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Mixture and non-mixture cure fraction models based on the generalized modified Weibull distribution with an application to gastric cancer data

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ABSTRACT

The cure fraction models are usually used to model lifetime time data with long-term survivors. In the present article, we introduce a Bayesian analysis of the four-parameter generalized modified Weibull (GMW) distribution in presence of cure fraction, censored data and covariates. In order to include the proportion of "cured" patients, mixture and non-mixture formulation models are considered. To demonstrate the ability of using this model in the analysis of real data, we consider an application to data from patients with gastric adenocarcinoma. Inferences are obtained by using MCMC (Markov Chain Monte Carlo) methods.

1. Introduction

In the lifetime data analysis, researchers commonly use standard non-parametrical techniques, such as Kaplan–Meier estimators or log-rank test [1], semi-parametrical models (for example, proportional hazards model in presence of covariates [2] or standard parametrical models using some popular lifetime distributions [3]. One of the distributions widely used in cancer research is the Weibull distribution [4], mainly due to the flexibility of its hazard function and the facility to estimate its parameters. However, in medical lifetime research, we usually have data sets which require more sophisticated parametric models. To achieve this goal, new classes of parametric distributions based on extensions of the Weibull distribution have been introduced in the literature. As special cases, we have the exponentiated Weibull (EW) [5,6], the generalized modified Weibull [7] and the log-beta Weibull distributions [8]. In addition, other common situation in the analysis of time-to-event data, particularly in cancer research, occurs when it is expected that a fraction of individuals will not experience the event of interest. In this case, it is assumed that the

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studied population is a mixture of susceptible individuals who experience the event of interest and non-susceptible individuals that supposedly will never experience it. The presence of immune or cured individuals in a data set is usually suggested by a Kaplan–Meier plot of the survival function, which shows a long and stable plateau with heavy censoring at the extreme right of the plot [9]. Different parametric and non-parametric approaches have been considered to model the proportion of immunes and interested readers can refer, for example, to Boag [10], Berkson [11], Haybittle [12], Meeker [13], Gamel et al. [14], Ghitany and Maller [15], Copas and Heydary [16], Ng and McLachlan [17], De Angelis et al. [18], Peng and Dear [19], Lambert et al. [20] and Yu et al. [21]. In addition, Bayesian inference methods for survival data with a surviving fraction were introduced by some authors such as Castro et al. [22], Chen et al. [23], Ibrahim et al. [24], Kim et al. [25] and Seltman et al. [26]. As a motivation for this paper, we consider a gastric cancer lifetime data introduced by Jácome et al. [27]. For a statistical analysis of this data set, we assume the four-parameter generalized modified Weibull distribution (GMW) [7] in presence of cure fraction, censored data and covariates. We implemented the statistical model under a Bayesian framework, where the parameter estimation is based on Markov Chain Monte Carlo (MCMC) techniques. We organize the rest of the paper as follows. The gastric cancer data set is described in Section 2. In Section 3, we describe the mixture and non-mixture cure fraction models, the GMW distribution [7] and some of their special cases. In this section we also introduce the formulation of the likelihood functions considering mixture and non-mixture cure fraction models based on the GMW distribution. The Bayesian analysis for the proposed models is described in Section 4. The obtained results of the Bayesian analysis for this medical data set, considering the proposed mixture and non-mixture models, are presented in Section 5. Finally, in Section 6, we present a discussion of the obtained results.

2. The gastric cancer data

Gastric cancer is one of the leading causes of cancer-related death [28] and the mucosal resection is accepted as a treatment option for early cases of the disease. In a review of the literature [29], it was found that the 5-year survival rate following all type of resections has increased significantly from 20.7% before 1970 to 28.4% before 1990. In addition, the 5-year survival rate following curative or radical resection has risen from 37.6 to 55.4% over the same period. Thus, new technologies to optimize medical decisions and the development of new therapies are of great importance to improve survival in gastric cancer. Jácome et al. [27] conducted a retrospective study in patients with gastric adenocarcinoma who underwent curative resection with D2 lymphadenectomy in the Barretos Cancer Hospital (Hospital de Câncer de Barretos, Brazil) between January 2002 and December 2007. The effectiveness of lymphadenectomy for cure in patients with early gastric cancer and lymph node metastasis is discussed by Okamura et al. [30]. It is known that adjuvant chemoradiotherapy (CRT) is the standard treatment in Western countries for gastric cancer patients submitted to curative resection. Aiming a more precise evaluation of the treatment, Jácome et al. [27] considered 185 patients with stage II to IV gastric adenocarcinoma with no distant metastases and compared the 3-year overall survival of the two treatments, that is, adjuvant CRT versus resection alone. In the present article, as an illustration for the use of the GMW distribution, we consider the entire data set obtained from this study, considering 201 patients of different clinical stages. Table 1 shows this data set, which includes 76 patients that received adjuvant CRT and 125 that received resection alone. The data in this table refer to the times until death in months since surgery, where a plus symbol (+) indicates censored data. We observe that we have 53.2% of censored data, that is, 57.9% if we consider the patients treated with CRT and 50.4% if we consider the patients treated with resection alone.

The Kaplan–Meier estimate of the survival function for the gastric cancer data is given in Fig. 1, where the presence of a plateau near to 0.5 observed in the graph presented in panel (a) suggests that models that ignore the proportion p of long-term survivors will not be suitable for these data. The graph presented in panel (b) of Fig. 1 describes the empiric survival functions for each type of treatment, where the presence of stable plateaus at the right tail of the plot also assures the adequacy of the cure fraction model approach.

3. Models

3.1. *Mixture and non-mixture cure fraction models*

Following Maller and Zhou [31], a mixture model for lifetime data sets assumes that the probability of the time-to-event to be greater than a specified time t is given by the survival function

$$S(t) = p + (1-p)S_0(t), \tag{1}$$

where p is a parameter which represents the proportion of "long-term survivors" or "cured patients", regarding the event of interest ($0<p<1$), and $S_0(t)$ is the baseline survival function for the susceptible individuals [10]. Common choices for $S_0(t)$ are the Gompertz, exponential and Weibull distributions. The probability density function for the lifetime T is

$$f(t) = \frac{dF(t)}{dt} = (1-p)f_0(t),$$

where $F(t) = 1 - S(t)$ and $f_0(t)$ is the baseline probability density function for the susceptible individuals. Considering a random sample (t_i, δ_i) of size n, $i = 1, \ldots, n$, the contribution of the ith subject for the likelihood function is given by

$$L_i = [f(t_i)]^{\delta_i}[S(t_i)]^{1-\delta_i} = [(1-p)f_0(t_i)]^{\delta_i}[p + (1-p)S_0(t_i)]^{1-\delta_i},$$

where δ_i is a censoring indicator variable, that is, $\delta_i = 1$ for an observed lifetime and $\delta_i = 0$ for a censored lifetime. Alternatively, a non-mixture formulation has been suggested by several authors [32,33]. This model defines an asymptote for

Table 1 – Data from 76 patients received adjuvant CRT and 125 receiving resection alone. A plus symbol (+) indicates censored data.

Treatment	Months since surgery
CRT	5.76, 7.89, 8.85, 8.95, 9.05, 9.47, 10.72, 11.97, 12.5, 12.83, 13.09, 13.49, 13.78, 13.82, 14.7, 14.77, 16.38, 16.51, 17.07, 17.14, 17.34+, 17.7, 18.39, 19.21, 19.38+, 20.49+, 20.76+, 21.02, 22.86, 23.39+, 23.82+, 24.21, 24.21+, 24.31, 24.28+, 24.97+, 25.23, 25.33+, 25.56+, 25.59+, 25.76+, 25.79, 25.79+, 26.05, 27.89+, 28.22+, 28.59, 28.65+, 29.08+, 29.31+, 30.26, 30.69+, 30.95+, 31.64+, 31.84+, 32.4+, 32.47+, 32.53+, 33.88+,34.74+, 34.9+, 35.72+, 35.89+, 36.0+,36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+
Surgery alone	0.1, 0.2, 0.23, 0.26, 0.3, 0.33, 0.49, 0.53, 0.56, 0.63, 0.66, 0.66, 1.18, 1.45+, 1.61, 1.78, 2.63+, 2.73, 2.8, 2.89, 2.96, 3.32, 3.49+, 4.01, 4.54, 4.67, 4.67, 4.93, 6.15, 6.55+, 6.91, 7.17, 7.7, 7.93+, 8.32, 8.36, 8.39, 8.78, 8.91, 9.28, 9.7, 10.03, 10.2, 10.53, 10.76, 11.41, 11.88, 12.5, 13.13+, 13.95, 14.01, 14.05, 14.34, 14.38+, 15.43, 15.76+, 16.09, 16.18, 16.94, 16.94+, 17.14, 17.24, 17.43, 18.62, 19.14, 19.44, 19.84+, 19.93, 20.49+, 21.38+, 21.48, 21.84+, 21.88+, 22.14, 22.99+, 23.39+, 23.52+, 23.55+, 23.85+, 24.01+, 24.57+, 24.8+, 25.26+, 25.3, 25.33+, 25.36+, 26.15+, 26.32, 26.32+, 26.78+, 27.37+, 28.98+, 29.28+, 29.31+, 29.97+, 30.16+, 30.49+, 30.63+, 31.38+, 31.68+, 32.5+, 32.8+, 33.09+, 33.36+, 33.65+, 33.91+, 34.08+, 34.21+, 34.41+, 35.0+, 35.03+, 35.2+, 35.3+, 35.59+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+, 36.0+

the cumulative hazard and hence for the cure fraction. In this case, the survival function is given by

$$S(t) = p^{F_0(t)} = \exp[\ln(p)F_0(t)], \tag{2}$$

where $F_0(t) = 1 - S_0(t)$. Assuming this model, the contribution of the ith subject for the likelihood function is given by

$$L_i = [h(t_i)]^{\delta_i} S(t_i) = [-(\ln p) f_0(t_i)]^{\delta_i} \exp[\ln(p)F_0(t_i)],$$

where $h(t) = f(t)/S(t)$ is the hazard function. In the literature, an extensive list of articles on modeling survival data including long-term survivors can be found, and interested readers can refer to Farewell [34], Tsodikov [35], Sposto [36], Cancho et al. [37], Mazucheli et al. [38], Rodrigues et al. [39], Perdoná and Louzada-Neto [40], among several others.

3.2. *The generalized modified Weibull distribution*

Let us assume a generalized modified Weibull (GMW) distribution for the susceptible individuals with probability density function given by

$$f_0(t) = \frac{\alpha\beta t^{\gamma-1}(\gamma + \lambda t)\exp[\lambda t - \alpha t^{\gamma}\exp(\lambda t)]}{\{1 - \exp[-\alpha t^{\gamma}\exp(\lambda t)]\}^{1-\beta}}, \tag{3}$$

$t > 0$, where $\alpha > 0$, $\beta > 0$, $\gamma > 0$ and $\lambda > 0$. This four-parameter distribution was introduced by Carrasco et al. [7], and it is flexible to accommodate many forms of the hazard rate function, including bathtub-shaped failure rates data. The respective survival function is given by

$$S_0(t) = 1 - \{1 - \exp[-\alpha t^{\gamma}\exp(\lambda t)]\}^{\beta}. \tag{4}$$

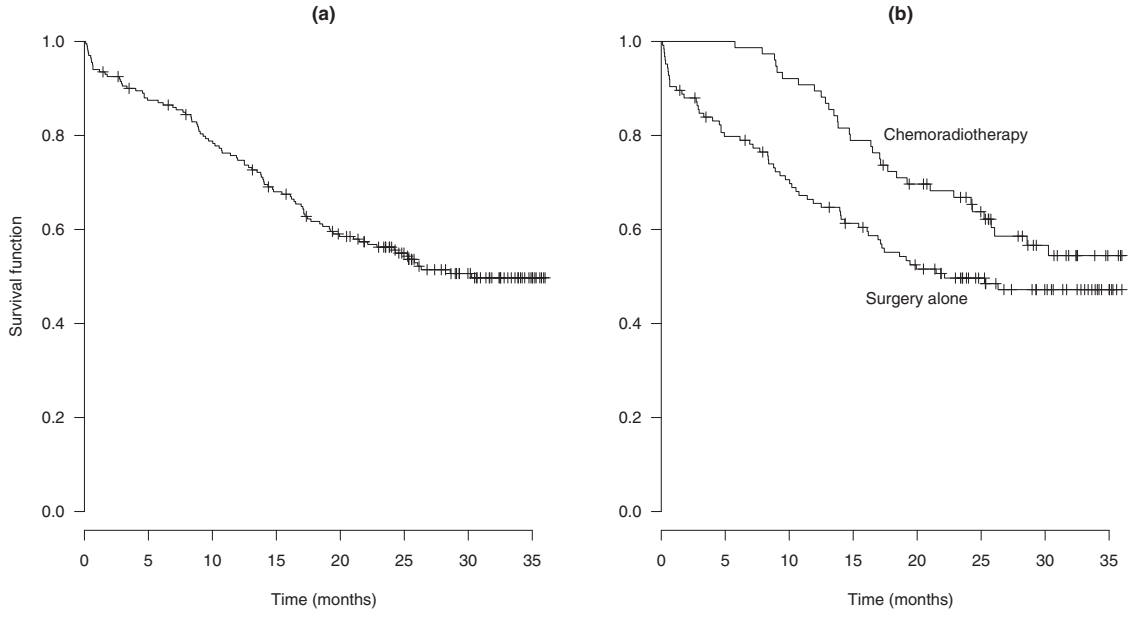

Fig. 1 – (a) Kaplan–Meier estimate of the overall survival function for the gastric cancer data. (b) Survival functions for each type of therapy.

The GMW distribution is denoted by $X \sim GMW(\alpha, \beta, \gamma, \lambda)$. The α parameter is a scale parameter and β and γ are shape parameters. Following Carrasco et al. [7], the λ parameter is related to an accelerating factor in the imperfection time and it works as a factor of fragility in the survival of the individual when the time increases. The corresponding hazard function for the lifetimes is given by

$$h_0(t) = \frac{\alpha\beta t^{\gamma-1}(\gamma+\lambda t)\exp[\lambda t - \alpha t^{\gamma}\exp(\lambda t)]\{1-\exp[-\alpha t^{\gamma}\exp(\lambda t)]\}^{\beta-1}}{1-\{1-\exp[-\alpha t^{\gamma}\exp(\lambda t)]\}^{\beta}}.$$

Several standard existing distributions are special cases of the four-parameter GMW distribution [7], given as follows:

(a) **Weibull distribution:** when $\lambda = 0$ and $\beta = 1$, the expression (3) is the probability density function of a two-parameter Weibull distribution.
(b) **Exponential distribution:** when $\lambda = 0$, $\beta = 1$ and $\gamma = 1$, the expression (3) is reduced to the probability density function of an exponential distribution. This distribution is characterized by a constant hazard function given by $h_0(t) = \alpha$.
(c) **Rayleigh distribution:** when $\lambda = 0$, $\beta = 1$ and $\gamma = 2$, the expression (3) is reduced to the probability density function of a Rayleigh distribution.
(d) **Extreme value distribution:** this type I extreme value distribution [41] is a special case of the GMW distribution with $\beta = 1$ and $\gamma = 0$. However, when considering survival outcomes some caution is required because its support spreads over the whole real line [42]. From (4), we note that its respective survival function is given by $S_0(t) = exp(-\alpha e^{\lambda t})$. Thus, we have $S_0(t) = e^{-\alpha}$ when $t = 0$, that is, $S_0(t = 0)$ is not equal to 1, as it is expected by considering survival data. Despite these problems, we also consider this distribution in the present study.
(e) **Exponentiated Weibull distribution (EW):** the EW distribution [5,6] is a special case of the GMW distribution with $\lambda = 0$. The statistical properties of the EW distribution are presented by Nassar and Eissa [43].
(f) **Exponentiated exponential distribution (EE):** the EE distribution [44] is a special case of the GMW distribution with $\lambda = 0$ and $\gamma = 1$. Some properties of the EE distribution are discussed by Gupta and Kundu [45].
(g) **Generalized Rayleigh distribution (GR):** the GR distribution [46] is a special case of the GMW distribution with $\lambda = 0$ and $\gamma = 2$.
(h) **Modified Weibull distribution (MW):** Lai et al. [42] introduced the three-parameter MW distribution, which is a special case of the GMW distribution with $\beta = 1$. Maximum-likelihood estimation of the parameters and statistical properties of the MW distribution are presented by Sarhan and Zaindin [47].

Carrasco et al. [7] introduced general formulas for the moments of the GMW distribution and also commented on obtaining maximum likelihood estimators for the parameters of the model and hypothesis tests of interest.

3.3. *The log-likelihood functions*

Assuming the mixture model (1), the log-likelihood function for $\boldsymbol{\theta} = (p, \alpha, \beta, \gamma, \lambda)$ is given by

$$\begin{aligned} l(\boldsymbol{\theta}) = {} & \sum_{i=1}^{n}[\ln(1-p)]\delta_i + (\ln\alpha)\sum_{i=1}^{n}\delta_i + \sum_{i=1}^{n}(\ln\beta)\delta_i + (\gamma-1)\sum_{i=1}^{n}\delta_i \ln t_i \\ & + \sum_{i=1}^{n}\delta_i \ln(\gamma+\lambda t_i) + \lambda\sum_{i=1}^{n}\delta_i t_i - \alpha\sum_{i=1}^{n}\delta_i t_i^{\gamma}\exp(\lambda t_i) \\ & - \sum_{i=1}^{n}(1-\beta)\delta_i \ln\{1-\exp[-\alpha t_i^{\gamma}\exp(\lambda t_i)]\} \\ & + \sum_{i=1}^{n}(1-\delta_i)\ln[p + (1-p)(1-\{1-\exp[-\alpha t_i^{\gamma}\exp(\lambda t_i)]\}^{\beta})]. \end{aligned} \quad (5)$$

Moreover, assuming the non-mixture model (2), the log-likelihood function for $\boldsymbol{\theta}$ is given by

$$\begin{aligned} l(\boldsymbol{\theta}) = {} & \sum_{i=1}^{n}\ln(-\ln p)\delta_i + (\ln\alpha)\sum_{i=1}^{n}\delta_i + \sum_{i=1}^{n}(\ln\beta)\delta_i + (\gamma-1)\sum_{i=1}^{n}\delta_i \ln t_i \\ & + \sum_{i=1}^{n}\delta_i \ln(\gamma+\lambda t_i) + \lambda\sum_{i=1}^{n}\delta_i t_i - \alpha\sum_{i=1}^{n}\delta_i t_i^{\gamma}\exp(\lambda t_i) \\ & - \sum_{i=1}^{n}(1-\beta)\delta_i \ln\{1-\exp[-\alpha t_i^{\gamma}\exp(\lambda t_i)]\} \\ & + \sum_{i=1}^{n}\{\ln(p)\{1-\exp[-\alpha t_i^{\gamma}\exp(\lambda t_i)]\}^{\beta}\}. \end{aligned} \quad (6)$$

In addition for these models, we also assume that the parameter p could be related to a vector of covariates $\mathbf{x}_i$ by replacing p in the expressions (5) and (6) by

$$p_i = \frac{\exp\left(\mathbf{x}_i^T\boldsymbol{\eta}\right)}{1+\exp\left(\mathbf{x}_i^T\boldsymbol{\eta}\right)},$$

where $\boldsymbol{\eta}$ is a vector of unknown parameters.

4. Bayesian inference

The joint posterior distribution for the parameters of the model is obtained via Bayes theorem [48] by combining the joint prior distribution with the likelihood function for $\boldsymbol{\theta}$. Although the joint posterior distribution for the parameters of the proposed model is of great complexity, samples of the joint posterior distribution can be generated using some existing MCMC (Markov Chain Monte Carlo) simulation methods. A great computational simplification to simulate these samples is obtained using the OpenBUGS software, where we only need to specify the distribution for the data and the prior distributions for the parameters. For a Bayesian analysis of the mixture and non-mixture models not including covariates, we assume a beta prior distribution for the proportion p of the long-term survivors denoted by $p \sim Beta(a,$

b) where a and b are known hyperparameters. Observe that since the parameter p is defined for values in the interval (0, 1), a natural choice for a prior distribution is given by a beta distribution. We also assume gamma prior distributions for the parameters α, β, γ and λ considering that these parameters are real and positive numbers. Thus, we have $\alpha \sim Gamma(c_\alpha, d_\alpha)$, $\beta \sim Gamma(c_\beta, d_\beta)$, $\gamma \sim Gamma(c_\gamma, d_\gamma)$ and $\lambda \sim Gamma(c_\lambda, d_\lambda)$, where c_α, d_α, c_β,d_β, c_γ,d_γ,c_λ and d_λ are known hyperparameters and $Gamma(c, d)$ denotes a gamma distribution with mean c/d and variance c/d^2. It is important to note that one or more of these parameters are alternatively fixed with constant values when considering the special cases of the GMW distribution. For example, if considering the exponentiated exponential (EE) distribution, we have $\alpha \sim Gamma(c_\alpha, d_\alpha)$, $\beta \sim Gamma(c_\beta, d_\beta)$, $\gamma = 1$ and $\lambda = 0$. When we have the presence of covariates, we can assume a normal prior distribution $N(e, f^2)$ with known mean e and known variance f^2 for each parameter included in the vector $\boldsymbol{\eta}$. In all cases we assume prior independence among the parameters included in the model. Posterior summaries of interest are obtained from simulated samples for the joint posterior distribution using standard Markov Chain Monte Carlo (MCMC) procedures. Interested readers can refer to Chib and Greenberg [49] for a review of standard MCMC methods. We generated 1,005,000 samples for each parameter of interest. The 5000 first simulated samples were discarded as a burn-in period, which is usually used to minimize the effect of the initial values. The posterior summaries of interest were based on 10,000 samples, taking every 100th sample to have approximately uncorrelated values. The Bayes estimates of the parameters were obtained as the median of Gibbs samples drawn from the joint posterior distribution. We used the median rather than the mean since some simulated distributions were quite skewed. For our study, we considered mixture and non-mixture models based on the four-parameter GMW distribution and some special cases of this distribution (Weibull, exponential, Rayleigh, extreme value, EW, EE, GR and MW distributions). Convergence of the MCMC algorithm was monitored by usual time series plots for the simulated samples and also using some existing Bayesian convergence methods considering different initial values (see for example Gelman and Rubin [50]).

4.1. *Model selection*

Comparison between mixture and non-mixture models assuming different distributions was assessed using the deviance information criteria (DIC) proposed by Spiegelhalter et al. [51], where a lower DIC value indicates better model fit. The deviance $D(\boldsymbol{\theta})$ is defined by $D(\boldsymbol{\theta}) = -2\ln L(\boldsymbol{\theta}) + k$, where $\boldsymbol{\theta}$ is the vector of unknown parameters included in the model, $L(\boldsymbol{\theta})$ is the respective likelihood function and k is a constant that does not vary across models. Thus, the DIC value is given by $DIC = D(\widehat{\boldsymbol{\theta}}) + 2n_P = 2\overline{D} - D(\widehat{\boldsymbol{\theta}})$, where $D(\widehat{\boldsymbol{\theta}})$ is the deviance evaluated at the posterior mean and n_P is the effective number of parameters of the model, given by $n_P = \overline{D} - D(\widehat{\boldsymbol{\theta}})$, considering $\overline{D}$ as the posterior deviance measuring the quality of the data fit for the model. We also obtained the expected Akaike information criterion (EAIC) introduced by Brooks [52], and the expected Bayesian (or Schwarz) information criterion (EBIC) proposed by Carlin and Louis [48]. The EAIC and EBIC values can be calculated by $EAIC = \overline{D} + 2q$ and $EBIC = \overline{D} + q\ln(n)$, respectively, where q is the number of parameters in the model and n is the sample size. OpenBUGS software was used to calculate the DIC, EAIC and EBIC values and in the generation of samples from the posterior distribution on the model parameters. The model code is given in Appendix A.

5. Results

For the Bayesian analysis of the mixture and non-mixture models considering the GMW distribution and not including covariates, it was assumed $p \sim Beta(1, 1)$ (a non-informative uniform prior distribution) and $Gamma(1, 1)$ prior distributions for α, β, γ and λ, that is, $c_\alpha = d_\alpha = c_\beta = d_\beta = c_\gamma = d_\gamma = c_\lambda = d_\lambda = 1$. The convergence of the MCMC algorithm was not obtained using the software OpenBUGS choosing values less than 1 for these hyperparameters, even when using a larger burn in period for the algorithm. In Tables 2 and 3 we have the posterior summaries considering the Bayesian approach assuming the mixture and non-mixture models, respectively. From 2 and 3, we observe similar results considering both models. We note that when we compare the obtained DIC values considering each one of the assumed probability distributions for the mixture and non-mixture models, we have very similar values. This suggests that both models (mixture and non-mixture) fit the data equally well. In addition, to evaluate the robustness of the method, we performed a small sensitivity analysis study in which the prior standard deviations for α, β, γ and λ are specified to be less than that assuming a $Gamma(1, 1)$ distribution, but the results (not shown) were quite similar. From both Tables 2 and 3 it is possible to note that the models that showed the smallest DIC values are those based on the GMW and EW distributions. However, when these models are compared, we observe that the smallest EAIC and EBIC values are those obtained using the MW distribution. In order to obtain a more visual representation of the fit of the model for the data based on the different distributions for the gastric cancer data, Fig. 2 shows plots of the Kaplan–Meier estimates for the survival function against the respective predicted values obtained from the parametric mixture models (results from Table 2) for each probability distribution. We omitted the plots considering the non-mixture models since they are similar to those obtained by considering the mixture model. Clearly, we observe from Fig. 2 that the predicted values obtained from the models based on the GMW and MW distributions are those closest to the empirical values, suggesting that these models give a better fit to the data. From Tables 2 and 3 we also note that the models based on the Weibull, Exponential, EW and EE distributions have estimated values for p smaller than that suggested by Fig. 1. Using the models based on the GMW and MW distributions we estimated more realistic values for the cure fraction p, which shows an additional evidence of a better fit according to these models, despite the observed DIC values.

The graphs in Fig. 3 show the survival functions (panels (a) and (b)) and the respective hazard functions (panels (c) and (d)) obtained from the fit of the mixture model (results in Table 2),

Table 2 – Posterior summaries, assuming the mixture model and not including covariates.

Model	Parameter	Posterior median	95% credible interval	DIC	EAIC	EBIC
GMW	α	0.1498	(0.0099; 0.6547)	879.3	897.9	914.4
	β	1.3150	(0.5451; 3.5900)			
	γ	0.4383	(0.1728; 1.1150)			
	λ	0.0565	(0.0248; 0.0985)			
	p	0.4906	(0.4003; 0.5660)			
Standard Weibull	α	0.0517	(0.0290; 0.0895)	898.6	902.6	917.8
	γ	0.8867	(0.7104; 1.124)			
	p	0.2683	(0.0181; 0.4737)			
Standard exponential	α	0.0462	(0.0259; 0.0699)	898.2	900.5	917.7
	p	0.3534	(0.0967; 0.4857)			
Standard Rayleigh	α	0.0046	(0.0035; 0.0058)	950.7	952.8	970.0
	p	0.4990	(0.4272; 0.5714)			
Extreme value	α	0.1324	(0.0843; 0.1985)	941.8	944.9	960.1
	λ	0.1247	(0.1057; 0.1448)			
	p	0.5006	(0.4282; 0.5735)			
Exponentiated Weibull (EW)	α	0.0709	(0.0039; 0.4047)	878.0	905.0	918.2
	β	1.1210	(0.5065; 2.8550)			
	γ	0.8094	(0.4087; 1.6420)			
	p	0.2437	(0.0126; 0.4812)			
Exponentiated exponential (EE)	α	0.0357	(0.0160; 0.0698)	898.5	902.4	917.6
	β	0.8791	(0.6695; 1.1660)			
	p	0.3031	(0.0310; 0.4728)			
Generalized Rayleigh (GR)	α	0.0017	(0.0001; 0.0031)	896.0	899.2	914.4
	β	0.4322	(0.3358; 0.5498)			
	p	0.4562	(0.2762; 0.5461)			
Modified Weibull (MW)	α	0.0808	(0.0455; 0.1346)	891.7	895.7	908.9
	γ	0.5566	(0.3307; 0.8550)			
	λ	0.0643	(0.0264; 0.0948)			
	p	0.4921	(0.4049; 0.5670)			

according to the GMW distribution and its special cases. The hazard function $h(t)$ is given by

$$h(t) = \frac{f(t)}{S(t)} = \frac{(1-p)f_0(t)}{p + (1-p)S_0(t)}, \quad (7)$$

where $f_0(t)$ and $S_0(t)$ are given by (3) and (4), respectively. Plots considering the non-mixture models (not shown) are quite similar to that obtained for the mixture models (Fig. 3). As expected, the survival curves associated to the models based on the GMW and MW distributions are the closest to the empirical values from Kaplan–Meier estimates (Fig. 3, panel (b)). The panel (d) of Fig. 3 shows that the hazard functions obtained from these distributions are quite close to each other. These curves suggest that the risk of dying during the period immediately after the surgery is high. After this peak, the risk decreases with a slight increase close to the twentieth month and with a further reduction until the end of follow up.

Table 4 shows the inferences for the models based on the GMW distribution and its special cases, not including the cure fraction p. We can note that the fit of models not including p gives larger DIC, EAIC and EBIC values than the fit of models including the cure fraction (see Tables 2 and 3). As expected, this suggests that the cure fraction models are more appropriate for the analysis of this medical lifetime data set.

To obtain inferences considering the type of treatment as a covariate, we initially considered the regression model

$$\ln\left(\frac{p_i}{1-p_i}\right) = \eta_0 + \eta_1 x_i,$$

where x_i is a "dummy" variable related to the treatment (1 = adjuvant chemoradiotherapy; 0 = surgery alone), $i = 1, \ldots, n$. Assuming the mixture and non-mixture models based on the GMW distribution, let us consider normal prior distributions $N(0, 100)$ for the parameters η_0 and η_1. Thus, we are assuming approximately non-informative priors for these parameters. Note that the parameter η_1 is related to the effect of the treatment on the cure fraction. If the credible interval for η_1 includes zero, we can conclude that there is no evidence of treatment effect. Assuming prior independence among the parameters, Table 5 shows posterior summaries obtained from simulated samples using the MCMC method and the graph representing the survival function obtained from the mixture model is shown in the panel (a) of Fig. 4. The DIC, EAIC and EBIC values for the two assumed models (Table 5) also give very close results. The values for p_0 and p_1 showed in Table 5 were obtained by the relations $p_0 = e^{\eta_0}/(1+e^{\eta_0})$ and $p_1 = e^{\eta_0+\eta_1}/(1+e^{\eta_0+\eta_1})$ and they refer to the cure fractions considering the patients treated by surgery alone and adjuvant chemoradiotherapy, respectively.

The graph in the panel (a) of Fig. 4 suggests that the model considering the GMW distribution and a covariate in the cure

Table 3 – Posterior summaries, assuming the non-mixture model and not including covariates.

Model	Parameter	Posterior median	95% credible interval	DIC	EAIC	EBIC
GMW	α	0.1176	(0.0052; 0.5719)	877.7	898.0	914.5
	β	1.3410	(0.5335; 3.593)			
	γ	0.4227	(0.1666; 1.1230)			
	λ	0.0626	(0.0276; 0.1100)			
	p	0.4918	(0.3997; 0.5671)			
Standard Weibull	α	0.0261	(0.0099; 0.0529)	899.6	903.4	918.6
	γ	0.9252	(0.7433; 1.1590)			
	p	0.2471	(0.0260; 0.4586)			
Standard exponential	α	0.0262	(0.0094; 0.0477)	898.5	901.0	918.2
	p	0.2996	(0.0664; 0.4606)			
Standard Rayleigh	α	0.0038	(0.0027; 0.0049)	947.5	949.5	966.7
	p	0.4929	(0.4165; 0.5665)			
Extreme value	α	0.0911	(0.0578; 0.1403)	939.3	942.3	957.5
	λ	0.1341	(0.1139; 0.1551)			
	p	0.4969	(0.4253; 0.5680)			
Exponentiated Weibull (EW)	α	0.0526	(0.0015; 0.3503)	874.6	905.8	919.0
	β	1.2860	(0.5272; 3.3440)			
	γ	0.7489	(0.3497; 1.6560)			
	p	0.2022	(0.0139; 0.4628)			
Exponentiated exponential (EE)	α	0.0219	(0.0055; 0.0522)	899.3	903.3	918.5
	β	0.9395	(0.7427; 1.2090)			
	p	0.2765	(0.0422; 0.4590)			
Generalized Rayleigh (GR)	α	0.0011	(0.0001; 0.0024)	897.8	901.5	916.7
	β	0.4680	(0.3716; 0.5836)			
	p	0.4369	(0.2021; 0.5415)			
Modified Weibull (MW)	α	0.0575	(0.0316; 0.0969)	891.8	895.8	909.0
	γ	0.5524	(0.3213; 0.8555)			
	λ	0.0723	(0.0349; 0.1043)			
	p	0.4931	(0.4081; 0.5675)			

Table 4 – Posterior summaries, not including the cure fraction *p* and not including covariates.

Model	Parameter	Posterior median	95% credible interval	DIC	EAIC	EBIC
GMW	α	0.1506	(0.0115; 0.6112)	883.9	906.1	919.3
	β	1.6030	(0.6819; 4.0630)			
	γ	0.5037	(0.2465; 1.0060)			
	λ	0.0055	(0.0002; 0.0175)			
Standard Weibull	α	0.0430	(0.0252; 0.0700)	898.6	900.7	907.3
	γ	0.8200	(0.6621; 0.9568)			
Standard exponential	α	0.0229	(0.0186; 0.0278)	901.3	902.3	905.6
Standard Rayleigh	α	0.00085	(0.0006; 0.0010)	1023.0	1024.0	1027.3
Extreme value	α	0.1038	(0.0705; 0.1462)	1005.0	1007.0	1013.6
	λ	0.0621	(0.0517; 0.0736)			
Exponentiated Weibull (EW)	α	0.1180	(0.0093; 0.5148)	882.9	903.2	913.1
	β	1.4710	(0.6771; 3.5800)			
	γ	0.6065	(0.3422; 1.1260)			
Exponentiated exponential (EE)	α	0.0172	(0.0111; 0.0241)	898.6	900.7	907.3
	β	0.7928	(0.6262; 0.9852)			
Generalized Rayleigh (GR)	α	0.00016	(0.00008; 0.00029)	899.6	901.7	908.3
	β	0.3647	(0.2953; 0.4434)			
Modified Weibull (MW)	α	0.0463	(0.0267; 0.0755)	900.3	904.1	914.0
	γ	0.7274	(0.5308; 0.9079)			
	λ	0.0056	(0.0002; 0.0198)			

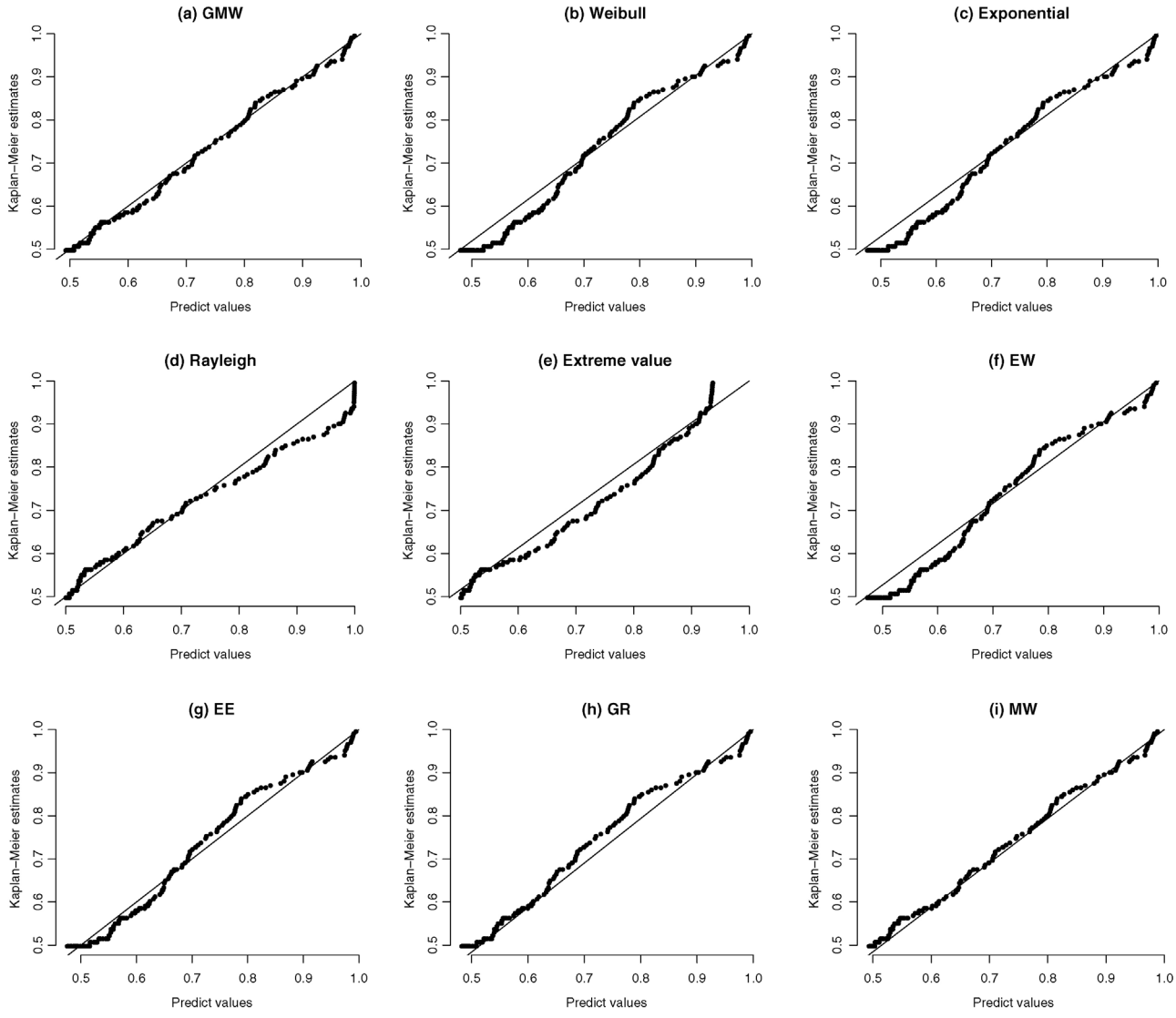

Fig. 2 – Plots of the Kaplan–Meier estimates for the survival function versus the respective predict values obtained from the parametric mixture models for each probability distribution of interest: (a) GMW, (b) Weibull, (c) Exponential, (d) Rayleigh, (e) Extreme value, (f) EW, (g) EE, (f) GR and (g) MW distributions. The diagonal straight lines represent a perfect agreement between Kaplan–Meier estimates and predicted values.

proportion p was not found to give a good fit for the data, given that the estimated survival curves are relatively distant from the Kaplan-Meier curves. Furthermore, we observed that the curves generated by the Kaplan–Meier for each treatment have different shapes (Fig. 1, panel (b)). Thus, considering the mixture and non-mixture models based on the GMW distribution, we can include the type of treatment as a covariate in the shape parameter β by replacing β by $\beta_i = \exp(\xi_0 + \xi_1 x_i)$ in the expressions (5) and (6). Thus, the parameter ξ_1 is related to the effect of the treatment on the shape of the survival curve. For a Bayesian analysis we assume normal prior distributions $N(0, 100)$ for the parameters ξ_0 and ξ_1. Including this covariate both in the cure proportion p and in the shape parameter, posterior summaries obtained from simulated samples are showed in Table 6, assuming mixture and non-mixture models. In this table we observe again that the DIC, EAIC and EBIC values for mixture and non-mixture models are quite similar. Table 6 also shows inferences for the ratio between the cure proportions p_0 and p_1. In both models, we observe that the 95% credible intervals for p_0/p_1 include the value 1, indicating that we do not have evidence of differences between the population cure fractions considering patients treated by adjuvant chemoradiotherapy and surgery alone. In addition, the 95% credible intervals for η_1 showed in Table 6 include the zero value.

Fig. 5 shows the hazard function for death assuming the mixture model based on the GMW distribution, with a covariate related to type of treatment included both in the cure proportion p and in the shape parameter β (results in Table 6). This figure evidences the non-proportionality of the hazard functions, making attractive the use of parametric models for the analysis of these data since these models do not consider

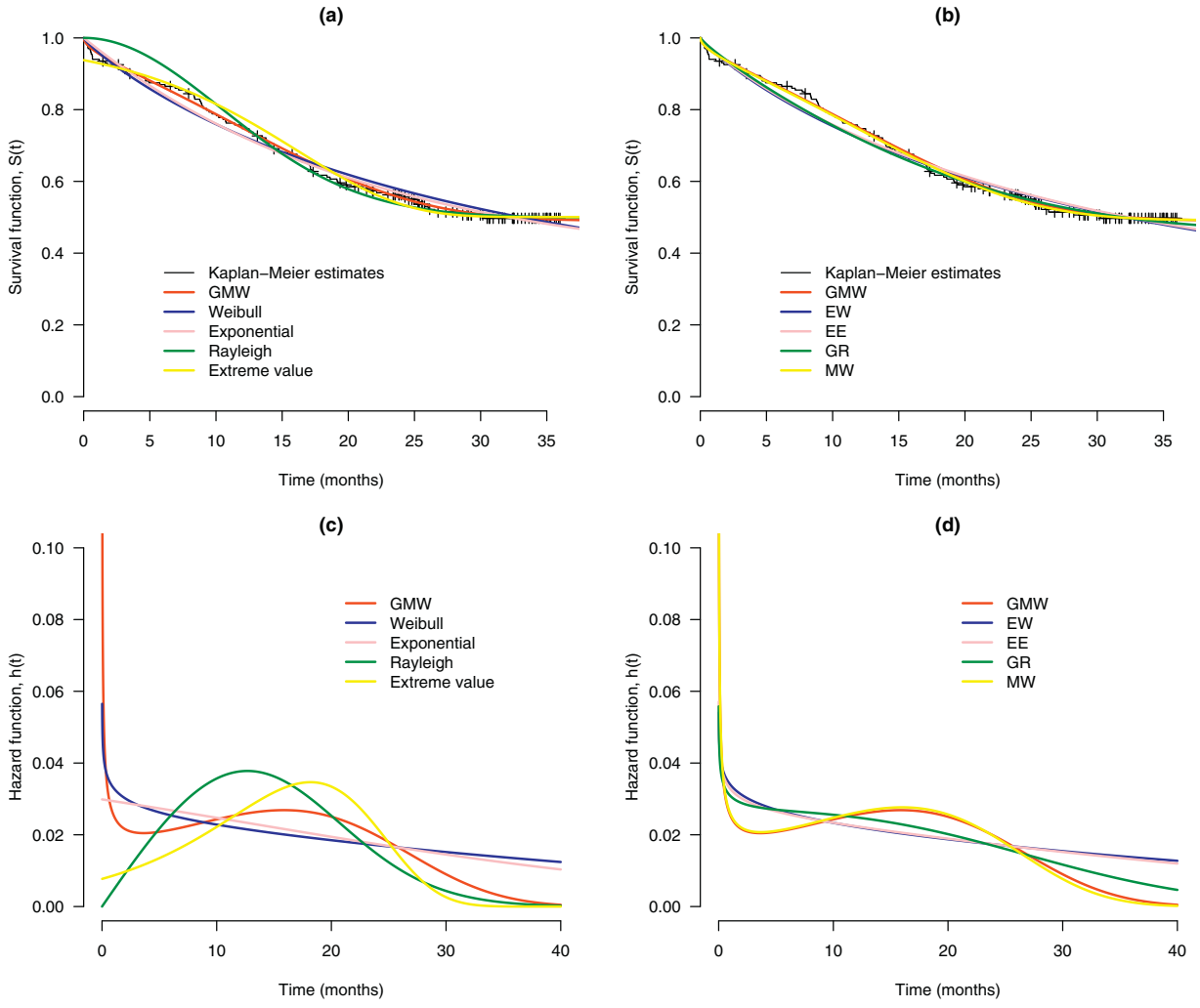

Fig. 3 – Plots of the survival functions estimated from the mixture model based on the GMW distribution and its special cases (panels (a) and (b)). Panels (c) and (d) exhibit the respective hazard functions. Curves considering the GMW distribution are showed in all plots for the purpose of comparisons.

Table 5 – Posterior summary, assuming mixture and non-mixture models based in the GMW distribution and with a covariate included in the cure proportion p.

Model	Parameter	Posterior median	95% credible interval	DIC	EAIC	EBIC
Mixture model	α	0.1512	(0.0095; 0.6359)	879.3	899.4	919.2
	β	1.3180	(0.5321; 3.5980)			
	γ	0.4396	(0.1750; 1.1220)			
	λ	0.0562	(0.0223; 0.0959)			
	η_0	−0.2185	(−0.7350; 0.1782)			
	η_1	0.4351	(−0.1880; 1.0830)			
	p_0	0.4456	(0.3241; 0.5444)			
	p_1	0.5534	(0.4153; 0.6678)			
Non-mixture model	α	0.1169	(0.0069; 0.5433)	878.2	896.6	916.4
	β	1.3430	(0.5791; 3.4980)			
	γ	0.4253	(0.1692; 1.0040)			
	λ	0.0630	(0.0283; 0.1144)			
	η_0	−0.2950	(−0.7710; 0.0986)			
	η_1	0.6265	(0.0350; 1.2210)			
	p_0	0.4268	(0.3163; 0.5246)			
	p_1	0.5821	(0.4536; 0.6904)			

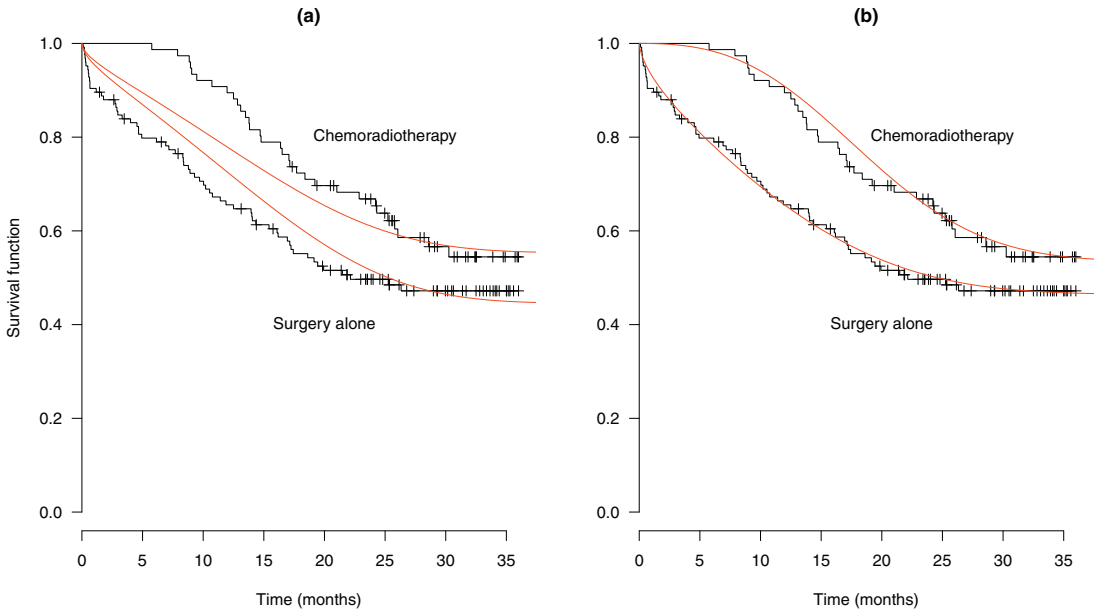

Fig. 4 – (a) Survival functions estimated by the Kaplan–Meier method (black lines) and assuming a mixture model based in the GMW distribution with a covariate included in the cure proportion p (red lines). (b) Survival functions from the mixture model with a covariate included both in the cure proportion p and in the shape parameter β (red lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

the assumption of proportional hazards used in the usual semi-parametric Cox model [2]. In addition, the shape of the curves are very different, suggesting that parametric models based on generalized probability distributions can be very useful in the analysis of data similar to those shown in Table 1, since these models can accommodate many forms of the hazard rate function. Note that the 95% credible intervals for ξ_1 showed in Table 6 do not include the zero value, suggesting a significant difference between the shapes of the hazard functions. The graphs in Fig. 5 suggest that the hazard of death is higher in the time immediately after the surgery considering the patients that received the surgery alone, and the hazard of death is higher around 20 months after the surgery intervention, considering the patients that received the chemoradiotherapy. In many studies published in medical journals, graphs similar to that showed in Fig. 5 may be employed in addition to the usual Kaplan-Meier curves and the correspondent survival functions obtained from

Table 6 – Posterior summary, assuming mixture and non-mixture models based in the GMW distribution and with a covariate included in the cure proportion p and in the shape parameter β.

Model	Parameter	Posterior median	95% credible interval	DIC	EAIC	EBIC
Mixture model	α	0.3843	(0.0190; 1.9280)	814.9	876.8	899.9
	ξ_0	0.6252	(−0.6666; 2.6400)			
	ξ_1	1.3070	(0.8114; 1.7820)			
	γ	0.3784	(0.1101; 1.1870)			
	λ	0.0385	(0.0140; 0.0694)			
	η_0	−0.1420	(−0.5489; 0.2407)			
	η_1	0.2831	(−0.4207; 0.8930)			
	p_0	0.4646	(0.3661; 0.5599)			
	p_1	0.5345	(0.3754; 0.6548)			
	p_0/p_1	0.8706	(0.6443; 1.2510)			
Non-mixture model	α	0.2967	(0.0120; 1.4900)	819.8	877.0	900.1
	ξ_0	0.5944	(−0.6499; 2.3390)			
	ξ_1	1.1490	(0.7026; 1.6070)			
	γ	0.3842	(0.1177; 1.3080)			
	λ	0.0427	(0.0155; 0.0766)			
	η_0	−0.1253	(−0.5396; 0.2367)			
	η_1	0.2571	(−0.4109; 0.8503)			
	p_0	0.4687	(0.3683; 0.5589)			
	p_1	0.5321	(0.3809; 0.6505)			
	p_0/p_1	0.8815	(0.6585; 1.2400)			

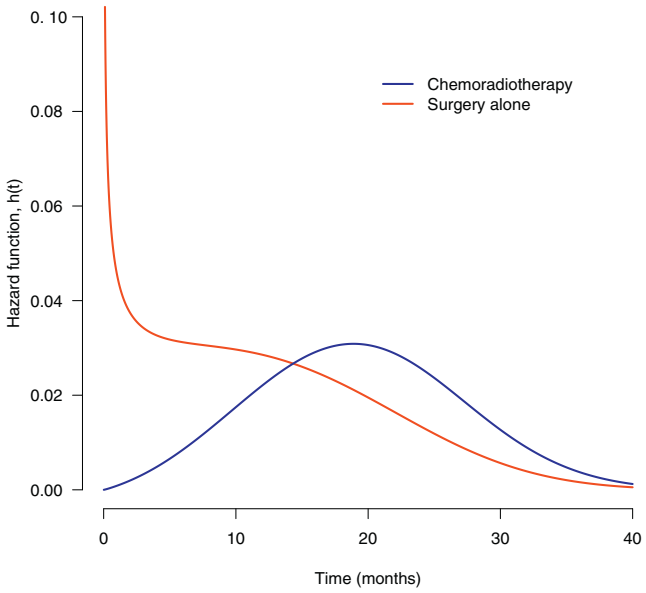

Fig. 5 – Hazard functions obtained from the mixture model with a covariate (type of treatment) included both in the cure proportion p and in the shape parameter β.

parametric models, since they are able to describe quite clearly the death rate at time t.

Graphs similar to that in Figs. 4 and 5 but considering the non-mixture models are not shown in this article because they are quite similar to these ones.

6. Discussion

Based on the GMW distribution, we propose in this article a cure fraction regression model very suitable for modeling censored and uncensored lifetime data. This model extends several distributions widely used in the lifetime data analysis allowing flexibility in modeling monotone and non-monotone shape hazard rates and it serves as a good alternative for the analysis of real data sets. Aiming to show the flexibility, practical relevance and applicability of this regression model, we provided an application to gastric cancer lifetime data. Other factors different of the treatments may also contribute to the variability of the results such as length of illness, the time from prognosis to treatment, age at diagnosis and stage of tumor. However, our aim in this study was to describe the utility of the GMW distribution considering a real data set, and more complete models can be developed to study the simultaneous effect of a large number of variables on the time until the event of interest. Bradburn et al. [1] argue that the Cox proportional hazards model [2] is the most commonly used approach for analyzing survival time data in applied medical research. However, this model assumes that for the comparison of two groups the respective hazards are proportional and not overlapping at all points in time. This assumption may not be valid in many practical situations and the hazard ratios obtained in this case are unrealistic. Clearly, the graph of Fig. 5 evidences non-proportionality in the hazard functions considering patients treated with chemoradiotherapy and with surgery alone. In addition, the standard Cox model usually does not consider the presence of long time survivors that are common in many clinical studies. There are in the literature, however, several extensions of the Cox model that account for a surviving fraction [53–55], but these approaches are not suitable for the assessment of non-proportional hazard functions. Thus, parametric models including a cure fraction are suitable tools for the analysis of time-to-event data since these models do not assume proportional hazards and they are able to estimate measures which are easily interpreted by physicians and other health professionals, as the proportions of long-term survivals and the mean survival time. Therefore, it is of fundamental importance that statisticians working in medical research have a good knowledge of different existing lifetime parametric models, including Bayesian procedures. It was shown that usual distributions such as Weibull do not fit well to the data presented in Table 1. The literature presents many models based on generalized distributions, such as the generalized F distribution [56] and the extended family of the generalized Gamma distribution [57]. These models can be satisfactorily used in the analysis of the data set introduced here, but the purpose of the present study is to describe the use of a distribution recently introduced in the literature [7]. New and more flexible probability distributions useful for lifetime analysis have been introduced in recent years by many researchers (we can cite as examples the works of Cordeiro et al. [58], Pascoa et al. [59], Cancho et al. [60] and Roman et al. [61], amongst others), and the use of statistical models based in these distributions can provide large benefits for the medical research, as observed in the medical application introduced in this paper. In addition, Bayesian inference methods show great potential for efficient computing likelihood-based inference in a large number of contexts and the application of models under a Bayesian framework is often greatly facilitated by the availability of softwares such as OpenBUGS, that only requires the specification of the distribution to the data and prior distributions for the parameters. Due to the development of MCMC algorithms the application of Bayesian methods became advantageous to fit models with many parameters, which may be difficult to be fitted by frequentist methods. Another advantage of the Bayesian model is that they also allow the incorporation of expert prior opinion for the parameters. In this way, the professional knowledge of an oncologist on expected proportion of patients who are immune to the event of interest can be incorporated into a prior distribution for the parameter p, resulting in more precise inferences.

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Appendix A. OpenBUGS codes

The OpenBUGS code used for the analysis of the gastric cancer data is given below, considering the mixture model.

```
model
  {
for (i in 1:N) {
  f0A[i] < -alpha*beta*pow(t[i],gamma-1)*(gamma+lambda*t[i])
    *exp(lambda*t[i]-alpha*pow(t[i],gamma)*exp(lambda*t[i]))
  f0B[i] < -pow(1-exp(-alpha*pow(t[i],gamma)*exp(lambda*t[i])),1-beta)
  f0[i] < - f0A[i]/f0B[i]
S0[i] < -1-pow(1-exp(-alpha*pow(t[i],gamma)*exp(lambda*t[i])),beta)
  L[i] < -pow(1-p,d[i])*pow(f0[i],d[i])*pow(p+(1-p)*S0[i],1-d[i])
  logL[i] < - log(L[i])
  zeros[i] < - 0
  zeros[i] ~ dloglik(logL[i])
}
# Prior distributions
p ~ dbeta(1,1)
alpha ~ dgamma(1,1)
beta ~ dgamma(1,1)
gamma ~ dgamma(1,1)
lambda ~ dgamma(1,1)
}
```

In this code, `N` is the sample size, `f0[i]` is the baseline probability density function given in expression (3), `S0[i]` is the respective survival function given in expression (4), `L[i]` is the likelihood function, `t[i]` is the time-to-event variable and `d[i]` is the censoring indicator variable (denoted by δ_i). Considering that the GMW distribution is not available directly as a choice in OpenBUGS we used the `dloglik()` distribution, which requires us to specify the logarithm of the likelihood function. Assuming the non-mixture model, we replace in the code the line for `L[i]` by

```
F0[i]< - 1-S0[i]
h[i] < - -(log(p))*f0[i]
L[i] < - pow(h[i],d[i])*exp(F0[i]*log(p))
```

In obtaining the posterior samples of the model parameters, we did not encounter a problem of convergence in any of the models. However, it is highly recommended that reasonable initial values are specified for the generation of samples.

REFERENCES

[1] M.J. Bradburn, T.G. Clark, S.B. Love, D.G. Altman, Survival analysis. Part II: Multivariate data analysis – an introduction to concepts and methods, British Journal of Cancer 89 (3) (2003) 431–436.

[2] D.R. Cox, Regression models and life tables (with discussion), Journal of the Royal Statistical Society Series B 34 (1972) 187–220.

[3] M.J. Bradburn, T.G. Clark, S.B. Love, D.G. Altman, Survival analysis. Part III: Multivariate data analysis – choosing a model and assessing its adequacy and fit, British Journal of Cancer 89 (4) (2003) 605–611.

[4] R. Peto, P.N. Lee, W.S. Paige, Statistical analysis of the bioassay of continuous carcinogens, British Journal of Cancer 26 (4) (1972) 258–261.

[5] G.S. Mudholkar, D.K. Srivastava, Exponentiated Weibull family for analyzing bathtub failure-rate data, IEEE Transactions on Reliability 42 (2) (1993) 299–302.

[6] M. Pal, M.M. Ali, J. Woo, Exponentiated Weibull distribution, Statistica 66 (2) (2006) 139–147.

[7] J.M.F. Carrasco, E.M.M. Ortega, G.M. Cordeiro, A generalized modified Weibull distribution for lifetime modelling, Computational Statistics and Data Analysis 53 (2008) 450–462.

[8] E.M.M. Ortega, G.M. Cordeiro, M.W. Kattan, The log-beta Weibull regression model with application to predict recurrence of prostate cancer, Statistical Papers 54 (2011) 113–132.

[9] F. Corbière, D. Commenges, J.M. Taylor, P. Joly, A penalized likelihood approach for mixture cure models, Statistics in Medicine 28 (3) (2009) 510–524.

[10] J.W. Boag, Maximum likelihood estimates of the proportion of patients cured by cancer therapy, Journal of the Royal Statistical Society Series B 11 (1949) 15–44.

[11] J. Berkson, R.P. Gage, Survival curve for cancer patients following treatment, Journal of the American Statistical Association 47 (1952) 501–515.

[12] J.L. Haybittle, A two parameter model for the survival curve of treated cancer patients, Journal of the American Statistical Association 53 (1965) 16–26.

[13] W.Q. Meeker, Limited failure population life tests: application to integrated circuit reliability, Technometrics 29 (1) (1987) 51–65.

[14] J.W. Gamel, I.W. McLean, S.H. Rosenberg, Proportion cured and mean log survival time as functions of tumor size, Statistics in Medicine 9 (1990) 999–1006.

[15] M.E. Ghitany, R.A. Maller, Asymptotic results for exponential mixture models with long term survivors, Statistics 23 (1992) 321–336.

[16] J.B. Copas, F. Heydari, Estimating the risk of reoffending by using exponential mixture models, Journal of the Royal Statistical Society A 160 (2) (1997) 237–252.

[17] S.K. Ng, G.J. McLachlan, On modifications to the long-term survival mixture model in the presence of competing risks, Journal of Statistical Computation and Simulation 61 (1998) 77–96.

[18] R. De Angelis, R. Capocaccia, T. Hakulinen, B. Soderman, A. Verdecchia, Mixture models for cancer survival analysis: application to population-based data with covariates, Statistics in Medicine 18 (4) (1999) 441–454.

[19] Y. Peng, K.B.G. Dear, A nonparametric mixture model for cure rate estimation, Biometrics 56 (1) (2000) 237–243.

[20] P.C. Lambert, J.R. Thompson, C.L. Weston, Estimating and modeling the cure fraction in population-based cancer survival analysis, Biostatistics 8 (3) (2007) 576–594.

[21] B. Yu, R.C. Tiwari, K.A. Cronin, E.J. Feuer, Cure fraction estimation from the mixture cure models for grouped survival data, Statistics in Medicine 23 (11) (2004) 1733–1747.

[22] M. Castro, V.G. Cancho, J. Rodrigues, Bayesian long-term survival model parametrized in the cured fraction, Biometrical Journal 51 (3) (2009) 443–455.

[23] M.H. Chen, J.G. Ibrahim, D. Sinha, A new Bayesian model for survival data with a surviving fraction, Journal of the American Statistical Association 94 (447) (1999) 909–919.

[24] J.G. Ibrahim, M.H. Chen, D. Sinha, Bayesian semiparametric models for survival data with a cure fraction, Biometrics 57 (2) (2004) 383–388.

[25] S. Kim, M.H. Chen, D.K. Dey, D. Gamerman, Bayesian dynamic models for survival data with a cure fraction, Lifetime Data Analysis 13 (2007) 17–35.
[26] H. Seltman, J. Greenhouse, L. Wasserman, Bayesian model selection: analysis of a survival model with a surviving fraction, Statistics in Medicine 20 (11) (2001) 1681–1691.
[27] A.A. Jácome, D.R. Wohnrath, C. Scapulatempo Neto, J.H. Fregnani, A.L. Quinto, A.T. Oliveira, V.L. Vazquez, G. Fava, E.Z. Martinez, J.S. Santos, Effect of adjuvant chemoradiotherapy on overall survival of gastric cancer patients submitted to D2 lymphadenectomy, Gastric Cancer (2013) (Epub ahead of print).
[28] B.J. Dicken, D.L. Bigam, C. Cass, J.R. Mackey, A.A. Joy, S.M. Hamilton, Gastric adenocarcinoma: review and considerations for future directions, Annals of Surgery 241 (2005) 27–39.
[29] J.A. Akoh, I.M. Macintyre, Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970, British Journal or Surgery 79 (1992) 293–299.
[30] T. Okamura, S. Tsujitani, D. Korenaga, M. Haraguchi, H. Baba, Y. Hiramoto, K. Sugimachi, Lymphadenectomy for cure in patients with early gastric cancer and lymph node metastasis, American Journal of Surgery 155 (3) (1988) 476–480.
[31] R.A. Maller, X. Zhou, Survival Analysis with Long-Term Survivors, Wiley, New York, 1996.
[32] A.D. Tsodikov, J.G. Ibrahim, A.Y. Yakovlev, Estimating cure rates from survival data: an alternative to two-component mixture models, Journal of the American Statistical Association 98 (464) (2003) 1063–1078.
[33] J.A. Achcar, E. Coelho-Barros, J. Mazucheli, Cure fraction models using mixture and non-mixture models, Tatra Mountains Mathematical Publications 51 (2012) 1–9.
[34] V.T. Farewell, The use of mixture models for the analysis of survival data with long-term survivors, Biometrics 8 (4) (1982) 1041–1046.
[35] A. Tsodikov, A proportional hazards model taking account of long-term survivors, Biometrics 54 (4) (1998) 1508–1516.
[36] R. Sposto, Cure model analysis in cancer: an application to data from the Children's Cancer Group, Statistics in Medicine 21 (2) (2002) 293–312.
[37] V.G. Cancho, J. Rodrigues, M. Castro, A flexible model for survival data with a cure rate: a Bayesian approach, Journal of Applied Statistics 38 (1) (2011) 57–70.
[38] J. Mazucheli, J.A. Achcar, E.A.C. Barros, F. Louzada, Infant mortality model for lifetime data, Journal of Applied Statistics 36 (2009) 1029–1036.
[39] J. Rodrigues, V.G. Cancho, M. de Castro, F. Louzada-Neto, On the unification of long-term survival models, Statistics and Probabilities Letters 79 (2009) 753–759.
[40] G.C. Perdoná, F. Louzada-Neto, A general hazard model for lifetime data in the presence of cure rate, Journal of Applied Statistics 38 (2011) 1395–1405.
[41] N.L. Johnson, S. Kotz, N. Balakrishnan, Continuous Univariate Distributions, vol. 2, Wiley, New York, 1995.
[42] C.D. Lai, M. Xie, D.N.P. Murthy, A modified Weibull distribution, IEEE Transactions on Reliability 52 (1) (2003) 33–37.
[43] M.M. Nassar, F.H. Eissa, On the exponentiated Weibull distribution, Communications in Statistics – Theory and Methods 32 (7) (2003) 1317–1336.
[44] R.D. Gupta, D. Kundu, Generalized exponential distributions, Australian and New Zealand Journal of Statistics 41 (1999) 173–188.
[45] R.D. Gupta, D. Kundu, Exponentiated exponential family: an alternative to gamma and Weibull distributions, Biometrical Journal 43 (1) (2001) 117–130.
[46] D. Kundu, M.Z. Rakab, Generalized Rayleigh distribution: different methods of estimation, Computational Statistics and Data Analysis 49 (2005) 187–200.
[47] A.M. Sarhan, M. Zaindin, Modified Weibull distribution, Applied Sciences 11 (2009) 123–136.
[48] B.P. Carlin, T.A. Louis, Bayes and Empirical Bayes Methods for Data Analysis, 2nd ed., Chapman and Hall, Boca Raton, 2001.
[49] S. Chib, E. Greenberg, Understanding the Metropolis–Hastings algorithm, The American Statistician 49 (4) (1995) 327–335.
[50] A. Gelman, R.D. Rubin, Inference from iterative simulation using multiple sequences, Statistical Sciences 4 (1992) 457–511.
[51] D.J. Spiegelhalter, N.G. Best, B.P. Carlin, A. van der Linde, Bayesian measures of model complexity and fit, Journal of the Royal Statistical Society Series B 64 (2002) 583–639.
[52] S.P. Brooks, Discussion on the paper by Spiegelhalter, Best, Carlin and van der Linde, Journal of the Royal Statistical Society Series B 64 (2002) 616–618.
[53] A.Y.C. Kuk, C.H. Chen, A mixture model combining logistic regression with proportional hazards regression, Biometrika 79 (3) (1992) 531–541.
[54] J.P. Sy, J.M.G. Taylor, Estimation in a Cox proportional hazards cure model, Biometrics 56 (1) (2000) 227–236.
[55] W. Lu, Maximum likelihood estimation in the proportional hazards cure model, Annals of the Institute of Statistical Mathematics 60 (3) (2008) 545–574.
[56] Y. Peng, K.B.G. Dear, J.W. Denham, A generalized F mixture model for cure rate estimation, Statistics in Medicine 17 (8) (1998) 813–830.
[57] K. Yamaguchi, Accelerated failure-time regression models with a regression model of surviving fraction: an application to the analysis of "permanent employment" in Japan, Journal of the American Statistical Association 87 (418) (1992) 284–292.
[58] G.M. Cordeiro, E.M.M. Ortega, G.O. Silva, The exponentiated generalized gamma distribution with application to lifetime data, Journal of Statistical Computation and Simulation 81 (7) (2011) 827–842.
[59] M.A.R. Pascoa, E.M.M. Ortega, G.M. Cordeiro, The Kumaraswamy generalized gamma distribution with application in survival analysis, Statistical Methodology 8 (5) (2011) 411–433.
[60] V.G. Cancho, F. Louzada, G.D.C. Barriga, The Geometric Birnbaum–Saunders regression model with cure rate, Journal of Statistical Planning and Inference 142 (4) (2012) 993–1000.
[61] M. Roman, F. Louzada, V.G. Cancho, J.G. Leite, A new long-term survival distribution for cancer data, Journal of Data Science 10 (2012) 241–258.