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An Application of Spatial Frailty Models to Recovery Times of COVID-19 Patients in India under Bayesian Approach

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Abstract: **The pandemic COVID-19, starts at the end of the year 2019, and rapidly blowout almost all over the sphere. There were more than 16.4 million people in the world pretentious by the disease up to the month of July 2020 and the miserable part was that we lost more than 0.6 million people in it. Still, an encouraging note for us was that most of the patients, more than 9.57 million people have recuperated from it. In the month of July 2020 India became the country with the third biggest amount of confirmed cases in the universe. In case of the recapture of COVID-19 patients, Spatial factor may play a significant role. To be mindful of this, the research was done to study the recovery time of the COVID-19 patients of India in respect of their spatial locations by means of spatial frailty model under Bayesian mechanism. The study time of the research was from 1st March, 2020 to 25th April, 2020. Arbitrarily selected a sample of 294 COVID-19 positive cases reported during the study period, in seven exceedingly pretentious states of India up to the month of March, 2020, were included in the study which were followed up to 25th April, 2020. Surprisingly the analysis showed that spatial effect actually plays an important role in the recovery time of the COVID-19 patients and it establishes the prominence of the application of frailty model in this circumstance. Besides this, the study also reveals the significant effect of the factors age and gender on their respective recovery times**

Index Terms: **COVID-19, Survival Analysis, Spatial Frailty model, Proportional Hazards model, Recovery time of patients.**

I. INTRODUCTION

COVID-19 pandemic, the most burning topic of today, affect almost every nation of the world. This current global pandemic is caused due to coronavirus disease 2019 (COVID-19). The COVID-19 patients were first detected in the Wuhan City of China in December 2019 (Hung et al., 2020). According to the reports of World Health Organization (WHO), it was declared as a "Public Health Emergency of International Concern" on 30 January 2020 and a "Pandemic" on 11 March, 2020 by them. Up to the month of July 2020, the total reported cases of COVID-19 across the world was more than 16.4 million in more than 189 countries and territories which caused more than 654,000 deaths and more than 9.57 million people have recovered from it (Johns Hopkins University, 2020). In India the first case of COVID-19 was reported on 30 January, 2020 which originated from China. At present India has the biggest number of confirmed cases in Asia (Hindustan Times, 29 May 2020) with 1.5 million (Ministry of Health and Family Welfare, 2020) people and has the third largest number of confirmed cases in the world (Kulkarni, 2020). Till now, among 1.4 million COVID-19 confirmed cases 0.99 million patients are being recovered from it and more than 33 thousand (Ministry of Health and Family Welfare, 2020) people lost their life due to this disease. According to a report of WHO-China Joint Mission (2019), a patient of COVID-19 takes on an average 2 weeks to recover from it. A report of India Today revels that in India the COVID -19 patients usually takes 14 days to recover but in some special cases it is observed to be up to eight weeks (India Today, 4 April 2020). Nemati et al. (2020) performed a research on machine learning based survival analysis and discharge time likelihood prediction using clinical data of COVID-19 patients. Ruan et al.(2020) conduct a study on 150 patients from Wuhan City, China on Clinical predictors of mortality due to COVID-19. Pandey et al. (2020) proposed SEIR and Regression Model to predict COVID-19 outbreak in India. Gupta & Shankar (2020) worked on the estimation the number of COVID-19 infections in Indian hot-spots using fatality data. Chatterjee et al. (2020)

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proposed a stochastic mathematical model for healthcare impact of COVID-19 epidemic in India. Barman et al. (2020) carried out a pilot study on COVID-19 pandemic and its recovery time of patients in India. However in this study and in any other studies so far our knowledge goes, no attempt has been made to estimate recovery time of COVID-19 patients using survival models with frailty.

Frailty model, a different kind of model used in survival analysis, offers us to analyse the unobserved heterogeneity in to the usual survival models, which cannot be explain by covariates of the model. In frailty model, in addition to the covariates of the survival model, a random effect factor - frailty is used in it which modifies the hazard function of an individual, or of correlated individuals. The idea of frailty was familiarised by Greenwood and Yule (1920) and the name "frailty" was introduced by Vaupel et al. (1979) and it was endorsed by Clayton(1978). Spatial factor plays a significant role in survival modeling due to the differences in socioeconomic status, access to health care, pollution, population density, weather conditions etc. In case of spatial frailty model, it is assumed that the random effects associated with the people of different geographical location are same or they share the same frailty. Henderson et al.(2002), Kneib(2006), Li & Lin(2006), Banerjee & Day (2005), Zhou et al.(2015) are some examples of application of Spatial frailty models of spatially correlated patients of different field like leukemia, childhood mortality, asthma, breast cancer etc.

Keeping all these points in mind, to analyse the recovery time of the COVID-19 patients of India a study was conducted among a group of patients from seven states of India, where highest numbers of positive cases are observed up to the month of March, 2020 using Spatial Survival model performed under Bayesian mechanism. The outcome of the analysis along with methodology adopted has been presented in this paper.

II. MATERIALS AND METHODS:

The time span of the study is from the first March of 2020 to the twenty-fifth April of 2020. The study subjects of confirmed COVID-19 cases (data source- https://www.kaggle.com/) were taken from -seven states of India- Maharashtra, Delhi, Tamil Nadu, Uttar Pradesh, Karnataka, Kerala and Telangana. These seven states have high positive Covid-19 cases during the period of our study. The study comprised of all the positive hospitalized cases in the seven states of India within March 1, 2020 to March 31, 2020. These cases were followed up to 25th April, 2020. During the period of follow-up, inclusion of new patients was restricted. A total number of 1090 COVID-19 positive patients were diagnosed in the different hospitals of these seven states of India. With the population size of 1090, using sample size determination formula for finite population (Yamane, 1967), the sample size for the study perched at 294 samples of Covid-19 positive patients. Simple random sampling is used to select 294 covid-19 patients from the population using MS-Excel. Age and sex of the patients are also collected from the same data source. The recovery time (in days) is the time between day of hospitalization and the day of recovery. The patients were contemplated as censored if he/she died or remain hospitalization after 25th April, 2020.

In this study spatial frailty model is used to analyse the recovery times of COVID-19 patients of India. To know the effectiveness of the spatial effect on the COVID-19 patients and for making a comparison we also fit the same survival model without the frailty term. In case of spatial frailty models it was assumed that the frailty factor associated with an individual was different with respect to different geographical locations. Let us consider a right censored survival data (t_{ij}, δ_{ij}), $i=1,2,\ldots,n$; $j=1,2,\ldots,m$ and assume that the censoring is non-informative. Let δ_{ij} denotes the indicator variable taking value 1 if we get the event of interest for the j^{th} subject ($j=1,2,\ldots,m$) of the i^{th} group ($i=1,2,\ldots,n$) and value 0 otherwise. Hence t_{ij} is a survival time if $\delta_{ij}=1$ and it is a censoring time if $\delta_{ij}=0$. Let x_{ij} be the covariate for each subject. Hence the triplet (t_{ij},δ_{ij}, x_{ij}) is observed for all i and j. Let (Y, X) denotes the collection of all such triplet (t_{ij}, δ_{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,

$$L(Z,Y,X)=\prod_{i=1}^{n}\prod_{j=1}^{m}[h_{ij}(t)]^{\delta_{ij}}S_{ij}(t) \qquad (2.1)$$

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. In this present study the groups will be different states. Given the unobserved frailty Z_i, t_{ij}'s are independent.

Proportional Hazards (PH) Frailty models are the extensions of the population hazards model which is best known as the Cox model (Cox, 1972) a widely pursued model in survival analysis. According to Cox the hazard rate of an individual is given by,

$$h(t,X)=h_0(t)e^{\beta' X} \qquad (2.2)$$

Where $h_0(t)$ denotes the baseline hazard function, assumed to be unique for all individuals in the study population. X is the vector of observed covariates and β is the respective vector of regression parameters to be estimated.

PH frailty model extends the Cox model such that the hazard of an individual depends in addition on an unobservable random variable Z, which acts multiplicatively on the baseline hazard function $h_0(t)$. Introducing an additive frailty term Z for each individual in the exponent of the hazard function as follows,

$$h(t,Z,X)=h_0(t)e^{\beta' X+Z} \qquad (2.3)$$

Here Z is the random variable varying over the population and it is unobservable. The corresponding survival function and the density is given by,

$$S(t,Z,X) = S_0(t)^{e^{\beta' X+Z}} \quad (2.4)$$

$$f(t,Z,X) = e^{\beta' X+Z}\, S_0(t)^{e^{\beta' X+Z}-1}\, f_0(t) \quad (2.5)$$

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

PH frailty model is the most popular type of frailty model. This model was first introduced by Clayton (1978) and Vaupel et al.(1979). Li and Ryan (2002), Banerjee et al.(2005), Diva et al. (2008), Zhou et al.(2015) and many others use the proportional hazards frailty model in case of Spatially correlated survival data using different non-parametric frailty prior and different parametric and semiparametric baseline hazard function. In this study we consider a Log-logistic distribution with parameter υ and *k* for modeling the baseline hazard function. The complete data likelihood for the multivariate Proportional Hazards Model using Log-logistic Hazard with and without frailty is given by equation (2.6) and (2.7)

$$L_1 = \prod_{i=1}^{n}\prod_{j=1}^{m}\left[\frac{\upsilon k(\upsilon t_{ij})^{k-1}}{1+(\upsilon t_{ij})^k} e^{\beta' X+Z_i}\right]^{\delta_{ij}} \frac{1}{1+(\upsilon t_{ij})^k} e^{\beta' X+Z_i} \quad (2.6)$$

$$L_2 = \prod_{i=1}^{n}\prod_{j=1}^{m}\left[\frac{\upsilon k(\upsilon t_{ij})^{k-1}}{1+(\upsilon t_{ij})^k} e^{\beta' X}\right]^{\delta_{ij}} \frac{1}{1+(\upsilon t_{ij})^k} e^{\beta' X} \quad (2.7)$$

Following Zhou et al. (2017) for the frailty parameter here we consider an independent Normal prior density, $Z_i \sim N(0, \tau^2)$, for $i=1,2,\ldots,n$. Considering appropriateness of gamma distribution as a conjugate prior in Bayesian statistics here a gamma prior is considered for τ i.e, $\tau^{-2} \sim Gamma(a_\tau, b_\tau)$. Following Sahu et al.(1997), Sahu and Dey (2004), Zhou et al. (2017) a normal prior for the regression parameters are considered here which is given by $\beta \sim N(0,m)$. For the hyper parameters of the baseline hazard function a gamma prior is assumed here due to its simplicity and flexibility as used by Sahu et al. (1997). In case of Log-logistic baseline hazard it is assumed that υ ~ Gamma(ρ,ρ) and *k*~Gamma*(a,b)*.The joint posterior distributions for all the parameters of the models are given by,

$$P_1 = \prod_{i=1}^{n}\prod_{j=1}^{m}\left[\frac{\upsilon k(\upsilon t_{ij})^{k-1}}{1+(\upsilon t_{ij})^k} e^{\beta' X+Z_i}\right]^{\delta_{ij}} \frac{1}{1+(\upsilon t_{ij})^k} e^{\beta' X+Z_i} \frac{1}{\tau\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{Z_i}{\tau}\right)^2} \pi(\beta)\pi(\upsilon)\pi(k)\pi(\tau^{-2}) \quad (2.8)$$

$$P_2 = \prod_{i=1}^{n}\prod_{j=1}^{m}\left[\frac{\upsilon k(\upsilon t_{ij})^{k-1}}{1+(\upsilon t_{ij})^k} e^{\beta' X}\right]^{\delta_{ij}} \frac{1}{1+(\upsilon t_{ij})^k} e^{\beta' X} \pi(\beta)\pi(\upsilon)\pi(k) \quad (2.9)$$

π (.) be the respective prior distributions.

To get the data likelihood of the various parameters given in equation (2.8) and (2.9) we have to integrate out the Z_i's with the specified independent Normal prior density. Here we use Markov chain Monte Carlo (MCMC) algorithms like Metropolis-Hastings algorithm (Hastings, 1970) and Gibbs sampling (Geman and Geman, 1984) to generate samples from the appropriate marginal posterior distributions.

A residual plot of Cox and Snell (1968) is used here for model diagnostics. If the model provides a good fit to the data we expect a straight line through the origin with slop 1. In this study to compare the fitted models we use two criteria, deviance information criteria (DIC) (Spiegelhalter et al., 2002) and the log pseudo marginal likelihood (LPML) (Geisser and Eddy,1979). Generally smaller DIC value shows good model fitting and large value of LPML indicates better predictive performance of the model. If the frailty model obtained to be better as compared to the other, it will establish the presence of spatial effect on the data.

III. RESULTS:

In this study a random sample of 294 COVID-19 positive individuals are taken from seven highly affected states of India. The patients are followed up to 25th April, 2020. Using this data set we have done the Bayesian Analysis of the two survival models mentioned in section 2 with the help of the R Software. Here we consider recovery times of the patients as the survival times and age and sex of the patients as the covariates of the models. Besides this to observe the spatial effect on the patients, different states are considered as different geographical locations. The patients of each state constitute a cluster and they share the same spatial frailty. In case of $e^{\beta' X+Z_i}$, $\beta = (\beta_{Age}, \beta_{Sex})'$ and we consider Sex_{ij}=1, if the j^{th} patient in the i^{th} state is a male and 0 otherwise. Where *i=1,2,…,7* and *j=1,2,…,42*. The MCMC is done using adaptive Metropoli samplers (Haario et al., 2001). 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. From the above analysis we have found the posterior inferences about the parameters of the model. Here the Table 3.1 and Table 3.2 shows the posterior mean, median, standard deviation and 95% credible intervals for the regression Coefficients and the frailty variance for the models. Fig 3.1 and Fig 3.2 shows the trace plots of the parameters for the two fitted models. For the two fitted models the Cox-Snell plots are given in Fig 3.3 and Fig 3.4. For the two fitted models the obtained LPML and DIC are given in table 3.3.

Table 3.1: Posterior Inference of Regression Coefficients

Models	Regres-sion Coeffi-cients	Mean	Median	Standard Deviation	95% CI-Low	95% CI-Upper
PH Frailty Model	β_{Age}	0.13492	0.127179	0.199196	-0.244719	0.536585
	β_{Sex}	-0.0017	-0.001646	0.005607	-0.012573	0.008886
PH Model without frailty	β_{Age}	0.13318	0.131906	0.191888	-0.244529	0.500415
	β_{Sex}	-0.0018	-0.001810	0.005430	-0.012060	0.009080

Table 3.2: Posterior Inference of Frailty Variance

Models	Mean	Median	Standard Deviation	95% CI- Low	95% CI- Upper
P H Frailty Model	0.129010	0.056849	0.234131	0.005632	0.711479

Table 3.3: LPML and DIC for different models

Models	Log Pseudo Marginal Likelihood: LPML	Deviance Information Criterion: DIC
PH Frailty Model	-501.1691	1002.731
PH Model without frailty	-508.8872	1010.656

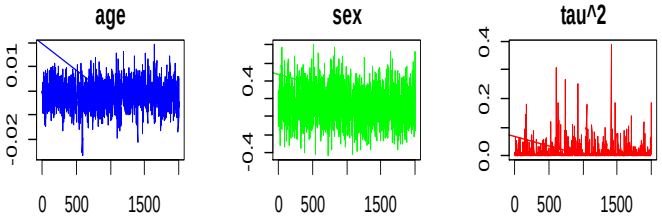

Fig 3.1: Trace plots of the Regression coefficients and Frailty variance for the frailty model

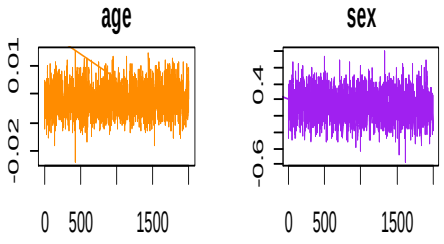

Fig 3.2: Trace plots of the Regression coefficients for the model without frailty

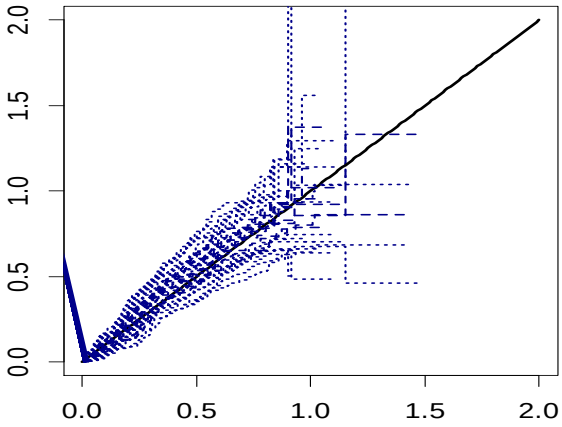

Fig 3.3: Cox and Snell plot for the frailty model

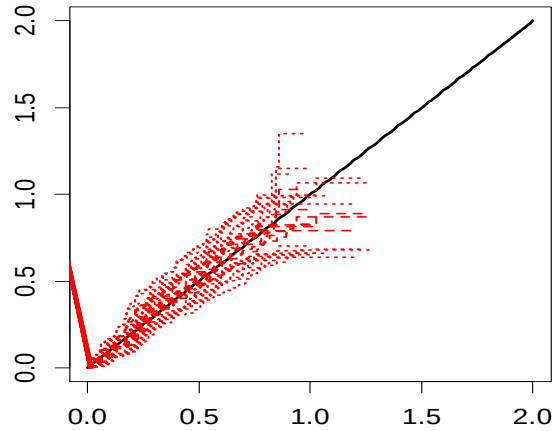

Fig 3.4: Cox and Snell plot for the model without frailty

IV. DISCUSSION:

The table 3.1 depicts that the recovery times of male patients is lower than the females. The factor age has also effect on the recovery times of the patients. The study indicates that when age increases the recovery time of a patient also increases. Voinsky et al. (2020) in their study observed that the recovery time of the patients aged more than 30 years had significantly longer recovery periods compared with younger patients. Though their result is statistically significant, the differences are very small. Yet, they conclude that younger individuals were less likely to have severe COVID-19 symptoms and take less time to recover from it. According to a study conducted in Singapore by Mollazehi et al. (2020) younger patients recovered faster compared to elderly patients. Lithander et al.(2020) observed an association between age and prognosis in COVID-19.The estimate of the frailty variance in the present study, in table 3.2 indicates presence of heterogeneity in the population of patients. It is observed that the recovery times of patients are different according to their geographical locations.

That is the area or state also has effect on the recovery times of the patients. The recovery time varies from state to state. In other words it also establishes impact of environmental factor on recovery time of COVID-19 patients. From the Cox-Snell plots of both the models in Fig 3.3 and Fig 3.4 it can be seen that the data fits the proposed models quite good and fit of the frailty model is better than the other. From the table 3.3 it is observed that the Proportional Hazards frailty Model using Log-logistic hazard has larger LPML and smaller DIC as compared to the other model. So it is clear that the fit of the frailty model is better than the model without the frailty term. Which indicates the presence of spatial effect on the COVID-19 patients in different states of India. The study of Mollazehi et al. (2020) also revealed that in Singapore, the Singaporean patients cure more quickly than non-Singaporean patients.

Besides these some other factors may also have some effect on the recovery time of the patients like health status, mental strength of the patients, presence of some other disease like diabetes, hypertension, respiratory disease, heart disease etc. may also affect the recovery time of COVID-19 patients. But due to unavailability of such kind of detail information about the patients, we are unable to study these factors. So there is scope for extension of this study considering such kind of valuable factors.

CONCLUSION

In this paper, the recovery times of the COVID-19 patients of India are studied with respect to the factors geographical locations, age and sex using spatial proportional hazard frailty model with Log-logistic hazard. For making a comparative analysis we have also fitted the same Proportional Hazards model without the frailty term. A random sample of 294 Covid-19 positive cases reported during the month of March, 2020, in seven highly affected states of India, viz, Maharashtra, Delhi, Tamil Nadu, Uttar Pradesh, Karnataka, Kerala and Telangana are considered here. The analysis is performed under Bayesian Mechanism with the help of R software. From the analysis it is observed that the recovery times of male patients are lower as compared to the females. Again, the factor age has effect on the recovery times of the patients. It is observed that the recovery times of patients are different according to their geographical locations. The model diagnostics has shown quite good fit of the spatial frailty model. That is spatial factors also play role on the recovery time of the patients. Due to inaccessibility of data, in the present study some important facts about the patients, which may have effect on recovery time of the patients, are not considered here. So there is a future scope for extension of this study incorporating more parameters related to the COVID-19 patients.

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