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Survival analysis in tuberculosis patients of exponential accelerated failure time model

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ABSTRACT

The survival analysis can be used in time to event data, this one of the tools to estimate the probability of survival in patients. To estimate the patient's survivorship based on time-independent variable this called nonparametric model. Acceleration failure model is considered the parametric model, it takes covariate and multiple effects of survivorship, is measured through a log-linear model taking the logarithm of survival time and the outcomes of the dependent variable. The model assumes that follow survival function is known as assuming the effect of a covariate is to accelerate or decelerate the life of patients by important constant. Hence the AFT model is alternative to proportional hazard models because in this model analysis the effect of a covariate to multiply the hazard by the constant. This study discusses the survival time of patients by acceleration failure time model in TB patients, like the variable is age, Regimen, sex, and weight are considered. We have been check the model fit from the failure distribution, whether it is fitting for the model in that distribution based on deviation method (-2LL) using partial log-likelihood functions.

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INTRODUCTION

Overview of Tuberculosis

Tuberculosis is an infectious disease which is caused by the bacterium, Mycobacterium tuberculosis and is spread from person to person via airborne droplets (e.g. when an infected person coughs or sneezes). Tuberculosis primarily affects the lungs (causing pulmonary tuberculosis), but it can also affect other organs, e.g. central nervous system, lymphatic system, and circulatory system among others, resulting in extrapulmonary tuberculosis. When a person first becomes infected, the tuberculosis bacteria generally lay dormant in the body and the person will not manifest any symptoms (this is termed "Latent Tuberculosis Infection". Persons with Latent Tuberculosis Infection are not infectious. However, in about 10% of healthy individuals with Latent Tuberculosis Infection, active tuberculosis disease may eventually develop over their lifetime. The highest risk of progressing to active tuberculosis disease is in the first two years after initial infection. In persons who are immune compromised (e.g. the elderly or those who are human immunodeficiency virus (HIV) positive), the rate of progressing to active tuberculosis disease will be higher than in healthy individuals. For example, individuals with untreated HIV co-infection may progress from Latent Tuberculosis Infection to active tuberculosis disease at the rate of 5-8% per year, with a lifetime risk of approximately 30%.

The general accelerated failure time model

According to the Collett David (2003) to the general acceleration failure time model, the ith individual at time t, the hazard function of $h_i(t)$, in such that

$$h_i(t) = e^{(\gamma i} h_*(t/e^{\gamma i})$$

Where $\eta i = \alpha_/ x_{/i} + \alpha_2 x_{2i} + \ldots + \alpha_p x_{pi}$

In this model is called linear component of the model, here x_{6i} the value of the j^{t9} is considered explanatory variable of $X_{6,}$ $j = 1,2,3, \ldots p$, for the i^{t9} individual, $i = 1,2,3, \ldots n$. Then the baseline of hazard function $h_*(t)$ in the proportional hazard model, the hazard of failure at time t for an individual value of p is the explanatory variable are equal to zero and the corresponding survivor function is

$$S_i(t) = S_*\{t/e(\eta_i)\}$$

Where $S_*(t)$ is the baseline of survival function. The acceleration failure time model for survival data analysis is nearly close related to the general linear model apply for regression analysis.

Log-linear from of the accelerated failure time model

The T the random variable is considered for a log-linear model, combine with the survival analysis of i^{t9} individual of lifetime according that Collett David (2003) explosed to

$$logT_i = \mu + \alpha_/ x_{/i} + \alpha_2 x_{2i} + \ldots + \alpha_p x_{pi} + \sigma\epsilon_i$$

This model provides the unknown coefficient are $\alpha_/$, α_2, … , α_p and the explanatory variable is p, then $X_/ , X_2$, … , X_P and μ, σ are two parametric is called as constant and scale parameter. We are apply this model the deviation of the value $logT_i$ from the linear part of the model. In this model given the α is parameters the parameter is follow the effect of explanatory variable on the survival time.

The equation considers the correlation between the model and survivor function of T_i , the time random variable related with survival time of the i^{t9} subject , show that the survival function is given by,

$$S_i(t) = P(T_i \geq t)$$

$$P = \{\exp(\mu + \alpha^R x_i + \sigma\epsilon_i) \geq t\}$$

Where $\alpha^R x_i = \alpha_/ x_{/i} + \alpha_2 x_{2i} + \ldots + \alpha_p x_{pi}$

Then $S_i(t) = P\{\exp(\mu + \sigma\epsilon_i) \geq t / \exp(\alpha^R x_i)\}$

Review of Literature

Rinku Saikia and Manash Pratim Barman we are delivered the acceleration failure time model give a good result compare to the cox proportional hazard model. In this model similarly easy to understand the inference. The AFT model was fitted in parametric distribution. Zhanshan (Sam) Ma Edward John Bechinski , they are applied and determine the acceleration failure time model to test the effect of covariance and dependence between covariates. Raman and Venkatesan said the acceleration failure time model is better alternative to the cox PH model in survival analysis. To account for more heterogeneity in weibull distribution is measure for other distribution by acceleration failure time model with gamma frailty model. The AFT without frailty model analyse give better fit the lognormal distribution approach other distribution model. Shankar Prasad Khana, V. Sreenivas and Subrat K. Acharya, they exposed the AFT model analysed the time to event data to estimate covariates on acceleration or deceleration of survival time. We suggested that outcome from the acceleration failure time model were easier to interpreted not only for medicine that incorporates the study of liver but also for used other clinicians for more relevant evidence the survival data. William R. Swindell Were gave the conclusion that the acceleration failure time model must be applied more general research. The acceleration failure time model along with quartile regression model as a complementary follow- up- approach. In these approaches bring valuables tools that may be give better outcome from the experimental studies of the survivorship. Jesus Orbe, Eva Ferreira and Vincent Nunez-Anton (2002), conferred the clinical research typical used most wide model to analysis the foreboding variables in cox PH model. This model cannot satisfied by data. AFT model directly considered the explanatory variable on the survival time.

Exponential Acceleration Failure time model

Elisa T. Lee John Wenyu Wang (2003) The survival time T following an exponential distribution is called exponential model. The exponential model is characterized by a constant hazard rate λ, its only parameter. A large λ indicates high risk and short survival while a small λ indicates low risk and long survival.

When λ=1, the distribution is often referred to as the unit exponential distribution.

When the survival time T follows the exponential distribution with a parameter λ, the

Probability density function is defined as (Lee 1992)

$$f(t) = \begin{cases} \frac{\lambda}{\Gamma(\gamma)} (\lambda t)^{\mathrm{WC}/} \mathrm{e}^{\mathrm{CX}t} ; \ \mathrm{t} > 0, \lambda > 0, \gamma > 0 \\ 0 \ ; \ otherwise \end{cases}$$

The cumulative distribution function is

$$F(t) = P(T \leq t) = F(t) = 1 - \mathrm{e}^{(\mathrm{ef}}$$

Now the survivorship function is

$$S(t) = 1 - F(t) = e^{(ef}, t \geq 0.$$

The Weibull Model in an AFT formulation

The exponential distribution and also the Weibull distribution can be treated a log-linear model of time, but the error is concluded. We can able do the Weibull distribution from acceleration failure time model formulation is given

$$T_i = \exp(X_i\gamma)\sigma u_i$$

The comparison of the acceleration failure time express the exponential model, then the Weibull model has the extreme value of the distribution charge the error u_i is not strained have the variance equal to one and variance of the errors can be taken to any positive integer. The weibull model to be estimate the covariates directly effect on the log of survival time is (γ) the variance of the error term is (σ). However the, weibull distribution considers the two parameterization then same time refers to σ kind of p.

1. P = $1/\sigma$ this mean that shape parameter and the function is considered the variance the residuals in the accelerated failure time form.
2. When we have minimum error of variance of σ will tend to be dependence positive period, in this relative lack of heterogeneity.
3. We have data with a maximum error of variances will tend to dependence negative.
4. 4. β = - γ/σ is equal to $\gamma = -\beta/p$
5. This distribution considers the parameters β and γ are equal to the scale parameter p or σ.

The Gompertz Model

The lognormal distribution and log-logistic distribution can estimate the survival time and the Gompertz distribution is can able to find out the hazard rate or failure time and this model is only is used, proportional model. In this model has been widely used in demography and biomedical then especially apply lesser extent in sociology. It have been two parameter distribution, its hazard out of the Weibull distribution is given by,

$$h(t) = \exp(\lambda)\exp(\gamma t)$$

And the corresponding survival function

$$S(t) = \exp(\lambda) \exp\left[-\frac{e^{X}}{\gamma}(e^{Wt} - 1)\right]$$

The above equation, the parameter λ model is considered the first moment, such that can estimate covariates that we believe the level of the hazard.

$$\lambda_i = \exp(X_i\beta)$$

Then another parameter γ is called a shape parameter and along with the lines P parameter in the weibull model. Here,

When we have $\gamma = 0$, that time the hazard is constant, and the model is largely corresponds to an exponential model,

We get $\gamma > 0$, can conclude the hazard are monotonically is raise the over time.

When $\gamma < 0$, the hazard are fall over time.

Gamma model

Elisa T. Lee John Wenyuwang (2003) said the random variable T is followed the Gamma distribution, this distribution has two parameters γ and λ are shape and scale parameter. In this distribution represent two different type failure time data analysis survival model and hazard rate is increase or decrease the overtime period. Hence, the parametric distribution model it can be used for engineering and industrial reliability problem.

The probability density function of a gamma distribution is

$$f(t) = \begin{cases} \frac{\lambda}{\Gamma(\gamma)}(\lambda t)^{WC/}e^{CXt}\ ;\ t > 0, \lambda > 0, \gamma > 0 \\ 0\ ;\ otherwise \end{cases}$$

The cumulative distribution function

$$F(t) = P(T \leq t) = \int_{*}^{t} \frac{\lambda}{\Gamma(\gamma)}(\lambda x)^{WC/}e^{CXx}\,dx$$

Reparametrise with $\alpha = \lambda^{y}$ so that taking derivative is easier (Miller, 1981),

And the survival function is

$$S(t) = e^{(afq}, f(t) = \alpha\gamma t^{yC/}e^{(afq}$$

When we have the $\gamma > 1$, is indicates positive and hazard rate rises monotonically from zero to infinity, then $\gamma = 1$, the hazard rate equal λ a constant same as follows the exponential model. Finally the $0 < \gamma < 1$, represent is negative and the hazard rate decrease monotonically from the infinity to λ as a time increase.

Deviation method (-2LL)

Elisa T. Lee John Wenyuwang (2003), proposed that the survival data including time-independent and time-dependent variables it can be able to compare and evaluate the particular model fitting or not. To check the process leads to maximum likelihood function when we have been the outcome is independent, if we have your outcome is dependent they are used maximised partial likelihood function. So that gets the value from the test statistics of -2log likelihood.

Table 1: Exponential regression from accelerated failure time model

Parameters	Coefficient	Std. Error	Z Value	P Value	[95% CI]	
Regimen	0.046	0.039	1.20	0.231	-0.029	0.123
Sex	0.264	0.078	3.38	0.001	0.111	0.417
Weight	-0.012	0.004	-2.65	0.008	-0.022	-0.003
Pre.TRT	-0.674	0.092	-7.28	0.000	-0.856	-0.493
Age	0.000	0.002	0.27	0.790	-0.004	0.006

Table 2: Weibull regression from accelerated failure time model

Parameters	Coefficient	Std. Error	Z Value	P Value	[95% CI]	
Regimen	0.0385	0.0205	1.87	0.061	-0.0018	0.0789
Sex	0.1954	0.0410	4.76	0.000	0.1149	0.2759
Weight	0.0094	0.0024	-3.92	0.000	-0.0141	-0.0047
Pre.TRT	0.0529	0.0495	-10.6	0.000	-0.6262	-0.4321
Age	0.0001	0.0015	0.12	0.906	-0.0028	0.0032
/ln_p |	0 .6326	0.02391	26.46	0.000	0.5857	0.6795
p	1.8826	0.04502	--			
1/p	0.5311	0.01270				

Table 3: Gompertz regression from accelerated failure time model

Parameters	Coefficient	Std. Error	Z Value	P Value	[95% CI]	
Regimen	-0.6297	0.0388	-1.62	0.105	-0.1391	0.0132
Sex	-0.3293	0.0776	-4.24	0.000	-0.4815	-0.1770
Weight	0.0168	0.0046	3.63	0.000	0.0077	0.0259
Pre.TRT	0.9202	0.0948	9.70	0.000	0.7344	1.1061
Age	-0.0000	0.0029	-0.03	0.908	-0.0058	0.0056
gamma	0.3120	0.0207	15.02	0.000	0.2713	0.3528

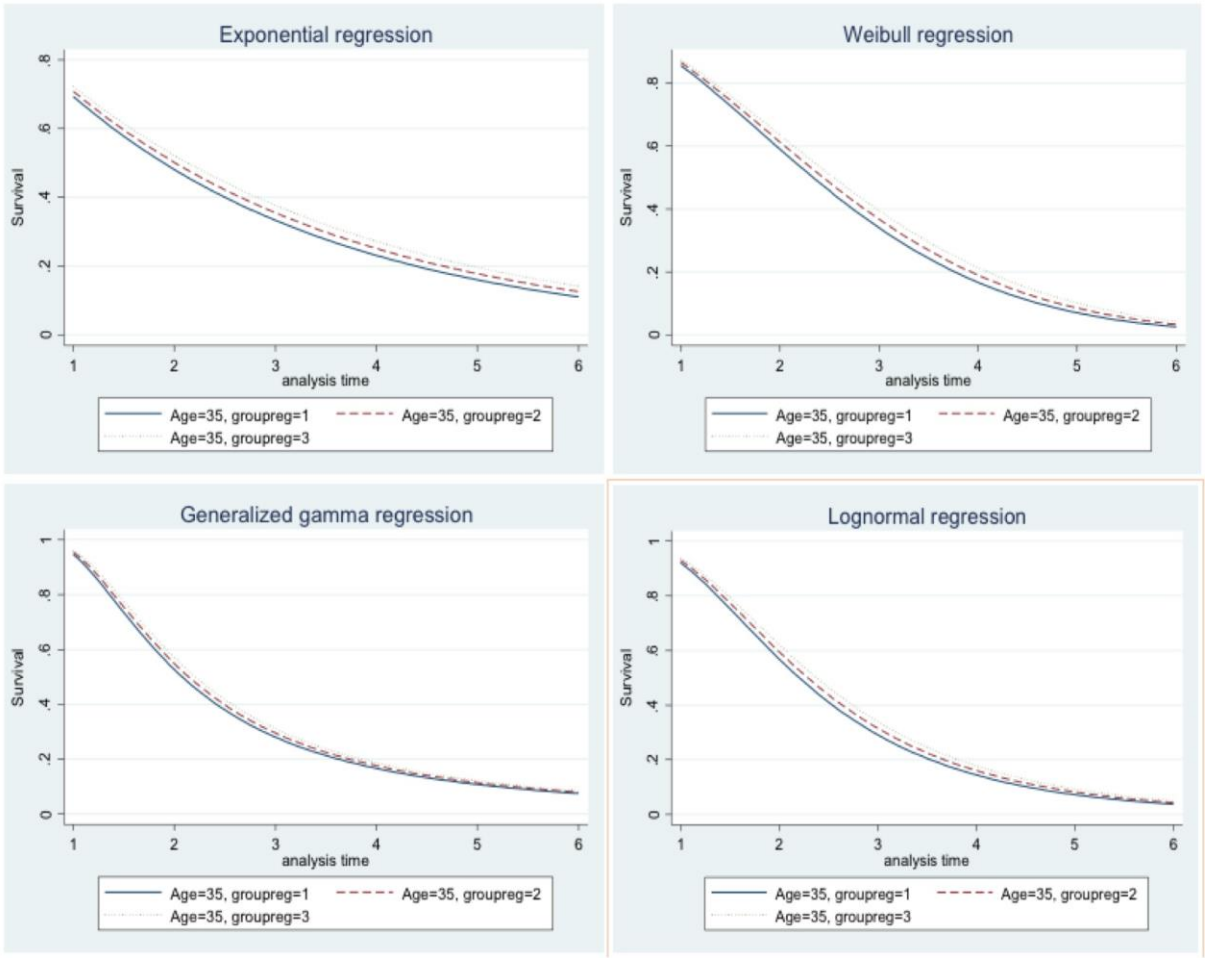

Figure 1: Age=35 vs. Treatments

Table 4: Exponential regression from accelerated failure time model

Parameters	Coefficient	Std. Error	Z Value	P Value	[95% CI]	
Regimen	0.0273	0.0203	1.34	0.179	-0.0125	0.0673
Sex	0.1959	0.0414	4.73	0.000	0.1147	0.2771
Weight	-0.0087	0.0026	-3.62	0.001	-0.0140	-0.0035
Pre.TRT	-0.3665	0.0434	-8.44	0.000	-0.4515	-0.2814
Age	0.0026	0.0014	1.76	0.079	-0.0003	0.0055
ln_sig	-0.6088	0.0233	-26.08	0.000	-0.6545	-0.5630
sigma	0.5439	0.0127			0.5196	0.5694

Table 5: Log-logistic regression from accelerated failure time model

Parameters	Coefficient	Std. Error	Z Value	P Value	[95% CI]	
Regimen	0.0259	0.0199	1.30	0.192	-0.0130	0.0650
Sex	0.1961	0.0406	4.83	0.000	0.1164	0.2757
Weight	-0.0082	0.0026	-3.06	0.002	-0.0135	-0.0029
Pre.TRT	-0.3432	0.0467	-7.34	0.000	-0.4350	-0.2517
Age	0.0029	0.0014	2.00	0.046	0.0000	0.0057
ln_gamma	-1.1718	.02705	-43.32	0.000	-1.2248	-1.1188
gamma	0.3097	0.0083			0.2938	0.3266

Table 6: Gamma regressions from accelerated failure time model

Parameters	Coefficient	Std. Error	Z Value	P Value	[95% CI]	
Regimen	0.0224	0.0193	1.16	0.247	-0.0155	0.0604
Sex	0.1590	0.0402	3.95	0.000	0.0801	0.2379
Weight	-0.0063	0.0025	-2.46	0.014	-0.0114	-0.0012
Pre.TRT	-0.2249	0.0444	-5.06	0.000	-0.3120	-0.1377
Age	0.0034	0.0013	2.51	0.012	0.0007	0.0661
ln_sig	-0.6557	0.0263	-24.91	0.000	-0.7073	-0.6041
kappa	-0.6987	0.1046	-6.68	0.000	-0.9039	-0.4936
sigma	0.5190	0.0136			0.4929	0.5465

Table 7: Model comparison using -2LL in acceleration failure time model

Parametric Distribution Covariates	Exponential	Weibull	Gompertz	Lognormal	Log Logistic	Gamma
Regimen	0.047	0.038	-0.062	0.027	0.025	0.022
Sex	0.264*	0.195*	-0.329*	0.195*	0.196*	0.159*
Weight	-0.012*	-0.009*	0.016*	-0.008*	-0.008*	-0.006*
Presence	-0.674*	-0.529*	0.920*	-0.366*	-0.343*	-0.224*
Age	0.000	0.000	-0.000	0.002	0.002*	0.802*
-2LL	2597	2102	2398	1876	1870	1832

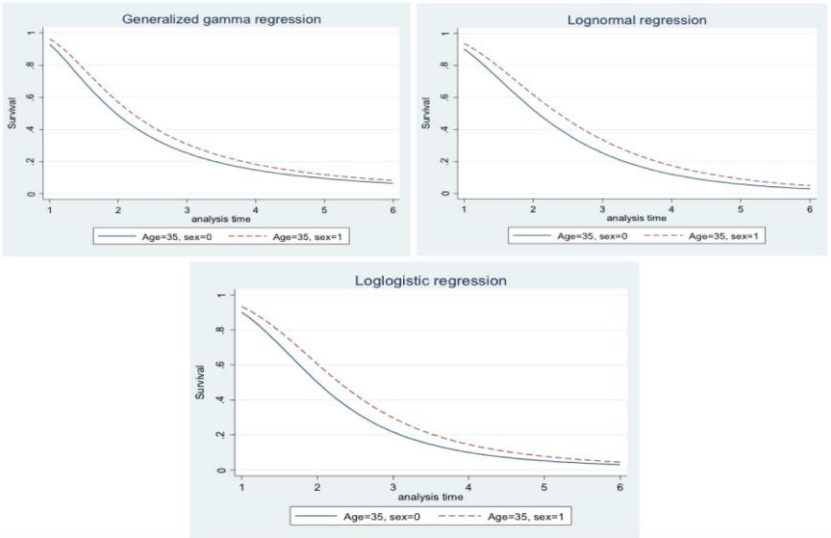

Figure 2: Age vs. Sex

Alternatively nested model may be compared to the percentage point of the chi-square distribution and with degrees of freedom balanced the difference in the value of parameters was fitted. C. Ponnuraja and P. Venkatesan (2010), explained sputum conversion and spell out clinical trial approached in tuberculosis data. Catherine Rexy D, Mokesh Rayalu. G and Ponnuraja C (2017) considered Unshared Gamma Frailty Model in Tuberculosis Patients.

Research Dataset Description

The data were collected from the National Institute of Tuberculosis (ICMR) Chennai. The patients admitted and gave the treatment based on randomized controlled clinical trial including into three type of treatment with control regimen, in this study contact since the patients admitted in the treatment to six months duration. The 1124 patients considered for in this research and my focus the event of interest is the conversion of sputum in positive into negative for this during the treatment period. There are five covariates examine is given below.

1. Regimen - (i) Standard Regimen- (0); (ii). New Split Regimen- (1)
2. Gender - (Male-1 and Female-0)
3. Weight at baseline (in Kg)
4. Pre treatment sensitivity - (Present-1 and Absent-0)
5. Age - The patients admitted in the age group between 9 to 68 years.

Application of Clinical Trial Data Using AFT Model

The above table.1 gives the result acceleration failure time model from an exponential distribution, We founded the coefficient of the regimen in acceleration failure time model is court by 100X [1-exp (0.046)] = 4.7, that reduces that nearly 53 present. However that the concluded the regimen 4.7 present of the survival time of TB patients. The same techniques applied for another coefficient like sex, weight, pre-treatment sensitivity and age then we have value for sex is 2.67 percentages, weight is 1.19 percentage, pre-treatment sensitivity is 49 percentage and age is 0.07 percentage survival time of the TB patients based on exponential distribution AFT model. We have to consider the P value less than 0.05 gets sex, weight and pre-treatment sensitivity is significant, and remaining other coefficients is not significant.

The table.2 represents the AFT model from Weibull distribution for p is a shape parameter, that the p-value is greater than one the result suggested hazard increase over time. The estimated acceleration factor of regimen exp (0.0385) = 1.0392. According that the result based on the median survival time is increased by a factor of 1.0392. P is the hazard value and 1/P is the survival time that is 0.5311 of TB patients in Weibull distribution. So that we can find out the Weibull model more feasibility than an exponential model for this tuberculosis patients dataset.

It can be concluded that from Gomperz distribution find out the hazard rate of the tuberculosis patients. This distribution has two parameters and the hazard is monotonic function over time. We considered above table value of shape (P) parameter in Gomperz distribution, is gamma value represents the hazard function the overtime, then when we have gamma = 0, the hazard is constant, and gamma = 0.3120 so the gamma value greater than zero in that meaning the hazards are monotonically increasing over time in this distribution. The hazard exponentially increases over time.

The lognormal regression from the acceleration failure time model exploring the data output of shape parameter is called sigma and the reciprocal ($1/\sigma$) of sigma is considered for P value. Similarly, the distribution assumed follows a standard normal distribution. However, the p-value is greater than zero hazards first time increase after that fall down. Hence the p-value is (1/0.5439) = 1.8385. So we conclude that the p-value is greater than one, hazard rises the first time and fall next time. In this particular, the log-logistic model and lognormal the most value of P >1 this model is unimodal.

Log-logistic from acceleration failure time model given that output and estimates the coefficients for like regimen and age is not significant based on the p-value ($p<0.05$). Another coefficient like sex, weight and pre-treatment sensitivity is significant. The STATA provides the estimates of the p-value is considered (gamma = 1/p) the reciprocal of gamma value.so estimated for P = 1/ (0.3097) = 2.18. In this particular the p-value indicates P>1, that means the hazard increases the first time and then decrease over time. In this case, the hazard model is said unimodal.

From the table.7 represent the result we can able to find out how many covariates have significant and contribute the outcome of sputum conversion positive to negative. Hence, the covariates like sex, baseline weight, and pre-treatment sensitive highly influence the outcomes. Then we have to consider other important covariates like regimen and sex is not significant so can able to interpret these variables do not influence the outcome.

The conclusion comes from the parametric distribution model namely exponential, Weibull, Gompertz, lognormal. Gamma and log-logistic distribution form acceleration failure model give up the output having four covariates significant in this distribution. Since the covariates relate to sex, baseline weight, pre-treatment and age impact of patient outcomes of sputum conversion.

The above table.7 can we come to an end which parametric distribution give a better model of the tuberculosis patients data set based on -2 log likelihood value. According to that -2LL which distribution has been the less value or minimum deviation compares to another distribution model that distribution model is called better model. We would calculate of -2LL deviation took the value from the corresponding distribution in log-likelihood value and multiple in two after that getting -2 log likelihood deviations.

Finally, the gamma distribution calculates the -2LL function the value taken from STATA output in gamma distribution is log likelihood value is -2(-916.06447) = 1823.The same concept applied other distribution and get the -2 log likelihood value showing table. So we find out gamma distribution is better distribution compared other distribution because this distribution having a minimum value.

CONCLUSION

The acceleration failure time model is predicated survival time and can be find out median of survival time. We can know the effect of covariates is to be accelerated or waiting the period of disability by a constant value. The failure family distribution applied the acceleration failure time model containing the Weibull AFT model, Gompertz log-logistic AFT model, log-normal AFT model, and gamma AFT model are applied to this tuberculosis patient data set. We can select better model for this distribution using -2LL deviation method.

Which distribution got the minimum value compare to another distribution model is consider better distribution model. The table show the result the gamma distribution get minimum value compares to another distribution model. Finally, in this study we conclude the tuberculosis patients data set describe the model of better distribution can estimated from the acceleration failure time gamma distribution.

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