Factors predicting diabetes mellitus among tuberculosis patients in public health facilities in Addis Ababa, Ethiopia

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A thesis submitted in partial fulfilment of the requirement for the degree of

Master of Science in Public Health

by

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LIST OF ABBREVIATIONS

AOR	Adjusted Odds Ratio
AUC	The area under the curve
BMI	Body Mass Index
CI	Confidence Intervals
DALYs	Disability-adjusted life years
DM	Diabetes Mellitus
DOT	Directly observed treatment
EPTB	Extra-pulmonary tuberculosis
HbA1c	Glycosylated haemoglobin
HIV	Human Immune Virus
IQR	Interquartile range
NCD(s)	Non-communicable diseases
NGOs	Non-profit organisation
OR	Odds Ratio
PTB	Pulmonary Tuberculosis
RBS	Random blood sugar
ROC	Receiver operating characteristic curve
SARA	Availability and Readiness Assessment
SES	Socioeconomic status
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
TBDM	Tuberculosis diabetes mellitus co-morbidity
WHO	World Health Organization

DEFINITION OF TERMS

Tuberculosis (TB):	is caused by Bacillus Mycobacterium tuberculosis; when infected people cough, the bacteria spreads through the air, which is the primary transmission mode. The lungs are the primary site for infection and are referred to as pulmonary tuberculosis; extrapulmonary TB is when other sites are involved (1).
Diabetes mellitus (DM):	is a chronic condition that occurs when the body is no longer able to produce enough of the hormone insulin to regulate the blood glucose level. There are two main types: type 1 DM and type 2 DM (2).
Receiver operating characteristic (ROC) curve:	is used to assess various diagnostic tests performance; when plotted on the Y axis, it corresponds to sensitivity versus the x-axis coordinates, which is 1- specificity (3).

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ABSTRACT

Background: The lethal combination between Diabetes Mellitus (DM) and tuberculosis (TB) in epidemiology and outcome necessitates bi-directional screening. The lack of simplified screening tools is one of the reasons for the limited screening of DM among TB patients. The current study aimed to assess the performance of risk scoring tools combined with clinical symptoms in predicting TB patients at higher risk of DM.

Methodology: This study was quantitative research conducted using secondary data based on primary cross-sectional study in Addis Ababa, Ethiopia, from September 2020 to December 2021. Data from a risk scoring tool and symptom checklists were analysed using the logistic regression method to assess factors associated with increased DM co-morbidity among TB patients and clusters. A two-step cluster analysis was done to identify characters of TB patients' clusters. To measure the performance of symptoms and risk scoring tools, Receiver operating characteristic curve was plotted.

Results; Clusters with a waist circumference of 85-89.9/78-83.9cm (OR 2.83, 95%CI,1.74-4.59), smoking history (OR 2.14, 95%CI,1.24- 3.71), and drinking alcohol (OR 2.09 95%CI: 1.13, 3.91), were significantly associated with DM. A family history of DM was the strongest predictor of DM [aOR4.94,95%CI,3.37-7.23], followed by age >40 (aOR,2.23 95%CI,1.43, 3.44). Merging symptoms with risk scoring tools showed moderate predictive accuracy with sensitivity of 88.3% (AUC= 0.70) and specificity of 41.9%.

Conclusion: Individual symptoms and risk scores predicted DM with lower accuracy, but a combination of symptoms and risk scoring tools predicted DM with moderate accuracy.

Keywords: Risk scoring, Tuberculosis, Diabetes mellitus.

word count: 10098

INTRODUCTION

The synergy between tuberculosis and diabetes Mellitus further worsens the overburdened health care system affecting the quality of care in resource-limited settings (4). In 2021, 24 million people were living with DM in Africa, projected to rise to 55 million in 2045. Of these, 416,000 people lost their lives due to DM. Ethiopia, one of the top 5 countries in Africa, had 26,448 deaths from DM in 2021, and 1.9 million people are living with the disease. Geographically, 25 per cent of TB cases were detected in Africa in 2020, with sub-Saharan Africa bearing the most burden. Tuberculosis is still a serious public health threat on this continent (1). Ethiopia is among the 30 high TB burden countries with an incidence of 132 per 100,000 population and a Mortality of 19.2 per 100,000 population (5).

The burden of DM in a country like Ethiopia, where there is high TB endemicity, is detrimental Since DM negatively affects the outcome of tuberculosis patients. A considerable part of DM cases is still undiagnosed, complicating matters further. Studies suggest that 53% of African DM patients are undiagnosed (2,6). According to a recent study, 5.75% of diabetic patients in Ethiopia remain undiagnosed (7). A recent Ethiopian study shows that the prevalence of diabetes in tuberculosis patients is high (8.3%) compared to the general population (8). This high prevalence necessitates the development of a simple screening tool in a resource-constrained setting such as Ethiopia. This tool will help triage TB patients at risk for DM for the possibility of early detection and treatment. This thesis aims to assess the performance of risk scoring tools combined with clinical symptoms in predicting TB patients at higher risk of being diagnosed with diabetes mellitus.

As a medical doctor, Having Worked for more than six years in St Paul's hospital, a tertiary hospital in Ethiopia, I witnessed first-hand how resource limitation affected the outcome of patients. Attending infectious disease cases such as TB referred from all over the country, I saw the interactions of TB co-infections with HIV or Dm could severely affect the outcome of the patients. It was a golden opportunity to work on my thesis on TB and DM and work with KNCV Tuberculosis foundation. The results from this thesis will help make a recommendation for policymakers for effective interventions to improve the lives of tuberculosis patients in Ethiopia.

1. CHAPTER ONE:

1.1 Background:

This section will give a piece of background information on Ethiopia in relevance to the objective of the study.

1.1.1 Geography, ethnicity, religion, and population distribution of Ethiopia

Ethiopia is a low-income county located on the horn of Africa with a land size of 1,100,000 square kilometres (420,000 sq mi). As a landlocked country, Ethiopia shares borders with Eritrea in the north, Djibouti and Somalia in the northeast, South Sudan and Sudan in the west, and Kenya in the south. The country comprises nine National Regional States- Tigray, Afar, Amhara, Oromia, Somali, Benishangul-Gumuz, Southern Nations Nationalities and Peoples Region, Gambella and Harari – and two administrative councils – Addis Ababa and Dire Dawa (9). Addis Ababa is the Capital city of Ethiopia with a location between 8055′ and 9005′ North Latitude and 38040′ and 38050′ East Longitude and administered in 10 sub-cities and 116 woredas (districts), as shown in figure 1 (10).

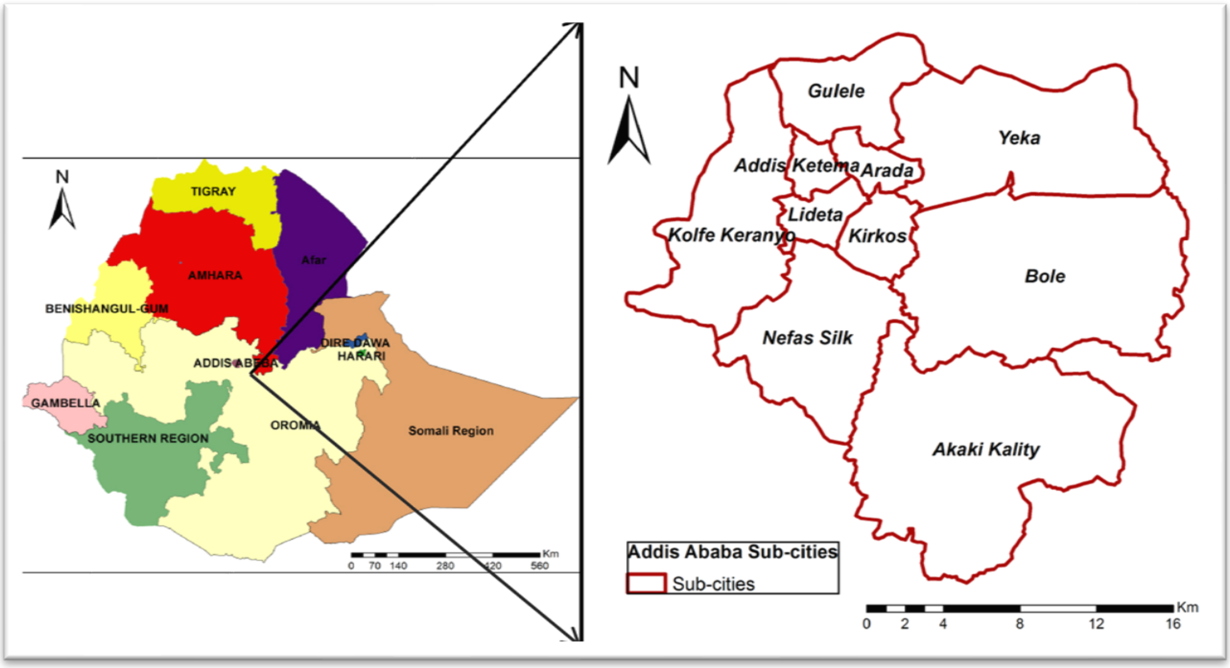

Figure 1: Map of Ethiopia showing the location of Addis Ababa (Adapted from Sisay Seifu,2020) (10).

Ethiopia is the second most populous country in Africa and the 12th-most populous in the world, with a population estimated to be 120 million, as shown in figure 2. Nearly half (49%) of the people are between the age of 15-64, and Only 4% are above the age of 65 years. The distribution of females and males in the population is 50.2% and 49.8%, respectively. Ethiopia's population is expected to reach 109.5 million by 2024, with a projected population of 122.3 million by 2030, based on a birth rate of 36 births per 1,000 people and a population growth rate of 3.02 percent per year. (11). The corresponding population density of the country is 108.1 people per square kilometre. The capital, Addis Ababa, is the most populous, with 4.5

million inhabitants living in an area of 527 square kilometres (9). There exist 80 distinct ethnic groups in Ethiopia, where Oromo (34.4%), Amhara (27%), Somali (6.2%), and Tigrayan (6.1%) are the major groups. There are 90 unique languages spoken in the country; however, the most common ones are Amharic, Oromo, Somali, and Tigrinya. Christianity makes up 67%, and Islam, with 30%, are the two largest religions in Ethiopia (9).

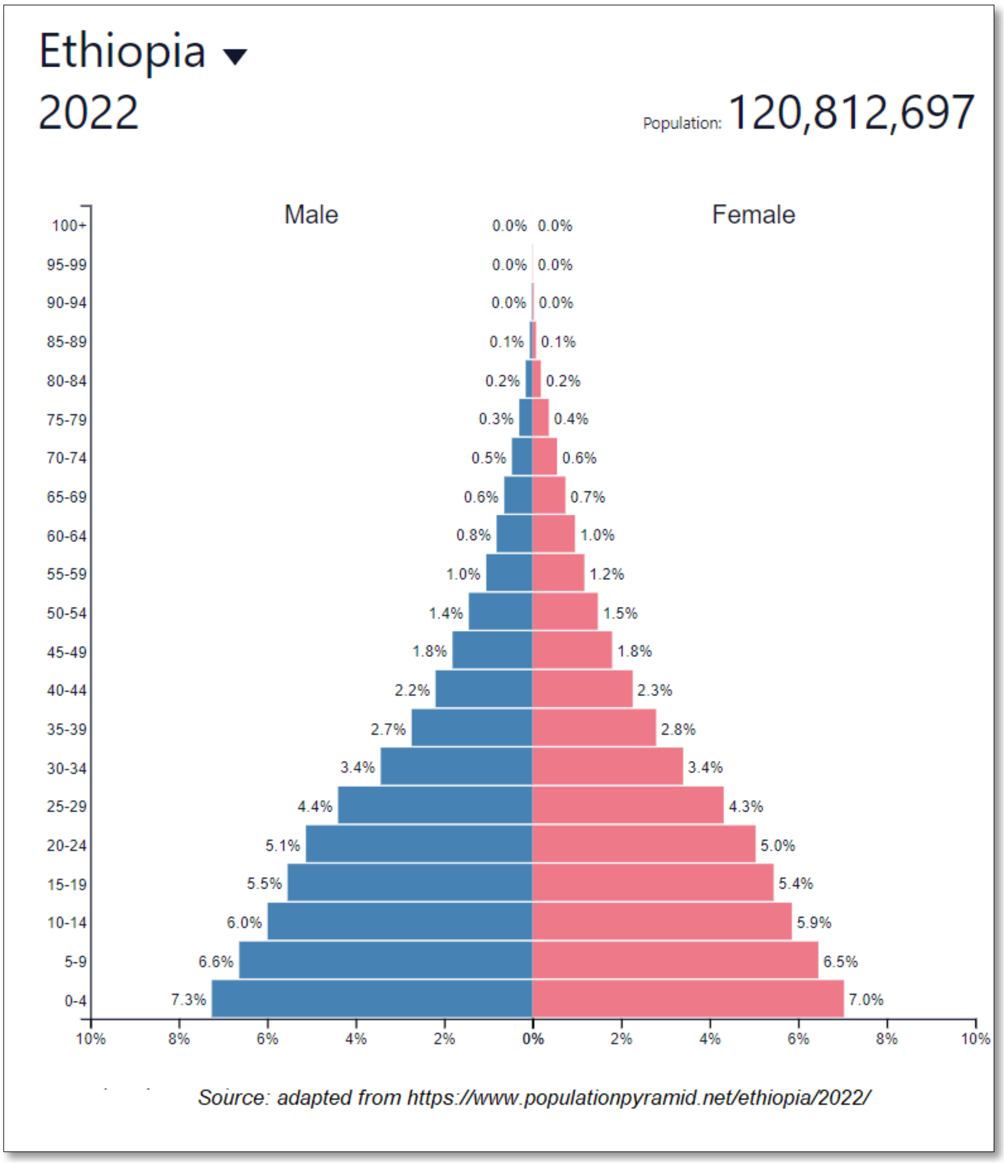

Figure 2: Ethiopian population pyramid (source; population pyramid.net, 2022) (11).

1.1.2 Socio-Economic Status of Ethiopia

Ethiopia’s per capita gross national income reaches only $890, making the country one of the poorest countries in the world, but it still has the fastest growing economy, with a 6.3% growth in the 2020/21 fiscal year. Economic increment resulted in a reduction of people living under the poverty line from 30 percent in 2011 to 24 percent in 2016. The economy depends on agriculture, with 46% of the gross domestic product and 85% of total employment. The industry and service sectors are the other significant contributors to economic growth. The unemployment rate was 3.69% in 2021, showing a 0.46% increment from 2020 (12). With the recent labour force survey done in the country, Addis Ababa (22.1%) shows the highest rate of unemployment, followed by Dire Dawa (15.9 %), while Benishangul-Gumuz Region (4.3 %) showed the lowest (13). The country's literacy rate is only 49% which showed an increment throughout the years, with a 57.2% literacy rate in males and 41.1% in females (9).

1.1.3 Health Care System and Health Problems

Ethiopian health service delivery is set up in a three-tier system at the primary, secondary, and tertiary levels of care. The primary level of care, which includes the primary hospital, health centre, and five health posts, serves 60,000 to 100,000 people. The general hospitals serve 1-1.5 million people and are at the second healthcare system level. Specialized hospitals that serve 3.5 to 5 million patients make up the top tier providing speciality care. Apart from the private sector, Addis Ababa currently has 96 health centres and 11 public hospitals (14).

Ethiopia showed notable improvement in health indicators between 2007 and 2019, with an increment in life expectancy at birth from 58.5 to 66.34yrs. Likewise, the under-5 mortality rate has decreased from 123 per 1,000 live births in 2005 to 59 in 2019. Additionally, maternal Mortality has decreased from 871 deaths per 100,000 live births in 2000 to 401 in 2017 (14). In 2019, Non-Communicable Diseases (NCDs) accounted for 35% of disability-adjusted life years (DALYs), with maternal and neonatal disorders, communicable diseases, and malnutrition accounting for 58% of DALYs. Over the last decades, the relative contribution of NCDs in the DALYs has increased from 17% to 35% (15). The top 5 risk factors leading to the most DALYs lost in the country include drinking alcohol, smoking, malnutrition, dietary risks, and unsafe sex (15). Tuberculosis screening and treatment services are provided through the three-tier system. Starting from the primary level, where directly observed treatment (DOTs) clinics are available to the secondary and tertiary levels, where they provide care for drug-resistant TB. Diabetic screening and diagnosis services are given throughout all the levels of care but need a referral to speciality treatment centres for some complicated cases (15).

1.1.4 Tuberculosis and Diabetes Program in Ethiopia

Ethiopia has endorsed the End TB strategy, which aims to end the TB epidemic by 2035. The national TB and leprosy strategy reports that TB treatment success and cure rates in 2019/20 were 95% and 80%, respectively. According to the 2018 Service Availability and Readiness Assessment (SARA), 50 percent of health facilities in the country performed TB diagnosis via sputum smear microscopy examination, and 12 percent used chest x-ray. Since 2019, there have also been 59 drug-resistant TB treatment clinics and over 700 treatment follow-up facilities (15). According to the SARA, 43 percent of health facilities in Addis Ababa provide TB services (16).

Ethiopia's federal health ministry issued a national strategic action plan for NCDs prevention and control in 2010. This policy focuses on four NCDs: cardiovascular disease, cancer, chronic respiratory illnesses, and diabetes. The policy strives to raise awareness, early detection, and management of NCDs to reduce morbidity and disability (17). According to SARA data from 2018, 36% of health facilities in the country provide diabetes diagnosis and treatment services. Eighty-two percent of the health facilities in Addis Ababa provide diabetes services. The mean commodities required to provide services for diabetes diagnosis and treatment (glucose strips, urine dipsticks, insulin injectables.) were available in 54% of the health facilities (16).

The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) have called for service integration to address the double burden of the diseases. The main goals of this collaboration include primary prevention of both diseases and bidirectional screening to detect the disease early and start treatment and follow-up. At last, the overall goal is to improve the outcome for TB and DM patients. Despite this, there is no system organized in most African countries for the provision of integrated service, which was shown to improve better follow-up, management, and early detection of both diseases. Services for Diabetes and TB are offered separately, including in Ethiopia (18).

2. CHAPTER TWO

2.1 Problem statement:

Diabetes Mellitus (DM) and tuberculosis (TB) have received the name 'the converging epidemics' and 'double burden' because of their increased prevalence at an epidemic level (19,20). Globally, in 2021, studies estimated that 536.6 million people were living with DM, and it is projected that by 2045, 783.2 million people will have diabetes. Currently, a high proportion of people with diabetes (80.6%, 432.7 million) live in low- and middle-income countries. The number is projected to increase dramatically, with growing prevalence in middle-income countries from 10.8% in 2021 to 13.1% in 2045 and in low middle-income countries from 5.5% to 6.1% in the coming decades (21). This rapid increment is associated with the shift in lifestyle, urbanization, and epidemiological changes.

The DM prevalence is much higher in areas where TB is already an epidemic (22). In 2021, 24 million people in Africa were living with DM, with 1 in 22 (54%) of people living with diabetes being undiagnosed. In the same year, 416,000 people died in the continent as a result of diabetes. Ethiopia is one of the top 5 countries in Africa, where 1.9 million people have DM, and in 2021 DM caused 26,448 deaths (2). A recent systemic review by Getachew et al. showed a pooled prevalence of undiagnosed diabetes mellitus to be 5.75% in Ethiopia among the general population (23).

TB remains globally a significant public health threat. In 2020, 1.4 million HIV-negative and 214 000 HIV-positive people died due to the disease (1). TB remains among the top 10 diseases with high Mortality (up to 30%) in underdeveloped countries. In 2020, next to COVID-19, it was the second cause of death because of a single infectious agent worldwide (1,24). Geographically, in 2020, 25 % of TB cases were in Africa, with sub–Saharan Africa having the most significant burden (1). Ethiopia is among the 30 high TB burden countries, with a drug-susceptible TB incidence of 164 per 100,000 people (25). In Ethiopia, out of the top 10 causes of death and disability, both TB and DM are in fifth and ninth place, respectively (26).

Diabetes will contribute 12% to the TB epidemic in 2030, a 25% increase from 2010 (27). One systematic review and meta-analysis of data from 2.3 million people with TB worldwide estimated that the Prevalence of DM in patients with TB is around 15% and was twice that of the general population (28). Another 2021 study found that the prevalence of DM was 13.7% among pulmonary TB patients globally, showing a 9.3% prevalence in Africa (29). A systemic review done in sub-Saharan countries in 2019 showed that the prevalence of DM among TB patients was 9.0%. Ethiopia was one of the three countries with the highest prevalence of 10% (4). A study done in Ethiopia showed that the prevalence of DM among newly diagnosed TB patients was 8.3% which showed increased DM prevalence in the general population (8). In general, diabetic patients are three times more likely to contract tuberculosis in countries with a high TB burden (27).

Studies also showed that the co-existence of DM worsens the outcome in TB-treated patients. Diabetes increases the risk of treatment failure, death, and relapse in tuberculosis patients (30). On the other hand, TB causes hyperglycaemia and glucose intolerance which predisposes DM patients to have impaired glycaemic control. This causes difficulty in management and may reveal masked DM that was undiagnosed in susceptible people (31).

2.2 Justification:

This lethal combination between DM and TB in terms of epidemiology and outcome necessitates bi-directional screening. The collaborative framework for care and control of TB and DM proposed by the World Health Organization (WHO) along with the International Union against TB and Lung recommends routine screening and reporting of patients with TB for DM (31). Despite the fact that diabetes is prevalent among TB patients, research has revealed that routine screening has not been implemented in many Sub-Saharan African countries, for example, in Ghana, Zambia, and Uganda (32–34). One study in Malawi showed that after implementing integrated care and bidirectional routine screening for TB patients, outcomes of patients improved, and a decrease in follow-up was seen (35). Another study conducted in Zimbabwe on the feasibility of screening for diabetes mellitus among tuberculosis patients found that there was a drop in patients from follow-up seen from the screening cascade due to various patient-related factors and a lack of data-driven supervision (36).

In Ethiopia, this routine screening does not take place on a broad scale, even though the links between the two diseases are recognized. Despite the fact that the national guideline recommends routine screening for diabetes in tuberculosis patients, TB clinics do not provide the service. One of the reasons for the limited screening for DM among TB patients is the lack of a simplified screening tool, as routine blood tests are not widely available in TB clinics. Some triaging approaches would be desirable to guide the best use of available resources, as suggested in a recent report by Jerene et al. (37). Findings from this current study will help further understand the optimum combination of risk factors and symptoms that can guide better-triaging patients into various risk groups. This will guide policymakers to formulate specific intervention strategies that will guide the efficient use of limited resources and further improve tuberculosis patients' outcomes and quality of life.

2.3 Research Objectives:

2.3.1 General objective:

This study aims to assess the performance of risk scoring tools combined with clinical symptoms in predicting TB patients at higher risk of being diagnosed with diabetes mellitus in Ethiopia to provide recommendations for policymakers and health planners to develop intervention strategies.

2.3.2 Specific objectives:

- To identify common socio-demographic and clinical factors associated with a higher risk of being diagnosed with diabetes mellitus among TB patients.
- To assess the performance of the risk scoring tools for predicting those at risk for DM among TB patients.
- To determine the most efficient combination of risk factors and clinical symptoms to identify TB patients at high risk of DM.
- To provide a recommendation to policymakers to justify the need for routine screening for DM in TB patients to improve the outcome and quality of care for patients.

3. CHAPTER THREE

3.1 Methodology

This section describes the different parts of the methodology and the conceptual framework used in the current study.

3.2 Research Design and Data Source

This study was a quantitative research design by conducting a secondary analysis based on a primary cross-sectional study conducted in public health facilities in Addis Ababa, Ethiopia, between September 2020 and December 2021. The data source was KNCV tuberculosis foundation. In the primary study, all consenting adult patients with confirmed TB diagnoses were included irrespective of their stage of TB treatment. The objective of the primary study was to see the performance of risk scoring tools combined with blood tests on the yield of DM screening among TB patients and assess TB treatment outcomes among TB/DM co-morbid patients in the study.

The steps taken in the primary study to screen for diabetes in patients with a confirmed TB diagnosis are attached in appendix A. A Finger-prick blood test was performed to confirm the diagnosis of diabetes. A Random Blood Sugar (RBS) of ≥ 200 gm/dl or Fasting Blood Sugar (FBS) of ≥ 126 gm/dl on two separate occasions or a previous diagnosis as confirmed by medical records was considered confirmatory of DM diagnosis.

3.3 Data Extraction

The data for this study was extracted from the KNCV tuberculosis foundation study data in SPSS 25. The primary study was a cross-sectional health facility-based study of 2381 TB patients who were screened for diabetes. Because data for two patients were missing, the current study included 2379 tuberculosis patients, 1247 male, and 1125 female, who were screened for diabetes. All participants in the study presented at public health facilities in Addis Ababa, Ethiopia, between September 2020 and December 2021.

3.4 Data Management

The dataset which is extracted from the primary study holds the participant's: socio-demographic information, clinical presentation and diagnosis, risk factors, and nine symptoms associated with acute and chronic complications of DM.

In the current study, the following listed variables were extracted in relation to their relevance to the above-stated research objectives and entered for logistic regression analysis. Risk factors include a family history of DM, age, waist circumference, smoking history, and alcohol use. Clinical Symptoms: which include the three poly symptoms (excessive urination, thirst, and hunger), unexplained weight loss, blurred vision, fatigue, tingling/numbness in the limbs, frequent infection, and delayed wound healing. Other variables such as sex of the patient type of TB diagnosed. Random or Fasting blood measurements were done in the primary study.

For a simpler organization of the extracted variables in the current study, the age of TB patients was categorized as (<=40 years and >40 years), the smoking variable was categorized as (never smoked and previous history of smoking), and Alcohol use in glasses per day categorized as (never or <1 drink per day and >= one drink per day). In the primary study, they used the median cumulative risk score value, which was 2 (interquartile range [IQR] = 0–3), as a reference to classify patients as high or low-risk groups. In this current study, we used the cut-off value of 3 to classify patients with a risk scoring value of <3 as low-risk TB patients and those >=three scoring value as high-risk TB patients. This risk scoring is calculated from the standard risk scoring checklist, which was used in the primary study, as seen in appendix A. Tuberculosis patients were classified as symptomatic if one of the abovementioned nine clinical symptoms were reported and asymptomatic if they did not report any symptoms.

3.5 Data Analysis

The statistical analysis and management of data related to this study were carried out in Statistical Package for Social Sciences (SPSS) version 25, using logistic regression with the composite of DM Random of 200mg/dl or Fasting blood FPG ≥126 mg/dl versus normal as the dependent variable. Descriptive analysis techniques were used to describe the socio-demographic factors and clinical characteristics of the study participants. It was also used to describe the frequency and percentage of risk factors and symptoms for DM. A staged approach to variable selection was used to analyse the study's first objective. First, I assessed the association of each variable and the outcome independently (DM). Other than Risk factors and symptoms, those variables in a univariate level analysis with a p-value of <0.25 were also selected and included in the multivariate logistic regression model. This process was then repeated for each variable. Binary logistic regression (LR) analyses with adjusted Odds Ratio (AOR) and 95% Confidence Interval (95%CI) to identify predictors of DM were used. A two-step cluster analysis was performed to identify whether tuberculous patients belong to distinct clusters, and logistic regression analysis was performed to evaluate whether the diagnosis of DM was significantly different between TB patient clusters. A p-value of <0.05 was used as a standard for statistical significance difference among the clusters.

To analyse the second and third objectives of the study, The receiver operating characteristic (ROC) curves were plotted. Sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC) were calculated with its 95% CIs to evaluate the predicting accuracy of the risk factors and symptoms against blood test results or DM as a reference standard. The AUC value of < 0.50 was considered suboptimal. Each variable was compared in terms of the area under the receiver operating characteristic (ROC) curve, with the aim of maximizing this.

3.6 Conceptual/Analytical framework

The conceptual framework for TB-Diabetes co-infection Proposed by Noureen was applied for this study (38). This framework which was used to study diabetes mellitus and associated risk factors among Tuberculosis Patients was used to analyse objective one of this study. The conceptual framework explained the interrelation of these two diseases at a demographic level. As explained in Figure 3, some factors are associated solely with TB or DM, and others can be associated with both diseases. For instance, smoking and a specific type of occupational exposure are directly associated with TB by causing lung damage and weak immunity. Smoking, in particular, affects the effectiveness of TB treatments, resulting in a more prolonged infection period and worse treatment outcomes. Marital status was explained as having a direct TB contact history as spouses get infected was another aspect of the framework. Locality, either as an urban dweller or rural, was associated with both diseases. Because of a sedentary way of life, unhealthy diet, and overcrowding, those from the urban side were associated with DM and those from rural areas with TB. Advanced age and Family History of

DM are also other factors associated with both diseases because of weak immunity and genetic susceptibility. Another interrelated factor is Socioeconomic status (SES), where those with High SES are associated with DM in relation to lifestyle, and those with low SES are associated with TB due to overcrowding. The framework also explains that both diseases co-relate with each other at a different level, at which one worsens the outcome of the other and makes individuals susceptible to both diseases, further worsening the co-pandemic.

This current study focuses on only exploring factors such as Age, Family history, smoking history, Type of TB diagnosed, co-morbidities, and sedentary lifestyle as variables in the framework since the primary study data was health facility data which focused on only these areas and clinical factors.

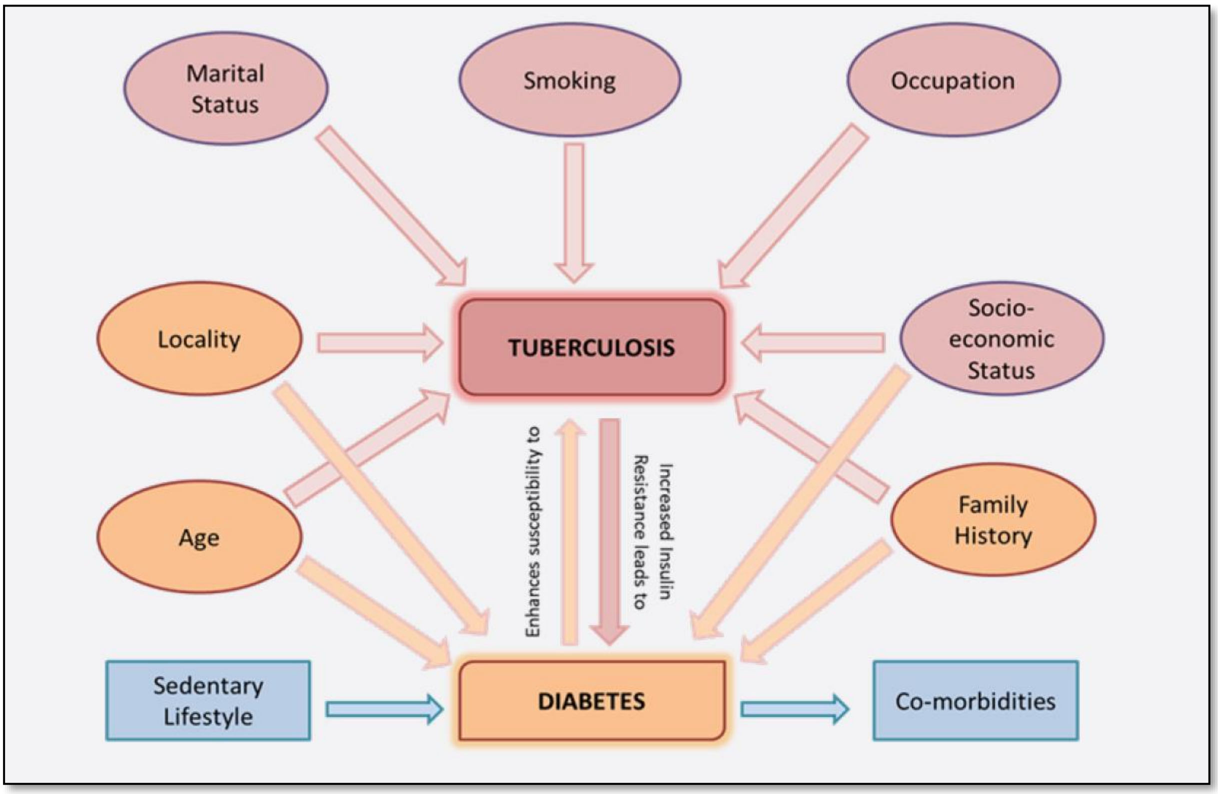

Figure 3: Conceptual Model of TB-Diabetes co-infection (Adapted from Noureensee,2017) (38).

3.7 Ethical consideration

For the current study, which is a secondary data analysis of the dataset from KNCV TB Foundation, a waiver from the KIT Royal Tropical Institute Research Ethics Committee was obtained on 28-05-2022. Furthermore, the Ethics review committee of Addis Ababa City Council Health Bureau reviewed and approved the study protocol for the original primary research. Any patient data was kept anonymized with no personal identification, and data was handled confidentially.

3.8 Limitation of Study Design/Methodology

The study used a data set that is from a cross-sectional study which makes it difficult to establish causal relationships. Since some of the factors which were explained in the framework, for example, occupation, marital status, locality, and socioeconomic status, were not collected in the original study, the framework will not be able to explain the interrelation between the two diseases firmly. The primary study data source was health facility-based, so it might not represent the true nature of the two diseases in the general population.

3.9 Operational Definition of Variables

The above-described conceptual framework was used as a reference to select and extract the independent and dependent variables from the primary data. Concerning the interest and objective of the study, Variables such as Alcohol use, Symptoms (excessive urination, thirst, and hunger, blurred vision, fatigue, tingling and numbness of the limbs, unexplained weight loss, frequent infection, and delayed wound healing) were included in the study though they are not part of the framework. Since some of the variables or factors selected in the framework cannot be measured directly, a proxy variable was used. For example, the variable' waist circumference' was used as a proxy for a sedentary way of life; 'HIV co-infection was used as a proxy for co-morbidities. The table1 below describes all the variables that were used in the regression model analysis.

Table 1: Operational definition of variables

Variable Name **(Independent variables)**	**Variable coding**	**Operational definition**	**Proxy variable**
Age	<=40 (0) Above 40(1)	the study included adult tuberculosis patients	
waist circumference in centimetres (men/women)	<=84/77(0) 85 to 89.9 / 78 to 83.9(2) >= to 90 /84(3)	Measured at the umbilicus and recorded by the health care worker	Proxy for Sedentary lifestyle
Family history of DM	No (0) Yes (1)	Self-reported whether a sibling/ parent has DM	
Smoking	Never (0) History of smoking (1)	self-reported history of smoking	
Alcohol use (Glasses per day)	Never or <1 drink/day (0)	Self-reported history of drinking irrespective of the kind of drink	

	More than 1drink/day (1)		
Type of Tuberculosis	Bacteriologically confirmed pulmonary TB (1) Clinically diagnosed pulmonary TB (2) Extrapulmonary TB (3) Drug-resistant TB (4)	Reported from medical record data on the current treatment phase	
HIV co-infection	HIV positive (1) HIV negative (2)	Medical record data of the diagnosis	Proxy for co-morbidity
Excessive urination,	Yes (1) No (2)	Self-reported urge to urinate frequently	
Excessive thirst	Yes (1) No (2)	Self-reported urge to drink frequently	
Excessive hunger	Yes (1) No (2)	self-reported urge to eat frequently	
Unexplained weight loss	Yes (1) No (2)	Self-reported decrement in body weight>5kgs in the last six months without no reason	
blurred vision	Yes (1) No (2)	Self-reported inability to see fine details of things	
fatigue	Yes (1) No (2)	self-reported feeling of extreme tiredness	
tingling/numbness in the limbs	Yes (1) No (2)	Self-reported description of burning feeling/ reduced ability to feel pain or temperature change in the feet	
frequent infection	Yes (1) No (2)	Self-reported infections of the different parts of the body	

delayed wound healing	Yes (1) No (2)	Self-reported experience of slowly healing wound	
Outcome Variable			
Diabetes mellitus	No DM (0) DM (1)	RBS ≥ 200 gm/dl or FBS ≥ 126 gm/dl on two occasions or medical record of the previous diagnosis	

4. CHAPTER FOUR

4.1 Results

This chapter discusses the study's findings, which are arranged in four parts. The first section describes the characteristics of the study respondents, which are shown in table 2. The second section, which includes table 3, shows the frequency of risk factors and symptoms of diabetes seen in TB patients. The third part, with table 4, figure 4, and table 5, describes the distribution of different TB patient clusters of the risk factors in a two-step cluster analysis and logistic regression analysis of the association of the clusters with the diagnosis of DM. The description of the univariate and multivariate analysis of the predictors of DM is mentioned in the fourth part, which also includes table 6. The last section, which includes table 7, figures 5, and 6, shows the specificity and the sensitivity of risk scores and individual symptoms in predicting DM and the performance of the prediction model of the risk scoring and the combination of the symptoms in the ROC curve.

4.2 Characteristics of the Study Participants

We included 2379 TB patients in this study out of the 2381 TB patients screened for DM since data for the two patients was missing. Table 2 below summarizes the study participants' baseline socio-demographic and clinical presentation. The study participants' median weight was 51 kilograms, with 52.6% males and 47.4% females. The median age of the TB patients who have been screened was 31 years. Eighty-two percent of TB patients visited health centres, while only 17.9% were evaluated in hospitals. Of these, 58.7% were diagnosed with Pulmonary TB, while 2.7 % had drug resistance TB, and 15% of them were HIV positive.

Table 2: Distribution of the baseline characteristics of the study participants

Variable		Frequency (n)	Percentage (%)
Sex	Male	1247	52.6
	Female	1125	47.4
	Missing	7	0.3
Body Weight in Kg	Median weight (IQR, 25%-75%)	51	45,59
Age in years	Median Age (IQR, 25%-75%)	31	24,42
Type of TB Diagnosed	Extrapulmonary TB	908	38.2
	Bacteriologically confirmed Pulmonary TB	868	36.5
	Clinically diagnosed pulmonary TB	528	22.2
	Drug-resistant TB	64	2.7
	Missing	11	0.5
Type of Health facility visited	Hospital	427	17.9
	Health centre	1952	82.1
HIV test	HIV negative	2005	84.3
	HIV positive	357	15
	Unknown	11	0.5
	Missing	6	0.3

4.3 Description of risk factors and symptoms of DM in TB patients

According to the risk scoring cut-off value, which was used in this study, 59.9% of the TB patients were classified as a low-risk group (risk score <3), and 39.1% were in the high-risk group (risk score >=3). This risk scoring is calculated from the standard risk scoring checklist as presented in appendix A.

The description of the risk factors shows that 26.1% of the TB patients were aged over 40 years, with the majority (72.6%) of men and women in the study were having a Waist circumference of <=84/77cm. Family history of Dm was seen in 8.4% of the screened TB patients. Of the study participants, 22.1% had a smoking history, and 11.8% drank>= one glass of alcohol per day.

Screened tuberculosis patients who were reported to have at least one symptom for DM were 38%, and 62% were asymptomatic or showed no symptoms. As shown below in table 3 of the poly symptoms, excessive urination (6.2%) was mentioned as a symptom more frequently than excessive hunger or thirst, which are reported as 4.0% and 5.3%, respectively. Fatigue, unexplained weight loss, and blurred vision were the three most frequently reported symptoms,27.2%, 21.9%, and 6.9%, respectively. On the other hand, a history of frequent infections, delayed wound healing, and numbness or tingling sensations on the limbs were the least reported symptoms at 2.2%,1.4%, and 4.4%, respectively.

Table 3: Frequency of risk factors and symptoms of DM seen in TB patients

Risk factor		**Frequency (n)**	**Percentage (%)**
Age of Tb patient	<=40	1752	73.6
	>40	620	26.1
	Missing	7	0.3
Waist circumference in centimetres (men/women)	<=84/77	1728	72.6
	85 to 89.9 / 78 to 83.9	532	22.4
	>=90 /84	111	4.7
	missing	8	0.3
Smoking history	Never	1850	77.8
	History of smoking	526	22.1
	Missing	3	0.1
Family history of DM	no	2175	91.4
	Yes	199	8.4
	Missing	5	0.2
Alcohol use (Glasses per day)	Never or <1drink per day	2094	88.0
	>=1 drink per day	280	11.8
	Missing	5	0.2
Symptoms			
Excessive urination	Yes	147	6.2
	No	2232	93.8

Excessive Thirst	Yes	126	5.3
	No	2253	94.7
Excessive hunger	Yes	95	4.0
	No	2284	96.0
Unexplained weight loss	Yes	522	21.9
	No	1857	78.1
Blurred vision	Yes	164	6.9
	No	2215	93.1
Fatigue	Yes	648	27.2
	No	1727	72.6
	missing	4	0.2
Tingling/numbness in the limbs	Yes	104	4.4
	No	2257	94.9
	missing	18	0.8
Frequent infection	Yes	53	2.2
	No	2326	97.8
Delayed wound healing	Yes	34	1.4
	No	2345	98.6

4.4 Description of distinct clusters of TB patients with respect to risk factors

According to the two-step cluster analysis performed, TB patients were divided into six clusters based on reported risk factors. Clusters six, four, and two made up the largest of the clusters with 38.6%,19%, and 14.5%, respectively. As shown in figure 4, Clusters three and five were the smallest of the clusters, with 8.4% and 9.6%, respectively.

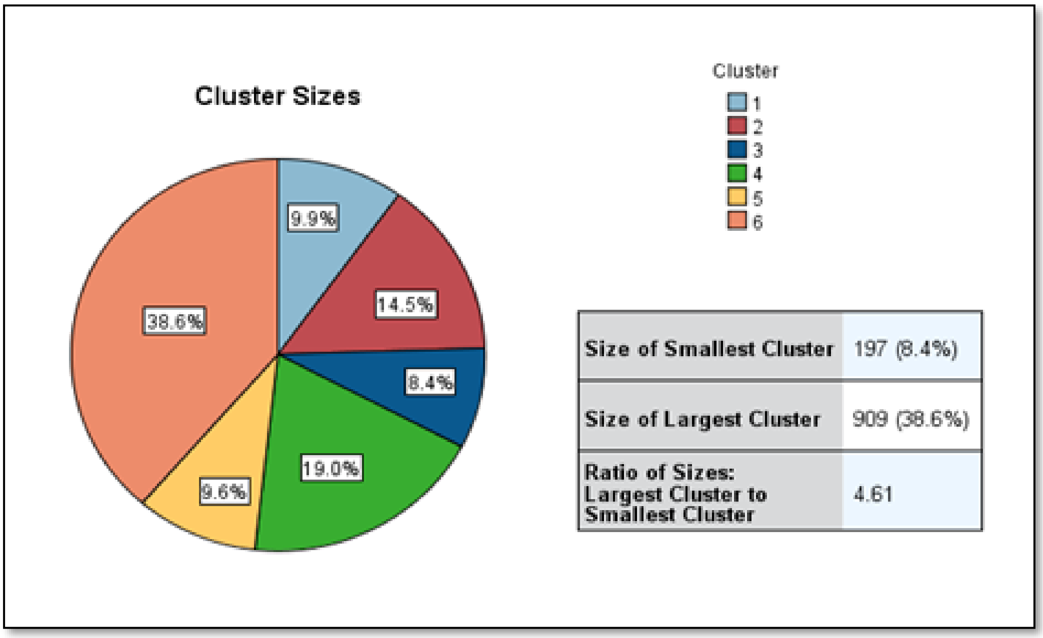

Figure 4: Description of tuberculosis patient cluster sizes

Different distinct characteristics of the clusters were identified in relation to the risk factors, as shown in Table 4 below. The largest cluster, which is cluster 6, is characterized by younger individuals younger than 40 with normal waist circumference and no history of alcohol, smoking, or family history of DM. Cluster 4 and cluster 2, which made the second and third largest clusters, are distinct from others by Waist circumference measurement of 85 to 89.9 / 77 to 83.9 cm and having a smoking history, respectively. The smallest of the TB patient clusters, which is cluster 3, is distinctly characterized by patients having a family history of DM.

Table 4: Distinctive characteristics of TB patients' clusters

Clusters	**1**	**2**	**3**	**4**	**5**	**6**
Size N (%)	9.9% (234)	14.5% (342)	8.4% (197)	19% (447)	9.6% (226)	38.6% (909)
Age	<=40yr	<=40yr	<=40yr	<=40yr	>40yr	<=40yr
Alcohol	>=1Drink per day	Never or <1drink/ day	Never or <1drink/ day	Never or <1drink/ day	Never or <1drink/ day	Never or <1drink/ day
Family history	No	No	Yes	No	No	No
Smoking	never	History of smoking	never	never	never	never
Waist circumference	<=84/77	<=84/77	<=84/77	85 to 89.9 / 78 to 83.9	<=84/77	<=84/77

The logistic regression analysis result shown in table 5 was performed to determine which clusters were associated with DM. The odds of having DM were 13.6 times higher among patients in cluster 3 with a distinct character of having a family history of DM [Odds Ratio (OR)=13.6; 95% Confidence Interval (CI):8.54,21.6; p<0.000]. Followed by cluster 5 with a distinct feature of age older than 40, who had 2.97 higher odds of having diabetes [OR=2.97; 95%CI: 1.67,5.26; p<0.000] compared to those with no risk factors. Another cluster significantly associated with Dm is cluster 4 with [OR=2.83.; 95%CI: 1.74, 4.59; p<.000], distinct features of TB patients having a Waist circumference(cm) of 85 to 89.9 / 78 to 83.9. Cluster 2 and cluster 1 are also significantly associated with DM with [OR=2.14.; 95%CI: 1.24, 3.71; p<.007], and [OR=2.09.; 95%CI: 1.13, 3.91; p<.0.019], and having a history of smoking and history of drinking alcohol, respectively.

Table 5: Logistic regression of the relationship between the clusters and DM

Variable (Distinct Character)	OR (95%CI)	P-value
Cluster 6 (Ref) (No risk factors)	1	
Cluster 1 (>=1Drink per day)	2.09 (1.13, 3.91)	0.019
Cluster 2 (History of smoking)	2.14 (1.24, 3.71)	0.007
Cluster 3 (Family history of DM)	13.6 (8.54 ,21.6)	0.000
Cluster 4 (Waist circumference 85 to 89.9 / 78 to 83.9cm)	2.83 (1.74, 4.59)	0.000
Cluster 5 (>40yrs old)	2.97(1.67, 5.26)	0.000

4.5 Detection of DM among TB patients

Of the 197 DM cases detected, 161 (81.7%) were identified at health centres and 36 (18.3%) at public hospitals. From the total number of DM cases identified, 98 (49.7%) were newly diagnosed diabetic patients. In terms of the type of TB diagnosed in DM cases, 7(3.6%) had drug-resistant TB, 53 (27.2%) had extrapulmonary TB, 48 (24.6%) had clinically diagnosed pulmonary TB, and the majority, 87 (44.6%) had bacteriologic confirmed pulmonary TB. HIV co-infection was seen in 27(13.7%) of the total 197 TBDM comorbid patients.

4.6 Factors associated with prediction of DM in TB patients

The univariate and multivariate regression analysis of factors predicting DM among screened TB patients is shown in table 6. After adjusting for confounders in the multivariate analysis, four factors were found to be significantly associated with DM (Age, Family history of DM, having a higher risk score >=3, and having one or more symptoms). Age was significantly associated with Dm at both the univariate and multivariate analysis levels. At the multivariate level, the odds of having DM among those who are >40 were 2.23 times higher [aOR= 2.23; 95%CI:1.43, 3.44; p<0.000] compared to those who aged <=40 yrs. A higher waist circumference measurement ≥90/84cm in both men & women was significantly associated with DM at a univariate level [OR=2.71; 95% CI: 1.60, 4.59; p<0.000]. In addition, those with a waist circumference measurement of 85–89.9/78–83.9 cm had 1.62 higher odds of predicting DM [OR=1.62; 95%CI: 1.17,2.26; p<0.004] compared to those with having <=84/77cm measurement at univariate analysis. Having a family history of DM is the strongest predictor of DM at both univariate and multivariate analysis levels. The odds of having DM among those with a family history were 4.94 times higher [aOR= 4.94; 95%CI: 3.37, 7.23; p<0.000] compared to those who do not have a family history.

Though those with a history of smoking (9.0%) had a higher rate of TB and DM infection than those who never smoked (7%), there was no statistically significant difference (P>0.106) at both levels of analysis. The same was true with the sex of the TB patient; though males were found to have a higher rate of infection (9.2%) than females (7.5%), this difference was not statistically significant at both univariate and multivariate levels (p>0.315). Consuming alcohol >= one glass of drink per day was significantly associated with predicting DM at a univariate level with [OR=1.51; 95% CI: 1.01, 2.26; p<0.044] but not at a multivariate analysis level (p>0.564). At both levels of analysis, having a risk score of >= three and having one or more symptoms of DM were strongly associated with the prediction of DM diagnosis with [aOR= 2.32; 95%CI: 1.37, 3.92; p<0.002] and [aOR=3.03; 95%CI: 2.18, 4.22; p<0.000] respectively.

Table 6: Logistic regression analysis of factors associated with prediction of DM

Variables	**UNIVARIATE(Unadjusted)**		**MULTIVARIATE (Adjusted)**	
	OR (95%CI)	**P-value**	**aOR (95%CI)**	**P-value**
Age (in years)				
<=40 yrs. (Ref)	1		1	
>40 yrs.	4.24(3.14, 5.72)	0.000	2.23 (1.43, 3.44)	0.000*
Waist circumference				
<=84/77 (Ref)	1		1	
85–89.9/78–83.9	1.62 (1.17, 2.26)	0.004	1.03 (0.69, 1.51)	0.899
≥90/84	2.71 (1.60, 4.59)	0.000	1.43 (0.78, 2.63)	0.251
Family History of DM				
no (Ref)	1		1	
yes	7.3 (5.1, 10.3)	0.000	4.94 (3.37, 7.23)	0.000*
Sex				
Female (Ref)	1		1	
male	1.26 (0.9, 1.69)	0.130	1.18 (0.85, 1.65)	0.315
Alcohol drinking history				
Never or <1drink/day (Ref)	1		1	
>=1Drink per day	1.51(1.01, 2.26)	0.044	0.87 (0.55, 1.39	0.564
Smoking History				
Never (Ref)	1		1	
History of smoking	1.10 (0.78, 1.55)	0.586	0.72 (0.49, 1.07)	0.106
Risk factors scored				
<3 (Ref)	1		1	
> =3	4.87(3.50, 6.77)	0.000	2.32 (1.37, 3.92)	0.002*
Presence of one or more symptoms				
no (Ref)	1		1	
yes	3.52 (2.58, 4.81)	0.000	3.03 (2.18, 4.22)	0.000*

*Significant P-value

4.7 Prediction models of risk factors and individual symptoms

Fatigue, unexplained weight loss, and blurred vision were the three most frequently reported symptoms mentioned above. However, when we look at the performance of individual symptoms as a predictor of DM in the model, fatigue predicted DM diagnosis with very low accuracy (AUC = 0.39, 95% CI = 0.33,0.43), with 50.7% sensitivity and 25.6% specificity. Unexplained weight loss (AUC=0.39) and blurred vision (AUC=0.40) have almost similar AUC with the worst performance to predict DM. As presented in table 7, symptoms such as delayed wound healing and frequent infection showed a better AUC of 0.46 and 0.44, respectively but with the lowest specificity. In the prediction model, almost all the symptoms individually have an AUC of lower than 0.50, which shows that symptoms individually have the lowest predictive accuracy of distinguishing patients with or without DM.

Table 7: ROC curve results showing the accuracy of different factors predicting newly diagnosed DM

		ROC curve results		
		AUC (95% CI)	**Sensitivity**	**Specificity**
Risk factors	Age of patient	0.66 (0.61, 0.71)	56.0	76.0
	Family history of DM	0.62 (0.57, 0.68)	31.3	93.1
	Waist circumference	0.57 (0.52, 0.62)	39.3	73.9
	History of alcohol use	0.52 (0.48, 0.58)	16.7	88.5
	Smoking history	0.51 (0.46, 0.56)	24.0	77.8
Individual symptoms	Delayed wound healing	0.46 (0.41, 0.51)	90.7	0.9
	Frequent infection	0.44 (0.39, 0.49)	86.0	1.5
	Tingling/numbness in the limbs	0.43 (0.37, 0.48)	81.6	3.5
	Blurred vision	0.40 (0.35, 0.45)	74.7	5.7
	Unexplained weight loss	0.39 (0.34, 0.44)	56.7	20.5
	Fatigue	0.39(0.33, 0.43)	50.7	25.6
	Excessive hunger	0.39 (0.34, 0.45)	76.0	2.6
	Excessive urination	0.34 (0.28,0.39)	63.3	4.1
	Excessive Thirst	0.34 (0.29, 0.39)	64.7	3.2
Risk score at cut-off (<3 VS >=3)		0.68 (0.64, 0.72)	73.3	63.1
Any one of the symptoms (yes or no)		0.64 (0.59, 0.69)	64.7	63.8
Symptom and Risk factors combined (Yes or No)		0.70 (0.61, 0.73)	88.3	41.9

As seen in figure 5 and table 7, the performance of individual risk factors such as the age of the patient predicted DM diagnosis with moderate accuracy as determined by the area under the ROC curve (AUC = 0.66, 95% CI = 0.61,0.71) with a sensitivity of 56.0% and 76.0% specificity. Family history of DM and Waist circumference also showed good performance in predicting DM with (AUC = 0.62, 95% CI = 0.57,0.68) and (AUC = 0.57, 95% CI = 0.52,0.62) respectively. However, both risk factors achieved a lower sensitivity of 31.3%and 39.3%, respectively. Other Risk factors such as a history of smoking and alcohol did not show a better predicting accuracy as determined by the area under the ROC curve with an (AUC = 0.51, 95% CI = 0.46,0.56) and (AUC = 0.52, 95% CI = 0.48,0.58) respectively.

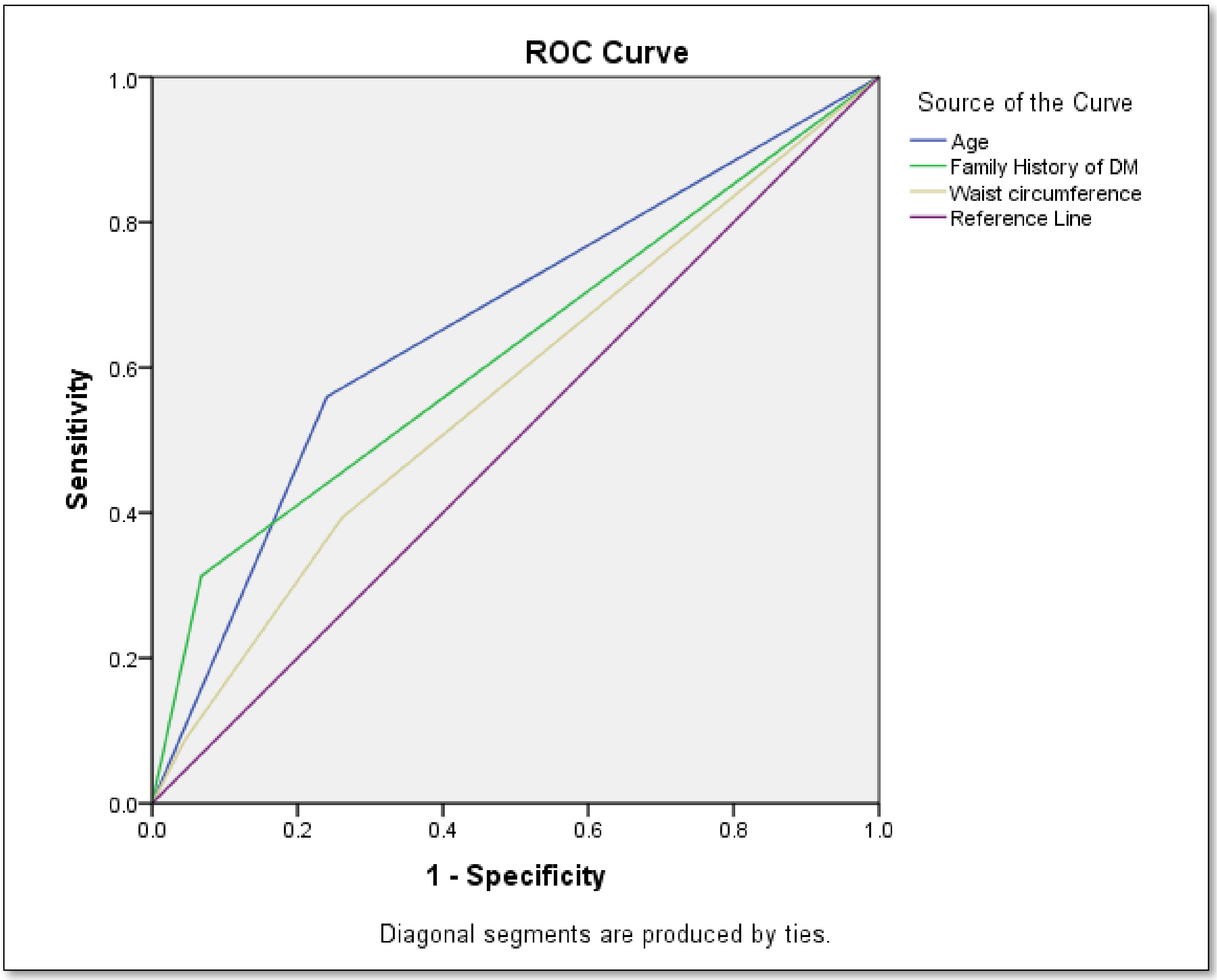

Figure 5: ROC curve showing the accuracy of risk factors as predictor models

As presented in table 7, the presence of any one or more of the symptoms predicted DM with lower accuracy as seen in the area under the ROC curve (AUC = 0.64, 95% CI = 0.59,0.69) with 64.7 sensitivity and specificity of 63.8. Relatively having risk score of >=3 predicted DM with a better accuracy of (AUC = 0.68, 95% CI = 0.64,0.72) with higher sensitivity of 73.3% and 63.1% specificity. As seen in figure 6, Combining symptoms with risk scoring increased the predictive value of the model, increasing sensitivity to 88.3% with (AUC= 0.70, 95% CI= 0.61, 0.73). with a relative drop in the specificity of 41.9%. This shows that combining the two was a stronger predictor of undiagnosed diabetes than the individual risk scoring tools and the symptoms.

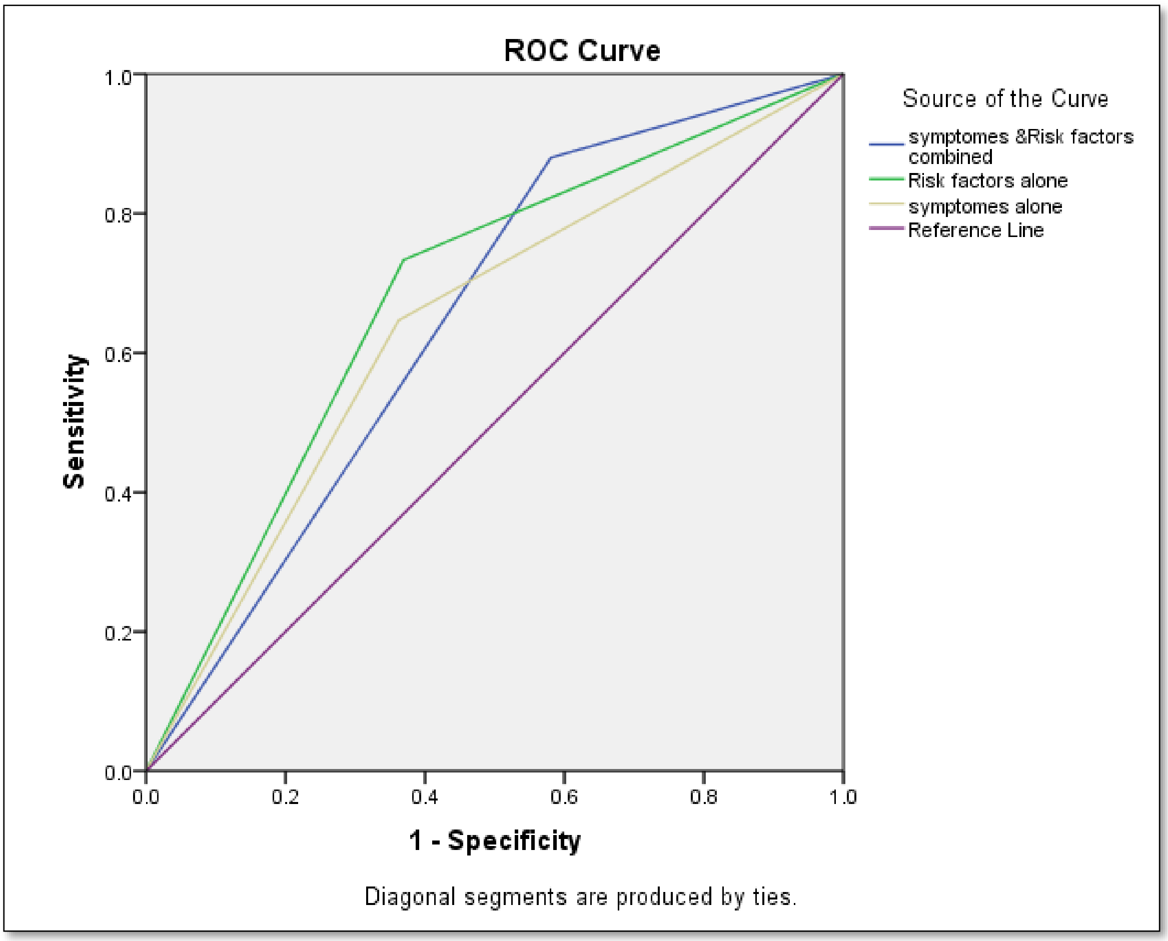

Figure 6: ROC curve showing the predicting accuracy of three different models

5. CHAPTER FIVE

5.1 Discussion

This section discusses the research findings in line with the study objectives.

5.2 Characteristics of TBDM co-morbid patients

The current study found that from the total screened TB patients,197 of them had DM. Of the total TB patients, 38% were reported to have at least one symptom of DM, and those symptoms were not specific to DM. The majority of TBDM patients had bacteriologically confirmed pulmonary TB. According to this study, almost half of the TB patients were unaware that they had diabetes, which means that undiagnosed DM patients with tuberculosis made up 49.7 percent of all detected DM patients. This study found that TB patients with a family history of the disease, who were older than 40, had a higher risk score >=3, and had one or more symptoms suggestive of DM were significantly associated with a higher TBDM co-morbidity rate. When TB patients were analysed in clusters, larger waist circumference and having a history of smoking and alcohol drinking were significantly associated with DM. Moreover, the risk factors mentioned above predicted the diagnosis of DM with moderate accuracy compared to Individual DM symptoms, which had lower accuracy in predicting the diagnosis of DM. Despite this, combining the risk factors and the symptoms improved the sensitivity and accuracy of DM prediction.

Our findings suggest that despite WHO's recommendations to screen all TB patients for diabetic Mellitus, a sizable portion of them continue to go undiagnosed due to either non-specific symptoms of the disease or presenting with no symptoms. Thus, combining the symptoms with the risk factors will be a simple and effective way to determine which TB patients require additional investigation. With further refinement and local validation, health care workers can apply this convenient tool in areas with limited resources. This tool could also be simplified and used for self-screening of TB patients.

Our results reveal that close to a half 87 (44%) of the DM patients had pulmonary TB (PTB) that was bacteriologically proven. Being smear-positive is significantly associated with having diabetes, as shown in a study conducted in Addis Ababa, Ethiopia (39). A similar study in Ethiopia (40%) and India (50%) found that PTB was more prevalent in TB and DM coinfected patients.(8,40) Another two studies in India showed that the risk of having DM was higher in those with bacteriologically confirmed PTB (41,42). Immune system abnormalities and decreased alveolar macrophage ability to clear mycobacterial infection in DM patients can be used to explain the findings mentioned above (43,44).

Of the total number of DM cases reported, 161 (81.7%) were identified in health centres and 36 (18.3%) at public hospitals. This result is comparable to the finding in the south-eastern Amhara region of Ethiopia, where 93 (85.3%) of 109 DM cases were identified at health centres, with the remaining 8 (7.3%) and 8 (7.3%) reported at government and private hospitals, respectively (45). Three studies conducted in three distinct Indian states (Saluru, Koolar, and Trivandrum) and one study from Mexico indicated that DM detection and screening are far more possible from peripheral health care centres than from referral hospitals (46–49). On the contrary, another study in India, which included eight hospitals and sixty health centres, found that most diabetes patients were diagnosed in the hospitals. This finding could be due to patients referred to the hospital who are already severely ill will receive different investigations, making diagnosing DM easy (50). As per the studies, TB patients who are diagnosed are commonly sent to a peripheral health center for a continuum of care, which could serve as an entry point for DM screening at the periphery level.

The study found that only 38% of evaluated TB patients had at least one symptom indicative of diabetes, whereas 62% were asymptomatic. Most of the patient's symptoms were fatigue and unexplained weight loss, neither of which were specific to diabetes and could be confused with the underlying illness or other disease symptoms (51). A study in Dar es Salaam found that most TB patients evaluated for DM had the symptoms of fatigue and weight loss. This overlap of symptoms made it difficult for health workers to differentiate the features and screen for diabetes (52). Another study in Ghana revealed that patients with TBDM co-morbidity were more likely to present to the clinic with weight loss, low appetite, night sweats, and fatigue symptoms. As a result, health professionals should be aware of the similarity of symptoms and have a strong index of suspension to screen for diabetes (53).

Almost half (49.7%) of tuberculosis patients in this study were unaware that they had the illness. These patients would have remained undiagnosed if the screening for DM for the primary study did not take place. Similar findings were seen in studies conducted in Gondor (53%) and in south-eastern Amhara region (58%) of Ethiopia and Eritrea (45.5%), where undiagnosed DM patients (45,54,55). The present study's findings are lower than those of a prior study conducted in Addis Ababa (84.2%) which had a higher prevalence of undiagnosed new cases of DM in TB patients who were screened (39). According to Studies conducted in Tanzania, Kenya, and Indonesia, which screened TB patients for DM, 73%, 69.5%, and 61%, respectively, were newly diagnosed patients (56–58). Our findings were higher than findings in Kohalar, India (14%) and one in Mexico (4.4%) (47,48). This proportionally high undiagnosed DM in this current study can be explained by the low awareness of health professionals about screening and unavailable diabetic screening programs in TB clinics. The significant difference in the magnitude of undiagnosed DM in different countries could be due to the socio-demographic differences, the lack of access to DM health service providers, and the different screening methods used to diagnose DM (45,48,59).

As discussed above, studies revealed that DM patients have non-specific symptoms that can persist for years without a diagnosis. As a result, patients remain unrecognized, resulting in delayed health care seeking, causing them to present late with complications (27,60). Undiagnosed DM, especially in TB patients, is fatal since it is associated with poor TB treatment outcomes. A cohort study conducted in Ethiopia showed TBDM co-morbid patients were four times more likely to die than those without DM (61). A study in Tanzania also revealed a fivefold increased risk of early Mortality in TB DM patients during the start of treatment (62). Another similar cohort study on TB patients in India showed that Mortality was 10% higher in TB DM co-morbid patients than in those with only TB (7%) (63). Poor glycaemic control and cell-mediated immunity dysfunction in TBDM patients can explain the above findings. This detrimental effect of diabetes could have significant consequences for meeting WHO's 2035 goal of reaching a 95% reduction in TB mortality (61). As a result, our findings suggest that all TB patients should be screened for DM so that the outcomes of TBDM co-morbid patients can be improved.

5.3 Factors associated with co-occurrence of DM in TB patients

This study showed that the odds of having DM among those with a family history were almost five times higher compared to those who do not have a family history. This finding was consistent with the cluster analysis done of screened TB patients. A systematic review done in

Ethiopia by Alemu et al. supported this result, which showed that there were 3.65 times higher odds of developing DM in those with family history than those with no history (64). Other similar studies done in different parts of Ethiopia showed that a family history of DM is a risk factor for TB dm co-morbidity (39,45,65,66). Studies in Tanzania also showed a 6.5 times risk of having DM in TB patients, and Another study in Kenya showed a significant association with TBDM co-morbidity (57,67). These findings were consistent with studies done in Tamilu Nadu state in India, Vietnam, and China, in which family history strongly influenced TBDM co-occurrence (68–70). The above findings may be explained by the fact that genes are passed down through the family to their offspring. Additionally, having a family history is also a risk factor for developing DM in the general population (71).

The current study also revealed there were 2.23 times higher odds of having DM in those Older age groups who are >40 compared to those who are <=40 yrs. A systemic review in 2021 in Ethiopia also found that older TB patients had 2.25 times higher odds of developing DM (64). Other studies done in Amhara and eastern Ethiopia also showed an increased risk for those older than 41 (45,66). Similar findings in Kenya, Dar es Salaam, and Eritrea revealed that ages greater than 40, 45, and 41 years were significantly associated with the risk of developing DM in TB patients (52,57). Other studies done in Kerela state, Tamil Nadu state in India, and China showed that increasing age was a significant risk factor for TBDM co-occurrence (46,68,70). Likewise, a cohort study in Portugal showed that as age increases every year, the odds of having DM among TB patients increase by 4.7% per year of age (72). The findings discussed above can be explained by the fact that ageing causes immune impairment, which predisposes individuals to TB and DM. Another explanation is that ageing causes increased inflammation in the body, leading to insulin resistance. Lipid metabolism disorders due to ageing also cause elevated free fatty acid concentrations, leading to severe insulin resistance and the development of DM (71).

Higher waist circumference measurement ≥90/84cm in men and women was significantly associated with DM at a univariate level. This finding was consistent with findings from India, which showed measurements above >=90 cm in men and >=80 cm in women were significantly associated with DM in TB patients (70). Two studies from India and Guinea revealed that obesity and a sedentary lifestyle were associated with diabetes. The body mass index (BMI) of TB DM co-morbid patients was higher than non-DM TB patients (73,74). These findings can be explained by the fact that obesity, particularly central obesity, increases inflammation, which disrupts beta cell function, resulting in low insulin sensitivity and resistance (71).

The cluster analysis done on TB patients showed that clusters with medium waist circumference measurements of 85 to 89.9 / 78 to 83.9cm were also significantly associated with DM. Similarly, an Eritrean study found that TB patients with normal BMI were at risk of developing diabetes (55). Another systematic review found that patients' BMI status had both a positive and negative association with TB DM co-morbidity (75). This can be explained by differences in the socio-demographics of study participants and the fact that TB patients have a lower median weight due to weight loss, which is a clinical feature of the disease.

In the present study Consuming alcohol >= one glass of drink per day was significantly associated with DM in the cluster analysis. A study conducted in Addis Ababa discovered that the odds of having DM were three times higher in TB patients who drank alcohol (76). Another study in Puducherry, India, showed a significant association between alcohol consumption and DM prevalence in TB patients (77). A systemic review on the effect of alcohol consumption found that moderate consumption of one to three drinks per day was associated with a lower risk of diabetes. In contrast, heavy consumption of more than three drinks per day was associated with a 43 percent increase in the incidence of diabetes. The explanation was, Heavy consumption causes beta cell dysfunction and insulin resistance, whereas moderate consumption increases insulin sensitivity. Because measures of daily alcohol use were different between studies, the interpretation of results may also differ (78).

This current research revealed that a cluster of TB patients with a smoking history were associated with diabetes. A systemic review done by Workneh and his colleagues showed that cigarette smoking is associated with TB DM co-morbidity (75). A study conducted in Tamil Nadu state India, Puducherry, India, and Nepal showed that a smoking history was significantly associated with DM. In the Nepal study, 78% of diabetic TB patients had a smoking history than their counterparts (70,77,79). The findings can be explained by the fact that increased nicotine uptake in the body reduces muscle glucose intake, leading to insulin resistance. In addition, oxidative stress and inflammation also increase the risk of DM (75).

5.4 Performance of the model for predicting risk for DM

This study found that the performance of risk factors such as the patient's age predicted DM diagnosis with moderate accuracy (AUC, 0.66) with a sensitivity of 56.0% and 76.0% specificity. Furthermore, other factors such as a Family history of DM (AUC, 0.62) and Waist circumference (AUC, 0.57) also predicted DM with a lower sensitivity of 31.3% and 39.3%, respectively. Furthermore, when we used risk scoring tools, those with a risk score cut-off value of more than or equal to three were significantly associated with a higher TBDM co-morbidity rate. Moreover, the performance of risk scoring tools with a risk score of >= three on predicting DM on the model showed better accuracy (AUC,0.68) with a sensitivity of 73.3% and 63.1% specificity. A similar study in Ethiopia found that screened TB patients with a risk score of >=5 were three times more likely to have abnormal blood glucose measurements (80). The difference in this Ethiopian study was that they added hypertension as a risk factor, and the risk scoring tool used was validated in a non-TB population in Korea. The performance of the above risk scoring tool, which was used in the Ethiopian study, yielded sensitivity, specificity, and AUC of 81%, 54%, and 0.73, respectively, in detecting DM (80,81). The above Ethiopian study was the only study in Ethiopia that tried to predict the diagnosis of DM using a risk scoring tool. The current study provides much more broad and detailed information, including a larger sample size of tuberculosis patients.

This present study confirmed that having one or more DM symptoms is significantly associated with TB DM co-morbidity. An Ethiopian study by Jerene et al. revealed that symptomatic patients are three times more likely to develop DM (82). A study in Dar es Salaam also found that having any symptoms suggestive of diabetes increased the odds of having DM 1.89 times (52). In this current study, individual DM symptoms have an AUC of less than 0.50, indicating the lowest predictive accuracy in the prediction model. However, the presence of any of the symptoms predicted diabetes with moderate accuracy (AUC, 0.64), 64.7 sensitivity, and 63.8 specificity.

This present study found that when symptoms were combined with risk scoring, the model's predictive value of DM diagnosis increased, increasing sensitivity to 88.3 percent with (AUC, 0.70) but decreasing specificity to 41.9 percent. One study done in the Netherlands in 1997 tried to see a combination of symptom and risk questionnaires to predict undiagnosed DM. Other symptoms added in addition to those used in this study were "pain and shortness of breath while walking, frequent thirst, sex of the patient, use of antihypertensive drugs, and not using a bicycle for transportation.". This symptom-risk questionnaire had an AUC of 0.80 with a sensitivity of 72% and specificity of 56% (82). This disparity in performance could be attributed to differences in the study population as well as the use of different cut-off points. A risk score developed in one population will perform worse in another when used in a completely different population. Most risk scoring systems validated and used to predict DM are in the general population. These vital risk scoring tools were developed and validated in Caucasian and Asian populations rather than African populations, making them difficult to adopt and use in the African context.

Another study by Glummer and colleagues used the Rotterdam risk score, including age, sex, use of antihypertensive medications, and BMI. They used the score to predict undiagnosed diabetes for more than eight ethnic populations, including Cameroon. The model performed well in the White population, with AUC (0.68), Sensitivity, and Specificity of 78 and 55 percent, respectively. The model's performance dropped with AUC, Sensitivity, and Specificity of 0.53, 16.7%, and 91%, respectively, which was explained by the different interaction between ethnicity and the predictor variables with DM (83). Both preceding studies were conducted in non-TB populations with poor performance in other ethnic populations. Our study showed promising findings with a combination of symptoms and risk scores which can be used for triaging tuberculosis patients for further workup for diabetes.

5.5 Relevance of the conceptual framework

The Conceptual Framework of TB-Diabetes co-infection used in this study explained that both diseases co-relate at a different level. The framework was used to analyse the first objective of our research: To identify common socio-demographic and clinical factors associated with a higher risk of being diagnosed with Diabetes mellitus among TB patients. It was most helpful to select variables from the primary data. Furthermore, using this framework helped to arrange the first objective's findings more coherently. Some of the framework's elements, such as marital status, locality, occupation, and socio-economic status relevant to explaining the TB-DM correlation, were not collected in the primary data, so they were not used. Two proxy variables were also used to replace co-morbidities and sedentary lifestyles. This would impact the research's capacity to be supported by a solid conceptual framework. Furthermore, factors such as a history of alcohol drinking, type of TB diagnosed, waist circumference measurement, and HIV co-infection could determine the co-occurrence of TB DM. If we consider such elements to add to the current framework, this conceptual framework might be more comprehensive.

5.6 Strength and limitations of the study

This study is one of the few studies that tried to see the performance of individual risk factors, symptoms, and their combination in predicting diabetes in TB patients. The study showed that the overall accuracy of the tool is promising and can be used to screen TB patients at the primary health care level. The current study provides much more information since the data enrolled a large number of study participants from both health centres and hospitals. It provides an overview of the TB/DM services provided.

The limitation of our study was that the primary data used was health facility data, and the study was conducted in Ethiopia's capital, Addis Ababa, so it did not represent the rural community. Even though the primary data was comprehensive, it would have been more helpful to see the associations if variables like residence, education level, occupation, and socio-economic status had been included. Individual measurement errors in waist circumference measurements are also possible. Some questions in the data were filled out through patients' self-reporting, so recall bias may be there. RBS and FBS tests were used to diagnose diabetes though they have lower sensitivity and specificity than glycated haemoglobin (HbA1c), which is the current recommended diagnostic test for DM.

6. CHAPTER SIX

6.1 Conclusions

This study provides important insights into the performance of risk scoring tools combined with clinical symptoms in predicting TB patients at higher risk of DM. The study also provides information about socio-demographic and clinical factors associated with a higher risk of being diagnosed with Diabetes mellitus among TB patients.

Undiagnosed DM was a common problem among patients receiving TB treatment in Addis Ababa. This may be attributed to the fact that most of the TB patients had non-specific symptoms that overlap with symptoms of the underlying disease. As a result, patients remain unrecognized and undiagnosed. This can have undesirable consequences for the patients as DM is associated with poor treatment outcomes for TB patients. This all adds up to implicating the need for screening all TB patients for DM through their first contact with the health system, if possible, before initiation of treatment. This requires the attention of health policymakers, as it has been demonstrated that this problem persists in African countries where tuberculosis is prevalent.

Simplified risk scoring tools such as the one used in this study can be helpful to aid in the early identification of patients at higher risk of DM. Factors associated with a higher DM co-morbidity rate among screened TB patients were those with a family history of DM, older age groups who are >40, those with a higher risk score >=3, and those with one or more symptoms suggestive of DM. In addition, having a larger waist circumference measurement and a smoking and alcohol drinking history were significantly associated with DM within the TB clusters. Some of These factors mentioned above were shown to be interrelated with both TB and DM in the framework that was used in this study. The two strongest predictors of DM were having a family history of diabetes and being over the age of 40. As a result, in a resource-constrained setting, a community screening system should focus on TB patients with these risk factors.

The performance of each individual DM symptom was also assessed in predicting DM on the prediction model, which showed (AUC< 0.50) the lowest predictive accuracy in the model. However, the presence of any of the symptoms predicted diabetes with moderate accuracy. Age of the patient, Family history of DM, and Waist circumference measurement showed moderate accuracy in the prediction model. Furthermore, the performance of Risk scoring tools on predicting DM with a risk score of >= three showed better accuracy on the model (AUC,0.68). Finally, when symptoms were combined with risk scoring, the model's predictive value of predicting DM diagnosis increased, increasing sensitivity to 88.3 percent and (AUC, 0.70) but decreasing specificity to 41.9 percent. To conclude, based on the findings of this study, every TB patient should be assessed for diabetes, using a combination of risk scoring tools and symptoms guide to assist in the timely identification of undiagnosed diabetes. This will improve TB patients' outcomes and quality of life.

6.2 Recommendations

In accordance with the results of this study, the following recommendations were made to justify the need for routine screening for diabetes in TB patients in order to improve patient outcomes and quality of care.

Recommendation to the ministry of health, policymakers, donors, and national TB & NCDs programs

- Our findings show that undetected diabetes is much more common in screened TB patients, highlighting the importance of using an effective screening system for TB patients to detect diabetes. The already organized infrastructure and program for TB control in the peripheral DOT (directly observed therapy) TB clinics and hospitals can be used as an entry point to screen for DM in TB patients before initiation of treatment. This continuous supervision for treatment and patent support service can also be used as an opportunity for patient health education and clinical management site for TBDM co-morbid patients. To accomplish this, the Government should first assemble an organizing body to ensure effective collaboration among existing TB and DM programs. This coordinating body had to be established at the national, regional, and district levels. This formed body should include critical stakeholders, such as sectors of the Ministry of Health in charge of TB and diabetes control programs, healthcare facilities, civil society, healthcare insurance, the private sector, health workers' professional associations, and diabetic and tuberculosis patients' groups. This joint body should have to devise a joint plan to incorporate this national routine screening of TB patients for DM and reflect upon it according to the national guideline or plan.

- Our study also discovered that because of the overlap of symptoms between TB and DM, first-line health workers should be informed and trained to have a high index of suspension. According to the findings in this study, due to the presentation of TB patients with unspecific symptoms, in a Resource-limited country like Ethiopia, it may be difficult to screen all patients. As a result, a targeted screening approach can be made considering the high-risk group: those with a family history of DM and those older than 40 years. The ministry of health should work and involve the joint collaborative body, which is formed to strengthen the already existing clinical guidelines by giving a step-by-step guide on how to screen patients and a clear description of patient presentation and management. This can be done by giving refresher training for health workers, putting posters and fliers in the TB clinics, and creating mass media platforms to increase awareness among health care workers and in the community.

- The main reason for not implementing routine screening in health facilities in Ethiopia was a lack of a simple tool and the lack of a standard blood test kit (RBS, FBS). According to our research findings, using a combination of symptom and risk scoring tools accurately predicted DM diagnosis in TB patients with the highest risk of developing DM. As a result, this simplified tool can be used in all health facilities that provide TB services to triage patients who are at risk of developing diabetes in the future. After the screening, identified patients can be sent for laboratory confirmation of DM before initiating anti-TB treatment. Since routine blood tests for DM in all TB clinics are not currently being tested, the ministry of health should work with the national joint coordinating body to implement this feasible and cost-effective strategy.

- Funding is necessary to implement this routine testing at a national level. As a result, first, the national Government should try to use domestic sources and, in case of need, be supported by external donors and non-profit organizations (NGOs) as per the national strategic plan. This generated fund can be used to mobilize resources for further standardization and validation of this screening tool to implement it at a national level in the future. Funding is also required for continuous provision and availability of routine Blood tests and HbA1c since it is the recommended diagnostic test for DM in TB patients.

- According to our findings, having a larger waist circumference, smoking history, and drinking are all associated with TBDM co-morbidity. As a result, community engagement through partnership in raising community awareness and providing counselling as part of primary prevention and lifestyle modification. Moreover, involving the community can help in TBDM patient case finding, care provision, and patient support. The Government can also use the already existing Health extension workers at the primary care level to strengthen this community partnership and engagement. To summarize, Advocacy using already structured TB control programs to improve DM primary prevention is recommended.

- The already structured monitoring strategy on TB control programs can be used for monitoring and evaluating the progress of this routine screening, and the Ministry of Health should work with regional health bureaus to see this through.

- The Government should show complete political commitment and support for the implementation of this screening tool because it will help achieve the end-of-TB strategy goal and improve the quality of life and outcomes for TB patients.

Recommendations for future research

- This current study was conducted in Addis Ababa, Ethiopia's capital city. For this reason, larger-scale studies involving rural and urban areas would give a better perspective. Prospective observational cohort study of newly diagnosed tuberculosis patients who begin anti-TB medication and are screened for diabetes could give broad information. This might provide data on the national prevalence of undiagnosed diabetes and contribute to determining which type of diabetes (type 1 or type 2 DM) is prevalent in the Ethiopian context. The relative outcome of TBDM co-morbid patients at the end of treatment can also be studied.
- **Other priority study topics include:**

    - Operational research focusing on how to effectively implement routine screening of TB patients for DM on already implemented DOTS TB control programs in some selected cities of Ethiopia. This will provide information on how to proceed with the next step of the implementation procedure.

    - Qualitative research on the assessment of the healthcare system challenges, which includes health workers' and donors' perspectives on implementing this routine screening. It will give in-depth insight into the possible opportunities and will provide answers about the feasibility of the screening program.

    - A cross-sectional population-based study to see further the performance and validation of the risk scoring tools in other African populations.

- A prospective observational cohort study for the impact of this routine screening of TB patients for DM on the treatment outcome of TB patients. It will help answer questions such as did the early diagnosis and co-management of DM improve the outcome of TB patients.

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APPENDICES

Appendix A: TB patient screening procedure

Screening of DM in patients with confirmed TB diagnosis was done in the following steps. Each consenting tuberculosis patient visiting the health facility, irrespective of their treatment stage, was asked about the current DM diagnosis and risk factors for DM with the standardized Diabetes risk scoring checklist see figure 7 below. The health worker checked the presence of clinical symptoms based on questioner checklist prepared by the team and categorized the patients as 'symptomatic' or 'asymptomatic.' To diagnose DM, Random Blood Sugar (RBS) of ≥ 200 gm/dl or Fasting Blood Sugar (FBS) of ≥ 126 gm/dl on two separate occasions or medical facility records showing the previous diagnosis of DM were taken.

DIABETES RISK SCORING CHECKLIST

SN	Risk factor		Weight
1	Family history of Diabeteses (any of parent/sibling)		
		No	0
		Yes	2
	Age group		
		<35 year	0
		35-44 year	2
		>=45 year	3
2	Waist circumference, taken at umbilicus (Men/Women)		
		<84/77cm	0
		85-89.9/77-83.9 cm	2
		>=90/84 cm	3
3	Smoking history		
		Never	0
		Ex-smoker	1
		Current smoker	2
4	Alcohol use daily, irrespective of the type		
		Never or <1 drink per day	0
		1-4.9 drinks per day	1
		>=5 drinks per day	2
	Total score: 0-12		

Figure 7: Diabetes risk scoring checklist (Adapted from Jerene D, 2022) (37)