The Influence of Diabetes Mellitus on Treatment Outcomes of Patients with Pulmonary Tuberculosis

A Retrospective Cohort Study

Master of Public Health Integrating Experience Project

Professional Publication Framework

by

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Yerevan, 2015

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LIST OF ABBREVIATIONS

AFB	Aid-fast bacilli
DM	Diabetes mellitus
HIV	Human immunodeficiency virus
IRB	Institutional Review Board
MDR	Multidrug-resistant
NTCC	National Tuberculosis Control Center
NIH	National Institute of Health
PTB	Pulmonary tuberculosis
SES	Socio economic status
SEL	Socio economic level
SS+/-	Sputum smear-positive/negative
TB	Tuberculosis
WHO	World Health Organization
XDR	Extensively drug resistant

ACKNOWLEDGMENTS

I want to express my deep gratitude to my adviser Dr. Varduhi Petrosyan for her priceless influence on my way of professional development. Her guidance, comments and advice made me explore and reveal the bests in me.

I am very grateful to my adviser Dr. Lusine Abrahamyan for enlarging my understanding of statistical analysis and techniques.

I wish to thank Dr. Tsovinar Harutyunyan for her dedicated and exemplary teaching, as well as her valuable comments.

I do appreciate the CHSR staff for being encouraging and supportive during two years of my study. Special thanks to Nune Truzyan for the time she dedicated to listening and sharing my concerns, and helping me throughout the project.

This project could not be accomplished without the support of the National TB Control Center (NTCC). Special thanks to NTCC director Mr. Armen Hayrapetyan, Drs. Karapet Davtyan and Hayk Davtyan. Thanks to all those TB health care specialists who were willing to help me during the data collection period.

Finally I am thankful to my classmate Zaruhi Grigoryan for her trust and motivation toward my work, and her valuable contribution to the data collection of the project.

ABSTRACT

Introduction: Tuberculosis (TB) is a communicable disease caused by the Mycobacterium tuberculosis. It is one of the ten leading causes of death worldwide. There were 8.6 million new cases of TB and 1.3 million TB related deaths in 2012. Epidemiological studies found that among patients infected with TB and having diabetes mellitus (DM), TB treatment has poor outcomes. Diabetes has been associated with an increased risk of failed TB treatment and death.

Objective: To investigate the impact of DM on treatment outcomes among pulmonary TB (PTB) patients in Yerevan, Armenia after adjusting for confounding factors.

Methods: The research team used a retrospective cohort study design to address the research question of interest. The study population included all adult patients registered in Yerevan TB care outpatient facilities whose treatment outcomes were recorded in the database of the Armenian National Tuberculosis Control Center for the period January 1, 2013 to December 31, 2014. The study had two comparison groups: TB patients who had diabetes mellitus were in the exposed group and those without DM were in the non-exposed group. Electronic database was reviewed to obtain the list of all eligible study population and necessary variables. Information on comorbidities, height and weight of patients were extracted from medical records of patients in eight outpatient TB facilities and prison hospital.

Results: In the sample of 621 patients 36 had diabetes (5.8%). The prevalence of DM among the TB patients was 2.2 times higher than the prevalence of DM in the general population in Armenia. The odds of failure treatment outcome was higher among TB patients with DM compared to TB patients without DM (OR=9.49; 95% CI: 2.65-33.98, p=0.001) after adjusting for confounding.

Conclusion: The study found that the prevalence of DM was much higher among the TB

patients in Armenia than the general public and having DM negatively influenced the TB treatment outcomes. TB patients with DM were more likely to fail their TB treatment than TB patients without DM. The result of this first investigation in Armenia to evaluate the association between DM and TB treatment outcome was consistent with the international literature.

INTRODUCTION

1. Literature review

1.1 Epidemiology of Tuberculosis

Tuberculosis (TB) is a communicable disease caused by the *Mycobacterium tuberculosis.*[1,2] Usually TB occurs in the lungs (pulmonary TB or PTB) or other organs (extra pulmonary TB) such as skin, bones, kidney, and liver.[2] Because of poor treatment practices TB may become drug resistant which has mono-resistant, poly-resistant, multidrug- resistant (MDR-TB) and extensively drug- resistant (XDR-TB) types.[3]

TB is one of the ten leading causes of death worldwide.[4] Most TB cases and deaths occur among men, but it remains one of the top three killers of women in the world.[5,6] World Health Organization (WHO) 2013 Global Tuberculosis report indicates that the worldwide incidence rate is reducing since 2001.[5] The rate of decrease from 2011-2012 was 2%, and the mortality rate has been reduced by 45% since 1990.[5] There were 8.6 million new cases of TB and 1.3 million TB related deaths in 2012[5]. The incidence and mortality rates vary between countries and WHO regions, which is mostly related to the social economic factors and migration patterns.[7] The lowest incidence rates are in high income countries including Western European countries, Canada, USA, and Australia.[5] The highest rates are in Asia and Africa; in particular, 26% and 12% of the global incident cases are in India and China, respectively.[5] The incidence is also high in South Africa, Indonesia and Nigeria. The African region has approximately 25% of the world's TB cases.[5] In WHO European region, TB incidence vary from 2-119 per 100 000 population among countries.[8] The majority of the cases occur in 18 high TB priority countries (including Armenia): 87% of incident cases, 87% of prevalent cases, 92% of mortality and 99% of the MDR TB.[8]

The key determinants for developing TB are socio-economic status (SES), household crowding, undernutrition, and conditions and diseases that lead to a weak immune system and increased susceptibility to infection such as diabetes, HIV, alcohol abuse, smoking, homelessness and being a prisoner.[6,7,9] Socio-economic factors have been widely researched.[10,11]

TB risk is higher in populations with low SES than those with high.[10,12,11] HIV is one of the greatest risk factors for TB. It has been estimated by WHO, that people with HIV are at 20-times higher risk to develop TB than people without HIV.[13] In 2011, globally, 1.1 million people living with HIV developed TB and 430 000 died because of TB.[13] Several studies also investigated possible associations between smoking, alcohol use and TB.[14,15,16,17] Evidence shows that people who smoke are more likely to have a positive tuberculin skin test, to have active TB and to die from TB, compared with people who do not smoke.[14] Regardless of alcohol use and other socio economic risk factors, smoking increases the risk of developing TB more than 2.5 times. A systematic review points out that heavy alcohol use is another risk factor for incidence of TB.[17]

Epidemiological studies found an association between diabetes mellitus (DM) and development of TB.[18,19] A systematic review of 13 observational studies showed that people with DM were at three times higher risk to develop TB than people without.[19] Diabetes itself is a global health challenge. About 8.3% of the population in the world have diabetes.[20] It is the fifth leading cause of death in most high income countries.[20] The prevalence of diabetes continues to rise. It is estimated that by 2035, about 592 million people, or one adult in 10 will have diabetes.[20] The confluence of these two epidemics may increase the incidence of TB, especially in the countries where high prevalence of TB and DM exist.

A number of investigations have shown that among patients infected with TB and having DM, TB treatment has poor outcomes.[21,22,23] Diabetes has been associated with an increased risk of failed TB treatment.[24] A systematic review of 33 studies concluded that diabetes increases the risk of failed treatment and death among patients with tuberculosis (risk ratio (RR) =1.69 (95% CI 1.36 to 2.12).[23] A retrospective cohort study of patients with active, culture-confirmed TB was conducted to assess the impact of DM on TB treatment outcomes.[21] Among 297 patients included in the study, 14% had DM. The final results suggested that patients with diabetes had 6.5 times higher odds of death compared to those without DM.[21] However, there is an inconsistency in the literature. A recent study, for example, reported similar treatment outcomes between PTB patients with and without DM.[25] Another study reported that PTB patients with diabetes had higher sputum conversion rates compared with PTB patients without diabetes at the end of the third month of treatment.[25] However, registered success in sputum conversion rates was preceded by higher pre-treatment bacterial load,[25] which itself is an interesting phenomenon to investigate. Another study identified that the PTB DM patients were more likely to be sputum smear positive (SS+) at the time of diagnosis and remain positive at the end of the first two months of the treatment.[26]

Considerable evidence demonstrates that DM impairs immune responses that body needs to resist to the Micobacterium Tuberculosis infection thus increasing susceptibility to develop active TB.[27] However, the mechanism how DM negatively influences on TB treatment is controversial. Recent studies showed that patients with diabetes had a risk for poor drug absorption including anti-tuberculosis drugs.[28] Particularly rifampicin was lower among TB patient with DM compared with TB patients without DM.[28] In contrast to this, another research stated that there is no difference between pharmacokinetics of antituberculosis

drugs between patients with and without DM and that the low exposure of rifampicin might be related with increased body weight.[29]

The association of DM and drug resistant types of TB is in dispute and not well researched yet. In one of the studies diabetes is reported as one of the risk factors for poor TB treatment outcome among MDR and XDR TB patients,[30] while another research found no significant association between DM and DR TB treatment outcomes.[26]

A number of potentially modifiable and non-modifiable risk factors have been identified that can also lead to unsuccessful TB treatment outcome.[31] These factors include age, gender, HIV/AIDS, DR TB, having cancer, SES, including unemployment, homelessness and malnutrition, being underweight, previous history of TB, alcoholism and smoking.[15,31,32,33] MDR TB is also shown to be a risk factor to fail the treatment of tuberculosis.[32,33] Higher lost to follow up rates are associated with being male and having previous history of TB treatment.[32,34] Males have twice higher risk to be lost to follow up than females.[35] Elderly people are more likely to present unfavourable outcomes compared with younger people.[36]

1.2 Situation in Armenia

TB is one of the major public health problems in Armenia. According to the WHO, Armenia is among the high-priority countries; it is one of the 27 high MDR-TB burden countries in the world ranked 14 in the list.[37] In 2012, in Armenia the incidence of TB has been reported to be 52 per 100 000 population, and the prevalence rate 79 per 100 000.[38] Among smear-positive TB patients in the pulmonary form of the disease the success rate of treatment is below the WHO target of 85%.[37]

Diabetes is the third leading cause of death in Armenia and reached 8.87% of total deaths in 2011.[39] According to the National Institute of Health (NIH) of the Republic of Armenia (RA), the incidence of DM among 15+ year old people has increased from 96.1 to 264.9 per 100 000 population during 2000 to 2010.[40] Among the population 15 years and over the prevalence of diabetes was 2603.9 per 100 000 population in 2013.[41] The situation is also burdened due to lack of appropriate care management at primary care level and lack of appropriate self-management among diabetes patients in Armenia.[42]

No prior study investigated the association of TB and DM in Armenia. An investigation of the association of diabetes mellitus and TB treatment outcome is very important and would help to improve the care and treatment outcomes of patients with DM and TB.

1.3 Aims and Research Questions of the Study

The aim of the study was to assess the association of diabetes mellitus and TB treatment outcome.

The objectives of the study were:

- To estimate the prevalence of diabetes mellitus among patients with PTB in Yerevan, Armenia.
- To investigate the impact of DM on treatment outcome among PTB patients in Yerevan, Armenia after adjusting for confounding factors.

Research Question: Does the outcome of the TB treatment differ among pulmonary TB patients (18 and over) with type 1 and type 2 DM compared to the TB patients (18 and over) without DM after adjusting for other factors that could influence the TB treatment outcome in Yerevan, Armenia.

2. METHODS

2.1 Study Design

The retrospective cohort study design was considered the most appropriate for this investigation. Using already an existing database and medical records was comparatively cost effective and not time consuming. The study had two comparison groups: TB patients who had diabetes mellitus were in the exposed group and those without DM were in the non-exposed group. The TB patients were considered having diabetes if they had a diagnosis of DM recorded in their medical cards.

Two groups of patients with and without diabetes had been followed from the day of diagnosis with TB to the day of their treatment outcome.

2.2 Study Population

The target population for the study were adults (18+ years old) with pulmonary TB. The study population included all adult patients registered in Yerevan outpatient TB care facilities whose treatment outcomes were recorded in the database of the Armenian National Tuberculosis Control Center (NTCC) for the period January 1, 2013 to December 31, 2014. The NTCC electronic database contained diagnosis and treatment related information for all TB cases identified at all inpatient and TB outpatient center in Armenia since 2011. The exclusion criteria for the study population were: missing or incomplete medical record, being transferred out of Yerevan during the TB treatment period, as the follow up of their entire treatment period was not possible.

Armenia follows the forth WHO treatment guideline for national TB programs[43] – all drug sensitive (regular) TB patients receive two months of intensive TB treatment at a TB inpatient

care facility followed by four months of Directly Observed Therapy (DOT) at a TB outpatient center. There are exceptions for sputum smear-negative (SS-) patients who may receive the intensive phase of the treatment in TB outpatient centers. Patients with DR TB (including MDR and XDR) have a treatment lasting 21-24 months including both the intensive and ambulatory treatment phases. [43]

2.3 Study Settings and Data Collection

For the feasibility reasons study setting was narrowed down only to Yerevan city. The data collection consisted of two main stages and conducted in the NTCC office, eight Yerevan TB outpatient centers and the Prison hospital of Yerevan. During the first stage, the study team had reviewed the NTCC electronic database to obtain the list of all eligible TB cases and the necessary variables (Appendix 2) and imported them into the SPSS database. During the second stage, the student investigator collected information on comorbidities and weight (Appendix 2) of each eligible TB case from their medical records in TB outpatient centers and the prison hospital. The heights of the patients were extracted from the online E-TB manager program, as most of the medical cards did not contain this data. The student investigator has developed a data abstraction form in order to abstract the data from medical records (Appendix 3).

2.4 Data Sources

The electronic database (MS Access software) of the NTCC contains information on patients' names, demographic characteristics, classification of cases, sputum smear status and the treatment outcome. The data for electronic database are collected from the journals of TB outpatient centers. Every three months the health care providers of the TB outpatient centers provide the hard copies of the journals that contain quarterly data (data for the previous three months) to the NTPCO, which the NTPCO data entry officer enters into the electronic database.

The journal forms are standard WHO recommended forms[44] and are used in all TB outpatient centers throughout Armenia. The NTPCO Monitoring and Evaluation (M&E) department is in charge of the database. The head of the M&E department and the data management specialist are responsible for the data collection, monitoring and update of the database. The NTCC updates the information on DR TB cases once a week and drug sensitive cases every three months. Though the NTPCO does not have a special quality assessment system, they ensure the validity and quality of data by checking the same information on each single TB case through different sources: inpatient and outpatient centers, as well as through TB outpatient centers monitoring visits. The WHO Mission evaluated the NTPCO database in August 2014.[45] They indicated that the database is designed in a way that prevents errors during the data entry process. Although some minor inconsistency exist, most of the variables are 100% complete, valid and internally consistent.[45]

2.5 Study Variables

The dependent variables of the study was the TB treatment outcome defined by the WHO (see Appendix 1): successful treatment (cured or treatment completed) and treatment failed, died, and lost to follow up.[44] Not evaluated was not included among the study outcome variables as the NTCC database did not have any case with not evaluated outcome.

The main independent variable of interest was the presence or absence of diabetes. The control variables were age, gender, weight, having HIV/AIDS, type of TB (drug sensitive or drug resistant), having a previous TB treatment history, the length of DM, having combined form of TB (pulmonary and extra-pulmonary), having cancer, hepatitis C, liver cirrhosis, CVDs, pneumonia and renal failure.[46,47,36,48,32,49,50,51]

2.6 Statistical analysis

The student investigator transferred data from NTCC electronic database into the SPSS, and entered data that were extracted during the second stage of the data collection. Data cleaning was conducted using frequencies and sort command for each variable to find missing values and/or unusual patterns of data and addressed the issues.

The difference of baseline characteristics between diabetic and non-diabetic groups were compared using independent samples t-test for continuous variables (after testing for assumptions) and chi-square for binary variables.

First, binary logistic regression was conducted to test the associations between the main independent and dependent variables. Then, multivariable logistic regression was used to construct the final model.

3. ETHICAL CONSIDERATIONS

The Institutional Review Board (IRB) of the American University of Armenia approved the study protocol. The study team obtained two permissions from the National Tuberculosis Control Center in Armenia to access the electronic database and medical cards of outpatient TB care facilities and from the Ministry of Justice to access the medical records of the prison hospital in Yerevan.

4. RESULTS

4.1 Administrative Results

The total number of eligible cases was 839 and included patients from nine outpatients TB facilities and the prison hospital in Yerevan. One of the TB facilities that had the medical

records of 159 patients refused to participate in the study resulting in a response rate of 81%. During the second stage of data collection 12 patients were excluded because in the beginning of their TB treatment they were transferred out of Yerevan or Armenia and therefore were not eligible for the study; and 47 patients were excluded because their medical records were missing or incomplete (the records were mainly lost during the restructuring of TB outpatient facilities in Yerevan in 2014). The final sample size included 621 patients. The student investigator conducted the chart review and data abstraction from February 20 to April 6, 2015.

4.2 Descriptive Statistics

In the sample of 621 patients 36 had diabetes (5.8%). The prevalence of DM among the TB patients was 2.2 times higher than the prevalence of DM in the general population in Armenia (2.6%) ($P < 0.001$) [41].

Table 1 presents baseline characteristics of the patients by their diabetes status. Patients in both groups were statistically significantly different only with respect to their age and weight. Patients with diabetes were older (mean age 52 versus 46, $P = 0.013$) and heavier than those without DM (mean weight 65.6kg versus 61.3kg, $P = 0.002$). The majority of patients in both diabetic and non-diabetic groups were male (81% and 82%, respectively) and had drug sensitive (DST) type of TB (86% and 85%, respectively). HIV prevalence in diabetic and non-diabetic groups was 2.8% and 6.2%, respectively. The previous history of TB treatment in diabetic and non-diabetic groups was 25% and 36%, respectively. SS+ rate in the beginning of the treatment in diabetic group was 50% and in non-diabetic group 31%. The combined form of TB in diabetic and non-diabetic groups was 2.8% and 2.4%, respectively.

4.3 Simple Logistic Regression

For the final analysis, we separated the cases with death and lost to follow-up as the risk factors associated with these treatment outcome categories are different (Table 4 & 5). In addition, when we calculated power for the model where the P among the groups represented all unsuccessful categories combined (failure, death and lost to follow-up) the estimated power was 0.41. The modified outcome variable has two options: treatment failure or success (cured and completed).[52] Table 2 presents the results of simple logistic regression analysis. The crude OR of the association between having DM and treatment failure outcome was 6.74 (95% CI: 2.00-22.62, P=0.002), suggesting that the odds of failing TB treatment was 6.74 times higher among TB patients with diabetes compared with TB patients without diabetes without adjusting for confounding.

4.4 Testing for Confounding

Table 3 shows the results of simple logistic regression analyses checking associations between the TB treatment outcome and DM status with other independent variables to identify confounding relationships. Age and weight were found to have a statistically significant association with having diabetes. However, only weight was associated with the dependent variable, hence confounding the association between the TB treatment outcome and DM status. The other independent variables did not confound the relationship between DM status and TB treatment outcome variables.

4.5 Multivariable Logistic Regression

The final multivariable logistic regression included the only variable that was confounding the relationship between DM and TB treatment outcome (Table 4). After adjusting for weight the OR of the association of DM and failure treatment outcome was 9.49 (CI: 2.65-33.98),

suggesting that the odds of failing TB treatment among patients with DM were 9.49 times higher compared to TB patients without DM after adjusting for confounders.

4.6 Predictive Model: Multiple Logistic Regression

The study team created a predictive model where they included variables associated with both independent and dependent variables with P value at 0.25 and lower[53] and variables that theory suggested to be related to the main outcome variable (Table 7). This included variables for weight, gander, age, SS status, HIV status, DR TB and having previous TB treatment history.

All the independent variables that were included in the final model were tested for multicollinearity using the VIF (variance inflation factor) statistics.[54] The analysis found no multicollinearity between the covariates. To evaluate the logistic regression model the Hosmer - Lemeshow goodness-of-fit test was used.[53] The Hosmer-Lemeshow test statistics was 3.22 (Prob > chi2 = 0.92) indicating acceptable calibration (Table 5). After adjusting for those factors the odds of failing TB treatment was 14.31 among TB patients with diabetes compared with TB patients without diabetes (95% CI: 3.45-59.38).

4.7 Power Analysis

The power was calculated based on two-sample comparison of proportions[55] where P_1 was the proportion of adverse outcome in the unexposed group and P_2 the proportion of the adverse outcome in the exposed group, n_1 and n_2 represented the numbers of unexposed and exposed groups respectively. When the failure treatment outcome was considered as the P among the groups, n_1 and n_2 were 495 and 30 respectively, with the level of significance 0.05 (one sided test) the estimated power was 0.75.

5. DISCUSSION

5.1 Main Findings

The presented retrospective cohort study investigated the association of DM and TB treatment outcome among adult patients with pulmonary TB registered in outpatient TB facilities and prison hospital in Yerevan. Similar to many other studies we found that the prevalence of DM was higher (2.2 times) among TB patients than the DM prevalence among the general population.[19,56] The prevalence of DM reported in our study (5.8%) was lower than other researchers reported for other countries.[18] This could be explained by higher prevalence of DM in those countries, where those studies were conducted (India, Indonesia and Mexico) [18,26] or varying diagnostic techniques that were used in the studies.[57,58]

The main hypothesis of our investigation whether DM was associated with less favorable outcome of TB treatment was supported by our research. The findings showed that TB patients with DM had higher probability to fail their TB treatment than TB patients without DM. Only the weight of the patients in the beginning of their TB treatment was confounding the relationship between DM and TB treatment outcome; after adjusting for this confounder the OR was 9.49 (95% CI: 2.65-33.98, P=0.001), which was higher than previously reported risk of TB treatment failure in the literature.[22,23,52] In the final predictive model we included all factors that according to the literature could be predictors for the outcome variable. The independent risk of failure treatment among DM patients after adjusting for other predictors was 14.33. Similar to our findings, a recent large prospective cohort study conducted in Southern Mexico revealed significantly higher rate of failure among DM patients than the failure rate among non DM patients.[52] This association between DM and TB possesses risk especially to the populations which carry high burden of both DM and TB. As DM is estimated to increase rapidly and it is

moving from high to low income countries, it is very likely that DM will soon surpass HIV as the most important risk factor for TB.[59]

In contrast to other studies we did not find any association between death of TB patients and DM.[21,23] The main predictors of death were other comorbidities rather than DM and HIV including cancer, CVDs, hepatitis C and combined form of TB that already had been identified by other research as predictors of death among TB patients.[49,50,52] We identified 9.5% lost to follow up among our study population. It is slightly higher than the rate of the lost to follow-up in similar studies reported to be 7.0-8.5%.[22,52] Our study, similar to others, did not detect difference in the lost to follow-up rates between the groups with and without DM.[22,52]

5.2 Limitations

The study revealed several limitations that should be considered. The type of medical cards varied between TB outpatient facilities and the way of recording information on comorbidities was different. Besides this limitation, it was impossible to control for some variables that based on the literature were related to the outcome variable of interest (SES, smoking status, alcohol and drug use, type of DM, length of DM, BMI and glucose level in the blood) since the information either was not available or the variable had more than 20% missing values.

5.3 Strengths

Our study was the first study designed to evaluate the relationship between DM and TB treatment outcome in Armenia. Only physician-established diagnoses were used to define cases with DM, HIV and other comorbidities and there were no self-reported diagnoses or a case defined by the study team. Another strength was the inclusion of all TB care facilities in Yerevan that provide outpatient TB care followed DOTs regimen (except one TB cabinet that

refused to participate in the study) and conducting a census of the target population. The sample size gave an opportunity to assess the association of DM and each TB treatment outcome category separately, which helped us to be more specific in our recommendations.

6. RECOMMENDATIONS

Based on the study results we would make the following recommendations for the NTBCC's consideration:

- To develop mechanisms to enforce the MOH guidelines for screening of DM patients for TB and TB patients for DM. TB care specialists should be encouraged to more attentively manage the TB treatment process among patients with DM.
- Future prospective studies need to evaluate the same hypothesis of the current study, however continuously collecting data on potential confounders that the current study missed such as length of DM, glucose level in the blood, alcohol, drug use and smoking status.
- Treatment guidelines might be revised to accurately address treatment of TB patients who have DM comorbidity.

7. CONCLUSIONS

The study found that the prevalence of DM was much higher among the TB patients in Armenia than the general public and having DM negatively influenced the TB treatment outcome. TB patients with DM were more likely to fail their TB treatment than TB patients without DM. This first investigation in Armenia to evaluate the association between DM and TB treatment outcome was consistent with the international literature.

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TABLES

Table 1. Baseline characteristics of study population

Characteristic	**%, Mean, SD**	**Total sample n=621**	**Patients with DM n = 36**	**Patients without DM n = 585**	**P value**
Age, years	Mean (SD) N	46.73 (16.31) 620	52.41 (13.09) 36	46.39 (16.43) 584	0.013
Weight (in the beginning of the treatment), kg	Mean (SD) N	61.85 (11.29) 599	67.53 (13.11) 34	61.51 (11.09) 565	0.002
Gender					
Male	% (n/N)	81.80 (508/621)	80.56 (29/36)	81.88 (479/585)	0.842
Female		18.20 (113/621)	19.44 (7/36)	18.12 (106/585)	
TB treatment outcome					
Successful (Cured and Completed)	% (n/N)	82.13 (510/621)	72.22 (26/36)	82.74 (484/585)	0.110
Death		5.96 (37/621)	8.33 (3/36)	5.81 (34/585)	0.535
Failure		2.42 (15/621)	11.11 (4/36)	1.88 (11/585)	0.008
Lost to follow-up		9.50 (59/621)	8.33 (3/36)	9.57 (56/585)	0.802
Type of TB					
DST	% (n/N)	84.70 (526/621)	86.11 (31/36)	84.62 (495/585)	0.809
DR		15.30 (95/621)	13.89 (5/36)	15.39 (90/585)	
TB treatment history					
New	% (n/N)	73.43 (456/620)	75.00 (27/36)	73.33 (429/585)	0.922
Previous history of TB treatment		26.57 (164/620)	25.00 (9/36)	26.67 (155/585)	
SS status					
SS+	% (n/N)	31.93 (198/620)	50.00 (18/36)	30.82 (180/584)	0.064
SS-		68.06 (422/620)	50.00 (18/36)	69.18 (404/584)	

HIV status					
HIV positive	% (n/N)	6.28 (39/621)	2.78 (1/36)	6.50 (38/585)	0.601
HIV negative		86.47 (537/621)	88.89 (32/36)	86.32 (505/585)	
HIV status unknown		7.25 (45/621)	8.33 (3/36)	7.18 (42/585)	
Time of DM diagnosis					
Newly diagnosed	% (n/N)	66.67 (12/18)			
Prior diagnosed		33.33 (6/18)			
Combined form of TB (pulmonary + extra pulmonary)	% (n/N)	2.42 (15/621)	2.78 (1/36)	2.39 (14/571)	0.886
Cancer	% (n/N)	1.94 (12/618)	0 (0/36)	2.06 (12/582)	0.228
Renal failure	% (n/N)	0.33 (2/610)	0 (0/36)	0.35 (2/574)	0.622
Cirrhosis	% (n/N)	0.32 (2/618)	5.56 (2/36)	0 (0/582)	0.001
Pneumonia	% (n/N)	0.97 (6/619)	0.00 (0/36)	1.03 (6/582)	0.395
Hepatitis C	% (n/N)	4.71 (29/616)	11.11 (4/36)	4.31 (25/580)	0.105
CVDs[1]	% (n/N)	4.32 (26/602)	4.23 (24/567)	5.71 (2/35)	0.617
Mental disorders	% (n/N)	4.37 (27/618)	2.78 (1/36)	4.47 (26/582)	0.608
Total number of comorbidities[2]	Mean (SD) N	0.31 (0.27-0.36) 613	0.57 (0.81) 35	0.30 (0.60) 578	0.183

DM=Diabetes mellitus; DST=Drug sensitive; DR=Drug resistant; HIV=human immunodeficiency virus; SS status= Sputum smear status; TB=Tuberculosis

[1] Cardiovascular diseases

[2] Excludes HIV and DM

Table 2. Simple Logistic Regression: TB treatment success (cured and completed) vs. failure

Factor	OR 95% CI	P-value
DM status	**6.74** (2.01-22.62)	0.002

Table 3. Risk factors associated with death

Factor	OR 95% CI	P-value
Combined form of TB	4.57 (1.05-7.92)	0.041
CVDs	14.74 (5.02-43.23)	<0.001
Cancer	9.29 (2.17-39.7)	0.003
Hepatitis C	6.27 (1.88-20.91)	0.003
Age	1.03 (1.00-1.06)	0.029
Weight	0.95 (0.92-0.99)	0.016
Type of TB	2.88 (1.05-7.92)	0.041

Table 4. Table 4. Risk factors associated with lost to follow up

Factor	OR 95% CI	P-value
Age	0.98 (0.96-0.99)	0.028
Gender	3.14 (1.21-8.20)	0.019
Type of TB	2.26 (1.18-4.33)	0.014

Table 5. Simple Logistic Regression: Testing for confounding

Factor	Association between TB treatment outcome and covariates	Association between DM status and covariates
	OR, (95% CI), P-value	**OR, (95% CI), P-value**
Age	0.99 (0.96-1.02) 0.531	**1.02** (1.00-1.05) 0.043
Weight	0.95 (0.90-1.00) 0.071	**1.04** (1.01-1.08) 0.004
Gender:		
Female	1.00	1.00
Male	0.97 (0.27-350) 0.961	0.79 (0.33-1.90) 0.599
Type of TB[3]		
DST	1.00	1.00
DR	2.39 (0.74-7.73) 0.145	0.69 (0.20-2.32) 0.545
Classification of TB case		
New	1.00	1.00
Previous TB treatment history	1.00 (0.89-1.12) 0.983	0.72 (0.29-1.79) 0.477
SS Status		
SS-	1.00	1.00
SS+	1.41 (0.91-2.18) 0.122	1.96 (0.93-4.11) 0.076
HIV status		
No	1.00	1.00
Yes	1.44 (0.18-11.52) 0.730	-
Unknown	2.34 (0.50-10.52) 0.278	1.57 (0.45-5.45) 0.481
Combined form of TB*	-	-
Cancer*	-	-
Renal failure*	-	-
Cirrhosis*	-	-
Pneumonia*	-	-
Hepatitis C	1.64 (0.21-13.06) 0.641	1.68 (0.37-7.54) 0.499

[3] TB=Tuberculosis; Cardiovascular diseases; HIV=human immunodeficiency virus; SS status= Sputum smear status

*For those variables, the data were insufficient to obtain interpretable results

Table 6. Multivariable Logistic Regression: TB treatment success (cured and completed) vs. failure

(n=511)

Factor	OR 95% CI	P-value
DM status	**9.49** (2.65-33.98)	0.001
Weight	0.94 (0.90-0.99)	0.028

Table 7. Predictive Model: TB treatment success (cured and completed) vs. failure

(n=510)

Factor	Unadjusted OR, 95% CI, P value	Adjusted Model OR, 95% CI, P value
Diabetes status	**6.77 (2.02-22.71) 0.002**	**14.31 (3.45-59.38) <0.000**
Weight*	0.95 (0.99-1.00) 0.071	0.92 (0.86-0.98) 0.013
Male**	0.98 (0.27-3.52) 0.970	2.61 (0.57-12.01) 0.219
Age**	0.99 (0.96-1.02) 0.534	0.98 (0.95-1.02) 0.313
SS +*	1.41 (0.91-2.18) 0.122	1.22 (0.69-2.13) 0.532
Previous history of TB treatment **	1.00 (0.90-1.12) 0.982	0.99 (0.89-1.11) 0.910
DR TB*	2.36 (0.73-7.63) 0.150	2.69 (0.70-10.37) 0.150
HIV/AIDS**		
Yes	1.45 (0.18-11.57) 0.727	2.04 (0.24-17.44) 0.516
Unknown	2.35 (0.51-10.97) 0.276	2.35 (0.46-13.14) 0.292

*Included in the model based on testing for confounding (p<0.25)

** Included in the model based on theory

APPENDICIES

Appendix 1: Treatment outcomes for TB patients according to WHO standards[44]

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of cured and treatment completed.

Appendix 2: Data dictionary

Variable	Type	Measure	Source of data
Age	Numeric (continues)	Years	NTC database
Gender	Binary	1=Male 2=Female	NTC database
Height*	Numeric (continues)	Cm	Med. Records
Weight*	Numeric (continues)	Kg	Med. Records
Date of diagnosis	Numeric (continues)	Year and month	NTC database
Classification of TB case	Nominal (binary)	1=New patient 2=Previously treated patient	NTC database
Type of TB	Nominal (binary)	1=DST 2=DR	NTC database
Sputum smear status*	Nominal (binary)	1=SS- 2=SS+	NTC database
Time to sputum conversion	Numeric (continues)	Months	NTC database
DM status*	Nominal (binary)	0=No 1=Yes	Med. Records
Type of DM	Nominal (binary)	1= type 1 2= type 2	Med. Records
Date of DM diagnosis	Numeric (continues)	Years	Med. Records
HIV status*	Nominal (binary)	0=No	Med. Records

		1=Yes	
Cancer status*	Nominal (binary)	0=No 1=Yes	Med. Records
CVD status	Nominal (binary)	0=No 1=Yes	Med. Records
History of CVD diseases (heart attack, stroke)	Nominal (binary)	0=No 1=Yes	Med. Records
Hypertention status	Nominal (binary)	0=No 1=Yes	Med. Records
Urological diseases	Nominal (binary)	0=No 1=Yes	Med. Records
Gastrointestinal diseases	Nominal (binary)	0=No 1=Yes	Med. Records
Respiratory diseases	Nominal (binary)	0=No 1=Yes	Med. Records
Gynecological diseases	Nominal (binary)	0=No 1=Yes	Med. Records
Other comorbidity status*	Nominal (binary)	0=No 1=Yes	Med. Records
Name of comorbidity	Nominal	Name of disease	Med. Records
TB treatment outcome	Nominal (polytomous)	1=Cured 2=Treatment completed	NTC database

		3=Failed 5=Died 6=Lost to follow up 7=Not evaluated	
Date of outcome	Numeric (continues)	Month	NTC database

*Defined at the time of diagnosis.

Appendix 3: Medical Record Data Abstraction Form

Administrative Data	
1. Patient ID_____	**2.** Outpatient TB facility ID _____
3. Height (cm) _____	
4. Weight (kg) _____	
Comorbidities	
5. DM status 1.□ Yes 2.□No 99.□ Unclear/missing **5a.** If yes the types of DM 1.□ 2.□ **5b.** Date of diagnosis_____d/m/y	
6. HIV status 1.□ Yes 2.□No 99.□ Unclear/missing	
7. Having any kind of cancer 1.□ Yes 2.□No 99.□ Unclear/missing **7a.** If yes type of the cancer _____ **7b.** Date of diagnosis_____d/m/y	
8. Having any kind of CVD disease 1.□ Yes 2.□No 99.□ Unclear/missing **8a.** If yes type of the CVD disease **8b**. Date of diagnosis_____d/m/y	
9. Having past history of any kind of CVD disease 1.□ Yes 2.□No 99.□ Unclear/missing **9a.** If yes type of the disease **9b.** Date of disease happen_____d/m/y	
10. Hypertension status 1.□ Yes 2.□No 99.□ Unclear/missing **10a.** If yes date of diagnosis_____d/m/y	
11. Having any kind of gastrointestinal disease 1.□ Yes 2.□No 99.□ Unclear/missing **11a.** If yes type of the disease_____	

11b. Date of diagnosis_____d/m/y
12. Having any kind of respiratory disease 1.□ Yes 2.□No 99.□ Unclear/missing **12a.** If yes type of the disease _____ **12b.** Date of diagnosis _____d/m/y
13. Having any kind of gynecological disease 1.□ Yes 2.□No 99.□ Unclear/missing **13a.** If yes type of the disease _____ **13b.** Date of diagnosis _____d/m/y
14. Other comorbidities 1.□ Yes 2.□No 99.□ Unclear/missing **14a**. If yes the name of disease (s) _____ _____ _____