

**EVALUATION OF TREATMENT OUTCOMES,
FACTORS AFFECTING TREATMENT
DEFAULTING AND HEALTH RELATED
QUALITY OF LIFE OF NEWLY DIAGNOSED
TUBERCULOSIS PATIENTS IN YEMEN**

AMMAR ALI SALEH JABER

UNIVERSITI SAINS MALAYSIA

2018

**EVALUATION OF TREATMENT OUTCOMES,
FACTORS AFFECTING TREATMENT
DEFAULTING AND HEALTH RELATED
QUALITY OF LIFE OF NEWLY DIAGNOSED
TUBERCULOSIS PATIENTS IN YEMEN**

by

AMMAR ALI SALEH JABER

**Thesis submitted in fulfilment of the requirements
for the degree of
Doctor of Philosophy**

July 2018

ACKNOWLEDGEMENT

All praise and thanks are due to my Lord, ALLAH SUBHANH WA TAALA, for giving me the health, strength, knowledge and patience to complete this work Whom His Majesty Said (And remember! your Lord caused to be declared (publicly): "If you are grateful, I will add more (favours) unto you." (Ibrahim: 7). Since the Prophet Muhammad "Peace be Upon Him" said: 'Whoever does not thank people (for their favours) has not thanked Allah (properly), therefore, I would like to express my sincere gratitude and deep thanks to my supervisor Dr Amer Hayat Khan for all his support, patience and guidance during this study. He has widened my horizon in conducting the research. His contributions was invaluable, extraordinary and his way of directing a student was unique. Without his support and encouragement, it remained unfinished work. I am privileged to be his student. No words can adequately express my indebtedness to my co-supervisor Prof. Syed Azhar Syed Sulaiman for his insightful remarks, thoughtful guidance, precious feedback and invaluable time. Every discussion conversation I had with him has been a great learning experience for me and educative in many ways. He is an epitome of expertise crowned with garlands of humanity; He is, in the true sense of the term, fed with intellectual commitment. I am greatly in him debt.

Words stand mute to express my gratitude for the indescribable love, patience, and endless encouragement of my inspiring father Ali Saleh Jaber, my lovely mother Nema Abdo Saleh, caring Father-in-law Abdo Saleh Alfageeh, warm-hearted, forbearing mother, loving mother-in-law, unfailingly helpful brother Salah and Abdulghani, sisters and brothers-in-law for making me realise the value of education. It is their endless financial and spiritual support that has sustained me

throughout my studies. I will be failing in my duty if I do not acknowledge the limitless efforts of my affectionate wife Amatalrahaman Abdo Saleh in the completion of this project. She has adorably sweetened my stay in Malaysia and done the impossible to keep me in the best state of mind. She has been all dutiful and never hesitated to extend any forms of help in critical times.

I would like to express my gratitude and thanks to the workers of Taiz and Al Hudaydah Tuberculosis center in Yemen for facilitating data collection stage, especially Dr Mohammed Alazazi and Dr Mohammed Saif. A great thanks to Dr Najib Al-Ashwal.

My debt to scholars whom I knew only from their works, needless to say, is felt all through this humble endeavour.

TABLE OF CONTENTS

ACKNOWLEDGEMENT	ii
TABLE OF CONTENTS.....	iv
LIST OF TABLES	ix
LIST OF FIGURES	xi
LIST OF ABBREVIATION.....	xii
ABSTRAK	xv
ABSTRACT.....	xviii
CHAPTR ONE: INTRODUCTION	
1.1 General Introduction.....	1
1.2 Tuberculosis as a global phenomenon.....	1
1.3 Epidemiology of Tuberculosis	2
1.3.1 Global epidemiology of Tuberculosis	2
1.3.2 Epidemiology of Tuberculosis in Yemen	3
1.4 Management and treatment of tuberculosis in Yemen	5
1.5 Operational Definitions adapted from NTCP.....	8
1.6 Problem statement	10
1.7 Rationale and Importance of overall study.....	12
1.8 Research contribution.....	14
1.9 Aim and objectives	15
1.9.1 General Objective	15
1.9.2 Specific Objective.....	15

CHAPTER TWO: LITERATURE REVIEW

2.1	Literature Review	16
2.2	Evaluation of treatment outcome of newly diagnosed pulmonary tuberculosis (PTB) patients	16
2.3	Risk factors associated with delayed sputum conversion at the end of intensive phase among newly diagnosed PTB patients.....	25
2.4	Overview of Prolong Treatment Duration (a total of 6 month) of newly diagnosed PTB patients.....	30
2.5	Health-Related Quality of life (HRQoL) of TB patients.....	31
2.6	Overview of TB treatment defaulting.....	40
2.7	Health Related Quality of Life (HRQoL) of TB treatment defaulters.....	50

CHAPTER THREE: METHODOLOGY AND MATERIALS

3.1	Evaluation of treatment and possible clinical outcome of newly diagnosed pulmonary tuberculosis	56
3.1.1	Study location and design	56
3.1.2	Sample size calculation for all newly diagnosed pulmonary tuberculosis	57
3.1.3	Study duration and population.....	57
3.1.4	Ethical consideration	57
3.1.5	Inclusion criteria and exclusion criteria.....	58
3.1.6	Questionnaire adaptation, validation and Pilot study	58
3.1.7	Final version of the questionnaire.....	59
3.1.8	Data collection	59
3.1.9	Statistical Analysis.....	60
3.2	Evaluation of Health Related Quality of Life among TB patients	61

3.2.1	Research Instrument/Measures	61
3.2.2	Pilot Study	62
3.2.3	Evaluation of HRQoL among all newly diagnosed TB patients ...	64
3.2.4	Sample Size for Health Related Quality of Life of TB patients	65
3.2.5	Inclusion and exclusion criteria for HRQoL of all newly diagnosed TB patients.....	65
3.2.6	Scoring and Statistical Tests for HRQoL among all newly diagnosed TB patients	65
3.3	Evaluation of newly diagnosed PTB Defaulters	67
3.3.1	Sample calculation for PTB defaulters	67
3.4	Evaluating Health Related Quality of Life of TB treatment Defaulter's	68
3.4.1	Sample calculation for Health Related Quality of Life of TB treatment Defaulter's	68

CHAPTER FOUR: RESULTS

4.1	Tuberculosis Treatment Outcome for Newly Diagnosed Pulmonary Tuberculosis	70
4.1.1	Selection of newly diagnosed PTB.....	71
4.1.2	Socio-Demographical Characteristics of Newly diagnosed Pulmonary Tuberculosis	72
4.1.3	Clinical characteristics	74
4.1.4	Tuberculosis Symptoms during various stage of treatment.....	77
4.1.5	Change in Patient Body Weight during Tuberculosis Treatment ..	78
4.1.6	Bacteriological test for pulmonary tuberculosis patients.....	78
4.1.7	Duration of Treatment for newly diagnosed PTB patients	79
4.1.8	Side Effect for newly diagnosed PTB patients	80

4.1.9	Treatment Outcomes for Newly Diagnosed Smear-Positive PTB	80
4.1.10	Risk Factors Associated with Unsuccessful Treatment Outcome	81
4.1.11	Risk factor associated with prolong sputum conversion.....	83
4.1.12	Risk factor associated with prolong treatment duration (> 6 months).....	86
4.2	Evaluation of Health Related Quality of Life of All Tuberculosis Patients	89
4.2.1	Description of patients included for evaluation of HRQoL.....	89
4.2.2	Patient's baseline socio-demographic characteristics.....	91
4.2.3	Clinical characteristics of TB patients evaluated for HRQoL.....	93
4.2.4	Changes in HRQoL at various stage of treatment	94
4.2.5	Predictors of changes in HRQoL component score over time	97
4.3	Evaluation of newly diagnosed Tuberculosis Defaulters	107
4.3.1	Socio-Demographic Characteristics for TB defaulters.....	107
4.3.2	Risk factors associated with Defaulters.....	110
4.3.3	Reason for TB defaulting (Open end questionnaire).....	114
4.3.4	Health conditions of defaulters patients end of study period	116
4.4	Evaluation of Health Related Quality of Life for TB Defaulters	118

CHAPTER FIVE: DISCUSSION

5.1	Evaluation of treatment outcome for newly diagnoses Smear Positive Tuberculosis (PTB).....	122
5.1.1	Socio Demographical Features for newly diagnoses Smear Positive Tuberculosis (PTB).....	122
5.1.2	Clinical manifestation of newly diagnosed pulmonary Tuberculosis	126
5.1.3	Side effect of newly diagnosed pulmonary Tuberculosis.....	128

5.1.4	Treatment Outcome of Newly Diagnosed Smear-Positive PTB Patients.....	129
5.1.5	Predictors of Unsuccessful Treatment Outcome	132
5.1.6	Predictors for prolong sputum conversion at the end of Intensive Phase.....	133
5.1.7	Predictors of prolonging treatment duration (> 6 months)	134
5.2	Health Related Quality of Life of TB patients	136
5.2.1	Description of patients included for evaluation of HRQoL.....	137
5.2.2	Change of HRQoL at various stage of treatment.....	137
5.2.3	Predictors of changes in HRQoL component score over time	142
5.3	Risk factor associated with newly diagnosed TB treatment defaulters....	144
5.3.1	Reason for TB defaulting (open end questionnaire).....	152
5.4	Evaluating HRQoL of TB defaulters by Normal Based Score (NBS)	156
5.4.1	Evaluating of HRQoL of TB defaulters by PCS and MCS score	157

CHAPTER SIX: SUMMARY, CONCLUSIONS, LIMITATION AND

FUTURE WORK

6.1	Summary and conclusion	159
6.2	Limitation	161
6.3	Future work	161

REFERENCE	163
------------------------	------------

APPENDICES

LIST OF PUBLICATIONS

CONFERENCE PRESENTATION

LIST OF TABLES

		Page
Table 1.1	Epidemiology of TB 2009 in Yemen	5
Table 1.2	Recommended dose, contraindication cases and side effect of TB drugs	7
Table 1.3	Operational definitions	8
Table 2.1	Risk factors associated with unsuccessful treatment outcome	18
Table 2.2	Risk factors associated with TB defaulters	43
Table 3.1	Item Internal consistency of Arabic Version of HRQoL SF-36V2	62
Table 3.2	Internal consistency of SF-36V2 (Arabic translation)	63
Table 3.3	Correlation between all domains score of SF-36V2	64
Table 3.4	Sample size calculation for Health Related Quality of Life TB patients	65
Table 4.1	Socio-demographic characteristics of the study population	72
Table 4.2	Clinical characteristics of study population	75
Table 4.3	Diagnostic and Laboratory Tests of both cities of Yemen	76
Table 4.4	Change of Tuberculosis Symptoms during various stage of treatment	77
Table 4.5	Changes in Patient Body Weight during Tuberculosis Treatment (kg)	78
Table 4.6	Sputum Smear Result at Different Stages of Treatment	79
Table 4.7	Duration of treatment for PTB	79
Table 4.8	Side Effects Associated with Anti-tuberculosis Drugs	80
Table 4.9	Treatment outcomes for all newly diagnosed PTB patients as per WHO criteria at the end of 6 th month	80
Table 4.10	Independent risk factors for unsuccessful treatment outcomes	81
Table 4.11	Univariate analysis of independent risk factors associated with prolong sputum conversion	83

Table 4.12	Multivariate analyses of independent risk factors associated with prolong sputum conversion	86
Table 4.13	Independent risk factors for prolonged treatment duration	87
Table 4.14	Socio-demographical characteristics of TB patients at the beginning of treatment	91
Table 4.15	Clinical characteristics for TB patient enrolled at the beginning of study	93
Table 4.16	Health-Related Quality of Life SF 36V2 scores using Norm-Based Scoring (NBS) at various stage of treatment	95
Table 4.17	Health-Related Quality of Life SF 36V2 scores using normative data (0-100 scores) at various stage of treatment	96
Table 4.18	Changes in mean Physical Component Score (PCS) and Mental Component Summary (MCS) during various stages of treatment	96
Table 4.19	General Linear Model Repeated measure ANOVA test for physical and mental component score within the subject effect	97
Table 4.20	General Linear Model Repeated measure ANOVA test for the physical and mental score in between the subject effect.	103
Table 4.21	Total number of newly diagnosed TB defaulter cases in Taiz and Al Hudaydah registered between April 2014 and March 2015	107
Table 4.22	Characteristics of TB defaulters registered between April 2013 and March 2014	108
Table 4.23	Predictors of risk factors associated with defaulters: Using Univariate logistic regression analysis (ULRA)	111
Table 4.24	Predictors of risk factors associated with defaulters determined using multi logistic regression analysis MLRA [‡]	114
Table 4.25	Reasons for defaulting from treatment	116
Table 4.26	Socio-Demographical Characteristics of TB defaulter	118
Table 4.27	Health-Related Quality of Life SF 36V2 scores using normative data (0-100 scores) for tuberculosis defaulters	120
Table 4.28	Health-Related Quality of Life SF 36V2 scores using Norm-Based Scoring (NBS) for tuberculosis defaulters	120
Table 4.29	Physical and Mental Component Summary (PCS and MCS) for tuberculosis defaulters	121

LIST OF FIGURES

	Page	
Figure 3.1	Conceptual Frame Work	55
Figure 4.1	Number of PTB patients enrolled in the study	71
Figure 4.2	Number of TB patients enrolled in the study	90
Figure 4.3	Taiz and Al Hudaydah Governance: Difference in estimated marginal mean of Physical Component Score (PCS)	99
Figure 4.4	Smoking Status: Difference in estimated marginal means of Physical Component Score (PCS)	100
Figure 4.5	Chewing Khat Status: Difference in estimated marginal means of Physical Component Score (PCS)	101
Figure 4.6	TB Symptoms at the beginning of treatment: Difference in estimated marginal means of Physical Component Score Physical Component Score (PCS)	102
Figure 4.7	Taiz and Al Hudaydah Governance: Difference in estimated marginal mean of Mental Component Score Mental Component Score (MCS)	104
Figure 4.8	Chewing Khat Status: Difference in estimated marginal means of Mental Component Score Mental Component Score (MCS)	105
Figure 4.9	Stigma and Non-Stigma Status: Difference in estimated marginal means of Mental Component Score Mental Component Score (MCS)	105
Figure 4.10	Total Treatment Duration: Difference in estimated marginal means of Mental Component Score Mental Component Score (MCS)	106
Figure 4.11	Tracing defaulters end of 2015	117

LIST OF ABBREVIATION

AFB	Acid Fast Bacilli
ANOVA	Analysis of Variance
AOR	Adjusted Odds Ratio
ATT	Antituberculosis Treatment
BCG	Bacille Calmette-Guerin
BMI	Body Mass Index
BP	Bodily Pain
CBC	Complete Blood Count
CDR	Case Detection Rate
CI	Confidence Interval
CP	Continuation Phase
DM	Diabetes Mellitus
DOT	Direct Observed Therapy
DST	Drug Sensitivity Tests
E	Ethambutol
EPTB	Extrapulmonary Tuberculosis
FBG	Fasting Blood Glucose
GH	General Health
H	Isoniazid
HRQoL	Health-Related Quality Of Life
HIV	Human Immunodeficiency Virus
HT	Health Transition

IUALTLD	International Union Against Tuberculosis And Lung Disease
IDP	Internally Displaced People
IFNg	Interferon-g
IP	Intensive Phase
KFT	Kidney Function Test
LAM	Lipoarabinomannan
LFT	Liver Function Test
LTB	<i>Latent Tuberculosis</i>
MCS	Mental Component Score
MDR-TB	Multi Drug Resistance Tuberculosis
MH	Mental Health
MID	Minimal Important Difference
MLRA	Multivariate Logistic Regression Analysis
Mtb	Mycobacterium Tuberculosis
NBS	Norm-Based Score
NTCP	National Tuberculosis Control Programs
NTP	National Tuberculosis Programs
OR	Odd Ratio
PCR	Polymerase chain reaction
PCS	Physical Component Score
PF	Physical Functioning
PPM	Public-Private Mix
PPT	Primary Public Health
PTB	Pulmonary Tuberculosis

PASW	Predictive Analysis Software
R	Rifampicin
RE	Role Emotional
RP	Role Physical
SD	Standard Deviation
SE	Standard Error
SF	Social Functioning
SF-36V2	Short-Form 36 Version 2
SLRA	Simple Logistic Regression Analysis
TB	Tuberculosis
ULRA	Univariate Logistic Regression Analysis
UNICEF	United Nations International Children's Emergency Fund
VT	Vitality
WHO	World Health Organization
Z	Pyrazinamide

**PENILAIAN HASIL RAWATAN TUBERKULOSIS, FAKTOR YANG
MEMPENGARUHI PESAKIT YANG TIDAK MENGIKUTI RAWATAN
SUSULAN (DEFAULTERS) DAN KUALITI KEHIDUPAN BERKAITAN
KESIHATAN DI YAMAN**

ABSTRAK

Meskipun rawatan tuberkulosis (TB) didapati berkesan, TB masih merupakan cabaran penyakit berjangkit utama di seluruh dunia akibat peningkatan mortaliti dan morbiditi. Tambahan pula di Yemen, TB berada di tangga keempat penyebab kematian. Kajian terkini direka bagi menilai TB tpalitan smear positif kalangan pesakit smear *positive pulmonary tuberculosis* (PTB) termasuklah hasil rawatan, kualiti kehidupan berkaitan kesihatan (HRQoL) dan faktor risiko ke atas pesakit TB yang tidak mengikuti rawatan susulan. Satu kajian pengamatan prospektif direka. Kajian dijalankan ke atas dua bandar dengan penyebaran tinggi TB iaitu Taiz dan Al Hudaydah di Yemen antara April 2014 dan Januari 2016 yang memperoleh nilai kejayaan yang rendah iaitu 83%. Kajian mendapati bahawa lelaki (nisbah ods terlaras (AOR: 0.248, 95% CI: 0.239–0.874), buta huruf (AOR: 2.294, 95% CI: 1.272–4.137), dan komorbiditi (AOR: 1.995, 95% CI: 1.108–3.590) merupakan faktor risiko berkaitan hasil yang tidak berjaya. Tambahan pula, mereka yang tinggal di kawasan pendalaman (AOR: 1.97, 95% CI: 1.280-2.919), mempunyai BMI \geq 18.5 kg/m² (AOR: 2.85, 95% CI: 2.194-3.652) adalah faktor risiko berkaitan fasa intensif semasa tempoh penukaran sputum. Penduduk yang tinggal di kawasan pendalaman (nisbah ods terlaras) (AOR: 2.358, 95% CI: 0.658–4.00), mengunyah daun khat (AOR: 2.615, 95% CI: 1.201–5.691), batuk selama >3 minggu pada awal rawatan (AOR:

2.672, 95% CI: 1.053–6.782), dan luka dua hala semasa radiografi (AOR: 2.134, 95% CI: 1.147–3.972) merupakan faktor risiko berkaitan tempoh rawatan lanjutan. Kualiti kehidupan berkaitan kesihatan (HRQoL) dalam kalangan pesakit TB dan semua pesakit baru yang mendaftar sebagai pesakit TB diminta melengkapkan sendiri soal selidik SF-36 pada awal rawatan, akhir fasa intensif (I.P) dan akhir fasa lanjutan (C.P). Pada akhir rawatan, skor komponen fizikal tinggi (PCS) (48.9) diperoleh sebagai perbandingan dengan skor komponen mental (MCS) (44.3) yang menunjukkan tekanan mental tinggi disebabkan aspek emosi. Oleh yang demikian, peramal perbezaan dalam min MCS yang tinggal di bandar Al Hudaydah, mengunyah daun khat, stigmatisasi dan tempoh rawatan lebih daripada 6 bulan. Kajian mendapati bahawa nilai pesakit yang tidak mengikuti rawatan susulan adalah 12.6% (52 pesakit). Pesakit berasal daripada kawasan pendalaman (nisbah ODS terlaras (AOR: 3.343, 95% CI: 1.362–8.208), buta huruf (nisbah ods terlaras (AOR: 13.362, 95% CI: 4.231–42.197), mempunyai tabiat merokok, (nisbah ods terlaras (AOR: 12.047, 95% CI: 4.307–33.696), stigmatisasi (nisbah ods terlaras (AOR: 3.365, 95% CI: 1.561–9.573), rendah BMI (nisbah ods terlaras (AOR: 4.016, 95% CI: 1.620–9.954), kos perjalanan tinggi (nisbah ods terlaras (AOR: 14.190, 95% CI: 4.560–44.156), dan kesan sampingan (nisbah ods terlaras (AOR: 2.780, 95% CI: 1.092–7.077) adalah seperti faktor risiko berkaitan dengan pesakit yang tidak mengikuti rawatan susulan. Tambahan lagi, dalam kalangan 52 pesakit, 32 pesakit diikuti untuk mengenal pasti sebab mereka meninggalkan rawatan susulan. Kos perjalanan tinggi (48.1%), kesan sampingan (32.7 %) dan stigmatisasi (30.8 %) merupakan sebab utama mereka tidak mengikuti rawatan dan diikuti dengan penambahbaikan dari aspek kesihatan (19.2 %), kos perubatan (15.4 %), tidak hadir bekerja semasa rawatan (13.5 %), jarak yang jauh untuk ke pusat TB (11.5 %), dan

ketidakpuasan hati dengan perkhidmatan kesihatan (11.5 %). Oleh itu, mengambil kira faktor risiko pesakit yang tidak mengikuti rawatan susulan dan sebab utama mereka meninggalkan rawatan susulan boleh membantu mengurangkan kadar pesakit meninggalkan rawatan susulan dan meningkatkan hasil rawatan. HRQoL bagi pesakit yang tidak menjalani rawatan susulan dilaporkan mempunyai skor MCS yang rendah iaitu 28.9 yang menandakan keaduan yang kurang memuaskan dan tinggi risiko untuk depresi. Oleh itu, skor MCS yang rendah boleh diguna pakai oleh pekerja pasukan TB untuk menjangkan pesakit yang mungkin tidak menjalani rawatan susulan di masa hadapan.

**EVALUATION OF TREATMENT OUTCOMES, FACTORS AFFECTING
TREATMENT DEFAULTING AND HEALTH RELATED QUALITY OF
LIFE OF NEWLY DIAGNOSED TUBERCULOSIS PATIENTS IN YEMEN**

ABSTRACT

Despite the effectiveness of tuberculosis (TB) treatment, TB remains the most challenging infectious disease worldwide due to augmented trend of mortality and morbidity. In addition, in Yemen, TB consider as the 4th causes of death. Present study is designed to evaluates TB among smear positive pulmonary tuberculosis (PTB) including treatment outcome, health related quality of life (HRQoL) and risk factors associated with TB defaulters. A prospective cohort study was designed. The study conducted in two high TB prevalent cities (Taiz and Al Hudaydah) of Yemen, between April 2014 and January 2016. Moreover, this study reported a lower success rate of 83% compare to WHO target of 85%. Likewise, the study report male gender (adjusted odds ratio [AOR]: 0.248, 95% CI: 0.239–0.874), illiterate (AOR: 2.294, 95% CI: 1.272–4.137), and comorbidity (AOR: 1.995, 95% CI: 1.108–3.590) were the risk factors associated with unsuccessful outcome. Moreover, living in rural areas (AOR: 1.97, 95% CI: 1.280-2.919),, having BMI \geq 18.5 kg/m² (AOR: 2.85, 95% CI: 2.194-3.652) were the risk factors related to prolonging sputum conversion during intensive phase. Moreover living in a rural area (adjusted odds ratio [AOR]: 2.358, 95% CI: 0.658–4.00), smoking (AOR: 0.054, 95% CI: 0.987–4.112), chewing khat (AOR: 2.615, 95% CI: 1.201–5.691), having a cough for >3 weeks at the start of treatment (AOR: 2.672, 95% CI: 1.053–6.782), and bilateral lesions during radiography (AOR: 2.134, 95% CI: 1.147–3.972) were a risk factor related to

prolonging treatment duration (> 6 months). Health related quality of life (HRQoL) among TB patients, all newly registered TB patients ask for the self-complete SF-36V2 survey at the beginning of treatment, end of the intensive phase (I.P) and end of the continuous phase (C.P). At the end of the treatment, a higher physical component score (PCS) (48.9) obtained as compared to mental component score (MCS) (44.3) showing higher mental distress due to emotional aspects. Likewise, the predictors of difference in mean MCS were living in Al Hudaydah city, chewing khat, stigmatization and treatment duration more than 6 months. This study reported defaulter rate of 12.6% (52 defaulters). The patients coming from rural areas (AOR: 3.343, 95% CI: 1.362–8.208), illiteracy (AOR: 13.362, 95% CI: 4.231–42.197),, having a smoking habit (AOR: 12.047, 95% CI: 4.307–33.696),, stigmatization (AOR: 3.365, 95% CI: 1.561–9.573), low BMI (AOR: 4.016, 95% CI: 1.620–9.954),, high travel cost (AOR: 14.190, 95% CI: 4.560–44.156), and side effects (AOR: 2.780, 95% CI: 1.092–7.077) reported as a risk factor associated with defaulters. Moreover, among 52 defaulters, 32 were followed to identify the reasons of default. High travel cost (48.1 %), side effect (32.7 %), and stigmatization (30.8 %) were the main reasons for defaulting, followed by improved health condition (19.2 %), medication cost (15.4 %) , Missed work during treatment period (13.5 %), far distance to TB centres (11.5 %) , and dissatisfaction with health services (11.5 %). Considering defaulting risk factors and the main reasons for defaulting may help to reduce future defaulter rates and improve the treatment outcomes. HRQoL of TB defaulters reported a low MCS score of 28.9 to indicate the poor condition and a higher risk of depression Thus; low MCS can assist TB workers to predict future TB treatment defaulters.

CHAPTR ONE

INTRODUCTION

1.1 General Introduction

This chapter comprises a brief overview of treatment outcomes and health-related quality of life (HRQoL) of tuberculosis (TB) patients in addition to causes of patients' defaulting from treatment. TB as a global phenomenon is also explained. In addition, the epidemiology, management and treatment of TB in Yemen and follow up drug treatment are discussed. This chapter also presents the problem statement, rationale and importance of the study, research contribution, aim and objectives.

1.2 Tuberculosis as a global phenomenon

TB is an infectious disease caused by an organism called *Mycobacterium tuberculosis* (*tubercle bacilli*). Despite an increase success rate against TB worldwide, it remains a globally serious problem. World Health Organization (WHO) estimates that over 30% of the world population is infected with either dormant or active tuberculosis (TB) (WHO, 2014). TB is a deadly disease that results in an estimated 1.5 million deaths annually (Sharpe *et al.*, 2016). In addition, any organ in the human body can be affected by TB, but the most infected organ is the lung. The case of lung infected with TB is referred to as pulmonary tuberculosis (PTB), while extrapulmonary tuberculosis (EPTB) is for cases where other organs are affected. PTB is spread very fast by small droplets (containing bacillus) from a cough or sneeze of an infected patient. However, TB only advances into a disease in low proportions of infected persons (WHO, 2011).

1.3 Epidemiology of Tuberculosis

1.3.1 Global epidemiology of Tuberculosis

In 2015, approximately 10 million people are infected with TB (of which 60% are considered new), in addition to 1.5 million deaths annually (Muliaditan *et al.*, 2016); (Hochberg *et al.*, 2016); (WHO, 2015). Furthermore, approximately 94% of overall TB cases and over 95% of death cases occurred in low-income nations (Bøhler, Mustafaa and Mørkve, 2005). Apart from the 60% reported cases, others are considered undiagnosed or not reported to national TB control programs (NTP). Similarly, studies reported that approximately 70% of TB cases infected with sputum smear-positive pulmonary TB died within 10 years (WHO, 2015). An estimated 13% of newly TB cases were diagnosed as HIV-infected, which is considered high, with the majority of cases reported in developing countries. Furthermore, TB was reported to have declined in industrial countries, but remains prevalent in poor and developing countries (Norheim *et al.*, 2015). India is considered the country with the highest number of TB cases followed by China with a global rate of 24% and 11%, respectively (WHO, 2014). The number of TB cases declined globally to an average of 1.5% per year between 2000 and 2013 (WHO, 2014). In 2014, WHO reported half million more cases of TB compared to 2013 (WHO, 2014). An estimated 95% of total world TB cases and 98% of the mortality due to TB are reported in developing countries, with 75% among the productive age group (15-50 years old) (WHO, 2010). The most recent WHO reports show that approximately 56% of global TB cases are in south-east Asian and western Pacific regions (WHO, 2016). African region comprises 25% of world TB cases and highest mortality rate.

Tuberculosis (TB) ranks globally as the second foremost cause of mortality among infectious diseases after HIV (WHO, 2013b). TB is directly associated with overpopulation and poverty. It also co-related to other diseases and addictive behaviours such as smoking, HIV and diabetes (Perrin, 2015). WHO estimates that the number of TB cases in 2020 will reach 1 billion. Among them, approximately 35 million will succumb to the disease if TB control is not strengthened globally (WHO, 2005). Legesse et al., (2010) reported that the key factors associated with increased risk of TB is poverty and lack of awareness. Several factors play a significant role in controlling TB such as adequate knowledge and awareness, and appropriate treatment.

1.3.2 Epidemiology of Tuberculosis in Yemen

Yemen is an Arabian country with 26 million population (WHO, 2015). Yemen is situated in WHO's Eastern Mediterranean Region (EMR) and rank as an intermediate TB-burdened country (WHO, 2013b). The countries in the EMR are categorized into three distinct epidemiological categories. The first group entails countries with an estimated incidence of 50 or more tuberculosis patients (all forms) per 100 000 population, consisting of Afghanistan, Djibouti, Iraq, Morocco, Somalia, Sudan, Yemen and Pakistan, which are among the 22 high burden countries in the world. The second category involves countries with an estimated incidence of 25–49 tuberculosis patients (all forms) per 100 000 population, consisting of Bahrain, Egypt, Islamic Republic of Iran, Kuwait, Saudi Arabia and Syrian Arab Republic. The last category entails countries with an estimated incidence of 0–24 tuberculosis patients (all forms) per 100 000 population consisting of Jordan, Lebanon, Libyan Arab Jamahiriya, Oman, Tunisia, United Arab Emirates and Palestine (WHO, 2015).

WHO had carried out a multi-country study on diagnosis and treatment delay in tuberculosis in seven high and middle burden countries of the EMR (WHO, 2006). In addition, out of the 22 countries of the EMR, 9 constitute 94% of the tuberculosis cases in the region: Pakistan (43% of tuberculosis cases), Afghanistan (12%), Sudan (8%), Iraq (7%), Islamic Republic of Iran (6%), Somalia (6%), Morocco (5%), Egypt (4%) and Yemen (3%). The low detection rate of TB in the EMR is mainly attributable to the low detection rates of 3% and 9% in Pakistan and Afghanistan in 2000, respectively (WHO, 2013b).

Tuberculosis in Yemen is considered a major public health problem, and ranks fourth on the priority list of the public health issue (NTCP, 2010a). The cities of Taiz and Al Hudaydah in Yemen have the highest TB prevalence (NTCP, 2010a). The main centres for the research and diagnosis of most TB patients via sputum examination and isolation culture are in these cities (NTCP, 2010a). Taiz city is located in the south of Sana'a (about 256 km away). Taiz city has the highest incidence of TB in Yemen, with a rate of 12.16%. Al-Hodeida city represents about 11% of the total population of Yemen and ranks second in the list of TB incidence rate (*Yemen National Information Center*, 2014) (NTCP, 2010a).

In Yemen, TB patients received standard treatment according to national tuberculosis control program (NTCP). The tuberculosis control program (NTCP) entails two months of intensive treatment involving the prescribed ingestion of ethambutol (E), pyrazinamide (Z), rifampicin (R) and isoniazid (H), followed by at least 4 months of isoniazid (H and Rifampicin (R) for both pulmonary (PTB) and extrapulmonary (EPTB) tuberculosis. In few cases of EPTB, the program duration

extends to 8 months, depending on the patient’s condition and decision of the physician involved (NTCP, 2010a).

In 2009, in Yemen scenario only 3576 new smear-positive PTB out of 8248 TB cases were reported at the rate of 15 per 100, 000 population, which indicates detection rate of only 60%. The case detection rate was 60%, and the estimated prevalent case was only 78 per 100,000 populations with 18720 estimated common cases. In 2009, there was approximately 1900 deaths due to TB, which indicates a mortality rate of 7.9 per 100,000. 73% of PTB cases fall in the productive age gap (15-49 years old), as evident in Table 1.1 (NTCP, 2010a). In 2016, WHO reported a notification rate of 3321 smear positives, 2808 smear negatives and 3486 EPTB patients (WHO, 2016). The detected TB cases among children was very low with fewer than 2 per 100,000, which suggests that TB remains under-detected. This may be as a result of several reasons such as difficulties in producing sputum and the diagnosis method used by primary health (NTCP, 2010a).

Table 1.1 Epidemiology of TB 2009 in Yemen

Descriptions	
Total population	26 million
Annual Incidence of smear positive PTB	6,000 (25/100,000 population)
Total incidence of all form of TB	14,400 (60/100,000 population)
Prevalence	18,720 (78/100,000 population)
Mortality	2000-2500 person (9.9/100,00 Population)

1.4 Management and treatment of tuberculosis in Yemen

In order to manage and increase the success rate of TB cure in Yemen, the National Tuberculosis Control Program (NTCP) adopted the directly observed

therapy (DOT) strategy, which involves the use of primary health care units to delivering health services to tuberculosis patients according to WHO recommendations. This comprehensive strategy was developed to prevent the re-emergence of tuberculosis in Yemen and to effectively treat tuberculosis patients. In 2015, DOT strategy increased the success rate of TB cure in Yemen to 84%, but still under the global success rate (90%) (WHO, 2016).

To confirm suspected pulmonary tuberculosis, a fast acid tuberculosis microscopic examination is performed. The direct smear examination is the main diagnostic method for pulmonary TB in Yemen, which is the most reliable method in developing countries due to its reliability and cost effectiveness. The subjects can also be subjected to direct smear examination that involves the testing of 3 specimens of the suspected patient's sputum. In addition, all TB patients are subjected to chest X-ray for validation. However, the sputum culture is not performed for all TB patients. Generally, the diagnosis of extra-pulmonary TB (EPTB) can only be performed by a medical officer or specialist, depending on the organ involved. The symptoms of TB include swelling with occasional pus drainage when lymph nodes are affected; pain and swelling when joints are involved; headache, fever, stiffness of the neck and mental disarray in the case of TB meningitis; loss of function in lower limbs when there is spinal involvement, and infertility when the genitalia is affected (WHO, 2008).

Based on WHO regulations, Yemen NTCP recommends the use of 4 main drugs for the treatment of TB, i.e. rifampicin (R), ethambutol (E), isoniazid (H) and pyrazinamide (Z). In 2005, NTCP initiated the use of HRE drugs for an intensive

phase of 2 months and HRZE for a continuous phase of 4 months (NTCP, 2010) (Table 1.2).

Table 1.2 Recommended dose, contraindication cases and side effect of TB drugs

Drug name	Dose (mg/kg)	Maximum dose (mg)	Contraindicated cases	Side effect
Isoniazid	5	300	Hepatic dysfunction -Known hypersensitivity to rifamycins	Hepatitis→ stop drug and hospitalise Neurotoxicity – >give pyridoxine Pellagra-like syndrome Various skin rashes
Rifampicin	10	600	-Hepatic dysfunction -Known hypersensitivity to rifamycins	Hepatitis → stop drug and hospitalize Respiratory syndrome associated with collapse and shock → immediate hospitalization Purpura, acute haemolytic anemia, shock, renal failure – > stop drug immediately, never given again, mandatory hospitalization flushing and/or pruritis with or without rash ≥ often self-limiting, symptomatic treatment flu syndrome ≥ symptomatic treatment abdominal syndrome ≥ symptomatic treatment and drug
Pyrazinamide	20-30 adult 30-40 child	2000	-Hepatic dysfunction -Known hypersensitivity to rifamycins	Hepatitis; joint pain; gout; hypersensitivity reactions (rare)

Drug name	Dose (mg/kg)	Maximum dose (mg)	Contraindicated cases	Side effect
Ethambutol	25: adult 15: child	1000	Pre-existing optic neuritis from any cause -Renal impairment- Inability (young children <6, unconscious patients)to report visual disturbances- Known hypersensitivity	Visual impairment ≥ stop drug

(NTCP, 2010a)

1.5 Operational Definitions adapted from NTCP

The following operational definitions were adopted as per MOH, National Tuberculosis Control Program guideline 2009, Table 1.3

Table 1.3 Operational definitions

Term	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment which was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Defaulter	TB patients consider as default if treatment interrupted for 2 or more consecutive months.
Cohort	A cohort is a group of patients diagnosed and registered for treatment during a specific period (usually one-quarter of a year).
New TB case	A patient who has never had treatment for TB or who has taken anti-TB drugs for less than 1 month
Pulmonary Positive (PTB)	Includes patients with at least two sputum specimens that are smear positive for acid-fast bacilli (AFB) as determined by microscopy analysis; patients with at least one sputum specimen that is smear positive for acid-fast bacilli as assessed through

Term	Definition
	microscopy analysis, with radiographic abnormalities consistent with PTB, and whose physician decided to treat with full course of chemotherapy; or patients with at least one sputum specimen that is smear positive for AFB as evaluated by microscopy and at least one sputum specimen that is culture positive for <i>Mycobacterium tuberculosis</i>
Extra Pulmonary Tuberculosis (EPTB)	comprises patients with diseases affecting sites other than the lung parenchyma, including isolated TB pleural effusion or isolated TB intrathoracic lymphadenopathy
Pulmonary Negative	patients whose initial sputum smears are negative (at least three specimens tested), who have sputum sent for culture initially, and whose subsequent sputum culture result is positive; or patients without bacteriological confirmation (also culture negative), with radiographic abnormalities consistent with active PTB, without response to a course of broad-spectrum antibiotics, and whose case is clinically judged to merit treatment by a full course anti-TB therapy
Stigma	Stigma is defined as an undesirable or discrediting attribute that an individual possesses, thus reducing the status of that individual in the eyes of the society.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who died of any cause during course of treatment
Transfer out	A patient who has been transferred to another TB register to continue treatment
Treatment success	The sum of cured and treatment completed. Moreover, Based upon this classification treatment cure and completed is consider to be treatment success while other classifications consider being unsuccessful treatment (WHO, 2013a)
Bacteriology	Bacteriology refers to the smear status of pulmonary cases and the identification of <i>M. tuberculosis</i> for any case by culture or newer methods. (WHO, 2010a)
Bilateral lungs involvement	It is a pathological state where a lesion appears in both lungs
High-grade sputum	Grading of sputum is classified based upon number of AFT identified during sputum smear microscopy test. Four types are identified (i.e., scanty positive, one positive, two positive and

Term	Definition
	three + positive). To shorten and simplify grading types. Scantly and one positive recognised as low grade. Moreover, two and three positive considered as high grade (Abdurrahman <i>et al.</i> , 2017).
Khat	Is a shrub plant that grows in East Africa and Yemen. It is a natural psych stimulant that has pharmacological effects similar to that of amphetamine. (Jaber, Khan, Sulaiman, Ahmad, Anaam, <i>et al.</i> , 2016) (Kassim, Croucher and Al'Absi, 2013)
Literate	TB patient can read in the Arabic language.
New case	Patients who had never received treatment for TB or who had received anti-TB drugs for <1 month.
Prolong duration	A course of treatment that was >6 months.
Treatment Failure	A patient who was initially sputum smear-negative and culture-positive and remained culture-positive at the end of treatment
Treatment after default	TB patients were considered return after default, if patient return to treatment following interruption of treatment for 2 or more consecutive months and bacteriologically positive.
prolonged sputum conversion	Patients who require longer duration of treatment to obtain a bactriological confirmed smear negative

1.6 Problem statement

1. In Yemen tuberculosis consider as 4th in disease-related causes of death. According to the recent WHO global report and the latest National Tuberculosis Control Program (NTCP) released in 2010, Yemen is close to WHO target of treatment success rate (90%). Despite this success rate, the prospective evaluation and risk factors associated with unsuccessful outcome during treatment has not been well recorded and assessed.
2. Several factors associated with treatment such as poverty, monthly income, malnutrition and urbanization, in addition to common habits such as chewing khat and smoking all continue to aggravate the problem of TB in Yemen.

However, these factors have not been evaluated. Assessing these factors can play a major role in improving treatment outcome.

3. Currently, a high human and financial cost is expended on the management and diagnosis of tuberculosis, whereas relatively less attention is given to the quality of life of TB patients, during and after treatment. The last WHO edition of TB management did not place emphasis on HRQoL (WHO, 2016). Meanwhile, several of the recent TB studies show a great relationship between HRQoL of TB patient and treatment outcome (Kakhki and Masjedi, 2015; Atif, Sulaiman, *et al.*, 2014; Kastien-Hilka *et al.*, 2016; Chamla, 2004; (Rajeswari *et al.*, 2005). Therefore, evaluating HRQoL can play an important role in improving quality of life after TB infection, consequently enhancing the treatment outcome particularly in countries with low fiscal budget.
4. The determination of risk factors associated with lengthy treatment course is considered crucial because prolonged duration may play a role in Multi-Drug Resistance (MDR) (Espinal *et al.*, 2001).
5. Recent studies have reported increased drug resistance cases in Yemen. Yemen remains among the 28 countries that have non-capacity or do not partner with laboratories for 2nd line drug susceptibility tests (WHO, 2015). In addition, defaulters are considered the main factor that leads to drug resistance. Earlier studies have not taken these factors into consideration. Therefore, this study hypothesized that determining the associated risk factors and reasons for defaulting can play a significant role in optimizing future drug resistance and increase success rates.

6. Determining the HRQol of defaulters as well as identifying the risk factor associated with defaulters HRQoL may play an significant role in optimizing future defaulters if considered.

1.7 Rationale and Importance of overall study

1. The analysis of clinical outcome is a marker to assess the long-term effectiveness of TB progress.
2. The prospective evaluation of treatment outcome of new tuberculosis (TB) patients acts as primary sources of measurement of national tuberculosis control program (NTCP) work. It allows the health workers to identify their main problems and to take action to improve their performance.
3. WHO highly recommends the evaluation of the treatment outcome of TB patients annually, which should be based on cities, district and national level. Also, the assessment of the treatment can give NTP workers the opportunity to improve future performance to significantly enhance their success rate.
4. As a developing country, TB disease remains a significant problem in Yemen. TB is ranked 4th on the priority list of diseases that affect public health. However, the medical services at the tuberculosis centres (consultation, laboratory investigation, X-ray and another service) are not made available for free, with the exception of TB medication which is supported by government and international organisations (World Health Organization, 2012). Approximately 20% of Yemen population live under \$1.25/day, hence they are considered one of the 20 poorest countries in the world (Peck and Pressman, 2013). Various kinds of medical test can be provided to the patient such as HIV glucose test to find the co-morbid

conditions associated with TB and study the effectiveness of these factors on TB patients.

5. Determination of risk factor associated with prolonging duration may play a major role in optimizing future MDR cases, especially in low-income countries like Yemen.
6. There is lack of published studies on treatment outcome as well as HRQoL of TB infected persons living in Yemen.
7. Global reports show higher success rates in most countries, but relatively less attention is given to the HRQoL of TB patients in poor countries such as Yemen. In addition, various studies have proved there is a relation between quality of life of a patient and treatment outcome.
8. This study contributes to assessing changes in HRQoL during treatment to quantify the impact of TB on the quality of life of persons. This research also provides vital information that cannot be obtained from conventional clinical and functional measurements.
9. Default in TB treatment can bring about major problems such as drug resistance and relapse. Therefore, this study will help identify and evaluate the risk factors associated with TB treatment defaulters in order to decrease the chances of drug resistance as well as increase the success rate and adherence to treatment.

1.8 Research contribution

1. Despite the high success rate of TB treatment in Yemen, the number of TB cases particularly in Taiz and Al Hudaydah, cities has increased. Therefore, evaluation of the risk factors associated with unsuccessful treatment outcome in Taiz and Al Hudaydah can help NTCP to focus more on susceptible patients, which may help in increasing the success rate.
2. This study describes the socio-demographical and clinical aspects of TB disease for 12 months and identifies the limitations observed in the diagnosis and follow up treatment period.
3. This study analyzes the HRQoL of TB patients as well as the impact of treatment on HRQoL of TB patients. Based on the analysis, the following recommendations were made:
 - a. Extensive care and support to TB patients in the first two months of treatment to improve HRQoL, particularly for MCS, so as to prevent patients from defaulting on treatment
 - b. Factors such as chewing khat habit, stigmatisation, and duration of treatment over 6 months should be considered during TB treatment to prevent poor outcome due to the negative role of MCS score.
 - c. Thirdly, health workers should focus on increasing the MCS HRQoL in Al Hudaydah because of its relatively low educational level.
4. Taiz and Al Hudaydah have the highest numbers of treatment defaulters in Yemen. Therefore, identifying the risk factors associated with defaulters may enable NTCP managers to address those factors during TB treatment, which can play a role in reducing the numbers of defaulters.

5. Evaluating the HRQoL of TB defaulters is essential in identifying future risk factors.

1.9 Aim and objectives

1.9.1 General Objective

To evaluate the treatment outcome, Health related quality of life of newly diagnosed tuberculosis patients and factors affecting treatment defaulting in Yemen

1.9.2 Specific Objective

1. To evaluate the patients socio demographic, clinical characteristics and risk factor associated with unsuccessful treatment outcome of newly diagnosed pulmonary tuberculosis patients (PTB).
2. To identify the risk factors associated with prolong sputum conversion at the end of intensive phase, and the prolong treatment duration (a total of 6 month) of newly diagnosed PTB patients
3. To evaluate the risk factors associated with treatment defaulting among newly diagnosed TB patients.
4. To evaluate the Health-Related Quality of Life (HRQoL) of newly diagnosed Tuberculosis patients and its associated risk factors.
5. To assess the Health-Related Quality of Life (HRQoL) among TB defaulters

CHAPTER TWO

LITERATURE REVIEW

2.1 Literature Review

This chapter consists mainly of 6 parts. The first part critically reviews the various studies associated with the evaluation of PTB treatment outcome. The second part provides an overview and detailed synopsis of several studies associated with delay sputum conversions. The third part explain the Prolonged Treatment Duration (PTD) studies. The fourth part elucidates the evaluation of HRQoL of TB patients. The fifth part explains various studies and factors associated with TB defaulters, and the sixth part discusses the HRQoL of TB defaulters.

2.2 Evaluation of treatment outcome of newly diagnosed pulmonary tuberculosis (PTB) patients

The evaluation of TB treatment outcome is valuable, because it monitors the treatment progress of TB patients and aids the identification of the risk factors associated with treatment success or failure (Mattos *et al.*, 2016). In addition, it can be used to assess the overall performance of the tuberculosis control program at the local and national levels, which can be useful to predict possible limitations in the treatment program and provide new strategies and recommendations for improving treatment outcomes (Fernandez, 2014) (WHO, 2010a). The effectiveness of the national tuberculosis program is reflected by the proportion of success rate of TB patient (Antoine and Che, 2013) (Antoine *et al.*, 2007). Therefore, this study aims to predict the risk factors associated with treatment outcome.

WHO and several studies recommended the early evaluation of TB patients to ensure higher treatment and success rate, particularly in developing countries (WHO, 2010a); (Vasankari *et al.*, 2007). Nonetheless, most countries have attained the success rate 85% posited by WHO, but the risk factors associated with unsuccessful treatment outcomes remain understudied. The review of related literature shows that no study has fully evaluated and identified the treatment outcome and risk factors associated with TB in Yemen. Only a few studies have identified the risk factors associated with TB relapse and TB compliance cases in Yemen (Anaam *et al.*, 2013); (Anaam *et al.*, 2012). This study focuses only on smear-positive pulmonary tuberculosis (PTB) based upon WHO recommendations for analysis of smear-positive, smear negative and extrapulmonary tuberculosis as a separate program (WHO, 2010a).

Furthermore, WHO reports show that Yemen remains below the revised projected target success rate of 90%. (WHO, 2016). Also, TB in Yemen is ranked the fourth cause of death and considered a major priority of Yemen ministry of health program (NTCP, 2010a). Therefore, prospective evaluation of treatment outcomes in Yemen is essential to preventing any future health catastrophe due to TB infection. The few studies conducted to evaluate the treatment outcome of TB patients are listed below (Table 2.1).

Table 2.1 Risk factors associated with unsuccessful treatment outcome

Study	Study Design & Place	Sample Size	Duration & Treatment Success Rate (%)	Risk Factor for Unsuccessful Outcome
(El-Shabrawy and El-Shafei, 2016)	Retrospective study/Sharkia/Egypt	480 TB	2013-2014/ 78	Sputum positive on second month, lungs cavities, retreatment TB
(SALEH, 2016)	Prospective study / Kashmir/India	72 PTB ^{'''}	June 2013-May 2015 / 88	Comorbidity such as HIV*, DM [‡]
(Vasankari <i>et al.</i> , 2007)	Retrospective study / Finland	629 PTB ^{'''}	1995-1996 / 70	Male, sex, old age, and previous TB ^{'''} treatment
(Vasankari <i>et al.</i> , 2010)	Cohort study / Finland	276 EPTB [°]	1995-1996 / 79	Male, older age.
(Ditah <i>et al.</i> , 2008)	Prospective study / Europe	2676 TB ^{''}	2001-2002	Male, old age, PTB ^{'''} and MDR [€] .
(Antoine <i>et al.</i> , 2007)	Retrospective study / England	6652 TB ^{''}	2001-2002 /79	Males, elderly patient, PTB ^{'''} , and MDR [€]
(Farah <i>et al.</i> , 2005)	Register-based cohort study / Norway	655 TB	1996 to 2002 / 79	Older age and Isoniazid resistance
(Horne <i>et al.</i> , 2010)	Cohort study / Washington state- USA	3451 TB	1993 to 2005	Older age, male, HIV* comorbidity and TB ^{''} treatment by private healthcare providers

Study	Study Design & Place	Sample Size	Duration & Treatment Success Rate (%)	Risk Factor for Unsuccessful Outcome
(Kherad <i>et al.</i> , 2009)	Retrospective study / Switzerland	252 TB	1999-2003 / 85	Age, sex, HIV*, Smoking
(Nguyen <i>et al.</i> , 2011)	Retrospective study / North Carolina	5311 TB	1993-2003 /	Older age, aggressive TB" disease, HIV*
(Singla <i>et al.</i> , 2003)	Retrospective study / Riyadh	514 PTB"	1998-1999	Multiple cavitations, numerous bacilli at the time of diagnosis
(Ukwaja <i>et al.</i> , 2016)	Retrospective study / Nigeria	1180 TB	2011- 2012 / 75.7	TB" in urban public health, smear negative, EPTB°, HIV*, received treatment more than 8months
(Chee <i>et al.</i> , 2006)	Retrospective study / Singapore	1646 TB	2001-2002	Chinese ethnicity, younger than 65 years old and patient enrolled under DOT [#]
(Mohammed <i>et al.</i> , 2017)	Retrospective study / Hosanna, Ethiopia	768 TB	2008-2014 / 43.3	Age, sex, place of residence, HIV* Type of TB
(Solliman <i>et al.</i> , 2012)	Retrospective study / Libya	327 TB	2007-2008 / 58.7	Libyan nationality
(Gebrezgabiher <i>et al.</i> , 2016)	Retrospective study / Ethiopia	1537 TB	2008- 2009 / 85	Rural area, PTB" and Negative PTB
(Ade <i>et al.</i> , 2014)	Retrospective cohort / Benin	383 EPTB°	2011	HIV*

Study	Study Design & Place	Sample Size	Duration & Treatment Success Rate (%)	Risk Factor for Unsuccessful Outcome
(Akhtar <i>et al.</i> , 2011)	A cohort study / Pakistan	582 TB	2003 to 2005 / 66	Family DOT [#] patients
(Amo-adjei and Awusabo-asare, 2013)	Mixed method approach study	240 TB	1997 to 20010 / 87	Diagnosis methods, stigma.
(Antoine and Che, 2013)	A surveillance report / France	3,787 PTB ^{'''}	2009	Male, born outside France, having the previous history of TB
(Babatunde, 2013)	A cross-sectional descriptive study / Nigeria	78 TB	2010	Smear positive, EPTB ^o , and HIV [*] patients
(Belo <i>et al.</i> , 2011)	Prospective study / Brazil	561 TB	2005 to 2008	Distance to the health centre, BMI [‡] , drug resistance and HIV [*]
(Berhe, Enquesslassie and Aseffa, 2012)	Retrospective study / Ethiopia	427 TB	2009 to 2011 / 89.2	PTB ^{'''} , age < 40 years, having family member more than 5, unemployment, retreatment TB cases.
(Bøhler, Mustafaa and Mørkve, 2005)	Retrospective study / Khartoum -Sudan	2000 PTB ^{'''}	2000 / 65	History of TB ^{''} , Born abroad
(Fatiregun, Ojo and Bamgboye, 2009)	A longitudinal study design / Nigeria	1245 PTB ^{'''}	2000 / 76.6	Male and Poor knowledge
(Feng <i>et al.</i> , 2011)	Prospective observational study / China	992 TB	2007-2009	Older age, the existence of a chronic cough, anorexia, and highly fever

Study	Study Design & Place	Sample Size	Duration & Treatment Success Rate (%)	Risk Factor for Unsuccessful Outcome
(Getahun <i>et al.</i> , 2013)	A historical cohort study / Addis Ababa	6451 TB	2005-2009 / 83	Tuberculosis treatment center
(Glynn <i>et al.</i> , 1998)	Retrospective study / Malawi	1655 TB	1986-1994	HIV*, BCG ^ε vaccination
(Ahmed, Hayat and Sciences, 2017)	A retrospective study/ Baluchistan	219 TB	2014 / 66.4	Retreated TB
(Harries <i>et al.</i> , 1999)	Retrospective study / Malawi	8243 PTB ^{''} and negative PTB	1995 / 72	Negative PTB ^{'''} , HIV* patients
(Nahid <i>et al.</i> , 2011)	Cohort study / Washington state- USA	3541 TB	1993 to 2005	Age, male gender, co-infection with HIV*, taking treatment by privates providers
(Kaur <i>et al.</i> , 2008)	A longitudinal study in Chandigarh / India	265 TB	2004-2005 / 90	Retreatment TB, Age, Sex
(Firdie, Dejene and Tewelde, 2015)	A cross-sectional study / Northern Ethiopia	1830 TB	2009 to 2013/ 79.4	Male, Urban residency
(Khan <i>et al.</i> , 2009)	Prospective study in Peshawar/Pakistan	306 TB	2007 / 99	Older age, sex
(Kherosheva <i>et al.</i> , 2003)	Retrospective study / oblast-Russia	749 TB	1999-2000 / 81	HIV* and MDR ^ε

Study	Study Design & Place	Sample Size	Duration & Treatment Success Rate (%)	Risk Factor for Unsuccessful Outcome
(Mohandas <i>et al.</i> , 2017)	Record-based study / Calicut, India	289 TB	2013 / 85	Absence of sputum conversion at second month, DM [‡]
(Lienhardt <i>et al.</i> , 1998)	Retrospective study / Gambia	1357 PTB ^{'''}	1994-1995 / 90	Absence of sputum conversion at 2 nd month, HIV*
(Manosuthi <i>et al.</i> , 2012)	Retrospective study / Thailand	812 TB	2008-2009 / 52	HIV* , low body weight, EPTB [°] and older patients
(Peltzer and Louw, 2014)	Prospective study / South Africa	1196 TB	2014 /70	Leaving in traditional houses, poverty and retreatment TB patients
(Pk <i>et al.</i> , 2011)	A descriptive study / Karnataka, India	181 TB	2013 / 84	Irregular treatment, alcoholism and HIV*
(Alemayehu <i>et al.</i> , 2017)	A cross-sectional study / Gondar, Ethiopia	352 TB	2015	Low income, low education, history of TB ^{''}
(Quy <i>et al.</i> , 2003)	Prospective study / Vietnam	400 TB	2001/60	No DOT [#] , Drug cost
(Raj <i>et al.</i> 2012)	Retrospective study / madhya Pradesh- India	10,964 TB ^{''}	2004 to 2009 / 85	Male, HIV*
(van Hest <i>et al.</i> , 2012)	A systematic review / European Union	79 datasets	2000 -2010	Several factors
(C. S. Wang <i>et al.</i> , 2008)	Retrospective study / Taiwan	157 PTB ^{'''}	2003-2006	Older age, low BMI [€] , comorbidity conditions

Study	Study Design & Place	Sample Size	Duration & Treatment Success Rate (%)	Risk Factor for Unsuccessful Outcome
(Woldeyohannes <i>et al.</i> , 2015)	Retrospective study / eastern Ethiopia	31,199 TB	2003-2012 / 85.5	Male, PTB ^{'''}
(Yen <i>et al.</i> , 2012)	Retrospective study / Taipei, Taiwan	1616 TB	2008 / 77.4	Older age, unemployment, tumour, MDR [€] and low education
(Sunday, 2014)	Retrospective study / Southwester Nigeria	965 TB	4 years / 85	HIV*, older age
(Pawar <i>et al.</i> , 2017)	A retrospective comparative study / Maharashtra, India	1915 TB	2015-2016 /	PTB ^{'''}
(Johnson <i>et al.</i> , 2016)	Retrospective cohort study / Malaysia	286 TB	2010-2014	Males, losing weight, smear-positive at the end of treatment and smoking
(Costa, Keny and Lawande, 2016)	Retrospective study / Goa, India	369 TB	2004 -2013 / 77	Not reported
(Tafess <i>et al.</i> , 2016)	Retrospective study/ Ethiopia	34,895 TB	2003 – 2012 / 97	Not reported
(Liew <i>et al.</i> , 2015)	Retrospective study / East region, Malaysia	21,500 TB	2012 / 78.5	Older age, non-Malaysian, low education, no BCG scars, smokers, HIV*, MDR [€] and EPTB [°]
(Belayneh <i>et al.</i> , 2016)	Retrospective study / Gondar, Ethiopia	3,800 PTB ^{'''}	2009 -2013 / 79	Not reported

Study	Study Design & Place	Sample Size	Duration & Treatment Success Rate (%)	Risk Factor for Unsuccessful Outcome
(Gebreegziabher, Yimer and Bjune, 2016)	Retrospective study / Punjab, India	15,140 TB	2007 – 2012 , 90	Recurrent TB and HIV*
(Bagga <i>et al.</i> , 2017)	Prospective study / Ludhiana, India	221 PTB ^{'''}	2010-2011, 82.8	Elderly age, DM [‡] , smear positive, longer distance to centre

PTB^{'''}: Smear positive Pulmonary Tuberculosis; EPTB[°] : Extra Pulmonary Tuberculosis; HIV*: Human Immunodeficiency Virus; BCG[€] : Bacille Calmette-Guerin; MDR[€]: Multi Drug Resistance DOT#, DM[‡]: Diabetic Mellitus