A joint model of longitudinal and competing risks survival data with heterogeneous random effects and outlying longitudinal measurements

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This article proposes a joint model for longitudinal measurements and competing risks survival data. The model consists of a linear mixed effects sub-model with t-distributed measurement errors for the longitudinal outcome, a proportional cause-specific hazards frailty sub-model for the survival outcome, and a regression sub-model for the variance-covariance matrix of the multivariate latent random effects based on a modified Cholesky decomposition. A Bayesian MCMC procedure is developed for parameter estimation and inference. Our method is insensitive to outlying longitudinal measurements in the presence of nonignorable missing data due to dropout. Moreover, by modeling the variance-covariance matrix of the latent random effects, our model provides a useful framework for handling high-dimensional heterogeneous random effects and testing the homogeneous random effects assumption which is otherwise untestable in commonly used joint models. Finally, our model enables analysis of a survival outcome with intermittently measured time-dependent covariates and possibly correlated competing risks and dependent censoring, as well as joint analysis of the longitudinal and survival outcomes. Illustrations are given using a real data set from a lung study and simulation.

Keywords and phrases: Joint model, Competing risks, Bayesian analysis, Cholesky decomposition, Mixed effects model, MCMC, Modeling random effects covariance matrix, Outlier.

1. INTRODUCTION

In the past decades, much work has been done in the field of joint modeling of longitudinal and survival data. Joint models have been proposed to adjust inferences on longitudinal measurements in the presence of nonignorable missing values due to dropout (Schluchter, 1992; DeGruttola and Tu, 1994; Little, 1995; Hogan and Laird, 1997; Henderson et al., 2000; Elashoff et al., 2007, 2008); to

solve difficulties in Cox proportional hazards model arising from time-dependent covariates which are possibly missing at some event times or subject to substantial measurement error (Faucett and Thomas, 1996; Wulfsohn and Tsiatis, 1997; Faucett et al., 1998; Wang and Taylor, 2001; Xu and Zeger, 2001; Song et al., 2002; Brown and Ibrahim, 2003; Tseng et al., 2005; Ye et al., 2008); and to assess covariates effects on both endpoints simultaneously (Henderson et al., 2000; Zeng and Cai, 2005; Elashoff et al., 2007, 2008; Liu et al., 2008).

Most joint models in the literature assume a normal random error for the longitudinal sub-model. The normal model, however, can be sensitive to outliers or heavy-tailed data. For example, the profile plot of repeated measured FVC (Forced Vital Capacity) in Figure 1 reveals several suspiciously large values. We demonstrate in Section 3 that the normal model is sensitive to the extreme values. We also observe in a simulation study (see Tables 2, 3) that the regression and random effects parameters in a normal model can be seriously biased in the presence of outliers.

This paper proposes a new joint model of longitudinal and competing risks survival data. Our model consists of three sub-models: a linear mixed effects sub-model with a t-distributed measurement error, a cause-specific hazards sub-model for the survival outcome, and a variance-covariance sub-model for the multivariate latent random effects based on a modified Cholesky decomposition. A Bayesian MCMC method is developed for estimation and inference. Our model has several distinct features from existing models. The inference resulting from the linear mixed effects sub-model with a t-distributed measurement error is more robust to outlying longitudinal measurements or heavy-tailed data than its normal-error counterpart. Secondly, the cause-specific hazards sub-model for the survival outcome allows one to account for possibly correlated competing risks and dependent censoring. The random effects of the two sub-models induce the correlation between the longitudinal and survival outcomes. Finally, by extending the idea of Pourahmadi (1999), the sub-model for the variance-covariance matrix of the multivariate latent random effects based on a modified Cholesky decomposition allows for high-dimensional heterogeneous covariance matrices of the multivariate random effects and the resulting estimated covariance matrices are guaranteed to be

positive definite. Our method also provides a framework for testing the homogeneous random effects assumption of a homogeneous joint model.

It is worth noting that compared to other robust methods such as Huber's robust regression (Huber, 1973), the t-distribution based method is mathematically more tractable and computationally simple. The use of the t-distribution in applications with heavy-tailed or outlying data is well-developed in the literature. Lange et al. (1989) and Liu (1996) used it in linear and nonlinear regressions. Rosa et al. (2003) applied a class of normal/independent distributions (Lange and Sinsheimer, 1993), which include the t-distribution as a special case, in linear mixed effects models with ignorable missing data. Li et al. (2009) extended the idea to a robust joint model for longitudinal and survival data with possible non-ignorable missing data due to some terminating events. Our approach is distinct from Li et al. (2009) in several aspects. Our Bayesian MCMC method can easily handle high-dimensional random effects that otherwise complicates the likelihood-based method of Li et al. (2009). Secondly, Li et al. (2009) assume a homogeneous variance-covariance matrix for the random effects, while we allow heterogeneous random effects. Finally, the homogeneous variance-covariance assumption is untestable under the Li et al. (2009) model. Our model provides a useful framework to test this assumption.

This paper is organized as follows: in Section 2 we define the robust joint model and derive a Bayesian estimation procedure. In Section 3, we illustrate our method using a data set from scleroderma lung study (Tashkin et al., 2006). In Section 4, the performance of our method is examined by simulation. A discussion of the method is provided in Section 5. Technical details of the MCMC algorithm are deferred to the Appendix.

2. MODEL AND ESTIMATION

2.1 Robust joint model

Suppose there are m subjects in the study. For the ith subject at time t, the longitudinal outcome $Y_i(t)$ follows a linear mixed effects model:

$$(1) \qquad Y_i(t) = X_i^{(1)}(t)^T \beta + Z_i(t)^T U_i + \epsilon_i(t)$$

where $X_i^{(1)}(t)$ and $Z_i(t)$ are vectors of covariates associated with the fixed effects β ($p \times 1$) and the random effects U_i ($q \times 1$) respectively. Assume that the measurement error $\epsilon_i(t)$ is $t(0, \sigma^2, \kappa)$ distributed with κ degrees of freedom. Assume further that $\epsilon_i(t) \perp U_i$ and $\epsilon_i(t_1) \perp \epsilon_i(t_2)$ for any $t_1 \neq t_2$.

During follow-up, each subject may experience one of g distinct competing causes of failure or may be right censored. Let $C_i = (T_i, D_i)$ be the competing risks survival data on subject i, where T_i is the failure or censoring time, and D_i assumes a value from $0, 1, \ldots, g$, with $D_i = 0$ indicating a noninformative censored event and $D_i = k$ indicating the kth failure type, $k = 1, \ldots, g$. Dependent (or

informative) censoring is treated as one of the g types of failures. The cause-specific hazards sub-model for the competing risks survival data is specified as follows:

(2)

$$\lambda_k(t; X_i^{(2)}(t), v_i, \gamma_k, \nu_k)$$
$$= \lim_{h \to 0} \frac{P[t \le T_i < t + h, D_i = k | T_i \ge t, X_i^{(2)}(t), v_i, \gamma_k, \nu_k]}{h}$$
$$= \lambda_{0k}(t) \exp\{X_i^{(2)}(t)^T \gamma_k + \nu_k v_i\}.$$

The function $\lambda_k(t; X_i^{(2)}, v_i, \gamma_k, \nu_k)$ is the instantaneous failure rate from cause k at time t given the vector of covariates $X_i^{(2)}(t)$ and the latent unknown factor v_i, in the presence of all other failure types. The regression coefficient ν_k represents the effect of the latent variable v_i with ν_1 set to 1 to ensure identifiability. The parameter γ_k represents the effects of the observed covariates $X_i^{(2)}(t)$ on cause k. We further assume that the kth baseline hazard is a step function, $\lambda_{0k}(t) = \lambda_{0k}^{(s)}$, for $t_k^{(s-1)} < t \le t_k^{(s)}$, where $0 < t_k^{(1)} < \cdots < t_k^{(S^k)} < \infty$ is a partition of $(0, \infty)$ and S^k indicates the number of steps for the kth baseline hazard. The competing risks model is one of the useful methods to handle dependent censoring. The identification of dependent competing risks models in which each risk has a mixed proportional hazard specification with regressors, and the risks are dependent by way of the unobserved heterogeneity, or frailty components, has been proved by Abbring and Van den Berg (2003).

Assume that

$$(3) \quad W_i = \begin{pmatrix} U_i \\ v_i \end{pmatrix} \sim N_{q+1}\left(\begin{pmatrix} \mathbf{0} \\ 0 \end{pmatrix}, \Sigma_i = \begin{pmatrix} \Sigma_{U_i} & \Sigma_{U v_i} \\ \Sigma_{U v_i}^T & \sigma_{v_i}^2 \end{pmatrix} \right).$$

Similar to Pourahmadi (1999), we model the covariance matrices Σ_i through a modified Cholesky decomposition $M_i \Sigma_i M_i^T = H_i$, where H_i is a diagonal matrix with positive entries and M_i is the lower triangular matrix with $-\phi_{i,jl}$ as its $(j, l)^{th}$ entry. This decomposition has a clear statistical interpretation: the below-diagonal entries of M_i are the negatives of generalized autoregressive parameters (GARP), $\phi_{i,jl}$, in the autoregressive model

$$(4) \quad W_{ij} = \sum_{l=1}^{j-1} \phi_{i,jl} W_{jl} + e_{ij}, \quad j = 1, \ldots, q+1.$$

The diagonal entries of H_i are the innovation variances (IV) $h_{ij}^2 = var(e_{ij})$ and we have $cov(e_{ij}, e_{jk}) = 0$ if $j \neq k$ ($1 \le j, k \le q + 1$ and $i = 1, \ldots, m$). The GARPs and the logarithms of the IVs are modeled with linear and log link functions:

$$(5) \quad \begin{cases} \phi_{i,jl} = a_{i,jl}^T \eta_1 & \text{for } i = 1, \ldots, m \\ \log h_{ij}^2 = b_{ij}^T \eta_2 & j = 1, \ldots, q+1, \ l = 1, \ldots, j-1 \end{cases}$$

where $a_{i,jl}$ and b_{ij} are covariates, and η_1 and η_2 are low-dimensional parameter vectors. For example, $a_{i,jl}$ and b_{ij}

may contain group indicators, implying that the random effects covariances are heterogeneous. The homogeneous random effects assumption in existing joint models becomes a testable assumption within our model framework. Furthermore, the resulting estimated covariance matrix is guaranteed to be positive definite. The latent association between the longitudinal measurements and survival outcomes can be assessed by testing the hypothesis $\Sigma_{Uv_i} = \mathbf{0}$.

2.2 Likelihood

The standard maximum likelihood method involves integrating out latent variables from the log-likelihood function which is difficult when dealing with high-dimensional variables. We develop a Bayesian estimation procedure and a Markov chain Monte Carlo (MCMC) method for estimation and inference. To make the sampling of σ^2 and β easier, we use the fact that the t-distributed error can be represented as $\epsilon_{ij} = \tau_{ij}^{-1/2}\varepsilon_{ij}$, where $\tau_{ij}|\kappa \sim Gamma(\kappa/2, \kappa/2)$ is independent of U_i and $\varepsilon_{ij} \sim N(0, \sigma^2)$. We define the parameter set in the joint model as: $\Omega = \{\beta, \sigma^2, \gamma, \nu, \lambda_0, \eta_1, \eta_2\}$, where $\gamma = (\gamma_1, \gamma_2, \ldots, \gamma_g)$, $\nu = (\nu_2, \ldots, \nu_g)$ and $\lambda_0 = (\lambda_{01}^{(1)}, \lambda_{01}^{(2)}, \ldots, \lambda_{0g}^{(S^g)})$. We assume that for each subject i the longitudinal data are independent of the survival data, given all the parameters in Ω, latent factors $\theta = (W, \tau)$, and covariates (X_i, Z_i). For simplicity, we assume κ is prespecified. Thus, the full likelihood function for Ω, conditional on the data (Y_i, C_i) for $i = 1, \ldots, m$ and covariates, is:

(6) $\quad L(\Omega|Y, C)$
$$\propto \prod_{i=1}^{m} p(Y_i, C_i|\Omega) = \prod_{i=1}^{m} \int_{\theta} p(Y_i|\theta, \Omega) p(C_i|\theta, \Omega) p(\theta|\Omega) d\theta$$

It is convenient to work directly with the joint distribution of the observed data (Y, C) and the unobservable random vector θ, conditional on Ω, which facilitates the MCMC implementation. The conditional joint density of (Y, C) and θ is:

(7)

$p(Y, C, \theta|\Omega)$
$$= \prod_{i}^{m} p(Y_i|\theta_i, \Omega) p(C_i|\theta_i, \Omega) p(\theta_i|\Omega)$$
$$\propto \prod_{i=1}^{m} \prod_{j=1}^{n_i} \left(2\pi \frac{\sigma^2}{\tau_{ij}}\right)^{-\frac{1}{2}} \exp\left\{-\frac{\tau_{ij}}{2\sigma^2}(Y_{ij} - X_{ij}^{(1)T}\beta - Z_{ij}^T U_i)^2\right\}$$
$$\times \prod_{k=1}^{g} ((\lambda_k(T_i))^{I(D_i=k)} \exp\{-H_k(T_i)\})$$
$$\times \exp\left\{-\frac{1}{2}\sum_{j=1}^{q+1}\left[b_{ij}^T\eta_2 + \left(W_{ij} - \sum_{l=1}^{j-1} a_{ijl}^T\eta_1 W_{il}\right)^2\right.\right.$$
$$\left.\left.\times \exp(-b_{ij}^T\eta_2)\right]\right\}$$

where $\lambda_k(T_i) = \lambda_{0k}(T_i)\exp\{X_i^{(2)}(T_i)\gamma_k + \nu_k v_i\}$ and

(8) $\quad H_k(T_i) = \exp(\nu_k v_i)\sum_{s=1}^{S^k} I(T_i > t_k^{(s-1)})\lambda_{0k}^{(s)}$
$$\times \int_{t_k^{(s-1)}}^{min(T_i, t_k^{(s)})} \exp(X_i^{(2)}(t)\gamma_k)dt$$

2.3 Estimation and inference

Our Bayesian method involves a combination of direct sampling from the full conditional distribution, Metropolis-Hastings (MH) sampling (Hastings, 1970; Chib and Greenberg, 1995) and adaptive rejection sampling (ARS) (Gilks and Wild, 1992). We estimate the parameters by their posterior medians. Approximate 95% probability intervals are based on the 2.5^{th} and 97.5^{th} percentiles. Standard errors are obtained from the standard deviations of the posterior samples. The convergence of the Gibbs sampler is monitored by examining time series plots of the parameters over iteration and the Gelman and Rubin (1992) approach of using multiple chains.

We assume independent priors for Ω. We specify Normal priors for the parameters β, γ, ν, η_1 and η_2, leading to conjugate posteriors for β and some components of the η_1. We use an inverse Gamma prior for the measurement error variance σ^2 and a gamma prior for each step of the kth baseline hazard function λ_{0k} by which conjugate posterior distributions are easy to obtain. Because the full conditional distributions of the parameters β, σ^2, and $\lambda_{0k}^{(s)}$, $(s = 1, \ldots, S^g, k = 1, \ldots, g)$ are standard distributions, drawing random variates from their full conditional distributions is straightforward. The full conditional distribution of the random variate τ_{ij} given κ is also known. For other parameters and the random effects (U_i, v_i), we either use a Metropolis-Hastings step with the normal approximation to the full conditional distribution as the candidate distribution or apply the adaptive rejection sampling technique. The technical details on the sampling distributions are given in the Appendix.

The initial values of the parameters for sampling are obtained by modeling the longitudinal data and survival data separately by a linear mixed model and a cause-specific proportional hazards model. The initial value for $\lambda_{0k}^{(s)}$ $(s = 1, \ldots, S^k, k = 1, \ldots, g)$ can be obtained by drawing a random variate from the gamma full conditional distribution described in the Appendix.

3. AN EXAMPLE

We apply the developed method to analyze a data set from a scleroderma lung study (SLS) (Tashkin et al., 2006) to evaluate the effectiveness of oral cyclophosphamide (CYC) for scleroderma lung disease. The SLS enrolled 158 patients, which were randomized to receive either CYC (79

patients) or placebo (79 patients) for 12 months. An additional year of follow-up was performed to determine if CYC effects persisted after treatment. The primary outcome is forced vital capacity (FVC, % predicted) which was measured at 3-month intervals from the baseline. Treatment failure was defined as a $\geq 15\%$ (absolute) decrement in %FVC from baseline occurring at least 3 months into treatment that was sustained for at least 1 month.

Our analysis is based on the 6–24 months %FVC scores of 141 patients. The longitudinal profile of %FVC over time for the two groups (Figure 1) reveals some potential outliers. We are particularly concerned how these outlying data points would affect the joint model inference. We observe 14 treatment failures or deaths, 32 informative dropouts and 5 noninformative dropouts. A dropout is noninformative if there is no evidence showing that the dropout is related to the disease or the treatment, and informative otherwise. Since the informative dropout is potentially related to the patient's disease condition, it causes not only non-ignorable missing data in %FVC, but also dependent censoring for treatment failure or death.

We consider two baseline factors in our joint model when assessing the CYC treatment effects: baseline %FVC (FVC_0), and lung fibrosis (FIB_0). It is suggested by clinicians that the beneficial effects of CYC on pulmonary function continue to increase after stopping treatment at 12 months and eventually begin to wane after 18 months. Therefore, we fit the following linear spline mixed effects model with a change point at month 18 for the longitudinal measurements %FVC:

(9)
$$
\begin{aligned}
\%FVC_{ij} &= \beta_0 + \beta_1 FVC_{0i} + \beta_2 FIB_{0i} + \beta_3 CYC_i \\
&\quad + \beta_4 Time_{ij} + \beta_5 (Time_{ij} - 18)_+ + \beta_6 FVC_{0i} \\
&\quad \times CYC_i + \beta_7 FIB_{0i} \times CYC_i + \beta_8 Time_{ij} \\
&\quad \times CYC_i + \beta_9 (Time_{ij} - 18)_+ \times CYC_i \\
&\quad + Z_{ij} U_i + \epsilon_{ij}
\end{aligned}
$$

where $U_i = (U_{i1}, U_{i2})^T$ is the subject-specific random effects and the ϵ_{ij} is the mutually independent measurement errors. Since we include baseline %FVC as a fixed effect covariate, we don't consider random intercept to avoid possible confounding effects and $Z_{ij} = (Time_{ij}, (Time_{ij} - 18)_+)$.

A cause-specific competing risks sub-model was applied to model disease-related dropout (risk 1) and treatment fail-
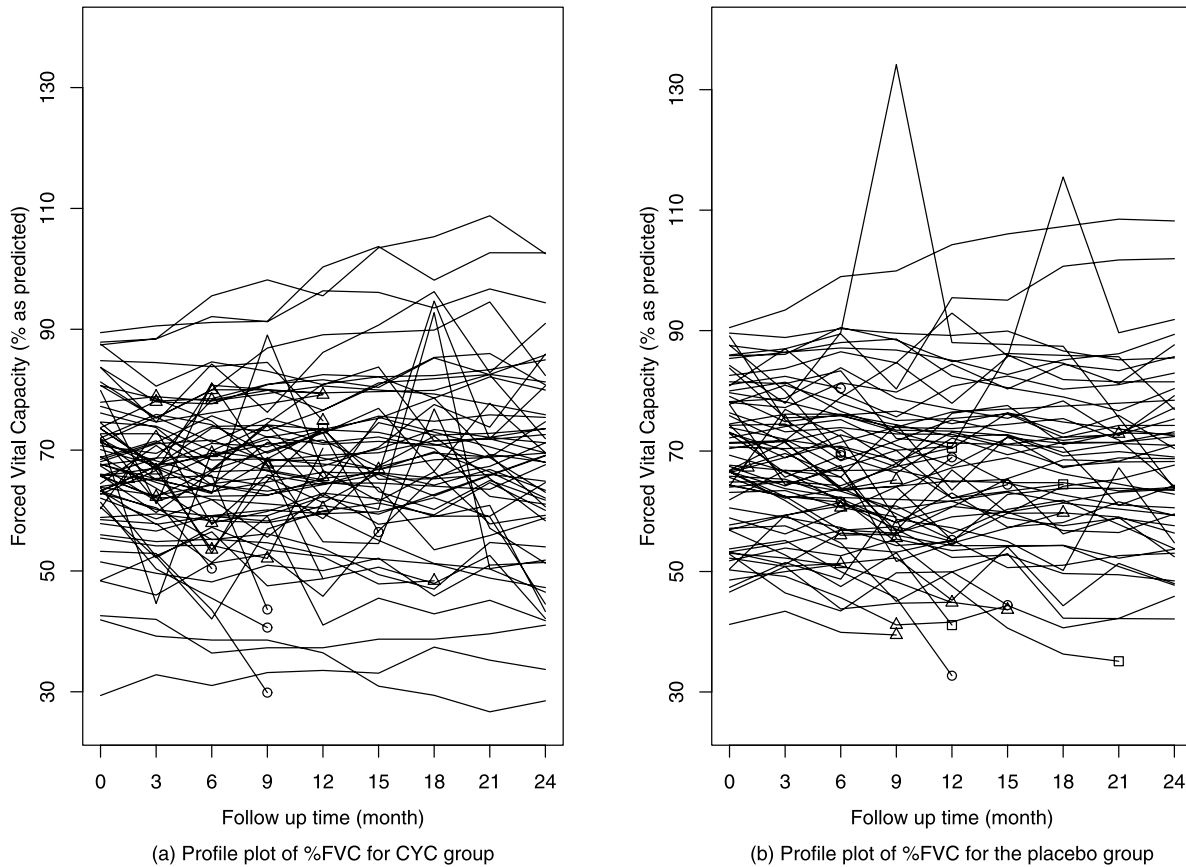

Figure 1. (a)–(b) Profile plots of observed %FVC for CYC group vs. placebo group including potential outlying measurements: ○ for treatment failure or death; △ for informatively censored events; □ for noninformatively censored events.

ure or death (risk 2):

(10)

$$\lambda_1(t) = \lambda_{01}(t) \exp(\gamma_{11}FVC_{0i} + \gamma_{12}FIB_{0i} + \gamma_{13}CYC_i + \gamma_{14}FVC_{0i} \times CYC_i + \gamma_{15}FIB_{0i} \times CYC_i + v_i)$$

and

(11)

$$\lambda_2(t) = \lambda_{02}(t) \exp(\gamma_{21}FVC_{0i} + \gamma_{22}FIB_{0i} + \gamma_{23}CYC_i + \gamma_{24}FVC_{0i} \times CYC_i + \gamma_{25}FIB_{0i} \times CYC_i + \nu_2 v_i).$$

The latent variables from both sub-models are assumed to have a multivariate normal distribution with mean zero and variance-covariance matrices

$$\Sigma_i = \left(\begin{array}{cc} \Sigma_{U_i} & \Sigma_{Uv_i} \\ \Sigma_{Uv_i}^T & \sigma_{v_i}^2 \end{array} \right).$$

We first test the homogeneous random effects covariance matrix assumption by considering subject-dependent covariates for a_{ijl} and b_{ij}. Specifically, we choose $a_{ijl} = b_{ij} = (1, CYC_i)$, which allows heterogeneous covariance matrices for different treatment groups, and test the null hypothesis by examining if the 95% credible interval of CYC effects contains zero for all the GARP and IV parameters. None of the 95% CIs for CYC of all the covariance parameters exclude zero (results not shown here), suggesting no obvious violation of the homogeneous random effects covariances assumption.

We use independent noninformative prior distributions for all the parameters with relatively large variances. A 3-step baseline hazard function, with the time points defining the steps being equally-split percentiles of the observed event times, is utilized for the informatively censored events and the event of treatment failure or death. Sensitivity analyses with 4- and 5-step baseline hazard functions are conducted and show no significant difference. The corresponding priors for the parameters are $\beta_0 \sim N(70, 10^3)$ and $\beta_l \sim N(0, 10^3)$ for $l = 1, \ldots, 9$; $\sigma^2 \sim IG(10^{-3}, 10^{-3})$; $\gamma_{kr} \sim N(0, 10^3)$ for $k = 1, 2$ and $r = 1, \ldots, 5$; $\lambda_{0k}^{(s)} \sim \Gamma(0.1, 0.1)$ for $s = 1, \ldots, S^k$ and $S^1 = S^2 = 3$; $\nu_2 \sim N(0, 10^5)$; and each element of η_1 and $\eta_2 \sim N(0, 10^5)$. We use 30,000 iterations of MCMC sampling chains following a 15,000-iteration "burn-in" period.

We identify 7 possible outlying data points by examining the residuals from our robust joint model. Table 1 compares results from a normal joint model with and without the outliers together with a model with a t-distributed error ($\kappa = 3$) using all data points. The estimation procedure for the normal joint model is the same except that there is no need to estimate parameter τ_{ij} (Huang, 2008). First, the outliers are observed to be influential to the parameter estimates for the longitudinal endpoint. The t-model with all data and the normal model without outliers yield consistent conclusions. For example, both methods reveal a significant time

trend in the placebo group before 18 months (β_1), which indicates a more steep decrease before 18 months in %FVC scores than that estimated from the normal joint model with all the data points. They also both identify a significant interaction (β_8) between the time trend (before 18 months) and the treatment group. In contrast, these effects are not significant using the normal method with all data points. Secondly, comparable estimates at the survival endpoint are obtained for all three models. Thirdly, all models identify a negative significant covariance Σ_{U1v} between the random slope before 18 months in the longitudinal model and the latent variable of the survival model, and a positive significant covariance Σ_{U2v} between the random slope after 18 months in the longitudinal model and the latent variable from the survival model, which indicates a dependence between the longitudinal measurement %FVC and the survival endpoint. We also observe a significant positive coefficient ν_2 which suggests a latent positive association between the two competing risks. Finally, the negative sign of Σ_{U1v} and positive sign of Σ_{U2v} together with the positive ν_2 indicate that before month 18, there is a lower risk of treatment failure or death and informative dropout for patients with higher than average increasing rate of %FVC over time; after 18 months, the trend is reversed due to the negative association between the two slopes. In summary, the longitudinal sub-model with a normal error is not robust against potential outliers in the longitudinal data, although the outliers may not have much impact on the estimation of the survival model parameters.

The models are assessed using the Deviance Information Criterion (DIC) (Spiegelhalter et al., 2002). The robust joint model gives the lowest DIC of 5089.35, which indicates the best fit. We note that there are several versions of DIC for missing data models (Celeux et al., 2006; Chen, 2006). Here we use the DIC constructed from the conditional distribution while treating both Ω and W as parameters because it is easy to compute. We conduct a small simulation to evaluate the DIC which selects 147 times out of 200 datasets and the effective dimension is always positive.

4. SIMULATION STUDY

We carry out a simulation study to assess the performance of our robust joint model and compare it to the joint model with a normal measurement error. The longitudinal measurements are simulated from the following random slope model:

(12)
$$Y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 X_{2i} + U_i t_{ij} + \epsilon_{ij}$$

where $t_{ij} = 0, 0.15, 0.3, \ldots, 3$, represents the scheduled visit time and $X_{2i} \sim Bernoulli(0.5)$ is a group indicator. We generate 1% outliers in the placebo group from normal distributions $N(60, 100)$ and $N(-60, 100)$ with rates 30% and 70%, respectively. The rest of the data have measurement error $\epsilon_{ij} \sim N(0, 5)$. We simulate two competing risks

	Normal distribution		t-distribution ($\kappa = 3$)
	With outliers	Without outliers	With outliers
	Estimate (95%CI)	Estimate (95%CI)	Estimate (95%CI)
Longitudinal outcome %FVC			
$Time$ (β_1)	$-0.13(-0.30, 0.05)$	$\mathbf{-0.18(-0.33, -0.02)}$	$\mathbf{-0.20(-0.36, -0.03)}$
$Time18$ (β_2)	$0.23(-0.25, 0.74)$	$0.15(-0.25, 0.53)$	$0.22(-0.13, 0.56)$
FVC_0 (β_3)	$0.92(0.83, 1.03)$	$0.88(0.79, 0.98)$	$0.93(0.85, 1.01)$
FIB_0 (β_4)	$-2.05(-3.22, -0.94)$	$-1.83(-2.84, -0.81)$	$-1.88(-2.75, -0.99)$
CYC (β_5)	$-1.38(-3.66, 1.00)$	$-1.00(-2.89, 0.88)$	$-1.12(-2.83, 0.59)$
$FVC_0 \times CYC$ (β_6)	$0.11(-0.04, 0.25)$	$0.15(-0.02, 0.27)$	$0.09(-0.01, 0.20)$
$FIB_0 \times CYC$ (β_7)	$2.03(0.43, 3.69)$	$1.74(0.32, 3.19)$	$2.25(0.92, 3.52)$
$Time \times CYC$ (β_8)	$0.26(-0.01, 0.51)$	$\mathbf{0.23(0.01, 0.45)}$	$\mathbf{0.24(0.01, 0.47)}$
$Time18 \times CYC$ (β_9)	$-0.64(-1.33, 0.07)$	$-0.43(-0.96, 0.13)$	$-0.41(-0.92, 0.09)$
p-value for H_0:Overall CYC Effects=0	$\mathbf{0.040}$	$\mathbf{0.022}$	$\mathbf{0.003}$
Cause-specific hazards (informatively censored events)			
FVC_0 (γ_{11})	$-0.06(-0.13, -0.01)$	$-0.06(-0.12, -0.01)$	$-0.06(-0.12, -0.01)$
FIB_0 (γ_{12})	$0.21(-0.28, 0.77)$	$0.21(-0.29, 0.76)$	$0.21(-0.27, 0.79)$
CYC (γ_{13})	$0.24(-0.61, 1.20)$	$0.29(-0.55, 1.21)$	$0.25(-0.57, 1.18)$
$FVC_0 \times CYC$ (γ_{14})	$0.11(0.03, 0.18)$	$0.10(0.03, 0.18)$	$0.11(0.04, 0.19)$
$FIB_0 \times CYC$ (γ_{15})	$0.13(-0.58, 0.83)$	$0.12(-0.61, 0.81)$	$0.08(-0.63, 0.78)$
Cause-specific hazards (treatment failure of death)			
FVC_0 (γ_{21})	$0.01(-0.07, 0.11)$	$0.02(-0.06, 0.10)$	$0.01(-0.07, 0.09)$
FIB_0 (γ_{22})	$0.25(-0.68, 1.22)$	$0.22(-0.62, 1.13)$	$0.25(-0.67, 1.20)$
CYC (γ_{23})	$-1.24(-3.20, 0.35)$	$-1.19(-3.29, 0.22)$	$-1.20(-3.50, 0.34)$
$FVC_0 \times CYC$ (γ_{24})	$-0.06(-0.20, 0.08)$	$-0.07(-0.20, 0.07)$	$-0.05(-0.19, 0.09)$
$FIB_0 \times CYC$ (γ_{25})	$-0.55(-2.26, 1.07)$	$-0.52(-2.12, 0.94)$	$-0.51(-2.22, 1.02)$
Random effects			
ν_2	$3.34(1.34, 8.35)$	$3.28(1.42, 8.81)$	$3.25(1.18, 7.84)$
Σ_{U11}	$0.27(0.20, 0.36)$	$0.28(0.21, 0.37)$	$0.25(0.19, 0.33)$
Σ_{U12}	$-0.36(-0.61, -0.18)$	$-0.32(-0.53, -0.17)$	$-0.27(-0.45, -0.15)$
Σ_{U22}	$1.60(0.89, 2.59)$	$0.93(0.51, 1.61)$	$0.73(0.39, 0.1.25)$
σ_v^2	$0.40(0.07, 1.59)$	$0.31(0.05, 1.16)$	$0.35(0.06, 1.31)$
Covariance of U_i and v_i			
Σ_{Uv1}	$-0.25(-0.53, -0.09)$	$-0.25(-0.50, -0.09)$	$-0.23(-0.47, -0.08)$
Σ_{Uv2}	$0.69(0.24, 1.50)$	$0.42(0.11, 1.02)$	$0.39(0.11, 0.93)$
Model fit			
DIC	5693.08	5295.18	5089.35

Note: The bold numbers indicate the significant results(p-value < 0.05).

failure times with the following cause-specific hazards:

$$(13) \quad \lambda_1(t; X_{1i}, X_{2i}, v_i, \gamma_1)$$
$$= \lambda_{01}(t)exp\{\gamma_{11}X_{1i} + \gamma_{12}X_{2i} + v_i\}$$
$$(14) \quad \lambda_2(t; X_{1i}, X_{2i}, v_i, \gamma_2, \nu_2)$$
$$= \lambda_{02}(t)exp\{\gamma_{21}X_{1i} + \gamma_{22}X_{2i} + \nu_2 v_i\}$$

where $X_1 \sim N(2, 1.0)$, and X_2 is shared with the longitudinal model. We use constant baseline hazards of 0.12 and 0.25 for risk 1 and risk 2, respectively, to generate the survival data. The random effects are generated from the multivari-ate normal distribution with covariance matrices Σ_i which are decomposed into the GARPs and IVs modeled with co-variates $a_{ijl} = b_{ij} = (1, X_{2i})$. In other words, the covariance matrices are different in the two groups: strong positive correlation in one group and strong negative correlation in the other. The parameter values are given in Table 2. With this setup, the rate of risk 1 is approximately 0.44, the rate of risk 2 is 0.36 and the censoring rate is 0.20. Longitudinal responses are missing after the observed or censored event times. The average number of total longitudinal observations is 7.8 per subject. We use a vague prior of $N(0, 10^5)$

Table 2. Comparison of the joint model with a normal distribution versus that with a t-distribution for ϵ_{ij} (sample size $= 250$)

m	Parameter	True	Normal distribution			t-distribution		
			Bias	SE	CP	Bias	SE	CP
250	Longitudinal							
	Fixed effects							
	β_0	10	**0.295**	0.352	0.655	0.020	0.137	0.903
	β_1	-1	0.059	0.735	0.927	-0.009	0.221	0.952
	β_2	1.5	**0.272**	0.340	0.807	-0.015	0.155	0.949
	Survival							
	Fixed effects							
	γ_{11}	0.8	-0.004	0.121	0.953	-0.011	0.130	0.923
	γ_{12}	-1	0.042	0.286	0.927	0.002	0.248	0.954
	γ_{21}	0.5	-0.025	0.128	0.927	-0.012	0.119	0.929
	γ_{22}	-1	0.026	0.260	0.960	-0.034	0.255	0.959
	Random effects							
	ν_2	0.5	**0.147**	0.688	0.895	-0.004	0.308	0.939
	σ_{u1}^2	2.5	**-0.117**	1.640	0.876	0.109	0.561	0.944
	σ_{uv1}	1.5	-0.018	0.890	0.931	0.036	0.514	0.949
	σ_{v1}^2	1	**0.253**	0.713	0.949	0.063	0.585	0.959
	σ_{u0}^2	0.5	**0.719**	0.967	0.887	0.039	0.259	0.938
	σ_{uv0}	-0.4	**-0.492**	2.905	0.840	0.002	0.297	0.908
	σ_{v0}^2	0.5	**0.054**	0.530	0.895	-0.018	0.416	0.929

Note: The bold numbers represent relatively large biases.

for each component of β, γ, ν, η_1 and η_2, $IG(10^{-3}, 10^{-3})$ for σ^2, and $\Gamma(10^{-3}, 10^{-3})$ for λ_0. The simulation is based on 200 Monte Carlo samples with a sample size of 250. The MCMC sampling is run using $5,000$ iterations, and the estimation results are based on the last $2,500$ iterations.

The bias, standard deviations of the posterior medians and coverage rate of 95% credible intervals are given in Table 2. In the presence of outliers, the joint model with a normal measurement error shows large bias for the longitudinal fixed effects β, the joint random effects covariance matrix parameters and ν_2. In particular, the group effect β_2 is overestimated since the outliers only exist in the placebo group and have a higher probability of being negative. Furthermore, these biases do not disappear for a large sample size of 500 (Table 3). In the contrast, our robust joint model yields much smaller biases for all the parameters. Both methods produce comparable estimates for the fixed effects for the competing risks survival endpoint.

5. DISCUSSION

We propose a robust joint model for longitudinal measurements and competing risks survival data with heterogeneous random effects. The robustness against potential outliers in the longitudinal measurements is achieved by specifying a t-distribution for the measurement error in the linear mixed effects sub-model. In addition, the proposed approach allows for high-dimensional random effects and heterogenous covariance matrices of the multivariate random effects, and

the resulting estimated covariance matrices are guaranteed to be positive definite.

The t-distribution model is a robust model in two ways. First, with t-distributed random errors, τ_{ij} reweights the observations according to their residuals, and thus we are able to obtain robust estimation by downweighting the outliers. Secondly, we carried out simulation to compare the two models (t-model and normal model) when there were no outliers, that is, the underlying measurement error followed a zero-mean normal distribution. There are almost unbiased estimates for all the parameters in both methods and the simulated coverage probabilities are close to 0.95, although the joint model with the t-distribution produces a little bit larger standard errors for the parameters at the longitudinal endpoint.

We did some sensitivity analyses of the estimates to misspecification of the variance-covariance structure and found out that we may obtain biased parameter estimates for the survival endpoint when combining the information of the longitudinal outcome if the correlation of the two endpoints is incorrectly modeled. Therefore, ignoring the heterogeneity can result in biased estimates and invalid inference.

The t-distributed error with $\kappa = 3$ has demonstrated nice properties for the purpose of guarding against outliers in the longitudinal data in our numerical study, even though it can also be estimated as a parameter. General principles of parsimony suggest that κ be fixed for small data sets and estimated for large ones (Lange et al., 1989). Lange et al. (1989) also suggest that estimated values of degree of freedom below 1 should be regarded with suspicion. In addi-

Table 3. *Comparison of the joint model with a normal distribution versus that with a t-distribution for ϵ_{ij} (sample size = 500)*

m	Parameter	True	Normal distribution			t-distribution		
			Bias	SE	CP	Bias	SE	CP
500	Longitudinal							
	Fixed effects							
	β_0	10	0.249	0.239	0.594	0.004	0.091	0.935
	β_1	-14	-0.064	0.413	0.934	-0.026	0.157	0.936
	β_2	1.5	0.231	0.239	0.791	-0.008	0.114	0.907
	Survival							
	Fixed effects							
	γ_{11}	0.8	0.007	0.085	0.955	-0.004	0.081	0.947
	γ_{12}	-1	-0.002	0.191	0.938	0.007	0.173	0.947
	γ_{21}	0.5	-0.005	0.084	0.934	-0.010	0.087	0.931
	γ_{22}	-1	0.011	0.182	0.934	-0.021	0.170	0.955
	Random effects							
	ν_2	0.5	-0.027	0.299	0.910	-0.006	0.192	0.931
	σ_{u1}^2	2.5	-0.375	0.540	0.796	0.072	0.388	0.951
	σ_{uv1}	1.5	-0.013	0.457	0.959	-0.009	0.385	0.943
	σ_{v1}^2	1	0.153	0.457	0.951	-0.015	0.396	0.927
	σ_{u0}^2	0.5	1.266	1.129	0.575	0.050	0.154	0.939
	σ_{uv0}	-0.4	-0.204	0.699	0.868	-0.022	0.170	0.923
	σ_{v0}^2	0.5	-0.051	0.292	0.877	-0.012	0.232	0.907

tion to the t-distribution, other normal/independent distributions (Lange and Sinsheimer, 1993), such as the slash distribution or the contaminated normal distribution, can be adapted for the measurement error in our robust joint model. Rosa et al. (2003) pointed out that the t process is the most commonly used thick-tailed distribution for robust inference which is often a good alternative to a Gaussian distribution; the contaminated normal distribution is more flexible but at the expense of an additional parameter, while the slash distribution is rarely encountered in the literature despite its relatively easier implementation in hierarchical modeling.

Our model can be extended to clustered data. Clustered data arise frequently from multi-site clinical trials, in which each site can be viewed as a cluster, or from studies across families, in which each family may be treated as a cluster. The cluster effect can easily be incorporated as a random effect or as a design vector for the GARP/IV parameters in order to take into account the heterogeneity across the cluster.

Finally, it is possible to extend our method to handle recurrent event data when each subject may repeatedly experience a certain event. Typical medical examples are multiple infection episodes and tumor recurrences. Zhang et al. (2008) considered a joint mixed-effects regression model for time series measures and recurrent events to analyze the air quality and respiratory symptom data. Their work may represent the first attempt to include a latent process in both the hazard and recovery rates of a recurrent event process. Extension of our joint model to incorporate recurrent event data would offer another promising approach. A possible choice of the sub-model for the recurrent

event data is the semiparametric transformation models with random effects described by Zeng and Lin (2007).

APPENDIX A: FULL CONDITIONAL DENSITIES

This section provides details for the full conditional distributions of the parameters used in the Gibbs sampling algorithm. We use $p(.)$ and $p(.|.)$ to denote marginal and conditional densities, respectively. We denote the prior distribution by $p_0(.)$. Based on the modified Cholesky decomposition, the random effects v_i can be written as $v_i = \sum_{l=1}^{q} a_{iql}^T \eta_1 U_{il} + e_{i,q+1}$ where $e_{i,q+1} \sim N(0, \exp(b_{i,q+1}^T \eta_2))$. Instead of sampling v_i directly, we sample $e_{i,q+1}$, leading to a faster convergence rate.

1. Sample τ_{ij} from

$$p(\tau_{ij}|.) \sim \Gamma\left(\frac{1+\kappa}{2},\right.$$
$$\left. \frac{1}{2}\left[\kappa + \frac{1}{\sigma^2}(Y_{ij} - \beta^T X_i^{(1)}(t_{ij}) - U_i^T Z(t_{ij}))^2\right]\right)$$

2. Sample σ^2 from

$$p(\sigma^2|.) \sim IG\left(\frac{\sum_{i=1}^{m} n_i}{2} + \alpha_1, \frac{1}{2}\sum_{i=1}^{m}\sum_{j=1}^{n_i} \tau_{ij}\right.$$
$$\left. \times (Y_{ij} - \beta^T X_i^{(1)}(t_{ij}) - U_i^T Z(t_{ij}))^2 + \alpha_2\right)$$

where $p_0(\sigma^2) = \Gamma(\alpha_1, \alpha_2)$.

3. Sample β from

$$p(\beta|.) \sim N\left(\left(\frac{\sum_{i=1}^{m} X_i^{(1)T} S_i X_i^{(1)}}{\sigma^2} + \Sigma_{\beta}^{-1}\right)^{-1}\right.$$
$$\times \left(\frac{\sum_{i=1}^{m} X_i^{(1)T} S_i (Y_i - Z_i U i)}{\sigma^2} + \Sigma_{\beta}^{-1}\beta_0\right),$$
$$\left.\left(\frac{\sum_{i=1}^{m} X_i^{(1)T} S_i X_i^{(1)}}{\sigma^2} + \Sigma_{\beta}^{-1}\right)^{-1}\right)$$

where $S_i = Diag(\tau_{ij})_{n_i}$ and $p_0(\beta) = N(\beta_0, \Sigma_\beta)$.

4. Sample the random effects U_i from

$$p(U_i|.) \propto N(\mu_{U_i|Y_i}, \Sigma_{U_i|Y_i})$$
$$\times \prod_{k=1}^{g} \exp\left\{\left(\sum_{l=1}^{q} a_{iql}^T \eta_1 U_{il} + e_{i,q+1}\right)\right.$$
$$\left.\times \nu_k I(D_i = k) - H_k(T_i)\right\}$$

where $\Sigma_{U_i|Y_i} = (\frac{Z_i^T S_i Z_i}{\sigma^2} + \Sigma_{u_i}^{-1})^{-1}$, $\mu_{U_i|Y_i} = \Sigma_{U_i|Y_i}[\frac{Z_i^T S_i(Y_i - X_i\beta)}{\sigma^2}]$, and $\Sigma_{u_i}^{-1} = M_i^{*T} H_i^{*-1} M_i^*$, M_i^* is a $q \times q$ matrix consisting of the first q columns and rows of M_i, H_i^* is a $q \times q$ matrix consisting of the first q columns and rows of H_i. We use the one-step Metropolis-Hastings algorithm to obtain the update in the sampling sequence with the normal density from the longitudinal data as the proposal density. The random effects U_i is obtained by first sampling a random variable form the conditional density based on the longitudinal data and then using the conditional likelihood contribution from the survival data to determine the acceptance of the new draw.

5. Sample η_1 from

$$p(\eta_1|.) \propto N\left(\left(\sum_{i=1}^{m} Q_i^T H_i^{*-1} Q_i\right)^{-1}\left(\sum_{i=1}^{m} Q_i^T H_i^{*-1} U_i\right),\right.$$
$$\left.\left(\sum_{i=1}^{m} Q_i^T H_i^{*-1} Q_i\right)^{-1}\right) \prod_{k=1}^{g} \exp\left\{\left(\sum_{l=1}^{q} a_{iql}^T \eta_1 U_{il}\right.\right.$$
$$\left.\left.+ e_{i,q+1}\right) \nu_k I(D_i = k) - H_k(T_i)\right\} p_0(\eta_1),$$

where Q_i is a $q \times q_1$ matrix with first row $Q_{i1} = 0$ and j^{th} row $Q_{ij} = \sum_{l=1}^{j-1} a_{ijl}^T U_{il}$ for $j = 2, \ldots, q$. We sample η_1 in two steps: sample the entries only involving U_i from the normal conditional density, sample the entries involving U_i and v_i with adaptive rejection sampling. It is worth noting that for the homogeneous case where the variance-covariance matrix Σ is diagonal, we have $\Sigma = H$ and $M = I$. In this case, there is no need to sample η_1 and it should be set to zero in the sampling procedure.

6. Sample η_2 from

$$p(\eta_2|.) \propto \exp\left[-\frac{1}{2} \sum_{i=1}^{m}\left(\sum_{j=1}^{q}\left\{b_{ij}^T \eta_2\right.\right.\right.$$
$$+ \left(U_{ij} - \sum_{l=1}^{j-1} a_{ijl}^T \eta_1 U_{il}\right)^2 \times \exp(-b_{ij}^T \eta_2)\Big\}$$
$$\left.\left.+ b_{i,q+1}^T \eta_2 + e_{i,q+1}^2 \exp(-b_{i,q+1}^T \eta_2)\right)\right] p_0(\eta_2).$$

We use a Metropolis-Hastings step with a normal approximation to the full conditional as the candidate distribution. For details, see Daniels and Pourahmadi (2002).

7. Sample γ_{kr}, $k = 1, \ldots, g$, $r = 1, \ldots, R$ from

$$p(\gamma_{kr}|.) \propto \exp\left[\gamma_{kr} \sum_{i=1}^{m} I(D_i = k) X_{ir}^{(2)}(T_i)\right.$$
$$\left.- \sum_{i=1}^{m} H_k(T_i)\right] p_0(\gamma_k).$$

We use a Metropolis-Hastings step within the single component sampler to update the values of these parameters. For each of these parameters, we propose a normal density as the proposal density, which has the current value of the parameter as its mean and its standard deviation is set equal to four times the standard error of a maximum partial likelihood estimate from a standard Cox model (Wang and Taylor, 2001).

8. Sample ν_k with ARS from

$$p(\nu_k|.) \propto \exp\left[\sum_{i=1}^{m} I(D_i = k)\nu_k\left(\sum_{l=1}^{q} a_{iql}^T \eta_1 U_{il} + e_{i,q+1}\right)\right.$$
$$- \sum_{i=1}^{m} \int_0^{T_i} \lambda_{0k} \exp\left(\gamma_k^T X_i^{(2)}\right.$$
$$\left.\left.+ \nu_k\left(\sum_{l=1}^{q} a_{iql}^T \eta_1 U_{il} + e_{i,q+1}\right)\right) dt\right] p_0(\nu_k).$$

9. Sample $e_{i,q+1}$ $(i = 1, \ldots, m)$ from

$$p(e_{i,q+1}|.) \propto N(0, \exp(b_{i,q+1}^T \eta_2))$$
$$\times \prod_{k=1}^{g} \exp[e_{i,q+1}\nu_k I(D_i = k) - H_k(T_i)].$$

The sample is obtained by first sampling a candidate from the normal densities as its assumption and then using the conditional likelihood contribution from the survival data to determine the acceptance of the new draw.

10. Sample each piece of λ_{0k} $(k = 1, \ldots, g)$ from

$$p(\lambda_{0k}^{(s)}|.) \propto \Gamma(\alpha_k^s, \beta_k^s) p_0(\lambda_{0k}^{(s)}),$$

where $\alpha_k^s = \sum_{i=1}^m I(D_i = k, t_k^{(s-1)} < T_i \leq t_k^{(s)}) + 1$ indicates the number of events occurring in the time interval $(t_k^{(s-1)}, t_k^{(s)}]$, and $\beta_k^s = \sum_{i=1}^m I(T_i > t_k^{(s-1)}) \int_{t_k^{(s-1)}}^{\min(T_i, t_k^{(s)})} \exp(\gamma_k^T X_i^{(2)} + \nu_k v_i) dt$, for $s = 1, \ldots, S^k$.

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