INDIAN JOURNAL OF SCIENCE AND TECHNOLOGY

RESEARCH ARTICLE

Check for updates

OPEN ACCESS

Received: 23-03-2023

Accepted: 26-06-2023

Published: 02-11-2023

Editor: Guest Editors: Dr. Madhuryya Saikia & Dr. Niranjan Bora

Citation: Mahanta KK, Hazarika J (2023) A Multivariate Proportional Odds Frailty Model with Weibull Hazard under Bayesian Mechanism. Indian Journal of Science and Technology 16(SP2): 30-37. https://doi.org/10.17485/IJST/v16iSP2.6447

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Funding: None

Competing Interests: None

Published By Indian Society for Education and Environment (iSee)

ISSN
Print: 0974-6846
Electronic: 0974-5645

A Multivariate Proportional Odds Frailty Model with Weibull Hazard under Bayesian Mechanism

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Abstract

Objectives: The objective of this study is to develop a new Proportional Odds frailty model by using a Weibull hazard function in context of Bayesian mechanism. **Methods:** Frailty models provide a convenient way to introduce random effects, association and unobserved heterogeneity into models for survival data. Proportional Odds (PO) model is a widely pursued model in survival analysis which extends the concept of Odds ratio considered for lifetime data with covariates. Proportional Odds models can be derived under frailty approach by introducing a frailty term for each individual in the exponent of the hazard function, which acts multiplicatively on the baseline hazard function. In this paper an attempt has been made to develop a new Proportional Odds frailty model by using a Weibull hazard function in context of Bayesian mechanism. **Findings:** The methodologies are applied to a real life survival data set and the posterior inferences are drawn using Markov Chain Monte Carlo (MCMC) simulation methods and model comparison tools like Deviance Information Criteria (DIC) and the Log Pseudo Marginal Likelihood (LPML) are also calculated and to check the fit of the model Cox-Snell residual plot is employed. The performance of the newly developed model is compared with an existing proportional odds model without the frailty term and it is observed that the newly developed frailty model perform well as compered to the traditional non frailty model. **Novelty:** A new Proportional Odds frailty model using Weibull hazard function under Bayesian mechanism is developed in this paper which is an added contribution in the field of Survival Analysis.

Keywords: Proportional Odds (PO) model; Frailty; MCMC simulation methods; DIC; LPML; Cox Snell residual plot

1 Introduction

Frailty models, a specific area in survival analysis provide a convenient way to introduce random effects, association and unobserved heterogeneity into models for survival data. Frailty is an unobserved random proportionality factor that modifies the hazard function of an individual, or of related individuals. The frailty approach is a statistical modeling concept which aims to account for heterogeneity, caused by unmeasured covariates. Proportional Odds (PO) model is another widely pursued model in survival analysis which extends the concept of Odds ratio considered for lifetime data with covariates. Proportional Odds models can be derived under frailty approach by introducing a frailty term for each individual in the exponent of the hazard function, which acts multiplicatively on the baseline hazard function.

In case of Bayesian analysis of frailty models[1] use exponential and Gompertz regression models in gamma shared proportional hazards frailty model and[2] developed a generalized log-logistic proportional hazard model.[3] proposed a Bayesian Parametric Proportional Hazard Model and applied it to a Right-Censored Healthcare Data. In case of the development of spatial frailty model[4] proposed a spatial Cox proportional hazard models,[5] develop a Spatial Survival Model with Non-Gaussian Random Effect.[6] developed a Semiparametric spatial frailty model using a non-parametric prior for modelling baseline survival function.[7] proposed a Semi-Parametric Cure Rate Proportional Odds Models with Spatial Frailties for Interval-Censored Data.[8] developed a Bayesian shared Proportional odds gamma frailty models for time to first birth of married women in Ethiopia.[9] in their study used a Bayesian hierarchical survival model in the setting of competing risks for the spatially clustered HIV/AIDS data.

Form the literature review it is observed that various researchers work in the field of Bayesian analysis of Multivariate Proportional hazards frailty model but so far our knowledge goes, it is observed that a very less amount of work have been done yet in case of Bayesian analysis of Proportional Odds frailty models. However, some researcher work in the fields of Bayesian analysis of Proportional Odds models under spatial frailty approach[7,8]. Still, some distributions exist, which are very simple but till now not used for modeling the baseline hazard function in case of Bayesian analysis of Multivariate Proportional odds frailty models. So in this paper an attempt has been made to develop a new Multivariate Proportional Odds frailty model by using a Weibull hazard function in context of Bayesian mechanism. For making a comparative analysis the same Proportional Odds model without the frailty term is also considered here. To illustrate the models a real life survival data set is used and posterior inferences are drawn accordingly.

2 Methodology

Since the odds ratio is a useful tool for comparison of the probabilities of occurrence of an event under different conditions so it is very natural that a proportional odds model should have been considered for lifetime data with covariates. This model was introduced[10] which can be written as,

$$\frac{S(t \mid X)}{1-S(t \mid X)} = \frac{S_0(t)}{1-S_0(t)} e^{-\beta' X} \tag{1}$$

Where, $S(t|X)$ is the survival function evaluated at time t conditional on the observed covariates X and β is the corresponding vector of regression coefficients and $S_0(t)$ is the baseline survival function.

Proportional Odds (PO) frailty model extends the PO model by introducing a frailty term Z for each individual in the exponent of the hazard function, which acts multiplicatively on the baseline hazard function. Thus,

$$\begin{gathered}\frac{S(t \mid Z,X)}{1-S(t \mid Z,X)} = \frac{S_0(t)}{1-S_0(t)} e^{-\left(\beta' X+Z\right)} \\ \Rightarrow S(t \mid Z,X) = \frac{e^{-\left(\beta' X+Z\right)} S_0(t)}{1+\left\{e^{-\left(\beta' X+Z\right)}-1\right\} S_0(t)}\end{gathered} \tag{2}$$

Thus the corresponding density and hazard functions are given by,

$$f(t \mid Z,X) = \frac{e^{-\left(\beta' X+Z\right)} f_0(t)}{\left[1+\left\{e^{-\left(\beta' X+Z\right)}-1\right\} S_0(t)\right]^2} \tag{3}$$

$$h(t \mid Z,X) = h_0(t) \frac{1}{1+\left(e^{-\left(\beta' X+Z\right)}-1\right\} S_0(t)} \tag{4}$$

Where $S_0(t)$, $f_0(t)$ and $h_0(t)$ are the baseline survival function, baseline density and baseline hazard function assumed to be unique for all individuals in the study population respectively.

Multivariate frailty modes deal with the multivariate survival data for example competing risk, recurrence of events in the same individuals, occurrence of a disease in relatives etc. Let us consider a right censored survival data *(tij,* δ_{ij}*), i=1,2,…,n ; j=1,2,…,m* and assume that the censoring is non- informative. Let δ_{ij}denotes the indicator variable taking value 1 if the j^{th} subject *(j=1,2,…,m)* of the i^{th} group *(i=1,2,…,n)* fails and value 0 otherwise. Hence, t_{ij} is a failure time if $\delta_{ij}=1$ and a censoring time otherwise. Let x_{ij} be the covariate for each subject. Hence, the triplet $(t_{ij}, \delta_{ij}, x_{ij})$ is observed for all i and j. Let (Y, X) denotes the collection of all such triplet $(t_{ij}, \delta_{ij}, x_{ij})$. The vector of unobserved frailty z_i*'s*, denoted by Z, is called the augmented data and the triplet (Z, Y, X) is called the complete data. If $h_{ij}(t)$ and $S_{ij}(t)$ be the hazard function and survival function of the j^{th} subject in the i^{th}group then the complete data likelihood for a multivariate frailty model is given by,

$$L(Z,Y,X) = \prod_{i=1}^{n} \prod_{j=1}^{m\delta} \left(h_{ij}(t)\right]^{\delta_{ij}} S_{ij}(t) \tag{5}$$

Where Z is the random variable known as frailty which varies over the population and it is unobservable. Z_i is the frailty variable for the i^{th} group of individuals. Given the unobserved frailty Z_i, t_{ij}'s are independent.

For the newly proposed multivariate proportional odds model let us consider a Weibull distribution with parameter μ and γ for modeling the baseline hazard function. The second parameter γ allows great flexibility to the model and different shapes of the hazard function. The respective density, survival function and hazard function in case of Weibull survival model are given by,

$$f(t) = \mu\gamma t^{\gamma-1} e^{-\mu t^{\gamma}},\ \mu > 0,\ \gamma > 0 \tag{6}$$

$$S(t) = e^{-\mu t^{\gamma}} \tag{7}$$

$$h(t) = \mu\gamma t^{\gamma-1} \tag{8}$$

The complete data likelihood for the multivariate PO frailty model is given by,

$$\begin{aligned} L_{POFM} &= \prod_{i=1}^{n} \prod_{j=1}^{m} \left(h_{ij}(t)\right]^{\delta_{ij}} S_{ij}(t) = \prod_{i=1}^{n} \prod_{j=1}^{m} \left[h_0 \frac{1}{1+\left\{e^{-(\beta' X+Z_i)}-1\right\} S_0(t)}\right]^{\delta_{ij}} \frac{e^{-\left(\beta' X+Z_i\right)} S_0(t)}{1+\left\{e^{-(\beta' X+Z_i)}-1\right\} S_0(t)} \\ &= \prod_{i=1}^{n} \prod_{j=1}^{m} \left[\mu\gamma t_{ij}^{\gamma-1} \frac{1}{1+\left\{e^{-(\beta' X+Z_i)}-1\right\} e^{-\mu t_{ij}\gamma'}}\right]^{\delta_{ij}} \frac{e^{-\left(\beta' X+Z_i\right)} e^{-\mu t_{ij}\,\gamma}}{1+\left\{e^{-(\beta' X+Z_i)}-1\right\} e^{-\mu t_{ij}\,\gamma}} \end{aligned} \tag{9}$$

And the complete data likelihood for the multivariate PO model without the frailty term (for comparison purpose this model is also considered in the study) is given by,

$$\begin{aligned} L_{POMWOF} &= \prod_{i=1}^{n} \prod_{j=1}^{m} \left[h_{ij}(t)\right]^{\delta_{ij}} S_{ij}(t) = \prod_{i=1}^{n} \prod_{j=1}^{m} \left(h_0 \frac{1}{1+\left\{e^{-(\beta' X)}-1\right\} S_0(t)}\right]^{\delta_{ij}} \frac{e^{-\left(\beta' X\right)} S_0(t)}{1+\left\{e^{-(\beta' X)}-1\right\} S_0(t)} \\ &= \prod_{i=1}^{n} \prod_{j=1}^{m} \left(\mu\gamma t_{ij}{}^{\gamma-1} \frac{1}{1+\left\{e^{-(\beta' X)}-1\right\} e^{-\mu t_{ij}\,\gamma}}\right]^{\delta_{ij}} \frac{e^{-\left(\beta' X\right)} e^{-\mu t_{ij}\,\gamma}}{1+\left\{e^{-(\beta' X)}-1\right\} e^{-\mu t_{ij}\,\gamma}} \end{aligned} \tag{10}$$

For the frailty parameter, let us consider an independent Normal prior distribution for the newly proposed model, defined as $Z_i \sim N(0, \tau^2)$, for $i=1,2,\ldots,n$. Then the density of the frailty variable Z is given by,

$$f(Z) = \frac{1}{\tau\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{Z}{\tau}\right)^2};\ -\infty < Z < \infty, \tau > 0 \tag{11}$$

Since gamma distribution is widely used as a conjugate prior in Bayesian statistics and it is the conjugate prior for the precision (i.e, inverse of the variance) of a normal distribution. So here we consider a gamma prior for τ i.e, $\tau^{-2} \sim Gamma(a_\tau\ , b_\tau\ )$.

Following[11] we consider a normal prior for the regression parameters which is given by $\beta \sim N(0, m)$. For the hyper parameters of the baseline hazard function we also consider a gamma prior due to its simplicity and flexibility. Here we assume that $\mu \sim$ Gamma(ρ,ρ) and γ~Gamma(a,b).

The joint posterior distribution for all the parameters of the newly proposed multivariate proportional odds frailty model with weibull hazard function is given by,

$$P_{POFM} = L_{POFM}\frac{1}{\tau\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{z}{\tau}\right)^2}\pi(\beta)\pi(\mu)\pi(\gamma)\pi\left(\tau^{-2}\right)$$
$$= \prod_{i=1}^{n}\prod_{j=1}^{m}\left(\mu\gamma t_{ij}^{\gamma-1}\frac{1}{1+\left\{e^{-(\beta' X+Z_i)}-1\right\}e^{-\mu t_{ij}^{\gamma}}}\right]^{\delta_{ij}}\frac{e^{-\left(\beta' X+Z_i\right)}e^{-\mu t_{ij}^{\gamma}}}{1+\left\{e^{-(\beta' X+Z_i)}-1\right\}e^{-\mu t_{ij}^{\gamma}}}\frac{1}{\tau\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{Z_i}{\tau}\right)^2}\pi(\mu)\pi(\gamma)\pi(\beta)\pi\left(\tau^2\right) \quad (12)$$

And the joint posterior distribution for all the parameters for the multivariate PO model without the frailty term is given by,

$$P_{POMWOF} = L_{POMWOF}\frac{1}{\tau\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{Z}{\tau}\right)^2}\pi(\beta)\pi(\mu)\pi(\gamma)\pi\left(\tau^{-2}\right)$$
$$= \prod_{i=1}^{n}\prod_{j=1}^{m}\left(\mu\gamma t_{ij}{}^{\gamma-1}\frac{1}{1+\left\{e^{-(\beta' X)}-1\right\}e^{-\mu t_{ij}'}}\right]^{\delta_{ij}}\frac{e^{-\left(\beta' X\right)}e^{-\mu t_{ij}{}^{\gamma}}}{1+\left\{e^{-(\beta' X)}-1\right\}e^{-\mu t_{ij}{}'}}\pi(\mu)\pi(\gamma)\pi(\beta) \quad (13)$$

π (.) be the respective prior distributions.

To get the data likelihood of the various parameters in (Equation (12)) we have to integrate out the Z_i's with the independent Gaussian prior density given in (Equation (11)). The final forms of the data likelihoods after integration are too complicated to work with. Thus, it is not so easy to evaluate the marginal posterior distributions analytically. To overcome this difficulty, we have to use Metropolis-Hastings algorithm[12] and Gibbs sampling[13] to generate samples from the appropriate marginal posterior distributions. Metropolis-Hastings algorithm and Gibbs sampling or a Gibbs sampler is a Markov chain Monte Carlo (MCMC) algorithm for obtaining a sequence of observations which are approximated from a specified multivariate probability distribution, when direct sampling is difficult.

3 Results and Discussion

In this section we consider a real life survival data set of 38 kidney patients on dialysis used by[14] to illustrate the proposed model and compare its performance with the traditional proportional odds model without the frailty term. The data set is recorded for time to first and second time of infection from the time of insertion of the catheter for 38 kidney patients using portable dialysis equipment. Age and sex of the patients along with the presence or absence of three kidney disease type GN, AN, PKD are considered as the covariates of the model.

Using this data set we have done the Bayesian Analysis of the newly proposed multivariate proportional odds frailty model and the traditional proportional odds model without the frailty term with the help of the R Software. In case of $e^{\beta' X+Z_i}, \beta = (\beta_{Age}, \beta_{Sex}, \beta_{GN}, \beta_{AN}, \beta_{PKD})'$ and we consider Sex $ij = 1$, if the j^{th} patient in the i^{th} group is a female and 0 otherwise. For the disease types GN, AN and PKD, GN $ij/AN_{ij}, /PKD_{ij} = 1$, if the j^{th} patient in the i^{th} group have the disease and 0 otherwise. Where $i = 1,2$ and $j = 1,2,\ldots,38$.

The MCMC is carried out through an empirical Bayesian approach coupled with adaptive Metropoli samplers[15]. The following hyper-parameter initial values were used in the simulation process. Here we consider τ = 1 and aτ = bτ=.001, ρ=0.001, a=0.01, b=0.01 and m=1. In case of Bayesian analysis sometimes it was difficult to sample from the resulting full conditional distribution due to computer underflow problems for different hyper-parameter initial values. Sometimes it is observed that Bayesian inference was largely insensitive to change in the values of the hyper-parameter.

From the analysis we have found the posterior inferences about the parameters of the models. Here the Table 1 and Table 2 show the posterior mean, median, standard deviation and 95% credible intervals for the regression Coefficients and the frailty variance respectively.

From the analysis it is observed that in case of the two fitted models β_{sex} shows the female patients have a slightly lower risk for infection. Also, β_{PKD} shows that presence of this disease has a lower impact on infection of the catheter.

Table 1. Posterior Inference of Regression Coefficients

Models	Regression Coefficients	Mean	Median	Standard Deviation	95% CI-Low	95% CI-Upper
Multivariate Proportional Odds (PO) Frailty Model using Weibull Hazard	β_{Age}	0.006715	0.007605	0.019258	-0.032534	0.042531
	β_{Sex}	-2.374729	-2.350184	0.634126	-3.662368	-1.134899
	β_{GN}	0.575931	0.581126	0.695671	-0.672068	1.945885
	β_{AN}	0.838527	0.839291	0.668901	-0.412312	2.230658
	β_{PKD}	-0.904540	-0.849033	1.062712	-2.950442	1.159998
Multivariate Proportional Odds (PO) Model using Weibull Hazard without Frailty	β_{Age}	0.004295	0.004156	0.016648	-0.027239	0.035148
	β_{Sex}	-2.350611	-2.347335	0.538348	-3.379441	-1.296205
	β_{GN}	0.622478	0.625729	0.627375	-0.675799	1.840597
	β_{AN}	0.880071	0.867046	0.617260	-0.294509	2.127648
	β_{PKD}	-0.805603	-0.775248	0.966528	-2.686374	1.004825

Table 2. Posterior Inference of Frailty Variance

Model	Mean	Median	Standard Deviation	95% CI-Low	95% CI-Upper
Multivariate Proportional Odds (PO) Frailty Model Using Weibull Hazard	0.355576	0.096441	0.578804	0.001952	2.016323

The estimates of frailty variance from the fitted frailty model shows presence of heterogeneity in the population of patients. Figure 1 and Figure 2 show the trace plots of the parameters for the fitted models and Figure 3 and Figure 4 show the Posterior Density Plots of the Parameters for the fitted models.

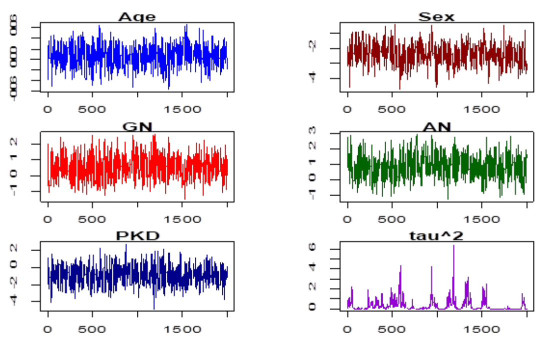

Fig 1. Trace plots for the Regression coefficients and Frailty variance for the Proportional Odds (PO) Frailty Model using Weibull hazard

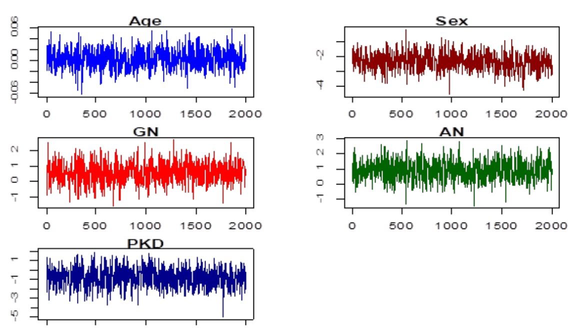

Fig 2. Trace plots for the Regression coefficients for the Proportional Odds (PO) Model using Weibull hazard without Frailty

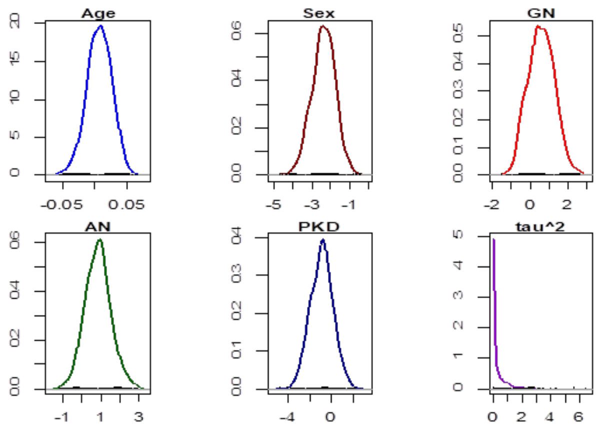

Fig 3. Posterior Density plots of the Regression coefficients and Frailty variance for the Proportional Odds Frailty Model using Weibull Hazard

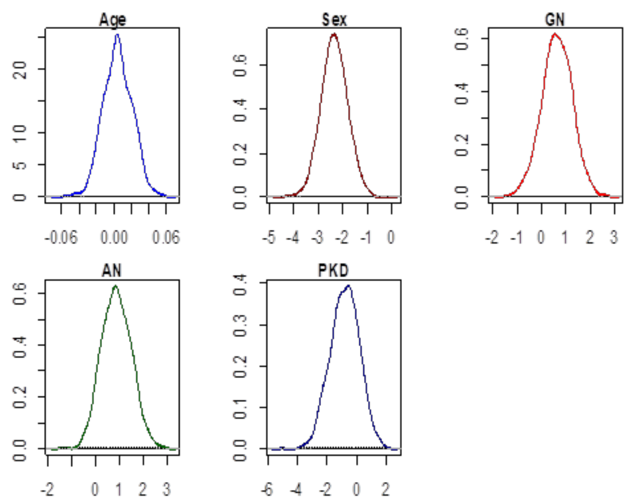

Fig 4. Posterior Density plots of the Regression coefficients for the Proportional Odds Model using Weibull Hazard without frailty

For model diagnostics, we consider a residual plot of[16] a plot of estimated cumulative hazard function (based on Cox and Snell residual and the censored data) versus the Cox and Snell residual. If the model provides a good fit to the data, we expect a straight line through the origin with slop 1. For the above fitted models the Cox-Snell plots are given in Figure 5 and Figure 6 from which it can be seen that the data fits the proposed models quite good and they are competing.

For model comparison, here two popular model choice criteria: the deviance information criteria (DIC)[17] and the log pseudo marginal likelihood (LPML)[18] are considered, where DIC (smaller is better) places emphasis on the relative quality of model filling and LPML (large is better) focuses on the predictive performance. For the above two fitted models the obtained LMPL and DIC are given in Table 3.

Table 3. LMPL and DIC of the fitted models

Models	Log Pseudo Marginal Likelihood: LPML	Deviance Information Criterion: DIC
Multivariate Proportional Odds(PO) Frailty model using Weibull Hazard	-180.786	352.7812
Multivariate Proportional Odds(PO) model using Weibull Hazard without Frailty	-334.7713	667.0212

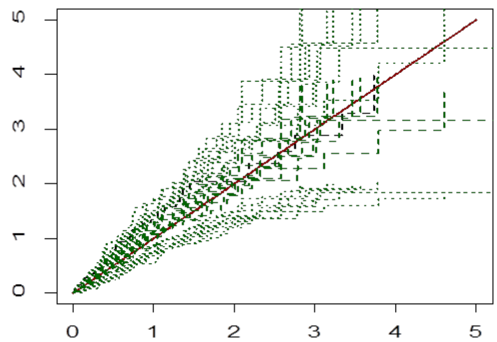

Fig 5. Cox and Snell plot for the Proportional Odds frailty model using Weibull hazard

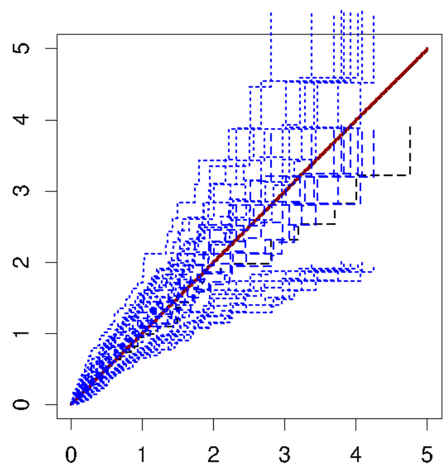

Fig 6. Cox and Snell plot for the Proportional Odds model using Weibull hazard without frailty

From the Table 3 it is observed that the Multivariate Proportional Odds Frailty Model using Weibull Hazard has a larger LMPL and Smaller DIC as compared to the Multivariate Proportional Odds (PO) Model without the frailty term. So in case of the above analysis it is observed that the Proposed Multivariate Proportional Odds Frailty Model using Weibull Hazard is better than the model without frailty term [1,8,19] also developed some new proportional hazards and proportional odds frailty models and compared its performance with other traditional survival models using AIC, BIC, DIC and many other criteria and observed that fit of the frailty models are better than the traditional survival models without the frailty term.

4 Conclusion

Frailty model is a random effect model for time to event data, where the random effect (the frailty) has a multiplicative effect on the baseline hazard function. In this paper, a new multivariate Proportional Odds frailty model is developed under Bayesian approach using Weibull baseline hazard function which is defiantly an added contribution in the field of Survival Analysis. For making a comparative analysis the traditional Proportional Odds model without the frailty term is also considered here. To explain the models a real life survival data set is used here and diagnostics checking and model comparisons are done by using some popular model choice criteria like Cox-Snell plot, LMPL and DIC etc. From the study it is observed that the newly

Proposed Multivariate Proportional Odds Frailty Model using Weibull Hazard perform better as compared to the traditional proportional odds model without the frailty term. Like the earlier works done by [1,7,8,19] etc. this study also recommended the application of frailty models instead of traditional survival model to analyse survival data. In near future researchers can use this newly developed multivariate Proportional Odds frailty model using Weibull baseline hazard function to analyze survival data under Bayesian Mechanism.

5 Declaration

Presented in Fourth Industrial Revolution and Higher Education (FIRHE 2023) during 23rd-25th Feb 2023, organized by DUIET, Dibrugarh University, India. The Organizers claim the peer review responsibility.

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