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Diabetes Reduces the Rate of Sputum Culture Conversion in Patients with Newly Diagnosed Multidrug Resistant Tuberculosis

Argita Salindri

ABSTRACT

DIABETES REDUCES THE RATE OF SPUTUM CULTURE CONVERSION IN PATIENTS WITH NEWLY DIAGNOSED MULTIDRUG RESISTANT TUBERCULOSIS

by

ARGITA DYAH SALINDRI

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Background: Risk factors for acquired multidrug resistant tuberculosis (MDR TB) are well described but risk factors of primary MDR TB is understudied. We aimed to 1) assess risk factors for primary MDR TB, including diabetes, and 2) determine if diabetes reduced the rate of sputum culture conversion in patients with primary MDR TB.

Methods: From 2011-2014 we conducted a prospective cohort study at the National Center for TB and Lung Disease in Tbilisi, Georgia. Adult (≥35 years) patients with primary TB were eligible. MDR TB was defined as resistance to at least rifampicin and isoniazid. Patients with HbA1c ≥6.5% were defined to have diabetes. Polytomous regression was used to estimate the association of patient characteristics with drug resistance. Cox regression was used to compare the hazard rate of sputum culture conversion in patients with and without diabetes.

Results: Among 318 patients, 268 had drug susceptibility test results. Among patients with DST results, 19.4% was primary MDR TB and 13.4% had diabetes. In adjusted analyses, diabetes (aOR 2.51 95%CI 1.00 – 6.31) and lower socioeconomic status (aOR 3.51 95%CI 1.56 – 8.20) were associated with primary MDR TB. Among patients with primary MDR TB, 44 (84.6%) converted sputum cultures to negative. The hazard rate of sputum culture conversion was lower among patients with diabetes (aHR 0.34 95%CI 0.13 – 0.87) and among smokers (aHR 0.16 95%CI 0.04 – 0.61).

Conclusions: We found diabetes to be associated with an increased risk of primary MDR TB; both diabetes and smoking were associated with a decreased rate of sputum culture conversion.

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APPROVAL PAGE

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Author's Statement Page

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CHAPTER I

INTRODUCTION

1.1 Background

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) that most commonly affects the lungs (WHO, 2013). The estimated global incidence of TB is 9.0 million in 2013 and it caused 1.5 million deaths in the same year (WHO, 2014). Although the global incidence of tuberculosis has decreased over the past 10 years, global TB control now faces new challenges posed by of the emergence of drug-resistant strains (Gandhi et al., 2010).

Drug-resistant tuberculosis happens when MTB is resistant to anti-tuberculosis drug(s) and it is classified as either primary or acquired (Cohn, Bustreo, & Raviglione, 1997). Primary drug-resistant TB is when a drug-resistant strain of MTB infects a person who had no prior history of tuberculosis treatment for more than one month, while acquired drug resistant TB is defined as the presence of MTB resistant strain in a patient who have history of receiving anti-TB treatment for at least a month (WHO Geneva & IUATLD, 1998). There are several categories for drug-resistant tuberculosis: mono-drug resistant tuberculosis, poly-drug resistant tuberculosis, multi-drug resistant tuberculosis, and extensively-drug resistant tuberculosis (Vashakidze et al., 2009).

Multi-drug resistant TB (MDR TB), defined as MTB resistant to at least Rifampicin and Isoniazid, is a major challenge in the global TB control and the

proportion of global TB cases that are MDR TB continues to increases (Nachega & Chaisson, 2003). Approximately 450,000 cases of MDR TB were reported in 2013 (WHO, 2013b) and it increased to 480,000 cases in 2014 (WHO, 2014). Among MDR TB cases in 2013, 3.5% were new TB cases and 20.5% were previously treated TB (WHO, 2014). The increasing incidence of MDR is simultaneous to the growing prevalence of diabetes worldwide. In 2013, there were 382 million adults that had prevalent diabetes mellitus (Shaw, Sicree, & Zimmet, 2010).

An association between diabetes and tuberculosis has been hypothesized for centuries but has re-emerged with the rising global prevalence of diabetes (Dooley & Chaisson, 2009). Approximately 15-25% of active TB cases are attributable to diabetes (Lönnroth, Roglic, & Harries, 2014), but whether diabetes is a risk factor for MDR TB remains unclear. While the majority of MDR TB cases are due to primary infection (Gandhi et al., 2010), risk factors for MDR TB are only well described for acquired MDR TB. A deeper understanding of risk factors of primary MDR TB will help TB control programs to break the chain of transmission.

Previous studies reported that diabetes is associated with poor TB treatment outcomes (Dooley, Tang, Golub, Dorman, & Cronin, 2009), but whether diabetes affects MDR TB treatment is still underreported. Well established factors that are associated with poor MDR TB treatment include male sex (Johnston, Shahidi, Sadatsafavi, & Fitzgerald, 2009), alcohol use (Shin et al.,

2006), HIV infection, resistance to fluoroquinolone drugs, and previous history of tuberculosis (Kliiman & Altraja, 2009). A previous study reported that diabetes was associated with larger median time to initial sputum culture conversion (Holtz et al., 2006), but additional studies that investigated if diabetes is associated with delayed or longer time to sputum culture are needed. Understanding the role of diabetes in MDR TB treatment will help clinicians to design better clinical guidelines to improve the quality of patient management.

Our study was conducted in Country of Georgia, a former Soviet Republic with high prevalence and incidence of tuberculosis (Mdivani et al., 2008). It is also one of the European countries with the highest burden of MDR TB, with an overall prevalence of MDR TB of 15% in 2009 (Lomtadze et al., 2009). In 2014, the prevalence of MDR TB cases was estimated around 11% among new TB cases, and 38% among previously-treated TB cases (WHO, 2014).

1.2 Gap and Purpose of Study

Previous studies about MDR-TB focused on risk factors of acquired MDR-TB. Given that nearly 21% MDR-TB cases worldwide occur among those who had never been exposed to anti-TB treatment (WHO, 2014), it is important to describe risk factors for primary MDR-TB. This study focuses on newly diagnosed or primary MDR TB as the outcome of interest. Using a prospective cohort study, we hypothesized that diabetes is associated with primary MDR TB

and that diabetes would be associated with poor MDR-TB treatment outcomes. Therefore, the objective of this study is to:

1. Investigate factors associated with the occurrence of newly diagnosed MDR TB
2. Determine the association of diabetes with drug-resistant profile in newly diagnosed MDR TB
3. Investigate the association of diabetes with time to sputum culture conversion in newly diagnosed MDR TB patients

CHAPTER II

REVIEW OF LITERATURE

2.1 Multi-Drug Resistant Tuberculosis

Resistance to isoniazid and rifampin is caused by mutations in bacterial genes (Ormerod, 2005). Resistance to isoniazid is due to mutation in either *kat*G or *inh*A gene (Piatek et al., 2000). *Kat*G gene encodes for catalase-peroxidase, an enzyme that is associated with virulence factor for MTB as it can act as the protective agent against oxidative stress during the host infection process, mutation in this gene will retain *kat*G gene activity (Gagneux et al., 2006). *Inh*A gene encodes for InhA as part of FAS-II (fatty acid elongation system) which is required to synthesize mycolic acid, mutation in this gene will result in up-regulation of InhA (Gagneux et al., 2006). Resistance to rifampicin is associated with mutation in the *rpo*B gene, which involves RNA polymerase alterations and will lead to the substitution of some highly conserved aminoacids in the resistant strain (Telenti et al., 1993).

Treatment of MDR TB requires prolonged antibiotic use (approximately 18 months) uses second-line drugs which are less effective (Ormerod, 2005), yet more expensive (Liang et al., 2012). MDR TB treatment is also associated with serious adverse effects such as ototoxicity, vision impairment, depression, hepatitis, and renal failure (Marks et al., 2014). With MDR TB, patients typically remain infectious for longer periods of time, both in community and hospital

settings. Consequently, it is important to generate new information regarding risk factors for primary MDR TB in order to improve clinical guidelines for MDR TB patients' management and to prevent transmission both in community level and nosocomial settings.

2.2 Risk factors for newly diagnosed MDR TB

Studies to date mainly report risk factors for acquired MDR TB, the primary risk factor for acquired MDR TB is non-adherence and poor outcome of the previous TB treatment. Previous TB treatment was reported to have increased risk of MDR TB in several study sites like Belarus (Skrahina et al., 2013), Australia (Francis, Blyth, Colby, Fagan, & Waring, 2014), Uzbekistan (Ulmasova et al., 2013), and Baja, California (Bojorquez et al., 2013). Longer duration of previous TB treatment (more than 6 months), being treated more than three times using anti TB drugs, and the presence of adverse effect during TB treatment are also known to be associated with acquired MDR TB (Chen et al., 2013).

Demographic characteristics that were associated with acquired MDR TB include female gender (Atre, D'Souza, Vira, Chatterjee, & Mistry, 2011), being under 45 years old (Ulmasova et al., 2013), unemployment (Skrahina et al., 2013), history of imprisonment (Skrahina et al., 2013; Ulmasova et al., 2013), history of hospitalization in the last 10 years (Ulmasova et al., 2013). Alcohol abusers, smokers, and HIV co-infection were reported to increase the risk of MDR TB (Skrahina et al., 2013). Patients with history of drug abuse are also at increased

risk in developing MDR TB (Anderson et al., 2014). Travel history (ever stayed more than 3 months in high prevalence countries) was associated with the occurrence of MDR TB in western Australia (Francis, Blyth, Colby, Fagan, & Waring, 2014). The presence of cavity on chest radiography and the infection of Beijing strain are found to statistically significant with the occurrence of acquired MDR-TB (He et al., 2011).

Only a few studies to date have reported risk factors for primary MDR TB. The current established risk factor for primary MDR TB is close contact with MDR TB patients. There were only limited and outdated studies that investigated the close proximity with MDR TB patients and its relation with the occurrence of MDR TB. MDR TB outbreaks also occur at healthcare facilities as the result of nosocomial infection (Breathnach et al., 1998). In a study conducted in Rio de Janeiro, Brazil, tuberculosis occurred in 17 (7.8%) of 218 healthy people that had close contact with 64 MDR TB cases (index). Samples were collected from 13 of 17 new TB cases observed. Of those 13 newly diagnosed TB cases, six (46%) had identical drug resistant profile as their index cases (MDR TB cases), 31% had different drug resistant profile with their index cases, and the remaining 23% were found to be susceptible TB cases (Kritski et al., 1996). This finding indicates that close contact with MDR TB cases has higher chance of developing the same resistance pattern.

A recent prospective cohort study conducted in Peru compared the incidence of active TB among household contacts with MDR TB index cases

versus drug susceptible TB index cases. Among household contacts contacted with MDR TB index cases, 3.3% (35/1055) developed active TB and 86% (24/28) patients with DST results available were MDR TB. The prevalence of active TB among household contacts contacted with drug susceptible TB index case was higher 4.8% (114/2362), but MDR TB was only 2% (2/73) among patients with DST results available (Grandjean et al., 2015).

One study conducted in Peru found that 23.2% of subjects studied reported to have at least one high risk factors for primary MDR TB including close contact with TB patients, previous prophylaxis (LTBI treatment), and tobacco use. Although the risk factors did not have a statistically significant association with primary MDR TB, the rate of MDR-TB was reported to be higher among patients with at least one of these risk factors (Otero et al., 2011).

Non-adherence during previous latent tuberculosis infection treatment (LTBI treatment) may be a risk factor for primary MDR-TB. However, chemoprophylaxis for people with LTBI is not commonly used in low- and middle-income settings, and therefore data on the association between LTBI treatment history and primary MDR TB is limited. However, one study conducted in Western Cape Province of South Africa estimated the efficacy of chemoprophylaxis given to children <5 years old who had a close contact with adult MDR TB index cases. Among 119 children that were followed up, 14 (12%) developed active TB. Of those remaining who had not developed the disease, 61 (51%) were infected and considered as LTBI cases while 44 (37%) were not

infected. Those who didn't develop the disease were prescribed LTBI treatment according to susceptibility test of the index cases. After 30 months follow up, 29 (24%) developed the disease and 64 (54%) were infected. TB disease was lower (5%) among children received appropriate LTBI chemoprophylaxis (based on index cases' susceptibility profile) versus children who did not receive chemoprophylaxis (20%). This study concluded that appropriate chemoprophylaxis might prevent the TB development among children contacted with adult MDR TB patients (Schaaf, Vermeulen, Gie, Beyers, & Donald, 1999).

2.3 Diabetes and drug-resistant tuberculosis

As MDR TB prevalence increases, the global prevalence of diabetes is also becoming another major challenges for global TB control. Diabetes is an established risk factors for tuberculosis (Jeon & Murray, 2008), but the association between diabetes and drug resistant tuberculosis remains controversial. Diabetes has been linked to lower plasma concentration of rifampicin (Ruslami et al., 2010), more severe TB infection manifestation (Chang et al., 2011), and it is proved to be one of potential risk factors for the development of MDR TB (Hsu et al., 2013).

Diabetes is associated with immunosuppression condition in which cytokines and chemokines are up-regulated due to chronic inflammatory state, resulting in higher susceptibility to bacterial infection including *Mycobacterium tuberculosis* because the production of reactive oxidative species (ROS) might be

altered (Fisher-Hoch et al., 2008). Although there is not enough evidence to date to say that the resistant strain of *Mycobacterium tuberculosis* is more infectious than the susceptible strain (Anderson et al., 2014), a study in Taiwan showed that the rate of drug-resistant tuberculosis (resistant to Isoniazid, Rifampicin, and Streptomycin) is higher among immunocompromised group (including patients with diabetes, lung cancer, end-stage renal disease, autoimmune disease) when being compared to immunocompetent group (25.8% vs 17.0%). There was only one MDR TB patient in the immunocompromised group and none in the immunocompetent group (Jiang, Yen, & Wang, 2011).

A case-control study conducted in Bangladesh showed that the adjusted odds of developing MDR TB was two times greater among patients with diabetes (Rifat et al., 2014). This finding is similar to a study conducted in Texas-Mexico border. The adjusted odds of developing MDR TB among patients with diabetes in a Texas site was 2.14 (95%CI 1.10-4.17) and 1.80 (95%CI 1.13-2.87) in Mexico site. Diabetes was prevalent among MDR-TB patients (31.6%) in overall study population. When breaking down the study site, Texas had higher rates of diabetes among its MDR TB patients (36.7%) compared to the Mexico site (29.5%) (Fisher-Hoch et al., 2008).

In a case control study conducted in New York City, the rate of MDR TB was higher among diabetes group (36%) compared to non-diabetes group (10%) with the crude odds ratio of 5.1 (95% CI 2.1-12.5) (Bashar, Alcabes, Rom, & Condos, 2001). A very similar finding was reported in a recent publication from

Mexico, which reported that the rate of diabetes is significantly different in MDR TB (47.2%) versus non MDR TB patients (28.1%) (OR 2.29; 95% CI 1.08 - 4.86) (Gómez-Gómez et al., 2015).

Some contradictive results were reported when comparing the association of diabetes and MDR TB among newly diagnosed patients and previously treated cases. A study in Taiwan found that diabetes can act as both protective factor for newly diagnosed MDR TB (aOR 0.95 95% CI 0.34-2.68) and independent risk factors for acquired MDR TB (aOR 1.52 95% CI 0.59-3.95)(Hsu et al., 2013). The rate of MDR TB among patients with diabetes was not significantly different among patients with and without diabetes in Thailand (Duangrithi et al., 2013), Korea (Reed et al., 2013), and Taiwan (Chang et al., 2011).

2.4 Diabetes and culture conversion among MDR TB patients

Although the role of diabetes and poor TB outcome has been reported worldwide (Baker et al., 2011), the role of diabetes and MDR TB treatment outcome is still understudied. Delayed culture conversion, indicators of progressive TB pulmonary disease and markers for additional drug resistance (Kurbatova et al., 2011), can be one of the predictors for poor MDR TB outcome. Evaluating the culture conversion time among patients can also be used as parameter whether the regimen given to the patient is effective or not (Laserson et al., 2005).

Some previous studies were conducted to examine the associations between diabetes and TB drugs pharmacokinetic. A clinical study with Indonesia as the study setting reported that there was no significant difference for the maximum plasma concentration, time to reach maximum concentration, and the half-lives for rifampin, pyrazinamide, and ethambutol during the intensive phase of TB treatment between patients with and without diabetes (Ruslami et al., 2010). However, two studies reported that diabetes is associated with lower concentration of rifampicin among TB patients, making it less potent for TB treatment (Alisjahbana et al., 2007; Nijland et al., 2006). The pharmacokinetics of second line TB drugs among patients with diabetes is still understudied. Further study to investigate the association between glycemic condition or the interaction between diabetes drug and the second line TB drugs is needed. Such study will give an idea if diabetes will reduce the efficacy of second-line TB drugs which can result in delayed culture conversion during MDR TB treatment.

In a multinational study involving 5 countries with DOTS-plus program, risk factors associated with delayed culture conversion included older age, alcoholism, cavitary disease, positive result in baseline AFB smear, history of previous treatment, poor outcome on previous TB treatment, and the presence of additional drug resistance (Kurbatova et al., 2012). A study in South Africa showed that 32% of MDR TB patients had culture conversion within the first two months of their MDR TB treatment. In the same study, cavity score and positive AFB smear were found to be associated with longer time to achieve culture

conversion (Brust et al., 2013). Similar finding were reported from a study in Peru, where the majority of the patients (87.7 %) converted with a median of 59 days. In the same study, aggressive regimen was found to have association with the culture conversion with the hazard ratio (HR) of 1.40 (Tierney et al., 2014). A study conducted in India showed that more than half (68%) of MDR TB patients studied converted within 9 months of their treatment. Of those who did not converted had poor MDR TB treatment outcomes (15 died, 18 default, 8 failed) (Jain, Desai, Solanki, & Dikshit, 2014).

Some interesting findings have been reported in regards of culture conversion time and the presence of some co-morbidity factors. Low body mass index (BMI) is reported to have association with delayed culture conversion in the study conducted in Indonesia (Putri et al., 2014). A study in Botswana reported that the median time of culture conversion was smaller in HIV infected patients (78 days) compared to non-HIV infected patients (95 days) with the unadjusted HR of 0.9 (Hafkin et al., 2013).

The role of diabetes in delayed culture conversion time has been understudied over the past few years. A study conducted in Latvia reported that concurrent diabetes was found to be associated with larger median time to culture conversion time with the p-value of 0.024 (Holtz et al., 2006). Our previous study in Georgia showed that the proportions of MDR TB patients with diabetes who got their culture converted is not significantly different from MDR TB patients without diabetes (Magee et al., 2014).

2.5 Summary of literature review

Highlights from the literature review of previous studies include:

- Studies to date primarily examined risk factors for acquired MDR TB while risk factors for primary MDR TB remain understudied
- The association between diabetes and drug resistant tuberculosis is controversial, as demonstrated by various discrepant results across study locations and populations
- The association between diabetes and sputum culture conversion is under studied

CHAPTER III

MANUSCRIPT

Introduction

Annually there are an estimated 9 million new cases of active tuberculosis (TB) disease including 480,000 cases of multidrug-resistant (MDR) TB, defined as resistance to at least rifampicin and isoniazid [1]. Importantly, the incidence of MDR TB is increasing rapidly; for example, there were 450,000 cases in 2012 [2] compared to 290,000 in 2010 [3]. Simultaneous to the increase of MDR TB, the global prevalence of type 2 diabetes mellitus (diabetes) has increased substantially in the past ten years and in 2013 an estimated of 382 million adults had prevalent diabetes[4]. While diabetes is an established risk factor for active TB and an estimated 15-25% of active TB cases are attributable to diabetes [5], whether diabetes is associated with MDR TB remains unclear.

Although diabetes is associated with a 2-3 fold increased risk of active TB [6], whether it is associated with either primary or acquired MDR TB remains controversial. Previous studies reported that diabetes is associated with MDR TB [7], [8] while others reported no increased prevalence of MDR TB among patients with diabetes compared to those without diabetes [9], [10]. The majority of global MDR TB cases are due to primary infection with a resistant strain [11], but risk factors for MDR TB are only well established for acquired MDR TB. Established risk factors for acquired MDR TB include female gender [12], previous TB treatment [13], [14], HIV infection [15], and infection of Beijing strain [16]. While less in known about risk factors for primary MDR TB, studies have reported that close contact with MDR TB patients, either household [17] or

nosocomial contact [18], was associated with primary MDR TB. Diabetes is associated with immunosuppression [19], but there is not enough evidence to date to suggest that patients with diabetes are at increased risk of primary MDR TB infection. Improved global control of TB will require improved prevention of primary MDR TB including a better understanding of the relationship between diabetes and risk of MDR TB.

Diabetes is also associated with poor TB treatment outcome [20], but whether diabetes affects response to MDR TB treatment outcomes is understudied. Risk factors for poor MDR TB treatment outcome are well described and include male gender [21], alcohol abuse [22], HIV infection, previous TB treatment, resistance to ofloxacin, and positive AFB smear at the start of anti TB treatment [23]. Given the paucity of information on the relationship between diabetes and MDR TB, the primary objective of this study was to determine the association of diabetes with drug-resistant profiles in patients without previous TB treatment. We also aimed to investigate the association between diabetes and time to sputum culture conversion in newly diagnosed MDR TB patients.

Methods

Setting and Study Design

We performed a prospective cohort study conducted between 2011 and 2014 at the National Center for TB and Lung Disease (NCTLD), the primary care center for the National TB Program in Tbilisi, Georgia. Patients aged 35 and older with new pulmonary laboratory confirmed TB (by *Mycobacterium tuberculosis* culture and/or sputum smear-positive) or clinically diagnosed (based on clinical symptoms and chest x-ray findings)

were eligible. Retreatment cases or patients with prior history of TB were excluded. Patients with MDR TB were followed during treatment to evaluate sputum culture conversion time.

Definitions

The primary outcomes in this study were presence of primary MDR TB and time to sputum culture conversion. We classified drug resistance pattern into three categories: fully susceptible, intermediate resistance, and multi or extensively drug resistant tuberculosis (M/XDR). Drug susceptibility tests were performed at the Georgia National TB Reference Laboratory (NRL) using LJ absolute concentration method, as previously described [24]. Fully susceptible TB was defined as TB that was susceptible to all of first-line TB drugs used in Georgia (Isoniazid, Rifampin, Ethambuthol, and Streptomycin). Intermediate resistance was defined as TB resistant to at least one first-line TB drug but not MDR TB. Included in intermediate resistance were patients with mono-drug resistant TB, poly-drug resistant TB, and patients with missing no more than 3 first-line drug susceptibility test results. Multi-drug resistant TB was defined as TB that was resistant to at least isoniazid and rifampin. We combined MDR and XDR TB cases as the prevalence of XDR-TB was very low in this study. We excluded patients with missing drug susceptibility results for all TB first line drugs. The second primary outcome, time to culture conversion, was defined as time (in days) from the beginning of TB treatment until the date of the first of two consecutive negative culture results that were at least 30 days apart. We classified MDR TB treatment outcome as favorable and

poor outcome, favorable included cured and patients who completed the treatment and patients who defaulted, failed, or died were defined to have poor outcome [25].

Diabetes status was determined by measuring patients' glycosolated hemoglobin (HbA1c) level within 60 days of TB treatment initiation. We classified diabetes status based on the 2014 American Diabetes Association clinical guidelines [26], patients with HbA1c ≥6.5% and/or with a history of diabetes diagnosis were considered to have diabetes.

Demographic and behavioral risk factor information was collected using a questionnaire at the time of enrollment. Participants were interviewed in Kartuli (official language of Georgia), or Russian. Patients were asked to self-report their education attainment, socioeconomic status, smoking status and alcohol use. Education attainment was classified into three categories: less than high school completed, high school degree, and more than high school. Socioeconomic status was categorized into three groups based on tertiles of income. We classified smoking status as never, past and current. We classified patients who reported no current or past use of tobacco as never smokers. Those who reported previous habitual or frequent use of tobacco were considered as past smoker. Those who smoked daily or less than daily were considered current smokers. Patients were also asked about their alcohol use with the classification of never; intermediate (≤ 4 drinks per setting), and heavy (≥ 5 drinks per setting).

Statistical Analyses

All statistical analyses were performed using SAS version 9.4. A two sided p-value <0.05 was considered significant in all analyses. Bivariate analyses for categorical

data were performed using polytomous logistic regression to examine association between patient characteristics and drug resistance profile. Continuous data were analyzed using Kruskal-Wallis test. Multivariable logistic regression models were used to estimate the association of diabetes with drug resistance profile. Hazard assessment was performed using Cox proportional hazard models to evaluate culture conversion time among MDR TB patients. Patients were censored if in the end of MDR TB treatment they did not have documentation of sputum conversion, were lost to follow up, or died (with no documentation of prior conversion). Proportional hazard assumptions were assessed graphically, with goodness-of-fit tests, and using time-dependent models [27]. Covariates included in multivariable models were based on previous literature and observed bivariate associations with the primary exposure and outcomes.

Ethical approval

This study has been reviewed and approved by Institutional Review Board at the NCLTD and Emory University.

Results

Study Samples and Baseline Characteristic

During the study period 586 eligible TB patients were treated at NCLTD in Tbilisi; 324 were screened for the HbA1c and 318 were enrolled in this study. Of the 318 patients, 268 (84.3%) had drug susceptibility test results and were included in final analyses. Among 268 patients with TB, 52 (19.4%) were M/XDR TB patients. The median HbA1c was 5.4 (IQR 5.1 – 5.7) and the prevalence of diabetes was 13.4% (36/268).

The majority of patients were male (75.4%) and the median age was 49 years (IQR 42 - 58). Most participants finished high school (56.9%) and were in the lower and middle socioeconomic status (61.9% combined) with the median income of $118 USD (IQR 41 – 412). Only 8.2% patients were internally displaced and previous imprisonment was reported by 14.6% of participants. Self-reported current smoking was high (49.1%) and any alcohol use was reported among 70.0%.

Diabetes and Drug Resistance Profile

Of the 268 patients with available drug susceptibility test results, 137 (51.1%) were fully susceptible to all first line drugs, 79 patients (29.5%) had intermediate resistance, and 49 (18.3%) had MDR TB, and 3 (1.1%) had XDR TB (Table 1). The prevalence of MDR TB among patients with diabetes was 30.6% versus 17.7% among patients without diabetes (p=0.07). In an adjusted model the odds of MDR TB was significantly higher among patients with diabetes compared to patients without diabetes (aOR 2.51 95% CI 1.00 – 6.31) (Table 2). In the same adjusted model, the odds of intermediate resistance was significantly higher among past smokers (aOR 3.94 95% CI 1.25 – 12.47) and current smokers (aOR 95% CI 4.56 1.149 – 14.02), while the odds of MDR TB was higher among patients with lower socioeconomic status (aOR 3.51 95% CI 1.56 – 8.20).

Diabetes and culture conversion time among MDR TB patients

Among 52 M/XDR TB patients, 44 (84.6%) converted sputum cultures to negative with a median time of 61 days (IQR 31.0-91.5) (Table 3). Median time to culture conversion among MDR TB patients with diabetes was 87 days (IQR 35-99) vs 38 (31-84) in MDR TB patients without diabetes (p=0.07). In an unadjusted model, the rate of sputum culture

conversion was lower among MDR TB patients with diabetes (cHR 0.75 95% CI 0.36 – 1.53) and current smokers (cHR 0.44 95% CI 0.19 – 0.98). After adjusting for age, sex, socioeconomic status, HIV status, cavitary disease, and grade of AFB smear, we found that the hazard rate of sputum culture conversion to be significantly lower among MDR TB patients with diabetes (aHR 0.34 95% CI 0.13 – 0.87) compared to MDR TB patients without diabetes. In the same model, we found that the hazard rate of sputum culture conversion was also lower among current smokers (aHR 0.16 95% CI 0.04 – 0.61) compared to non-smokers. In a supplementary secondary model we found that age (aHR 0.39 95% CI 0.16 – 0.97) was associated with lower hazard rate of sputum culture conversion, while and cavitary disease was associated with higher hazard rate of sputum culture conversion (aHR 3.39 95% CI 1.25 – 9.23) among patients with MDR TB.

At the end of follow-up, 50 (96.2%) patients with MDR TB had treatment outcome information. One patient had missing treatment outcome and one patient remained on treatment. Of 50 patients who had treatment outcome information, 54% (27/50) had favorable treatment outcome (cured or completed) while 46% (23/50) others had poor treatment outcome (died or defaulted). Of those who had poor treatment outcome, 21.74% (5/23) had diabetes. The risk of poor treatment outcome was similar among those with diabetes (45.4%) and those without diabetes (46.1%). The risk of poor treatment outcome among those who reported current use of tobacco was 72.7% compared to 25.0% among those who reported past or no history of tobacco use ($p=<0.01$).

Discussion

Overall, we found that diabetes was a risk factor for primary MDR TB and that among patients with MDR TB the rate of sputum culture conversion was lower in those with diabetes. These associations were observed even after adjusting for confounding factors. Our findings suggest diabetes may have a more important role in MDR TB and response to MDR TB treatment than previously indicated. Importantly, we also observed that lower household income was associated with MDR TB and that current smoking was associated with intermediate drug resistance. We also reported that patients with MDR TB who reported to be current smokers has a significantly lower rate of sputum culture conversion.

Diabetes is associated with altered immune function likely leading to increased susceptibility to bacterial infections like *Mycobacterium tuberculosis* [7]. Whether resistant strains of *M. tuberculosis* are more infectious than the susceptible strains is unknown [28], however, previous studies reported that mutations in bacterial genes may increase pathogenicity. For example, a molecular analysis of isoniazid-resistant strains found that *kat*G gene mutations in isogenic MTB resulted in increased coding of catalase-peroxidase, an enzyme that may prevent bacterial susceptibility to oxidative stress during the host infection process [29]. Given MDR TB patients in our study were due to primary infection, and resistant to isoniazid and rifampin, it is possible that resistant MTB strains were better able to survive host oxidative stress among patients with diabetes in whom the production of reactive oxidative species (ROS) is likely reduced due to glycation [7].

Whether diabetes is associated with increased prevalence or risk of MDR TB has been inconsistently reported in previous studies. Consistent with our findings that patients with diabetes have more than twice the odds of MDR TB, a retrospective cohort study conducted on the Texas-Mexico border also found that the risk of developing MDR TB was higher among patients with diabetes among both Texas (aOR 2.14 95% CI 1.10 – 4.17) and Mexican patients (aOR 1.80 95% CI 1.13 – 4.17) [7]. A case control study conducted in Bangladesh also reported greater risk of MDR TB among patients with diabetes (OR 2.25 95% CI 1.4 – 3.6) [30]. However, both Texas and Bangladesh studies included patients with previously treated TB. A cross-sectional study conducted in Taiwan reported that diabetes did not increase the odds of prevalent MDR TB among newly diagnosed patients (aOR 0.95 95% CI 0.34 – 2.68) [9].

Few other studies reported that diabetes status is associated with time lower rate of sputum culture conversion. Consistent with this study's findings, our previous work reported lower but not significant culture conversion rate among patients with diabetes (aHR 0.95, 95% CI 0.71–1.28) in an adjusted model [31]. A multinational cohort of patients with MDR TB also reported lower but non-significant unadjusted rate of sputum culture conversion among patients with diabetes (cHR 0.76 95% CI 0.54 – 1.06) [32]. Also consistent with our finding, a retrospective cohort study conducted in Latvia reported that concurrent diabetes is associated with longer time to culture conversion with difference in initial conversion time of 373 days (95% CI 23 – 1725; p=0.02) [33].

Similar to this study's findings, previous studies consistently report that low SES and smoking play critical roles in risk of TB and response to TB treatment. For example,

studies that examined risk factors for MDR TB also reported that lower socioeconomic status is associated with resistance [34]–[36]. Consistent with our finding that patients with lower socioeconomic status had three times greater odds of MDR TB, a study in Turkey reported that the risk of MDR TB is increased by 6 fold among patients with low socioeconomic status. Higher prevalence of MDR TB among lower socioeconomic groups in our study suggests that the infection may be related to poverty. We run a separate bivariate analysis and found that the proportion of contacts with MDR TB patients is significantly different in lower socioeconomic group (10.1%) versus higher socioeconomic group (2.4%) (p=0.02). Increasingly studies have found smoking to be an important risk factor for poor TB treatment outcome [37], [38] and increased risk of relapse after successful treatment [39]. Although the association between smoking and poor MDR TB treatment outcomes is under studied, this study's finding that smoking lowers the rate of sputum culture conversion is consistent with our previous study in Georgia (aHR 0.82, 95%CI 0.71 – 0.95) [31]. Our results suggest that low SES is a risk factor for MDR TB and that smoking importantly delays culture conversion rates among MDR TB patients. In regions with high rates of MDR TB like Georgia, expanded surveillance and prevention programs should be targeted among low SES settings where smoking rates are typically higher.

This study was subject to limitations. First, our study population came from one TB hospital in Tbilisi and the generalizability to other countries may be limited. Nonetheless, patients from the entire country of Georgia seek care at the facility where our study was conducted and consequently findings are likely relevant to other former

Soviet Republics and other low- and middle-income settings with high rates of MDR TB. Moreover, our study was conducted in a TB facility supported with high quality laboratory testing so that the lab results including the drug sensitivity test results were reliable and bias due to misclassification was of limited concern. Second, 15.7% of enrolled patients in our study did not have complete DST available and were excluded from analyses. We compared basic demographic and clinical characteristics among patients with and without DST results. We found that patients with missing DST were older (median 56 vs 49 years) but similar with respect to gender, socioeconomic status, baseline AFB, and HIV status. We do not believe missing DST introduced internal systematic error in our results. More importantly, only two patients with MDR TB had a missing treatment outcome, providing an exceptional follow-up rate in our prospective analyses (96.2%). Third, some of the key covariates in our analysis, like smoking status and alcohol use, were self-reported and may have resulted in misclassification. However, previous studies have reported high validity of self-reported smoking and alcohol use behaviors compared to biomarker measurement [40], therefore we do not believe the misclassification led to substantial bias in our reported measures of association.

Conclusion

Previous studies assessing the relationship between diabetes and MDR TB primarily were among patients with prior history of TB treatment, while in our study we found that diabetes was associated with primary infection with MDR TB and reduced rate of sputum culture conversion during MDR TB treatment. Expanding our understanding

of the risk factors for primary infection of MDR TB, including the role of diabetes, is urgently needed in order to improve effective MDR TB prevention efforts.

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TABLE – RESULT

Table 3.1. Baseline characteristics and drug resistant profile among newly diagnosed adult TB patients in Tbilisi, Georgia, 2011 – 2014

Variable	Type of Resistance			Total N=268	P-Value
	Fully susceptible[A] N % = 137 (51.12)	< Fully Susceptible <MDR[B] N % = 79 (29.48)	MDR and XDR TB[C] N % = 52 (19.40)		
	N %	N %	N %	N %	
Age					
Median (IQR)	50 (41 – 58)	48(42 – 54)	47 (42.5 – 58)	49 (42 – 58)	0.82
35 – 54	89 (64.96)	60 (75.95)	35 (67.31)	184 (68.66)	0.24
≥ 55	48 (35.05)	19 (24.05)	17 (32.69)	84 (31.34)	
Sex					
Female	37 (27.01)	14 (17.72)	15 (28.85)	66 (24.63)	0.24
Male	100 (72.99)	65 (82.28)	37 (71.15)	202 (75.37)	
Education (formal years)					
Median (IQR)	11 (10 – 14)	11 (10 -14)	10 (10 – 11)	11 (10 – 14)	0.07
< High School completed (≤9)	16 (11.76)	10 (12.66)	4 (7.69)	30 (11.24)	**<0.01**
High school (10 – 11)	68 (50.00)	42 (53.16)	42 (80.77)	152 (56.93)	
> High School (≥12)	52 (38.24)	27 (34.18)	6 (11.54)	85 (31.84)	
Household Income (USD/Month)					
Median (IQR)	176.47 (58.82 – 529.41)	117.65 (5.88– 411.76)	62.94 (0 – 205.88)	117.65 (41.18 – 411.77)	**<0.01**
≤ $59	36 (26.28)	27 (34.18)	25 (48.08)	88 (32.84)	0.07
$60 - $176	42 (30.66)	22 (27.85)	14 (26.92)	78 (29.10)	
≥ $177	59 (43.07)	30 (37.97)	13 (25.00)	102 (38.06)	
Internally Displaced					
No	124 (90.51)	76 (96.20)	46 (88.46)	246 (91.79)	0.24
Yes	13 (9.49)	3 (3.80)	6 (11.54)	22 (8.21)	

Variable	Type of Resistance			Total N=268	P-Value
	Fully susceptible[A] N % = 137 (51.12)	< Fully Susceptible <MDR[B] N % = 79 (29.48)	MDR and XDR TB[C] N % = 52 (19.40)		
	N %	N %	N %	N %	
Imprisonment					
No	118 (86.13)	66 (83.54)	45 (86.54)	229 (85.45)	0.85
Yes	19 (13.87)	13 (16.46)	7 (13.46)	39 (14.55)	
Smoking Status					
Never smoker	39 (28.68)	8 (10.13)	14 (26.92)	61 (22.85)	**0.04**
Past smoker	36 (26.47)	24 (30.38)	15 (28.85)	75 (28.09)	
Current smoker	61 (44.85)	47 (59.49)	23 (44.23)	131 (49.06)	
Alcohol Use					
Never	45 (33.09)	16 (20.25)	19 (36.54)	80 (29.96)	0.18
Intermediate	35 (25.74)	20 (25.32)	10 (19.23)	65 (24.34)	
Heavy	56 (41.18)	43 (54.43)	23 (44.23)	122 (45.69)	
Contact with MDR-TB Patient					
No	126 (92.65)	68 (90.67)	47 (92.16)	241 (91.98)	0.88
Yes	10 (7.35)	7 (9.33)	4 (7.84)	21 (8.02)	
BMI					
Median (IQR)	21.19 (19.23 – 22.89)	21.55 (20.15 – 23.38)	21.48 (19.59 – 24.61)	21.30 (19.71 – 23.56)	0.34
<18.5	28 (21.05)	14 (18.42)	8 (15.38)	50 (19.16)	0.44
18.5 – 24.9	91 (68.42)	51 (67.11)	33 (63.46)	175 (67.05)	
≥ 25	14 (10.53)	11 (14.47)	11 (21.15)	36 (13.79)	
Diabetes					
Median Hba1c (IQR)	5.4 (5.1 – 5.7)	5.5 (5.2 – 5.7)	5.3 (5.2 – 5.85)	5.4 (5.1 – 5.7)	0.61
No Diabetes	120 (87.59)	71 (89.87)	41 (78.85)	232 (86.57)	0.18
Diabetes	17 (12.41)	8 (10.13)	11 (21.15)	36 (13.43)	
HIV Status					
Negative	128 (97.71)	75 (94.94)	49 (94.23)	252 (96.18)	0.45
Positive	3 (2.29)	4 (5.06)	3 (5.77)	10 (3.83)	

Variable	Type of Resistance			Total N=268	P-Value
	Fully susceptible[A] N % = 137 (51.12)	< Fully Susceptible <MDR[B] N % = 79 (29.48)	MDR and XDR TB[C] N % = 52 (19.40)		
	N %	N %	N %	N %	
Hypertension					
No	113 (82.48)	68 (86.08)	41 (78.85)	222 (82.84)	0.56
Yes	24 (17.52)	11 (13.92)	11 (21.15)	46 (17.16)	
Liver Disease					
No	118 (86.76)	70 (88.61)	39 (75.00)	227 (85.02)	0.08
Yes	18 (13.24)	9 (11.39)	13 (25.00)	40 (14.98)	
Kidney Disease					
No	126 (91.97)	69 (90.79)	44 (84.62)	239 (90.19)	0.32
Yes	11 (8.03)	7 (9.21)	8 (15.38)	26 (9.81)	
Cavitary disease					
None	105 (81.40)	57 (73.08)	31 (59.62)	193 (74.52)	**0.01**
Any Cavity	24 (18.60)	21 (26.92)	21 (40.38)	66 (25.48)	

Abbreviations: MDR – multi drug resistant; XDR – extensively drug resistant; IQR – interquartile range; HbA1c – hemoglobin A1c;

A. Patients known to have all susceptible results for the TB first line drugs used in Georgia (Isoniazid, Rifampicin, Ethambutol, Streptomycin)
B. Patients known to have at least one resistance to any TB first line drug (including patients with one or more missing susceptibility results for the TB first line drugs, but not MDR case)
C. Patients known to have resistance for isoniazid and rifampicin, there were 49 patients of MDR TB and 3 patients of XDR TB

Bold indicates that the finding is statistically significant at level of confidence of 5% (P value <0.05

Table 3.2 Polytomous regression for type of resistance among newly diagnosed adult TB patients in Tbilisi, Georgia, 2011 – 2014

Variable	Type of Resistance			
	< Fully Susceptible (Not MDR)[B] vs Fully Susceptible[A]		M/XDR[C] vs Fully Susceptible	
	COR (95%CI)	AOR (95%CI)[D]	COR (95%CI)	AOR (95%CI)[D]
Age				
35 – 54	1	1	1	1
≥ 55	0.59 (0.32 – 1.10)	0.72 (0.36 – 1.42)	0.90 (0.46 – 1.77)	0.94 (0.44 – 2.00)
Sex				
Female	1	1	1	1
Male	1.72 (0.86 – 3.42)	0.71 (0.25 – 2.04)	0.91 (0.45 – 1.85)	0.84 (0.27 – 2.61)
Education (formal years)				
< High School completed (≤9)	1.20 (0.48 – 3.01)		2.17 (0.54 – 8.64)	
High school (10 – 11)	1.19 (0.65 – 2.18)		**5.35 (2.12 – 13.55)**	
> High School (≥12)	1		1	
Household Income				
≤ $59	1.48 (0.76 – 2.87)	1.65 (0.81 – 3.36)	**3.15 (1.43 – 6.93)**	**3.51 (1.56 – 8.20)**
$60 - $176	1.03 (0.52 – 2.03)	1.14 (0.54 – 2.43)	1.51 (0.65 – 3.55)	1.78 (0.72 – 4.41)
≥ $177	1	1	1	1
Internally Displaced				
No	1		1	
Yes	0.38 (0.10 – 1.36)		1.24 (0.45 – 3.47)	
Imprisonment				
No	1		1	
Yes	1.22 (0.57 – 2.63)		0.97 (0.38 – 2.45)	
Smoking Status				
Never smoker	1	1	1	1
Past smoker	**3.25 (1.30 – 8.15)**	**3.94 (1.25 – 12.47)**	1.16 (0.49 – 2.73)	1.52 (0.48 – 4.76)
Current smoker	**3.76 (1.60 – 8.79)**	**4.56 (1.49 – 14.02)**	1.05 (0.48 – 2.28)	1.52 (0.50 – 4.59)

Variable	Type of Resistance			
	< Fully Susceptible (Not MDR)[B] vs Fully Susceptible[A]		M/XDR[C] vs Fully Susceptible	
	COR (95%CI)	AOR (95%CI)[D]	COR (95%CI)	AOR (95%CI)[D]
Alcohol Use				
Never	1	1	1	1
Intermediate	1.61 (0.73 – 3.55)	1.14 (0.42 – 3.07)	0.68 (0.28 – 1.64)	0.82 (0.27 – 2.47)
Heavy	**2.16 (1.08 – 4.33)**	1.28 (0.48 – 3.44)	0.97 (0.47 – 2.01)	0.93 (0.32 – 2.72)
Contact with MDR-TB Patient				
No	1		1	
Yes	1.30 (0.47 – 3.56)		1.07 (0.32 – 3.59)	
BMI				
<18.5	0.89 (0.43 – 1.85)		0.79 (0.33 – 1.90)	
18.5 – 24.9	1		1	
≥ 25	1.40 (0.59 – 3.31)		2.17 (0.90 – 5.25)	
Diabetes				
No Diabetes	1	1	1	1
Diabetes	0.80 (0.33 – 1.94)	1.20 (0.46 – 3.14)	1.89 (0.82 – 4.38)	**2.51 (1.00 – 6.31)**
HIV Status				
Negative	1	1	1	1
Positive	2.28 (0.50 – 10.45)	1.86 (0.39 – 8.89)	2.61 (0.51 – 13.38)	2.57 (0.47 – 14.05)
Hypertension				
No	1		1	
Yes	0.76 (0.35 – 1.65)		1.26 (0.57 – 2.81)	
Liver Disease				
No	1		1	
Yes	0.84 (0.36 – 1.98)		2.19 (0.98 – 4.86)	
Kidney Disease				
No	1	1	1	1
Yes	1.16 (0.43 – 3.13)	1.01 (0.35 – 2.91)	2.08 (0.79 – 5.51)	1.65 (0.59 – 4.63)
Cavitary Disease				
No	1		1	
Yes	1.61 (0.83 – 3.15)		**2.96 (1.48 – 6.03)**	

Abbreviations: MDR – multi drug resistant; XDR – extensively drug resistant; COR – Crude odds ratio; AOR – Adjusted odds ratio; CI – Confidence Interval

A. Patients known to have all susceptible results for the TB first line drugs used in Georgia (Isoniazid, Rifampicin, Ethambutol, Streptomycin)
B. Patients known to have at least one resistance to any TB first line drug (including patients with one or more missing susceptibility results for the TB first line drugs, but not MDR case)
C. Patients known to have resistance among isoniazid and rifampicin
D. Adjusted odds ratio after controlling for age, sex, socioeconomic status, smoking status, alcohol use, HIV status, diabetes status, and kidney disease. Empty cells mean that the variables were not included in the multivariate model.

Bold indicates that the finding is statistically significant at level of confidence of 5% (P value <0.05)

Table 3.3 Univariate and multivariate hazard rate ratio analysis of patients' characteristics and sputum culture conversion time among adult newly diagnosed MDR-TB patients in Tbilisi, Georgia, 2011 – 2014

Characteristic	**Converted 44/52 (84.62%)** N %	**Median (IQR)[A]**	**cHR (95% CI)**	**aHR[B] (95% CI)**
Age				
35 – 54	30/35 (85.71)	60 (31 – 91)	1	1
≥ 55	14/17 (82.35)	63 (32 – 94)	0.90 (0.47 – 1.72)	0.45 (0.19 – 1.06)
Sex				
Female	12/15 (80.00)	60 (29 – 63)	1	1
Male	32/37 (86.49)	62 (32 – 94)	0.50 (0.24 – 1.02)	1.45 (0.49 – 4.28)
Household Income				
≤ $59	22/25 (88.00)	63 (32 – 92)	0.97 (0.45 – 2.09)	0.66 (0.25 – 1.72)
$60 - $176	12/14 (85.71)	47.5 (29 – 63)	1.66 (0.71 – 3.87)	0.93 (0.32 – 2.69)
≥ $177	10/13 (76.92)	61 (31 – 94)	1	1
Smoking Status				
Never smoker	12/14 (85.71)	61.5 (29 – 87)	1	1
Past smoker	15/15 (100.00)	60 (29 – 92)	0.97 (0.45 – 2.10)	0.60 (0.20 – 1.79)
Current smoker	17/23 (73.91)	61 (32 – 99)	**0.44 (0.19 – 0.98)**	**0.16 (0.04 – 0.61)**
Alcohol Use				
Never	17/19 (89.47)	62 (31 – 87)	1	
Intermediate	9/10 (90.00)	31.5 (27 – 99)	1.06 (0.46 – 2.41)	
Heavy	18/23 (78.26)	60 (32 – 94)	0.58 (0.29 – 1.15)	
Imprisonment				
No	38/45 (84.44)	61 (32 – 92)	1	
Yes	6/7 (85.71)	31 (29 – 84)	1.89 (0.78 – 4.57)	
Contact with MDR-TB Patient				
No	41/47 (87.23)	61 (32 – 92)	**1**	
Yes	2/4 (50.00)	14.5 (0 – 31.5)	3.54 (0.80 – 15.62)	

Characteristic	Converted 44/52 (84.62%) N %	Median (IQR)[A]	cHR (95% CI)	aHR[B] (95% CI)
Diabetes				
No	34/41 (82.93)	38 (31 – 84)	1	1
Yes	10/11 (90.91)	87 (35 – 99)	0.75 (0.36 – 1.53)	**0.34 (0.13 – 0.87)**
HIV Status				
Negative	42/49 (85.71)	61 (31 – 91)	1	1
Positive	2/3 (66.67)	35 (29 – 126)	0.65 (0.15 – 2.73)	0.51 (0.09 – 3.06)
BMI				
<18.5	7/8 (87.50)	30.5 (13.5 – 57)	**2.82 (1.18 – 6.75)**	
18.5 – 24.9	29/33 (87.88)	60 (32 – 94)	1	
≥25	8/11 (72.73)	63 (34 – 87)	1.19 (0.53 – 2.68)	
Cavitary Disease				
None	25/31 (80.65)	61 (31 – 94)	1	1
Any cavity	19/21 (90.48)	60 (31 – 91)	1.31 (0.71 – 2.40)	**2.48 (1.04 – 5.90)**
AFB Smear (among Culture Positive)				
Negative	5/8 (62.50)	30.5 (24 – 57.5)	1	1
Positive	35/39 (89.74)	61 (32 – 94)	0.66 (0.25 – 1.73)	0.56 (0.17 – 1.88)

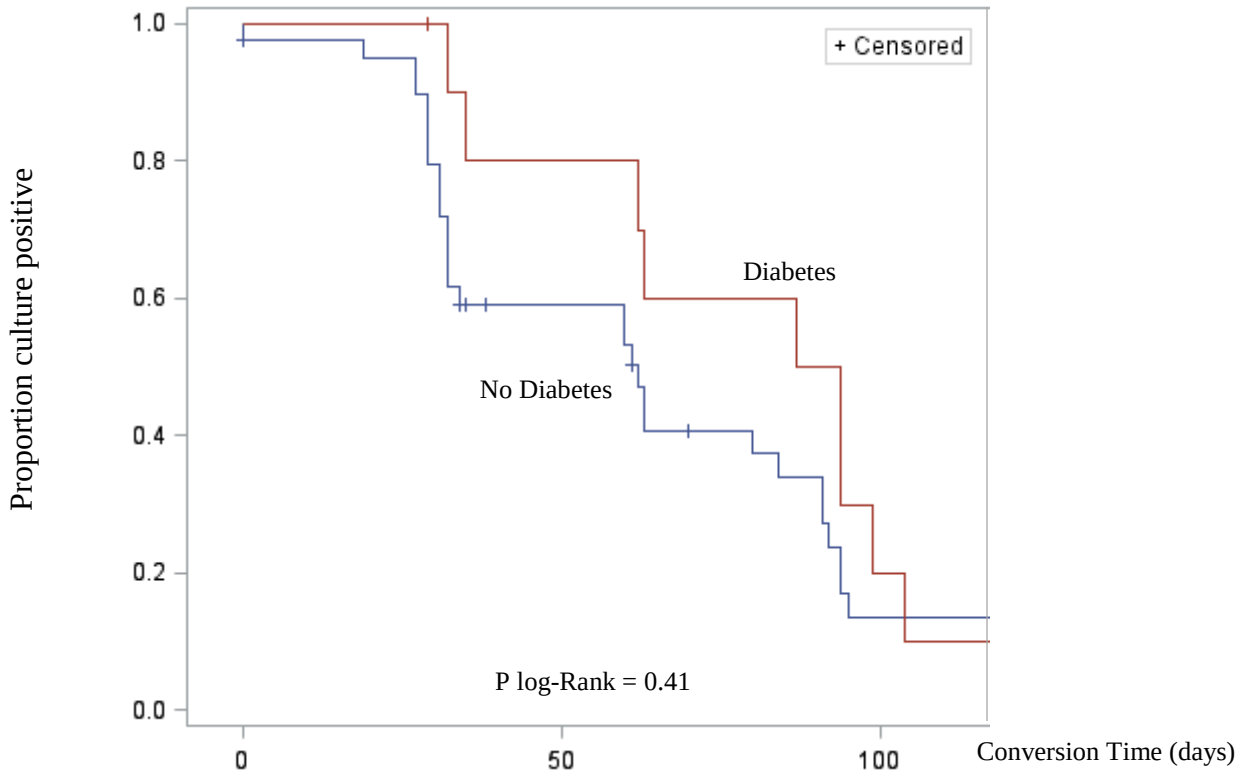
Abbreviations: MDR – multi drug resistant; IQR – interquartile range; cHR – crude hazard rate ratio; aHR – adjusted hazard rate ratio; BMI – body mass index; HbA1c – hemoglobin A1c;

A. Among patients who converted, median time (measured in days) from the initial MDR-Treatment until the first two consecutive negative culture results (≥30 days apart)

B. Hazard rate ratio after controlling for age, sex, socioeconomic, smoking status, diabetes status, HIV status, cavitary disease, and AFB smear. Empty cells mean that the variables were not included in the multivariate model

Bold indicates that the finding is statistically significant at level of confidence of 5% (P value <0.05)

Figure 3.1. Time to sputum culture conversion among 52 primary MDR TB patients with and without diabetes in Tbilisi, Georgia, 2011 – 2014



Number at risk			
Diabetes	11	9	3
No Diabetes	41	21	5

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APPENDICES

Table a. Distribution of multidrug resistant tuberculosis and baseline characteristic among adult TB patients in Tbilisi, Georgia, 2011 – 2014

Characteristic	Non MDR-TB N = 266	MDR-TB[A] N = 52	Total	OR (95% CI)	P value[B]
	N %	N %	N = 318		
Demographic Characteristic					
Age					
Median, IQR	50.0 (42 – 58)	47.0 (42.5 – 58)	49.0 (42 – 58)		0.41
35 – 44	86 (32.3)	20 (38.5)	106 (33.3)	1	0.54
45 – 54	85 (32.0)	15 (28.8)	100 (31.5)	0.76 (0.36 – 1.57)	
55 – 64	58 (21.8)	13 (25)	71 (22.3)	0.96 (0.44 – 2.07)	
≥ 65	37 (13.9)	4 (7.7)	41 (12.9)	0.47 (0.13 – 1.33)	
35 – 44	86 (32.3)	20 (38.5)	106 (33.3)	1	0.69
45 – 54	85 (32.0)	15 (28.9)	100 (31.5)	0.76 (0.34 – 1.57)	
≥ 55	95 (35.7)	17 (32.6)	112 (35.2)	0.77 (0.38 – 1.56)	
35 – 54	171 (64.3)	35 (67.3)	206 (64.8)	1	0.68
≥ 55	95 (35.7)	17 (32.7)	112 (35.2)	0.87 (0.47 – 1.64)	
Sex					
Female	64 (24.1)	15 (28.8)	79 (24.8)	1	0.47
Male	202 (75.9)	37 (71.2)	239 (75.2)	0.78 (0.40 – 1.52)	
Education (formal years)					
Median (IQR)	11.0 (10 – 15)	10.0 (10 – 11)	11.0 (10 – 14)		**0.02**
< High School completed (≤9)	33 (12.4)	4 (7.7)	37 (11.7)	2.00 (0.49 – 7.44)	**<0.01**
High school (10 – 11)	133 (50.2)	42 (80.8)	175 (55.2)	**5.21 (2.29 – 14.09)**	
> High School (≥12)	99 (37.4)	6 (11.5)	105 (33.1)	1	

Characteristic	Non MDR-TB N = 266	MDR-TB[A] N = 52	Total	OR (95% CI)	P value[B]
	N %	N %	N = 318		
≤ High School (≤11)	166 (62.6)	46 (88.5)	212 (66.9)	**4.57 (2.03 – 12.29)**	**<0.01**
> High School (≥12)	99 (37.4)	6 (11.5)	105 (33.1)	1	
Household Income (USD/Month)					
Median (IQR)	176.5 (58.5 – 470.6)	62.9 (0 – 205.9)	117.7 (41.2 – 411.8)		**<0.01**
≤ $59	77 (28.9)	25 (48.1)	102 (32.1)	**2.75 (1.34 – 5.85)**	**0.02**
$60 - $176	79 (29.7)	14 (26.9)	93 (29.25)	2.28 (0.79 – 6.16)	
≥ $177	110 (41.4)	13 (25.0)	123 (38.68)	1	
Low SES (< $177)	156 (58.7)	39 (75.0)	195 (61.3)	**2.12 (1.11 – 4.29)**	**0.03**
High SES (≥ $177)	110 (41.3)	13 (25.9)	123 (38.7)	1	
Internally Displaced					
No	245 (92.1)	46 (88.5)	291 (91.5)	1	0.39
Yes	21 (7.9)	6 (11.5)	27 (8.5)	1.5 (0.58 – 3.98)	
Imprisonment					
No	231 (86.8)	45 (86.5)	276 (86.8)	1	0.95
Yes	35 (13.2)	7 (13.5)	42 (13.2)	1.03 (0.43 – 2.46)	
Smoking Status					
Never smoker	61 (23.0)	14 (26.9)	76 (23.9)	1	0.57
Past smoker	65 (24.5)	15 (28.9)	80 (25.2)	1.02 (0.45 – 2.31)	
Current smoker	139 (52.5)	23 (44.2)	162 (50.9)	0.73 (0.36 – 1.55)	
Never/Past smoker	126 (47.5)	29 (55.8)	155 (48.9)	1	0.28
Current smoker	139 (52.5)	23 (44.2)	162 (51.1)	0.72 (0.40 – 1.31)	
Alcohol Use[C]					
Never	75 (28.4)	19 (36.5)	94 (29.8)	1	0.56
Frequent/infrequent intermediate	68 (25.8)	10 (19.2)	78 (24.7)	0.58 (0.24 – 1.31)	
Infrequent heavy	77 (29.2)	16 (30.8)	93 (29.4)	0.82 (0.39 – 1.71)	
Frequent heavy	44 (16.6)	7 (13.5)	51 (16.1)	0.63 (0.23 – 1.56)	

Characteristic	Non MDR-TB N = 266	MDR-TB[A] N = 52	Total	OR (95% CI)	P value[B]
	N %	N %	N = 318		
Never	75 (28.4)	19 (36.5)	94 (29.8)	1	0.42
Frequent/Infrequent intermediate	68 (25.8)	10 (19.2)	78 (24.7)	0.58 (0.24 – 1.31)	
Frequent/Infrequent Heavy	121 (45.8)	23 (44.2)	144 (45.5)	0.75 (038 – 1.48)	
Never	75 (28.4)	19 (36.5)	94 (29.8)	1	0.24
Frequent/Infrequent	189 (71.6)	33 (63.5)	222 (70.2)	0.69 (0.37 – 1.31)	
Contact with MDR-TB Patient					
No	243(93.1)	47 (92.2)	290 (92.9)	1	0.77
Yes	18 (6.9)	4 (7.8)	22 (7.1)	1.15 (0.37 – 3.55)	
Symptoms					
Cough					
No	58 (23.2)	10 (19.2)	68 (22.5)	1	0.53
Yes	192 (76.8)	42 (80.8)	234 (77.5)	1.27 (0.60 – 2.69)	
Hemoptysis					
No	191 (76.7)	42 (80.8)	233 (77.4)	1	0.52
Yes	58 (23.3)	10 (19.2)	68 (22.6)	0.78 (0.37 – 1.66)	
Chest Pain					
No	159 (64.1)	34 (65.4)	193 (64.3)	1	0.86
Yes	89 (35.9)	18 (34.6)	107 (35.7)	0.95 (0.50 – 1.77)	
Fever					
No	69 (39.9)	3 (13.0)	72 (36.7)	1	**0.01**
Yes	104 (60.1)	20 (87.0)	124 (63.3)	4.42 (1.27 – 15.46)	
Missing	93	29	122		
Weight loss					
No	62 (36.5)	4 (17.4)	66 (34.2)	1	0.07
Yes	108 (63.5)	19 (82.6)	127 (65.8)	2.73 (0.89 – 8.38)	
Missing	96	29	125		
Night sweats					
No	57 (33.7)	10 (45.5)	67 (35.1)	1	0.28

Characteristic	Non MDR-TB N = 266	MDR-TB[A] N = 52	Total	OR (95% CI)	P value[B]
	N %	N %	N = 318		
Yes	112 (66.3)	12 (54.5)	124 (64.9)	0.61 (0.25 – 1.50)	
Missing	97	30	127		
Weakness					
No	38 (22.2)	6 (27.3)	44 (22.8)	1	0.59
Yes	133 (77.8)	16 (73.7)	149 (77.20)	0.76 (0.28 – 2.08)	
Missing	95	30	125		
Clinical Information					
Symptom to TB treatment time (days)					
Median (IQR)	33 (18.5 – 105)	44 (22 – 136)	35 (19 – 108)		0.37
0 – 21	63 (33.9)	7 (19.4)	70 (31.5)	1	
22-70	65 (35.0)	15 (41. 7)	80 (36.0)	2.08 (0.82 – 5.75)	0.23
≥71	58 (31.1)	14 (38.9)	72 (32.5)	2.17 (0.84 – 6.08)	
Missing	80	16	96		
Seek care to TB treatment time (days)					
Median (IQR)	14 (1 – 37)	14.5 (0.5 – 28.5)	14 (1 – 14)		0.51
0 – 14	114 (49.1)	19 (46.4)	133 (48.7)	1	0.42
15 – 35	58 (25.0)	14 (34.1)	72 (26.4)	1.45 (0.67 – 3.08)	
≥36	60 (25.9)	8 (19.5)	68(24.9)	0.80 (0.31 – 1.88)	
Missing	34	11	45		
BMI					
Median (IQR)	21.3 (19.7 – 23.4)	21.5 (19.6 – 24.6)	21.3 (19.7 – 23.6)		0.47
<18.5	46 (17.9)	8 (15.4)	54 (17.5)	0.92 (0.37 – 2.04)	0.47
18.5 – 24.9	174 (67.7)	33 (63.5)	207 (70.0)	1	
≥25	37 (14.4)	11 (21.1)	48 (15.5)	1.57 (0.70 – 3.31)	
Diabetes					
Median HbA1c	5.4 (5.1 – 5.7)	5.3 (5.2 – 5.85)	5.4 (5.1 – 5.7)		0.87

Characteristic	Non MDR-TB N = 266	MDR-TB[A] N = 52	Total	OR (95% CI)	P value[B]
	N %	N %	N = 318		
No Diabetes	240 (90.2)	41 (78.9)	281 (88.4)	1	**0.02**
Diabetes	26 (9.8)	11 (21.1)	37 (11.6)	2.48 (1.14 – 5.40)	
No Diabetes	194 (72.9)	35 (67.3)	229 (72.0)	1	0.05
Pre Diabetes	46 (17.3)	6 (11.5)	52 (16.4)	0.72 (0.26 – 1.71)	
Diabetes	26 (9.8)	11 (21.2)	37 (11.6)	2.35 (1.03 – 5.08)	
HIV Status					
Negative	249 (93.6)	49 (94.2)	298 (93.7)	1	0.37
Positive	9 (3.4)	3 (5.8)	12 (3.8)	1.69 (0.37 – 5.91)	
Unknown	8 (3)	0 (0.0)	8 (2.5)	<0.001 (. – 1.40)	
Hypertension					
No	213 (81.0)	41 (78.9)	254 (80.6)	1	0.72
Yes	50 (19.0)	11 (21.1)	61 (19.4)	1.14 (0.55 – 2.38)	
Liver Disease					
No	226 (85.9)	39 (75.0)	265 (84.1)	1	0.05
Yes	37 (14.1)	13 (25.0)	50 (15.9)	2.04 (0.99 – 4.17)	
Kidney Disease					
No	240 (92.3)	44 (84.6)	284 (91.0)	1	0.11
Yes	20 (7.7)	8 (15.4)	28 (9.0)	2.18 (0.90 – 5.26)	
AFB Smear					
Negative	89 (33.6)	10 (19.2)	99 (31.2)	1	**0.04**
Positive	176 (66.4)	42 (80.8)	218 (68.8)	2.12 (1.02 – 4.43)	
Missing	1	0	1		
AFB Smear (among Culture Positive)					
Negative	44 (21.2)	8 (17.0)	52 (20.4)	1	
Positive	164 (78.8)	39 (83.0)	203 (79.6)	1.31 (0.57 – 3.00)	0.53
Missing	58	5	63		

Characteristic	Non MDR-TB N = 266	MDR-TB[A] N = 52	Total	OR (95% CI)	P value[B]
	N %	N %	N = 318		
Grade (Among AFB positive)					
1+	48 (27.4)	8 (19.0)	56 (25.8)	1	0.31
2+	54 (30.9)	16 (38.1)	70 (32.3)	1.78 (0.72 – 4.73)	
3+	39 (22.3)	13 (31.0)	53 (24.0)	2.0 (0.77 – 5.52)	
4+	34 (19.4)	5 (11.9)	39 (17.9)	0.88 (0.25 – 2.88)	
Cavitary disease					
None	206 (81.1)	31 (59.6)	237 (77.5)	1	**<0.01**
Any cavity	48 (18.9)	21 (40.4)	69 (22.5)	**2.9 (1.53 – 5.50)**	
Any cavity, unilateral	33 (68.8)	19 (90.5)	52 (75.4)	1	0.05
Any cavity, bilateral	15 (31.2)	2 (9.5)	17 (24.6)	0.23 (0.05 – 1.12)	
Unilateral, left cavity	14 (42.4)	10 (52.6)	24 (46.2)	1	0.47
Unilateral, right cavity	19 (57.6)	9 (47.4)	28 (53.8)	0.66 (0.21 – 2.06)	
Infiltrate, upper left side					
No	109 (42.6)	22 (42.3)	131 (42.5)	1	0.97
Yes	147 (57.4)	30 (57.7)	177 (57.5)	1.01 (0.55 – 1.85)	
Infiltrate, lower left side					
No	169 (66.3)	39 (75.0)	208 (67.8)	1	0.22
Yes	86 (33.7)	13 (25.0)	99 (32.2)	0.66 (0.33 – 1.30)	
Infiltrate, upper right side					
No	65 (25.2)	18 (34.6)	83 (26.8)	1	0.16
Yes	193 (74.8)	34 (65.4)	227 (73.2)	0.64 (0.34 – 1.20)	
Infiltrate, lower right side					
No	158 (62.0)	43 (82.7)	201 (65.5)	1	**<0.01**
Yes	97 (38.0)	9 (17.3)	106 (34.5)	0.34 (0.15 – 0.73)	

Abbreviations**:** MDR-TB-Multidrug resistant tuberculosis; IQR-interquartile range; BMI-body mass index; AFB-acid-fast bacilli

A. MDR-TB is defined as TB disease where the bacilli is resistant to at least isoniazid and rifampicin
B. Two sided p-value acquired from Chi square and Fisher's Exact test (categorical data) and Kruskal-Wallis test (continuous data)
C. Alcohol use: heavy ≥5 drinks/setting; intermediate ≤4 drinks/setting; frequent ≥3days/week; infrequent ≤2days/week

Statistical Tests**:** *Categorical:* Chi square test and Fisher's exact test. *Continuous:* Kruskal-Wallis test
Bold indicates that the finding is statistically significant at level of confidence of 5% (P value <0.05)

Table b. Distribution of low socioeconomic status and baseline characteristic among adult TB patients in Tbilisi, Georgia, 2011 – 2014

Characteristic	Low SES[A] N = 195	High SES[B] N = 123	Total	OR (95% CI)	P value[C]
	N %	N %	N = 318		
Demographic Characteristic					
Age					
Median, IQR	51 (43 – 61)	47 (41 – 58)	49.0 (42 – 58)		
35 – 44	61 (31.3)	45 (36.6)	106 (33.3)	1	0.87
45 – 54	59 (30.1)	41 (33.3)	100 (31.5)	1.21 (0.73 – 2.03)	
55 – 64	43 (22.1)	28 (22.8)	71 (22.3)	1.09 (0.62 – 1.93)	
≥ 65	32 (16.4)	9 (7.3)	41 (12.9)	0.98 (0.52 – 1.83)	
35 – 44	61 (31.3)	45 (36.6)	106 (33.3)	1	0.73
45 – 54	59 (30.3)	41 (33.3)	100 (31.5)	1.21 (0.73 – 2.03)	
≥ 55	75 (38.5)	37 (30.1)	112 (35.2)	1.04 (0.64 – 1.71)	
35 – 54	120 (61.5)	86 (69.9)	206 (64.8)	1	0.79
≥ 55	75 (38.5)	37 (30.1)	112 (35.2)	0.94 (0.62 – 1.43)	
Sex					
Female	48 (24.6)	31 (25.2)	79 (24.8)	1	0.91
Male	147 (75.4)	92 (74.8)	239 (75.2)	0.97 (0.58 – 1.63)	
Education (formal years)					
Median (IQR)	10.0 (10 – 11)	13.0 (11 – 15)	11.0 (10 – 14)		
< High School completed (≤9)	30 (15.5)	7 (5.7)	37 (11.7)	**9.35 (3.91 – 25.18)**	**<0.01**
High school (10 – 11)	131 (67.5)	44 (35.8)	175 (55.2)	**6.50 (3.84 – 11.22)**	
> High School (≥12)	33 (17.0)	72 (58.5)	105 (33.1)	1	
≤ High School (≤11)	161 (83.0)	51 (41.5)	212 (66.9)	**6.89 (4.14 – 11.69)**	**<0.01**

Characteristic	Low SES[A] N = 195	High SES[B] N = 123	Total	OR (95% CI)	P value[C]
	N %	N %	N = 318		
> High School (≥12)	33 (17.0)	72 (58.5)	105 (33.1)	1	
Internally Displaced					
No	176 (90.3)	115 (93.5)	291 (91.5)	1	0.39
Yes	19 (9.7)	8 (6.5)	27 (8.5)	1.6 (0.68 – 3.87)	
Imprisonment					
No	167 (85.6)	109 (88.6)	276 (86.8)	1	0.45
Yes	28 (14.4)	14 (11.4)	42 (13.2)	1.31 (0.67 – 2.66)	
Smoking Status					
Never smoker	47 (24.1)	29 (23.6)	76 (23.9)	1	0.52
Past smoker	53 (27.2)	27 (21.9)	80 (25.16)	1.24 (0.64 – 2.39)	
Current smoker	95 (48.7)	67 (54.5)	162 (50.94)	0.89 (0.50 – 1.56)	
Alcohol Use[D]					
Never	64 (32.8)	30 (24.8)	94 (29.8)	1	0.06
Frequent/infrequent intermediate	43 (22.1)	78 (24.7)	78 (24.7)	0.58 (0.31 – 1.07)	
Infrequent heavy	51 (26.2)	93 (28.4)	93 (29.4)	0.57 (0.31 – 1.03)	
Frequent heavy	37 (18.9)	51 (16.1)	51 (16.1)	1.24 (0.59 – 2.68)	
Never	64 (32.8)	30 (24.8)	94 (29.8)	1	0.22
Frequent/infrequent intermediate	43 (22.1)	35 (28.9)	78 (24.7)	0.58 (0.31 – 1.07)	
Frequent/infrequent Heavy	88 (45.1)	56 (46.3)	144 (45.5)	0.74 (0.43 – 1.27)	
Never	64 (32.8)	30 (24.8)	94 (29.8)	1	0.13
Frequent/infrequent	131 (67.2)	91 (75.2)	222 (70.2)	0.68 (0.40 – 1.12)	
Contact with MDR-TB Patient					
No	170 (89.9)	120 (97.6)	290 (92.9)	1	**0.02**
Yes	19 (10.1)	3 (2.4)	22 (7.1)	**4.47 (1.48 – 19.32)**	
Clinical Information					
BMI					
Median (IQR)	20.9 (18.8 – 23.1)	22.7 (20.4 – 24.7)	21.3 (19.7 – 23.6)		

Characteristic	Low SES[A] N = 195	High SES[B] N = 123	Total	OR (95% CI)	P value[C]
	N %	N %	N = 318		
<18.5	44 (23.5)	10 (8.2)	54 (17.5)	**3.07 (1.52 – 6.76)**	**<0.01**
18.5 – 24.9	122 (65.9)	85 (69.7)	207 (70.0)	1	
≥25	21 (11.2)	27 (22.1)	48 (15.5)	0.54 (0.29 – 1.02)	
Diabetes					
Median Hba1c (IQR)	5.4 (5.1 – 5.7)	5.4 (5.2 – 5.6)	5.4 (5.1 - 5.7)		
No Diabetes	176 (90.3)	105 (85.4)	281 (88.4)	1	0.18
Diabetes	19 (9.7)	18 (14.6)	37 (11.6)	0.97 (0.70 – 1.35)	
No Diabetes	138 (70.8)	91 (74.0)	229 (72.0)	1	0.10
Pre Diabetes	38 (19.5)	14 (11.4)	52 (16.4)	1.79 (0.94 – 3.59)	
Diabetes	19 (9.7)	18 (14.6)	37 (11.6)	0.70 (0.35 – 1.41)	
HIV Status					
Negative	182 (93.3)	116 (94.3)	298 (93.7)	1	0.45
Positive	6 (3.1)	6 (4.9)	12 (3.8)	0.64 (0.20 – 2.08)	
Unknown	7 (3.6)	1 (0.8)	8 (2.5)		
Hypertension					
No	161 (83.9)	93 (75.6)	254 (80.6)	1	0.07
Yes	31 (16.1)	30 (24.4)	61 (19.4)	0.59 (0.34 – 1.05)	
Liver Disease					
No	160 (82.9)	105 (86.1)	265 (84.1)	1	0.45
Yes	33 (17.1)	17 (13.9)	50 (15.9)	1.27 (0.68 – 2.45)	
Kidney Disease					
No	167 (88.4)	117 (95.1)	284 (91.0)	1	**0.05**
Yes	22 (11.6)	6 (4.9)	28 (9.0)	**2.57 (1.07 – 7.15)**	
Cavitary Disease					
No	132 (71.0)	105 (87.5)	237 (77.5)	1	**<0.01**
Yes	54 (29.0)	15 (12.5)	69 (22.5)	**2.86 (1.56 – 5.52)**	

Characteristic	Low SES[A] N = 195	High SES[B] N = 123	Total	OR (95% CI)	P value[C]
	N %	N %	N = 318		
Infiltrate, upper left side					
No	70 (37.2)	61 (50.8)	131 (42.5)	1	
Yes	118 (62.8)	59 (49.2)	177 (57.5)	**1.74 (1.10 – 2.78)**	**0.02**
Infiltrate, lower left side					
No	120 (63.8)	88 (73.9)	208 (67.8)	1	
Yes	68 (36.2)	31 (26.1)	99 (32.2)	1.61 (0.98 – 2.69)	0.06
Infiltrate, upper right side					
No	54 (28.6)	29 (24.0)	82 (26.8)	1	
Yes	135 (71.4)	92 (76.0)	227 (73.2)	0.79 (0.46 – 1.32)	0.37
Infiltrate, lower right side				1	
No	121 (64.7)	80 (66.7)	201 (65.5)	1.09 (0.67 – 1.78)	0.72
Yes	66 (35.3)	40 (33.3)	106 (34.5)		

Abbreviations**:** SES-socioeconomic status; IQR-interquartile range; BMI-body mass index;

A. Low SES is defined as household income less than US $177 per month
B. High SES is defined as household income greater or equal to US $177 per month
C. Two sided p-value acquired from Chi square and Fisher's Exact test (categorical data) and Kruskal-Wallis test (continuous data)
D. Alcohol use: heavy ≥5 drinks/setting; intermediate ≤4 drinks/setting; frequent ≥3days/week; infrequent ≤2days/week

Statistical Tests**:** *Categorical:* Chi square test and Fisher's exact test. *Continuous:* Kruskal-Wallis test
Bold indicates that the finding is statistically significant at level of confidence of 5% (P value <0.05)

Table c. Multivariate analysis for estimation of MDR-TB prevalence among new adult TB patients in Tbilisi, Georgia, 2011 – 2014

Variables	N =318			
	Prevalence of MDR TB (%)	COR (95%CI)	AOR (95%CI)	P multivariate
Age				
35 – 54	16.99	1	1	0.50
≥ 55	15.18	0.87 (0.47 – 1.64	0.79 (0.40 – 1.54)	
Sex				
Female	18.99	1	1	0.80
Male	15.48	0.78 (0.40 – 1.52)	0.91 (0.43 – 1.97)	
SES				
Low SES (<177)	20.00	**2.12 (1.11 – 4.29)**	**2.09 (1.03 – 4.44)**	0.05
High SES ≥ $177	10.57	1	1	
Smoking Status				
Never/past smoker	18.71	1	1	0.53
Current smoker	14.20	0.72 (0.40 – 1.31)	0.80 (0.40 – 1.60)	
HIV Status				
Negative	16.96	1	1	0.42
Positive	25.00	1.69 (0.44 – 6.48)	1.79 (0.37 – 6.77)	
Diabetes				
No Diabetes	14.59	1	1	0.06
Diabetes	29.73	**2.48 (1.14 – 5.40)**	2.24 (0.93 – 5.16)	
Kidney Disease				
No	15.49	1	1	0.29
Yes	28.57	2.04 (0.99 – 4.17)	1.65 (0.62 – 4.07)	
Cavitary Disease				
No	13.08	1	1	**0.02**
Yes	30.44	**2.9 (1.53 – 5.50)**	**2.24 (1.14 – 4.36)**	

Abbreviations: COR - crude odds ratio; AOR – adjusted odds ratio; CI – confidence interval

A. Adjusted model when variable age, smoking status, and household income were categorized as dichotomous (Age: 35 – 54/ ≥55; Smoking: never/past and current smoker; Household income: <$177/≥177)
B. In addition to age and sex, adjusted model included household income as indicators for Socio-economy status

Bold indicates that the finding is statistically significant at level of confidence of 5% (P value <0.05)