Application of Survival Analysis of TB Patients Using Parametric Model: A Case Study of General Hospital Bayara

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Authors’ contributions

This work was carried out in collaboration among all the authors. Author SD designed the study and carried out the research and the analysis. Authors KEL and JB interpreted the result. All the authors approved the final manuscript.

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Abstract

Aim: We evaluate the performance of parametric models, mixture of generalized gamma frailty model with Gompertz distribution and compare it with Cox proportional hazard model that is commonly used in the analysis of TB patients and also by [1].

Place and the Duration of the Study: The study was carried out in Bauchi State, Nigeria from January, 2017 to January, 2020.

Methodology: In this study secondary data was used and gotten from the patients’ treatment card and TB registers from January 2015 to December 2017. The covariates used were, drug, age, marital status, smoking habit, educational level, weight, category, and risk factor. We used AIC and BIC selection tool to select the model with the lowest value and then compare it with Cox hazard model. Data analysis was done in Stata version 14.

Results: The result of the analysis shows that mixture of frailty model with Gompertz baseline distribution has the lowest AIC and BIC value when compared to Cox Proportional model therefore shows a better goodness of fit for our dataset.

Conclusion: We therefore conclude that mixture of frailty model with Gompertz baseline distribution model can serve as an alternative to Cox Proportional Model.

Keywords: Tuberculosis (TB); gamma frailty model; Gompertz distribution; Cox proportional hazard model.

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1 Introduction

Tuberculosis (TB) remains one of the main causes of morbidity and mortality in many countries and is considered a global health problem [2]. Although it can be treated if diagnosed on time, every year not less than nine million people develop active disease and two million die from it [3] WHO has coordinated multiple and various efforts towards global TB control. One of the goals of the Global Plan to Stop TB is to reduce TB deaths to the barest minimum [4]. In recent studies evidence has shown that TB prevalence and mortality have been under-estimated in many high-burden countries with rising estimates from Nigeria. Nigeria being the most populous country in Africa has an estimated population of over 180 million people. Among the identified 22 high burden countries, Nigeria is ranked 4th in the high burden countries and 1st in Africa with an estimate of 460,000 new cases and 5,000 leprosy per year [5].

Survival analysis is a branch of statistics for analyzing the expected duration of time until one or more events happen. Despite the advantages of parametric model due attention has not been given to this model in the study of non HIV TB patients as a control group. Hence this study tries to compare the performance of several parametric models and compare it with Cox proportional model that was often used by researchers in modeling time to event data in survival analysis.

A number of studies have been conducted in which various survival regression methods are compared with parametric models to model time to event data [6,7,8,9,3,10].

2 Materials and Methods

Secondary data was obtained from the treatment card and TB register of the patients in the hospital. The following covariates were used in the analysis drug, age, marital status, smoking habit, educational level, weight, category and risk factor. Kaplan Meier curve was used to estimate the survival pattern of the patients; log rank test was used to identify factors affecting TB survival. Parametric model (exponential, weibull, log logistic, log normal, Gompertz distribution), and compared with Cox proportional model. The model with the lowest AIC and BIC was selected as the best goodness of fit for the dataset.

2.1 Method of analysis

This study included 255 non HIV TB patients in General Hospital Bayara, Opportunistic and infection unit Bauchi. Parametric model, mixture of generalized gamma frailty model based on Gompertz baseline distribution, will be analyze and compared with Cox proportional model in the analysis of non HIV Tb Patients as a control group. Data of the patients were collected and recorded over time from the Tb register and treatment cards of the patients. The parametric models considered in this study are as follows:-

- Propose mixture of generalized gamma frailty model based on Gompertz baseline distribution [11]

The conditional likelihood for the frailty model is given as

\[ L = \prod_{i=1}^{G} \prod_{j=1}^{n_i} \left[ h(t_{ij} | z_i, X_{ij}) \right]^{\delta_{ij}} S(t_{ij} | z_i, X_{ij}) \]

Integrating L over the entire range of the frailty variable Z. the unconditional likelihood function L is obtained as:

\[ L = \int \cdots \int \prod_{j=1}^{G} \prod_{i=1}^{n_i} \left[ h(t_{ij} | z_i, X_{ij}) \right]^{\delta_{ij}} S(t_{ij} | z_i, X_{ij}) f(z_i) dz_i \]

Where \( f(.) \) denotes the pdf of the generalized gamma frailty distribution (GGD (b,d,k)) given by
Note that $d$ and $k$ are the shape parameters and $b$ is the scale parameter of the GGD, to make the parameters of the model identifiable we set the mean of the frailty parameter equal to 1 hence

$$E(z) = \frac{b\Gamma(k + \frac{1}{d})}{\Gamma(k)} \Rightarrow b = \frac{\Gamma(k)}{\Gamma(k + \frac{1}{d})}$$

This gives

$$V(z) = \frac{\Gamma(k)\Gamma(k + \frac{2}{d})}{\Gamma(k + \frac{1}{d})^2} - 1$$

- Gompertz Distribution

$$f(t) = \omega e^{\alpha t} e^{-\frac{\omega}{\alpha}[e^{\alpha t} - 1]}, \quad \omega > 0, t > 0$$

**Parametric models used in this study**

- Exponential model

$$f(t) = \lambda \exp(-\lambda t), \quad t > 0, \lambda > 0$$

- Weibull model

$$f(t) = \frac{\alpha}{\lambda} \left(\frac{t}{\lambda}\right)^{\alpha-1} \exp\left(-\left(\frac{t}{\lambda}\right)^\alpha\right), \quad 0 < t < \infty, \lambda, \alpha > 0$$

- Log-normal model

$$f(t) = \frac{1}{\alpha t \sqrt{2\pi}} \exp\left(-\frac{1}{2\alpha^2}[\ln t - \ln \mu]^2\right), \quad 0 < t < \infty$$

- Log-logistic model

$$f(t) = \frac{\alpha \lambda - (\alpha \lambda)^{\lambda-1}}{[1 + (\alpha t)\lambda]^2}, \quad \alpha > 0, \lambda > 0 \text{ and } t > 0$$

- Cox proportional hazard model

$$\lambda (t/X_i) = \lambda_0 (t) + \beta_1 X_{ij} + \cdots + \beta_p X_{ip} = \lambda_0 (t) + X_i \beta$$

The data was analyzed in Stata version 14 using all the models and then compared with (Cox proportional model) used by [1].
3 Data Analysis

This chapter provides the results of the analysis done on expert’s opinion on the best alternative model in the study of non HIV TB patients, and then compared with Cox model.

3.1 Presentation of tables and results

A total of 255 non HIV TB patients were followed for a period of 18 months.

| Covariates and health factors | Total | Death | Percentage of covariates |
|-------------------------------|-------|-------|--------------------------|
| Sex                           |       |       |                          |
| Male                          | 157   | 10    | 61.57                    |
| Female                        | 98    | 5     | 38.43                    |
| Marital status                |       |       |                          |
| Single                        | 93    | 5     | 36.47                    |
| Married                       | 159   | 10    | 62.36                    |
| Widow                         | 2     | 0     | 0.78                     |
| Divorce                       | 1     | 0     | 0.39                     |
| Smoking record                |       |       |                          |
| Yes                           | 17    | 12    | 6.67                     |
| No                            | 238   | 3     | 93.33                    |
| Education level               |       |       |                          |
| Non formal                    | 181   | 10    | 70.98                    |
| Primary                       | 8     | 0     | 3.14                     |
| Secondary                     | 28    | 2     | 10.98                    |
| Tertiary                      | 38    | 3     | 14.90                    |
| Category of TB                |       |       |                          |
| I                             | 79    | 6     | 30.98                    |
| II                            | 127   | 8     | 49.80                    |
| III                           | 49    | 1     | 19.22                    |
| Weight                        |       |       |                          |
| <20                           | 46    | 1     | 18.04                    |
| 22 – 30                       | 51    | 1     | 20.00                    |
| >31                           | 158   | 13    | 61.96                    |
| Age                           |       |       |                          |
| 15 – 25                       | 91    | 2     | 35.69                    |
| 26 – 35                       | 84    | 2     | 32.94                    |
| 36 – 59                       | 68    | 5     | 26.67                    |
| >60                           | 12    | 6     | 4.70                     |

Table 3.1. Summary of survival data

. stset months, failure (status==0) scale(1)

| total observations | exclusions |
|--------------------|------------|
| 255                | 0          |

255 observations remaining, representing
15 failures in single-record/single-failure data
4173 total analysis time at risk and under observation
at risk from
earliest observed entry
t = 0
t = 0
last observed exit
t = 39
The table above indicates 255 total observations, 15 failures and 4,173 total analysis times at risk. There were no exclusions. The event of interest is recovery from TB (0 = failure, 1 = recovery).

![Figure 3.0. Kaplan Meier graph by gender](image1)

The Kaplan Meier graph above indicates that gender is not significant in predicting survival since there is no much difference between the subjects.

![Figure 3.1. Kaplan Meier survival estimate by drug adherence](image2)

Figure 3.1 shows that survival is dependent on drug adherence, those with poor adherence end up having complications and dying than those who adhere. Drug adherence is significant in the survival of TB patients.
Table 3.2. Log rank test by smoking habit

. stset _SmokingHabit, logrank
    failure _d: status ==0
    analysis time _t: months

log-rank test for equality of survivor functions

| Smoking habit | Events observed | Events expected |
|---------------|----------------|-----------------|
| 1             | 3              | 6.84            |
| 2             | 12             | 8.16            |
| Total         | 15             | 15.00           |

Chi2 (1) = 3.99
Pr>chi2 = 0.0459

The log rank test above shows that the significant level of the test is less than (α =0.05) indicating that smoking habit is affecting the survival of TB patients.

Table 3.3. Log rank test by risk factor

. stset _riskfactor, logrank
    failure _d: status ==0
    analysis time _t: months

log-rank test for equality of survivor functions

| risk factor | Events observed | Events expected |
|-------------|----------------|-----------------|
| 0           | 12             | 13.33           |
| 1           | 0              | 0.31            |
| 2           | 2              | 0.44            |
| 3           | 0              | 0.33            |
| 4           | 1              | 0.10            |
| 5           | 0              | 0.48            |
| Total       | 15             | 15.00           |

Chi2 (5) = 14.57
Pr>chi2 = 0.0124

From the log-rank test above with 5 df, the significance level of the test is below (α=0.05) indicating that risk factor is significant and therefore affecting the survival of TB patients. The following risk factors are coded into Stata software for the analysis.

None = 0
High fever = 1
Diagnosis delay = 2
Hypertension = 3
Diabetes = 4
Substance abuse = 5
Table 3.4. Stata output of gamma frailty model with Gompertz distribution

| Failure _d: status ==0 | Analysis time _t: months |
|------------------------|---------------------------|
| Gompertz regression – log relative hazard form |
| Gamma frailty |

No. of subjects = 255  
Number of obs = 255  
No. of failures = 15  
Time at risk = 4173  

LR chi2 (8) = 25.93  
Prob > chi2 = 0.0011  
Log likelihood = -43.597888  

| _t | Hazard ratio | Std error | z | P>|z| | [95% conf. Interval] |
|----|--------------|-----------|---|------|---------------------|
| drug | 0.085779 | 0.0926379 | -2.27 | 0.023 | 0.0103304 - 0.7122693 |
| age | 1.090521 | 0.0568851 | 1.66 | 0.097 | 0.9845385 - 1.207913 |
| _MaritalStatus | 0.5908347 | 0.7088084 | -0.44 | 0.661 | 0.0562733 - 60203394 |
| _SmokongHabit | 4.390093 | 4.513256 | 1.44 | 0.150 | 0.585318 - 32.92725 |
| _Educationallevel | 0.7547019 | 0.3412641 | -0.62 | 0.534 | 0.3110826 - 1.830944 |
| weight | 1.04367 | 0.0450470 | 0.99 | 0.322 | 0.9589694 - 1.135852 |
| category | 0.2650246 | 0.2046013 | -1.72 | 0.085 | 0.0583648 - 1.203431 |
| _riskfactor | 1.135659 | 0.4123552 | 0.35 | 0.726 | 0.5574152 - 2.313755 |
| _cons | 0.000287 | 0.0012359 | -1.89 | 0.059 | 0.0583648 - 1.203431 |
| /gamma | 0.2469574 | 0.0930287 | 2.65 | 0.008 | 0.0646244 - 0.4123552 |
| /In_the | 2.037338 | 0.8591983 | 2.37 | 0.018 | 0.3533996 - 3.721277 |
| theta | 7.670168 | 6.589965 | 1.4239 | 0.149 | 141.31714 |

Likelihood-ratio test of theta=0: chibar2 (01) = 2.66  
Prob>=chibar2 = 0.052

. estat ic

Akaike’s information criterion and Bayesian information criterion

| Model | Obs 11(null) | 11(model) df | AIC | BIC |
|-------|--------------|--------------|-----|-----|
| -     | 255 -56.56181 | -43.59789 10 | 107.1958 | 142.6084 |

Note: N=obs used in calculating BIC; see [R] BIC note

From the gamma frailty model with Gompertz distribution above, 1 unit increase in smoking habit is associated with 4.39 times greater the chance that it affects TB survival. The hazard ratio of drug is 0.08 and has a P value less than (α = 0.05) which is significant. We will conclude by saying it reduce the hazard of TB mortality.

Table 3.5. Stata output of cox proportional hazard regression model

| failure _d: status ==0 | analysis time _t: months |
|------------------------|---------------------------|

Iteration 0:  
log likelihood = -67.869635
Iteration 1:  
log likelihood = -56.98712
Iteration 2:  
log likelihood = -56.833897
Iteration 3:  
log likelihood = -56.833616
Refining estimates:
Iteration 0:  
log likelihood = -56.833616
Cox regression – Breslow method for ties

|               | Hazard ratio | Std error | z    | P>|z|  | [95% conf. Interval] |
|---------------|--------------|-----------|------|------|-----------------------|
| drug          | 0.3102259    | 0.1340739 | -2.71| 0.007| 0.1329855 – 0.7236883 |
| age           | 1.038266     | 0.0282921 | 1.38 | 0.168| 0.9842695 – 1.095225  |
| _MaritalStatus| 0.6470829    | 0.4877549 | -0.58| 0.564| 0.1476881 – 2.835139  |
| _SmokingHabit | 2.960524     | 2.187533  | 1.47 | 0.142| 0.6956891 – 12.59859  |
| _EducationalLevel| 1.114541  | 0.2636522 | 0.46 | 0.647| 0.7010333 – 1.771958  |
| weight        | 1.017039     | 0.0281065 | 0.61 | 0.541| 0.9634164 – 1.073646  |
| category      | 0.4466932    | 0.1860506 | -1.93| 0.053| 0.1974597 – 1.010509  |
| _riskfactor   | 1.184179     | 0.2260777 | 0.89 | 0.376| 0.814536 – 1.72157    |

. estat ic

Akaike’s information criterion and Bayesian information criterion

| Model | Obs 11(null) | 11(model) | df | AIC     | BIC     |
|-------|--------------|-----------|----|---------|---------|
| -     | 255          | -56.83362 | 8  | 129.6672| 157.9973|

Note: N=obs used in calculating BIC; see [R] BIC note

From the above table of Cox proportional hazard ratio drug and category are not significant predictors of mortality.

![Cox proportional hazards regression](image)

Figure 3.2. Cox hazard plot

The hazard regression plot of Cox model is above zero on the hazard function. It starts to go up from 12 in the analysis time and increases rapidly from 23 showing the hazard rate of the model.
Figure 3.3. Gompertz hazard plot

The hazard regression plot of Gompertz distribution shows a lower hazard when compared to Cox hazard model. The hazard function is on zero. It starts to go up from 8 in the analysis time and increases rapidly from 17 showing the hazard rate of the model. From the hazard plot of the two models Gompertz distribution has a lower hazard rate than Cox proportional hazard model.

4 Discussion of Results

The following covariates were used in the analysis of the data they include drug, age, marital status, smoking habit, educational level, weight, category of TB and risk factor. A total number of 255 HIV negative TB cases were recorded from January 2014 to December 2017. The median followed up period is 18 months. 15 patients died representing (5.88%) of the total number of patients of which 6 (2.35%) are in category I, 8 (3.14%) in category II and 1 (0.39%) in category III. Most of the death occurred within patients who default in taking their drugs and loss to follow-up. 125 patients were lost-to-follow-up during the study period after diagnosis. 220 were censored due to incomplete information.

A total of 94.12% of the TB patients survived the study period, which signifies that TB patients had a high survival rate if they adhere to taking their drugs.

The Kaplan Meier graph in Figure 3.0 indicates that gender is not significant in predicting survival. Figure 3.1 shows that survival is dependent on drug, those with poor adherence end up having complications and dying than those who do not adhere. Drug is significant in the survival of TB patients. From Figure 3.2 the hazard regression plot of Cox model is above zero on the hazard function. It starts to go up from 12 in the analysis time and increases rapidly from 23 showing the hazard rate of the model. Figure 3.3 of hazard regression plot of Gompertz baseline distribution shows a lower hazard when compared to Cox hazard model. The hazard function is on zero. It starts to go up from 7 in the analysis time and increases rapidly from 12. From the hazard plot of the two models Gompertz baseline distribution has a lower hazard rate than Cox proportional hazard model.

The Multivariate analysis showed an increased risk of survival for patients with smoking habit [HR=2.960524 SE= 2.187533 (P=0.05) CI (0.6956891 12.59859)], in Cox PH model.

Smoking habit and risk factor are a strong and independent factor affecting the survival of TB patients. From the Gompertz baseline distribution output of Table 3.4, 1 unit increase in smoking habit is associated with 4.39 times greater the chance that it affects TB survival. The hazard ratio of drug is 0.08 and is significant with a probability value of 0.023 less than (α =0.05) we will conclude by saying it reduce the hazard of TB
mortality. The evaluation criteria indicated that parametric model form the best models in multivariate analysis and can lead to more precise result as an alternative to Cox proportional hazard model.

4.1 Model selection based on AIC and BIC

Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) is both a model selection tool, they are used in selecting models that have the lowest value from a given set of data. The formula to calculate AIC = -2logL+2k and BIC = -2 * log-likelihood + k * ln (N)

The whole parametric models considered in this study have 2 ancillary model parameter except exponential model that have 1 ancillary model parameter. Cox proportional model doesn’t have ancillary model parameter.

Exponential model  
AIC = -2(-52.212701) + 2(8+1) = 122.425402  
BIC = -2(-25.212701) + (8+1) ln 255 = 154.2967739

Exponential regression --- log relative hazard form

| No. of subjects | Number of obs | 255 |
|-----------------|---------------|-----|
| No. of failures | 15            |     |
| Time at risk    | 4173          |     |
| Log likelihood  | -52.212701    |     |
| LR chi2 (8)     | 15.34         |     |
| Prob > chi2     | 0.0529        |     |

Weibull regression --- log relative hazard form

| No. of subjects | Number of obs | 255 |
|-----------------|---------------|-----|
| No. of failures | 15            |     |
| Time at risk    | 4173          |     |
| Log likelihood  | -46.029683    |     |
| LR chi2 (8)     | 21.66         |     |
| Prob > chi2     | 0.0056        |     |

Lognormal regression --- accelerated failure-time form

| No. of subjects | Number of obs | 255 |
|-----------------|---------------|-----|
| No. of failures | 15            |     |
| Time at risk    | 4173          |     |
| Log likelihood  | -45.12726     |     |
| LR chi2 (8)     | 24.45         |     |
| Prob > chi2     | 0.0019        |     |

Loglogistic regression --- accelerated failure-time form

| No. of subjects | Number of obs | 255 |
|-----------------|---------------|-----|
| No. of failures | 15            |     |
| Time at risk    | 4173          |     |
| Log likelihood  | -45.840609    |     |
| LR chi2 (8)     | 22.29         |     |
| Prob > chi2     | 0.0044        |     |

Gompertz regression --- log relative - hazard form

| No. of subjects | Number of obs | 255 |
|-----------------|---------------|-----|
| No. of failures | 15            |     |
| Time at risk    | 4173          |     |
| Log likelihood  | -44.365325    |     |
| LR chi2 (8)     | 24.39         |     |
| Prob > chi2     | 0.0020        |     |
Table 4.0. AIC and BIC of the models for non HIV TB patients

| Parametric model                                      | Log-likelihood value | AIC            | BIC            |
|-------------------------------------------------------|----------------------|----------------|----------------|
| Exponential                                           | -52.212701           | 122.4254       | 154.2968       |
| Log-normal                                             | -45.12726            | 110.2545       | 145.6672       |
| Log-logistic                                           | -45.840609           | 111.6812       | 147.0939       |
| Weibull                                               | -46.02968            | 112.0594       | 147.4720       |
| Generalized gamma shared frailty with Gompertz         | -43.59788            | 107.1958       | 142.6084       |
| distribution                                          |                      |                |                |
| Gompertz                                              | -44.365325           | 108.7306       | 144.1433       |
| Cox Prop Hazard                                       | -56.833616           | 129.6672       | 157.9973       |

From the AIC and BIC table above, gamma shared frailty model with Gompertz baseline distribution shows a better goodness of fit among the rest of the models with the lowest value of AIC and BIC [12,13].

5 Conclusion

In this study we have demonstrated that parametric model can be use to model outcome of TB patients, the propose model mixture of gamma shared frailty model with Gompertz baseline distribution having the lowest value of AIC and BIC, shows a better performance and can be used as an alternative to Cox proportional hazard model.

Competing Interests

Authors have declared that no competing interests exist.

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