Journal of the Royal Statistical Society
SERIES C Applied Statistics

Appl. Statist. (2012)
61, *Part* 1, *pp.* 135–149

Estimating progression-free survival in paediatric brain tumour patients when some progression statuses are unknown

Ying Yuan and Peter F. Thall

M. D. Anderson Cancer Center, Houston, USA

and Johannes E. Wolff

Tufts University Medical Center, Cambridge, USA

[Received August 2010. Revised June 2011]

Summary. In oncology, progression-free survival time, which is defined as the minimum of the times to disease progression or death, often is used to characterize treatment and covariate effects. We are motivated by the desire to estimate the progression time distribution on the basis of data from 780 paediatric patients with choroid plexus tumours, which are a rare brain cancer where disease progression always precedes death. In retrospective data on 674 patients, the times to death or censoring were recorded but progression times were missing. In a prospective study of 106 patients, both times were recorded but there were only 20 non-censored progression times and 10 non-censored survival times. Consequently, estimating the progression time distribution is complicated by the problems that, for most of the patients, either the survival time is known but the progression time is not known, or the survival time is right censored and it is not known whether the patient's disease progressed before censoring. For data with these missingness structures, we formulate a family of Bayesian parametric likelihoods and present methods for estimating the progression time distribution. The underlying idea is that estimating the association between the time to progression and subsequent survival time from patients having complete data provides a basis for utilizing covariates and partial event time data of other patients to infer their missing progression times. We illustrate the methodology by analysing the brain tumour data, and we also present a simulation study.

Keywords: Latent variables; Missingness at random; Missing values; Survival analysis

1. Introduction

A clinical outcome that is commonly used to characterize the effects of treatments for cancers and other potentially fatal diseases is the progression-free survival (PFS) time, which is defined as the time from the start of treatment to disease progression (worsening) or death, whichever occurs first. Denote the time to death without progression by T_0, the time to progression by T_1 and the time from progression to death by T_2. Thus, aside from censoring, either T_0 or (T_1, T_2) is observed for each subject, the PFS time is $\min\{T_0, T_1\}$, and overall survival (OS) time is $T = \min\{T_0, T_1 + T_2\}$. For diseases where progression always precedes death, i.e. T_0 is never observed, T_1 and the PFS time are identical and the OS time is $T = T_1 + T_2$. In this case, a wide variety of time-to-event regression models and methods may be applied (Therneau and Grambsch, 2000; Ibrahim *et al.*, 2001; Klein and Moeschberger, 2003) for estimating the

Address for correspondence: Ying Yuan, Department of Biostatistics, M. D. Anderson Cancer Center, Unit 447, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
E-mail: yyuan@mdanderson.org

 0035–9254/12/61135

distributions of T_1, T_2 and T as functions of a vector $\mathbf{Z} = (Z_1, \ldots, Z_q)$ of covariates and treatment variables. In this setting, the problem of estimating the distribution of $[T_1|\mathbf{Z}]$ becomes more difficult if, for some subjects, either T is known but T_1 is not known, or T is right censored and it is not known whether the subject's disease progressed before the censoring time. For data that have either of these missingness structures, we formulate a family of parametric likelihood functions and present methods for estimating the progression time distribution. Intuitively, the idea underlying our approach is that estimating the joint distribution of T_1 and T_2 from subjects having complete data including $\mathbf{Z}$ provides a basis for utilizing the partial information in the value of T or its censoring time and $\mathbf{Z}$ to infer T_1 when data for T_1 are missing in either of the two ways that were described above.

Our research is motivated by a data set that arose from 780 patients with choroid plexus tumours. These are rare brain tumours that typically occur in young children, subclassified histologically by the World Health Organization as the comparatively more benign choroid plexus papilloma, the intermediate atypical choroid plexus papilloma and the most malignant histology choroid plexus carcinoma (CPC). Each patient received surgery, and possibly some combination of radiation and chemotherapy. Surgery achieving gross total resection (GTR) is traditionally believed to be of high prognostic relevance (Wolff *et al.*, 2002), whereas the roles of radiation and chemotherapy are less well understood (Wolff *et al.*, 1999). As these tumours are rare, sufficient prospectively collected data to evaluate PFS and OS reliably and thus to establish benchmarks for treatment have not been available. Therefore, the data came from two sources: literature and a prospective clinical study. A systematic literature search was undertaken to collect and codify all published case reports (Wolff *et al.*, 1999, 2002), resulting in 674 cases. These case reports typically included the OS time but rarely included the PFS time. In contrast, the data resulting from a prospective study of 106 patients (Wrede *et al.*, 2009) did include both PFS and OS times. Consequently, among the total of 780 patients, 674 patients had observed or censored values of T without observing the value of T_1, whereas 106 patients had observed or censored values of T_1 and T_2.

Considerable research has been conducted for survival data analysis with missing failure indicators. Dinse (1982) proposed a Kaplan–Meier-type estimator using the non-parametric maximum likelihood method and the EM algorithm. Lo (1991) developed two alternative estimators that are strongly consistent and converge to Gaussian processes. In the context of a competing risks model, Goetghebeur and Ryan (1990) derived a modified log-rank test to compare survival in two groups when failure types are missing for some individuals and later extended that approach to proportional hazards regression models (Cox, 1972; Goetghebeur and Ryan, 1995). Lu and Tsiatis (2001) and Tsiatis *et al.* (2002) took a different approach and proposed the use of multiple imputation to address the problem of missing information on the cause of failure. More recently, Gijbels *et al.* (2007) introduced a class of estimating functions for the regression parameter of the Cox proportional hazards model to allow unknown failure statuses on some study subjects. Although related, the problem that we consider here is rather different from the situations that were considered in the literature noted above. First, in our case the missing information is more severe in the sense that, in addition to missing failure indicators, T_1 is completely missing for some patients, with only T observed. Moreover, we consider a bivariate survival function for (T_1, T_2), whereas the above literature focused on the univariate case.

Our data structure also shares some similarity to semicompeting risks data (Fine *et al.*, 2001) in the sense that disease progression can be viewed as an intermediate non-terminating event, with death a terminating event. However, there are some important differences. For the choroid plexus tumour data, death must be preceded by disease progression owing to the nature

of the disease; in other words, the terminating event cannot censor the non-terminating event. This is different from semicompeting risks data, which are characterized by the feature that the terminating event can censor the non-terminating event. In addition, in semicompeting risks data, for subjects who experienced the terminating event it typically is known whether or not they experienced the intermediate non-terminating event. However, in our data set, the status of disease progression may be missing.

Section 2 describes a general probability model that accounts for missing information of the forms that were described above and presents a family of accelerated failure time (AFT) models for the marginals of T_1 and T_2. Numerical methods for model fitting and estimation are presented in Section 3. In Section 4, the methods are illustrated by an analysis of the data set that motivated this paper. In Section 5, we assess the goodness of fit of the proposed model by using a Bayesian χ^2-test, and we present sensitivity analyses to assess effects of between-study heterogeneity, the copula that is assumed to obtain a bivariate distribution for (T_1, T_2) and the values of prior parameters characterizing association between T_1 and T_2 as well as location and scale in the marginal distributions. We evaluate the performance of the proposed method by using a simulation study in Section 6, and we close with a brief discussion in Section 7.

2. Probability model

2.1. General form of the likelihood

Let $\boldsymbol{\theta}$ denote the vector of model parameters. For $j = 1, 2,$ denote the marginal probability density function, cumulative density function and survivor function of $[T_j|\mathbf{Z}]$ by $f_j(t|\mathbf{Z}, \boldsymbol{\theta})$, $F_j(t|\mathbf{Z}, \boldsymbol{\theta})$ and $S_j(t|\mathbf{Z}, \boldsymbol{\theta}) = 1 - F_j(t|\mathbf{Z}, \boldsymbol{\theta})$. Denote the administrative right censoring time by C, with observed times $T_1^{\mathrm{o}} = \min\{T_1, C\}$, $T_2^{\mathrm{o}} = \min\{T_2, C - T_1\}$ and $T^{\mathrm{o}} = \min\{T, C\}$. In addition to right censoring, we account for the possibilities that either it is known that progression occurred but the value of T_1 is not known, or $T^{\mathrm{o}} < T$ and it is not known at T^{o} whether progression has occurred. To keep track of all possible cases, we define the following categorical indicator variable:

$$\Delta = \begin{cases} 1 & \text{if } T_1 \text{ and} T_2 \text{ both are observed,} \\ 2 & \text{if } T_1 \text{ is observed and } T_2 \text{ is censored,} \\ 3 & \text{if } T_1 \text{ is censored,} \\ 4 & \text{if } T \text{ is observed and } T_1 \text{ is unknown,} \\ 5 & \text{if } T \text{ is censored and it is not known whether progression occurred.} \end{cases}$$

We define the corresponding indicators $\delta_j = I(\Delta = j)$ for $j = 1, \ldots, 5$. For brevity, we denote $\mathbf{T}^{\mathrm{o}} = (T_1^{\mathrm{o}}, T_2^{\mathrm{o}}, T^{\mathrm{o}})$ and $\boldsymbol{\delta} = (\delta_1, \ldots, \delta_5)$.

Each subject's likelihood contribution takes one of five possible forms. Denote the joint probability density function of $[T_1, T_2|\mathbf{Z}]$ by $f_{1,2}(t_1, t_2|\mathbf{Z}, \boldsymbol{\theta})$. If T_1 and T_2 are both observed, then the likelihood is

$$\mathcal{L}_1(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) = f_{1,2}(T_1^{\mathrm{o}}, T_2^{\mathrm{o}} \mid \mathbf{Z}, \boldsymbol{\theta})^{\delta_1}. \tag{1}$$

If T_1 is observed but T_2 is censored, then the likelihood is

$$\mathcal{L}_2(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) = \left\{ \int_{t_2 = T_2^{\mathrm{o}}}^{\infty} f_{1,2}(T_1^{\mathrm{o}}, t_2|\mathbf{Z}, \boldsymbol{\theta}) \, \mathrm{d}t_2 \right\}^{\delta_2}. \tag{2}$$

If T_1 is censored, then it is known that $T_1 > T_1^{\mathrm{o}}$ but nothing is known about T_2, and it follows that the likelihood is

$$\mathcal{L}_3(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) = S_1(T_1^{\mathrm{o}})^{\delta_3}. \tag{3}$$

The above three cases are those seen most commonly in practice. The next two cases may be considered non-standard in that they are seen less often. If the time of death $T^{\mathrm{o}} = T = T_1 + T_2$ is observed but T_1 is not known, possibly because T_1 was not recorded, then the likelihood is

$$\mathcal{L}_4(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) = \left\{ \int_{t_1=0}^{T^{\mathrm{o}}} f_{1,2}(t_1, T^{\mathrm{o}} - t_1|\mathbf{Z}, \boldsymbol{\theta})\, \mathrm{d}t_1 \right\}^{\delta_4}. \tag{4}$$

This is the convolution of T_1 and T_2 evaluated at the observed survival time $T = T^{\mathrm{o}}$. The fifth possibility is that the subject is known to be alive but it is not known whether disease progression has occurred, formally, $T > T^{\mathrm{o}}$ but T_1 is not known. In this case, since

$$\begin{aligned}\Pr(T > T^{\mathrm{o}}|\mathbf{Z}, \boldsymbol{\theta}) &= \Pr(T_1 \leqslant T^{\mathrm{o}}|\mathbf{Z}, \boldsymbol{\theta}) \Pr(T > T^{\mathrm{o}}|T_1 \leqslant T^{\mathrm{o}}, \mathbf{Z}, \boldsymbol{\theta}) \\ &\quad + \Pr(T_1 > T^{\mathrm{o}}|\mathbf{Z}, \boldsymbol{\theta}) \Pr(T > T^{\mathrm{o}}|T_1 > T^{\mathrm{o}}, \mathbf{Z}, \boldsymbol{\theta}) \\ &= \Pr(T_1 + T_2 > T^{\mathrm{o}} \text{ and } T_1 \leqslant T^{\mathrm{o}}|\mathbf{Z}, \boldsymbol{\theta}) + \Pr(T_1 > T^{\mathrm{o}}|\mathbf{Z}, \boldsymbol{\theta}),\end{aligned}$$

the likelihood contribution is

$$\mathcal{L}_5(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) = \left\{ \int_{t_1=0}^{T^{\mathrm{o}}} \int_{t_2=T^{\mathrm{o}}-t_1}^{\infty} f_{1,2}(t_1, t_2|\mathbf{Z}, \boldsymbol{\theta})\, \mathrm{d}t_2\, \mathrm{d}t_1 + S_1(T^{\mathrm{o}}|\mathbf{Z}, \boldsymbol{\theta}) \right\}^{\delta_5}. \tag{5}$$

The likelihood thus is the product $\mathcal{L}(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) = \Pi_{k=1}^{5} \mathcal{L}_k(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta})$.

To obtain a joint distribution $f_{1,2}$ for given marginals, we assume the Clayton (1978) copula,

$$S(t_1, t_2|\mathbf{Z}, \boldsymbol{\theta}) = \{S_1(t_1|\mathbf{Z}, \boldsymbol{\theta})^{-1/\phi} + S_2(t_2|\mathbf{Z}, \boldsymbol{\theta})^{-1/\phi} - 1\}^{-\phi}, \qquad \phi \geqslant 0. \tag{6}$$

Under this model, the correlation parameter ϕ is related to Kendall's τ by the equation $\tau = 1/(2\phi + 1)$. Either a large positive value of τ or a small value of ϕ corresponds to a large positive correlation between T_1 and T_2, with $\tau = 1$ if $\phi = 0$. Independence of T_1 and T_2 corresponds to $\tau = 0$, which is obtained if $\phi \to \infty$. Thus, the Clayton copula assumes that the correlation between the time to progression T_1 and the time from progression to death T_2 is non-negative. This assumption is quite reasonable here because choroid plexus tumour patients with longer time to progression T_1 are more likely to have a longer subsequent survival time T_2, which also is the case with many other types of cancer. Below, we shall assess the effects of assuming the particular form (6) by repeating the model fit using a bivariate copula (Hougaard, 1986) that has a very different form. Shih and Louis (1995) discussed inferences on the association parameter in copula models for bivariate survival data.

To simplify the notation, we temporarily suppress the arguments $\mathbf{Z}$ and $\boldsymbol{\theta}$ in f_1, f_2, S_1 and S_2, and we denote $\zeta = (\phi + 1)/\phi$. Under the Clayton copula, the general forms of the likelihood given by equations (1), (2), (4) and (5) take the following forms:

$$\mathcal{L}_1(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) = [\zeta\{S_1(T_1^{\mathrm{o}})^{-1/\phi} + S_2(T_2^{\mathrm{o}})^{-1/\phi} - 1\}^{-\phi-2} f_1(T_1^{\mathrm{o}}) f_2(T_2^{\mathrm{o}})\{S_1(T_1^{\mathrm{o}})\, S_2(T_2^{\mathrm{o}})\}^{-\zeta}]^{\delta_1},$$

$$\mathcal{L}_2(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) = [\{S_1(T_1^{\mathrm{o}})^{-1/\phi} + S_2(T_2^{\mathrm{o}})^{-1/\phi} - 1\}^{-\phi-1} f_1(T_1^{\mathrm{o}}) S_1(T_1^{\mathrm{o}})^{-\zeta}]^{\delta_2},$$

$$\mathcal{L}_4(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) =$$
$$\left[\int_{t_1=0}^{T^{\mathrm{o}}} \zeta\{S_1(t_1)^{-1/\phi} + S_2(T^{\mathrm{o}}-t_1)^{-1/\phi} - 1\}^{-\phi-2} f_1(t_1) f_2(T^{\mathrm{o}}-t_1)\{S_1(t_1)\, S_2(T^{\mathrm{o}}-t_1)\}^{-\zeta}\, \mathrm{d}t_1\right]^{\delta_4}$$

and

$$\mathcal{L}_5(\mathbf{T}^{\mathrm{o}}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}) = \left[\int_{t_1=0}^{T^{\mathrm{o}}} \{1 + S_1(t_1)^{1/\phi} S_2(T^{\mathrm{o}}-t_1)^{-1/\phi} - S_1(t_1)^{1/\phi}\}^{-\phi-1} f_1(t_1)\, \mathrm{d}t_1 + S_1(T^{\mathrm{o}})\right]^{\delta_5}.$$

2.2. Specific distributional forms for the marginals

To incorporate covariates, we assume that each marginal belongs to the family of AFT models, characterized by the hazard function

$$\lambda(t|\mathbf{Z}, \boldsymbol{\beta}) = \exp(\eta)\,\lambda_0\{t\exp(\eta)\} \qquad \text{for } t > 0,$$

where the covariate and treatment effects are the parameters $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_q)$ in the linear term $\eta = \beta_1 Z_1 + \ldots + \beta_q Z_q$. Under the AFT model, the cumulative hazard function is

$$\Lambda(t) = \exp(\eta) \int_0^t \lambda_0\{u\exp(\eta)\}\, \mathrm{d}u$$

and the survivor function is $S(t) = \exp\{-\Lambda(t)\}$. The AFT family is quite broad, with a particular distribution obtained by assuming a specific form for the baseline hazard function λ_0. To obtain a good fit to the brain tumour data, we shall consider four possible distributional forms for each of the baseline hazards corresponding to T_1 and T_2. These are the exponential, Weibull, log-normal and log-logistic distributions, for a total of 16 possible models. To choose a single best model for analysis of the data at hand, we shall assess the goodness of fit by using the Bayesian information criterion (Schwarz, 1978).

Index the event times by $j = 1, 2$ and denote the linear components $\eta_j = \beta_{j,1} Z_1 + \ldots + \beta_{j,q} Z_q$. Since the exponential distribution is characterized by constant baseline hazard function $\lambda_0(t) \equiv \gamma$ for $\gamma > 0$, the covariate-adjusted exponential AFT hazard of T_j is

$$\lambda_{j,\exp}(t|\mathbf{Z}, \boldsymbol{\beta}_j, \gamma_j) = \exp(\eta_j)\gamma_j. \tag{7}$$

The Weibull model has baseline hazard $\lambda_0(t) = \gamma\alpha t^{\alpha-1}$, for $\gamma, \alpha > 0$, so the covariate-adjusted Weibull AFT hazard of T_j is

$$\lambda_{j,\mathrm{weib}}(t|\mathbf{Z}, \boldsymbol{\beta}_j, \alpha_j, \gamma_j) = \gamma_j\alpha_j \exp(\alpha_j\eta_j) t^{\alpha_j - 1}. \tag{8}$$

Denoting the probability density function and survivor function of the log-normal distribution having mean $\exp(\mu + \gamma/2)$ and variance $\{\exp(\gamma) - 1\}\exp(2\mu + \gamma)$ for real-valued μ and $\gamma > 0$ by $f_{\mathrm{LN}}(t; \mu, \gamma)$ and $S_{\mathrm{LN}}(t; \mu, \gamma)$, since the baseline log-normal hazard function is $\lambda_0(t; \mu, \gamma) = f_{\mathrm{LN}}(t; \mu, \gamma)/S_{\mathrm{LN}}(t; \mu, \gamma)$, it follows that the covariate-adjusted log-normal AFT hazard function of T_j is

$$\lambda_{j,\text{log-norm}}(t|\mathbf{Z}, \boldsymbol{\beta}_j, \mu_j, \gamma_j) = \exp(\eta_j)\frac{f_{\mathrm{LN}}\{t\exp(\eta_j); \mu_j, \gamma_j\}}{S_{\mathrm{LN}}\{t\exp(\eta_j); \mu_j, \gamma_j\}}. \tag{9}$$

Finally, the log-logistic baseline hazard function is $\lambda_0(t) = \gamma\alpha t^{\alpha-1}/(1+\gamma t^{\alpha-1})$, so the covariate-adjusted log-logistic AFT hazard function of T_j is

$$\lambda_{j,\text{log-logist}}(t|\mathbf{Z}, \boldsymbol{\beta}_j, \alpha_j, \gamma_j) = \exp(\eta_j)\frac{\gamma_j\alpha_j\{t\exp(\eta_j)\}^{\alpha_j-1}}{1+\gamma_j\{t\exp(\eta_j)\}^{\alpha_j-1}}. \tag{10}$$

3. Numerical methods and estimation

Although we adopt a parametric approach, the likelihood does not have a simple closed form because the non-standard cases given by $\mathcal{L}_4(\mathbf{T}^{\circ}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta})$ and $\mathcal{L}_5(\mathbf{T}^{\circ}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta})$ involve integrals that must be evaluated numerically. This makes it challenging to evaluate the first and second derivatives of the likelihood, which is often needed for maximum likelihood methods such as Fisher scoring. To avoid this difficulty, we fit the model by using the Gibbs sampler by generating unknown parameters sequentially from their full conditional posterior distributions. This approach does not require evaluating the derivatives of the likelihood. Let $p(\boldsymbol{\theta})$ denote the prior distribution of $\boldsymbol{\theta}$. We assume that the components of $\boldsymbol{\theta}$ are mutually independent *a priori*. Given data from n subjects, the posterior distribution of $\boldsymbol{\theta}$ is

$$p(\boldsymbol{\theta}|\text{data}) \propto p(\boldsymbol{\theta}) \prod_{i=1}^{n}\prod_{k=1}^{5} \mathcal{L}_k(\mathbf{T}^{\circ}, \boldsymbol{\delta}|\mathbf{Z}, \boldsymbol{\theta}).$$

Following Ibrahim *et al.* (2001), chapter 2, we assume independent improper priors on the elements of $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$, which we denote by $\beta_{jr} \propto 1$, for $j = 1, 2$ and $r = 1, \ldots, q$. Thus, the posteriors are determined mainly by the observed data. For the exponential distributions, we assume gamma priors for the scale parameter, $\gamma_j \sim \text{Ga}(a_1, b_1)$, where $\text{Ga}(a, b)$ denotes a gamma distribution with mean a/b and variance a/b^2. For the Weibull baseline hazards, we assume $\alpha_j \sim \text{Ga}(a_2, b_2)$ and $\gamma_j \sim \text{Ga}(a_3, b_3)$. For the log-normal baseline hazards, we assume a uniform improper prior for the location parameter and a gamma prior for the scale parameter, $\mu_j \propto 1$ and $\gamma_j \sim \text{Ga}(a_4, b_4)$. For the log-logistic baseline hazard, we assume that $\alpha_j \sim \text{Ga}(a_5, b_5)$ and $\gamma_j \sim \text{Ga}(a_6, b_6)$. We set $a_j = b_j = 0.01$ for each $j = 1, \ldots, 6$, which is a gamma distribution with mean 1 and variance 100, to reflect vague prior information on the unknown positive parameters.

Under these priors, because the posterior full conditional distributions of the parameters do not have closed forms, we computed the posteriors by using the adaptive rejection Metropolis sampling method of Gilks *et al.* (1995). We evaluated the integrals appearing in the likelihoods $\mathcal{L}_4$ and $\mathcal{L}_5$ numerically by using adaptive Gaussian–Kronrod quadrature (Piessens *et al.*, 1983). In the Markov chain Monte Carlo algorithm we used 500 iterations to burn in the chains and 5000 iterations to compute the posterior samples. For initial values in the Markov chain Monte Carlo algorithm, we used the maximum likelihood estimates of the parameters of the marginals for T_1 and T_2 based on the smaller data set consisting of 106 patients having complete data.

4. Analysis of the brain tumour data

In this section, we apply the proposed methodology to the brain tumour data. Although T_1 and T_2 or their censoring times were recorded for 106 out of a total of 780 patients, the censoring rate was very high. Among the smaller sample of 106, only 20 disease progression times T_1 were observed, with 81.1% of the T_1-values censored. Because T_2 is observable only if T_1 is observed, the information regarding T_2 was even more limited. Among the 20 patients with observed T_1-values, 10 values of T_2 were observed and 10 were censored. Among the 674 patients with missing values of both T_1 and T_2, the sum $T = T_1 + T_2$ was observed for 182 patients and the

remaining 492 values of T were censored. Thus, although the total sample size was 780, most of the information consisted of values of $T_1 + T_2$, with uncensored (T_1, T_2) pairs fully observed in only 10 patients. Consequently, our analyses relied heavily on covariate information, as well as the strong assumption that the two data sets were exchangeable. Below, we shall conduct a sensitivity analysis to assess potential between-study effects.

As noted above, we conducted a preliminary model selection and goodness-of-fit analysis to choose one best parametric model by considering four distributional forms for each marginal, including the exponential, Weibull, log-normal and log-logistic models, given by expressions (7)–(10). For each regression model, the linear terms η_1 and η_2 each include four covariates: age (z_1), histology ($z_2 = 1$ for CPC and $z_2 = 0$ for atypical choroid plexus papilloma or choroid plexus

Table 1. Bayesian information criterion values for each of the 16 models obtained from combinations of the marginal distributions for T_1 and T_2, assuming the Clayton copula†

Distribution of T_2	*Results for the following distributions of* T_1*:*			
	Exponential	*Weibull*	*Log-normal*	*Log-logistic*
Exponential	3901	2915	3358	2327
Weibull	3745	2721	3103	*2153*
Log-normal	4176	2484	3523	2739
Log-logistic	2472	2402	2978	2782

†The model that fits the data best is in italics.

Table 2. Posterior means, standard deviations SD and 95% credible intervals of the model parameters, under the best fitting model with T_1 log-logistic and T_2 Weibull, using either all of the available data or only the complete cases of the 106 patients with no missing values†

Covariate	*Parameter*	*Results for available data* $(n = 780)$			*Results for complete cases* $(n = 106)$		
		Mean (SD)	*95% credible interval*	$Pr(\beta > 0)$	*Mean (SD)*	*95% credible interval*	$Pr(\beta > 0)$
Marginal distribution of T_1							
Age	β_{11}	−0.09 (0.06)	(−0.23, 0)	0.02	−0.02 (0.05)	(−0.13, 0.08)	0.40
Histology, CPC	β_{12}	2.24 (0.87)	(0.71, 4.15)	1	2.15 (0.56)	(1.16, 3.36)	1
Surgery, GTR	β_{13}	−1.29 (0.82)	(−3.04, 0.22)	0.05	−0.80 (0.61)	(−2.02, 0.4)	0.09
Metastases, yes	β_{14}	1.49 (1.02)	(−0.49, 3.57)	0.93	0.27 (0.73)	(−1.21, 1.72)	0.65
	α_1	0.69 (0.14)	(0.45, 0.98)		1.14 (0.22)	(0.74, 1.62)	
	γ_1	0.03 (0.02)	(0.01, 0.08)		0.23 (0.13)	(0.07, 0.56)	
Marginal distribution of T_2							
Age	β_{21}	0.08 (0.28)	(−0.51, 0.65)	0.63	0.09 (0.29)	(−0.48, 0.66)	0.64
Histology, CPC	β_{22}	6.86 (3.50)	(1.84, 15.82)	1	7.50 (3.97)	(2.19, 17.78)	1
Surgery, GTR	β_{23}	2.30 (2.17)	(−1.56, 7.30)	0.88	2.58 (2.31)	(−1.36, 7.94)	0.90
Metastases, yes	β_{24}	0.73 (2.44)	(−3.85, 6.09)	0.61	0.63 (2.47)	(−4.03, 6.04)	0.59
	α_2	0.47 (0.14)	(0.22, 0.78)		0.46 (0.15)	(0.22, 0.78)	
	γ_2	0.88 (0.58)	(0.16, 2.43)		1.07 (0.74)	(0.24, 3.11)	
	ϕ	2.73 (2.57)	(0.28, 9.17)		2.54 (2.49)	(0.28, 9.00)	

†A positive value of β_{jr} corresponds to a higher hazard or, equivalently, a smaller value of T_j.

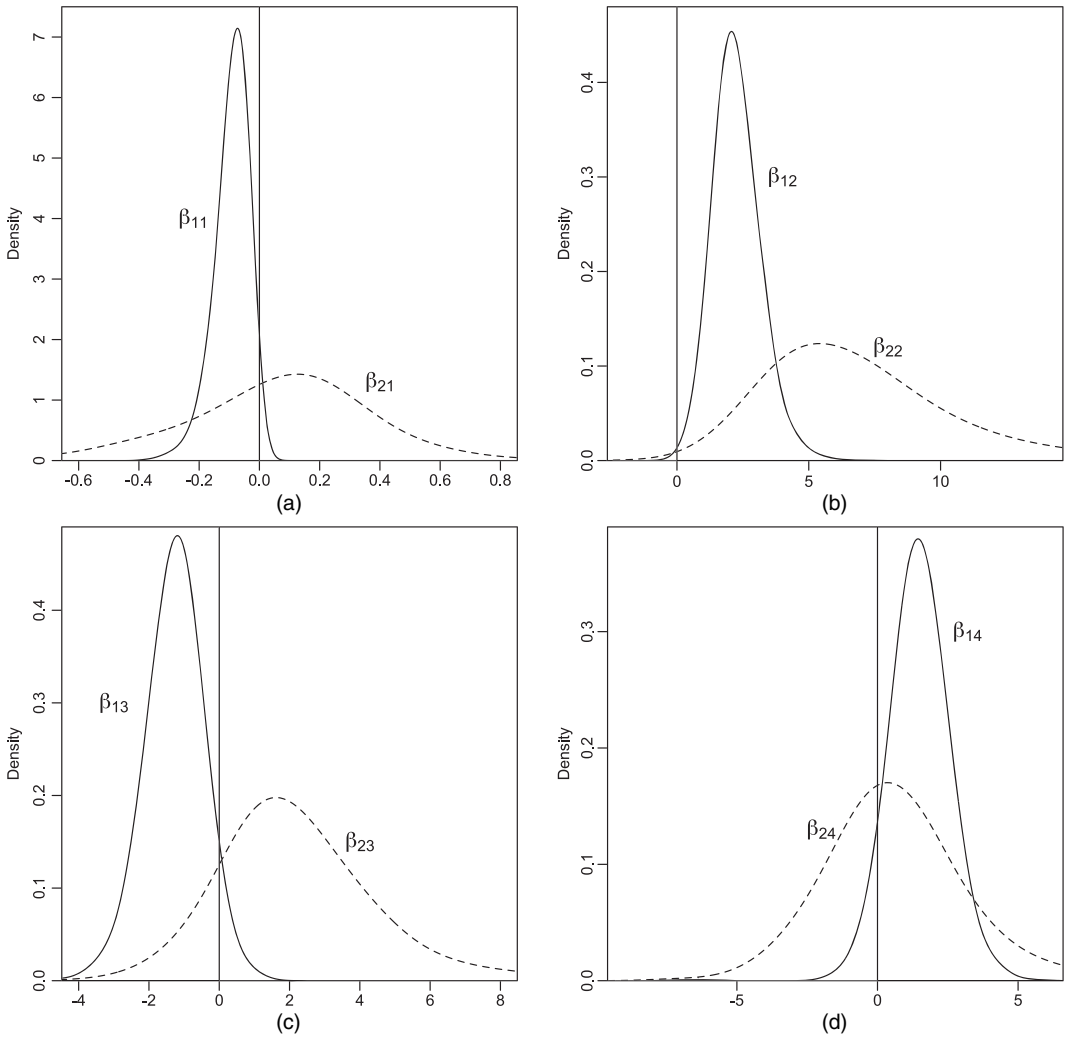

Fig. 1. Posterior distributions of regression parameters (———, regression parameters for T_1; -------, regression parameters for T_2): (a) age effect β_{11} and β_{21}; (b) CPC effect β_{12} and β_{22}; (c) GTR effect β_{13} and β_{23}; (d) metastases effect β_{14} and β_{24}

papilloma), surgery group ($z_3 = 1$ for GTR and $z_3 = 0$ if less than GTR) and primary metastases ($z_4 = 1$ if yes and $z_4 = 0$ if no). Table 1 shows the Bayesian information criterion values of the 16 models that were considered. On the basis of this analysis, the model that fits the data best has log-logistic baseline hazard for T_1 and Weibull baseline hazard for T_2. The posterior parameter estimates under this model are given in Table 2, and Fig. 1 shows the posterior distributions of the covariate parameters.

In the model, for each outcome $j = 1, 2$, a positive value of the coefficient $\beta_{j,k}$ corresponds to a larger hazard and thus on average a smaller value of T_j. Table 2 shows that, for T_1, a CPC histology and presence of metastatic disease are prognostic factors for faster progression, whereas older age and achieving a GTR with surgery are both desirable. This is shown graphically by Fig. 1. The posteriors of β_{11} for age and β_{13} for GTR are mostly below 0, and the posteriors of β_{12} for CPC and β_{14} for metastases are mostly above 0. For the covariate parameter estimates of the

distribution of T_1 in Table 2, the magnitude of the negative posterior mean effect of age is larger when using all available data compared with the complete-case analysis, with $\Pr(\beta_{11} > 0|\text{data})$ decreasing from 0.40 based on the fit using only the 106 complete cases to 0.02 based on the fit using all 780 cases. Similarly, going from the complete cases to the full data set, the magnitude of the positive posterior mean effect of metastases is larger, with $(\beta_{14} > 0|\text{data})$ increasing from 0.65 to 0.93. The posterior standard deviations of all four covariate parameters were larger in the fit using all available data, probably because of the extra variability that is introduced by the heterogeneous observations collected from the literature. In contrast, there were no substantive differences between the fits for any of the covariate parameters of T_2 by using the complete cases *versus* using all available cases. This result might be expected on the basis of the consideration that the information regarding T_2 in the combined data set essentially came from the smaller data set, since T_2 was never observed directly in the larger data set.

5. Model diagnostics and sensitivity analyses

We assessed the goodness of fit of the proposed model by using the Bayesian χ^2-test for censored data that was proposed by Cao *et al.* (2010). The Bayesian χ^2-test is based on squared differences between observed and expected frequencies for a given partition of the sample space and assesses the adequacy of the posited model by graphically comparing the posterior distribution of the squared difference with its null χ^2-distribution. Specifically, to construct the Bayesian χ^2-test statistic, we first defined a uniform residual r for each of the observed failure times, T_1^{o} and T_2^{o}, as follows. Given T_s^{o} and C,

$$r = \Pr(T_s \leqslant T_s^{\text{o}} | T_s < C, \tilde{\boldsymbol{\theta}}) = F_s(T_s^{\text{o}}|\tilde{\boldsymbol{\theta}}) / F_s(C|\tilde{\boldsymbol{\theta}}), \qquad s = 1, 2, \tag{11}$$

where $\tilde{\boldsymbol{\theta}}$ is a posterior draw of $\boldsymbol{\theta}$. For patients with observed failure times, since their censoring time C was not unobserved it was sampled from its posterior distribution according to the procedure that is described in Cao *et al.* (2010). It follows that the residuals are independent and follow a uniform distribution when the model assumed is correctly specified. We partitioned the unit interval into $K = 3$ equiprobable subintervals. Letting O_k denote the number of r-values in the kth cell, and m the total number of observed failure times, the χ^2-test statistic is given by

$$S = \sum_{k=1}^{3} \frac{(O_k - m/3)^2}{m/3}. \tag{12}$$

If the model assumed is correctly specified, S approximately follows a χ^2-distribution with 2 degrees of freedom, χ_2^2. Fig. 2 shows the histogram estimates of the posterior distribution of S, which was very close to its null distribution χ_2^2, suggesting that the model provides an adequate fit to the data.

Although the model diagnostic does not indicate any significant lack of fit, given the high rate of censoring, the power of the diagnostic is limited. Therefore, it is also useful to examine the sensitivity of our analyses to the model assumptions. An important assumption underlying our analyses is that the 674 observations from the literature and the 106 from the prospective study are exchangeable. This assumption is quite reasonable because clinical practice in treating choroid plexus tumours has not changed substantively over the time period encompassing the two data sets. Still, it is important to investigate potential effects of between-study heterogeneity. Although one may attempt to account for possible between-study heterogeneity by specifying distinct regression parameters for the prospective study and the literature review data in each of the marginal regression models of T_1 and T_2, unfortunately such a model is not identifiable. This is because, since only $T_1 + T_2$ is observed in the literature review data set, the marginal

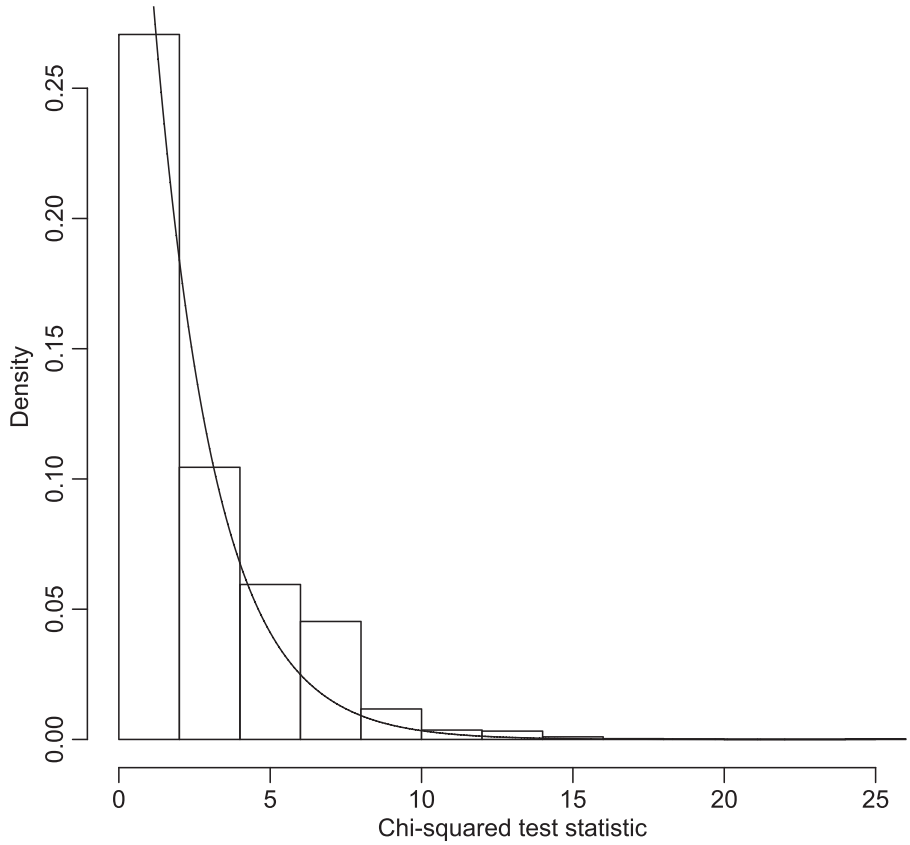

Fig. 2. Histogram estimate of the posterior distribution of the χ^2-test statistic S: ———, χ^2-distribution with 2 degrees of freedom for reference

distributions of T_1 and T_2 are not identifiable for the literature review data. Intuitively, adding an arbitrary value Δ to T_1 and then subtracting Δ from T_2 does not change the value of $T_1 + T_2$. Consequently, parameters that characterize the between-study effects are not identifiable.

To address this issue, we conducted a sensitivity analysis to investigate how the inferences are affected when the homogeneity assumption is violated. Let λ_{jk}, $j, k = 1, 2$, denote the hazard of T_j for the literature data set ($k = 1$) and the prospective study ($k = 2$). Our sensitivity analysis is based on the following Bayesian hierarchical model for the marginal distributions of T_1 and T_2. Denoting $\eta_{jk} = \beta_{j1k} Z_1 + \ldots + \beta_{jqk} Z_q$, the model for the hazard of T_j in data set k for a patient with covariates $\mathbf{Z}$ is

$$\begin{aligned} \lambda_{jk}(t|\mathbf{Z}, \boldsymbol{\beta}) &= \exp(\eta_{jk})\, \lambda_0\{t \exp(\eta_{jk})\}, \\ \beta_{jrk} &\sim N(\tilde{\beta}_{jr}, \tilde{\sigma}^2_{jr}), \qquad r = 1, \ldots, q, \\ \tilde{\beta}_{jr} &\propto 1 \end{aligned}$$

where $\tilde{\sigma}^2_{jr}$ is a known parameter that shrinks the literature data set parameter β_{jr1} and the prospective study parameter β_{jr2} towards the common hyperparameter $\tilde{\beta}_{jr}$, i.e. $\tilde{\sigma}^2_{jr}$ characterizes the heterogeneity between the literature data set and the prospective study. A large value of $\tilde{\sigma}^2_{jr}$ corresponds to high between-study heterogeneity, whereas if $\tilde{\sigma}^2_{jr} \to 0$ the covariate effects are homogeneous between the two data sets, i.e. $\beta_{jr1} = \beta_{jr2}$ for all j and r. To accommodate

different scales of $\{\beta_{jrk}\}$ and to facilitate the sensitivity analysis, we set $\tilde{\sigma}_{jr} = \tau\hat{\beta}_{jr}$ where $\hat{\beta}_{jr}$ is the estimate of β_{jr} under the homogeneity assumption (see Table 2) and τ can be interpreted as the coefficient of variation, i.e. the ratio of the standard error to the mean. We fitted the above Bayesian hierarchical model, with the Clayton copula (6), using a range of values of τ. Fig. 3 shows how the posterior mean estimates of the β_{jr}s vary with τ, the between-study heterogeneity. Although some covariate effects (e.g. β_{12} and β_{22} for histology) appear relatively more sensitive to τ than others (e.g. β_{11} and β_{21} for age), overall the covariate effects are not particularly sensitive to between-study heterogeneity.

To investigate the sensitivity of our results to the assumed Clayton copula, we also fitted the data by using the Gumbel–Hougaard copula (Hougaard, 1986),

$$S(t_1, t_2|\mathbf{Z}, \boldsymbol{\theta}) = \exp\{-([-\log\{S_1(t_1|\mathbf{Z}, \boldsymbol{\theta})\}]^{\varphi} + [-\log\{S_2(t_2|\mathbf{Z}, \boldsymbol{\theta})\}]^{\varphi})^{1/\varphi}\}.$$

We chose this copula because its functional form is very different from that of the Clayton copula. Under this model, the association parameter φ is related to Kendall's τ via the formula $\tau = 1 - 1/\varphi$. A summary of the fitted model under the Gumbel–Hougaard copula model is given in Table 3. With the exceptions of γ_2 and β_{24}, the posterior parameter estimates are very similar to those obtained under the Clayton copula. This indicates that, for this data set, inferences are not sensitive to the choice of copula that is used to obtain a bivariate survival model for the given marginals. Although the estimate of the association parameter φ under the Gumbel–Hougaard copula model is numerically similar to that of the association parameter

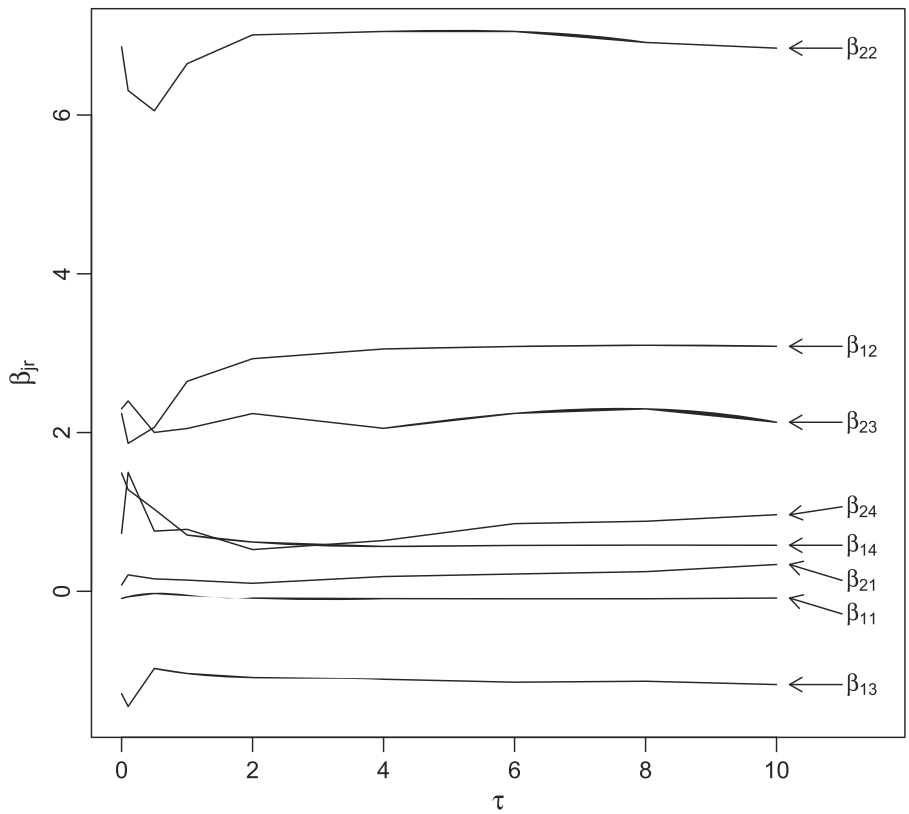

Fig. 3. Sensitivity analysis of covariate effects with respect to the study heterogeneity

Table 3. Sensitivity analyses†

	β_{11}	β_{12}	β_{13}	β_{14}	α_1	γ_1	β_{21}	β_{22}	β_{23}	β_{24}	α_2	γ_2	ϕ	φ
Gumbel–Hougaard copula model using gamma priors with $a_j = b_j = 0.01$														
Mean	−0.09	2.26	−1.25	1.30	0.67	0.04	0.05	6.65	1.80	3.30	0.53	0.24	—	1.97
Standard error	0.06	0.91	0.81	1.01	0.14	0.02	0.22	2.83	2.13	2.57	0.20	0.31	—	0.70
Clayton copula model using gamma priors with $a_j = b_j = 0.1$														
Mean	−0.09	2.28	−1.31	1.45	0.68	0.04	0.10	6.93	2.22	0.70	0.47	0.82	2.36	—
Standard error	0.14	0.90	0.81	1.01	0.28	0.02	0.06	3.50	2.20	2.47	0.14	0.55	2.29	—
Clayton copula model using gamma priors with $a_j = b_j = 0.01$														
Mean	−0.09	2.24	−1.29	1.49	0.69	0.03	0.08	6.86	2.30	0.73	0.47	0.88	2.73	—
Standard error	0.06	0.87	0.82	1.02	0.14	0.02	0.28	3.50	2.17	2.44	0.14	0.58	2.57	—
Clayton copula model using gamma priors with $a_j = b_j = 0.0001$														
Mean	−0.09	2.27	−1.30	1.45	0.68	0.04	0.10	6.85	2.27	0.73	0.47	0.84	2.63	—
Standard error	0.06	0.89	0.81	1.01	0.14	0.02	0.29	3.43	2.21	2.46	0.14	0.58	2.56	—

†To assess sensitivity to the assumed variance 100 for the gamma priors ($a_j = b_j = 0.01$), the model was refitted by using gamma priors for the shape and scale parameters assuming variances of 10 ($a_j = b_j = 0.1$) or 10000 ($a_j = b_j = 0.0001$). To assess sensitivity to the assumed Clayton copula, the model was refitted by using a Gumbel–Hougaard copula. To facilitate comparisons, the estimates under the Clayton copula with gamma priors from Table 2 are repeated.

ϕ under the Clayton copula model, the estimated associations between T_1 and T_2 are quite different under the two models. This is because the association parameters of the two models have different meanings, with Kendall's τ-value 0.16 under the Clayton copula and 0.49 under the Gumbel–Hougaard copula. Such a difference is not completely unexpected, however, since data typically contain much less information about association parameters compared with covariate effect parameters. In the present setting, information about the association parameter comes mainly from the small data set of 106 patients for whom both T_1 and T_2 were observed. Moreover, given the small number of events in this data set, it is difficult to estimate the association parameter reliably, as demonstrated by the large posterior standard deviations of these parameters.

We conducted another sensitivity analysis by refitting the model, assuming the Clayton copula, for each of a series of values of the prior mean of ϕ. This strategy was advocated by Rotnitzky *et al.* (1998, 2001). We assumed informative gamma distributions for ϕ with a small variance of 0.004 and the mean fixed, successively, at the values 0.1, 0.2, 0.5, 1, 2, 4, 8 and 16. Fig. 4 shows the resulting posterior mean model parameter values as functions of the prior mean of ϕ. Fig. 4 shows that all parameters, except γ_2, are robust to the prior mean of ϕ. The sensitivity of γ_2 to the prior mean of ϕ is consistent with the observation that the value of $\hat{\gamma}_2$ is different under the Clayton and Gumbel–Hougaard copulas, since these two models yielded different estimates of the association between T_1 and T_2 in terms of Kendall's τ.

We also assessed the sensitivity of our results to prior specifications of the location and scale parameters under the log-logistic model and to the shape and scale parameters under the Weibull model. To do this, we considered two more priors for these positive parameters: a relatively informative prior Ga(0.1, 0.1), which has variance 10, and a very diffusive prior Ga(0.0001, 0.0001), which has variance 10000. The results under these priors, which are given in Table 3, are quite similar to those displayed in Table 2. This suggests that our results are not sensitive to the gamma prior's variances in this range, when the prior mean is set equal to 1.

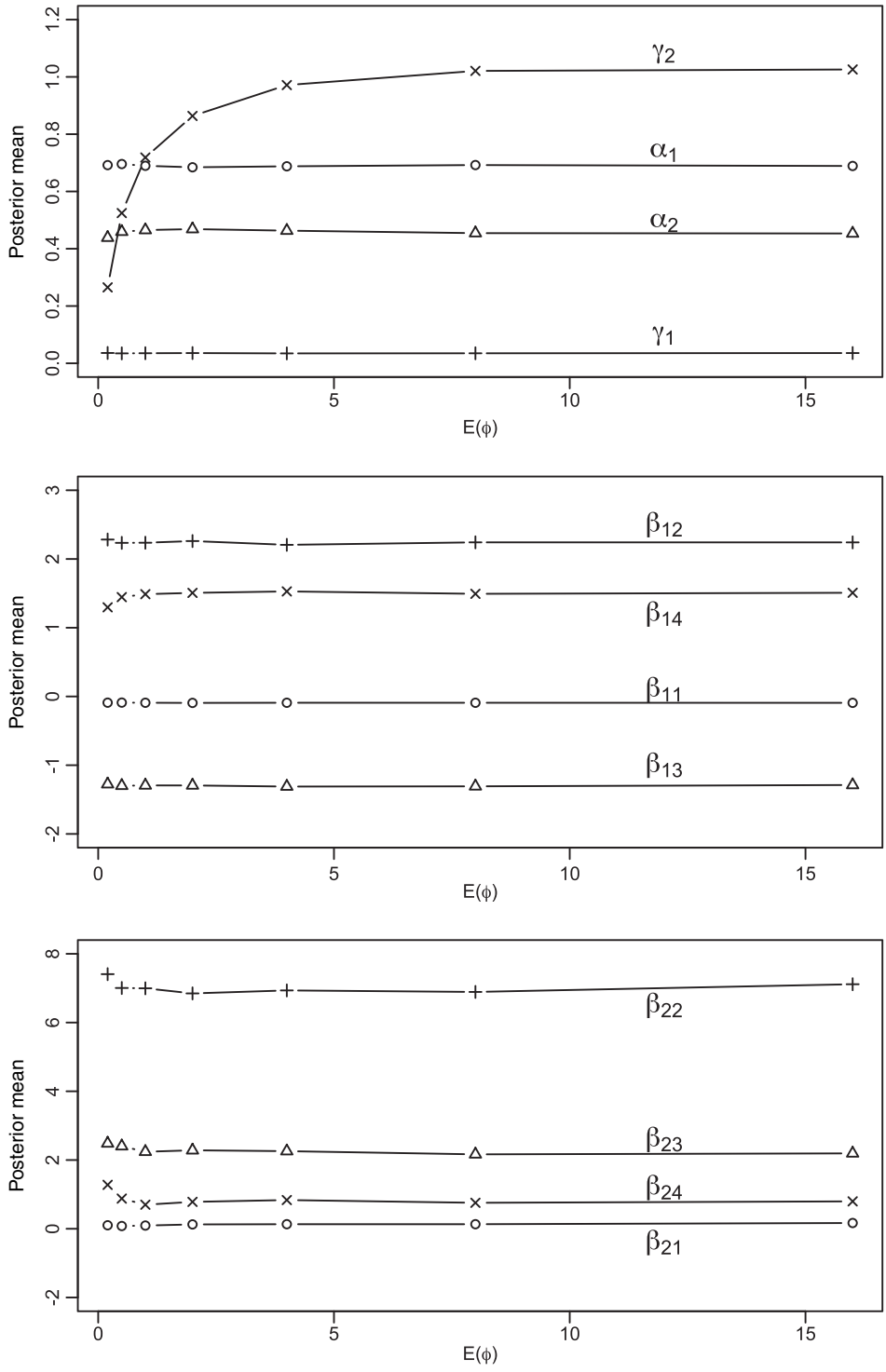

Fig. 4. Sensitivity analysis by assigning informative gamma distributions with a small variance of 0.004 and mean fixed successively, at the values 0.1, 0.2, 0.5, 1, 2, 4, 8 and 16, and as the prior distribution of ϕ

Table 4. Simulation results

	α_1	λ_1	α_2	λ_2	β_1	β_2	β_3	β_4	ϕ
True parameter value	0.45	0.03	0.30	0.12	0.50	0.50	0.50	0.25	1.00
Empirical bias	0.002	0.005	0.001	−0.006	−0.031	−0.044	−0.064	−0.034	−0.066
Standard error	0.076	0.014	0.052	0.040	0.483	0.893	0.589	0.992	0.899
Coverage probability	0.931	0.940	0.942	0.935	0.941	0.948	0.951	0.961	0.985

6. Simulation study

We conducted a simulation study to evaluate the performance of the proposed method when the data are heavily censored, as in the case of the motivating example. We generated bivariate time-to-event data (T_1, T_2) based on the Clayton copula with T_1 and T_2 marginally following the log-logistic and Weibull AFT models respectively. In the AFT models, we included two covariates: a continuous covariate Z_1 generated from a standard normal distribution and a binary covariate Z_2 generated from a Bernoulli distribution with probability parameter 0.5. In the log-logistic AFT model (10) for T_1, we set $\alpha_1 = 0.45$, $\lambda_1 = 0.03$ and the two regression coefficients $\beta_1 = \beta_2 = 0.5$. In the Weibull AFT model (8) for T_2, we set $\alpha_2 = 0.3$, $\lambda_2 = 0.12$ and the two regression coefficients $\beta_3 = 0.5$ and $\beta_4 = 0.25$. We set the copula association parameter $\phi = 1$, corresponding to moderate correlation between T_1 and T_2 with Kendall's τ equal to $\frac{1}{3}$. We assumed a total of 206 patients, with 106 patients having observed or censored values of T_1 and T_2 and the remaining 100 patients having missing progression statuses. We chose a uniform censoring distribution with the percentage of censoring in the simulated data matching that seen in the brain tumour data, i.e., in the simulated data, on average about 20 patients had T_1 observed (i.e. 81.1% of the T_1-values were censored), 10 patients had T_2 observed (i.e. 90.6% of the T_2-values were censored) and 28 patients had $T = T_1 + T_2$ observed (i.e. 72.0% of the T-values were censored). We simulated 1000 data sets. Table 4 summarizes the simulation results, including the empirical bias, standard error and coverage probability of the 95% credible interval. The simulations show that the estimates of all parameters had small biases, with the coverage of all 95% credible intervals, except for that of ϕ, close to the nominal value. The 98.5% mean coverage of the posterior credible interval for the association parameter is not surprising, given the general difficulty of estimating such parameters reliably, as well as the structure and high level of missingness that are imposed in the simulation study. These simulation results suggest that the methodology proposed performs well with heavily censored data of the form that is considered here.

7. Discussion

We have proposed a Bayesian model-based method to estimate PFS when the progression status of some subjects is unknown. Our approach models the marginal distributions of the time to progression and the time from progression to death separately by using AFT models and then links these marginals to obtain a joint distribution by using a copula. Under the Bayesian paradigm, our method incorporates all available information, including both completely observed and partially observed time-to-event data, to make inferences about PFS time. Our sensitivity analyses indicated that the approach proposed is robust to the choice of both the copula model and the prior specification in settings with this type of missing value structure, even when there are high levels of censoring and missingness.

Acknowledgements

Ying Yuan and Peter Thall acknowledge support from National Cancer Institute grants R01 CA154591 and R01 CA83932 respectively.

References

Cao, J., Moosman, A. and Johnson, A. E. (2010) A Bayesian chi-squared goodness-of-fit test for censored data models. *Biometrics*, **66**, 426–434.

Clayton, D. G. (1978) A model for association in bivariate life tables and its application in epidemiological studies of familial tendency in chronic disease incidence. *Biometrika*, **65**, 141–151.

Cox, D. R. (1972) Regression models and life-tables (with discussion). *J. R. Statist. Soc.* B, **34**, 187–220.

Dinse, G. E. (1982) Nonparametric estimation for partially-complete time and type of failure data. *Biometrics*, **38**, 417–431.

Fine, J. P., Jiang, H. and Chappell, R. (2001) On semi-competing risks data. *Biometrika*, **88**, 907–919.

Gijbels, I., Lin, D. and Ying, Z. (2007) Non- and semi-parametric analysis of failure time data with missing failure indicators. *IMS Lect. Notes*, **54**, 203–223.

Gilks, W. R., Best, N. G. and Tan, K. K. C. (1995) Adaptive rejection Metropolis sampling within Gibbs sampling. *Appl. Statist.*, **44**, 455–472.

Goetghebeur, E. and Ryan, L. (1990) A modified log rank test for competing risks with missing failure type. *Biometrika*, **77**, 207–211.

Goetghebeur, E. and Ryan, L. (1995) Analysis of competing risks survival data when some failure types are missing. *Biometrika*, **82**, 821–833.

Hougaard, P. (1986) A class of multivariate failure time distributions. *Biometrika*, **73**, 671–678.

Ibrahim, J. G., Chen, M.-H. and Sinha, D. (2001) *Bayesian Survival Analysis*. New York: Springer.

Klein, J. P. and Moeschberger, M. L. (2003) *Survival Analysis: Methods for Censored and Truncated Data*, 2nd edn. New York: Springer.

Lo, S. H. (1991) Estimating a survival function with incomplete cause-of-death data. *J. Multiv. Anal.*, **39**, 217–235.

Lu, K. and Tsiatis, A. (2001) Multiple imputation methods for estimating regression coefficients in the competing risks model with missing cause of failure. *Biometrics*, **57**, 1191–1197.

Piessens, R., de Doncker-Kapenga, E., Uberhuber, C. W. and Kahaner, D. K. (1983) *QUAD-PACK: a Subroutine Package for Automatic Integration*. New York: Springer.

Rotnitzky, A., Robins, J. M. and Scharfstein, D. O. (1998) Semiparametric regression for repeated outcomes with non-ignorable non-response. *J. Am. Statist. Ass.*, **93**, 1321–1339.

Rotnitzky, A., Scharfstein, D., Su, T. L. and Robins, J. (2001) Methods for conducting sensitivity analysis of trials with potentially nonignorable competing causes of censoring. *Biometrics*, **57**, 103–113.

Schwarz, G. (1978) Estimating the dimension of a model. *Ann. Statist.*, **6**, 461–464.

Shih, J. H. and Louis, T. (1995) Inference on the association parameter in copula models for bivariate survival data. *Biometrics*, **51**, 1384–1399.

Therneau, T. M. and Grambsch, P. M. (2000) *Modeling Survival Data: Extending the Cox Model*. New York: Springer.

Tsiatis, A., Davidian, M. and McNeney, B. (2002) Multiple imputation methods for testing treatment differences in survival distributions with missing cause of failure. *Biometrika*, **89**, 238–244.

Wolff, J. E., Sajedi, M., Brant, R., Coppes, M. J. and Egeler, R. M. (2002) Choroid plexus tumours. *Br. J. Cancer*, **87**, 1086–1091.

Wolff, J. E., Sajedi, M., Coppes, M. J., Anderson, R. A. and Egeler, R. M. (1999) Radiation therapy and survival in choroid plexus carcinoma. *Lancet*, **353**, 21–26.

Wrede, B., Hasselblatt, M., Peters, O., Thall, P. F., Kutluk, T., Moghrabi, A., Mahajan, A., Rutkowski, S., Diez, B., Wang, X., Pietsch, T., Kortmann, R. D., Paulus, W., Jeibmann, A. and Wolff, J. E. (2009) Atypical choroid plexus papilloma: clinical experience in the CPT-SIOP-2000 study. *J Neuroncol.*, **95**, 383–392.