MODELS FOR PREDICTING TIME TO SPUTUM CONVERSION AMONG MULTI-DRUG RESISTANT TUBERCULOSIS PATIENTS IN LAGOS, NIGERIA

By

Oluwatosin Jonadab AKINSOLA

B.Sc. (Hons) MSc, MPhil.

Matriculation Number: 88323

A Thesis Submitted to the Department of Epidemiology and Medical Statistics,

Faculty of Public Health, College of Medicine, University of Ibadan, Nigeria

In partial fulfillment for the requirement of the Award of

Ph.D Biostatistics

June, 2018

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Declaration

I hereby declare that this work is original otherwise acknowledged. The work has neither been presented to any other University for an academic award nor has it been submitted elsewhere for other purpose.

30/07/2018

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Oluwatosin Jonadab AKINSOLA

Certification

I hereby certify that this work is original and was carried out by Oluwatosin Jonadab AKINSOLA of the Department of Epidemiology and Medical Statistics, Faculty of Public Health, College of Medicine, University of Ibadan, Nigeria under my supervision. I also certify that this work has neither been presented for any purpose to any other Institution or examination body nor has it been submitted elsewhere for other purpose

OB Yusuf 31/07/2018

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Dedication

This thesis for award of Ph.D. Biostatistics is dedicated to Almighty God (Jehovah),

To my darling wife and son. Christiana and Richard

And my beloved mother, Mrs Florence Jadesola AKINSOLA,

And to

All my teachers: Both past and present

Acknowledgement

I thank the Almighty God for seeing me through this study; it was indeed a long wait. I am greatly indebted to many people too numerous to mention, who have contributed their expertise in specific areas and participated in the development of technical content of this study. First and foremost, I sincerely appreciate my supervisor, Dr. Oyindamola Bidemi Yusuf. Despite her tight and competing schedules as the incumbent Head of Department, she painstakingly took time to read every aspect of this work; her personal efforts ensured the present quality of this thesis. I appreciate her constructive criticism, patience, support and accessibility.

I am particularly grateful to my second supervisor, Dr Olusoji Mayowa Ige who is a Consultant Pulmonologist (UCH), for his splendid and unequalled technical inputs to this research work. I am highly indebted to Dr Abimbola Bowale, Medical Director of Infectious Disease Hospital, Lagos Mainland and Mrs Olanike Morounfolu, Principal Officer, Ministry of Health, Lagos State who gave immeasurable help in getting the data used for this study. I say many thanks. I also appreciate my Dean, Professor O.I. Fawole, Professor Olusola Ayeni, Professor Elijah Bamgboye, Dr David Dairo, Dr Mattew Akpa, Dr Stephen Adebowale, Dr Babatunde Gbadebo, Dr Adeniyi Fagbamigbe, Dr Joshua Akinyemi, Dr Babatunde Adedokun, Dr Rotimi Afolabi, Dr Eniola Bamgboye and Mr Nathaniel Afolabi and all other staff members of the department for their support in one way or the other.

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This acknowledgment would be incomplete if I fail to mention my in-laws; Mrs Olubunmi Alaran, Brother Raphael Alaran, Dorcas Adunbarin. Peter Adunbarin and Mrs Adenike Lawal. I thank you all for your prayers, love, care, understanding, trust, support, advice, motivation, faith, confidence and belief.

Abstract

Multi-drug resistant tuberculosis (MDR-TB) develops due to problems such as irregular drug supply, poor drug quality, inappropriate prescription and poor adherence to treatment. These factors allow the development and subsequent transmission of resistant strains of the pathogen. With the advancements in statistics, mixture cure models provide the insight to the covariates that are related with the treatment outcomes. However, potential modifiable factors such as demographic and clinical characteristics are not clearly known in poor resource settings such as Nigeria. Therefore, this study was designed to determine the factors that can predict time to sputum conversion among MDR-TB patients using cure model.

A retrospective clinic-based cohort study was conducted on 413 patients who were diagnosed of multi-drug resistant tuberculosis and met inclusion criteria from April 2012 to October 2016 at the Infectious Disease Hospital, Lagos. The main outcome measure (sputum conversion time) was the time from the date of commencement of MDR-TB treatment to the date of specimen collection for the first of two-consecutive negative smear and culture taken 30 days apart. The predictor variables of interest include: demographic (age, gender and marital status) and clinical characteristics (registration group, number of drugs resistant to during treatment initiation, HIV status, diabetes status and adherence with medication). Mixture Cox cure models were fitted to the main outcome variable using Log-normal, Log-logistic and Weibull distributions as alternatives to the violation of Proportional Hazards (PH) assumption. Akaike Information Criterion (AIC) was used for models comparison based on different distributions, while the effect of predictors of time to sputum conversion was reported as Hazard Ratio (HR) at $\alpha_{0.05}$.

Age was 36.8±12.7 years, 60.8% were male and 67.6% were married. Majority of the patients (58.4%) converted to sputum negative. Patients who were resistant to two drugs at treatment initiation had 39.0% rate of conversion than those resistant to at least three drugs [HR: 1.39 (CI: 0.98, 1.98)]. The likelihood of sputum conversion time was shorter among non-diabetic patients compared to diabetics [HR: 0.55: (CI: 0.24, 0.85)]. The overall median time for sputum conversion was 5.5 (IQR: 1.5-11.5) months. In the cure model, resistance to more drugs at the time of initiation was significantly related with a longer sputum conversion time for Log normal Cox mixture [HR: 2.06 (CI: 1.36-3.47)]; Log-logistic Cox mixture cure [HR: 2.56 (CI: 1.85-4.09)] and Weibull Cox mixture [HR: 2.81 (CI: 1.94-4.19)]. Diabetic patients had a significantly

higher sputum conversion rate compared to non-diabetics; Log-normal Cox mixture [HR: 2.03 (CI: 1.17-3.58)]; Log-logistic Cox mixture cure [HR: 2.11 (CI: 1.25-3.82)] and Weibull Cox mixture [HR: 2.02 (CI: 1.17-3.34)]. However, Log-normal PH model gave the best fit and provided the fitness statistics [(-2LogL: 519.84); (AIC: 1053.68)]. The best fitting Log-normal PH model was $Y=1.00X_1+2.06X_2+0.98X_3+2.03X_4+\varepsilon$ where Y is time to sputum conversion and Xs are age, number of drugs, adherence and diabetes status.

The models confirmed the presence of some factors related with sputum conversion time in Nigeria. The quantum of drugs resistant at treatment initiation and diabetes status would aid the clinicians in predicting the rate of sputum conversion of patients.

Keywords: Mixture Cure Model, Sputum Conversion Time, MDR-TB, Log-normal, Prediction
Word count: 500

Contents

CHAPTER ONE

Introduction

Contemporary trends in the burden of tuberculosis point to poor global health indicators. According to Tuberculosis Factsheet 2013, Tuberculosis is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. "Nigeria is now the 3rd highest TB country in the world and the first in the African region. It is among the 22 high burden countries with an annual incidence of 338 per 100,000 and prevalence of 322 per 100,000 individuals. The national TB survey also confirmed a worrisome situation with regard to Multi-Drug Resistance Tuberculosis (MDR-TB) (National TB Prevalence Survey, 2012).

Consequently, Nigeria is now the 13th highest MDR-TB country globally and 2nd highest in the African region" (WHO, 2014). In 2014, an estimated 480,000 new cases of MDR-TB occurred and about 190,000 people died of MDR-TB. Since then MDR-TB has emerged as a worldwide problem with an estimated incidence of 425,000 cases occurring annually and the worldwide prevalence estimated to be 2 to 3 times the incidence (WHO, 2014). Yearly, over 8 million people develop tuberculosis and nearly 1.8 million die from it, despite extensive vaccination and drug treatment programmes. In Nigeria, the estimated number of patients with multi-drug resistant tuberculosis is between 2,700 and 4,500 while the prevalence rate of MDR-TB was 2.9% among new patients and 14.5% among previously treated cases in Nigeria (Oladimeji et al, 2016).

Documented cases of MDR-TB have been reported by almost 90 countries and it has been recognized by the international community as a clinical and public health threat (Shah et al, 2007). The prevalence of MDR-TB and Extra-Drug Resistance (XDR-TB) appears to be increasing particularly in low and middle income settings (CDC, 2004). MDR-TB develops through the misdiagnosis, mismanagement and treatment of TB diseases such as irregular drug supply, poor drug quality, inappropriate prescription and/or poor adherence to treatment. These factors allow the development and subsequent transmission of resistant and strains of the pathogen. With the advancement in bio-medical statistics, mixture cure models provide insight to the covariates that are related with the treatment results.

Sputum conversion (which is used to monitor program performance) is one the most important interim indicators of pulmonary tuberculosis treatment outcome, measuring efficacy and identifying the constraints. Culture-based monitoring of MDR-TB patients is used to evaluate treatment efficacy and helps to identify those who remain infectious. The internationally agreed-upon definition of culture conversion is two consecutive negative smear/culture from sputum samples collected ≥30 days apart (WHO, 2011). Early conversion is very important to prevent transmission of MDR-TB, reduce hospitalization time, and reduce cost related to infection control measures. There is also some evidence that delayed sputum conversion is associated with amplifications of drug resistance. Few published studies had examined sputum conversion among MDR-TB patients and factors associated with conversion, but they often neglect the influence of correlates and prognostic differentials in the serial assessment of sputum smear and culture status for effectiveness of treatment and case management of individual patients.

Addressing these gaps are particularly relevant in a developing country characterized by major challenges to public health and epidemic of infection with the human immunodeficiency virus (HIV) through increasing pressing need for new drugs, vaccines and diagnostic procedures. It is equally important, however, to identify correlates (Age, number of drugs the initial isolate was resistant to at treatment initiation and time in days to initial sputum culture conversion) and prognostic differentials (Gender, HIV status, Diabetes status, Alcohol intake, Medical compliance and Social support) for predicting the sputum conversion rate in ensuring adequate standards of care for treatment efficacy, improved clinical management of tuberculosis and where increased attention should be paid in future prevention strategies. However, potential modifiable factors such as demographic and clinical characteristics are not clearly known in poor resource settings such as Nigeria. A patient with tuberculosis disease is capable of experiencing three outcomes: cure, relapse or death (Multi-Drug Resistant) when monitored over a period of time.

1.1 Research Problem

Tuberculosis is an increasing cause of morbidity among person with human immune-deficiency virus (HIV) infection in Nigeria. As the number of patients hospitalized with HIV infection and tuberculosis increases, the risk nosocomial transmission of tuberculosis arises. Moreover, HIV induced immune-suppression may amplify the spread of tuberculosis in hospitals because it greatly increases the risk of rapid progression to active and infectious tuberculosis.

Indeed, advancement has been achieved to lower global incidence of drug-susceptible tuberculosis. the emergence of multi-drug resistant (MDR) and extra-drug resistant (XDR) tuberculosis during the past decade threatens to undermine these advances. However, countries such as India, Indonesia, China and Pakistan are responding far too slowly. Of the estimated 440,000 cases of MDR tuberculosis that occurred in 2008, only 7% were identified and reported to World Health Organization (WHO). Of these cases, only a fifth was treated according with WHO standards (Gandhi et al, 2010). Although treatment of MDR and XDR tuberculosis is possible with currently available diagnostic techniques and drugs, the treatment course is substantially more costly and laborious than for drug-susceptible tuberculosis, with higher rates of treatment failure and mortality.

Nonetheless, a few countries provide examples of how existing technologies can be used to reverse the epidemic of MDR tuberculosis within a decade. Major improvements in laboratory capacity, infection control, and performance of tuberculosis control programmes with treatment regimens for both drug-susceptible and drug-resistant disease will be needed, together with a massive scale-up in diagnosis and treatment of MDR and XDR tuberculosis to prevent drug-resistant strains from becoming the dominant form of tuberculosis. New diagnostic tests and drugs are likely to become available during the next few years and should accelerate control of MDR and XDR tuberculosis. Equally important, especially in the highest-burden countries of India, Indonesia, China, Nigeria, Pakistan and South Africa will be a commitment to tuberculosis control including improvements in national policies and health systems that remove financial barriers to treatment, encourage rational drug use, and create the infrastructure necessary and sufficient in the management of MDR tuberculosis.

1.2 Long-term effects of MDR-TB

Untreated multi-drug resistant tuberculosis can give rise to serious debilitating effects on the neurological parts of the body including the bones, brain, liver, kidney and heart. These affected in addition to complications of the lungs. When tuberculosis spreads to other parts of the body, it exposes those areas to further infection and undermines their ability to function. Mycobacterium tuberculosis causes this contagious but curable disease according to Public Health England (CDC, 2004).

Accordingly, once tuberculosis reaches the bones, it can cause long-term destruction of joints. Tuberculosis in the bones can damage the ribs as well. Tuberculosis also negatively impacts organ function. For instance, an affected liver or kidney loses optimal capacity to filter waste substances from the blood circulatory system. When tuberculosis infects the human heart, the organ's capacity to aid in blood circulation is substantially compromised. If tuberculosis penetrates the brain, it can cause meningitis. This condition can lead to death due to swelling of membranes around the brain and spinal column.

The United Kingdom's NHS explains that pulmonary tuberculosis affects only the lungs, and it can typically be treated using antibiotics, such as Isoniazid and Rifampicin. This treatment method requires a long-term, six-month course of medication. The medication is to be taken every day until completion of the prescribed dosage. This type of treatment works on other tuberculosis affected organs as well but may require a 12-month course of antibiotics. The NHS confirms that tuberculosis can result in death if the lungs become too severely damaged to function properly.

1.3 Justification for the study

In the field of biostatistics, the analysis of survival data is often the goal of studies. The methods currently available to do this analysis are numerous and varied. Some of most commonly used methods in survival analysis include the Proportional Hazards (PH) model and the Accelerated Failure Time (AFT) model. Both of these methods assume that every subject will eventually experience the event of interest, given enough follow-up time. However, there are some instances, especially with the advancements in modern medicine, in which a proportion of the population of interest are "cured" and will therefore, never experience the event of interest. This situation motivates the incorporation of a cure fraction in a statistical model in order to analyse the ability of a certain treatment to cure a disease of interest.

The common established method for predicting time to sputum conversion among multi-drug resistant tuberculosis outcomes is the use of Cox proportional hazard model. Indeed, survival analysis attempts to answer questions such as: what is the proportion of a population which will survive certain time? Of those that survive, at what rate will they die or fail? Can multiple causes of death or failure be taken into account? How do particular circumstances or characteristics increase or decrease the probability of survival? More generally, survival analysis involves the modelling of time to event data; in this context, death or failure is considered an "event" in the survival analysis literature-traditionally only a single event occurs for each subject, after which the organism or mechanism is dead or broken. Recurring event or repeated event models relax that assumption. The object of primary interest is the survival function, conventionally denoted S, which is defined as

$$S(t) = \Pr(T>t) \quad \text{.....equation 1.1}$$

Where t is some time, T is a random variable denoting the time of death, and "Pr" stands for probability. That is, the survival function is the probability that the time of death is later than some specified time t. The survival function is also called the survivorship function in problems of biological survival. Usually one assumes $S(0) = 1$, although it could be less than 1 if there is the possibility of immediate death or failure.

The survival function can be expressed in terms of probability distribution and probability density functions

$$S(t) = \Pr(T > t) = \int_t^{\infty} f(u)\,du = 1 - F(t). \quad \text{.....equation 1.2}$$

Similarly, a survival event density function can be defined

$$s(t) = S'(t) = \frac{d}{dt}S(t) = \frac{d}{dt}\int_t^{\infty} f(u)\,du = \frac{d}{dt}[1 - F(t)] = -f(t).$$

.....equation 1.3

The hazard function, conventionally denoted by λ, is defined as the event rate at time t conditional on survival until time t or later (that is, $T \geq t$),

$$\lambda(t) = \lim_{dt \to 0} \frac{\Pr(t \leq T < t + dt)}{dt \cdot S(t)} = \frac{f(t)}{S(t)} = -\frac{S'(t)}{S(t)}.$$

.....equation 1.4

Force of mortality is a synonym of hazard function which is used particularly in demography and actuarial science, where it is denoted by μ. The term hazard rate is another synonym. The hazard function must be non-negative, $\lambda(t) \geq 0$, and its integral over $[0, \infty]$ must be infinite, but is not otherwise constrained; it may be increasing or decreasing, non-monotonic, or discontinuous.

Several studies have consistently reported that different socio-economic problems have influenced outcomes of patients with tuberculosis condition. However, very few of these studies, particular in Nigeria and in Africa have studied any correlates and prognostic differentials for predicting time to sputum conversion among MDR-TB patients (Howhannesyan and Breeze, 2012). The knowledge of the correlates and prognostic differentials of time to sputum conversion of Multi-Drug Resistant TB can give an insight into the cause and timing of the relapse and factors that influence drug failure. This would assist considerably in the management of patients with MDR-TB condition and facilitate the reduction of the degree as well as the frequency of the ailment. Therefore, this study was designed to develop suitable cure models that can predict time to sputum conversion among MDR-TB patients.

1.4 Objectives of the study

The main objective of this work was to develop a model for time to sputum conversion among multi-drug resistant tuberculosis patients in Lagos, South-West, Nigeria.

The specific objectives are to:

- Describe the background characteristics of MDR-TB patients with respect to sputum conversion status
- Determine and compare median time to sputum conversion between new and retreatment Cases of MDR-TB patients
- Determine the mortality experience among the MDR-TB patients
- Develop a fitting statistical model of overall sputum conversion time among MDR-TB patients
- Examine the predictors of sputum conversion time among MDR-TB patients
- Examine the predictors of treatment initiation period among MDR-TB patients

1.5 Research Questions

In order to establish the linkages between predictors of time to sputum conversion among multi-drug resistant tuberculosis patients, the following research questions were proposed:

- What are the background characteristics of the patients who experienced conversion and non-conversion sputum at six months or more?
- Is there any significant difference between sputum conversion time of MDR-TB patients of new and retreatment cases?
- What are the predictors of time to sputum conversion?
- What are the predictors of treatment initiation period?

CHAPTER TWO

Literature Review

2.1 Definition

Isoniazid, the most powerful mycobactericidal drug available, ensures early sputum conversion and helps in decreasing the transmission of TB. Rifampicin, by its mycobactericidal and sterilizing activities is crucial for preventing relapses. Thus, isoniazid and rifampicin are keystone drugs in the management of TB. While resistance to either isoniazid or rifampicin may be managed with other first-line drugs, resistance to both isoniazid and rifampicin (MDR-TB) demands treatment with second-line drugs. These drugs have limited sterilizing capacity and are not suitable for short-course treatment. Thus, patients with MDR-TB require prolonged treatment with drugs that are less effective and more toxic. Therefore, it is necessary to distinguish MDR-TB from mere drug-resistant tuberculosis by performing mycobacterial culture and sensitivity testing because the therapeutic implications are different.

It is possible to strictly define a given isolate of *M .tuberculosis* as multidrug-resistant only after performing mycobacterial culture and *in vitro* sensitivity testing. Under programme conditions, these facilities are usually not available and patients are labelled as "treatment failure", "re-treatment failure" and "chronic cases" as per the guidelines issued by the WHO, 2015. It is likely that several of these patients may be excreting multidrug-resistant organisms. Keeping these facts in mind, the term MDR-TB has been used in this review in the strict sense of the definition referring to isolates resistant to both isoniazid and rifampicin with or without resistance to other drugs.

2.2 Terminology of Drug Resistance

Primary resistance is that which has not resulted from the treatment of the patient with the drug concerned. It includes resistance in wild strains which have never come into contact with the drug (natural resistance) and the resistance occurring as a result of exposure of the strain to the drug but in another patient. Initial resistance is the resistance in patients who give a history of never having received chemotherapy in the past. It includes primary resistance and resistance to previous treatment concealed by the patient or of which the patient was unaware. The term "acquired resistance" has often been used with the implication that resistance has developed due to exposure of the strain to anti-tuberculosis drugs and the consequent selecting out of resistant mutant bacilli.

However, some of the drug-resistant isolates in previously treated patients may actually represent primary resistance among patients who remain uncured. In the strict sense, the term "acquired resistance" can be used to refer to strains proven to have drug resistance in a reliable laboratory which were subsequently isolated from a patient in whom initial susceptibility testing was done to document the presence of a drug susceptible strain earlier. If initial drug susceptibility testing has not been done, the term "resistance among previously treated patients" would be a more appropriate term than "acquired drug resistance".

Susceptible strains are those that have not been exposed to the main anti-tuberculosis drugs and respond to these drugs in a uniform manner. Resistant strains differ from the sensitive strains in their capacity to grow in the presence of higher concentration of a drug. Wild strains are those that have never been exposed to anti-tuberculosis drugs. Naturally resistant strains are wild strains resistant to a drug without having been in contact with it. It is species specific and has been used as a taxonomic marker.

2.3 Epidemiology of Multi-Drug Resistant Tuberculosis

Although studies presented from global perspective proposed the potential problem of drug resistance, however it was in 1990s when multi-drug resistant tuberculosis emerged in United States of America that it came to public health attention. The prevalence of resistance to four first-line anti-tuberculosis drugs in 35 countries has been reported (WHO, 1997). The range of prevalence was 5.3 percent for the acquired resistance in New Zealand compared to 100% in Ivanovo Oblast which is located in Russia with a median of 36 percent.

There are separate "hot spots" with high prevalence of MDR-TB scattered around the globe which could hamper control programmes. Few of these countries include: Latvia, Estonia and two Russian territories in Europe; Dominican Republic and Argentina in Americas and Côte d'Ivoire in Africa. The temporal changes associated with the survey of the prevalence of resistance were excluded. In addition, surveys were carried out in some high burden countries such as India, China and Russia which was not a reflection of their national outlook. Therefore WHO-IUATLD survey was extended to define this problem further.

From 1996 and 1999, situations in 58 geographic sites were appraised (WHO, 1999). The range of newly diagnosed patients was between 1.7 percent in Uruguay compared to 36.9 percent in Estonia. A significant fall in multi-drug resistance was documented in United States and France. However, there was a sharp increase in prevalence from 11.7 percent in 1994 to 18.1 percent in 1998 in Estonia. The combination of results of resistance surveys from 64 countries and predictive resistance from 72 others intimated that over 273,000 newly diagnosed cases of MDR-TB were documented globally in 2000 and these gave 3.2 percent of new cases of tuberculosis.

2.4 Prevalence of Multi-Drug Resistant Tuberculosis in developing countries

Apparently, concerning the burden of tuberculosis, South Africa was adjudged third in global raking, behind China and India with larger populations. Therefore, the quantum of MDR-TB and XDR-TB patients has become greater in amount as a result of ineffective management of tuberculosis and HIV pandemic. A total of 9070 multi-drug resistant tuberculosis cases and 594 extra-drug resistant tuberculosis cases were documented in 2009 while 7386 multi-drug resistant tuberculosis cases and 741 extra-drug resistant tuberculosis cases in 2010 respectively by the National Health Laboratory Services (NHLS) in South Africa. However, there has been a steady increase since 2006, which can be attributed to case detection strategy.

In the nine provinces of South Africa, approximately 9070 cases of MDR-TB were confirmed in 2009. With respect to the treatment diagnosis, out of the 7838 cases, 5313 commenced treatment. However, the differential between number of diagnosis and treatment commencement still need to be narrowed. Previous estimates exhibited that up to 73 percent started treatment from those diagnosed while studies conducted later proposed that the conditions were being treated effectively and cured in South Africa (Holtz et al, 2001).

The management of treatment outcomes of MDR-TB inpatients in South Africa are not encouraging. A detailed account in Western Cape showed that out of 240 MDR-TB patients; thirty-three percent were cured; thirteen percent failed while 33% died (Schaaf, Marais, 2011). Consequently, a national study conducted among 671 patients for a period of three years between 1991 and 2001 presented a report of 67 defaulters while among these defaulters, 27 had positive sputum culture at the time of default. These large defaulters emphasize the importance of public health integration (Holtz et al. 2001). Moreover, the comparison of treatment success to defaulters' rates was 45 percent and 15 percent respectively in a Durban tertiary hospital (SA Department of Health, 2009).

Treatment models have succeeded with its application in the community-based settings for MDR-TB in other countries (Lockman et al, 2001) but the situation in South African is unambiguous. Therefore, suitable models should take into considerations by the health services planning in the interventions for high burden of MDR-TB, XDR-TB, HIV and TB with TB-HIV co-infection rates.

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2.5 Epidemiology of Multi-Drug Resistant Tuberculosis in Nigeria

An intensifying number of MDR-TB in Nigeria currently constitutes a major source of concern. Medical professionals have given a stern warning on the alarming trend that this condition should be addressed so as to avoid what can be described as "imminent and total collapse of the efficacy of the available first-line drugs for TB treatment." Normally, a patient diagnosed for MDR-TB would be treated for a period of eighteen to twenty-four months which is dissimilar to the normal tuberculosis that needs six months to handle.For MDR-TB patients, a hospitalization for six months would precede an ambulatory care for about eighteen months. "A Tuberculosis patient is confirmed to have developed MDR-TB when the patient becomes resistant to the two important and potent anti-tuberculosis drugs. The bottom line of TB control is to detect active cases of TB and render them non-infectious with capable treatment".

Information from the national agency in charge Tuberculosis and Leprosy Control (NTLCP) have demonstrated that presently, there are over 7,000 MDR-TB documented cases in the country. Worldwide, there are over 500,000 cases of MDR-TB reported, out of which a paltry 3 percent get adequate treatment. Nigeria ranks 4th out of the 22 countries that have 75 percent of the global burden of Tuberculosis (WHO, 2017). To address this condition effectively, the World Health Organisation (WHO) advocates that the affected countries must detect at least 75 percent of active case and reach 85 percent treatment. In Nigeria, about 36 percent are detected and majority of the (over 60 percent) cases are missed. The import of this, according to physicians is that no one is immuned to Tuberculosis infection. However, a close interaction with a Tuberculosis patient over a long period can increase the probability of being infected with Tuberculosis.

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2.6 Pathophysiology of Multi-Drug Resistant tuberculosis

Multi-drug resistant tuberculosis (MDR-TB) is defined as a form of TB infection caused by bacteria that are resistant to treatment with at least two of the most powerful first-line anti-TB drugs, Isoniazid (INH) and Rifampicin (RMP). Five percent (5%) of all TB cases across the globe in 2013 were estimated to be MDR-TB cases, including 3.5% of newly diagnosed TB cases and 20.5% of previously treated TB cases. While rates of MDR-TB infections are relatively low in North America and Western Europe, they are an increasingly serious problem worldwide, in particular in areas of the sub-Saharan Africa, Russian Federation, the former Soviet Union and other parts of Asia.

MDR-TB infection may be classified as either primary or acquired. Primary MDR-TB occurs in patients who have not previously been infected with TB but who become infected with a strain that is resistant to treatment. Acquired MDR-TB occurs in patients during treatment with a drug regimen that is not effective at killing the particular strain of TB with which they have been infected. Rates of primary MDR-TB are low in North America and Western Europe: in the US in 2000, the rate of primary MDR-TB was 1% of all cases of TB nationally. Most cases of acquired MDR-TB are due to inappropriate treatment with a single anti-TB drug, usually INH. This can occur due to a medical provider, such as a doctor or nurse, improperly prescribing ineffective treatment, but may also be due to the patient not taking the medication correctly, which can be due to a variety of reasons, including expense or scarcity of medicines, patient forgetfulness, or patient stopping treatment early because they feel better.

Treatment of MDR-TB requires treatment with second-line drugs, usually four or more anti-TB drugs for a minimum of 6 months, and possibly extending for 18-24 months if rifampicin resistance has been identified in the specific strain of TB with which the patient has been infected. In general, second-line drugs are less effective, more toxic and much more expensive than first-line drugs. Under ideal program conditions, MDR-TB cure rates can approach 70%.

2.7 Prevention of Multi-Drug Resistant Tuberculosis

There are various ways for the prevention of drug resistance tuberculosis. These include:

- Rapid diagnosis and treatment of Tuberculosis: In most developing countries, the adjudged greatest risk factors for drug resistant TB are due to problems in diagnosis and treatment. If this condition is established and treated as soon as possible, drug resistance can be averted.
- Completion of treatment: A pointer to MDR-TB is regarded as previous treatment of tuberculosis. Irregular drug supply, poor drug quality, inappropriate prescription by the physician and poor adherence to treatment by the patient can lead to development of resistance.
- Diagnosed MDR-TB patients who have comorbidity with HIV/AIDS should be isolated and be given immediate proper attention because of their compromised immunity.
- Close contacts identification that may be susceptible to Tuberculosis such as relatives, acquaintances and people in close contact
- A cutting-edge research is essential for the prevention, diagnosis and therapy of Tuberculosis and multi-drug resistant.

2.8 Predictors for the development of Multi-Drug Resistant Tuberculosis

Certain factors have been documented to be associated with the development of MDR-TB. In an analysis to identify determinants of drug resistant TB, population-based representative data on new and previously treated patients with TB collected within an international drug resistance surveillance network were studied. Of the 9,615 patients, 85.5 per cent were new cases and 14.5 percent were previously treated cases. Compared with new cases, patients who received treatment in the past were more likely to have resistance to anti-tuberculosis drugs. An approximately linear increase was observed in the likelihood of having MDR-TB as the total time of prior anti-tuberculosis treatment measured in months increased. Multivariate analysis revealed that prior anti-tuberculosis treatment but not HIV positivity, was associated with MDR-TB.

In a study from Saudi Arabia, previous history of anti-tuberculosis treatment and young age were found to be risk factors associated with the development of MDR-TB. In a study from New Delhi, the presence of past history of tuberculosis, poor compliance to treatment, low socio-economic status and body mass index (BMI, kg/m^2) <18 kg/m^2 were independent contributors to the risk of developing MDR-TB. In most of the published studies, previous history of tuberculosis and past history of anti-tuberculosis treatment have been implicated in the causation of MDR-TB.

2.9 Management of Multi-Drug Resistant Tuberculosis Patients

In the early reports of outbreaks of MDR-TB in HIV co-infected patients in hospitals and prisons, the mortality rate was very high ranging from 72 to 89 percent. However, subsequent studies have documented decreased mortality and improvement in ciinical outcome for HIV sero-positive patients with MDR-TB who were started on at least two drugs with *in vitro* susceptibility against thc MDR-TB isolate. Even in HIV sero-negative patients, treatment of MDR-TB has been difficult and may only give response rates of the order of 50 percent with a high mortality rate with persistent positive cultures.

In resource-poor nations, the treatment of MDR-TB has been considered to be very expensive and available only at referral centres. In a recently published study, results of community-based out-patient treatment of MDR-TB were reported from Peru. While the results of susceptibility testing were pending, the patients were treated empirically under direct observation with regimens containing at least five drugs to which the strains were likely to be susceptible. The definitive regimens, determined on the basis of the results of drug susceptibility, contained a minimum of five drugs and lasted for at least 18 months. Of the 66 patients who completed four or more months of therapy, 55 (83%) were probably cured (defined as at least 12 months of consecutive negative cultures during therapy). Five of these 66 patients (8%) died while receiving treatment. Only one patient continued to have positive cultures after six months of treatment. Low haematocrit [hazard ratio (HR) 4.09; 95% CI, 1.35 to 12.36] and a low BMI (kg/m^2) (HR, 3.23; 95% CI, 0.90 to 11.53) were found to be the predictors of the time to treatment failure or death. These observations suggest that community-based out-patient treatment of MDR-TB has the potential to yield high cure rates even in resource-poor settings. Sparse data are available from published literature regarding the treatment of patients with MDR-TB from India. In a study from New Delhi, additional administration of oral ofloxacin was found to be effective and safe for the treatment of MDR-TB.

A prospective uncontrolled study from New Delhi reported that sparfloxacin, in combination with kanamycin (for the initial 3 to 4 months) and ethionamide treatment was useful in achieving sputum conversion, clinical and radiological improvement in nine patients with pulmonary tuberculosis who had received adequate anti-tuberculosis treatment with first-line drugs, including supervised category II treatment regimen as per WHO guidelines for five months, and were still sputum smear positive. In a study from Vellore, Tamil Nadu, combination therapy containing ofloxacin was useful in achieving sputum conversion in 26 of 49 (53%) patients and culture conversion occurred in 16 of 26 (61.5%) patients. Clinical and radiological response was noted in 31 (56%) and 13 (32.5%) out of 40 patients respectively.

2.10 Prognostic Markers of Multi-Drug Resistant Tuberculosis

Park et al reported that extra-pulmonary involvement was a risk factor for shorter survival, while a cavitary lesion on initial chest film and institution of appropriate treatment were positive predictors of survival in patients with MDR-TB. In a recently published study from the United Kingdom, overall median survival time was 1379 days (95% CI: 1336 to 2515). Median survival time was 858 days (95% CI: 530 to 2515) in immune-compromised individuals and 1554 (95% CI: 1336 to 2066) days in immuno-competent persons. Median survival in patients treated with three drugs to which the bacterium was susceptible on *in vitro* testing was 2066 days (95% CI: 1336 to 2515), whereas, in those not so treated survival was 599 days (95% CI: 190 to 969). Immuno-compromised status, failure to culture the bacterium in 30 days or to apply appropriate treatment with three drugs to which the organism is susceptible, and age were significant factors in mortality. An immuno-compromised patient was nearly nine times more likely to die, while application of appropriate treatment reduced the risk. Increasing age was associated with increasing risk of death (risk ratio 2.079; 95% CI: 1.269 to 3.402) suggesting that, for every 10 yr increase in age the risk almost doubled112. In a study from France, in patients with MDR-TB, HIV co-infection, treatment with less than two active drugs, and knowledge regarding the multidrug-resistant status at the time of diagnosis were found to be associated with a poor outcome. In study from Turkey, older age and history of previous treatment with a larger number of drugs were found to be associated with a poor outcome.

2.11 Guidelines for the management of patients with Multi-Drug Resistant Tuberculosis

When MDR-TB is suspected on the basis of history or epidemiological information, the patient's sputum must be subjected to culture and anti-tuberculosis drug sensitivity testing and the WHO re-treatment regimen or the empirical regimens employing second-line reserve drugs (Tables III and IV) suggested by the American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society of America (ATS/CDC/IDSA) must be initiated pending sputum culture report. Further therapy is guided by the culture and sensitivity report. These guidelines clearly mention that a single drug should never be added to a failing regimen. Furthermore, when initiating treatment, at least three previously unused drugs must be employed to which there is *in vitro* susceptibility.

When susceptibility testing reports are available and there is resistance to isoniazid and rifampicin (with or without resistance to streptomycin) during the initial phase, a combination of ethionamide, fluoroquinolone, another bacteriostatic drug such as ethambutol, pyrazinamide and aminoglycoside (kanamycin, amikacin, or capreomycin) are used for three months or until sputum conversion. During the continuation phase, ethionamide, fluoroquinolone, another bacteriostatic drug (ethambutol) should be used for at least 18 months after smear conversion. If there is resistance to isoniazid, rifampicin and ethambutol (with or without resistance to streptomycin) during the initial phase, a combination of ethionamide, fluoroquinolone and another bacteriostatic drug such as cycloserine or PAS, pyrazinamide, and aminoglycoside (kanamycin, amikacin, or capreomycin) are used for three months or until sputum conversion. During the continuation phase, ethionamide, ofloxacin, another bacteriostatic drug (cycloserine or PAS) should be used for at least 18 months after smear conversion.

The recently published ATS/CDC/IDSA guidelines suggest that among the fluoroquinolones, levofloxacin is most suited for the treatment of MDR-TB given its good safety profile with long-term use. These observations need to be confirmed in prospective studies with a large sample size.

2.12 DOTS-Plus Strategy

DOTS is a key ingredient in the tuberculosis control strategy. In populations where MDR-TB is endemic, the outcome of the standard short-course regimen remains uncertain. Unacceptable failure rates have been reported and resistance to additional agents may be induced. As a consequence, there have been calls for well-functioning DOTS programmes to provide additional services in areas with high rates of MDR-TB. These "DOTS-plus for MDR-TB programmes" may need to modify all five elements of the DOTS strategy: (*i*) the treatment may need to be individualized rather than standardized; (*ii*) laboratory services may need to provide facilities for on-site culture and antibiotic susceptibility testing; (*iii*) reliable supplies of a wide range of expensive second-line agents; (*iv*) operational studies would be required to determine the indications; and (*v*) financial and technical support from international organizations and Western governments would be needed in addition to that obtained from local governments. WHO has established a Working Group on DOTS-Plus for MDR-TB, to develop policy guidelines for the management of MDR-TB and to develop protocols for pilot projects intended to assess the feasibility of MDR-TB management under programme conditions.

The WHO has also established a unique partnership known as the Green Light Committee (GLC) in an attempt to promote access to and rational use of second-line anti-tuberculosis drugs for the treatment of MDR-TB. If DOTS-Plus programmes are established, they may prove beneficial not only for patients with MDR-TB but for all patients with tuberculosis.

2.13 Treatment of Multi-Drug Resistant Tuberculosis Patients

Usually, multi-drug resistant tuberculosis can be cured with long treatments of second-line drugs, but these are more expensive than first-line drugs and have more adverse effects. The treatment and prognosis of MDR-TB are much more akin to those for cancer than to those for infection. MDR-TB has a mortality rate of up to 80%, which depends on a number of factors, including

- How many drugs the organism is resistant to (the fewer the better)
- How many drugs the patient is given (patients treated with five or more drugs do better)
- Whether an injectable drug is given or not (it should be given for the first three months at least)
- The expertise and experience of the physician responsible
- How co-operative the patient is with treatment (treatment is arduous and long, and requires persistence and determination on the part of the patient)
- Whether the patient is HIV positive or not (HIV co-infection is associated with an increased mortality).

The majority of patients suffering from multi-drug resistant tuberculosis do not receive treatment, as they are found in underdeveloped countries or in poverty. Denial of treatment remains a difficult human rights issue, as the high cost of second-line medications often precludes those who cannot afford therapy.

A study of cost-effective strategies for tuberculosis control supported three major policies. First, the treatment of smear-positive cases in DOTS programs must be the foundation of any tuberculosis control approach, and should be a basic practice for all control programs. Second, there is a powerful economic case for treating smear-negative and extra-pulmonary cases in DOTS programs along with treating smear-negative and extra-pulmonary cases in DOTS programs as a new WHO "STOP TB" approach and the second global plan for tuberculosis control. Last, but not least, the study shows that significant scaling up of all interventions is needed in the next 10 years if the millennium development goal and related goals for tuberculosis control are to be achieved. If the case detection rate can be improved, this will guarantee that people who gain access to treatment facilities are covered and that coverage is widely distributed to people who do not now have access.

In general, treatment courses are measured in months to years; MDR-TB may require surgery, and death rates remain high despite optimal treatment. However, good outcomes for patients are still possible. The treatment of MDR-TB must be undertaken by physicians experienced in the treatment of MDR-TB. Mortality and morbidity in patients treated in non-specialist centres are significantly higher to those of patients treated in specialist centres.

In addition to the obvious risks (i.e., known exposure to a patient with MDR-TB), risk factors for MDR-TB include HIV infection, previous incarceration, failed TB treatment, failure to respond to standard TB treatment, and relapse following standard TB treatment. Treatment of MDR-TB must be done on the basis of sensitivity testing: it is impossible to treat such patients without this information. When treating a patient with suspected MDR-TB, pending the result of laboratory sensitivity testing, the patient should be started on SHREZ (Streptomycin+isonicotinylHydrazine+Rifampicin+Ethambutol+pyraZinamide)+moxifloxacin+ cycloserine. There is evidence that previous therapy with a drug for more than a month is associated with diminished efficacy of that drug regardless of *in vitro* tests indicating susceptibility. Hence, a detailed knowledge of the treatment history of each patient is essential.

A gene probe for *rpoB* is available in some countries. This serves as a useful marker for MDR-TB, because isolated RMP resistance is rare (except when patients have a history of being treated with rifampicin alone). If the results of a gene probe (*rpoB*) are known to be positive, then it is reasonable to omit RMP and to use SHEZ+MXF+cycloserine. The reason for maintaining the patient on INH is that INH is so potent in treating TB that it is foolish to omit it until there is microbiological proof that it is ineffective (even though isoniazid resistance so commonly occurs with rifampicin resistance).

When sensitivities are known and the isolate is confirmed as resistant to both INH and RMP, five drugs should be chosen in the following order (based on known sensitivities):

- an aminoglycoside (e.g. amikacin, kanamycin) or polypeptide antibiotic (e.g., capreomycin)
- pyrazinamide
- ethambutol
- a fluoroquinolone (e.g., moxifloxacin (ciprofloxacin) should no longer be used);
- rifabutin

- cycloserine
- a thioamide: prothionamide or ethionamide
- PAS
- a macrolide: e.g, clarithromycin
- linezolid
- high-dose INH (if low-level resistance)
- interferon-γ
- thioridazine
- Ampicillin

Note: Drugs placed nearer the top of the list are more effective and less toxic; drugs placed nearer the bottom of the list are less effective or more toxic, or more difficult to obtain.

In general, resistance to one drug within a class means resistance to all drugs within that class, but a notable exception is rifabutin: Rifampicin-resistance does not always mean rifabutin-resistance, and the laboratory should be asked to test for it. It is possible to use only one drug within each drug class. If it is difficult finding five drugs to treat then the clinician can request that high-level INH-resistance be looked for. If the strain has only low-level INH-resistance (resistance at 0.2 mg/l INH, but sensitive at 1.0 mg/l INH), then high dose INH can be used as part of the regimen. When counting drugs, PZA and interferon count as zero; that is to say, when adding PZA to a four-drug regimen, another drug must be chosen to make five. It is not possible to use more than one injectable (STM, capreomycin or amikacin), because the toxic effect of these drugs is additive: If possible, the aminoglycoside should be given daily for a minimum of three months (and perhaps thrice weekly thereafter). Ciprofloxacin should not be used in the treatment of tuberculosis if other fluoroquinolones are available.

There is no intermittent regimen validated for use in MDR-TB, but clinical experience is that giving injectable drugs for five days a week (because there is no-one available to give the drug at weekends) does not seem to result in inferior results. Directly Observed Therapy helps to improve outcomes in MDR-TB and should be considered an integral part of the treatment of MDR-TB. Response to treatment must be obtained by repeated sputum cultures (monthly if possible). Treatment for MDR-TB must be given for a minimum of 18 months and cannot be stopped until the patient has been culture-negative for a minimum of nine months. It is not unusual for patients with MDR-TB to be on treatment for two years or more.

Patients with MDR-TB should be isolated in negative-pressure rooms, if possible. Patients with MDR-TB should not be accommodated on the same ward as immunosuppressed patients (HIV-infected patients, or patients on immunosuppressive drugs). Careful monitoring of compliance with treatment is crucial to the management of MDR-TB (and some physicians insist on hospitalization if only for this reason). Some physicians will insist that these patients remain isolated until their sputum is smear-negative or even culture-negative (which may take many months, or even years). Keeping these patients in hospital for weeks (or months) on end may be a practical or physical impossibility, and the final decision depends on the clinical judgment of the physician treating that patient. The attending physician should make full use of therapeutic drug monitoring (in particular, of the aminoglycosides) both to monitor compliance and to avoid toxic effects. Some supplements may be useful as adjuncts in the treatment of tuberculosis, but, for the purposes of counting drugs for MDR-TB, they count as zero (if four drugs are already in the regimen, it may be beneficial to add arginine or vitamin D or both, but another drug will be needed to make five).

2.14 New Drugs in the Management of Drug Resistant Tuberculosis

BEDAQUILINE (SIRTURO®)

This is the first drug in a novel class approved for the therapy of TB since rifampin was approved in 1971.Bedaquiline is indicated as part of combination therapy in the treatment of adults (≥18 years) with pulmonary Multi-Drug Resistant Tuberculosis. Chemical Class: Diaryl-quinolone. It belongs to World Health Organization Group 5 drugs.

PHARMACOLOGY

This Bedaquiline drug has a Half-life of 5.5 months. Hepatically metabolized; the major enzyme involved is CYP3A4. It can prolong the QT interval (26.6% vs 8.6% >450ms). Moreover, it can cause hepatotoxicity and increased risk of death in the Bdq arm of the clinical trial (9/79 vs. 2/81).

MECHANISM OF ACTION

Bedaquiline is the first anti-tuberculosis drug to interfere with bacterial energy metabolism. Bedaquiline kills both torpid and actively replicating mycobacteria by interfering with energy production and disrupting intracellular metabolism.Bedaquiline specifically suppresses mycobacterial ATP (adenosine 5-triphosphate) synthase, by binding to subunit c of the enzyme that is essential for the generation of energy in Mycobacterium tuberculosis.

BEDAQUILINE monotherapy (efficacy)

Bedaquiline MICs were superior to both rifampin and isoniazid when tested against a number of drug susceptible MTB strains: (Andries*et al*). Bedaquiline monotherapy was also superior to all presently available first-line drugs in a murine model of pulmonary TB with a high initial bacillary load (Ibrahim *et al*, 2007). In a murine model, use of Bedaquilinefor 4 months was as effective as standard 6-month first-line therapy (Ibrahim *et al*, 2009). Therapy with Bedaquiline for 2 months was more effective than the combination of isoniazid, rifampin & pyrazinamide in mice infected with a drug susceptible TB strain, H37Rv (Louni*et al*, 2006).

2.15 Operational Definition of Variables

- **Loss to follow-up**

Lost to follow-up refers to patients who at one point in time were actively honouring their appointments at the MDR-TB clinic but who are censored (either being incommunicado or by being unreachable) at the point of data collection of the research study. These patients could not be accounted for many reasons i.e. without properly informing the Health Care Worker in the MDR-TB clinic about the situation of their treatment regimen they may have opted to withdraw or discontinue treatment, moved away from the particular study site during their treatment period or become ill and unable to communicate or are deceased.

- **Adherence**

A patient was regarded as being adhered if he/she takes the drugs for at least 40 days out of the 60 days (i.e. two months period). If the total number of days a patient takes the drugs is >= 40 {Patients that had >0.5 of the fraction were regarded as having adhered to treatment} days which excludes Saturdays and Sundays for two months, it was regarded as "Yes" (Adhered) and "No" (Not Adhered).

- **Culture Conversion**

Culture conversion is a diagnostic criterion indicating the point at which samples taken from a patient infected with tuberculosis can no longer produce tuberculosis cell cultures. Culture conversion is a positive prognostic marker indicating that a patient is cured of, or is recovering from tuberculosis.

- **Sputum Conversion Rate**

Sputum conversion rate is the rate at which all smear positive patients become negative. In this context, the conversion rate is defined as the number of negative results divided by the number of smear-positive patients for whom the 2 months follow-up examination was completed.

Rate = (No of negative results/No of smear-positive patients) x 100%

2.15.1 Operationlization of Terms

- **Cured**

  This is defined as consistent completion of treatment on negative culture for at least five negative results in the last twelve to fifteen months.

- **Treatment completed**

  This is defined as completion of treatment in agreement with laid down procedures without adherence to specification for therapy failure due to lack of laboratory results.

- **Died**

  This is defined as fatal experience for any reason during the course of MDR-TB treatment.

- **Treatment failure**

  This is defined as failure of at least two of the five cultures documented during the period of 12-15 months of treatments of positive cultures.

- **Lost to follow up**

  This refers to patients who at one point in time were actively participating in the study, but have become lost (either by error in a computer tracking system or by being unreachable) at the point of follow-up in the study.

- **Transferred out**

  This is defined as transferring of patient to another documenting unit which involves recording and reporting activities of an unknown treatment outcome.

- **Time to sputum conversion**

  This is defined as the time from the date of commencement of MDR-TB treatment to the date of specimen collection for the first of two-consecutive negative smear and culture taken 30 days apart.

2.16 Cox Regression

The Cox (proportional hazards) model (Cox, 1972) is the most commonly used multivariate approach for analyzing survival time data in medical research. It is a survival analysis regression model, which describes the relation between the event incidence, as expressed by the hazard function and a set of covariates. Briefly, the hazard is the instantaneous event probability at a given time, or the probability that an individual under observation experiences the event in a period centered on that point in time.

Mathematically, the Cox model is written as

$$h(t) = h_o(t) \times \exp(b_1X_1 + b_2X_2 + \ldots\ldots + b_pX_p) \quad \text{Equation 2.1}$$

where the hazard function h(t) is dependent on (or determined by) a set of p covariates (x_1, $x_2,\ldots x_p$), whose impact is measured by the size of the respective coefficients ($b_1,b_2,\ldots b_p$). The term ho is called the baseline hazard, and is the value of the hazard if all the X_i are equal to zero (the quantity exp(0) equals 1). The 't' in h(t) reminds us that the hazard may (and probably will) vary over time. An appealing feature of the Cox model is that the baseline hazard function is estimated non-parametrically, and so unlike most other statistical models, the survival times are not assumed to follow a particular statistical distribution.

The Cox model is essentially a multiple linear regression of the logarithm of the hazard on the variables X_i, with the baseline hazard being an 'intercept' term that varies with time. The covariates then act multiplicatively on the hazard at any point in time, and this provides us with the key assumption of the PH model: the hazard of the event in any group is a constant multiple of the hazard in any other. This assumption implies that the hazard curves for the groups should be proportional and not cross.

Proportionally implies that the quantities exp (b_i) are called hazard ratios. A value of b_i greater than zero, or equivalently a hazard ratio greater than one, indicates that as the value of the ith covariate increases, the event hazard increases and thus the length of survival decreases. Put another way, a hazard ratio above 1 indicates a covariate that is positively associated with the event probability, and thus negatively associated with the length of survival. This proportionality assumption is often appropriate for survival time data but it is important to verify that it holds.

2.16.1 Assumptions of Cox (Proportional Hazard) Model

First and foremost is the issue of non-informative censoring. To satisfy this assumption, the design of the underlying study must ensure that the mechanism giving rise to censoring of individual subjects are not related to the probability of an event occurring. In a regression type situation, this means that the survival curves for two strata must have hazard functions that are proportional over time (i.e. constant relative hazard).

Since the Cox proportional hazards model relies on the hazards to be proportional, i.e. that the effect of a given covariate does not change over time, it is very important to verify that the covariates satisfy the assumption of proportionality. If this assumption is violated, the simple Cox model is invalid, and more sophisticated analyses are required. If this interest centres upon a binary covariate, Z_1, whose relative risk changes over time, one approach is to introduce a time-dependent covariate as follows. Let

$Z_2(t) = Z_1 \times g(t) = g(t)$ if the covariate Z_1 takes on the value 1

$= 0$ if the covariate Z_1 takes on the value 0,

where $g(t)$ is a known function of time. One difficulty with this approach is that the function $g(t)$ is usually unknown. In such cases, it may be preferable to use a procedure that would allow the function $g(t)$ to be estimated from the data. One approach to this problem is to fit a model with an indicator function for $g(t)$.

However. Cure models can be a useful alternative to the standard Cox proportional hazards models for data with survival trends for quite a number reason (Cox. 1972). First. the assumption of proportional hazards can fail when survival curves have plateaus at their tails. Secondly. survival plots with long plateaus may indicate heterogeneity within a patient population that can be useful to describe explicitly. Cure models allow to us investigate what covariates are associated with long-term effects. For example. Cure models can allow evaluating whether a new therapy is associated with an increase or decrease in the probability of being a long-term survivor or an improvement or detriment in survival for those who are not long-term survivors. While Cure models have been a popular component of statistical literature for the past 20 years. they have not been extensively implemented in Epidemiology and Public Health Hence. there is need to device another approach in order to determine. predict and establish the time to sputum conversion among multi-drug resistant tuberculosis condition in individuals in an effective and efficient way.

2.17 Cure Models

A cure is the end of a medical condition; the substance or procedure that ends the medical condition, such as a medication, a surgical operation, a change in lifestyle, or even a philosophical mindset that helps end a person's sufferings. It may also refer to the state of being healed, or cured. A remission is a temporary end to the medical signs and symptoms of an incurable disease. A disease is said to be incurable if there is always a chance of the patient relapsing, no matter how long the patient has been in remission.

The proportion of people with a disease that are cured by a given treatment, called the cure fraction or cure rate, is determined by comparing disease-free survival of treated people against a matched control group that never had the disease. Another way of determining the cure fraction and/or "cure time" is by measuring when the hazard rate in a diseased group of individuals' returns to the hazard rate measured in the general population. Inherent in the idea of a cure is the permanent end to the specific instance of the disease. When a person has the common cold, and then recovers from it, the person is said to be *cured*, even though the person might someday catch another cold. Conversely, a person that has successfully managed a disease, such as diabetes mellitus, so that it produces no undesirable symptoms for the moment, but without actually permanently ending it, is not cured.

In complex diseases, such as cancer, researchers rely on statistical comparisons of disease-free survival (DFS) of patients against matched, healthy control groups. This logically rigorous approach essentially equates indefinite remission with cure. The comparison is usually made through the Kaplan-Meier estimator approach. The simplest cure rate model was developed by Berkson and Gage in 1952. In this model, the survival at any given time is equal to those that are cured plus those that are not cured, but who have not yet died or, in the case of diseases that feature asymptomatic remissions, have not yet re-developed signs and symptoms of the disease. When all of the non-cured people have died or experienced relapse of the disease, only the permanently cured members of the population will remain, and the DFS curve will be perfectly flat. The earliest point in time that the curve goes flat is the point at which all remaining disease-free survivors are declared to be permanently cured. If the curve never goes flat, then the disease is formally considered incurable (with the existing treatments).

Therefore, Berkson and Gage equation is written as: $S(t) = p + [(1-p)\, S^*(t)]$.....Equation 2.2

In addtion, Maller & Zhou (1996) gave an extensive discussion of classic methods of inference for the mixture cure rate model. The two available types of cure models are mixture and non-mixture models. For mixture cure models, it concerns modelling the survival two group of patients: cured and uncured individuals. Similarly, logistic regression is used to model the probability of curing a patient while survival model is used for uncured individuals. It is noteworthy that this can be achieved with both Weibull and the Cox models. Mixture cure model is based on the assumption of two different populations which is contrary to a single population of Cox model. In a typical logistic Weibull model, it propounds the interpretation of Odds ratios and Hazard Ratios. Odds Ratio is the probability for cured patient while Hazard Ratio is the survival of uncured individuals.

Non-mixture cure models assume a different procedure to modelling survival. The Non-mixture survival equation can be written as:

$S(t) = p^{1\text{-}Sx(t)}$.....Equation 2.3

The probability of being cured and in $S\times(t)$can be incorporated in the non-mixture model.

Where $S(t)$ is the proportion of people surviving at any given point in time, p is the proportion that are permanently cured, and $S^*(t)$ is an exponential curve that represents the survival of the non–cured people. In addition, Maller & Zhou (1996) gave an extensive discussion of classic methods of inference for the mixture cure rate model.

Cure rate curves can be determined through an analysis of the data. The analysis allows the statistician to determine the proportion of people that are permanently cured by a given treatment, and also how long after treatment it is necessary to wait before declaring an asymptomatic individual to be cured. Several cure rate models exist, such as the *Expectation-Maximization Algorithm* and *Markov Chain Monte Carlo* Model. It is possible to use cure rate models to compare the efficacy of different treatments. Generally, the survival curves are adjusted for the effects of normal aging on mortality, especially when diseases of older people are being studied.

From the perspective of the patient, particularly one that has received a new treatment, the statistical model may be frustrating. It may take many years to accumulate sufficient information to determine the point at which the DFS curve flattens (and therefore no more relapses are expected). Some diseases may be discovered to be technically incurable, but also to require treatment so infrequently as to be not materially different from a cure. Other diseases may prove to have a multiple plateaus, so that what was once hailed as a "cure" results unexpectedly in very late relapses. Consequently, patients, parents and psychologists developed the notion of psychological cure, or the moment at which the patient decides that the treatment was sufficiently likely to be a cure as to be called a cure. For example, a patient may declare himself to be "cured", and to determine to live his life as if the cure were definitely confirmed, immediately after treatment.

There are two major classes of cure models, mixture and non-mixture models. Mixture cure models, as the name suggests, explicitly model survival as a mixture of two types of patients: those who are cured and those who are not cured. Typically, the probability a patient is cured is modelled with logistic regression. The second component of the model is a survival model for patients who are not cured. There are many options for this, but two common models are the Weibull and the Cox models. In words, a mixture cure model can be written as follows:

Probability alive at time t = probability cured + probability not cured X probability alive at time t if not cured..... .....Equation 2.4

Standard survival models, such as the Cox model, do not assume 2 different populations as the mixture cure model does. Many variations of mixture cure models have been proposed in the statistical literature. A nice feature of the logistic Weibull model (and some other mixture models) is that a wide range of researchers understand how to interpret ORs and HRs. The results of the model provide ORs for the probability of being cured and HRs for the survival for patients who are not cured. A benefit of the mixture cure model is that it allows covariates to have different influence on cured patients and on patients who are not cured. For example, a therapy may increase the proportion of patients who are cured (evidenced by a significant OR) but not affect survival for patients who are not cured (evidenced by a non-significant HR). A mixture cure model allows us to tease out that relationship.

Non mixture cure models take a different approach to modelling survival. Many non-mixture cure models can be thought of as Cox proportional hazards models that allow for a cure fraction. Non mixture survival models can be written as follows:

Probability alive time t = probability cured$^{1-Sx(t)}$ .....Equation 2.5

where $1\text{-}S\times(t)$ is an exponent of the probability of being cured and $S\times(t)$ is a survival function. Equation 2.5 has a very different form than the mixture cure model in equation 2.4. Non mixture cure models may fit some data better than mixture cure models and vice versa.

For the non-mixture model, covariates can be incorporated both in the model for the probability of being cured and in $S\times(t)$. The interpretation of covariates is different with the non-mixture cure model than with the mixture model. Covariates included in $S\times(t)$ characterize a "short-term" effect, but the covariates do not describe the survival for those who are not cured because the non-mixture model does not directly model a mixture population.

2.17.1 Mixture Cure Model

As previously stated, the motivation behind mixture cure modeling is the desire to predict time to sputum conversion in which there are cured proportions of individuals and the resulting consequence that those individuals will never experience conversion to sputum negative of multi-drug resistant tuberculosis. This has led to the exploration into cure rate estimation and development of the first mixture cure models by Boag, Berkson, Gage, and Hay Bittle (1965). From these developed models, various studies have proposed and assessed parametric and semi-parametric mixture cure models such as Default time from tuberculosis treatment in the Southern Republic of Benin Using Mixture Cure Model for Survival Analysis (Tchibozo Anicet Sylvere et al, 2015). This cohort assessed the cured fraction, the conditional probability of default (CPD) from treatment course and identified the risk factors predicting its timing. With Cox proportional hazards (PH), predictors of default time were HIV/AIDS, TB history and Age. However, with logistic Cox mixture cure model, HIV/AIDS and Age significantly increased the probability of default, whereas TB history significantly reduced default probability from previous TB infection.

Moreover, the study provides the first evidence that HIV/AIDS, TB history and Age were the major predictive factors of default time from anti-TB treatment in Benin Republic. Therefore, additional efforts to improve the compliance of patients with anti-TB treatment through a better management of the co-infection with HIV/AIDS in accordance with patient's specific age group may be an important feature of a prospective TB control strategy in the future.

Besides, another study has recently used mathematical models to predict the future burden of multi-drug resistant tuberculosis. These models suggest the threat of multi-drug resistant to TB control will depend on the relative 'fitness' of MDR strains and imply that if the average fitness of MDR strains is considerably less than that of drug-sensitive strains, the emergence of resistance will not jeopardize the success of tuberculosis control efforts. These results imply that current epidemiological measures and short-term trends in the burden of MDR-TB do not provide evidence that MDR-TB strains can be contained in the absence of specific efforts to limit transmission from those with MDR disease (Cohen and Murray, 2004).

Several authors such as Persson (2002) and David et al (2013) have studied the parametric approach to mixture cure models. However, semi-parametric models are often of greater interest than parametric models since the parametric assumption can be hard to meet. When this situation arises, violations of the assumptions of the analysis impact the ability to trust the results and validly draw inferences about the results. If this assumption is violated, the simple Cox model is invalid, and more sophisticated analyses are required to achieve the set objectives.

Therefore, many studies more recently such as Tchibozo Anicet Sylvere et al, (2015) and Cohen et al (2004) have explored modeling and estimation with semi-parametric mixture cure models. To start, we give the expression for the mixture cure model. Let T denote the failure time for the event of interest and let Y be the indicator of an individual's susceptibility to the event of interest (Y=1 for susceptible, while Y=0 for not susceptible). Also, define $1-\pi(z)$ as the probability of being cured given the vector of covariates z. $S(t|Y=1, x)$ gives the survival probability for susceptible, uncured patients at time t, given a certain covariate vector x. Covariate vectors x and z may affect the survival and the cure function, respectively. The expression for the mixture cure model is as follows:

$$S_{pop}(t|x, z) = \pi(z)\, S(t|Y = 1, x) + 1-\pi(z) \quad \text{.....Equation 2.6}$$

where $S_{pop}(t|x, z)$ is the unconditional survival function of T for the entire population. Here, $S(t|Y = 1, x)$ is defined as the latency and $\pi(z)$ is defined as the incidence. The modeling strategy for the mixture cure model involves separately modeling the cure proportion and the survival distribution of the uncured patients.

2.18 Log-normal Distribution

In statistics, a log-normal distribution can be described to be normally distributed when a random variable fits a continuous probability distribution. Therefore, if the random variable X is log-normally distributed, then $Y = \ln(X)$ has a normal distribution. Likewise, if Y has a normal distribution, then $X = \exp(Y)$ has a log-normal distribution. A log-normal distribution data takes an only positive real value which was developed by Francis Galton (hald, 1998). The procedure of combination of a variety of independent random variables with positive values is associated with log-normal distribution. This distribution process can function efficiently with mean and standard deviation of the variable's natural logarithm. Therefore, given a log-normally distributed random variable X and two parameters μ and σ that are, respectively, the mean and standard deviation of the variable's natural logarithm, then the logarithm of X is normally distributed, and we can write X as

$X = e^{\mu+\sigma Z}$ with a standard normal variable.

Probability Density Function

A random positive variable x is log-normally distributed if the logarithm of x is normally distributed,

$$\mathcal{N}(\ln x; \mu, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left[-\frac{(\ln x - \mu)^2}{2\sigma^2}\right], \quad x > 0. \qquad \text{.....Equation 2.7}$$

A change of variables must conserve differential probability. In particular,

$$\mathcal{N}(\ln x)d\ln x = \mathcal{N}(\ln x)\frac{d\ln x}{dx}dx = \mathcal{N}(\ln x)\frac{dx}{x} = \ln \mathcal{N}(x)dx, \qquad \text{.....Equation 2.8}$$

where

$$\ln \mathcal{N}(x; \mu, \sigma) = \frac{1}{x\sigma\sqrt{2\pi}} \exp\left[-\frac{(\ln x - \mu)^2}{2\sigma^2}\right], \quad x > 0 \qquad \text{.....Equation 2.9}$$

is the log-normal probability density function.

Cumulative Distribution Function

The cumulative distribution function is

$$\int_0^x \ln\mathcal{N}(\xi;\mu,\sigma)d\xi = \frac{1}{2}\left[1 + \operatorname{erf}\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right] = \frac{1}{2}\operatorname{erfc}\left(-\frac{\ln x-\mu}{\sigma\sqrt{2}}\right) = \Phi\left(\frac{\ln x-\mu}{\sigma}\right),$$

.....Equation 2.10

Where erfc is the complementary error function, and Φ is the cumulative distribution function of the standard normal distribution.

2.19 Weibull Distribution

In probability theory and statistics, the Weibull Distribution is a continuous probability distribution. It is named after Swedish mathematician Waloddi Weibull, who described it in detail in 1951, although it was first identified by Fréchet (1927) and first applied by Rosin & Rammler (1933) to describe a particle size distribution.

The probability density function of a Weibull random variable is:

$$f(x;\lambda,k) = \begin{cases} \frac{k}{\lambda}\left(\frac{x}{\lambda}\right)^{k-1} e^{-(x/\lambda)^k} & x \geq 0, \\ 0 & x < 0, \end{cases} \quad \text{.....Equation 2.11}$$

Where $k > 0$ is the *shape parameter* and $\lambda > 0$ is the *scale parameter* of the distribution. Its complementary cumulative distribution function is a stretched exponential function. The Weibull distribution is related to a number of other probability distributions; in particular, it interpolates between the exponential distribution ($k = 1$) and the Rayleigh distribution ($k = 2$ & $\lambda = \sqrt{2}\sigma$).

If the quantity X is a "time-to-failure", the Weibull distribution gives a distribution for which the failure rate is proportional to a power of time. The *shape* parameter, k, is that power plus one, and so this parameter can be interpreted directly as follows:

- A value of $k < 1$ indicates that the failure rate decreases over time. This happens if there is significant "infant mortality", or defective items failing early and the failure rate decreasing over time as the defective items are weeded out of the population.
- A value of $k = 1$ indicates that the failure rate is constant over time. This might suggest random external events are causing mortality, or failure.
- A value of $k > 1$ indicates that the failure rate increases with time. This happens if there is an "aging" process, or parts that are more likely to fail as time goes on.

In the field of materials science, the shape parameter k of a distribution of strengths is known as the Weibull modulus.

Density Function

The form of the density function of the Weibull distribution changes drastically with the value of k. For $0 < k < 1$, the density function tends to ∞ as x approaches zero from above and is strictly decreasing. For $k = 1$, the density function tends to $1/\lambda$ as x approaches zero from above and is strictly decreasing. For $k > 1$, the density function tends to zero as x approaches zero from above, increases until its mode and decreases after it. It is interesting to note that the density function has infinite negative slope at $x = 0$ if $0 < k < 1$, infinite positive slope at $x = 0$ if $1 < k < 2$ and null slope at $x = 0$ if $k > 2$. For $k = 2$ the density has a finite positive slope at $x = 0$. As k goes to infinity, the Weibull distribution converges to a Dirac delta distribution centred at $x = \lambda$. Moreover, the skewness and coefficient of variation depend only on the shape parameter.

Distribution Function

The cumulative distribution function for the Weibull distribution is

$$F(x; k, \lambda) = 1 - e^{-(x/\lambda)^k} \quad \text{.....Equation 2.12}$$

For $x \geq 0$, and $F(x; k; \lambda) = 0$ for $x < 0$.

The quantile (inverse cumulative distribution) function for the Weibull distribution is

$$Q(p; k, \lambda) = \lambda(-\ln(1-p))^{1/k} \quad \text{.....Equation 2.13}$$

for $0 \leq p < 1$

The failure rate h (or hazard function) is given by

$$h(x; k, \lambda) = \frac{k}{\lambda}\left(\frac{x}{\lambda}\right)^{k-1} \quad \text{.....Equation 2.14}$$

2.20 Log-Logistic Distribution

The log-logistic distribution is the probability distribution of a random variable whose logarithm has a logistic distribution. It is similar in shape to the log-normal distribution but has heavier tails.

The cumulative distribution function is

$$F(x; \alpha, \beta) = 1 / (1 + (x/\alpha)^{-\beta}$$

$$= (x/\alpha)^{\beta} / (1 + (x/\alpha)^{\beta}$$

$$= x^{\beta} / (\alpha^{\beta} + x^{\beta}) \quad \text{Equation 2.15}$$

where $x > 0$, $\alpha > 0$, $\beta > 0$

The probability density function is

$$f(x; \alpha, \beta) = (\beta/\alpha)(x/\alpha)^{\beta-1} / (1 + (x/\alpha)^{\beta})^2 \quad \text{Equation 2.16}$$

2.21 Log-rank Test

In statistics, the log-rank test is a hypothesis test to compare the survival distributions of two samples. It is a non-parametric test and appropriate to use when the data are right skewed and censored (technically, the censoring must be non-informative). It is widely used in clinical trials to establish the efficacy of a new treatment in comparison with a control treatment when the measurement is the time to event (such as the time from initial treatment to a heart attack). The test is sometimes called the Mantel-Cox test, named after Nathan Mantel and David Cox. The log-rank test can also be viewed as a time-stratified Cochran Mantel-Haenszel test. The test was first proposed by Nathan Mantel and was named the log-rank test by Richard and Julian Peto. The log-rank test statistic compares estimates of the hazard functions of the two groups at each observed event time. It is constructed by computing the observed and expected number of events in one of the groups at each observed event time and then adding these to obtain an overall summary across all-time points where there is an event.

Let $j = 1, \ldots, J$ be the distinct times of observed events in either group. For each time j, let N_{1j} and N_{2j} be the number of subjects "at risk" (have not yet had an event or been censored) at the start of period j in the two groups (often treatment vs. control), respectively. Let $N_j = N_{1j} + N_{2j}$. Let O_{1j} and O_{2j} be the observed number of events in the groups respectively at time j, and define $O_j = O_{1j} + O_{2j}$.

Given that O_j events happened across both groups at time j, under the null hypothesis (of the two groups having identical survival and hazard functions) O_{1j} has the hyper geometric distribution with parameters N_j, N_{1j}, and O_j. This distribution has expected value

$$E_{1j} = \frac{O_j}{N_j} N_{1j}$$ and variance $$V_j = \frac{O_j (N_{1j}/N_j)(1 - N_{1j}/N_j)(N_j - O_j)}{N_j - 1}$$ .....Equation 2.17

The log-rank statistic compares each O_{1j} to its expectation E_{1j} under the null hypothesis and is defined as

$$Z = \frac{\sum_{j=1}^{J}(O_{1j} - E_{1j})}{\sqrt{\sum_{j=1}^{J} V_j}}.$$

.....Equation 2.18

2.21.1 Asymptotic Distribution

If the two groups have the same survival function, the log-rank statistic is approximately standard normal. A one-sided level α test will reject the null hypothesis if $Z > z_\alpha$ where z_α is the upper α quartile of the standard normal distribution. If the hazard ratio is λ, there are n total subjects. d is the probability a subject in either group will eventually have an event (so that nd is the expected number of events at the time of the analysis), and the proportion of subjects randomized to each group is 50%, then the log-rank statistic is approximately normal with mean $(\log \lambda)\sqrt{\frac{nd}{4}}$ and variance 1. For a one-sided level α test with power $1-\beta$, the sample size required is

$$n = \frac{4(z_\alpha + z_\beta)^2}{d \log^2 \lambda}$$

.....Equation 2.19

where z_α and z_β are the quartiles of the standard normal distribution.

Joint Distribution

Suppose Z_1 and Z_2 are the log-rank statistics at two different time points in the same study (Z_1 earlier). Again, assume the hazard functions in the two groups are proportional with hazard ratio λ and d_1 and d_2 are the probabilities that a subject will have an event at the two time points where $d_1 \leq d_2$. Z_1 and Z_2 are approximately bivariate normal with means $\log \lambda \sqrt{\frac{n d_1}{4}}$ and $\log \lambda \sqrt{\frac{n d_2}{4}}$ and correlation $\sqrt{\frac{d_1}{d_2}}$

.....Equation 2.20

2.22 Likelihood and Akaike Information Criterion

Many statistical models in medical research are estimated using a technique called *maximum likelihood*. This technique attempts to estimate the parameters of a model, which we denote generically by β, by maximizing the likelihood function. The likelihood function, denoted L(β), is the product of the probability density functions (or probability mass functions for discrete distributions) evaluated at the observed data values. Given the observed data, maximum likelihood estimation seeks to find values for the parameters, β, that maximize L(β).

Instead of maximizing the likelihood function L(β), it is easier to work with the negative of the natural logarithm of the likelihood function, -*Log* L(β). The problem of maximizing L(β) is reformulated as a minimization problem where you seek to minimize -LogLikelihood = -*Log* L(β). Therefore, smaller values of -LogLikelihood or (-2LogLikelihood) indicate better model fits.

One can use the value of -LogLikelihood to choose between models and to conduct custom hypothesis tests that compare models fit using different platforms. This is done through the use of likelihood ratio tests. One reason that -2LogLikelihood is reported in many medical research is that the distribution of the difference between the full and reduced model -2LogLikelihood values is asymptotically Chi-square. The degrees of freedom associated with this likelihood ratio test can be equated in value to the difference between the numbers of parameters in the two models (Wilks, 1938). The corrected Akaike's Information Criterion (AICc) and the Bayesian Information Criterion (BIC) are information-based criteria that assess model fit. Both are based on -2LogLikelihood.

AICc is defined as follows:

$$AICc = -2LogLikelihood + 2k + 2k\,(k + 1)/(n-k-1)$$

where *k* is the number of estimated parameters in the model and *n* is the number of observations in the data set. This value can be used to compare various models for the same data set to determine the best-fitting model. The model having the smallest value, as discussed in Akaike (1974), is usually the preferred model.

BIC is defined as follows:

$$BIC = -2LogLikelihood + k \ln(n)$$

where k is the number of estimated parameters in the model and n is the number of observations in the data set. When comparing the BIC values for two models, the model with the smaller BIC value is considered better.

CHAPTER THREE

Methodology

3.1 Study Design

Secondary data was employed for this retrospective study. This secondary dataset came from patients who attended Lagos Mainland (Infectious Disease Hospital) Hospital, Lagos, Nigeria.

3.2 Study Population

The target population consisted of patients who were diagnosed of multi-drug resistant tuberculosis disease in Infectious Disease Hospital, Mainland Hospital, Lagos and University College Hospital, Ibadan. This involved a 54-month (April 2012-October 2016, except December 2015) of 413 involving treated multi-drug resistant tuberculosis patients who met inclusion criteria out of 469 since the programme inception. The patients received treatment at the facility. Consequently, ethical approval and data accessibility for this study was granted by Health Research and Ethics Committee of Lagos State University Teaching Hospital (LASUTH) and Health Service Commission, Lagos respectively.

3.3.1 Inclusion Criterion

The criteria for inclusion of patients in this study was

- Patient (aged 15 years or more) who had earlier had an episode of multi-drug resistant tuberculosis condition.

3.3.2 Exclusion Criterion

The criteria for exclusion of patients in this study was

- Patient less than 15 years who had earlier had an episode of multi-drug resistant tuberculosis condition.

3.4 Selection of Records

This was achieved by consecutively extracting information about each multi-drug resistant patient who met the inclusion criterion. A right censoring technique was employed for the selection of the patients. Right censoring occurs when a subject or patient leaves the study before the event occurs or the study ends before the event has occurred. Therefore, one hundred and twenty-three (123) patients were censored out of four-hundred and thirteen (413) patients. So, two-hundred and ninety (290) patients were left at the end right censoring period. Conversely, left censoring is when the event of interest has already occurred before enrolment in the study. This is very rarely encountered.

3.5 Description of Data Extraction

The main outcome measure (time to sputum conversion) was the time from the date of MDR-TB treatment started or date of making diagnosis to the date of specimen collection for the first of two consecutive negative smear/culture taken 30 days apart. Time was computed as the period of months each patient was measured for sputum conversion. The predictor variables of interest include: demographic (age and gender) and clinical characteristics (registration group, number of drugs resistant to at treatment initiation, HIV status, diabetes status and adherence with medication).

In addition, variables such as patients status: (transferred in, previously exposed with both first line and second line anti-TB drugs and others), type of test (smear/culture), history of TB treatment, treatment outcomes (cured, completed, failed, died, defaulted, transferred out) Type of Test (Gene Expert and Drug Sensitivity Test), Result (Resistant, Susceptible and Contaminated), ART status (Yes/No), bacillary load and negative sputum smear and culture at the beginning of treatment, drug-resistant pattern at initiation of treatment, treatment initiation period, number of drugs the initial isolate was resistant to at treatment initiation and time in days to initial sputum culture conversion were also extracted.

3.6 Data Management and Analysis

R statistical software was used in carrying out the Kaplan-Meier Estimation and Modelling. Statistical Package for Social Sciences (IBM SPSS) version 20.0 was used to produce life tables so as to give a detailed survivorship pattern among multi-drug resistant tuberculosis patients and also to assess the effect of other socio-biological factors using Cox regression models. The Cox proportional hazard model was used to determine which of the explanatory variables explained differences in survival time of patients (the lifespan or period that the patients on multi-drug resistant tuberculosis drugs were visible during the study). In the analyses, descriptive statistics (frequency distribution tables, measures of location and variation) was used to examine the distribution of the patients according to some socio-economic and demographic variables of interest.

Also, survival analysis was performed to compare the time to initial sputum conversion by various levels of variables (HIV status, gender, medical compliance, social support, period of enrolment). For each categorical variable (Gender, HIV status, Medical compliance and Social support), Kaplan-Meier survival curves was constructed and stratified for each level of the variables. The log-rank test was used to test for statistical differences in the observed time to sputum conversion between new and retreatment cases. Unadjusted and adjusted hazard ratios for sputum conversion were determined from a Cox proportional hazard regression. Factors associated with time to sputum conversion at 5% level of significance in Kaplan-Meier analysis were forwarded to the multivariate Cox regression model. Mixture Cox cure models were also fitted to the main outcome variable which is time to sputum conversion using Lognormal, Log-logistic and Weibull distributions as alternative to the violation of Proportional Hazard assumption.

First, the standard Cox regression was fitted under the proportional hazard assumption. That is: $h(t; X_1, X_2, \ldots X_k) = \lambda_0(t) \exp(\lambda_1 X_1 + \lambda_2 X_2 + \ldots\ldots + \lambda_k X_k)$. Where $\lambda_0(t)$ is the baseline hazard of time to sputum conversion at time t and $X_1, X_2, \ldots X_k$ are the k independent covariates. Here, t is the time to sputum conversion. This was implemented in R using the PARFM procedure. Second, the logistic Cox PH mixture model was used to account for the cure fraction of the sample. It assumes a binary distribution to model the incidence probability and a parametric sputum conversion time distribution to model the latency. Collett and Dave (2003), extended the model by using Cox proportional hazards regression for the latency. That is:

$$S[t, x, z] = \pi[z]\, S[t / U\ 1, x] + [1 - \pi(z)]$$

Where S [t/x,z] is the conditional survival function for the entire cohort. S [t/U=1,x] = P[T> t/U = 1,x] is the survival function for susceptible individuals given a covariate vector $X = [X_1, X_2, \ldots X_k]'$ and $\pi[z] = P[U = 1/z]$ is the probability of being susceptible given a covariate vector $Z=[z_1, z_2, \ldots z_p]'$ which may include the same covariates as x. These were also implemented through PARFM in R software. Sputum conversion time can take the form of parametric distributions such as Weibull, Log-normal and Log-logistic which are commonly used to model survival data. Estimates were computed using the R PARFM procedure for the parametric component and through the Expectation Maximization (EM) algorithm for the Cox PH mixture cure component. Three models (Weibull, Log-normal and Log-logistic) were proposed and the best one was selected based on the goodness of fit statistics: Deviance (-2LogL), Akaike Information Criterion (AIC). That is the model with the smallest criteria while the effect of predictors of time to sputum conversion was reported as Hazard Ratios at $\alpha_{0.05}$

Besides, data was designed such that each of the selected covariates has an effect on both the cured fraction and the survival of the uncured patients who experienced sputum conversion. The use of the standard Cox PH model is linked to the hypothesis that, if complete follow-up were possible for all patients, each would have eventually experienced the sputum conversion from treatment. This hypothesis, however, did not hold for the dataset at hand. Some individuals were cured or immune against the event, resulting in the fact that time to sputum conversion distribution was improper as it has total mass less than 1. Indeed, from the figure 4.1, the Kaplan-Meier Estimate (KME) curve levels off at nonzero proportion (around 95%) at the right tail and exhibit a relatively long and stable plateau (Figure 4.1). Combined with the fact that the last sputum conversion time was censored, this supported the applicability of the mixture cure model. Another evidence of the presence of immune individuals in the 2016 cohort of MDR-TB patients was based on the largest event time. The largest sputum conversion time was censored. This led to the rejection of the hypothesis of no immune patient in the source population of the cohort which establishing the evidence of sufficient follow-up. Added to this, we found 64.9% of sputum conversion, satisfying the cut-off criterion of at least 5% of event needed to apply the mixture cure model.

3.7 Confidentiality

All information collected from this study was given code numbers and no name was also recorded. The name or the identity of the patient was not used and would not be used in any publication or report from this study.

3.8 Ethical Approval

The ethical approval for this study was granted by the Ethical Research Committee of the Lagos State University Teaching Hospital (LASUTH), Lagos, Nigeria.

CHAPTER FOUR

The demographic, clinical, social and lifestyle characteristics are presented in this chapter, four. The results of factors associated with sputum conversion time among multi-drug resistant tuberculosis patients in bivariate analysis were presented. Moreover, covariates associated with time to sputum conversion using mixture cure models and its models goodness-of-fit statistics were also displayed. Finally, clinical life tables which relate to life expectancy and mortality experience of the multi-drug resistant tuberculosis patients were summarized. A total of 413 records of multi-drug resistant tuberculosis patients were included for this analysis.

4.1 Demographic, Clinical, Social and Lifestyle Characteristics

The demographic characteristics of the multi-drug resistant tuberculosis patients were summarized in table 4.1.1. The mean age of the respondents was 36.8 ± 12.7 years. About a third of them (32.0) were between 25-34 years. A larger percent of the patients (60.8%) were male with a sex ratio of 1.7 while some of them (41.4%) acquired secondary education. About two-third (67.6%) of them were married and 68.8% had normal Body Mass Index. Most of them (47.7%) were of Yoruba ethnic tribe. More than three-quarter (77.7%) of the patients reside within Lagos.

Table 4.1.1: Demographic Characteristics of Multi-Drug Resistant Tuberculosis Patients

Variables	Frequency	Percentage
Age group (years)		
15–24	62	15.0
25–34	132	32.0
35–44	103	24.9
45–59	82	19.9
>60	24	5.8
Unknown	10	2.4
Total	**413**	**100.0**
Gender		
Male	251	60.8
Female	148	35.8
Unknown	14	3.4
Total	**413**	**100.0**
Level of Education		
None	78	18.9
Primary	127	30.8
Secondary	171	41.4
Tertiary	29	7.0
Unknown	8	1.9
Total	**413**	**100.0**
Marital Status		
Single	84	20.3
Married	279	67.6
Separated	19	4.6
Widow/Widower	24	5.8
Unknown	7	1.7
Total	**413**	**100.0**
Tribe		
Yoruba	197	47.7
Igbo	73	17.7
Hausa	28	6.8
Others	98	23.7
Unknown	17	4.1
Total	**413**	**100.0**
Body Mass Index		
Normal	284	71.6
Overweight	103	25.9
Obese	10	2.5
Total	**397**	**100.0**

Variable	Frequency	Percentage
Location of Patients		
Lagos	321	77.7
Outside Lagos	92	22.3
Total	**413**	**100.0**

Table 4.1.2 shows the clinical characteristics of the multi-drug resistant tuberculosis patients. A larger percentage (86.9%) of the patients was of pulmonary tuberculosis status. The distribution ratio of the registration category of the patients in respect to new and retreatment cases was 1:3. More than half of them (58.4) converted within the duration of study period while among the non-converted, 11.4% extended into extensive drug resistant category. A paltry percentage (13.3%) of the patients were HIV positive and on anti-retroviral treatment (11.1%). Less than a fifth of the patients (15.5%) were cured while 7.3% died, 8.2% are lost to follow-up, 9.2% defaulted and 5.3% relapsed.

Table 4.1.2: Clinical Characteristics of Multi-Drug Resistant Tuberculosis Patients

Variables	Frequency	Percentage
Form of Tuberculosis		
Pulmonary Tuberculosis	359	86.9
Extra Pulmonary Tuberculosis	54	13.1
Total	**413**	**100.0**
Registration Category		
New	94	22.8
Retreatment	319	77.2
Total	**413**	**100.0**
Conversion status		
Converted	241	58.4
Not Converted	172	41.6
Total	**413**	**100.0**
XDR-TB		
Yes	47	11.4
No	79	19.1
Unknown	46	69.5
Total	**172**	**100.0**
HIV Status		
Positive	55	13.3
Negative	307	74.3
Unknown	51	12.4
Total	**413**	**100.0**
Anti-Retroviral Treatment		
Yes	46	11.1
No	308	74.6
Unknown	59	14.3
Total	**413**	**100.0**

Variable	Frequency	Percentage
Colony count at initial culture		
1+ or 2+	164	39.7
3+ or 4+	172	41.6
Unknown	77	18.7
Total	**413**	**100.0**
Bacilloscopy before treatment		
Positive	303	73.4
Negative	49	11.9
Unknown	61	14.8
Total	**413**	**100.0**
Clinical outcome		
Sputum converted	268	64.9
Died	30	7.3
Defaulted	38	9.2
Relapses	22	5.3
Loss to follow-up	34	8.2
Transferred out	21	5.1
Total	**413**	**100.0**

Table 4.1.3 shows the social and lifestyle characteristics of multi-drug resistant tuberculosis patients. A larger percentage of the patients (42.6%) had ever taken alcohol while a paltry percentage 17.4% had ever smoked. Less than half of them (16.9%) were known diabetic. Less than half of them (47.4%) adhered with their medication. The average number of drugs resistant to at treatment initiation by the patients was five (4.83 ± 1.9). Majority of the patients were resistant to streptomycin (79.7) while 16.2% were resistant to ofloxacin.

Table 4.1.3: Social and Lifestyle Characteristics of Multi-Drug Resistant Tuberculosis Patients

Variables	Frequency	Percentage
Ever taken alcohol		
Yes	176	42.6
No	199	48.2
Unknown	38	9.2
Total	**413**	**100.0**
Ever smoked		
Yes	72	17.4
No	293	70.9
Unknown	48	11.6
Total	**413**	**100.0**
Diabetes status		
Yes	70	16.9
No	298	72.1
Unknown	45	11.0
Total	**413**	**100.0**
Adherence with medication		
Yes	196	47.4
No	179	43.4
Unknown	38	9.2
Total	**413**	**100.0**
Number of drugs resistant to at treatment initiation		
2–4 drugs	192	46.5
5–6 drugs	131	31.7
>=7 drugs	90	21.8
Total	**413**	**100.0**
Resistant to Streptomycin		
Yes	329	79.7
No	58	14.0
Unknown	26	6.3
Total	**413**	**100.0**

Variable	Frequency	Percentage
Resistant to Ethambutol		
Yes	265	64.2
No	107	25.9
Unknown	41	9.9
Total	**413**	**100.0**
Resistant to Kanamycin		
Yes	69	16.7
No	81	19.6
Unknown	263	63.7
Total	**413**	**100.0**
Resistant to Ofloxacin		
Yes	67	16.2
No	270	65.4
Unknown	76	18.4
Total	**413**	**100.0**
Resistant to Capreomycin		
Yes	73	17.7
No	228	55.2
Unknown	112	27.1
Total	**413**	**100.0**
Resistant to Amikacin		
Yes	88	21.3
No	214	51.8
Unknown	111	26.9
Total	**413**	**100.0**

4.2 Factors associated with time to sputum conversion among multi-drug resistant tuberculosis patients

Factors associated with time to sputum conversion among multi-drug resistant tuberculosis patients are shown in table 4.2. The overall median time for sputum conversion was 5.5 (IQR: 1.5-11.5) months among those who converted. The median sputum conversion time of patients who reside within Lagos was 3.5 (IQR: 1.5-6.0) months compared to 5.5 (IQR: 3.0-8.5) months among those who reside outside Lagos [p=0.037]. The median sputum conversion time for patients who are less than or equal to 40 years was 4.5 (IQR: 2.0-11.5) months compared to 6.0 (IQR: 2.33-9.5) months among patients who are older than 40 years [p<0.001]. The median sputum conversion time for patients who adhered to drug medication was 3.5 (IQR: 1.5-6.5) months compared to 6.5 (IQR: 2.0-11.33) months among patients who did not adhere to drug medication [p<0.001]. Also, the median sputum conversion time for diabetic patients was 6.67 (IQR: 2.5-10.5) months compared to 3.33 (IQR: 2.0-6.0) months among non-diabetic patients [p<0.001]. Finally, there was a significant difference in sputum conversion time for patients who had successful treatment outcome; 3.0 (IQR: 1.67-6.33) months compared to 8.33 (IQR: 2.0-11.50) months from patients who had poor treatment outcome [p<0.001].

Table 4.2: Factors associated with time to sputum conversion among MDR-TB patients

ariables	No of Patients	Converted		Not Converted		Median duration of conversion (months)	*P*-value (log-rank test)
		Freq.	(%)	Freq.	(%)		
ntire group	413	241	(58.3)	172	(41.7)	5.5 (1.5-11.5)	NA
ocation							0.037**
agos	321	190	(59.1)	129	(40.1)	3.5 (1.5-6.0)	
utside Lagos	92	51	(55.4)	43	(44.6)	5.5 (3.0-8.5)	
ge of patients							<0.001**
=40 years	265	171	(64.5)	94	(35.5)	4.5 (2.0-11.5)	
40 years	138	69	(50.0)	69	(50.0)	6.0 (2.33-9.5)	
nknown	10	1	(10.0)	9	(90.0)		
ender							0.198
ale	251	161	(64.1)	90	(35.9)	5.4 (0.75-6.5)	
emale	148	99	(66.9)	49	(33.1)	6.45 (0.7-8.0)	
nknown	14	6	(42.9)	8	(57.1)		
eg. Group							0.894
ew	94	60	(63.8)	34	(36.2)	5.5 (0.8-7.5)	
etreatment	319	206	(64.6)	113	(35.4)	5.0 (0.85-6.0)	
o of drugs esistant at reatment nitiation							<0.001**
-2	60	46	(76.7)	14	(23.3)	3.75 (2.9-6.2)	
3	353	195	(55.2)	158	(44.8)	5.5 (4.6-9.8)	
olony count at nitial culture							0.073
+ or 2+	157	92	(58.6)	65	(41.4)	4.4 (0.93-5.60)	
3+ or 4+	164	116	(70.7)	48	(29.3)	5.25 (0.65-8.50)	
Unknown	92	58	(63.0)	34	(37.0)		
Bacilloscopy before treatment							0.485
Positive	303	194	(64.0)	109	(36.0)	5.55 (0.73-6.85)	
Negative	49	35	(71.4)	14	(28.6)	4.6 (0.65-6.33)	
Unknown	61	37	(60.7)	24	(39.3)		
dherence with nedication							<0.001**
es	196	147	(75.0)	49	(25.0)	3.5 (1.5-6.5)	
o	179	74	(41.3)	105	(58.7)	6.5 (2.0-11.3)	
Unknown	38	22	(57.9)	16	(42.1)		
Diabetes status							<0.001**
es	70	17	(24.3)	53	(75.7)	6.67 (2.5-10.5)	
o	298	214	(71.8)	84	(28.2)	3.33 (2.0-6.0)	
Unknown	45	8	(17.8)	37	(82.2)		

Variable	No of Patients	Converted		Not Converted		Median duration of Conversion (months)	P-value (log-rank test)
		Freq.	(%)	Freq.	(%)		
HIV status							0.228
Positive	55	30	(54.5)	25	(45.5)	5.7 (0.80-7.75)	
Negative	307	204	(66.4)	103	(33.6)	5.25 (0.65-7.33)	
Unknown	51	32	(62.7)	19	(37.3)		

4.3 Multivariate Analysis (Cox Regression) of factors influencing time to sputum conversion

The factors significantly associated with time to sputum conversion in bivariate analysis were harvested and subjected to multivariate analysis. The result of the Cox regression analysis for time to sputum conversion is shown in table 4.3. Patients who are aged less than or equal to forty years had 18% increased rate of conversion than those who are aged greater than forty years (HR=1.18, p=0.361, 95% CI: 0.83, 1.68). Patients who reside within Lagos had 12% decreased rate of conversion than those who reside outside Lagos (HR=0.88, p=0.456, 95% CI: 0.62, 1.24). Non-diabetic patients had 55% rate of conversion than diabetic patients (HR=0.55, p=0.014**, 95% CI: 0.24, 0.85). Patients who adhered with medication had about twenty-percent (19%) rate of conversion than those who did not adhere (HR=1.19, p=0.263, 95% CI: 0.88, 1.63).

Table 4.3: Test of association of variables with time to sputum conversion in the Cox model for Multi-Drug Resistant TB patients

Variables	Crude Hazard Ratio (95% CI)	P-value	Adjusted Hazard Ratio (95% CI)	P-value
Age of patients				
≤40 years	2.09 (1.38-3.18)	0.001**	1.18 (0.83-1.68)	0.361
>40 years	RC			
Location of patients				
Lagos	0.61 (0.38-0.97)	0.038**	0.88 (0.62-1.24)	0.456
Outside Lagos	RC			
No of drugs resistant at treatment initiation				
1-2	0.80 (0.58-1.12)	0.002**	1.39 (0.98-1.98)	0.036**
>3	RC			
Diabetes status				
Yes	RC	<0.001**	0.45 (0.24-0.85)	0.014**
No	0.13 (0.07-0.23)			
Adherence with medication				
Yes	4.26 (2.74-6.61)	<0.001**	1.19 (0.88-1.63)	0.263
No	RC			

4.4: Test of statistical comparison for the observed time to sputum conversion between new and retreatment groups of MDR-TB patients

The result of statistical comparison (log-rank test) for the observed time to sputum conversion between new and retreatment groups of MDR-TB patients are shown in table 4.4. There was no significant difference between the sputum conversion time of new and retreatment groups of MDR-TB patients (p=0.894). In addition, figure 4.1 showed no clear differentials in survival pattern of time to sputum conversion between new and retreatment cases of multi-drug resistant tuberculosis patients.

Table 4.4: Test of statistical comparison for the observed time to sputum conversion between new and retreatment groups of MDR-TB patients

Registration Group	Median duration of conversion (months)	IQR	P-value (log-rank test)
New	5.50	4.0-7.5	0.894
Retreatment	5.00	3.5-7.5	

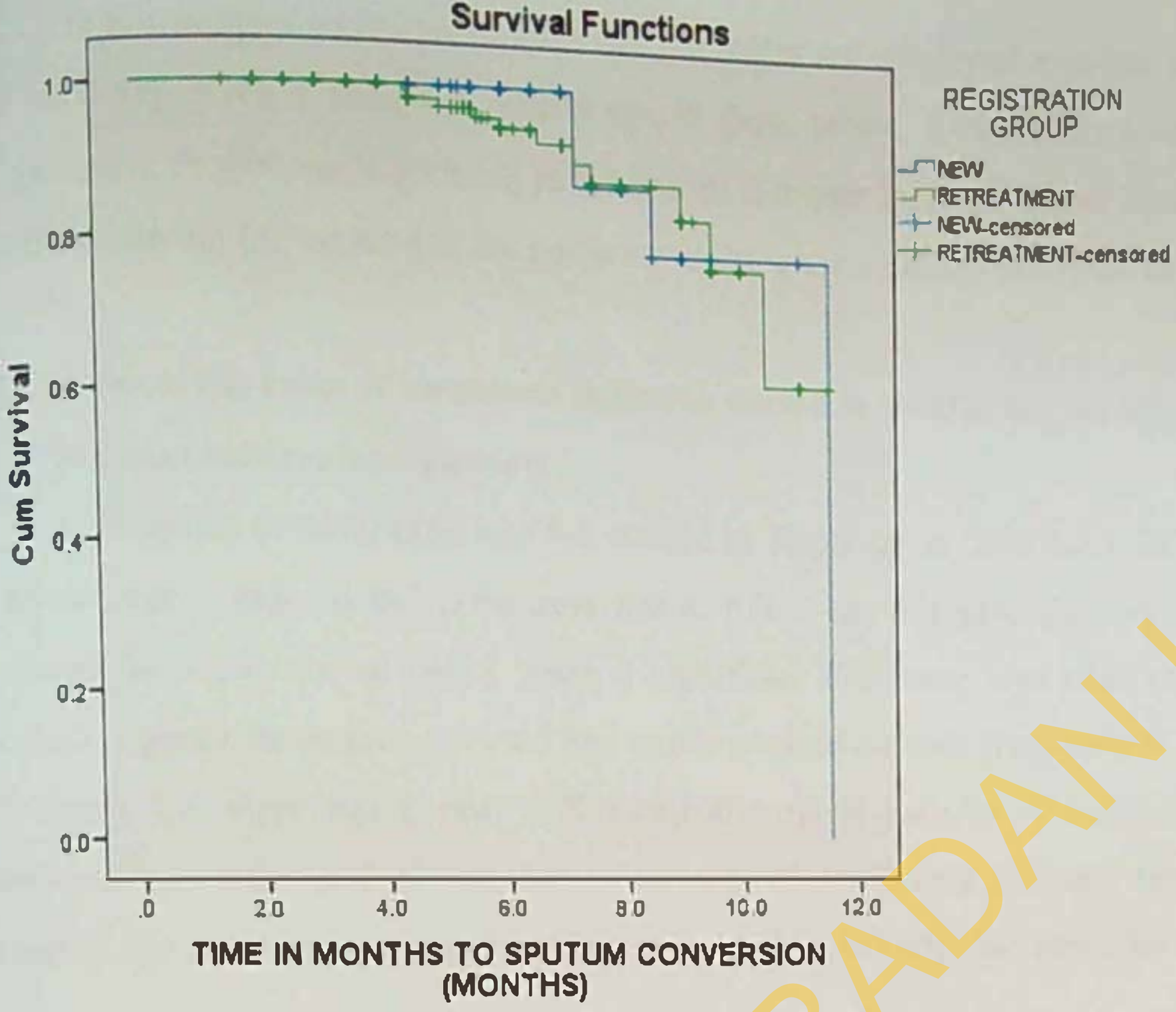

Figure 4.1: Survival function of time to sputum conversion by registration group using the KME and the Mixture cure model

4.5: Clinical Life Tables

In this section, techniques of clinical life tables are employed to summarize the probability of surviving given a period of follow-up. In these tables, a steady drop was observed in the Cumulative Proportion Suriviving at the end of 2-month Interval. These statistics are computed in the following life tables that are constructed using the methods described earlier.

4.5.1: Clinical life table of treatment initiation period in months for the whole multi-drug resistant tuberculosis patients

The median survival time was 9.0 months as displayed in table 4.5.1. In the first interval, 2 patients were censored and none were lost to follow-up, this gave the number of patients who entered the next interval (411). Also, a significant difference was observed in the treatment initiation period between converted and non-converted patients (Log-rank = 129.747, $p<0.001$). In figure 4.2, there was a clear differential in survival patterns of treatment initiation period between converted and non-converted patients of multi-drug resistant tuberculosis patients. Overall, the converted patients had a better survival probability than non-converted patients.

Table 4.5.1. Clinical Life Time Table of treatment initiation period for the whole multi-drug resistant tuberculosis patients

Interval Start Time (Months)	Number Beginning Interval	Cumulative Event (LFU)	Number of Terminal Events	Proportion Surviving	Cumulative Proportion Surviving	Standard Error of Proportion Surv.
0	413	0	2	0.9952	0.9952	0.0034
2	411	1	10	0.9879	0.9832	0.0054
4	400	37	10	0.9564	0.9403	0.0101
6	353	59	21	0.9196	0.8647	0.0137
8	273	59	31	0.8327	0.7200	0.0200
10	183	27	15	0.7461	0.5372	0.0251
12	141	25	18	0.6525	0.3505	0.0297
14	98	12	11	0.5992	0.2100	0.0322
16	75	14	10	0.5151	0.1082	0.0357
18	51	10	7	0.4401	0.0476	0.0383
20	34	13	7	0.3378	0.0161	0.0420
22	14	9	3	0.2807	0.0045	0.0462
24	2	1	0	0.1403	0.0006	0.0739
26	1	1	0	0.1403	0.00009	0.0737

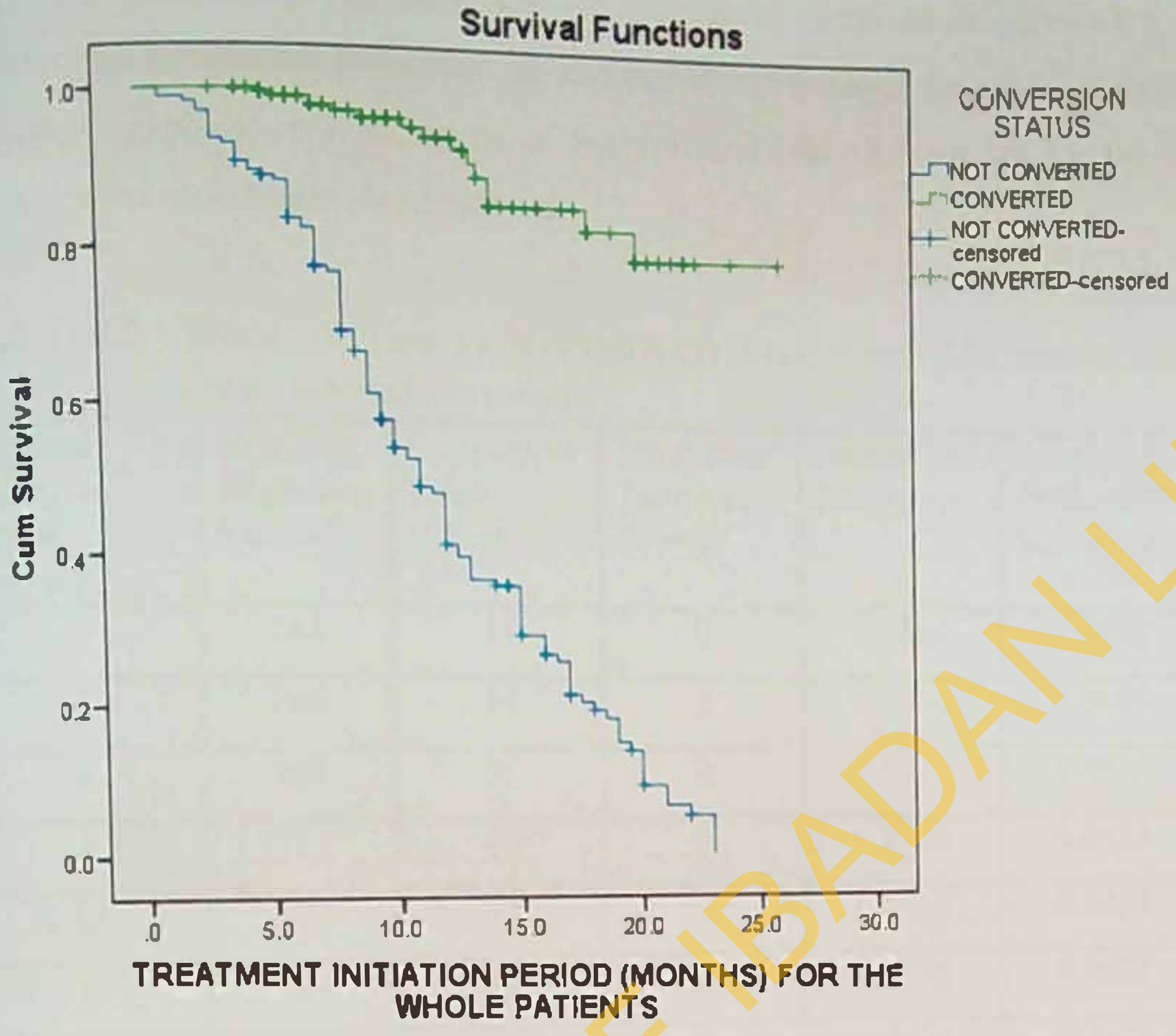

Figure 4.2: Survival function of treatment initiation period by conversion status

4.5.2: Clinical life table of treatment initiation period (months) for converted multi-drug resistant tuberculosis patients

The median survival time was 7.5 months as displayed in table 4.5.2. There was an observance of constant proportion of terminal events between four to ten-month follow-up. In addition, graphical representations of Survival and Hazard functions for the two conversion status of the patients are also displayed.

Table 4.5.2. Clinical Life Time Table of treatment initiation period for converted multi-drug resistant tuberculosis patients

Interval Start Time (Months)	Number Beginning Interval	Cumulative Event (LFU)	Number of Terminal Events	Proportion Surviving	Cumulative Proportion Surviving	Standard Error of Proportion Surviving
0	241	11	0	1.0000	1.0000	0.0000
4	240	34	2	1.0000	1.0000	0.0000
6	204	51	2	0.9913	0.9913	0.0061
8	151	47	2	0.9740	0.9655	0.0116
10	102	23	2	0.9568	0.9238	0.0167
12	77	24	3	0.9335	0.8624	0.0230
14	50	8	2	0.8672	0.7479	0.0386
16	40	9	0	0.8672	0.6485	0.0386
18	31	8	1	0.8393	0.5443	0.0464
20	22	12	1	0.8011	0.4361	0.0579
22	9	7	0	0.8011	0.3493	0.0579
24	2	1	0	0.8011	0.2798	0.0579
26	1	1	0	0.8011	0.2242	0.0579

4.5.3: Clinical life table of treatment initiation period (months) for non-converted multi drug resistant tuberculosis patients

The median survival time was 9.5 months as displayed in table 4.5.3. There was a steady progression of proportion of terminal events between four to eight-month follow-up, which suggests that patients must be closely monitored to avoid subsequent fatal events.

Table 4.5.3. Clinical Life Time Table of treatment initiation period for the non-converted multi-drug resistant tuberculosis patients

Interval Start Time (Months)	Number Beginning Interval	Cumulative Event (LFU)	Number of Terminal Events	Proportion Surviving	Cumulative Proportion Surviving	Standard Error of Proportion Surviving
0	172	0	2	0.9884	0.9884	0.0082
2	170	10	0	0.9709	0.9596	0.0128
4	160	3	8	0.8953	0.8592	0.0233
6	149	8	19	0.8243	0.7082	0.0291
8	122	12	28	0.6688	0.4736	0.0367
10	81	4	13	0.5291	0.2506	0.0402
12	64	1	15	0.4017	0.1007	0.0407
14	48	4	9	0.3631	0.0365	0.0403
16	35	5	10	0.2631	0.0096	0.0382
18	20	2	6	0.1878	0.0018	0.0354
20	12	1	6	0.0957	0.0002	0.0296
22	5	2	1	0.0547	0.0000	0.0246
23	2	0	2	0.0000	0.0000	–

4.5.4: Clinical life table of time to sputum conversion (months) for the multi-drug resistant tuberculosis patients

The median survival time was 5.5 months as displayed in table 4.5.4. About 85% of the patients cumulatively survived at 3 months while 25% survived at 6 months.

Table 4.5.4. Clinical Life Time Table of time to sputum conversion in months for the multi-drug resistant tuberculosis patients

Interval Start Time (Months)	Number Beginning Interval	Cumulative Event (LFU)	Number of Terminal Events	Proportion Surviving	Cumulative Proportion Surviving	Standard Error of Proportion Surviving
1	241	1	0	1.0000	0.9884	0.0000
2	240	12	0	1.0000	0.9596	0.0000
3	228	41	0	1.0000	0.8592	0.0000
4	187	45	2	0.9893	0.7082	0.0075
5	140	32	2	0.9752	0.4736	0.0124
6	106	32	2	0.9568	0.2506	0.0177
7	72	26	4	0.9036	0.1007	0.0308
8	42	15	1	0.8821	0.0365	0.0368
9	26	13	2	0.8142	0.0096	0.0573
10	11	4	1	0.7402	0.0018	0.0877
11	6	5	1	0.6169	0.0002	0.1343

4.6: Effect of covariates using the mixture cure model

Data was designed such that each of the selected covariates has an effect on both the cured fraction and the survival of the uncured individuals or patients who experienced a conversion. The use of the standard Cox PH model is linked to the hypothesis that, if complete follow-up were possible for all patients, each would have eventually experienced the sputum conversion from treatment. This hypothesis, however, did not hold for the dataset at hand. Some individuals were cured or immune against the event, resulting in the fact that time to sputum conversion distribution was improper as it has total mass less than 1. Indeed, from the figure 4.1, the Kaplan-Meier Estimate (KME) curve levels off at nonzero proportion (around 95%) at the right tail and exhibit a relatively long and stable plateau (Figure 4.1). Combined with the fact that the last sputum conversion time was censored, this supported the applicability of the mixture cure model. Another evidence of the presence of immune individuals in the 2016 cohort of MDR-TB patients was based on the largest event time. The largest sputum conversion time was censored. This led to the rejection of the hypothesis of no immune patient in the source population of the cohort which establishing the evidence of sufficient follow-up. Added to this, we found 64.9% of sputum conversion, satisfying the cut-off criterion of at least 5% of event needed to apply the mixture cure model.

Table 4.6.1 and 4.6.2 showed the results of time to sputum conversion among MDR-TB patients using mixture cure model. In log-normal model, non-diabetic patients are two times more likely to experience sputum conversion than diabetes [2.03 (1.17-3.58)] while patients who are resistant to two drugs are two times more likely to experience sputum conversion than those who are resistant to at least three drugs [2.06 (1.36-3.47)]. For Log-logistic model, non-diabetic patients are two times more likely to experience sputum conversion than diabetes [2.11 (1.25-3.82)] while patients who are resistant to two drugs are about three times more likely to experience sputum conversion than those who are resistant to at least three drugs [2.56 (1.85-4.09)]. Moreover, for Weibull model, non-diabetic patients are two times more likely to experience sputum conversion than diabetes [2.02 (1.17-3.58)] while patients who are resistant to two drugs are about three times more likely to experience sputum conversion than those who are resistant to at least three drugs [2.81 (1.94-4.19)]. However, amongst the entire model, the Log normal cure model has the best fitted data as it gave the lowest goodness of fits criteria as shown table 4.6.1 [(-2LogL: 519.84); (AIC: 1053.68)]. The best fitting model was Log-normal mixture cure was $Y=1.00X_1+2.06X_2+0.98X_3+2.03X_4+\varepsilon$ where Y is time to sputum conversion and Xs are age, number of drugs, adherence and diabetes status.

Table 4.6.1: Factors associated with time to sputum conversion among MDR-TB patients using mixture cure model

Variable	Log-normal Cox Mixture Cure OR (95% CI)	Log-Logistic Cox Mixture Cure OR (95% CI)	Weibull Cox Mixture Cure OR (95% CI)
Age	1.00 (0.99-1.02)	1.00 (0.96-1.02)	1.00 (0.98-1.02)
Diabetes status	2.03 (1.17-3.58)**	2.11 (1.25-3.82)**	2.02 (1.17-3.58)**
Adherence status	0.98 (0.80-1.19)	0.98 (0.80-1.19)	0.95 (0.78-1.16)
Number of drugs resistant at treatment initiation	2.06 (1.36-3.47)**	2.56 (1.85-4.09)**	2.81 (1.94-4.19)**

** Significant p-value

Table 4.6.2: Models' goodness-of-fit statistics (time to sputum conversion)

Fit Statistics	Log-normal Cox Mixture Cure	Log-Logistic Cox Mixture Cure	Weibull Cox Mixture Cure
-2LogL	519.84	522.22	521.694
AIC	1053.68	1058.44	1057.39

4.7: Factors associated with treatment initiation period among MDR-TB patients (conversion) using mixture cure model

The results of the effect of selected covariates on the treatment initiation among the patients that experienced conversion were shown in tables 4.7.1 and 4.7.2 showed the results of treatment initiation period among MDR-TB patients using mixture cure model. In log-normal model, non-diabetic patients are two times less likely to complete treatment initiation period than diabetes [0.54 (0.38-0.79)], patients who adhered to treatment medications are about two times less likely to complete treatment initiation period than those who did not adhere [0.63 (0.57-0.92)], while patients who are resistant to two drugs have eight percent increase to complete treatment initiation period than those who are resistant to at least three drugs [1.08 (0.85-1.36)]. For Log-logistic model, patients who are less than or equal to forty-years old have eight percent decrease in completing treatment initiation period compared to patients who are more than forty-years old [0.92 (0.98-1.09)] while non-diabetic patients are have sixteen-percent percent decrease in completing treatment initiation period compared two times more likely to experience sputum conversion than diabetes [0.84 (0.69-1.15)]. Moreover, for Weibull model, non-diabetic patients have a paltry four percent decrease in completing treatment initiation period than diabetes [0.96 (0.62-1.07)] while patients who adhered to treatment medications have a paltry four percent decrease in completing treatment initiation period than those who did not adhere [0.96 (0.78-1.11)]. However, amongst the entire model, the Log normal cure model has the best fitted data as it gave the lowest goodness of fits criteria as shown table 4.6.1 [(-2LogL: 519.84); (AIC: 1053.68)]. However, among the entire model, the Log-Logistic cure model has the best fitted data as it generated the least value goodness of fits as shown table 4.7.1 [(-2LogL: 694.28); (AIC: 1402.55)].

Table 4.7.1: Factors associated with treatment initiation period among MDR-TB patients (conversion) using mixture cure model

Variable	Log-normal Cox Mixture Cure OR (95% CI)	Log-Logistic Cox Mixture Cure OR (95% CI)	Weibull Cox Mixture Cure OR (95% CI)
Age	1.01 (0.96-1.23)	0.92 (0.98-1.09)	1.00 (0.99-1.02)
Diabetes status	0.54 (0.38-0.79)	0.84 (0.69-1.15)	0.96 (0.62-1.07)
Adherence status	0.63 (0.57-0.92)	0.96 (0.78-1.18)	0.96 (0.78-1.11)
Number of drugs resistant at treatment initiation	1.08 (0.85-1.36)	0.97 (0.94-1.06)	1.00 (0.94-1.07)

NA (Not Applicable)

Table 4.7.2: Models' goodness-of-fit statistics (treatment initiation period of conversion)

Fit Statistics	Log-normal Cox Mixture Cure	Log-Logistic Cox Mixture Cure	Weibull Cox Mixture Cure
-2LogL	737.07	694.28	707.16
AIC	1488.13	1402.55	1428.32
BIC	1512.49	1426.92	1452.69

4.8: Factors associated with treatment initiation period among MDR-TB patients (non-conversion) using mixture cure model

The results of the effect of selected covariates on the treatment initiation among the non-converted patients were shown in tables 4.8.1 and 4.8.2 showed the results of treatment initiation period among MDR-TB patients using mixture cure model. In log-normal model, patients who are less than or equal to forty-years old are two times more likely to complete treatment initiation period compared to patients who are more than forty-years old [2.23 (1.85-3.37)], non-diabetic patients have over twenty percent increase to complete treatment initiation period than diabetes [1.23 (0.94-1.61)] while patients who adhered had over thirty-percent increase to complete treatment initiation period than those who did not adhere [1.33 (0.97-1.85)]. For Log-logistic model, non-diabetic patients are have eighteen-percent percent increase to completing treatment initiation than diabetes [1.18 (0.92-1.51)] while patients who adhered had thirty-percent increase to complete treatment initiation period than those who did not adhere [1.30 (0.94-1.79)]. Moreover, for Weibull model, patients who adhered to treatment medications had about twenty-percent increase in completing treatment initiation period than those who did not adhere [1.21 (0.87-1.66)]. However, among the entire model, the Weibull cure model has the best fitted data as it yielded the lowest goodness of fits criteria as displayed table 4.8.1. [(-2LogL: 488.57); (AIC: 991.15)].

Table 4.8.1: Factors associated with treatment initiation period among MDR-TB patients (non-conversion) using mixture cure model

Variable	Log-normal Cox Mixture Cure	Log-Logistic Cox Mixture Cure	Weibull Cox Mixture Cure
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age	2.23 (1.85-3.37)**	1.02 (1.01-1.04)**	1.01 (0.99-1.03)
Diabetes status	1.23 (0.94-1.61)	1.18 (0.92-1.51)	0.96 (0.70-1.32)
Adherence status	1.33 (0.97-1.85)	1.30 (0.94-1.79)	1.21 (0.87-1.66)
Number of drug resistant at treatment initiation	1.04 (0.95-1.13)	1.03 (0.94-1.11)	0.99 (0.91-1.08)

** Significant CI values

Table 4.8.2: Models' goodness-of-fit statistics (treatment initiation period of non-conversion)

Fit Statistics	Log-normal Cox Mixture Cure	Log-Logistic Cox Mixture Cure	Weibull Cox Mixture Cure
-2LogL	497.13	492.07	488.57
AIC	1008.27	998.14	991.15

CHAPTER FIVE

5. 1 Discussion

This study has been designed with the aim to develop a model to predict time to sputum conversion among multi-drug resistant tuberculosis patients. The application of the findings, the contributions to knowledge, the conclusions and recommendations are presented sequentially in this chapter.

5.1.1 Demographic characteristics of multi-drug resistant tuberculosis patients

An overwhelming majority of the patients were male. This is in agreement with the findings of Hovhannesyan and Brecze (2012) that there are fewer females than males in cases of multi-drug resistant TB condition. Nigerian women are so sensitive about the stigma associated with TB disease and negative social consequences have been shown to be more of importance to women. Moreover, studies have shown that women with pulmonary TB are diagnosed on average two weeks later than men due to a delay from the health care provider, and in a study on cough patients it was found that men more often than women were asked for sputum specimen (Thorson et al, 2010).

More than half of the patients studied were above forty years old. According to this finding, there is an increasing risk of TB drug adverse events when age increases. Sylvere (2015) reported that about two-third of the male population were multi-drug resistant tuberculosis patients. In previous reports, the occurrence of any major side effects has been linked with aging, which are predominant amongst the old people. The frequency of adverse reactions has demonstrated a steady increase and direct correlation with age. Overall, susceptibility to adverse reactions are frequent with old people especially at a hepatotoxic level due to a significant reduction in clearance rate of metabolized drug agents by the cytochrome P450 enzyme, changes in the hepatic blood flow distribution as well as other factors affecting liver function (Chung-Delgado et al, 2011).

The findings that 67.6% of the multi-drug resistant TB patients are married substantiate similar findings by Javaid et al, 2016. The latter reported that 66.8% of the study population were married. According to a study conducted by Communicable Diseases Health Service Delivery (COMDI-HSD), married women are particularly vulnerable to the social, economic and mental impacts of MDR-TB, including isolation, financial hardship and depression. Wives and mothers give crucial family support to their husbands and children with MDR-TB, but are sometimes denied even basic support from husbands and family when they are the patients.

In this study, patients who resided within Lagos had a lower rate of time to sputum conversion than those who resided outside Lagos. This variation could be attributed to salient health care delivery systems provided by the state which invariably translated to TB care delivery in Lagos. Also, patients who were resistant to two drugs at treatment initiation had approximately forty-percent rate of sputum conversion than those who were resistant to at least three drugs. This finding was consistent with a previous study on Intensive-Phase Treatment of MDR-TB patients. (Oladimeji et al, 2014).

This study confirmed the knowledge of a association between MDR-TB and Diabetes Mellitus diseases due to the co-morbidity nature which makes the management of MDR-TB challenging. Indeed, majority of the non-diabetic patients in this study had a higher rate of sputum conversion time than diabetic patients. This finding was corroborated by a study on the relationship between multi-drug resistant tuberculosis and diabetes which showed that diabetes mellitus is a risk factor for tuberculosis infection and the reactivation of latent tuberculosis can be adduced to the compromised immune system as a result of certain infections and diseases like diabetes mellitus (Yorke et al, 2017).

Moreover, number of drugs resistant to treatment initiation emerged as a significant risk factor in predicting time to sputum conversion after controlling for other variables. The results suggested that patients who had fewer numbers of drugs significantly predicted the sputum conversion time for the converted patients. The reasons for this require further investigation. One explanation might be due to misclassification in proper case definition of the MDR-TB patients since the study was purely based on analytical retrospective study. Another reason could be adduced to the confounding effect of other concomitant variables that cannot be explicitly explained at the commencement of the study (Kolappan et al, 2002).

5.1.2: Clinical Characteristics of Multi-Drug Resistant Tuberculosis Patients

The results showed a higher proportion of pulmonary TB (86.9%) compared to extra-pulmonary TB (13.1%). However, a study carried out by Sreeramareddy et al (2000), in a tertiary care hospital in western Nepal, there was a sharp contrast in the prevalence of pulmonary TB (51.5%) and extra-pulmonary TB (48.5%) with a relatively equal distribution. The reasons for a paltry proportion of extra-pulmonary TB can be adduced to the rigorous diagnostic procedures of extra-pulmonary TB which was based on fine needle aspiration cytology or biochemical analyses of cerebrospinal/pleural/ascetic fluid or histopathological examination. These procedures also include imageological methods, blood tests for laparotomies for excision biopsies and Mantoux tests. These facilities wherever available are not functional optimally for the investigation and diagnosis of extra-pulmonary tuberculosis.

The findings from this study revealed that majority of cases were retreatment compared to fewer new cases. The results showed a clear contrast to the study conducted by Serge Ade et al (2016) in Republic of Benin where about ninety-five percent of the cases were new cases. Improper records and database, case report/misclassification may be attributed to this sharp difference in this study due to lack of proper case definitions.

In respect of conversion status among multi-drug resistant TB patients, there were clear variations and reports in the proportion of conversion to non-conversion status. Epidemiological reports from a study on Intensive-Phase Treatment Outcomes among Hospitalized Multi-drug Resistant Tuberculosis Patients, nationwide cohort in Nigeria (Oladimeji, et al 2014), had 88.0% converted multi-drug resistant TB patients to 12.0% non-converted while Hovhannesyan and Breeze (2012), reported study had 69.0% conversion to 31.0% non-conversion patients. A study by Heunis et al (2014) from Free State Province South-Africa, reported similar findings of non-conversion between gender groups. In addition, the decline in the trend of 2-month sputum smear non-conversion confirms the relative success of the DOTS strategy in TB control, with better performance among females than males. Interventions should consider the age and sex of patients to improve the 2-month sputum smear-conversion rate.

5.1.3: Social and Lifestyle Characteristics of Multi-Drug Resistant Tuberculosis Patients

The findings from this study revealed that the level of alcohol intake and use of cigarette among the multi-drug resistant TB patients can worsen the treatment outcomes of MDR-TB patients. However, studies conducted by Deiss et al (2009) and Duraisamy et al (2014) were at variance with the results of this study. The implications of substance abuse stem from the fact that drug and substance use whether narcotic or alcohol diminishes the capacity to make and implement rational decisions.

5.1.4 Factors associated with sputum conversion time among multi-drug resistant tuberculosis patients

Specifically, patients whose location are outside Lagos, those who are at least forty-years old, and those diagnosed with diabetes mellitus condition had prolonged sputum conversion at treatment induction. However, the identified factors are assessed either before the condition was diagnosed or during treatment programme. These afford the clinicians to have an insight on the progress the patients made individually with respect to treatment management. Also, in low-resource setting, it is necessary to have an adequate monitoring system for sputum cultures conversion in patients with high risk for longer or delayed conversion in order to manage the cost-effectiveness of the programme. Also, earlier reports on sputum conversion time have insufficient data on history of drug resistance which are germane information for the existing literature. In this study, diabetes status and number of drugs resistant to at treatment initiation emerged as significant risk factors after controlling for other variables. The reasons for this require further investigation.

The study revealed that a fewer patients experienced conversion from MDR-TB treatment programme compared with the level found by a previous study conducted in Armenia (Hovhannesyan and Breeze, 2012). This decrease in proportion may suggest one of the shortcomings in MDR-TB surveillance strategy and still far from the rate recommended by the World Health Organization. However, a higher proportion was found in sub-Saharan African which was between 45.0% to 60.0% (Berhan et al, 2013).

Concerning the intensity of conversion, approximately 6 out of 10 patients experienced conversion within the period. Consequently, a significant difference in sputum conversion was documented based on HIV status. That is a survival rate of 0.10 per month. However, a study on sputum conversion among HIV Co-infected with multi-drug resistant tuberculosis patients in, South Africa revealed 89% conversion rate (Brust et al, 2011) and another one from Zimbabwe (Metcalfe et al, 2014) claimed 62.0% conversion rate. This wide variation in conversion rates can be attributed to the differences in the study designs. Multi-Drug Resistant was found to be resistant to both isoniazid and rifampicin whether there is resistance to other drugs or not (Sharma SK and Mohan A, 2006). This study indicates that much intervention is still needed such as health education.

5.1.5 Factors associated with time to sputum conversion and treatment initiation period among MDR-TB patients using mixture cure model

With respect to mixture cure model, number of drugs resistant to during treatment initiation and diabetes status were found to be significantly associated with time to sputum conversion while Log-normal Cox mixture cure has the best fitted data as it generated the least goodness of fits criteria among multi-drug resistant tuberculosis patients in this study. However, in a similar study on the application of mixture cure model which focussed on the time to default from tuberculosis infection in Southern Republic of Benin. Age, HIV/TB co-infection were found to be significantly associated with default time from tuberculosis treatment while Log-logistic Cox mixture has the best fitted data as it generated the least goodness of fits criteria (Sylvere et al, 2015).

Indeed, juxtaposing the factors associated with treatment initiation period between converted and non-converted multi-drug resistant tuberculosis patients, the model showed no significant association among converted MDR-TB patients whilst Log-logistic Cox mixture has the best fitted data as it yielded the lowest goodness of fits criteria whereas age was significantly associated with the non-converted MDR-TB patients while Weibull Cox mixture has the best fitted data as it generated the least goodness of fits criteria.

From some developed models, various studies have proposed and assessed parametric and semi-parametric mixture cure models such as Default time from tuberculosis treatment in the Southern Republic of Benin Using Mixture Cure Model for Survival Analysis (Tchibozo Anicet Sylvere et al, 2015). This cohort assessed the cured fraction, the conditional probability of default (CPD) from treatment course and identified the risk factors predicting its timing. With Cox proportional hazards (PH), predictors of default time were HIV/AIDS, TB history and Age.

However, with logistic Cox mixture cure model, HIV/AIDS and Age significantly increased the probability of default, whereas TB history significantly reduced default probability from previous TB infection. Moreover, the study provides the first evidence that HIV/AIDS, TB history and Age were the major predictive factors of default time from anti-TB treatment in Benin Republic. Therefore, additional efforts to improve the compliance of patients with anti-TB treatment through a better management of the co-infection with HIV/AIDS in accordance with patient's specific age group may be an important feature of a prospective TB control strategy in the future.

In comparison, a study of modelling epidemics of multi-drug resistant tuberculosis of heterogeneous fitness was emphasized. These models suggest the threat of multi-drug resistant to TB control will depend on the relative 'fitness' of MDR strains and imply that if the average fitness of MDR strains is considerably less than that of drug-sensitive strains, the emergence of resistance will not jeopardize the success of tuberculosis control efforts. These results imply that current epidemiological measures and short-term trends in the burden of MDR-TB do not provide evidence that MDR-TB strains can be contained in the absence of specific efforts to limit transmission from those with MDR disease (Cohen and Murray 2004).

5.2 Conclusion

In view of high rate of drug resistance propounded by the study, about two-third of the cases attained sputum conversion within a period of two months. Some variables were confirmed to be associated with time to sputum conversion. This could assist in employing further strategies in the patients' care and management. Sputum culture conversion can be used regularly as a signal of the achievement of the management of multi-drug resistant TB despite insufficient information to provide benchmarks against progress monitoring. In addition, the findings of time to sputum culture conversion may be useful as a gold standard for determining the treatment outcome for multi-drug resistant tuberculosis patients.

Finally, factors revealed to be associated with culture conversion within a period of two months in the research can be detected during the course of MDR-TB therapy. This can assist in future management of MDR-TB patients. Further studies are needed to unravel and confirm the finding of negative association between resistance to streptomycin and culture conversion at two months observed in the present study.

5.3 Recommendations

1. More prospective clinical studies are required to assess other possible underlying potential factors that cause delays in sputum conversion such as urban and rural differentials, delay in presentation, adverse drug reaction and treatment interruption.
2. There is need for a paradigm shift in the management of MDR-TB patients such that fewer patients are hospitalized in favour of community-based treatment care with measures put in place to ensure compliance.

5.4 Contributions to knowledge

1. The use of mixture cure model in the analysis of MDR-TB data instead of descriptive statistics is a substantial contribution to the body of knowledge.
2. Diabetes mellitus and quantum of drugs resistant at treatment initiation have been identified as factors associated with time to sputum conversion.

R COMMAND CODES FOR Tables 4.5 and 4.51

```
library(survival)
library(parfm)
packageDescription("parfm", fields = "Version")
library(OIsurv)
library(KMsurv)
mydata<-read.csv('akinsola2.csv', header =T)
#fix(mydata)#spreadsheet
attach(mydata)
mydata$adherence <- mydata$adherence - 1
.....Conversion Patient with Time(t) .....
model <- parfm(Surv(time,conversion) ~ adherence + drugs +age + outcome + diabetes, cluster =
"location", data = mydata, dist = "weibul", frailty = "none")
model
confAd<- ci.parfm(model, level = 0.05)["adherence",]
confAd
confAg<- ci.parfm(model, level = 0.05)["age",]
confAg
confDia<- ci.parfm(model, level = 0.05)["diabetes",]
confDia
confDr<- ci.parfm(model, level = 0.05)["drugs",]
confDr
confOut<- ci.parfm(model, level = 0.05)["outcome",]
confOut
AIC(model)
BIC(model)
model1 <- parfm(Surv(time,conversion) ~ adherence + drugs +age + outcome + diabetes, cluster
= "location", data = mydata, dist = "loglogistic", frailty = "none")
model1
confAd1<- ci.parfm(model1, level = 0.05)["adherence",]
confAd1
confAg1<- ci.parfm(model1, level = 0.05)["age",]
confAg1
confDia1<- ci.parfm(model1, level = 0.05)["diabetes",]
confDia1
confDr1<- ci.parfm(model1, level = 0.05)["drugs",]
confDr1
confOut1<- ci.parfm(model1, level = 0.05)["outcome",]
confOut1
AIC(model1)
BIC(model1)
```

```
model2 <- parfm(Surv(time,conversion) ~ adherence + drugs +age + outcome + diabetes, cluster
= "location", data = mydata, dist = "logistics", frailty = "none")
model2
confAd2<- ci.parfm(model2, level = 0.05)["adherence",]
confAd2
confAg2<- ci.parfm(model2, level = 0.05)["age",]
confAg2
confDia2<- ci.parfm(model2, level = 0.05)["diabetes",]
confDia2
confDr2<- ci.parfm(model2, level = 0.05)["drugs",]
confDr2
confOut2<- ci.parfm(model2, level = 0.05)["outcome",]
confOut2
ci.parfm(model2, level = 0.05)["drugs",]
AIC(model2)
BIC(model2)
model23 <- select.parfm(Surv(time, conversion) ~ drugs + age + diabetes + outcome+ adherence
+ censoring, cluster = "location", data = mydata, dist = c("exponential", "weibull","gompertz",
"loglogistic", "lognormal"),frailty = c("gamma", "possta"))
```

R COMMAND CODES FOR Tables 4.6 and 4.6.1

```
library(survival)
library(parfm)
library(OIsurv)
library(KMsurv)
mydata<-read.csv('akinsola2.csv', header =T)
#fix(mydata)#spreadsheet
attach(mydata)
mydata$adherence <- mydata$adherence - 1
..... Period 2... Conversion patients
model <- parfm(Surv(period2.conversion) ~ adherence + drugs +age + outcome + diabetes,
cluster = "location", data = mydata, dist = "weibul", frailty = "none")
model
confAd<- ci.parfm(model, level = 0.05)["adherence",]
confAd
confAg<- ci.parfm(model, level = 0.05)["age",]
confAg
confDia<- ci.parfm(model, level = 0.05)["diabetes",]
confDia
confDr<- ci.parfm(model, level = 0.05)["drugs",]
confDr
confOut<- ci.parfm(model, level = 0.05)["outcome",]
confOut
AIC(model)
BIC(model)
model1 <- parfm(Surv(period2.conversion) ~ adherence + drugs +age + outcome + diabetes,
cluster = "location", data = mydata, dist = "loglogistic", frailty = "none")
model1
confAd1<- ci.parfm(model1, level = 0.05)["adherence",]
confAd1
confAg1<- ci.parfm(model1, level = 0.05)["age",]
confAg1
confDia1<- ci.parfm(model1, level = 0.05)["diabetes",]
confDia1
confDr1<- ci.parfm(model1, level = 0.05)["drugs",]
confDr1
confOut1<- ci.parfm(model1, level = 0.05)["outcome",]
confOut1
AIC(model1)
BIC(model1)
model2 <- parfm(Surv(period2.conversion) ~ adherence + drugs +age + outcome + diabetes,
cluster = "location", data = mydata, dist = "lognormal", frailty = "none")
```

```
model2
confAd22<- ci.parfm(model2, level = 0.05)["adherence",]
confAd22
confAg22<- ci.parfm(model2, level = 0.05)["age",]
confAg22
contDia22<- ci.parfm(model2, level = 0.05)["diabetes",]
contDia22
confDr22<- ci.parfm(model2, level = 0.05)["drugs",]
confDr22
confOut22<- ci.parfm(model2, level = 0.05)["outcome",]
confOut22
AIC(model2)
```

R COMMAND CODES FOR Tables 4.7 and 4.7.1

```
library(survival)
library(parfm)
library(Olsurv)
library(KMsurv)
mydata<-read.csv('akinsola3.csv', header =T)
#fix(mydata)#spreadsheet
attach(mydata)
 mydata$adherence <- mydata$adherence - 1
..... Uncured (Code) Patients
model <- parfm(Surv(period3,conversion) ~ adherence + drugs +age + outcome + diabetes,
cluster = "location", data = mydata, dist = "weibul", frailty = "none")
model
confAd<- ci.parfm(model, level = 0.05)["adherence",]
confAd
confAg<- ci.parfm(model, level = 0.05)["age",]
confAg
confDia<- ci.parfm(model, level = 0.05)["diabetes",]
confDia
confDr<- ci.parfm(model, level = 0.05)["drugs",]
confDr
confOut<- ci.parfm(model, level = 0.05)["outcome",]
confOut
 AIC(model)
 BIC(model)
model1 <- parfm(Surv(period3,conversion) ~ adherence + drugs +age + outcome + diabetes,
cluster = "location", data = mydata, dist = "loglogistic", frailty = "none")
model1
confAd1<- ci.parfm(model1, level = 0.05)["adherence",]
confAd1
confAg1<- ci.parfm(model1, level = 0.05)["age",]
confAg1
confDia1<- ci.parfm(model1, level = 0.05)["diabetes",]
confDia1
confDr1<- ci.parfm(model1, level = 0.05)["drugs",]
confDr1
confOut1<- ci.parfm(model1, level = 0.05)["outcome",]
confOut1
 AIC(model1)
 BIC(model1)
model2 <- parfm(Surv(period3,conversion) ~ adherence + drugs +age + outcome + diabetes,
cluster = "location", data = mydata, dist = "lognormal", frailty = "none")
```

```
model2
confAd22<- ci.parfm(model2, level = 0.05)["adherence",]
confAd22
confAg22<- ci.parfm(model2, level = 0.05)["age",]
confAg22
confDia22<- ci.parfm(model2, level = 0.05)["diabetes",]
confDia22
confDr22<- ci.parfm(model2, level = 0.05)["drugs",]
confDr22
confOut22<- ci.parfm(model2, level = 0.05)["outcome",]
confOut22
AIC(model2)
BIC(model2)
```

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DEPARTMENT OF EPIDEMIOLOGY AND MEDICAL STATISTICS

FACULTY OF PUBLIC HEALTH, COLLEGE OF MEDICINE, UNIVERSITY OF IBADAN, NIGERIA

Ph.D (Biostatistics) Data Collection Instrument

MODELS FOR PREDICTING TIME TO SPUTUM CONVERSION AMONG MULTI-DRUG RESISTANT TUBERCULOSIS PATIENTS IN LAGOS, SOUTH-WEST NIGERIA.

A CASE STUDY OF MAINLAND (INFECTIOUS DISEASE) HOSPITAL, LAGOS

S/No	Date of Reg.	Gender	Education	Marital Status	Tribe	BMI	Patients' Location	Form of MDR-TB	Registration Category	XDR-TB Status	HIV Status	ARV Status
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												

S/No	Colony count	Baccilloscopy	Clinical outcome	Ever taken alcohol	Ever smoke	Diabetes status	Adherence with medication	No of drugs resistant	Resistant to streptomycin	Resistant to ethambutol	Resistant to kanamycin
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
15											
16											
17											
18											
19											
20											

S/No	Resistant to ofloxacin	Resistant to capreomycin	Resistant to amikacin	Time in month(s) to sputum conversion	Treatment initiation period in month(s) of sputum conversion
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					

LAGOS STATE GOVERNMENT

LAGOS STATE
UNIVERSITY TEACHING HOSPITAL,
IKEJA

HEALTH RESEARCH AND ETHICS COMMITTEE
REG. NO. NHREC04/04/2008
(www.nhrec.net)

PROJECT TITLE: MODELLING TIME TO SPUTUM CONVERSION AMONG MULTI DRUG RESISTANT TUBERCULOSIS PATIENTS IN LAGOS, SOUTH WESTERN NIGERIA.
REF. NO.: LREC /06/10/700
PRINCIPAL INVESTIGATOR: AKINSOLA OLUWATOSIN JONADAB
ADDRESS: DEPT. OF EPIDEMOLOGY & MEDICAL STATISTICS, U
DATE OF RECIEPT OF VALID APPLICATION: 08/04/16
DATE OF APPROVAL: 12/07/16

This is to inform you that the research described here in the submitted protocol, the consent forms, advertisements and other participant information materials have been reviewed and given full approval by the Health Research and Ethics Committee of LASUTH (LREC)

This approval dates from 12/07/2016 to 12/07/2018. If there is any delay in starting the Research, Please inform the HREC LASUTH so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. All informed consent forms used in this study must carry the HREC LASUTH assigned number and duration of HREC approval. In a multiyear research endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research

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