2019February

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BAHIR DAR UNIVERSITY

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DETERMINANTS OF TRATMENT OUTCOMES OF MDR-TB AT SAINT PETER HOSPITAL, ADDIS ABABA ETHIOPIA: A CASE - CONTROL STUDY

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A THESIS SUBMITTED TO THE DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS, SCHOOL OF PUBLIC HEALTH, COLLEGE OF MEDICINE AND HEALTH SCIENCES, BAHIR DAR UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMNTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN EPIDEMIOLOGY

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Acknowledgment

First and for most, I would like to express my deepest gratitude to my advisors Mr. Zelalem Mehari (M.Sc. in biostatistics) & Kebadnew Mulatu (MPH in Epidemiology and Biostatistics) for their guidance and support starting from the beginning to produce this thesis.

I would like to acknowledge Bahir Dar University, College of Medicine and Health Sciences School of public health department of epidemiology and biostatistics for giving me a chance to pursue my education.

I would also like to thank the participants and Saint Peter Specialized Hospital for allowing me to undertake the research, the MDR-TB focal persons for facilitating data collection and give orientation for data collectors.

Last but not least my special thanks goes to data collectors and my parents and friends who are always there for me.

Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body Mass Index
CI	Confidence Interval
DM	Diabetes Mellitus
DST	Drug Sensitivity Test
ETB	Ethiopian Birr
G.C	Gregorian calendar
Hgb	Hemoglobin
K	Potassium
MDR	Multi Drug Resistance
SPSS	Statistical Package for Social Science
TB	Tuberculosis
WBC	White blood cell count

Table of contents

Content **Page**

List of tables

List of figures

Abstract

Background: Multidrug-resistant tuberculosis is tuberculosis due to resistance of M. tuberculosis to at least isoniazid and rifampicin. In spite of increased testing, the number of MDR-TB cases detected in 2016 reached 153 000, a slight increase from 2015. The two reasons why MDR-TB continues to emerge and spread are mismanagement of tuberculosis (TB) treatment and person to person transmission. To reduce the burden of MDR-TB, Ethiopia has designed a strategy to provide treatment and culture and drug susceptibility testing (DST) services at least to all MDR-TB suspected cases. However, there are limited data on the determinants of treatment outcome of MDR-TB in the country to guide the National TB Program.

Objective: To identify the determinants of treatment outcome of MDR-TB in St. Peter Specialized Hospital, Addis Ababa Ethiopia

Methods: An institution based unmatched case control study design was employed on MDR-TB patients. A total of 354 (71 case and 283 controls) MDR-TB treated patients between 2010 and 2018 were included. Patients were selected by simple random sampling method. Data were extracted from patients' MDR-TB registration books and medical records. A Binary Logistic regression analysis was performed; bi-variable logistic regression was employed to identify candidate variables for multivariable logistic regression at $P \leq 0.2$. Factors associated with treatment outcome of MDR-TB was identified in multivariable logistic regression at $P<0.05$ and odds ratio with 95% CI. Model was diagnosed by Hosmer - Lemeshow goodness of fit test with a P value of 0.68; it shows that the model was well fit for the data in this study.

Results: In the multivariable logistic regression, individuals with a history of taken second line drug were 4.465 times [95% CI: 2.141-9.312] more likely to have poor treatment outcomes. And also individual with more than two first line TB drug resistant were 3.092 times [95% CI: 1.092 - 8.696] more likely to have poor treatment outcome. The study also revealed that individuals with a history of developing adverse effect on the course of treatment were 6.305 times [95% CI: 1.536-25.881] more likely to have poor treatment outcome. In addition individuals with primary education were 77.7 % (OR=0.223 [95% CI: 0.104-0.489]) less likely to have poor treatment outcome and patients with low hemoglobin level were also 52.5 % (OR=0.475 [95 % CI: 0.227-0.996]) less likely to have poor treatment outcome.

Conclusion and Recommendation: This study concluded that patients with a history of taken second line TB drugs, developing adverse effect on the course of treatment, and resistance of more than two first lines TB drugs at the commencement of treatment are important determining factor for treatment outcome. Thus, this study urges that hospitals should strengthen follow up system for a patients with adverse effect, history of taken second line TB drug and resistance of more than two MDR TB drugs.

Keywords: MDR-TB, treatment outcome, determinants

1. Introduction

1.1. Background

Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis due to resistance of mycobacterium tuberculosis to at least isoniazid and rifampicin, which are the two most effective anti-tuberculosis drugs. The two reasons why MDR-TB continues to emerge and spread are mismanagement of tuberculosis (TB) treatment and person to person transmission which can then be transmitted especially in crowded settings (1).

Worldwide and in most countries with a high burden of MDR-TB, WHO estimates that in 2014 only 41% of those with MDR-TB were actually diagnosed by laboratory testing. Finally, improvements in early identification and enrollment into treatment must also be followed by quality of care measures that ensure treatment success. Only three high-burden countries reported a treatment success rate for MDR-TB of 75% or higher (2).

Treatment of MDR-TB is very complex. The treatment is given at least for two years. The drugs are more toxic and expensive than those used to treat patients without MDR-TB (3-5). As a result, recently new MDR-TB drugs regimen are started in order to shorten, simplify and make MDR-TB treatment more effective. Moreover, public health strategies have been developed to promote treatment and prevent the occurrence of drug resistance, which usually results from human mistakes (6, 7).

Treatment outcomes are assigned by a team of physicians working in the hospital based on the patient's progress (i.e. based on adherence to treatment and signs of clinical improvement), and culture results. In the surveillance system, treatment outcomes are re-corded as cured, treatment completed, died, treatment failure (failure due to side effects, or failure due to other reasons), lost to follow-up (i.e. default) or not evaluated (others). These treatment outcomes are based on WHO recommendations (8).

To reduce the burden of MDR-TB, Ethiopia has designed a strategy to provide culture and drug susceptibility testing (DST) services at least to all MDR-TB suspected cases (9). There for the

treatment outcome is still having high gap and need further study. In this research addressed the determinant factors for poor treatment outcome of MDR TB patients.

1.2. Statement of the Problem

Tuberculosis (TB) still continues to be a big public health problem worldwide. It is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people (down from 1.7 million in 2000) and an additional 374 000 deaths among HIV-positive people. An estimated 10.4 million people fell ill with TB in 2016 (8).

Most deaths from TB could be prevented with early diagnosis and appropriate treatment. Millions of people are diagnosed and successfully treated for TB each year, averting millions of deaths (53 million, 2000–2016), but there are still large gaps in detection and treatment(10).

The main barrier that challenges the control of TB is high burden of multidrug-resistant TB (MDR-TB). It is a major public health problem globally and is an obstacle for national TB control programs. According to the WHO 2017 Global Tuberculosis Report, The latest anti-TB drug resistance surveillance data show that 4.1% of new and 19% of previously treated TB cases in the world are estimated to have rifampicin- or multidrug-resistant tuberculosis (MDR-TB). In 2016, an estimated 600 000 new cases of MDR-TB emerged globally. MDR-TB caused 240 000 deaths in 2016 (10).

And also the number of patients diagnosed with MDR-TB and started treatment has increased over time but the treatment outcomes have not improved over time. The proportion of patients who experienced poor treatment outcomes was higher in patients who started treatment during 2011 and 2012 than patients who started treatment during 2014. This might indicate limited improvements in care over time, including improved diagnostic services, treatment and follow up (11).

Treatment outcome of MDR/RR-TB is still only 54% (WHO target 75%) of the MDR-TB patients who started treatment in 2014 were successfully treated, while 16% of patients died and in 8% of patients their treatment failed (21% were lost to follow-up or not evaluated) (10).

Ethiopia is a high TB-burden country and reports approximately 127, 407 cases of TB each year. And also Ethiopia is one of the 30 high MDR-TB countries; it is ranked 15th with more than 5,800 estimated MDR-TB patients each year. According to the WHO report, the incidence rate of MDR-TB has been 5.7% per 100,000 and its prevalence is 2.7% in newly diagnosed patients; it is reportedly even higher in patients who have previously received anti-TB treatment 14% (12).

A study in Ethiopia shows that 63% (WHO target 75%) were successful treatment outcome whereas 13% died, 2% experienced treatment failure, 11% were lost to follow-up, and 2% transferred out (13).

However, there are limited data on the determinants of treatment outcome of MDR-TB in the country to guide the National TB Program in designing an evidence-based algorithm to prioritize access to MDR-TB diagnostic implemented services (culture and DST) and tailor treatment, prevention and control strategies.

Therefore, this study was conducted to identify determinants of MDR-TB treatment outcome in a case control study of patients managed in Saint Peters Specialized Hospitals Addis Ababa, Ethiopia, between November 15, 2018 and December 15, 2018. This study aims at producing reliable and valid determinants of poor treatment outcome of MDR TB which may assist the Hospitals, Ministry of Health and potential stakeholders to improve the effectiveness of treatment outcome of MDR-TB.

1.3. Significance of the Study

The results of this study have implications for policy makers, health care providers, educators and researchers, to improve or strengthen policies related to treatment outcome of MDR-TB.

The problem of poor treatment outcome of MDR-TB cannot be solved only by the effort of government with the common treatment regimen only, it needs research based MDR TB treatment follow up based on patients exposure status and focus areas to improve or strengthen policies and strategies related to TB/MDR-TB.

And also it will be supported MDR-TB patients to get research based appropriated treatment follow up according to their exposure status; and it improves patient's treatment outcome and decrease infection rate with in a community through direct person to person contact.

Moreover it is hoped that information obtained from this study will add to the existing body of knowledge in the area of MDR-TB treatment outcome. Consequently, the findings might help to enhance family and social support system for MDR-TB patients.

2. Literature Review

In the literature review addressed socio-demographic factors, clinical factors and laboratory finding factors that have associated with treatment outcome of MDR-TB in formers similar studies. Literatures were collected from web through EndNote and google scholar.

2.1. Socio-demographic Factors Associated with MDR TB treatment Outcome

A study conducted in Pakistan and South Korea shows age were significantly associated with MDR-TB patient's failed, died and defaulted treatment outcomes (14, 15). Similar study in Taiwan also patients who were aged ≥65 years were more likely to die during treatment compared with patients who were <45 years old (16). And also a retrospective study conducted in Ethiopia (Boru Meda Hospital and Saint Peter Specialized Hospital) shows the same finding that age were significantly associated with poor treatment outcome of MDR-TB (13, 17).

A systematic review study in 21 countries (including African countries) revealed, patients sex (male gender) were significantly associated with poor treatment outcome of multi-drug resistance tuberculosis (18). And also the cohort study conducted in India also revealed males were associated with unfavorable treatment outcome (19).

A study conducted in South Koria, India and China shows BMI<18.5 kg/m^2 were significantly associated with poor treatment outcome (15, 19, 20) A systematic review study in 21 countries also show the same finding that BMI<18.5 kg/m^2 were associated with poor treatment outcome (18). And also the study conducted in Saint Peter Specialized Hospital Ethiopia revealed that BMI<18.5 kg/m^2 is allied with poor treatment outcome (21).

A Case control study in Kenya on treatment outcome of MDR-TB revealed having primary education or no education were independent risk factors for unfavorable treatment outcome (treatment failed, died and defaulted) (22).

A cohort study conduct in Northwest Ethiopia shows that patients came from rural area (Farmers) were prone to result poor treatment outcome of MDR-TB. Farmers were more than four times at risk to have a poor treatment outcome at any time than employees (13).

2.2. Clinical Factors Associated with MDR-TB treatment Outcome

A study conducted in Estonia shows that HIV infection increased the risk of poor treatment outcome 10-fold and previous TB treatment increased the risk almost three-folds. Resistance to ofloxacin and positive AFB smear at the start of anti-TB treatment were independent risk factors of poor treatment outcome in MDRTB. Alcohol abuse was close to be significantly associated with poor treatment outcome in MDR-TB (23).

Another study in Pakistan shows that unsuccessful interim outcomes demonstrated statistically significant association with history of streptomycin use, ofloxacin resistance and sputum culture positivity at two months of treatment were; ofloxacin resistance, , and being culture positive at the second month of treatment (14).

A study in South Korea show that diabetes, and MDR-TB history were significantly associated with treatment failure, death, or relapse. Treatment interruption was associated with service sector employees or laborers, bilateral lesions on chest X-ray, and previous treatment failure or treatment interruption history (15).

A study in China shows in multivariate logistic regression analysis, poor outcomes were associated with duration of previous anti-TB treatment of more than one year, retreatment, diabetes, tumor, decreased albumin, and cavitation. In multivariate logistic regression analysis, having a tumor was the only independent risk factor associated with death (20). Another study in china revealed there were 90.7% patients experienced at least 1 type of adverse event and 55.2% of them required a changed MDR-TB treatment; 6.8% patients required permanent discontinuation of the offending drug due to adverse events. The occurrence of adverse events was associated with poor treatment outcome (24).

A study conducted in India revealed factors significantly associated with unfavorable treatment outcomes were baseline seven missed doses in intensive phase and continuation phase; cavity disease; prior treatment episodes characterized by re-treatment regimen taken twice, longer duration and more episodes of treatment; any weight loss during treatment and additional

resistance to first line drugs (Ethambutol, Streptomycin). Baseline to Ofloxacin also significantly reduced the odds of unfavorable treatment outcomes in multinomial logistic regression model (16).

Another study on risk factors for poor multidrug-resistant tuberculosis treatment outcomes in Kyiv Oblast, Ukraine shows that 18.1% achieved treatment cure or completion while 36.4% died, 31.9% defaulted, and 10.3% failed treatment. In the multivariate analysis, the strongest baseline predictors of poor outcomes were HIV infection without anti-retroviral therapy initiation and presence of extensively-drug resistant TB (25).

The study conducted in Brazil shows that the overall success proportion was 60%. Success was more likely in non-HIV patients, sputum-negative at baseline, with unilateral disease and without prior DR-TB. Adjusted for these variables, those receiving standardized regimens had 2.7-fold odds of success compared to those receiving individualized treatments when failure/relapse were considered, and 1.4-fold odds of success when death was included as an unsuccessful outcome. When loss to follow-up was added, no difference between types of treatment was observed. Patients who used levofloxacin instead of ofloxacin had 1.5-fold odds of success (26).

A study in Taiwan patients who were with cancer or chronic kidney disease were significantly more likely to die compared with those without these diseases. Retreatment cases were more likely to be lost to follow-up compared with new cases the proportion of patients who were lost to follow-up was particularly high among patients who received treatment after loss to follow-up (27). Another study in Taiwan also shows receiving second-line drugs with ofloxacin, 59.2% were cured. Those who received ofloxacin had a lower risk of relapse than those receiving only first-line drugs and a lower risk of TB-related death than those receiving second-line drugs but not ofloxacin (16).

A Case control study in Kenya on treatment outcome of MDR-TB revealed independent risk factors associated with unfavorable treatment outcome were; having primary or no education, poor housing and CD4 count less than 200/µl. Taking 30 minutes or less on travelling to, or waiting for treatment less than at facility and availability of DOTs supporter daily were found to be protective factors (22).

In Egypt a treatment success rate of approximately 69% was achieved with the first national treatment cohort of MDR-TB under the Egyptian program. Predictors of unsuccessful treatment were delayed culture conversion, moderate or extensive lung affection, and diabetes (28).

A systematic review study in 21 countries (including African countries) shows that, 62% of patients had successful outcomes, while 13% defaulted, 11% died, and 2% were transferred out. Factors associated with worse outcome included alcohol abuse, smear positivity at diagnosis, fluoroquinolone resistance and the presence of an XDR resistance pattern. Factors associated with successful outcome were surgical intervention, no previous treatment, and fluoroquinolone use (18)

A study in St. Peter Hospital in Ethiopia shows that a composite treatment success was 78.6% with 64.7% cured,13.9% who completed treatment, 1.6% who failed, 13.9%who died and 5.9% who were lost to follow-up. HIV confection, corpulmonale and confirmed MDR TB were predictive of treatment failure or death (21).

A retrospective study in Boru Meda Hospital, Northeast Ethiopia also shows that 61.1% patients were cured, 24.4% of them died, 8.9% were defaulted, 3.3% have completed, and 2.2% failed. Patients having a negative culture result by six month were associated with successful treatment outcome (17).

2.3. Laboratory Factors Associated with MDR-TB treatment outcome

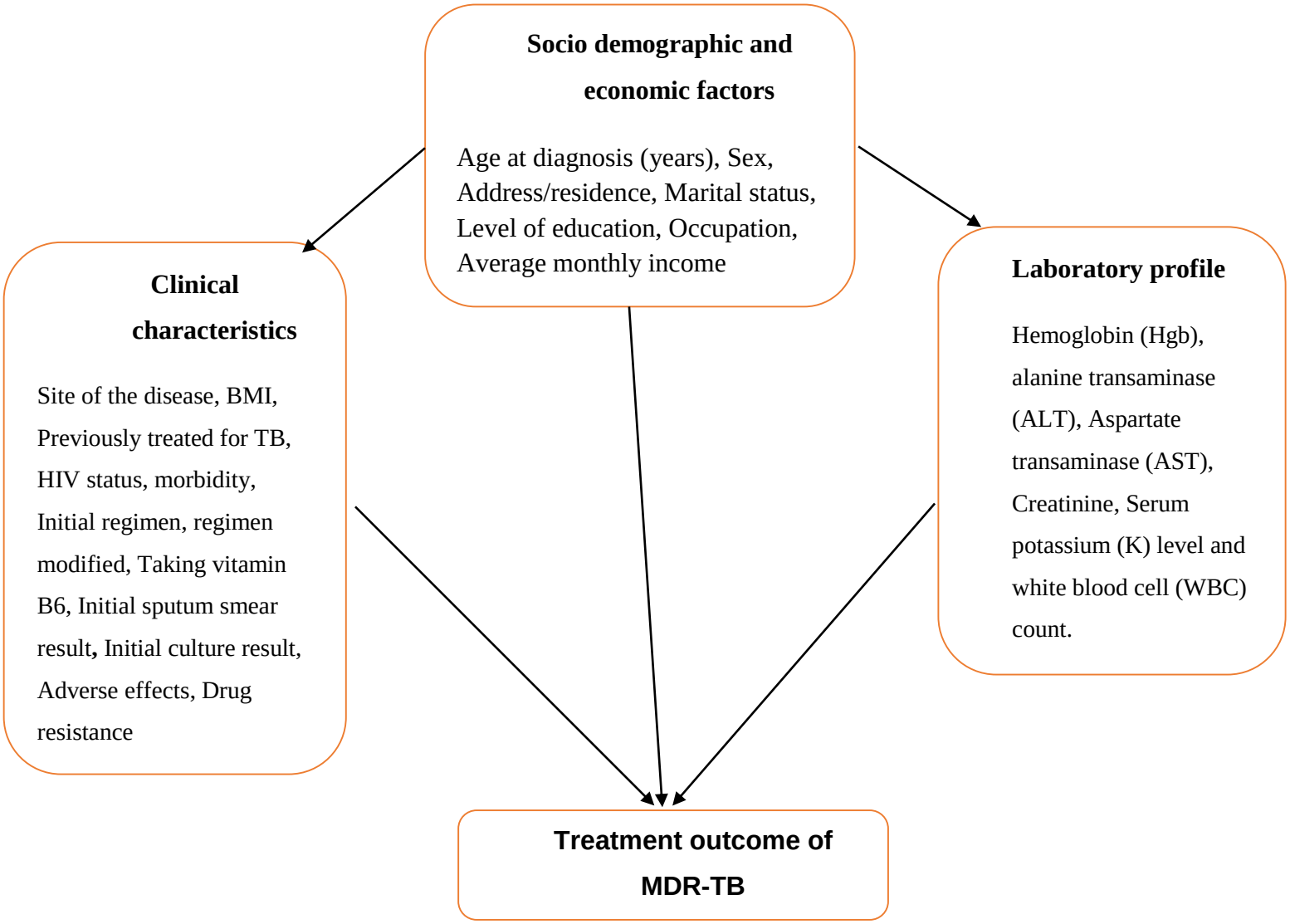
Another study in Northwest Ethiopia shows that in multivariate analyses being anemic were the independent predictors of time to poor treatment outcome. Those who had low hemoglobin levels (i.e. Patients with anemia) were more than two times at risk to have a poor treatment outcome at any time than those who had normal hemoglobin levels (13).

A study conducted in Pakistan shows that above normal baseline serum creatinine level were significantly associated with poor treatment MDR-TB (14).

In the literature some available factors were now well addressed especially initial laboratory finding were not assessed. In this study available recorded data were added and tried to assess the effect on treatment outcomes.

2.4. Conceptual frame work

A conceptual frame to assess treatment outcome of MDR-TB developed from the above different literatures.



3. Objective of the Study

To identify determinants of treatment outcome of MDR-TB in St. Peter Specialized Hospital, Addis Ababa Ethiopia.

4. Methods and Materials

4.1. Study area and Period

4.1.1. Study Area

The study was conducted in Addis Ababa City at St. Peter TB Specialized Hospital which is established 40 years ago and MDR TB treatment were started in 2010 G.C. It's located in Gulled Sub city, woreda 02. St. Peter specialized hospital is one of the tuberculosis hospitals in patients and out patients do to their large experience in the management of TB, this center has been chosen as the facility that will be response of providing treatment and follow up of the first cohort of 45 patients with MDR-TB in the country under supervision of national TB control program.

The estimated population size of Addis Ababa is 4.6 million and the male population constitutes 48% (29). The Hospital provides healthcare services for a population of approximately 5 million people. Patients are enrolled in the MDR-TB treatment centre if they have bacteriological evidence of rifampicin resistance (RR), determined by culture; bacteriological evidence of MDR-TB, determined by a line-probe assay (i.e. Geno Type MTBDR plus V.2.o, HAIN Life, Science), Gene Xpert or conventional drug susceptibility testing (DST); or clinical evidence of MDR-TB based on multiple treatment failures, or a history of contact with someone with MDR-TB. All patients enrolled at the MDR-TB treatment centre are eligible for treatment.

4.1.2 Study Period

The study was conducted from November 15- December 15, 2018 on the above study area (Saint Peter Specialized Hospital Addis Ababa, Ethiopia).

4.2. Study Design

An institution based unmatched case control study design was employed among MDR-TB patients who registered at the MDR-TB treatment center. Cases and controls was identified according to the WHO definition of successful and unsuccessful treatment outcome categories.

4.3. Population

4.3.1 Source Population

The source population of this study was all MDR-TB patients who were attending in the MDR clinic of Saint Peter Specialized Hospital.

4.3.2 Study Population

Case: the study population for cases was MDR-TB patients whose treatment outcomes were assigned treatment outcome either died, failed, or defaulted.

Control: the study population for controls was all MDR-TB patients whose treatment outcome were assigned treatment outcome either cure or treatment completed.

4.3.3. Eligibility Criteria's

Inclusion criteria

- Complete registries of patients MDR-TB treatment outcome were included

Exclusion Criteria

- Patients who were transferred were excluded from the study

4.4. Sample size and Sampling Technique

4.4.1. Sample size determination

Sample size was determined using Epi Info statCalc table by taken variables from similar study in Kenya (It is included in literature review). Three variables namely taking chronic illness, HIV status, and none or primary education (with high school and tertiary school) (22), which were significantly associated with time to poor treatment outcome was taken for sample size determination and it is calculated using EPI INFO version 7 (unmatched case control) computer software and using 95% CI, power of 80%.

Table 1: *Sample size determination using power method*

Variable	Ratio (Case to control)	% of controls exposed	OR	% of case exposed	Sample size			Remark
					Case	Control	Total	
Chronic illness (Yes/No)	1:4	16.3	2.48	32.6	71	283	354	
HIV Status	1.4	19.4	2.41	36.7	69	275	344	
EDUCATION LOWER (Prim. or none) (Yes/No)	1:4	53.7	4.09	82.6	30	119	149	
Housing Poor/Good house	1:4	57.1	2.5	69.5	63	249	312	

From the above calculated sample size the largest sample was taken as the study sample. There for 354 (71 case/283 control) randomly selected clients cards was included in the study.

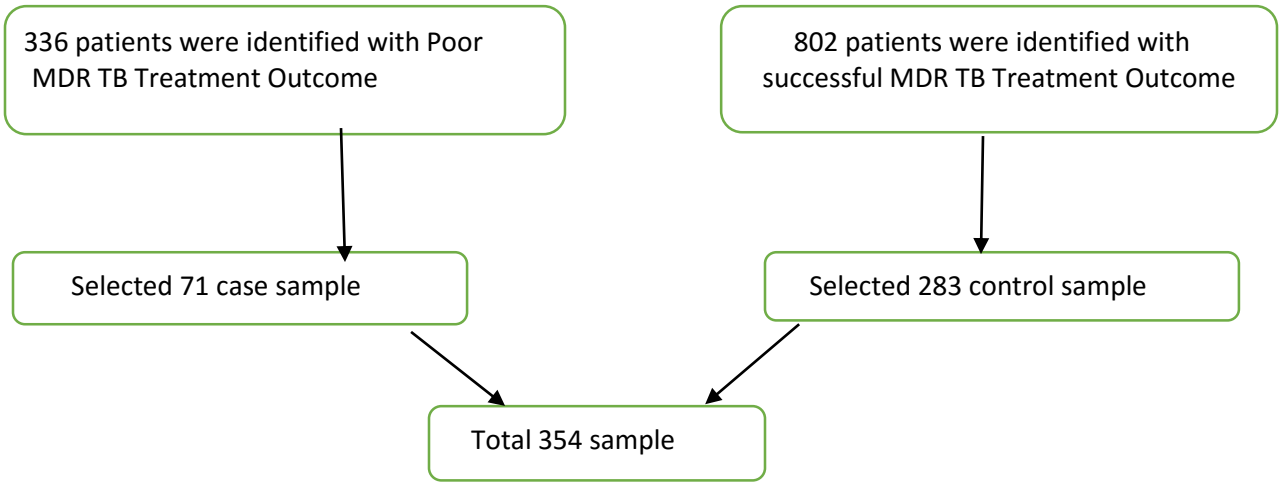
4.4.2. Sampling Technique

Simple random sampling technique was employed in total clients underwent for MDR-TB treatment in Saint Peter Specialized Hospital starting from 2010 to 2018.

Case was sampled from complete register of patients with poor treatment outcome and controls was sampled from a complete record of MDR-TB patients with successful treatment outcome.

First identified all cases and selected 71 sample by simple random sampling and next identified all controls and selected 283 sample by simple random sampling technique

Figure 2: Sampling process steps



4.5. Study Variables

4.5.1. Dependent Variables

Treatment Outcome of MDR-TB

4.5.2. Independent Variables

Socio-demographic factors

- Age at diagnosis (years)
- Sex/Gender
- Address/residence
- Level of education
- Average monthly income
- Religion

Clinical characteristics

- Site of the disease
- Registration group
- History of taken second line TB drug use
- BMI
- Previously treated for TB/Treatment History

- Risk Factors
- Adverse Effect
- HIV status
- Any comorbidity
- Taking vitamin B6
- Initial sputum smear result
- Initial culture result
- Drug resistance
- Treatment regimen

Laboratory profile

- Hemoglobin (Hgb),
- Alanine transaminase (ALT),
- Aspartate transaminase (AST),
- Creatinine,
- Serum potassium (K) level and
- White blood cell (WBC) count.

4.6. Standard and Operational Definition

4.6.1 Standard Definition

Cured: Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least30 days apart are negative after the intensive phase (11).

Treatment completed: Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase (11).

Treatment failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:

- Lack of conversion b by the end of the intensive phase, or

- Bacteriological reversion b in the continuation phase after conversion b to negative, or
- Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or
- Adverse drug reactions (ADRs) (11).

Died: A patient who dies for treatment failure during the course of treatment (11).

Lost to follow-up/Defaulted: A Patients whose treatment was interrupted for 2 consecutive months or more (11).

Not evaluated: A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown) (11).

Treatment success: The sum of cured and treatment completed (11).

4.6.2. Operational Definition

Successful treatment outcome (Control): is defining as all patients who were taking their MDR-TB treatment for the recommended duration and who were declared as either cured or completed (excluding not evaluated patients).

Poor treatment outcome (Case): is define as the MDR-TB patients who died, defaulted or failed treatment (excluding those who were not evaluated).

4.7. Data Collection Procedure

Data were extracted from patients' MDR-TB registration books and medical records. The registration book contained a number of variables including socio-demographic characteristics (age, sex, residence, educational status, and Income), and clinical variables (HIV status and other comorbidities, site of TB disease, number of previous TB treatments, initial MDR-TB regimen, vitamin B6 supplementation, initial sputum and culture result, adverse drug effects, height and weight) and laboratory profile (hemoglobin (Hgb), alanine transaminase (ALT),aspartate transaminase (AST), creatinine, serum potassium(K) level and white blood cell (WBC) count).

Data were collected by healthcare professionals who were working in the MDR-TB treatment center, and trained in study procedures. The collected data from the registration books were cross-checked with the medical records of the patients by the investigators.

4.8. Data Quality Assurance

To ensure the quality of data, pre-test was done on 5% of subjects in St. Peter TB specialized hospital MDR TB clinic. The pre-test was used to determine the clarity of the questions, terms, and time required to complete the checklist. Following the pre-test, checklist formats evaluated and improved (remove variables Religion, Marital Status) Give training to data collectors on data encoding and closely supervised by principal investigator at the time of data collection. Training help to get common understanding (familiar to the check list) and to avoid confusion on the check list between the data collectors and principal investigator. Data completeness and consistency were checked by running frequencies of each variable.

4.9. Data Processing and Analysis

Data were checked for completeness and entered into a form designed in EPI data version 3.1 and then exported to SPSS version 23 for analysis. A descriptive analysis was done based on frequency distribution of selected socio-demographic characteristics. The respondents were categorized into those that have unsuccessful treatment outcome (cases) and those have successful treatment outcome (controls).

Bivariable logistic regression was employed to identify candidate variables for multivariable logistic regression at $P \leq 0.2$. Factors associated with poor treatment outcome of MDR-TB treatment was identified in multivariable logistic regression at $P < 0.05$ and odd ratio with 95% CI. Model was diagnosed by Hosmer-Lemeshow goodness of fit test with a P value of 0.68; it shows that the model was well fit for the data in this study.

4.10. Ethical Consideration

Ethical approval was obtained from Bahir Dar University college of Medicine and Heath Science. Permissions letter was obtained again from the concerned body, Amhara Regional Health Bureau. Written permission was requested from Saint Peter Specialized Hospital.

5. Result

5.1. Socio-demographic characteristics of study participants

A total of 1254 patients were registered and commenced on MDR-TB treatment between 2010 and 2017. From these total of 354 former patients were recruited; 71 cases and 283 controls.

The mean age of case participant was 34.2 (SD=10.4) years, whereas the mean age of the control participant was 29.1 (SD=9.9) years. Majority of the study participants of case 48 (67.6 %) were in the economically productive age group; like the case, majority of control 220 (80.92 %) participants were in the economically productive age group, 20-40 years. A female participant constitutes half of the study participant in both cases 37 (52.12%) and controls 145 (52. 11 %) groups. Regarding to educational status, majority of the participants 50 (71.4 %) were unable to read & write and primary education in the case group, whereas in control group less than the half of control participants 110 (39.7 %) was unable to read & write and primary education. Concerning to the residence majority of the participants were from urban areas in both case 45 (63.4) and control 202 (71.3) groups. In both case and control groups majority of 16 (76.12 %) & 77 (70%) participants respectively was in poor economic status.

Table 2: *Baseline of socio-demographic of MDR-TB patients stratified by treatment outcome in from 2010 to 2018*

		Treatment Outcome	
Variables		**Poor treatment outcome**	**Successful Treatment outcome**
Gender	Male	37 (10.4)	138 (38.5)
	Female	34 (9.6)	145 (40.9)
Age Group	Under 25	9 (2.5)	24 (44.4)
	19-29	28 (7.9)	138 (39)
	30-40	20 (5.6)	82 (23.1)
	41-64	12 (33.9)	35 (9.9)
Residence	Rural	26 (7.3)	81 (22.9)
	Urban	45 (12.71)	202 (58.5)
Economic status	Poor	16 (11.3)	77 (54.6)
	Medium	5 (3.5)	27 (19.1)
	Good	0 (0)	6 (4.2)
	Dependent	0 (0)	10 (7.1)
Educational Status	Primary	50 (14.4)	110 (31.7)
	Secondary	19 (5.4)	168 (48.4)

5.2. Clinical characteristics of the study participants

Almost all patients had pulmonary TB in both case 64 (90.1) and control 257 (90.8 %) groups with initial positive sputum smear results of 38 (53.5%) for case and 149 (53.2%) for controls and also a positive culture result for case and control was 25 (35.2%) and 106 (38.1%) respectively. The majority of both case 52 (82.5%) and control 200 (72.4%) participants was both rifampicin and ionized resistance, and the rest patients was resist more than two first line TB drugs. All most all patients case 65 (94.2) and control 257 (94.8%) had TB treatment history, from this 49 (71.0%) cases and 184 (67.9%) controls had two or more than two time's history of TB treatment. Regarding to second line drug intake history more than a half of case 44 (62.0%) was taken second line TB drugs, whereas control only 104 (36.7%) was taken second line TB drugs.

A majority of both case 63 (88.7%) and control 273 (96.4%) participants were experienced one or more adverse events. The most prevalent adverse event was gastrointestinal and hearing disturbances. The occurrence of adverse event with life threatening potential was rare. Concerning to a registration group 43 (60.5%) case and 162 (57.2%) controls was started treatment after the failure of retreatment (fall in registration group 5). All patients were checked their HIV status and 21 (29.5%) cases and 60 (21.2%) were HIV positive. Among the HIV infected, 223 (81.8 %) were on ART during TB treatment. At the beginning of treatment, the majority of both cases 39 (73.6%) and controls 67.3 % were underweight (BMI<18.5 kg/m2).

Table 3: *Baseline clinical characteristics of MDR-TB patients stratified by treatment outcome from 2010 to 2018*

Variables		Treatment Outcome	
		Successful treatment outcome	**Poor Treatment outcome**
Site	Pulmonary	257 (72.6)	64 (18.1)
	Extra pulmonary	19 (5.3)	3 (0.8)
	Both	7 (1.9)	4 (1.1)
	New	18	6
	Relapse	39 (11)	12 (3.9)
Reg Group			
	After Failure of treatment	57 (16.1)	6 (16.9)
	After failure of retreatment	162 (45.7)	43 (12.1)
2nd Line	N0	179 (50.5)	27 (7.6)
	Yes	104 (29.37)	44 (12.4)
BMI	Under BMI	163 (55.2)	39 (13.2)
	Normal BMI	74 (25.08)	14 (4.7)
	Over BMI	5 (1.7)	0 (0)
	Never treated before	14 (14.1)	4 (1.2)
Tx History	One times treated	73 (21.4)	16 (4.7)
	Two Times Treated	113 (33.2)	30 (8.8)
	Three time treated	47 (13.8)	17 (5)
	More than three times treated	24 (7)	2 (0.5)
	No Risk factor	238 (70.6)	59 (17.5)
Risk Factor	Alcohol intake	12 (3.5)	1 (0.3)
	Sigarate smoking	6 (1.8)	5 (1.9)
	Both Sigarate and alcohol	13 (3.8)	2 (0.6)
Comorbidities	No comorbidity	229 (64.9)	55 (15.9)
	DM	11 (3.1)	3 (0.9)
	Hypertension	2 (0.8)	2 (0.8)
	Hypoxia	2 (0.8)	2 (0.8)
	Hepatitis	3 (0.9)	0 (0)
	Peptic Ulcer	0 (0)	1 (0.3)
	Other	35 (9.9)	8 (2.2)

Variables		Treatment Outcome	
		Successful treatment outcome	Poor Treatment outcome
Adverse Effect	No	10 (2.8)	8 (2.2)
	Yes	273 (77.1)	63 (17.8)
HIV	Positive	60 (16.9)	21 (5.9)
	Negative	223 (63)	50 (14.1)
Smear	Positive	149 (42.6)	38 (10.8
	Negative	105 (30)	23 (6.5)
	Unavailable	26 (7.4)	9 (2.6)
Culture	Positive	106 (30.4)	25 (7.1)
	Negative	31 (8.9)	9 (2.6)
	Unavailable	141 (40.4)	37 (10.6)
	H, R, S, E	76 (22.4)	10 (2.9)
rug resistant	R, S	200 (59)	52 (15.3)
Treatment Regimen	Z, E, Cm, Lfx, Eto, Cs	17 (3.9)	4 (1.1)
	Z, Cm, Lfx, Eto, Cs	241 (60.3)	63 (17.8)

5.3. Laboratory Findings

At the commencement of MDR TB treatment many laboratory test was conducted. Almost all participants' lab result was in normal range in both case and control individuals. Participants ALT result of case and control was 54 (79.4%) and 211 (84.4%) respectively in normal range and also AST result was 48 (69.5%) case and 199 (84.3%) control fall in normal range. Regarding to initial lab result of creatinine half of the case (50.7%) and majority of control 188 (70%) participants was in normal level. At the initial lab result potassium level of case (72.3%) and control 211 (77.8) of participants was in normal level. And also the majority of both case 49 (66.6) and control 182 (65.4%) participants WBC count was normal. Concerning to hemoglobin level half of case 35 (50%) participants was under low hemoglobin level whereas control groups majority of participants 171 (61.5%) was in normal hemoglobin level.

Table 4: *Baseline clinical laboratory finding of MDR-TB patients stratified by treatment outcome in from 2010 to 2018*

Variables		Treatment Outcome	
		Successful treatment outcome	Poor Treatment outcome
ALT	Low	33 (10.37)	8 (2.5)
	Normal	211 (66.3)	54 (17)
	High	6 (1.9)	6 (1.9)
AST	Low	8 (2.6)	2 (0.6)
	Normal	199 (65.2)	48 (15.7)
	High	29 (9.5)	19 (6.2)
Creatinine	Low	68 (20.3)	28 (8.4)
	Normal	188 (56.3)	33 (9.9)
	High	13 (3.9)	4 (1.2)
K	Low	29 (8.6)	11 (3.2)
	Normal	211 (62.7)	47 (13.9)
	High	31 (9.2)	7 (2.0)
Hgb1	Normal	91 (26.1)	35 (10)
	Low	187 (53.7)	35 (10)
WBC	Low	9 (2.6)	5 (1.4)
	Normal	182 (52.4)	46 (13.2)
	High	87 (25.7)	18 (5.1)

5.4. Treatment Outcome

In the 71 case patients with MDR TB the proportion of patients with died, defaulted and treatment failed was 44 (61.9%), 24 (33.8%) and 3 (0.4%) respectively. And also in the 283 control patients with MDR-TB, the proportion of patients with successful treat completed and cured was 157 (55.4%) and 126 (45.6 %) respectively transferred out patients were excluded.

5.5. Factors Associated with Treatment outcome of MDR-TB

Factors found to be significant by bi-variable logistic regression analysis were subjected to multivariable logistic regression analysis. Using logistic regression; nine variables were found to be independently associated with MDR-TB treatment outcome in the study. Taken second line TB drug and education status with a P value of <0.001 was independent factors associated with MDR-TB treatment outcome. Other independent factors were having adverse effect (P=0.012), residence in rural area (P=0.191) registration group at the commencement of treatment (P=0.146), Risk factors (P=0.141), HIV positive patients (P=0.135), Developing drug resistance (P=0.066), low level of creatinine (P=0.014) and low hemoglobin levels (P=0.022).

In the multivariable logistic regression, individuals with a history of taken second line TB drugs were 4.465 times [95% CI: 2.141-9.312] more likely to have poor treatment outcomes than individuals who don't have history of taken second line TB drugs. And also individual with drug sensitivity test result of more than two first line TB drugs resistant were 3.092 times [95% CI: 1.099 - 8.696] more likely to have poor treatment outcome than individuals who don't have resistance of two and less than two first line TB drugs.

The study also revealed that individuals with a history of developing adverse effect through treatment were 6.305 times [95% CI: 1.536-25.881] more likely to have poor treatment outcome than individuals haven't a history of developing adverse effect in the course of treatment. In addition individuals with primary education were 77.7 % (OR=0.223 [95% CI: 0.0104-0.489]) less likely to have poor treatment outcome than individuals with secondary school educational level. And also patients with low hemoglobin level were 52.5 % (OR=0.475 [95 % CI: 0.227-0.996]) less likely to have poor treatment outcome than patients with normal hemoglobin level.

Table 5: *Determinants of MDR TB Treatment outcome at St. Peter Specialized Hospital, Addis Ababa*

n=334

Variable		Control	Case	COR (95% CI)	AOR (95% CI)
Second line drug use	N0	171	24	2.805 [1.640-4.797]	4.465 [2.141-9.312]
	Yes	98	41		
Drug Resistance	H, R, S, E	76	10	2.216 [1.144-4.293]	3.092 [1.099 - 8.696]
	R, S	196	52		
Educational status	Primary	106	47	0.249 [0.139-0.449]	0.223 [0.104-0.489]
	Secondary	162	19		
Adverse Effect	Yes	260	58	3.467 [1.315-9.138]	6.305 [1.536-25.881]
	Yes	9	7		
Hgb	Low	94	31	0.511 [0.316-0.827]	0.475 [0.227-0.996]
	Normal	176	33		
Residence	Rural	61	26	0.694 [0.401-1.200]	0.706 [0.335-1.487]
	Urban	202	45		
Reg Group	New	18	6	1.011 [0.836-1.223]	0.250 [0.053-1.181]
	Relapse	39	12		
	After Failure of treatment	57	6		
	After failure of retreatment	153	43		
HIV	Positive	55	20	1.561 [0.071-2.799]	0.692 [0.305-1.570]
	Negative	214	45		
Creatinine	Low	68	28	0.558 [0.334-0.832]	0.541 [0.259-1.130]
	Normal	188	33		
	High	13	4		

** Due to the missing values of factors multivariable logistic regression analysis was done with the n value of 334.

6. Discussions

The study revealed that individuals with resistance of more than two first line drug at the commencement of MDR TB treatment has a positive relationship with poor treatment outcome. The same finding was seen in a systematic review study conducted on twenty one countries (including Africa countries) and a study conducted in China ; the study also revealed that individuals with resistance of more than two first line TB drug on drug sensitivity test were significantly associated with poor treatment outcome (18, 20).

And also the same study conducted in Pakistan shows the same finding with this study resistance of more than two first line TB drug at the commencement of MDR-TB treatment is associated with poor treatment outcome (14). This might be due to the reason, patients were started their treatment with second line TB drugs; due to that they can prone to develop resistance to second line drug and it's difficult to change the regimen easily.

In this study individuals with history of taken second line has a positive relationship with poor treatment outcome of MDR TB. This finding in line with previous study conducted in Taiwan (16). And also the same study in Estonia shows the same result with this study finding (23). In addition to the above studies the study conducted in Brazil and Pakistan also shows the same finding; history of taken second line TB drugs were associated with poor treatment outcome (14, 26). This might be due to patients were developing resistance to the standard and modified MDR-TB treatment regimens.

Developing adverse effect on the course of MDR-TB treatment has a positive relationship with MDR-TB poor treatment outcome in the study. Similar studies conducted in Egypt also revealed that developing nausea, vomiting and other related adverse effect were statistically associated with unsuccessful treatment outcome (28).

Another study in China on Adverse Events Associated with Treatment of Multidrug-Resistant Tuberculosis also shows the same result with this study, the occurrence of adverse events on the course of treatment was associated with poor treatment outcome of multi-drug resistance tuberculosis patients (24). This might be due to patients was changing treatment regimen frequently and vulnerable for drug resistance.

Studies conducted in Kenya demonstrated that illiterate and primary educations were statistically associated with poor treatment outcome. But in this study odd of poor treatment outcome was negatively associated with patients with illiterate and primary education than primary and secondary schools. This signals that illiterate and primary education was not affecting treatment outcome. This might be due to the reason that the illiterate and primary education is more eager to take the hectic treatment seriously and properly accepted the guidance of the health care providers (22).

The study conducted in Northwest Ethiopia shows patients with low hemoglobin level were statistically associated with poor treatment outcome. But in this study patients with low hemoglobin level has negatively associated with poor treatment outcome. This might be due to MDR TB patients with low hemoglobin level were taken high dose of vitamin B6 on the course of treatment with MDR-TB treatment regimen (13)

In this study individuals live in rural area were less likely to result poor treatment outcome. But the same study conducted in Northwest Ethiopia shows farmers were more likely to result poor treatment outcome (13). This may be due to the difference of the study area, in this study 63.4% of the cases were from urban areas and most of them are from Addis Ababa it signaling that the disease was clustered in the urban areas while in Gonder University Hospital most of the patients are came from rural area around Gonder town.

7. Strength and Limitation of the study

7.1. Strength

- The study was representative of MDR-TB case; it was conducted in the first MDR-TB treatment hospital in Ethiopia and included all patients starting from the beginning of MDR-TB treatment (2010 G.C) until today.
- The data were collected by trained professionals.

7.2. Weakness

- Since it was secondary data some important variables such as marital status, family size, Religion, Adherence, action taken for adverse effect had not available totally (not registered).
- Adherence is a critical variable for treatment outcome but it was not recorded in the registration book as well as in the patient's card.

8. Conclusion

- MDR-TB patients with a history of developed adverse event on the course of treatment, resistant to more than two first line drug and a history of taken second line TB were the most important determinant of treatment outcome.

- Whereas patients with primary education was not associated with treatment outcome of MDR-TB.

- Also the same as educational status; low level of hemoglobin at the commencement of MDR-TB treatment were not associated with treatment outcome of MDR-TB.

9. Recommendation

9.1. Saint Peters Specialized Hospital

- Strengthen follow up system for a patient with a history of taken second line drug before starting the treatment.
- Strengthen follow up system for a patient with resistance of more than two first line TB drugs at the commencement of the treatment.
- Strengthen follow up system for a patient with developing adverse effect on the course of treatment.
- Continue drug sensitivity test without interruption at the commencement of MDR-TB treatment.

9.2. Federal Ministry of Health

- Give emphasis during policies and strategies development for MDR-TB treatment; because poor treatment outcome of MDR-TB public health factors is need structural and consortium effort.
- Conduct further study why patients with a history of taken second line TB drugs, develop adverse event on the course of treatment and develop resistance of more than two TB drugs patients are vulnerable to MDR-TB poor treatment outcomes.

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Annex

Checklist

Part I Socio-demographic data

S/N	Question	Choice	Remark
101	Age at diagnosis (years)	_____	
102	Sex	1. Male 2. Female	
103	Residence	1. Urban 2. Rular	
104	Level of education	1. Unable to read and write 2. Primary 3. Secondary 4. Tertiary	
105	Average monthly income	_____	

Part II Clinical characteristics

S/N	Question	Choice	Remark
201	Site of the disease	1. Pulmonary 2. Extra pulmonary	
202	BMI	Wight_____ Height_____	
203	Previously treated for TB	1. Not treated (new) 2. Once 3. Twice 4. Three times 5. Four times and above	
204	HIV status	1. Positive 2. Negative	
205	Any comorbidity	1. None recorded 2. Diabetes mellitus 3. Congestive heart failure 4. Hypertension 5. Hepatitis	
206	Initial regimen	1. Z, E, Cm, Lfx, Eto, Cs 2. Z, Cm, Lfx, Eto, Cs	
207	History of taken second line drug	1. Yes 2. No	

208	Taking vitamin B6	1. Yes 2. No	
209	Initial sputum smear result	1. Positive 2. Negative 3. Not recorded	
210	Adverse effects	1. Yes 2. No	
211	Drug Resistance	1. H,E,R & S 2. R & S	
212	Reg Group	1. New 2. Relapse 3. After Failure of treatment 4. After failure of retreatment	

Part III: Laboratory profile

S/N	Question	Choice	Remark
301	Hemoglobin (Hgb) level	_____	
302	Alanine transaminase (ALT)	_____	
303	Aspartate transaminase (AST	_____	
304	Creatinine	_____	
305	Potassium (K)	_____	
306	White blood cell count (WBC),	_____	