Treatment Outcomes and Risk Factors for Poor Outcome among Patients with Multidrug-Resistant Tuberculosis at ALERT and University of Gondar Hospitals, Ethiopia

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Abstract

Background: *Multidrug-resistant tuberculosis (MDR-TB) presents an increasing threat to the global tuberculosis control. MDR-TB emerged as one of priority public health problem in Ethiopia. There has been a study reporting on predictors for death only. In this study, default and treatment failure, while arguably distinct from death, was included in our definition of poor outcome to allow for a more complete program evaluation. Therefore, we assessed the treatment outcomes and risk factors associated with poor outcome among MDR-TB patients at two national MDR-TB treatment centers, ALERT and University of Gondar hospitals, Ethiopia.*

Methods: *Hospital based retrospective general cohort study was conducted at ALERT and University of Gondar hospitals, Ethiopia, from December 2010 to May 2014. We reviewed medical records of confirmed MDR-TB patients treated with a standardized regimen. The data was analyzed using SPSS version 20 computer software. To identify the risk factors related to poor treatment outcome(failure, default and death), bivariate comparison and multiple logistic regressions was performed .we used P < 0.2 in bivariate analysis to include variables in the original multivariate logistic regression model, and P< 0.05 considered as cut off point for presence of statistical significance.*

Results: *Of 113 MDR-TB patients assessed, 6 (5.3%) had been diagnosed with primary MDR-TB, 107(94.7%) as secondary MDR-TB, and there had been no patients treated with second-line anti-TB drugs for this disease previously. Assessment of treatment outcomes showed that 68 (60.2%) patients were cured or completed therapy, 29 (25.6%) died, 15 (13.5%) defaulted, and treatment failed in 1 (0.9%). In a multivariate logistic regression model of these patients, independent risk factors for poor outcome included having baseline weight ≤ 45kg (adjusted odds ratio [AOR],* 4.99*;95% confidence interval [CI],*1.270-19.582*), positive smear at treatment initiation* (AOR, 4.62; 95% CI, 1.406-15.185*), and HIV co-infection (*AOR, 3.77*; 95% CI,* 1.145-12.436*).*

Conclusion: *Our study showed lower success rate in treating MDR-TB patients using a standardized regimen compared with WHO target. HIV co-infection, baseline weight ≤45kg, and positive smear at treatment initiation were shown to be independent risk factors for poor outcome. To decrease the poor outcome, ensuring adherence and paying special attention to this risky group of patients in addition to use of early diagnosis and initiation tuberculosis treatment is warranted.*

Key-words: *Multidrug-resistant tuberculosis; treatment outcomes; risk factors, Ethiopia.*

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List of abbreviations

AHRI	Armauer Hansen Research Institute
ALERT	All-Africa leprosy, Tuberculosis Rehabilitation, Research and Training Center
AAERC	AHRI/ALERT Ethics Review Committee
ADE	Adverse drug event
AFB	Acid-fast bacilli
AIDS	Acquired Immuno-Deficiency Syndrome
Am	Amikacin
ART	Anti-Retroviral Therapy
Cm	Capreomycin
CPT	Cotrimoxazole Preventive Therapy
Cs	Cycloserine
DOT	Directly Observed Therapy
DOTS	Directly Observed Treatment, Short course
DR-TB	Drug Resistance TB
DST	Drug Susceptibility Testing
E	Ethambutol
EPTB	Extra Pulmonary TB
Eto	Ethionamide
FLDs	First-line drugs
FMoH	Federal Ministry of Health, Ethiopia
GFATM	Global Fund to fight against AIDS, Tuberculosis and Malaria
H	Isoniazid
HBCs	High Burden Countries
Km	Kanamycin
Lfx	Levofloxacin
MDR-TB	Multi-Drug Resistant TB

Mfx	Moxifloxacin
NTP	National TB Program
PAS	Para-aminosalicylic acid
PFSA	Pharmaceuticals Fund and Supply Agency
PTB	Pulmonary Tuberculosis
R	Rifampicin
RRL	Regional Reference Laboratory
S	Streptomycin
SLDs	second-line drugs
SPSS	Statistical Package for Social Sciences
SPTSH	Sent Peters TB Specialized hospital
TB	Tuberculosis
TDR-TB	Totally Drug-Resistant TB
WHO	World Health Organization
XDR-TB	Extensively Drug Resistance TB
Z	Pyrazinamide

CHAPTER ONE: INTRODUCTION

1.1. Background

The global burden of tuberculosis (TB) remains enormous(1).Efforts to control the global TB epidemic have now been complicated by the emergence of strains of Mycobacterium tuberculosis, which are resistant to one or more anti-TB drugs. There were estimated to be 8.6 million cases of incident TB cases in 2012.There were also 1.3 million deaths from TB (1, 2). Drug resistance originates from misuse of anti-TB drugs by physicians, patients and producers (3).The spread of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) is a major medical and public health concern for the world. These two forms of highly drug-resistant TB threaten to make TB into an untreatable and highly fatal disease, particularly in resource-poor countries with a high prevalence of AIDS(4).

MDR-TB is defined as *Mycobacterium tuberculosis* resistance to at least both isoniazid (H) and rifampicin(R).XDR-TB is MDR as well as any fluoroquinolone, and any of the second line injectable anti TB drugs (capreomycin, kanamycin, and amikacin).MDR-TB, like drug susceptible TB, is a droplet infection and is easily transmitted to immune compromised individuals, especially to the HIV infected and the clinical manifestations are also similar(5).

MDR-TB is a rapidly-emerging disease that is characterized by difficult treatment and high rates of morbidity and mortality, because the treatment of MDR-TB with second line drugs is long, complex and costly, and has a considerable rate of adverse effects than treatment of drug susceptible TB(5, 6). It is important to treat MDR-TB patients both to prevent morbidity, mortality and to limit the spread of drug-resistant TB in the community(7).

Worldwide and in most countries with a high burden of MDR-TB, less than 25% of the people estimated to have MDR-TB were detected in 2012 (1).Globally, 83 715 cases of MDR-TB were notified. According to 2012 WHO, 3.6% of new TB cases and 20.2% of previously treated cases are estimated to have MDR-TB in 2012. The highest levels are

in eastern Europe and central Asia where in several countries, more than 20% of new cases and more than 50% of previously treated cases have MDR-TB (1).

There are scanty data about MDR-TB trends in Africa. The WHO estimate of the number of MDR-TB cases emerging in 2008 in Africa, most likely an underestimate, is 69 000 cases(8).

According to WHO 2012 report, there were an estimated 15,000 deaths (18 per 100,000 populations) due to TB, excluding HIV related deaths, in Ethiopia in 2011 .According to the Ministry of Health hospital statistics data, tuberculosis is one of the leading causes of morbidity, the fourth cause of hospital admission, and the second cause of hospital death in Ethiopia ,and the third leading cause of death in Ethiopia(5, 7).

Ethiopia is 15th of the world's 27 countries with the highest burden of MDR-TB. MDR-TB emerged as one of priority public health problem in Ethiopia. Among 804 newly diagnosed TB cases 1.6% was found to be infected with MDR TB. The rate of MDR TB among specimens from 76 previously treated TB cases was 12 %.(5).There were an estimated 1700 and 550 MDR TB cases among notified new and re-treatment pulmonary TB cases in 2011, respectively in Ethiopia(9).Because culture and DST are only performed for retreatment cases and patients failing first-line therapy, these numbers are likely a substantial underestimate of the actual current MDR TB burden(7)

In 2011, the World Health Organization (WHO) recommended that the MDR-TB treatment regimen should ideally consist of at least four second-line anti-TB drugs likely to be effective, as well as Pyrazinamide during the intensive phase of treatment(10).As standard in Ethiopia, all patients receive Pyrazinamide, Capreomycin, Levofloxacin, Ethionamide, and Cycloserine. Ethambutol is continued if DST suggests susceptibility to the drug. However, Ethambutol will not count as one of the 4 effective drugs. Pyrazinamide will be used throughout in all patients as resistance uncommon and no reliable DST available, but it will also not be counted as an effective drug(7).

1.2. Statement of the problem

Globally, only 48% of MDR-TB patients in the 2010 cohort of detected cases were successfully treated, reflecting high mortality rates and loss to follow-up. The Global Plan's target of achieving at least 75% treatment success in MDR-TB patients by 2015 was only reached by 34/107 countries reporting outcomes for the 2010 cohort(1).

In 2012, among the 1.3 million deaths from TB, there were an estimated 170 000 from MDR-TB, a relatively high total compared with 450 000 incident cases of MDR-TB(1).

An unfortunate consequence of treating MDR-TB with second-line drugs, however, is the inevitable emergence of further drug resistance. If the same factors that produce MDR-TB remain in force, then MDR-TB becomes XDR-TB, and their also be TDR-TB(11).Failure to act rapidly to contain local outbreaks, develop tools and strategies for identifying and treating XDR-TB, and investing in longer term improvements to TB control could transform the magic bullets for TB into blanks, and assure a return to the grim prospects of the Magic Mountain(12).

The particular determinants for poor MDR-TB treatment outcomes have been reported (13-21).Male sex, positive smear at treatment initiation, HIV-coinfection, treatment with < 2 active drug ,previously treatment for MDRTB, the use of ≤5 drugs for 3 months or more ,greater baseline resistance, prior TB, low BMI, fluoroquinolone resistance have all been found to be related to poor MDR-TB treatment outcome.

Previous research has described predictors for death among MDR-TB patients treated at St.Peters TB specialized hospital, Ethiopia (22). However, to our knowledge, there were no published studies conducted on composite risk factors for poor outcome in Ethiopia. In this study, default and treatment failure, while arguably distinct from death, was included in our definition of poor outcome to allow for a more complete program evaluation.

With the listed risk factors in mind, this study was, therefore, aimed to assess the treatment outcomes among MDR-TB patients treated at ALERT and University Gondar hospitals, Ethiopia. Specifically, this study will focus on identification of independent risk factors for poor outcome of MDR-TB treatment in order to improve the program's future performance to attain WHO goal.

CHAPTER TWO: LITERATURE REVIEW

2.1. Literature Review

Most studies were done in developed countries: China, France, England, and South Korea. Some were done in low-income or middle-income countries—Peru, Estonia, Latvia, South Africa and Turkey.

This review consists of almost retrospective cohort studies. Monitoring the outcome of MDR-TB treatment and understanding the independent risk factors for poor treatment outcome are important in evaluating the effectiveness of MDR-TB control program. There were different risk factors associated with poor treatment outcomes. The following literatures were reviewed to assess the treatment outcome and independent risk factors for poor MDR-TB treatment outcomes.

2.1.1. Review on treatment outcomes of MDR-TB

A systematic review and meta-analysis on treatment outcomes of multidrug-resistant tuberculosis patients published in 2009 showed in a pooled analysis, 62% [95% CI 57–67] of patients had successful outcomes, while 13% [9–17] defaulted, 11% [9–13] died, and 2% [1–4] were transferred out (18).

A retrospective evaluation in Turkey revealed that the overall success rate of treatment was 77%,with cures in 78 patients (49%) and probable cures in 43 (27%). Treatment failed in 13 patients (8%). Seven patients died (4%). (23) Seventeen patients (11%) did not complete the treatment regimen. In another retrospective study in Israel indicated that cure was achieved in 50.3% and 30.4% died(13).

A retrospective cohort study conducted in patients with MDR-TB at 3 TB referral hospitals in the public sector of Korea showed that from 202 MDR-TB patients, 75 (37.1%) had treatment success and 127 (62.9%) poor outcomes. Default rate was high (37.1%) comprising 59.1% of poor outcomes. Similarly, in another study on an individualized treatment regimen for MDR-TB, from January 1995 through December 2004 outcome assessment revealed that 102 patients (66%) were cured or completed therapy and 53(34%) with unfavorable outcome(24).In another study in china in 2013

showed that there were a total of 240 patients (40.95%) had treatment success, and 346 (59.05%) had poor treatment outcomes(21).

A prospective study from five resource-limited countries: Estonia, Latvia, Peru, the Philippines, and the Russian Federation to evaluate the management of MDR-TB showed that treatment was successful in 70% of 1,047 patients (range 59%–83%). Failure occurred in 3.3% to 11% of patients, default in 6.3% to 16%, and death in 3.7% to 19%. (25).Similarly, in the same countries, a meta-analysis from 2000-2004,showed that from 1768 patients, treatment outcomes were: cure/completed – 1156 (65%), died – 200 (11%), default - 241 (14%), failure - 118 (7%)(19).

A retrospective study conducted in Peru in 2003 on community-based therapy for MDR-TB showed that among 66 patients who completed four or more months of therapy, 83% (55) were probably cured at the completion of treatment. Five of these 66 patients (8%) died while receiving therapy(26).

A retrospective cohort study in Latvia, between January 1, and December 31, 2000 showed that from the 04 patients assessed, 55 (27%) had been newly diagnosed with MDRTB, and 149 (73%) had earlier been treated with first-line or second-line drugs for this disease. Treatment outcomes showed that 135 (66%) patients were cured or completed therapy, 14 (7%) died, 26 (13%) defaulted, and treatment failed in 29 (14%). Of the 178 adherent patients, 135 (76%) achieved cure or treatment completion(20).Similarly, in Estonia, overall successful treatment outcome was 60.4%, rising to 72.8% among adherent patients(27).

A retrospective study was performed to determine factors associated with the outcome of pulmonary MDR-TB in Taiwan indicated that 153 (51.2%) were cured, 31 (10.4%) failed, 28 (9.4%) died and 87 (29.1%) defaulted. Of the 125 patients receiving second-line drugs with ofloxacin, 74 (59.2%) were cured(28).In Iran, over 76% of the patients responded to the treatment (negative smear and culture). Cure and probable cure were documented in seven (41.2%) and four (23.5%) of the patients, respectively(29).

A retrospective observational study in South Africa on treatment outcomes showed that 491 (41%) were cured, 35 (3%) completed treatment, 208 (17%) failed treatment, 223 (18%) died and 252 (21%) defaulted.52% of patients with known HIV status were HIV-

infected(14).similarly, in a prospective Cohort,348 patients (46.0%) were successfully treated, 74 (9.8%) failed therapy, 177 (23.4%) died and 158 (20.9%) defaulted(16).

2.1.2. Review on factors associated with poor MDR-TB treatment outcomes

A systematic review and meta-analysis on treatment outcomes of multidrug-resistant tuberculosis patients published in 2009 showed that male gender 0.61 (or for Successful outcome) [0.46–0.82], low BMI 0.41[0.23–0.72], smear positivity at diagnosis 0.53 [0.31–0.91], fluoroquinolone resistance 0.45 [0.22–0.91] and the presence of an XDR resistance pattern 0.57 [0.41–0.80] as factors associated with worse outcome. This analysis includes 36 articles that represent 31 treatment programmes from 21 countries and a systematic search (to December 2008) to identify trials describing outcomes of patients treated for MDRTB were undertaken. However, this analysis doesn't show the risk with HIV–co infected patients ,and relied exclusively on observational data for treatment outcomes and also treatment outcome definitions were heterogeneous between populations(18).

A Nationwide Case-Control study in France in 1996 revealed HIV-coinfection ([HR] 41), treatment with less than two active drugs (HR 9.9), and MDR status knowledge at the time of diagnosis (HR 3.3) as factors related to a poorer outcome (17).

A retrospective evaluation in Turkey showed that 38% of the patients with unsuccessful outcomes were infected with organisms that were resistant to more than five drugs(23).similarly in another study, an unfavorable response was significantly associated with resistance to a greater number of drugs before the current courses of treatment (30).Similarly, in Israel patients' age, smear positivity at diagnosis and XDR-TB resistance pattern were identified as factors independently associated with death(13).

A retrospective cohort study conducted in patients with MDR-TB at 3 TB referral hospitals in the public sector of Korea showed that male sex, positive smear at treatment initiation, and XDR-TB were independent predictors of poor outcome(31).

A retrospective multi-center investigation to identify risk factors for poor treatment outcomes in Patients with MDR-TB and XDR-TB in China in 2013 showed that poor outcomes were associated with duration of previous anti-TB treatment of more than one year (OR, 0.077; 95% CI, 0.011-0.499, P<0.001), a BMI less than 18.5 kg/m^2 (OR,

2.185; 95% CI, 1.372-3.478, P<0.001), XDR (OR, 13.368; 95% CI, 6.745-26.497, P<0.001), retreatment (OR, 0.171; 95% CI, 0.093-0.314, P<0.001), diabetes (OR, 0.305; 95% CI, 0.140-0.663, P=0.003)(21).

A meta-analysis to identify predictors of poor outcomes among patients treated for MDR-TB at DOT-plus projects in Estonia, Latvia, Philippines, Russia, and Peru, 2000–2004 found that: age>45 years (RR = 1.90 (95%CI 1.29–2.80), HIV infection (RR = 4.22 (2.65–6.72)), BMI<18.5 (RR = 2.71 (1.91–3.85)), previous use of fluoroquinolone (RR = 1.91 (1.31–2.78)), resistance to any thioamide (RR = 1.59 (1.14–2.22)), baseline positive smear (RR = 2.22 (1.60–3.10)), no culture conversion by 3rd month of treatment (RR = 1.69 (1.19–2.41)) as independent predictors of death; cavitary disease (RR = 1.73 (1.07–2.80)), resistance to any fluoroquinolone (RR = 2.73 (1.71–4.37)) and any thioamide (RR = 1.62 (1.12–2.34)), and no culture conversion by 3rd month (RR = 5.84 (3.02–11.27)) as independent predictors of failure; unemployment (RR = 1.50 (1.12–2.01)), homelessness (RR = 1.52 (1.00–2.31)), imprisonment (RR = 1.86 (1.42–2.45)), alcohol abuse (RR = 1.60 (1.18–2.16)), and baseline positive smear (RR = 1.35 (1.07–1.71)) as independent predictors of default (19).

A retrospective study conducted in Peru in 2003 on community-based therapy for MDR-TB showed that inclusion of Pyrazinamide and Ethambutol in the regimen (when susceptibility was confirmed) was associated with a favorable outcome (hazard ratio for treatment failure or death, 0.30; 95 percent confidence interval, 0.11 to 0.83)(26).

A retrospective case series of 52 HIV-positive individuals receiving treatment for MDR-TB in Peru showed that low baseline weight predicted a three-fold increased rate of death while individuals receiving highly active ART experienced a significantly lower rate of death compared to those who were not(32).

A retrospective cohort study on Clinical outcome of individualized treatment of MDR-TB in Latvia between Jan 1, and Dec 31, 2000 showed that having previously received treatment for MDR-TB (HR 5·7, 95% CI 1·9–16·6), the use of five or fewer drugs for 3 months or more (3·2, 1·1–9·6), resistance to ofloxacin (2·6, 1·2–5·4), and BMI less than 18·5 at start of treatment (2·3, 1·1–4·9) as an independent predictors of poor outcome (death and treatment failure)(20).

Similarly, in another study in Estonia showed that HIV infection, previous TB treatment, resistance to ofloxacin and positive acid-fast bacilli (AFB) smear at the start of treatment as risk factors for poor treatment outcome in MDR-TB(27).In other study in Czech republic in 2010,resistance to capreomycin was an important predictor of poor outcome(33).

In a retrospective review of prospective single cohort in outcomes and follow-up of patients treated for multidrug-resistant tuberculosis in Orel, Russia, 2002–2005 showed that among 192 patients, factors significantly associated with poor outcome in multivariate analysis include three or more treatment interruptions during the intensive phase of therapy and alcohol or drug addiction (adjusted OR [aOR] 2.1, 95%CI 1.0–4.3 and aOR 1.9, 95%CI 1.0–3.7). Previous treatment was associated with poor outcome, but only among smear-positive patients (aOR 3.1, 95%CI 1.3–7.3)(15).

A retrospective observational study in South Africa on treatment outcomes showed greater baseline resistance, prior TB, and diagnosis in years 2001, 2002 or 2003 were independent risk factors for treatment failure. HIV co-infection was a risk factor for death and both HIV and male sex were risk factors for treatment default(14).similarly, in a prospective Cohort, HIV and Low baseline weight (less than 45 kg and less than 60 kg) was also associated with a higher hazard of death. (16).

In a study from south Africa which was done on risk of death among HIV co-infected MDR-TB patients, compared to mortality in the general population found that out of the 1413 patients that tested for HIV infection, 554 (39.2%) tested positive. Excess mortality was higher in HIV infected, compared to HIV uninfected, MDR-TB patients (adjusted excess hazard ratio, 5.6 [95% CI, 3.2-9.7]); in patients whose TB isolates' resistance to ethambutol and kanamycin was unknown (3.7 [2.1-6.2] and 4.87 [1.9-13.3], respectively) vs. known(34).

In a retrospective analysis of records conducted from Oct, 2011 - May, 2012 among cohorts of MDR-TB patients admitted in SPTSH, Addis Ababa, Ethiopia showed that smoking (HR: 4.01, 95% CI 1.42 - 11.37, $P = 0.009$), therapeutic delay > 1 month (HR: 3.61, 95% CI 1.41 - 9.20, $P = 0.007$), HIV-seropositive (HR: 5.94, 95% CI 2.40 - 14.72, $P < 0.0001$) and clinical complication (HR: 1.90, 95% CI 1.52 - 2.39, $P < 0.001$)as factors independently associated with mortality of patients(22).

In general, according to the different studies that we mentioned on the review section, socio-demography, co-morbidity, initial drug regimen, drug resistance pattern, previous TB history and type of TB affect MDR-TB treatment outcome. Being male sex, positive smear at treatment initiation, HIV-coinfection, treatment with less than two active drugs, previously received treatment for MDRTB, the use of five or fewer drugs for 3 months or more, resistance to ofloxacin, greater baseline resistance, prior TB, low BMI, fluoroquinolone resistance and the presence of an XDR resistance pattern have all been found to be related to poor MDR-TB treatment outcomes (Figure 1).

2.2. Conceptual frame work

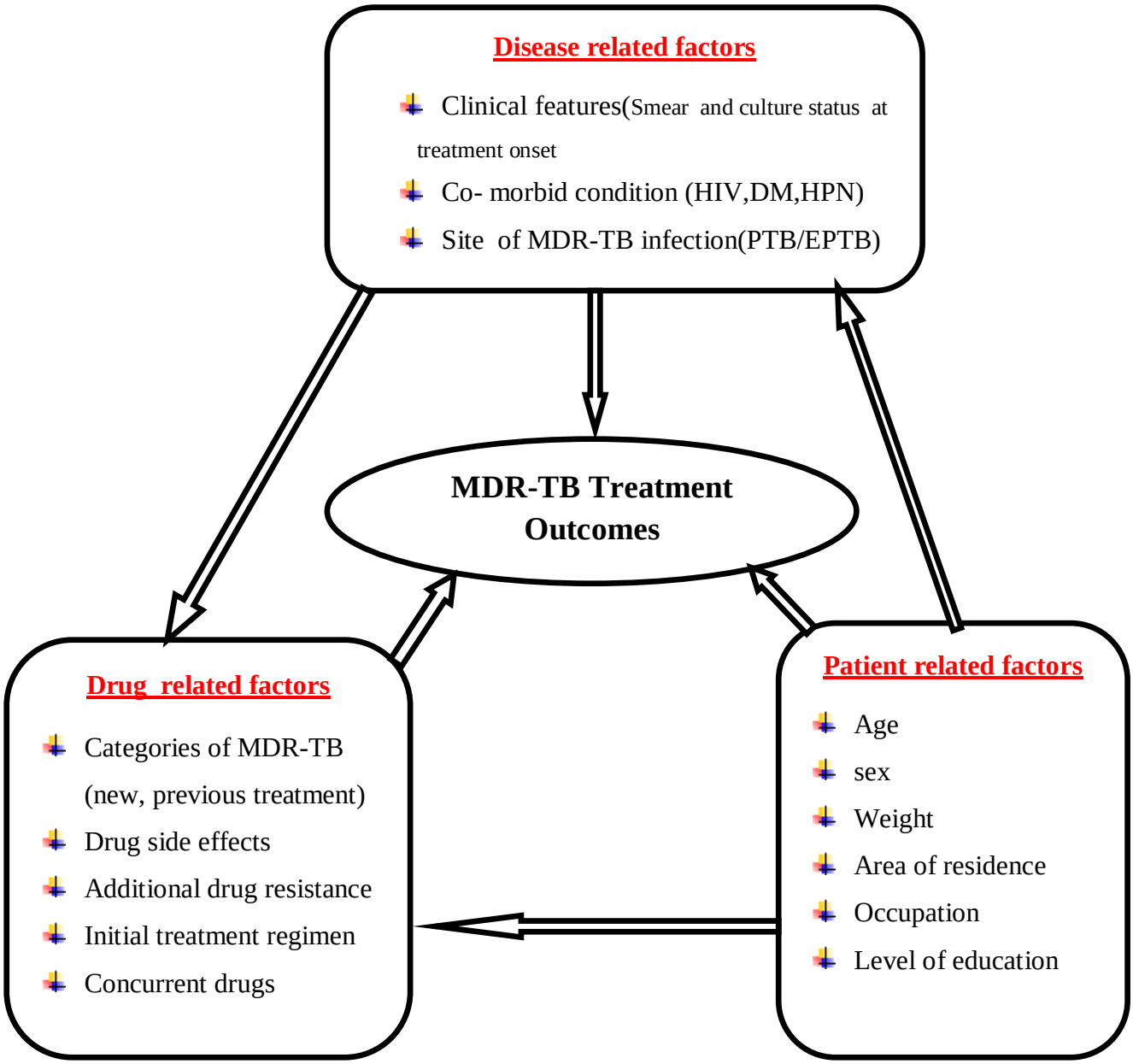

Figure 1: Conceptual frame work for risk factors associated with MDR-TB treatment outcome among MDR-TB patients at ALERT and University of Gondar hospitals, Ethiopia

2.3. Significant of the study

The present study, designed to asses treatment outcomes and to identify independent risk factors for poor treatment outcomes in patients with MDR-TB, highlights opportunities for improvement in treatment outcomes for MDR-TB, their by enhance the countries structured program for the management of MDR-TB in collaboration with the health centers, hospitals and relevant stake holders in the country, Ethiopia.

Previously predictors for death(22) have been studied at St.Peters TB specialized hospital, which was the first national referral MDR-TB treatment center in the country. However, factors associated with poor MDR-TB treatment outcome in general were not clearly identified, and studied. Thus, this study will also contribute to increase the knowledge about outcome of standard treatment of MDR-TB, and associated risk factors with poor MDR-TB treatment outcomes in our country Ethiopia, and this will be an input to health centers and hospital staffs who are involved in the management of this disease so as to develop strategies to alleviate the occurrence of the problem.

Finally, this paper, as baseline to other researchers for further studies on similar problems, and identifies risk factors associated with poor MDR-TB treatment outcomes in the country, which is essential in order to guide program planning, and organizing health service so as to reach the success rate set by WHO in Ethiopia.

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CHAPTER THREE: OBJECTIVES

3.1. Research questions

- ☞ What is the treatment outcomes of MDR-TB patients treated at ALERT and University of Gondar hospitals, Ethiopia?
- ☞ What are the risk factors for poor outcome of MDR-TB patients treated at ALERT and University of Gondar hospitals, Ethiopia?

3.2. General Objective

- ☞ To assess the treatment outcomes and risk factors associated with poor outcome among MDR-TB patients treated at ALERT and University of Gondar hospitals, Ethiopia.

3.3. Specific Objectives

- ☞ To assess the treatment outcomes among MDR-TB patients treated at ALERT and University of Gondar hospitals, Ethiopia.
- ☞ To determine risk factors associated with poor outcome among MDR-TB patients treated at ALERT and University of Gondar hospitals, Ethiopia.

CHAPTER FOUR: METHODS AND PARTICIPANTS

4.1. Study Area and period

4.1.1. ALERT CENTER

ALERT consists of a specialized, tertiary referral hospital, a research institute and a training center. It is located 7km south west of Addis Ababa`s city center, on the Jimma road , at the Capital City of the Federal Democratic Republic of Ethiopia .The hospital started MDR-TB services for patients who referred from different part of the country and from central Addis Ababa since November 2011 and has a total of 30 beds for admission.

4.1.2. UNIVERSITY OF GONDAR HOSPITAL

Gondar is located in the Semien Gondar Zone of the Amhara Region, Northwest Ethiopia and 727 km. far from Addis Ababa. University of Gondar hospital found in this town and has teaching hospital. The hospital provides health services for the population of Gondar town and remote areas of northwest Ethiopia. The total population served by the hospital is more than 5 million. The hospital has started MDR-TB treatment since December 2010 and has 24 beds for admission.

The study period was from April 30 to May 31/2014.

4.2. Treatment regimen and management

Among the 113 patients who began treatment the duration was recorded for 97.3% (110/113). All patients were admitted for initial therapy, then discharged for ambulatory DOT .Treatment lasted a median of 21 months (range 1·0–27).

The drugs in both hospital MDR-TB clinic consists similar groups of first and second line anti-TB medications. All patients in our study group were started on nationally standardized regimen for MDR-TB treatment. The regimen is Pyrazinamide(Z), Capreomycin (Cm),Levofloxaciline(Lfx),Ethionamide(Eto),Cycloserine (Cs).Ethambutol (E) is added when susceptibility dictates, and Para-aminosalicylic acid (PAS) is reserved to be used when other drugs can’t be used due to side effects. This regimen may be modified as needed in various co morbid states (called special conditions in MDR-TB

treatment) like pregnancy, diabetes, psychiatric disorders, seizure disorders, liver and renal diseases).

4.3. Study design

Hospital based retrospective general cohort study was employed.

4.4. Population

All patients treated for MDR-TB in the country.

4.4.1. Source population

All patients treated for MDR-TB at ALERT and University of Gondar Hospitals.

4.4.2. Study participants

All patients treated for MDR-TB at ALERT and University of Gondar Hospitals from December 2010 to May 31/2014, and who were eligible only.

4.5. Eligibility criteria

4.5.1. Inclusion criteria

- Patients who had active TB as evidenced by positive culture or by previous treatment failure with clinical evidence of active disease
- Patients who had documented MDR-TB or suspected MDR-TB based on a history of previous treatment failures, and
- Full patient registries and documented outcome

4.5.2. Exclusion criteria

- Monoresistance, polyresistance
- Double outcome registers for single patient
- MDR-TB patients who are on treatment
- MDR-TB patients documented as transfer out.
- incomplete documentation

4.6. Sample size and sampling technique/procedure

All patients treated for MDR-TB at ALERT and University of Gondar Hospitals from December 2010–May 2014 that fulfill the inclusion criteria were included, and no sampling technique/procedure was used.

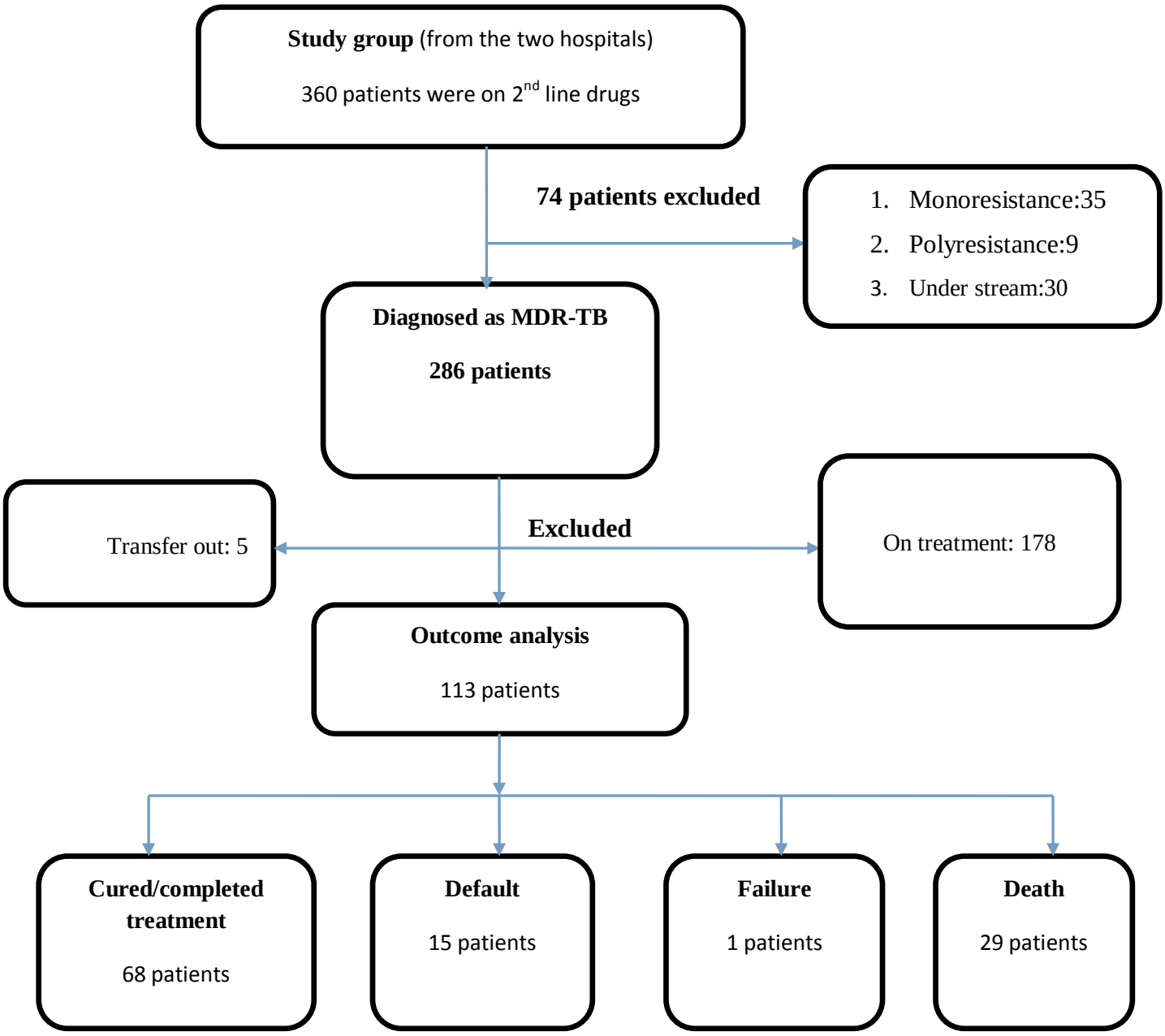


Figure 2 .Flow charts showing the study profile

4.7. Variables in the study

*4.7.*1. Dependent variables

- MDR-TB treatment outcomes
  - Cured
  - Treatment completed
  - Default
  - Failure
  - Death

*4.7.*2. Independent variables

- **Patient related factors :**
  - ☞ **Socio-demographic factors:**
    - Age
    - Sex
    - Weight
    - Occupation
    - Level of education
    - Area of residence

- **Disease related factors :**
  - Clinical features
    - ✓ Smear +ve at treatment onset
    - ✓ Culture +ve at treatment onset
  - Co morbid condition (HIV or others)
  - Site of MDR-TB infection(PTB/EPTB)
- **Drug related factors :**
  - Categories of MDR-TB: new, previously treated
  - Adverse drug events
  - Additional drug resistance
  - Initial treatment regimens
  - Concurrent medication

4.8. Data collection instrument and Procedure

Data was collected through medical records review of patients using a prepared standard checklist from MDR-TB register books and medical chart from April 30 to May 31,2014 from a cohort of MDR-TB patients (N = 113) enrolled in a study of programmatic management of MDR-TB in Ethiopia from 2010 to 2014.

The data collected included patients' baseline demographic, treatment and clinical variables (for example; sex, age, baseline weight, HIV status, previous treatment for TB and MDR-TB, drug susceptibility). Adverse drug events data for most commonly identified drug reactions related to second line drugs treatment were also collected and were analyzed descriptively. Treatment outcome variables collected included completion or cure, failure, default and death and transfer out.

4.9. Data Quality Assurance

In order to assure the quality of data the following measures were undertaken:- Pre-test was done at Shenen Gibe hospital found at Jimma town, Southwest Ethiopia. Data was collected by Bsc nurses and a pharmacist (supervisor) working at the MDR-TB clinic at SPTSH and University of Gondar hospital for ALERT hospital and University of Gondar hospital data collections, respectively. The data collectors and supervisor were trained for one day on the data collection format and techniques for data collection. Supervisor was closely followed the data collectors daily, and the principal investigator also reviewed all filled checklist.

4.10. Statistical analysis

Data was checked and cleaned for its completeness. The baseline characteristics and treatment outcomes were identified for all patients and were described using simple frequencies and medians. Student's t-test was performed to compare continuous variables. To identify the risk factors for poor outcome, we compared variables between treatment success and poor outcome using bivariate analysis. Variables with a $p < 0.2$ on bivariate analysis were then incorporated in to a multivariate logistic regression model for the composite poor outcome, and also checked for correlation between variables included in multivariate analysis. All analysis were performed using SPSS version 20.0

(SPSS Inc, Chicago, IL, USA), and the results with $P < 0.05$ were considered statistically significant.

4.11. Ethical consideration

Letter of ethical clearance was obtained from Research and Ethics Committee of Jimma University and AAERC. The patient's data were accessed upon the approval from Clinical Service director of ALERT and University of Gondar Hospitals at each treatment centers, respectively. The information that was taken from patients' medical record was used only to identify factors related to poor treatment outcome. The data collection process was carefully guided by the principal investigator, and data collectors were trained on data collection tool, handling patient data confidentiality and appropriate data abstraction as per the data collection tools only. The name of individual patient was not required or mentioned in data collection tool, instead only the variables that are mentioned on checklist were collected during the data collection time to ensure confidentiality.

4.12. Dissemination plan

The result of the study will be disseminated to responsible bodies such as Jimma university department of Pharmacy, Federal Ministry of Health, Ethiopian food, medicine and health administration and control agency, pharmaceutical fund and supply agency, to ALERT hospital, University of Gondar hospital, and also to all new MDR-TB treatment centers.

The findings will be presented at each hospital, and on scientific conferences, and also be submitted to professional journal for publication so as to serve as baseline for further studies.

4.13. Operational Definitions and Definition of Terms:

Definition of Terms (7)

A **bacteriologically confirmed TB case** is one from whom a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.

A **clinically diagnosed TB case** is one who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment.

Extra pulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

Extra-pulmonary MDR-TB refers to organs other than the lungs.

Extensive drug-resistance (XDR): Resistance to isoniazid and rifampicin (i.e. MDR) as well as any fluoroquinolone, and any of the second line injectable Anti TB drugs (Capreomycin, kanamycin, and amikacin).

Empiric Treatment: Each regimen is individually designed based on the patient's past history of TB treatment and with consideration of DRS data from the representative patient population. An empirical regimen is adjusted when DST on individual patient becomes available.

Individualized Treatment: Each regimen is adopted according to guidelines based on the patient's past history of TB treatment, individual FL- and SL-DST results and possible side-effects.

Pulmonary MDR-TB refers to disease involving the lung parenchyma. A patient with both pulmonary and extra-pulmonary MDR-TB constitutes a case of pulmonary MDR-TB.

Previously treated with first-line drugs only: a patient who has been treated for one month or more for TB with only first-line TB drugs.

Previously treated with second-line drugs: a patient who has been treated for one month or more for TB with one or more second-line drugs, with or without first-line TB drugs.

Poly-resistance: Resistance to more than one first line anti-TB drugs, but not to both isoniazid and rifampicin.

Mono-resistance: Resistance to only one first line anti-TB drugs.

New: a patient who has received no or less than one month of anti-tuberculosis treatment.

Standardized treatment: Drug Resistance Survey (DRS) data from representative patient populations are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen.

Treatment Outcome Definitions:

MDR TB treatment outcome was classified according to standardized definitions(35).

- **Cure:** was defined as completion of treatment while remaining consistently culture-negative (with at least five results) in the final 12 months of treatment. Clinicians may mark a patient as cured if only one of the cultures is positive, but it is followed by three consecutive negative cultures and there is no concomitant clinical evidence of deterioration.
- **Treatment completion:** was defined as completion of the entire treatment course but without bacteriologic documentation of cure.
- **Treatment failure:** was defined as having more than one positive culture in the last 12 months of treatment, with a minimum of five monthly cultures performed during the last 12 months. Treatment was also considered to have failed if one of the last three cultures taken during treatment was positive, or if the patient was persistently culture positive and a clinical decision was made to terminate treatment.
- **Default:** was defined as treatment interruption for 2 or more consecutive months for any reason.
- **Death:** was defined as death from any cause during MDR-TB treatment.
- **Transfer out:** was defined as transferred to another reporting and recording unit and for whom the treatment outcome is unknown.
- **No outcome assigned**: was defined as a patient in treatment program whose final outcome cannot be determined as he/she is still on treatment at the end of reporting period.

Stream patients: MDR-TB patients under clinical trial

For the purpose of analysis:

- **Successful outcome:** was defined as Patients who were cured or who successfully. completed treatment
- **Poor outcome or composite poor outcome:** was defined as treatment failure, default or death from any cause.
- **Far from the facility:** patients who are living outside the city of the treatment centers
- **Near to the facility:** patients who are living inside the city of the treatment centers.
- **Contact person:** responsible person during the course of treatment.
- **Additional drug resistance:** presence of additional resistance than the two, isoniazid and rifampicin.
- **Primary MDR-TB:** newly acquired infection from a patient already infected with the resistant strain.
- **Secondary MDR-TB:** infection that evolve in a patient with a sensitive strain who was inadequately treated.

CHAPTER FIVE: RESULTS

In total, from December 2010–May 2014,360 patients were registered and took 2nd line drugs at both hospitals. From which, 286 patients were diagnosed as MDR-TB. Out of these confirmed patients, 178 patients were still on treatment. Out of all MDR-TB patients, 118 patients had documented outcomes at both hospitals. Five patients who had documented outcome as transfer out were excluded, hence, 113 patients were included in the cohort under assessment, 42 (37.2%) from ALERT Hospital, and 71 (62.8%) from the University of Gondar Hospital, Ethiopia.

5.1. Socio-demographic characteristics of patients

MDR-TB outcomes were thus assessed for 113 patients: 62(54.9%) were men, and median age was 30 years (IQR: 24.0-40.5) and the median baseline weight was 46kg (IQR: 43.0-51.6). There were only one child with the age of one year old, and no pregnant women were identified, and the majorities, 56(49.6%) were between the ages of 25 to 44 years old. Most of the patients, 98(86.7%) had contact person during the course of treatment. Over half of the patients, 58(51.3%) were located far from the treatment center. Of 107 patients, 43(40.2%) were at secondary school levels (Table 1).

TABLE 1: Socio-demographic characteristics of patients with MDR-TB at ALERT and University of Gondar hospitals, Ethiopia, 2014 (N=113)

Demographics	Number of patients (%)
Age, years ,median (IQR)	**30.0(24.0-40.5)**
≤ 24	33(29.2)
25-44	56(49.6)
≥ 45	24(21.2)
Sex	
Male	62(54.9)
Female	51(45.1)
Baseline weight ,(Kg), median(IQR)	**46.0(43.0-51.6)**
≤ 45	51(45.1)
46-54	42(37.2)
≥ 55	20(17.7)
Place of residence*	
Near	55(48.7)
Far	58(51.3)
Contact person	
Yes	98(86.7)
No	15(13.3)
Occupational status	
Employed**	30(26.5)
Unemployed	30(26.5)
Merchant	17(15.0)
Farmer	10(8.8)
House wife	10(8.8)
Unknown	16(14.2)
Educational level(n=107)	
Illiterate	14(13.1)
Primary	27(25.2)
Secondary	43(40.2)
Higher	23(21.5)

*place where the patients reside near or far from the treatment centers.
IQR=interquartile range)

5.2 Disease characteristics

Pulmonary disease was most common 102(90.3%); 81(79.4%) of these cases were sputum smear positive at the time of treatment initiation. HIV tests were performed for all patients and the majority 91(80.5%) were sero-negative. Of 113 patients, 30(26.5%) had at least 1 co morbidity. HIV positive was the most common (n=22, 19.5%), followed by Diabetes mellitus (n=10, 8.8%).

When patients were categorized on the basis of their previous treatment histories: 6(5.3%) were new patients, and 107 (94.7%) had been treated previously with first-line drugs only, and no patients had been treated with second-line drugs previously in this study subjects (Table 2).From the previously treated patients with first-line drugs, majority of them were failure after re-treatment (n=89, 83.2%) (Fig.3)

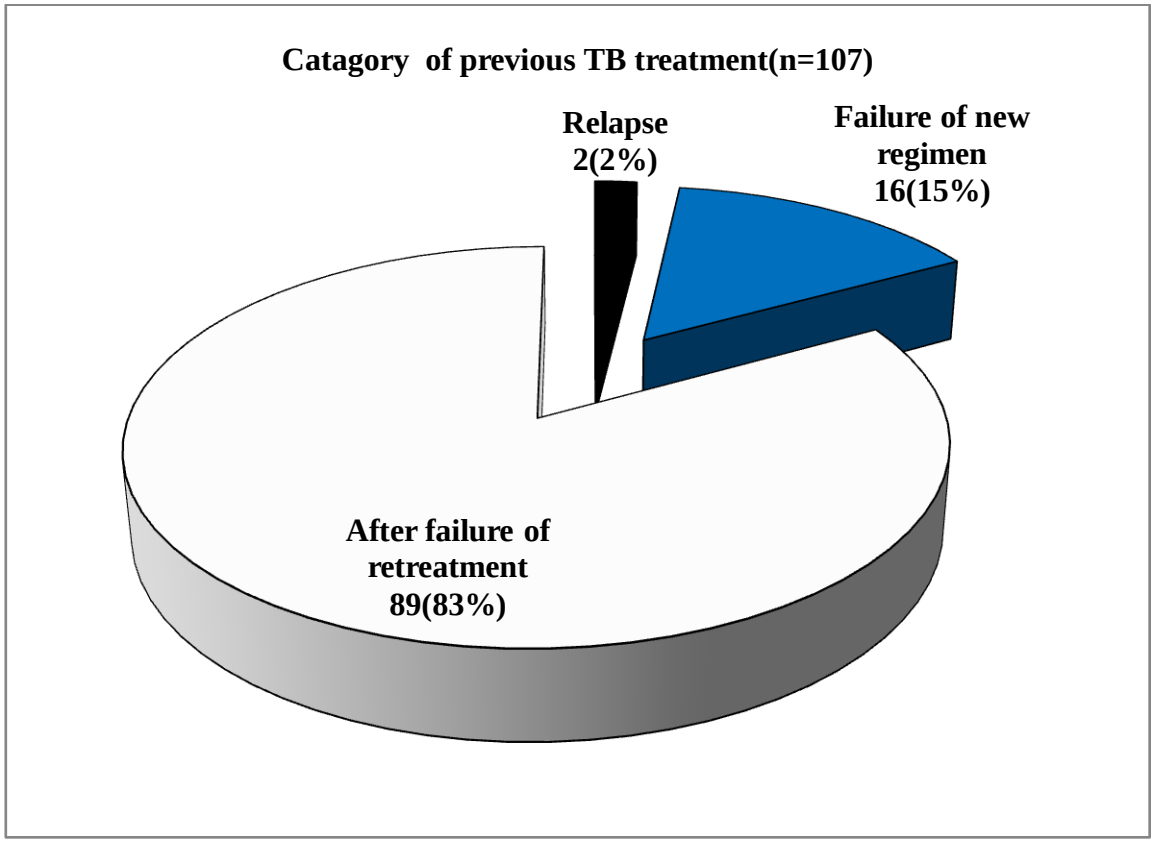


Figure 3: MDR-TB patients by previous TB treatment category at ALERT and University of Gondar Hospitals, Ethiopia

TABLE 2: Disease characteristics of patients with MDR-TB at ALERT and University of Gondar hospitals, Ethiopia, 2014 (N=113)

Clinical Characteristics	n (%)
Category of MDR-TB	
New	6(5.3)
Previously treated for TB	107(94.7)
Co-morbidity(n=30,26.5%)	
None	83(73.5)
Any	30(26.5)
HIV positive(n=113)	16(14.2)
Diabetes(n=113)	5(4.4)
Renal failure(n=113)	1(0.9)
Hypertension(n=113)	3(2.7)
HIV and diabetes(n=113)	5(3.5)
HIV and DVT(n=113)	1(3.3)
HIV status	
Positive	22(19.5)
Negative	91(80.5)
Site of MDR-TB	
Pulmonary, smear positive	81(71.7)
Pulmonary, other**	21(18.6)
Extraplumonary disease only	11(9.7)

** Patients with negative smear at initiation of treatment.

5.2.1. Sputum smears and culture examination

Sputum smear and culture examination were conducted every month for all patients during the entire follow-up period. At the start of treatment 34.5% patients were registered as unknown sputum culture status.

Among patients with pulmonary TB, 81(80.2%) were sputum smear–positive. In 13 (16.0%) of these 81 patients, the sputum smear did not convert to negative. Of the remaining 67 patients, the median time to initial sputum smear conversion was 2 month (range, 1 to 6).

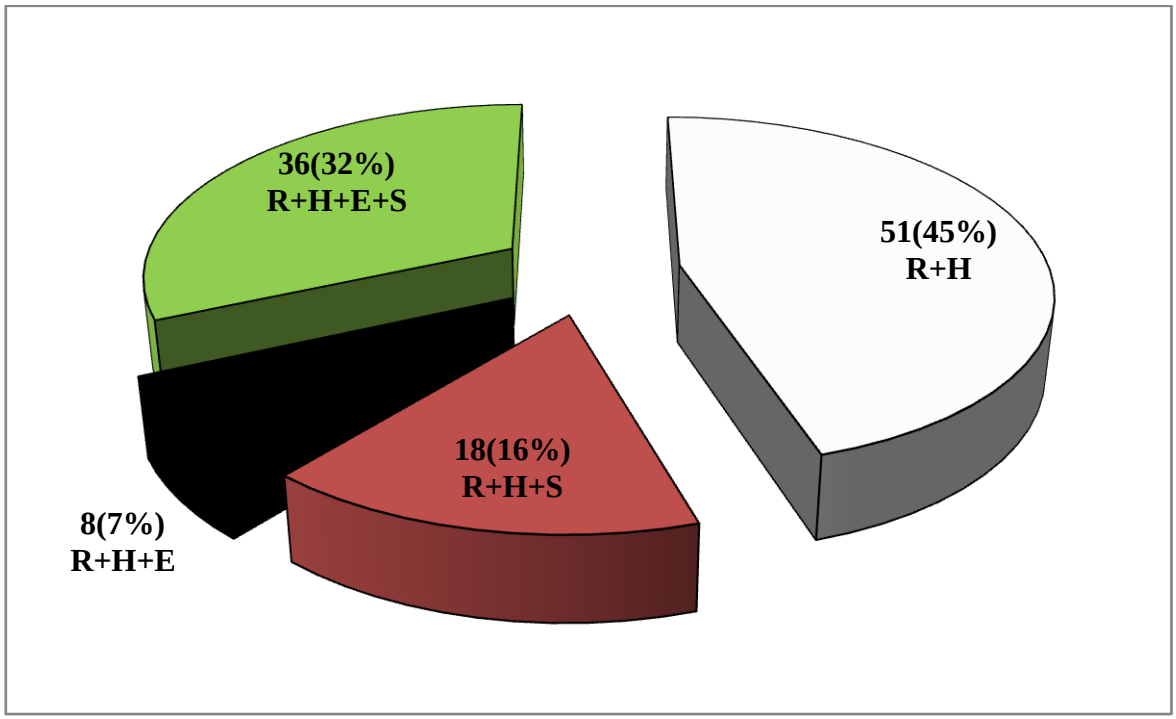
In our cohort, from the total of 88 patients that had data on culture conversion, 68 patients (86%) achieved sputum culture conversion and 11 (14%) did not. Among the 68 patients who converted, 13.2 % did so after 1 month of treatment, 26.5% did so after 2 months of treatment, 26.5% did so after 3 months of treatment and 33.9 % had converted after 4 months of treatment. For these patients, the median initial sputum culture conversion time was 3 months (range, 1 to 7 months).

TABLE 3: Sputum smears and culture examination of MDR-TB patients at ALERT and University of Gondar hospitals, Ethiopia, 2014

Smear conversion(n=101)	n(%)	Median(range)
Smear positive at treatment onset	81(80.2)	
Smear negative at treatment onset	20(19.8)	
Time to initial conversion, months (n=67)		2(1-6)
Culture conversion(n=88)		
Culture positive at treatment onset	40(81.6)	
Culture negative at treatment onset	9(18.4)	
Unknown initial status *	39(34.5)	
Time to initial conversion, months (n=68)		3(1-7)
***unknown status at presentation**		

5.3. Drug related characteristics

Of all 113 confirmed MDR-TB patients, 51(45%) had resistance to isoniazid and rifampicin only, 26(23%) to isoniazid, rifampin and one additional drug, 36(32%) to isoniazid, rifampin and two additional drugs. Isolates were resistant to a median of 3 drugs (range 2-4). The baseline resistance patterns are shown by figure 4.



H, isoniazid; R, rifampicin; E, ethambutol; S, streptomycin;

Figure 4.Drug resistance patterns of patients with MDR-TB at ALERT and University of Gondar Hospitals, Ethiopia

The proportions resistant to Streptomycin and Ethambutol were 47.8% and 38.9%, respectively (figure 5). There were no cases of XDR-TB identified.

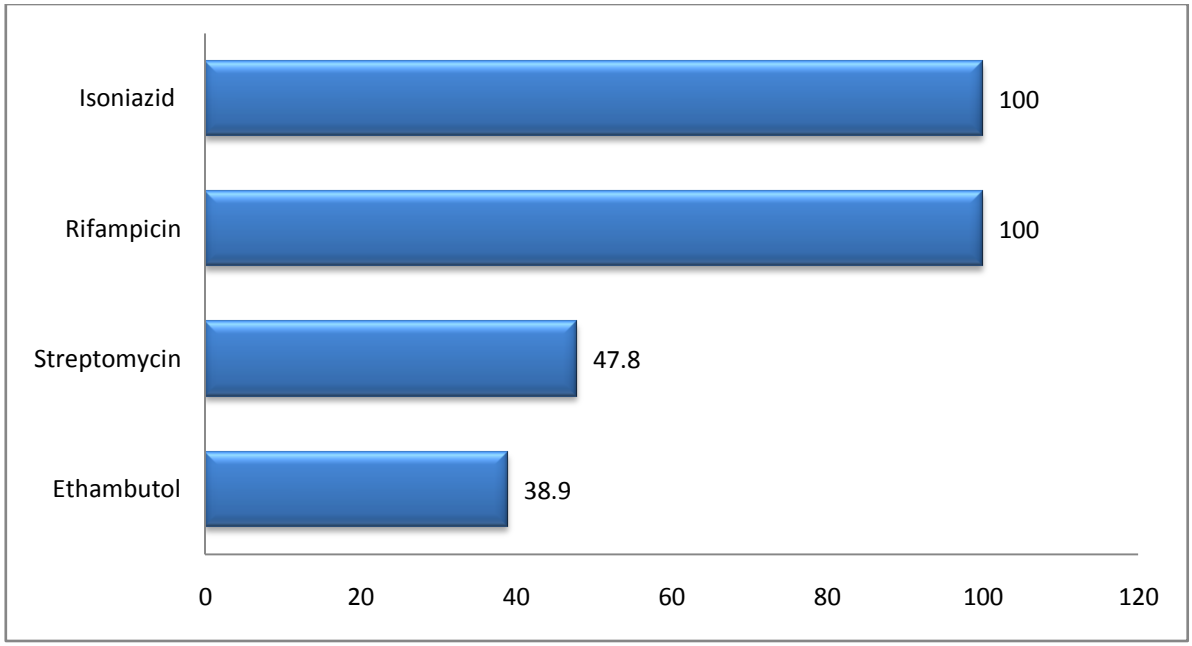


Figure 5.Drug resistance of M. tuberculosis in 113 patients on admission

5.4. Adverse drug events

Ninety two (89.3%) patients had recorded adverse drug events associated with treatment, with the frequency of gastrointestinal disturbance 75(72.8%), psychiatric disorders 29(28.2%), dermatological effects 13(12.6%), neurological disorders 56(54.4%), Hypokalemia 58 (56.3%), Arthralgia 23(22.3%), and hepatitis 4(3.9%) (Table 4).

TABLE 4: Adverse events of drugs used in the treatment of MDR-TB patients at ALERT and University of Gondar hospitals, Ethiopia, 2014

Adverse effects	**n (%)**
Any	92(89.3)
None	11(10.7)
Adverse drug events reported per person, median(range)	**3(0-7)**
Gastrointestinal disturbance	75(72.8)
Psychiatric disorders	29(28.2)
Dermatological disorders	13(12.6)
Neurological disorders	56(54.4)
Hypokalemia	58(56.3)
Arthralgia	23(22.3)
Hepatitis	4(3.9)
***Adverse effect reports not mutually exclusive.**	

5.5. Treatment Outcomes

Of the 113 patients, the assessment of treatment outcomes revealed that 68 (60.2%) had successful outcome: 55 (48.7%) were cured and 13 (11.5%) completed treatment; 45 (39.8%) had a poor outcome: treatment resulted in failure in 1 (0.9%) cases, 15 (13.3%) defaulted treatment and another 29 (25.6%) patients died.

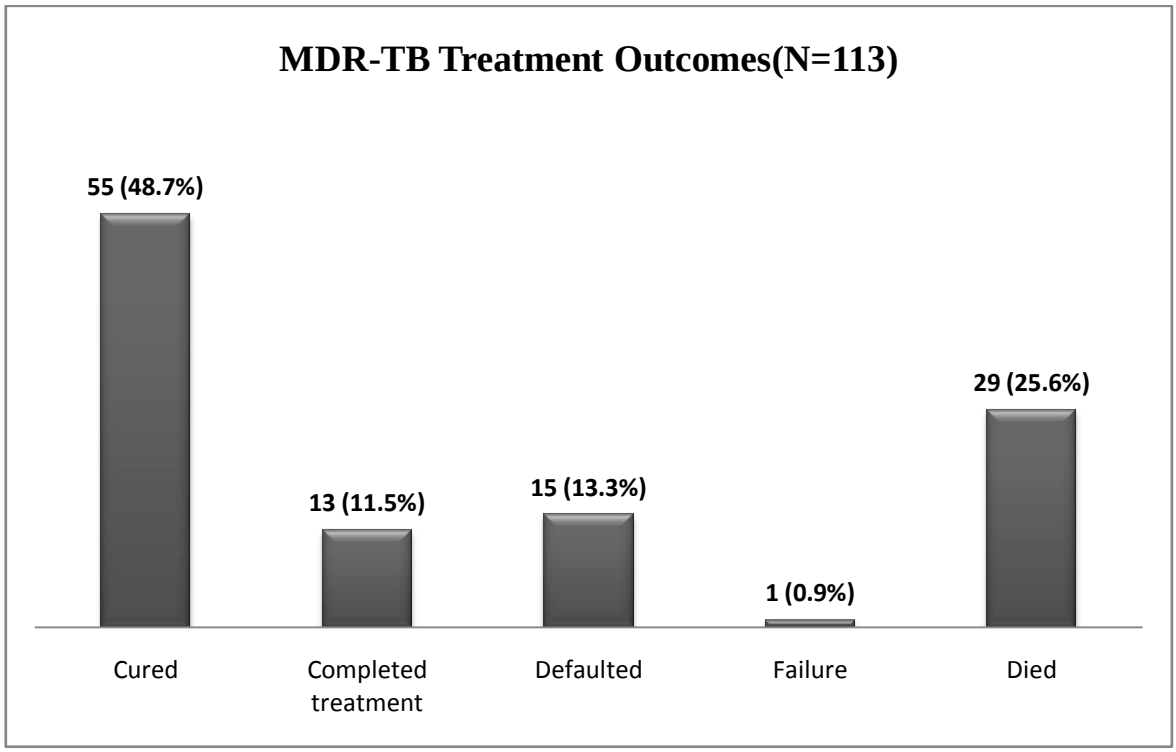


Figure 6: MDR-TB treatment outcomes of patients treated at ALERT and University of Gondar hospitals, Ethiopia.

5.6. Association of patient related factors with poor MDR-TB treatment outcome

Bivariate analysis of the socio-demographic factors indicated that poor treatment outcome were statically significant for baseline weight ≤45kg (P=0.007), age ≥45 years (P=0.043), and for illiterate ones (P=0.019).But, the other factors didn't showed significance at P <0.05 (Table 5).

TABLE 5: Bivariate analysis of association of socio-demographic characteristics with poor treatment outcome in patients with MDR-TB at ALERT and University of Gondar hospitals, Ethiopia, 2014 (N=113)

Variables	Poor Treatment Outcome (n=45)	Treatment Success (n=68)	COR (95% CI)*	P value
Sex				
Male	25(40.3)	37(59.7)	1.047(0.491-2.233)	0.905
Female	20(39.2)	31(60.8)	1	
Age, Years				
≤ 24	9(27.3)	24(72.7)	1	
25-44	23(41.1)	33(58.9)	1.859(0.731-4.724)	**0.193**
≥ 45	13(54.2)	11(45.8)	**3.152**(1.039-9.561)	**0.043**
Baseline Weight(Kg)				
≤ 45	31(62.0)	19(38.0)	**4.895**(1.531-15.647)	**0.007**
46-54	9(20.9)	34(79.1)	0.718(0.227-2.774)	0.794
≥ 55	5(25.0)	15(75.0)	1	
Place of residence				
Near	18(33.3)	36(66.7)	1	
Far	27(45.8)	32(54.2)	1.687(0.787-3.620)	**0.179**
Contact person				
Yes	34(37.4)	57(62.6)	1	
No	11(50.0)	11(50.0)	1.676(0.657-4.281)	**0.28**
Educational level, n=107				
Illiterate	10(71.4%)	4(28.6%)	5.71(1.326-24.62)	**0.019**
Primary	12(44.4%)	15(55.6%)	1.83(0.568-5.882)	0.311
Secondary	15(34.9%)	28(69.6%)	1.22(0.413-3.632)	0.715
Higher	7(30.4%)	16(69.6%)	1	

*COR=cruds odds ratio,1=referent

5.7. Association of disease related factors with poor MDR-TB treatment outcome

Bivariate analysis of the disease related factors indicated that poor treatment outcome were statically significant for pulmonary smear positive at presentation (P=0.006), and for HIV co infected ones (P=0.004).But, the other factors didn't showed significance at P <0.05(Table 6).

TABLE 6: Bivariate analysis of association of disease related characteristics with poor treatment outcome in patients with MDR-TB at ALERT and University of Gondar hospitals, Ethiopia, 2014 (N=113)

Variables	Poor Treatment Outcome (n=45)	Treatment Success (n=68)	COR(95% CI)*	P value
Site of disease				
Pulmonary, smear positive	39(48.1)	42(51.9)	**4.024**(1.497-10.817)	**0.006**
Pulmonary/Extraplumonary	6(18.8)	26(81.2)	1	
HIV status				
Positive	15(68.2)	7(31.8)	**4.357**(1.606-11.820)	**0.004***
Negative	30(33.0)	61(67.0)	1	
Co-morbidity, other than HIV				
Yes	5(55.6)	4(44.4)	2.0(0.51-7.89)	**0.322**
No	40(38.5)	64(61.5)	1	

*COR=cruds odds ratio,1=referent

5.8. Association of drug related factors with poor MDR-TB treatment outcome

Bivariate analysis of drug related factors indicated that poor treatment outcome were statically significant for additional drug resistance at treatment initiation (P=0.043).But, the other factors didn't showed stastical significance at P <0.05(Table 7).

Having analyzed the data, the difference in treatment outcome was not statistically significant for category of MDR-TB (*P* = 0.261). Likewise, all patients received PZA and 55.8%, 63/113) received EMB based on their DST results. Nevertheless, treatment outcomes did not indicate any significant difference between those who had received PZA and EMB vs. those cases who received PZA, and not EMB based standard combination treatment of six drugs(P=0.46).

TABLE 7: Bivariate analysis of association of drug related factors with poor treatment outcome in patients with MDR-TB at ALERT and University of Gondar hospitals, Ethiopia, 2014 (N=113)

Variables	Poor Treatment Outcome (n=45)	Treatment Success (n=68)	COR(95% CI)*	P value
Category of MDR-TB				
New	1(16.7)	5(83.3)	1	
Previously treated for TB	44(41.1)	63(58.9)	3.492(0.394-30.932)	**0.261**
Additional drug resistance**				
No	26(50.0)	26(50.0)	1	
Yes	19(31.1)	42(68.9)	0.452(0.21-0.975)	**0.043**
Drug combinations at initiation of treatment				
Lfx+Cm+Z+E+others	27(42.9)	36(57.1)		
Lfx+Cm+Z+others(not E)	18(36.0)	32(64.0)	0.75(0.350-1.609)	**0.460**

**in addition to isoniazid and rifampicin resistance at initiation of treatment
*COR=cruds odds ratio
Lfx=Levofloxacilin, Cm=Capreomycin ,Z=Pyrazinamide, E=Ethambutol ,

5.9. Factors independently associated with poor MDR-TB treatment outcome

Our bivariate regression analysis showed that certain demographic, disease as well as drug related characteristics were shown to have associations at $p<0.05$.

From the risk factors identified on bivariate analysis, age ≥45 years (COR, 3.152; 95% confidence interval [CI], 1.039-9.561; *P* = 0.043), the presence of additional drug resistance (COR, 0.452; 95% CI, 0.21-0.975; *P* = 0.043) were shown associations, but this variables didn`t showed in multivariate logistic regression analysis, P values, 0.171 Vs 0.607, respectively.

In our multivariate logistic regression model, risk factors: HIV infection, (AOR, 3.774; 95% confidence interval [CI], 1.145-12.436; *P* = 0.029), positive smear at treatment initiation (AOR, 4.621; 95% CI, 1.406-15.185; *P* = 0.012), and baseline body weight ≤45kg at treatment initiation (AOR, 4.987; 95% CI, 1.270-19.582; *P* = 0.021) were remained independently associated with poor treatment outcome**.**

TABLE 8: Multivariate analysis of factors independently associated with poor treatment outcome in patients with MDR-TB at ALERT and University of Gondar hospitals, Ethiopia, 2014 (N=113)

Variables	Poor Treatment Outcome (n=45)	Treatment Success (n=68)	AOR (95% CI)*	P value
Age, Years				
≤ 24	9(27.3)	24(72.7)	1	
25-44	23(41.1)	33(58.9)	1.997(0.629-6.345)	0.241
≥ 45	13(54.2)	11(45.8)	2.657((0.656-10.761)	0.171
Baseline Weight(Kg)				
≤ 45	31(62.0)	19(38.0)	**4.987**(1.270-19.582)	**0.021**
46-54	9(20.9)	34(79.1)	0.579(0.144-2.329)	0.442
≥ 55	5(25.0)	15(75.0)	1	
Place of residence				
Near	18(33.3)	36(66.7)	1	
Far	27(45.8)	32(54.2)	1.198(0.452-3.176)	0.717
HIV status				
Positive	15(68.2)	7(31.8)	**3.774**(1.145-12.436)	**0.029**
Negative	30(33.0)	61(67.0)	1	
Site of disease				
Pulmonary, smear positive	39(48.1)	42(51.9)	**4.621**(1.406-15.185)	0.012
Pulmonary/Extraplumonary	6(18.8)	26(81.2)	1	
Additional drug resistance				
No	26(50.0)	26(50.0)	1	
Yes	19(31.1)	42(68.9)	0.773(0.289-2.067)	0.607
1=referent, AOR=adjusted odds ratio				

CHAPTER SIX: DISCUSSION

In this study, hospital based retrospective general cohort study was conducted to describe the treatment outcomes and risk factors from the cohort of MDR-TB patients who took a standard treatment regimen at two national MDR-TB referral hospitals, ALERT and University of Gondar hospitals, Ethiopia, from December 2010 to May 2014.

According to the finding of this study, 60.2% of patients achieved successful treatment outcome, comprising 48.7% cured and 11.5% completed treatment, from the cohort of MDR-TB treated patients at the two treatment centers. Compared with the WHO target of 75% success rate, and published reports from resource-limited settings (19, 20, 23, 25), that demonstrated success rate above 65%, treatment success rate in our study was lower. This is due to the higher rate of poor outcome in our study, and the reason for this difference is explained in terms of poor outcome discussion section. It is also known that interruption of the drug-resistant tuberculosis transmission cycle is possible if the cure rate is 60%. A cure rate of 80% is needed to achieve a 10-fold reduction in MDR-TB incidence within 20 yrs (36). This success rate could be a feasible target in Ethiopia if we learn from the experiences of other countries, and by giving due considerations for risk group of patients.

The rate of poor outcome in our study was 39.8%, comprising 25.6% died, 13.3% defaulted and 0.9% failed from treatment. Despite the fact in settings without the history of previous exposure with second-line drugs that yields better outcome(25), the rate of poor outcome in our study was similar with studies from high exposure to second-line drugs, Estonia 39.6%(27) and Russia(40%) (15). Compared with a report from the cohorts of MDR-TB patients in resource limited setting (19, 20, 25), that ranges from 23% to 34%, the percentage of poor outcome in our study was higher. One reason for higher rate of poor outcome in our study than the published reports were , First, treatment approach difference, individualized based treatment regimen(Latvia, Korea, Turkey), and also consider surgical resection for patients who were candidate, as this increases the success rate (24), thereby a decrease in poor outcome. Second, sputum culture and DST to first- and second-line drugs are performed at the project site , but in our case ,samples were collected and sent to the regional laboratory for analysis, and this may delay in initiation of therapy, as this is indicated as independent risk factor for poor

outcome by different studies(2, 22). Third, countries have well-established TB control programs such as DOTS (directly observed treatment, short-course)-Plus. Fourth, the high poor outcome in this study is probably with high mortality rate (64.4%).

However, the rate of poor outcomes was lower than the reports from South Korea 62.9% (31), China(59.05%) (21),South Africa (56%,54%) (14, 16), and Taiwan (48.9%) (28).The low rate of poor outcome in our study explained by; all patients in our study are not previously treated or exposed to second line drugs, less burden of M(X)DR-TB setting, sample size(china, multi-center investigation),from high HIV prevalent setting and before the era of HAART(south Africa), treatment outcome definitions difference(south Korea).

Areas of concern for management of MDR-TB in Ethiopia remain, with respect to treatment interruption, although patients received treatment under direct observation, 13.5% defaulted. Similar proportions of defaulters have been found in studies from Latvia(20),Russia(15) and meta-analysis(18). In another report from resource limited settings, the percentage of defaulters ranging from 6.3% to 16.0%(25), which is high to the range, and the percentage of defaulters was somewhat lower in Turkey(23), being 11.0% in MDR-TB patients, but according to a report on MDR-TB patients from South Korea, the proportion of defaulters was almost three times as high, reaching 37.1% (31) and twice in Taiwan 29.1%(28).

Despite the difference in composite poor outcome between studies, the death rate in our study was 25.6 %, which comprised 64.4% of the poor outcomes, with the exception in Israel (30.4%) (13), making these death rates among the worst seen in the published literature. A recent meta-analysis from 34 published MDR-TB cohorts in 20 countries. The pooled death rate was 11%% (range 9% to 13%)(18), and other published cohorts, such as from Peru, Latvia, Turkey and Taiwan, also demonstrate death rates of less than 10%. All of our patients were previously exposed to first line drugs only; with few to fail the treatment, 0.9%.

Our multivariate logistic regression analysis revealed: risk factors independently associated with increased odds of poor outcomes were patients' with baseline weight ≤45kg, positive sputum smear at presentation and HIV co infection. Additional drug

resistance (than isoniazid and rifampicin) and ages of ≥ 45 years were found association only on the bivariate analysis.

In our study, as in several previous studies that showed HIV positive patients were found to have high rate of poor outcome than HIV negative patients (17, 19, 27, 34, 37), an association of poor MDR-TB treatment outcome with HIV infection was found. Despite the prevalence (only 19.5% of MDR-TB patients were HIV infected) the risk of poor treatment outcome in that particular subpopulation was nearly 3.8 times higher (AOR, 3.77; 95%CI, 1.145-12.436; $P = 0.029$). A study done on MDR-TB patients at SPTSH, HIV infection was identified as the predictors for mortality (HR:5.94, 95% CI 2.40 - 14.72, $P < 0.0001$)(22). However, in a studies from Israel (13) and Latvia(20) found that HIV co infection was not showed as a risk factor for poor outcome. This might be due to lesser prevalence among the study subjects, 6.1%, 1%, respectively, and the difference in poor outcomes considered between studies. In addition, these studies were from settings that follow individualized based treatment approach. The rising HIV prevalence is intimidating and attention to early diagnosis of drug-resistant TB and early MDR-TB treatment should hence be particularly focused on HIV/MDR-TB-co-infected patients(2). Although not addressed in the present study, a combination of TB treatment and early antiretroviral therapy has been shown to improve treatment results in HIV co- infected patients (32, 38), thus providing limited grounds for optimism for this vulnerable patient group.

Regarding the site of disease, in our study nearly 80% of the patients were smear positive ,it was found that patients with smear positive at presentation is nearly 4.6 fold increase in risk for poor treatment outcome than patients diagnosed with smear negative at presentation and extraplumonary only cases (AOR, 4.62; 95% CI, 1.406-15.185; $P = 0.012$). Similar findings were reported from other studies, in which smear positivity at diagnosis was found in 85% and 82% of patients with MDR-TB reported from Korea and Latvia, respectively (19, 27, 31). However , a study from Latvia, smear positivity at baseline was not found to be a predictor for poor outcome(20). This is probably due to : Smear-positive patients often have more advanced disease, highly infectious, in our study 80% vs 44%, the difference in treatment approach, sample size, and adjuvant surgical resection(9%) than none in our study subjects ,and it has been shown that a

delay to start treatment results in poor outcome(22), and this is probably true in our study subjects since this study was from the cohort of patients who had been treated with many difficulties for the first time by this treatment centers.

In our study, we found a strong, independent association between baseline weight ≤45kg and 5 fold increase in odds of poor treatment outcome than those who had baseline weight ≥55kg (AOR, 4.99; 95% CI, 1.270-19.582; *P* = 0.021).Similarly, previous cohort studies also demonstrated a direct relationship to low body weight and poor MDR-TB treatment outcomes (16, 20, 32). This may be related to several factors operating in resource-poor settings, such as the high proportion of patients with HIV co infection, malnutrition, re-infection and strain dynamics, among other factors for poor outcome of MDR-TB patients(2). However , this finding is inconsistent with a study in SPTSH, Ethiopia, in which baseline weight was not showed to have a risk for poor outcome(22).This might be due to: high death rate in our study, 25.6% Vs 15.4%, categorization of the baseline weight in our study for analysis and may also be due to small sample size that we had. Little is known about the impact of weight on adverse drug reactions pharmacodynamics. We believe this is an important area for continued investigation, particularly correlations of low body weight with both adverse drug reactions and therapeutic drug levels of MDR-TB treatments focused on these subjects to explain this observation and shed light on its clinical importance.

STRENGTH AND LIMITATION OF THE STUDY

Strengths

- Its capacity to include patients at different MDR-TB referral centers in the country to make country-wide data.
- Good recording systems, both by computer database and manually on register book by the responsible persons only.
- Despite the listed limitations below, this study highlights the management, treatment outcomes and risk factors for composite poor outcome in a cohort of MDR-TB patients in the country.

Limitations

- This is a retrospective study that relied on routinely collected clinical data
- It is possible that some AEs, clinical conditions, or co morbidities were not documented in patient records and were therefore presumed to be absent during data analyses. The likely consequence of this would be under-reporting of these events and reduced statistical power in multivariable analyses.
- Finally, our small sample size limited our statistical power to detect associations for some predictors and may have precluded our ability to adequately adjust for potential confounders**.**

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATION

7.1. CONCLUTIONS

Our study showed lower success rate in treating MDR-TB patients using a standardized regimen compared with WHO target. From the composite poor outcome, the proportion of death was higher than those published from other MDR-TB cohorts. Our analysis showed that HIV co-infection, baseline weight ≤45kg, and positive smear at treatment initiation were identified as independent risk factors for poor treatment outcome.

7.2. RECOMMENDATIONS

Efforts to improve MDR-TB treatment outcome in the country must therefore be multifaceted to address such risk factors for poor outcome.

To ALERT and University of Gondar hospitals MDR-TB treatment program coordinator:

- ✓ As the risk factor of poor MDR-TB treatment outcome is HIV infection, extensive use of rapid diagnostic methods and early commencement of anti-TB treatment together with antiretroviral therapy is the way to improve treatment outcomes of HIV-infected MDR-TB patients.
- ✓ The current results indicate that special attention should be paid to patients who are smear positive at initiation of treatment, and adults having baseline weight ≤45kg , this may indicate the nutritional impact on the poor outcome, and the program should closely follow the nutritional status and should consider special support and follow up throughout the course of treatment for this particular group of patients.
- ✓ Regardless of the reasons for defaulting, the MDR-TB treatment program must have the resources to track and prevent defaults, as treatment interruption is a significant cause for amplifying resistance.
- ✓ Well organized prospective study is recommended in order not to miss risk factors that result in composite poor outcome of MDR-TB treatment (death, default and treatment failure) as well as individual risk factors for death, default and treatment failure at multicenter level.

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ANNEX: Data collection checklist

To assess treatment outcomes of MDR-TB treatment and risk factors for poor treatment outcomes at ALERT and University of Gondar hospitals, Ethiopia.

Instruction

A. For each checklist, mark "√" in the box provided and also put numbers if needed
If your answer is out of the choice; write your answer in the space provided

I. Patient related factors		
I. Socio-demographic characteristics		
1	Age, years	
2	sex	
3.	Baseline weight (Kg)	
4.	Area of residence(address)	
5.	Occupation	
6.	Level of education	
7.	Contact person (yes/No)	

	II Drug related factors	
1.	Category of MDR-TB	New ☐ Previously treated with first-line drugs only ☐ Previously treated with second-line drugs: ☐

2.	Additional drug resistance at the start of treatment	None….. ☐ Etambotol….. ☐ pyrazinamide… … ☐ levofloxaciline ……. ☐ ☐ Moxifloxacilline	Ethionamide …… ☐ Cycloserine…… ☐ Amicacine …… ☐ Kanamicine ..... ☐ Specify……
3.	Drugs used during intensive Phase of MDRTB treatment and date started		
4.	Drugs used during continuous Phase of MDRTB treatment and date started		
4.	Treatment side effects noted		
6.	Duration of MDR-TB treatment		
7.	Concurrent medications used		
III. Disease related factors			
1.	Site of MDR-TB	Pulmonary ☐ Sputum smear positive ☐ other ☐	Extraplumonary disease only ☐

2.	HIV status of the patient	HIV positiv☐... ☐ HIV negative……. Unknown…… ART initiated? Yes…☐ No☐ CPT initiated? Yes ..☐ No.☐
3.	Co-morbidity	
4.	Clinical features	Smear +ve at treatment onset ☐ Culture +ve at treatment onset ☐
5.	mean time of sputum smear and culture negativity	smear ….. ☐ cultur…… ☐
Treatment outcomes		
1.	MDR-TB treatment outcome	Cured… ☐ Completed treatment … ☐ Transferred out.☐ Died … ☐ Failure… ☐ Defaulted..☐