that mean estimates of the natural cubic splines (dashed curves: Mean JM est.) were very close to the true function (the top panels of Figures 2 & 3). Results from a piecewise linear approach [23] and a naïve approach were also presented in the figures for comparison which will be discussed later in this section. The pointwise coverage probabilities (CP) for 95% CI (dashed curves: JM 95% CP) were plotted in the bottom panels of Figures 2 & 3 with the mean coverage probabilities being 94.9% and 93.6% for $\beta_\mu(t^*)$ and $\beta_A(t^*)$ respectively. The average number of knots was 5.72 when AIC was used and 5.03 for BIC. Estimation results looked similar when BIC was used for model selection. The Wald-type 95% CI of estimators for the regression coefficient

parameters ψ_1 , ψ_2 , α_A , α_1 and α_2 (Table 1) had proper CP. The mean of the standard error estimators correctly reflected the empirical variability of the parameter estimators.

We compared our semiparametric modeling method with the piecewise linear modeling approach proposed by Li et al. (2013). The piecewise linear approach drastically overestimated the standard errors (SE) of both nonparametric and parametric parts in the longitudinal model due to misspecification of the non-linear terminal trend. The SE's were 3 to 11 times bigger than those from the semiparametric approach (Table 1). Overestimation of the variation was also reflected in the huge bias of estimates for the standard deviation parameters σ and τ , which consequently lead to zero CP for σ and τ (Table 1). The width of pointwise 95% CI for the terminal trend curves was more than three times wider than that from the semiparametric approach (see top panels of Figures 2 and 3). CP for the terminal trend curves was 100% due to the inflated SE. Parameter estimates and SE for the survival sub-model looked fine since the true survival distribution in the simulation setting is essentially an exponential distribution conditional on covariates.

We also compared our results with the naïve approach which performs two independent analyses for the data: a longitudinal analysis omitting all censored subjects and a survival analysis using all subjects. Our joint modeling method was much more efficient and it achieved comparable CP with 26.1% narrower 95% CI for $\beta_{\mu}(t^*)$ and 34.4% narrower for $\beta_A(t^*)$ (see top panels of Figures 2 and 3). The gain of efficiency were also reflected in the standard error (SE) estimates. The point-wise SE for $\beta_A(t^*)$ from joint modeling is (on average) 35% smaller and is more than 60% smaller when $t^* > 25$. For parametric regression coefficients in the model (Table 1), our approach achieves slightly better CP with 26.2% and 28.4% narrower 95% CI for ψ_1 and ψ_2 respectively, and 2.4%, 3.1% and 3.1% narrower 95% CI for α_A , α_1 and α_2 respectively. Therefore, our joint modeling method was much more efficient than the naïve approach for estimating the longitudinal parameters. It also increased estimation efficiency for survival parameters with a smaller magnitude. When the longitudinal and survival outcomes were independent, we observed significant gain in efficiency as well for estimating the longitudinal parameters (results not shown) although the survival parameter estimates were exactly the same as the naïve analysis.

The overall censoring rate in ENABLE III study is on the high end relative to other palliative care studies including ENABLE II [4] and Temel et al. [5]. ENABLE II had 28.26% overall censoring. We performed a simulation study with the 28.26% censoring rate and the results looked similar. In both ENABLE II and III studies, the rates of CBLS happened to be the same and equal to 4.4%. It is unlikely to see a very high CBLS rate in palliative care studies since all patients have relatively short prognosis. We carried out a sensitivity study to examine the technique that set the longest censoring time to be a death time when there are CBLS in group 3. In the simulation settings described above, the average CBLS rate was set at 5% to mimic real studies. We increased CBLS rate by lowering c , the upper bound of the censoring variable, to get 10%, 12.5% and 15% CBLS. We found that some CP fell below 90% for 12.5% and 15% CBLS although the CP for the parametric regression coefficients were relatively more stable.

5. APPLICATION

We applied our model to the recently completed two-arm ENABLE III RCT [6] as introduced in Section 2. There were 103 and 104 subjects in the early treatment arm and delayed treatment arm respectively. There were 38.2%, 14.5%, 36.7% and 10.6% subjects in groups 1, 2, 3 and 4 respectively and the CBLS rate was 4.35%. All censoring were due to study end. We adjusted the baseline QOL (QoL_0) and sex variables in both sub-models:

$$Y_i(t^*) = \beta_\mu(t^*) + A_i\beta_A(t^*) + \psi_1 QoL_0 + \psi_2 \text{sex} + b_i + \varepsilon_i(t^*), \quad (5)$$

$$\text{and } \lambda_i(t) = \lambda_o(t) \exp[A_i\alpha_A + \alpha_1 QoL_0 + \alpha_2 \text{sex}]. \quad (6)$$

Based on the AIC criterion, the estimated number of knots for the nonparametric curves was 7. The fitted longitudinal trajectories are shown in Figure 4 with 95% pointwise CI. Other parameters are given in Table 2. As we can see that there is an obvious decline of QOL in the last 6 months of life (Figure 4) which makes sense for cancer patients. The slope of cumulative hazard function (Figure 5) decreased after 12 months in both arms which indicates that the hazard of death was lower after 12 months. This can explain the increasing pattern of QOL in Figure 1 because patients who survived beyond 12 months were likely healthier and thus had better QOL. Data analysis results using the naïve approach (results not shown) had much larger SEs for the longitudinal parameter estimates. This is consistent with the conclusions from the simulation study. Estimates and comparisons for QALY were also estimated and presented in Section S3 of the supplemental material.

6. DISCUSSION

With the intention to establish a cutting-edge statistical approach for analyzing longitudinal QOL and survival data in palliative care research, we developed a novel semiparametric joint modeling method that directly estimates terminal trends of longitudinal QOL outcomes while incorporating censored survival information. The terminal trend estimation can help understand how patients may die in the (relatively) near future which is the key to caring well and plan appropriately [3]. The nonparametric components of longitudinal QOL trajectory are not subject to misspecification which makes the model applicable to all kinds of terminal trends. This approach appropriately accounts for the association between survival and longitudinal QOL outcomes, and thus it provides a clinically meaningful estimate of the palliative care treatment effect. This is accomplished by modeling the trajectories of the longitudinal QOL outcomes on a retrospective time scale. One can also make inferences about QALY using this novel joint modeling approach. An R program to run the model is available upon request. Our approach can be applied to a variety of longitudinal outcomes and EOL research studies although the focus in this paper is longitudinal QOL outcome in palliative care studies. It is worth noting that medical cost needs to be treated differently than QOL-type outcomes because cost is a cumulative measure over certain interval [10] whereas QOL is an instant measure.

Compared with the parametric piecewise linear approach developed in Li et al. [23], this semiparametric model has more flexible nonparametric structure for the longitudinal trajectory that can appropriately model nonlinear smooth longitudinal terminal trends for studies with cancer or non-cancer patients. Compared with other joint models briefly reviewed in the introduction, our approach directly models the longitudinal QOL outcomes prior to death on a retrospective time scale. As a result, interpretation of such an analysis in palliative care research is likely more reflective of the nature of study purposes. Our joint model is more efficient (generating smaller SE) than the naïve analysis although the gain in efficiency is small for the survival model (3.1%).

A few possible extensions of our model are worth mentioning. Besides regression splines that were employed in the model, other nonparametric approaches (e.g., penalized splines, smoothing splines) could also be used and the estimation procedure will need to be modified accordingly. In the current approach, only the intercept and treatment effect are modeled with nonparametric functions in the longitudinal model. It can be easily extended to a more general case where the coefficients of other covariates are nonparametric functions as well. Another possible extension of the model is to add a shared random effect in the survival model [10] to account for another level of association between survival and the longitudinal QOL outcomes. To the best of our knowledge, there are limited developments for model diagnostic techniques for joint modeling in the literature. For shared parameter models, some informal diagnostic graphical procedures and multiple-imputation-based approaches to construct residuals and diagnostic plots can be found in the literature [37, 38]. Developments for model diagnostic tools under the terminal trend model may warrant further investigation.

A referee suggested that QOL might converge to the same value at the time of death for all patients. Under such circumstance, it would make sense to impose the constraint $\beta_A(0) = 0$ in the model such that the treatment group and control group has the same average QOL at death time (ie, at $t^* = 0$). This is a very interesting feature and can be incorporated by modifying the boundary conditions of the natural cubic splines at $t^* = 0$. We will consider it in future model developments. Another suggestion is that the sub-model for survival times could have time-varying treatment effect given that the longitudinal model has time-varying treatment effect. This makes perfect sense because the hazard ratio may not be a constant over the whole timespan of a study. Estimation approaches for Cox models with time-varying coefficients [39] can be adapted for this case. We have planned to extend our model in the future to accommodate time-varying treatment effect and time-varying coefficients for other covariates as well.

Comorbidities could be a potential issue because terminal trajectories are usually different for different types of illnesses. Patients with multiple disorders may have multiple trajectories running concurrently, with the more rapidly progressing trajectory typically dominating others [3]. This is not uncommon in older patients with slowly progressive cancers and thus more complicated models may be needed for this case. Comorbidities could also be related to another issue as pointed out by Currow et al. [40] that in palliative care RCTs, subjects often die as a direct result of disease progression or drop out for reasons unrelated to the treatment. Improper handling of those patients could make estimates systematically biased away from the true effect. They proposed a modified intent-to-treat

analysis approach to address this issue by identifying those who withdraw or die unrelated to the treatment and dropping them from the analysis. An alternative and better way to address this issue might be a joint modeling approach that appropriately models the survival and censoring distribution in terms of the treatment status.

Longitudinal QOL data missing at random is an assumption that is oftentimes unverifiable in practice. In the ENABLE III RCT, longitudinal QOL measurements were missing with an intermittent pattern and the reasons include “too busy”, “lost interest in the study”, “too ill to respond” and “unknown”. Missing data as a result of being “too ill” might indicate that the missing longitudinal data was not missing at random; in such cases missing data could result in efficiency loss due to bias. The semiparametric mixed effects model in the sub-model (1) for longitudinal QOL measurements should account well for missing at random assumption since that is one of the advantages of mixed effects models. In this paper, the censoring distribution is assumed to be independent of the longitudinal outcomes conditional on the adjusted baseline covariates including baseline QOL. In general, this might not be the case, but it is true in ENABLE III since survival status of all patients was identified at the end of ENABLE III trial, and hence there was only administrative censoring, a form of non-informative censoring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the referees for their review comments. *Funding:* Zhigang Li, H. R. Frost and Tor D. Tosteson were partially supported by R03NR014915. Zhigang Li is also partially supported by P01ES022832 and P20GM104416. H. R. Frost is also partially supported by K01LM012426 and P20GM103534. Tor D. Tosteson was also partially supported by the Dartmouth Clinical and Translational Science Institute, under award number UL1TR001086, and award number P30CA023108 to the Norris Cotton Cancer Center. Lei Liu was partially supported by AHRQ R01HS020263. Kathleen D. Lyons was supported by a Mentored Research Scholar Grant in Applied and Clinical Research (MRSG 12-113-01 – CPPB) from the American Cancer Society. Marie Bakitas was supported by the National Institute for Nursing Research (R01NR011871), National Cancer Institute (R01 CA101704), Foundation for Informed Medical Decision-Making and a Cancer and Leukemia Group B Foundation Clinical Scholar Award.

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Figure 1.

A. Mean QOL, 95% confidence intervals (CI) and number of patients alive (on the right y-axis) in the two arms on the prospective time scale. B. Mean QOL and 95% CI on the retrospective time scale.

Figure 2.

Estimation results for $\beta_{\mu}(t^*)$. The top panel shows the fit of the mean estimated curves along with the mean point-wise 95% CI using the joint modeling approach (JM), the piecewise approach and the naïve approach. The true function is plotted as a solid line, the mean estimated curves are plotted in black and the 95% CIs are plotted in grey. Dashed lines are used for the JM approach, dotted for naïve approach and dot-dashed for piecewise linear approach. The bottom panel shows the point-wise 95% coverage probabilities for all three methods using the same line types as in the top panel.

Figure 3.

Estimation results for $\beta_A(t^*)$. The top panel shows the fit of the mean estimated curves along with the mean point-wise 95% CI using the joint modeling approach (JM), the piecewise approach, and the naïve approach. The bottom panel shows the point-wise 95% coverage probabilities for the three methods. Please see the caption for Figure 2 for further details regarding figure line types, colors and interpretation.

Figure 4. Fitted longitudinal trajectories for early and delayed treatment arms and the point-wise 95% CI using ENABLE III data.

Figure 5.
Fitted cumulative hazard functions at the mean values of the adjusted covariates for early and delayed treatment arms using ENABLE III data.

Table 1

Simulation results for the estimation of the parametric parameters. Bias is the mean of estimates minus the true values; Percent of Bias is the bias as a percentage of the true value. SE is the empirical standard error of the estimates; Mean SE is the mean of estimated standard errors; CP is the empirical coverage probability of the 95% CI for the parameters. PW bias, PW mean.SE and PW CP are the counterparts from piecewise model; Naïve Mean SE and Naïve CP are the counterparts from the naïve model.

Longitudinal Model											
Parameter	TRUE	Bias	PW bias	Percent of Bias (%)	SE	Mean.SE	PW mean.SE	Naïve Mean.SE	CP (%)	PW CP (%)	Naïve CP (%)
ψ_1	0.3	0.004	-0.001	1.3	0.03	0.025	0.088	0.035	95	100	94.8
ψ_2	1	-0.27	0.098	-27.29	0.68	0.71	2.6	1	94.9	100	94.8
σ	6	0.21	18.66	3.53	0.26	0.26	3	--	89	0	--
τ	4	<0.0001	5.78	<0.0001	0.04	0.04	0.24	--	93.6	0	--
Survival Model											
α_A	-0.2	-0.18	0.005	-10.82	0.12	0.12	0.12	0.13	94.4	95	95
α_1	-0.01	-0.0001	0.0002	2.13	0.004	0.004	0.004	0.004	94.3	93.6	93.7
α_2	0.2	0.002	-0.008	1.25	0.12	0.12	0.12	0.13	95.1	95.8	94.4

Table 2

Estimates of model parameters

Longitudinal Model		Survival Model	
Parameter	Estimate (SE)	Parameter	Estimate (SE)
ψ_1	0.59 (0.05)	α_A	-0.31 (0.19)
ψ_2	2.58 (2.23)	α_1	-0.01 (0.005)
σ	11.57 (0.99)	α_2	0.34 (0.20)
τ	11.93 (0.41)		