Predictors of Smear non-conversion among Adult Patients Newly Treated for Bacteriologically Confirmed Pulmonary Tuberculosis at Shashemenne Referral Hospital – A Retrospective Cohort Study

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Jimma, Ethiopia

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Abstract

Introduction: Sputum smear non-conversion at the second month of tuberculosis treatment is a major predictor of patient infectivity and treatment failure. We aimed to identify the factors associated with smear non-conversion in patients newly treated for bacteriologically confirmed pulmonary tuberculosis.

Method and Material: A retrospective cohort study was conducted on adult patients newly treated for bacteriologically confirmed pulmonary tuberculosis enrolled from 2002 to 2011 at Shashemenne Referral Hospital. Data on socio-demographic factors, comorbidities, drug-related factors, substance use, and baseline bacilli grading were extracted from TB registered and patient cards by using a structured tool. Two nurses and one supervisor collected the data after being trained. Finally, a binary logistic regression was employed for analysis to determine the predictor of the smear non-conversion with a 95% confidence interval and 0.05 significance level.

Result: Of the 521 who had included in the analysis, 10.7% (56) overall smear non-conversion rate was found at their 2nd months of treatment. The mean age was 38.9 ± 13.2 SD, and 52.9% (276) were male sex. Being BMI < 18.5 kg/m2 [AOR = 2.15, (1.08, 4.27)], having history of smoking [AOR = 2.53, (1.13, 5.64)], and grade 3+ smear bacilli density [AOR= 2.57, (1.19, 5.58)] were found to be an independent predictor of smear non-conversion at 2nd months of treatment.

Conclusion: Pulmonary tuberculosis patients with the above independent predictors were the major reservoirs for TB transmission both before treatment and after treatment. The longer smear conversion period in those patients could further prolong the exposure period for the contacts. Hence, comprehensive infection prevention measures should be applied for patients with a history of smoking, undernutrition, and grade 3+ pretreatment bacilli density.

Keywords: Bacteriologically confirmed pulmonary tuberculosis, sputum smear conversion.

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List of abbreviations and acronyms

ADRs	Adverse Drug Reactions
AFP	Acid Fast Bacilli
AOR	Adjusted Odd Ratio
BCPTB	Bacteriologically Confirmed Pulmonary Tuberculosis
BMI	Body Mass Index
CBC	Complete Blood Count
CDC	Communicable Disease Control
COR	Crude Odd Ratio
DM	Diabetes Mellitus
DOTs	Directly Observed Therapy
DR-TB	Drug-Resistant Tuberculosis
DST	Drug Susceptibility Test
EFY	Ethiopian Fiscal Year
ESR	Electrolyte Sedimentation Rate
EPTB	Extra Pulmonary Tuberculosis
FMOH	Federal Ministry of Health
FBS	Fasting Blood Sugar
GC	Gregorian Calendar
HCT	Hematocrit
Hgb	Hemoglobin
HIV	Human Immune deficiency Virus
HIV/AIDS	Human Immune deficiency Virus/Acquired Immuno Deficiency Virus
HIV/TB	Human Immune deficiency Virus and Tuberculosis
HPF	High Power Field
IPC	Infection Prevention and Control
JUSH	Jimma University Specialized Hospital
LED-FM	Light Emitting Diode Fluorescent Microscopy
LTFUP	Lost To Follow Up
MDR-TB	Multi Drug-Resistant Tuberculosis
OR	Odds Ratio
PTB	Pulmonary tuberculosis
RBS	Random Blood Sugar
RHZE	Rifampicin, Isoniazid, Pyrazinamide, Ethambutol
RR	Relative Risk
RR-TB	Rifampicin Resistant Tuberculosis
SSC	Sputum Smear Conversion
SDG	Sustainable Development Goal
SRH	Shashemenne Referral Hospital
TB	Tuberculosis
WHO	World Health Organization

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CHAPTER 1: INTRODUCTION

1.1. Background

Tuberculosis is the world's deadliest infectious disease which remained a major global health challenge (1). Globally, over 10 million people will lose their lives to this preventable and curable disease. There were cases in all countries and age groups, but about 90% were adults (aged ≥ 15 years), 9% were people living with HIV of which 72% were in Africa (2).

WHO has declared TB as a global public health emergency in 1993 and then, formally launched the DOTs as a standard treatment strategy in 1994 (3). Since then, significant progress has been made in reversing the incidence of TB which enabled in 41% global prevalence reduction. However, still there are 30 high TB burden countries recognized by WHO, where about 87% of the global cases of tuberculosis were occurring. Ethiopia is one of the high burden countries where TB remained a major public health threat being one of the top ten causes of admission and deaths in adults (4)(5).

Tuberculosis poses a major challenge in resource-limited settings, particularly in Africa and some regions of Asia, leading to loss of healthy life years as it leads to a reduction in the global workforce, which in a way has impacts on the economy. TB serves as one of the main causes of deaths related to antimicrobial resistance and the number one killer of people living with HIV, especially in Africa (3). Progress towards UHC and actions to address health-related risk factors for TB (as well as broader social and economic determinants of TB) will be fundamental to achieving the targets and milestones for reductions in TB cases and deaths, for two reasons (3) (5).

The 2030 targets are a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate, compared with levels in 2015. The 2035 targets are a 95% reduction in TB deaths and a 90% reduction in the TB incidence rate, compared with levels in 2015 (6). Worldwide, TB incidence (new cases per 100 000 population per year) is falling at about 2% per year. The fastest regional declines were in the WHO European Region (5% per

year) and WHO African Region (4% per year). In the same 5 years, particularly impressive reductions (4–8% per year) occurred in southern Africa (e.g. Eswatini, Lesotho, Namibia, South Africa, Zambia, Zimbabwe) following a peak in the HIV epidemic, and the expansion of TB and HIV prevention and care, and in the Russian Federation (5% per year) following intensified efforts to reduce the burden of TB (7).

Ethiopia has adopted the DOTs strategy since 1997 after a successful pilot program with the development of the first combined Tuberculosis and Leprosy Prevention and Control Program manual (6). In Ethiopia, the annual TB incidence declines 42% annually from 369 cases per 100,000 populations in 1990 to 177 per 100,000 populations in 2016. However, Ethiopia is remained to be among the 30 countries reported with a high burden of TB, TB/HIV, and DR-TB for 2015 to 2020. This could be due to the high number of missed and infectious TB cases in the community as well as the failure in infection prevention strategies (7).

In resource-limited countries, patients with suspected symptoms of PTB are normally diagnosed based on sputum smear microscopy. According to the Ethiopia national TB guideline which adopted from the WHO guideline, once patients were diagnosed to have bacteriologically confirmed PTB they should be initiated with the standard anti-tuberculosis regimen comprising Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E) for intensive phase of two months, and HR in the continuation phase of four months (2).

In assessing the effectiveness of treatment and infectiousness of patients during anti-TB therapy in newly treated patients, sputum specimen is evaluated at 2^{nd}, $5^{th,}$ and 6^{th} months during treatment (6). Surveillance on smear conversion is currently used as an operational indicator for clinical management, the effectiveness of TB treatment, and evaluation upon the performance of the DOTs strategy.

Bacteriologically confirmed PTB patients are a significant source of infection. As a result, successful control of TB depends on early and effective tackling of the transmission from the prominent source of infectious. Studies have reported that most PTB patients are no longer infectious after 2 weeks on DOTs due to a reduction in coughing and a decrease in viable *mycobacterium tuberculosis*. This could reduce the infectiousness of bacteriologically confirmed PTB patients by 50% when compared with the period before chemotherapy (5) (6).

However, studies conducted on smear conversion at the end of the intensive treatment phase indicated variability in both magnitude and factors associated with persistent smear positivity. In Ethiopia, there is limited information on both the magnitude and determinants of smear non-conversion among the prominent source of infection at their most infectivity period. Knowledge of these factors could have an important role in controlling the transmission by establishing a necessary approach of airborne isolation both at home and health facility setting.

1.2. Statement of the problem

Despite the established DOTs strategy at the global and national level, TB has remained a major cause of morbidity and mortality. WHO estimated nearly one billion more new infections, 200 million illnesses, and 70 million deaths from TB between the years 1999 and 2020 unless effective and comprehensive IPC measures are strengthened at all levels (5). Sub-Saharan Africa, including Ethiopia, has the highest prevalence of TB infection in the world. Hence, 80% of TB cases and 78% of global TB deaths occur in these countries, primarily due to the high prevalence of HIV/AIDS, poor TB control efforts, social inequalities, drug resistance, and inadequate access to TB care (5)(2,8).

Patients with bacteriologically confirmed pulmonary tuberculosis are a major source of infection and capable of infecting up to 15 people a year (2). This might need to require an extensive prevention strategy in interrupting the transmission. Early diagnosis and prompt treatment initiation of smear-positive patients are an important strategy with a goal-line of smear conversion at two months of the intensive phase of potent anti-tuberculosis treatment. However, monitoring treatment response to chemotherapy remains unsatisfactory in resource-limited countries where sophisticated and expensive tests are not readily available. According to the MOH TB national guideline, microscopic examination is used as the measure of determining sputum smear status at all follow-up schedules (9).

Patient with persistent sputum smear non-conversion at 2 months presages poor outcome, higher rates of treatment failure, and relapse. In the same way, a prolonged infectivity period due to the persistent smear positivity could lead to a prolonged period of exposure of others individuals at home, community, and health facility level (10,11).

Previous studies on smear conversion reveal varied magnitude as per the study setting and study design employed. Accordingly, the highest rate of smear non-conversion was reported from prospective studies in Lithuania and Iran, where 25.3% and 35.3% smear non-conversion rate was reported at 2^{nd} months of treatment respectively (12)(13).

Similarly, retrospective studies from Italy (14) and India (15) had also reported as high as 21.3% and 33.2% respectively.

On contrary, a prospective study conducted in Sri Lanka (16) reported 14.2% persistent smear positivity at the end of the intensive phase whereas a retrospective study in Rural Tanzania (17) and Eden district of South Africa (18) revealed only 8.3% and 12.8% of bacteriologically confirmed PTB patients were remained smear positive at 2nd months of treatment respectively. The studies from the Eden district of South Africa also found that the magnitude of smear non-conversion varied among newly treated (13.3%) and previously treated cases (9.9%) (18).

In Ethiopia limited studies related to the area were conducted in two settings; East Gojjam, Amhara region, Jimma, and Addis Ababa city. A prospective study in East Gojjam part of Amhara region, Ethiopia was conducted in 2019 which finally come up with 15% of smear non-conversion whereas, on contrary, the crossectional studies conducted in Addis Ababa reported 6.15% which is much less when compared with the others (19),(20).

Therefore, limited information on the magnitude of the problem as well as much variability of smear non-conversion rate at setting previously studied first initiated for further studies on the area of the topic. Similarly, previous studies have also identified multiple factors which determine such varied smear non-conversion rate particularly at 2nd month of follow-up examination. These factors were also varied depending on the study setting, design, and statistical method used in the study.

Factors including socio-demographic characteristics, comorbidities (DM, HIV, anemia, under-nutrition), behavioral factors (smoking, alcoholic consumption), drug-related factors (Dosage, regimen, adverse effect, immunosuppressant drug use), and microbiological factors (baseline bacilli grading) were studied as to determine the smear non-conversion (12,14,16,19,21–24). However, almost all the studies agree only on a high pretreatment bacilli density as an independent predictor of smear non-conversion (14,16,19,21,22). But several studies were reported varied predictors in terms of socio-

demographic, comorbidity, drug-related and behavioral factors, which initiated me to conduct further studies (13,18,20,25–28).

In Ethiopia, as far as this research is concerned although sufficient information is documented on predictors of TB treatment failure, treatment outcome, and Drug resistance, there is limited information on both magnitude and predictors of smear non-conversion particularly at the intensive phase of treatment. The intensive period is considered as the time of maximum possibility of transmission despite the initiation of treatment.

In a country with a high TB burden and limited information on the determinants of smear non-conversion, this kind of study could bring new insight to further TB prevention and control particularly in a resource-limited country like Ethiopia. This study was intended to be conducted in Shashemenne Referral Hospital located in West Arsi Zone, southeast Ethiopia, where the first DOTS strategy was applied even at the national level. The study area is selected on basis of better TB diagnostic and treatment settings and as well as better documentation on patient records. The finding from this study could add to the limited information on the area of study despite that the expected limitation in the documentation might affect the finding.

1.3. Significance of the study

In a country with resource-limited and high TB burden like Ethiopia, knowing the potential risk factors of persistent smear positivity enable the service providers in stratifying patients according to the risk of prolonged infectivity and adverse outcome. Thus, extensive emphasis on those major sources of infection and having the risk of protracted smear conversion could further reduce the transmission. Hence, the finding from this study could help the reduction in global TB burden by giving an insight into the track of TB transmission even after initiation of treatment.

In the same way, the finding could also have an impact on the current drug resistance as it gives attention to those patients with the risk of late smear conversion. Several studies also reported as smear non-conversion had an association with treatment failure. Thus, identification and early prevention or treatment measures on the predictors of smear non-conversion could reduce the chance of developing the drug-resistant form of tuberculosis (10, 11).

This kind of study could also give insight into the cons and pros of the current DOTs service for TB transmission and any strategy that enhances patient mobility rather than isolation should be reevaluated for successful TB prevention and control. The more mobility reduced the less chance of contact and TB transmission.

Focusing on the study that insight both the reduction of new TB cases and Drug-resistant TB cases could have an indispensable role in for global TB program, and for the resource-limited country like Ethiopia in particular. So that, this study was focused on setting were first DOTS service at country level initiated, highly populated, and TB prevalent area. This could also help the countries TB Programme for better planning on measures of TB prevention and control.

CHAPTER 2: LITERATURE REVIEW

2.1. Overview of TB prevention and Control

World Health Organization has been subsequently introduced different TB prevention and control strategies that have been employed in all countries worldwide. These strategies include; DOTS strategy (1994-2005), The Stop TB Strategy (2006-2015), The END TB strategy (2015-2035) designed in line with an SDG target mainly aimed at ending the global TB epidemic, with targets to reduce TB deaths by 95% and cut new cases by 90% between 2015 and 2035, and ensure that no family is burdened with catastrophic expenses due to TB (29).

In 1992 EC, Ethiopia has initiated the DOTS services in the pilot area and the TB and Leprosy programs were merged to National Tuberculosis and Leprosy Control Program in 1994 (6). Ethiopia has also successfully achieved the millennium development goals set for TB in 2015 and currently, the country has expressed its commitment to accelerate the fight to end the TB epidemic by 2035 by endorsing the new post-2015 Global "END TB strategy" and has already aligned the National TB Strategic Plan within the framework of National Health Sector Transformation Plan (30)

2.2. TB diagnostic methods, treatment, and monitoring

Diagnosis of Tuberculosis may be reached by proper investigations using either bacteriologic examination, imaging techniques, histopathology, or biochemical analysis of body parts/fluids (31). Specifically, there are about four bacteriological methods to reach a diagnosis which is currently employed in Ethiopia as well at the different service level. This includes; smear microscopy which has two staining methods (Ziel-Neelsen staining or fluorescent auramine staining), TB Culture, Phenotypic DST diagnostic methods, and Genotypic/Molecular Diagnostic methods, which are specifically designed to detect/confirm genetic mutations associated with drug resistance. It is currently

recommended as an initial diagnostic method in previously treated patients, patients with a history of MDR TB contact, HIV patient, and children (32).

TB case detection rate and the treatment success rate are the two key indicators while monitoring TB performance program. For all newly treated TB patients WHO and the national TB guideline currently recommend a treatment regimen of four fixed drug combinations (HRZE) for two months (intensive phase) and two fixed drug combinations (RH) for the next four months (continuation phase) which tend to be given on daily basis under observation whereas the dose of the drug should also be given based on the weight of the patient as recommended on the guideline. Additionally, routine follow-up smear examinations at the 2^{nd}, 5^{th}, and 6^{th} months of treatment are recommended according to the national guideline (5).

2.3. The magnitude of smear non-conversion

According to the WHO and national guidelines, all sputum-positive patients on TB treatment must have one sputum specimen examined at the end of the 2nd month to achieve smear conversion within 2 months in most patients (1) (5). Sputum smear conversion after two or three months of treatment is a good predictor of an eventual cure if treatment is completed and is also strongly recommended in shortening the period of infectivity as it enhances the control of TB (2). A prospective study conducted in India on time for smear conversion reveals that the median time to smear and culture conversion was the end of the 5th week [day 35] and 6 ½ weeks [day 45] respectively (27).

A cross-sectional study from India (27) conducted in 2017 reveals as 97.33% underwent sputum and culture conversion at the end of the intensive phase of treatment whereas another prospective and retrospective cohort studies from India reported a higher rate of smear conversion which was 85.8% and 66.7% respectively (15)(33). Sputum conversion rate also tends to vary in subsequent weeks after treatment. Hence, studies in Morocco stated as the sputum conversion rate was 42% after two weeks, 73% after one month, and 95% after two months (34).

A similar prospective cohort study conducted in India resulted in the smear conversion rate of 71%, 84%, and 92% at 1st, 2nd and 3rd months of treatment respectively (35). On the other hand, the study conducted in South Africa revealed variability in persistent smear positivity among new and re-treatment cases as 13.3 % of the new cases and 9.9 % of the re-treatment cases do not undergo smear conversion (18)

2.4. Predictors of smear non-conversion

2.4.1. Socio-demographic factors

Several studies conducted on determinants of TB treatment outcome identified that TB patients with old age are more likely to end with unfavorable outcomes. A case-control study conducted in Arba Minch, Ethiopia in 2014 stated as patients with age group ≥ 35 years were less likely to end with treatment success when compared with those young age group. Other retrospective studies conducted in a different area of Ethiopia (Harar, Afar, Jimma, Arsi) dictated that old age were more at risk of treatment failure (36–41)

Several studies reported that patients with prolonged sputum conversion at the intensive phase were identified as one of the independent risk factors to be associated with unfavorable outcomes and also probably considered as a predictor for MDR-TB cases (10,11,42,43). As a result, the study conducted in different countries Italy (14), Tanzania (17), and South Africa (18) reported that old age significantly determines the time for sputum smear conversion. However, a retrospective study conducted in Burkina Faso (44) in 2015 resulted as age determine the smear conversion only among new cases while it has no chance on those patients with retreatment cases.

Unlike the age, a five years retrospective study conducted on treatment outcomes in Harar, Ethiopia reported that the male sex was more likely to have the unsuccessful outcome (36). On contrary, studies from Jimma Referral Hospital (41), and Debre Tabor General Hospital (38) reported as the sex of the patient has no association with the treatment outcome. Another retrospective study conducted in Iran in 2014 resulted in that

patient sex had a significant association with the treatment outcome so that male sex is more likely to end with unfavorable outcomes (45)

On the other hand, studies in different settings also reported contradictory findings on sex determinants on persistent smear conversion at the intensive phase. Studies from Lithuania, South Africa, Tanzania, and Ghana were conducted on sputum conversion dictate as male patients sex are more likely to develop persistent sputum positivity at the end of 2 months of treatment (12)(17) (18).

2.4.2. Behavioral factors

Nearly one-fifth of the world's population smokes tobacco or uses other tobacco products while smoking remained a major risk factor for the infection of tuberculosis. Smoking is more prevalent in countries with a high prevalence of TB. Currently, substantially large proportions of tobacco smokers (82%) live in low- and middle-income countries with a high burden of TB as well (46). A study conducted revealed that smoking increases the risk of latent TB by a factor of 1.9, active tuberculosis by two-fold, and that of death from TB by 2.6 after being adjusted for socioeconomic status (47).

Smoking also enhances the risk of treatment failure, the risk of relapse, and the number of defaults (46)(48). In India, 38% of deaths from TB among middle-aged men are attributed to smoking, costing the Indian economy three times its TB budget (49). The previous study also associates tobacco smoking considerably with TB diseases, increased risk of advanced and more severe disease in the form of cavitation, sputum positivity, and slower conversion of sputum after treatment initiation (50,51).

Prospective studies conducted on smear conversion in India (33), and East Gojjam, Ethiopia (19) also revealed that smoking and alcohol consumption are the two factors mostly determining the patient sputum conversion at the intensive phase. Another prospective cohort study in India (52) also resulted in tobacco smoking [AOR: 2.18; 95% CI: (1.03-4.61)] emerged as independent predictors of delayed sputum smear conversion. However, another study from Sri Lanka (16) contradictory reported as a smoker are less

likely to have sputum conversion at 2 -3 months as compared to non-smokers (90.2% vs. 82.1%, p = 0.045). Studies from Brazil reported as tobacco smoking significantly affects both smear conversion and treatment outcome (53).

In the same way, several studies also related alcohol consumption with early sputum conversion and treatment outcome. A retrospective study in Lithuania in 2017 reveals that alcohol abuse [AOR: 6.56; 95% CI: (2.27–18.94)]; was determined as an independent factor associated with persistent sputum positivity at the end of 2 months of treatment. Similarly, studies in East Gojjam, Ethiopia, and Sri Lanka also come up with similar findings (16)(19)(25)(54).

2.4.3. Clinical/Patient factors

HIV/AIDS is one of the most common causes of the incidence and death of tuberculosis (55). Globally, TB is the leading cause of death among people with HIV, accounting for an estimated 1.3 million (range, 1.2–1.4 million) deaths from TB among HIV-negative people in 2017 and an additional 300,000 (range, 266,000–335,000) deaths from TB among HIV positive people and Africa accounted for 84% of all deaths (2,55) However, the treatment regimens are largely the same for HIV-infected and non-HIV-infected patients (2).

HIV infection is also considered as the primary reason for the failure to meet tuberculosis control targets (at least 85% cure rate among new sputum smear-positive TB cases) in countries with high HIV infection. Studies conducted on TB/HIV show that the risk of death is 2 times higher in TB/HIV co-infected patients than those HIV negative patients on TB treatment (56). In addition, several studies also revealed contradictory ideas on the statistical significance of association between HIV co-infection and time of smear conversion (14,19,22,52).

A previous study conducted in Eden district of South Africa countries identified as HIV co-infected TB patients were more likely to remain smear-positive at the end of the intensive phase of DOTS therapy (18). On the contrary, studies conducted on the same

area of a topic in Tanzania (17) and Burkina Faso (44) revealed as HIV co-infection was not significantly associated with delayed sputum conversion. Besides this, the risk of death among the two groups of patients was not found different during the intensive phase, despite that significantly higher among the HIV-positive TB patients during the continuation phase (10).

Not only HIV but the recent increasing burden of diabetes mellitus also threatens the progress in reducing TB-related mortality, particularly in developing countries. In recent years, diabetic co-morbidity among TB patients continues to remain high in countries where diabetes mellitus cases are rampant. Thus, WHO has recently identified DM as a neglected, important, and reemerging risk factor for TB (57–59).

The effect of diabetes mellitus on tuberculosis infection is contradictory according to the studies in different study settings. A systematic review of seven studies showed that diabetic people have a 1.5-fold increased risk of developing active TB when compared with those patients without diabetic co-morbidity (95% CI 1.28–1.76), with relatively small heterogeneity (I2 = 44%) (58). A cross-sectional study conducted at Adare Hospital in Hawassa town, Ethiopia reported that the prevalence of pulmonary tuberculosis among diabetic patients was 5.3% [95% CI: (2.2, 8.4)]. This study also reported that patients with diabetes mellitus affected the clinical presentation and course of tuberculosis (60).

Previous studies from India (33) and Iran (45) conducted on sputum conversion in pulmonary positive TB patient also illustrated as uncontrolled DM significantly affect the time for sputum conversion. A retrospective cohort study in India and Iran identified DM co-morbidity as an independent risk factor for the delay in sputum conversion at the intensive phase of TB chemotherapy. Another study from India also resulted that DM patients have observed higher sputum positivity [OR: 1.247; 95% CI: (0.539–2.886)] at the end of 2-month treatment and poor outcome [OR: 1.176; 95% CI; (0.310–4.457)] after treatment compared with non-diabetic patients (52).

A case-control study conducted in Malaysia in 2015 also founded that diabetes mellitus [AOR: 4.01; 95% CI: (1.61–9.96)] being independently associated with the risk of persistent sputum smear positivity after 2 months of intensive treatment (61). Diabetic co-morbidity was also found significant association [OR: 3.578; 95% CI; (1.114– 11.494)] with the development of ADRs (58) These might be due to the dysfunctional immune response in DM patients, hyper-reactive T cells, that may affect the clinical presentation of TB and where chronic hyperglycemia also alters immune function (57).

The nutritional status of the patient is also another factor that influences the treatment outcome of TB patients. Weight loss is a common symptom in pulmonary tuberculosis and one of the signs of response to treatment is weight gain. Malnutrition has long been known to be strongly associated with TB treatment outcomes (36). Several studies recognized as underweight significantly determine the time for sputum conversion (16)(12).

A retrospective study in Lithuania in 2017 identified as lower BMI significantly determine the sputum conversion at the end of the intensive phase (12), despite that other study ruled out from those independent risk factors of delayed sputum smear conversion (14,19,21,23). A retrospective follow-up study conducted at the JUSH TB clinic in Southwest Ethiopia resulted in a strong inverse association [AOR: −0.698; SE=0.134, $p<0.001$)] between change in body weight and change in sputum conversion was observed (24).

On the other side, being anemic is also considered as the factor associated with prolonged the infectivity of the patient having persisting smear conversion (62). The prevalence of anemia among TB patients usually ranges between 30–94% (63). It has been shown that anemia is more likely to occur among TB patients compared to healthy controls. More importantly, anemia is associated with more severe forms of TB and poorer TB outcomes, including deaths.

A prospective cohort study conducted in the 14 largest TB clinics from Tanzania come up with 86% anemic and 7% sputum smear-positive at two months of anti-tuberculosis therapy. Anemic patients were three times more likely to have sputum-positive smear as compared to non-anemic patients at two months [RR=3.05; 95% CI (1.11–8.40)] (17). However, a study from Italy conducted in 2019 disagrees with the association of anemia with smear conversion (14).

2.4.4. Microbiological factors

All most of the studies regarding the risk factors of poor TB treatment outcome identified a baseline bacillary load as the most important independent risk factor for unsuccessful treatment outcome (12,14,16,19,21–24,52). According to a prospective study in Lithuania in 2017**,** the most important factor predicting sputum culture conversion was sputum smear grade at the beginning of treatment where patients with AFB grading of 2+ or more had more than 20-fold higher relative risk for no conversion at the intensive phase (12)

In addition, most retrospective studies from Burkina Faso (44), South Africa (18), Italy (14), India (27,64), and Iran (13) also agreed on the significant influence of initial bacillary load on sputum conversion at the intensive phase and outcome in general. The patients who have a high bacillary load are mostly accompanied by a radiological extension (cavitation) of the disease, which is also found to be associated with persistent sputum positivity (20). In a study conducted in East Gojjam, Ethiopia, delay in treatment initiation is also the other factor accompanied by enhancing the severity of the diseases leading to heavy bacillary load and in other words not enabling shorter period of smear conversion (19,23).

2.4.5. Drug-related factors

Drug-related factors like the stock of the required drugs; storage conditions, doses or combination, and adherence are all linked with the effectiveness for the successful treatment of tuberculosis. For any drug to be able to react potently, it should be stored in

a good condition. In this case, to evaluate the storage condition of an anti-TB drug, it might be expected to observe the drug condition from a different perspective on the spot while the patients pick it (2).

A dose and combination of the drug also determine the treatment outcome despite that the dose of the regimen is determined according to national standards based on the patient weight. There might be a case when the patient took under or overdose due to different reasons like health professional negligence, lack of knowledge or skill, not abide by guidelines. In addition, a fixed regimen is more likely to be associated with good treatment outcomes as compared with a single tablet (5)(65).

In the same way, non-adherence to anti-TB treatment is the major factor in the emergence of prolonged infectiousness, poor TB treatment outcomes, and MDR-TB (66). Non-adherence to anti-TB drug treatment was also significantly associated with drug side effects, being in the continuation phases of chemotherapy, pill burden, lack of adequate communication with health professionals, and lack of family support. A cross-sectional study conducted at Alamata District, northeast Ethiopia reported a high level of adherence to anti-TB treatment accompanied by a high TB treatment success rate (67).

2.5. Conceptual framework

Following the different works of literature on the area of the topics, the factors categorized under socio-demographic factors, behavioral factors, comorbidity (HIV, DM, Anemia, Under-nutrition), drug-related factors, and microbial related factors were considered as predictors of smear non-conversion which were inconsistently reported among kinds of literature (22,24,68–74). The following figure shows predictor variables that were studied under predictors of smear non-conversion status.

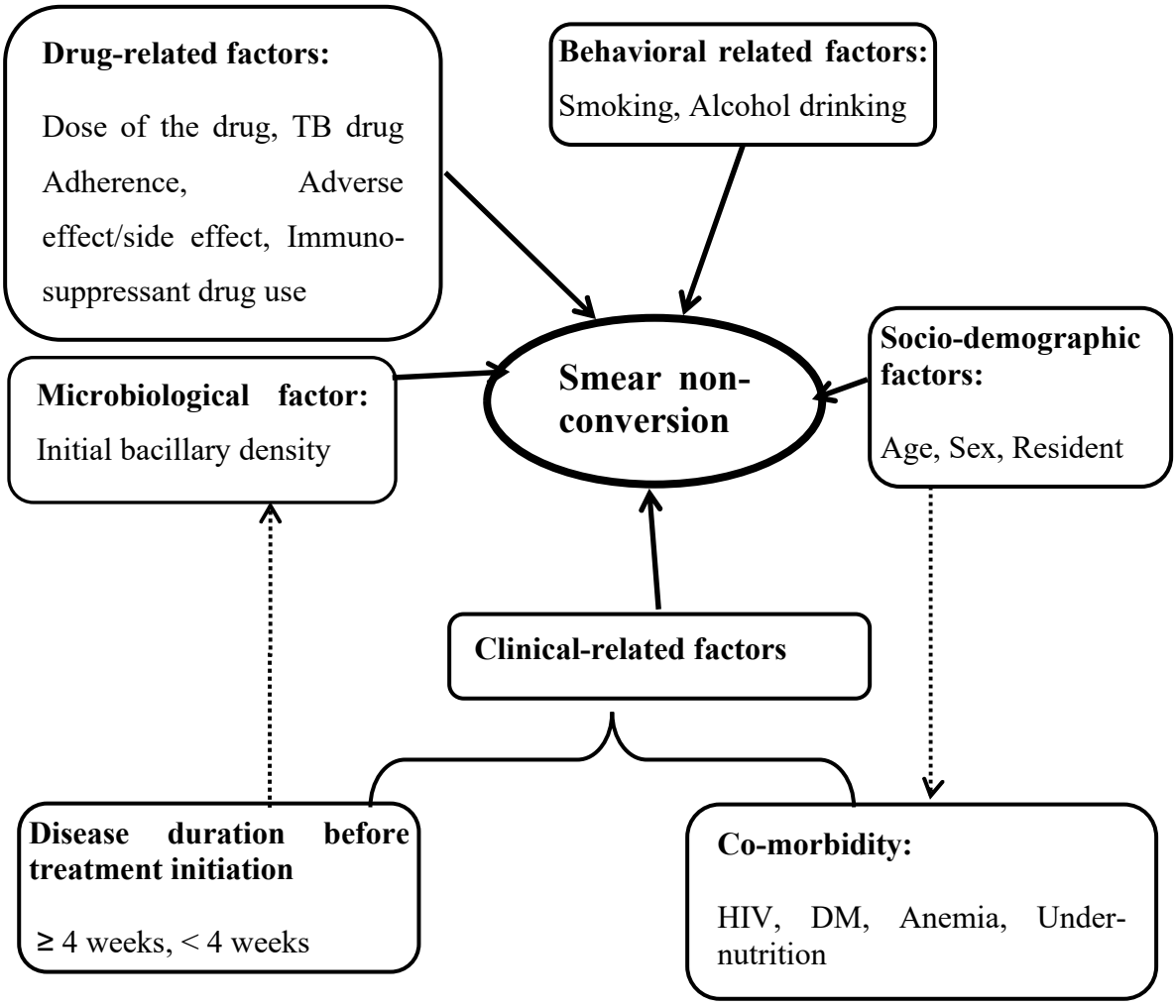


Figure 1: Conceptual framework for risk factors associated with delayed smear conversion among pulmonary positive TB patients.

CHAPTER 3: OBJECTIVE OF THE STUDY

3.1. General objective:

- To determine the magnitude and predictors of smear non-conversion at the end of intensive phase among patients newly treated for bacteriologically confirmed PTB enrolled at Shashemenne Referral Hospital from 2002 to 2011 EFY.

3.2. Specific objectives:

- To determine the magnitude of smear non-conversion rate at the end of intensive phase among patients newly treated for bacteriologically confirmed PTB.
- To identify predictors of smear non-conversion at the end of the intensive phase among patients newly treated for bacteriologically confirmed PTB.

CHAPTER 4: METHODOLOGY

4.1.Study Setting:

The study was conducted in the West Arsi zone Where Shashemenne referral hospital is found, Oromia region, Southern Ethiopia. The hospital is currently equipped with tuberculosis diagnosis with Gene Xpert alongside the pre-existing microscopic investigation. In addition to the diagnostic and TB treatment service, the hospital is also currently serving as a treatment initiation center for MDR-TB. In the hospital, an average of 125 bacteriologically confirmed PTB patients have been diagnosed annually.

Diagnosis of new smear-positive pulmonary tuberculosis was based on the National Tuberculosis Guidelines (5). All presumptive TB cases submitted two sputum samples on the spot, within an hour interval. Sputum smears sample is stained using Ziel-Neelsen technique and then, acid-fast bacilli graded according to the national guideline (5). New bacteriologically confirmed pulmonary tuberculosis patients were followed up at the 2nd, 5th, and 6th months following chemotherapy. For follow-up studies, each patient submitted one sample.

4.2. Study design and period

A retrospective cohort study on bacteriologically confirmed PTB patients was conducted from February 15 to May 30, 2013, for those enrolled at Shashemenne referral hospital from 21 June 2002 to 20 June 2011 EFY.

4.3. Populations

4.3.1. Source population:

All newly treated bacteriologically confirmed adult (≥15 years) pulmonary tuberculosis patients were diagnosed at Shashemenne referral hospital from 2002 to 2011 EFY.

4.3.2. Study population:

All newly treated bacteriologically confirmed adult (≥15 years) pulmonary tuberculosis patients who completed intensive phases at Shashemenne referral hospital from 2002 to 2011 EFY.

4.4. Eligibility criteria*:*

4.4.3. Inclusion criteria:

All bacteriologically confirmed adult PTB patient enrolled at SRH during the study period was involved in the study.

4.4.4. Exclusion criteria:

All bacteriologically confirmed adult PTB patients enrolled at SRH and either having the following characteristics within 2 months of treatment:

- ✓ Lost to follow up,
- ✓ died,
- ✓ transferred-out,
- ✓ Pregnant mothers
- ✓ PTB patient along with EPTB
- ✓ has no recorded smear status at 2nd month of treatment

4.5. Source of data

All data of adults newly treated with BC-PTB patients who were registered for ten years from June 21, 2002, to June 20, 2011 EFY, and those who fulfilled the inclusion criteria were incorporated in the study. Data on both the outcome variable (smear status) and predictors were extracted from Unit TB register and patient medical cards. Among a total of 1479 adults patients with BC-PTB, 1335 (90.3%) were newly treated BC-PTB cases. Of the newly diagnosed adult cases, 825 (61.8%) cases were enrolled at the TB unit of

Shashemenne referral hospital whereas 510 (38.2%) were excluded as they were transferred out to other health facilities.

Among the newly enrolled cases at SRH, 304 (36.8%) were excluded for their unknown outcome status due to 11(2.1%) death, 21(4%) defaulted, and 304(36.8%) unrecorded smear status at 2nd month of treatment. Finally, a total of 521 patients who were newly treated for BC-PTB at Shashemenne Referal Hospital and as well as had complete records on outcome variables were identified. Hence, about 521 of adult patients newly treated for BC-PTB were found to be eligible data to be involved in the study. The following flow chart shows the selection procedure of eligible data that were extracted in the study.

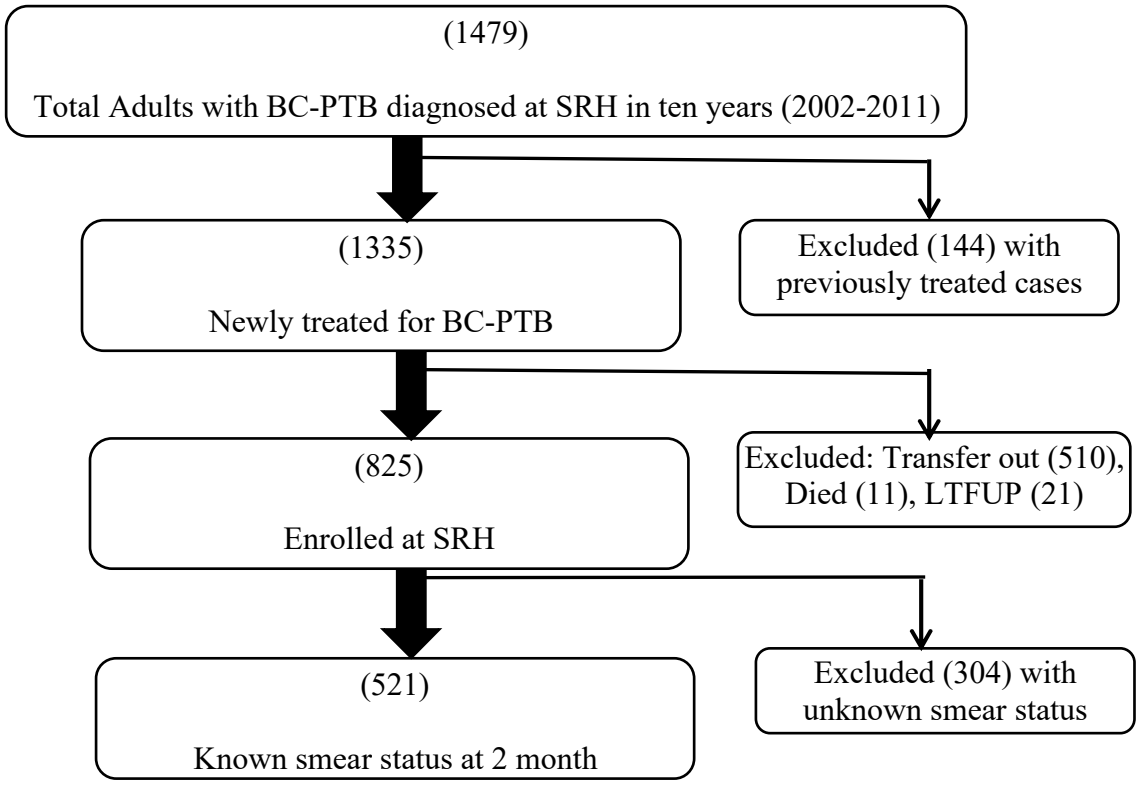


Figure 2: Study flow diagram showing data extraction procedure among adult patients diagnosed with bacteriologically confirmed PTB from the Unit TB register at Shashemenne Referral Hospital, 2002 - 2011.

4.6. Variables:

4.6.1. Dependent variable

- Smear non-conversion

4.6.2. Independent variables:

- Socio-demographic characteristics: (Age, Sex**,** Residence)
- Co-morbidity (Diabetes mellitus**,** HIV/AIDS**,** Anemia**,** and under-nutrition or low BMI)
- Baseline bacilli grading: (Scanty, 1+, 2+, 3+)
- Drug-related variables: **(**TB drug dosage, TB drug adherence**,** Adverse effect/side effect**,** Concomitant use immunosuppressant drug)
- History of substance use: (Alcohol consumption**,** Tobacco use)
- Disease duration before TB diagnosis

4.7. Data collection instrument and Procedure

All the data were extracted from the TB unit register and patient medical card by using a pre-prepared structured checklist adapted from different literature on the same area of study (16,21–23,52). Data were extracted by two trained nurses and laboratory personnel from the TB units and Laboratory unit of the hospital and being supervised every three days a week by a senior health expert working from TB unit who have training on national TB guideline.

Data on predictor variables including Socio-demographic, BMI, TB drug dosage, HIV serostatus, drug adherence, and smear grading were extracted from the TB Unit register while comorbidities (DM, and anemia), diseases duration before treatment initiation, adverse drug reaction/side effects, immunosuppressant drug use, and recorded behavioral factors were extracted from patient medical cards.

The smear status of patients at baseline and smear non-conversion (outcome) at 2nd month of treatment was needed to be recorded on both the Unit TB register and Laboratory TB register. Hence, data on the outcome (smear non-conversion) was extracted from the TB unit register and being cross-checked from the laboratory TB register. Those patients with negative sputum smear status at the 2nd month were categorized as smear non-conversion (24, 69–72).

Data on diabetic status was reviewed based on the FBS/RBS result at the time of TB diagnosis if performed or a history of diagnosis of or treatment for DM. A diagnosis of DM was reviewed from the patient card that was considered if the subject has a history of DM and is on insulin and/or an oral hypoglycemic agent or is being diagnosed with DM during PTB treatment (based on two or more fasting blood glucose levels ≥ 126 mg/dl on different days, but if no data on the diabetic status of the patient at the time of TB diagnosis, the DM results were recorded as unknown status (58,60).

The determination of anemia was also identified based on the HGB or HCT level being recorded on the patient card and remained unknown if not recorded. The patient is categorized as anemic per the WHO guideline which is < 11 g/dl for females and <12 g/dl for males (75). The data regarding the adverse reaction/ side effects, immunosuppressant drug uses, and duration of diseases before Anti-TB drug initiation were extracted from patient cards depending on the diagnosis and records of the clinician. Following previous literature, disease duration was extracted based on two categories (≤ 4 weeks and > 4 weeks).

For the data regarding smoking and alcohol consumption, a previously self-reported record from the patient card at the time of TB diagnosis was extracted from the patient medical card. In this study, patients were considered as tobacco use and alcohol consumption if any recorded data on the patient medical card regardless of the duration, frequency, and type they used (70).

4.8. Data Quality Assurance

Pre-test on the standard checklist was conducted on 5% data from nearby Melka Oda hospital and thus, correction on an ambiguous question was taken to the data collection tool before retrieval of the final data. Data were collected by trained nurses on the national guideline on TB treatment and control being supervised by a senior health professional. The data collectors and supervisor were initially oriented for one day on the data collection format and techniques for data collection.

A supervisor has closely followed the data collectors daily, and the principal investigator also reviewed all filled checklists. Data on predictors and outcome variables were cross-checked from patient cards, TB unit registers, and Laboratory TB register. The completeness of data on each predictor and outcome variable was checked every week throughout the data collection period. Finally, the overall completeness of the total data was checked before the submission of the completed tools.

4.9. Statistical analysis

Only BC-PTB Patients with recorded data on smear status at 2nd month of treatment were included in the analysis. Data cleaning and completeness were checked before entry. Then, data were entered into Epidata version 3.1 and exported to SPSS version 25.0 for analysis. Univariate analysis was used for describing proportion and mean for categorical and continuous variables respectively and presented using tables and graphs.

Then, a binary logistic regression was used for statistical analysis. Initially, a bivariate analysis was used for identifying candidate variables predicting smear non-conversion using a 25% significance level. Finally, a multivariate analysis was employed to have the final model in determining independent predictors of smear non-conversion using the backward stepwise method having considered a 5% significance level and 95% confidence interval. Hosmer-Lemeshow was also finally checked for the good fitness of the model which was found significant with a p-value above 0.05.

4.10. Ethical consideration

Initially, a letter of ethical clearance was obtained from the Research and Ethics Committee of Jimma University. The patient's data were accessed upon verbal approval from the medical director of Shashemenne Referral Hospital and the service provider at the candidate service unit.

Data collectors were initially trained on how to handle patient's data confidentiality and appropriate data extraction as per the data collection tools only and the data collection process was carefully guided by the principal investigator and supervisor. The name of an individual patient was not required or mentioned in the data collection tool, instead only the serial number and MRN were used to extract the required data to ensure confidentiality.

4.11. Dissemination plan

The result of the study is intended to be presented and finally submitted to Jimma University Institute of Health, Faculty of Public Health, and Department of Epidemiology. The finding is also intended to be disseminated to scientific communities by presenting at a scientific conference, and publication as possible.

4.12. Operational definition

According to the standard definitions of the NLCP adopted from WHO (1) and national guideline(5) the following clinical case and treatment outcome operational terms were used:

Smear non-conversion: Those initially bacteriologically confirmed PTB patients who remained smear positive at 2nd months of TB treatment and are persistently become infectious (confirmed by at least one positive sputum acid-fast bacilli of two samples).

Smear conversion: Those bacteriologically confirmed PTB patients whose smear status changed into negative at the end of the intensive phase of treatment and are therefore no longer infectious (confirmed by at least two consecutive negative sputum acid-fast bacilli (AFB).

Bacteriologically confirmed pulmonary TB cases: Those TB patients diagnosed to be sputum smear-positive on AFB smear microscopy or Gene Xpert MTB/RR and tested according to national TB guidelines.

The intensive phase of treatment: the first two months of TB treatment for new cases and the first three months for previously treated cases.

New cases: patients **t**hat have never been treated for TB or have taken anti-TB drugs for less than 1 month**.**

Previously-treated cases: Those patients who had received anti-TB drugs for one or more months in the past years.

Defaulted cases: Those patients who have received the anti-TB drug for one month and interrupted the drug for the rest of intensive phases.

Treatment interrupted: A patient who treatment interrupted Anti-TB drug for ≤14 days during the intensive phase.

Died: Those BCPTB patient**s** on TB treatment and died of any causes during the intensive phase of treatment.

Transfer-Out: Transfer-out is a patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown (33).

Treatment adherent: Those patients who received at least 80% of Ant-TB drug during intensive phases (68).

Baseline bacillary load: categorized as 3+ (when there is the presence of more than 10 AFB/field in at least 20 fields), 2+ (when 1–10 AFB/field are present in at least 50 fields), 1+ (when 10–99 AFB/field are seen at least in 100 fields), or Scanty (exact number when19 AFB/100 fields) are seen (22, 24, 68–74).

Immuno-suppressant drugs: are those immunosuppressing drugs listed under the National essential drugs list (76) (77).

Adverse reaction/side effect: Any BCPTB patients who were diagnosed to have any adverse reaction and/or any side effects of Anti-TB drug listed in the national TB guideline during the intensive phases of treatment.

CHAPTER 5: RESULTS

Of the total eligible BC-PTB enrolled at SRH, 521 (63.2%) had recorded smear status at their 2nd month and were included in the analysis despite the variability in the availability of data on the predictor variables.

5.1. Socio-demographic characteristics

The mean age of patients was observed to be 38.9 years with a 13.2 standard deviation and ranges from 15 to 82 years. Of the record incorporated in the analysis 216 (41.5%) were $31-45$ years of age, 276 (52.9%) were male and 262 (50.3%) were rural residents. The mean baseline weight of patients was 48kg with 8 standard deviations and 340 (67.3%) were observed to have a baseline weight range of 41 to 54kg. (Table 1)

Table 1: Socio-demographic characteristics of study patients enrolled in Shashemenne referral hospital from 2002 – 2011 EFY.

Variables		Frequency N (%)
Age (n=521)	15-30	151 (28.9%)
	31 - 45	216 (41.5%)
	> 45	154 (29.6%)
Sex (n=521)	Male	245 (47%)
	Female	276 (52.9%)
Resident (n=521)	Rural	262 (50.3%)
	Urban	259 (49.7%)
Baseline weight (n= 505)	< 40kg	87 (17.2%)
	40-54 kg	340 (67.3%)
	≥55 kg	78 (15.4%)

5.2.Clinical characteristics

Of the 521 patients enrolled and known smear status at 2nd months of treatment about 456 (87.7%) had recorded BMI whereas 164 (36%) and 148 (32.4%) were BMI of 18.5-20.9 kg/m2 and 16 – 18.4% kg/m2 respectively. Of the 521 patients, 375 (72%) were used three doses of TB drugs despite that all the newly treated PTB patients were expected to give similar drug combinations as per the National TB guideline. Of those who completed the intensive phase of treatment about 21 (4%) were recorded to take less than 45 TB doses (<80%) of the total dose of intensive phases. On the other way, among enrolled patients with recorded comorbidity, 45 (11.2%), 37 (11.9%), and 149 (40.4%) were found to have comorbidity with HIV, DM, and anemia respectively. (Table 2)

On the other hand, about 56 (19.3%) and 52 (18.4%) of TB patients with recorded status on their respective behavioral character had a history of tobacco and alcohol use respectively regardless of the dose, frequency, and type they used. On the side of bacteriological characteristics, 227 (55.9%) of recorded patients had grade 3 bacilli load at the baseline period. (Table 2)

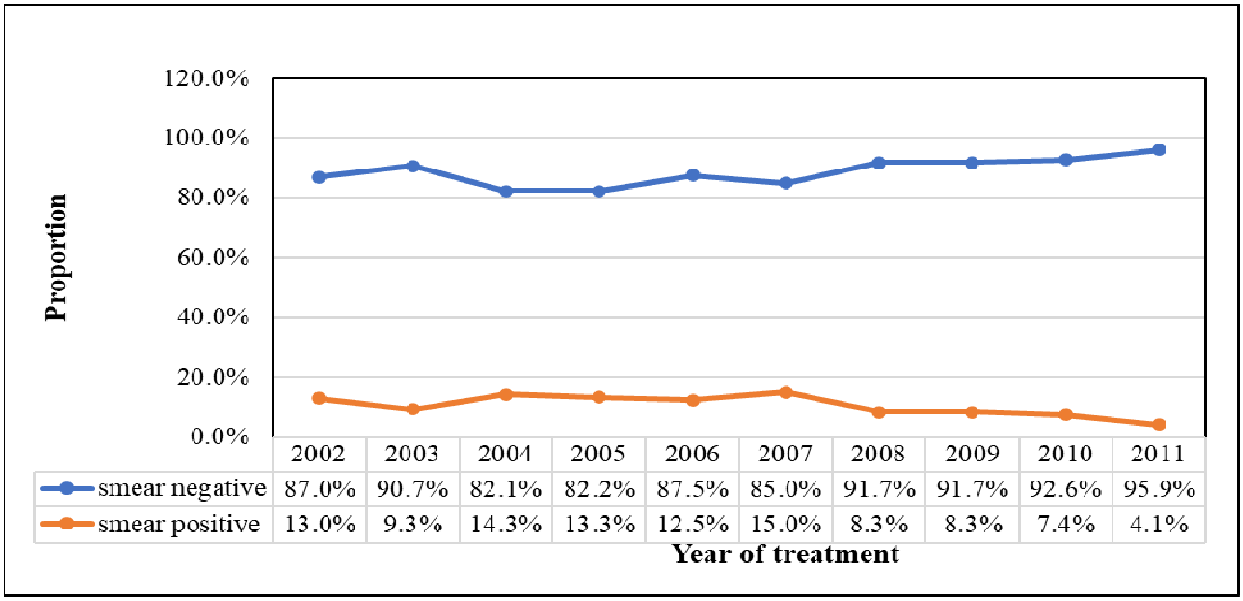
Table 2: Clinical characteristics of study patients enrolled in Shashemenne referral hospital from 2002 – 2011 EFY.

Variables		Frequency (%)
BMI (n=456)	< 16 kg/m2	73 (16%)
	16 -18.4 kg/m2	148 (32.4%)
	18.5 –20.9 kg/m2	164 (36%)
	21 – 24.9 kg/m2	64 (14%)
	≥25 kg/m2	7 (1.5%)
Baseline Drug dosage (n=521)	2 tablets	62 (11.9%)
	3 tablets	375 (72%)
	4 tablets	84 (16.1%)
Adverse reaction/side effects (n= 125)	Yes	11 (8.8%)
	No	114 (91.2%)
Immunosuppressant drug use (n= 137)	Yes	15 (10.9%)
	No	122 (89.1%)
TB drug adherence (n= 521)	< 45 pills (< 80%)	21 (4%)
	≥ 45 pills (≥80%)	500 (96%)
HIV status (n=403)	Negative	358 (88.8%)
	Positive	45 (11.2%)
Tobacco use (n=290)	Yes	56 (19.3%)
	No	234 (80.7%)
Alcohol use (n=283)	Yes	52 (18.4%)
	No	231 (81.6%)
Comorbidity with DM (n=328)	Yes	39 (11.9%)
	No	289 (88.1%)
Anemia (n=369)	Yes	149 (40.4%)
	No	220 (59.6%)

Baseline Bacilli smear Grading (n=406)	Scanty	5 (1.2%)
	AFB+	38 (9.4%)
	AFB++	136 (33.5%)
	AFB+++	227 (55.9%)

5.3. The magnitude of Smear non-conversion

Of the total 521 patients with known smear status, 56 (10.7%) were recorded to have positive sputum smear status at end of 2nd month of treatment. A high proportion of smear positivity at the end of the intensive phase of treatment was recorded in 2004 and 2007 when about 8 (14.3%) and 9 (15%) were come to be smear-positive respectively. (Fig 2)



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
smear negative	87.0%	90.7%	82.1%	82.2%	87.5%	85.0%	91.7%	91.7%	92.6%	95.9%
smear positive	13.0%	9.3%	14.3%	13.3%	12.5%	15.0%	8.3%	8.3%	7.4%	4.1%

Figure 3: Trends in the proportion of smear non-conversion at 2nd month of treatment from 2002 to 2011 EFY.

5.4.Predictors of smear non-conversion

5.4.1. Socio-demographic and drug-related factors

A bivariate analysis from all records of data on socio-demographic and drug-related factors shows that variables like age, residence, and BMI, are those candidate variables ($p < 0.25$) whereas sex and drug dosage are not a candidate in predicting smear non-conversion at 2 months of treatment.

Nearly one in ten BCPTB patients with smear non-conversion were found at above 36 age and, whereas, a nearly similar rate of smear non-conversion has occurred among both sex group and residence. In the case of drug-related factors, nearly one in ten of BCPTB patients taking the three different Ant-TB drug doses (2-4 doses) were finally smear non-converted at 2nd month of their treatment.

About 96.2% (501) of the total 521 BCPTB patients were received more than or equal 45 TB doses (≥80%) of which 10.4% were found smear non-converted at 2nd month of treatment. Among the total 521 records, only 23.9% (125) and 26.3% (137) records on the patient card had status on adverse reaction and/or side effects, and any of immunosuppressant drug use respectively.

Table 3: Bivariate analysis on socio-demographic and drug-related factors that predict smear non-conversion among patients treated at Shashemenne Referral Hospital, South-East Ethiopia, 2013.

Socio-demographic variables	smear non-conversion		COR	95% CI	P-Value
	Yes (n/%)	No (n/%)			
Age group (521)					
15 – 35	17 (8%)	195 (92%)	1		
> 35	39 (12.6%)	270 (87.4%)	1.66	0.91, 3.01	0.09*
Sex (n=521)					
Male	28 (11.4%)	217 (88.6%)	1.14	0.65, 1.99	0.63
Female	28 (10.1%)	248 (89.9%)	1		
Residence (n=521)					
Rural	19 (7.3%)	243 (92.7%)	0.47	0.26, 0.84	0.01*
Urban	37 (14.3%)	222 (85.7%)	1		
TB drug dosage (521)					
Two doses	6 (7.5%)	74 (92.5%)	0.76	0.26, 2.26	0.63
Three doses	39 (11.3)	305 (88.7%)	0.67	0.32, 1.40	0.29
Four doses	11 (11.3%)	86 (88.7%)	1		
Adherence (n=521)					
< 80 %	3 (15%)	17 (85%)	1.49	(0.42,5.26)	0.53
≥ 80 %	53 (10.4%)	448 (89.6%)	1		
Adverse reaction and/or side effect (n=125)					
Yes	2 (18.2%)	9 (81.8%)	1.59	(0.11, 8.11)	0.58
No	14 (12.3%)	100 (87.7%)	1		
Immunosuppressant drug use (n=137)					
Yes	2 (13.3%)	13 (86.7%)	1.41	(0.28. 7.01)	0.67
No	12 (9.8%)	110 (90.2%)			
*** Candidate variable selection with p-value < 0.25**					

5.4.2. Clinical and behavioral related factors

Of the 521 records of BCPTB patients, 95.2% (496) disease duration recorded on patient cards either in days or weeks or months or year which later converted into weeks. Hence, more than half of the TB cases were diagnosed after 4 weeks stayed with the illness, but a nearly similar smear non-conversion rate was found among both TB patients being diagnosed after 4 weeks and below 4 weeks of illness before treatment initiation.

About 77.4% (403) records of patients had HIV serostatus and of which 11.2% (45) HIV co-infection encountered. Smear non-conversion was encountered in 20% and 9.5% of HIV positive and HIV negative TB patients respectively. In this case, 116 (22.3%) of cases had unknown HIV serostatus which might be due to missing status during record or not tested. On the other way, only 62.9% (326) records of total BCPTB patients had documented status on diabetic Mellitus. However, one in four BCPTB patients comorbidity with DM had non converted smear status at 2 months of treatment. On the other hand, 2 of 5 TB patients with recorded hemoglobin levels during TB diagnosis encountered smear non-conversion at the intensive phase.

Of the total 459 records of patients with BMI, 224 (48.8%) were those with BMI less than 18.5 kg/m2 or under-nutrition and, 14.3% (32) were found to be smear non-converted. Similarly, 406 (78%) of the reviewed document had recorded status on baseline bacillary load or AFB, of which more than half were baseline bacillary grading of 3+. In addition, 15.7% (32) of them finally tested positive for smear status at 2 months of treatment. (Table 4)

Table 4: Bivariate analysis of clinical and behavioral related factors predicting smear non-conversion in a patient treated at Shashemenne Referral Hospital, South-East Ethiopia, 2013.

Predictor variables	Smear non-conversion		COR	95% CI	P-value
	Yes (n/%)	No (n/%)			
Disease duration before diagnosis (n=496)					
≤ 4 weeks	15 (7.9%)	175 (92.1%)	1		
> 4 weeks	40 (13.1%)	266 (86.9%)	1.77	0.95, 3.30	0.07*
BMI category (n=456)					
≥18.5 kg/m2	19 (8.2%)	213 (91.8%)	1		
< 18.5 kg/m2	32 (14.3%)	192 (85.7%)	1.86	1.02, 3.41	0.04*
Baseline bacilli load (n=406)					
Scanty, 1+, and 2+	13 (7.3%)	164 (92.7%)	1		
3+	36 (15.7%)	193 (84.3%)	2.35	1.21, 4.58	0.01*
HIV status (n=403)					
Negative	34 (9.5%)	324 (90.5%)	1		
Positive	9 (20%)	36 (80%)	2.38	1.05, 5.36	0.04*
DM comorbidity (n=328)					
No	36 (12.5%)	253 (87.5%)	1		
Yes	10 (25.6%)	29 (74.4%)	2.43	1.09, 5.38	0.03*
Anemia (n=369)					
No	18 (8.2%)	202 (91.8%)	1		
Yes	25 (16.8%)	124 (83.2%)	2.26	1.18, 4.36	0.01*
History of alcohol use (n=283)					
No	26 (11.3%)	205 (88.7%)	1		
Yes	8 (15.4%)	44 (84.6%)	1.43	0.61, 3.37	0.41
History of smoking (n=290)					
No	25 (10.7%)	209 (89.3%)	1		

Yes	13 (23.2%)	43 (76.8%)	2.52	1.19, 5.33	0.02*
*** Candidate variable selection by p-value < 0.25**					

Clinical-related factors incorporated in the analysis include the disease duration before initiation of treatment, behavioral factors, comorbidity, and the initial baseline bacillary density. Among those clinical factors, candidate variables with a significant value less than 0.25 were found to be the disease duration > 4 weeks, alcohol use, tobacco use, HIV co-infection, comorbidity with DM, comorbidity with anemia, under-nutrition, and baseline bacillary density 3+.

5.4.3. Independent predictors related to smear non-conversion

Among the candidate variables the following factors were found to be independent predictors: history of tobacco use (AOR=2.53, 95% CI = 1.13, 5.64), under-nutrition (AOR= 2.15, 95% CI= 1.08, 4.27), and grade 3+ bacilli load (AOR= 2.57, 95% CI= 1.19, 5.58), whereas being co-morbid with DM and other candidate variables being significant in bivariate analysis were not found to have statistical significance with smear non-conversion at 2nd months of treatment. (Table 5)

Table 5: Multivariate analysis of predictors independently associated with smear non-conversion in a patient treated at Shashemenne Referral Hospital, South-East Ethiopia, 2013.

Predictor variables	Smear non-conversion		AOR	95% CI	P-value
	Yes (n/%)	No (n/%)			
History of smoking (n=290)					
No	25 (10.7%)	209 (89.3%)	1		
Yes	13 (21%)	49 (79%)	2.53	1.13, 5.64	0.02*
DM comorbidity (n=328)					
No	36 (12.5%)	253 (87.5%)	1		
Yes	10 (25.6%)	29 (74.4%)	1.87	0.71, 4.97	0.11
BMI category (n=459)					
≥ 18.5 kg/m2	19 (8.2%)	213 (91.8%)	1		
< 18.5 kg/m2	32 (14.3%)	192 (85.7%)	2.15	1.08, 4.27	0.03*
Baseline bacilli load (n=406)					
≤ 2+	13 (7.3%)	164 (92.7%)	1		
3+	36 (15.7%)	193 (84.3%)	2.57	1.19, 5.58	0.01*
* significant < 0.05					

The above multivariate table indicates that regardless of the frequency, duration, and type of cigarettes they use, the odd of smear non-conversion is conversion 2.5 times higher in a patient with any history of tobacco use than those patients without tobacco use. However, the missing data as a result of the study design might affect the variability of the result.

In the same way, from the total 456 recorded cases on the Body Mass Index, the odd of smear non-conversion is 2.15 times higher among those BMI < 18.5 kg/m2 than those TB patients categorized under BMI ≥ 18.5 kg/m2. That means those patients with moderate to severe malnutrition have higher odds of smear non-conversion at their 2nd month of treatment than those patients with mild malnutrition and above.

Similarly, the odd of smear non-conversion in patients with initial grade 3+ bacilli load is 2.57 times higher than those having fewer bacilli load. However, Those TB patients co-morbid with diabetes are not independently associated with the smear non-conversion despite the enormous data missing which might affect the final model. In other words, the variability in the surplus missing data from many independent variables might bring about the different results on determining the smear non-conversion at their 2nd month of treatment.

CHAPTER 6: DISCUSSION

Of the total 521 patients included in the analysis, 10.7% were found to be smear non-converted at their 2nd month of treatment. However, it is worth noting that this data only represents almost 2/5th of all the newly diagnosed bacteriologically confirmed PTB who have been diagnosed at Shashemenne Referral Hospital respectively.

This finding was nearly similar to the study conducted in Tanzania (8.3%) but lower than the study in East Gojjam (14.2%) (19)(17). In the same way, it is also lower when compared with studies in Iran (16.4%), and Sir Lanka (16.8%) (13)(16). There were also studies showing a much higher proportion of smear non-conversion including 21.2% (Italy), 25.3% (Lithuania), 35.2% (Afghanistan), and 33.2% (India) (14)(12)(22)(15). The variability in the proportion might be due to the difference in study setup and study design which might have an effect on the detection of micro bacterium tuberculosis at both diagnostic and follow-up periods.

In this study, different factors were found to be independent factors associated with smear positivity during the two months of treatment. In these cases, undernutrition, tobacco use, and higher smear grading were independently associated with persistent smear non-conversion whereas comorbidity with DM, HIV, anemia, as well as disease duration, alcohol use, residence, and other drug-related factors was not independently associated with smear non-conversion. However, variability among various studies was reported on cases of independent risk factors predicting smear conversion. Finding from the different areas showed almost similarity on high bacillary density to be independently associated with smear conversion while other factors vary according to the study design and statistical methods used (14,16,19,21–24,44,52,69).

This study also showed that the odd of sputum non-conversion at 2nd month of treatment is 2.2 folds higher among patients with BMI < 18.5 kg/m2 as compared to those patients having BMI ≥ 18.5 kg/m2. This finding is comparable with the retrospective study conducted in Jimma, Ethiopia which dictated that change in weight of patients come to

have an independent association with smear conversion. Similarly, studies from Sir Lanka (19) and Lithuania (12) also reported that having lower BMI or Under-nutrition had a statistically significant association with smear non-conversion during 2nd month of treatment. Thus, finding from this study strengthens the importance of the routine implementation of nutritional screening and interventions through dietary counseling and nutrient supplementation.

In this study, the presence of high bacilli density (3+) at pre-treatment sputum smears is found one of the major predictors that are independently associated with smear non-conversion after 2 months of chemotherapy. The odds of smear non-conversion TB patients with grade 3+ pre-treatment bacilli density is 2.6 folds higher than those having ≤ 2+ bacilli load. Almost all studies conducted on factors of smear conversion agreed upon the independent association of baseline bacillary load and sputum conversion at two months of chemotherapy (12,13,15–20,22,24–28,33,44,52,63,65,68,69,72).

As far as this study is concerned, we did not find any study finding showing the bacilli grading as having no significant association with smear conversion. Hence, unless a comprehensive prevention measure is employed on such patients with high initial bacilli load, there could be a high chance of *mycobacterium tuberculosis* transmission both at the community and health facility level (1).

In cases of behavioral characteristics of patients, several studies contradict the behavioral character like smoking and alcohol consumption in determining the smear conversion status in accordance to the study design, setting, and statistical method used in the respective study. In this study, limited information on such behavioral character was recorded which could hinder the real association with smear conversion. However, this study obtained a significant association between patients with any history of tobacco use and smear non-conversion during 2nd month of chemotherapy.

Hence, the odd of smear non-conversion in those patients having a history of tobacco use is 2.5 folds higher than those without a history of tobacco use. This finding is comparable when compared with the study conducted in East Gojjam of Ethiopia (19), India (52), and Sir Lanka (16). On contrary, studies from Morocco (34) and Lithuania (25) did not find a statistically significant difference between the two groups of the population.

In the same way, statistical significance between patients with any history of alcohol consumption and smear conversion was found from the study in Sri Lanka (16) and Lithuania (12). Such difference in the finding might be due to the study design and statistical method used. The habit of hiding such behavioral character in the community might also affect the finding and expose to such contradictory results.

6.1. Limitation of the study

In finding from this study incorporated both the magnitude and predictors of smear non-conversion at the same time. This could enable any concerned body to have initial awareness of both magnitudes of smear conversion rate and its predictors for further study. However, the retrospective nature of the study came up with incomplete data on both predictor variables and outcome variables which could hinder the real association. Thus, the study finding may vary from other studies having any complete information. However, to solve the enormous incomplete data, data on each predictor variable that was missed from records were separately analyzed and seen for significance.

On the other hand, variables in this study were measured by different health workers at different time which the researcher has no control over it. This might lead to biases on both predictors and outcome variable measurements. The patients enrolled and completed their intensive phases at a similar health facility with better diagnostic and monitoring set-up were tried to be included in the study and this might minimize the measurement biases particularly the outcome variable measurement. Variability in instruments and personnel might bring about variability in measurements.

CHAPTER 7: CONCLUSION AND RECOMMENDATION

7.1. Conclusions

In conclusion, sputum non-conversion among new bacteriologically confirmed pulmonary tuberculosis patients at the end of 2nd month of treatment was 10.7%. Hence, there would be a long exposure time to such a major source of TB infection. On the other hand, patients having BMI < 18.5 kg/m2, any history of smoking, and higher bacillary load were identified to be the risk for prolonged smear conversion.

Identifying these groups of patients before treatment initiation and strict monitoring as per their risk of prolonged infectivity would help in tackling the transmission particularly among bacteriologically confirmed PTB patients who were the significant source of infection.

7.2. Recommendations

The health service provider should work on the comprehensive TB infection prevention measures during the first 2 months of treatment by grouping his patients according to the level of infectivity. In TB patients with independent predictors of smear non-conversion, very close treatment monitoring and strict IPC measures should be applied effectively during the intensive phase in particular. The health care provider should also apply a detailed counseling approach to such major sources of infection and also including all the family members.

Not only the patients but also special emphasis on those individuals who have possibly close contact with such patients is very mandatory in preventing the transmission. It is also better if the health care provider prioritizes community-based DOTs service than health facility-based DOTs services to limit the movement of patients with a high risk of TB transmission. The administrative unit should enforce a full package of IPC within the health facility as it further reduces the chance of transmission since those patients are expected to visit the health facility on daily basis.

Policymakers and MOH should do further on emphasizing touching the factors that predicting smear non-conversion particularly at the intensive period when a high chance of transmission is expected. Most importantly, research institutions and TB programmers should also further investigate the drawback of DOTs services in TB transmission as it enhances the patients' daily mobility of patient which can facilitate the contact at home, neighbor, community, and health facility.

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Annexes

Annex 1: General introduction and purpose of research for the administrative unit

Tuberculosis is the leading cause of death in the world. Even where free medication is available, many patients are not successfully treated for tuberculosis due to several factors that prolong smear conversion time thus enhancing the chance of persistent infectivity, especially among the most contagious TB patient. Understanding the specific reasons for poor treatment outcomes is important in preventing transmission of TB among contacts of pulmonary positive TB patients and for effective treatment as well.

This study aims to assess whether pretreatment bacilli smear load led to delayed smear conversion at the intensive phase of treatment among the pulmonary positive TB cases. So, if you agree on the importance of the study and I will proceed with data collection up on your consent.

Annex 2: Data extraction tool

Instruction:

A. Select your answer for the questions by encircling the possible answer for the multiple-choice question in the box provided.

B. For those open questions fill in the actual results from the register/patient medical record on the space provided for each of them.

C. All the data should be extracted from registers (TB unit register and Laboratory TB register) and Patient Medical records.

Code of a patient: _____

Part I. Data extraction tool from TB unit register			
MRN: _____Lab. Serial no: _____ Date started treatment: _____			
S.no	Variables	Response	Remark
1.	Age of patient in years	_____	
2.	Sex of patient	1. Male 2. Female	
3.	Residents of patient	1. Urban kebele 2. Rural kebele	
4.	Weight of patient recorded before treatment initiation.	_____	
5.	Height of patient recorded at treatment initiation	_____	

6	Dosage of anti-TB treatment at initiation	1. One tablet 2. Two tablets 3. Three tablets 4. Four tablets 5. Unknown	
7.	HIV status of the patient	1. Negative 2. Positive 3. Unknown	

8.	If positive, was she/he on ART at the time of TB diagnosis?	1. Yes 2. No 3. Unknown	
9.	If yes, final CD4 count for the previously initiated on ART or baseline CD4 count per cc for newly HIV positive patient	1. > 1000 2. 500 – 1000 3. 200-500 4. > 200	
10.	Any recorded adverse reaction of Ant-TB drug occurred?	1. Yes 2. No 3. Unknown	
11.	Number of pills received by the patient	_____	
12.	Duration of the disease before initiation of treatment	_____days/ weeks	
13.	Was there any history of alcohol consumption recorded at the time of diagnosis?	1. Yes 2. No 3. Unknown	
14.	If yes, is the patient recorded as the current consumer at the time of diagnosis?	1. Yes 2. No 3. Unknown	

15.	Was there any history of tobacco use (any type) recorded at the time of diagnosis?	1. Yes 2. No 3. Unknown	
16.	If yes, is the patient recorded as the current consumer at the time of diagnosis?	1. Yes 2. No 3. Unknown	
17.	Does the patient record as to be antidiabetic at the time of	1. Yes, 2. No 3. Unknown 2. No 3. Unknown	
18.	If yes, how about the time of diagnosis?	1. Newly diagnosed 2. Previously known	
19.	Was the patient put on treatment for DM at the time of TB diagnosis?	1. Yes 2. No 3. Unknown	
20.	Was the serum hemoglobin or hematocrit level know at the time of TB diagnosis?	1. Yes 2. No 3. Unknown	
21.	If yes, what was the serum hemoglobin/hematocrit level of the patient at the time of TB diagnosis?	____% Hct, or ____g/dl Hgb	
22.	Any use of immunosuppressant drugs (Corticosteroids) at the time of diagnosis?	1. Yes 2. No 3. Unknown	

23.	The level of bacilli loads recorded at time of diagnosis	1. Scanty 2. AFB + 3. AFB++ 4. AFB+++ 5. Unknown	
24.	Methods of diagnosis used	1. Microscopy 2. Gene-Xpert 3. Culture 4. Other(specify------)	
26.	If yes, smear result at 2nd month of treatment	1. Negative 2. Positive 3. Unknown	

Annex 3: DECLARATION

I, the undersigned, declare that this thesis is my original work, and has not been presented for a degree in this or any other university and that all sources of materials used for the thesis have been fully acknowledged.

Name and Signature of researcher:

Assegid Tesfaye

September 15/2021

Name of the institution: Jimma University

Date of submission: _____

This thesis has been submitted for examination with my approval as a University advisor

Name and signature of the first advisor

____Chernet Hailu___

September 15, 2021

Name and Signature of the second advisor

_____

Name and signature of the internal examiner

_____