

1 **MODELLING TIME TO RECOVERY FROM**  
2 **MULTIDRUG RESISTANT TUBERCULOSIS IN**  
3 **SOUTHERN ETHIOPIA**  
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7 **ABSTRACT**  
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**Introduction:** Multidrug resistant tuberculosis (MDR-TB) is a global health threat, resistant to key anti-TB drugs. It is ranked among the top 10 causes of death worldwide. Therefore, the current study investigated time to recovery from MDR-TB in southern Ethiopia.

**Data, materials and Methods:** Restrospective data from selected hospitals in SNNPR (January 2016 to December 2021) were analyzed. A cluster sample of 301 MDR-TB patients (131 NEMMCH, 121 BH, 49 AGH) was considered.

**Results:** Among the 301 cases, 116 (38.5%) were censored. While 185 (61.5%) were recovered. Parametric shared frailty models were employed to account unobserved heterogeneity among the Hospitals and patients and AFT models were employed. the median recovery time of MDR-TB is 22 months. The clustering effect of frailty model was hospitals. Weibull-gamma shared frailty model was appropriate for this data.

**Conclusion:** the final model showed that males have higher recovery rates than females. Extra pulmonary MDR-TB and Urban residency correleted with longer recovery times. The recovery rate 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 SNNP region By providing on early case detection and appropriate treatment of drug-susceptible MDR-TB, since it is essential to shorten the recovery time of MDR-TB patients in line with WHO guidelines.

9  
10 **Keywords:** Multidrug resistance tuberculosis, Time to recovery, parametric shared frailty, Treatment centers, accelerated  
11 failure time.  
12

## 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, 2].

“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. 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, Rwanda<sup>1</sup>, and South Africa<sup>4</sup> are 54%, 9.5%, 9.4%, and 73%, respectively” [5]. “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”. [33]

“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” [3]. “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”. [33] 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” [4]. “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” [5, 6]. “Moreover, the emerging and rapid transmission of XDR-TB is also another challenge for TB control program, 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” [2].

Investigating the survival duration of patients with MDR-TB serves as a means to address health challenges within the community. This involves identifying the significant factors associated with the time until recovery from MDR-TB patients. The findings of this study could offer valuable evidence to governmental and non governmental organizations, as well as other concerned bodies. This evidence could inform the development of policies, strategies, plans and further investigation

The findings of this study could offer valuable evidence to governmental and non-governmental organizations, as well as other concerned entities. This evidence could inform the development of policies, strategies, plans and further investigations can be directed towards enhancing recovery rates and improving the control and management of MDR-TB patient mortality. Moreover, this study can serve as a foundation future research endeavors focused on MDR-TB patients. 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

66 **2.1.1. Study area:** This research was carried out on MDR-TB treatment centers of SNNPR, Ethiopia. Southern Nations  
67 Nationalities and Peoples Region is the country's third-largest administrative region and the most diversified in terms of  
68 language, culture, and ethnic origin, covering more than 10% of the country's land area. More than 56 ethnic groups live  
69 in the region. The capital city of SNNPR is Hawassa. It is 273 kilometers south of Addis Ababa. The SNNPR is bordered  
70 from the south by Kenya, from the west by South Sudan, from the northwest by Gambela, and from the north and east by  
71 Oromia. The data for this research took place between January 2016 to December 2021. The region is divided into 17  
72 administrative zones and additionally, there are 6 special woreda's. In the region, there are six MDR-TB treatment  
73 centers. In the SNNPR, there are over 45 indigenous ethnic groups, each with their own cultural heritage and identity. In  
74 2018, the population was estimated to be 20,768,000. [32]

75 **2.1.2. Study population:** The study population was all MDR-TB patients who had been registered in the Hospitals. The  
76 totals of 301 patients with MDR-TB from the Hospital were included in the study. The total population was proportionally  
77 allocated to the three Hospitals: Nigist Ellen Mohammed memorial Comprehensive Hospital (211), Butjira Hospital (199)  
78 and Arbamich General Hospital (89).

79 **2.1.3. Study design:** A retrospective study design was employed and the data were obtained from MDR-TB patients  
80 admitted to the hospitals and also it was carried out in three selected hospitals of SNNP region which have MDR-TB  
81 treatment center. Which is a 72-months follow-up period. The time was measured by months in this study.

## 82 **2.2. Data source and data collection**

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

## 87 **2.3. Sampling techniques and Sample size Determination**

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

### 91 **2.3.1. Sample size determination:**

92 The sample size was determined using at 95% CI with a prevalence of MDR-TB rate of 15% [7] and a margin error of  
93 0.036. "Then a total sample of 499 MDR-TB patients was considered using cluster random sampling methods. Further  
94 discussions on sampling are available at Cochran" [8]. Thus, from a total sample of 301 MDR-TB patients that fulfill the  
95 inclusion-exclusion criteria was considered by applying cluster random sampling methods. Subsequently, all individuals  
96 within the designated clusters are included within the sample. Following this protocol, samples were collected from  
97 specified hospitals in the southern region.

## 98 **Inclusion and exclusion criteria**

99 Patients with insufficient recorded information in either the registration book or their card were excluded from the study.  
100 Additionally, those who had not initiated second-line MDR-TB treatments and XDR-TB patients were also excluded.  
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## 104 **2.4. Study Variables**

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

109 **Predictor variables:** The study considered predictor variables consisting of MDR-TB patients' background traits and their  
110 previous epidemiological, clinical, and laboratory findings, as outlined in table 1.

111 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 [9], Kaplan-Meier Survival functions [10] and median survival time [11]. “Besides estimating the survival functions, comparing two or more estimated survival curves is the most frequently used statistical tool of recent clinical research” [12].

The simplest way of comparing the survival times obtained from two or more groups are the Kaplan-Meier curves and log-rank test [13]. However, to explore the relationship between the survival experience of individual and explanatory variables, an approach based on statistical modeling has been used [14]. Also used with a modeling approach to the analysis of survival data are the Cox Proportional Hazard [15], Accelerated Failure Time [15] and parametric shared frailty models [16].

128 **2.5.2. Accelerated failure time model**

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

135 
$$Y_i = \log T_i = \mu + \beta_1 X_{1i} + \dots + \beta_{pi} X_{pi} + \sigma \varepsilon_i \dots Eq(1),$$

136 where,

- 137 ✓  $\log T_i$  represents the log-transformed survival time,
- 138 ✓  $\mu$  is the intercept
- 139 ✓  $\sigma$  is the scale parameter,
- 140 ✓  $x_1, \dots, x_p$  are the explanatory variables with the coefficients  $\beta$  reflecting the effect that each explanatory
- 141 variable have on the survival time and estimated by maximum likelihood method using a Newton-
- 142 Raphson procedure and
- 143 ✓  $\varepsilon_i$  is the error term which is assumed to follow a specific distribution such as Weibull [17], log-normal
- 144 [18], log-logistic [15] and gamma [19] among many.

146 **2.5.3. Parametric shared frailty models**

147 To address unobserved variations, the concept of frailty term was initially introduced by Hougaard in 1991 as an extension  
148 of proportional hazards. In a shared frailty model, observations within a cluster exhibit the same level of frailty, and the  
149 common frailty variance quantifies the interdependence among lifetimes within that cluster [20].

150 Consider a scenario with  $i$  clusters, where each cluster  $i$  comprises  $n_i$  observations, and the total sample size is given by  
151  $\sum_1^i n_i = n$  is the total sample size and  $t_{ij} = \min(c_{ij}, t_{ij}^*)$  is the observed failure time of a right censoring scheme for  $k^{th}$  ( $k =$   
152  $1, \dots, n_i$ ) observation in  $i^{th}$  cluster and  $c_{ij}$  is the censoring time, where  $t_{ij}^*$  and  $c_{ij}$  are independent random variables [16].

153 Then the observed censoring indicator  $\delta_{ij}$  is equal to 1 if  $t_{ij}^* < c_{ij}$ , and 0 otherwise and conditional on frailty  $y_i$  ( $> 0$ ) and  $X_{ij}$ ,  
154 the hazard function of  $i^{th}$  cluster has the form:

155 
$$h(t_{ij}, x_{ip}, y_i) = y_i h_o(t_{ij}) \exp(\beta^{x_{ij}}) \dots Eq(2),$$

156 Where

- 157 ✓  $h_o(\cdot)$  is the baseline hazard function
- 158 ✓  $x_{ij}$  is a vector of observed predictors for the  $k^{th}$  observation and
- 159 ✓  $\beta$  is a vector of regression parameters.

160 The frailties, represented by  $y_i$ , are independent and identically distributed (**i. i. d.**) variables with a shared probability  
161 density function  $g(y_i)$ . Numerous investigations have explored the selection of continuous distributions for frailty random  
162 variables, including Gamma [37], inverse Gaussian [20], log-normal [18], and positive stable [21]. And a limited number of  
163 studies have explored discrete distributions [22].

164 **2.5.4. Models comparison and diagnostics**

165 Model comparison and selection are among the most common problems of statistical practice, with numerous procedures  
166 for choosing among a set of models. There are several methods of model selection. One of the most commonly used  
167 model selection criteria is Akaike Information Criterion (AIC). we were compare the models study by using AIC, BIC,  
168 Likelihood ratio test [24] criteria's was used to compare various candidate models and the model with the smallest AIC  
169 and BIC value is considered as a better fit [25]. This is defined as:

170 
$$AIC = -2\log L + 2(p+k) \dots Eq(3),$$

171 Where,  $k$  is the number of covariates and  $p$  the number of model specific distributional parameters. This research used  
172 the AIC to compare various candidates of non- nested parametric models. The preferred model is the one with the lowest  
173 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 [15].

### 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 [15].

## 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%)
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

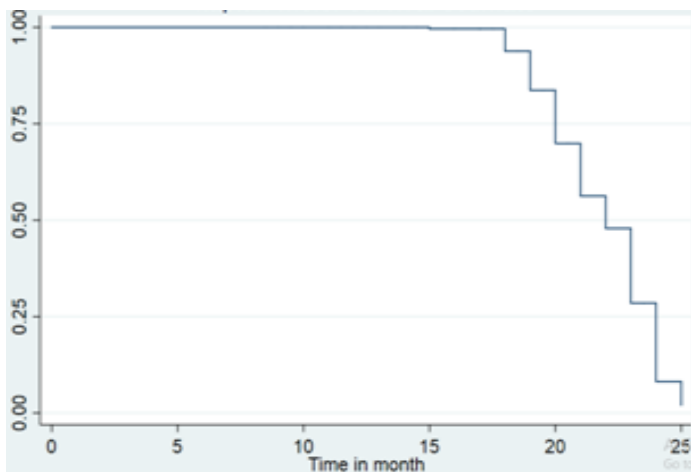
Residence	Rural	156(51.8%)	94(60.3%)	48	22
	Urban	142(47.2%)	89(62.7%)	67	23
HIV status	Negative	265(88.0%)	162(61.1%)	103	22
	Positive	36(12.01%)	13(36%)	23	24
Smoking status	Smoker	64(21.3)	40(42.5%)	24	22
	Non smoker	237(78.7%)	145(61)	92	21
Adherence	Poor	62(20.6)	35(56.5%)	27	23
	Fair	61(20.3%)	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

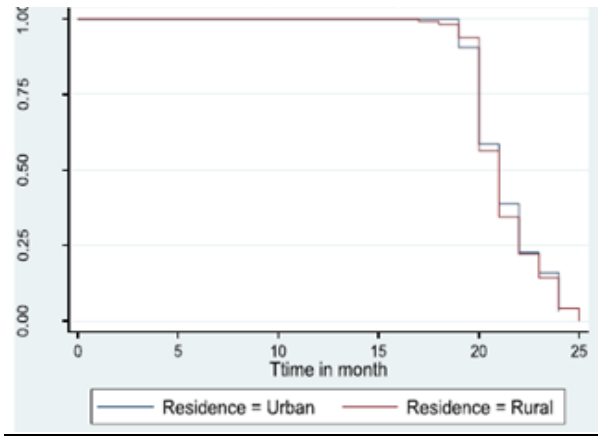
#### 3.1.1. Comparison of survivorship functions

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

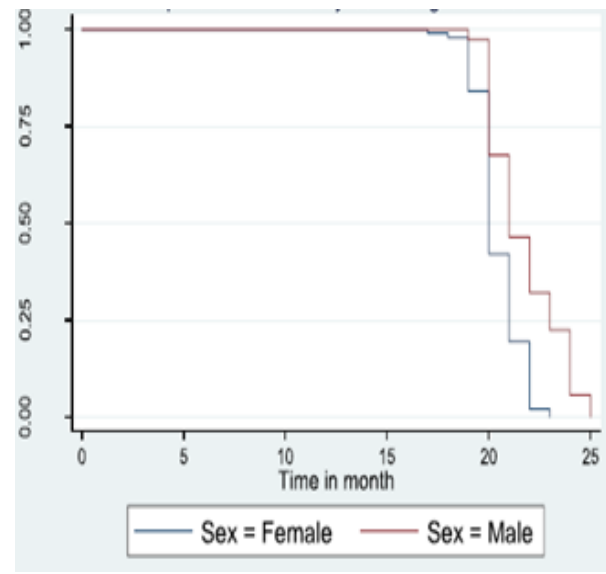
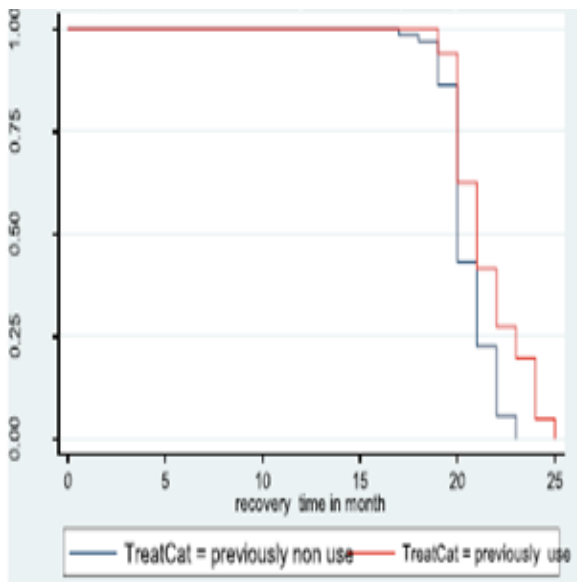


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c) MDR TB by drug use history

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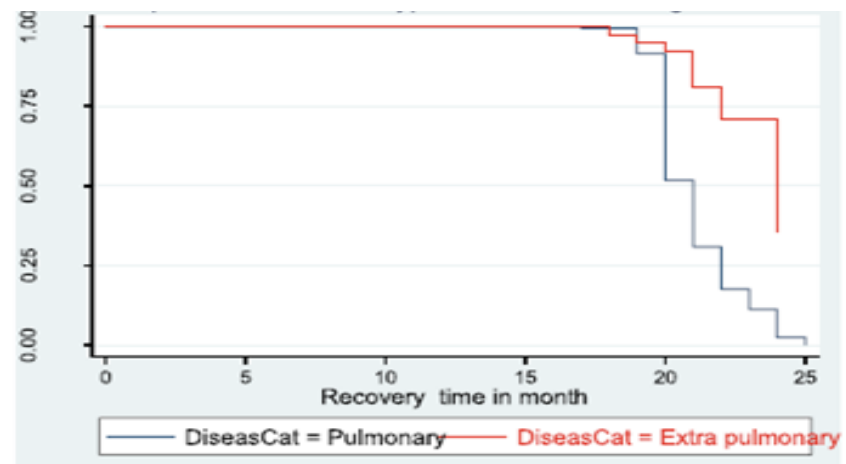
d) MDR TB by Sex



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e) MDR TB by type of MDR TB



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251 *Figure 1 Estimate of the KM Survival function for the recovery time of MDR-TB patients in SNNP among category*  
252 *of categorical variables by (a) overall (b) residence (c) drug use history (d) sex (e) type of MDR-TB.*  
253

254 The survival curve generated by the Kaplan-Meier estimator illustrated both the collective estimated survivor function and  
255 distinct predictor groups. Evidently, the overall estimated survivor function indicated that individuals with MDR-TB  
256 experienced recovery following 22-month treatment duration.

257 As we can see from above km estimated categorical variables the recovery time of patients was the difference between  
258 HIV status, smoking status, Residence, education level, Alcohol use and MDR-TB type, sex whereas, marital status,  
259 Adherence; history of TB and occupation did not show a clear difference in the figure above.  
260

### 261 3.1.2. Parametric shared frailty model Results

262  
263 Parametric-shared frailty models were applied, considering the Exponential, Weibull, and log-normal distributions for the  
264 baseline hazard function. The Gamma distribution, commonly employed in literature to assess frailty effects [23, 26], was  
265 specifically chosen. Consequently, the study involved fitting both the Gamma frailty model and the Weibull Gamma shared  
266 frailty model, with hospitals serving as the random (frailty) component, to determine the most suitable model.

267 The AIC for the Weibull gamma shared frailty (-2375.33) was smaller than the AIC for the Weibull AFT (- 222.56) models.  
268 The frailty for the selected model was estimated to be 1.467 (chi-square = 53.42, df = 1, p-value = 0.0000) which indicated  
269 existence of unobserved heterogeneity between the hospitals and it was observed that the inclusion of the frailty  
270 component in the model was significant. The result also showed that the value of the shared frailty ( $\theta$ ) is 1.467, 1.36,  
271 0.527 and 0.157 for Weibull, Log-logistic, Exponential and Lognormal gamma shared frailty models respectively; the  
272 heterogeneity between clusters was high when estimated by Weibull gamma shared frailty model, which were 1.46. The  
273 Kendall's tau ( $\tau$ ) is higher for higher values of theta ( $\theta$ ) which measure the association within region. The estimated  $\tau$  =  
274 0.424 shows that there is strong dependence within the cluster or region. This indicates Weibull-gamma shared frailty  
275 model is more efficient model to describe time-to-recovery from MDR-TB. And also it implied that the frailty component  
276 had significant contribution to the model.  
277

### 278 3.1.3. The Cox Snell Residual Plots

279 The Cox-Snell residuals offer a distinctive approach to assess the goodness of fit of the model to the data. It's notable that  
280 the plot depicting the cumulative hazard function against Cox-Snell residuals closely aligns with the 45-degree straight  
281 lines originating from the origin for the Weibull model when compared to exponential, Log-normal and Log-logistic.  
282 Therefore overall goodness of fit for the AFT model was checked by these Cox-Snell residual plots [15]. This suggests  
283 that Weibull model provided the best fit for the recovery time of MDR-TB patients. The plots indicate that the Weibull  
284 model fits the data best and that the other model fits poorly.

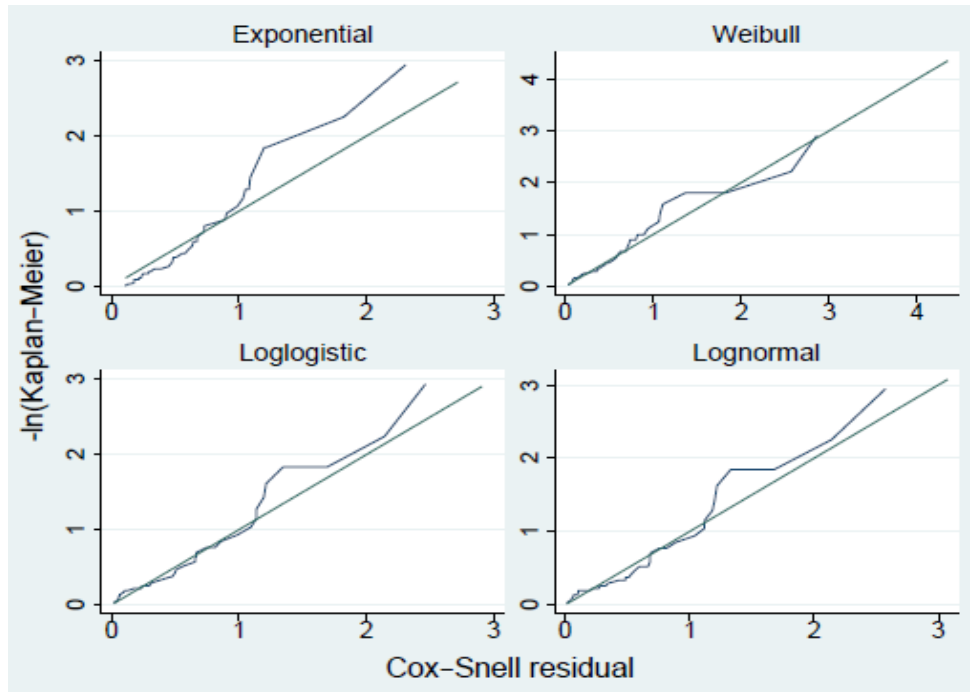


Figure 2 the Cox-Snell residual plots to evaluate model fit of four regression models Exponential, Weibull, log logistic and lognormal distributions.

### 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	Weibull
Log-normal	-221.68	123.5	
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( $\Phi$ )	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 <sup>R</sup>				1		
	18-64 year	0.517	0.0967	5.34	1.053	0.120	[0.327,0.7070]

Sex	Above 65	0.193	0.0754	4.49	1.21	0.750	[0.120,0.2312]
	Male <sup>R</sup>				1		
HIV_status	Female	0.182	0.0713	2.56	1.20	0.011	[0.0425,0.322]
	Negative <sup>R</sup>				1		
Smoking status	Positive	0.0973	0.0956	1.02	1.102	0.309	[-0.090,0.285]
	Non Smok <sup>R</sup>				1		
Residence	Smoker	0.0234	0.078	0.30	1.023	0.00	[-0.13,0.176]
	Rural <sup>R</sup>				1		
Adherence	Urban	0.230	0.042	0.64	1.26	0.002	[0.04,0.47]
	Good <sup>R</sup>				1		
Co-morbidities	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]
	No <sup>R</sup>				1		
Previous drug history	Yes	0.196	0.083	2.35	1.216	0.019	[0.033,0.36]
	No <sup>R</sup>				1		
MDR-TB type	Yes	0.45	0.112	4.03	1.57	0.00	[0.231,0.67]
	Pulmonary <sup>R</sup>				1		
Occupation	Extra pulmonary	-0.068	0.115	-0.59	0.934	0.006	[-0.293,0.159]
	Farmer <sup>R</sup>				1		
Education level	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				1		
History of TB	Secondary <sup>R</sup> & above				1		
	Primary	-0.007	0.014	-0.053	0.993	0.613	[-0.966,1.021]
Alcohol use	No	0.114	0.0354	3.14	1.12	0.002	[0.0419,0.180]
	Yes <sup>R</sup>				1		
Constant Frailty variance ( $\theta$ )	No	0.213	0.074	2.90	1.24	0.004	[0.069,0.358]
	Yes <sup>R</sup>				1		
Constant Frailty variance ( $\theta$ )	No	0.048	0.076	0.63	0.510	0.000	[-0.526,0.103]
	Yes <sup>R</sup>				1		
Constant Frailty variance ( $\theta$ )		0.126	0.035	89.09	1.13	0.000	[3.057,3.195]
	<b><math>\theta = 1.47, \lambda = 1.87, \tau = 0.424</math></b>						

305 R: Reference, Coef: Coefficient of parameter, SE ( ): standard error for;  $\varphi$ = Acceleration factor; (\*): 95%CI: 95%  
306 confidence interval for ( $\varphi$ );  $\theta$ = frailty variance;  $\lambda$ = scale parameter;  $\gamma$  = Shape parameter,  $\tau$ , Kendall's tau

307 The recovery time from MDR-TB in southern parts of Ethiopia was carried out by the Weibull Gamma shared frailty model  
308 with hospitals as a clustering effect. Table 5 depicted the result of Weibull Gamma shared frailty model of parameter  
309 estimates, standard error of estimates, z-value, p-values, Time ratios and 95% CI. the Weibull-Gamma shared frailty  
310 model result depicted the covariates are baseline weight, sex, smoking history, co-morbidities, residence of patients,  
311 previous drug history, education level, occupation of patients, history of TB, MDR-TB type and alcohol use were  
312 significantly determine the time to recovery from MDR-TB.

313 An acceleration factor (time ratio) ( $\Phi$ ) greater than 1 specifies prolonging the time of recovery. the acceleration factors ( $\Phi$ )  
314 for patients with non alcohol use were 0.51. This implies that the non alcohol users had a shorter time to recovery,  
315 compared to alcohol users. in addition the result shows that the increase of baseline weight ( $\Phi =1.03$ ; coeff= 0.0244;  
316 95%CI of coefficient: 0.01954, 0.0292) led to an increase in the recovery time. The study showed that the Patients with  
317 extra-pulmonary had an acceleration factor (time ratio) of 0.934 [95%CI of estimate: -2933, 0.1578] which indicated that

318 the patients with pulmonary MDR-TB have shorter Recovery time in comparison with extra-pulmonary MDR-TB patients.  
319 Patients who live in urban areas have a longer recovery time than those who live in rural areas ( $\Phi=1.26$ ; 95%CI[ 0.04,  
320 0.47]. female MDR-TB patients were experiencing longer recovery time than that of male MDR-TB patients. This means  
321 that female MDR-TB patients significant when we see it with reference group (male MDR-TB) [52]. The MDR-TB patients  
322 with co-morbidity also experienced longer recovery time than that of the reference groups. Acceleration factor of MDR-TB  
323 Patients who have previous drug history ( $\Phi =1.57$ ) had a longer recovery time than patients with no previous drug history  
324 of MDR-TB patients. And also MDR-TB patients with smoking history ( $\Phi= 1.023$ ; Coeff = 0.0234; 95CI of coefficient = -  
325 0.13, 0.176) had longer recovery time than MDR-TB patients who had No smoking history (reference group). Finally the  
326 result showed for employed of MDR-TB patients takes more time to recovery than reference group.

### 327 **3.2. Discussion**

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

331 “Given the close monitoring of patients while taking these medications, the median recovery duration of MDR-TB patients  
332 in the southern region was 22 months, which indicates that the recovery period of patients is within the advised treatment  
333 interval of 18 to 24 months or longer” [1].

334 “In comparison to the Log-normal, Log-logistic, Exponential, Gamma, and Gamma AFT models, the Weibull AFT model  
335 had the lower AIC. After selecting the Weibull AFT model, the data onto the Weibull AFT, Gamma frailty, and Weibull  
336 Gamma shared frailty models were effectively fitted. This is because of the model lifetime, Weibull distribution is mostly  
337 used in the literature as the Hazard rate for Weibull distribution is a monotone function” [16, 27].

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

342 “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  
343 agreement or in line with the results of studies conducted in Amhara region of Ethiopia” [28]. These kind of findings may  
344 attributed to the increased mobility observed in this age group, which could be driven by economic and social factors.

345 “This study showed that extra pulmonary MDR-TB patients had longer recovery time than that of pulmonary MDR-TB  
346 patients in Southern region, Ethiopia”, and it was supported by Limenih.A et.al, 2019 [28].

347 “Female MDR-TB patients were associated with a high likelihood of experiencing treatment outcomes. Some other studies  
348 have disagree shown that male MDR-TB patients tend to have shorter recovery time” [27, 28]. But this study means that  
349 female MDR-TB patients were experiencing longer recovery time than that of male MDR-TB patients. The MDR-TB  
350 patients with co-morbidity also experienced longer recovery time than that of the control groups. This result is in line with  
351 the previous findings in Ethiopia [29] and in India [27].

352 “In this study, the patients with not educated MDR=TB patients had longer recovery time in comparison with the reference  
353 group. This finding was supported with those of the studies performed in Ethiopia this could be due to the lack of  
354 awareness of people with lower levels of education about their health issues. Moreover, they might have had no access to  
355 media, such as social media” [28].

356 The study's participants were smokers and Khat users in proportions of 7.3% and 20,1%, respectively, in terms of social  
357 drug usage. Getachew et al. (2017) found that 5.32% of study participants who were smokers in St. Peter TB Specialized  
358 Hospital were equivalent to the study's results [29].

359 The findings of this study are comparable to those of a study done in Tanzania, where cigarette smoking was 5% and  
360 alcohol consumption was 18% (Nyaki et al., 2016) [30].

361 According to the study's findings, smoking habits and a history of drug use were both significant predictors of recovery  
362 time in the southern region.this demonstrates that patients without a history of smoking take longer to recover than  
363 patients who have used drugs in the past. This was in line with the findings of Kuaban et al's study [31].

#### 364 4. CONCLUSION

365 The objective of this study was to investigate recovery time of MDR-TB patients in selected treatment centers (Hospitals)  
366 at the Southern parts of the country. Retrospectively we obtained a cluster random sample of 301 patients from selected  
367 treatment centers. Among the 301 patients, 185 (61.5%) were recovered, and the remaining 38.5% were censored. Due  
368 to the clustering effects of patients within the treatment centers in relationship with recovery time from MDR-TB the study  
369 employed parametric shared frailty model and also employed accelerated failure time models.  
370

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

378 Weibull-Gamma shared frailty model was the final selected model based on AIC to explain time to recovery dataset of  
379 MDR-TB patients. The finding from the final fitted model indicated, the variables significantly influencing the MDR-TB  
380 patients time to recovery were sex, baseline weight, Alcohol use, smoking cigarette, History of TB, Co-morbidities and  
381 category of MDR-TB or MDR-TB type, education level, previous drug history, occupation of patients and place of  
382 residence.

383 Based on this study we recommend that the regional and federal Government of Ethiopia need to take immediate steps to  
384 address the causes of long recovery time of MDR-TB patients in SNNP region by promoting adherence to treatment, early  
385 detection of cases, and proper management of drug susceptibility in alignment with WHO guidelines, efforts can be  
386 directed towards improving recovery rate and effectively managing MDR-TB patient death. Further studies with a possible  
387 revision to the MDR-TB and XDR-TB management strategy at the centers are necessary.

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391

#### 392 AUTHORS' CONTRIBUTIONS

393 This work was carried out in collaboration among all authors. Author SSA designing study, performing analysis, writing the  
394 first draft of the manuscript; reading and approving the final manuscript analyzing data by using statistical software's.  
395 Author DSW and DAT managing the analysis and searching all possible literatures, reading and approving the final  
396 manuscript. Author managing the analysis and follow up the research. All authors read and approved the final manuscript.  
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#### 401 REFERENCES

- 402 1. World Health Organization. Global tuberculosis report 2019. Geneva: World Health Organization, 2019.
- 403 2. Teramaji W. and Abiyot N. Modeling Time to Death on MDR TB in Jimma: JRHS, 2021.
- 404 3. Federal ministry of health. Federal Ministry of Health and health related indicators 2005 E.C (2012/2013). 2014.
- 405 4. Federal Ministry of Health. Guideline for program and clinical management of drug resistant tuberculosis. 2019.
- 406 5. World health Organization. Treatment of tuberculosis guidelines. Geneva: World health Organization; 2020.  
407 <https://www.ncbi.nlm.nih.gov/books/NBK138748/>.
- 408 6. Chung-Delgado K, Guillen-Bravo S, Revilla-Montag A, Bernabe-Ortiz A. Mortality among MDR-TB cases:  
409 Comparison with drug-susceptible tuberculosis and associated factors. PLOS ONE. 2018; 10(3):e0119332.  
410 <https://doi.org/10.1371/journal.pone.0119332> PMID: 25790076

- 411 7. Nigus D, Lingerew W, Beyene B, Tamiru A, Lemma M, Melaku M. Prevalence of multi drug resistant tuberculosis  
412 among presumptive multi drug resistant tuberculosis cases in Amhara National Regional State, Ethiopia. *J*  
413 *Mycobac Dis.* 2014;4(152):2161-1068.1000152.
- 414 8. Cochran WG. *Sampling Techniques*. 3rd. New York: Wiley; 1977.
- 415 9. Fan J. *Local polynomial modelling and its applications: monographs on statistics and applied probability 66*. New  
416 York: Routledge; 2018.
- 417 10. Van der Meulen A. *Life tables and survival analysis*. The Hague: Statistics Methods Statistics Netherlands; 2012.
- 418 11. Brookmeyer R: Median survival time. *Wiley StatsRef: Statistics Reference Online* 2014.
- 419 12. Reid N. Estimating the median survival time. *Biometrika*. 2001;68(3):601–8.
- 420 13. Kleinbaum DG, Klein M. Kaplan-Meier survival curves and the log-rank test. In: *Survival analysis*. New York:  
421 Springer; 2016. p. 55–96.
- 422 14. Collett D. *Modelling survival data in medical research*. New York: Chapman and Hall/CRC; 2015.
- 423 15. Cox DR. Regression models and life-tables. In: *Breakthroughs in statistics*. New York: Springer; 2008. p. 527–41.  
424 p.30(2) 248-75
- 425 16. Gutierrez RG. Parametric frailty and shared frailty survival models. *Stata J.* 2002;2(1):22–44.
- 426 17. Pike M. A method of analysis of a certain class of experiments in carcinogenesis. *Biometrics*. 1966;22(1):142–61.
- 427 18. Bennett S. Analysis of survival data by the proportional odds model. *Stat Med*. 1983;2(2):273–7.
- 428 19. Van den Berg GJ. Duration models: specification, identification and multiple durations. In: *Handbook* 2016
- 429 20. Aalen O, Borgan O, Gjessing H. *Survival and event history analysis: a process point of view*. New York: Springer  
430 Science & Business Media; 2008.
- 431 21. Hougaard P. Survival models for heterogeneous populations derived from stable distributions. *Biometrika*.  
432 1986;73(2):387–96.
- 433 22. Caroni C, Crowder M, Kimber A. Proportional hazards models with discrete frailty. *Life time Data Anal*.  
434 2010;16(3):374–84
- 435 23. Askin OE, Inan D, Buyuklu AH. Parameter Estimation of Shared Frailty Models Based on Particle Swarm  
436 Optimization. *Int J Stat Probab*. 2017;6(1): 48–58.
- 437 24. Akaike H. A new look at the statistical model identification. *IEEE Trans Autom Control*. 1974;19(6):716–23.
- 438 25. Munda M, Rotolo F, Legrand C. Parfm: parametric frailty models in R. *J Stat Softw*. 2012;51(11):1–20.
- 439 26. Wienke A. *Frailty models in survival analysis*. New York: Chapman and Hall/ CRC; 2010.
- 440 27. Tavakoli A. Incidence and prevalence of tuberculosis in Iran and neighboring countries. *Zahedan J Res Med Sci*.  
441 2017;19(7):e9238.
- 442 28. Limenih.A and Workie Limenih.D. Survival analysis of time to cure on multidrug resistance tuberculosis patients  
443 in Amhara region, Ethiopia *BMC Public Health* (2019).
- 444 29. Girum T, Tariku Y, Dessu S. Survival status and treatment outcome of multidrug resistant tuberculosis (MDR-TB)  
445 among patients treated in treatment initiation centers (TIC) in South Ethiopia: a retrospective cohort study. *Ann*  
446 *Med Health Sci Res*. 2017;7(5):331–36.

- 447 30. Mitku AA, Dessie ZG, Muluneh EK, Workie DL. Prevalence and associated factors of TB/HIV co-infection among  
448 HIV infected patients in Amhara region, Ethiopia. *Afr Health Sci.* 2016;16(2):588–95.
- 449 31. World Health Organization Companion handbook to the WHO guidelines for the programmatic management of  
450 drug-resistant tuberculosis. Geneva:: WHO; 2019.
- 451 32. Ababa A. Federal democratic republic of Ethiopia central statistical agency population projection of Ethiopia for  
452 all regions at wereda level from 2014 – 2017; 2017.
- 453 33. Limenih YA, Workie DL. Survival analysis of time to cure on multi-drug resistance tuberculosis patients in Amhara  
454 region, Ethiopia. *BMC public health.* 2019 Dec;19:1-1.

455 **ABBREVIATIONS**

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

462 **APPENDIX**

464 **Table 6. Unavailable analysis using Weibull shared Gamma frailty model for the recovery time of MDR-**  
465 **TB patients in SNNP region, Ethiopia**

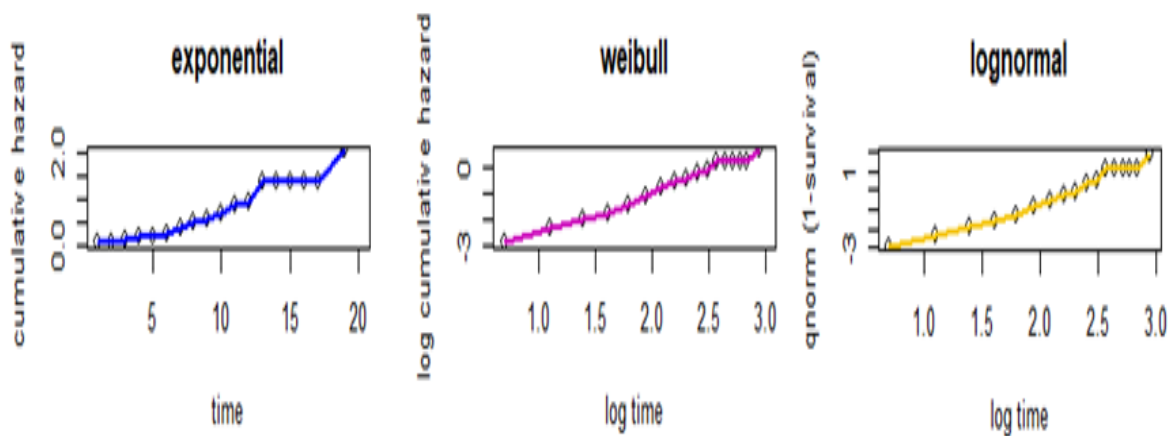
Variables	Categories	Estimates( $\beta$ )	Std.err	Z	T.R( $\Phi$ )	p> z	95% CI for estimate
Baseline Weight (kg)	continuous	0.079	0.0021	37.68		0.000	[0.0765,0.082]
Treatment center	NEMMCSH <sup>R</sup>				1		
	Butajira	3.76	0.29	12.82		0.123	[3.42,4.09]
	Arbaminch	1.267	0.05	5.32		0.531	[1.12, 1.45]
Age	0-17 years <sup>R</sup>				1		
	18-64 year	3.80	0.155	24.4		0.000	[3.61, 3.97]
	Above 65	0.70	0.045	3.45		0.012	[0.52, 2.10]
sex	Male <sup>R</sup>						
	Female	4.61	0.362	12.75		0.000	[4.2, 5.03]
HIV_status	Negative <sup>R</sup>				1		
	Positive	5.25	1.062	4.95		0.000	[4.03, 6.47]
Smoking status	Non Smok <sup>R</sup>				1		
	smoker	5.25	0.76	6.90		0.001	[4.37, 6.13]
Residence	Rural <sup>R</sup>				1		
	Urban	3.76	0.30	12.82		0.0001	[3.18, 4.35]
Adherence	Good <sup>R</sup>				1		
	Poor	1.47	0.012	19.45		0.002	[1.44, 1.50]
	Fair	3.96	0.264	14.21		0.000	[3.39, 4.43]
Co-morbidities	No <sup>R</sup>						
	Yes	6.13	1.02	6.00		0.002	[4.96, 7.31]
Previous drug history	No <sup>R</sup>				1		
	Yes	4.34	0.24	18.42		0.000	[3.87, 4.80]

MDR-TB type	Pulmonary <sup>R</sup>				1		
	Extra pulmonary	5.50	1.178	4.66		0.001	[4.14, 6.85]
Occupation	Farmer <sup>R</sup>				1		
	Employee	2.85	0.155	18.37		0.004	[2.55, 3.16]
	Merchant	0.95	0.12	11.23		0.045	[0.5, 1.25]
	Others	1.25	0.026	1.21		0.780	[0.96, 2.31]
Education level	Secondary <sup>R</sup> & above				1		
	Primary	0.93	0.048	9.03		0.850	[0.56, 1.53]
	No education	2.11	0.111	19.02		0.043	[1.90, 2.34]
History of TB	No	4.63	0.33	14.0		0.000	[3.98, 5.30]
	Yes <sup>R</sup>				1		
Alcohol use	No	4.32	0.34	12.30		0.002	[2.38, 4.75]
	Yes <sup>R</sup>				1		

466 Univariable analysis in order to see the effect of each covariate on time-to recovery from MDR-TB to the  
467 multivariable analysis at 25% level significance [25]

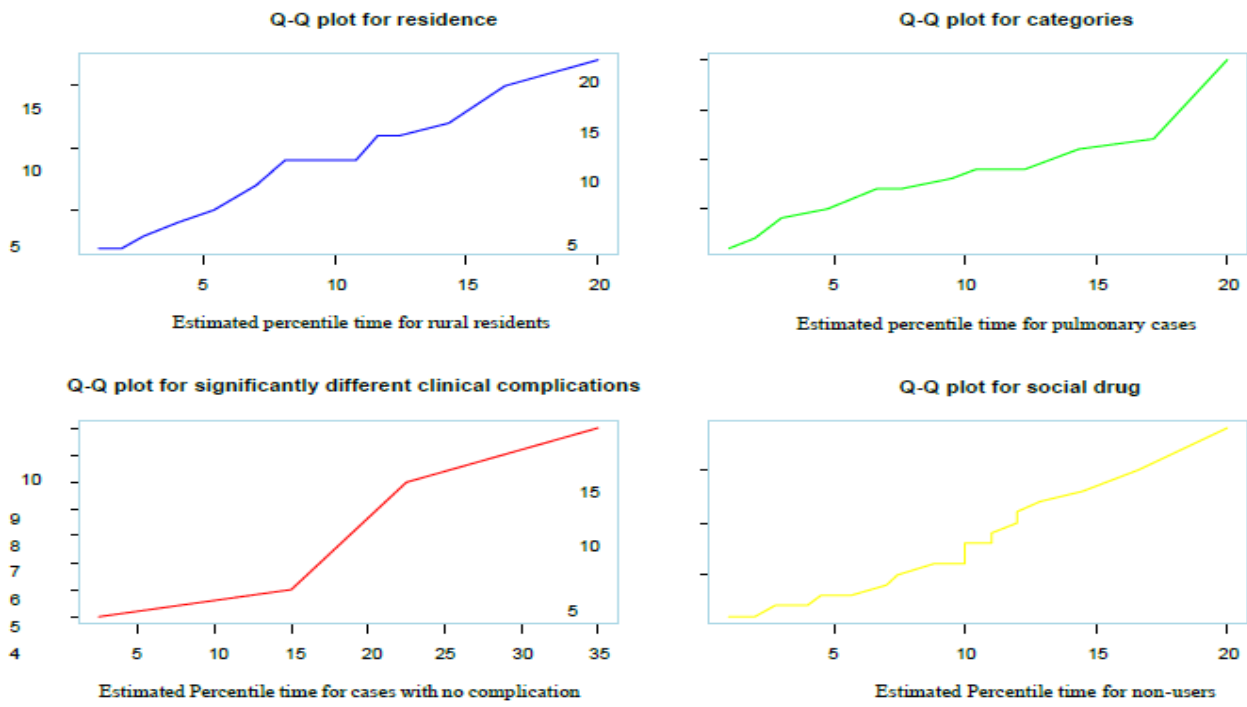
#### 468 4.1. Model Diagnostics

##### 469 Checking adequacy of parametric baselines using graphical methods



470

471 **Figure 3: Parametric assumption testing models**



472

473

**Figure 4:** Quantile-quantiles plot (Q-Q plot) to check the adequacy of the accelerated failure time models

474