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Parametric Frailty Models for Clustered Survival Data: Application to Recurrent Asthma Attack in Infants

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Abstract: This paper demonstrates the application of Gamma frailty models with parametric (Log-Normal, Log Skew Normal and Inverse Weibull) baseline hazards functions to estimate the effect of prognostic factors on the survival of recurrent asthma attack on infants. Maximum likelihood method of estimation was used as to obtain our estimates. Our results demonstrate a good fit, showing that frailty model with Log-Normal baseline performs better (infants are less frail), followed by the model with Log skew Normal and least by inverse Weibull baseline hazard judging from the results of AIC and BIC as well as other evidence.

Keywords: Gamma frailty, Parametric (AFT) models, Asthma, Log-Normal distribution , Log-Skew Normal distribution , inverse Weibull distribution

1 Introduction

Asthma is a chronic inflammatory (long-term) disease of the lungs and airways (bronchioles), (www.babycenter.com). These airways are irritated and swollen, and affect ability of child to breathe. An acute asthma attack in baby could be caused by production of mucus in lining of airways. The muscles around this airways will tighten and breathing tubes will become narrow. Rapidly breathing, cough, or wheeze (make a whistling sound) are common symptoms. Causes includes exposure to allergens such as dust mites, cockroaches mold, pollens or animal dander, cold air, viral infections,tobacco smoke,and other air pollutants can trigger or worsen symptoms in some children with asthma. This is referred to as allergic asthma. More than 80 percent of children with asthma have symptoms that started before they turned 5 [Aderele, 1979]. Seasonal allergies to outdoor pollens (also called hay fever) wouldn't usually be a problem until a child is 4 or 5, because it can take that long for him to be exposed to enough pollens. With doctor's help, asthma diagnose in children younger than 2, becomes easier. Although, conditions other than asthma can also cause wheezing or wheezing-like sounds. In fact, viral respiratory infections are probably the most common cause of wheezing in babies. With right medications, education, asthma action plan, and regular medical follow-up, most asthmatic children can get improved quality of life. A clinical and laboratory study on bronchial asthma of 200 Nigerian children was conducted by [Aderele, 1979]. In that paper, climate is found to be an important prognostics factor with rainy season as an important precipitating factor of asthma. A survey to assess the knowledge, attitude, and practices of doctors in South-East Nigeria regarding bronchial asthma was conducted [Chima et al., 2017]. It was concluded that there is a wide gap between Global Initiative for Asthma (GINA) guidelines and knowledge, attitude and practices of doctors in that part of the country. A survey of prevalence symptoms and Management of childhood asthma between urban and rural Nigeria revealed that there is an increasing trend in the prevalence of childhood asthma [Adiele,]. Asthma in infants as well as the challenges faced in diagnosis and treatments was reported by [Ewa et al., 2017]. The variabilities in time to the attack or recurrent after the last attack and treatments together with some risk factors are modeled. When studying recurrent events over time or other kinds of multivariate survival data, one may find it useful to construct random effects models. In the event history setting, it is a common phenomenon to approach such problem using frailty models.

Many statistical methods have been developed to adjust and evaluate the unobserved heterogeneity. Modeling unobserved heterogeneity in survival data is of great importance that have appeared in a large number of articles in recent

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decades. Unobserved Heterogeneity, often referred to as hidden variability, is one of the important sources of variability in medical and biological applications. Variability is of two types: the one accounted for by observable risk factors and those caused by unknown covariates which are theoretically unpredictable. Our study interest is about the asthma disease in infants. Frailty models are best used to describe such unobserved heterogeneity in survival analysis. The effect of heterogeneity, or frailty, has been recognized for a long time, [Strehler and Mildvan, 1960]. Different choices of distributions for unobserved covariates are possible. [Beard, 1959], [Vaupel et al., 1979], [Lancaster, 1979] and lots of researchers have worked on this problem. Ignoring heterogeneity resulting in omitting important (unmeasurable) variables in the models as studied by [Flinn and Heckman, 1982], [Clayton, 1978], [Oakes, 1986] and [Oakes, 1989] among others, suggested a shared Gamma frailty model for the analysis of the correlation between clustered survival times in genetic epidemiology. The paper by [Zare and Moradi, 2012], applied parametric shared frailty models to waiting time to first pregnancy and found that height, age at marriage and menstruation regularity to be the important predictors of waiting time to pregnancy. A shared frailty model [Mahmood et al., 2013], to identify important factors associated with length of birth intervals of Bangladeshi women. Frailty models are extension of Cox proportional hazard model, in this model the hazard rate will not just be a function of covariates but also a function of frailties [Cox, 1972]. Several works, [Hanagal, 2006], [Hanagal, 2007], [Hanagal, 2011] , [Hanagal and Dabade, 2013], and [Hanagal and Pandey, 2016] have discussed Shared Gamma frailty models and its applications. [Andersen et al., 2012] applied the Gamma frailty model to check the Proportional Hazard Model (PHM) in malignant melanoma data. Many of the applications of Gamma frailty models are as discussed by [Andersen et al., 1997] who estimated the variance in Cox regression model with shared Gamma frailties. [Bjarnason and Hougaard, 2000] form two Gamma frailty bivariate Weibull model, [Glidden, 1999] checked adequacy of Gamma frailty model for multivariate failure times. [Shih and Louis, 1995] assessed the Gamma frailty models for clustered failure time. A paper by [Aalen, 1994] discussed the application of Gamma frailty to expulsion of intrauterine contraceptive devices. [Ellermann et al., 1992] applied Gamma-Weibull to the study of recidivism among criminals. An extension of Gamma-frailty was constructed by [Geerdens et al., 2012] and the fitness was checked. Recently, [Adham and AlAhmadi, 2016] studied the comparison of Gamma and Inverse Gaussian frailty models using log-logistic baseline hazard distribution.

The choice of baseline hazard distribution matters, as it could also be a contributing factor to frailty [Abiodun and Oyejola, 2012]. In the frailty model, assuming a distribution for a baseline function makes frailty model parametric. Choosing from an extreme values distribution and or any positive distribution apart from among the trio (Exponential, Weibull and Gompertz) distributions makes a frailty distribution either full parametric of Accelerated Failure Time frailty distribution. The AFT shared frailty model is an appropriate choice for multivariate clustered survival time data, especially when observations within a cluster share a common unobservable frailty, [Swain and Grover, 2016]. It is a known fact that Log skew Normal and Log-Normal are nested distributions while Inverse Weibull is not nested with the duo. These AFT models perform differently apart from nested models that performed closely. Hence this study.

In this paper, asthma disease in infants are considered following a study application of Gamma frailty model compared on three different baseline hazards functions; estimation of the variance to determine the degree of heterogeneity in the study population; the estimates of the model without frailty (i.e parametric Accelerated Failure Time (AFT) models) are obtained and compared with frailty model. Fitness of the model is checked using AIC, BIC and log-likelihood.

2 The Model

We begin from the Cox PHM for an individual which depends on observed time-independent random variable X and acts multiplicatively on the baseline hazard function. [Cox, 1972],

$$h(t;x) = h_0(t)\exp(X'\beta), \qquad t \geq 0. \tag{1}$$

If however there is unobserved time-fixed covariate Z (random) which act multiplicatively on the hazard function. For subject j, $j = 1,\ldots,n_i$ from cluster $i, i = 1,\ldots,k$. Let τ_{ij} be the time to event for the subject j in the cluster i, and C_{ij} be the censoring time. We observed that the survival time $t_{ij} = min(\tau_{ij}, C_{ij})$ and status $\delta_{ij} = I(\tau_{ij} \leq C_{ij})$ where τ_{ij} and C_{ij} are independent. The number of observed events in the ith cluster is $d_i = \sum_{j=1}^{n_i} \delta_{ij}$.

Thus the frailty model is given as

$$h_{ij}(t|X,Z) = Zh_0(t_i j)\exp(X'\beta). \tag{2}$$

Equation (2) is a conditional hazard model, condition on Z. If however the frailty distribution degenerate to 1 for all individuals, the usual PHM (1) is obtained. We then consider the distribution for the frailty Z, i.e. Gamma distribution.

Frailty Model.
Following the works of [Duchateau and Janssen, 2008], [Hanagal, 2011], [Hougaard, 2012] and [Wienke, 2010]. Gamma distribution and its applications has been used widely as a frailty model, due to its simplicity in obtaining some statistical properties. The distribution is defined for a non-negative random variable Z as;

$$f(z) = \frac{1}{\Gamma(k)}\lambda^k z^{k-1}\exp(-\lambda z), \qquad z>0, \lambda>0. \tag{3}$$

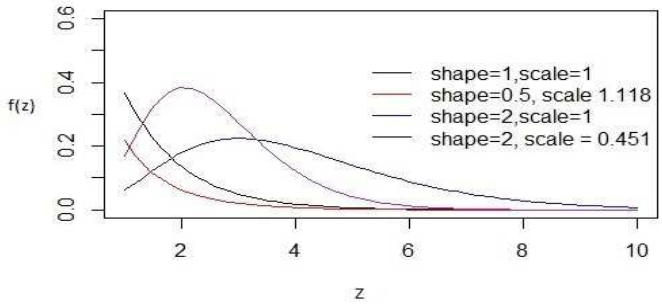

Fig. 1. Gamma density plot with different shape and scale parameters

The support of f_Z is $[0,\infty)$. In making sure that the model is identifiable, the restriction $k=\lambda$ is used and $E(Z)=1$ with $\theta=\frac{1}{\lambda}\Rightarrow\lambda=\frac{1}{\theta}$, thereby having the random variable $Z\sim\Gamma(\frac{1}{\theta},\frac{1}{\theta})$ given as

$$f(z) = \frac{1}{\Gamma(\frac{1}{\theta})}\theta^{-\frac{1}{\theta}}Z^{\frac{1}{\theta}-1}\exp(-\frac{Z}{\theta}), \qquad Z>0, \theta>0. \tag{4}$$

Baseline Hazard Functions
We adopt the following baseline hazard functions and cumulative hazard functions with parameter λ, ω and α
[1.] **Inverse-Weibull distribution.**
The hazard function is defined as;

$$h_0(t) = \frac{\lambda\alpha t^{-\alpha+1}}{\exp(\lambda t^{-\alpha})-1}. \tag{5}$$

and cumulative hazard as

$$H_0(t) = \int_0^t h_0(s)ds.$$

$$H_0(t) = -\ln[1-\exp(-\lambda t^{-\alpha})]h_0(s)ds. \tag{6}$$

and

$$S_0(t) = 1-\exp(-\lambda t^{-\alpha}) \quad ,\alpha,\lambda>0 \tag{7}$$

[2.] **Lognormal**

The hazard function is defined as;

$$h_0(t) = \frac{\phi\left(\frac{\log(t)-\lambda}{\omega}\right)}{\omega t\left[1-\Phi\left(\frac{\log(t)-\lambda}{\omega}\right)\right]} \tag{8}$$

Cumulative Hazard as;

$$H_0(t) = -\log\left[1-\Phi\left(\frac{\log(t)-\lambda}{\omega}\right)\right]$$

and

$$S_0(t) = 1 - \Phi\left(\frac{\log(t) - \lambda}{\omega}\right), \qquad \lambda \in \mathbb{R}, \omega > 0 \tag{9}$$

[3.] **log-skewed Normal**
The hazard function is defined as;

$$h_0(t) = \frac{2\phi\left(\frac{log(t)-\lambda}{\omega}\right)\Phi\left(\frac{\alpha\log(t)-\lambda}{\omega}\right)}{t\omega[1 - SN(\log(t);\lambda,\omega,\alpha)]} \tag{10}$$

$$H_0(t) = -log[1 - SN(log(t); \qquad \lambda,\omega,\alpha)]$$

and

$$S_0(t) = [1 - SN(log(t);\lambda,\omega,\alpha); \qquad \lambda,\alpha \in \mathbb{R}; \omega > 0 \tag{11}$$

3 Estimation Method

Likelihood Approach.
In order to obtain the parameters of interest, we follow a maximum likelihood of the marginal likelihood function. This is achieved as follows: within the context of multivariate clustered survival data, where we have observed information X_{ij} and event times $t_{ij} = min(\tau_{ij}, C_{ij})$, censoring indicators $(\delta_{1j}, \ldots, \delta_{kn_k})$ and unobserved clustered specific random variable $Z = (Z_1, \ldots, Z_k)$. From (2), the conditional likelihood of data with quadruple $(t_j, \delta_{ij}, X_{ij}, Z_{ij})(j = 1, \ldots, n_i, i = 1, \ldots, k)$ is similar to what we have in PHM. i.e

$$L(\pi, \beta|Z) = \prod_{j=1}^{n_i}(Z_{ij}h_0(t_{ij})\exp(X'_{ij}\beta))^{\delta_{ij}}\exp[-Z_{ij}H_0(t_{ij})\exp(X_{ij}\beta)] \tag{12}$$

conditionally on $Z_1, \ldots, Z_n$. Where $h_0(t_{ij})$ is the baseline hazard function with parameter $\pi = (\lambda, \omega)$ Lognormal, $\pi = (\lambda, \alpha)$ inverse Weibull and $\pi = (\lambda, \alpha, \omega)$ (log-skewed normal). Suppose the frailty $Z \sim \Gamma(\frac{1}{\theta}, \frac{1}{\theta})$ and following the above likelihood, the marginal likelihood (l_{marg}) for ith cluster is

$$l_{marg} = \int_0^{\infty}\prod_{j=1}^{n_i}(Z_{ij}h_0(t_{ij})\exp(X'_{ij}\beta))^{\delta_{ij}}\exp[-Z_{ij}H_0(t_{ij})\exp(X_{ij}\beta)]f(z)dz \tag{13}$$

where f(z) is as indicated in (4), then

$$l_{marg} = \frac{\prod_{j=1}^{n_i}(h_0(t_{ij})\exp(X'_{ij}\beta))^{\delta_{ij}}}{\Gamma(\frac{1}{\theta})\theta^{\frac{1}{\theta}}}\int_0^{\infty} z_{ij}^{\frac{1}{\theta}+d_i-1}\exp[-z_{ij}v - z_{ij}/\theta]dz$$

where $v = \sum_{j=1}^{ni} H_0(t_{ij})\exp(X'_{ij}\beta)$ and $d_i = \sum_{j=1}^{ni}\delta ij$.
Without loss of generality, we let $z_{ij} = z, X_{ij} = X$

$$l_{marg} = \frac{\prod_{j=1}^{n_i}(h_0(t_{ij})\exp(X'\beta))^{\delta_{ij}}}{\Gamma(\frac{1}{\theta})\theta^{\frac{1}{\theta}}}\int_0^{\infty} z^{\frac{1}{\theta}+d_i-1}\exp -z[\frac{1}{\theta}+v]dz$$

$$l_{marg} = \frac{\prod_{j=1}^{n_i}(h_0(t_{ij})\exp(X'\beta))^{\delta_{ij}}}{\Gamma(\frac{1}{\theta})\theta^{\frac{1}{\theta}}\left(\frac{1}{\theta}+v\right)^{\frac{1}{\theta}+d_i}}\Gamma(\frac{1}{\theta}+d_i) \tag{14}$$

$$l_{marg} = \frac{\prod_{j=1}^{n_i}(h_0(t_{ij})\exp(X'\beta))^{\delta_{ij}}\Gamma(\frac{1}{\theta}+d_i)}{\Gamma(\frac{1}{\theta})\theta^{-d_i}(1+\theta v)^{\frac{1}{\theta}+d_i}}$$

taking the logarithm and sum over ith strata, we obtain marginal loglikelihood i.e.

$$\log l_{marg} = \sum_{i=1}^{k}\left[\sum_{j=1}^{n_i}\delta_{ij}\log(h_0(t_{ij})+\exp(X'\beta))+\log\Gamma(\frac{1}{\theta}+d_i)-\log\Gamma(\frac{1}{\theta}) + d_i\log\theta-\left(\frac{1}{\theta}+d_i\right)\log(1+\theta v)\right] \tag{15}$$

$$\log l_{marg} = \sum_{i=1}^{k}\left(d_i\log\theta+\log\Gamma(\frac{1}{\theta}+d_i)-\log\Gamma(\frac{1}{\theta})-(\frac{1}{\theta}+d_i)\log(1+\theta v) + \sum_{j=1}^{n_i}\delta_{ij}(\log(h_0(t_{ij}))+(X'\beta))\right) \tag{16}$$

The Maximum Likelihood Estimates for π, θ, and β can be found by maximizing (16) using Newton Raphson approach. See [Duchateau and Janssen, 2008].

4 Application

We have considered 232 asthmatics infants between the age of 6 weeks and 24 months, [Duchateau and Janssen, 2008] (www.vetstat.ugent.be/research). An application of an existing anti-allergic drug(s) was administered to children who were at higher risk to develop asthma in order to prevent it. A prevention trial is set up with such children randomized to placebo or drug, and the asthma events that developed over time are recorded in a diary. Typically, a patient has more than one asthma event. These different events are thus clustered within a patient and are ordered in time. This ordering can be taken into account in the model. Such data can be presented in different formats, but here, we choose to use the calendar time representation. In the calendar time representation, the time at risk for a particular event is the time from the end of the previous event (asthma attack) to the start of the next event (start of the next asthma attack). In describing recurrent event data, we need a somewhat more complex data structure to keep track of the sequence of events within a patient. A particular patient has different periods at risk during the total observation period which are separated either by an asthmatic event that lasts one or more days or by a period in which the patient was not under observation. The start and end of each such risk period is required, together with the status indicator to denote whether the end of the risk period corresponds to an asthma attack or not. Below is the summary of the results of the data analysed by R-programming language software.

Table 1. Parameter Estimates of Gamma Frailty with Inverse Weibull, Log Skew Normal and Log Normal baseline hazard distributions

Parameters	IN-WEI	LSN	LN
θ(SE)	0.05(0.024)	0.082	0.082 (0.024)
λ(SE)	5.682(0.184)	3.518	3.683(0.068)
ω(SE)		1.521(0.021)	1.517(0.032)
α(SE)	0.564(0.015)	-2.274	
β_1(SE)	0.179(0.064)	-0.024(0.066)	-0.025 (0.064)
β_2(SE)	-0.102(0.074)	-0.247(0.053)	-0.247(0.075)

Table 2. Parameter Estimates of Parametric AFT distributions: Inverse Weibull, Log (skewed) Normal and Log Normal

Parameters	IN-WEI	LSN	LN
λ(SE)	5.533(0.177)	3.491(0.018)	3.538(0.053)
ω(SE)		1.526(0.019)	1.524(0.030)
α(SE)	0.585(0.013)	-3.228	
β_1(SE)	0.118(0.051)	-0.044(0.024)	-0.044(0.051)
β_2(SE)	-0.151(0.072)	-0.320(0.030)	-0.322(0.072)

Table 3. Comparison of Frailty Model relative to baseline hazard distribution

Baseline haz	AIC	BIC
inweibull	17085	17112
lognormal	16733	16761
logskewnormal	16735	16768

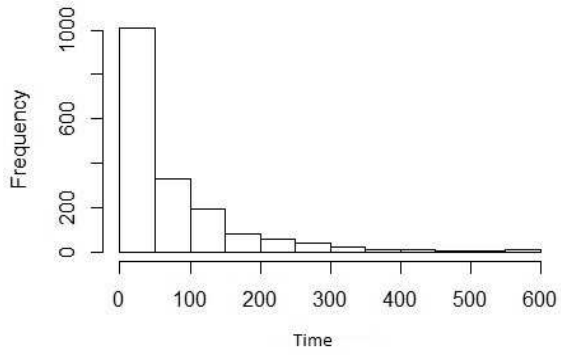

Fig. 2. Histogram of Survival time

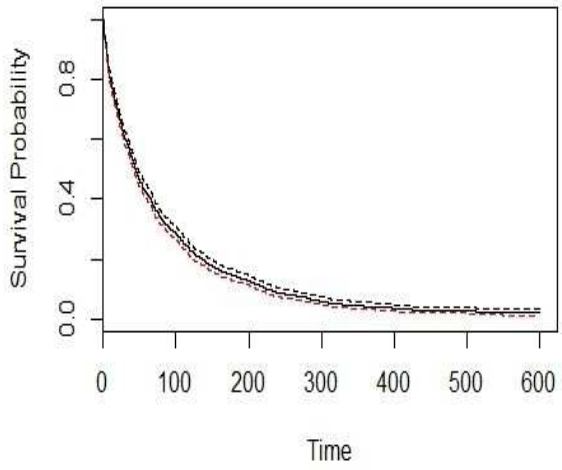

Fig. 3. Kaplan Meier Plot of Recurrent Asthma attacks in Infant

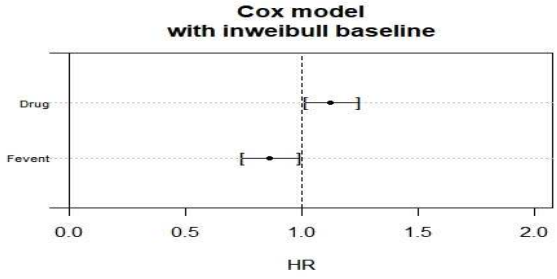

Fig. 4. The plot Hazard Ratio for Gamma frailty Model with inverse Weibull baseline

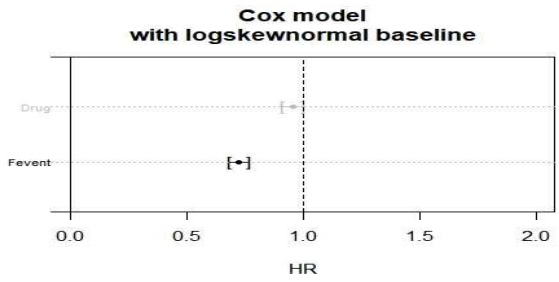

Fig. 5. The plot Hazard Ratio for Gamma frailty Model with Log skewed Normal baseline

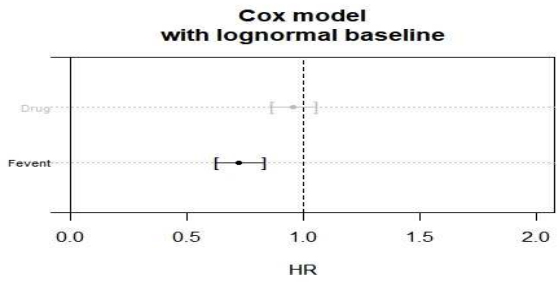

Fig. 6. The plot Hazard Ratio for Gamma frailty Model with Log Normal baseline

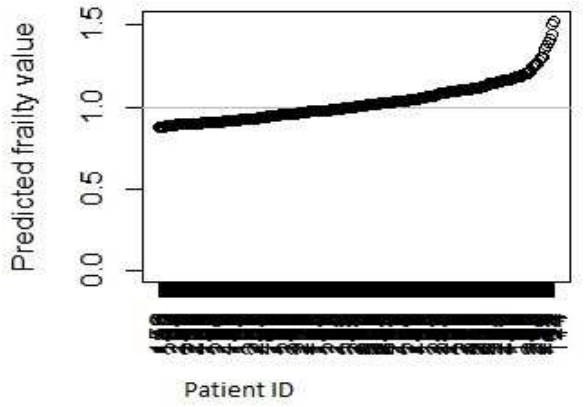

Fig. 7. The plot of predicted frailty values for Gamma frailty Model with inverse Weibull baseline

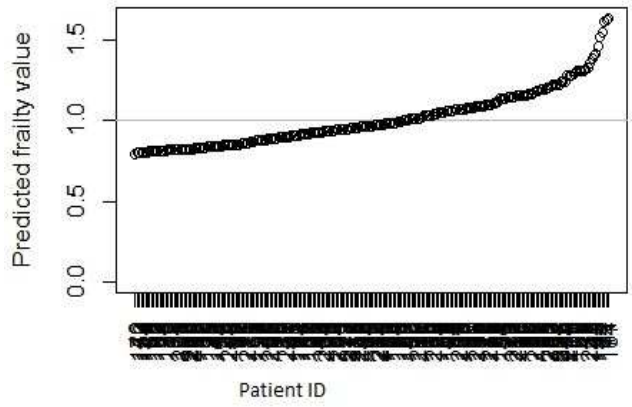

Fig. 8. The plot of predicted frailty values for Gamma frailty Model with Log skewed Normal baseline

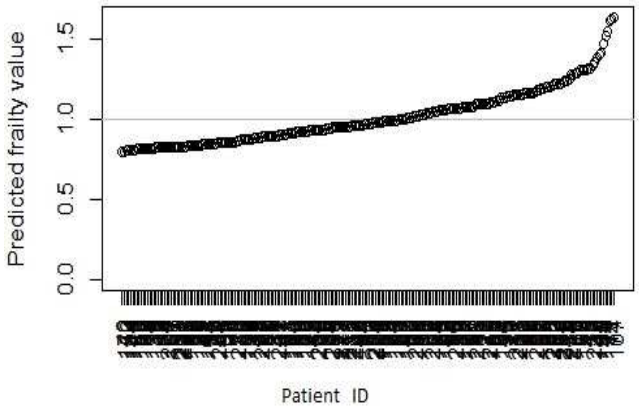

Fig. 9. The plot of predicted frailty values for Gamma frailty Model with Log Normal baseline

5 Interpretation of Results

The results of the estimated parameters for parametric gamma frailty and non frailty are as shown in Tables 1 and 2. From table 1,the maximum likelihood estimates of parameters obtained for the three different baseline hazards of Gamma frailty are; estimated parameters of the baseline distribution, its standard error, and frailty parameters (θ) and its standard errors, all are presented in table 1. Infants who used anti-allergic drug to reduce risks of asthma attack has higher risk of attack using Inverse-Weibull baseline (i.e. lower survival) by a factor of approximately 0.179 times higher than their counterpart using LN and LSN (approximately -0.024 each respectively) baseline distributions. That is, for using anti-allergic drug,the risk of attack is high when using Inverse Weibull baseline distribution and least with LN baseline distribution. infants are less frails using LN and LSN distributions. Infants with first time exposure (attack) have negative impact/effect on the hazard of survival time. It is also clear from Table 1 that the parameter θ of the gamma frailty (IWEI) is less than the parameter θ of the gamma frailty (LSN and LN), which indicates that including Inverse Weibull gives a better fit than other baseline hazards, although not totally supported. In the absence of frailty Table 2, (parametric AFT's model), it is clear that the regression coefficients (β_1, β_2) of the effect of the two covariate Drug and Fevent are biased down. Whereas, for the gamma frailty models, Table 1, the regression estimates and their standard errors (SE) increase, which is predictable because the frailty variable z is included in the model. The p-values of the regression coefficients (β_1, β_2)

of drug and fevent (IN-WEI) are 0.005 and 0.168, respectively; which is an indication that β_1 is significant while β_2 is not significant. For the gamma frailty (LSN and LN baseline hazards) and the results are found to be non significant for β_1 (p-values 0.719, 0.694) and significant for β_2 (p-value < 0.001). The p-value of θ's (IN-WEI = 0.0011), ($LSN = 9.776469e-07 < 0.001$) and ($LN = 9.468525e-07 < 0.001$), respectively show that the heterogeneity parameters θ are significant in the frailty models. The AIC and BIC values are computed for the gamma frailty models with (IN-WEI- AIC =17085, BIC=17112), (LSN- AIC =16735, BIC=16768) and (LN- AIC=16733, BIC=16761) baseline hazards functions respectively. The smallest AIC and BIC values suggest the model that gives better fit for the data than other models. It can be seen from Table (3), that the gamma frailty model with Log Normal baseline hazard gives the best fit to the data with AIC=16733, BIC=16761. followed by LSN and least by INWEI. Fig 2 is the histogram plot of the survival time which is right skewed and somehow has a long tail to the right. It is an indication that the distribution of time to recurrent attack of asthma is right skewed. The chance of surviving is high in the first 50 days of the experiment as there exist less frequent asthma attack, Fig 3. The median survival time is approximately 50 days. And high frequent of asthma attack occur as from 20% downward. Fig 4-6 Show the hazard ratio of the gamma frailty models. In Fig 4, the hazard ratio of infants who take drug is 1.2 days (28 hours, 48 minutes) time higher compared to infant on placebo given the same value of frailty. Also, tha HR of infant on Fevent is 0.023 days times lower compared to infant on placebo, given the same value of frailty. In fig 5, The HR for drug is approximately 1 and for fevent it's lower compared to those on placebo, given the same value of frailty. The result is the same in Fig 6. Predicted frailty values plots Fig 7-9 indicate that there exist unobserved term (frailty). Once the predicted value of an observation(s) is/are above 1, an indication of frailty set in. These also corroborate the significances of variances in table 1.

6 Conclusion

This study has greatly demonstrated the modeling and application of gamma frailty models when assuming the Inverse Weibull (IN-WEI), Log skew Normal(LSN) and Log Normal distributions as baseline hazards functions. The maximum likelihood estimation method is considered to estimate the parameters of the considered models in order to compare them through estimation and testing the significance of the parameters of the models under consideration. A real data set on Asthma recurrent attack is applied to compare the three baselines. The AIC and BIC were computed to assess the considered frailty model which of them gives the best fit to this data set. It has been found that the gamma frailty model with Log Normal baseline hazard is the best model that fits this data set among the others (infants are less frail). Furthermore, it has been found that, the heterogeneity parameter(s) θ is/are significant in all.
There are some limitations to our study; first, we were unable to get a reliable primary data set for this study as it requires a lots of hick-ups and lack of grants. Second, the unobserved risk factors to be the same for two baseline hazards function is as a result that the two models are nested.

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