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Research Article

Time to Cure and Predictive Factors Among Patients with Multi-Drug Resistance Tuberculosis in Puntland, Somalia: A Retrospective Cohort Study

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Abstract

Background: Multi-drug-resistant tuberculosis, also known as MDR-TB, is caused by bacteria that are resistant to the most effective first-line anti-tuberculosis medications, which are rifampicin and isoniazid. MDR-TB is an increasing global concern, and its spread has varying cure times for patients affected. Thus, this study was intended to investigate the median time to cure and identify predictive factors for patients with MDR-TB in Puntland, Somalia.

Methods: A retrospective cohort study was carried out at the MDR-TB center in Galkayo, Puntland, Somalia between the years of July 2017 and August 2023. The study utilized data that were collected from the inquiry form and monitoring cards of a randomly selected sample of 130 patients over a 6-year period. The data were entered into Epi-Data version 4.3 and analyzed using R Programming version 4.4.0. Non-parametric methods were used to estimate the median time to cure for patients with MDR-TB. Semi-parametric and parametric models were employed to determine predictive factors that influence the time to cure for MDR-TB patients. The Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) of different survival models were compared to select the model that offers the best fit.

Results: Out of the total of MDR-TB patients, 109(83.85%) were cured and 21(16.15%) were censored during the follow-up period. The median time to cure from MDR-TB was found to be 619 days which is approximately 20 months. In accordance with the AIC and BIC, the Log-logistic accelerated failure time model was the best fit for the data as compared to the other AFT models. The result of the Log-logistic AFT model revealed that age, sex, disease site, and comorbidities significantly affect the time to cure for MDR-TB. According to this study, older age with MDR-TB patients, male MDR-TB patients, MDR-TB patients with comorbid conditions, and extrapulmonary MDR-TB patients had a longer time to cure than their reference categories.

Conclusion: Based on the findings of the study, the median time to cure for patients with MDR-TB in Puntland was found to be 20 months. Sex, disease site, comorbidities and age were predictive factors of time to cure from MDR-TB.

Keywords: Puntland State; Multi-drug resistance tuberculosis; Median time to cure; Log-logistic Accelerated Failure time model.

INTRODUCTION

Tuberculosis (TB), a disease that is both preventable and curable, continues to be an important root cause of global morbidity and mortality. In 2021, TB was responsible for the deaths of 1.6 million individuals and affected over 10 million others [1]. The exact cause of TB was unknown until March 1882, when Dr. Robert Koch identified the pathogenic Mycobacterium tuberculosis [2].

In 2019, global estimates indicated that 10 million people contracted tuberculosis (TB). Of these, approximately 1.2 million deaths caused by tuberculosis (TB) were reported in individuals who did not have HIV infection, while an additional 208,000 fatalities occurred in individuals who were HIV positive. Around 88% of TB cases were diagnosed in adults, while the remaining 12% were accounted for children under the age of 15. Regionally, the Southeast Asia region was responsible for the highest burden, accounting for 44% of the global TB cases, followed by the African region (25%), and the Western Pacific region (18%). The proportions of TB cases in the Eastern Mediterranean, the Americas, and Europe accounted for 8.2%, 2.9%, and 2.5%, respectively. Notably, eight nations comprised two-thirds of the total global weight: India had the highest proportion of burden, accounting for 26%, followed by Indonesia (8.5%), China (8.4%), the Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%), and South Africa (3.6%) [3].

The World Health Organization (WHO) defines multidrug-resistant tuberculosis (MDR-TB) as tuberculosis that shows resistance to the two most powerful first-line anti-TB drugs, which are rifampicin (RFP) and isoniazid (INH) [4]. This type of TB is a major contributor to the global problem of antimicrobial resistance and continues to be an important public health concern. Annually, about 500,000 people globally are impacted by MDR-TB and rifampicin-resistant TB [5]. Additionally, the treatment duration for drug-resistant tuberculosis is prolonged, often ranging from 18 to 24 months, with successful outcomes approximating 50% [6].

The global impact of tuberculosis (TB) continues to be enormous. In 2012, it was estimated that there were 8.6 million new cases of TB, resulting in 1.3 million deaths (940,000 deaths among individuals without HIV infection and 320,000 deaths among those with HIV infection). Significantly, out of these fatalities, around 170,000 were caused by multidrug-resistant tuberculosis (MDR-TB), which is a relatively large number as compared to the 450,000 reported cases of MDR-TB [7].

The African Region accounts for around 29% of the global tuberculosis (TB) cases, with the high prevalence of HIV being a significant factor contributing to the spread of the TB epidemic in this region [8]. Moreover, among the estimated 450,000 individuals who had MDR TB in 2012, only 77,000, or less than 20%, received treatment, with the most significant disparity in treatment access observed in African [9]. A study conducted in Kenya successfully performed drug susceptibility testing on 184 isolates to determine their susceptibility to first-line medicines. Drug resistance was detected in 33% of the isolates. The medicine with the highest occurrence of resistance is isoniazid (INH), with a frequency of 23.9%. This is followed by ethambutol (EMB), which has a prevalence of 13.6%. The largest percentage of monoresistance was seen against isoniazid (INH), with a rate of 13.6% (25 cases). 4.4% of the new patients had multidrug resistance (MDR). There was no significant difference in the percentage of resistance seen based on gender, age, or prior therapy [10]. The treatment of MDR-TB is lengthy, and a significant number of the drugs are not well tolerated by patients [11]. For example, according to a study conducted in the Amhara region of Ethiopia the median time to cure from MDR-TB was found to be 21 months [12]. Which means that 50% of the patients cured in 21 months or less. Another study conducted in Southern Ethiopia found the median time to cure from MDR-TB to be 22 months [13].

The World Health Organization (WHO) has recognized Somalia as a country with a high burden of multidrug-resistant tuberculosis (MDR-TB) [2]. In a comprehensive national survey conducted in 2011, the burden of multidrug-resistant tuberculosis (MDR-TB) in Somalia was identified in 5.2% of patients with new cases of TB and a significantly higher 40.8% among those with previously treated TB. These rates of drug resistance represent some of the most elevated ever recorded in Africa and the Middle East [14]. According to a 3-year retrospective study conducted in Galkayo, Puntland, a total of 714 positive GeneXpert-MTB results were identified: with 619 (86.7%) showing susceptibility to drugs (no detection of Rifampin resistance [RR]), and 95 (13.3%) showing detection of RR or defined as MDR-TB. The majority of MDR-TB patients were male (71.6%, 68/95) and were aged between 15 and 24 (31.6%, 30/95) [15].

Despite many studies on the prevalence of multi-drug resistance and treatment outcomes in Somalia [15-17], there remains a lack of research on time to cure and predictive factors among patients with MDR-TB in Somalia, particularly within Puntland State. To the best of our knowledge, this is the first ever research study of its kind that has been carried out and published in Somalia, providing foundational data and insights that have not been previously addressed within the context of Somalia. This study makes a contribution that is both distinctive and answers a gap in the existing body of work. The absence of data on median time to cure and predictive factors for those with MDR-TB in Puntland impedes the implementation of effective control measures and customized interventions. Studying the time needed for MDR-TB patients in Puntland to achieve a state of cure and identifying the influential factors is crucial for establishing practical expectations, enhancing patient care, and boosting treatment results. Accordingly, this study was intended to fill this knowledge gap by performing advanced modeling techniques to estimate the median time to cure and identify predictive factors among patients with MDR-TB in Puntland.

METHODS AND MATERIALS

Study area

Puntland is the first federal state founded in Somalia, established in 1998. It is located in the northeastern part of the country. The state has a population of 4 million, accounting for approximately a third of Somalia's total population. The state also covers around a third of the overall geographical area of the nation. Puntland shares borders with several regions including the northern part of Somalia (Somaliland) to the west, the Gulf of Aden to the north, the Indian Ocean to the southeast, central regions to the south, and Ethiopia to the southwest [18].

Within Puntland, this study was conducted at the MDR-TB Center situated in Galkayo, which is the capital city of the Mudug Region. This center functions as a specialized treatment facility for all individuals with multidrug-resistant tuberculosis (MDR-TB) from Puntland. Patients diagnosed with MDR-TB in Puntland are transferred to this center to receive the necessary specialized care. Galkayo, the third-largest city in Somalia, serves as the capital city of the north-central Mudug region, Somalia.

Study period

The data were collected from June 27, 2024 to July 10, 2024, at the MDR-TB center in Galkayo, Somalia.

Study design

An institutional-based retrospective cohort study was conducted.

Source population

All MDR-TB patients who were admitted to the MDR-TB center in Galkayo from July 2017 to August 2023.

Study population

All selected MDR-TB patients who have been admitted to the MDR-TB center in Galkayo from July 2017 to August 2023.

Inclusion criteria

All MDR-TB patients who had complete medical records, were aged five years or above, and registered at the MDR-TB center between July 2017 and August 2023 were included.

Exclusion criteria

Patients who had incomplete medical records, were under the age of five years, or were not registered at the MDR-TB center between July 2017 and August 2023 were excluded.

Sample size determination

The sample size determination formula introduced by Cochran [19] with the correction factor has been selected for use.

$$n_0 = \frac{z^2 p(1-p)}{d^2} \Rightarrow n = \frac{n_0}{1 + \frac{1}{N}(n_0 - 1)}$$

Where,

n: sample size

N: the total population size

Z: Z score at 95% confidence interval=1.96

P= the proportion of MDR-TB patients who are anticipated to be successfully cured, which is 0.646, based on a study conducted in the Amhara region of Ethiopia [12].

d= marginal error, which is desired to be 0.05.

Accordingly, the sample size, given N = 205 and the aforementioned specifications, is determined to be n = 130.

Sampling technique

To ensure a fair representation of subjects, a simple random sampling technique was employed to select participants from the MDR-TB center in Galkayo. A comprehensive sampling frame, consisting of all MDR-TB patients treated during the study period, was utilized, and participants were selected using a random number generator.

Data collection methods

Using standardized tools, all information was taken from patients' monitoring cards and inquiry form. The checklist was adapted and modified from different related studies and then organized according to the objectives of the study. 2 data collectors who are nurses in their profession and work in facilities other than the study area were recruited for collecting data; one supervisor with a master's degree was assigned to oversee the collection of data.

Study variables

Dependent variable

The dependent variable is the time it takes for a patient to cure from MDR-TB. A patient is considered cured if they complete the treatment and achieve a negative bacteriology result at the end of the treatment. Patients who experienced death, lost to follow-up, treatment failure, or whose time to cure exceeded the intended duration of the study were considered censored in the analysis.

Independent variables:

The independent variables that were considered include both demographic (sex, age, weight, marital status, and employment status) and clinical factors (disease site, and comorbidities).

Data quality control and management

Data quality was ensured through the development of appropriate data abstraction tools. A pre-test was conducted on 5% of the sample size to facilitate any required modifications. Data collectors received two days of training on the data abstraction checklist. Throughout the data collection phase, rigorous supervision and monitoring were implemented on daily basis. Ultimately, completeness and consistency were verified for all collected data during the data cleaning process.

Data processing and analysis

The completeness of the data was carefully verified and coded accordingly. Errors were identified and addressed at the time after a review of the original data using the code numbers. After this, the data were entered using Epi-Data version 4.3 and exported to R Programming version 4.4.0 for analysis. Survival modeling was utilized to estimate the median time to cure from MDR-TB and identify predictive factors. The analysis began with descriptive statistics; survival curves, such as Kaplan-Meier curves, were generated. Additionally, non-parametric methods, such as the log-rank test were used to identify if there were any significant differences between the levels of the categorical variables in their cure rates. To further investigate the relationship between covariates and time to cure, both semi-parametric and parametric approaches were employed. The Cox-proportional hazard regression model assumption was checked using the Schoenfeld residual test. Both bivariate and multivariate analyses were performed. On bivariable analyses, any variable having a p-value less than or equal to 0.20 was selected to be a candidate for multivariable analysis. Variables whose p-value is less than or equal to 0.05 on multivariable analysis were used to determine predictive factors that influence the survival time to cure from MDR-TB. In the modeling approach, different Accelerated Failure Time (AFT) models were compared and the best-fit model was selected using the Akaike Information Criteria (AIC) and

Bayesian Information Criteria (BIC), selecting the model with the smallest AIC and BIC.

RESULTS AND DISCUSSION

Descriptive results

For this study, 109(83.85%) of the patients were cured, while 21(16.15%) were censored during the follow-up period. As the result summarized in **table 1** revealed, 75(57.69%) of the patients were male while 55(42.31%) were female. The cure rate was slightly lower for male patients at (80.00%), compared to (89.09%) for females. However, the proportion of censored cases was higher among male patients at (20.00%), versus (10.91%) for females. Examining marital status, 53(40.77%) of patients were married, 43(33.08%) were single, 18(13.85%) were divorced, and 16(12.30%) were widowed. Married patients demonstrated the highest cure rate at (92.45%), followed by divorced (83.33%), widowed (81.25%), and single (74.42%) individuals. In terms of employment status, 76(58.46%) of patients were employed while 54(41.54%) were unemployed. Employed patients had a cure rate of (84.21%), compared to (83.33%) for those who were unemployed.

Regarding clinical characteristics, 69(53.08%) of patients had extrapulmonary TB, while 61(46.92%) had pulmonary TB. Patients with pulmonary disease achieved a remarkably high cure rate of (90.16%), while those with extrapulmonary TB had a substantially lower rate of (78.46%). The presence of comorbidities also emerged as a significant factor, where 74(56.92%) of patients had no comorbidities, and this group exhibited an exceptionally high cure rate of (90.54%). In contrast, the 56(43.08%) of patients with comorbid conditions had a much lower cure rate of (75.00%).

Finally, the study revealed 85(65.38%) of patients were newly registered at the MDR-TB center and achieved a cure rate of (83.53%) while 45(34.62%) of patients were transferred into the center and demonstrated a slightly higher cure rate of (84.44%).

As shown in **table 2**, the patients in the study were followed up for a median duration of 618 days. The shortest follow-up period recorded was 75 days, while the longest follow-up period was 800 days. On average, the patients had an age of 36 years and a weight of 58.78 kilograms. The youngest patient was 9 years old, while the oldest patient was 80 years old. In terms of body weight, the patients ranged from a minimum of 27.00 kilograms to a maximum of 87.00 kilograms.

Table 1: Summary result for MDR-TB patients at the MDR-TB center in Galkayo, Somalia from 2017 up to 2023

Variable	Labels		Status of patients	
		Total	Cured	Censored
Sex	Male	75(57.69)	60(80.00)	15(20.00)
	Female	55(42.31)	49(89.09)	6(10.91)
Marital status	Married	53(40.77)	49(92.45)	4(7.55)
	Single	43(33.08)	32(74.42)	11(25.58)
	Divorced	18(13.85)	15(83.33)	3(16.67)
	Widowed	16(12.30)	13(81.25)	3(18.75)
Employment	Employed	76(58.46)	64(84.21)	12(15.79)
	Unemployed	54(41.54)	45(83.33)	9(16.67)
Disease site	Pulmonary	61(46.92)	55(90.16)	6(9.84)
	Extra pulmonary	69(53.08)	54(78.26)	15(21.74)
Comorbidities	No	74(56.92)	67(90.54)	7(9.46)
	Yes	56(43.08)	42(75.00)	14(25.00)
Treatment category	New	85(65.38)	71(83.53)	14(16.47)
	Transferred in	45(34.62)	38(84.44)	7(15.56)

Table 2: Descriptive statistics for continuous variables recorded from the MDR-TB patients in Galkayo, Somalia.

Variable	Total	Mean	SD	Min.	Max.	Median
Age (in years)	130	36	15.13	9.00	80.00	33.00
Weight (in kg)	130	58.78	11.99	27.00	87.00	56.70
Time (in days)	130	588	142.99	75.00	800.00	618.00

SD.= Standard deviation; Min.= Minimum; Max.= Maximum

The Kaplan-Mier Estimator

Survival time distributions of time-to-cure of MDR-TB patients were estimated for each group using the KM method. From **Figure 1** below of the KM curve, the horizontal axis shows the time-to-cure from multi-drug resistance tuberculosis, whereas the vertical axis shows the probability of survival p ($T>t$). At the beginning, the survival curve is increasing, at t= 0 S(t) = 1. This demonstrates that the estimated survival function, which measures the probability of surviving beyond a specific time point, progressively grows approximately until the 490-day mark. This shows that during the early stages of treatment, patients have a high chance of being event-free. However, after 490 days, the graph makes a turn, indicating a progressive drop in the survival chance over time. This dropping portion of the curve indicates that the survival probability decreases as time goes by.

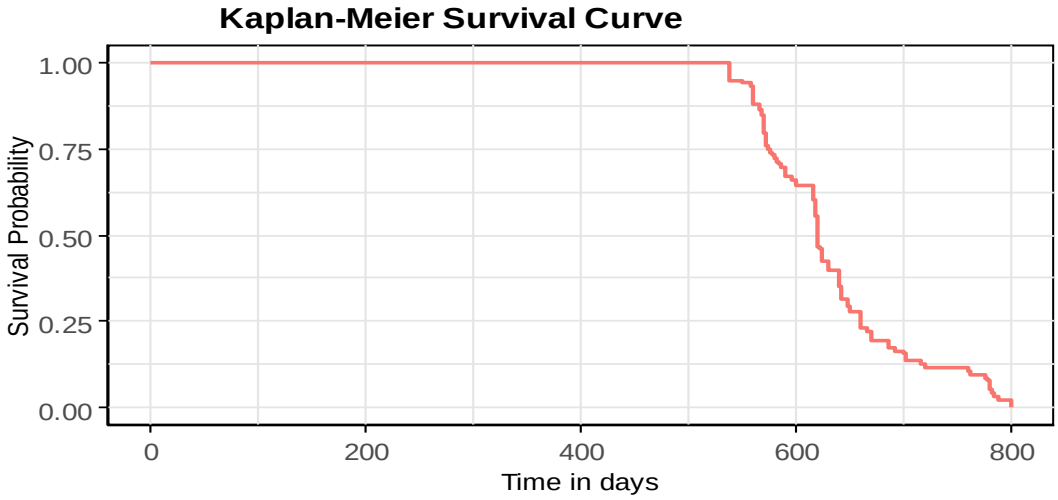

Figure 1: Kaplan Meier curve for survival time from MDR-TB

Comparing the survival time of pulmonary and extrapulmonary MDR-TB patients

As we can visually see from **figure 2**, the median time to cure for patients with extrapulmonary and pulmonary MDR-TB were compared, and the KM plot indicates that the median time to cure for pulmonary and extra pulmonary MDR-TB patients were approximately 590 and 641 respectively.

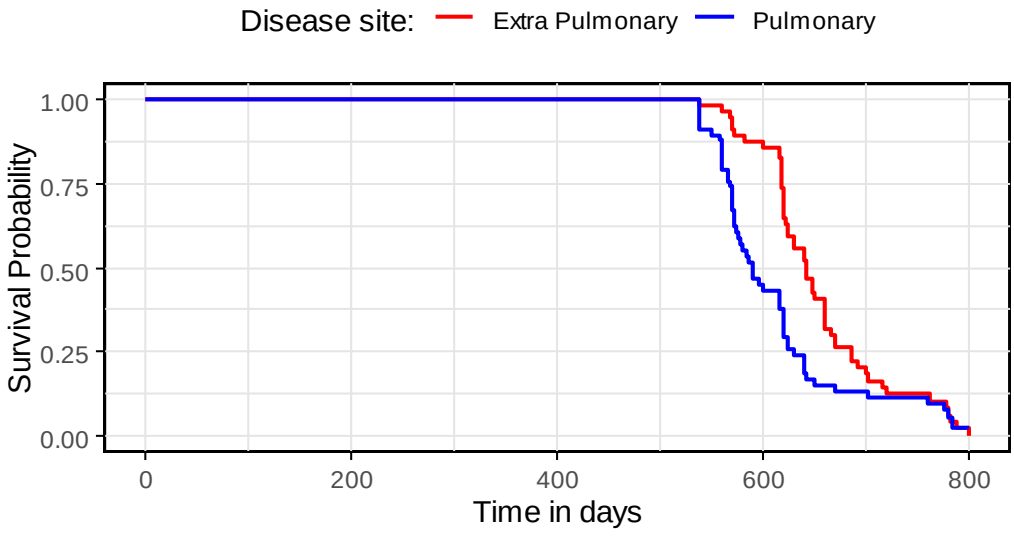

Figure 2: Estimated survival time of MDR-TB patients for the disease site category

Log-rank test for survival curves of MDR-TB patients

The log-rank test was employed to examine whether there is a significant difference in the time to cure across different levels of the assessed categories. There is no difference between the probabilities of an event occurring between the levels of categories at any time point was the null hypothesis that has been tested. The p-values obtained from the log-rank test are provided in **table 3**. According to the result, sex, employment, disease site, and comorbidities exhibited statistically significant differences in the time to cure from MDR-TB. The p-values for these variables were less than the predetermined alpha level of 0.05, indicating that there are significant disparities in time to cure among different levels of these categories. However, marital status, and treatment category did not demonstrate statistically significant differences in the time to cure from MDR-TB. The p-values for these variables were greater than the alpha level of 0.05, suggesting that there is no evidence of a significant variation in the probabilities of time to cure based on the levels of marital status and treatment category.

Table 3: The log lank test for the categorical variables of MDR-TB patients

Variables	DF	Chi-square	p-value
Sex	1	10.1	0.002
Marital status	3	4.2	0.20
Employment	1	8.2	0.004
Disease site	1	8.7	0.003
Comorbidities	1	20.9	0.000
Treatment category	1	0.7	0.40

DF= Degree of freedom

Univariate Cox regression model for MDR-TB patients

As shown in **table 4**, univariate Cox regression analysis was conducted to examine the effect of different covariates on the time it takes for patients with MDR-TB to achieve a cure and determine the variables that should be included in the multivariate Cox regression analysis. The findings of the univariate analysis indicated that sex, marital status, employment, comorbidities, and disease site were statistically significant for the univariate Cox regression model at a significance level of 20%. On the other hand, weight, and treatment category did not demonstrate statistical significance at a 20% level. Therefore, all predictive factors that demonstrated statistically significant were included in the multivariate Cox regression analysis.

Table 4: Univariate Cox regression model for MDR-TB patients

Variable	Category	Haz. Ratio	Std. Err	P-value	95%Conf.Inter.	
Sex	Male ®					
	Female	1.826	0.3567	0.0021	1.245	2.678
Age		0.955	0.0073	0.000	0.9407	0.9695
Weight		0.991	0.0090	0.31	0.9733	1.009
Disease site	Pulmonary ®					
	Extra pulmonary	0.5691	0.1108	0.0038	0.3885	0.8336
Treatment category	New ®					
	Transferred in	0.8338	0.1722	0.379	0.5563	1.25
Marital status	Single ®					
	Married	0.9006	0.2068	0.648	0.3336	1.156
	Divorced	0.6209	0.1968	0.133	0.3336	1.156
	Widowed	0.5854	0.1959	0.110	0.3038	1.128
Comorbidities	No ®					
	Yes	0.388	0.0826	0.000	0.2557	0.5887
Employment	Employed ®					
	Unemployed	0.5527	0.1155	0.0046	0.367	0.8326

Haz. Ratio = Hazard Ratio; Std. Err. = Standard Error; Conf. Interval = Confidence interval; ® = Reference

Multivariate Cox regression model for MDR-TB patients

The multivariate Cox regression analysis of time to cure for MDR-TB patients was performed by excluding the insignificant variables in the univariate Cox regression model. The backward elimination method was used to select the final significant covariates. According to the result in **table 5**, sex, age, disease site, and comorbidities were statistically significant for the multivariate Cox regression model at a significance level of 5%. The p-values for these variables were less than the predetermined alpha level of 0.05, indicating that they are statistically significant.

Table 5: Multivariate Cox regression model for MDR-TB patients

Variable	Category	Haz. Ratio	Std. Err	P-value	95%Conf.Inter.	
Sex	Male ®					
	Female	1.686	0.3373	0.00897	1.1396	2.4957
Age		0.960	0.0074	0.000	0.9453	0.9745
Disease site	Pulmonary ®					
	Extra pulmonary	0.649	0.1291	0.0297	0.4392	0.9583
Comorbidities	No ®					
	Yes	0.625	0.1369	0.03180	0.4066	0.9599

Haz. Ratio= Hazard Ratio; Std. Err. = Standard Error; Conf. Interval = Confidence interval; ® = Reference

Checking the proportional hazard assumption using Schoenfeld residual

The Schoenfeld residual was used to determine whether the proportional hazards (PH) assumption was fulfilled or not. A variable that has an insignificance p-value is said to have fulfilled the proportionality assumption. As **table 6** demonstrates, most variables have a p-value greater than the predetermined significance value, which is 0.05, which means they did not demonstrate any violation regarding the proportionality assumption. However, sex, comorbidities, and disease site have shown a small p-value, which means these three variables have violated the assumption. To test those two controversial findings, the global test result was used and it indicates that the p-value is significant (p-value = 0.00143). This implies that there is enough evidence to conclude that the proportional hazard assumption is violated.

Table 6: Test of proportional hazard assumption

Covariate	Chi-Square	DF	p-value
Sex	4.086	1	0.04324
Age	0.247	1	0.61901
Marital status	2.011	3	0.57021
Weight	0.468	1	0.49413
Employment	0.166	1	0.68407
Disease site	13.201	1	0.00028
Comorbidities	5.453	1	0.01953
Treatment category	2.819	1	0.09315
Global test	**28.633**	**10**	**0.00143**

DF = Degree of freedom

Accelerated Failure Time Models

As the proportional hazards assumption was violated, accelerated failure time (AFT) models were employed. When the assumption of proportional hazards is not met, it is advisable to use a parametric AFT model instead of the Cox model. The AFT models assume a particular distribution for the survival time and can model non-proportional hazards. Therefore, using the AFT model can provide more precise estimates of the effect of covariates on survival time in situations where the assumption of proportional hazards is not satisfied. As such, to select the most appropriate model for modeling time to cure for MDR-TB patients, several Accelerated Failure Time (AFT) models, including the Weibull, exponential, lognormal, and log-logistic distributions were compared. Each model was evaluated using the two

common model selection criteria, the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), the model with the smallest AIC and BIC values was then selected among the other models. From **table 7**, the value of AIC and BIC for all AFT models are displayed, model with the smallest AIC and BIC shows the best fit. Accordingly, the log logistics Accelerated Failure Time demonstrated the smallest AIC value and BIC value, indicating it is the best fit for analyzing the MDR-TB patient's data.

Table 7: Comparison of Accelerated Failure Time Parametric Models

	Model name			
	Exponential	Weibull	Lognormal	Log-logistic
AIC	1665.732	1208.815	1179.958	**1174.503**
BIC	1697.275	1243.226	1214.369	**1208.914**

AIC: Akaike Information Criterion BIC: Bayesian Information Criterion

Log-logistic Accelerated Failure Time model

The predictor factors assessed in the multivariate Cox proportional hazards model were included in the final Log-logistic accelerated failure time (AFT) model to examine their effect on time to cure from MDR-TB. The Log-logistic AFT distribution was found to be the best model for assessing the time to cure for patients with multidrug-resistant tuberculosis. The decision was based on the Log-logistic AFT model having the lowest Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values.

In **Table 8**, the result of the multivariate log-logistic AFT model is presented. The accelerated factor greater than one (ϕ>1) indicates a prolonged time to cure while the accelerated factor (ϕ<1) indicates a shortened time to cure. Sex, age, disease site, and comorbidities have a p-value less than the predetermined level of significance, which is 0.05. This indicates that these variables are the predictive factors that significantly affect the time it takes for MDR-TB patients to achieve a state of cure. Patients with comorbid conditions, and those who were affected by an extrapulmonary MDR-TB have an accelerator factor greater than one, which means that they have a prolonged time to cure from MDR-TB as compared with their reference group. However, female patients demonstrated an accelerator factor less than one, which indicates that they have a shortened time to cure from MDR-TB as compared to males. The estimated accelerator factor of patients with comorbidities is 1.05(ϕ:1.05; 95%CI:1.02—1.08), which indicates that patients with comorbid conditions prolonged the time to cure by a factor of 1.05 as compared with those without comorbid conditions when other predictors are considered to be constant. Female patients have an accelerator factor of 0.969(ϕ:0.969; 95%CI: 0.943—0.997), which means female patients shortened time to cure from MDR-TB by a factor of 0.969 when compared to male patients. The accelerator factor for age is 1.003 (ϕ:1.003; 95%CI: 1.002—1.004), which demonstrates that older age is associated with a slightly prolonged time to cure from MDR-TB, holding all other variables constant.

Table 8: Multivariate Log-logistic Accelerated Failure Time model

Variable	Category	Coefficient	ϕ	Std. Err	P-value	95% Conf. Interval
Sex	Male ®					
	Female	-0.0310	0.9694	0.0138	0.0289	0.9428, 0.9968
Age		0.0029	1.0029	0.0005	0.000	1.0018, 1.0040
Disease site	Pulmonary ®					
	Extra pulmonary	0.0472	1.0483	0.0150	0.0010	1.0193, 1.0782
Comorbidities	No ®					
	Yes	0.0471	1.0482	0.0156	0.0015	1.0182, 1.0792
Intercept		6.3059	547.7714	11.7754	0.000	525.17, 571.34

® = Reference; ϕ= Accelerated Factor; Std. Err= Standard Error; Conf. Interval= Confidence Interval

DISCUSSION

The study aimed to estimate the median time to cure for MDR-TB patients treated at the MDR-TB center in Galkayo, Puntland-Somalia under a follow-up of a 6-year-period, and identify predictive factors that influence the time it takes for patients with MDR-TB to achieve a state of cure.

Initially, the median time to cure for patients with MDR-TB was estimated, both univariable and multivariable analyses using the Cox-PH model were performed, and the assumption of proportionality in the Cox-PH model was then tested. However, the proportionality assumption was violated. To address this, the AFT models with common baseline distribution including Exponential, Weibull, Log-logistic, and Log-normal were

considered and compared their AIC, BIC, and the standard error of each variable among those AFT models.

Based on the evaluation of the AFT models, the log-logistic AFT model was found to be the best fit for the time to cure of MDR-TB patient data than others as it had the smallest AIC, BIC. The multivariate analysis using the log-logistic analysis was performed, showing age, disease site, comorbidities, sex as the predictive factors that significantly affect the time to cure for patients with MDR-TB.

The findings of this study showed that 69(53.08%) of patients had extrapulmonary TB, while 61(46.92%) had pulmonary TB. Patients with pulmonary achieved a cure rate of (90.16%), while those with extrapulmonary TB had a substantially lower rate of (78.26%). The presence of comorbidities also emerged as a significant factor, where 74(56.92%) of patients had no comorbidities, and this group exhibited an exceptionally high cure rate of (90.54%). In contrast, the 56(43.08%) of patients with comorbid conditions had a much lower cure rate of (75.00%).

The median time to cure for patients with MDR-TB was found to be 619 days which is approximately 20 months. Which means that, on average, 50% of the patients cured within 20 months, while other half took longer than 20 months. This shows that the recovery time is within the recommended treatment interval of 18 to 21 months or longer [20]. The study findings regarding treatment outcomes revealed that 109(83.85%) of the patients were cured, while 21(16.15%) were censored. This finding is close to a study conducted in the Amhara region of Ethiopia [12, 13]. This slight difference may be due to different MDR-TB distributions, different study duration, and the sample size.

The findings of this study revealed that male MDR-TB patients were found to have less likelihood of experiencing the event of interest, which is cured in this case. Several other studies have similarly shown that male MDR-TB patients tend to have longer recovery time [21] and [22]. The finding that males were a significant predictor of prolonged cure times for MDR-TB patients could relate to higher rates of alcohol and drug addiction among men, as well as increased treatment interruptions. However, further research is needed to determine the underlying biological, behavioral, and social factors that contribute to this sex discrepancy.

The study also showed that MDR-TB patients with comorbid conditions have a prolonged time to cure as compared to those without comorbidities. This result is in line with the previous findings in Ethiopia [23, 24], and India [21]. Patients with comorbid conditions may often have challenges sustaining prolonged MDR-TB treatment regimens. The increased physiological stress of dealing with several simultaneous health concerns may hinder the body's ability to properly tackle drug-resistant TB infection.

The results presented in this study demonstrated that the extrapulmonary disease site has a significant effect on the time to cure from MDR-TB with an accelerator factor of 1.05(ϕ:1.05; 95%CI:1.02—1.08). This implies that extrapulmonary patients have a longer time to cure as compared to pulmonary MDR-TB patients. This finding is consistent with the study conducted by Parmar et al study [21]. The findings of this study also revealed that as age increases by one year, the expected time to cure from MDR-TB increases by a factor of 1.003. While this effect is statistically significant, it is relatively small. This indicates that older patients are expected to take slightly longer to cure from MDR-TB compared to younger patients. This result aligns with a study conducted by [25], suggesting that age may play a role in recovery times.

LIMITATIONS OF THE STUDY

Due to the reliance on retrospective data, some potentially relevant variables affecting the time to cure from MDR-TB, such as smoking status, and treatment adherence, were not included in this study as the clinicians at the MDR-TB health center in Galkayo do not record these variables. The absence of these factors posed a significant challenge, as they may have influenced the predictive models developed in this study.

CONCLUSION

The median time to cure for patients with MDR-TB was estimated to be 619 days (approximately 20 months). The log-logistic AFT model was found to be the best fit and the result of the multivariate log-logistic failure time model indicted that sex, age, comorbidities and disease site were predictive factors for patients with MDR-TB in Puntland, Somalia.

The study also showed that patients with extrapulmonary MDR-TB and those with comorbid conditions had a prolonged time to cure compared to those with their reference categories, while female patients had a shortened time to cure as compared to male patients.

Recommendations

Based on the findings of this study, the researcher provides the recommendations below: -

- The Galkayo MDR-TB center should implement intensive monitoring as well as tailored interventions for MDR-TB patients who face longer treatment timelines to achieve a cure. This includes older patients, male patients, those with comorbid conditions, and extrapulmonary MDR-TB patients. Meanwhile, the Puntland health authorities ought to provide the necessary funding, equipment, and staffing to enable the Galkayo MDR-TB center to strengthen this effort.
- Researchers should conduct further studies to address factors contributing to longer cure times from MDR-TB for males, extrapulmonary MDR-TB patients, and those with comorbid conditions.

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REFERENCES

1. WHO G. Global tuberculosis report 2020. Glob Tuberc Rep. 2020;2020. https://www.who.int/teams/global-tuberculosis-programme/tb-reports

2. WHO. WHO consolidated guidelines on tuberculosis 2023.

3. Chakaya J, Khan M, Ntoumi F, Aklillu E, Fatima R, Mwaba P, et al. Global Tuberculosis Report 2020-Reflections on the Global TB burden, treatment and prevention efforts. International journal of infectious diseases. 2021;113:S7-S12. https://doi.org/10.1016/j.ijid.2021.02.107 PMid:33716195 PMCid:PMC8433257

4. Du L, Zhang Y, Lv X, Duan Y, Shi X, Ji H, et al. Prevalence of multidrug-resistant tuberculosis in Dalian, China: a Retrospective Study. Infection and Drug Resistance. 2021:1037-47. https://doi.org/10.2147/IDR.S294611 PMid:33758518 PMCid:PMC7981151

5. WHO. Global Tuberculosis Report 2019. 2019. https://www.who.int/teams/global-tuberculosis-programme/tb-reports

6. Oladimeji O, Ushie BA, Udoh EE, Oladimeji KE, Ige OM, Obasanya O, et al. Psychosocial wellbeing of patients with multidrug resistant tuberculosis voluntarily confined to long-term hospitalisation in Nigeria. BMJ global health. 2016;1(3):e000006. https://doi.org/10.1136/bmjgh-2015-000006 PMid:28588950 PMCid:PMC5321341

7. WHO. Global tuberculosis report 2013. World Health Organization; 2013. Report No.: 9241564652. https://www.who.int/teams/global-tuberculosis-programme/tb-reports

8. WHO. Global Tuberculosis Report. 2017. https://www.who.int/teams/global-tuberculosis-programme/tb-reports

9. Organization WH. Global tuberculosis report 2013. 2013. https://www.who.int/teams/global-tuberculosis-programme/tb-reports

10. Kerubo G, Amukoye E, Niemann S, Kariuki S. Drug susceptibility profiles of pulmonary Mycobacterium tuberculosis isolates from patients in informal urban settlements in Nairobi, Kenya. BMC infectious diseases. 2016;16:1-7. https://doi.org/10.1186/s12879-016-1920-5 PMid:27756241 PMCid:PMC5070164

11. Wu S, Zhang Y, Sun F, Chen M, Zhou L, Wang N, et al. Adverse events associated with the treatment of multidrug-resistant tuberculosis: a systematic review and meta-analysis. American journal of therapeutics. 2016;23(2):e521-e30. https://doi.org/10.1097/01.mjt.0000433951.09030.5a PMid:24284652

12. Limenih YA, Workie DL. Survival analysis of time to cure on multi-drug resistance tuberculosis patients in Amhara region, Ethiopia. BMC public health. 2019;19:1-11. https://doi.org/10.1186/s12889-019-6500-3 PMid:30732601 PMCid:PMC6367739

13. Abdo SS, Wanore DS, Teni DA, Ejamo LA. Modelling Time to Recovery from Multidrug Resistant Tuberculosis in Southern Ethiopia. Journal of Pharmaceutical Research International. 2024;36(6):88-103. https://doi.org/10.9734/jpri/2024/v36i67525

14. Sindani I, Fitzpatrick C, Falzon D, Suleiman B, Arube P, Adam I, et al. Multidrug-resistant tuberculosis, Somalia, 2010-2011. Emerging infectious diseases. 2013;19(3):478. https://doi.org/10.3201/eid1903.121287 PMCid:PMC3647667

15. Mohamed MA, Ali OA, Osman AM, Abatcha MG, Ahmed AA, Ali AM, et al. Assessment of drug-susceptible and multidrug-resistant tuberculosis (MDR-TB) in the Central Region of Somalia: A 3-year retrospective study. PLOS Global Public Health. 2023;3(9):e0002319. https://doi.org/10.1371/journal.pgph.0002319 PMid:37676848 PMCid:PMC10484424

16. Dirie AMH, Çolakoğlu S, Abdulle OM, Abdi BM, Osman MA, Shire AM, et al. Prevalence of multidrug-resistant TB among smear-positive pulmonary TB patients in Banadir, Somalia: a multicenter study. Infection and Drug Resistance. 2022:7241-8. https://doi.org/10.2147/IDR.S386497 PMCid:PMC9749408

17. Ali MM, Weldegebreal F, Kabew G, Urgesa K. Rifampicin resistant Mycobacterium tuberculosis and associated factors among presumptive pulmonary tuberculosis patients in Mogadishu, Somalia. SAGE Open Medicine. 2023;11:20503121221148603. https://doi.org/10.1177/20503121221148603 PMid:36643204 PMCid:PMC9834785

18. Puntlad Facts and Figures. Puntland Facts and Figures; Ministry of Planning and International Cooperation; Department of Statistics. 2017. https://bareedo.org/wp-content/uploads/2019/10/Puntland-Facts-and-Figures-2017-Year-book-2018-1.pdf

19. Cochran WG. Sampling techniques: john wiley & sons; 1977.

20. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. European Respiratory Journal. 2017;49(3). https://doi.org/10.1183/13993003.02308-2016 PMid:28331043 PMCid:PMC5399349

21. Parmar MM, Sachdeva KS, Dewan PK, Rade K, Nair SA, Pant R, et al. Unacceptable treatment outcomes and associated factors among India's initial cohorts of multidrug-resistant tuberculosis (MDR-TB) patients under the revised national TB control programme (2007-2011): evidence leading to policy enhancement. PloS one. 2018;13(4):e0193903. https://doi.org/10.1371/journal.pone.0193903 PMid:29641576 PMCid:PMC5894982

22. Brust JC, Gandhi NR, Carrara H, Osburn G, Padayatchi N. High treatment failure and default rates for patients with multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa, 2000-2003. The international journal of tuberculosis and lung disease. 2010;14(4):413-9.

23. Girum T, Tariku Y, Dessu S. Survival status and treatment outcome of multidrug resistant tuberculosis (MDR-TB) among patients treated in treatment initiation centers (TIC) in South Ethiopia: a retrospective cohort study. Annals of medical and health sciences research. 2017;7(5).

24. Mitku AA, Dessie ZG, Muluneh EK, Workie DL. Prevalence and associated factors of TB/HIV co-infection among HIV Infected patients in Amhara region, Ethiopia. African health sciences. 2016;16(2):588-95.

25. Hawulet M. Survival Analysis of Time to Recovery And Associated Factors of Tuberculosis Patients in Dessie Comprehensive Specialised Hospital, South Wollo, Ethiopia 2021.