SPATIAL FRAILTY MODELLING FOR MULTIDRUG-RESISTANT TUBERCULOSIS MORTALITY IN NAMIBIA

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Abstract

Multidrug-resistant Tuberculosis (MDR-TB) is fast becoming a major public health concern, with 80% of the reported global MDR-TB deaths occurring in high burden countries such as Congo, Kenya, Tanzania, South Africa, Ethiopia, and Namibia where drug susceptibility testing is not routinely performed, making the reported prevalence of MDR-TB in the country an underestimate of the true burden. Thus, the main aim of this study was to examine the spatial variation of mortality among MDR-TB patients in Namibia by estimating the survival time of mortality among the patients under treatment for MDR-TB, in addition to identifying the risk factors of MDR-TB mortality. To accomplish this, this study adopted a retrospective cohort study design using the 2014-2017 MDR-TB records from the Ministry of Health and Social Services, with Kaplan Meier used to estimate the survival functions and two sets of regression models (with and without frailty) fitted to determine the best fit model to use in modelling the MDR-TB mortality and identify its associated risk factors. Spatial mapping was used to map the spatial variation of the MDR-TB mortality among the patients. Results from this study showed that out of the 1432 MDR-TB patients in 2014-2017, 224 deaths were recorded. This study revealed more MDR-TB deaths among female patients, as well as high MDR-TB deaths among 35-54 years old HIV positive patients with Pulmonary TB in the Khomas region, who have had more than three previous TB treatments. The Gompertz PH regression model (AIC=1452.833, BIC=1589.625) was identified as the best fit model to use, while the Gompertz PH regression model with Gamma (shared) frailty (AIC=1451.836, BIC=1604.411) was identified as the best fit model to use for the frailty modelling of the MDR-TB mortality. Furthermore, MDR-TB patient's characteristics such as sex, age category, HIV status, region, number of previous TB treatments and treatment type had a significant effect on their MDR-TB mortality. MDR-TB mortality was less likely to occur for patients who were males (HR=0.684, p=0.018, 95% CI: 0.50-0.937) and new to treatment (HR=0.646, p=0.042, 95% CI: 0.424-0.984) compared to patients who came in after defaulting

on their treatment. Moreover, MDR-TB mortality was more likely to occur for patients who were aged 55 years and above (HR=3.586, p<0.001, 95% CI: 2.176-5.911), HIV positive (HR=2.066, p<0.001, 95% CI: 1.387-3.078), and from the Khomas (HR=3.681, p=0.001, 95% CI: 1.723-7.866), Kunene (HR=4.446, p=0.022, 95% CI: 1.242-15.913), Omusati (HR=2.7, p=0.022, 95% CI: 1.154-6.311), Oshana (HR=2.506, p=0.021, 95% CI: 1.145-5.481) and Otjozondjupa (HR=2.232, p=0.066, 95% CI: 0.948-5.254) regions compared to patients from the Erongo region. It is therefore recommended that the Namibian government and policy makers consider conducting outreach sessions to increase awareness on MDR-TB including early detection and screening programs, and patient's adherence, most especially among female patients aged 55 years and above, with HIV and those living in the Khomas, Kunene, Omusati, Oshana and Otjozondjupa regions.

Keywords: Multidrug-resistant Tuberculosis; Cox Proportional Hazard; Survival function; Frailty modelling; Namibia

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List of Abbreviations and/or Acronyms

AIDS	Acquired Immuno-Deficiency Syndrome
AIC	Akaike Information Criterion
AFT	Accelerated Failure Time
ART	Antiretroviral Therapy
BIC	Bayesian Information Criterion
CAR	Conditional Autoregressive
CD4	Cluster of Differentiation 4
CI	Confidence Interval
CPH	Cox Proportional Hazard
CUMSPH	Columbia University Mailman School of Public Health
DOTS	Directly Observed Treatment Strategy
DST	Drug Susceptibility Testing
DS-TB	Drug Susceptibility-Tuberculosis
ECDPC	European Centre for Disease Prevention and Control
eTB	electronic Tuberculosis
HBC	High Burden Country
HIV	Human Immunodeficiency Syndrome
HR	Hazard Ratio
KM	Kaplan Meier
MDR-TB	Multi Drug Resistant- Tuberculosis
MCMC	Monte Carlo Markov Chain
MoHSS	Ministry of Health and Social Services
NDP	National Development Plan
SPSS	Statistical Packages for Social Science

PH	Proportional Hazard
PLHIV	People Living with Human Immunodeficiency Syndrome
RR	Rifampicin-Resistant
TB	Tuberculosis
UNAM	University of Namibia
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant-Tuberculosis

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Dedication

This study is wholeheartedly dedicated to my son Dunbar Thandolwethu Mushwena.

Declarations

I, Paulina Mweshitya Shikongo, hereby declare that this study is my own work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

Paulina M Shikongo	PMShikongo	April 2024
Name of Student	Signature	Date

Chapter 1: Introduction

1.1 Background of the Study

Tuberculosis (TB) is a chronic respiratory infectious disease caused by the pathogen Mycobacterium tuberculosis and spreads through air droplets by sneezing and coughing of an infected person (Dube, 2015). It is treatable using drugs such as Isoniazid and Rifampin, two of the most potent TB drugs (World Health Organization [WHO], 2018). However, the bacteria that cause TB can develop resistance to the antimicrobial drugs used to cure the disease. Such TB bacteria is referred to as the Multidrug-Resistant TB (MDR-TB) and is associated with a higher fatality rate, especially among Human Immunodeficiency Virus (HIV) infected patients (WHO, 2019).

MDR-TB is much more difficult and becoming costly to treat than a drug susceptible TB. It has become a major public health problem and an obstacle to global TB control (Matteelli, 2018; WHO, 2013). Ou et al. (2021) reported that globally MDR-TB occurred in an estimated 460,000 cases and resulted in 230,000 deaths in 2017 and accounted for 3.6% of all new cases and 17% of treated cases. Furthermore, the highest burden of MDR-TB has been reported to be in China, India, Russia, and South Africa, and these countries have more than 60% of all cases combined worldwide. China has the second highest case burden of MDR-TB worldwide, with an estimated 58 000 MDR-TB/RR (Rifampicin-Resistant) -TB incidents in 2017, accounting for approximately 10% of the global burden (WHO, 2018). A study by Li et al. (2020) discovered that, MDR-TB, especially untreated MDR-TB, would rise rapidly under China's current MDR-TB control strategies and as such interventions designed to promote effective detection and treatment of MDR-TB are imperative in the fights against MDR-TB epidemics.

According to a report done by WHO (2021) nine of the world's 30 countries with the highest burden of MDR-TB are within the WHO European regions, namely, Azerbaijan, Belarus,

Kazakhstan, Kyrgyzstan, the Republic of Moldova, the Russian Federation, Tajikistan, Ukraine and Uzbekistan. These regions have the highest number of new and retreated cases of MDR-TB in the European region, with an estimated 74 000 cases in 2015. Moreover, in 2015, MDR-TB cases account for 16% of new TB cases (about 1 in 6) and 48% of previously treated TB cases (nearly 1 in 2). Of the estimated 74 000 cases of MDR-TB in 2015, only 60% were diagnosed (due to limited access to rapid and quality diagnosis) and treated. Over 2000 cases of Extensively Drug Resistant-Tuberculosis (XDR-TB) in the European region were detected in MDR-TB patients in 2015, meaning that 1 in 4 MDR-TB patients had XDR-TB, with most XDR-TB cases occurring in countries with a high burden of MDR-TB (WHO, 2021). In Africa, the true burden of Drug resistant TB is poorly described with only 51% of countries having a formal survey completed on it. In the absence of such, modelled estimates were used and a total of 92 629 drug resistant tuberculosis cases were estimated with 42% of these occurring in Nigeria and South Africa (Ismail et al., 2018).

Drug resistant TB is one of the greatest threats to ending TB in Namibia (WHO, 2019**).** According to the Ministry of Health and Social Services [MoHSS] (2016), the number of reported cases of MDR-TB in Namibia increased from 137 in 2014 to 190 in 2015 and to 387 in 2016. This was partly due to the scaling up of laboratory testing for TB drug resistance during the anti-TB drug resistance survey organized by MoHSS' National TB and Leprosy Programme, in 2015. Furthermore, looking at the trend in reported cases of drug resistance in Namibia from 2010 to 2020 inclusive of MDR-TB cases, it was observed that the number of people developing DR-TB and those on treatment has been decreasing from 2017 whilst the number of people with DR-TB who were successfully treated started increasing from 2014 (MoHSS, 2016). Similarly, looking at the reported cases of MDR-TB from 2007 to 2015, it was revealed that there was an increase in the number of MDR-TB cases between 2007 and 2009 (from 116 to 201) and then in 2014 to 2015 (from 137 to 190), while across the age and sex distribution for 2015, more males between

the ages of 25 to 44 years were resistant to the anti-TB drugs than their female counterparts (MoHSS, 2016). MoHSS (2016) further states that the treatment outcome in Namibia for MDR-TB patients in 2015 showed that 35% of the MDR-TB patients were cured, 29% had completed their treatment, 21% died, and 10% were lost to follow up, while 5% were still on treatment, failed or transferred to other facilities.

Throughout the centuries, the survival analysis technique has been popularly used in the biomedical research fields and solely linked to the investigation of mortality rates. With its development dated far back as to the 17th century (Liu, 2012). In the last few decades, the applications of survival analysis in biomedical researches have been widely used in evidence-based medicine to examine the time-to-event series as well as to predict survival/death events, with the time-to-event series used in illustrating the occurrence time to any dichotomous event (Flynn, 2012). As the year progresses and with more innovative statistical methods being developed and used in the health sciences fields, so were the modifications of the survival analysis technique with the implementation of these innovative statistical methods within its framework. In 1972, David Cox developed a proportional hazard model, which derives robust, consistent, and efficient estimates of covariate effects using the proportional hazards assumption with the baseline hazard rate unspecified (Liu, 2012; Deo et al., 2021).

To date, the Cox Proportional Hazard (CPH) model is the most widely used semi-parametric survival data modelling in the health sciences and medical research fields for investigating the association between the survival time of patients and one or more predictor variables (Andersen, 2022) while taking into account the effect of censored observations. However, now and again, the hazard for all the predictor variables can be proportional and there can be more than a single event types under consideration with each individual understudy undergoing exactly one type of event as can be the case for TB patient treatment outcomes (dead, stopped, transferred out, defaulted and interrupted). As a result, more advanced model modification of the CPH model such as the

stratified CPH and extended CPH models will be applicable to use for handling the non-proportional hazard while techniques such as the competing risk survival models can be applied to situations with more than one single event types under consideration. Qi (2009) suggested techniques such as the Accelerated Failure Time (AFT) model, Weibull and Gompertz models, in addition to the general CPH model, for the analysis of survival time data. Although not commonly used for the analysis of clinical trial data and medicinal researches, the AFT model measures the direct effect of the predictor variables on the survival time instead of the hazard as done in the general CPH model framework.

One of the CPH model assumptions is that the survival times be independent. However, there are situations when these times are not independent due to each individual understudy having some common features or some study characteristics that are shared by more than one observed event time. Thus, the frailty and shared frailty survival models are applicable to these situations (Qi, 2009). Frailty models are the survival data analog to regression models, which account for heterogeneity and random effects. A frailty is a latent multiplicative effect on the hazard function and is assumed to have unit mean and variance θ, which is estimated along with the other model parameters, while a frailty model is a heterogeneity model where the frailties are assumed to be individual- or spell-specific (Hevi et al., 2022). Similarly, Chen et al. (2014) discussed that a frailty is an unobservable random effect. For multivariate time-to-event data, it represents the unobserved covariates shared by correlated event times. On the other hand, a shared frailty model is a random effects model where the frailties are common (or shared) among groups of individuals or spells and are randomly distributed across groups (Hevi et al., 2022). The shared frailty model assumes that the common random effect (frailty) has a multiplicative effect on the individual hazard. Conditional on the frailty, the event times are independent and thus have hazards that are similar to the univariate model (Ballan & Putter, 2020).

1.2 Statement of the Problem

Despite TB being a long-standing and widespread disease, the global burden attributable to TB continues to be a major public health concern. In 2013 alone the estimated new cases of TB worldwide were 9.0 million of which 1.5 million resulted in deaths (Noppert, 2015). According to WHO (2019), 80% of these deaths occurred in 30 High-Burden Countries (HBCs) such as Congo, Kenya, Tanzania, South Africa and Ethiopia and Namibia is not excluded from such. WHO (2018) estimating that about 30% of patients with TB in Namibia go undiagnosed, untreated, or unreported. Although, MDR-TB treatment requires a course of second line drugs for at least 9 months up to 20 months, supported by counselling and monitoring for adverse events, Drug Susceptibility Testing (DST) is not routinely performed in Namibia, making the reported prevalence of MDR-TB in the country an underestimate of the true burden. Moreover, investigations into the relative contributions of specific risk factors of the development of MDR-TB and its mortality in Namibia are very few to non-existent. Further studies are therefore required to ascertain and understand these factors associated with the development and mortality of MDR-TB. Thus, this study aimed at performing an epidemiologic investigation of MDR-TB mortality in Namibia, by fitting a spatial frailty model to capture spatial variation in different geographical regions and possible identification of associated risk factors, which are therefore, required to understand the factors associated with MDR-TB mortality.

1.3 Objectives of the Study

The main objective of this study was to fit a spatial frailty model to examine the spatial variation of mortality among MDR-TB patients treated at different hospitals in various regions in Namibia. This was accomplished by the following specific objectives:

(a) Estimating the survival of patients under treatment for MDR-TB in Namibia using the Kaplan-Meier (KM) method.

(b) Fitting a CPH model to investigate the association between the survival time of the patients and covariates.

(c) Identifying the risk factors of mortality among MDR-TB patients under treatment in the country.

(d) Fitting spatial maps to investigate the spatial pattern of deaths among MDR-TB patients in Namibia.

1.4 Significance of the study

Although several studies reported MDR-TB mortality as well as the spatial variation of mortality among MDR-TB patients in many countries around Africa and globally, there are very few to non-existent epidemiologic reports from survival analysis perspective in Namibia. Hence, it is anticipated that findings from this study will contribute to the body of knowledge that informs the Namibian government, policy makers, TB program planners, decision makers and project implementers by providing the risk factors associated with deaths among MDR-TB patients treated across different hospitals in Namibia, as well as the spatial variation of mortality among the patients. In addition, this study will provide useful insights for evidence-based health policies and programs on TB and MDR-TB in the country, thereby further aiding in the effective allocation and utilization of public health programs and resources in the prevention of high MDR-TB mortality rates within the country. Moreover, the results from this study can be used to further guide other researchers to be knowledgeable about the risk factors associated with MDR-TB mortality in Namibia, while adding value to the body of scientific knowledge on MDR-TB mortality in Namibia and globally.

1.5 Limitation of the study

The study used secondary data obtained from the MoHSS' electronic Tuberculosis (eTB) database for the period of 2014 to 2017 and was limited to available variables within the dataset.

1.6 Delimitation of the study

The study focused on patients who were listed as MDR-TB patients in state health districts from 2014 - 2017. However, this may not necessarily reflect the true and current MDR TB statistics for 2022 in Namibia.

1.7 Organization of the thesis

Chapter 1 presented the background on MDR-TB, survival analysis, as well as the statement of the research problem, research objectives of the study, significance of the study, limitations of the study, and delimitations of the study. Chapter 2 begins with a short review of the MDR-TB globally, in different continents, different countries and in Namibia, as well as a review of the different survival analysis models used in MDR-TB studies. Furthermore, this chapter provides the research gap for this study. Chapters 3 and 4 present the research methodology and results obtained from the data analysis performed using the different survival analysis models and spatial mapping. Chapter 5 provides the discussion, conclusion, and recommendations for future research. Finally, the references and appendix that includes all STATA codes and additional information used for this study are presented.

Chapter 2: Literature Review

2.1 Introduction

This literature review gives a brief global overview of TB as well as an overview of the studies done on MDR-TB globally, in Europe, Asia, United States of America, Australia, and Africa, including Namibia. The chapter also discusses how different survival models such as Kaplan Meier, Log-Rank test, and Cox Proportional Hazard, as well as frailty and shared frailty models were applied in MDR-TB studies. This will be followed by the presentation of the research gap and summary of the literature.

2.2 Global overview of TB

Various studies on TB have been published with key concerns on its incidence and co-infection with HIV, as well as on the incidence of Drug Susceptible-Tuberculosis (DS-TB) and HIV co-infection, with the latter reported to have increased over the past two decades. Both TB and HIV have been discovered to be strongly co-linked, especially among HIV positive patients. It is estimated that People Living with HIV (PLHIV), especially with fewer than 200 cells/mm^3 CD4 count, showed a 19 (15-22)-fold increased risk of developing active TB compared with those who were HIV-negative (Singh, 2020). According to WHO (2019), 8.6% (7.4%–10%) of 10 million (range, 9-11.1 million) incident cases with active TB were also co-infected with HIV in 2018 while a third of 37 million PLHIV cases were infected with TB bacillus. Compared to other region, the Sub-Saharan Africa is the region with the highest burden of co-infection, comprising of 71% of the global co-infected cases (Mollel et al., 2020). Singh et al. (2020) further discovered that among 30 high-burden countries with TB and HIV co-infection in the world, HIV infection has been detected in 70% of the patients with TB, with South Africa (177,000 cases) having the highest number of TB cases among PLHIV, followed by India (92,000 cases) and Mozambique (58,000 cases). WHO (2019) also reported that 0.25 million (16.8%) of the 1.5 million deaths

from TB showed HIV co-infection worldwide. On the global scale, 862,000 new TB cases among PLHIV were reported, of which 86% were placed on Antiretroviral Therapy (ART). Singh et al. (2020) also discovered that, the global cure rate for TB in PLHIV has been reported to be 75%, although the mortality rate has reduced by 60% worldwide since 2000, there is still marked regional variation. However, this reduction was most evident in Europe and lowest in Sub-Saharan Africa.

2.3 MDR-TB and its associated risk factors review

Globally, in 2017, MDR-TB was reported to have occurred in an estimated 460,000 cases (accounting for 3.6% of all new cases and 17% of treated cases) and resulted in 230,000 deaths (Ou et al., 2021). According to WHO (2021), nine of the world's 30 countries with the highest burden of MDR-TB were within the WHO European regions, with these regions having the highest number of new and retreated cases of MDR-TB (an estimated 74,000 cases as of 2015). Furthermore, the highest burden of MDR-TB was reported to be in China, India, Russia, and South Africa, with these countries having more than 60% of all cases combined worldwide (WHO, 2018). In 2013/2014, several international health bodies such as WHO and European Centre for Disease Prevention and Control (ECDPC) revealed that MDR-TB is much more difficult and costly to treat than a DS-TB, thus becoming an obstacle to global TB control (WHO, 2013; ECDPC, 2014).

2.3.1 Europe

Acosta et al. (2014) reported that to address the MDR-TB and XDR-TB situation in the WHO European region, a Consolidated Action Plan to Prevent and Combat M/XDR-TB (2011-2015) was developed by the WHO regional office for all 53 Member States and implemented in 2011. Since the implementation of the Action Plan, the proportion of MDR-TB cases appeared largely to have levelled off among bacteriologically confirmed TB cases in high-burden countries with

universal or near universal (>95%) first-line DST. The treatment success rate, however, continued to decrease due to the substantial proportion of MDR-TB cases that were additionally resistant to either a fluoroquinolone, a second-line injectable agent or both (Seung, Keshavjee & Rich, 2015). Despite much progress in Eastern Europe, critical challenges remained such as appropriate treatment regimens, patient hospitalization, and scale-up of laboratory capacity, including the use of rapid diagnostics and second-line DST; vulnerable populations; human resources; and financing (ECDPC, 2014).

2.3.2 Asia

Srinivasan, Ponnuraja, & Rajendran (2017) introduced a frailty effect model in their study to account for the risk factor associated with MDR-TB in the Chennai regions of India. Their model captured the correlation and variation between neighboring locations using Conditionally Autoregressive (CAR) prior in Bayesian parametric survival model for studying dual infection of tuberculosis and HIV, while the Monte Carlo Markov Chain (MCMC) technique and the WinBUGS software were used for their Bayesian Survival model estimation. Results from their study revealed that the spatial frailty model accounted for a higher heterogeneity, with the weight at baseline identified as one of the significant factors associated with death. They further concluded that there were unmeasured covariates and risk factors influencing death in the Chennai regions. On the other hand, Balabanova et al. (2011) asserted that social factors, rural living, HIV infection and Beijing strain family impacted the survival of MDR-TB patients, while their survival period was short. They further concluded that rapid drug resistance identification, early administration of appropriate treatment and achieving high cure rates, expansion of HIV testing and antiretroviral treatment were necessary for optimal management of MDR-TB. Additionally, Chen et al. (2013) conducted a case–control study from July through August 2011 in five cities of Zhejiang Province in China to ascertain the risk factors for MDR-TB in this particular population, where cases were for the previously treated TB patients who had disease resistant to

at least isoniazid and rifampin, while the controls group were the previously treated TB patients who had disease sensitive to isoniazid and rifampin. Particular clinical diagnostic results, such as more than three TB foci in the lung, non-standard or irregular therapy, and adverse effects of anti-TB medication, were found to be associated with MDR-TB in previously treated TB patients.

2.3.3 United States of America

MDR-TB remains relatively rare in the United States. The MDR-TB data, from 2015, included 88 cases, which represented about 1% of persons with TB disease, of which 85% were foreign-born persons, and nearly 82% were individuals without a history of TB disease. These statistics emphasize how global control have undoubtedly affected the progress toward national TB elimination (Bailey, & Salleb, 2017). Chen, Miramontes, & Kammerer (2020) discovered that the characteristics and risk factors for MDR-TB differ between non-US-born and US-born persons. On comparing the results between the two groups, it was revealed that age groups 15-44 and 45-64 years, being a known contact of an MDR-TB patient, previous TB disease, and recent transmission were statistically significant risk factors for both non-US-born and US-born persons. Residing in the United States for ≤4 and 5-19 years and being white were additional risk factors for non-US-born persons; age group ≤14 years and being Asian were additional risk factors for US-born persons. Chen et al. (2020) further states that a known contact with an MDR-TB patient and previous TB disease were the two risk factors most strongly associated with MDR-TB cases. Therefore, unlike excess alcohol use and HIV co-infection, which vary in their associations with MDR-TB in different countries, previous TB disease remained a major risk factor universally; however, the magnitude might vary in different settings. They further concluded that MDR-TB intervention strategies in low-incidence countries will differ from those in higher TB incidence countries. In a small-scale MDR-TB risk factor study conducted in Ethiopia, previous contact with TB and MDR-TB patients was reported to be a risk factor for acquiring MDR-TB, while other studies such as Ying, et al. (2022) and Bailey, & Salleb (2017) revealed that a history of

previous TB disease was a contributing risk factor for MDR-TB. Although the majority of these MDR-TB studies had limited sample sizes, they were done across different environmental settings, from low- to high-incidence countries (e.g., France, Western and Eastern European countries, Malaysia, China, Brazil, and Ethiopia) (Asgedom, Teweldemedhin, & Gebreyesus, 2018).

2.3.4 Australia

Camphor et al. (2020) demonstrated that while Australia's MDR-TB burden was low, cases will continue to occur until TB control improves in countries with which Australia shares cultural and migration links. They further recommended that Australia should continue to support national and regional TB control programs to sustain progress towards national elimination of TB. Their study findings supported a review of data fields in the national TB dataset with potential expansion or adjustment to improve national data reporting, including the monitoring of evidence-based recommendations for the prevention and management of MDR-TB. Similarly, Baird et al. (2018) concluded that MDR-TB cases in Queensland were largely a result of cross-border Papua New Guinea nationals, with poorer outcomes seen in this cohort, and thus recommended continued strengthening of the region's TB programs, with a focus on cross-border patients.

2.3.5 Africa

A retrospective study was carried out by Limenih & Workie (2019) across seven hospitals having MDR-TB treatment centres in the Amhara region in Ethiopia from September 2015 to February 2018, among the different factors considered, research showed that the MDR-TB type, clinical complication, adherence, co-morbidities, sex, and smoking status were observed to have had a significant effect on the recovery time of MDR-TB patients in the region. Their study used an accelerated failure time and parametric shared frailty models and further concluded that the regional and federal government of Ethiopia should take immediate steps to address causes of

recovery time of MDR-TB patients in Amhara region through encouraging adherence, early case detection, and proper handling of drug-susceptibility according to WHO guideline. Furthermore, Zetola et al. (2013) compared the level of alcohol used among MDR-TB patients against three control groups (non MDR-TB patients, HIV infected patients without a history of TB, and the general population) in Botswana and it was revealed that MDR-TB patients had high rates of alcohol use and abuse, while among TB patients, alcohol abuse was associated with the diagnosis of MDR-TB and concluded to be an important modifiable factor. Another study done in South Africa by Lygizos et al. (2013) to assess the treatment outcomes, monthly cultures, Cluster of Differentiation 4 (CD4) count and viral load every 6 months of 80 patients initiated on a MDR-TB therapy from February 2008 to April 2010 of which 66 were HIV co-infected showed a high retention rate (5% defaults and 93% of visits attended) and favorable preliminary outcomes (77% cured/still on treatment and 82% undetectable viral load). The study further revealed that 9% of the patients had required care escalation, 8% had severe adverse events and 6% died, thereby prompting their conclusion that an integrated, home-based treatment for MDR-TB and HIV patients can be a promising treatment model to expand capacity and achieve improved outcomes in rural, resource-poor, and high-HIV prevalent settings.

2.3.6 Namibia

To the knowledge of the author of this mini-thesis, the only known epidemiological MDR-TB related study done in Namibia was by Ricks et al. (2012) while Shipanga (2019), although not MDR-TB related study, looked into the survival of TB and HIV co-infections among TB and HIV co-infected patients in the Erongo region of Namibia (one of the 14 regions of Namibia). Ricks et al. (2012) used medical records and patient questionnaires to describe the epidemiology and possible risk factors for the development of MDR-TB in Namibia by conducting a case-control study among patients diagnosed with TB between January 2007 and March 2009 in Namibia. Cases were defined as patients with laboratory-confirmed MDR-TB; while as the controls group

had laboratory-confirmed drug-susceptible TB or were being treated with WHO Category I or Category II treatment regimens. It was revealed that MDR-TB was associated with previous treatment for TB, previous hospitalization, and having had a household member with MDR-TB, suggesting that TB control practices had been inadequate. They further concluded that strengthening basic TB control practices, including expanding laboratory confirmation, directly observed therapy, and infection control, can be critical to the prevention of MDR-TB. Shipanga (2019) examined the spatial distribution of TB and HIV mortality in the Erongo region of Namibia (out of the 14 regions) from 2003-2017 and concluded that the detection of space-time clustering was useful in identifying higher risk areas in the regions. From his study it was recommended that there was a need to have targeted intervention among these areas to ensure that Namibia strives to attain its 5th National Development Plan (NDP5) which is intended to reduce the mortality of TB among HIV patients and that patients aged 50+ years and those with bedridden functional status should be strictly followed to reduce mortality.

2.4 Survival analysis review

Tolley, Barnes & Freeman (2016) stated that survival analysis is one of the primary statistical methods for analyzing data on time to an event such as death, heart attack, device failure, etc. It is a branch of empirical science that entails gathering and analyzing of data on time until failure or death and includes a variety of specific types of data analysis such as "life table analysis," "time to failure" methods, and "time to death" analysis. Turkson, Ayiah-Mensah, & Nimon (2021) discovered that sometimes, researchers have partial information about their subjects' survival times and are not privy to the exact survival times. Thus, censoring is needed in such situation. Censoring occurs when the event of interest is not observed for some subjects before the study is terminated. There are three general types of censoring, namely the right-censoring, left-censoring, and interval-censoring. The most common type of censoring encountered in survival analysis data is the right censored. According to Katsonaki (2016) right censoring occurs when an individual is

followed up from a time origin t_0 up to some later time point t_c and he/she has not had the event of interest, or their event has not occurred up to their censoring time t_c.

2.4.1 Kaplan Meier (KM)

Etikan (2017) defines Kaplan-Meier (KM) as a statistical method used in the analysis of time to event data. Time to event means the time from entry into a study until a particular event, for example onset of illness. This method is very useful in survival analysis as it is used by the researchers to determine and/or analyze the patients or participants who were lost to follow up or dropped out of the study, as well as those who developed the disease of interest or survived it. Etikan (2017) further states that KM is also used to compare two groups of subjects such as a control group (the one that is given placebo) and the other treatment group (the one given the genuine drug). The KM method is not only applicable to the fields of public health, medicine, and epidemiology, but it is also useful in other disciplines such as engineering, economics, among others. The KM method is widely used in clinical research (Rai, Mishra, & Ghoshal, 2021).

2.4.2 Cox Proportional Hazard

According to Elhafeez et al. (2021), the Cox model is a regression technique used mostly for performing survival analyses in epidemiological and clinical research. The Cox model, also known as the Cox proportional hazards regression analysis, is a semi-parametric survival modelling method because there is no assumption about the distribution of survival times, but it assumes that the effects of different variables on survival are constant over time (proportionality assumption) and additive over a particular scale.

2.4.3 Log rank test

LaMorte (2016) defines log rank test as a popular test that test the null hypothesis of no difference in survival between two or more independent groups. The test compares the entire survival experience between groups and can be thought of as a test of whether the survival curves are

identical (overlapping) or not. Furthermore, Bland, & Altman (2004) explains that the log rank test is used to test the null hypothesis that there is no difference between the populations in the probability of an event (such as death) at any time point. The analysis is based on the times of events (such as deaths). For each such time event, the observed number of deaths in each group and the number expected if there were in reality no difference between the groups are calculated. Additionally, the log rank test is most likely to detect a difference between groups when the risk of an event is consistently greater for one group than another (Subsahree, 2017). However, it is unlikely to detect a difference when survival curves cross, as can happen when comparing a medical treatment with a surgical intervention. When analyzing survival data, the survival curves should always be plotted for graphical inspection, before the model fittings (Bland, & Altman, 2004).

2.5 Frailty and shared frailty modelling

Occasionally, there are situations when survival times are not independent due to each individual understudy having some common features or some study characteristics that are shared by more than one observed event time. Thus, the frailty and shared frailty survival models are applicable to these situations (Qi, 2009). A frailty, a concept introduced by Vaupel et al. (1979), is an unobservable random effect. For multivariate time-to-event data, it represents the unobserved covariates shared by correlated event times.

2.5.1 Frailty models

To account for related subjects in the proportional hazard model, frailty models, which are mixed effects survival models, have been proposed where event times are assumed to be independent conditional on unobserved random effects called "frailties" (Dey et al., 2022**).** According to the Columbia University Mailman School of Public Health [CUMSPH] (2022), frailty models account for the heterogeneity caused by unmeasured covariates by adding random effects, which

act multiplicatively on the hazard function. Frailty models are essentially extensions of the Cox proportional hazards model with the addition of random effects. Although there are various classification schemes and nomenclature used to describe these models, four common types of frailty models are commonly used. These are the shared, nested, joint, and additive frailty models (Peace, Chen, & Menon, 2018).

2.5.2 Shared frailty models

A shared frailty model is a random effects model where the frailties are common (or shared) among groups of individuals or spells and are randomly distributed across groups (Hevi et al., 2022). This model assumes that the common random effect (frailty) has a multiplicative effect on the individual hazard. Conditional on the frailty, the event times are independent and thus have hazards that are similar to the univariate model (Chen, Ibrahim, & Chu, 2014). According to Dey et al. (2022) previous researchers have extensively studied shared frailty models with Gamma-distributed frailties. However, the shared frailty model assumes that the subjects in a cluster share common frailty and thus is limited in its scope to model more complicated dependency structures that arise in cohort-based association studies. Dey et al. (2022) further states that bivariate extensions to the shared frailty model such as the correlated Gamma or the correlated compound Poisson frailty model allow the frailties to be correlated among two subjects. However, these models are also too restrictive because they model the correlations using one parameter, although they are more appropriate for twin studies, and cannot model arbitrarily complex relationship structures.

2.6 Research gap

Although quite a number of TB infections and mortality studies have been done in Namibia, none of the studies focused on MDR-TB mortality in Namibia, as well as examining/identifying its specific risk factors. To the knowledge of the author of this mini-thesis, the only known

epidemiological MDR-TB related studies done in Namibia was by Ricks et al. (2012) using a retrospective cohort study from 2007 to 2009, while the latest epidemiological study done on TB mortality in Namibia was done by Shipanga (2019) using a retrospective cohort study from 2003 to 2017. While Ricks et al. (2012) was a MDR-TB study in Namibia, the study by Shipanga (2019) was not, but rather a TB-HIV co-infection survival study among TB and HIV co-infected patients in the Erongo region of Namibia (out of the 14 regions). Moreover, Ricks et al. (2012) focused on identifying the risk of developing MDR-TB as well as the characteristics of MDR-TB in Namibia and not on MDR-TB mortality nor on identifying the risk factors of MDR-TB mortality in the country. Thus, using a retrospective cohort study from 2014 to 2017, this current study aimed at performing an epidemiological investigation of MDR-TB mortality in Namibia, by fitting a spatial frailty model to capture spatial variation in different geographical regions and possible identification of associated risk factors, which are therefore, required to understand the factors associated with MDR-TB mortality, in juxtaposition with the risk factors for the development of MDR-TB findings of Ricks et al. (2012). This research study will be the first of its kind as previous related studies were only focused on finding spatial distribution of TB mortality, TB and HIV co-infection and describing the epidemiology and possible risk factors for the development of MDR-TB in Namibia. The identified risk factors associated with deaths among MDR-TB patients from this current study can further be considered as useful insights for evidence-based health policies and programs on TB and MDR-TB in the prevention of high MDR-TB mortality rates in the country, while adding value to the body of scientific knowledge on MDR-TB mortality in Namibia and globally.

2.7 Literature summary

It can be concluded that the global MDR-TB mortality rate has reduced but there is still marked regional variation and this reduction was most evident in Europe and lowest in Sub-Saharan Africa. The studies have identified risk factors that are associated with MDR-TB mortality such

as known contact of an MDR-TB patient, previous TB treatment, HIV infection, co-morbidities, and age (older people). Studies recommended that, there is a need for continuous support to national and regional TB control programs to sustain progress towards national elimination of TB, encouraging adherence, early case detection, and proper handling of drug-susceptibility, scale up human recourses, directly observed therapy, and infection control, can be critical to the prevention of MDR-TB. Moreover, previous related studies done in Namibia were only focused on finding spatial distribution of TB mortality, TB and HIV co-infection and describing the epidemiology and possible risk factors for the development of MDR-TB in the country. Thus, this current study will be first of its kind to perform an epidemiological investigation of MDR-TB mortality in the country by fitting a spatial frailty model to capture spatial variation in different geographical regions and possible identification of associated risk factors, which are therefore, required to understand the factors associated with MDR-TB mortality in the country.

Chapter 3: Methodology

3.1 Research Design

The study adopted a retrospective cohort study design using the 2014 to 2017 MDR-TB records from the MoHSS's electronic Tuberculosis (eTB) database. The eTB database is a system that was created by MoHSS to provide the monthly summaries information of TB patients across regions in Namibia since 2010.

3.2 Sample

The records of all MDR-TB patients registered on the eTB database from 2014 to 2017 were considered as the sample of the study. The study only used records of patients who were diagnosed with MDR-TB and classified as MDR-TB patients in the eTB database, and not all forms of DR-TB. Figure 1 shows how the sample of the study was selected. A total of 1514 DR-TB patients were recorded from 2014-2017 with 1432 classified as MDR-TB and 82 as XDR in the eTB database. Since this study's focus was on MDR-TB patients (see section 1.3), all patients classified as XDR were excluded from this study. Of the 1432 MDR-TB patients, 1208 were captured as alive while 224 were recorded as dead in the eTB database. Since this study was focusing on MDR-TB mortality, the 1208 patients were classified as censored patients in this study, while the 224 patients were classified as the patients who experienced the event, with the event being death in this study.

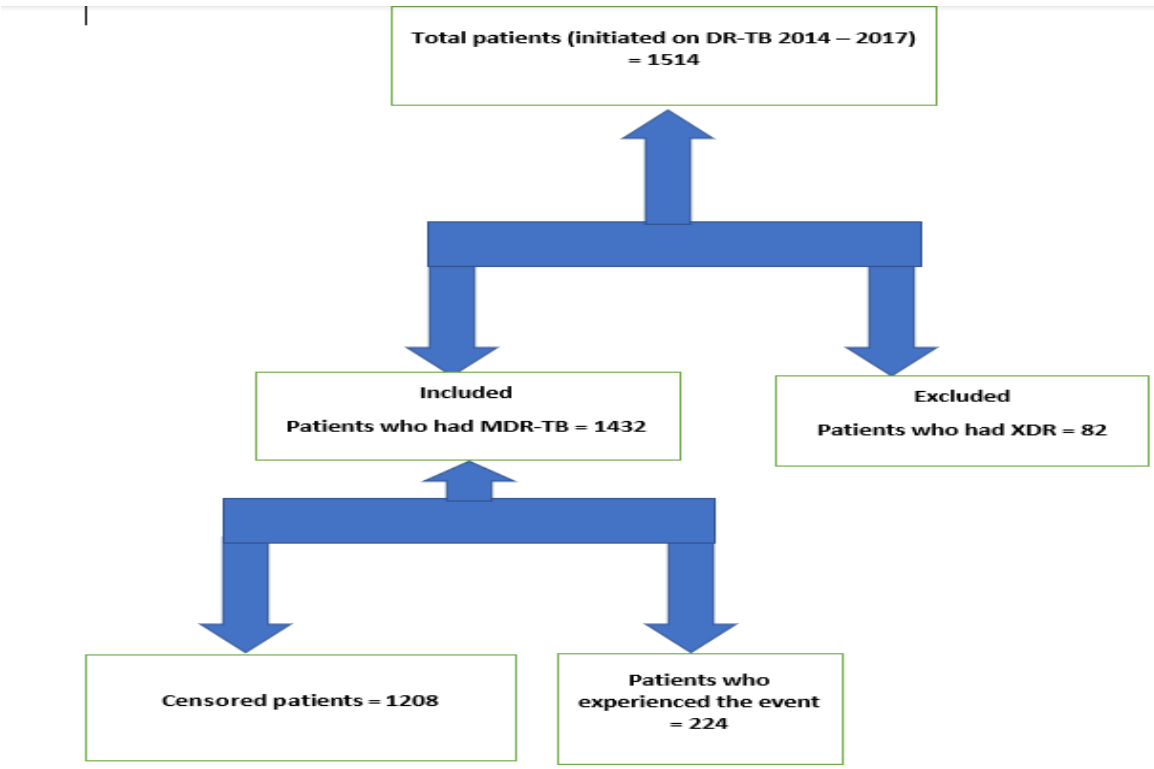

Figure 1: Selection of the sample of the study

3.3 Data Analysis

Microsoft Excel (2013) was used to clean the data, prior to performing the data analysis of this study, while the Statistical Package for Social Scientist (SPSS) version 22 was used to construct the KM graphs. STATA version 16 was used to perform the descriptive statistics, CPH modelling, survival parametric modelling and spatial modelling.

3.3.1 Data Variables

Variables within the eTB databases included the time to event variable which was the length of stay (i.e., the difference between the date the MDR-TB patient started the treatment and the date the patient experienced the event, discharged, lost to follow up or finished the treatment), as well as the patients' socio-demographic characteristics such as their sex, age category, and region, and clinical characteristics such as HIV status, treatment type, site of TB disease, number of previous TB treatments, and patient status. Table 1 gives a brief description of the study variables.

Table 1: List of study variables

Characteristic	Variable name	Brief description
Time to event variable	Length of stay (in months)	The difference between the date the MDR-TB patient started the treatment and the date the patient experienced the event, discharged, lost to follow up or finished the treatment as recorded in the eTB database. Here, the event variable was death since this study was focusing on MDR-TB Mortality
Socio-demographic	Sex	The MDR-TB patient's sex as recorded in the eTB database: Male & Female
	Age category (in years)	The age group of the MDR-TB patient: <18, 18-34, 35-54 & 55+
	Region	The region where the patient received treatment as recorded in the eTB database: Erongo, Hardap, //Karas, Kavango, Khomas, Kunene, Ohangwena, Omaheke, Omusati, Oshana, Oshikoto, Otjozondjupa & Zambezi
Clinical	HIV status	The HIV status of the MDR-TB patient as recorded in the eTB database: Positive, Negative & Unknown
	Site of TB disease	The TB site of the MDR-TB patient as recorded in the eTB database: Extrapulmonary, Pulmonary, both & Unknown
	Treatment type	The type of treatment category of the MDR-TB patient: Failure after 1st treatment, Failure re-treatment, After default, New & Others
	Number of previous TB treatments	The number of previous TB treatments the MDR-TB patient had: <2, 2-3 & >3
	Patient status	Current status of the MDR-TB patient as recorded in the eTB database: discharged, lost to follow up & Deceased

Spatial variation	Organisation units	The regions where the MDR-TB patients received their TB treatment as recorded in the eTB database (see the Regions variable above)

3.3.2 Survival Analysis

Survival analysis is a collection of statistical procedures for data analysis for which the outcome variable of interest is time until an event occurs, with time defined in terms of years, months, weeks, or days from the beginning of a follow-up of an individual until an event occurs. Also, time can refer to the age of an individual when an event occurs, with event defined in terms of death, disease incidence, relapse from remission, recovery (e.g., return to work) or any designated experience of interest that may happen to an individual (Kleinbaum & Klein, 2015). There are three basic goals for performing survival analysis, namely, (i) to estimate and interpret survivor and/or hazard functions from survival data, (ii) to compare survivor and/or hazard functions, and (iii) to assess the relationship of explanatory variables to survival time (Kleinbaum & Klein, 2015). Most often the event of interest is not observed for some individuals under consideration. Thus, this situation is often referred to as censoring. Turkson, Mensah, & Nimoh (2021) defines censoring as when the event of interest is not observed for some subjects before the study is terminated. It can occur when the researcher has partial information about the subjects' survival times but is not privy to the exact survival times. There are generally three types of censoring namely, right censoring, left censoring and interval censoring. Kleinbaum & Klein (2015) defines right-censoring as the censoring that occurs when the true survival time is equal to or greater than observed survival time, while left-censoring occurs when the true survival time is less than or equal to the observed survival time. On the other hand, interval-censoring occurs when the true survival time is within a known time interval (Kleinbaum & Klein, 2015).

3.3.2.1 Kaplan-Meier (KM)

The KM method is a statistical method used in the analysis of time to event data. The time to event means the time from entry into a study until a particular event, for example the time a patient is diagnosed with MDR-TB to the time of the event of interest (death). This method is very useful in survival analysis as it is used by the researchers to determine and/or analyze the patients or participants who were lost to follow up or dropped out of the study, as well as those who experienced the event of interest or survived it (Etikan, Abubakar, & Alkassim, 2017). Irvine, Waise, & Green (2020) discussed in their study that the KM method is used frequently for comparing the survival times for the subjects with different statuses. The statuses can be assigned by: (i) the treatment methods or/and circumstances under which they were applied; (ii) some biological, physiological, or/and genetical peculiarities such as sex, age, body mass index, genomic alterations; and (iii) the lifestyle, education, and socioeconomic level The group membership of the subjects is predetermined by the status. The KM estimator has a few assumptions namely, (i) the survival probability is the same for censored and uncensored subjects; (ii) the likelihood of the occurrence of the event is the same for the participants enrolled early and late; (iii) the probability of censoring is the same for different groups; and (iv) the event is assumed to occur at the defined time (Lee & Lim, 2019).

Moreover, Kleinbaum & Klein (2015) argued that KM is the most widely used non-parametric method of estimating the survival function (t) and utilizes information from both subjects who have experienced an event as well as right-censored subjects. Survival function $S(t)$ can be defined as the probability that a subject survives longer than time t. That is,

$$S(t) = P(T > t) \tag{1}$$

where T is the survival time and $S(t)$ is a monotonically decreasing function of t with

$$S(t) = \begin{cases} 1 & t = 0 \\ 0 & t = \infty \end{cases} \tag{2}$$

(Petrus, 2019). Theoretically, at the start of the study, since no one has experienced the event yet, the probability of surviving past time 0 is one, and if the study period increased without limit, eventually nobody would survive, so the survivor curve must eventually fall to zero. According to Etikan, Bukirova, & Yuvali (2018), the KM estimator at time t when it comes to the survival function is given by:

$$S(t) = \prod_{i|t_i \leq t} \left(\frac{n_i - d_i}{n_i} \right) \quad (3)$$

where t_i is the time passed to the next observation from the beginning of the study, n_i is the number of subjects at risk of death at the time t_i and d_i is the number of deaths at time t_i.

3.3.2.2 Log-rank Test

The log-rank test, a nonparametric procedure for comparing two or more survival functions, is a test of the null hypothesis that all the survival functions are the same, versus the alternative that at least one survival function differs from the rest (Ali & Mohammed, 2022). Kleinbaum & Klein (2015) suggested that this (log-rank) statistic, like many other statistics used in other kinds of chi-square tests, makes use of observed versus expected cell counts over categories of outcomes, with the categories for the log-rank statistic defined by each of the ordered failure times for the entire set of data being analysed. The log-rank statistic tests the null hypothesis that at all time points the survival functions for all groups are equal, against the alternative hypothesis that at least one survival function is different from the others for some time periods, with the (general) log-rank statistic given by:

$$\chi^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i} \quad (4)$$

where n is the number of groups being compared, O_i and E_i are the observed and expected number of deaths in each group i respectively, calculated for each time when an event occurs.

3.3.2.3 Cox Proportional Hazard (CPH) Model

The CPH model is essentially a regression model used for investigating the association between the survival time of patients and one or more predictor/explanatory variables (Cox, 1972). This model works for both quantitative predictor variables and categorical variables. In addition, the CPH regression model simultaneously assesses the effects of several risk factors on survival time (LaMorte, 2016). Two key assumptions of the CPH model is that the hazard curves for the groups of observations (or patients) must be proportional and these curves must not interact (LaMorte, 2016). A key reason for the popularity of the CPH is that, even though the baseline hazard is not specified, reasonably good estimates of regression coefficients, hazard ratios of interest, and adjusted survival curves can be obtained for a wide variety of data situations (Kleinbaum, & Klein, 2015). The CPH model relies on the assumption of proportional hazards (PH) across different covariates, thus the PH assumptions should be assessed and handled if violated (Kuitunen, et al. 2021). The CPH model makes two assumptions:

(i) The survival curves for different strata must have hazard functions that are proportional over the time *t*, and

(ii) The relationship between the log hazard and each covariate is linear, which can be verified with residual plots (Kleinbaum, & Klein, 2015).

The hazard function, denoted by $h(t)$, can be defined as the probability of failure during a very small-time interval, assuming that the individual has survived to the beginning of the interval. It gives the instantaneous potential per unit time for the event to occur, given that the individual has survived up to time t. The hazard function describes the instantaneous rate of occurrence over time, which can conceptually be viewed as the hazard rate during an infinitesimally small-time interval (Schober, & Vetter, 2018). In contrast to the survival function $S(t)$ which focuses on not failing, $h(t)$ focuses on failing, that is, on the event occurring. Thus, $h(t)$ can be considered as giving the opposite side of the information given by $S(t)$ (Shipanga, 2019). That is,

$$h(t) = \frac{P(t \leq T \leq t+\Delta t | T \geq t)}{\Delta t} \quad (5)$$

(Petrus, 2019), with $h(t)$ always nonnegative (i.e., equal to or greater than zero) and having no upper bound. The cumulative hazard function can be defined as the total number of failures or deaths over an interval of time and it is obtained by:

$$H(t) = \int_0^t h(u)du \quad (6)$$

where $h(u)$ is hazard risk and u is accumulated risk (Petrus, 2019). In the CPH regression model, the hazard function for an individual can be defined as

$$h(t, X) = h_0(t)\, exp[\sum_{i=1}^{P} (\beta_i x_i)] \quad (7)$$

where $\beta = (\beta_1, \beta_2, \cdots, \beta_P)$ is avector of regression coefficients, $x_1, x_2, \cdots, x_P$ are the values of P covariates $X_1, X_2, \cdots, X_P$ and $h_0(t)$ is the baseline hazard function (Srinivasan et al., 2017; Limenih & Workie, 2019). This model was fitted to investigate the association between the survival time of the patients and the covariates in this study, with the covariates been the patients' socio-demographic characteristics (such as sex, age category and region), and clinical characteristics (such as HIV status, site of TB disease, treatment type and number of previous TB treatments). Since the CPH regression model relies on the hazards being proportional, i.e., on the effect of a given covariate not changing over time, it is very important to verify that the covariates satisfy the assumption of proportionality (Cox, 2018).

3.3.2.4 Frailty models

According to Kleinbaum & Klein (2015), frailty is a random component designed to account for variability due to unobserved individual-level factors that are otherwise unaccounted for by the other covariates/predictors in the model. The frailty α is an unobserved multiplicative effect on the hazard function assumed to follow some distribution $g(\alpha)$ with $\alpha > 0$ and the mean of α equal to 1. The variance of α is a parameter $\emptyset$ that is typically estimated from the data. Individuals with $\alpha > 1$ have an increased hazard and decreased probability of survival compared to those of

average frailty ($\alpha = 1$). Similarly, individuals with $\alpha < 1$ have a decreased hazard and increased probability of survival compared to those of average frailty (Kleinbaum, & Klein, 2015). The model can be expressed as:

$$h(t|\alpha) = \alpha h(t) \quad (8)$$

where α is an unobserved multiplicative effect on the hazard function $h(t)$ assumed to follow some distribution. The frailty effect is defined as when the population level hazard eventually decreases over time because the "at risk group" has an increasing proportion of less frail individuals (Kleinbaum, & Klein, 2015).

3.3.2.5 Shared Frailty Model

In a shared frailty model, the subjects of a group of observations in the same cluster share the same level of frailty, that is, the common frailty variance measures of dependence among lifetimes within a cluster (Jabir et al., 2022). Since the observations in this current study were clustered into groups such as hospitals, the shared frailty modelling was the most appropriate model type to consider in order to account for the unobserved heterogeneity in individual risk to diseases and death (Jung et al., 2018). This is because shared frailty models are often used when observations in the same group share common unknown risk factors or frailty. In such models, the known effect on survival time can be described using the baseline distribution and regression coefficients while the unknown effect can be described through a frailty distribution (Sidhu, Jain, & Sharma, 2019). The conditional hazard function for the jth subject from the kth cluster can be expressed as:

$$h_{kj}(t|\alpha_k) = \alpha_k h_{kj}(t) \quad (9)$$

where $h_{kj} = h(t|x_{kj})$, for $j = 1,2, \cdots, n_k$, with n_k being the total number of subjects in the kth cluster and α_k is the (unobservable) frailty effect term. From (7), the hazard function of a Cox shared frailty survival model can be defined by:

$$h_{kj}(\alpha_k) = \alpha_k h_0(t) exp[\sum_{i=1}^{P} (\beta_{ikj} x_{ikj})] \quad (10)$$

for $k = 1,2, \cdots, n$, and $j = 1,2, \cdots, n_k$ observation in cluster k, where $h_0(t)$ is a baseline hazard, and $(\beta_{ikj}x_{ikj})$ is the covariate term.

3.3.3 Frailty and non-frailty model fittings description

In order to determine the best fit model to use in modelling the MDR-TB mortality, five model techniques were considered, each fitted with frailty effect and without frailty effect. These models are briefly described below.

3.3.3.1 Exponential Accelerated Failure Time (AFT) model

Exponential AFT model is used when the researcher assumes a constant failure rate **(**Mietlowski, 2012). This model assumes that the hazard rate is *constant*. In other words, the risk of the event of interest occurring remains the same throughout the period of observation (Kleinbaum, & Klein, 2015). The hazard function of an exponential AFT model can be defined as:

$$h(t) = \lambda \tag{11}$$

where $\lambda = exp(\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n)$. With frailty effect, (11) becomes:

$$h_j(t|\alpha_j) = \alpha_j h(t) \tag{12}$$

for $j = 1,2, \cdots, n$, where α_j is an unobserved multiplicative effect and $h(t)$ is the exponential hazard function defined in (11).

3.3.3.2 Weibull Proportional Hazard (PH) model

Weibull PH model is commonly used to assess product reliability**,** analyze life data and model failure times (Harry, 2003)**.** The Weibull model has the property that if the AFT assumption holds then the PH assumption also holds (and vice versa). This property is unique to the Weibull model (Cox & Oakes, 1984) and holds if p, shape parameter, does not vary over different levels of covariates (Kleinbaum, & Klein, 2015). The hazard function of a Weibull PH model can be defined as:

$$h(t) = \lambda p t^{p-1} \tag{13}$$

where $\lambda = exp(\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n)$, p is the shape parameter and t is the failure time. With frailty effect, (13) becomes:

$$h_j(t|\alpha_j) = \alpha_j h(t) \tag{14}$$

for $j = 1, 2, \cdots, n$, where α_j is an unobserved multiplicative effect and $h(t)$ is the Weibull hazard function defined in (13).

3.3.3.3 Log-normal AFT model

Log-normal AFT model is used when the variable is the product of a large number of independent, identically distributed variables in the same way that a normal distribution results when the variable is the sum of a large number of independent, identically distributed variables (Kleinbaum, & Klein, 2015). The hazard function of a log-normal AFT model can be defined as:

$$h(t) = \frac{\frac{1}{\sigma t}\boldsymbol{\Phi}\left(\frac{log\, t - \mu}{\sigma}\right)}{1 - \boldsymbol{\Phi}\left(\frac{log\, t - \mu}{\sigma}\right)} \tag{15}$$

where μ and σ are the unknown parameters, t is the failure time, Φ is the standard normal distribution function. With frailty effect, (15) becomes:

$$h_j(t|\alpha_j) = \alpha_j h(t) \tag{16}$$

for $j = 1, 2, \cdots, n$, where α_j is an unobserved multiplicative effect and $h(t)$ is the log-normal hazard function defined in (15).

3.3.3.4 Log-logistic AFT model

Log-logistic AFT model is applicable in cases where the logarithmized outcome variable follows a logistic distribution. In survival analysis, it is used to model hazard rates that are initially increasing and finally decreasing (Nussbeck, 2014). This model assumes that the density function of the residual in the regression predicting the logarithm of the time until occurrence of the event follows a logistic distribution. Additionally, the covariates are assumed to accelerate or decelerate

the waiting time until the event occurs (Nussbeck, 2014). The hazard function of a log-logistic AFT model can be defined as:

$$h(t) = \frac{\lambda p(pt)^{p-1}}{1+(pt)^{k}} \quad (17)$$

where $\lambda = exp(\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n)$, p is the shape parameter, and t is the failure time. With frailty effect, (17) becomes:

$$h_j(t|\alpha_j) = \alpha_j h(t) \quad (18)$$

for $j = 1, 2, \cdots, n$, where α_j is an unobserved multiplicative effect and $h(t)$ is the log-logistic hazard function defined in (17).

3.3.3.5 Gompertz PH model

The Gompertz PH model describes rates of aging and age-independent mortality with the parameters a and b, respectively. Estimates of these parameters have traditionally been based on the assumption that mortality rates are constant over short to moderate time periods (Mueller, Nusbaum, & Rose, 1995). The hazard function of a Gompertz PH model can be defined as:

$$h(t) = ae^{bxi} \quad (19)$$

where a and b are aging and age-independent mortality parameters and x represents values of the covariates. With frailty effect, (19) becomes:

$$h_j(t|\alpha_j) = \alpha_j h(t) \quad (20)$$

for $j = 1, 2, \cdots, n$, where α_j is an unobserved multiplicative effect and $h(t)$ is the Gompertz hazard function defined in (19).

3.3.4 Model comparison and diagnostics

In this study, the Akaike Information Criterion (AIC) and Bayesian Information Criteria (BIC) techniques were used to choose the best fit model to use in modelling the MDR-TB mortality among the 10 fitted models described in section 3.3.3 above. The model with the lowest AIC & BIC values was considered as the better fit and, thus, further used in the identification of the risk

factors associated with MDR-TB mortality. In this study, the event of interest was the death of MDR-TB patients during treatment and was coded as 1 for death occurring by TB and 0 for censor (no death). The time to event variable in this study was the length of stay of MDR-TB patients (calculated as the difference between the date the patient started the treatment and the date the patient experienced the event of interest (death) or when the study ended), while the spatial variation variable was the organisation units (i.e. the different hospitals/clinics where the patients were enrolled for TB care, categorized by regions). The censoring variable was the patient status - whether the patient completed the treatment and got discharged, lost to follow up or died, while the frailty variable was derived from the age variable considering elderly patients (aged 55+). The covariates were the patients' socio-demographic characteristics (such as sex, age category and region), and clinical characteristics (such as HIV status, site of TB disease, treatment type and number of previous TB treatments).

3.4 Research Ethics

Ethical clearance certificate for this study was obtained from the University of Namibia Decentralized Committee (see Appendix B). Permission to use the secondary data from the MoHSS' eTB database was obtained from MoHSS (see Appendix C) and the collected data was treated with confidentiality. In addition, the data was used for nothing else besides the purpose of the study and the information was not to be revealed to any other parties. Moreover, the collected data did not contain patient's names or information that could identify or reveal the patients' identity.

Chapter 4: Results

4.1 Descriptive Statistics

Out of the 1432 MDR-TB patients considered in this study, a total of 224 (15.6%) events (deaths) and 1208 (84.4%) censored cases were recorded from 2014 to 2017 as shown in Table 2. Of the 1432 MDR-TB patients, 801(55.936%) were males and 631(44.064%) were females of which 112 (17.75%) MDR-TB deaths were recorded among the females whilst 112 (13.983%) MDR-TB deaths were recorded among the males. Thus, it can be said that there were more MDR-TB deaths recorded among the females than in males during 2014-2017. Additionally, the highest number of MDR-TB deaths were recorded among patients who were aged 35-54 years (n=106) and in the Khomas region (n=48) as shown in Table 2. However, the lowest number of MDR-TB deaths were recorded among patients who were less than 18 years old (n=9) and in the Omaheke (n=1) and Zambezi (n=1) regions.

Table 2: Distribution of MDR-TB patients' by socio-demographic characteristics (2014-2017)

	Case status		
	Censored	Death	Total
	Count (%)	Count (%)	Count (%)
Sex			
Female	519 (82.250)	112 (17.750)	631 (44.064)
Male	689 (86.017)	112 (13.983)	801 (55.936)
Total	1208 (84.358)	224 (15.642)	1432 (100)
Age category (in years)			
<18	110 (92.437)	9 (7.563)	119 (8.310)
18-34	542 (88.852)	68 (11.148)	610 (42.598)
35-54	479 (81.880)	106 (18.120)	585 (40.852)
55+	87 (67.969)	41 (32.031)	128 (8.939)
Total	1208 (84.358)	224 (15.642)	1432 (100)
Region			
Erongo	121 (91.667)	11 (8.333)	132 (9.218)
Hardap	53 (84.127)	10 (15.873)	63 (4.399)
//Karas	40 (83.333)	8 (16.667)	48 (3.352)

Kavango	178 (83.178)	36 (16.822)	214 (14.944)
Khomas	184 (79.310)	48 (20.690)	232 (16.201)
Kunene	19 (73.077)	7 (26.923)	26 (1.816)
Ohangwena	167 (89.305)	20 (10.695)	187 (13.059)
Omaheke	18 (94.737)	1 (5.263)	19 (1.327)
Omusati	70 (76.923)	21 (23.077)	91 (6.355)
Oshana	132 (81.988)	29 (18.012)	161 (11.243)
Oshikoto	77 (84.615)	14 (15.385)	91 (6.355)
Otjozondjupa	117 (86.667)	18 (13.333)	135 (9.427)
Zambezi	32 (96.970)	1 (3.030)	33 (2.304)
Total	1208 (84.358)	224 (15.642)	1432 (100)

Table 3 shows the distribution of MDR-TB patients by their clinical characteristics from 2014 to 2017. Out of the 224 MDR-TB deaths reported, the highest number were recorded among patients who were HIV positive (n=128), had more than three previous TB treatments (n=107) after defaulting on their treatment (n=92) and have Pulmonary TB (n=203).

Table 3: Distribution of MDR-TB patients' by clinical characteristics (2014-2017)

	Case status		
	Censored	Death	Total
	Count (%)	Count (%)	Count (%)
HIV status			
Negative	553 (89.482)	65 (10.518)	618 (43.156)
Positive	454 (78.007)	128 (21.993)	58 (40.642)
Unknown	201 (86.638)	31 (13.362)	232 (16.201)
Total	1208 (84.356)	224 (15.642)	1432 (100)
Number of previous TB treatment			
<2	181 (79.386)	47 (20.614)	228 (15.922)
2-3	338 (82.843)	70 (17.157)	408 (28.492)
>3	689 (86.558)	107 (13.442)	796 (55.587)
Total	1208 (84.358)	224 (15.642)	1432 (100)
Treatment type			
After default	391 (80.952)	92 (19.048)	483 (33.729)
Failure 1st treatment	139 (87.421)	20 (12.579)	159 (11.103)
Failure re-treatment	46 (69.697)	20 (30.303)	66 (4.609)
New	589 (87.649)	83 (12.351)	672 (46.927)

Others	43 (82.692)	9 (17.308)	52 (3.631)
Total	1208 (84.358)	224 (15.642)	1432 (100)
Site of TB disease			
Both	3 (100)	0 (0)	3 (0.209)
Extrapulmonary	19 (73.077)	7 (26.923)	26 (1.816)
Pulmonary	1128 (84.748)	203 (15.252)	1331 (92.947)
Unknown	58 (80.556)	14 (19.444)	72 (5.028)
Total	1208 (84.358)	224 (15.642)	1432 (100)

Moreover, it can be concluded that the average duration of deaths among the MDR-TB patients was approximately 5 months and 3 days in 2014 to 2017, with a lower and upper bound of 5 to 6 months.

4.2 Life table and KM survival graphs

Looking at the life table shown in Table 4, it can be observed that about 92% of the MDR-TB patients survived the first month of treatment, while about 53% survived the fourth and ninth months.

Table 4: Life table of MDR-TB patients

*Time Interval (in months)	Beg. Total	Deaths	Lost	Survival	Std. Error	95% Conf. Int.	
0-<1	1432	101	214	0.924	0.007	0.908	0.937
1-<2	1117	79	576	0.836	0.012	0.812	0.857
2-<3	462	37	380	0.722	0.020	0.681	0.760
3-<4	45	7	37	0.531	0.064	0.400	0.646
8-<9	1	0	1	0.531	0.064	0.400	0.646

* There were no MDR-TB patient cases recorded for 4 to 7 months duration in 2014-2017
Beg. Total = Number of patients at the beginning of the study; Std. Error = Standard Error; Conf. Int. = Confidence Interval
Time interval is measured in months since diagnosis.

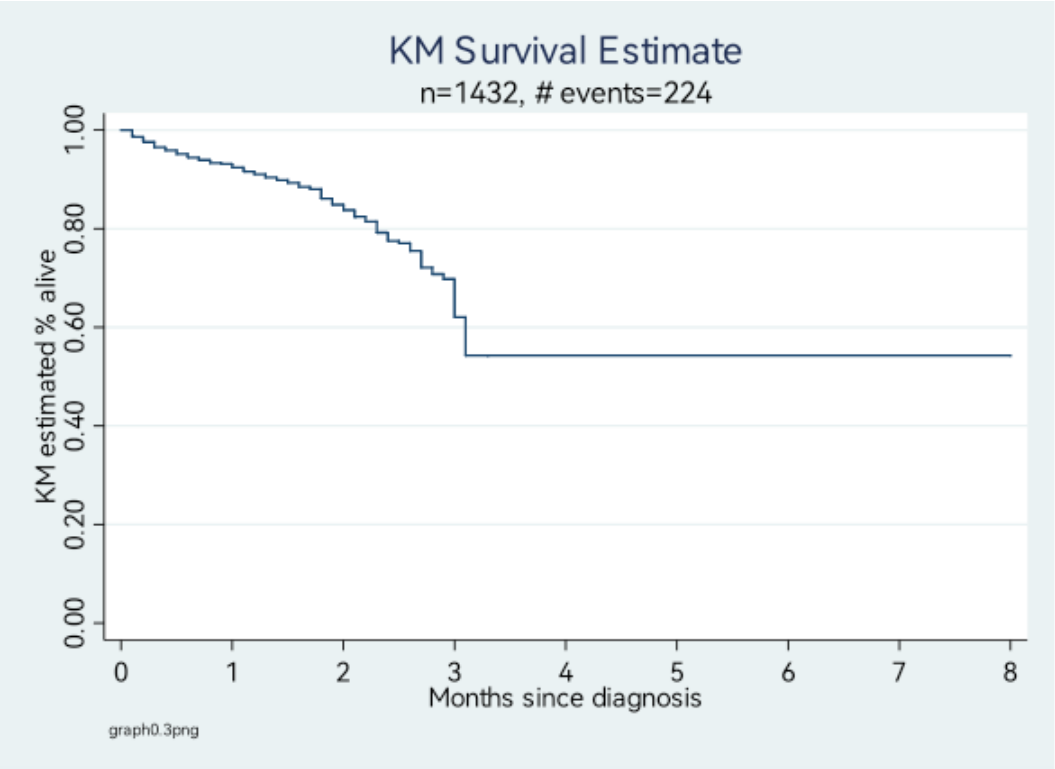

Figure 2: KM graph of survival time estimate from 2014 to 2017

From Figure 2, it can be observed that, overall, all MDR-TB patients had high survival chances at the beginning of their treatment, however, their survival rate started decreasing as the duration of their stay (in months) on the TB treatment increases. In other words, the longer a MDR-TB patient stayed on treatment the lower their chances of survival. In addition, the curve showed that mortality hazard was high in the first 3 months, after which the survival rate had reduced to 0.55 (55%) till the end of the study period. In other words, no MDR-TB deaths were recorded after month 4 as the patients had either survived or were lost to follow up or transferred to other facilities.

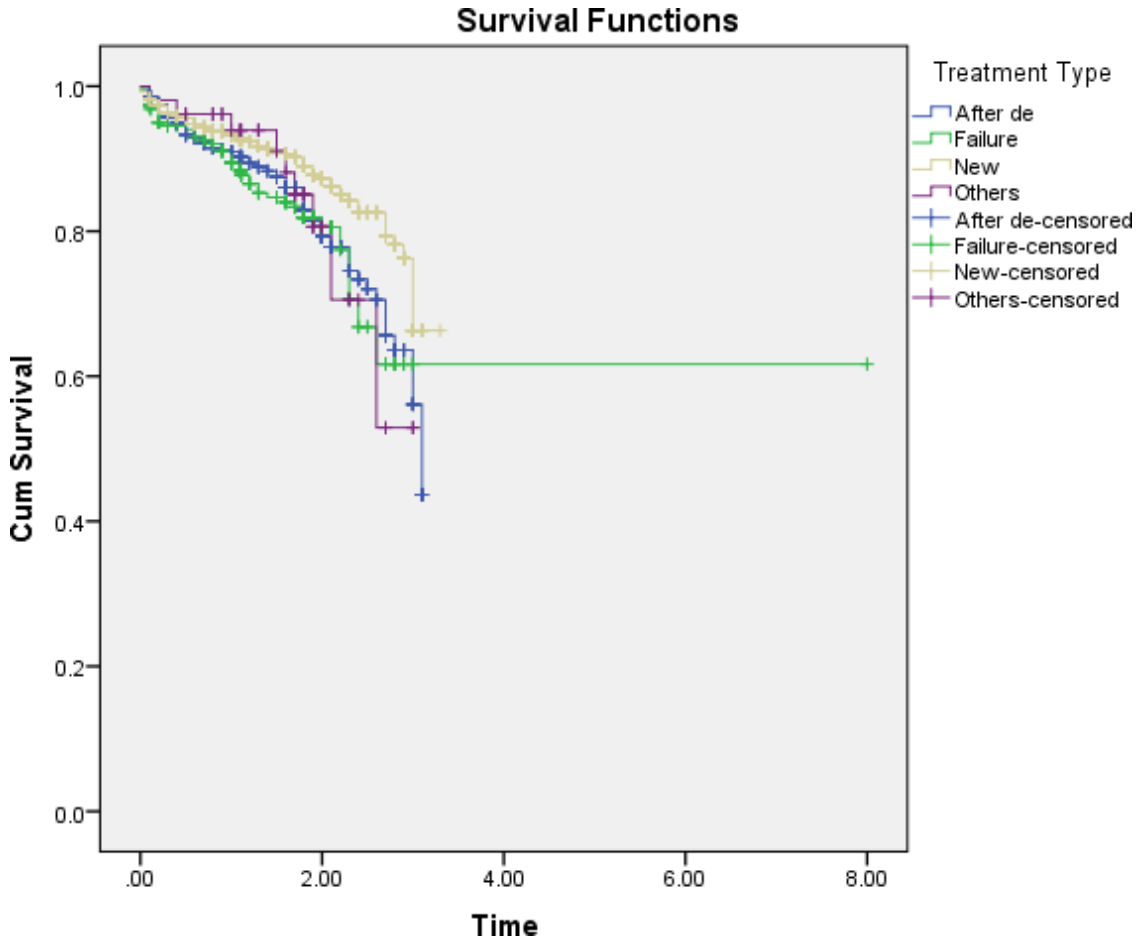

Figure 3: KM plot for treatment type since diagnosis

Figure 3 shows the survival rates of MDR-TB patients by their treatment type. At time zero, the survival probability was 1.0 (i.e., 100% of the MDR-TB patients were still alive), while at month 8, the probability of survival was approximately 0.62 (i.e., 62% of the MDR-TB patients were still alive) for MDR-TB patients whose treatment type was failure re-treatment. Also, as the months increased, the survival rates of MDR-TB patients were decreasing. Thus, it can be concluded that MDR-TB patients whose treatment type was failure re-treatment had a longer survival time than those who were on other types of treatments.

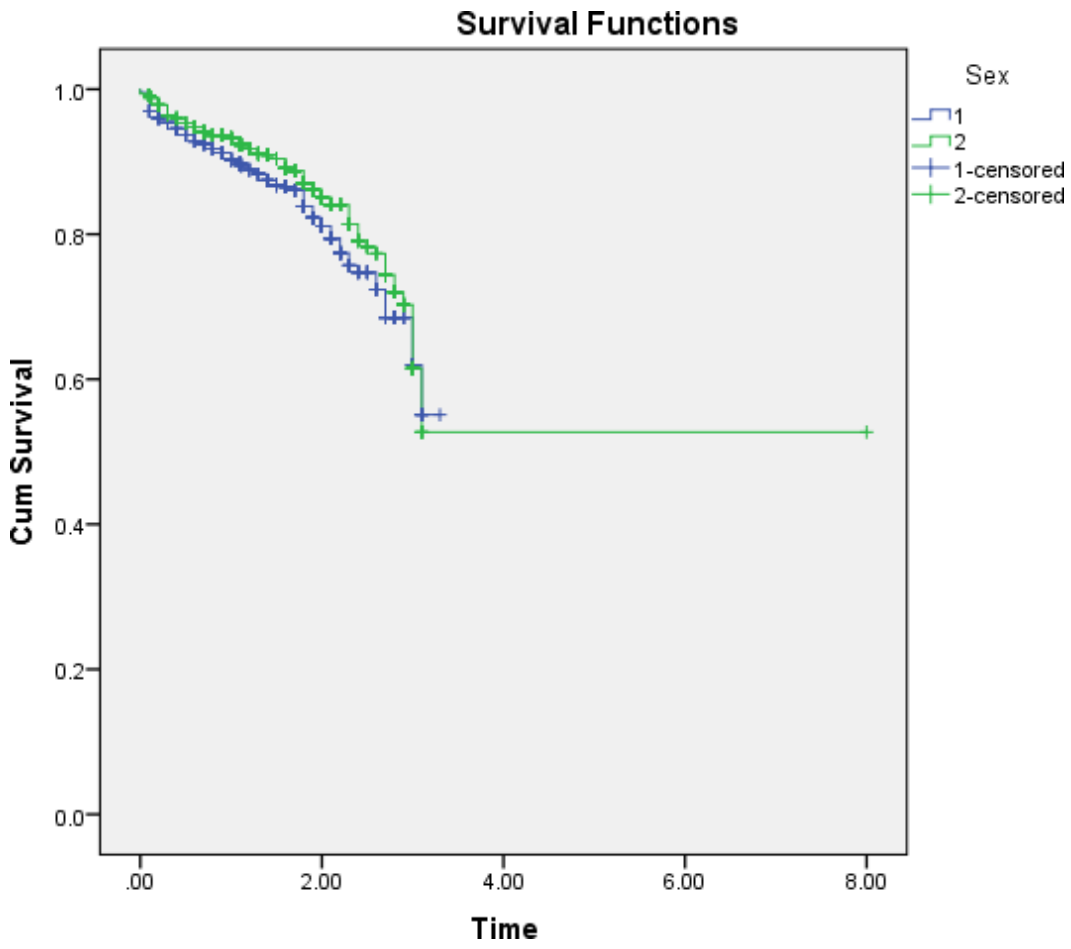

Figure 4: KM plot for sex since diagnosis

Figure 4 above shows the survival rates of patients by sex, with 1 denoting females and 2 for males. At month 0, the survival probability was 1.0 (i.e., 100% of the MDR-TB patients were alive) while at month 8, the probability of survival was approximately 0.54 (i.e., 54% of the MDR-TB patients were still alive) for male patients.

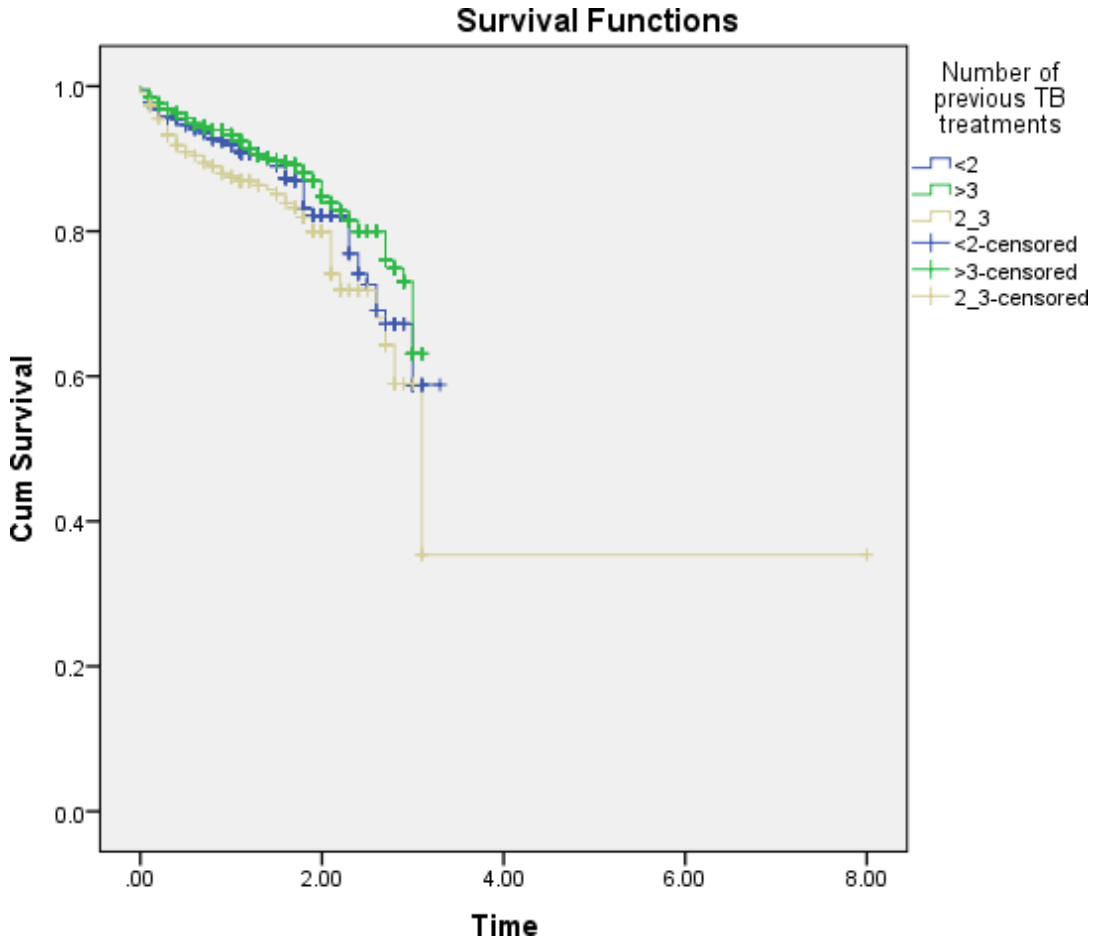

Figure 5: KM plot for number of previous TB treatments since diagnosis

Looking at the survival rates of MDR-TB patients by the number of previous TB treatments they have had in the past as shown in Figure 5 above, it can be observed that all patients had a high survival rate at the beginning of their treatment, however, their survival rates started decreasing as the duration (in months) of their stay on the TB treatment increases. In addition, it can be observed that MDR-TB patients who had 2-3 previous TB treatments had a longer survival time, while MDR-TB patients who had >3 previous TB treatments had a shorter survival time.

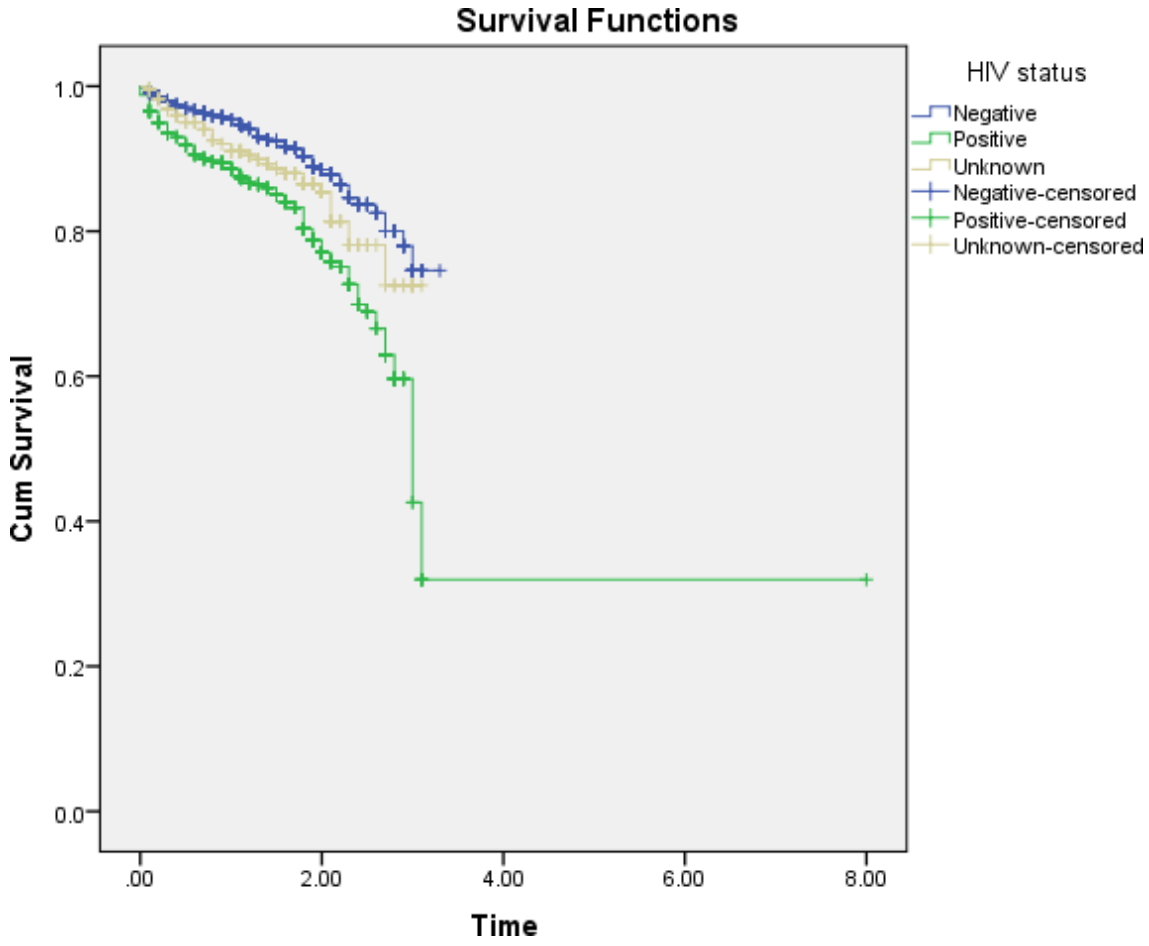

Figure 6: KM plot for HIV status at diagnosis

From Figure 6, it can be observed that HIV positive MDR-TB patients had a lower survival rate than MDR-TB patients who were HIV negative and those whose test results were unknown. Additionally, at month 2 the probability of survival was approximately 0.70 (70%) while at month 8, the probability of survival was approximately 0.30 for HIV positive MDR-TB patients.

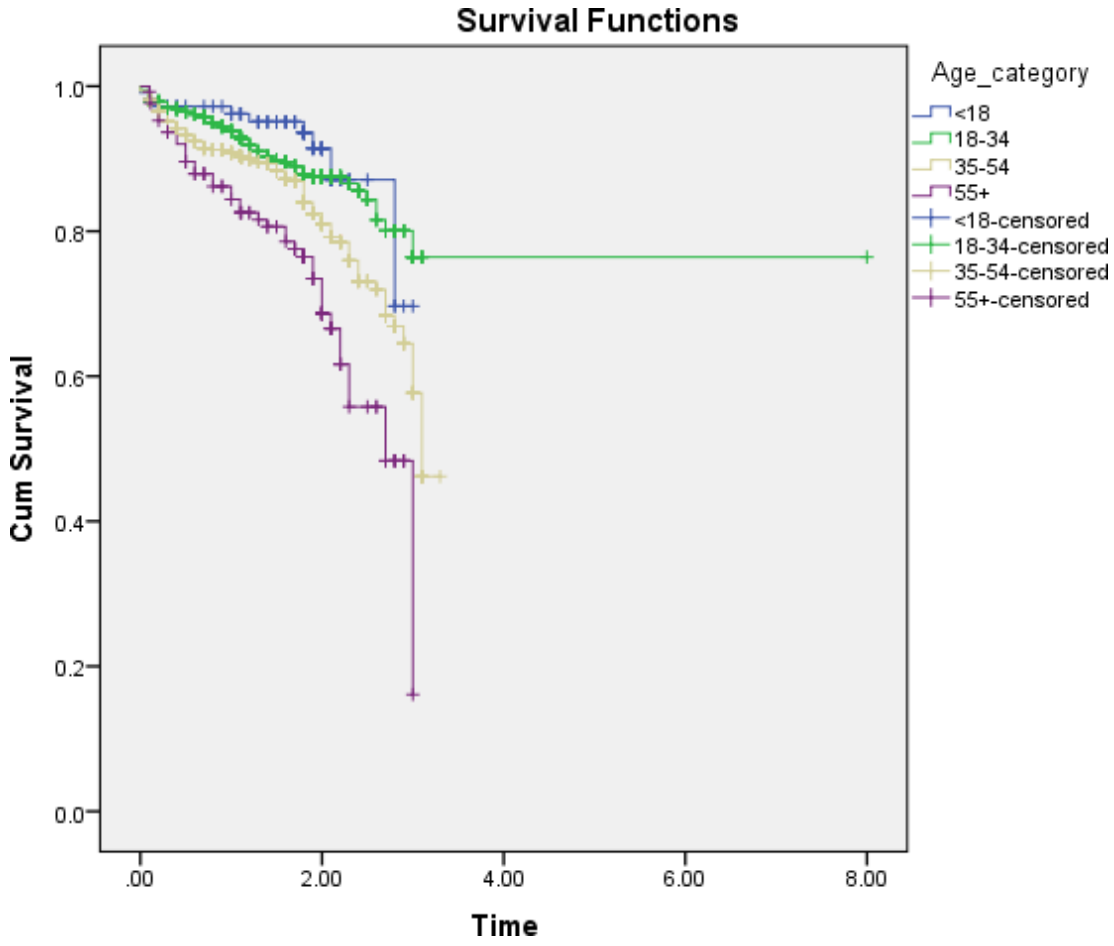

Figure 7: KM plot for age category since diagnosis

From Figure 7 above, it can be observed that, at month 2, the survival probability was 0.90 (90%) for MDR-TB patients aged less than 18 years and those aged 18-34 years, while at month 8, the probability of survival was approximately above 0.75 (75%) for MDR-TB patients aged 18-34 years. It can also be concluded that MDR-TB patients aged 55 years and above had a shorter survival time of only up to 3 months.

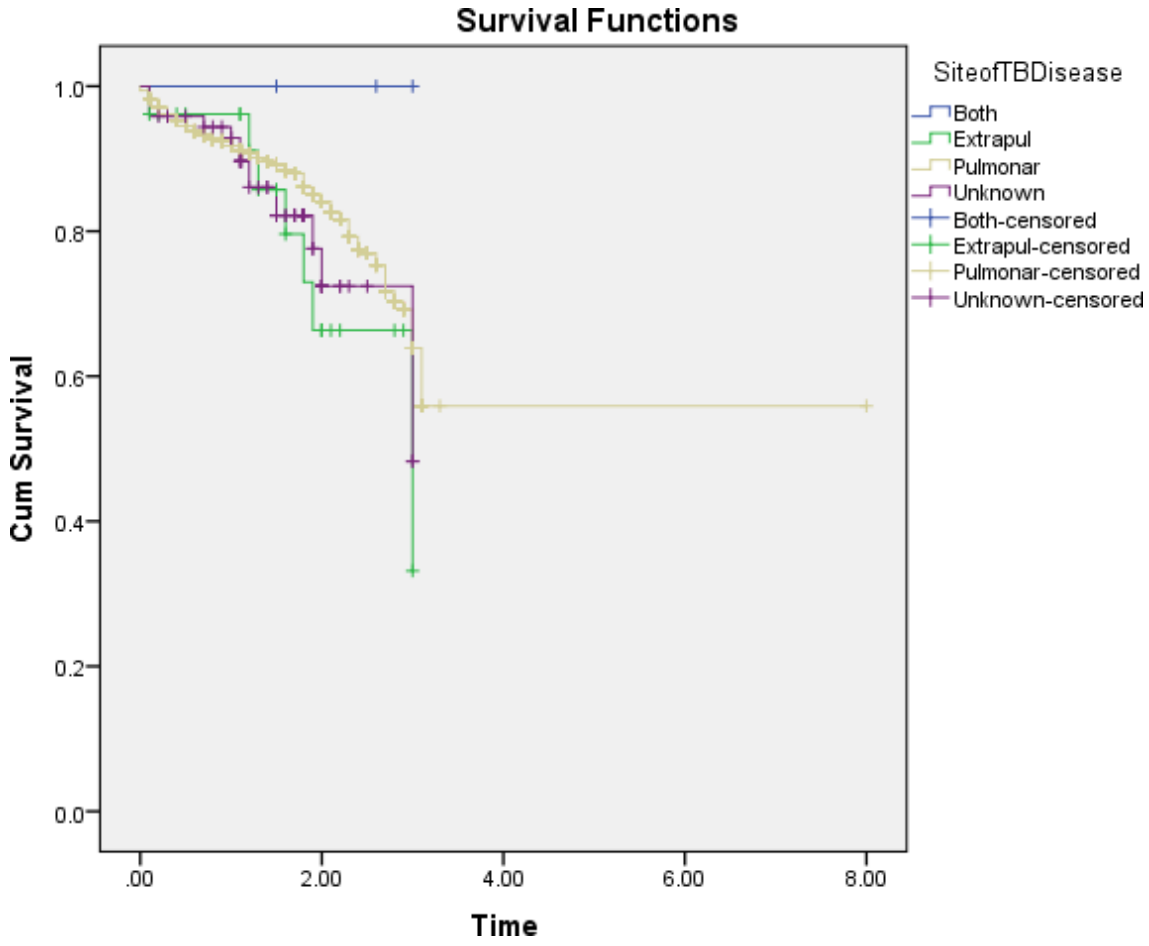

Figure 8: KM plot for site of TB disease from 2014 to 2017

From Figure 8 above, it can be observed that, at month 1, the survival probability was 0.9 (90%) for MDR-TB patients who had pulmonary and extrapulmonary TB, while at month 8, the probability of survival was approximately 0.55 (55%) for MDR-TB patients who had pulmonary TB.

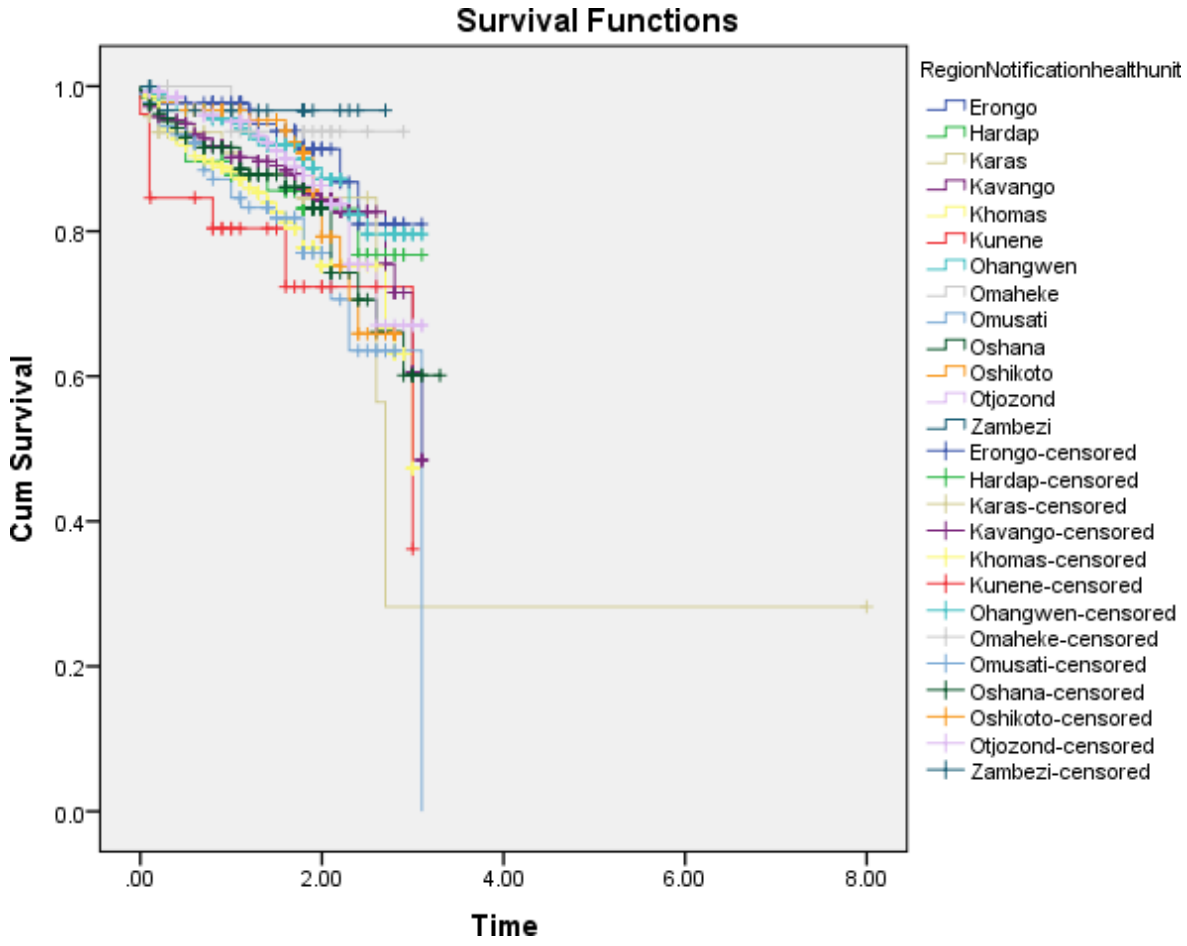

Figure 9: KM plot for region from 2014 to 2017

From Figure 9 above, it can be observed that, at month 8, the probability of survival was approximately 0.25 (25%) for MDR-TB patients in the Khomas region, while MDR-TB patients in the Omusati region had a shorter survival time than MDR-TB patients in other regions.

4.3 Log-rank test

Looking at the Log-rank test for equality of survivor functions output shown in Table 5, at a 5%-10% significance level, it can be concluded that the survival distributions across the MDR-TB patients' sex ($p=0.067$), number of previous TB treatments done ($p=0.022$), HIV status ($p<0.001$), treatment type ($p<0.001$), region ($p=0.004$) and age category ($p<0.001$) characteristics differ significantly. However, the survival distributions did not differ significantly across the patients'

site of TB disease (p=0.169). These significant characteristics were later used in the MDR-TB mortality modelling (sections 4.4 & 4.5).

Table 5: Log-rank test for equality of survivor functions

	Chi-square	P-value
Sex	3.35	0.067**
Age category	37.74	<0.001*
HIV status	26.61	<0.001*
Site of TB disease	5.04	0.169
Treatment type	30.29	<0.001*
Region	29.09	0.004*
Number of previous TB treatments	7.61	0.022*

*5% level of significance; **10% level of significance

4.4 Cox Regression

From Table 6, since the p=0.468 is greater than a 5% level of significance, it can be concluded that the (fitted) Cox model met the assumption of proportionality and the resulting regression output shown in Table 7.

Table 6: Test of proportional hazard assumption

	Chi-square	P-value
Global test	5.61	0.468

From Table 7, at a 5%-10% level of significance, it can be concluded that the MDR-TB patients who were males (HR=0.745, p=0.039, 95% CI: 0.562-0.986) had a low risk of mortality compared to the patients who were females. Looking at the age category characteristic, the MDR-TB patients who were aged 35-54 (HR=1.483, p=0.018, 95% CI: 1.071-2.053) and 55+ (HR=3.463, p<0.001, 95% CI: 2.297-5.223) years had a higher risk of mortality compared to the patients who were aged 18-34 years. It can be observed that MDR-TB patients from the //Karas (HR=0.01, p<0.001, 95% CI: 0.008-0.012) and Ohangwena (HR=0.01, p<0.001, 95% CI: 0.008-0.012) regions had lower

risk of mortality compared to the patients who were from the Erongo region. However, MDR-TB patients who were from the Khomas (HR=3.000, p=0.008, 95% CI: 1.335-6.743), Omusati (HR=9.042, p=0.001, 95% CI: 2.460-33.236), Oshana (HR=2.160, p=0.074, 95% CI: 0.928-5.027), Oshikoto (HR=4.263, p=0.039, 95% CI: 1.076-16.891) and Otjozondjupa (HR=3.858, p=0.059, 95% CI: 0.951-15.655) regions had high risk of mortality. Similarly, it can be observed that MDR-TB patients who had failure re-treatment (HR=2.102, p=0.017, 95% CI: 1.145-3.861) had high risk of mortality compared to patients who had come in after defaulting on their treatment. However, MDR-TB patients who were new to treatment (HR=0.699, p=0.068, 95% CI: 0.476-1.027) had low risk of mortality. Furthermore, MDR-TB patients who were HIV positive (HR=2.110, p<0.001, 95% CI: 1.510-2.950) had a high risk of mortality compared to patients who were HIV negative.

Table 7: Output from the Cox regression Breslow method for ties

	HR	SE	P-value	95% CI lower	95% CI upper
Sex					
Male	0.745	0.107	0.039*	0.562	0.986
Female (Ref)					
Age category					
<18	0.893	0.341	0.767	0.423	1.886
35-54	1.483	0.246	0.018*	1.071	2.053
55+	3.463	0.726	<0.001*	2.297	5.223
18-34 (Ref)					
Region					
Hardap	1.267	0.892	0.737	0.319	5.035
//Karas	0.010	0.001	<0.001*	0.008	0.012
Kavango	0.679	0.732	0.719	0.082	5.622
Khomas	3.000	1.240	0.008*	1.335	6.743
Kunene	2.245	1.620	0.263	0.546	9.238
Ohangwena	0.010	0.001	<0.001*	0.008	0.012
Omaheke	0.635	0.683	0.673	0.077	5.230
Omusati	9.042	6.005	0.001*	2.460	33.236
Oshana	2.160	0.931	0.074**	0.928	5.027
Oshikoto	4.263	2.995	0.039*	1.076	16.891

Otjozondjupa	3.858	2.757	0.059**	0.951	15.655
Zambezi	0.321	0.347	0.293	0.039	2.661
Erongo (Ref)					
Treatment type					
Failure 1st treatment	0.895	0.242	0.681	0.527	1.519
Failure re-treatment	2.102	0.652	0.017*	1.145	3.861
New	0.699	0.137	0.068**	0.476	1.027
Others	1.143	0.408	0.708	0.568	2.301
After default (Ref)					
Number of previous TB treatments					
<2	0.807	0.175	0.321	0.527	1.234
>3	0.801	0.185	0.336	0.509	1.259
2-3 (Ref)					
HIV status					
Positive	2.110	0.361	<0.001*	1.510	2.950
Unknown	1.321	0.300	0.221	0.846	2.063
Negative (Ref)					
_cons	0.038	0.015	<0.001	0.018	0.081

*5% level of significance; **10% level of significance; HR=Hazard Ratio; SE=Standard Error; CI=Confidence Interval; (Ref)=Reference group

4.5 Modelling the risk factors of MDR-TB mortality

Since the observations in this current study were clustered into groups such as regions, in order to account for the unobserved heterogeneity in individual risk to diseases and death, the shared frailty modelling technique was consider when modelling the MDR-TB mortality. Thus, as explained in sections 3.3.2.4, 3.3.2.5 and 3.3.3, in order to determine the best fit model to use in modelling the MDR-TB mortality, two sets of models were considered – one set was the models with frailty, while the other one was without frailty. As a result, 10 models were fitted, namely, (i) an Exponential Accelerated Failure Time (AFT) Regression model, (ii) a Weibull Proportional Hazard (PH) Regression model, (iii) a Lognormal AFT Regression model, (iv) a Loglogistic AFT Regression model, (v) a Gompertz PH Regression model, (vi) an Exponential AFT Regression model with a Gamma frailty, (vii) a Weibull PH Regression model with a Gamma frailty, (viii) a Lognormal AFT Regression model with a Gamma frailty, (ix) a Loglogistic AFT Regression

model with a Gamma frailty, and (x) a Gompertz PH Regression model with a Gamma frailty, and their respective AIC and BIC values shown in Table 8.

Table 8: AIC and BIC values of the fitted 10 models

	Without frailty		With frailty	
Models	AIC	BIC	AIC	BIC
Exponential	1470.171	1601.701	1469.372	1614.055
Gompertz	1452.833	1589.625	1451.836	1604.411
Weibull	1462.592	1599.384	1461.647	1611.591
Loglogistic	1470.292	1599.384	1470.760	1619.705
Lognormal	1483.713	1620.504	1482.734	1630.048

From Table 8, among the models fitted without (Gamma) frailty, it can be seen that the fitted Gompertz PH regression model (AIC=1452.833, BIC=1589.625) had the lowest AIC and BIC values. This meant that a Gompertz PH regression model was the best fit model to use when modelling the MDR-TB mortality without frailty consideration. Likewise, among the models fitted with frailty, it can be seen that the fitted Gompertz PH regression model (AIC=1451.836, BIC=1604.411) had the lowest AIC and BIC values. This meant that a Gompertz PH regression model with Gamma frailty was the best fit model to use when modelling the MDR-TB mortality with frailty consideration. Thus, it can be concluded that the Gompertz PH regression model is the best fit model to use for modelling the MDR-TB mortality, with the Gompertz PH regression with Gamma frailty model the best fit for the frailty modelling of the MDR-TB mortality. Table 9 shows the outputs obtained from the fitted Gompertz PH regression with and without Gamma frailty models.

4.5.1 Gompertz without frailty

From Table 9 at a 5%-10% level of significance, it can be concluded that the MDR-TB patients who were males (HR=0.700, p=0.012, 95% CI: 0.529-0.924) had a low risk of mortality compared to the patients who were females. Looking at the age category characteristic, the MDR-TB patients

who were aged 35-54 (HR=1.539, p=0.009, 95% CI: 1.112-2.129) and 55+ (HR=3.288, p<0.001, 95% CI: 2.186-4.946) years had high risk of mortality compared to the patients who were aged 18-34 years. Additionally, MDR-TB patients who were from the Khomas (HR=3.374, p=0.001, 95% CI: 1.686-6.75), Kunene (HR=3.551, p=0.018, 95% CI: 1.248-10.106), Omusati (HR=2.463, p=0.022, 95% CI: 1.141-5.32), Oshana (HR=2.432, p=0.018, 95% CI: 1.165-5.075) and Otjozondjupa (HR=2.127, p=0.065, 95% CI: 0.954-4.743) regions had high risk of mortality compared to the patients from the Erongo region. Similarly, MDR-TB patients who had failure re-treatment (HR=2.036, p=0.021, 95% CI: 1.114-3.722) had a high risk of mortality compared to patients who had come in after defaulting on their treatment. However, MDR-TB patients who were new to treatment (HR=0.659, p=0.031, 95% CI: 0.452-0.962) had a low risk of mortality. Moreover, MDR-TB patients who were HIV positive (HR=1.862, p<0.001, 95% CI: 1.348-2.571) had a high risk of mortality compared to the patients who were HIV negative.

Table 9: Output from the best fit models

	Gompertz (without frailty)					Gompertz (with Gamma frailty)				
	HR	SE	P-value	95% CI lower	95% CI Upper	HR	SE	P-value	95% CI lower	95% CI upper
Sex										
Male	0.700	0.110	0.012*	0.529	0.924	0.684	0.110	0.018*	0.500	0.937
Female (Ref)										
Age category										
<18	0.800	0.304	0.556	0.380	1.685	0.764	0.304	0.499	0.350	1.667
35-54	1.539	0.268	0.009*	1.112	2.129	1.483	0.268	0.029*	1.041	2.114
55+	3.288	0.914	<0.001*	2.186	4.946	3.586	0.914	<0.001*	2.176	5.911
18-34 (Ref)										
Region										
Hardap	1.473	0.697	0.413	0.582	3.724	1.620	0.840	0.352	0.587	4.474
//Karas	0.984	0.544	0.976	0.333	2.906	1.270	0.754	0.692	0.394	4.067
Kavango	1.753	0.654	0.132	0.844	3.644	1.809	0.719	0.136	0.830	3.942
Khomas	3.374	1.194	0.001*	1.686	6.750	3.681	1.426	0.001*	1.723	7.866
Kunene	3.551	1.895	0.018*	1.248	10.106	4.446	2.892	0.022*	1.242	15.913
Ohangwena	1.270	0.511	0.549	0.579	2.795	1.320	0.559	0.518	0.573	3.025
Omaheke	0.662	0.698	0.696	0.084	5.233	0.623	0.677	0.663	0.074	5.239
Omusati	2.463	0.968	0.022*	1.141	5.320	2.700	1.170	0.022*	1.154	6.311
Oshana	2.432	0.913	0.018*	1.165	5.075	2.506	1.001	0.021*	1.145	5.481
Oshikoto	1.558	0.662	0.297	0.677	3.585	1.490	0.677	0.383	0.610	3.631
Otjozondjupa	2.127	0.870	0.065**	0.954	4.743	2.232	0.975	0.066**	0.948	5.254
Zambezi	0.347	0.366	0.316	0.044	2.750	0.325	0.352	0.299	0.039	2.712
Erongo (Ref)										

Treatment type										
Failure 1st treatment	0.923	0.237	0.754	0.558	1.527	0.959	0.276	0.886	0.546	1.687
Failure re-treatment	2.036	0.627	0.021*	1.114	3.722	2.239	0.796	0.023*	1.116	4.496
New	0.659	0.127	0.031*	0.452	0.962	0.646	0.139	0.042*	0.424	0.984
Others	1.060	0.375	0.878	0.527	2.117	0.989	0.391	0.977	0.456	2.146
After default (Ref)										
Number of previous TB treatment										
<2	0.899	0.192	0.618	0.591	1.367	0.835	0.207	0.466	0.513	1.358
>3	0.902	0.206	0.650	0.577	1.410	0.823	0.221	0.469	0.486	1.394
2-3 (Ref)										
HIV status										
Positive	1.862	0.307	<0.001*	1.348	2.571	2.066	0.420	<0.001*	1.387	3.078
Unknown	1.277	0.289	0.279	0.82	1.989	1.359	0.340	0.221	0.832	2.221
Negative (Ref)										
_cons	8.49e-08	<0.001	0.974	0	.	3.03e-10	2.21e-06	0.998	0	.
/gamma	0.374	0.080	<0.001	0.218	0.530	0.524	0.162	0.001	0.205	0.842
/Intheta						-0.505	1.084	0.642	-2.629	1.620
theta						0.604	0.654		0.072	5.052

*5% level of significance; **10% level of significance; HR=Hazard Ratio; SE=Standard Error; CI=Confidence Interval; (Ref)=Reference group

4.5.2 Gompertz with Gamma frailty

From Table 9 at a 5%-10% level of significance, it can be concluded that the MDR-TB patients who were males (HR=0.684, p=0.018, 95% CI: 0.50-0.937) had a low risk of mortality compared to the patients who were females. Looking at the age category characteristic, the MDR-TB patients who were aged 35-54 (HR=1.483, p=0.029, 95% CI: 1.041-2.114) and 55+ (HR=3.586, p<0.001, 95% CI: 2.176-5.911) years had high risk of mortality compared to the patients who were aged 18-34 years. Additionally, MDR-TB patients who were from the Khomas (HR=3.681, p=0.001, 95% CI: 1.723-7.866), Kunene (HR=4.446, p=0.022, 95% CI: 1.242-15.913), Omusati (HR=2.7, p=0.022, 95% CI: 1.154-6.311), Oshana (HR=2.506, p=0.021, 95% CI: 1.145-5.481) and Otjozondjupa (HR=2.232, p=0.066, 95% CI: 0.948 -5.254) regions had high risk of mortality compared to the patients from the Erongo region. Similarly, MDR-TB patients who had failure re-treatment (HR=2.239, p=0.023, 95% CI: 1.116-4.496) had a high risk of mortality compared to patients who had come in after defaulting on their treatment. However, MDR-TB patients who were new to treatment (HR=0.646, p=0.042, 95% CI: 0.424-0.984) had a low risk of mortality. Moreover, MDR-TB patients who were HIV positive (HR=2.066, p<0.001, 95% CI: 1.387-3.078) had a high risk of mortality compared to the patients who were HIV negative.

4.6 Spatial pattern of deaths among MDR-TB patients

4.6.1 Duration of Stay

The spatial map in Figure 10 shows the duration (in months) of stay of the MDR-TB patients at hospitals across the different regions in Namibia while on TB treatment. It can be observed from the map that MDR-TB patients tended to stay longer (2 to 2.7 months) at hospitals in the Otjozondjupa and Kavango regions (dark blue color), long (1.7 to 2 months) in hospitals at the Erongo, Omusati, Oshikoto and Zambezi regions (sky blue color), but tended to stay for a short period (1 to 1.7 months) in hospitals at the //Karas, Omaheke and Ohangwena regions (light blue

color) and for a shorter period (0.8 of 1 month) in hospitals at the Khomas, Hardap, Oshana and Kunene regions (very light blue color). This map appears to be clustered, which suggests that there are spillover effects between regions. Overall, the shortest duration of stay among the MDR-TB patients was 0.8 month whilst the longest duration of stay was 2.7 months. See Appendix C for the names of the regions in Namibia.

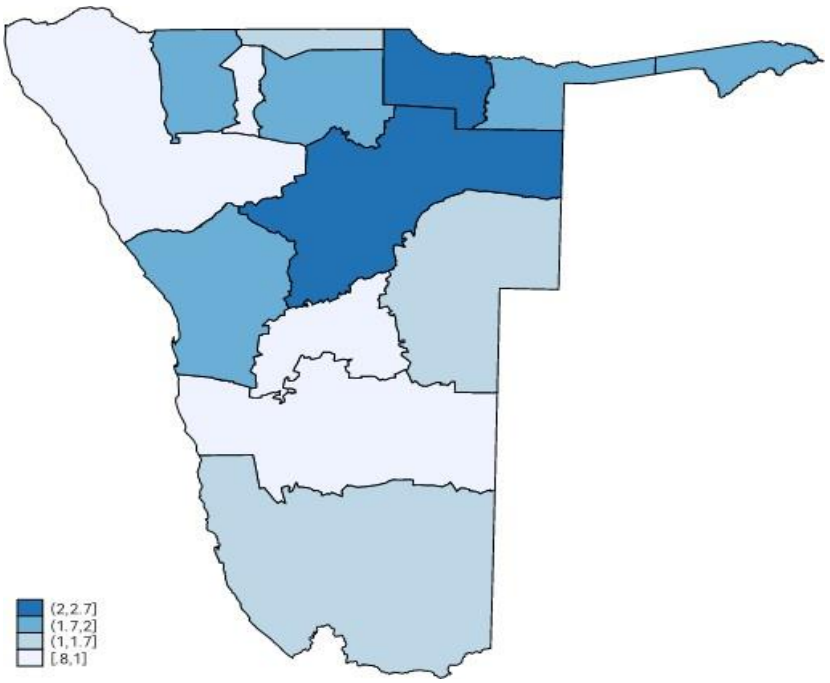

Figure 10: A clustered map of the MDR-TB patients' duration of stay variation in Namibia

4.6.2 Sex

Figure 11 shows that there was no difference between the MDR-TB mortality dispersion between males and females. However, there were less female mortality as well as male mortality in the Omusati, Kavango, Zambezi, Erongo, Omaheke and //Karas regions.

Sex=Female

Sex = Male

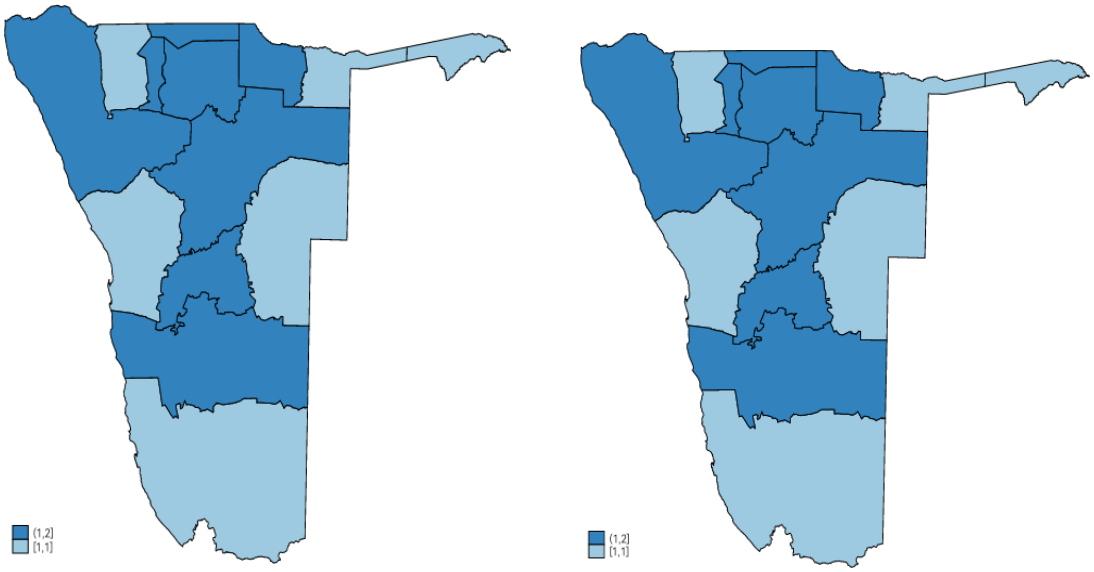

Figure 11: A spatial map for the MDR-TB patients' mortality variation per sex in Namibia

4.6.3 Region

Figure 12 shows the MDR-TB mortality dispersion across the 14 regions of Namibia. It can be observed from the map that higher MDR-TB mortality cases were recorded in the Hardap, Omaheke and Omusati regions (dark blue color), while a high number of MDR-TB deaths cases were recorded in the Kavango, Erongo, Zambezi and Ohangwena regions (sky blue color). However, a low number of MDR-TB deaths cases were recorded in the Kunene and Khomas regions (light blue color), while a lower number of MDR-TB mortality cases were recorded in the //Karas, Otjozondjupa, Oshikoto and Oshana regions (very light blue color).

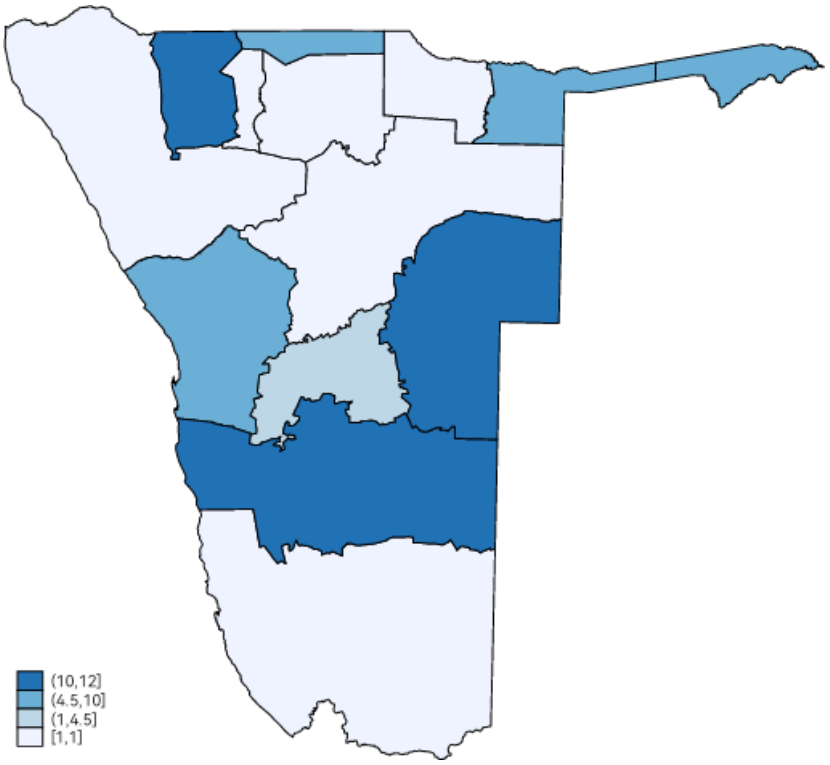

Figure 12: A spatial map of MDR-TB patients' mortality variation per region in Namibia

Chapter 5: Discussion, Conclusion and Recommendations

5.1 Discussion

The main aim of this study was to examine the spatial variation of mortality among MDR-TB patients treated at different hospitals in Namibia by estimating the survival time among patients under treatment for MDR-TB in Namibia, in addition to identifying the risk factors of mortality. Of the 10 different regression models fitted to determine the best fit model to use in modelling the MDR-TB mortality, the Gompertz PH regression model was identified as the best fit model to use, while the Gompertz PH regression model with Gamma (shared) frailty was identified as the best fit model to use for the frailty modelling of the MDR-TB mortality, due to their minimum AIC and BIC values. Moreover, MDR-TB patient's characteristics such as sex, age category, HIV status, region, treatment type and number of previous TB treatments had a significant effect on MDR-TB mortality. However, the MDR-TB patient's site of TB disease did not have a significant effect.

5.1.1 Sex and Age Characteristics

From this study, it was revealed that out of the 1432 MDR-TB patients between 2014 and 2017, majority were males. This can be due to the high tendencies towards alcohol and drug abuse among men, and the interruption of their medications and treatments due to a number of behavioural and psychosocial factors such as peer pressure, anxiety, and rejection of diagnosis, stigma and cultural beliefs. This finding is similar to the findings found by Limenih & Workie (2019) in Ghana who reported that there were more MDR-TB patients among the males than females and that male MDR-TB patients were associated with a high likelihood of experiencing unsuccessful treatment outcomes. This study further reveals that majority of the MDR-TB deaths recorded were among patients who were aged 35-54 years old, although MDR-TB patients who were at least 55 years old had a higher risk of mortality compared to those who were younger. In

other words, as the age of the patient increases, their survival probability were declining. This may be due to the fact that older patients might have underlying conditions such as high blood pressure which lead to weak immune systems, which then lead to poor response to medication. Additionally, the older the patients gets, the more prone they are to contracting other adult-related health illnesses or diseases such as diabetes, arthritis, osteoporosis, stroke and hypertension (to mention a few) thereby affecting their immune system that is already weakened by TB (Oyedele & Ntusi, 2021). Similar findings have been observed in a study done by An et al. (2020) in China where MDR-TB patients aged 40-60 and 60+ years were identified to be at a significant risk of death.

5.1.2 HIV Status and Region Characteristics

Out of the MDR-TB deaths, majority were recorded among patients who were diagnosed with HIV, with such patients having higher risk of mortality. This finding is not surprising as HIV weakens the immune system which is supposed to protect the body from any attacks, thereby increasing the risk of mortality (Oyedele & Ntusi, 2021) in people with TB as they have weaker immune systems than HIV negative patients and the co-infections of TB with HIV can be very fatal on their immune system. Also, HIV positive patients in general have a higher rate of adverse reactions. This study findings concurs with Shipanga (2019) and Woya et al. (2019) where it was revealed that TB patients co-infected with HIV had shorter survival duration than HIV negative patients, with Woya et al. (2019) concluding the same for MDR-TB patients. Furthermore, majority of the MDR-TB deaths recorded were among patients who were from the Khomas and Kavango regions. This is not surprising as the Khomas region has the largest population in the country and receives the highest number of MDR-TB and non-MDR-TB patients countrywide (including referrals from other regions) due to it being the capital city with two of the largest state hospitals and the main referral centres in the country with operational implications such as high patient load, huge patient turn over, extensive surgical operation and exhaustive waiting list.

While for the Kavango region, the hospitals are often understaffed, under equipped and lack sufficient medical supplies to adequately treat MDR-TB patients. Additionally, MDR-TB patients' from the Khomas, Kunene, Omusati, Oshana and Otjozondjupa regions had a higher risk of mortality compared to those from the Erongo region. This can be attributed to the fact that majority of the hospitals in these regions are referral centres for all patients from clinics and health centres in the regions and from neighbouring regions, regardless of the type of illnesses they are experiencing, which bring about operational challenges in terms of high patient load, manpower, treatment materials and equipment, huge patient turn over and extensive surgical operation among others. However, hospitals in the Omusati, Oshana and Otjozondjupa regions can be attributed to poor medical facilities operation and shortage of high skilled personnel.

5.1.3 Treatment Type and Number of Previous TB Treatments Characteristics

The study reveals that there was a uniform dispersal of high MDR-TB mortality cases among MDR-TB patients who had come in after defaulting on their treatment and those new to treatment. This can be due to the patients' immune system which might already be compromised at the time of reactivation of their (prescribed) TB treatment while for patients new to treatment, it can be due to the late diagnosis and commencement of their TB treatment. This also concurs with the findings made by Woya et al. (2019) where it was concluded that newly enrolled MDR-TB patients were at high risk than those who were previously enrolled. However, this study found that there were more MDR-TB mortality cases among MDR-TB patients' who had more than three previous TB treatments. This can be attributed to weak immune systems, where the body becomes resistant to certain (repeated) drugs.

5.2 Conclusions

From this study, it was revealed that there were more MDR-TB deaths among female patients, as well as high MDR-TB deaths among 35-54 years old HIV positive patients with Pulmonary TB in the Khomas region, who have had more than three previous TB treatments. In addition, patient's characteristics such as sex, age category, HIV status, region, number of previous TB treatments and treatment type had a significant effect on their MDR-TB mortality. Furthermore, from this study, it was revealed that the frailty and non-frailty modelling of the MDR-TB mortality can be done via the Gompertz PH regression model. MDR-TB mortality was less likely to occur for patients who were males and new to treatment compared to patients who came in after defaulting on their treatment, while MDR-TB mortality was more likely to occur for HIV positive patients who were at least 55 years old, from the Khomas, Kunene, Omusati, Oshana and Otjozondjupa regions compared to patients from the Erongo region.

5.3 Recommendations

MDR-TB mortality is a complex issue that has no simple solution and requires intervention from all government and non-governmental organizations. It can be prevented at all costs by implementing an effective Directly Observed Treatment Short Course (DOTS) strategy. It is therefore recommended that good control measures in hospitals and other congregate settings be implemented to protect HIV positive patients who were at least 55 years old, from the Khomas, Kunene, Omusati, Oshana and Otjozondjupa regions, as well as other patients and health care workers. All efforts have to be made to provide MDR-TB patients with tailored services and by ensuring family members and treatment supporters are fully involved in the care and support of the patients. Moreover, health care workers should ensure that MDR-TB patients fully understand why their (TB/MDR-TB) treatment should not be interrupted and the consequences of poor adherence (such as poorer prognosis, higher risk of failure, putting family members and contacts at risk, and having to receive more complicated and longer treatments).

In addition, from this research study's findings, it is strongly recommended that the Namibian government and policy makers consider conducting outreach sessions/courses to increase awareness on MDR-TB including early detection and screening programs, patient's adherence and mortality, most especially among female patients aged 55 years and above, with HIV and those living in the Khomas, Kunene, Omusati, Oshana and Otjozondjupa regions. Also, this research study recommends that more health facilities be built in the Khomas, Kunene, Omusati, Oshana and Otjozondjupa regions to take off pressure from already-existing facilities, while at the same time, government should employ more skilled medical personnel to cover backlogs and ensure that sufficient medical supplies are provided to health facilities.

Further studies on this topic need to consider other factors that might have an effect on MDR-TB mortality such as COVID-19 status, body weight, pregnancy, lactation, anaemia, nutrition status, smoking, alcohol/drug abuse, and place of work. Likewise, future research can make use of latest TB datasets and use a longitudinal study design which can enable the researcher to focus on a longer study period. Moreover, since this study revealed a high MDR-TB deaths among HIV positive patients with Pulmonary TB who have had more than three previous TB treatments, a further epidemiological study is recommended for the possible identification of associated risk factors of these deaths among this specific patient types.

References

Acosta, C. D., Dadu, A., Ramsay, A., & Dara, M. (2014). Drug-resistant tuberculosis in Eastern Europe: Challenges and ways forward. *Public Health Action, 4,* S3–S12. https://doi.org/10.5588/pha.14.0087

Ali, H.K.A, & Mohammed, A.I.A. (2022). Log-Rank Test for Comparing Survival Curves of Neonatal Mortality Characteristic Groups in River Nile State-Sudan. *Scientific Research an Academic Publisher: Open Journal of Statistics, 12(4).* Doi: 10.4236/ojs.2022.124032

An, Q., Song, W., Liu, J., Tao, N., Liu, Y., Zhang, Q., Xu, T., Li, S., Liu, S. Q., Li, Y., Yu. C., & Li, H. (2020). Primary drug-resistance pattern and trend in elderly Tuberculosis patients in Shandong, China, from 2004 to 2019. *Infection Drug Resistant*. 2(13),4133-4145 https://doi.org/10.2147/IDR.S277203

Andersen, P.K. (2022). Fifty Years with the Cox Proportional Hazards Regression Model. *Journal of the Indian Institute of Science*. https://doi.org/10.1007/s41745-021-00283-9

Asgedom, S.W., Teweldemedhin, M., & Gebreyesus, H. (2018). Prevalence of multidrug-resistant tuberculosis and associated factors in Ethiopia: a systematic review. *Journal of Pathogens* 2018: 7104921. https://doi.org/10.1155/2018/7104921

Bailey, J., & Saleeb, P. (2017). Exploring the threat of MDR-TB in the United States. *Contagion Live, 2(4).* https://www.contagionlive.com/view/exploring-the-threat-of-mdr-tb-in-the-united-states

Baird, T., Donnan, E., Coulter, C., Simpson, G., Konstantinos, A., & Eather, G. (2018). Multidrug-resistant tuberculosis in Queensland, Australia: an ongoing cross-border challenge. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease*, *22*(2), 206–211. https://doi.org/10.5588/ijtld.17.0180

Balabanova, Y., Radiulyte, B., Davidaviciene, E., Hooper, R., Ignatyeva, O., Nikolayevskyy, V., & Drobniewski, F. A. (2011). Survival of drug resistant Tuberculosis patients in Lithuania: Retrospective national cohort study. *British Medical Journal Open, 1(2).* https://doi.org/10.1136/bmjopen-2011-000351

Balan, A.T., & Putter, H. (2020). A tutorial on frailty models. *SAGE Journals*, 29(11). https://doi.org/10.1177/0962280220921

Bland, J. M., & Altman, D. G. (2004). The log rank test. *British Medical Journal (Clinical research ed.)*, *328*(7447), 1073. https://doi.org/10.1136/bmj.328.7447.1073

Camphor, H. S., Viney, K., Polkinghorne, B., & Pennington, K. (2020). Retrospective analysis of multidrug-resistant tuberculosis case notifications in Australia (1999-2018). *Communicable diseases intelligence (2018)*, *44*, 10.33321/cdi.2020.44.68. https://doi.org/10.33321/cdi.2020.44.68

Chen, S., Huai, P., Wang, X., Zhong, J., Wang, X., Wang, K., Wang, L., Jiang, S., Li, J., Peng, Y., & Ma, W. (2013). Risk factors for multidrug resistance among previously treated patients with Tuberculosis in eastern China : A case – control study. *International Journal of Infectious Diseases*, *17*(12), e1116–e1120. https://doi.org/10.1016/j.ijid.2013.06.006

Chen, L. M., Ibrahim, J. G., & Chu, H. (2014). Sample size determination in shared frailty models for multivariate time-to-event data. *Journal of biopharmaceutical statistics*, *24*(4), 908–923. https://doi.org/10.1080/10543406.2014.901346

Chen, M. P., Miramontes, R., & Kammerer, J. S. (2020). Multidrug-resistant tuberculosis in the United States, 2011-2016: patient characteristics and risk factors. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease*, *24*(1), 92–99. https://doi.org/10.5588/ijtld.19.0173

Columbia University Mailman School of Public Health. (2022). Population Health Methods: Time to Event Data Analysis. New York, USA.

Cox, D. R., & Oakes, D. (2018). Analysis of survival data. Routledge. London, UK

Deo, S. V., Deo, V., & Sundaram, V. (2021). Survival analysis-part 2: Cox proportional hazards model. *Indian journal of thoracic and cardiovascular surgery*, *37*(2), 229–233. https://doi.org/10.1007/s12055-020-01108-7

Dey, R., Zhou, W., Kiiskinen, T., Havullina, A., Elliot, A., Karjaleinen, J., Kurki, M., Qin, A., Gen, F., Lee, S., Palotie, A., Neale, B., Daly, M., & Lin, X. (2022). Efficient and accurate frailty

model approach for genome-wide survival association analysis in large-scale biobanks. *Nature Communications* **13**, 5437. https://doi.org/10.1038/s41467-022-32885-x

Dube, N. (2015). Application and comparison of time series methods on Tuberculosis incidence data: A case study of Zimbabwe 1990-2013. MSc thesis, Texas Tech University.

Elhafeez, A.S., D'Arrigo, G., Leonardis, D., Fusaro, M., Tripepi, G., & Roumeliotis, S. (2021). Methods to Analyze Time-to-Event Data: The Cox Regression Analysis. *Oxidative medicine and cellular longevity*. https://doi.org/10.1155/2021/1302811

European Centre for Disease and Control. (2014). Tuberculosis surveillance and monitoring in Europe. Stockholm, Sweden.

Etikan, İ., Abubakar, S., & Alkassim, R. (2017). The Kaplan Meier Estimate in Survival Analysis. *MedCrave - Biometrics & Biostatistics International Journal,* 5(2):55-59. doi: 10.15406/bbij.2017.05.00128

Etikan, I., Bukirova, K., & Yuvali, M. (2018). Choosing statistical tests for survival analysis. *Biometrics and Biostatistics International J*ournal, 7(5),477-481. https://doi.org/10.15406/bbij.2018.07.00249

Flynn, R. (2012). Survival analysis. *Journal of Clinical Nursing.* 21(19), 2789-2797.

Harry F. M. (2003). Encyclopedia of Physical Science and Technology (Third Edition). *Academic Press*, 143-159. https://doi.org/10.1016/B0-12-227410-5/00659-1

Hevi, J.H., & Mohammad, M.F. (2022). Apply Parametric Shared Frailty Models to Colorectal Cancer Patients. *Cihan University-Erbil Scientific Journal (CUESJ),* 6 (2): 119-124. http://journals.cihanuniversity.edu.iq/index.php/cuesj

Ismail, N., Ismail, F., Omar, S. V., Blows, L., Gardee, Y., Koornhof, H., & Onyebujoh, P. C. (2018). Drug resistant tuberculosis in Africa: Current status, gaps and opportunities. *African Journal of Laboratory Medicine*, *7*(2). https://doi.org/10.4102/ajlm.v7i2.781

Irvine, A.F., Waise, S., Green, E.W., & Stuart, B. (2020). A non-linear optimisation method to extract summary statistics from Kaplan-Meier survival plots using the published *P* value. *BMC Medical Research Methodology*. https://doi..org/10.1186/s12874-020-01092-x

Jabir, Y. N., Aniley, T. T., Bacha, R. H., Debusho, L. K., Chikako, T. U., Hagan, J. E., Seidu, A.A., & Ahinkorah, O.B. (2022). Time to Death and Associated Factors among Tuberculosis Patients in South West Ethiopia: Application of Shared Frailty Model. *Diseases*, *10*(3), 51. MDPI AG. http://dx.doi.org/10.3390/diseases10030051

Jung, T. H., Kyriakides, T., Holodniy, M., Esserman, D., & Peduzzi, P. (2018). A joint frailty model provides for risk stratification of Human Immunodeficiency Virus-infected patients based on unobserved heterogeneity. *Journal of clinical epidemiology*, 98,16–23. https://doi.org/10.1016/j.jclinepi.2018.02.007

Kartsonaki, C. (2016). Survival analysis. *Diagnostic Histopathology*, 22(7), 263 – 270. https://doi.org/10.1016/j.mpdhp.2016.06.005.

Kleinbaum, D. G., & Klein , M. (2015). Survival Analysis - A Self-Learning Text. New York: Springer-Verlag.

Kuitunen, I., Ponkilainen, V.T., Uimonen, M.M., Eskelinen, A., & Reito, A. (2021). Testing the proportional hazards assumption in cox regression and dealing with possible non-proportionality in total joint arthroplasty research: methodological perspectives and review. *BMC Musculoskelet Disor*ders **22**(489). https://doi.org/10.1186/s12891-021-04379-2

LaMorte, W.W. (2016). Survival Analysis: Comparing Survival Curves. School of Public Health, Boston University.

Lee, S., & Lim, H. (2019). Review of statistical methods for survival analysis using genomic data. *Gemonics & Informatic,17(4).* https://doi.org/10.5808/GI.2019.17.4.e41

Li, B. Y., Shi, W. P., Zhou, C. M., Zhao, Q., Diwan, V. K., Zheng, X., Li, Y., Hoffner, S., & Xu, B. (2020). Rising challenge of multidrug-resistant Tuberculosis in China: A predictive study using Markov modelling. *Infectious Diseases of Poverty*, *9*(1). https://doi.org/10.1186/s40249-020-00682-7

Limenih, Y. A., & Workie, D. L. (2019). Survival analysis of time to cure on multi-drug resistance Tuberculosis patients in Amhara region, Ethiopia. *BioMed Central Public Health*, *19*(1). https://doi.org/10.1186/s12889-019-6500-3

Liu, X. (2012). Survival analysis: models and applications. John Wiley & Sons.

Lygizos, M., Shenoi, S. V., Brooks, R. P., Bhushan, A., Brust, J. C., Zelterman, D., Deng, Y.,

Matteelli, A., Rendon, A., Tiberi, S., Al-Abri, S., Voniatis, C., Carvalho, A., Centis, R., D'Ambrosio, L., Visca, D., Spanevello, A., & Battista Migliori, G. (2018). Tuberculosis elimination: where are we now? *European respiratory review: an official journal of the European Respiratory Society*, *27*(148), 180035. https://doi.org/10.1183/16000617.0035-2018

Mietlowski, W. (2012). A Review of: Modeling Survival Data Using Frailty. *Journal of Biopharmaceutical Statistics*, 22:2, 420-423, DOI: 10.1080/10543406.2012.635981

Ministry of Health and Social Services. (2016). National Tuberculosis and Leprosy programme: Annual report 2015 - 2016. Windhoek, Namibia.

Mollel, E.W., Todd, J., & Mahande, M. J. (2020). Effect of Tuberculosis infection on mortality of HIV-infected patients in Northern Tanzania. *Tropical Medicine and Health*, 48(26). https://doi.org/10.1186/s41182-020-00212-z

Mueller, L.D., Nusbaum, T.J., & Rose, M.R. (1995). The Gompertz equation as a predictive tool in demography. Experimental Gerontology, 30(6), 553-569. https://doi.org/10.1016/0531-5565(95)00029-1.

Noppert, G.Y. Z. (2015). Trends of sputum-smear positive Tuberculosis in Zimbambwe (8 ed.). BioMed Central Research Notes.

Nussbeck, F.W. (2014). Log-Logistic Models. In: Michalos, A.C. (eds) Encyclopedia of Quality of Life and Well-Being Research. Springer, Dordrecht. https://doi.org/10.1007/978-94-007-0753-5_1691

Oyedele, O.F. and Ntusi, N.S. (2021). A Multinomial modelling of the factors that impact viral load levels in adults on Anti-Retroviral Therapy in Namibia: A case study of Nankudu health district. *International Science and Technology Journal of Namibia,* 14, 73-82.

Ou, Z. J., Yu, D. F., Liang, Y. H., He, W. Q., Li, Y. Z., Meng, Y. X., Xiong, H. S., Zhang, M. Y., He, H., Gao, Y. H., Wu, F., & Chen, Q. (2021). Trends in burden of multidrug-resistant Tuberculosis in countries, regions, and worldwide from 1990 to 2017: Results from the global

burden of disease study. *Infectious Diseases of Poverty*, *10*(1). https://doi.org/10.1186/s40249-021-00803-w

Peace, K.E, Chen, D., & Menom, S. (2020). Biopharmaceutical Applied Statistics Symposium: Volume 1 Design of Clinical Trials. doi=10.1007/978-981-10-7829-3

Petrus, A. (2019). An application of survival analysis on the prevalence and risk factors of breast cancer in Namibia. MSc Thesis, University of Namibia.

Qi, J. (2009). Comparison of proportional hazards and accelerated failure time models. MSc thesis, University of Saskatchewan.

Rai, S., Mishra, P. & Ghoshal, U.C. Survival analysis: A primer for the clinician scientists. *Indian Journal of Gastroenterol* **40**, 541–549 (2021). https://doi.org/10.1007/s12664-021-01232-1

Ricks, P. M., Mavhunga, F., Modi, S., Indongo, R., Zezai, A., Lambert, L. A., Deluca, N., Krashin, J. S., Nakashima, A. K., & Holtz, T. H. (2012). Characteristics of multidrug-resistant Tuberculosis in Namibia. *BMC Infectious Diseases*, *12*(1). https://doi.org/10.1186/1471-2334-12-385

Schober, P., & Vetter, T.R. 2018. Survival Analysis and Interpretation of Time-to-Event Data: The Tortoise and the Hare. *Anesthesia & Analgesia* 127(3):p 792-798. DOI: 10.1213/ANE.0000000000003653

Singh, A., Prasad, R., Balasubramanian, V., & Gupta, N. (2020). Drug-resistant Tuberculosis and HIV infection: Current perspectives. *HIV/AIDS - Research and Palliative Care* 12, 9–31. https://doi.org/10.2147/HIV.S193059

Shipanga, A. (2019). A Spatial temporal analysis of survival among TB and HIV. MSc Thesis, University of Namibia.

Sidhu, S., Jain, K., & Sharma, S.K. (2019). The Generalized Gamma Shared Frailty Model under Different Baseline Distributions. *International Journal of Mathematical, Engineering and Management Sciences, 4(1):* 219-231. DOI:10.33889/IJMEMS.2019.4.1-019

Srinivasan, R., Ponnuraja , C., & Rajendran, S. (2017). Spatial frailty survival model for infection of Tuberculosis among HIV infected individuals. *SSRG International Journal of Medical Science, 4(2), 5-10*

Subhasree, C. (2017). Survival Analysis Part – I. https://datascienceplus.com/survival-analysis-part-i/

Tolley, H. D., Barnes, J. M., & Freeman, M. D. (2016). Survival Analysis in Forensic Epidemiology. ScienceDirect, 261 - 284.

Turkson, A.J., Ayiah-Mensah, F., & Nimoh, V. (2021). Handling Censoring and Censored Data in Survival Analysis: A Standalone Systematic Literature Review, *International Journal of Mathematics and Mathematical Sciences.* https://doi.org/10.1155/2021/9307475

Seung, K. J., Keshavjee, S., & Rich, M. L. (2015). Multidrug-Resistant Tuberculosis and extensively drug-resistant Tuberculosis. *Cold Spring Harbor perspectives in medicine*, *5*(9). https://doi.org/10.1101/cshperspect.a017863

WHO. (2013). Global Tuberculosis Report. Geneva, Switzerland.

WHO. (2018). Global Tuberculosis Report. Geneva, Switzerland.

WHO. (2019). Global Tuberculosis Report. Geneva, Switzerland.

WHO. (2021). Global Tuberculosis Report. Geneva, Switzerland.

Woya, A. A, Tekile, A. K, & Basha, W. G. (2019). Spatial frailty survival model for MDR-TB mortality in Amhara Region, Ethiopia. *Tuberculosis Research and Treatment.* https//doi.org/10.1155/2019/8742363

Ying, X., Wei, Z., Rui-Jun, Q., & Jun, T. (2022). Risk factors for multidrug-resistant tuberculosis: A worldwide systematic review and meta-analysis. *Plos One Collection: Public Health Implications of Changing Climate.* https://doi.org/10.1371/journal.pone.0270003

Zetola, N.M, Modongo, C., Kip, E.C., & Gross, R. (2013). *National Institutes of Health Public Access, 16(11), 1529-1534.* http://doi.org/10.5588/ijtld.12.0026.Alcohol

Appendices

Appendix A: STATA commands

. tab1 Sex RegionNotificationhealthunit SiteofDisease TreatmentType NumberofpreviousTBtreatments HIVstatus Age_category, subpop(Patientstatus)

. stset Durationofstay, failure(Patientstatus==1)

. estat phtest

. encode RegionNotificationhealthunit, gen(Region)

. encode SiteofDisease, gen(SiteofTBdisease)

. encode TreatmentType, gen(Treatmenttype)

. encode NumberofpreviousTBtreatments, gen(numberofpreviouseTBtreatments)

. encode HIVstatus, gen(HIVstatus1)

. encode Age_category, gen(Agecat)

. ltable Durationofstay Patientstatus, graph survival

. sts test Sex Region SiteofTBdisease Treatmenttype numberofpreviouseTBtreatments HIVstatus1 Agecat, logrank

. stcox i.Sex i.Region i.SiteofTBdisease i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1 i.Agecat

. streg i.Sex i.Agecat, i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1, distribution(exponential)

. estat ic

. streg i.Sex i.Agecat, i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1, distribution(gompertz)

. estat ic

. streg i.Sex i.Agecat, i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1, distribution(loglogistic)

. estat ic

. streg i.Sex i.Agecat, i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1, distribution(weibull)

. estat ic

. streg i.Sex i.Agecat, i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1, distribution(lognormal)

. estat ic

. streg i.Sex i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1 i.Agecat, distribution(exponential) frailty(gamma)

estat ic

. streg i.Sex i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1 i.Agecat, distribution(gompertz) frailty(gamma)

estat ic

. streg i.Sex i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1 i.Agecat, distribution(loglogistic) frailty(gamma)

estat ic

. streg i.Sex i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1 i.Agecat, distribution(weibull) frailty(gamma)

estat ic

. streg i.Sex i.Region i.Treatmenttype i.numberofpreviouseTBtreatments i.HIVstatus1 i.Agecat, distribution(lognormal) frailty(gamma)

estat ic

. cd "C:\Users\pauli\Dropbox\My PC (LAPTOP-C77AESFG)\Desktop\maps"

C:\Users\pauli\Dropbox\My PC (LAPTOP-C77AESFG)\Desktop\maps

. shp2dta using ADMIN_Regional_Boundaries_2014, database(Namibia) coordinates(Namibiacoord) genid(id)

type: 5

. use Namibia, clear

. describe

. use Namibiacoord, clear

. describe

. tab _ID

. use MDR-TB, clear

. describe

```
. use Namibia, clear
. merge 1:1 REGION_NAM using "C:\Users\pauli\Dropbox\My PC (LAPTOP-
C77AESFG)\Desktop\maps\Namibia.dta"
merge 1:1 _n using "C:\Users\pauli\Dropbox\My PC (LAPTOP-
C77AESFG)\Desktop\maps\Namibia.dta"
. spmap COUNT_ using Namibiacoord,id(id)
(note:  _restyle could not find style indexed 79 in the current scheme for class shadestyle)
. encode( REGION_NAM), gen(Reg_NAM)

. spset Reg_NAM, coord(Shape_Leng Shape_Le_1) coordsys(latlong)
  Sp dataset Namibia.dta
                data:  cross sectional
     spatial-unit id:  _ID (equal to Reg_NAM)
         coordinates:  _CY, _CX (latitude-and-longitude, kilometers)
    linked shapefile:  none

. spset Reg_NAM, modify
  Sp dataset Namibia.dta
                data:  cross sectional
     spatial-unit id:  _ID (equal to Reg_NAM)
         coordinates:  _CY, _CX (latitude-and-longitude, kilometers)
    linked shapefile:  none

. spset, modify shpfile(Namibiacoord)
  (creating _ID spatial-unit id)
  (creating _CX coordinate)
  (creating _CY coordinate)
  Sp dataset Namibia.dta
                data:  cross sectional
     spatial-unit id:  _ID
         coordinates:  _CY, _CX (latitude-and-longitude, kilometers)
    linked shapefile:  Namibiacoord.dta
. spset Reg_NAM, coord(_CX _CY) coordsys(latlong)
data already spset
```

. grmap COUNT_, fcolor(green) ocolor(red)

. grmap COUNT_, fcolor(green) ocolor(red)

. grmap COUNT_, ytitle(Clustered map of MDR-TB deaths)fcolor(green) ocolor(red)

Appendix B: Ethical Clearance Certificate (UNAM)

UNAM
UNIVERSITY OF NAMIBIA

ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: SOS-0040 Date: 04 March 2022

This Ethical Clearance Certificate is issued by the University of Namibia Ethics Committee (REC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the ethics committee.

Title of Project: SPATIAL FRAILTY MODELLING FOR MULTIDRUG RESISTANCE TUBERCULOSIS IN NAMIBIA

Student: SHIKONGO PAULINA

Student Number: 201310225

Supervisor(s): DR. OPE-OLUWA OYEDELE (UNIVERSITY OF NAMIBIA)

Centre for Research Services

Take note of the following:

1. Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the ethics committee. An application to make amendments may be necessary.
2. Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the ethics committee
3. The Principal Researcher must report issues of ethical compliance to the ethics committee (through the Chairperson) at the end of the Project or as may be requested by the ethics committee
4. The ethics committee retains the right to:

i) Withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,

ii) Request for an ethical compliance report at any point during the course of the research.

The ethics committee wishes you the best in your research.

Dr. Zivayi Chiguvare (Chairperson Ethics Committee)

Prof. Davis Mumbengegwi (Head, Multidisciplinary Research)

Appendix C: Research Approval Letter (MoHSS)

Received
23/10/2020
Acting TB Head

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198
Windhoek
Namibia

Ministerial Building
Harvey Street
Windhoek

Tel: 061 – 203 2507
Fax: 061 – 222558
E-mail: itashipu87@gmail.com

OFFICE OF THE EXECUTIVE DIRECTOR

Ref: 17/3/3 PMS
Enquiries: Mr. A. Shipanga

Date: 30 July 2020

Ms. Paulina Mweshitya Shikongo
PO Box 40240
Ausspannplatz
Windhoek

Dear Ms. Shikongo

Re: Spatial Frailty Model for Multidrug Resistant Tuberculosis Mortality in Namibia.

1. Reference is made to your application to conduct the above-mentioned study.

2. The proposal has been evaluated and found to have merit.

3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;

3.2 No other data should be collected other than the data stated in the proposal;

3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;

ID: 14006

3.4 A quarterly report to be submitted to the Ministry's Research Unit;

3.5 Preliminary findings to be submitted upon completion of the study;

3.6 Final report to be submitted upon completion of the study;

3.7 Separate permission should be sought from the Ministry for the publication of the findings.

4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,

EXECUTIVE DIRECTOR
MINISTRY OF HEALTH AND SOCIAL SERVICES

BEN NANGOMBE
EXECUTIVE DIRECTOR

"Health for All"

Appendix D: Map of Namibian regions