Original Research Article

MODELLING TIME TO RECOVERY FROM MULTIDRUG RESISTANT TUBERCULOSIS IN SOUTHERN ETHIOPIA

ABSTRACT

Introduction: Multidrug resistant tuberculosis (MDR-TB) is a type of tuberculosis caused by Mycobacterium tuberculosis that is resistant at least to isonized and rifampicin first-line anti-TB drugs. It is ranked among the top 10 causes of death worldwide and has increasing global burden and the recovery time differ from patient to patient. Therefore, the current study investigated time to recovery from MDR-TB in southern Ethiopia.

Data, materials and Methods: we obtained data from selected Hospitals in the SNNPR retrospectively for the period between January 2016 to December 2021. Cluster random samples of 301 MDR-TB patients information were considered (131 from NEMMCH, 121 from BH and 49 from AGH).

Results: Among the 301 MDR-TB cases, 116 (38.5%) were censored. While the remaining 185 (61.5%) were recovered. Parametric shared frailty models were employed in order to account unobserved heterogeneity among the Hospitals and patients. Moreover, accelerated failure time models were employed to analyze the data. The exploratory data analysis prevailed; the median recovery time of MDR-TB is 22 months. The clustering effect of frailty model was hospitals (treatment centers). Weibull-gamma shared frailty model was found to be appropriate for this data among others.

Conclusion: The result from the final fitted model indicated, males are more likely to recover than females. Patients with extra pulmonary MDR-TB had longer recovery time than pulmonary MDR-TB and also patients who live in urban areas have a longer recovery time than those who live in rural areas. The recovery rate of patients increases with increasing baseline weight, education level, and occupation. But, the recovery rate decreases with smoking, co-morbidities, previous drug history, history of TB, and alcohol use.

Recommendation: All concerned bodies should be cognizant on the risk factors of MDR-TB. In addition, IMPROVEMENT and strengthening of comprehensive and targeted MDR TB–Addiction control program are recommended.

Keywords: Multidrug resistance tuberculosis, Time to recovery, parametric shared frailty, Treatment centers, accelerated failure time.

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacterium mycobacterium tuberculosis. Typically, it affects the lungs and other organs as well as it is transmitted from person to person via droplets, and over 90% of people infected with the tubercle bacillus will not develop TB disease. And it remains a major public-health problem in the world, despite several efforts to improve case identification and treatment compliance. It is also the single highest curable infectious disease today in the world [1].

Tuberculosis can be effectively treated with first line drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) for six months. But when this first line drugs are not properly used (erratically used, poor quality of drugs, poor clinical practice and low completion rate) this leads to Multidrug-resistant Tuberculosis [1, 3].

Globally TB incidence is falling at about 2% per year by 2020; these figure need to improve to 4–5% per year, to reach the first 2020 milestones to end TB Strategy [4]. In china, 98% of bacteriologically confirmed patients were diagnosed with MDR-TB. Additionally, the continent of Africa has reported a notably high incidence rate of MDR-TB. Africa accounts for 46% of all TB cases in the world and the highest reported incidence rate of 475 cases per 100,000 people. Research suggests that MDR-TB is widespread in numerous regions across Africa. For instance, recent investigations have shown that the prevalence rates of MDR-TB in Nigeria, Zambia, Rwanda1, and South Africa4 are 54%, 9.5%, 9.4%, and 73%, respectively. [7, 9]. Multidrug-resistant tuberculosis (MDR-TB) continues to be a public health problem. Globally in 2019, a total of 465,000 people developed rifampicin-resistant TB (RR-TB), of which 78% had MDR-TB.

MDR TB is treated with second line drugs which need longer treatment (18-24 months), toxic and complication prone, high cost. Currently, the majority of MDR-TB cases are due to one strain of TB bacteria called the Beijing lineage [1]. It is well known cause of ill-health among millions of people each year. Latest estimate, 10.4 million people fell ill with TB in 2016 and 1.6 million died from the disease [4]. By rising trend of TB, affecting mainly developing countries, there is a need to re-examine the characteristics of the patients and understanding the contributing factors, in order to adjust and adapt TB control policies. In an effort to intensify the battle against tuberculosis, the government has devoted significant resources to ensure that essential drugs are readily available and that healthcare staff are properly trained in all government and selected mission hospitals. Nonetheless, the current endeavor to identify, treat and care all individuals affected by the disease falls short of sufficiency.

Ethiopia is one of the 20 high burdens MDR-TB country and MDR-TB has been a major health problem of the society in the Southern region of Ethiopia, a strategy to provide culture and drug susceptibility testing services has been designed [5,10]. Even though various studies done on the prevention and control of the cross-transmission of healthcare-acquired infections between hospitalized patients have been carried out, the prevalence is still increasing [16, 17]. Moreover, the emerging and rapid transmission of XDR-TB is also another challenge for TB control program [63], XDR-TB is defined as MDR-TB with additional resistance to any fluoroquinolone (FQ) and at least one of the three second-line injectable drugs: Consequently, controlling and preventing the emergence and overflow of MDR-TB organisms is of vital importance. The Ethiopia National TB program has backed a continuous public awareness initiative via the media. this campaign aims to educate the public about TB symptoms, transmission methods, the significance of seeking medical care, the risks associated with MDR-TB, and the fact that TB is curable. Thus, the aim of this study is to investigate the recovery time of MDR-TB patients in three selected Hospitals of southern Ethiopia (NEMMCH, Arbamich General Hospital, Butajira Hospital), using accelerated failure time and parametric shared frailty models.

2. MATERIAL AND METHODS

2.1. Study Area, population and Design

2.1.1. Study area: This research was carried out on MDR-TB treatment centers of SNNPR, Ethiopia. Southern Nations Nationalities and Peoples Region is the country's third-largest administrative region and the most diversified in terms of language, culture, and ethnic origin, covering more than 10% of the country's land area. More than 56 ethnic groups live in the region. The capital city of SNNPR is Hawassa. It is 273 kilometers south of Addis Ababa. The SNNPR is bordered from the south by Kenya, from the west by South Sudan, from the northwest by Gambela, and from the north and east by Oromia. The data for this research took place between January 2017 to December 2022. The region is divided into 17 administrative zones and additionally, there are 6 special woredas. In the region, there are six MDR-TB treatment centers. In the SNNPR, there are over 45 indigenous ethnic groups, each with their own cultural heritage and identity. In 2018, the population was estimated to be 20,768,000. [64, 65]

2.1.2. Study population: The study population was all MDR-TB patients who had been registered in the Hospitals. The totals of 301 patients with MDR-TB from the Hospital were included in the study. The total population was proportionally allocated to the three Hospitals: Nigist Ellen Mohammed memorial Comprehensive Hospital (211), Butjira Hospital (199) and Arbamich General Hospital (89).

2.1.3. Study design: A retrospective study design was employed and the data were obtained from MDR-TB patients admitted to the hospitals and also it was carried out in three selected hospitals of SNNP region which have MDR-TB treatment center. Which is a 72-months follow-up period. The time was measured by months in this study.

2.2. Data source and data collection

The required data were extracted from follow-up charts and cards of MDR-TB patients admitted to the selected hospitals from January 2016 to December 2021. The data collectors of our study were trained healthcare professionals (nurses) under the supervision of investigators and the data quality had been checked for their completeness, consistency, and accuracy by investigators every day.

2.3. Sampling techniques and Sample size Determination

Cluster sampling technique was used. Currently, a total of six MDR-TB treatments centers are available, of which Nigist Ellen Mohammed Memorial Comprehensive specialized Hospital, Butajira Hospital and Arbamich General Hospital were selected randomly. We included all patients under follow up in these selected treatment centers consecutively.

2.3.1. Sample size determination:

The sample size was determined using at 95% CI with a prevalence of MDR-TB rate of 15% [21] and a margin error of 0.036. Then a total sample of 499 MDR-TB patients was considered using cluster random sampling methods. Further discussions on sampling are available at Cochran [22]. Thus, from a total sample of 301 MDR-TB patients that fulfill the inclusion-exclusion criteria was considered by applying cluster random sampling methods. Subsequently, all individuals within the designated clusters are included within the sample. Following this protocol, samples were collected from specified hospitals in the southern region.

Inclusion and exclusion criteria

Patients with insufficient recorded information in either the registration book or their card were excluded from the study. Additionally, those who had not initiated second-line MDR-TB treatments and XDR-TB patients were also excluded.

2.4. Study Variables

Outcome variables: Time to Recovery from MDR-TB, defined as duration from the starting of MDR-TB treatment until the patient achieves recovery. Time was measured interms of months. The event of interest was recovery from MDR-TB (1= recovered and 0 =Not recovered or censored). Data was entered by using SPSS-23 and it was cleaned and analyzed by using stata-15 software.

table 1 : **Predictor variables**

Predictor variables	**Categories**
Sex	1 = Male 0 = Female
Age (in year)	0 = 0-17 years 1= 18- 64 years 2= above 65 years
Residence	1 = Urban 0 = Rural
Marital status	0 = Married 1 = Single 2 = Divorced 3 = Widowed
HIV status	0 = HIV Negative 1 = HIV Positive

Smoking history	1 = Smokers, 0 = Non-smokers
Adherence based on Pill count	0 = Poor 1 = Fair 2 = Good
Co-morbidities	1 = Yes 0 = No
Previous drug use history	1 = yes 0 =No
MDR-TB type	0 = pulmonary 1 = Extra pulmonary
Baseline weight	Continuous (kg)
Occupation	0 = Employee, 1 = Farmer, 2 = Merchant
Family size	**0**= Less than 4 1= between 4 to 6 2= greater than 6
History of TB in Family	1 = Yes 0 =No
Status	1= Recovered 0 = Censored
Education status	0= Not educated 1= Primary 2=Secondary 4= Higher level educated
Alcohol use	1=Yes, 0= No

2.5. Statistical Models
2.5.1. Survival Analysis
Survival analysis is a statistical methodology used to analyze time-to-event data, where the focus on understands the time until a specific event of interest happens. When we refer to time, we are considering years, months, weeks, or a day starting from the commencement of follow up for an individual until a specific event takes place. Survival analysis is a significant statistical method utilized to depict and analyze time to event data. In any applied set, a survival data can summarize through life tables [23], Kaplan-Meier Survival functions [24] and median survival time [25, 26]. Besides estimating the survival functions, comparing two or more estimated survival curves is the most frequently used statistical tool of recent clinical research [27].
The simplest way of comparing the survival times obtained from two or more groups are the Kaplan-Meier curves and log-rank test [29–31]. However, to explore the relationship between the survival experience of individual and explanatory variables, an approach based on statistical modeling has been used [32]. Also used with a modeling approach to the analysis of survival data are the Cox Proportional Hazard [33], Accelerated Failure Time [33] and parametric shared frailty models [34].

2.5.2. Accelerated failure time model

The Accelerated Failure Time (AFT) model serves as a parametric alternative to the Proportional Hazards (PH) model. While the PH model assumes that covariates multiply the hazard by a constant, the AFT model posits that covariates either speed up or slow down the progression of an event by a constant factor. Parametric models, particularly AFT models, are well-suited for analyzing survival data, as there are limited probability distributions for survival time that can be employed in these models. In AFT models, the focus is on directly measuring the impact of explanatory variables on the survival time, rather than the hazard. For AFT models it is common to use the log-linear representation:

$$Y_i = \boldsymbol{logT_i} = \boldsymbol{\mu} + \boldsymbol{\beta_1 X_{1i}} + \cdots + \boldsymbol{\beta_{pi} Xp_i} + \boldsymbol{\sigma\varepsilon_i} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \boldsymbol{Eq}(\mathbf{1})$$

where, $logT_i$ represents the log-transformed survival time, **μ** is the intercept and **σ** is the scale parameter, the x1,…, xp are the explanatory variables with the coefficients β reflecting the effect that each explanatory variable have on the survival time and estimated by maximum likelihood method using a Newton-Raphson procedure and **εi** is the error term which is assumed to follow a specific distribution such as Weibull [35], log-normal [36], log-logistic [33] and gamma [37] among many.

2.5.3. Parametric shared frailty models

To address unobserved variations, the concept of frailty term was initially introduced by Hougaard in 1991 as an extension of proportional hazards. In a shared frailty model, observations within a cluster exhibit the same level of frailty, and the common frailty variance quantifies the interdependence among lifetimes within that cluster [38-39].
Consider a scenario with i clusters, where each cluster i comprises ni observations, and the total sample size is given by $\sum_1^r ni = n$ is the total sample size and $t_{ij}=\min(c_{ij}, t^*_{ij})$ is the observed failure time of a right censoring scheme for k^{th} (k = 1,... ,ni) observation in i^{th} cluster and c_{ij} is the censoring time, where t^*_{ij} and c_{ij} are independent random variables [34]. Then the observed censoring indicator $\boldsymbol{\delta_{ij}}$ is equal to 1 if $t^*_{ij} < c_{ij}$, and 0 otherwise and conditional on frailty y_i (> 0) and X_{ij}, the hazard function of **i^{th}** cluster has the form:

$$\boldsymbol{h(t_{ij}, x_{ip}, y_i) = y_i h_o(t_{ij}) \exp(\beta' x_{ij})} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \boldsymbol{Eq\ (2)}$$

Where

- ✓ $h_o(.)$ is the baseline hazard function
- ✓ x_{ij} is a vector of observed predictors for the **k^{th}** observation and
- ✓ β is a vector of regression parameters.

The frailties, represented by yi, are independent and identically distributed (**i.i.d.)** variables with a shared probability density function g(yi). Numerous investigations have explored the selection of continuous distributions for frailty random variables, including Gamma [37], inverse Gaussian [39], log-normal [36], and positive stable [40]. And a limited number of studies have explored discrete distributions [41].

3.6. 2.5.4. Models comparison and diagnostics

Model comparison and selection are among the most common problems of statistical practice, with numerous procedures for choosing among a set of models. There are several methods of model selection. One of the most commonly used model selection criteria is Akaike Information Criterion (AIC). we were compare the models study by using AIC, BIC, Likelihood ratio test [44] criteria's was used to compare various candidate models and the model with the smallest AIC and BIC value is considered as a better fit [45]. This is defined as:

$$\text{AIC} = -2\log L + 2(p+k)\ldots\ldots\ldots\ldots\ldots Eq(3)$$

Where, k is the number of covariates and p the number of model specific distributional parameters. This thesis used the AIC to compare various candidates of non- nested parametric models. The preferred model is the one with the lowest value of the AIC.
After a model fitted, the adequacy of the fitted model needs to be assessed. The methods that involved the model checking for this study used evaluation of the Parametric Baselines, log rank test and the Cox-Snell Residuals [46].

Cox-Snell Residuals

The Cox-Snell residuals method can be applied to any parametric model and the residual plots can be used to check the goodness of fit of the model. For the parametric regression problem, analogs of the semi-parametric residual plots can be made with a redefinition of the various residuals to incorporate the parametric form of the baseline hazard rates [46].

3. RESULTS AND DISCUSSION

3.1. Exploratory data analysis

In the event that the study's primary goal of determining how long MDR-TB patients in southern Ethiopia take to recover is accomplished. A total of 301 MDR-TB patients from NEMMCSH (131), BH (121) and AGH (49) were included in the study during the data collecting period. Of the total sample, 116 (38.5%) were censored, and 185 (61.5%) MDR-TB patients were recovered.

According to the study, the average recovery time or overall median time for MDR-TB patients in each hospital was 22 months, with the minimum and maximum recovery times being 18 and 24 months, respectively.

table 2. Status of the patients

Status of patients	Frequency (%)
Censored	116(38.5%)21.4
Recovered	185(61.5%)
Total N, %	301(100%)

The Recovery rate of MDR-TB was higher in males (64.2%) than in females (58.08%) (Males are more likely to recover than females). According to a study, 31 patients are extrapulmonary among the 301 recorded MDR-TB patients, 270 of whom had pulmonary TB. Extra pulmonary MDR-TB (10.3%) had a lengthier recovery time than pulmonary MDR-TB (89.7%). 166 (61.5%) of the 270 patients with pulmonary tuberculosis recovered, while 19 of the 31 additional patients experienced extra pulmonary recovery. (Extra pulmonary MDR-TB had longer recovery time than pulmonary MDR-TB).

Due to MDR-TB, patients who reside in urban areas (62.7%) have a higher likelihood of recovering than those who reside in rural areas (60.3%). recovery rates for MDR-TB among drinkers and smokers were 61.9% and 42.5%, respectively. Most of the patients (61.4%) were recovered at the age group between 18 to 64 years. HIV negative individuals recovered from MDR-TB at a higher incidence (61.1%) than HIV positive patients (36%). Patients with no prior drug history had a greater recovery rate (64.28%) than patients with a history of drug use (60.6%).

The recovery rate of patients increases with increasing baseline weight, education level, and occupation. But, the recovery rate decreases with smoking, co-morbidities, previous drug history, history of TB, and alcohol use.

Table 3. Descriptive results on demographic, clinical, and epidemiological characteristics of patients with MDR-TB from three selected Hospitals in southern Ethiopia.

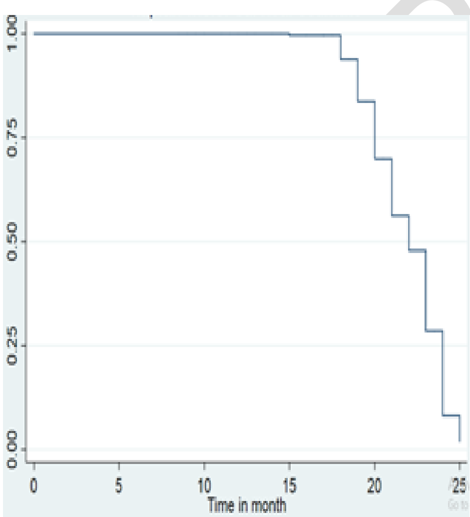
Covariates	Categories	Total (%)	Recovered (%)	Censored	Median
Sex	Female	136(43.51%)	79(58.08%)	45	22
	Male	165(54.8%)	106(64.2%)	59	21
Treatment center	NEMMCSH	131(43.5%)	86(65.6%)	59	22
	Butjira	121(40.51%)	72(59.5%)	49	22
	Arbamich	49(16.3%)	27(55.1%)	22	21
Age	0-17 years	31(10.3%)	17(54.84%)	14	20
	18-64 years	259 (86.4%)	159(61.4%)	100	23
	Above 65 years	11(3.65%)	9(81.81%)	2	24
Residence	Rural	156(51.8%)	94(60.3%)	48	22
	Urban	142(47.2%)	89(62.7%)	67	23
HIV status	Negative	265(88.0%)	162(61.1%)	103	22
	Positive	36(12.01%)	13(36%)	23	24
Smoking status	Smoker	64(21.3)	40(42.5%)	24	22
	Non smoker	237(78.7%)	145(61)	92	21
Adherence	Poor	62(20.6)	35(56.5%)	27	23
	Fair	61(20.3%)	41(67.2%)	20	21
	Good	178(59.1%)	109(61.2%)	69	22
Co-morbidities	Yes	46(15.3%)	24(52.2%)	22	22
	No	255(84.7%)	161(63.1%)	94	22
Drug use history	Yes	231(76.7%)	140(60.6%)	91	22
	No	70(23.3%)	45(64.28%)	25	22
MDR TB type	Pulmonary	270 (89.7	166(61.5%)	104	21
	Extra pulmonary	31(10.3%)	19(61.3)	12	23
Occupations	Employed	51(16. 5%)	29(56.8%)	22	22
	Farmer	153(50.8%)	106(69.3%)	47	22
	Merchant	67(22.3%)	36(53.7%)	31	23
	Other	30(10%)	14(46.6%)	16	21
History of TB	Yes	184(61.1%)	113(61.4%)	71	23
	No	117(38.9%)	72(60.5%)	45	22

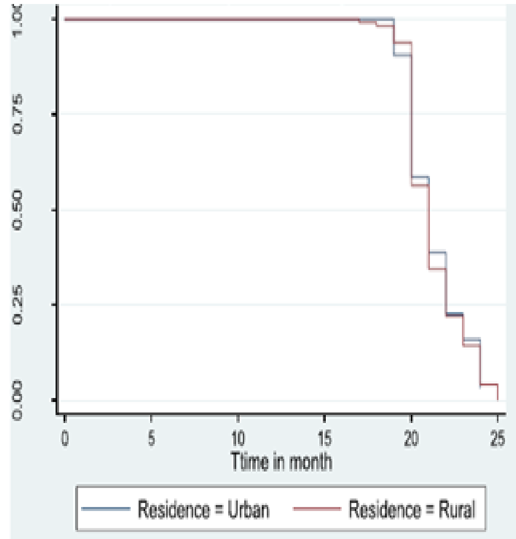
Education status	Not educated	41(13.6%)	25(60.9%)	16	23
	Primary	93(30.9%)	55(59.1%)	38	23
	Secondary	100 (33.2)	63(63%)	37	22
	Above all	67(22.3)	42(62.7%)	25	23
Using Alcohol	Yes	181(60.1%)	112(61.9)	69	23
	No	120(39.9%)	73(60.8)	47	22
Clinical completion	Completed	109(36.2 %)	42(38.5%)	67	17
	Not complete	191(63.5%)	74(38.7%)	117	20
Summary statistics of baseline continuous variables					
Continuous variables	Mean	Standard deviation	Minimum	Maximum	Median
Weight	46.52	13.20	6.50	85.50	48.50
Time	20.16	3.3	8.50	24	22.01

3.1.1. Comparison of survivorship functions

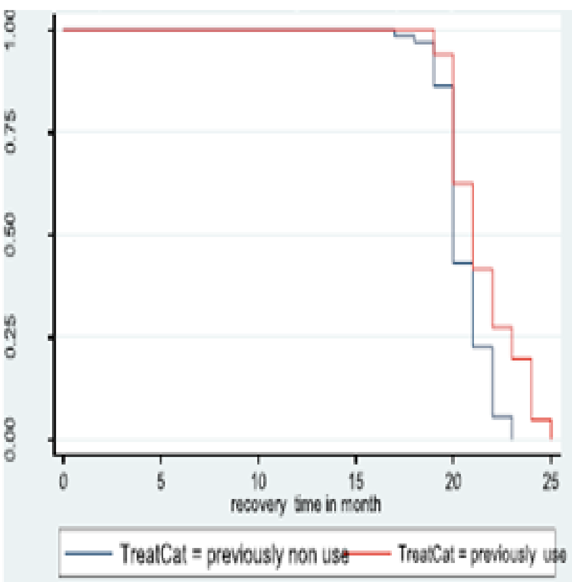
The main focus was on estimating the survival function for time to recovery across various covariate groups to compare their distributions. To obtain a more detailed estimate of the survival time, we employed the Kaplan-Meier estimation techniques. This method is crucial for analyzing censored data [34, 47]. The resulting Kaplan-Meier survival function curve illustrated both the overall estimated survivor function and distinct groups of predictors. Notably, the overall estimated survivor function indicated that patients with MDR-TB achieved recovery after a 22-month treatment period.

a) Over all kaplaian meier survival estimate b) MDR TB by Residence

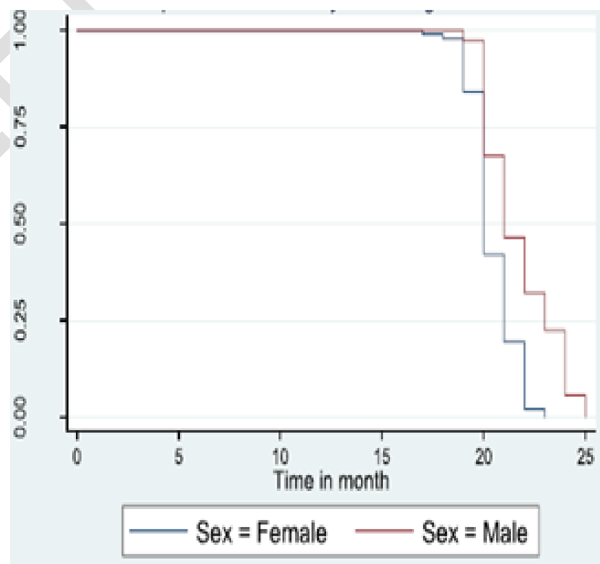




c) MDR TB by drug use history



d) MDR TB by Sex



e) MDR TB by type of MDR TB

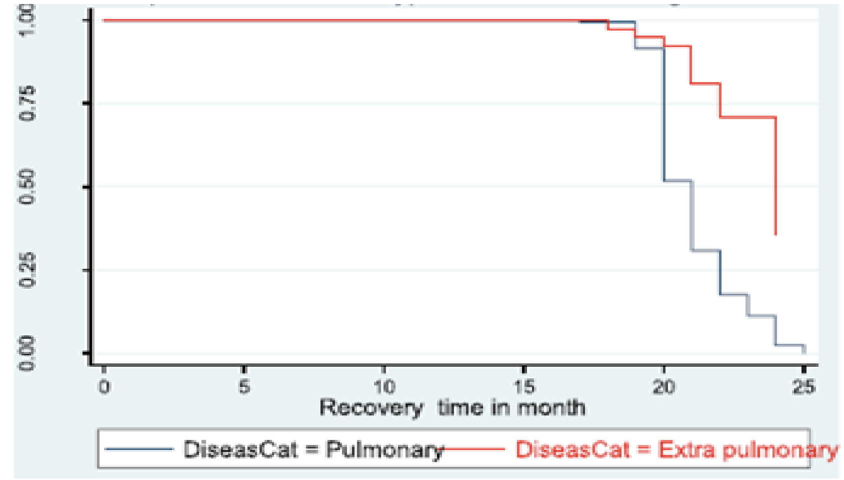


Figure 1 Estimate of the KM Survival function for the recovery time of MDR-TB patients in SNNP among category of categorical variables by (a) overall (b) residence (c) drug use history (d) sex (e) type of MDR-TB.

The survival curve generated by the Kaplan-Meier estimator illustrated both the collective estimated survivor function and distinct predictor groups. Evidently, the overall estimated survivor function indicated that individuals with MDR-TB experienced recovery following 22-month treatment duration.
As we can see from above km estimated categorical variables the recovery time of patients was the difference between HIV status, smoking status, Residence, education level, Alcohol use and MDR-TB type, sex whereas, marital status, Adherence; history of TB and occupation did not show a clear difference in the figure above.

3.1.2. Parametric shared frailty model Results

Parametric-shared frailty models were applied, considering the Exponential, Weibull, and log-normal distributions for the baseline hazard function. The Gamma distribution, commonly employed in literature to assess frailty effects [43, 48], was specifically chosen. Consequently, the study involved fitting both the Gamma frailty model and the Weibull Gamma shared frailty model, with hospitals serving as the random (frailty) component, to determine the most suitable model.
The AIC for the Weibull gamma shared frailty (−2375.33) was smaller than the AIC for the Weibull AFT (− 222.56) models. The frailty for the selected model was estimated to be 1.467 (chi-square = 53.42, df = 1, p-value = 0.0000) which indicated existence of unobserved heterogeneity between the hospitals and it was observed that the inclusion of the frailty component in the model was significant. The result also showed that the value of the shared frailty (θ) is 1.467, 1.36, 0.527 and 0.157 for Weibull, Log-logistic, Exponential and Lognormal gamma shared frailty models respectively; the heterogeneity between clusters was high when estimated by Weibull gamma shared frailty model, which were 1.46. The Kendall's tau (τ) is higher for higher values of theta (θ) which measure the association within region. The estimated τ = 0.424 shows that there is strong dependence within the cluster or region. This indicates Weibull-gamma shared frailty model is more efficient model to describe time-to-recovery from MDR-TB. And also it implied that the frailty component had significant contribution to the model.

3.1.3. The Cox Snell Residual Plots

The Cox-Snell residuals offer a distinctive approach to assess the goodness of fit of the model to the data. It's notable that the plot depicting the cumulative hazard function against Cox-Snell residuals closely aligns with the 45- degree straight lines originating from the origin for the Weibull model when compared to exponential, Log-normal and Log-logistic. Therefore overall goodness of fit for the AFT model was checked by these Cox-Snell residual plots [46]. This suggests that Weibull model provided the best fit for the recovery time of MDR-TB patients. The plots indicate that the Weibull model fits the data best and that the other model fits poorly.

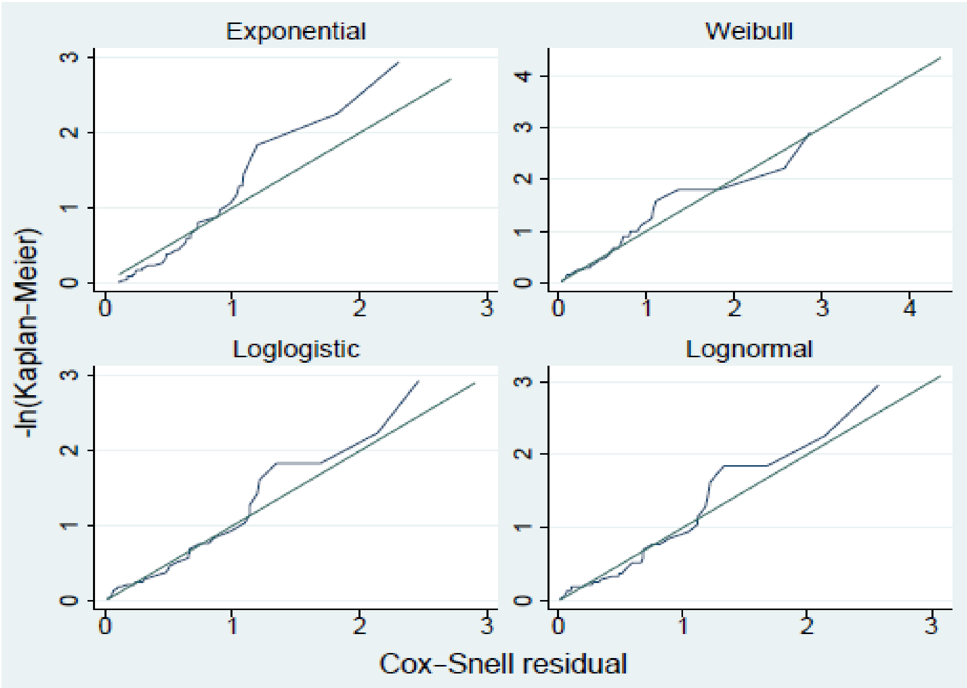


Figure 2 the Cox–Snell residual plots to evaluate model fit of four regression models Exponential, Weibull, log logistic and lognormal distributions.

3.1.4. Multivariable Analysis and Model Comparison results

The multivariable survival analysis was performed supposing the Exponential, Log-logistic, Weibull, and log-normal for the baseline hazard function and the gamma frailty distributions. Covariates that were not significant in the univariable analysis were not included in the multivariable analysis. It is done by using all significant covariates in Univariate analysis at 25% level of significance. Model comparison was done using the covariates that are significant in multivariable analysis. To compare the efficiency of different models. the AIC value of the Weibull-AFT model was -222.56 which was the minimum value, compared to all the other models and the largest value of log likelihood is Weibull-AFT model, compared to all others model. Hence, the Weibull-AFT model was the most efficient model to describe the dataset of patients with MDR-TB.

Table 4. Model selection based on information criteria from AFT

AFT models	Information criteria (IC)		
	AIC	log-likelihood	Best model
Exponential	554.86	-264.43	
Log-normal	-221.68	123.5	Weibull
Weibull	-222.56	124.28	
Log-logistic	-211.256	118.628	

AIC Akaike's information criteria, AFT Accelerated failure time

Table 5. Multivariable analysis using Weibull shared Gamma frailty model for the recovery time of MDR-TB patients in SNNP region, Ethiopia

Variables	***Categories***	***Estimates***	***Std.err***	***Z***	***T.R(Φ)***	***p>|z|***	***95% CI for estimate***
Weight (kg)	Continuous	0.024	0.00247	9.87	1.025	0.00	[0.0195,0.029]
Age	0-17 years[R]				1		

	18-64 year	0.517	0.0967	5.34	1.053	0.120	[0.327,0.7070]
	Above 65	0.193	0.0754	4.49	1.21	0.750	[0.120,0.2312]
Sex	Male[R]				1		
	Female	0.182	0.0713	2.56	1.20	0.011	[0.0425,0.322]
HIV_status	Negative[R]				1		
	Positive	0.0973	0.0956	1.02	1.102	0.309	[-0.090,0.285]
Smoking status	Non Smok[R]				1		
	Smoker	0.0234	0.078	0.30	1.023	0.00	[-0.13,0.176]
Residence	Rural[R]				1		
	Urban	0.230	0.042	0.64	1.26	0.002	[0.04,0.47]
Adherence	Good[R]				1		
	Poor	0.031	0.032	1.32	1.35	0.201	[0.01,1.06]
	Fair	0.184	0.0466	3.94	1.20	0.765	[0.093,0.275]
Co-morbidities	No[R]				1		
	Yes	0.196	0.083	2.35	1.216	0.019	[0.033,0.36]
Previous drug history	No[R]				1		
	Yes	0.45	0.112	4.03	1.57	0.00	[0.231,0.67]
MDR-TB type	Pulmonary[R]				1		
	Extra pulmonary	-0.068	0.115	-0.59	0.934	0.006	[-0.293,0.159]
Occupation	Farmer[R]				1		
	Employee	0.071	0.025	3.09	1.073	0.002	[1.026,1.12]
	Merchant	0.152	0.0383	3.98	1.164	0.231	[0.078,0.23]
	Others						
Education level	Secondary[R] &above				1		
	Primary	-0.007	0.014	-0.053	0.993	0.613	[-0.966,1.021]
	No education	0.114	0.0354	3.14	1.12	0.002	[0.0419,0.180]
History of TB	No	0.213	0.074	2.90	1.24	0.004	[0.069,0.358]
	Yes[R]				1		
Alcohol use	No	0.048	0.076	0.63	0.510	0.000	[-0.526,0.103]
	Yes[R]				1		
Constant		0.126	0.035	89.09	1.13	0.000	[3.057,3.195]
Frailty variance (***θ***)	***θ* = 1.47, *λ* = 1.87,** $\tau = 0.424$						

R: Reference, Coef: Coefficient of parameter, SE ( ): standard error for; φ= Acceleration factor; (*): 95%CI: 95% confidence interval for (φ); θ= frailty variance; λ= scale parameter; γ = Shape parameter, τ , Kendall's tau

The recovery time from MDR-TB in southern parts of Ethiopia was carried out by the Weibull Gamma shared frailty model with hospitals as a clustering effect. Table 6 depicted the result of Weibull Gamma shared frailty model of parameter estimates, standard error of estimates, z-value, p-values, Time ratios and 95% CI. the Weibull-Gamma shared frailty model result depicted the covariates are baseline weight, sex, smoking history, co-morbidities, residence of patients, previous drug history, education level, occupation of patients, history of TB, MDR-TB type and alcohol use were significantly determine the time to recovery from MDR-TB.

An acceleration factor (time ratio) (Φ) greater than 1 specifies prolonging the time of recovery. the acceleration factors (Φ) for patients with non alcohol use were 0.51. This implies that the non alcohol users had a shorter time to recovery, compared to alcohol users. in addition the result shows that the increase of baseline weight (Φ =1.03; coeff= 0.0244; 95%CI of coefficient: 0.01954, 0.0292) led to an increase in the recovery time. The study showed that the Patients with extra-pulmonary had an acceleration factor (time ratio) of 0.934 [95%CI of estimate: -2933, 0.1578] which indicated that the patients with pulmonary MDR-TB have shorter Recovery time in comparison with extra-pulmonary MDR-TB patients. Patients who live in urban areas have a longer recovery time than those who live in rural areas (Φ=1.26; 95%CI|[0.04, 0.47]. female MDR-TB patients were experiencing longer recovery time than that of male MDR-TB patients. This means that female MDR-TB patients significant when we see it with reference group (male MDR-TB) [52]. The MDR-TB patients with co-morbidity also experienced longer recovery time than that of the reference groups. Acceleration factor of MDR-TB Patients who have previous drug history (Φ =1.57) had a longer recovery time than patients with no previous drug history of MDR-TB patients. And also MDR-TB patients with smoking history (Φ= 1.023; Coeff = 0.0234; 95CI of coefficient = -0.13, 0.176) had longer recovery time than MDR-TB patients who had No smoking history (reference group). Finally the result showed for employed of MDR-TB patients takes more time to recovery than reference group.

3.2. Discussion

The main goal of the study was to investigate time to recovery from multidrug resistance tuberculosis among selected hospitals in southern Ethiopia using AFT and parametric shared frailty models by considering baseline distributions Weibull and gamma frailty.

Given the close monitoring of patients while taking these medications, the median recovery duration of MDR-TB patients in the southern region was 22 months, which indicates that the recovery period of patients is within the advised treatment interval of 18 to 24 months or longer [13].

In comparison to the Log-normal, Log-logistic, Exponential, Gamma, and Gamma AFT models, the Weibull AFT model had the lower AIC. After selecting the Weibull AFT model, the data onto the Weibull AFT, Gamma frailty, and Weibull Gamma shared frailty models were effectively fitted. This is because of the model lifetime, Weibull distribution is mostly used in the literature as the Hazard rate for Weibull distribution is a monotone function [34, 49–52].

The clustering effect of the hospitals was one of the elements this study found to be connected to the recovery times of MDR-TB patients in Southern Ethiopia. the clustering effect was substantial (p-value 0.001) in the Weibull-gamma shared frailty model, indicating that there is heterogeneity between institutions and that individuals within the same hospital share similar risk factors on recovery time.

The finding of this study showed that the percentage of MDR-TB was highest in the age group (18-64 years) and it was in agreement or in line with the results of studies conducted in Amhara region of Ethiopia [54]. these kind of findings may attributed to the increased mobility observed in this age group, which could be driven by economic and social factors.

This study showed that extra pulmonary MDR-TB patients had longer recovery time than that of pulmonary MDR-TB patients in Southern region, Ethiopia, and it was supported by Limenih.A et.al, 2019 [54].

Female MDR-TB patients were associated with a high likelihood of experiencing treatment outcomes. Some other studies have disagree shown that male MDR-TB patients tend to have shorter recovery time [52–54]. But this study means that female MDR-TB patients were experiencing longer recovery time than that of male MDR-TB patients. The MDR-TB patients with co-morbidity also experienced longer recovery time than that of the control groups. This result is in line with the previous findings in Ethiopia [55, 58] and in India [52].

In this study, the patients with not educated MDR=TB patients had longer recovery time in comparison with the reference group. This finding was supported with those of the studies performed in Ethiopia this could be due to the lack of awareness of people with lower levels of education about their health issues. Moreover, they might have had no access to media, such as social media. [54].

The study's participants were smokers and Khat users in proportions of 7.3% and 20,1%, respectively, in terms of social drug usage. Getachew et al. (2017) found that 5.32% of study participants who were smokers in St. Peter TB Specialized Hospital were equivalent to the study's results [58].

The findings of this study are comparable to those of a study done in Tanzania, where cigarette smoking was 5% and alcohol consumption was 18% (Nyaki et al., 2016) [59].

According to the study's findings, smoking habits and a history of drug use were both significant predictors of recovery time in the southern region.this demonstrates that patients without a history of smoking take longer to recover than patients who have used drugs in the past. this was in line with the findings of Kuaban et al's study [60].

4. CONCLUSION

The objective of this study was to investigate recovery time of MDR-TB patients in selected treatment centers (Hospitals) at the Southern parts of the country. Retrospectively we obtained a cluster random sample of 301 patients from selected treatment centers. Among the 301 patients, 185 (61.5%) were recovered, and the remaining 38.5% were censored. Due to the clustering effects of patients within the treatment centers in relationship with recovery time from MDR-TB the study employed parametric shared frailty model and also employed accelerated failure time models.

Analyses of exploratory data were conducted using graphical and numerical methods. the results showed that individuals with MDR-TB experienced a median recovery time of 22 months, with a minimum and maximum recovery time of 18.5 and 24 months, respectively. Patients with MDR-TB who were included in the analysis had baseline mean and median weights of 46.52 and 48.5, respectively. Based on the findings from the KM estimate; females, rural residents, pulmonary MDR-TB type, none alcohol users, none smokers, educated patients, patients who have co-morbidities, and patients who have previous drug history have relatively better recovery rate. This was evidenced from the Logrank and Breslow test results.

Weibull-Gamma shared frailty model was the final selected model based on AIC to explain time to recovery dataset of MDR-TB patients. The finding from the final fitted model indicated, the variables significantly influencing the MDR-TB patients time to recovery were sex, baseline weight, Alcohol use, smoking cigarette, History of TB, Co-morbidities and category of MDR-TB or MDR-TB type, education level, previous drug history, occupation of patients and place of residence.
Based on this study we recommend that the regional and federal Government of Ethiopia need to take immediate steps to address the causes of long recovery time of MDR-TB patients, A thorough and focused MDR TB-Addiction control program needs to be strengthened, Further studies and action with a possible revision to the MDR-TB and XDR-TB management strategy at the centers are necessary, there should be robust early case detection and proper treatment of drug-susceptible MDR-TB to shorten the recovery time of MDR-TB in accordance with WHO guidelines and It is advisable for future researchers to employee Weibull-Gamma shared frailty model to analyze survival data having clustering effects.

CONSENT FOR PUBLICATION

Not Applicable

ETHICAL APPROVAL

Not applicable

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ABBREVIATIONS

AIDS, Acquired Immune Deficiency Syndrome; AFT, Accelerated Failure Time; AIC, Akakei Information Criteria; ART, Antiretroviral therapy; CI, Confidence Interval; CSA, Central statistical agency; HIV, Human Immunodeficiency Virus; MDR-TB, Multidrug resistance tuberculosis; PH, Proportional Hazard; TB, Tuberculosis; WHO, World Health Organization; XDR, Extensively drug resistant; FQ, fluoroquinolone; RR, Rifampicin; NEMMCSH, Nigist Ellen Mohammed Memorial Comprehensive Specialized Hospital; AGH, Arbaminch General hospital; BH, Butajira Hospital.