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BAYESIAN ACCELERATED FAILURE TIME AND ITS APPLICATION IN CHEMOTHERAPY DRUG TREATMENT TRIAL

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ABSTRACT

The Cox proportional hazards model (CPH) is normally applied in clinical trial data analysis, but it can generate severe problems with breaking the proportion hazard assumption. An accelerated failure time (AFT) is considered as an alternative to the proportional hazard model. The model can be used through consideration of different covariates of interest and random effects in each section. The model is simple to fit by using OpenBugs software and is revealed to be a good fit to the Chemotherapy data.

Key words: Survival Analysis, Faliure Time, Metronomic, Cisplatin.

1. Introduction

Accelerated Failure Time (AFT) models for time to event data give the scope to work with a parametric form of the hazard function. It is possible to accumulate random effects as frailty part, and they can be easily fitted with statistical software. However, standard statistical methods for survival analysis are dependent on asymptotic statistical inference. Bayesian methods can be an alternative choice for survival data analysis. This work was influenced by the analysis of data for drug treatment effect, comparison among chemotherapeutic patient on a duration of survival. This primary application is then applied to illustrate the methodology in this paper, but the illustrated approach is also appropriate to other types of study. The paper is organized as follows. A discussion of accelerated failure time models is given in section 3. The models are then illustrated in the Chemotherapy data and their fitness evaluated in different sections. The Data methodology is explained

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in section 4. Section 5 provides the data modelling problem. Availability of different methods and their extension are detailed in section 6. Data analysis and results are provided in section 7. Section 8 gives the discussion and concluding remarks.

2. Accelerated Failure Time (AFT) Model

An Accelerated Failure Time (AFT) is a parametric model to give the alternative of the proportional hazard model. In the case of the proportional hazard model the effect of covariates is measured in terms of multiplication by a constant. In contrast to the proportional hazards model, the AFT model measured the effect of covariates with positive or negative terms by some constant discussed by David (2003). Let the $S_1(t)$ and $S_2(t)$ be the survival function in treatment Group-I and Group-II respectively. The AFT defines that $\phi > 0$ and

$$S_1(t) = S_2(\phi t) \tag{1}$$

The interpretation as follows : the percentage of individuals in the treatment Group-I that lives longer than time-(t) equal the percentage of individuals in the Group-II that lives longer than ϕt. Now the survival time t can be replaced by M_{1t} and M_{2t} as median survival time for treatment Group-I and Group-II. Now we have the hypothesis

$$S_1(M_{1t}) = S_2(M_{2t}) = 0.5 \tag{2}$$

and

$$\phi M_{1t} = M_{2t} \tag{3}$$

The AFT is an extension over limited application of the Proportional Hazard (PH) model. The parameters of interest in regression analysis become more robust in AFT than PH models, especially for ignored covariates (Hougaard (1994). In this paper, we propose an AFT regression model by adding a random effect to explore the influencing factor for survival duration among chemotherapy-treated patients. The aim of this work is to explore the treatment effect of Metronomic chemotherapy in comparison with Cisplatin chemotherapy. Three methods are applied to compare the treatment effectiveness,i.e (I) AFT regression with right-censored observation (II) AFT through consideration of Correlation Structure and (III) Bayesian extension of AFT models. The data are analyzed using OpenBugs code. The DIC value is used to select the best fit parametric model (Spiegelhalte 2002).

3. Data Motivation

Conventional MTD based chemotherapy dosing approach has lead to unsatisfactory efficacy results with excess of toxicity in comparison with new modality of drug administration termed as metronomic chemotherapy. It is an alternative to the traditional chemotherapeutic treatments (Hanahan 2000). The experimental work of metronomic chemotherapy was done by Folkman and his colleagues (Folkman 1971 and Hanahan 1996). The efficacy of metronomic chemotherapy on tumor with lack of toxicity of metronomic chemotherapy in mouse model was encouraging (Klement 2002). Multiple clinical studies in different tumors at different body sites have confirmed the efficacy of metronomic chemotherapy. In head and neck cancers too; metronomic chemotherapy in a palliative setting has shown a promise. The standard Cisplatin based palliative chemotherapy in head and neck cancers leads to a marginal improvement in overall survival. This improvement comes at a cost of severe side effects; Cisplatin in high dose causes emesis, nephrotoxicity, electrolyte disturbances and neurotoxicity. Hence an alternative treatment strategy was warranted in this situation. The proposed study was conducted in the department of Medical Oncology. Tata Memorial Hospital (TMH), Mumbai between 2011 to 2013, India. Patients attending the outpatient department of Medical Oncology (TMH) were selected for the present study subject to fulfillment of the selection criteria. Patients warranting palliative chemotherapy in head and neck cancers were randomized into 2 arms. One arm received 3 weekly Cisplatin for 6 cycles and another arm received oral metronomic chemotherapy untill progression. These patients were followed untill death. In this study, we were interested in the survival disparities between Metronomic and Cisplatin. The duration of survival was of two types: Overall survival and Progression Free Survival. The individual-specific information for a patient that is used in this study is age (age of the patient at diagnosis in complete years), Overall survival time, Progression-free survival time, Previous treatment and type of treatment (Metronomic or Cisplatin). We have 110 patients of chemotherapeutic effect, 57 patients from Metronomic and 53 patients from Cisplatin therapeutic groups. Table 1 provides a summary of the characteristics of the chemotherapeutic patients included in this study. In Figure 1, we plot the median duration estimates for both Metronomic, and Cisplatin groups of overall survival and progression-free survival.

4. Modeling Problems

The PH and AFT models are two attractive choices for survival analysis. The non-parametric Kaplan-Meier (K-M) curve can be used as the pointer for selection of suitable models. Figure 1 reveals the comparison of treatment groups in terms of survival duration. The graphical exploration of K-M curve and cumulative survival function are given in Figure 2. As basic assumption about proportional hazards, it is expected that the difference between the two functions will be constant. But Figure 2 does not give the strong evidence about the pattern of such expectation. We find that the survival rate does alter noticeably with the duration and it emerges that the metronomic group tends to have higher survival rates than the Cisplatin therapeutic group. So, considering random effects in survival models should develop the estimates of the contributing factors. Instead, the both functions are nearly same for the initial few days of time, almost up to the 50 days and then differentiate. It gives an idea about the possible violation of the proportional hazard model's assumptions. It is reasonable that the hazard functions are nontrivial but identical at any time t=0 through gradual difference with the increment of t. However, it breaks the assumptions about constant hazard ratio assumption for the proportional hazard model. In the presence of non-proportionality occurrences, the accelerated failure time model is applicable into two sample frameworks. It assumes the equality about scale change in the hazard function over the period.

5. Methods

5.1. Regression with Right-Censored Observations

Let T be the follow-up times, C is the censoring indicator and X is the baseline covariates. The actual survival time is defined as $Z \sim Weibull(\gamma, \lambda)$. The density and hazard fnction of Z is denoted as

$$f_0(z) = \lambda \gamma z^{\gamma-1} exp(-\lambda z^{\gamma}), h_0 = \lambda \gamma z^{\gamma-1} \tag{4}$$

Further, the hazard function is defined with

$$h(z|X) = exp(\beta^T X) h_0(z) = exp(\beta^T X) \lambda \gamma z^{\gamma-1} \tag{5}$$

It is possible to formulate the AFT from Weibull distribution through con-

sideration of $-\mu/\sigma$, as Intercept, α as a regression parameter by

$$\gamma = \sigma^{-1}, \lambda = exp(-\mu/\sigma), \beta = -\alpha/\sigma \tag{6}$$

5.1.1 Maximum Likelihood Estimation of Parameters

The aim is to estimate the parameter vector (γ, λ, β) based on this data through maximum likelihood. The corresponding likelihood function is defined as ,

$$L_1(\gamma, \lambda, \beta) = \prod_{i=1}^{n} h(T_i|X)^{c_i} S(T_i|X) \tag{7}$$

In order to account for X_{1i} potentially being censored, make additional assumptions and modify the likelihood function as follows: first, we explicitly specify a distribution for X_{1i} by specifying the density f_θ where $\theta \in R^d$ indicates the parameterization of f, for $d \geq 1$. Note that they assume the same distribution for all observations. Often it seems sensible to assume $f_\theta = f_{\mu,\sigma^2}$ as Normal, maybe after taking the logarithm of X_{1i}. Define for each observation the binary random variable $R_i = 1\{X_{1i} \geq c_i\}$ that indicates the status of the observation, i.e. whether it is observed or left-censored. The probability mass function p_{R_i} of R_i is a simple Bernoulli distribution with success probability $\pi_i = P(X_{1i} > c_i) = \int_{c_i}^{\infty} f_\theta(x)dx$ that X_{1i} is observed.

5.2. AFT through consideration of Correlation Structure

Let T_i, C_i and X_i be the failure time, censoring time and $p \times 1$ covariate for the i^{th} subject. Further, T_i is conditionally not dependent on $C_i|Xi$. The semi-parametric AFT model is defined with

$$T_i = X_i^T \beta + \varepsilon_i, i = 1, ..n \tag{8}$$

The term β is a regression parameter, ε_i(error) is identically distributed with random variables. It is assumed that ε_i are free from X_i. The i^{th} individuals observed data is defined as $Y_i = min(C_i, T_i)$. The matrix representation of X_i is very crucial for estimation of regression coefficients. There are several features that may occur about the representation of X_i like margin-specific regression coefficient, identical regression coefficient or mixture of margin-specific regression and identical regression. The presence of correlations between measurements is a natural problem for estimation procedures. In this work the ε_i are assumed to have I.I.D and correlation structure without spec-

ification and correlation with "Exchangeable" are considered to perform this analysis. The general extension of Generalized Estimating Equation (GEE) is applied in this work to carry the algorithm. (Chiou 2014a, Chiou 2014b).

5.3. Bayesian Modeling

The AFT model is defined as

$$log(t_{ij}) = \alpha + x_{ij}\beta + \Omega_{ij} + \sigma\varepsilon_{ij} \tag{9}$$

The term $\alpha + x_{ij}\beta$ is the linear predictor of a subset of intercept and linear dependence of regression predictor and parameters. The term Ω_{ij} effects model and ε_i is the error term. Now, we can write

$$f(t_0/\lambda_{it}) = \frac{1}{\sigma t_0} f_0(\frac{\log(t_0) - \lambda_0}{\sigma}) \tag{10}$$

$$S(t_0|\lambda_0) = S_0(\frac{log(t_{ij}) - \lambda_{ij}}{\sigma}) \tag{11}$$

$$h(t_0|\lambda_{ij}) = \frac{1}{\sigma t_{ij}} h_0(\frac{log(t_{ij}) - \lambda_{ij}}{\sigma}) \tag{12}$$

The terms $f_0(.)$ and $s_0(.)$ are the base failure distribution and corresponding survival function. In case of logistic model, it can be defined with

$$V_{ij} = \alpha + x_{ij}\beta + \Omega_{ij} \tag{13}$$

$$S_0(\varepsilon) = \frac{1}{1 + exp(\varepsilon)} \tag{14}$$

and

$$S(t_0/V_{ij}) = S_0(\frac{log(t_{ij}) - V_{ij}}{\sigma}) \tag{15}$$

$$S(t_0/V_{ij}) = \frac{1}{1 + [t_{ij} exp(-V_{ij})]^{1/\sigma}} \tag{16}$$

$$f(t_{ij}|V_{ij}) = S_0(\frac{log(t_{ij}) - V_{ij}}{\sigma})^2 exp(\frac{log(t_{ij}) - V_{ij}}{\sigma}) \tag{17}$$

It is assumed that $S_0(.)$ is following logistic distribution. Further, the Likelihood is defined as

$$L_2 = \prod_{i=1}^{n} \prod_{j=1}^{n_i} [\frac{1}{\sigma t_{ij}} f_0(\frac{log(t_{ij}) - V_{ij}}{\sigma})]^{V_i} S_0(\frac{log(t_{ij}) - V_{ij}}{\sigma})^{1-c_{ij}} \tag{18}$$

Let $p(a)$ gives the prior distribution for the parameter a and $p(b)$ for the parameter b. The posterior distribution can be stated as

$$p(b,V,a/t) \propto L(t|b,V)p(W/a)p(b)p(a) \tag{19}$$

In Model1, it is assumed that $t_i \sim weibull(\rho,\lambda_i)$. The rate is defined as

$$\log(\lambda_i) = \beta_0 + \mu_{j(i\in j)}, (j = 1,2) \tag{20}$$

The terms β_0 , μ_j and $\log(\rho)$ are assumed to have prior distributions with $N(0,\sigma_\beta^2)$,$N(0,\sigma_\mu^2)$ and $N(0,\sigma_\rho^2)$ respectively.

The Model2, is defined as

$$\log(\lambda_i) = \beta_0 + \mu_{j(i\in j)} + v_i, (j = 1,2) \tag{21}$$

and v_i is enclosed to take care about random effect. The prior distribution of v_i is obtained through $v_i \sim N(0,\sigma_v^2), \tau_v = \sigma_v^2, \sigma_v \sim U(0,3)$.

In Model3, the shape parameter is attached for individual specific observation through $t_i \sim Weibull(\rho_i,\lambda_i)$. The prior distribution of ρ_i is assumed through $log(\rho_i) \sim N(0,\sigma_\rho^2)$ The individual specific random effect has not been considered in this model.

The model performance is observed through p_D,$\bar{D}$ and DIC respectively. The model with the smallest DIC value is considered as suitably fitted in this scenario. The posterior mean estimates observed from three models are given in Table 2 and the corresponding p_D,$\bar{D}$ and DIC values of the model parameters are detailed in Table 4.

6. Data Analysis and Results

Based on the two retrospective data and related studies the predicted PFS for Arm B and Arm A were assumed with 5 months and 2.5 months respectively. Power of 80% was adopted and a total of 33% increment of PFS by the metronomic arm over cisplatin was expected. A type one error of 0.05 was taken; with a 2 tailed p value of 0.05% considered as significant. A total sample size was calculated as 110. The intention to treat the patients was adopted to conduct the primary endpoint analysis. The PFS between both the arms were compared by Kaplan-Meier curve, with the unstratified log-rank test. The multivariate Cox proportional hazard was carried on PFS and OS. The covariates were selected through forward LR method. The hazard

Table 1: Demographic, baseline characteristics and important prognostic details according to the arm

Parameters	Cisplatin=53	Metronomic=57
Median	45(29-70)	48(31-69)
M:F ratio	44.9	49.8
Median monthly Income (USD)	30.7 (7.7-461.5)	38.4 (7.7-461.5)
Localization		
Local	11 (20.7%)	13(22.8%)
Regional	22(41.5%)	21(36.8%)
National	20(37.8%)	23(40.4%)
Tobacco chewer	39(73.6%)	36 (63.2%)
Cigarette smoker	17 (32.1%)	16 (28.1%)
Median pack years	20 (1-30)	20 (2-80)
Subsite of tumour		
Oral cavity	41(77.4%)	43 (75.4%)
Oropharynx	8(15.1%)	10 (17.5%)
Larynx	3(05.7%)	1 (01.8%)
Hypopharynx	1(01.8%)	3 (05.3%)
Locally advanced disease/relapse	50(94.3%)	54 (94.7%)
Metastatic disease	03(05.7%)	03 (05.3%)

ratio with 95% confidence interval was documented.

The median duration of PFS was higher in Arm B (i.e. median 101 days, 95% CI: 58.2-143.7 days) in comparison with Arm A(i.e. median 66 days, 95% CI; 55.8-76.1 days). The log-rank test shows there is a significant difference between both the arms ($p = 0.014$). The factors [age(0.07) and arm(0.015)] influencing the better PFS were obtained through Cox PH model. The hazard ratio in Arm A was 1.58 (95% CI,1.09,2.38). The median OS was significantly higher in Arm B (i.e. median 249 days , 95% CI: 222.48-275.52 days)) in comparison to Arm A(i.e. median OS 152 days (134.19-247.81 days). The log-rank test also confirms a significant difference between both the arms ($p = 0.02$). The only factor arm was found influencing for better OS and it was obtained through Cox PH model. The hazard ratio not in favor of Arm A was 1.63 (95% CI, 1.05, 2.50). The goal of this work is to explore whether Metronomic therapy provides more survival duration of cancer patients. Table 3 gives the estimates of λ and γ for PFS and OS separately. The Hazard Ratio(HR) and Event Time Ratio(ETR) estimates

Table 2: Posterior Mean estimates of parameters based on 20,000 MCMC runs

Parameters	Model1	
	Mean(SD)	(2.5%, 97.5%)
σ_0	1.63(0.32)	(0.78,1.98)
σ_1	1.02(0.60)	(0.07,1.95)
μ_1	0.78 (1.01)	(0.06,0.56)
μ_2	1.05 (1.03)	(0.06,0.86)
β_0	3.32(1.04)	(0.61,4.64)

Parameters	Model2	
	Mean(SD)	(2.5%, 97.5%)
σ_0	2.27(1.25)	(0.49,4.74)
σ_1	3.22(0.96)	(1.55,4.92)
μ_1	3.94 (0.09)	(0.01,3.92)
μ_2	0.53 (0.03)	(0.00,0.55)
β_0	0.94(0.05)	0.80,0.996)

Parameters	Model3	
	Mean(SD)	(2.5%, 97.5%)
σ_0	1.67(0.28)	(0.97,1.98)
σ_1	0.91(0.58)	(0.06,1.95)
μ_1	0.55 (0.91)	(0.05,0.29)
μ_2	0.82 (0.92)	(0.05,0.56)
β_0	3.56(0.91)	3.83,4.68)

Table 3: Posterior Mean estimates of parameters based on 20,000 MCMC runs

Parameters	PFS	OS
	Estimate(SE)	Estimate(SE)
λ	0.00(0.00)	0.00(0.00)
γ	1.16(0.09)	0.00(0.11)
Arm	0.63(0.21)	0.41(0.22)
Age	-0.02(0.01)	-0.01(0.01)

Table 4: Bayesian Model goodness of fit with Model 1, Model2 and Model3

Model	$\bar{D}$	*DIC*	p_D
1	2183	2179	2.98
2	2185	2183	20.16
3	2178	2186	3.96

Table 5: HR estimates obtained through Cox PH and AFT Model

Parameters	Cox PH	
	PFS	OS
Age	0.61(0.35, 1.11)	0.63(.335,1.105)
Arm	1.58(1.09,2.38)	1.63(1.05,2.50)
Parameters	AFT Model	
	PFS	OS
Age	0.97(0.95,0.99)	0.48(0.96,1.00)
Arm	1.88(1.22,2.83)	1.51(0.98,2.34

Table 6: Estimates obtained through regression models

Parameters	PFS		OS	
	Estimate(SE)	p-value	Estimate(SE)	p-value
Intercept	4.23(0.47)	0.00	5.18(0.43)	0.00
Arm	-0.54 (0.19)	0.00	-0.30(0.16)	0.00
Age	-0.02(0.00)	0.00	0.01(0.00)	0.00

Table 7: Estimates obtained through aftgee regression modeling

Parameters	Model1		Model2	
	Estimate(SE)	p-value	Estimate(SE)	p-value
Intercept	3.84(0.57)	0.00	3.84(0.48)	0.00
Age	0.01(0.01)	0.14	0.01(0.01)	0.09
Sex	-0.05(0.26)	0.82	-0.05(0.28)	0.83

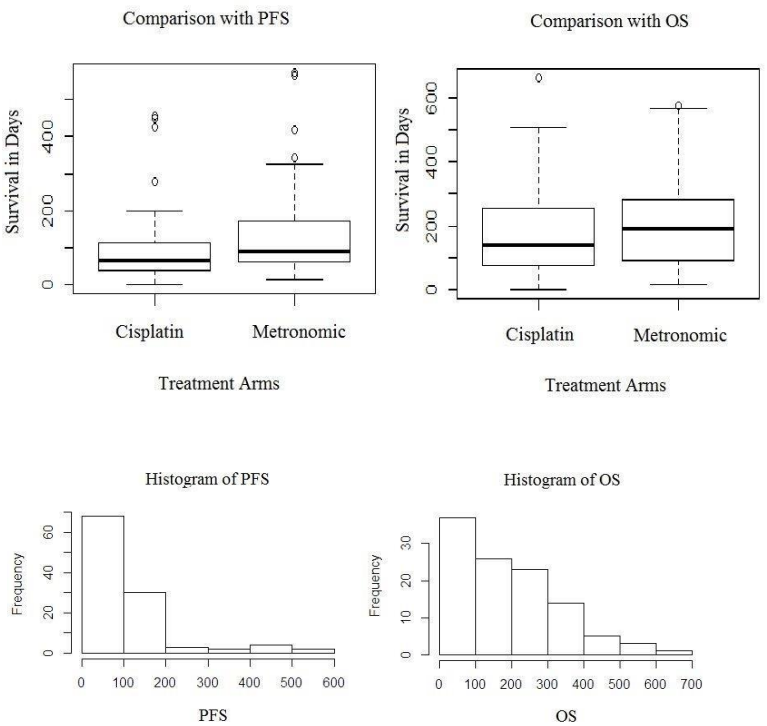

Figure 1: Comparison of Treatment Groups in Terms of Survival Duration

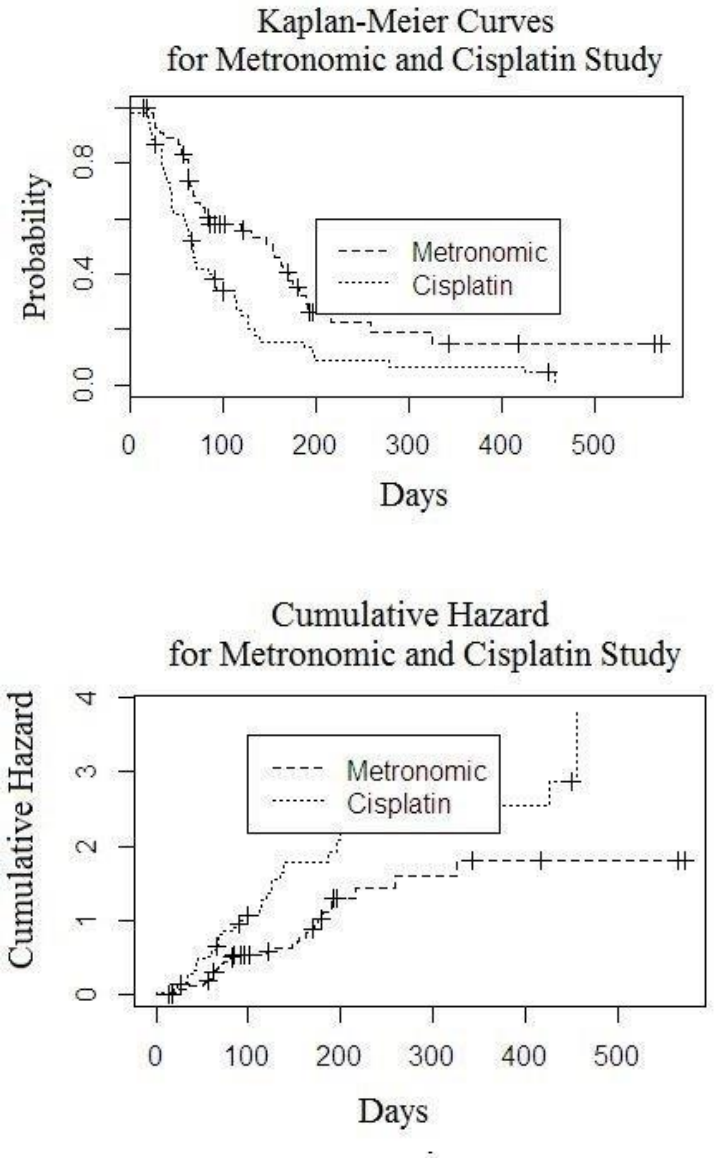

Figure 2: Treatment effect comparison

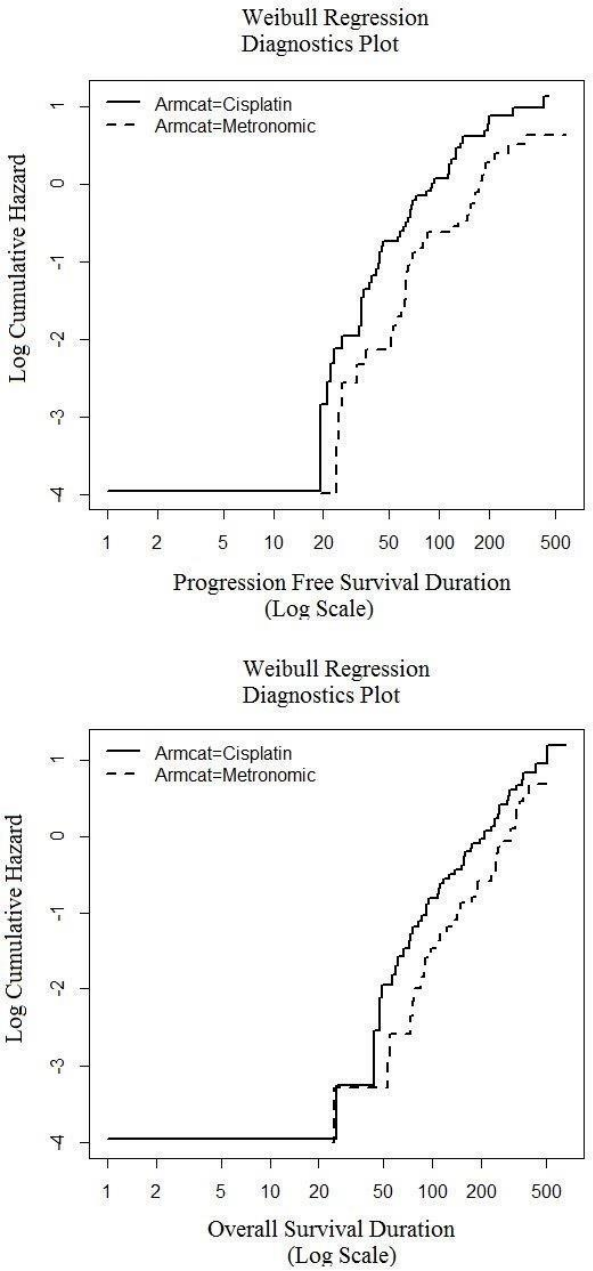

Figure 3: Diagnostic Plot for PFS and OS

obtained through regression models are detailed in Table 5. The mean and median survival duration in days is compared. In both the tables, duration of survival in Metronomic therapy is found better in comparison with Cisplatin. Further, the work contributes to the exploration of the influence of factors for the different survival between the groups. The work is carried out through the model to try to explain the effect of therapy on the time of survival. The coefficient of Arm is found to be significantly related to both models. It provides that patients treated with Cisplatin are likely to have more hazard in comparison with Metronomic arm(Table 5). The estimates of the regression coefficient of Arm and Age are observed with -.54(0.19) and -.02(0.00) respectively (Table 5). The coefficient of Sex is found to be non-significantly related to both models. It proposes that male and female patients are likely to have equal recurrence durations (Table 7). The data analysis is carried out through Bayesian approach. The prior distributional assumption is points for each parameter of interest. We desired to dominate the data information for posterior distribution value formulation. The non-informative prior is used to dominate the data value for posterior distribution for all parameters. The posterior sampling-based procedures Markov Chain Monte Carlo (MCMC) is applied for model generation. Model 1 is observed with minimum DIC value, i.e. 2179. It can be concluded that Model1 is more appropriate in this study data.

7. Discussion and Conclusion

This study provides that PFS is better in a metronomic arm in comparison to cisplatin arm. The result of cisplatin is similar with recently published studies with single-agent platinum (morton 1985,wittes 1976,clavel 1994). The CPH models are widely explored for censored regression modeling for covariates of interest. Accelerated failure time (AFT) models are another and rarely explored approaches for regression modeling for censored data model. The CPH modeling (Cox 1972) and AFT modeling (Kalbeisch 2002) are available methods for right-censored observations for survival data analysis. The frailty effects are widely applied into PH model through consideration of parametric model or with arbitrary distribution (Klein 1999,Horowitz 1999,Anderson 1995,Walker 1997,Sargent 1998,Pickles 1995).Recently, the parametric and non-parametric frailty distribution is applied through AFT (Sargent 1998). The gamma frailty has also been explored into AFT models (Pan 2001). The PH model is widely applicable tool for survival analysis. But exposure to address different types of distribution is limited. The widely applied

distributional assumption, i.e. Weilbull and Gompertz are only suited for monotonically increase or decrease distribution. It is very difficult to avail different types of distributional assumption through PH model. In contrast, AFT is open to carry different distributional assumption into the model assumptions (David 2003). Recently, Bayesian approach for AFT models has been explored. A Bayesian Semi-parametric approach is elaborated to an AFT model (Walker 1999). It also applied for an AFT model with interval-censored and structured correlated data (Komarek 2007). The random effect into AFT model is applied for multivariate doubly censored data for cluster observations (Komarek 2008). Dirichlet process prior is used for mixing distribution to deal with Semi parametric regression model for censored data (Ghosh 2006). A fully Bayesian approach for the median regression by Polya tree prior is proposed (Walker 1999). An application of normal mixture prior distribution has also been illustrated for AFT model (Komarek 2007,Komarek 2005). The AFT can be directly linked with expected death time to the covariates of interest through linear regression modeling. The semi parametric extension of AFT is more appropriate for undetermined error distributions. The rank-based approach (Prentice 1978) and least squares (Buckley 1979, Jin 2007) are two methods to handle the semi parametric extension of AFT. The specified distribution for error is called as parametric AFT model(Tsiatis 1990,Therneau 2014). Failure to specify the proper distribution for the error may generate the bias estimation about censored data. The Buckley-James (BJ) estimator (Buckley 1979) is the tool to work with parametric AFT.

In this paper, we examine the chemotherapeutic data by the Bayesian parametric AFT model. The OS and PFS were observed separately for better information about survival duration on chemotherapeutic effect. The OpenBUGS is utilized for data analysis through parametric AFT models. The DIC criterion is used to know the best fitted models. The K-M curve is plotted for non-parametric statistical inference. It is found that the Bayesian AFT model with random effect is suitable for analysis of chemotherapy data. The results observed in this study shows that metronomic arm is having significant influence on duration of survival on chemotherapeutic patients. The model can be more robust by allowing other parametric assumption. However, it can be difficult to carry the computational work (Anderson 1995,Sargent 1998,Folkman 1971). The DIC is applied as diagnostic criteria to test the model. The DIC is adopted to check the model fitting suitability. It is avaliable in OpenBugs. However, other model comparision tools can be

used to compare the models in different computational platforms. The parametric AFT model is applied to chemotherapeutic data. The computational difficulties may be greater if we shift from parametric approach (Anderson 1995,Sargent 1998,Folkman 1971). Although, the semiparametric approach can also be applied and it has been found successful in survival data analysis. However, semi-parametric approach can also be applied to AFT model as an extension of this work (Anderson 1995, Sargent 1998,Komarek 2007,Komarek 2005,Christensen 1988).

8. Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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