Determinant Factors of Treatment Failure among Tuberculosis Patients under Directly Observed Therapy in Tigray Regional State Public Hospitals, North Ethiopia: A Case-Control Study

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Abstract

Introduction: Tuberculosis continues to be one of the major public health problems in Ethiopia. In 2009 the country ranked 7th from the 22 TB high burden countries by estimated number of case. It is also showed that the country has lower treatment success rate sated by World Health Organization. Therefore, the aim of this study is to assess determinant factors of tuberculosis treatment failure among patients directly Observed therapy in Northern Ethiopia.Methods: Unmatched case-control study was conducted among randomly selected health facilities found in northern Ethiopia from February to October 2013. Samples were 77 cases and 153 controls recruited during the course of TB treatment. Cases were TB patients those declared as treatment failure and control were as cured after completion of the treatment (after 5 months of treatments). Both cases and controls were selected from TB clinics. Data were analyzed by SPSS version 16.0. Bivariate and multivariate logistic regression (Odds Ratio) with 95

Index terms— tuberculosis, treatment failure, determinant factors, northern Ethiopia.

1 Introduction

uberculosis (TB) is one of a contagious disease which spreads through the air. When infectious persons cough, sneeze, talk or spit, they transmit the disease causing germs into the air which is inhaled with air and transmitted to another person [1]. After the disease introduced in to the person it is broadly classified in to pulmonary TB (smear positive and smear negative) and extra pulmonary TB and the disease is commonly diagnosed by sputum smear microscope [2].

The treatment progress of the patient with the disease is assessed by sputum examination for pulmonary TB patient. The new pulmonary TB patients with smear positive at the start of treatment should be monitored by sputum smear microscopy at the end of the fifth and seventh months. If results at the fifth or seventh month are positive, treatment has failed, and outcome is labeled as treatment failure and patient is treated as treatment failure type [3].

Tuberculosis is a global health concern. It is a major cause of illness and death worldwide second to HIV/AIDS, especially in low and middle income countries where it is fuelled by the presence of HIV/AIDS [4]. The World Health Organization (WHO) report on tuberculosis indicated that, in 2010, there were 8.8 million incident cases of tuberculosis, and 1.1 million deaths from TB among HIV-negative people and an additional 0.35 million deaths from HIV-associated TB. Majority of cases were (40%) occurred in India and China and 82% of TB cases were from the 22 high-TB burden countries which includes Ethiopia. From the global cases Africa also accounts for 24% notified cases ??5]. In addition, the incidence in Sub-Saharan Africa is twice that of South Asia which has highest prevalence from the world ??6].

After the introduction of directly observed therapy (DOT), the number of people being cured from TB are increasing, but millions will remain ill because they lack access to high-quality care **??**7]. And the treatment success rate among smear positive pulmonary TB reached 87% globally in 2009, but in the Africa region it is 80% which is lower than WHO target. Among the 22 high burden countries 15 of the reached the target and Ethiopia is one of the 7 countries from which treatment success rate lower than the target **??**6].

2 II.

3 Methods

Study setting: The study was conducted in health centers and hospitals found in north Ethiopia from February to October 2013. In the region there are 16 governmental, 2 private hospitals and 211 health centers **??**11].

Sample size and study design: Unmatched case-control study was conducted by taking patient who completed tuberculosis treatment course. New smear positive TB cases who registered at TB clinic was included in the study. Patients declared as treatment failure were taken as case and cured were as controls. All adult patients (age 15 years and above) who were smear positive at the beginning of the treatment and declared as cured (smear negative) at the end of DOTS course was included as control. All adult Patients who were smear positive at the beginning of the treatment and declared as treatment failure (smear positive) was included as a case.

Sampling procedures: Cases and controls were selected from randomly selected health facilities (4 hospitals and 6 health centers) providing TB treatment based on proportional to population size ratio allocation be treatment failed, i.e. if the patient had smear positive result at fifth month and later. Controls were selected randomly from patient who declared cured from the disease. Systematic simple random sampling was used in selection of control, but the cases were enrolled to the study until the required sample size was filled.

Data collection: We considered as "cured":-if patient whose sputum smear or culture was positive at the beginning of the treatment but who was sputum smearor culture-negative in the last month of treatment; and "Treatment Failure":-if patient who was initially smearpositive and who remained smear-positive at month 5 or later during treatment or a patient on re-treatment.

The instrument was prepared by reviewing similar literatures **??**12] **??**13] **??**14]22]. The questionnaire was prepared in English and translated to Tigrigna and it was checked for its consistency by back translation to English by two different individual. The data was collected using pre-tested interviewer guided semistructured questionnaire. Data was collected through interviewer guided face to face interview and medical record reviews of patients. Information on sociodemographic characteristics, patient's disease status, treatment regimen, disease co-morbidity, knowledge to ward TB treatment, treatment adverse effect, personal habits, nutritional related factors and health service related factors was collected directly from the respondents. Information on treatment regimen, sputum re-examination and treatment outcome was taken from TB clinic patient registration. Data was collected by a 10 nurses who has experience in TB treatment and care. Data collection process was strictly supervised by supervisors and the data were checked for consistency and completeness. Incomplete and unclearly filled questionnaires were given back to the interviewer to be completed.

Data processing and analysis: Data entry and cleaning was done using EPI Info version 3.5.1 and was analyzed by SPSS version 16. The data was summarized and descriptive statistics was computed for all variables according to type. Frequency, mean and standard deviation were obtained for continuous variables while the categorical variables were assessed by computing frequencies.

A bivariate analysis was used to describe the association between independent and dependent variables and a multivariate analysis also was used to show the factors determining outcome variables. To determine the factors most strongly associated treatment failure, odds ratio at 95% CI was determined by using logistic regressions analysis and P ? 0.05 will be considered significant for all the independent variables in the model. The final model was fitted using the Hozmer and Lem show Goodness of test.

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Confounders, interaction and Muti-collinarity were checked to minimize bias. methods. Cases was selected if the patient declared to Even though, Ethiopia adopted and fully implemented the DOT, TB continues to be a major public health problem which puts the countries at 7th rank from the 22 TB high burden countries by estimated number of case **??**8]. In 2009 TB is the 5th cause of admission, the 3rd leading cause of death with 67% cure rate for registered patient in the same year in Ethiopia **??**9]. In addition to these, for all new TB cases, 20% of them have a chance to be multidrug-resistant (MDR) TB **??**10].

Since, there is limited study about determinants treatment failure among TB patient in the country and study area, thus, this study is aimed to identify the determinants factors of treatment failure among tuberculosis treated patients in health settings found in Northern Ethiopia using case control study.

Sample was taken by two population proportion formulas by considering proportion of exposure among the patients with treatment failure place of residence was taken to calculate the sample size by considering 20% exposure among poor treatment outcome from south region of Ethiopia study and odd ratio 2.5 [12] and is calculated using Epi-info version 3.5.1. We use 95% CI and 80% power of test with 1:2 ratio of case to control. Accordingly, a total sample size of 230 (77 cases and 153 controls) were included from the selected hospitals and health centers. After considering 10% of non response a total sample size 253 will be required.

Ethical clearance: The study protocol was reviewed and approved by health research ethics review committee of the College of Health Sciences at Mekelle University. Permission to undertake the study was obtained from every relevant authority in Tigray regional health bureau, hospitals and health centers. Written informed consent was obtained from the participants prior to participation in the study, and data collection was conducted confidentially.

5 III.

6 Result

Scio-demographic characteristics of respondents: Of the total study population who visited the TB clinic in northern Ethiopia during study period; 230 study participants completed the interview in all study sites, a response rate of 91%. Among these 64(27.8%) were cases (failure) and 166(72.2%) were controls (cured rest were females. Majority of the failure as well as cured patient after TB treatment were between 40 and above years of age. The median age of patients among failure was 40 years and 29 years among cured. Majority of the study subjects were married; (35.9% of failures and 47.6% of cured TB patients). About 21.9% of failure and 10.8% of cured patients were not employed. Major proportion of failure and cured patients after TB treatment were Orthodox Christian follower (98.4% vs. 97.6% respectively). About 26.6% of failure and 17.5% of cured patients' complete 1-6 grade and most of the failure (71.9%) and cured patients (57.8%) live in urban area. The mean ± SD family size of study subjects was 3.7 ± 2.1(SD). About 48.4% failure and 11.4% cured patients were infected with HIV among those HIV positive participant; 27.2% of failure and 89.5% of cured parents' were started ART (Table 1 The study participants were also compared with respect to the experience of side effect of TB treatments, subject who experience vomiting as side effect of TB treatment had higher risk TB treatment failure (AOR=32.9, 95% CI=3.27, 330.2); patient with headache also higher risk (AOR=7.87, 95% CI= 1.3, 47.38), and patient with numbness of the hand and leg were also higher likelihood risk of TB treatment failure (AOR=27.81, 95% CI=2.6, 297) compared with patients who don't experienced vomiting, headaches and numbness of the hand and leg after adjusting for other variables (Table 5). IV.

7 Discussion

Assessment of factors responsible for unsuccessful treatment outcome in DOTS programs is of paramount importance particularly in smear-positive PTB patients as they harbor a highly contagious form of Microbactorium tuberculosis that can be monitored for speed of bacteriologic conversion on chemotherapy **??**13].

Hence, the aim of this study was to assess the determinant factors of tuberculosis treatment failure among smear positive PTB in DOTS program and was assessed at 4 months (new protocol), 5(old) or 7 months of taking TB treatment. Accordingly the factors which were associated with TB treatment failure include: having cough for more than 9 weeks before TB diagnosis, experience of side effect of TB treatments such as vomiting as side effect of TB treatment, patient with headache and patient with numbness of the hand and leg were positively associated with TB treatment failure where as being in age between 30-39 years and being farmers by occupation were a negatively risk factors.

In this study being male or female showed no statistically significant associations for the development of TB treatment failure. However, a study in Addis Ababa found that being male was a risk factor for development of treatment failure **??**14]. Similarly a study in Nigeria showed that being male was a risk factor for defaulting from anti-TB medication **??**15]. The reason for the difference may be due to the different in study population between the studies.

Another study showed that individuals who do not take anti-TB medication regularly have increased risk for treatment failure **??**16]. In our study the bivariate analysis also showed that individuals who missed to take one or more first-line anti-TB drugs whether forgot or intentionally missed had increased risk for development of TB treatment failure. It is also similarly with study conducted in Addis Ababa showed that individuals who did not take first-line anti-TB drugs regularly had increased risk for development of MDR-TB **??**14]. Other study conducted in Addis Ababa reported are major factors influencing treatment adherence **??**17].

Different studies have shown that poor treatment adherence was a risk factor for MDR-TB [6]. However, the current study showed that individuals who were incomplete the treatment for previous TB infection (history) had no increased risk of developing Treatment failure. In Ethiopia, the previous guideline for first-line anti-TB treatment was 8 months' duration, but the standard has been changed to 6 months. TB therapy requires more than 90% adherence to facilitate cure **??**18].

As it is known, coming early to health institutions to make TB diagnosis at the start of the symptoms has strong relationship with the successfulness of any treatment rather than coming after becoming severely complications. Having this, in this study individuals who had 9 weeks and more cough before TB diagnosis were risk factor for TB treatment failure. In this study, TB drug side effect were significantly associated with TB treatment failure which is similarly with study conducted with Addis Ababa, individuals who encountered drug side effects during the first course of TB treatment had a 4.5 times increased risk of developing MDR-TB [14]. Studies done in three districts of Arsi Zone, Ethiopia, found that anti-TB drug side effects were significantly associated with a high rate of defaulting **??**19]. When patients develop side effects, they tend to stop treatment, which favors the development of TB treatment failure. If the DOTS strategy of the nation were followed in all cases, there would be a chance to counsel patients and even treat adverse drug reactions before treatment interruption.

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In the current study, being age 40 years and above compared to age between 30-39 years had higher risk of TB treatment failure. Similarly a cross sectional study in Tigray showed that the risk of unsuccessful treatment outcome was 2.5 (95% CI: 1.12-5.59) times higher among PTB patients older than 40 years of age compared to those aged 15-40 years **??**13]. Similarly another study in Thailand showed that an age of above 60 years was significantly correlated with treatment interruption and treatment failure [20].

(adjusted OR = 3.10, 95% CI: 1.33-7.24) unsuccessful outcome when compared to their counterparts **??**13]. This is consistence with the current study that having no job has higher risk of TB treatment failure than farmer.

In this study previous history of both self and family member TB infection and treatment has statistical significant at bivariate level but not significant in the multiple logistic regression model. Similarly in study in Ethiopia showed that that having more than one TB episode also increased risk for TB treatment failure. This may be related to the previous treatment outcome, default, treatment failure, or relapse, or the patient may have had MDR-TB initially. A systematic review of 29 published reports on risk factors associated with TB treatment failure in Europe revealed that previous treatment was the strongest determinant of MDR-TB and that the pooled risk of TB treatment failure was 10.23 times higher in previously treated than in never-treated cases [21]. A study in Uganda also showed that multiple TB episodes and treatment failure were significantly associated with treatment failure [22]. Similarly, in Ethiopia, according to a nationwide anti-TB drug resistance survey conducted in 2005, 1.6% of newly diagnosed TB cases were infected with MDR-TB, while 11.8% of the MDR-TB cases were previously treated TB cases.

In the current study, HIV status had no significant association with TB treatment failure. A study in Thailand and Addis Ababa showed also that HIV status was not significantly associated with TB treatment failure [23,2]. A study in Ukraine showed that HIVpositive individuals had a 50% higher risk of developing TB treatment failure at their first TB infection [24]. This is because being HIV positive is one risk factor for drugsusceptible TB, which is related to immune system suppression. Being HIV positive might carry the same risk of infection with MDR-TB but may not contribute to the change of a drug-susceptible strain of TB to MDR-TB.

In current study marital status, residence, distance from treatment center, number of rooms in house, educational status, ever smoking cigarette were no risk factors for the development of TB treatment failures, which is similar in study conducted in Addis Ababa and Tigray [14, 13]. As limitation, in this study the sample size was small which makes to generalizing findings due to the cases were very rare events and difficult to get a patient with treatment failure after DOTs during the 9 months study periods. In addition, there may be also a interviewer bias since the data collectors were recruited from the health facilities. So, it is better to consider in interpretation of this findings. As strength, the design of the study is unique in trying to minimize potential bias by using the unconditional cases and controls. Used standard structured questionnaire factors from patient, health provider, and medical practice sides.

V.

9 Conclusion

Forgetting to take TB drug, missing TB drug intentional due to different reasons and taking different treatment drugs for other medical problems during the course of TB treatment drug cause more risk of experiencing TB treatment failure. Being in age group between 30-39 years had reduced likely hood of risk of TB treatment failure compared to those 40 years old and similarly being farmers by occupation were a reduction likelihood of risk compared with a person with no job. Subjects who had more than 9 weeks cough before TB diagnosis were more likely to have treatment failure compared with those who had less than 4 week cough. Subject who experience vomiting, head ache and numbness of the hand and leg as side effect of TB treatment had more likely risk to TB treatment failure compared with patients who don't experienced vomiting, headaches and numbness of the hand and leg after TB treatment. Considering this, early treatment of TB, giving especial care to older patients and possible and appropriate sustained activities to bring behavior change regarding effective use of drug at home during the continuation phase are important interventions. In addition, there should be a system for regular supervision, follow-up training and means of quality control and possible referral system for patient with treatment failure.

10 VI.

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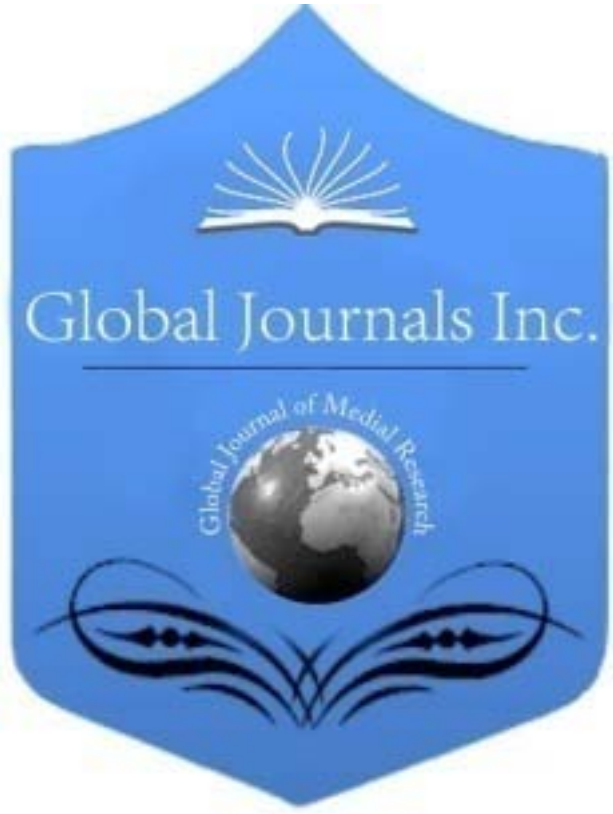

Figure 1: F

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from TB). Male participants were 139(60.4%) and the

Variables	Cases N= 64	Control N=166	Total
Age (years)	No(%)	No(%)	No(%)
<=19	6(9.4)	30(18.1)	36(15.7)
20-29	11(17.2)	55(33.1)	66(28.7)
30-39	13(20.3)	36(21.7)	49(21.3)
40+	34(53.1)	45(27.1)	79(34.3)
Sex Male	41(64.1%)	98(59%)	139(60.4%)
Female	23(35.9%)	68(41%)	91(39.6%)
Religion			
Orthodox	63(98.4)	162(97.6)	225(97.8)
Muslim	1(1.6)	4(2.4)	5(2.2)
Educational status			
Illiterate	7(01.9)	24(14.5)	31(13.5)
Read and write	5(7.8)	25(15.1)	30(13)
1-6 grade	17(26.6)	29(17.5)	46(20)
7-8 grade	8(12.5)	21(12.7)	29(12.6)
9-12 grade	13(20.3)	32(19.3)	45(19.6)
Above 12 grade	14(21.9)	35(21.1)	49(21.3)
Marital status			
Single	20(31.2)	65(39.2)	85(37)
Married	23(35.9)	79(47.6)	102(44.3)
Divorced	17(26.6)	17(10.2)	34(14.8)
Widowed	2(3.1)	3(1.8)	5(2.2)
Separated	2(3.1)	2(1.2)	4(1.7)
Owen income			
Yes	37(57.8)	94(56.6)	131(57)
No	27(42.2)	72(43.4)	99(43)
Residence			
Urban	46(71.9)	96(57.8)	142(61.7)
Rural	18(28.1)	70(42.2)	88(38.3)
HIV status			

Figure 2: Table 1 :

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Figure 3: Table 2 :

3

Nutritional status of study participants: Most of the study participant were under weight with BMI <=19 which 68.8% of failure and 51.2% of cured patients were malnourished. During the treatment of TB; most of the patients, 79.6% failure 69.9% cured had developed loss

Figure 4: Table 3 :

4

Health care system related factors: According to the study participants most of the time the opening time o

very good interaction by 46.9% of failure and 51.2%

Health related factors	caresystem	Cases N= 64 No(%)	
TB clinic opening time convenient for Pt			
Yes		60(93.8)	152(91.6) 212(92.2)
No		4(6.2)	
Waiting time at TB clinic in minute			
<=30 minutes		57(89.1)	
31-60 minutes		4(6.2)	
>=61 minutes		3(4.7)	
Care	giverduring intensive phase		
Health worker	extension	4(6.2)	
Nurse at TB clinic		59(92.2)	
Others		1(6.6)	
View of patient toward attitude professional at TB clinic	of health		
Very good		30(46.9)	
Good		24(37.5)	

Figure 5: Table 4 :

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Variables	Cases n(%)	Control n(%)	Crude OR (95%CI)	Adjusted OR (95%CI)
Age (years)				
<=19	6(9.4)	30(18.1)	0.47(0.178, 1.24)	0.49(0.16, 1.51)
20-29	11(17.2)	55(33.1)	0.44(0.196, 1.002)	0.5(0.2, 1.28)
30-39	13(20.3)	36(21.7)	0.123(0.028, 0.54)*	0.56(0.028, 0.56)*
40+	34(53.1)	45(27.1)	1	1
Occupation				
Government worker	12(18.8)	32(19.3)	0.48(0.18, 1.26)	0.52(0.18, 1.49)
Private	4(6.2)	9(5.6)	0.57(0.14, 2.25)	0.76(0.17, 3.33)
NGO	1(1.6)	4(2.4)	0.32(0.03, 3.21)	0.28(0.025, 3.18)
Merchant	6(9.4)	15(9)	0.51(0.16, 1.67)	0.38(0.11, 1.32)
Farmer	8(12.5)	31(18.7)	0.33(0.12, 0.94)*	0.248(0.077, 0.8)*
House wife	5(7.8)	10(6)	0.64(0.18, 2.31)	0.47(0.12, 1.87)
Daily laborer	9(14.1)	18(10.8)	0.64(0.22, 1.86)	0.73(0.24, 2.25)
Student	5(7.8)	29(71.5)	0.222(0.068, 0.72)*	0.29(0.074, 1.12)
No job	14(21.9)	18(10.8)	1	1
Number of people live in the same house				
<=2	25(39.1)	67(40.4)	1	1
3-4	31(48.4)	59(35.5)	1.866(0.77, 4.53)	2.2(0.97, 4.94)

Figure 6: Table 5 :

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Prevalence community.PLoS One 2010, 5(12

Figure 7:

.1 Acknowledgement

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