ASSESSMENTOFTREATMENT OUTCOME AND ASSOCIATED FACTORS AMONG MDR-TB PATIENTS IN SHANAN GIBE GENERAL HOSPITAL, SOUTH WEST ETHIOPIA: A CROSS-SECTIONAL STUDY

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ASSESSMENT OF TREATMENT OUTCOME AND ASSOCIATED FACTORS AMONG MDR-TB PATIENTS IN SHANAN GIBE GENERAL HOSPITAL, SOUTH WEST ETHIOPIA: A RETROSPECTIVE CROSS-SECTIONAL STUDY

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ABSTRACT

Background*: The emergence of drug resistance tuberculosis, particularly MDR-TB has become a major public health problem in a number of countries and an obstacle to the global TB control efforts. Information on treatment outcomes among patient with multi drug resistant tuberculosis (MDR-TB) were limited from different parts of treatment initiation centers like Jima, even if there are MDR-TB initiation Centers in our country.*

Objective*: We aimed to assess the treatment outcome and associated factors of MDR-TB patients in Shanan Gibe MDR-TB Treatment Initiation Center; during March 2013 to March 2020.*

Methods*: Health facility based retrospective cross-sectional study was conducted. Check-list containing Socio-demographic, clinical characteristics and investigations were used. Data were cleaned, coded and entered into Epi-Data manager 4.6 and exported to STATA version 16.0 for analysis. A multivariable logistic regression were employed.*

Result*: A total of 70 MDR-TB patients were managed from March 2013 to March 2020. And 68.6% were cured, 17.1% died, 11.4% had treatment completion, and 2.9% lost to follow up. Overall favorable MDR-TB treatment outcome was 80%. As the age increases by one year the odds of having favorable treatment outcome decreases by 6% (AOR=0.94 [95% C.I, .88, .99]). Patients who did develop adverse drug side effect were 99.03% (AOR=0.07 [95% C.I, .01, .71]) less likely to have favorable treatment outcome as compared with their counterparts.*

Conclusion: *About one in five MDR-TB patients had unfavorable treatment outcome. Being younger age and not experiencing adverse drug side effects were found to be statistically significant factors associated with favorable MDR-TB treatment outcome. Early initiation of treatment and appropriate drugs with minimal side effects are recommended to increase the favorable treatment outcome for MDR-TB patients and further study should be done to determine other factors that are associated with poor treatment outcome.*

Key words: *Retrospective Cross-sectional, MDR-TB, Treatment outcome*

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ABBREVIATION

AIDS----Acquired Immune Deficiency Syndrome

DOTS ---Directly Observed Treatment Short course

DR- -----Drug Resistant

DRC-----Democratic Republic of Congo

DRS-----Drug Resistant Survey

DST -----Drug Susceptibility Testing

EPTB----Extra pulmonary tuberculosis

HCW----Health Care Worker

HIV----- Human Immunodeficiency Virus

H/INH—Isoniazid

JUMC-Jima University Medical Center

MDR- --Multi-Drug Resistant

MTB----Mycobacterium Tuberculosis

PTB-----Pulmonary Tuberculosis

R--------Rifampicin

RHB----- Regional Health Bureau

RR-MDR-TB-Rifampicin Resistance MDR-TB

SS^+----Sputum Smear Positive

SS^- ----Sputum Smear Negative

TB ----Tuberculosis

TBL---Tuberculosis and Leprosy

TIC---treatment Initiation Center

TFC--Treatment Follow up Center

WHO -World Health Organization

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CHAPTER ONE

1. INTRODUCTION

1.1. Background

Drug-resistant TB, which is a man-made problem, remains a major public health concern in many countries. Three major categories; Multi-Drug Resistance Tuberculosis (MDR-TB), Rifampicin Resistant Tuberculosis (RR-TB) and Extensive Drug Resistance Tuberculosis (XDR-TB) are used for global surveillance and treatment. MDR-TB is Tuberculosis (TB) that is resistant to rifampicin and isoniazid, the two most powerful anti-TB drugs. Both MDR-TB and RR-TB requires treatment with a second-line regimen. Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB plus resistance to at least one drug from both fluoroquinolones and second-line injectable agents (amikacin, capreomycin or kanamycin) (1).

The development of drug-resistant tuberculosis is largely the consequence of human error as a result of individual or combination of factors related to management of drug supply, patient management, prescription of chemotherapy, and/or patient adherence. The treatment of MDR-TB with second line drug is long, complex and costly, and also associated with significant rate of adverse drug effects(2).

After bacteriological confirmation of TB, the detection of MDR/RR-TB requires testing for drug resistance using rapid molecular tests, culture methods or sequencing technologies. Treatment requires a course of second-line drugs for at least 9 months, even up to 20 months, which should be supported by counseling and monitoring for adverse drug events(3).

1.2. Statement of the Problem

Globally in 2018, 51% of people with bacteriologically confirmed TB were tested for rifampicin resistance, up from 41% in 2017 and the coverage of testing was 46% for new and 83% for previously treated TB patients. Globally, a total of 186 772 cases of MDR/RR-TB were detected and notified in 2018, up from 160 684 in 2017, and 156 071 cases were enrolled in treatment, up from 139 114 in 2017(3).

Among 27 high burden countries (HBC), Eastern European and central Asian have the highest levels of MDR-TB, with 35% of new cases and 75% of previously treated cases. Africa had 2.1% (0.5%–3.7%) new TB cases with MDR-TB and 11% (6.7%–16%) retreatment TB cases with MDR-TB; while Ethiopia is 15th from 27 HBC of MDR TB(1).

A systematic review and meta-analysis of the prevalence, determinants and treatment outcome of MDR-TB in Ethiopia show that the overall prevalence of MDR-TB to be 7.24 %(95% CI 6.11-8.37), with 2.18% (95% CI 1.44–2.92%) among newly diagnosed and 21.07% (95% CI 11.47–30.67%) in previously treated patients(4).

A 6-month case–control study performed at different zones of Oromiya Region in 2013–14 show that, out of 265 patients with confirmed M. tuberculosis infections,88 (33%) of them had laboratory-confirmed MDR-TB(5).

According to cross-sectional health facility-based study conducted from March 2012 to April 2013 in Jimma area, Southwest Ethiopia, the prevalence of MDR-TB among retreatment cases was found to be 31.4% (22/70)(6).

The latest treatment outcome data for people with MDR/RR-TB show a global treatment success rate of 56% which is even lower than that of WHO 2015 target of 75%. Examples of high MDR-TB burden countries with better treatment success rates (>70%) are Bangladesh, Ethiopia, Kazakhstan and Myanmar(3, 7).

However, Outcomes of the treatment and associated factors were not described in peripheral Treatment Initiation Centers (TIC) of Ethiopia like Shanan Gibe MDR-TB initiation center. Examining a population who received a second-line therapy, for the management of MDR-TB, to determine the overall survival rate has a great importance for proper planning and effective implementation. Therefore, this study aimed at assessing the treatment outcome and associated factors of Multidrug Resistant Tuberculosis (MDR-TB) among Patients Treated in Treatment Initiation Centers (TIC) at Shanan Gibe General Hospital, Jimma; South West Ethiopia.

1.3. Significance of the Study

The treatment of resistant tuberculosis (TB) is complex, long and expensive. It requires many anti-TB drugs that are more toxic and less effective than the first line medicines and it often results in poor treatment outcomes.

However there is no research conducted in the area of MDR-TB treatment outcome and associated risk factors in Jimma and surrounding area, though the MDR-TB cases are being increasing and Cost to treat MDR-TB is highly expensive. Data on this is highly needed in order to evaluate the efficiencies/deficiencies of MDR-TB treatment program.

This study will determine the treatment outcome for this new ambulatory care model and identify the factors associated with unfavorable treatment outcome of MDR-TB in Shanan Gibe MDR-TB treatment initiation center (TIC). It will help service providers to improve MDR-TB treatment outcome and attain intended control of MDR-TB. It will also help as a baseline for the future studies.

CHAPTER TWO

2. LITERATURE REVIEW

2.1. INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is a type of TB that is resistant to at least the first line anti-TB drugs (Rifampicin and Isoniazid). MDR-TB results from either primary infection or may develop in the course of a patient's treatment (8). Since MDR-TB patients respond poorly to short course chemotherapy, they need to be treated intensively for up to 24 months with a regimen based on reserve anti tuberculosis drugs (9).

The emergence of MDR-TB is a threat for the populations of resource-limited countries like Ethiopia in which low socioeconomic status of the people, high prevalence of infectious diseases and limited access to appropriate health care facilities worsens the effect of MDR-TB. Furthermore, MDR-TB is even more complicated disease than drug susceptible TB due to poor treatment outcomes, longer treatment time, higher treatment costs, and many more complications(10, 11).

The latest treatment outcome data for people with MDR/RR-TB show a global treatment success rate of 56% which is even lower than the WHO target of 2015. Examples of high MDR-TB burden countries with better treatment success rates (>70%) are Bangladesh, Ethiopia, Kazakhstan and Myanmar(3).

2.2. Burden of Multidrug-resistance Tuberculosis

Globally in 2018, 51% of people with bacteriologically confirmed TB were tested for rifampicin resistance, up from 41% in 2017 and the coverage of testing was 46% for new and 83% for previously treated TB patients. A global total of 186 772 cases of MDR/RR-TB were detected and notified in 2018, up from 160 684 in 2017, and 156 071 cases were enrolled in treatment, up from 139 114 in 2017. Ten countries; including China, India, Indonesia, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation and Viet Nam; accounted for 75% of the global gap between treatment enrolments and the estimated number of new cases of MDR/RR-TB in 2018, and thus will have a strong influence on progress in closing this gap. China and India alone accounted for 43% of the global gap(3)

Among 27 high burden countries (HBC), Eastern European and central Asian have the highest levels of MDR-TB, with 35% of new cases and 75% of previously treated cases. Africa had 2.1% (0.5%–3.7%) new TB cases with MDR-TB and 11% (6.7%–16%) retreatment TB cases with MDR-TB; while Ethiopia is 15th from 27 HBC of MDR TB(1).

A retrospective study done from 1997 to 2009 in 309 hospitals, China Beijing; among 5523 patients 3752 (67.9%) were male; 3430 (62.1%) were out of previous treatment cases; 1999 (36.2%) were live in Beijing. The mean age was 45.8 ± 20.2 years (range 0.5–98.0 years) and majority of patients (n=3851, 69.7%) had age between 15-65 years and the rest were < 15 years (n=125, 2.3%) and > 65 years (n=1547, 28%) old. In this study 47.1% (2604) had resistance to any anti-TB drug; the resistance type by each ant-TB drug was: ethambutol (n=1455, 26.3%), streptomycin (1477, 26.6%), kanamycin (828, 15%), ofloxacin (536, 9.7%), levofloxacin (308, 5.6%) and para-amino salicylic acid (912, 16.5%). Patients with mono-resistant TB were 14.8%, poly-resistant TB were 19.8%, MDR TB were 19.4% and XDR TB were 1.3%(12).

A retrospective cohort was done in Chennai and Madurai, India from June 2012 to May 2013, on multidrug-resistant tuberculosis based on positive follow-up smear results; among 520 smear and culture positive patients 389 (75%) were male, 176 (34%) were HIV infected, and mean age was 34.1 years (standard deviation 10.3); patients with culture negative during follow-up was 98%(13).

A cross-sectional survey in Mumbai, India from March 2013 to January 2014 on Alarming Levels of Drug-Resistant Tuberculosis in HIV-Infected Patients; of 1724 total patients 60% were male, median age 35 (Inter-quartile range, IQR: 24–44), 98% patients had pulmonary TB, 80% were on ART and 52% had CD4 cell counts less than 500 cell/ml at the last ART visit, 72 (4.2%) had smear positive TB, 202 (11.7%) had culture positive TB, 11 TB patients were smear positive but culture negative and 141 patients were culture positive but smear negative(14).

A retrospective cohort study on treatment out came and follow up MDR TB patients in West Coast/Wineland, South Africa from 1992 to 2002; out of 747 culture confirmed MDR TB patients, 491 (66%) started at least two Second Line Drugs (SLD), 112 (15%) were treated with

first line drugs and the remaining 144 (19%) didn't start treatment due to death or default by TB treatment before laboratory confirmation of MDR TB(15).

Institution based case-control study on determinants of MDR TB patients under first-line treatment in Addis Ababa, from November 2011 to February 30, 2012; among 134 cases, 81 (60.5%) were male but out of 134 controls, 70 (52.5%) were female; mean age in case group was 25.1 (SD=10.94) years and 30.72 (SD=11.4) years in control group. In this research 96 (71.6%) out of 134 cases had previous TB treatment more than two episodes, in control groups 14 (10.4%) had TB treatment two round(16).

A hospital based retrospective study on pattern of anti-TB drug resistance among previously treated TB patients, St. Peter Ethiopia, from January 2004-December 2008; out of 376 culture positive M-tuberculosis, 274 (72.9%) were resistance to at least one anti-TB drug; resistance to STM (67.3%), resistance to INH (56.1%), resistance to RIF (46.1%) and resistance to ETM (43.5%). Poly resistance was 29 (7.7%), prevalence of MDR-TB was 174 (46.3%) and among MDR-TB cases 140 (80.5%) were resistance to all first line anti-TB drugs(17).

A cross-sectional study on primary drug resistance TB in major towns of Amhara region, Ethiopia from January 2008 to October 2008; come across the following findings; of 93 patients 25 (26.9%) had HIV positive results and the rest 68 (73.1%) were negative for HIV test. HIV positive patients were likely to develop resistance to any one of ant-TB drugs compared with HIV-negative cases (OR 2.76: p=0.09)(18).

A facility based cross-sectional study on assessment of MDR TB burden in Khayelitsha, South Africa between May and November 2008; among 1842 suspected pulmonary TB patients, culture positive result was diagnosed in 271/732(37%) cases among those not previously treated and 264/843 (31%) cases among those with more than one month of previous tuberculosis treatment. Eighty eight percent (88%) of new cases were tested for HIV and 55% of them had positive result; 90% of previously treated patients were tested for HIV and 71% of them had positive result(19).

2.3. Factors Associated with Multi Drug-Resistant Tuberculosis Treatment outcome

The treatment of MDR-TB in Ethiopia started recently in TB specialized hospital and expanded to MDR-TB treatment initiation centers (TIC) in selected hospitals of the regions(20).

According to prospective study done in Zhejiang, China, 2009–2013, the treatment success rate of MDR-TB was 69.6% (374/537). Independent predictors of poor treatment outcomes included age >60 years (hazard ratio (HR) 2.3, 95% confidence interval (CI) 1.2e4.2), patients registered as experiencing relapse (HR 2.2, 95% CI 1.1e4.4), patients registered as receiving treatment after failure (HR 2.4, 95% CI 1.2e4.9), use of standardized MDR-TB regimens (HR 0.6, 95% CI 0.4e1.0), cavitary disease (HR 4.9, 95% CI 2.8e8.6) and adverse events (HR 2.5, 95% CI 1.2e5.5) (21).

A retrospective medical record review in, Seoul, Korea, from January 1 to December 31, 2004 on treatment outcome and mortality among MDR TB patients in 3 public TB hospitals; had the following findings, out of 202 patients 75 (37.1%) treatment successes (n=46, 22.8% cured and n=17, 8.4% treatment completed); and 127 (62.9%) had poor outcome;(75 (37.1%) defaulted, 9 (4.5%) died on treatment, 3 (1.5%) treatment failed)(22).

According to retrospective observational study conducted in KwaZulu-Natal, South Africa from 2000-2003 on high treatment failure and default rates for patients with MDR TB; among 1209 patients whose MDR TB treatment outcome is accessed, 491 (41%) were cured, 252 (21%) defaulted, 223 (18%) passed away, and 208 (17%) failed on treatment; and 35 (3%) treatment completed. In general 526 (44%) had favorable outcome (cured or completed) but 683 (56.5%) had unfavorable outcome (defaulted, died, failed) (23).

A retrospective cohort study in Nigeria from July 2010 to October 2012, on intensive phase treatment outcome among hospitalized MDR TB patients showed; out of 162 MDR TB patients on treatment 138 (85%) were alive and the remaining 24 (15%) were passed away at the end of intensive phase treatment. All patients alive at the end of intensive phase had culture and sputum smear negative(24).

A systematic review and meta-analysis of the prevalence, determinants and treatment outcome of MDR-TB in Ethiopia show that the overall prevalence of MDR-TB of 7.24 %(95% CI 6.11-

8.37), with 2.18% (95% CI 1.44–2.92%) among newly diagnosed and 21.07% (95% CI 11.47–30.67%) in previously treated patients. History of previous treatment is the major determinant (pooled OR = 4.78 (95% CI 3.166.39)), while contact history and adherence also contributed. From this review the pooled death computed among 5 articles showed that 12.25% (95% CI 9.39–15.11%) of MDR-TB patients were died in the course of treatment, and complication, drug side effects and HIV infection were the main determinants for the death(4).

An aggregated and individual patients' data analysis for outcome and effectiveness of the current regimens in Ethiopia, included six studies reporting treatment outcome of 1993 MDR-TB patients, came with the treatment success rate of 59.2% (95%CI, 48.1–70.4), while 23.3% (95%CI, 19.7–27.0%) of patients had a poor outcome. In sub-group analysis,46.1% (95%CI, 34.2–58.0) were cured, 12.8% (5.7–20.0) treatment completed, 14.3% (11.5–17.2) died, 7.5% (3.7–11.3) lost to follow up, and 1.6% (1.1–2.2%) experienced treatment failure(25)

From retrospective cohort study done at St. Peter's TB Specialized Hospital January 1, 2009 to December 31, 2010, the treatment outcome of 166 patients with MDR-Tb was shown as, cure 7(4.2%), death 15(9.6%), default 1(0.6%), still on treatment 143 (86.1%) and no treatment failure was observed in the study period(26).

Study done in Addis Abeba at St. peter TB specialized Hospital, by Meresa D. et al, 2015,shows the highest MDR-TB treatment success outcomes(78.6%) so far achieved in Africa, in a setting with severe resource constraints and patients with advanced disease. Intensive treatment of adverse effects, nutritional supplementation, adherence interventions and NGO-MOH collaboration were key strategies contributing to success(27)

The treatment outcome of MDR-TB from institution based retrospective cohort study carried out in two Treatment Initiation Centers (TIC) of SNNPR; Yirgalem hospital and Queen Eleni Memorial Hospital, show that 39 (25.3%) of patients were cured, 26 (16.9%) were completed their treatment, 13 (8.4%) died during treatment, 20 (13%) defaulted or lost to follow up, 5 (3.2%) of patients required medical transfer and the remaining 51 (33.1%) are on treatment and all of the deaths were recorded with in the first five months of treatment initiation(28).

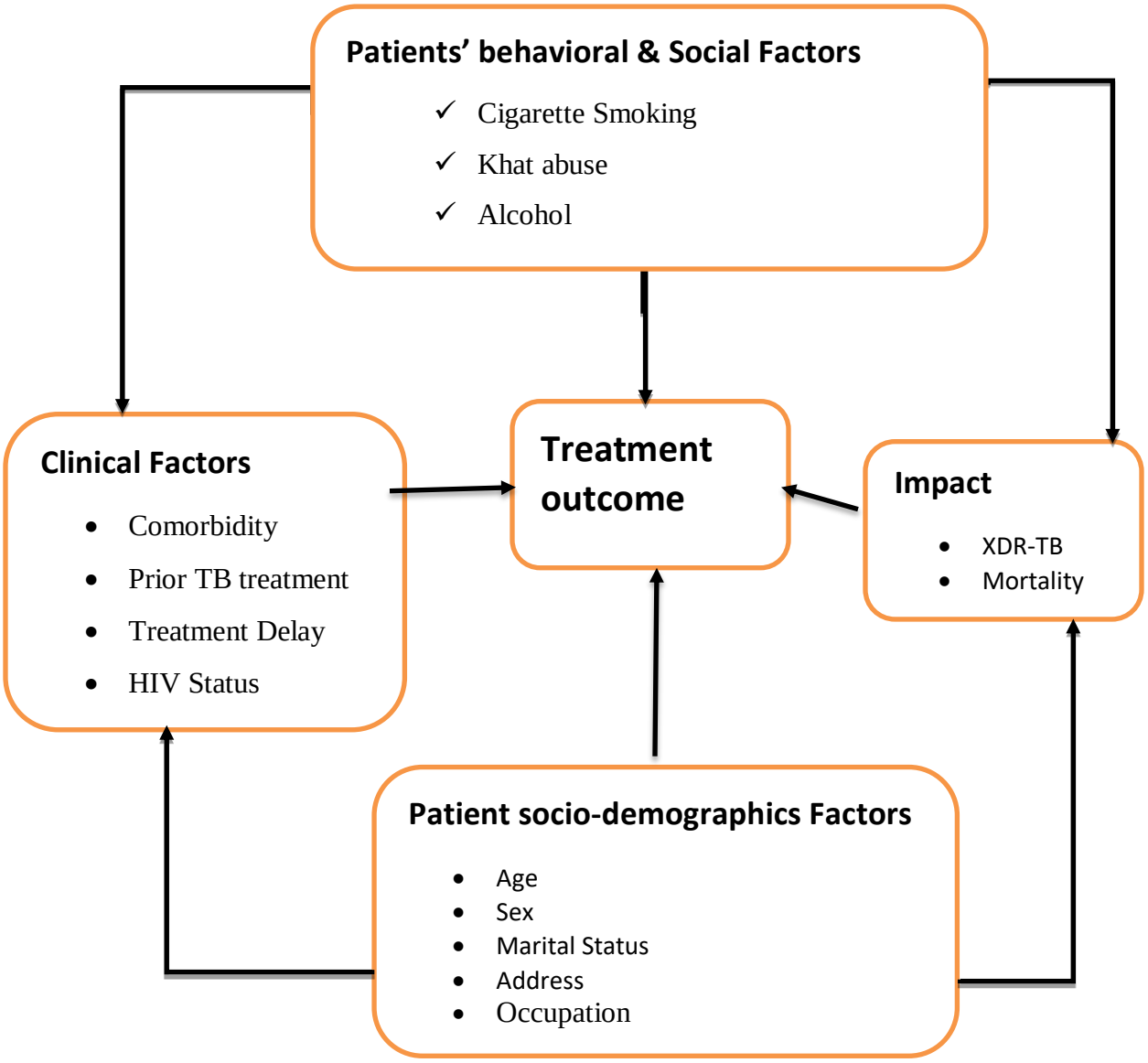

Figure 1: Conceptual framework showing treatment outcome and associated factors of MDR-TB patients at Shanan Gibe General Hospital from March 2013 to March 2020

CHAPTER THREE

3. Objective

3.1. General objective

- ✓ To assess the treatment outcome and associated factors of MDR-TB patients in Shanan Gibe MDR-TB Treatment Initiation Center from March 2013 G.C to March 2020 G.C, Jimma, Ethiopia.

3.2. Specific objectives

- ✓ To determine treatment outcome of MDR-TB among patients in Shanan Gibe treatment center from 2013 G.C to March 2020 G.C, Jimma, Ethiopia.
- ✓ To identify factors associated with MDR-TB treatment outcome among patients in Shanan Gibe treatment center from 2013 G.C to March 2020 G.C, Jimma, Ethiopia.

CHAPTER FOUR

4. METHODS AND METERIALS

4.1. Study Area and Period

This study was conducted in Shanan Gibe General Hospital, which is located in Jimma town, Oromiya region, Southwest of Ethiopia 342 km from Finfinnee/Addis Ababa, from March 2013 to March 2020. Shanan Gibe General Hospital, having 5 wards (Pediatric, Obs/Gyn, Surgery, Medical and MDR-TB) and about 65 beds, was established in 2011 G.C as primary hospital in Jimma town and gives TB service since then and also started MDR TB service since 2013 GC.

In addition to TB and MDR TB treatment and care services, Shanan Gibe hospital gives several services to the community. Among them; ART treatment and care service, Emergency service, pharmacy service, Anti-natal care service, delivery service and psychiatry services are some of the services the hospital gives to the community.

Duration: The study was conducted from October 15-25/ 2020

4.2. Study design

A Hospital based cross-sectional study was employed

4.3. Source population

The source population was all patients with tuberculosis on treatment at Shanan Gibe General Hospital during March 2013 to march 2020.

4.4. Study population

The study population was all bacteriologically confirmed and clinically diagnosed MDR-TB patients who were on second line anti-TB treatment at Shanan Gibe General Hospital, from March first 2013 to last March of 2020.

4.5. Eligibility criteria

4.5.1. Inclusion criteria

MDR TB patients whose age was greater than 14 were included

4.5.2. Exclusion criteria

Patient under follow up and with incomplete information such as date of entry and exit, age, sex were excluded.

Those who were transferred in/out and patients with XDR-TB diagnosis at the start of treatment were also excluded.

4.6. Sample size determination and sampling procedure

All charts of MDR-TB patients at Shanan Gibe General Hospital were reviewed.

4.7. Study Variables

4.7.1. Dependent variable

Treatment outcome

4.7.2 Independent Variables

- **Demographic variables**
  - ✓ Age
  - ✓ Sex
  - ✓ Address
  - ✓ Marital Status, Occupation
- **Behavioral Variables**
  - ✓ Cigarette Smoking
  - ✓ Khat abuse
  - ✓ Alcohol
- **Clinical Variables**
  - ✓ Comorbidity
  - ✓ Prior TB treatment
  - ✓ Treatment Delay
  - ✓ HIV Status

4.8. Operational Definitions

Treatment outcomes were categorized according to the Global Fund MDR-TB Project

Cure: Defined as patient who completed treatment and at least five final consecutive cultures of his or her sputum during the final 12 months of treatment were negative; or if one culture was positive, then at least three of its following consecutive cultures had to be negative

Treatment completed: Defined as patients who had completed their treatments without evidence of failure but with inadequate bacteriologic records to be defined as cured

Treatment failure: Defined when two or more positive sputum cultures of the 5 final cultures, or one positive culture of the final 3 cultures during the final 12 months of treatment

Death: Defined as patients who died of any cause during treatment

Lost to follow-up (default): Defined as patients whose treatment was interrupted for two or more consecutive months against their clinician's advice

Favorable Treatment outcome: Defined as cure or completed treatment outcome

Unfavorable Treatment outcome: Defined as treatment failure, default or death

Read and Write: A person who has no formal education but can read and write

4.9. Data Collection Procedure

Data extraction formats was adapted from similar literature and patients' registration and follow up charts (appendix 1). All relevant variables were extracted from patient log book and follow up charts and patient cards. Data were extracted by two trained data collectors, who were supervised by principal investigator.

4.10. Data processing and analysis

The data were checked for completeness, coded and entered into Epi-Data Manager 4.6 and exported to STATA version 16 for analysis. Summary statistics such as percentage was computed and odds ratio calculated with 95% confidence interval. Bivariate logistic regression model was used to test association between each independent factor with outcome variable. Variables that showed significance during bivariate analysis at $P<0.25$ was included in multivariable logistic regression. Variables with statistically significant association at P value of <0.05 with outcome variable was expressed as potential risk factor for MDR TB outcome.

4.11 Data quality control

Data collection tool and check list had been adopted and modified from previous similar studies and guidelines. Pretest was conducted for 5% of charts to ensure the consistence of the information to be collected. Two expertise on data collection (nurses) working at the TB ward were selected as data collectors and oriented on basic procedures of data collection as well as data collection system was closely supervised by principal Investigator to ensure the quality of data. The collected data were checked for completeness manually and were done a double data entry system to control the missing data.

4.12. Ethical Concern

Ethical clearance of this study was obtained from Jimma University health Science Ethical Review Board. Since it was secondary data that was taken retrospectively; I did not take any informed consent from individuals (study subjects). To ensure confidentiality, patient records was coded and accessed only by personnel working in the hospital after permission was obtained from Administration of Shanan Gibe General Hospital.

4.13. Dissemination Plan

The findings of the study will be submitted to internal medicine department of JUMC, Shanan Gibe General Hospital, and also distributed to other interested bodies. The article will be submitted for publication on peer reviewed journals to communicate the finding for the scientific community.

CHAPTER FIVE

5. RESULT

5.1 Socio-demographic characteristics

A total of 114 MDR-TB patients were enrolled to MDR-TB treatment initiation at Shanan Gibe General Hospital from March 1, 2013 to last March of 2020. Seventy (70) patients fulfilled the inclusion criteria, while 44 were excluded (n=25-on treatment n=14- were ≤14 years and n=5- charts with incomplete data). About 54.3% of the study participants were in the age15-29 years group, with the mean age of 30.51 (95%CI 28.02, 33.01) years. Female accounts for 61.43% of the participants, while 72.86% of the participants were from urban area (Table1).

Table 1: Socio-demographic characteristics of the study participants

Variables	Categories	Frequency(n=70)	Percentage
Age group (in years)	15-29	38	54.29
	30-39	19	27.14
	>=40	13	18.57
Sex	Male	27	38.57
	Female	43	61.43
Marital status	Single	16	22.86
	Married	47	67.14
	Divorced	7	10.00
Residence	Urban	51	72.86
	Rural	19	27.14
Occupation	Public and private employee	16	22.86
	Housewife	26	37.14
	Farmer	17	24.29
	Merchant	4	5.71
	Daily labor	7	10.00

5.2 MDR-Treatment outcome

Overall favorable (Cured + Completed) MDR-TB treatment outcome was 80.0%. The rate of treatment outcome of the patients were 68.6% had cure, followed by 17.1% died, 11.4% had completed treatment, and 2.9% were lost to follow up (Figure 1).

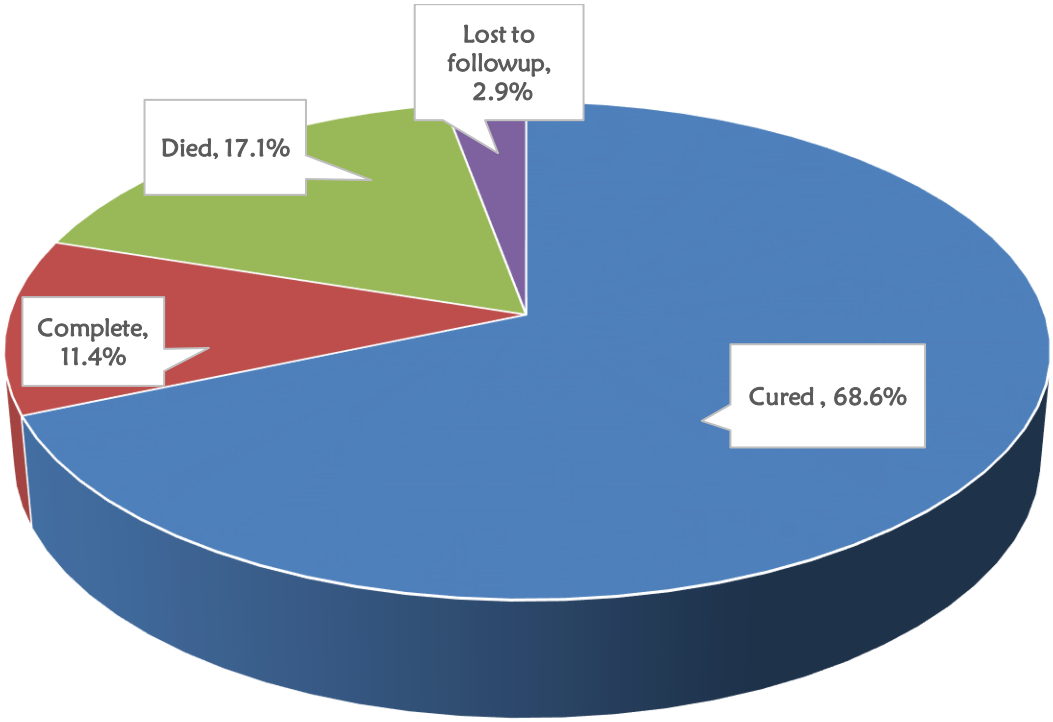

Figure 2: MDR-TB treatment outcome in Shanan Gibe General hospital, Southwest Ethiopia

5.3 Patients' behavioral & health related characteristics

Among the study participants, 21.43% had social and behavioral risk factors which include drug abuse 10 (13.33%), alcohol misuse 10(66.67%), and khat chewing 7 (46.67%). The MDR-TB patients had also different comorbidities which accounted for 10% of the study participants. Among them 2 patients had chronic kidney disease, and 1 patient had chronic liver disease (Table 2).

Table 2: Patients' behavioral & health related characteristics of the study participants

Variables	Categories	Frequency (n=70)	Percentage
Patients behavioral risk factors			
	Yes	15	21.43
	No	55	78.57
Drug abuse	Yes	2	13.33
	No	13	86.67
Alcohol misuse	Yes	10	66.67
	No	5	33.33
Khat chewing	Yes	7	46.67
	No	8	53.33
Hypertension	Yes	7	10.00
	No	63	90.00
Chronic kidney disease			
	Yes	2	28.57
	No	5	71.43
Chronic liver disease			
	Yes	1	14.29
	No	6	85.71

5.4 Clinical characteristics

Twenty six (37.14%) of the participants were categorized as new and 23 (32.86%) were categorized after failure of first treatment. Five patients (7.14%) were having HIV co-infection. Pulmonary TB accounts for 88.57% by site of MDR-TB, while 44(63.77%) of the study participants had history of previous TB treatment with first line anti-tuberculosis. Thirteen patients had history of drug interruption, of which, three patients interrupted due to adverse drug side effects and 10 patients due to poor adherence. AFB/GeneXpert was positive for 60(85.71%) of cases and baseline culture result was positive for 66 (94.29%) study participants. Sixty percent of the patients with MDR-TB started treatment within 7 days of diagnosis and the mean delay in treatment initiation after diagnosis was 10.41[95% CI 6.96,13.86] days (Table 3).

Table 3: Clinical characteristics of the study participants

Variables	Categories	Frequency	Percentage
Registration	New	26	37.14
Category of	Relapse	10	14.29
MDR-TB	After lost to follow up	3	4.29
	After failure of first treatment	23	32.86
	After failure of retreatment	8	11.43
HIV status	Positive	5	7.14
	Negative	64	91.43
	Unknown	1	1.43
History of previous	New	26	36.23
TB treatment	Treated with first line	44	63.77
Site of MDR-TB	PTB	62	88.57
	EPTB	8	11.43
History of drug interruption			
	Yes	13	18.57
	No	57	81.43
Reason for drug interruption* (n=13)			
	Adverse drug effect	3	23.07
	Failure	1	7.69
	poor adherence	10	76.92
Did the Patient develop adverse drug side effect?			
	Yes	62	88.57
	No	8	11.43
Adverse drug side effects*			
	Hepatitis(jaundice)	10	16.13
	GI Upset	57	91.94
	Psychiatric illness	8	12.90
Result of AFB/GeneXpert at baseline			
	Detected	60	85.71
	Not detected	8	11.43
	Not done	2	2.86
Baseline Culture	Positive	66	94.29
result	Unknown	4	5.71
Delay in treatment	<7 days	42	60.00
initiation	7-14 days	12	17.14
	>/=14 days	16	22.86

*More than one reason possible for one participant, + declined to answer, GI= gastrointestinal, PTB=pulmonary tuberculosis, EPTB= extra-pulmonary tuberculosis

5.5 Factors associated with MDR-TB treatment outcome in Shanan Gibe General hospital, Southwest Ethiopia

A bi-variable logistic regression revealed timely initiation of treatment; absence of drug interruption and not developing adverse drug side effect were found to be statistically significant association with favorable outcome of MDR-TB treatment.

The number of days it took to start MDR-TB treatment was significantly associated with its outcome. As the number of days to initiate treatment increase by one day, the odds of being favorable treatment outcome decreases by 5% (COR= .95, [95% C.I, .92, .99].

After controlling for potential confounding factors, a multivariate logistic regression revealed that being younger age and not experiencing adverse drug side effects were found to be statistically significant factors associated with favorable MDR-TB treatment outcome. Delay in treatment initiation was significant in bi-variable logistic regression; however, it became insignificant after controlling for confounders.

As the age increases by one year the odds of being favorable outcome decreases by 6% (AOR=0.94 [95% C.I, .88, .99]). Patients who did develop adverse drug side effect were 99.03% (AOR=0.07 [95% C.I, .01, .71]) less likely to have favorable outcome as compared with their counterparts (Table 4).

Table 4: Bi-variable and multivariable logistic regression for MDR-TB treatment outcome in Shanan Gibe General hospital, Southwest Ethiopia

Variables		COR (95%CI)	P-value	+AOR(95%CI)	P-value
Sex	Male	1.0	0.117	1.0	0.963
	Female	2.59 [.78, 8.57]		1.08 [.13, 8.48]	
Age (in years)	-	.96[.92, 1.02]	.232	0.94[.88, .99]*	**0.044**
Delay in treatment initiation (days)	-	.95[.92, .99]*	**.018**	0.98[.93, 1.03]	0.456
Registration Category of MDR-TB	New	1.0		1.0	
	Relapse	.23[.05, 1.15]	.075	.46[.01, 20.29]	.089
	After failure of first treatment	5.24 [.56, 48.65]	.145	8.92[.05, 24.04]	.152
	After failure of retreatment	0.71 [.12, 4.65]	.725	9.74[.02, 16.65]	.247
No history of drug interruption	-	8.33 [2.17, 32.05]*	**.002**	++	
Develop adverse drug side effect	Yes	.05[.01, .29]**	**.001**	0.07 [.01, .71]*	**.024**
	No	1.0		1.0	

***p<.01 * P <0.05* 1.0 reference category ++ omitted from the final model because of multi-collinearity

+ Adjusted for sex, age, Delay in treatment initiation (days), Registration category of MDR-TB, History of drug interruption, Develop adverse drug side effect, Radiological(X-ray) pattern of lung lesion

CHAPTER SIX

6. DISCUSSION

This study was designed to assess treatment outcome and determine predictors of unfavorable treatment outcomes of MDR-TB patients who were treated at Shanan Gibe General Hospital, Southwest of Ethiopia. We found that the overall treatment success (i.e. having an outcome of cured and treatment completed) at the end of the treatment (24 months) was 80%, which is in accordance with the WHO target (>75%), and the treatment outcomes so far done for inpatient model of care in Addis Ababa at St peter hospital in 2015(78.6%)(7, 27). This favorable outcome is higher than findings in other countries such as South Africa, Korea and China (21-23). It is also better than the outcome of studies done in different MDR-TB treatment centers in Ethiopia like St. Peter's TB Specialized Hospital and in two Treatment Initiation Centers (TIC) of SNNPR; as well as an aggregated and individual patients' data analysis for outcome and effectiveness of the current regimens in Ethiopia, included six studies, that showed the treatment success rate of 59.2% (95%CI, 48.1–70.4) (25, 27, 28)

This encouraging MDR-TB treatment outcome in Shanan Gibe General Hospital, South West Ethiopia may be due to several reasons, related to the study population and the treatment program. The patients in our study were generally young with mean age of 30.51 (±10.47) years and there were no significantly associated comorbidities that would negatively affect the treatment outcome of such kinds of patients. In addition, all patients who participated in this study were started treatment as outpatient ambulatory model of care and as an inpatient at MDR-TB ward and followed at treatment initiation center during the first month of treatment and received directly observed therapy at various treatment follow up center. In the continuation phases of treatment, patients were followed and traced using several strategies: health professionals from the treatment centers visited the patients every month; the patients were appointed monthly to visit the treatment initiation site; treatment supporters were assigned from the patient's family to assist the patient with directly observed therapy; and food baskets were provided regularly for the patient.

The treatment outcome of MDR-TB may be significantly affected by age of the study population and the presence of adverse drug side effects. In this study, as the age increases by one year the odds of being favorable outcome decreases by 6% (AOR=0.94 [95% C.I, .88, .99]). Patients who did not develop adverse drug side effect were 99.03% (AOR=0.07 [95% C.I, .01, .71]) less likely to have unfavorable outcome as compared with their counterparts. This is in line with different studies done elsewhere(22, 28)

The number of days it took to start MDR-TB treatment was significantly associated with its outcome. As the number of days to initiate treatment increase by one day, the odds of being favorable treatment outcome decreases by 5% (COR= .95, [95% C.I, .92, .99].

Even though there was high percentage (21.43%) of social and behavioral risk factors and HIV co-infection was also found in 7.14% among the study participants, these were not significantly associated with unfavorable treatment outcome in this study, unlike other study done elsewhere(27, 28). A fundamental aspect of the program presented here was the implementation of adherence strategies successfully employed in the outpatient program; including monthly home visits and monthly patient visits to the treatment initiation site's outpatient department, identification of a patient supporter to assist with DOT, psychosocial support, monthly food baskets and social support for the patients who have no family supporter. We note that other program that have reported high rates of favorable treatment outcome also provide some nutritional, social and/ or economic support(27). We assume that such measures are integral to the success of outpatient treatment program, especially in settings of resource constrained countries like Ethiopia.

LIMITATION

All the data for necessary variables could not be obtained and the reliability of the data may not be ascertain because it is retrospective study and based on records. The side effect of medication could not be analyzed by MDR TB regimen properly due to limited biochemical findings. Small sample size might have limited the statistical power of the study.

CHAPTER SEVEN

7.1 CONCLUSION AND RECOMMENDATION

About one in five MDR-TB patients had unfavorable treatment outcome. Being younger age and not experiencing adverse drug side effects were found to be statistically significant factors associated with favorable MDR-TB treatment outcome.

Based on this study, Federal ministry of health and other responsible bodies (Companies and Scientists) as well as Zonal and Districts health bureaus are recommended to deal with the program of early initiation of treatment and appropriate drugs with minimal side effects to increase the favorable treatment outcome for MDR-TB patients and further study should be done to determine other factors that are associated with poor treatment outcome. A mixed method study employing qualitative data of live experiences are recommended to explore other determinants of unfavorable treatments outcomes.

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ANNEX

Annex-I. Information sheet and Data Collection Tool

Annex 1.1 Information sheet

Data Extraction Format for Research Project in Shanan Gibe General Hospital MDR-TB Treatment Initiating Center

Title: ***Assessment of MDR-TB Treatment Outcome and associated factors among MDR-TB patients >14 years; and Diagnosed and enrolled into Shanan Gibe Hospital Treatment Initiating Center during March 2013 G.C to March 2020 G.C.***

Dear my data collectors thank you for your time, energy and willingness to participate in this study. All the data are to be collected from MDR-TB patient registries and patient treatment card. The data collected need to be logical, and based only on the information from the records, not arbitrarily. So I kindly request you to collect the actual data from patient logbook/card honestly. The data extraction form contains three sections, including socio-demographic characteristics, patient's baseline laboratory factors and patient's clinical characteristics to treatment outcome. The choice form should be selected by encircling. Other data should be filled as it obtained from the information card. The data should be filled with a pencil.

Dear my data collectors; I want to remind you that we have to protect ourselves from COVID-19 using face mask, keeping our distance and other necessary measures during data collection.

Thank you again and if you need any additional information or had any difficulties contact me with the following address.

Name: Dita Bira (MD)

Telephone number……

E-mail= biradita0@gmail.com

Annex 1.2: Data collection tool (checklist):

This checklist is prepared to assess MDR-TB treatment outcome and factors associated with unfavorable treatment outcome.

Part I: Checklist for socio demographic characteristics of the patient:

Patient's unique MDR-TB registration no. =……...

No	Questions	Response
1	Sex	1. Male 2. Female
2	Age	_____age in complete year
3	Marital status	1. Single 2. Married 3. Widowed 4. Divorced(legally)
7	Occupation	1. Government employee 2. Private sector employee 3. Daily laborer 4. House Wife 5. Others (specify_____
8	Residence	1. Urban 2. Rural

Part II. Checklist for clinical characteristics of patient:

1. Time from diagnosis to treatment initiation of MDR-TB
    1. Date of diagnosis……. /……./……..
    2. Date of treatment initiation……/……. /…….
    3. Delay of treatment initiation……. days
    4. Date of treatment completion……/……. /……
2. HIV status of the patient
    1. Positive 2. Negative 3. None
3. If HIV positive, what was the treatment status of HIV at the diagnosis of HIV
    1. New 2. On HAART
4. If HIV positive, what is the CD4 count at the time of MDR-TB diagnosis?
    1. Number (……) 2. Percentage (%)……..
5. Registration category of MDR-TB patient:
    1. New
    2. Relapse
    3. After lost to follow up
    4. After failure of first treatment
    5. After failure of retreatment
    6. Other, specify……
6. History of previous TB treatment
    1. New
    2. Treated with first line
    3. Treated with second line
7. Site of MDR-TB
    1. Pulmonary TB
    2. Extra-pulmonary TB
    3. Disseminated TB
8. MDR-TB patient's treatment regimens (specify the regimen code in front of the choice)
    1. Standard regimen……
    2. Individualized regimen……..
    3. Empirical treatment…….

9. Presence of comorbidities
    1. COPD
    2. DM
    3. HTN
    4. Chronic renal disease
    5. Chronic liver disease
    6. Others/specify……
    7. none
10. History of drug interruption
    1. Yes
    2. No
11. If yes to question number 10, what was the reason for interruption?
    1. Failure
    2. Adverse drug effect
    3. Drug stock out
    4. Poor adherence
    5. Others (specify…..)
12. Patients social/behavioral risk factor(more than one response-possible)
    1. Homelessness
    2. Drug abuse
    3. Alcohol misuse
    4. Smoking
    5. Khat chewing
    6. Others (specify……)
    7. None

13. Does the patient have treatment and nutritional support?

    1. Yes 2. No

14. If 'yes' to 14, who give the support?
    1. Family member
    2. Government
    3. NGO
    4. Others (specify……)
    5. None

15. Did the patient develop adverse drug side effect?
    1. Yes
    2. No

16. If yes to question 16, what was the side effect and how frequent?

(Write frequency in number in front of the system affected)

1. Hepatitis (jaundice)……..
2. GI upset ……..
3. Renal toxicities ……
4. Psychiatric illness…….
5. Ototoxicity……..
6. Severe hypokalemia……
7. Others (specify**)…**

Part III. Checklist for laboratory characteristics of patient:

1. Smear result(AFB and/or Gene Xpert) at base line
   1. Detected
   2. Not Detected
2. Results of baseline culture
   1) Positive
   2) Negative
   3) Unknown
3. Baseline DST result
   1) RIF resistance only
   2) Resistance to RIF,INH
   3) Resistance to RIF,INH,EMB,SM
   4) Others (specify…..)
4. Date of the first culture conversion after treatment initiation (fill the month at which the culture or smear converted to negative)…….
5. Radiological (x-ray) pattern of lung lesion
   1) Cavitary lesion
   2) Consolidative
   3) Reticulo-nodular
   4) None
   5) Other ,specify_____
6. Radiological extent of lung lesion
   1) Unilateral
   2) Bilateral
   3) Normal
7. What was the final treatment outcome of the patient?
   1) Cured
   2) Completed
   3) Failed
   4) Died
   5) Lost to follow up

8. Date of treatment outcome_____

Annex-II: Declaration

I the undersigned, declare that this is my original work and all sources of materials used for this thesis have been acknowledged.

Name: Dita Bira Chala (MD)

Signature _____

Date of submission _____

This thesis has been submitted with our approval as University

Advisors

Name: Dr. Daniel Yilma (MD, Associate Professor, Consultant Internist)

Signature _____

Date of submission _____

Name: Mr. Abraham Lomboro (BSc, MPHE)

Signature_____

Date of submission _____

The End