Factors associated with mortality among Tuberculosis patients on treatment in Limpopo Province, South Africa, from 2013 to 2018

BY

Mamba Gugu Glorance (11553616)

Mini-Dissertation submitted in partial fulfilment of the requirements for the degree of

Master's in Public Health

Faculty of Health Sciences

Department of Public Health

University of Venda

Supervisor: **Dr JT Mabunda**

Co-supervisor: **Prof A Samie**

December 2021

© University of Venda

DECLARATION

I, Gugu Glorance Mamba (11553616), hereby declare that the mini-dissertation titled: **"Factors associated with mortality among Tuberculosis patients on treatment in the Limpopo Province, South Africa, from 2013 to 2018"** for the degree, Master of Public Health (MPH), at the University of Venda, hereby submitted by me, has not previously been submitted for a degree at this or any other university, that it is my own work in design and execution and that all reference materials contained therein have been duly acknowledged.

Signature  **……. Date** 25 JANUARY 2022**……**

© University of Venda

DEDICATION

I dedicate this work to my late mother who encouraged me at a very young age not to ever give up on my dreams, and also to my family (husband and kids) who supported me during my study time. To my family, thank you, this would not have been possible without your support.

© University of Venda

ACKNOWLEDGEMENTS

I would like to sincerely thank my supervisor, Dr J.T Mabunda and Co-Supervisor, Prof A Samie, for helping me to initiate and finalize this study. Their comments, suggestions and guidance have been extremely helpful; without them this study would not have been a success. I would also like to express my sincere gratitude to the Department of Health for granting me permission to conduct the study in their institution.

© University of Venda

ABSTRACT

Background

Tuberculosis is among the leading causes of morbidity and mortality worldwide, despite the availability and implementation of directly-observed treatment, and all other intervention strategies for its treatment; more than 70% of deaths among tuberculosis patients occurs during the first 2 months of treatment. This study, therefore, aims at identifying factors that contribute to death among tuberculosis patients during treatment, in Limpopo Province, South African, between 2013 and 2018.

Method

A quantitative retrospective cohort study design, using secondary data was applied. Data on all patients who were registered for tuberculosis treatment in the Province from 2013 to 2018 was extracted from the electronic tuberculosis register (ETR.Net) into an excel spread sheet; Statistical Package Social Science version 20, and Statistics and Data version 12 were used for analysis. As part of the descriptive statistics, the Chi square test ($\chi 2$) was used to establish the association between other variables and the main outcome - death. Summary tables described the variables in terms of their frequency and univariate, as well as multivariate models were developed in order to identify the factors that significantly impacted on the death of these patients.

Results

A total of 79589 patient's records were selected for the study; of these 48892 (61.4%) were HIV positive. Their treatment outcomes showed that patients cured were 80.6%, died were 12.5% (which is still high), the defaulted were 5.7%, the MDR cases were 0.2, the Rifampicin resistance were 0.3% and 0.6% for treatment failure. There is a gradual decrease in the death rate, from 2013 at 14.7 % to 7.4% in 2018. There was a statistically significant association between death and gender. The mortality rate among the male gender was 12.8% and for the female gender was 12.2%, with a Chi square value of 4.4 and a p value of 0.032. There was a clear association between CD4 cell count range among TB patients and mortality. The mortality among TB patient with a CD4 count less than 50 was 20.4%, which

© University of Venda

was the highest and the difference was statistically significant with a p value less than 0.0001. Mortality among the other groups was much lower and decreased progressively with the lowest mortality rate among those with a CD4 cell count higher than 350 at 3.3%. The Kaplan-Meier Survival analysis provides special techniques that are required to compare the risks for death associated with different groups (in this case, HIV positive and HIV negative patients) where the risk changes over time in measuring survival time. The case processing summary shows that the number of events in both HIV negative and HIV positive groups were almost similar and 91.5% of the HIV negative were censored as compared to 85%.

Discussion

A retrospective review of data collected on patients receiving anti-TB treatment was conducted in Limpopo Province where TB incidence rate is the highest compare to all provinces of South Africa. A low treatment success rate was observed in this study; the treatment outcomes showed that patients cured were 80, 6 %, and patients who died were 12, 5%. In Cameroon, patients' treatment success outcome was 76.4% and 6.9% died. There was a statistical significant association between death and gender. The gender that had high mortality among TB patients on treatment, between the years 2013 -2017 was the male gender.

Recommendation

All patients that are diagnosed with TB should be tested for HIV. Their HIV status should be known before starting with the TB treatment so they can be given proper treatment for both diseases, concurrently. The TB data (ETR.net) needs improving as There are a lot of missing values causing this study to have some limitations.

Conclusion

All the factors that are associated with high death in this study highlighted the urgency of early initiation of TB treatment and ART. DOT-intensive treatment should be initiated as soon as possible for males and patients over the age of 60, for those with extrapulmonary TB infection and those who are HIV positive with CD4 cell count less than 350 ul. The TB data (ETR.net) needs improving; there are a lot of missing values putting some limitations on this study.

© University of Venda

LIST OF ACRONYMS AND ABBREVIATIONS

AIDS: Acquired Immunodeficiency Syndrome

ART: Antiretroviral Treatment

ARV: Antiretroviral

CDC: Centre for Disease Control and Prevention

CPT: Cotrimoxazole Preventive Therapy

DOT: Directly Observed Treatment

ETR. Net: Electronic TB Registers

HAST: HIV and AIDS, STI and TB

HIV: Human Immunodeficiency Virus

ISTC: International Standard for Tuberculosis

MDR-TB: Multi-Drug Resistant Tuberculosis

NACP: National AIDS Control Programme

NHLS: National Health Laboratories Services

NICD: National Infectious Communicable Disease

NTP: National TB Programme

NTSSA: National TB Statistics for South Africa

PSP: Provincial Strategic Plan

RIF: Rifampicin

SANTA: South African National Tuberculosis Association

SDG: Sustainable Development Goal

STATA: Statistics and Data

STI: Sexually-Transmitted Infection

SPSS Statistical Package for Social Sciences

© University of Venda

TB: Tuberculosis

WHO: World Health Organization

XDR-TB: Extreme Drug Resistant Tuberculosis

© University of Venda

University of Venda
Creating Future Leaders

TABLE OF CONTENT

Contents

DECLARATION I
DEDICATION II
ACKNOWLEDGEMENTS III
ABSTRACT IV
LIST OF ACRONYMS AND ABBREVIATIONS VI
TABLE OF CONTENT VIII
LIST OF FIGURES XI
LIST OF TABLES XII
CHAPTER 1 1
INTRODUCTION AND BACKGROUND OF THE STUDY 1
1.1 INTRODUCTION 1
1.2 Statement of the problem 2
1.3 Rationale 3
1.4 Significance of the study 3
1.5 Purpose of the study 3
1.6 Objectives of the study 3
1.7 Definition of Terms 4
1.8 Outline of the chapters 4
1.9 Conclusion 5
CHAPTER 2 6
LITERATURE REVIEW 6
2.1 Introduction 6
2.2 Extent of Tuberculosis 6
2.3 Tuberculosis types 7
2.4 Microbiology of Tuberculosis 7
2.5 TB treatment 8
2.6 TB Treatment failure 8
2.7 Other diseases that cause death among TB patients 9
2.8 TB treatment default 9
2.9 TB drug resistance 10
2.10 HIV/TB co-infection 10
2.11. Health system failures responsible for spread of M/XDR-TB 11

© University of Venda

2.12 Treatment of M/XDR-TB 12
2.13 Morbidity and Mortality of TB 13
2.13 Conclusion 14
CHAPTER 3 15
RESEARCH METHODOLOGY 15
3.1 Introduction 15
3.2 Study design 15
3.3 Study setting 15
3.4 Target population 17
3.5 Sampling and sample 17
3.6 Data collecting tool 17
3.7 Data collection methods 17
3.8 Data management and analysis 18
3.9 Validity of the study 18
3.10 Reliability of the study instrument 18
3.11 Variables 19
3.11.1 Exposure variable 19
3.12 Ethical Consideration 19
3.12.1. Ethical clearance and permission 19
3.12.2 Confidentiality 19
3.12.3 Anonymity 20
3.13 Dissemination of results 20
3.14 Conclusion 20
CHAPTER 4 21
RESULTS 21
4.1 Introduction 21
4.2 Socio-demographic and clinical characteristics of the study from 2013-2018 21
4.3 Treatment outcome 23
4.4 Mortality in Limpopo - 2013 to 2018 24
4.5 Mortality rate among TB patient in different age groups 24
4.6 Mortality among TB patient in different district municipalities 25
4.7 Regimens used for treatment 27
4.8 Factors associated with mortality among TB patients taking treatment in different treatment centres in Limpopo Province 28
4.9 Estimates of the survival curve of HIV - and HIV + and ART started and ART not started TB patients using Kaplan -Meier method 32

© University of Venda

4.10 Conclusion..... 36
CHAPTER 5 37
DISCUSSION 37
5.1 Introduction..... 37
5.2 Discussion 37
5.3 Conclusion..... 40
CHAPTER 6 42
SUMMARY, CONCLUSION AND RECOMMENDATIONS 42
6.1 Summary 42
6.2 Conclusion..... 42
6.3 Recommendation 42
REFERENCES……44
APPENDICES 52
Appendix 1: Time from Treatment start to outcome 52
Appendix 2: Ethical clearance approval……..53
Appendix 3: Letter of Approval from the Department of Health……54
Appendix 4: Data collection sheet……55

© University of Venda

LIST OF FIGURES

Figure 1: Hospitals in SA Limpopo Province

Figure 2: Overall TB treatment outcome among patient attending different centres in Limpopo Province, SA

Figure 3: Mortality rate among TB patients in Limpopo Province, SA, from 2013-2018

Figure 4: Mortality among TB patients in Limpopo, in different age groups

Figure 5: Mortality among TB patients in the different district municipalities in Limpopo Province, SA

Figure 6: Mortality among TB patient on different regimens

Figure 7: Plot of Kaplan-Meier product limit estimates of survival of HIV-Positive and HIV-Negative patients

Figure 8: Plot of Kaplan-Meier product limit estimates of survival of ART-started and ART-not started patients

© University of Venda

LIST OF TABLES

Table 4.1: Socio-demographic and clinical characteristics of the study participants

Table 4.2: Clinical characteristics of the study

Table 4.3: Kaplan-Meier results of survival analysis of the HIV-negative and HIV-positive TB patients

Table 4.4: The Mean and Median survival of TB/ HIV-positive and TB/HIV-negative patients

Table 4.5: Kaplan-Meier results of survival analysis of the ART-started and ART-not started TB/HIV patients

Table 4.6: The Mean and Median survival of ART-started and ART-not started on TB/HIV patients

© University of Venda

CHAPTER 1

INTRODUCTION AND BACKGROUND OF THE STUDY

1.1 INTRODUCTION

Tuberculosis (TB) remains a leading cause of death worldwide and TB deaths have consistently been used as a target and indicator to measure progress towards its control. An estimated 1.5 million individuals died of TB in 2014, affecting mainly, countries in Sub-Saharan Africa and South-East Asia (Adamu, Gadanga, Abubakar, Abubakar, Bello, Gajida, Babashani & Abubakar, 2017). TB has become a great concern in recent history, and despite highly-effective drugs, the disease and deaths due to *Mycobacterium tuberculosis* are increasing in countries, including in South Africa where it is also fuelled by the Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) epidemic (National Department of Health, 2013).

According to Birlie, Tesfaw, Dejene & Woldemichael. (2015), it is estimated that more than 70% of deaths amongst TB patients occur during the first two months of its treatment. Studies have identified as some of the major risk factors that lead to death amongst TB patients as the Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome, old age, being underweight and undergoing re-treatment of TB.

Over recent years, there has been increasing literature concerning TB treatment failures which has led to the development of multi-drug resistant tuberculosis (MDR-TB) and an increase in the death of patients. Of particular interest to this research are those patients who are also HIV positive. Studies conducted around the world have shown that TB treatment outcome on TB/HIV co-infected patients worsens with time (WHO, 2017). In Conakry, a study was conducted on 573 TB patients and 86 (15%) of them died before the end of the treatment; 52% of these deaths occurred within eight weeks of treatment onset and all those who died were also HIV-positive patients (Camara, Sow, Toure, Diallo, Kaba, Bah, Diallo, Guilavogui & Sow, 2017). In Brazil, a study was conducted on TB treatment outcomes among HIV patients and results showed that older patients (over 60 years) were at high risk of mortality, while the HIV-positive patients and those who returned to treatment after defaulting had similar outcomes (Do Prado, Rajan, Miranda, Dias, Cosme, Possuelo, Sanchez, Golub, Riley & Maciel, 2016).

In South Africa, a number of studies have been conducted on TB and its treatment outcome in different parts of the country. In the Free State Province, the study revealed that TB/HIV patients have more risk of unsuccessful treatment outcome than those with HIV-negative

© University of Venda

status (Engelbrecht, Kigozi, Chikobvu, Botha & Van Rensburg, 2017). Multi-drug resistant tuberculosis (MDR-TB) is another major public health concern in Limpopo Province. TB can be cured within 6-8 months of effective treatment, however, many patients fail to adhere to the treatment, resulting in failure to get cured and the possible development of MDR TB. Diagnosis and management of MDR TB remains a crucial and challenging task, necessitating an effective co-operation of hospitals and community-based out-patient management (Alobu, Oshi, Oshi &Ukwaja, 2014).

The number of MDR TB and possible Extensively Drug Resistant TB (XDR TB) are increasing in the Limpopo Province. For the best possible chance of treatment and cure of MDR and XDR TB patients, they must be hospitalized for at least 6 months and kept relatively isolated from other patients to reduce the risk of cross infection. Existing facilities for MDR TB patients are currently over utilized in the Province, hence, patients are getting treatment at home due to lack of beds at the MDR TB hospital at Witbank (Department of Health, 2013). This compounds the burden of the disease on the Province and the country at large, therefore, it is important to regularly evaluate the circumstances surrounding the treatment leading to outcomes, such as death. This process should assist in identifying measures for intervention that would alleviate the effect of the disease on the population.

Limpopo Province is one of the most affected by TB, from the nine provinces of South Africa. According to the 2017 Provincial Strategic Planning, between 2015/16, the Limpopo TB incidence rate was 301/100 000 people, which was much higher than the provincial target of 150/100 000 new TB infections. In 2014, a study was conducted on mortality rates associated with TB/HIV co-infection among patients and results showed that some 18074 patients had started the TB treatment but 2242 of them had died (Mabunda, Ramalivhana & Dambisya, 2014). No known study, however, has been conducted in the Limpopo Province in order to identify local factors that could be associated with the high death rate among TB patients.

1.2 Statement of the problem

TB can be a very important barrier to the achievement of the 90-90-90 targets to both HIV/TB patients, it requires a specific attention to TB patient care. There is availability and implementation of Directly-Observed Treatment Short Course (DOTS), and all other intervention strategies for TB treatment, despite this, patients are still dying while on treatment, in areas like the Limpopo Province. The factors contributing to death of TB patients while on treatment in the Province are not well documented.

© University of Venda

Mabunda *et al.,* (2014) revealed that in 2014, 18074 TB patients started treatment and 12.4% of these patients died while on TB treatment. In the absence of objective accurate evidence, it can be assumed that there are contributing factors leading to the death of these patients. Finding out these contributing factors will enhance the understanding and the development of new strategies to prevent, reduce and eradicate mortality amongst TB patients. This study, therefore, seeks to found out the factors that are associated with death of TB patients while on treatment, in the Limpopo Province.

1.3 Rationale

Birlie *et al.,* (2015) estimate that more than 70% of deaths amongst TB patients occur during the first two months of TB treatment. Studies have identified major risk factors that lead to early death amongst TB patients as HIV/AIDS, old age, being underweight and undergoing re-treatment of TB (Gunda *et al.,* 2016). No known study, however, has been conducted in the Limpopo Province to identify local factors that could be associated with the high mortality among TB patients.

1.4 Significance of the study

The results of this study may assist the Limpopo Provincial Department of Health in understanding the contributory factors to TB mortality and develop new strategies to prevent or reduce deaths amongst TB patients. It may also assist the National TB Programme (NTP) in the management of TB patients within the communities. In addition, findings of the study may also help primary health-care professionals in taking appropriate care of TB patients on treatment in the Province. By doing so, the researcher hopes to have contributed to the body of scientific knowledge on the topic and to open doors for further studies in this very same field.

1.5 Purpose of the study

The purpose of the study is to investigate the factors associated with mortality among patients on TB treatment in the Limpopo Province, South Africa, between 2013 and 2018.

1.6 Objectives of the study

The specific objectives of this study are to:

© University of Venda

- Determine the case fatality and crude mortality rates due to TB in the Limpopo Province during the period 2013 to 2018;
- Measure the survival curves among TB patients in Limpopo Province during the period of 2013 to 2018;
- Determine the risk factors for mortality among TB patients in Limpopo Province between the years 2013 and 2018;
- Determine factors associated with death among TB patients in the Limpopo Province between the years 2013 and 2018, and
- Describe the association between the variables among TB patients in the Limpopo Province during the period of study.

1.7 Definition of Terms

Tuberculosis - is an illness caused by the bacteria *Mycobacterium* tuberculosis that most often affect the lungs and is curable and preventable (WHO, 2018) In this study, Tuberculosis will be defined as an illness for which treatment will commence, with either a smear or culture-positive or extra pulmonary symptoms.

Factor - is a constituent or element that brings about certain effects or results (WHO, 2019). In this study, a factor is the variable that is under investigation.

Patient - is a person receiving or registered to receive medical treatment (Shield, 2009). In this study, a patient, is a person who is receiving TB treatment.

Mortality - is the condition of being mortal, losing of life or the circumstance of an accident which produced a fatal injury (WHO, 2019). In this study, it is the number of deaths in a given period.

Treatment - it is the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of life (WHO, 2007). In this study, treatment is the taking of anti-TB drugs that are administered to TB patients.

1.8 Outline of the chapters

The chapters are arranged as follows:

© University of Venda

Chapter 1- Introduction and background of the study

Chapter 2-Literature review

Chapter 3- Research methodology

Chapter 4- Results

Chapter 5- Discussion

Chapter 6- Summary, conclusion and recommendation

1.9 Conclusion

TB remains one of the biggest threats to public health in South African provinces. The Limpopo Province experiences poor TB treatment outcome in spite of the adoption of strategies that have been proven all over the world, to be controlling and improving the outcome of TB Treatment, however, the factors associated with the high mortality rate among TB patients on treatment in Limpopo province are as yet undocumented. This chapter presented the introduction and background of the study and the next chapter will present the literature review.

© University of Venda

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter will cover the literature on TB - its extent, other diseases that cause death of TB patients other than HIV/AIDS, types, treatment, treatment failure, treatment default, inadequate treatments that lead to TB drug resistance, Health system failures responsible for spread of M/XDR-TB and Treatment of M/XDR-TB.

2.2 Extent of Tuberculosis

Tuberculosis (TB) is a leading cause of infectious disease morbidity and mortality worldwide (Lewinsohn *et al.,* 2017). In 2017, there was a total number of 10 million new TB cases and of whom 1.6 million died including 0.2 million children with HIV. This is, therefore, an indication that TB is a leading killer of HIV-positive patients (WHO, 2017). The Sustainable Development Goal (SDG) aimed at reducing the TB incidence rate by 90% to less or equal to 10 cases per 100,000 populations per year and to reduce the absolute number of TB deaths by 95% compared with a baseline of 2015.

There is, therefore, an overall goal of ending the global TB epidemic by 2035 (WHO,2015), however, tuberculosis, in places like Ethiopia, has been recognized as a major public health problem, hence, the country has been listed among the 14 TB, TB/HIV and Multi-Drug Resistant TB high-burden countries. The first national TB prevalence survey conducted in 2011 revealed smear-positive pulmonary prevalence of 108/100,000, of which 55% were not detected before the survey (Asres *et al.,* 2018). Similarly, South Africa, in 2015, was among 22 countries with the highest burden of TB, since the country had the fourth highest estimated incidence of TB and highest number of HIV – infected TB cases and deaths (Heunis *et al.,* 2017). TB patients with or without HIV co-infection have been shown to have a similar pattern of bacteriologic response to anti-tuberculosis treatment, however, TB has been shown to be the leading cause of death among individuals with HIV infection. Before the advent of antiretroviral treatment (ARVs) the prognosis of TB/HIV co-infection was quite poor (Amante & Ahemed, 2015) and despite the fact that there is an available and effective treatment for HIV, it still causes death among TB patients (Camara *et al.,* 2017). There are a number of factors that can cause death to TB patients on anti-TB treatment, some of which may include other diseases, treatment default and TB patient's education about its treatment.

© University of Venda

2.3 Tuberculosis types

TB has two forms, latent TB, in which the bacteria is in your body but your immune system is preventing it from spreading, hence, there are no symptoms and no contagiousness, but the infection is alive and can one day become active (Iseman, 2013). Active TB, the germs multiply and make you sick and you can spread the disease to others (Khatri, 2020).

2.4 Microbiology of Tuberculosis

Mycobacterium is an etiological agent of tuberculosis; a successful pathogen that adapts to survive within a host. Robert Koch identified the etiological agent of human TB over a century ago, over 150 years, but even today it is still a problem for human's health (Chai, Zhang & Liu,2018). It has been hypothesised that the genus *Mycobacterium* originated more than 150 million years ago. In the middle ages, scrofula, a disease affecting cervical lymph nodes, was described as a clinical form of TB. In 1720, for the first time the infectious origin of TB was conjugated by the English physician Benjamin Marten, while the first successful remedy against TB was the introduction of the sanatorium cure. Robert Koch a scientist isolated the tubercle bacillus and presented his extraordinary result to the society of physiology in Berlin on the 24th of March 1882. After the discovery of the famous scientist, Robert Koch, over the years, there have been the development of Parquet and Mantoux tuberculin skin tests, Albert Chalmette and Camille Guerin (BCG) vaccine, Selman Waksman Streptomycin and other anti- tuberculosis drugs have followed (Barberis, Bragazzi, Galluzzo & Martini, 2017).

Mycobacterium tuberculosis has a unique cell envelop structure and composition containing a peptidoglycan layer that is essential for maintaining cellular integrity for virulence (Maitra, Munshi, Hearly, Martin, Vollmer, Keep & Bhakta, 2019). Tuberculosis is a communicable disease, the *tubercle bacilli* establish infection in the lungs after they are carried in small droplets. These are small enough to reach the alveolar space and if the host's first line of defence fails to destroy the infection, the bacilli will increase rapidly inside the alveolar macrophages and destroy the cells.

TB bacterium has a rod-shape and it is a purple organism. Its name, meaning "fungus-bacteria" refers to the shape of the bacillus when it grows in the laboratory. When it is viewed under a microscope if forms a heap of small rods with protective layers around them, thus, looks like a fungus (Mukhophadhyay & Ghosh, 2017). TB can be diagnosed using Xpert and smear microscopy (Ziehl-Neelsen); Xpert-positive samples are then inoculated in liquid culture media and solid media using Lowenstein Jensen tubes. Microscopy of specimens

© University of Venda

stained with fluorochrome dye provides an easier, more efficient and more sensitive alternative, however microscopic detection of mycobacteria does not distinguish *Mycobacteria* tuberculosis from non-*Mycobacteria* tuberculosis (Wani, 2013). The exposure of the *Mycobacterium* tuberculosis to direct sunlight will rapidly kill it, however, if protected from the sunlight, it might remain alive and infectious for up to ten weeks.

2.5 TB treatment

In TB patient's treatment, a combination of different drugs must be taken; the patients must take the drugs properly and it is the doctor's responsibility to make sure that the patients are taking the correct medication (Ambardekar, 2019). A patient is said to have relapsed if he / she improved while taking TB treatment but becomes ill again after they have finished their treatment. Patient with active TB disease should receive at least three drugs as their initial TB treatment, fewer than three drugs can cause a development of drug resistance TB. (Koo, Min & Lee, 2020). The drugs that patients should take when they have never had any TB treatment before are, Isoniazed, Rafampicin, Pyyrazinamide and Ethambutol. It is assumed that the bacteria in the patient's body will respond, as these drugs are generally the drugs with the greatest activity against TB bacteria (Kanabus, 2021). With new patients with presumed drug susceptibility pulmonary TB, the WHO recommends that they should have six months of treatment - two months of intensive phase and four months of continuation phase (CDC, 2016).

2.6 TB Treatment failure

It is often assumed that TB Treatment failure is because a patient did not take their TB drugs correctly, however, there can be a number of different reasons for TB treatment failure. It is true that if a patient does not take the drugs correctly it may lead to the development of drug resistant TB, however, the patient may already have drug resistance TB, if that is the situation, the treatment that the patient is taking now will fail even if the drugs are taken correctly (Dialo, Dahouron, Dah, Tassembedo, Sawadoga & Meda, 2018).

2.7 Other diseases that cause death among TB patients

There are other diseases, such as renal and liver diseases, which may change the presentation of TB, making it more difficult to diagnose and treat the patients. These conditions may also be associated with increased risk of toxicity caused by the anti-TB drug;

© University of Venda

patients on anti-TB drug with chronic Hepatitis B Virus co-infection are more susceptible to developing liver failure and have poor TB treatment outcome (Chen *et al.,* 2018). In a study by Stijnberg *et al.,* (2019) diseases like chronic kidney disease and malignancies were correlated with mortality among TB patients on treatment; in another study it was found that the all-cause mortality of TB was 12% and this was mainly due to non-TB-related causes at 82,7% due to malignancy, liver cirrhosis, renal failure as well as military and pneumonic radiographic pattern mortality in TB deaths. The patients who died of TB-progressed rapidly band at 37, 2% were not diagnosed ante-mortem (Lin *et al.,* 2014). The effect of the underlying diseases other than HIV/AIDS on the risk of death due to TB has not been well explained, as sometimes the actual diseases that caused the death is unknown, because there was only one indicated one cause of death (Xin *et al.,* 2009).

2.8 TB treatment default

Treatment default is also another factor that causes death among TB patients. WHO (2013) defines 'treatment default' as interrupting treatment for at least two consecutive months. Patients who default from treatment can undermine efforts to control TB because such persons have an increased risk of mortality, treatment failure and the emergence of MDR and XDR-TB (WHO, 2013). There are various factors that cause TB patient to default treatment, especially in a resource-limited setting. In a study that was done in Nigeria by Alobu *et al.,* (2014) more than one third of the patients defaulted TB treatment very early after they started treatment, thus, a substantial number of patients who had sputum smear-positive pulmonary TB may still have had positive smear at the time they discontinued treatment. The recommendations of the study included the administering of a long-term anti-tuberculosis regimen. Most patient stop taking the treatment after feeling better, therefore, if the treatment regimen is long, they will probably stop before finishing the course. Knowledge and awareness about TB and its treatment are essential for TB patients (Mohammed & Mustafa, 2016). A TB patient's education at the start of a treatment is a crucial step in the management and will enhance patient's understanding and awareness about TB and its treatment.

2.9 TB drug resistance

As soon as the first antibiotic (streptomycin) to fight TB became available in the 1940s, drug resistance began to evolve (Shenoi & Friedland, 2009). Whenever a bacillus or virus is

© University of Venda

exposed to a drug or treatment that is not potent enough to totally clear it, the microbe will continue to reproduce; eventually, a mutation will occur that makes the bacilli less sensitive to the effects of treatment, and the microbe will flourish. This is essentially the reason why a potent combination drug regimen attacking the bacillus on multiple fronts is needed to stop TB. The current standard first-line regimen for TB ought to cure 95% of cases provided that the full course of treatment is taken as recommended (Department of Health, 2013), however, whenever an active TB infection receives inadequate treatment, drug resistance can develop and once it has, it can be transmitted from one person to another. Data suggest that having an MDR-TB infection that is resistant to even one drug when starting a TB treatment regimen can reduce the chances of curing TB, increase the risk of relapse and the likelihood of further resistance developing to other drugs within the treatment regimen (Department of Health, 2009), but it should also be pointed out that there are degrees of resistance to individual drugs or within drug classes.

Many people with isoniazid 'resistance' have an infection which is less sensitive to standard doses of the drug, but which may still respond to higher isoniazid doses (International Standard for Tuberculosis (ISTC, 2009). There are also accumulating data which suggest that moxifloxacin may work against TB that is resistant to some of the weaker fluoroquinolone drugs (WHO, 2013). Multidrug-resistant tuberculosis (MDR-TB) is defined as TB caused by MDR-TB that has become resistant to at least isoniazid and rifampicin, the two most critical first-line anti-TB drugs, although resistance may develop to the other drugs in the regimen as well. Extensively drug-resistant TB (XDR-TB) is MDR-TB that is also resistant to any one of the fluoroquinolones and to at least one of three injectable second-line drugs - amikacin, capreomycin or kanamycin (ISTC, 2009). Sometimes, MDR-TB that is only resistant to the injectable second line drugs is referred to as being 'pre-XDR-TB.'

2.10 HIV/TB co-infection

The results of a study that was done in 2008 in 212 countries showed that an estimated 13 TB/HIV deaths occurred per 100,000 populations globally. This study also revealed that the highest death rate was in the African region with HIV positive TB mortality rates that were 29.9 times higher than non-African countries (Morb Martal, 2011). The KwaZulu-Natal registration rate for the TB cases for 2012/14 was 1128 per 100 000 in 2012, 1200 per 100 000 populations in 2013 and 1016 per 100 000 populations in 2014.

Persons with HIV are at increased risk for TB disease, and a high risk of death, however, this link has been evidenced mainly in resource-limited settings (Alobu *et al.,* 2014). Studies have shown that although TB/HIV mortality is a global problem, the African region is leading in

© University of Venda

deaths related to TB and HIV. The other reason for high mortality among TB patients is that HIV infection has mostly been diagnosed towards the end stages of HIV disease. With such high burden of morbidity and mortality, tuberculosis seems to exert a great impact on the economic growth of low and middle-income countries in sub-Saharan Africa (Das & Horton, 2010). It is, therefore, important to examine through a cross-sectional study the relationship between HIV status and TB mortality from a programmatic point, using routine data collected and entered on an electronic TB register. The results emanating from this study would be ideal to help motivate reinforcement of the TB/HIV service integration with the ultimate goal of giving an early opportunity to TB patients to access HIV care and ARV. This approach would ultimately lead to reduction of TB deaths among HIV-positive individuals.

In a study done in Ghana, TB/HIV co-infection rate was quite high and more females were infected than male. The study findings also demonstrated that HIV co-infection affects TB treatment outcome, adversely. In 2013, Malawi reported high early death rate of HIV infected TB patients, within the first two months of treatment. The causes of these deaths included late presentation for treatment leading to severe TB or HIV-related illnesses like bacteraemia or cryptococcal meningitis (Tweya *et al.,* 2013) It has been shown that persons with HIV are at increased risk for TB disease, and those have a high risk of death, however, this link has been evidenced only in resource-limited settings, where limited access to antiretroviral therapy (ART) and other health-care services contribute to high mortality (Alobu *et al.,* 2014). The association between HIV status and mortality from TB while on treatment, has been demonstrated in previous studies, however, in this project we will analyse the association between HIV status and death while on TB treatment, in the Limpopo Province.

2.11. Health systems' failures responsible for spread of M/XDR-TB

Epidemics of drug-resistant TB begin with a failure to effectively manage drug-sensitive TB. In the past, there was a tendency to blame the patient, but now more of the responsibility is being shifted to programme failures (Mohammed & Mustafa, 2016). Consistently adhering to a long-term treatment regimen is difficult for anyone, but a range of social barriers and situations can make it more unlikely that a person will complete a course of treatment for MDR-TB. People who are poorly informed about the need to take the whole course of treatment may quit or simply forget to keep taking it as soon as they feel well. People who are homeless or live in remote areas far from the clinic may not always make it to the clinic on time, or the latter may have difficulty delivering treatment to them (Alobu *et al.,* 2014). Household responsibilities and employment can get in the way of adherence. Alcohol and drug use have been associated with people not adhering to or defaulting on treatment and

© University of Venda

this has been a particular problem in many countries, particularly, of the former Soviet Union, such as Russia and Ukraine. Ultimately, it is the responsibility of the national TB control programme (NTP) to take people's needs and foibles into account, and to find and implement culturally-appropriate ways to support adherence and ensure that people with TB take all of their treatment (Department of Health, 2013). Many countries fail to do this, or worse, implement policies that discourage people from staying with their care.

Partly for this reason, the emergence of M/XDR-TB is often said to be the result of a weak TB control programme (WHO, 2008). This is also the case when the NTP does not comply with evidence-based treatment guidelines, does not adequately train, supervise or monitor the clinicians treating TB, or the counsellor and community-based carers supporting treatment. If the NTP cannot keep a consistent supply of high-quality drugs in stock, or when it charges for treatment - choosing between food and TB care is a choice no one should have to make. (Department of Health, 2013). Sometimes these failings are due to poor management, but often NTPs have become disorganised or have failed to update policies after periods of political upheaval, or economic or social crises that have disrupt health systems. The challenge is often one of political will in making health and TB-control, national priorities.

2.12 Treatment of M/XDR-TB

Treating someone with MDR-TB and especially XDR-TB requires a longer course of therapy (eighteen months to two years) with drugs that are more expensive and toxic, yet less potent (Department of Health, 2013). Drug-resistant TB can be difficult to diagnose and respond to in a timely manner, but failure to put someone on a regimen that is effective against the TB they are infected with, and then support their adherence, can lead to poor outcomes and death, particularly, in people with HIV as well as lead to onward transmission (WHO, 2013).

Treatment for XDR tuberculosis does not differ according to its cause, although, the intervention to prevent acquired versus transmitted diseases, differ. Acquired-drug resistance can be reduced by providing effective treatment and ensuring completion of the treatment. Halting transmission requires identifying and separating infectious patient, improving ventilation in congregate settings and promptly initiating of effective treatment (Shan *et al.,* 2017).

© University of Venda

2.13 Morbidity and Mortality of TB

Globally a total number of 1.4 million people, annually, die from TB, including 208 000 people with HIV. TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS) (WHO, 2020) In the South African context, where almost 60% of people with TB are HIV positive, integration of HIV and TB services are essential to improve accessibility and reduce barriers to care (Osman *et al.,* 2021)

An estimated number of 360 000 people developed Tuberculosis in South Africa, 58% of these individuals were HIV positive and 17% of them died (WHO, 2020) According to death certificates, TB remains South Africa's leading natural cause of death, which is higher in HIV-positive people, particularly, those admitted to hospitals (STATS SA, 2018).

Identifying risk factors of death following diagnosis of TB is essential to predict progress in TB patients and for planning effective interventions to reduce death rates (Alavi-naini *et al.,* 2013). Population-based studies have identified a number of risk factors including age, male gender, HIV/TB co-infection, drug resistance, disease severity as a factor associated with mortality following a diagnosis of TB (Stijnberg *et al.,* 2019). A study by Lin *et al.,* (2014), found that male gender, age 74 and above, extra-pulmonary TB, malignancy, liver cirrhosis, renal failure, military and pneumonic radiography patterns were all significant predictive factors for TB-related death.

In 2019, an estimated 10 million people fell ill with Tuberculosis worldwide; 5,6 million were men, 3,2 million women and 1,2 million children. TB is present in all countries and all age groups but is curable and preventable (WHO, 2019). Globally 7 million persons were notified of their positive-TB results in 2018, representing 70% of the estimated number of persons with TB incident, an increase from the 6,4million, 64%, notified in 2017. In 2018, 69% of all persons with TB incident, received anti-TB treatment compare with 64% notified in 2017. The estimated number of TB-related death declined 5% from 1,5 million in 2017 to 1,49 million in 2018 (CDC, 2020).

In a study by Abdullahi in 2019, during the six months' follow-up of TB patients on TB treatment 9,234(86%) patients completed TB treatment and 1,483 (14%) did not. Overall, 585 (5,5%) died, 280 (2,6%) were lost to follow-up and 618 (5,8%) outcomes were not evaluated. The researcher found most deaths occur within the first 3 months and an increasing mortality rate during the time under review among patients on TB treatment. A high mortality rate was observed among patients with MDR-TB globally. Different patient health status and programme-related factors are contributing to this high mortality rate. Patients-related

© University of Venda

determinants include, demographic characteristics, behavioural factors and clinical factors (Alemu, Bitew, Gamtesa & Alebel, 2021).

2.14 Conclusion

In this chapter details of TB, such as - type, treatment, causes of treatment failure, other diseases that causes TB patients' death, treatment default, inadequate treatment lead to TB-drug resistance, HIV/TB co-infections, health system failures, MDR and XDR TB, morbidity and mortality of, microbiology were discussed in this chapter. This chapter presented the literature review while, the next chapter will present the methodology of the study.

© University of Venda

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Introduction

In this chapter will be discussed the research design, area or study setting, population and sampling method, data collection, source of data, measurement instrument, data management, data analysis, validity and reliability of the study, ethical consideration and dissemination of the results.

3.2 Study design

A quantitative retrospective cohort study design, using secondary data was applied. Retrospective study involves a situation where the outcome of an interest has already occurred at the time the study is initiated (Salkind, 2010). Retrospective design was used as it would allow the investigator to examine the factors or assess possible associations between an outcome and an exposure or variables.

3.3 Study setting

The study took place in Limpopo Province, South Africa. Limpopo Province was previously called Northern Province because it is situated in the northern part of South Africa. It consists of 5 districts - Capricorn, Mopani, Vhembe, Sekhukhune and Waterberg and has about 35 government hospitals and about 7 private hospitals. Figure 1 shows the hospitals in the Province, including the private hospitals.

Information on TB is routinely captured in the ETR.Net. This tool is valuable for collating and analysing TB surveillance data and for monitoring programme performance (Nadol *et al.,* 2008). At the facility level, a TB nurse collates patient information from clinic cards and enters this in a paper-based TB register on a daily basis. The same nurse reviews the patient data for completeness and correctness at the clinic level. Information from the paper-based TB register is then sent from the clinic to the sub-district level for electronic capturing. The sub-district office is responsible for further data validation and analysis at the end of a cohort period. The sub-district TB coordinator, in informed by the data capturers at this level, performs random checks to ensure that data are captured completely and accurately (National Department of Health, 2014).

© University of Venda

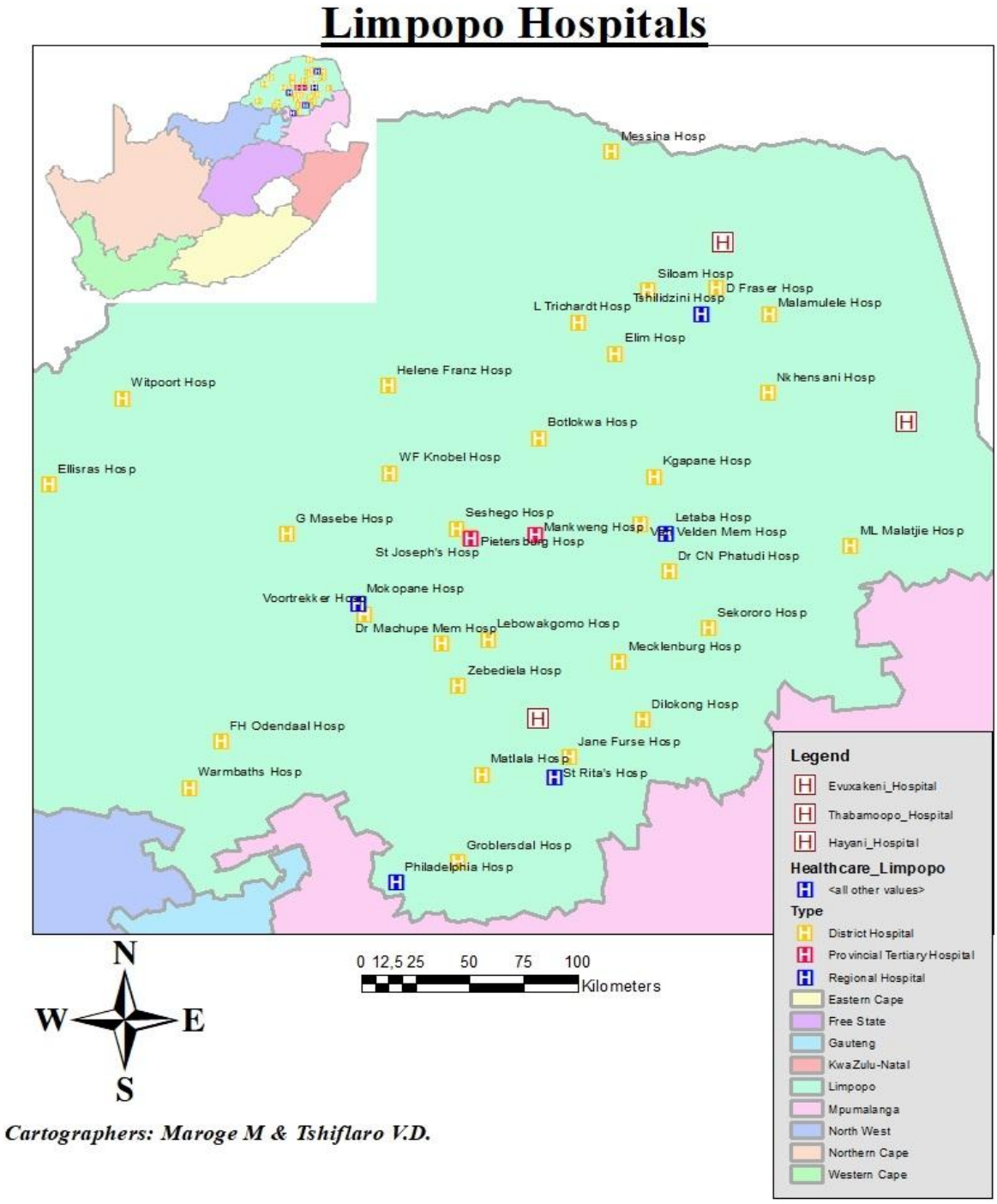

Figure 1: Hospitals in Limpopo Province

© University of Venda

3.4 Target population.

The target population consists of records of all patients diagnosed with TB, irrespective of age and who started TB treatment in Limpopo Province between January 2013 to December 2018.

3.5 Sampling and sample

Sampling is referred to as the researcher's process of selecting a portion of the population in a way that it represents the population of interest, in order to obtain information regarding a phenomenon. The total population sampling was used; this is a type of purposive sampling technique that involves examining the entire population that have a particular set of characteristics, hence, all records of TB patients who were registered on the ETR.net, and who were on TB treatment from January 2013 to December 2018 were included (Laerd, 2012).

3.6 Data collecting tool

Data was exported from ETR.Net onto a spread sheet (Appendix 7). The spread sheet consisted of variables such as age, TB type, gender, socio economic status, HIV status and other disease and treatment outcome (survived or died).

3.7 Data collection methods

The data source for this study was the ETR.net located at the provincial TB program offices. Data on all patients who were registered for TB treatment in Limpopo Province from 2013-2018 was extracted from the electronic TB register on to the data collection sheet. The report was run firstly with all personal details including names and were stored in a coded form. The original document including patient personal information was then extracted, including names, address, date of birth or identity number, age, type of TB diagnosed, treatment start date, treatment outcome, which is death (for the purpose of this study), date of death, HIV status and ARV start-date. A second working document with all the above patients' details without names and surnames but with codes linking them to the original was created.

© University of Venda

3.8 Data management and analysis

Data was exported from ETR.Net onto a spread sheet. This step was followed by a thorough checking to assess missing values. Data was then coded into numerical values and continuous data, categorised. Clean data was thereafter exported into Statistical Package for Social Science (SPSS) version 20, and Statistics and Data (STATA) version 12 for further analysis. Quantitative data was summarized and presented in the form of frequency tables. As part of the descriptive statistics for the population under study, a Chi-square test was used to assess the association between independent variables and main outcome variables. Summary tables described the variables in terms of their frequency. Odds ratios were computed to assess the association between HIV status and TB mortality, as well as other variables. Precision of estimate of the odds ratio was set at 5% significance level. All factors that were significant at $p < 0.05$ on univariate and multivariate analysis were further analysed using logistic regression model. Survival analysis using the Kaplan-Meier survival curves was applied (Adamu *et al.,* 2017).

3.9 Validity of the study

Validity in a quantitative study refers to the extent at which the survey measures the right elements that need to measure; in simple terms it refers to how well an instrument measures what it was intended to do (Heale & Twycross, 2015). To validate this data, spot checks on ETR.net for data completeness and consistency were performed. The facility, sub-district and district TB coordinators were contacted for cross-verification of the information captured on the paper-based TB register.

3.10 Reliability of the study instrument

Reliability refers to how consistently a method measures something, if the same results can be consistently achieved by using the same method under the same circumstances, then the measurement is considered reliable (Middleton, 2020). To ensure the reliability of this study, the instrument was administered on the same information on more than two occasions, then, the results were compared to test the reliability of the instrument.

© University of Venda

3.11 Variables

Variables comprised of outcome and exposure

The main outcome variable is death while on TB treatment.

3.11.1Exposure variable

The main exposure is the HIV status of the TB patients.

Other potential exposure factors are:

- Gender
- Age
- Socio-economic profile
- Other associated diseases
- Type of TB
- Antiretroviral treatment start-date
- Health facility
- Year of TB registration

3.12 Ethical Consideration

3.12.1. Ethical clearance and permission

The proposal was presented to the Higher Degree Committee of the School of Health Sciences at the University of Venda and submitted to the University Higher Degrees Committee for approval. Ethical clearance (Appendix 2) was obtained from the University of Venda Research and Ethics committee. Permission to conduct the study was sought from the Limpopo Department of Health (Appendix 3)

3.12.2 Confidentiality

Data or information on the study were treated confidentially, therefore, the data collected was kept in a secure place in the computer, under password protection (Brink, 2009).

© University of Venda

3.12.3 Anonymity

Anonymity was achieved by assigning a special number to each file, hence, linking the data to the patient or the hospital was not possible.

3.13 Dissemination of results

The results of this study will be submitted to the University of Venda library for referencing by other researchers will also be presented at local occasions, such as provincial primary health care conference and the annual public health conference. The results from this study will be submitted to a peer review journal for publication and a written report with recommendations will be presented to the Limpopo Health Department's TB programme section.

3.14 Conclusion

Data was collected, cleaned and analysed after the University of Venda Higher Degree Committee granted an ethnical clearance certificate and the Department of Health, Limpopo granted permission to conduct the study. This chapter presented the study methodology and the next chapter will present the results of the study.

© University of Venda

CHAPTER 4

RESULTS

4.1 Introduction

In this chapter, the results of this study are presented in tables and charts. The results of this study were obtained from 2013-2018 data.

4.2 Socio-demographic and clinical characteristics of the study from 2013 - 2018

A total of 79589 patient's records were selected for the study; of these 48892 (61.4%) were HIV positive. The age varied from 0 to 119 years. The mean was 38.104 and the standard deviation was 16.541. In terms of Gender distribution, more males had TB at 56% while females were 43%. The district with more numbers of TB patients was Capricorn representing 21.6% of the whole study population, followed by Vhembe with 21.3%, then Waterberg with 20.4%, Mopani with 18.4% and Sekhukhune had the least of them all with 18.3%. In relation to TB treatment regimen, most patients were on regimen I at 94.4%, followed by regimen III at 9% and the last one was regimen II with 4.5%. For existing disease classification, Pulmonary TB was found in 87% patients and 12% for extra pulmonary.

In terms of patient category, new patients were 95.2%, followed by those on retreatment after defaulting at 0.9%, then those on retreatment after failure at 0.5% and relapsed patients were 2%. For HIV status, HIV positive patient were 61.4%, while HIV negative patients were 33.7%, while the rest of the patients' HIV status was unknown. For transfer type, most patients were not transferred at 94.6% while 1.7% of the patients were transferred out of the primary facility and 3.7% of the had patients moved out. Of the HIV positive patients, 89.5% had started receiving ART, this represented a total of 55% of all patients. Those who had not started ART were 3.2% and the rest were those who were HIV negative and those with an unknown HIV status representing 41.8% of our study population. With Cotrimoxazole Preventive Therapy (CPT), 53% had started while 11.3 had not and 35.8% were unknown. The results are shown in Table 4.1.

Table 4.1 Socio-demographic and clinical characteristics of the study participants

© University of Venda

Characteristics		Frequency	Percent
Gender	Females	34665	43.6
	Males	44924	56.4
District	Capricorn DM	17176	21.6
	Mopani DM	14635	18.4
	Sekhukhune DM	14569	18.3
	Vhembe DM	16966	21.3
	Waterberg DM	16243	20.4
TB treatment regimen	Regimen 1	75157	94.4
	Regimen 2	755	4.5
	Regimen 3	3593	9
	Other regimen	1	.0
	INH chemoprophylaxis	21	.0
	Other chemoprophylaxis	62	.1
Disease Classification	Unknown	82	.1
	Extra pulmonary TB	9549	12.0
	Pulmonary TB	69958	87.9
Patient Category	Unknown	81	.1
	New	75776	95.2
	Other	1045	1.3
	Re-treatment after default	750	.9
	Re-treatment after failure	378	.5
	Relapse	1559	2.0
HIV Status	Negative	26797	33.7
	Positive	48892	61.4
	Unknown	3900	4.9
Transfer Type	Have not changed facility.	75281	94.6
	Moved out	2942	3.7
	Transferred out	1366	1.7
ART Started?	(HIV negative patients)	33243	41.8
	NO	2561	3.2
	YES	43785	55.0

© University of Venda

CPT Started?	Unknown	28462	35.8
	NO	8964	11.3
	YES	42163	53.0
	Total	79589	100.0

4.3 Treatment outcome

Treatment outcome of this study shows that cured patients were 80.6%, patients who died were 12,5% while the default patients were (5,7%). Those who had developed multidrug-resistance (MDR) cases were (0.2%), Rifampicin-resistance were 0,3% and treatment failure at 0,6 %. The different treatment outcomes can be seen in Figure 2.

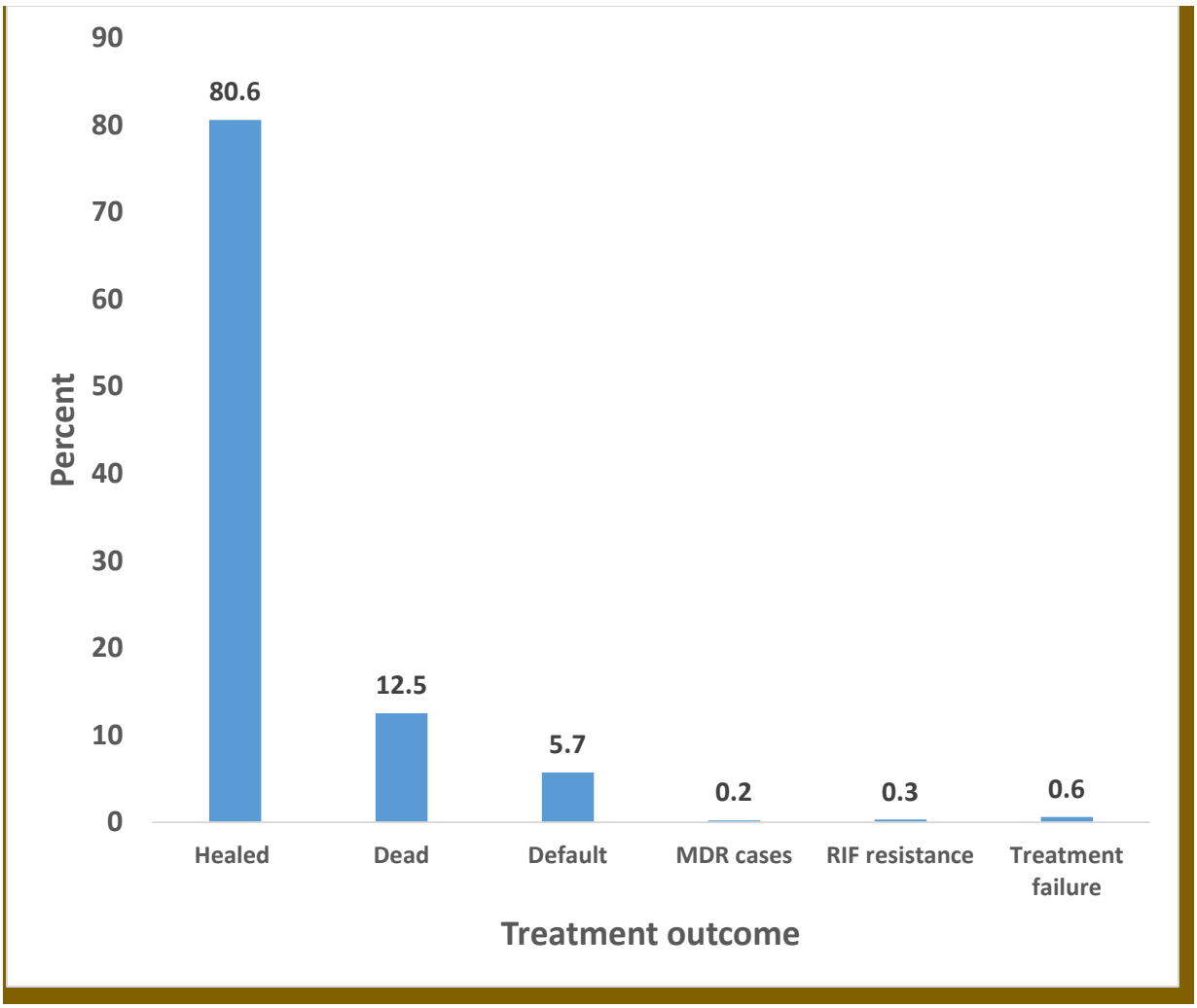

Figure 2. Overall Tuberculosis treatment outcome among patients attending different centres in the Limpopo Province for TB treatment

© University of Venda

4.4 Mortality in Limpopo from 2013 to 2018

There is a gradual decrease in death rate from 2013 which was 14.7 % to 7.4% in 2018. See figure 3 below.

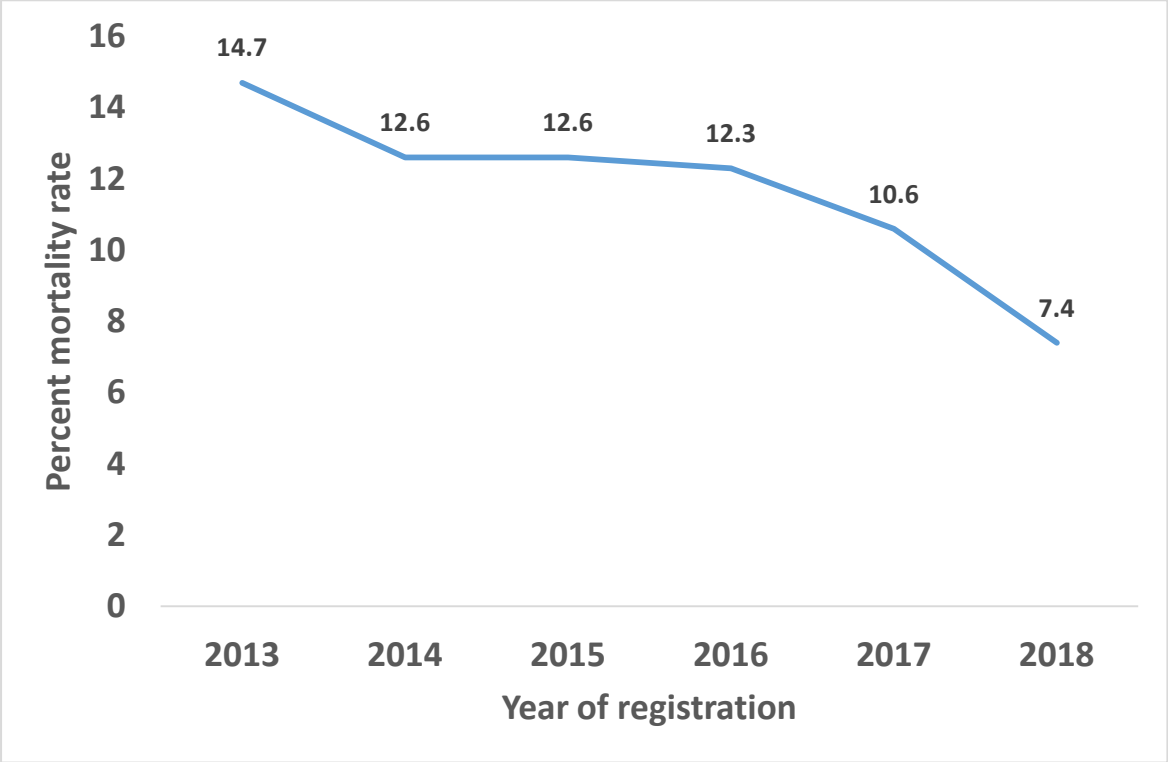

Figure 3. Mortality rate among TB patients in the Limpopo Province from 2013 to 2018

4.5 Mortality rate among TB patient based on different age groups

The mortality rate among TB patients in the Limpopo increased with age from 5.8% among patients aged between 0-4 (from birth to 4 years) to 23.3% among patients who were aged 65years and above.

© University of Venda

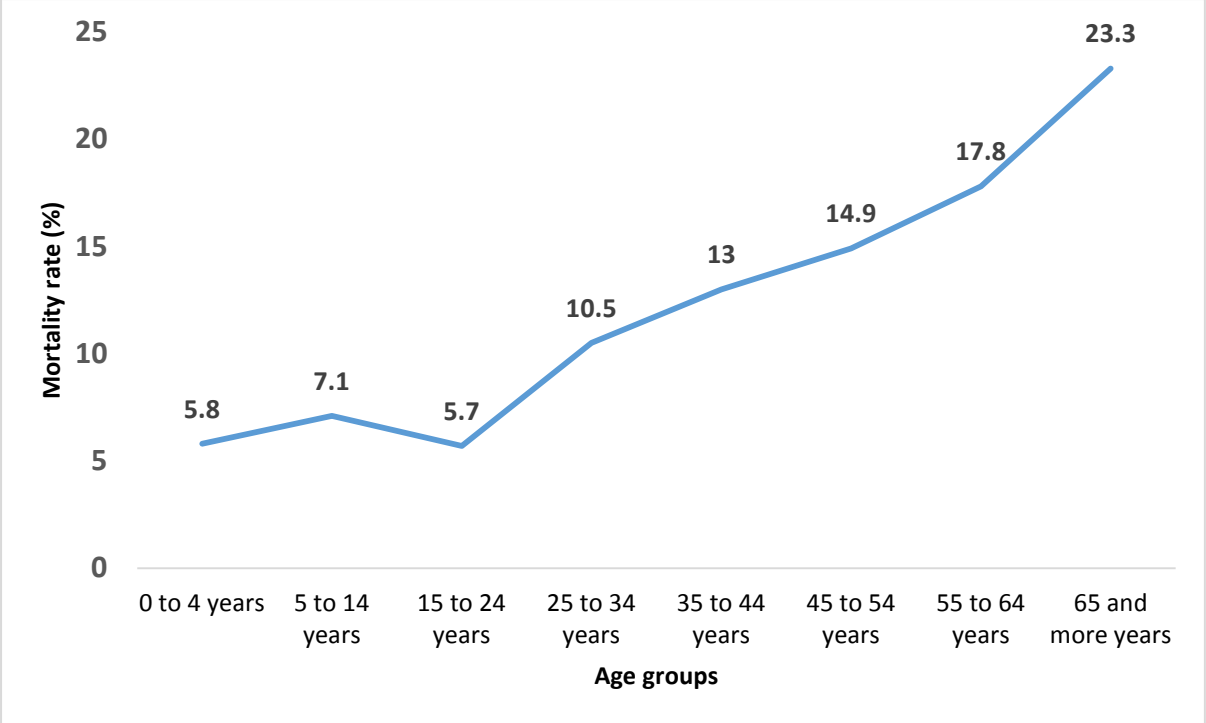

Figure 4. Mortality among TB patients in Limpopo among different age groups

4.6 Mortality among TB patient in different district municipalities

Capricorn District Municipality had 15% of patients' mortality rate, followed by Sekhukhune with 14.1 %, Waterberg with 13.2% and Mopani at 12%. Vhembe District had the lowest mortality rate among TB patients attending treatment centres in Limpopo with 8.4% mortality rate. See figure 5 below.

© University of Venda

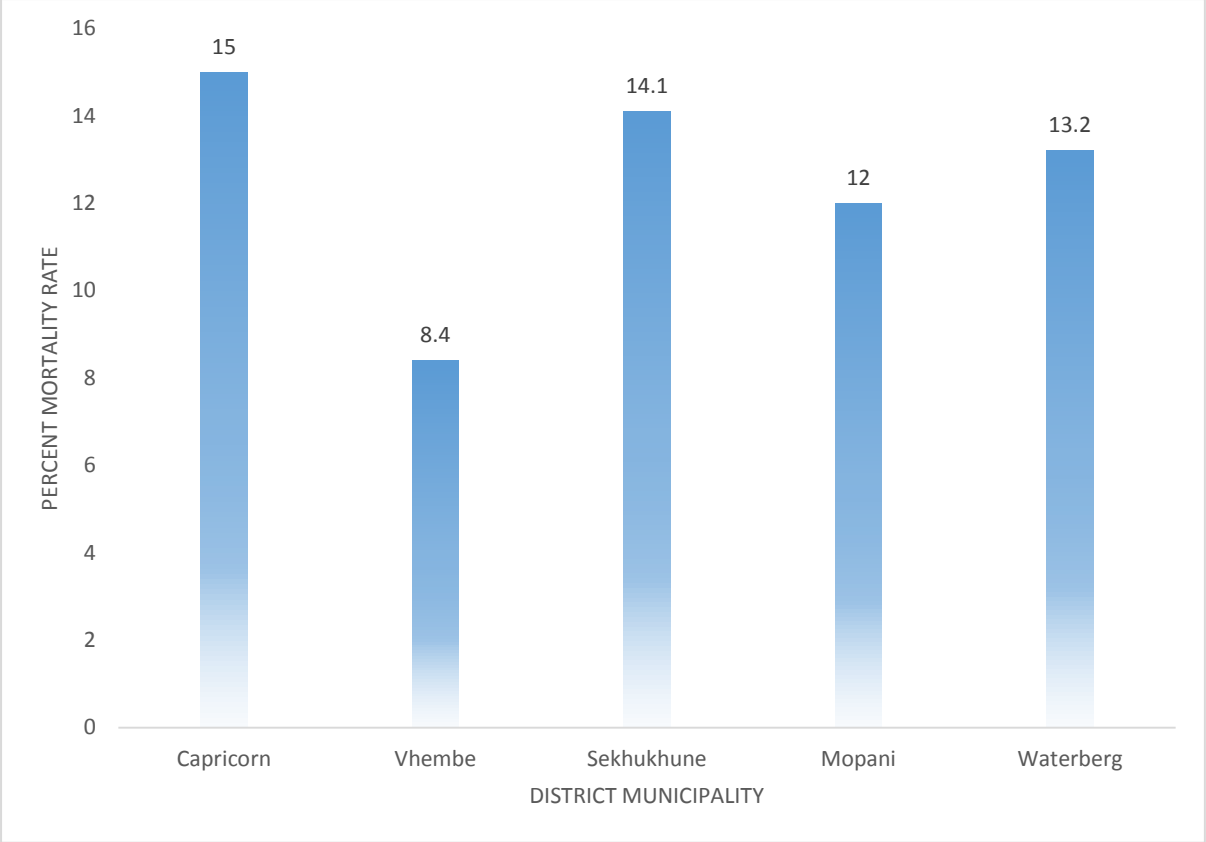

Figure 5. Mortality among TB patients in the different district municipalities in the Limpopo Province of SA

© University of Venda

4.7 Regimens used for treatment

This graph shows mortality according to different regimens taken by the patients. The standard regimen for TB treatment is the combination of Isoniazid (INH), Rifampin (RIF), Ethambutol (EMB) and Pyrazinamide (PZA). Regimen II produced 15.9% mortality while regimen I had 12.8% and regimen III was 5.5%. Figure 6 below illustrates this data.

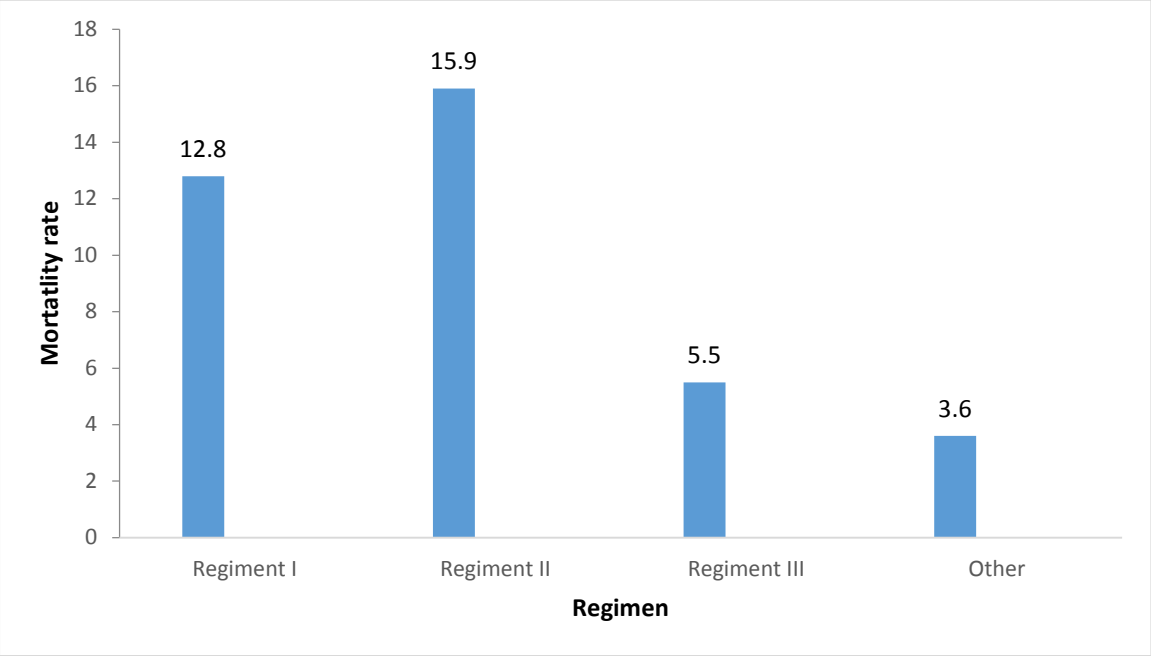

Figure 6. Different regimens used for treating TB patient.

© University of Venda

4.8 Factors associated with mortality among TB patients taking treatment in different treatment centres in Limpopo Province

Table 2 below shows the association between the different variables and death among TB patients taking medication in Limpopo Province between 2013 and 2018. In terms of treatment, the mortality among patients taking regimen 1 was 12.8% compared to 15.9% among those taking regimen 2. It can be observed that regimen 2 had the highest mortality rate and the difference was statistically significant with a p value less than 0.0001, with an ODD Ratio of 1.3 and a confidence interval between 1.1 and 1.6.

There was a statistically significant association between death and gender. The mortality rate among the male gender was 12.8% and for the female gender was 12.2%. With a Chi square value of 4.4 and a p value of 0.032.

In terms of disease classification**,** patients suffering from extra pulmonary TB had a mortality rate of 20.5% while those with pulmonary TB was 11.5%. This clearly indicates that there is a higher risk of dying among patients who had extrapulmonary TB compared to those with pulmonary TB.

Mortality in different categories of patients did not vary significantly. Mortality for the patients who were in the group for retreatment after default was 12.8%, followed by new patients at 12.5%. Patients that relapsed had 10.5% mortality while those in retreatment after failure were 9.3%. It can be seen that patients who were retreated after failure had a much lower mortality rate of 9.3%. This means that changing regimen after failure was a positive action and had a significant effect in terms of the reduction of mortality among the patients.

In terms of HIV counselling, the mortality amongst TB patients who were HIV counselled**,** was not significantly different from that of those who were not counselled. The mortality among HIV patients who were counselled was 7.8% and the TB patients who were not counselled had 6.9%, however**,** mortality amongst patients who were HIV positive, was far higher at 15%, compared to those that were HIV-negative at 7.8 %. There was a clear association between CD4 cell count range among TB patients and mortality. The mortality among TB patient with a CD4 count less than 50 was 20.4%, which was the highest of all those with CD4 count and the difference was statistically significant with a p value less than 0.0001. Mortality among the other groups was much lower and decreased progressively with the lowest mortality rate among those with a CD4 cell count higher than 350 at 3.3%.

There was an association between death and the start of ART among TB/HIV patients. This means that antiretroviral treatment was a significant factor among these patients. The mortality among those who had started on ART was 13.4%, while among those who had not

© University of Venda

started with ART was 35.1%; the difference was statistically significant. Cotrimoxazole preventive therapy (CPT) did not seem to make any positive change, instead, it seems that it worsened the situation. The death rate was higher among patients that took the CPT compared to those who did not take such measures. The mortality rate among patients that started CPT was 15.2% while among those who did not start with the therapy was 9.9%, however, directly observed therapy (DOT intensive) seemed to significantly decrease the death rate among the patients. We observed 12% mortality rate for the patients who were not on the DOT intensive programme and 8.4% for those who were.

The movement of patients was also reported. Two types of transfers could be observed. Those that moved out and those that were transferred out of the facility. Those patients who were transferred out of the facility had a mortality rate of 6.1% while those who moved out had a mortality rate of 12.4%. This shows that the decision to move patients that was taken by the health facility were more beneficial as compared to movements that were initiated by the patients themselves. The results are shown in Table 2 below.

© University of Venda

Table 4.2. Association between death and different variables.

DIFFERENT VARIABLES	TOTAL ON TREATMENT	NUMBER DIED	CHI-SQUARED	P-VALUE
REGIMEN USED				
Regimen I	75157	9652(12.8%)		
Regimen II	755	120(15.9%)		
Regimen III	3593	199(5.5%)	180.862	0.000
Other	84	3(3.6%)		
GENDER				
Female	34665	4245(12.2%)		
Male	44924	5729(12.8%)	4.486	0.032
DISEASE CLASSIFICATION				
Pulmonary TB	69958	8016 (11.5%)		
Extra pulmonary TB	9549	1955 (20.5%)	625.855	0.000
Other	82	3(3.7%)		
PATIENT CATEGORY				
New	755776	9488 (12.5%)		
Relapse	1559	163 (10.5%)		
Retreatment after default	750	96 (12.8%)	30.866	0.000
Retreatment after failure	378	35 (9.3%)		
Other	1126	192 (17.1%)		
HIV COUNSELLED				
Yes	4246	331 (7.8%)		

© University of Venda

No	4177	287 (6.9%)	2.648	0.104
HIV STATUS				
Positive	48892	7355 (15%)		
Negative	26797	2097 (7.8%)	836.498	0.000
CD4 COUNT				
>50	1446	295 (20.4%)		
51-100	2909	335 (11.5%)		
101-200	1570	110 (7%)	227.705	0.000
201-349	816	51 (6.3%)		
350<	814	27 (3.3%)		
ART STARTED				
No	2561	899(35.1%)		
Yes	43785	5872(13.4%)	1475.687	0.000
Unknown	33243	3203(9.6)		
CPT				
No	8964	891(9.9%)		
Yes	42163	6410(15.2%)		
Unknown	28462	2673(9.4%)		
DOT INTENSIVE				
No	26000	3129(12%)	26.272	0.000
Yes	2268	191(8.4%)		
TRANSFER TYPE				
Transfer in	1366	83 (6.1%)	40.473	0.000

© University of Venda

Moved out	2942	366 (12.4%)		
SPUTUM SMEAR				
Positive smear	20610	2355(11.4%)		
Negative smear	16703	1181(7.1%)	757.917	0.000
No smear	42276	6438(15.2%)		

4.9. Estimating the survival curve of HIV-negative and HIV-positive and also ART-started and ART-not started TB patients, using the Kaplan – Meier Method

Kaplan-Meier is one of the best options used to measure the survival time from diagnosis to death. Survival analysis provides special techniques that are required to compare the risk of death associated with different groups (HIV-positive and HIV-negative patients) where the risk changes over time, in measuring survival time. Table 3 below presents the case processing-summary and it shows that the number of events in both HIV-negative and HIV-positive groups were almost similar as 91.5% of the HIV-negative patients were censored as compared to 85%. Table 4 below shows that the median survival was not recorded for patients who were HIV-negative as most patients were censored and not on ART and the median survival was approximately 21 months for patients who were HIV-positive. Table 5 shows the case processing-summary and that the ART-started patients had more events than those who were not on ART. Figure 7 below shows that at time zero, the survival probability was 1.0 (or 100% of the patients were alive. Table 6 presented that at time 22 months, the probability of survival is approximately 0.50 or 50% for HIV-positive patients and 0.75 or 75% for HIV-negative patients. The median survival of patients not on ART was 13 months and for patients on ART was 28 months. This suggests a good survival for patients on ART compared to patients not on ART. Figure 8 presented that at time zero, the survival probability was 1.0 or 100% of the participants were alive. At 13 months, the probability of survival is approximately 0.50 or 50% for patients not on ART and 0.78 or 78% for patients on ART. The median survival was approximately 13 months for patients not on ART and 22 months for patients on ART.

© University of Venda

Table 4.3. Kaplan-Meier results of survival analysis of the HIV-negative and HIV-positive TB patients

Case Processing Summary				
HIV Positive	Total N	N of Events	Censored	
			N	Percent
HIV negative	30695	2619	28076	91.5%
HIV positive	48885	7355	41530	85.0%
Overall	79580	9974	69606	87.5%

Table 4.4. The Mean and Median survival of TB/ HIV-positive and TB/HIV-negative patients

Means and Median for Survival Time								
	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
HIV Positive	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
HIV negative	19.377	.374	18.645	20.110	.	.	.	.
HIV positive	24.200	2.257	19.777	28.623	21.000	3.717	13.715	28.285
Overall	25.536	2.295	21.038	30.034	28.000	4.864	18.466	37.534

a. Estimation is limited to the largest survival time, if it is censored.

© University of Venda

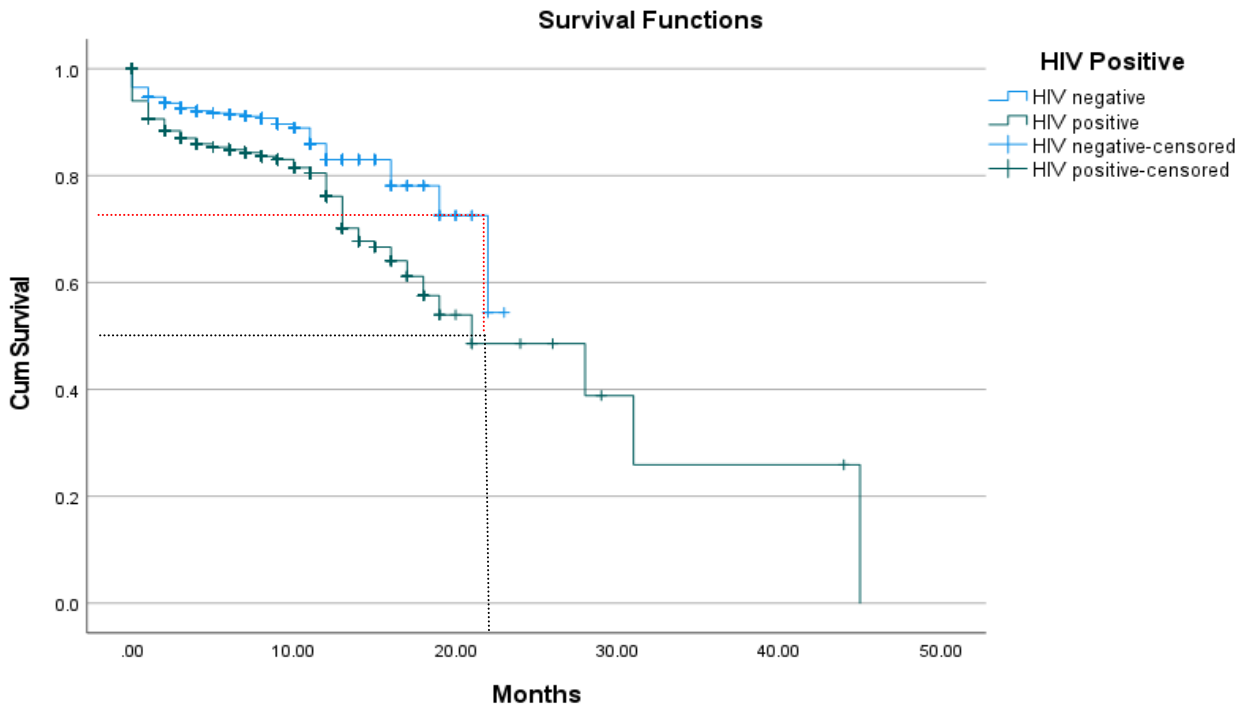

Figure 7: Plots of Kaplan-Meier product-limit estimates of survival of HIV-positive and HIV-negative patients.

Table 4.5**.** Kaplan-Meier results of survival analysis of the ART-started and ART-not started TB/HIV patients

Case Processing Summary				
ART Started?	Total N	N of Events	Censored	
			N	Percent
Not on ARV	2560	899	1661	64.9%
Has started ART	43780	5872	37908	86.6%
Overall	46340	6771	39569	85.4%

© University of Venda

Table 4.6**.** The Mean and Median survival of ART-started and AR- not started on TB/HIV patients

Means and Median for Survival Time

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
ART Started?	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
Not on ARV	10.358	.579	9.224	11.493	13.000	1.250	10.549	15.451
Has started ART	24.856	2.390	20.172	29.540	28.000	6.024	16.192	39.808
Overall	24.305	2.320	19.758	28.852	21.000	3.812	13.529	28.471

a. Estimation is limited to the largest survival time, if it is censored.

© University of Venda

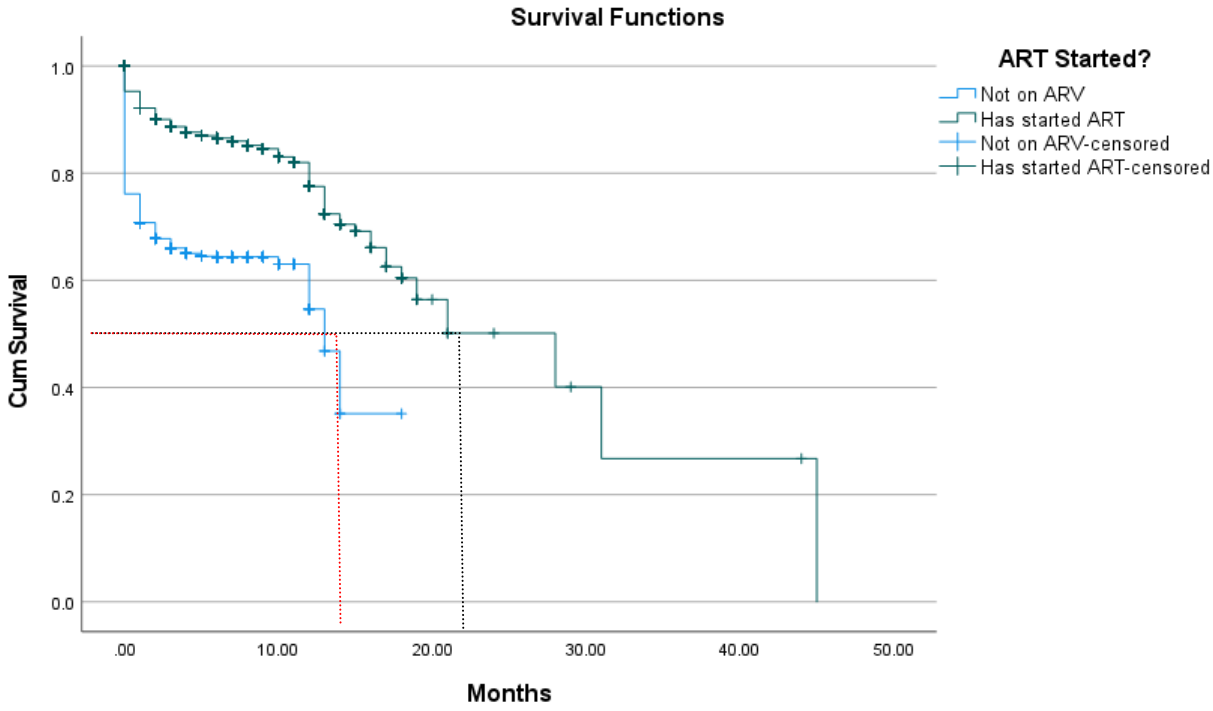

Figure 8: Plots of Kaplan-Meier product-limit estimates of survival of ART-started patients and patients that are not on ART

4.10 Conclusion

Most patients who were on ART, DOT intensive, HIV-negative, younger than 60 years of age and female were on the safe side. They had a much higher survival rate, but the TB patients who were older than 65 years old, HIV positive with CD 4 count below 50µl and whose sputum smear results were positive, had a higher risk of dying. The Kaplan-Meier estimates showed that HIV-negative patients were censored compare to HIV-positive and there was a good survival rate for patients on ART than those not on ART. This chapter presented the results, the next chapter will present the discussions.

© University of Venda

CHAPTER 5

DISCUSSION

5.1 Introduction

In this chapter treatment outcome, association between death and different variables will be discussed. Intervention measures to control the number of deaths on TB patients who were on treatments were also discussed and suggestions made because TB patients are still dying while on treatment as shown in this study. The following objectives were discussed: to

- Determine the case fatality and crude mortality rates due to TB in the Limpopo Province during the period 2013 to 2018;
- Measure the survival curves among TB patients in Limpopo Province during the period of 2013 to 2018;
- Determine the risk factors for mortality among TB patients in Limpopo Province between the years 2013 and 2018;
- Determine factors associated with death among TB patients in the Limpopo Province between the years 2013 and 2018, and
- Describe the association between the variables among TB patients in the Limpopo Province during the period of study.

5.2 Discussion

A retrospective review of data collected on patients receiving anti-TB treatment was conducted in Limpopo Province where TB patients' rate is the highest compare to all 9 provinces of South Africa (National TB Statistics for SA, 2017).

Limpopo Province consists of 5 districts; the mortality rates amongst these districts are different with Capricorn District having the highest followed by Sekhukhune then Waterberg, Mopani and the lowest was Vhembe. In Gauteng Province, South Africa, Marais, Mlambo, Rastogi, Zozio, Grobusch, Duse, Victor & Warren (2014) and Berry *et al.,* (2019) also found different mortality rates in the different municipalities.

According to the 2017 Limpopo provincial strategic planning, between 2015/16, the Limpopo TB incidence rate was 301/100000 people, which was much higher than the Provincial target of 150/100000 new TB infections.

The treatment outcomes of this study showed that patients cured were 80, 6 %, patients who died were 12, 5%. A study by Tola, Mishore, Ayele, Mekuria & Legese (2019) showed that

© University of Venda

the treatment outcome was - 30.1% were cured and 7.7% died; a similar study conducted by Tanue, Nsagha, Njamen & Assob (2019) in Cameroon indicated that the treatment success outcome was 76.4% while 6.9% died. These results are below the WHO target of 90% in the End TB strategy (WHO, 2018). Even the global study, which was conducted in 2019 by Torres, Rodriguez, Andrade, Arriga & Netto (2019), showed that the TB treatment outcome was also below the WHO threshold of 85%. Atif, Fatima, Ahmed & Babar (2020) speculated that the reason for low treatment success rate could be that patients did not adhere to TB treatment or they did not know the consequences of neglecting to follow-up or that the treatment centres are far from them.

Our study revealed that the number of patients who died while on TB treatment in the Limpopo Province is high, however, a study conducted by Takarinda *et al.,* (2017) in Zimbabwe indicated that TB patient who died while on anti-TB treatment in the southern region were 22% which is much higher than the findings of this study. In Tanzania, a study by Gunda *et al.,* (2016) indicated that most TB patients on treatment survived, while 12, 98% of them died during the course of their anti-TB treatment with 71, 43% of the patients being positive for HIV. The study by Gunda *et al.,* (2016) has similar outcome with Mabunda *et al.,* (2014) in Limpopo Province of in 2013 where 13% of TB patients died while on TB treatment.

Our study further shows that a large number of patients on TB treatment died in 2013, however, the mortality rate has decreased over the years; the mortality rate was very high in 2013 as compare to 2018. Our findings are similar to those of Holden, Lillebaek & Jahansen (2019) where mortality rate decreased over the years of the study, from 12.3% in 2009 to 4.1% in 2014. Even though the number of death has decreased over the years these results are still above the WHO target of less than 3%.

The survival curve was measured using the Kaplan-Meier method. It is one of the best options to use when measuring the fraction of subjects living for a certain amount of time after treatment (Goel, Khanna & Kishore, 2011). The survival analysis in this study compared the HIV-positive patients from day of registration until outcome, which is death, in this study. All the other outcomes except death are considered censored when the event is death. Censored occurs when patients are, for example, unable to trace or follow-up to the end of the study (Etikan, Abubarkar & Alkassin, 2017). In this study the number of events in both HIV-negative and HIV-positive groups were almost similar, although, the HIV-negative patents were censored as compare to HIV positive. This implies that many patients were either unable to be followed-up or did not complete their treatment during the study period. The median survival was not recorded of patient who were HIV-positive as most patients were censored and not on ART and the median survival was approximately 21 months for

© University of Venda

patients who were HIV-positive. The median survival of patients not on ART was 13 months, and for patients on ART was 28 months. This suggests a good survival for patients on ART compared to patients not on ART (Naidoo, Baxter & Abdool Karim, 2013). The current data is censored which implies that the information about a patients' survival time is incomplete. This is a problem which most survival analyses suffer from. This in the current study, might be due to a patient not experiencing the event -TB cured - before the study ended, or a patient is lost to follow-up during the study period and / or a patient has withdrawn from the study because of some reason.

This study shows that death of patients on TB treatment is age-related, with older patients at a greater risk of dying than younger patients. Patients at 65 years of age and above are even at a higher risk of dying; this showed that there was an association between age and mortality. Our study agrees with the study conducted by Gunda *et al.,* (2016) which showed that patients at the age 40 and older are more likely to die of TB than patients aged 35 and below. Gunda *et al.,* 2016 speculated that this might be due to the fact that this age group has disrupted immunity caused by chronic obstructive pulmonary diseases.

The study by Takarinda *et al.,* (2017) is in agreement with the findings of our study in that the older the patient the more chances of them dying while on TB treatment.

There was an association between death and regimen used for TB treatment. Regimen I is preferred for patients with a newly-diagnosed Pulmonary TB, regimen II is the preferred alternative regimen in situations in which more frequent DOT, during continuation phase, is difficult to archive. Regimen III is used with caution in patients with HIV and or cavitary diseases. Missed doses can lead to treatment failure, relapse and acquired drug resistance (Ndjeka, Hughes, Reuter, Conradie, Enwerem, Ferreira, Ismail, Kock, Master, Meintjes, Padanilam, Romero, Schaaf, Teriele & Maartens, 2020). In this study, many of the TB patients were newly-diagnosed and they were all in regimen I. Regimen II had a high number of deaths, while a low number of deaths were observed on regimen III.

The gender which was significantly associated with mortality among TB patients on treatment between the years 2013 -2017 was the male gender, however, in a study done by Gafar *et al.,* (2013), there was no association between gender and death. There was no favourable outcome between the male and female; the death rate was the same for both genders. In 2017, Zerbini *et al.,* found that most patient who died while on treatment were males; also in a study by Nanzaluka, Chibuye, Kasapo, Langa, Nyimbili, Moonga Kapata, Kumar & Chongwe.(2019), males patients had unfavourable outcomes and it was suggested that males may be more exposed to TB infections associated with behavioural factors such as previously smoking and working in mines also put men at a higher risk of TB infection,

© University of Venda

coupled with the fact that woman take better care of themselves than men. It is suggested that TB prevention and early accurate diagnosis recognition of the role of HIV and shorter pathways to TB treatment initiation may reduce death (Tola *et al.,* 2019)

HIV-positive TB patients are more likely to die while on TB treatment because their immune system is compromised by the virus, and they were found to be significantly associated with poor TB treatment outcome (Getie & Alemnew, 2020). This study also proved that HIV-positive TB patient were the ones with high mortality compared to HIV-negative patients. Patients who had already started ART were safer than the ones who did not start ART and the patients with lower Cluster of Differentiation 4 (CD4) cell count were at a higher risk of death compared to those with higher CD4 cell count. Sawadogo, Ciza, Nzeyimana, Shingiro, Ndikumana, Demeulenaere, Khogali, Edginton, Reid, Kumar & Harries, (2015) in their study concluded that the ART and CPT uptake increased the chances of a favourable treatment outcome, while in this study CPT was statistically associated with death. Woldeamanuel & Mingude. (2013) had the same results in their study, where HIV positive patients with lower CD4 cell count were more likely to die during TB treatment.

The type of TB with a high number of deaths was extra-Pulmonary TB while Pulmonary TB had a lower number of deaths, hence, extra -Pulmonary TB is the one that was statistically associated with death. In Pakistan, Atif *et al.,* (2020) got the same results - extra- Pulmonary TB had more mortality; Tola *et al.,* (2019) and Holden et al., (2019) studies find extra-Pulmonary to have higher chances of death during treatment than Pulmonary TB. Zerbini *et al.,* (2017), however, found Pulmonary TB to have higher deaths than extra-Pulmonary in their study in Argentina.

The sputum smear examination is normally performed at the end of the second month of TB treatment. A study by Dialo *et al.,* (2018) found that the sputum-smear positive results was a factor associated with treatment failure. In our study the group of patients with no smear sputum results were the ones who were statistically associated with mortality, however, in Ethiopia a study by Woldeamanuel & Mingude. (2018) showed a significant association between sputum smear results and risk of death among TB patients; smear-negative TB patients had a higher risk of mortality than smear-positive cases; this therefore has an impact on the diagnosis of TB.

5.3 Conclusion

Overall outcomes of the study indicated that male patients, patients who are older than 65 years of age or patients who were infected by extra-pulmonary TB, or were HIV positive and

© University of Venda

who were not on ART and had low CD4 cell count, were not on DOT intensive and their sputum-smear results was positive, were at a higher risk of death. The next chapter will be presenting the summary, conclusion and recommendation.

© University of Venda

CHAPTER 6

SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 Summary

TB remains the leading cause of death worldwide. This study aimed at identifying the factors associated with death among TB patients who were on treatment in Limpopo Province. A quantitative retrospective cohort study design using secondary data was applied. TB data was extracted from the ETR.net TB register onto a spread sheet. Statistical package for the social science version 20 and statistic and data version 2 were used for data analysis. The results of the study showed 12, 5% death, 5, 2% defaulted, MDR cases were 0, 2%, drug resistance 0, 3% and cured 80, 6%. Factors associated with death were male gender, over 60 years of age, extra-pulmonary TB, HIV- positive with no ART, CD4 cell count less than 350ul. With all the preventive methods in place, TB death could have been the issue of the past if the preventive methods were used properly.

6.2 Conclusion

The risk factors for mortality with TB patients on anti-TB treatment were male gender, older than 60 years of age, extra-pulmonary TB, being HIV positive with no ART and CD4 cell count less than 350ul, not on Dot intensive programme and having sputum-smear results positive. All these factors that are associated with high death rates in this study have highlighted the necessity for early initiation of TB treatment and ART. DOT intensive should be initiated as soon as possible for males, patients over the age of 60, those with extra-pulmonary TB infection, those who are HIV positive and those with low CD4 cell count. TB death can still be prevented, if all the identified factors associated with high death rates can be controlled properly; the government has all the preventive measures in place, thus, TB death could be an issue of the past in Limpopo Province and South Africa, as a whole.

6.3 Recommendation

All patients who are diagnosed with TB should be tested for HIV and their HIV status should be known before starting with TB treatment so they can be given proper treatment for both diseases. HIV-positive patients with low CD4 count should be initiated early on TB treatment

© University of Venda

and on ART. Patients older than 60 years, male patients, those with a positive sputum smear should be on Dot intensive programme as soon as they are diagnosed.

The TB data (ETR.net) needs improving. There are a lot of missing values and that placed some limitations on this study. There are many patients who are ‘lost’ or unable to follow and they end up not having any treatment; that shows that the DOT intensive programme is not really effective because it should know where to find the patients and follow them up.

© University of Venda

REFERENCES

Adamu AL, Gadanga MA, Abubakar IS, Abubakar MJ, Bello MM, Gajida AV, Babashani MM and Abubakar I (2017). High mortality among TB patients on treatment in Nigeria: a retrospective cohort study. *BMC infectious diseases:* Vol 17:170

Alavi-naini R, Moghtaderi A, Metanat M, Mohammedi M and Zabetien M (2013). Factors associated with mortality in tuberculosis patients. *Journal of Research in Medical Science* vol 18(1) pages 52-55

Ali SA, Mavundla TB, Fantu R and Awoke T (2016). Outcomes of TB treatment in HIV co-infected TB Patients in Ethopia a cross-sectional analytic study. *BMC infectious diseases:* Vol 16(1) 640

Alobu I, Oshi SN, Oshi DC, Ukwaja KN (2014). Risk factors of treatment default and death among tuberculosis patient in resource- limited setting. *Asia Pacific Journal of Tropical Medicine.* Vol 7(12) 977

Alobu I, Oshi SN, Oshi DC, Ukwaja KN (2014). Risk factors of treatment default and death among tuberculosis patient in resource-limited setting. *Asia Pacific Journal of Tropical Medicine.* Vol 7(12) 977

Amante TD and Ahemed TA (2015). Risk factors for unsuccessful tuberculosis treatment outcome(failure,default and death) in public health institutions, Eastern Ethiopia. *Pan African Medical Journal*. Vol 16; 20:247

Ambardekar N, MB 2019. What is the treatment for Tuberculosis? http://webmd.com. Last accessed on 28 June 2021.

Asres A, Jerene D and Deressa W (2018). Delays to treatment initiation is associated with tuberculosis treatment outcome among patients on directly observed treatment short course in Southwest Ethiopia: a follow up study. *BMC Pulmonary Medicine.* Vol 18:64

Atif M, Fatima R, Ahmed N and Babar Z (2020). Treatment outcome of extra-Pulmonary TB in Bahamalpur, Pakistan, a record review. Journal of pharmaceutical policy and practice vol 13 (35)

Au – Yeung, C, Kanters, S, Ding, E, Glaziou, F, Anema, A, Cooper, CL, Montaner, JSG, Hogg, RS, and Mills, EJ (2011). Tuberculosis mortality in HIV- infected individuals: a cross-

© University of Venda

national systematic assessment. *Journal of clinical epidemiology* 2011;3:21 -29. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3035603

Babbie, E. (2010). *The practice of social research.* 12th Edition. London: Wardsworth Cengage Leaning.

Badri M, Ehrlich R, Wood R, Pulerwitz T and Maartens G.(2001) Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area. *International Journal of Tuberculosis and lung disease*. 2001 Mar; 5(3):225-32

Berry K M, Rodriguez C A, Berhanu R H, Ismail N, Mvusi L, Long L and Evans D (2019). Treatment outcome oin treatment for Tuberculosis in 2 Metropolitan Municipalities in Gauteng Province South Africa. *BMC public health*. Vol 19(1): page 973

Birlie A, Tesfaw G, Dejene T, Woldemichael K (2015). Time to Death and Associated Factors among Tuberculosis Patients in Dangila Woreda, North Ethiopia. *Plos one journal*, vol 10:1371

Biruk M, Yimam B, Abrha H, Biruk S and Amdie FZ (2016). Treatment Outcomes of Tuberculosis and Associated Factors in an Ethiopian University Hospital" *Advances in public health journal,* vol 2016, pages 5-6, 2016.

Blumber H, Burman W, Chaisson R, Daley C, Etkinds, Friedman L, Fujiwara P, Grzemska M, Hopewell P and Iseman M (2003). American Thoracic Society/Center for disease control and prevention/infectious diseases society of America: treatment of tuberculosis. *American Journal of Respiratory and critical care medicine.* 167(4): 603-633.

Burn SN and Grove S.K (2009). The practice of nursing research: appraisal, synthesis and generation of evidence. St Louis, M O: Saunders Elsevier

Brink H (2009). *Fundamentals of research methodology for health care professionals.* Pennsylvania State University, Juta and company 1996

Camara A, Sow MS, Toure A, Diallo OH, Kaba L, Bah B, Diallo MS, Guilavogui T and Sow OY (2017). Treatment outcome, Survival and their risk factors among new tuberculosis patients Co-infected with HIV during the ebola outbreak in Conakry. *Rev Epidemiology Sante Publique* vol 65(6): 419-426

Centres for Disease Control and Prevention (CDC) (2000). Targeted Tuberculin Testing and Treatment of latent tuberculosis infection. *Morbidity Mortality Weekly Reports* 49(RR-06): 1-54.

© University of Venda

Centres for Disease Control and Prevention (CDC) (2016). Treatment for TB disease: http://www.cdc.gov. last accessed 28 June 2021

Chen L,Bao D, Gu L, Gu Y, Zhou L, Gao Z and Huang Y(2018). Co-infection with hepatitis B virus among tuberculosis patients is associated with poor outcomes during anti-tuberculosis treatment. *BMC Infectious Disease.* Vol 18:295

Cobert LE, Marston B. (2006) Tuberculosis in sub Saharan Africa: Opportunities, challenges, and change in the era of antiretroviral treatment. *Lancet* 2006; 367:926-37.

Corbett, EL, Watt, CJ, Walker, N, Maher, D, Williams, BG, Raviglione, MC and Dye,C.(2003) The growing burden of Tuberculosis: Global trends and interactions with the HIV epidemic. *Archives of Internal Medicine.* 2003; 163:1009-21. [PubMed 12742798]

Das P and Horton, (2010). Early treatment outcome and HIV status in patients with XDR-TB in South Africa: retrospective cohort study. *Lancet.* 375 (9728): 1755- 1757. ETR. Net Report , Limpopo Province. www.etrnet.info. Last access 15 October 2010.

Department of Health. *National Tuberculosis Management Guidelines* 2009: 1, 73.

Department Of Health (2013). *Management of drug resistance tuberculosis*, Policy Guideline

Dialo A, Dahourou DL, Dah TTE, Tassembedo S, Sawadoga R and Meda N. (2018) Factors associated with tuberculosis treatment failure in the central East health region of Burkina Faso. *Pan African Medical Journal* article number 30 page 293

Do Prado TN, Rajan JV, Miranda AE, Dias ES, Cosme LB Possuelo LG, Sanchez MN, Golub JE, Riley LW and Maciel E.L(2016). Clinical and Epidemiological Characteristics associated with unfavourable tuberculosis treatment outcome in TB/HIV co-infected patient in Brazil: a hieracchial polytomous analysis. *The Brazilian Journal of Infectious disease.* Vol 21(2): 162-170

Engelbrecht M.C, Kigozi N.G, Chikobvu P, Botha S and Van Resburg HC(2017). Unsuccessful TB treatment outcomes with a focus on HIV Co-infected cases: a cross-sectional retrospective record review in a high-burdened province of South Africa. *BMC Health Services Research journal.* Vol 17: 470.

Getre A and Alemnew B (2020). Tuberculosis treatment outcome and association factors among patients treated at Woldia general hospital in Northeast Ethiopia. An institution-based cross-sectional study. *Infection and drug resistance Journal* vol 13 pages 3423-3429.

© University of Venda

Goel MK, Khanna P and Kishore J C (2011) Understanding survival analysis: Kaplan-Meier estimate. *International journal of Ayurveda Research* vol1.

Gunda D W, Kilonzo S B, Bulegesi S M, Mpondo B C T, Shao E R (2016). Risk factors for mortality among Tuberculosis patients on treatment at Bugando medical center in North-Western Tanzania: A retrospective cross-sectional study. *Tanzania Journal of Health Research* vol 18: 4

Heale R and Twycross A (2015). Validity and Reliability in quantitative studies. *Evidence based nursing,* vol 18(3)

Heunis JC, Kigozi NG, Chikobvu P, Botha S and Van Resburg HCJD (2017). Risk factors for mortality in TB patients: 10-year electronic record review in South Africa. *BMC Public Health.* Vol 17: 38

Holden I K, Lillebaek T, Johansen I S (2019). Predictors for Pulmonary TB treatment outcome in Denmark from 2009-2014. *Scientific reports* vol 9 page 12995. https://www.ncbi.nlm.nih.gov

Howell E, Kigozi NG and Heunis JC(2018). Community-based directly observed treatment for TB patients to improve HIV services: a cross-sectional study in South African Province. *BMC Health Services Research.* Vol 18:255

International Standard for Tuberculosis Care (ISTC) (2009). The Hague: *Tuberculosis Coalition for Technical Assistance* (2nd edition).

Iseman M 2020. Tuberculosis. https://www.nationaljewish.org

Kanabus A 2021. TB treatment-drugs,length of treatment, treatment failure. http://tbfacts.org. (last accessed on 28 June 2021)

Khatri M, MD 2020. Tuberculosis (TB). http://www.webmd.com

Koo H K, Min J, Lee S S. (2020) Prediction of treatment failure and compliance in patients with Tuberculosis. *BMC infectious Disease* vol 20 article number 622

Limpopo Provincial Strategic Plan for HIV/AIDS/STI and TB 2012- 2016 (HAST) (2008). Programme NAC. The Republic of South Africa.175: 43 - 349.

Mabunda TE, Ramalivhana NJ and Dambisya Y (2014). Mortality associated with TB/HIV co-infection among patient on TB treatment in Limpopo Province, South Africa. *African health sciences,* vol 14(4) 849-854

© University of Venda

Marais E, Mlambo C K, Rastogi N, Zozio T, Grobusch M P, Duse A, Victor T and Warren R W (2014). Treatment outcome of multidrug-resistance Tuberculosis patients in Gauteng, Johannesburg South Africa. *Infection* vol 42(2) pages 405-413.

Middelkoop K, Bekker LG, Myer L, Johnson LF, Kloos M, Morrow C, Wood R.(2011) Antiretroviral Therapy and TB Notification Rates in a High HIV Prevalence South African Community. *Journal of Acquired Immune Deficiency Syndrome.* 2011 Mar 1; 56(3):263-9.

Middleton F (2020). Validity and Reliability. https://www.sribbr.com. Last accessed 18 July 2021

Mohammed M. Gafar Norman Z. Nyazema Yoswa M. Dambisya (2010) Factors influencing treatment outcomes in tuberculosis patients in Limpopo Province, South Africa, from 2006 to 2010. *Journal of the Democratic Nursing Organization of South Africa*. Vol 37, No1

MMWR Morb Mortal, Wkly Rep. 2010 Nov26; 59(46): 1509 – 13. Erratum in: MMWR Morb Mortal, Wkly Rep. 2011 Feb 4; 60(4):115. Mortality among patients with tuberculosis and associations with HIV status. United States, 1993 – 2008. *PubMed PMID*: 21102404.

National Department of Health. *National tuberculosis management guidelines*. Pretoria: NDoH; 2014

National TB Statistics for South Africa (2017). https:/www.TBfactors.org/TB-Statistics-South Africa/ (last accessed 25 June 2018)

Nadol P, Stinson K, Cogging W, Naiker M, Wells CD, Miller B, Nelson LJ(2008). Electronic Tuberculosis Surveillance systems: a tool for managing today's TB programs. *International Journal of Tuberculosis and Lung Disease.* Vol 12(3): 8-16

Naidoo K, Baxter C, Abdool Karim SS (2013). When to start antiretroviral therapy during Tuberculosis treatment. *Current Opinion on Infectious Disease.* Vol 26(1): 35-42

Nanzaluka F H, Chibuye S, Kasapo C C, Langa N, Nyimbili S, Moonga G, Kapata N, Kumar R and Chongwe G (2019). Factors associated with unfavourable Tuberculosis treatment outcome in Lusaka Zambia 2015, a secondary analysis of routine surveillance data. *Pan African Medical Journal,* vol 32.

Ndjeka N, Hughes J, Reuter A, Conradie F, Enwerem M, Ferreira H, Ismail N, Kock Y, Master I, Meintjes G, Padanilam X, Romero R, Schaaf H S, te Riele J and Maartens G (2020). Implementation of novel regimes for drug-resistance Tuberculosis in South Africa. What can

© University of Venda

the world learn? *International Journal of Tuberculosis and lung disease* vol 24(10) pages 1-73-1080.

Osman M, Karat AS, Khan M, Meehan SA, Delft AV, Brey Z, Charalombous S, Hesseling AC, Naidoo P and Loveday M (2021). Health system determinants of Tuberculosis mortality in South Africa a casual loop model. *BMC Health Services Research* vol 21 article no 388

Polit D.F and Beck C.T (2012). *Nursing research: generating and assessing evidence for nursing practice.* Philadelphia: Wolters Kluwer health/Lippincott William and Wilkins

Provincial profile (2004): Limpopo\ Statistic South Africa- Pretoria: *Statistic South Africa, 2006* 110p {report NO. 00- 91- 09)

Rich JT, Neely JG, Paniello RC, Voelker CCJ, Phil, Oxono D, Nussenbaum B and Wang E.W (2010). *A practical guide to understanding Kaplan-Meier curves.* Vol 143(3) pages 331-336.

Robinson J, MD 2020. Tuberculosis prevention, what to know. https://www.webmd.com. Last accessed 01 July 2021

Roy E, Lowrie DB, Jolles SR. (2007) Current strategies in TB immunotherapy. *Journal of molecular medicine* 2007 Jun; 7(4): 373-86.

Salkind NJ (2010). Retrospective study. Encyclopaedia. https://dx.doi.org/10.4135/9781412961288.n390. last accessed 02November2017

Sawadogo M,Ciza F, Nzeyimana S D, Shingiro A, Ndikumana T, Demeulenaere T, Khogali M, Edgiton M, Reid A J, Kumar M V and Harries A D (2015). Effect of increase ART-CPT uptake on tuberculosis outcomes and association factors, Burundi 2009-2013. *Public health action* vol 5(4).

Shan S.N, M.D., M.P.H, Auld S.C, M.D., Jones C.M. Brust, M.D, and Barum M (2017). Transmission of Extensively Drug-resistance Tuberculosis in South Africa, *New England Journal of Medicine.* 376: 243-253

Shenoi S and Friedland G (2009). Extensively drug resistant tuberculosis: A new face to an old pathogen, *Annual Review of Medicine,* 60:307-320

South African National Tuberculosis Association (SANTA) (2008). Tuberculosis speech delivered at SANTA Provincial Conference 1OTH - 12TH. http://www.dhsd.Limpopo.gov.za\docs\speech last accessed *25/October/2017*

© University of Venda

South Africa, National Institute for Communicable Diseases (NICD) & National Health Laboratory Services (NHLS) 2010. *Communicable Diseases Surveillance Bulletin.* Volume 8, NO. 4.

Statistics South Africa (STATS SA) (2018). *Mortality and causes of death in South Africa in 2016, findings from death notification*. Pretoria statistics South Africa.

Sterling T, Zhoa Z, Khan A, Chaisson R, Schluger N, Mangura B, Welner M and Vernon A(2009). Mortality in a large Tuberculosis treatment trial: modifiable and non-modifiable risk factors. *International Journal of Tuberculosis and Lung Disease* 10(5): 542-549

Stijnberg D, Commiesie E, Marfn D, Schrooten W, Perez F and Sanchez M (2019). Factors associated with mortality in person co-infected with TB and HIV in Sariname: a retrospective cohort study. *Pan American Journal of Public Health* vol 43 pages 103

Takarinda C K, Sandy C, Masuka N, Hazangwe P, Choto R C, Matasa- Apollo T, Khomo B, Sibanda E, Mugurungi O, Harries A D and Siziba (2017). Factors associated with mortality among patients on TB treatment in the Southern Region of Zimbabwe 2013. *Tuberculosis Research Treatment.* Vol 9 pages 1-11

Tanue E A, Nsagha D S, Njamen T N and Assob N J C (2019). Tuberculosis treatment outcome and its associated factors among people living with HIV and AIDS in Fako Division of Cameroon. *Plos one journal* vol 14(7).

Tola A, Mishore K M, Ayele Y, Mekuria A N and Legese N (2019). Treatment outcome of Tuberculosis and Association factors among TB-HIV Co-infected patients at public hospitals of Harar town, Eastern Ethiopia, a five year retrospective study. *BMC Public Health*. Vol 19.

Torres N M C, Rodriguez J J Q, Andrade P S P, Arriga M B and Netto E M (2019). Factors predictive of the success of TB treatment. A systematic review with meta-analysis. *Plos one Journal* vol 14(12)

Tweya H, Feldacker C, Phiri S, Ben-Smith A, Fenner L, Jahn A, Kalulu M, Weigel R, Khamba C, Banda R, Egger M and Keiser O(2013). Comparison of treatment outcomes of new smear-positive pulmonary tuberculosis patients by HIV and Antiretroviral status in TB/HIV clinic, Malawi. *National Institutes of Health.* Vol 8(2)

Tuberculosis and HIV in India.(2007) The challenges ahead. *Journal of medical science* 2007 March, 356; 12.

© University of Venda

Umeokonkwo C D and Disu Y O (2020). Trend and determinants of Tuberculosis outcome in a tertiary hospital in Southeast Nigeria. *Journal of infection and public health* vol 13(7) pages 1029-1033.

Woldeamanuel G G & Mingude A B. (2018) Factors associated with mortality in Tuberculosis patients at Debre Birhan Referral Hospital Ethiopia: A retrospective study. *Journal of Tropical Diseases* vol 7:1

World Health Organisation (WHO) (2007). Global tuberculosis control: surveillance, planning. financing. *WHO/HTM/TB/2007.387* last accessed 03 November 2017

World Health Organization (WHO) (2008). Guideline for the programmatic management of drug-resistance tuberculosis: emergency update Genava *WHO/HTM/TB*:2008.402

World Health Organization (WHO) (2008). Global Tuberculosis Control: Surveillance planning and financing. WHO report. Geneva *WHO/HTM/TB/2008*.393

World Health Organization (WHO) (2009). *Epidemiology. Global Tuberculosis Control: Epidemiology Strategy financing* pp 6-33. *WHO/HTM/TB/2009.426*

World Health Organization (2013). *Definition of Tuberculosis cases and treatment outcomes*. Geneva, Switzerland

World Health Organization (2013), HIV testing and Counselling. Online available : http://www.who.int/hiv/topics/vct/en/ last accessed 13April2017

World Health Organization(2015), implementing the end TB strategy: The Essentials.

World Health Organization (2017). Reviewed Tuberculosis, global health observatory data. Geneva www.WHO.int/gho/TB/epidemic/case-death/ last accessed 11May2018

World Health Organization (2019). Health topics: Risk factor. https:/www.who.int/topics/risk_factors/en/. Last accessed 16My2019

World Health Organization (2020). *Global Tuberculosis report*. Geneva

Xin S, Kathryn D, Zhengan Y, Mei S, Zhen X, Xiaohony G, Lili W and Jian M (2009) Deaths among tuberculosis cases in Shangai China, Who is at risk? *BMC Infectious Disease* 9:

Zerbini E, Greco A, Estranda S, Cisneros M, Colombo C, Beltrame S, Boncompain C & Genero S. Risk factors associated with tuberculosis mortality in adults in six provinces of Argentina. *Medicina vol* 77 pages 267-2

© University of Venda

APPENDICES

Appendix 1: Time from Treatment start to outcome

	Frequency	Percent	Cumulative Percent
.00	5129	6.4	6.5
.00	2927	3.7	10.1
.00	2196	2.8	12.9
.00	1726	2.2	15.1
.00	1555	2.0	17.0
.00	25897	32.5	49.6
.00	26568	33.4	82.9
.00	6132	7.7	90.6
.00	3364	4.2	94.9
.00	2438	3.1	97.9
0.00	762	1.0	98.9
1.00	419	.5	99.4
2.00	245	.3	99.7
3.00	77	.1	99.8
4.00	37	.0	99.9
5.00	22	.0	99.9
6.00	14	.0	99.9
7.00	17	.0	99.9
8.00	25	.0	100.0
9.00	10	.0	100.0
0.00	4	.0	100.0
1.00	5	.0	100.0
2.00	3	.0	100.0
3.00	1	.0	100.0
4.00	1	.0	100.0
6.00	1	.0	100.0
8.00	1	.0	100.0
9.00	1	.0	100.0
1.00	1	.0	100.0
4.00	1	.0	100.0
5.00	1	.0	100.0
otal	79588	100.0	

Appendix 2: Ethical clearance approval.

© University of Venda

RESEARCH AND INNOVATION
OFFICE OF THE DIRECTOR

NAME OF RESEARCHER/INVESTIGATOR:
Ms GG Mamba

Student No:
11553616

PROJECT TITLE: **Factors associated with mortality among Tuberculosis patients on treatment in Limpopo Province, South Africa from 2013 -2018.**

PROJECT NO: **SHS/19/PH/19/0612**

SUPERVISORS/ CO-RESEARCHERS/ CO-INVESTIGATORS

NAME	INSTITUTION & DEPARTMENT	ROLE
Dr JT Mabunda	University of Venda	Supervisor
Prof A Samie	University of Venda	Co - Supervisor
Ms GG Mamba	University of Venda	Investigator – Student

Type: Masters Research
Risk: Minimal risk to humans, animals or environment (Category 2)
Approval Period: December 2019 – October 2022

The Human and Clinical Trails Research Ethics Committee (HCTREC) hereby approves your project as indicated above.

General Conditions
While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following.

- The project leader (principal investigator) must report in the prescribed format to the REC:
  - Annually (or as otherwise requested) on the progress of the project, and upon completion of the project
  - Within 48hrs in case of any adverse event (or any matter that interrupts sound ethical principles) during the course of the project.
  - Annually a number of projects may be randomly selected for an external audit.
- The approval applies strictly to the protocol as stipulated in the application form. Should any changes to the protocol be deemed necessary during the course of the project, the project leader must apply for approval of these changes at the REC. Should there be deviation from the project protocol without the necessary approval of such changes, the ethics approval is immediately and automatically forfeited.
- The date of approval indicates the first date that the project may be started. Should the project have to continue after the expiry date, a new application must be made to the REC and new approval received before or on the expiry date.
- In the interest of ethical responsibility, the REC retains the right to:
  - Request access to any information or data at any time during the course or after completion of the project.
  - To ask further questions; Seek additional information; Require further modification or monitor the conduct of your research or the informed consent process.
  - withdraw or suspend approval if:
  - Any unethical principles or practices of the project are revealed or suspected.
  - It becomes apparent that any relevant information was withheld from the REC or that information has been false or misrepresented.
  - The required annual report and reporting of adverse events was not done timely and accurately.
  - New institutional rules, national legislation or international conventions deem it necessary

ISSUED BY:
UNIVERSITY OF VENDA, RESEARCH ETHICS COMMITTEE
Date Considered: November 2021

Name of the HCTREC Chairperson of the Committee: Dr NS Mashau

Signature:

UNIVERSITY OF VENDA
OFFICE OF THE DIRECTOR
RESEARCH AND INNOVATION
2021 -11- 15
Private Bag X5050
Thohoyandou 0950

University of Venda
PRIVATE BAG X5050, THOHOYANDOU, 0950 LIMPOPO PROVINCE SOUTH AFRICA
TELEPHONE (015) 962 8504/8913 FAX (015) 962 8260
"A quality driven financially sustainable, rural-based Comprehensive University"

© University of Venda

Appendix 3. Letter of approval from the Department of Health

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Department of Health

Ref : LP- 201912 - 010
Enquiries : Ms PF Mahlokwane
Tel : 015-293 6028
Email : Kurhula.Hlomane@dhsd.limpopo.gov.za

G G Mamba

PERMISSION TO CONDUCT RESEARCH IN DEPARTMENTAL FACILITIES

Your Study Topic as indicated below;

Factors associated with mortality among Tuberculosis patients on treatment in Limpopo Province, South Africa from 2010 – 2016

1. Permission to conduct research study as per your research proposal is hereby Granted.
2. Kindly note the following:
   a. Present this letter of permission to the institution supervisor/s a week before the study is conducted.
   b. In the course of your study, there should be no action that disrupts the routine services, or incur any cost on the Department.
   c. After completion of study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
   d. The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
   e. The approval is only valid for a 1-year period.
   f. If the proposal has been amended, a new approval should be sought from the Department of Health
   g. Kindly note that, the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated

Head of Department

Date

Private Bag X9302 Polokwane
Fidel Castro Ruz House, 18 College Street. Polokwane 0700. Tel: 015 293 6000/12. Fax: 015 293 6211.
Website: http/www.limpopo.gov.za

The heartland of Southern Africa – Development is about people!

© University of Venda

Appendix 4: Data collecting sheet

TB reg No.	Age	Gender	Other diseases	substance use	Classification of disease	Treatment start date	HIV status	Treatment start date	Treatment outcome			Date of death	House income
									Death	survived	defaulted		

© University of Venda

© University of Venda