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Cured Fraction Models on Survival Data and Covariates with a Bayesian Parametric Estimation Methods

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Abstract: A cure fraction models are usually meant for survival data that contains a proportion of non subject individuals for the event under study. In order to estimate the cure fraction, two models namely mixture model and non-mixture model were commonly deployed. In this work, mixture and non-mixture cure fraction models were presented with survival data structure based on the beta-Weibull distribution. The beta-Weibull distribution is a four parameter distribution developed in this work as an alternative extension to the Weibull distribution in the analysis of lifetime data. The proposed extension allows the inclusion of covariates analysis in the model, in which the estimation of parameters were done under Bayesian approach using Gibbs sampling methods.

Keywords: Bayesian analysis; Beta-Weibull distribution; Cure fraction models; Survival analysis; MCMC algorithm.

Introduction

A suitable distribution is often of interest in the analysis of survival data proposed by (Pal et al., 2014), as it provides insight into characteristics of failure times and hazard functions such as Weibull, Beta and Gamma distributions respectively given by, the probability density function of the 2-parameter Weibull distribution is:

$$f_0(t) = \gamma\lambda t^{\gamma-1}e^{-\lambda t^{\gamma}}, t \geq \gamma, \lambda > 0 \quad (1)$$

where γ is the shape parameter and λ is the scale parameter (mechanics & 1951, n.d.).

The probability density function of the general Beta distribution is:

$$f_0(t) = \frac{(t-a)^{p-1}(b-t)^{q-1}}{B(\alpha,\beta)(b-1)^{p+q-1}}, \qquad a \leq t \leq b; \alpha, \beta \geq 0 \quad (2)$$

Where α and β are the shape parameters, a and b are the lower and upper bounds, respectively, of the distribution, and $B(\alpha,\beta)$ is the beta function (Pal et al., 2014).

The probability density function of the general Gamma distribution is:

$$f_0(t) = \frac{\left(\frac{t-\mu}{\beta}\right)^{\gamma-1}\exp\left(\frac{-t-\mu}{\beta}\right)^{\gamma-1}}{\beta\Gamma(\gamma)}, \qquad t \geq \mu; \beta, \gamma \geq 0 \quad (3)$$

where γ is the shape parameter, μ is the location parameter, β is the scale parameter, and Γ is the gamma function (Stacy, 1962) and α, β, λ are positive. The Weibull distribution is a very popular distribution which was named after (Waloddi & Stockholm, 1951), in 1951 a Swedish physicist. He used it in 1939 to analyze the breaking strength of materials (Carrasco et al., 2008). Due to the relative flexibility of its hazard function and the ease for estimation of its parameters, ever since it has been

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widely used for analyzing lifetime data. It is one of the most commonly used families for modeling such data. However, only monotonically increasing and decreasing hazard functions can be generated from the classic two-parameter Weibull distribution (Carrasco et al., 2008). One of the limitation in Beta-Weibull (BW) distribution is that the survival and hazard functions cannot be expressed in a closed form, specifically when more covariates are considered, thus numerical approach that is the integration techniques are required to determine the estimate of parameters in the model.

The cure fraction model (Achcar et al., 2012) is an extension to the conventional parametric survival models, which account for the fraction of individuals that will not experience the event of interest. Cure fraction models can also be referred to as long-term survival models in respect of the kind of event being specified. the two most typical cure models are the mixture and non-mixture models. The mixture cure rate model, otherwise called standard cure rate model, assumes that the studied population is a mixture of susceptible individuals, who experience the event of interest "p" which is the proportion of "long-term survivors" or "cured patients" regarding the event of interest $(0 < p < 1)$ and non-susceptible individuals that will never experience it "$(1 - p)$",

The survival function for the entire population, denoted by $S(t)$ for this model is given by

$$S(t) = p + (1 - p)S_0(t), \qquad t > 0 \tag{4}$$

Where $S_0(t)$ is the standard parametric survival curve function for the susceptible individuals. The non-mixture cure rate model defines an asymptote for the cumulative hazard, and hence for the cure fraction. The survival function can be written as:

$$S(t) = p^{F_c(t)} = \exp\left(\ln(p)\, F_c(t)\right), \qquad t > 0 \tag{5}$$

Any parametric family of distribution can be incorporated into larger families through an application of the probability integral transform (Gelman et al., 2013; Wahed et al., 2009). So also, the BW density can be expressed as a mixture of Weibull density a contribution by (Cordeiro et al., 2013) who further drive an expression for their moment generating function and investigated that the potential usefulness of the BW distribution for modeling censored survival data from a breast cancer research. Recently, it has been found out in (Schwertman & de Silva, 2007) that the extension of the beta-Weibull distribution was proposed in the content of (Cordeiro et al., 2013). The beta modified Weibull distribution is another generalization of the Weibull distribution (Cordeiro, Nadarajah, et al., 2013). The distribution has an edge due to its flexibility upon accommodation of multiple forms of risk function while handling various problems in survival data modeling (Wahed et al., 2009). Several literature suggest Bayesian formulation of the cure fraction model (Achcar et al., 2012). Numerous attempt on techniques for estimation of cure rates in the context when there are partially observed or missing covariate (Aljawadi et al., 2011; Gelman et al., 2013; Mudholkar et al., 1996; Tsodikov et al., 2003)

Method

Distributional assumptions and derivations

We denote $G_0(t)$ as the cummulative distribuion function (cdf) of a random variable T, which has a generalized class of distribution defined by:

$$\begin{aligned} F_0(t) = I_{G_0(t)}(\alpha, \beta) &= \frac{B_{G_0(t)}(\alpha, \beta)}{B(\alpha, \beta)} \\ &= \frac{\int_0^{G_0(t)} w^{\alpha-1}(1-w)^{\beta-1} dw}{B(a, b)} \end{aligned} \tag{6}$$

Where $\alpha > 0, \beta > 0, B(\alpha, \beta) = \frac{\Gamma(\alpha)\Gamma(\beta)}{\Gamma(\alpha,\beta)}$ is the beta function,with associated gamma function given by $\Gamma(\alpha) = \int_0^\infty z^{\alpha-1} e^{-z} dz$ and $B_{G_0(t)}(\alpha, \beta)$ is the incomplete beta function. If $G_0(t)$ in Equation (6) assumes a cdf of a normal distribution with mean μ and variance σ^2, we then have beta-normal distrbution, (Eugene et al., 2002). A model based on the cdf of the Weibull distribution with shape parameter γ and scale parameter λ assumes:

$$G_0(t) = 1 - \exp\left[-\left(\frac{t}{\lambda}\right)^{\gamma}\right], \; t > 0 \tag{7}$$

And from Equation (6), we subtitutute Equation (7) to have

$$F_0(t) = \frac{1}{B(\alpha,\beta)} \int_0^{1-\exp\left[-\left(\frac{t}{\lambda}\right)^{\gamma}\right]} w^{\alpha-1}(1-w)^{\beta-1} dw,\ t > 0 \quad (8)$$

Now, in the context of survival analysis, the baseline survival function or standard parametric survival curve function for
the susceptible individuals is given by

$$S_0(t) = 1 - F_0(t). \quad (9)$$

We observed that the function cannot be expressed in a closed form reference to the limitation. The baseline probability density function of the BW distribution with four parameters is written as

$$f_0(t) = \frac{\gamma}{\lambda^{\gamma} B(\alpha,\beta)} \exp\left[-\beta\left(\frac{t}{\lambda}\right)^{\gamma}\right]\left\{1-\exp\left[-\beta\left(\frac{t}{\lambda}\right)^{\gamma}\right]\right\}^{\alpha-1}, t > 0 \quad (10)$$

Where α, β, γ and λ are all positive numbers. The corresponding hazard function is given by:

$$h(t) = \frac{f_0(t)}{S_0(t)} = \frac{\gamma t^{\gamma-1}\lambda^{\gamma}\exp\left[-\beta\left(\frac{t}{\lambda}\right)^{\gamma}\right]\left\{1-\exp\left[-\beta\left(\frac{t}{\lambda}\right)^{\gamma}\right]\right\}^{\alpha-1}}{B(\alpha,\beta)\int_0^{1-\exp\left[-\left(\frac{t}{\lambda}\right)^{\gamma}\right]} w^{\alpha-1}(1-w)^{\beta-1} dw}, t > 0 \quad (11)$$

Assuming the Mixture model, the likelihood function for $\theta = (\alpha, \beta, \gamma, \lambda, p)$ is given by

$$L_I(\theta) = \prod_{i=1}^{n}\left[\frac{(1-p)\gamma}{\lambda^{\gamma}B(\alpha,\beta)} t_i^{\gamma-1}\exp\left(-\beta\left(\frac{t_i}{\lambda}\right)^{\gamma}\right)\left(1-\exp\left[-\beta\left(\frac{t_i}{\lambda}\right)^{\gamma}\right]^{\alpha-1}\right)^{\delta_i}\right] \times \prod_{i=1}^{n}[p+(1-p)S_0(t_i)]^{1-\delta_i} \quad . \quad (12)$$

Moreover, assuming the Non-mixture model, the likelihood function for $\theta = (\alpha, \beta, \gamma, \lambda, p)$ is given by:

$$L_{II}(\theta) = \prod_{i=1}^{n}\left[-\frac{\gamma \ln(p)}{\lambda^{\gamma}B(\alpha,\beta)} t_i^{\gamma-1}\exp\left(-\beta\left(\frac{t_i}{\lambda}\right)^{\gamma}\right)\left(1-\exp\left[-\beta\left(\frac{t_i}{\lambda}\right)^{\gamma}\right]^{\alpha-1}\right)^{\delta_i}\right] \times \prod_{i=1}^{n}[p+(1-p)S_0(t_i)]^{1-\delta_i} \quad . \quad (13)$$

Further Incorporation

Implementation of the conventional estimation methods especially maximization or direct methods on the likelihood functions $L_I(\theta)$ and $L_{II}(\theta)$ are tedious and usually computationally expensive due to complexity of some distributional expressions. Bayesian Inference based on Markov Chain Monte Carlo (MCMC) estimation methods bring down those complexities without compromise to precision and thus utilized in our implementation in this work which was appropriately justified in . The vector of covariate X_i which are closely related with proportion p of cure rate fraction models were incorporated by replacing p in the likelihood function expressions $L_I(\theta)$ and $L_{II}(\theta)$ with:

$$p_i(t) = \frac{\exp(x_i'\eta')}{1-\exp(x_i'\eta')}. \quad (14)$$

Where $x_i' = (1, x_1, \ldots, x_n)$ is J covariates's vector of observations for the ith individual and $\eta' = (\eta_0, \eta_1, \ldots, \eta_n)$ is the unknown parameters vector. To study the effect of vector of covariates W_i on the parameter λ, λ is replaced in both mixture and non-mixture expression of the likelihood function $L_I(\theta)$ and $L_{II}(\theta)$ by:

$$\lambda_i(t) = \exp(w_i'\zeta') \quad (15)$$

Where $\mathbf{w_i'} = (\mathbf{1}, \mathbf{w_1}, \ldots, \mathbf{w_n})$ is the vector of the observations of K covariates for the i-th individual and $\boldsymbol{\zeta}' = (\boldsymbol{\zeta_1}, \boldsymbol{\zeta_2}, \ldots, \boldsymbol{\zeta_n})$ is the vector of unknown parameters

Bayesian Analysis

We first consider a Bayesian analysis of the longterm survival models without considering covariates (Martinez et al., 2013), on the other hand we also presume the beta prior for the given probability of proportion "p" of cure models which is denoted by by $p \sim B(a, b)$ where a and b are known hyper parameters (Achcar et al., 2012; Martinez et al., 2013). We also assume a gamma prior distribution for the parameters $\alpha, \beta, \gamma \; and \; \lambda$. That is $\alpha \sim \Gamma(c_\alpha, d_\alpha), \beta \sim \Gamma(c_\beta, d_\beta), \gamma \sim \Gamma(c_\gamma, d_\gamma), \lambda \sim \Gamma(c_\lambda, d_\lambda)$ where c_α, d_α , $c_\beta, d_\beta, c_\gamma, d_\gamma c_\lambda, d_\lambda$ are known hyperparameters and $\Gamma(c, d)$ denotes a gamma distribution with mean $\frac{c}{d}$ and variance $\frac{c}{d^2}$. In all the cases the joint prior distributionis then establish by assuming prior independence between the parameters, or say,

$$\pi(\theta) = \pi(\alpha), \pi(\beta), \pi(\gamma), \pi(\lambda) \propto \alpha^{c\alpha-1}\beta^{c\beta-1}\lambda^{c\lambda-1}\gamma^{c\gamma-1}\exp\left(-\frac{\alpha}{d_\alpha} - \frac{\beta}{d_\beta} - \frac{\lambda}{d_\lambda} - \frac{\gamma}{d_\gamma}\right)p^{\alpha-1}(1-p)^{b-1} \quad (16)$$

for models incorporating the following covariates, the prior distribution for the unknown parameters are assumed: $\alpha \sim \Gamma(c_\alpha, d_\alpha), \beta \sim \Gamma(c_\beta, d_\beta), \gamma \sim \Gamma(c_\gamma, d_\gamma), \lambda \sim \Gamma(c_\lambda, d_\lambda)$, $\boldsymbol{\zeta_j} \sim N(c_{\zeta_j}, d_{\zeta_j}^2)$, $j = 0,1, \ldots, J,$ and $\eta_k \sim N(c_{\zeta_k}, d_{\zeta_k}^2), k = 0,1, \ldots, K$. where $N(c, d^2)$ denotes a normal distribution with mean c and variance d^2: are hyper parameters. In this situation we should focus on the independence between the prior distributions in a similar approach by (Martinez et al., 2013).

Log Pseudo Maximum Likelihood

Log Psuedo Marginal Likelihood (LPML) and the Pseudo Factor is an efficient tool for comparison of mixture and non-mixture models based on varied distributional assumption. The derivation of LPML $\boldsymbol{D}, \boldsymbol{D}[\boldsymbol{i}]$ is done through conditional predictive ordinate (CPO) statistics (Gelfand et al., 1992). That is, for the ith observation, $\boldsymbol{CPO_i}$ is given by

$$f(D_i/y_{|i|}t) = \int f(D_i/\Theta) f(f(\Theta/D_i) d\Theta \quad (17)$$

Where Θ is the incomplete vector of parameters, Di is each instance of the full data is D without the current observation i

And $f(\Theta/D_i)$ is the posterior density of given $D[i]$; $i = 1,2, \ldots, n$: An MCMC approximation of CPOi is given by:

$$\widehat{CPO_i} = \left[\frac{1}{B}\sum_{b=1}^{b}\frac{1}{f(D_i/\Theta_{(b)})}\right]^{-1}, i = 1,2, \ldots, n \quad (18)$$

such that, B is the iteration count for the MCMC implementation procedure after burn-in period and $\Theta_{(b)}$ is vector of the obtained samples at 4th and 5th iterations (Tsodikov et al., 2003). Thus, for a given model, the LPML value is given by:

$$\widehat{LPML} = \sum_{i=1}^{n}\log(\widehat{CPO_i}), i = 1,2, \ldots, n \quad (19)$$

The larger the value of LPML, the better is fit of the model (Gelfand et al., 1992). Alternatively, the Pseudo Bayes factor (PMF) for comparing models m and m' is:

$$PBF_{mm'} = \exp(\widehat{LPML}_m - \widehat{LPML}_{m'}) \quad (20)$$

So also, the highest probability density (HPD) intervals was obtained for parameters of interest (Gelfand et al., 1992). A $100(1-\omega)\%$ HPD interval for a generic parameter θ is a subset of the parameter space $C\Theta$ given by $C = \{\theta; \pi(\theta/D) \geq k\}$ where $\pi(\theta/D)$ is the posterior distribution for θ given the data D and k is the largest number such that

$$\int_{\pi(\theta/D)\geq k} \pi(\theta/D) = 1-\omega$$

German Breast Cancer Study

In this study, we first consider the case where the cure fraction parameter and covariates are not included in the model. for this reason, we use the data set from German Breast Cancer (GBC) study. The data set comprises 686 patients under 65 years of age where 299 had an event recurrence-free survival and 171 died. We used the time to death as the event of interest. The maximum follow-up time available was 7 years. already published should be indicated by a reference: only relevant modifications should be described. Do not repeat the details of established methods.

Bone Marrow transplant patients

We also presented a data set of 137 bone marrow transplant patients with acute myeloctic leukemia (AML) and acute lymphoblastic leukemia where treated in four North American hospitals. Bone marrow transplants are the standard treatment for acute leukemia. Conclusions**.**

Result and Discussion

A sample 30,000 was generated for each parameter of interest based on each cases under consideration. Assuming a burn-in sample of 10,000 data size which can minimize the initialization effect on the simulation process. However, a 15,000 sample size, with each of the 200th sample having approximately uncorrelated values was utilized to achieve a posterior summaries of interest.

Table 1. The posterior summaries of the model parameters excluding a cure fraction while considering GBC study dataset.

Model	Parameter	Posterior median	95% HDP^a	$LPML^b$	HW^c p value	Geweke's p value
BW	α	3.8116	(1.5334,6.7999)	-864.148	0.314	0.112
	β	0.0806	(0.0166,0.2681)		0.392	0.251
	γ	0.9084	(0.5611,1.2922)		0.618	0.307
	λ	2.3126	(1.1376,4.3364)		0.099	0.223
EW	α	7.4618	(4.5975,11.2487)	-835.774	0.232	0.076
	γ	0.4409	(0.3456,0.5518)		0.324	0.234
	λ	4.0185	(1.4213,7.6297)		0.122	0.166
BE	α	3.3499	(1,9664,5.2017)	-844.909	0.463	0.334
	β	0.0590	(0.0250,0.1167)		0.818	0.772
	λ	2.2978	(1.2235,4.1378)		0.699	0.394
Weibull	γ	1.654	(1.4712,1.8571)	-825.444	0.736	0.757
	λ	3.850	(2.788,3.293)		0.710	0.842

From Table 1, we observed that the convergence of the MCMC algorithm was not obtained choosing values less than 1 for these hyper parameters, even when using a very large burn-in -period for the algorithm. These results were shown in Table 1, considering the beta-Weibull (BW), exponentiated Weibull (EW), beta-Exponentiated (BE) and Weibull distributions respectively. Estimated parameters were obtained as median estimate of Gibbs samples drawn as a join posterior distribution. Median is preferred here over mean due to skewed nature of the distribution in the simulation process.. The p values from Heidelberger and Welch (HW) convergence diagnostic criteria do not reject the null hypothesis of stationary of the chains, for being larger or equal than 0.10. In the case of Geweke's p value which also suggest convergence. The result further suggest that, among the models in consideration, Weibull distribution has the lowest Log pseudo marginal likelihood (LPML) value unlike BW, BE and EW distributions all having similar LPML value.. However, an additional evidence of a better fit is the non convergence of the MCMC estimation on fitting BW distribution in presence of cure fraction as against standard Weibull distribution (Sauerbrei et al., 1999).

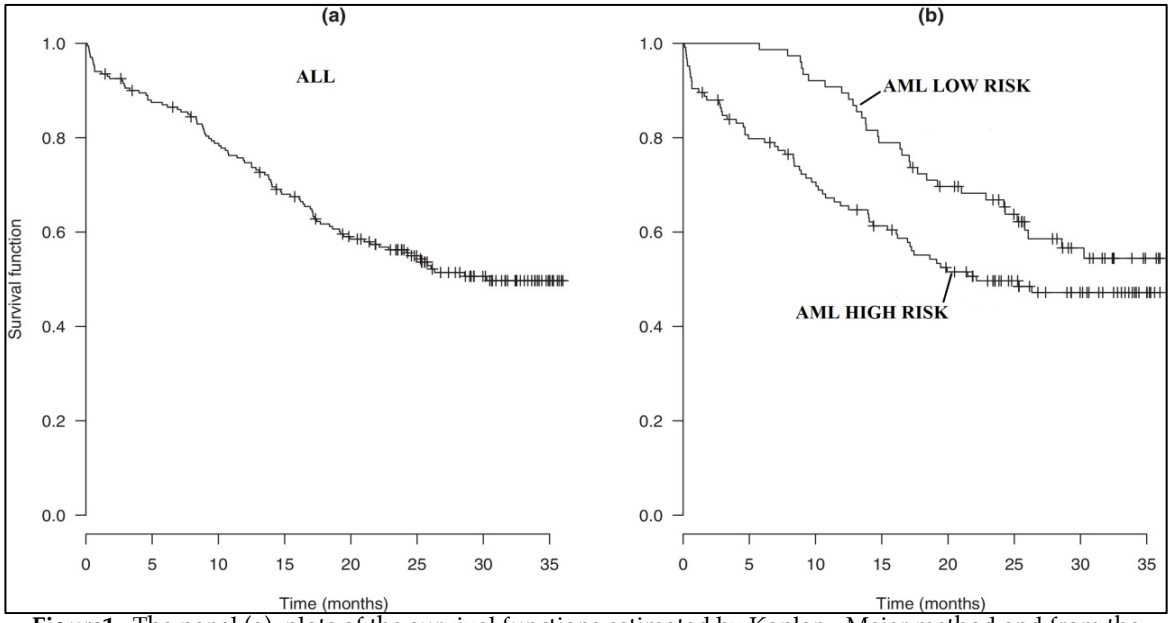

Figure1 : The panel (a), plots of the survival functions estimated by Kaplan - Meier method and from the models based on the BW and Wiebull distributions

Where (ALL) stands for "Acute Lymphoblastic Leukemia". While Panel (b), shows the hazard functions based on the Bone-Marrow Transplant data, where (AML) low risk and (AML) high risk stands for "Acute Myelocticm Leukemia".

The inferences for the non-mixture and mixture model which are based on the Beta-Weibull distribution with its special cases are clearly demonstrated in Table 2. Based on highest LPML of the models, mixture models get a better fit (Klein & Moschberger KM, 2003). Furthermore, the 95% credible interval for η_2 based on its non zero value inclusion suggest that the subjects in the AML high risk and low risk groups have contrasting cure fractions. The Bayesian estimates for the cure fractions for every risk group can be obtain by considering the simulated samples for n0,n1 and n2 and the relation $P(AML\ lowrisk) = exp(\eta_0)$, $P(AML\ highrisk) = exp(\eta_0 + \eta_1)$ and $P(all) = exp(\eta_0 + \eta_2)$. Therefore, the estimated results obtained for the cure fractions of the patients classified as AML low risk, ALL and AML high risk are shown above respectively. The graphs in Figure 2, shows that Kaplan - Meier survival curves for bone marrow transplant patients based on the BW distribution fit the mixture model at all level of risks. Note that the curves obtained from the model are close to those estimated by Kaplan -Meier method, a great indication of good fit based on the models for the (Klein & Moschberger KM, 2003).

Table 2. The posterior summaries assuming the mixture model with covariate and considering the data set of 137 bone marrow transplant patients

Model	Parameter	Posterior median	95% HDP^a	$LPML^b$	HW^c p value	Geweke's p value
BW	α	1.0129	(0.3684,2.1799)	-67.403	0.453	0.729
	β	1.2932	(0.1107,3.2681)		0.224	0.251
	γ	1.0381	(0.5337,1.6854)		0.338	0.607
	ζ_0	-0.3526	(-1.1376,0.3364)		0.069	0.533
	ζ_1	-0.6706	(-0.0166,0.2681)		0.152	0.651
	ζ_2	-0.9889	(-0.5611,-.2922)		0.148	0.307
	η_0	-0.1337	(-1.1376,0.3364)		0.799	0.343
	η_1	-0.4843	(-0.2611,0.2922)		0.618	0.707
	η_2	-0.9124	(-1.1376, 0.3364)		0.779	0.243
EW	α	0.9930	(4.5975,11.2487)	-67.374	0.232	0.076
	γ	1.0456	(0.5611,1.2922)		0.618	0.307
	ζ_0	-0.5640	(1.1376,0.3364)		0.099	0.223
	ζ_1	-0.6876	(0.0166,0.2681)		0.372	0.351
	ζ_2	-1.0025	(0.5611,1.2922)		0.618	0.307
	η_0	-0.1466	(-1.1376,1.3364)		0.099	0.256
	η_1	-0.4688	(-0.0350,1.1427)		0.834	0.435
	η_2	-0.9530	(0.0150,0.2147)		0.568	0.872
BE	α	1.0649	(1,9664,5.2017)	-66.561	0.483	0.007

Model	Parameter	Posterior median	95% HDP^a	$LPML^b$	HW^c p value	Geweke's p value
Weibull	β	1.2006	(0.0166,0.2681)	-65.557	0.392	0.251
	ζ_0	-0.4126	(-1.1376,0.3364)		0.099	0.223
	ζ_1	-0.6561	(-.0166,0.2681)		0.692	0.281
	ζ_2	-0.9876	(-1.5611,1.2922)		0.618	0.307
	η_0	-0.1365	(-0.1376,1.9864)		0.099	0.223
	η_1	-0.4753	(-.5611,1.2922)		0.618	0.337
	η_2	-0.9146	(-1.1376,0.2324)		0.099	0.223
	γ	1.654	(1.4712,1.8571)		0.10	0.265
	ζ_0	-0.3126	(-1.1376,4.3364)		0.023	0.123
	ζ_1	-0.0806	(-1.0166,-0.2881)		0.362	0.281
	ζ_2	-1.9084	(-1.5611,-0.4922)		0.618	0.237
	η_0	-0.3126	(-0.1376,0.3364)		0.099	0.243
	η_1	-0.9084	(-1.4621,0.2322)		0.228	0.417
	η_2	-0.3126	(-1.2346,-0.5364)		0.565	0.287

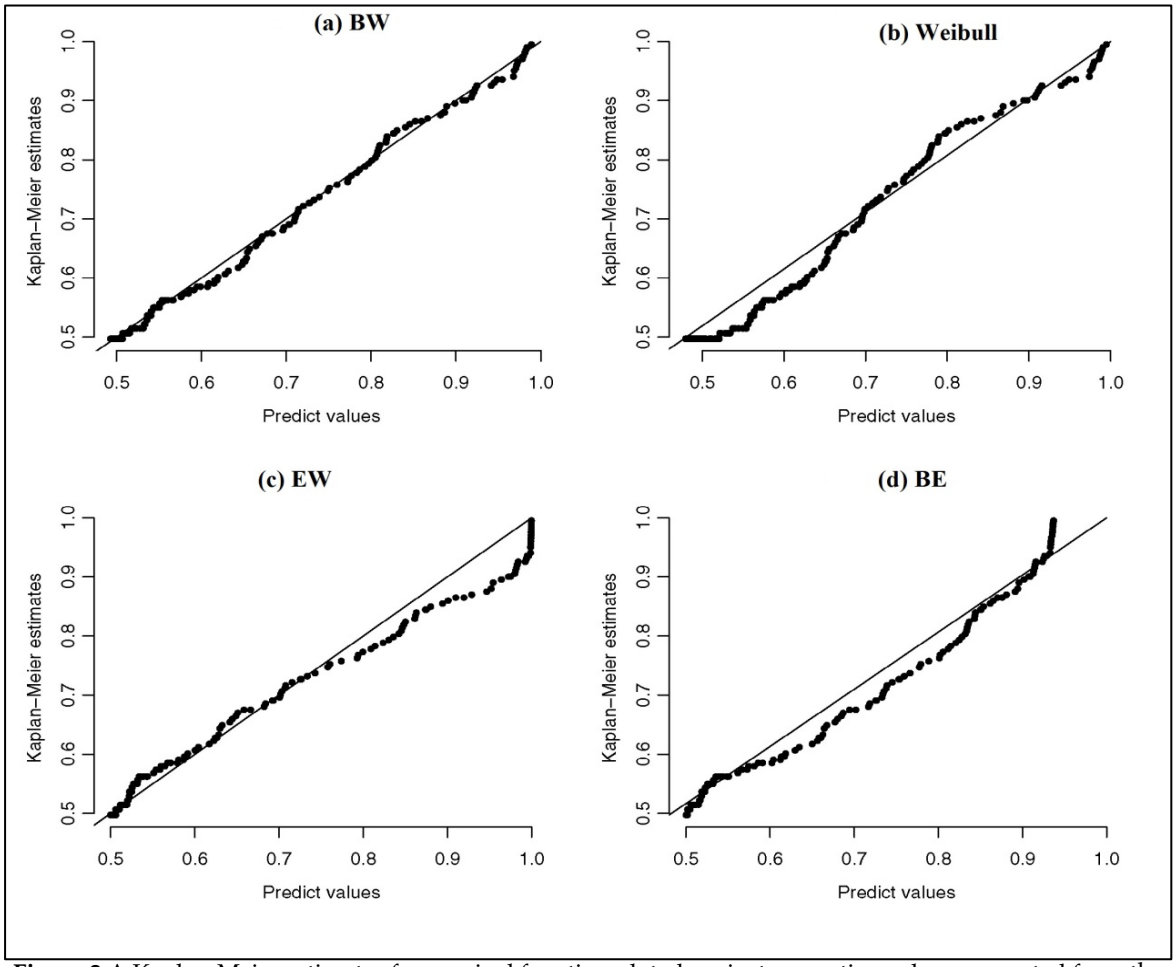

Figure 2:A Kaplan-Meier estimates for survival function ploted against respective values generated from the parametric mixture models for each of the distribution of interest: (a) BW (b) Weibull, (c) EW, (d) BE.

Conclusion

The cure fraction model and covariates analysis are strong features of a life time data analysis. Deployment of different parametric formulations for the analysis of such data can be done as mixture or non mixture models. This paper establish a parametric models approach based on BW distribution with special cases useful in analyzing medical data set (Wahed et al., 2009). Also the Bayesian methodology using MCMC methods was demonstrated in this work as a suitable tool to establish certain inferences about parameters of the model. As highlighted by (Carrasco et al., 2008), the limitation of the BW distribution is that the survival function has no closed form of expression and thus numerical integration techniques were utilize for parameter estimate of the model. Same limitations were more critical in terms of covariates because the likelihood function become more

complex. An advantage of Bayesian approach over other conventional method is it explicit incorporation of an expert prior opinion for the parameters. In clinical application, the knowledge of a specialist of the expected proportion of patience who are immune to the event of interest can be added into a prior distribution for the cure fraction p to have a more precise inference

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