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Diabetes mellitus is associated with cavities, smear grade, and multidrug resistant tuberculosis in Georgia

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SUMMARY

Setting—National tuberculosis (TB) treatment facility, country of Georgia.

Objective—To determine the prevalence of diabetes mellitus (DM) and pre-DM among patients with TB using glycosylated-hemoglobin (HbA1c), and to estimate the association between DM and clinical characteristics and response to TB therapy.

Design—A cohort study was conducted (2011–2014) at the National Center for TB and Lung Disease in Tbilisi. Patients ≥35 years with pulmonary TB were included. HbA1c was used to define DM (≥6.5%), pre-DM (≥5.7%–6.4%), and no DM (<5.7%). Interviews and medical chart abstraction were performed. Regression analyses estimated associations between DM and 1) baseline TB characteristics and 2) TB treatment outcomes.

Results—A total of 318 newly diagnosed patients with TB were enrolled. Prevalence of DM was 11.6% and pre-DM prevalence was 16.4%. In multivariable analyses, patients with TB-DM had more cavitation (aOR 2.26), higher smear (aOR 2.37), and more MDR-TB (aOR 2.27) compared to patients without DM. Risk of poor TB treatment outcome was similar among patients with and without DM (28.1% vs. 23.6%).

Conclusion—Diabetes and pre-DM were common among adults with newly diagnosed pulmonary TB in Tbilisi, Georgia and DM was associated with more clinical symptoms at presentation including MDR-TB.

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Keywords

hyperglycemia; hemoglobin A1c; treatment failure; epidemiology

INTRODUCTION

Diabetes mellitus (DM) increases the risk of active tuberculosis (TB) by approximately three-times.[1, 2] Impaired immune responses that predispose persons with DM to active TB[3–5] may also confer a greater likelihood of severe TB disease and poor response to TB therapy, thus threatening recent gains in global TB control.[6] Global increases in DM prevalence and persistently high incidence of TB increase the importance of clarifying how DM affects TB disease presentation and response to TB treatment.[7, 8]

Studies have inconsistent findings regarding how DM affects TB therapy. Some observational studies reported that patients with DM and TB require more time to convert sputum cultures from positive to negative,[9–11] are at increased risk of TB treatment failure,[12] and have higher rates of death during TB treatment.[13–15] Other studies have not observed significant differences between these groups.[16, 17] An important limitation of most studies to date is the reliance on self-reported DM status. Further, few studies have investigated the prevalence of pre-DM among patients with TB.[18] Moreover, most studies examining the relation between DM and TB were retrospective and did not adjusted for important known confounders.[2, 12]

The aims of this study were to 1) estimate the prevalence of DM and pre-DM using a glycosolated hemoglobin A1c (HbA1c) test among new adult patients with TB in Tbilisi, Georgia; 2) estimate the association between DM and clinical characteristics at the time of diagnosis, including MDR-TB; and 3) estimate the association between DM status and response to anti-TB treatment.

METHODS

Setting and Participants

Between October 2011 and May 2014 a prospective cohort study was conducted at the National Center for TB and Lung Disease (NCTLD) in Tbilisi, the largest TB treatment and referral facility in Georgia. Eligible participants included newly diagnosed patients with pulmonary TB with no history of prior TB treatment, aged ≥35 years, with confirmed TB (sputum AFB smear-positive and/or culture-positive for *Mycobacterium*, or met NCTLD's clinical definition [symptoms with chest x-ray [CXR] findings]). Physicians and study staff recruited eligible participants from NCTLD inpatient and ambulatory outpatient clinics. Participants were treated with standard WHO recommended anti-TB treatment regimens[19] and were monitored for study outcomes after two months of treatment and at the conclusion of TB treatment.

Definitions and Study Measures

HbA1c was measured by rapid, point-of-care HbA1c device (Afinion, Axis Shield). Capillary blood sample was collected from participants' fingers at study enrollment; samples were analyzed for HbA1c within 30 seconds of collection. HbA1c levels were included in the patient's medical record and reported to physicians. Treatment for DM was at the discretion of physicians. For the primary measure of DM status, we categorized HbA1c according to American Diabetes Association's recommended scale: DM ≥6.5%, pre-DM 5.7–6.4%, and no DM <5.7%.[20] Participants with HbA1c <6.5% with previous DM diagnosis by a physician or health-care worker and documented use of DM medication were also defined as DM. In secondary analyses, we categorized DM by history of DM diagnosis, use of DM medication, or uncontrolled DM (HbA1c ≥8.0%).

Clinical TB characteristics (CXR findings, body mass index [BMI], and HIV status) were abstracted from participants' medical records at the time of TB diagnosis. Laboratory results were obtained from the Georgia National TB Reference Laboratory, which receives annual WHO external quality assessment.[21] Ziehl-Neelsen staining was used for sputum smear AFB, Lowenstein-Jensen and BACTEC-MGIT for *M. tuberculosis* culture, and the absolute concentration method for TB drug susceptibility (DST), as previously described.[21] Sputum AFB smears were graded following CDC guidelines[22], those with 3+ or 4+ were defined as high AFB smear grade. Multidrug-resistant TB was defined as resistance to at least INH and RIF. HIV serologic testing was performed for all participants.

At enrollment, patients were interviewed in Georgian (Kartuli) or Russian to determine socio-demographics, smoking and alcohol use, TB symptom history, and previous DM diagnosis. Patients were asked about tobacco use, those indicating they smoked were considered current smokers; patients who were not current smokers but indicated previous regular tobacco use were considered past smokers, and those without current or past tobacco use were considered never smokers. Alcohol use was defined as heavy (≥5 drinks per day), intermediate (≤4 drinks per day), frequent (≥3 days per week), and infrequent (≤2 days per week).

Sputum for AFB smear and culture were repeated after two months of anti-TB treatment when participants visited the NCTLD directly observed therapy short-course (DOTS) clinic or in the hospital for admitted patients. At the end of the study follow-up period (May 2014), treatment outcomes were assessed using NCTLD treatment database. Treatment result was categorized according WHO guidelines: cured, completed, lost to follow-up, failed, died, or transferred.[19] Favorable outcome was defined as participants who were cured or completed after six months of treatment and poor outcome included participants who defaulted, failed, or died.

Data analyses

Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Categorical baseline characteristics were compared by DM status using Fisher's exact or $\chi 2$ tests, and the Kruskal-Wallis test was used for continuous variables. Logistic models were used to estimate the association between DM status and baseline patient characteristics (self-

reported symptoms, radiograph results, sputum microscopy, and drug susceptibility). Log-binomial or log-Poisson regressions were used to estimate the association between DM status and longitudinal outcomes (poor/favorable treatment outcome, two-month AFB status, two-month culture status). Covariates included in multivariable models were chosen based on previous literature, bivariate associations in the data, and directed-acyclic graph theory.[23]

Ethical approval

The study protocol and materials were reviewed and approved by Institutional Review Boards at the NCTLD and Emory University.

RESULTS

Of 586 eligible TB patients who sought treatment at NCTLD during the study period, 324 were approached to participate and 318 were enrolled (2 were ineligible, 4 refused). Enrolled participants were demographically similar to all patients with TB from Georgia (data not shown). Among the 318 enrolled participants, 291 (91.5%) had final TB treatment outcome information available. Of the remaining participants, 26 were still on treatment (20 with MDR-TB) and the outcome for 1 was missing.

Median age of study participants was 49 years (IQR 42–58) and 75.2% were male (Table 1). Most participants received a high school education (55.2%), the median income was equivalent to $132 USD per month. Current smoking was reported by more than half the study subjects (51.1%) and 45.5% indicated heavy alcohol use. Median BMI was 21.3 (IQR 19.4–23.6); most (N=298) participants were HIV seronegative (93.7%), and MDR-TB prevalence was 15.4% (N=49).

The prevalence of DM was 11.6% (95%CI 8.4–15.5%); 31 (9.7%) participants with had baseline HbA1c >6.5% and six (1.9%) participants were previously diagnosed DM and had HbA1c <6.5%. Among 37 patients with DM, 24.3% were not previously diagnosed with DM (N=9) and 32.4% were not receiving DM medications (N=12). Median time with DM among those with previous DM diagnosis was 2.5 years (IQR 0.0–8.0). Median HbA1c among patients with TB and DM was 7.9% and non-significantly higher among patients with previous DM diagnoses (8.0% vs. 7.6%, p-value=0.63) and lower among those currently receiving DM medications (7.9% vs. 8.2%, p-value=0.26). There were 52 (16.4%, 95%CI 12.6–20.8%) patients with TB and pre-DM. The total proportion of participants with any hyperglycemia (DM and pre-DM combined) was 28.0% (95% CI 23.3–33.1%).

Diabetes status and TB clinical presentation

Among patients enrolled, 80.4% were sputum culture positive for *M. tuberculosis*, 68.6% were sputum AFB smear positive, 270 (85.2%) were either culture or AFB positive, and 47 (14.5%) were clinical cases. Compared to patients with TB but without DM, participants with TB and DM were more likely to have hemoptysis, positive baseline AFB smear, positive baseline culture, MDR-TB, and cavitary disease but less likely to have upper lung infiltration (p-value <0.05 for all comparisons).

In multivariable analyses (adjusted for age, sex, HIV status, and smoking status), TB patients with DM were more likely to have cough (aOR 3.43, 95%CI 1.00–11.79) and hemoptysis (aOR 2.21, 95%CI 1.02–4.78) compared to those without DM (Table 2). Patients with TB and DM were also more likely to have any cavitary disease (aOR 2.26, 95%CI 1.04–4.90), higher AFB smear grade (aOR 2.37, 95%CI 1.14–4.94), and MDR-TB (aOR 2.27, 95%CI 1.02–5.08) compared to those without DM (Table 3). The adjusted odds of having any lung cavity among patients with DM but not currently taking DM medications was 3.63 (95%CI 1.05–12.60) times the odds among patients without DM or with pre-DM. In an adjusted model, each percentage increase in HbA1c increased the odds of having higher AFB smear grade (3+ or 4+) by 1.26 (95%CI 1.03–1.54) times. Compared to patients without DM or with pre-DM, MDR-TB was significantly more prevalent among patients with previous DM diagnosis (aOR 3.09, 95%CI 1.31–7.32), and among those currently using DM medications (aOR 3.71, 95%CI 1.51–9.07). The adjusted odds of prevalent MDR TB among patients with HbA1c ≥ 8.0% was 3.31 (95%CI 1.19–9.16) times the odds among patients HbA1c <8.0%.

Diabetes status and response to TB treatment

Among 291 patients with TB that had complete treatment follow-up, 70 (24.1%) had a poor TB outcome (Table 4) including 46 who were lost to follow-up, 17 who failed, and 7 who died. In primary outcome analyses, patients with DM (compared to those without DM) did not have a significantly greater risk of poor TB outcome in unadjusted (28.1% vs. 23.6%) or adjusted models (aRR 1.29, 95%CI 0.55–3.06). In the multivariable analysis for poor TB outcome, only baseline MDR-TB (aRR 2.96, 95%CI 1.71–5.13) was significantly associated with an increased risk.

We performed additional analyses of response to TB treatment among patients without MDR TB. After two months of TB treatment, 170 of 176 baseline AFB smear positive patients without MDR TB had a follow-up AFB performed and 164 of 208 baseline culture positive patients had a follow-up culture performed. Among those who were initially positive, 31.8% remained AFB smear positive and 34.1% remained culture positive after two months of treatment. Compared to patients without DM, there was a non-significant trend toward increased risk of remaining AFB smear positive after two months among patients with DM (aRR 1.82 95%CI 0.68–4.81), but the trend was not observed for sputum culture. Among 259 patients without MDR-TB who had complete final treatment information, 19.3% had a poor outcome. In a multivariable model, the risk of poor TB outcome among patients with DM was 1.39 (95%CI 0.44–4.39) times the risk of patients without DM.

DISCUSSION

At the time of TB diagnosis and treatment initiation, we found a high proportion of new adult patients with pulmonary TB also had DM (11.6%). Among those identified with DM, a quarter did not have a previous diagnosis of DM and nearly a third were not receiving DM treatment. We also identified a high proportion of patients pre-diabetes (16.4%); together 28.0% of patients with TB in our study had either DM or pre-DM. Patients with TB and DM

had significantly more severe clinical disease at the time of TB diagnosis compared to those without DM, including more hemoptysis, higher AFB smear grade, cavitary lung disease, and were more likely to have MDR-TB.

The present study prospectively screened new adult TB patients for DM and pre-DM by directly measuring HbA1c, a key strength to our study. Compared to most previous studies of DM and TB that relied on self-reported DM and could not examine pre-DM, we used a valid average measure of hyperglycemia. Another advantage of our study was a rigorous analysis of responses to TB therapy, including three outcome measures. Our analyses were appropriately designed to estimate the association between DM and longitudinal TB outcomes with proper modeling procedures (log binomial and Poisson).

Most previous studies that examined baseline smear results among patients with TB-DM reported a greater proportion AFB-positive[11, 15, 24–27] and higher smear grade[26, 28] among patients with DM. Consistent with our results, a study of TB among patients in Texas reported that patients with DM were more likely to be baseline AFB smear positive (aOR 1.8, 95% CI 1.3–2.4).[25] Also similar to our results, previous studies comparing TB symptoms at time of presentation have reported more cough[24, 25], hemoptysis[15, 24, 25], and lung cavitation[15, 25–27] among patients with DM.

We found that patients with TB and DM were significant more likely (aOR=2.27) to have MDR-TB at the time of diagnosis compared than those without DM. To our knowledge, this is the first study to find DM associated with MDR-TB in patients without previous history of TB treatment. A study from Texas found more MDR-TB among those with TB-DM, but that study included retreatment TB cases where MDR-TB is much more common.[29] Despite excluding patients with previous TB, our observed association (aOR 2.27) between DM and MDR-TB was similar to Texas (aOR 2.14). Additional studies from settings with high MDR-TB burdens are needed to confirm the association between DM and primary MDR-TB.

Our study has several limitations. Patients were enrolled at a limited number of sites and 54% of those eligible were enrolled. However, we compared demographic characteristics to national TB data and found that patients enrolled in our study were similar to patients with TB from the entire country of Georgia. Second, HbA1c screening was not performed at a standard time for all patients, and anti-TB regimens or anemia from iron deficiency may influence blood-glucose levels for some individuals.[30] We analyzed HbA1c results by time between treatment initiation and study enrollment and found TB regimens did not substantially affect our results. Third, we measured HbA1c once. Because TB disease may cause prolonged inflammation,[8] hyperglycemia at the time of TB treatment initiation may be transient for some participants. This has the potential to introduce misclassification of DM or pre-DM status. Ideally patients with new DM according to HbA1c should be confirmed by repeat testing with fasting plasma glucose or oral glucose tolerance tests although this may not be feasible in low- and middle-income countries. If DM status was misclassified, our prevalence estimates of DM may be overestimated. However, the relationship between HbA1c, TB severity, and TB outcomes is of clinical importance regardless of DM classification, consequently bias from misclassification of DM status is of minimal concern

because reported measures of association between HbA1c and study outcomes were unaffected. Fourth, we did not have complete data on treatment adherence or duration of intensive phase treatment. However, DOTS was the standard of care during the study. If clinicians extended intensive phase therapy (due to suspected risk) for TB-DM, our results would likely under-estimate the effect of DM on poor outcomes.

Conclusions

We found a high prevalence of DM and pre-DM in adult TB patients in Tbilisi. TB-DM patients had more severe clinical disease at time of treatment initiation than patients without DM. We also found DM was associated with MDR-TB among patients without a previous history of TB. Our findings suggest that clinical guidelines should recommend DM screening in patients with TB and MDR TB. Data from our study also highlight the importance of expanding public health programs that link TB and DM diagnostic and treatment services. Additional studies are needed to better understand the risk of poor TB treatment outcomes in patients with TB and DM.

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Table 1

Distribution of hemoglobin A1c blood glucose levels and baseline characteristics of culture positive adult pulmonary TB patients in Tbilisi, Georgia, 2011–2012

Baseline patient characteristic	**Total No.=318 No. (%)**	**No diabetes HbA1c ≤ 5.6% No.=229 (72.0) No. (%)**	**Pre diabetes HbA1c 5.7–6.4% No.=52 (16.4) No. (%)**	**Diabetes[*] HbA1c ≥ 6.5% No.=37 (11.6) No. (%)**	**P-value[†]**
Demographics					
Age, median years (IQR)	49.0 (42–58)	49.0 (41–57)	52.5 (44–61)	50.0 (42–59)	0.99
Sex, female	79 (24.8)	60 (26.2)	7 (13.5)	12 (32.4)	0.26
Monthly income[‡], median USD (IQR)	132 (47–412)	147 (47–412)	117 (41–294)	177 (88–412)	0.46
Internally displaced person	27 (8.5)	21 (9.2)	4 (7.8)	2 (5.4)	0.47
Ever imprisoned	42 (13.5)	33 (14.8)	7 (14.0)	2 (5.4)	0.12
Smoking Status					
Never smoker	75 (23.7)	54 (23.7)	9 (17.3)	12 (32.4)	0.05
Past smoker	80 (25.2)	54 (23.7)	13 (25.0)	13 (35.1)	
Current smoker	162 (51.1)	120 (52.6)	30 (57.7)	12 (32.4)	
High alcohol use[§]	51 (16.1)	39 (17.1)	10 (19.2)	2 (5.6)	0.06
Self-reported symptoms					
Cough	234 (77.5)	162 (73.6)	40 (85.1)	32 (91.4)	**0.04**
Hemoptysis	68 (22.6)	46 (21.0)	9 (19.1)	13 (37.1)	**0.03**
Chest pain	107 (35.7)	71 (32.4)	22 (47.8)	14 (40.0)	0.57
Fever[¶]	124 (63.3)	95 (60.7)	17 (60.7)	12 (66.7)	0.75
Weight loss[¶]	127 (65.8)	90 (61.2)	22 (78.6)	15 (83.3)	0.10

Baseline patient characteristic	Total No.=318 No. (%)	No diabetes HbA1c ≤ 5.6% No.=229 (72.0) No. (%)	Pre diabetes HbA1c 5.7–6.4% No.=52 (16.4) No. (%)	Diabetes* HbA1c ≥ 6.5% No.=37 (11.6) No. (%)	P-value†
Night sweats¶	124 (64.9)	91 (62.8)	21 (75.0)	12 (66.7)	0.46
Weakness¶	149 (77.2)	110 (74.8)	25 (89.3)	14 (77.8)	0.95
Symptom to diagnosis time, days (IQR)	35 (20–108)	35 (19–108)	40 (19–141)	35 (17–102)	0.96
Clinical information					
BMI					
<18.5	54 (17.5)	44 (19.6)	8 (16.0)	2 (5.7)	**0.02**
18.5–24.9	207 (67.0)	148 (66.1)	36 (72.0)	23 (65.7)	
≥25	48 (15.5)	32 (14.3)	6 (12.0)	10 (28.6)	
HIV positive	12 (3.8)	11 (4.8)	0	1 (2.7)	0.93
Baseline AFB smear positive	218 (68.8)	150 (65.5)	36 (70.6)	32 (86.5)	**0.01**
Baseline sputum culture					0.06
Negative	50 (16.2)	40 (17.5)	9 (17.3)	1 (2.7)	
Positive	255 (82.5)	181 (79.0)	39 (75.0)	35 (94.6)	
Contaminated/missing	13 (4.1)	8 (3.5)	4 (7.7)	1 (2.7)	
Treatment regimen					
First-line therapy	266 (83.7)	194 (84.7)	46 (88.5)	26 (70.3)	**0.01**#
MDR	49 (15.4)	32 (14.0)	6 (11.5)	11 (29.7)	
XDR	3 (0.9)	3 (1.3)	0	0	
Drug susceptibility					
Sensitive	214 (67.3)	153 (66.8)	36 (69.2)	25 (67.6)	**0.04**
MDR or XDR	52 (16.4)	35 (15.3)	6 (11.5)	11 (29.7)	
Clinical case	52 (16.4)	41 (17.9)	10 (19.2)	1 (2.7)	
Any lung cavity	69 (22.5)	45 (20.4)	11 (22.4)	13 (36.1)	**0.04**

Baseline patient characteristic	Total No.=318 No. (%)	No diabetes HbA1c ≤ 5.6% No.=229 (72.0) No. (%)	Pre diabetes HbA1c 5.7–6.4% No.=52 (16.4) No. (%)	Diabetes* HbA1c ≥ 6.5% No.=37 (11.6) No. (%)	P-value†
Infiltrate, upper	298 (95.8)	218 (96.9)	49 (98.0)	31 (86.1)	**0.01**
Infiltrate, lower	133 (42.9)	100 (44.4)	19 (38.8)	14 (38.9)	0.67

Abbreviations: HbA1c-hemoglobin A1c; STD-standard deviation; IQR-interquartile range; GEL- Georgian Lari; BMI-body mass index; AFB-acid-fast bacilli; XDR-extremely drug resistant; MDR-multi-drug resistant

*Diabetes mellitus defined by HbA1c ≥ 6.5%, and 5 patients with HbA1c <6.5% who self-reported physician diagnosed diabetes and current use of diabetes medications.

†Two sided p-value, chi-square tests or Fisher's Exact test for categorical variables and Kruskal-Wallis tests for continuous variables. Comparing diabetes to pre-diabetes and no diabetes combined.

‡Household monthly income in USD, Exchange rate from Georgian Lari (GEL) used was 1 USD ≈ 1.7 GEL.

§High alcohol use defined as ≥ 5 drinks per day and ≥ 3 days/week.

¶Fever (No.=122), weight loss (No.=125), night sweats (No.=127), and weakness (No.=125) had >30% missing.

#MDR status was dichotomous (Yes/No).

Table 2

Multivariable analyses for self-reported tuberculosis (TB) symptoms at the time of TB presentation among new adult TB patients with diabetes mellitus in Tbilisi, Georgia, 2011–2012

	Cough*		Hemoptysis*	
DM status	**OR (95% CI)**	**aOR (95% CI)†**	**OR (95% CI)**	**aOR (95% CI)†**
DM	**3.86 (1.13, 12.93)**	**3.43 (1.00, 11.79)**	**2.22 (1.04, 4.75)**	**2.21 (1.02, 4.78)**
Pre-DM	2.05 (0.87, 4.82)	1.91 (0.80, 4.56)	0.89 (0.40, 1.97)	0.85 (0.38, 1.90)
No DM	1.00	1.00	1.00	1.00
DM no med	3.22 (0.40, 25.60)	2.97 (0.37, 23.88)	3.20 (0.94, 10.87)	3.23 (0.94, 11.10)
DM med	3.54 (0.81, 15.44)	3.22 (0.72, 14.49)	1.92 (0.78, 4.71)	1.89 (0.75, 4.78)
Pre-DM/No DM	1.00	1.00	1.00	1.00
HbA1c ≥8.0%	2.10 (0.47, 9.48)	2.03 (0.44, 9.42)	0.47 (0.11, 2.14)	0.49 (0.11, 2.24)
HbA1c <8.0%	1.00	1.00	1.00	1
HbA1c, per 1% increase	**1.55 (1.03, 2.34)**	1.48 (0.99, 2.21)	1.02 (0.81, 1.29)	1.02 (0.81, 1.29)

Abbreviations: DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; aOR, multivariable adjusted odds ratio; Pre-DM, pre-diabetes mellitus; NA, not available; HbA1c, hemoglobin A1c

*Self-reported by patients at baseline, cough (No.=302) and hemoptysis (No.=301).

†In addition to diabetes status, adjusted models included age, sex, HIV status, smoking status.

Table 3

Multivariable analyses of chest radiograph, sputum microscopy, and drug susceptibility at the time of tuberculosis (TB) presentation among new adult TB patients with diabetes mellitus in Tbilisi, Georgia, 2011–2012

	Cavity*		High AFB grade†		MDR TB‡	
DM status§	**OR (95% CI)**	**aOR (95% CI)**	**OR (95% CI)**	**aOR (95% CI)**	**OR (95% CI)**	**aOR (95% CI)**
DM	**2.21 (1.04, 4.70)**	**2.26 (1.04, 4.90)**	**2.30 (1.12, 4.71)**	**2.37 (1.14, 4.94)**	**2.35 (1.06, 5.18)**	**2.27 (1.02, 5.08)**
Pre-DM	1.13 (0.54, 2.39)	1.18 (0.55, 2.54)	1.70 (0.89, 3.25)	1.55 (0.80, 3.01)	0.72 (0.29, 1.82)	0.80 (0.31, 2.04)
No DM	1.00	1.00	1.00	1.00	1.00	1.00
Previous DM	1.53 (0.64, 3.65)	1.50 (0.61, 3.68)	1.76 (0.79, 3.93)	1.95 (0.85, 4.49)	**3.25 (1.40, 7.54)**	**3.09 (1.31, 7.32)**
New DM	**6.37 (1.48, 27.44)**	**6.81 (1.56, 29.84)**	3.40 (0.89, 13.00)	3.00 (0.77, 11.64)	0.73 (0.09, 6.01)	0.72 (0.09, 5.99)
Pre-DM/No DM	1.00	1.00	1.00	1.00	1.00	1.00
DM no med	3.19 (0.94, 10.81)	**3.63 (1.05, 12.60)**	2.72 (0.85, 8.69)	2.46 (0.76, 7.98)	0.53 (0.07, 4.23)	0.54 (0.07, 4.30)
DM med	1.80 (0.74, 4.38)	1.71 (0.68, 4.31)	1.81 (0.78, 4.21)	2.05 (0.85, 4.95)	**3.90 (1.64, 9.28)**	**3.71 (1.51, 9.07)**
Pre-DM/No DM	1.00	1.00	1.00	1.00	1.00	1.00
HbA1c ≥8.0%	1.47 (0.50, 4.31)	1.62 (0.54, 4.91)	**2.63 (1.01, 6.87)**	**3.06 (1.13, 8.28)**	**3.61 (1.33, 9.80)**	**3.31 (1.19, 9.16)**
HbA1c <8.0%	1.00	1.00	1.00	1.00	1.00	1.00
HbA1c, per 1% increase	1.12 (0.91, 1.38)	1.14 (0.92, 1.41)	**1.25 (1.03, 1.53)**	**1.26 (1.03, 1.54)**	1.18 (0.95, 1.47)	1.18 (0.95, 1.46)

Abbreviations: DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; aOR, multivariable adjusted odds ratio; Pre-DM, pre-diabetes mellitus; NGT, normal glucose tolerance; HbA1c, hemoglobin A1c

*Any cavitary disease, N=306.

†Baseline sputum AFB smear 4+ or 3+ vs. 2+, 1+, or negative, No.=316.

‡Any resistance pattern that includes resistance to both rifampin and isoniazid, No.=318.

§In addition to diabetes status, adjusted models included age, sex, HIV status, smoking status.

Table 4

Patient characteristics associated with two-month acid-fast bacilli (AFB) sputum smear positive results among adult pulmonary TB patients in Tbilisi, Georgia, 2011–2012

Baseline patient characteristic	Poor TB outcome* 70/291 (24.1) Positive/Total (%)	Risk ratio (RR) RR (95% CI)	Adjusted RR aRR (95% CI)†
DM status			
No DM	50/212 (23.6)	1.00	1.00
Pre-DM	11/47 (23.4)	0.99 (0.56, 1.76)	0.95 (0.45, 1.99)
DM	9/32 (28.1)	1.19 (0.65, 2.18)	1.29 (0.55, 3.06)
Age (years)			
35–44	25/98 (25.5)	1.00	1.00
45–54	28/94 (29.8)	1.17 (0.74, 1.85)	1.01 (0.56, 1.81)
55–64	14/64 (21.9)	0.86 (0.48, 1.52)	0.68 (0.34, 1.39)
≥65	3/35 (8.6)	0.37 (0.11, 1.04)	0.62 (0.18, 2.19)
Sex			
Female	7/70 (10.0)	1.00	1.00
Male	63/221 (28.5)	**2.85 (1.37, 5.93)**	1.82 (0.68, 4.91)
Income, household USD/Month‡			
≤$59	21/85 (24.7)	1.00	
$60–$176	19/85 (22.4)	0.90 (0.53, 1.56)	
≥$177	29/117 (24.8)	1.00 (0.62, 1.63)	
Internally displaced person			
No	63/264 (23.9)	1.00	
Yes	6/26 (23.1)	0.97 (0.46, 2.01)	
Ever Imprisoned			
No	55/244 (22.5)	1.00	
Yes	13/39 (33.3)	1.48 (0.90, 2.44)	
Smoking Status			
Never smoker	7/67 (10.5)	1.00	1.00
Past smoker	6/71 (8.5)	0.81 (0.29, 2.28)	0.49 (0.14, 1.73)
Current smoker	57/153 (37.3)	**3.57 (1.72, 7.40)**	1.94 (0.67, 5.60)
Alcohol use§			
Never	10/82 (12.2)	1.00	1.00
Frequent/infrequent intermediate	21/75 (28.0)	**2.30 (1.16, 4.55)**	1.26 (0.49, 3.25)
Infrequent heavy	23/84 (27.4)	**2.25 (1.14, 4.42)**	0.99 (0.38, 2.60)
Frequent heavy	16/48 (33.3)	**2.73 (1.35, 5.53)**	1.34 (0.48, 3.73)
Cough			

Baseline patient characteristic	Poor TB outcome* 70/291 (24.1) Positive/Total (%)	Risk ratio (RR) RR (95% CI)	Adjusted RR aRR (95% CI)†
No	21/63 (33.3)	1.00	1.00
Yes	46/213 (21.6)	**0.65 (0.14, 1.00)**	0.76 (0.44, 1.33)
Hemoptysis			
No	54/213 (25.4)	1.00	
Yes	13/62 (21.0)	0.83 (0.48, 1.41)	
BMI			
<18.5	7/51 (13.7)	1.00	1.00
18.5–24.9	46/191 (30.0)	1.75 (0.84, 3.65)	1.28 (0.55, 2.96)
≥25	15/40 (37.5)	**2.73 (1.23, 6.06)**	2.13 (0.80, 5.69)
HIV status			
Negative	66/274 (24.1)	1.00	
Positive	3/10 (30.0)	1.25 (0.47, 3.28)	
Unknown	1/7 (14.3)	0.59 (0.10, 3.69)	
AFB smear			
Negative	26/97 (26.8)	1.00	
1 or 2+	28/112 (25.0)	0.93 (0.59, 1.48)	
3 or 4+	16/81 (19.8)	0.74 (0.43, 1.28)	
Drug susceptibility			
Drug susceptible	50/259 (19.3)	1.00	1.00
XDR/MDR	20/32 (62.5)	**3.24 (2.25, 4.67)**	**2.96 (1.71, 5.13)**
Cavitary Disease			
None	56/223 (25.1)	1.00	
Any	11/58 (19.0)	0.76 (0.42, 1.35)	

Abbreviations: RR-risk ratio; aRR-adjusted risk ratio; HbA1c-hemoglobin A1c; BMI-body mass index; AFB-acid-fast bacilli; MDR-multi-drug resistant; XDR-extremely drug resistant

*Poor outcome was defined as default, failure, or death according to 2013 WHO criteria. Patients still on treatment (No.=27) at the end of follow-up were excluded from the analysis.

†Age was also included in the multivariable model as a continuous variable.

‡Exchange rate from Georgian Lari (GEL) used was 1 USD ≈ 1.7 GEL.

§Alcohol use: Heavy ≥5 drinks/day, intermediate ≤4 drinks/day, frequent ≥3 days/week, infrequent ≤2 days/week.