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Bayesian Survival Analysis of Recovery for Tuberculosis Patients in Bulsa Traditional Area

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Abstract: Tuberculosis (TB) is a contagious infection that affect the lungs and caused majorly by a bacterium known as *Mycobacterium tuberculosis*. The study sought to discover factors that influence recovery of patients using Bayesian Continuous-Time Survival model and the Log-logistic model. The factors that were seen to be linked to treatment outcome are; Age, treatment time, smear results and HIV. It was further realized that, age, HIV and their interactions were significant determinants of TB treatment outcomes in the Bulsa traditional area. The recoveries for males and females were 79.32%, and 87.32% respectively. Also, the recovery for children(100%), adults(81.28%), and aged (80.28%) were realized. Patients who were diagnosed with TB as first timers(New patients) had lower recovery rates compared to nonnew(relapsed) patients. A rigorous HIV testing rate of 97.73% was identified with TB/HIV coinfection rate of 10.39%. HIV/TB Co-infection was seen to have link to TB related deaths with a mortality rate of about 18.75%. The most prevalent disease category was found to be Pulmonary positive TB. Therefore, prudent Health education and voluntary testing should be intensified to enable early diagnosis and treatment of the disease.

Keywords: Tuberculosis, Covariates, HIV/TB Con-infection, Relapse, Bayesian Analysis.

1 Introduction

Tuberculosis (TB) is a dreadful disease mainly caused by a bacilli whose mode of transmission is through droplets, vapour or a varying period of latency of infections [1,2]. There exist diverse ways of screening for the *bacterium*. Some of which include using X-rays, culture test, skin test, Smear tests, molecular test etc [3,4]. TB is an opportunistic disease that confounds with some immune weakening diseases or comorbidities such as diabetes, sickle cell anemia, ageing and HIV/AIDS which can be disastrous if not detected on time[5]. TB is most prevalent in HIV patients and persons with immuno-compromised systems and this is worse in the under-developed regions. TB screening and early detection is therefore paramount in the control of TB among persons living with HIV [6]. According to Cui et al.[7], TB and HIV co-infected patients is estimated to be 173 times more than the number of HIV negative patients in Guangxi. The prevalence of TB worldwide was estimated to be around 10 million newly registered cases annually with a worldwide fatality rate of 1.24 million and an estimated death rate of 16 per 100,000 persons in 2018 [8]. The prevalence rate in Ghana for 2019 stood at 144 per 100,000 persons [9]. This is a reduction in the incidence of 290 patients per 100,000 individuals in the year 2013 [10].

Although the global prevalence rate declined between 2015 and 2019 by 9%, its effect on Africa and Asia cannot be overlooked. Moreover, the WHO aim of reducing the prevalence of the disease by the year 2020 by a rate of 20% was not achieved [9].

Even though there was a 14% reduction in TB related deaths between 2015 and 2019, it fell short of the WHO target of 35% by 2020 [9]. According to Global TB Report [9], some few analyses that were carried out using the 2019 data compared the condition in Ghana as a country to Africa as a continent is as follows; the population for Ghana and Africa were estimated to be 30 million and 1 billion respectively. Ghana had a prevalence rate of 144 per 100,000 against 226 per 100,000 people in Africa resulting in decrease rates of prevalence of 10% and 16% within the period of 2015 to

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2019. Tuberculosis and HIV Co-infection rate for Ghana was 30 whereas that of Africa was 54 per 100,000. Multi Drug Resistance (MDR) was 4 and 7 per 100,000 people respectively, and HIV positive TB patients mortality was 16 per 100,000 for both Ghana and Africa. The rate of decrease in terms of TB related deaths for Ghana and Africa were 4.3% and 19%. Additionally, the TB/HIV co-infected patients in Ghana that are on ART is very low(75%) as against the 92% that are on ART in the region. It is therefore not surprising that the recovery is very low in Ghana (77%) compared to the regional average treatment success of 79%. According to the Global TB report, about 4.1% of TB patients in Ghana were on ART in the year 2019 while the regional average for Africa was 53% [9].

According to Terefe et al. [11], treatment success was 75% with a median recovery of about 185 days in South-West Ethiopia. Also, Japerik et al. [12] reported 73.75% treatment success in Upper West Region. Similarly, median recovery time for Northern Region, Northern Ghana and Upper West Region were found to be 22 weeks, 24.14 weeks and 25.43 weeks [12,13,14]. The study thus seeks to determine the factors responsible for recovery of patients suffering from tuberculosis by using Bayesian Continuous-Time modeling.

2 Methodology

2.1 Data Source

The study used secondary data from the Municipal Health Directorate of the Builsa North Municipality. The Builsa North Municipal health Directorate coordinates all health facilities within Builsa North Municipal and Builsa South District. Patients from Kassena-Nankana West District and Kassena-Nankana Municipal of the Upper East Region, Sissala East District of the Upper West Region and the Mamprugu Moagduri District of the North East Region among others also visit health facilities within Bulsa traditional area for healthcare, thus giving the data a wider coverage. The map of the Bulsa traditional area is painted blue in Figure 1 below.

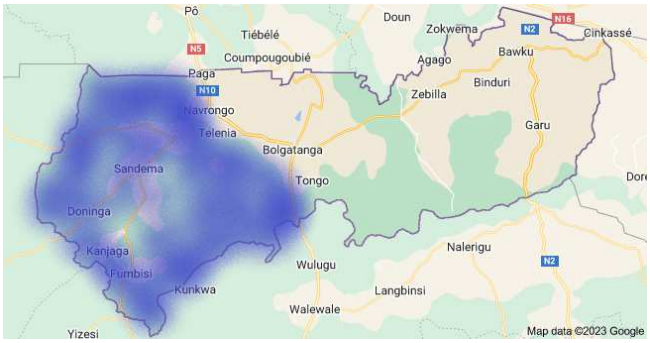

Fig. 1: Map of Upper East Region

The Data collected covered individual patients enrolled for TB treatment within the period of January 25, 2012 and March 20, 2020. Some of the Variables that were of interest during the data collection was the registration date, when the treatment started, the date that the patient completed the treatment, gender, age, disease category, HIV, type of patient, smear results and treatment outcome. All these variables were collected on each patient that visited a health facility to register for TB treatment. Ethical clearance was not necessary since the study did not directly involved patients. Patients' identification numbers and their personal details were not included in the data hence ensured absolute confidentiality of the patients whose data were used for the study. About 308 patients in total were registered for treatment, patients who died while on treatment, those who defaulted, patients transferred out, those who could not be traced after commencement of treatment regimen and patients whose treatment time has gone pass the regular six months duration were all considered censored observations.

2.2 Limitations of the study

The major limitation of the study is the fact that the study relied on secondary data for analysis, as such some important covariates which would have enhance the scope of the study such as geo-spatial coordinates were not included in the study. This could have helped produce a geospatial map of TB cases in the Bulsa traditional area.

2.3 Covariates Description

Below are the description of various variables used and their codes:

2.3.1 Prognostic factors

–*Age:* This is the age of the patient at the time of registration.
–*Gender:* it refers to the gender or sex of a patient. *Male = 0 and Female = 1*
–*HIV Status:* This refers to the HIV screening status of the patients and how they are coded. HIV negative, *N = 0*, HIV positive, *P=1* and Patients who were not screened for HIV, *DN = 2*
–*Treatment time:* Calculated as the interval between date of treatment commencement and the date treatment completed, *TT.*
–*Type of patient (TP):* This refers to type of TB patients as recorded in the TB register: First time (new) TB patients and nonnew (default) TB patients.
a)*New patients(NP)*. TB patients who registered for treatment as first timers and given a code as '0'
b) *Non-new patients(NNP).* Patients who have ever received some form of tuberculosis medication or treatment. They are mostly relapsed patients and coded as '1'
–*Disease category:* It is simply the grouping of the patients as Pulmonary positive(PP), pulmonary negative(PN) or extra-pulmonary TB patients which are coded as '1', '0' and '2' respectively

–*Smear results* : This refers to the categorization of patients into smear negative(SN) and smear positive(SP) and coded as '0' and '1' respectively.

2.3.2 Treatment Outcomes

–*Cured*: refers to patients who were tested smear positive before the commencement of medication but became smear/culture negative at the last month of treatment.
–*Treatment completed*: a patient who remains positive or could not achieve a culture/ smear negative after taking a complete dosage of TB medications.
–*Died*: Patients who died of the disease during treatment.
–*Defaulted*: a patient who has his/her treatment interrupted for at least two months in a roll.
–*Lost-to-follow-up*: Refers to patients whose whereabout is unknown by TB care givers after the commencement of treatment for proper monitoring.
–*Treatment failure*: this refers to those TB patients who after at least five months of treatment still remains smear/culture positive. These include patients who are *Rifampicin or multi-Drug Resistant (MDR*).
–*Transfer-out*: This refers to patients who are transferred from one facility to another (probably an upgraded facility) out of the jurisdiction of the DHD for further treatment where the treatment outcome of those patients is untraceable.
–*Treatment outcome*: this is an appraisal measuring the efficacy and results of the treatment and care given to the patients. The treatment outcomes of patients were categorized as successful or good treatment outcomes and unsuccessful or poor treatment outcomes
–*Successful/Good treatment outcomes:* this refers to TB patients who are cured and/or completed the full TB regimen without a bacteriological result [15].
–*Unsuccessful/Poor treatment outcome*: this refers to patients who either abandoned the drugs and were not traceable by TB care givers (lost-to-follow-up), or those who unfortunately passed on while on the regimen or defaulting patients.

2.4 Censored

When an observation being studied fail to experience the event during the time of follow-up, the observation is said to be censored. In most cases, an object's event time information is well known during censoring, what however is unknown is the actual time of the event. Some times incomplete times are observed due to;
a) The observation inability to experiencing the event by the time the study ends.
b) Individuals not traceable to complete the medication.
c) A patient opting out of the study willingly for personal reasons.

2.5 Bayesian Accelerated Failure Time Model

The accelerated failure time (AFT) model can be represented mathematically in the log-linear form is given by:
$log(T_{ij}) = \alpha + \beta x_{ij} + \sigma_{\varepsilon_{ij}}$

Where $\alpha + \beta x_{ij}$ being linear predictor and ε_{ij} being error term.

The likelihood function generally defined as: $L = \prod_{i=1}^{n} \prod_{j=1}^{n_i} [\frac{1}{\sigma t_{ij}} f_0(\frac{log(t_{ij}) - v_{ij}}{\sigma})]^{v_{ij}} s_0(\frac{log(t_{ij}) - v_{ij}}{\sigma})^{1-c_{ij}}$
The AFT model parameters were estimated by means of posterior sampling based on MCMC simulation approach. Let the prior distributions be p(a) and p(b), then the posterior distribution is defined as
$p(b, v, a/t) \propto L(t/b, v)p(w/a)p(b)p(a)$
[16].
The Bayesian results were obtained using GENMOD Built-in procedure in SAS.

Model Assumptions

–The predictors should be multiplicative with respect to survival time
–The estimated time ratios are required to be constant.

2.5.1 Model Selection

The AFT models considered for modeling the data are: Weibull, Gamma, log-normal, log-logistic and Exponential distributions. The model selection process was based on the use of accuracy measures such as Log-likelihood values, Deviance Information Criterion (DIC), corrected Akaike's Information Criterion (AICc), Bayesian Information Criterion (BIC) and Akaike's Information Criterion (AIC) to identify the Distribution that best model data set [16].

2.5.2 Log-logistic Distribution

The Log-logistic distribution takes a similar form just like the standard logistic distribution. However, the log-logistic comes with an error term. The log-logistic is mostly a better substitute for the Weibull distribution. The log-logistic distribution can be used to fit non-monotonic hazards. The log-logistic distribution is mostly the best distribution for modeling diseases like Tuberculosis which have hazards that rise, fall or hump-shaped. The advantage of the log-logistic is that, the coefficients can be interpreted as odd ratios.

The probability density function is $f(t) = \alpha\lambda(\alpha t)^{\lambda-1}(1 + (\alpha t)^{\lambda})^{-2}$.

The hazard function is defined as; $h(t) = \frac{\alpha\lambda(\alpha t)^{\lambda-1}}{1+(\alpha t)^{\lambda}}$

The survival function, $S(t) = \frac{1}{1+(\alpha t)^{\lambda}}$

Where $\alpha > 0, \lambda > 0$ and $t > 0$. The log-logistic is tractable compared to Weibull or lognormal especially when it has to do with censored events [16].

3 Results

3.1 Preliminary analysis

The number of TB patients who reported for treatment at various health facilities and treatment centers within Bulsa traditional are from January 25, 2012 to March 20, 2020 were 308. About 250(81.16%) of the patients were successfully treated and 27(8.77%) died along the way. A total of 237(76.95%) were males with females being the less affected gender group. The recoveries based on gender were 188(79.32%) and 62(87.32%) for males and females respectively with a total percentage recovery of 250(81.16%). The minimum, maximum and median ages were 17 years, 87 years and 43 years respectively with a mean age of 47.08. The study identified the youngest patient who died while receiving treatment to be 27 years old were as the oldest was 85 years. But the median and mean age for patients who unfortunately lost their lives while receiving treatment was 49 years and 53.07 years.

New cases constituted 265(86%) of cases under study. Recovery was high among non-new case patients 36(83.72%) than new case patients 214(80.75%). Pulmonary positive TB was the highest recorded (70.45%) followed by Pulmonary

negative TB (28.90%) with extra-pulmonary TB (0.65%) being the least in terms of prevalence. However, Pulmonary Positive had the lowest treatment success rate of 78.80% followed by Pulmonary negative (86.52%) and the highest being extra-pulmonary TB(100%). Out of the 308 patients, 196 (63.6%) were smear positive and 112 (36.3%) smear negative. A total of 301 (97.73%) of the patients screened for HIV/AIDS which revealed an alarming 10.39% TB and HIV co-infection. Details of the results is contained in Table 1.

Table 1: Descriptive Statistics

PARAMETER	TOTAL N(%)	CENSORED(%)	RECOVERED(%)
GENDER			
MALES	237(76.95)	49(20.68)	188(79.32)
FEMALES	71(23.05)	9(12.68)	62(87.32)
AGE			
0-17	2(0.65)	0(0)	2(100)
18-60	235(76.30)	44(18.72)	191(81.28)
ABOVE 60	71(23.05)	14(19.72)	57(80.28)
PATIENT TYPE			
NP	265(86.04)	51(19.26)	214(80.75)
NNP	43(13.96)	7(16.28)	36(83.72)
SMEAR TEST			
SP	196(63.64)	41(20.92)	155(79.08)
SN	112(36.36)		95(84.82)
HIV TESTING			
POSITIVE	32(10.39)	9(28.13)	23(71.88)
NEGATIVE	269(87.34)	48(17.84)	221(82.16)
NO TEST DONE	7(2.27)	1(14.29)	6(85.71)
DISEASE TYPE			
PP	217(70.45)	46(21.20)	171(78.80)
PN	89(28.90)	12(13.48)	77(86.52)
EXTRA-PULMONARY	2(0.65)	0(0)	2(100)

NB: N=Number.

3.2 Goodness of Fit Test

According to the results of the accuracy measures, AIC, AICc,BIC and DIC showed smaller values for log-logistic and a higher LOGL estimate as seen in Table 2. This is an indication the Log-logistic accelerated failure time model provides the best fit for the data. Details of the results for the comparative performance of the distributions are contained in Table 2 below.

Table 2: Accuracy Measures for Various Distributions

Model	AIC	AICc	BIC	DIC	LOGL
Weibull Distribution	264.05	264.72	296.66	264.19	-123.02
Log-logistic Distribution	**98.73**	**99.73**	**138.60**	**96.64**	**-38.37**
Exponential Distribution	561.12	561.79	593.74	560.56	-271.56
Gamma Distributions	445.00	445.74	482.30	445.32	-212.50
Log-Normal Distribution	300.68	301.50	336.92	300.79	-140.34

3.3 Log-Logistic Distribution

Following the selection of the log-logistic distribution as the best model for analyzing the data, it was used to analyze the TB data without interactive effects and the results is contained in Table 3. The effects of individual covariates as

presented in Table 3 revealed that the factors such as age, treatment time, and smear results are significantly associated with treatment outcome (Recovery).

Table 3: Posterior Distribution Estimates for Log-Logistic Regression

Parameter	DF	Mean Estimate	Standard Error	95% Confidence Interval	
Intercept	1	13.305	61113.210	-119766	119793
Age	**1**	**0.013**	**0.006**	**-0.001**	**0.024**
Gender0	1	-0.024	0.237	-0.488	0.441
Gender1	0	0.000			
DC0	1	-4.807	60476.11	-118536	118526.2
DC1	1	-5.561	60476.110	-118537	118525.4
DC2	0	0.000			
TP0	1	-0.330	0.293	-0.904	0.245
TP1	0	0.000			
SR 0	**1**	**-0.848**	**0.405**	**-1.642**	**-0.054**
SR1	0	0.000			
HIV0	1	-5.912	8800.315	-17254.20	17242.39
HIV1	1	-5.843	8800.315	-17254.12	17242.461
HIV2	0	0.000			
TIME	**1**	**0.032**	**0.003**	**0.027**	**0.038**
Scale	**1**	**0.340**	**0.051**	**0.253**	**0.457**

A further probe conducted by interacting some covariates in the log-logistic model to identify possible interactive effects among the explanatory variables. The results revealed that HIV, age and their interactions were statistically significant as contained in Table 4.

Table 4: Posterior Distribution Estimates for Log-Logistic Regression

Parameter	DF	Mean Estimate	Standard Error	95% Confidence Limits	
Intercept	**1**	**13.7734**	**2.0371**	**9.7808**	**17.7660**
AGE	**1**	**-0.1536**	**0.0297**	**-0.2119**	**-0.0954**
GENDER0	1	-0.1727	0.1914	-0.5478	0.2023
GENDER1	0	0.0000			
DC	1	-0.0385	0.2009	-0.4322	0.3553
TP0	1	0.1607	0.1476	-0.1287	0.4500
TP1	0	0.0000			
SR0	1	0.2316	0.2730	-0.3035	0.7666
SR1	0	0.0000			
HIV0	**1**	**-8.6377**	**2.0541**	**-12.6637**	**-4.6117**
HIV1	**1**	**-9.5312**	**2.1324**	**-13.7105**	**-5.3518**
HIV2	0	0.0000			
AGE * HIV0	**1**	**0.1584**	**0.0298**	**0.0999**	**0.2168**
AGE * HIV1	**1**	**0.1811**	**0.0337**	**0.1150**	**0.2473**
AGE * HIV2	0	0.0000			
SR * TP0 0	1	-0.1633	0.2823	-0.7167	0.3900
SR * TP0 1	0	0.0000			
SR * TP1 0	0	0.0000			
SR * TP1 1	0	0.0000			
DC *GENDER 0	1	0.1447	0.2222	-0.2908	0.5801
DC * GENDER 1	0	0.0000			
Scale	**1**	**0.3576**	**0.0311**	**0.3016**	**0.4240**

4 Discussion

Out of a total of 308 patients included in the study, about 18.83% of the patients were censored. The case fatality rate was 8.77% and the recovery (treatment success) was 81.16%. The percentage of males were 76.95% whereas females were 23.05%. A recovery of 81.16% was achieved. Although this looks very impressive comparatively, it is however below the 85% World Health Organization [17] target and 90.2% success that was achieved between the years 2012 and 2016 at the Central Region of Ghana [18]. That not withstanding, a recovery of 81.16% is seen to be better than a treatment success of 75% at Ethiopia [11] and a 73.75% treatment success in the Upper West Region of Ghana [12].

The results reveals a mortality of 8.77% higher than the 4.4% and 8.5% recorded for the South-West Ethiopia and the central region but lower than 17.7% by a university hospital in Ethiopia [11,18,19]. A TB recovery of 79.32% for males and a 87.32% for females is consistent with findings in the Upper West Region where chances of females recovering from the infection is higher than males [12]. According to literature, alcohol consumption, smoking and manual works like mining, construction and farming (which involves the use of agrochemicals and mineral purification chemicals such as cyanide) are male dominated activities and these are risk factors that are associated with TB [20,21]. This probably is the reason for the high number of male cases than females recorded since majority of the male patients are either involved in farming or mining. This is partly due to the fact that Bulsa traditional area is a rural setting and one of the poor areas of the Upper East region with majority of the people engaged in peasant farming. These, coupled with opportunistic diseases increase maternal mortality and worsened their health outcomes in women when not detected early[22,23]. The study revealed a 97.73% HIV testing among TB patients and a 10.39% rate of HIV/TB co-infection. Mortality and treatment success (recovery) among TB/HIV co-infected patients was 18.75% and 71.88% respectively. The increased mortality among HIV/TB co-infected patients seems to be a confirmation of the fact that TB/HIV co-infection can be very fatal if not detected early for proper care.

Although the TB/HIV co-infection rate seems high, it is still viewed as among the lowest when compared with the 14.7% and 22.6% in literature [24,25]. There is a high rate of HIV testing (97.73%) among TB patients in Bulsa traditional area compared to studies in other areas. This maybe as a result of previous knowledge of the negative impact that HIV/AIDS has on TB patients. According to literature, the best and most appropriate way to minimize the impact of TB/HIV co-infection is early screening for timely diagnosis and treatment [26]. For an opportunistic disease like Tuberculosis, rigorous screening for early detection of HIV and other immuno-compromise diseases is required for the better management and possible reduction in the prevalence of the disease. This study revealed a higher pulmonary TB (70.45%) against low reported cases of extra pulmonary TB (0.65%). The pulmonary tuberculosis (70.45%) is seen to be very similar to the 78.2% reported in earlier study in Accra [26].

The log-logistic model was identified to be the best fitted model for the data since it produced the biggest Log-likelihood value and the least AIC, DIC, BIC, AICc values as presented in Table 2.

The analysis using log-logistic first identified smear results, age and treatment time as the significant prognostic factors. But, when some of the parameters were interacted, factors such as HIV was seen to be significantly related to the recovery while type of patient and disease category showed no signs of significance. The study discovered that one unit increase in the age of a TB patient in Bulsa traditional area will result in the reduction of the chances of recovering from the infection by 1.2%. However, a unit increase in the time of treatment was seen to be linked to about 3.9% increase in recovery of patients. Also, Recovery among HIV negative TB patients was 13.6% higher than HIV positive TB patients.

Age was seen to be a contributing factor as far as the treatment of tuberculosis is concerned.This seems to be consistent with past studies [13,14,26,27,28]. This suggest that TB treatment success is inversely proportional to the age of the patient. Hence, the chances of a younger patient recovering from the disease is higher than the aged under the same conditions.

One reason that could explain why treatment success of TB is inversely proportional to Age is that, as one gets older, he/she turns to have relatively weak immune system compared to the younger folks. Hence, the inability of the aged to quickly respond to treatment.

HIV is an immuno-compromising disease that lowers the white blood cell count of the patient and hence making the patient more vulnerable and prone to other infections such as TB. Patient who are co-infected with HIV have relatively weaker immune system to aid fast recovery. This maybe the reason HIV negative patients had about 13.6% chance of recovery from the infection over patients who are co-infected with HIV.

Although the percentage of recoveries among non-new patients (83.72%) is a bit higher than new cases (80.75%),there was no significance among the type of TB patients in this study. On the other hand, the significance of time is an indication that the duration of treatment has an impact on the success or failure in the treatment of tuberculosis.

5 Conclusions

The best model for the tuberculosis data was found to be log-logistic accelerated failure time model. The age of the patient, HIV status, sputum smear results and treatment time were the significant factors responsible for the recovery of tuberculosis patients in Buluk. Therefore, various stakeholders in the treatment of TB in the Bulsa traditional area should coordinate their efforts and intensify health education, HIV and TB screening for early detection and treatment to improve treatment outcomes for this dreaded disease.

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