The effect size of type 2 diabetes mellitus on tuberculosis drug resistance and adverse treatment outcomes

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1. Abstract

Objective: To evaluate the effect size of type 2 diabetes mellitus (T2DM) on tuberculosis (TB) treatment outcomes and multi drug resistance (MDR).

Methods: A cohort with 507 individuals with diagnosed TB included 183 with coexistence of T2DM and TB (TB-T2DM). Participants were identified at the time of TB diagnosis and followed during the course of TB treatment. Then we computed relative risks and adjustments by Cox proportional hazards for outcome variables (drug resistance, death, relapse, treatment failure), and the size of their effect as Cohen's-d.

Results: Patients with TB-T2DM were more likely to remain positive for acid-fast bacilli after two months of anti-TB treatment RR= [2.01 (95% CI: 1.3, 3.1)], to have drug resistant (DR) [OR 3.5 (1.8, 6.7)] and multi-drug resistant (MDR) TB [OR 3.5 (1.8, 7.1)]. The Cohen's-d for DR or MDR in T2DM was 0.69 when compared with non-DM subjects. The T2DM patients had higher odds of resistance to isoniazid (OR 3.9, 95% CI 2.01, 7.9), rifampicin (OR 3.4, 95%CI: 1.6, 7.2) and pyrazinamide (OR 9.4, 95% CI 2.8, 25.6), and their effect sizes were ≥ 0.67. Patients with TB-T2DM (versus no DM) were more likely to present with MDR TB (HR 3.1; 95% CI 1.7, 5.8; *p* <0.001), treatment failure (HR 2.04; 95% CI 1.07, 3.8; *p* 0.02) and relapse (HR 2.1; 95% CI 1.2, 3.8; *p* 0.002), with effect sizes ≥0.39.

Conclusion: T2DM showed a substantial contribution to the presence of DR or MDR-TB and to adverse clinical outcomes during and after TB treatment. Our findings support the importance for routine screening of T2DM among newly-diagnosed TB patients in order to stratify them for immediate DR assessment, and highlight the need for clinical trials to evaluate variations to the standard TB treatment in TB-T2DM to prevent adverse treatment outcomes.

Keywords: Tuberculosis, type 2 diabetes mellitus, effect, size

2. Introduction

The overall prevalence of diabetes mellitus (DM) has increased rapidly as a result of an aging population, urbanization and associated changes lifestyle during the last decades. The International Diabetes Federation (IDF) estimated in 2015 the worldwide prevalence of type 2 diabetes mellitus (T2DM) was 8.8% (415 million people) (IDF). In Mexico, the prevalence of T2DM increased by 4.7% from 1998 to 2012, with a morbidity rate of 358.2 per 100 000 in 2012 (Sistema.Nacional.de.Vigilancia.Epidemiológica, 2013). Meanwhile, the World Health Organization (WHO) reported 9.5 million new cases of TB in 2014 and 1.5 million deaths. (WHO, 2015) In Mexico, the tuberculosis (TB) incidence was 23 per 100,000, reflecting a serious public health problem (Delgado-Sanchez et al., 2015).

The increase in prevalence of T2DM has had a significant impact on tuberculosis comorbidity, with prevalence rates ranging from 10% to 30%, mainly affecting developing countries, including Latin America (Goldhaber-Fiebert, Jeon, Cohen, & Murray, 2011; IDF, 2015; Perez-Navarro, Fuentes-Dominguez, & Zenteno-Cuevas, 2015; Restrepo et al., 2011; Shetty, Shemko, Vaz, & D'Souza, 2006; Singla et al., 2006). The number of TB cases linked with T2DM increased by 134% in the last decade in Mexico. During 2014, the coexistence of T2DM and TB (TB-T2DM) represented 21% of new cases of TB and 45% of multidrug resistance (MDR). (Delgado-Sanchez et al., 2015).

Some studies report that T2DM increased two to three times the risk of TB (Dooley & Chaisson, 2009; Jeon & Murray, 2008; Perez-Navarro et al., 2015), and diminishes the success of treatment cure (Baker et al., 2011; Jimenez-Corona et al., 2013).

In addition, T2DM has been recognized as an important risk factor for transmission, treatment failure, hospitalization, relapse, drug (DR), multidrug resistance (MDR), and delay in smear conversion (Baker et al., 2011; Dooley & Chaisson, 2009; Perez-Navarro et al., 2015; Restrepo et al., 2008; Thanh, Khue, Sy, & Strobel, 2015). However, these outcomes are not consistent across studies, perhaps due to variations in study populations (Balde et al., 2006; Magee et al., 2013; Shetty et al., 2006).

Our previous study in Veracruz, Mexico, showed that subjects with TB-T2DM have more than 3.5 times greater risk of developing drug resistance and multi-drug resistance, as well as increased risk of persisting with smear positive in the second month of treatment (OR 2.3) compared to the TB subjects. (Perez-Navarro et al., 2015) To expand on these findings, the goal of the present study was to evaluate the effect size of T2DM on the TB clinical severity at the time of diagnosis and on its treatment outcomes.

3. Methods

3.1 Population

This is an open cohort study that included patients with pulmonary TB who were 15 years or older and received anti-tuberculosis treatment from the Mycobacteriosis State Program of Veracruz Health Services (*SESVER*) during the period March 2006 to July 2015. TB diagnosis was based on positive smear or clinical findings (chest imaging studies). Newly-diagnosed TB patients who consented to participate were followed from the initial diagnosis of TB (time zero) until the record of any outcome variables (failure to treatment, drug resistance, relapse or death) or had completed treatment and had a negative smear by July 1st 2015. HIV-positive individuals were excluded.

The diagnosis of T2DM was based on the patient's medical records following the guidelines for the TB program in the state of Veracruz, which includes evidence of hyperglycemia (fasting glucose ≥126 mg/dl), self-reported history of diabetes and/or use of anti-diabetes medications. (Mexican Official Standard: NOM-015). Individuals with Type 1 DM were excluded. TB patients were classified as TB-noT2DM or TB-T2DM.

3.2 Epidemiological and clinical data

Epidemiological data and self-reported medical history were documented at the time of TB diagnosis using a questionnaire developed previously (Perez-Navarro, Fuentes-Dominguez, Morales-Romero, & Zenteno-Cuevas, 2011). Socio-economic status was stratified into high (professionals, managers and business owners); medium (employees, office workers, housewives and students) and low (workers, peasants, unemployed and prisoners). Domestic overcrowding was based on the presence of three or more persons per room in the home of the patient. Indigenous origin, when the patients recognized as indigenous. Self-reported consumption of alcohol, at least once a week, and smoking within the six months, prior to the diagnosis of TB, were recorded. Sedentary lifestyle was based on reporting the absence of a physical activity more than 3 times a week for 30 minutes each time. Medical records were used to obtain information on sputum smear extracted taken at the time zero and monthly until the end of treatment. DR was based on the isolation of *M. tuberculosis* resistant to one or more first or second line drugs based

drug sensitivity testing in vitro at any time during the course of treatment. TB relapse was documented when the patient was newly diagnosed with TB after at least three months of successful completion of treatment. Treatment failure indicated persistence of culture-confirmed bacilli in the sputum or other specimens at the end of treatment, or after a period of defaulting from treatment during the course of it, or death from any cause during the course of treatment was registered (WHO, 2015).

3.3 Statistics, survival analysis and ethical considerations

Estimation of mean differences was determined with a *t* test, while for proportions a z test was used for obtaining and odds ratio. Logistic regression was used for odds ratio (OR), adjusted for age (no gender differences were noted). Survival analysis was done following the Cox method (Bradburn, Clark, Love, & Altman, 2003) for hazards ratio (HR) adjusted by age (<35 and ≥35 years), sex, overcrowding and smoking. The effect size calculation was done with Cohen's-d (Cohen, 1998), after OR and HR transformations. The statistical packages SPSS 22 and Epidat 3.0 were used data analysis. A difference between groups was considered statistical significant if a value of $p < 0.05$ was reached.

Ethical considerations were strictly observed following guidelines from the committee of the Public Health Institute of the University of Veracruz, which oversaw the ethical issues related to this study.

4. **Results**

4.1 Characteristics that distinguish TB-T2DM versus TB-noT2DM at the time of diagnosis

During the period from March 2006 to July 2015, we enrolled 507 new TB patients, including 183 (36%) individuals with TB-T2DM; the mean age was 43 (SD 16) years old; men were more frequent (67%) than women. Patients with TB-T2DM are older with mean age 50 (SD 11) years old, also more likely to live under crowded conditions (43% *vs* 34%, p= 0.05) and to have an indigenous origin (9% *vs* 4%, p=0.06), additional demographic variables are shown in Table1.

T2DM was diagnosed 6.1 (SD 5.2) years before TB for 90% (165/183) of subjects, and the remaining 10% were diagnosed simultaneously with TB. Patients with TB-T2DM were more likely to be overweight (31% *vs* 15%, p<0.005), to have a family history of T2DM (68% *vs* 30%, p<0.005), and less likely to be smokers (30% *vs* 43%, p<0.005). The presence of malnutrition was higher among TB-no T2DM patients (25% *vs* 7%, p<0.005). (Table 1)

At the time of TB diagnosis, TB-T2DM (versus TB-noT2DM) were more likely to be smear positive, but among the smear-positive there were no further differences in smear bacillary load (Table 1). Clinical signs and symptoms at the time of TB diagnosis were similar for TB-noT2DM and TB-T2DM, except for fever (TB-T2DM subjects had OR= 1.8, 95% CI 1.2, 2.9) and a trend for more hemoptysis. The hospitalization after diagnosis with TB was higher in subjects with TB-T2DM (OR=1.8, 95% CI 1.04, 3.3). (Table 2)

4.2 Adverse events during the course of TB treatment by T2DM status

During the course of treatment, one-third of all TB patients remained with smear positive after two months of TB treatment, and this was twice as likely among the TB-T2DM group (OR=2.01, 95% CI 1.3, 3.1). (Table 3)

It is unclear as to whether DR occurred at the time of TB diagnosis or emerged during the course of treatment, given that DR testing is generally done once a patient has “failed” treatment with the standard regimen of first line medications. We found that TB-T2DM was associated with resistance to isoniazid, rifampicin and pyrazinamide (OR=3.9, 95% CI 2.1, 7.9; OR=3.4, 95% CI

1.6, 7.2; OR=9.4, 95% CI 2.8, 25.6, respectively) and a Cohen's d ≥ 0.7 was attributed to T2DM. Resistance to streptomycin and ethambutol were not associated with T2DM. T2DM was also associated with resistance to more than one drug and MDR with an effect size Cohen's-*d* of 0.69, respectively. (Table 3)

Drug resistance was found in 24% of TB-T2DM, HR=3.1 (95% CI 1.7, 5.8, p <0.001), this is equivalent to effect size Cohen's-d 0.62 for T2DM (Fig. 1). After 2 years of follow up DR in TB-T2DM was 17.5% versus 6% in TB no-T2DM individuals.

4.3 Adverse treatment outcomes by T2DM status

Mortality did not show difference by T2DM status, with an effect size Cohen's-*d* of 0.1. (Figure 2). Treatment failure was 24% among the TB-T2DM group, compared with 11% of the subjects with TB-noT2DM, the HR was 2.04 (95% CI 1.07, 3.8, p= 0.02) and size of effect Cohen's-*d* 0.39. (Figure 3) Finally, those with TB-T2DM showed 30% of relapse after completion of the anti-tuberculosis treatment, compared with only 15% in those with only TB, HR= 2.1 (95% CI 1.2, 3.8, p= 0.01), and Cohen's-*d* 0.42 (Figure 4).

Stratification of the TB patients by T2DM and smear-positivity at 2 months, showed that those with T2DM and smear positivity were more likely to have DR TB (OR= 2.4, 95% CI 1.09, 5.2; p= 0.02) with a Cohen's-*d* effect size for T2DM of 0.48, and relapse (OR= 2.7, 95% CI1.2, 6.1; p= 0.01) and a Cohen's-*d* effect size for T2DM of 0.54. Smear positivity at 2 months and T2DM was not associated with death or treatment failure. (Table 4)

5. Discussion

This is the first cohort of newly-diagnosed Mexican TB patients that were followed from the time of TB diagnosis until completion of TB treatment, over a period of seven years, including 507 patients with TB (n=324) and TB-T2DM (n=183). The calculated proportion of coexistence of both conditions is 36%, which is among the highest reported to date. While it is similar to that reported in the Mexican border with Texas, it is higher than the 21% from other cities in Mexico (Delgado-Sanchez et al., 2015; Restrepo et al., 2011; WHO, 2015), and higher than that from other studies in Latin America, which range from 10-30%. (Carrion-Torres, Cazorla-Saravia, Torres Sales, Yhuri Carreazo, & De La Cruz Armijo, 2015; Delgado-Sanchez et al., 2015; Garcia-Garcia et al., 2001; Jimenez-Corona et al., 2013; Magee et al., 2013). To our knowledge this is the first time that the effect size (Cohen's d) of T2DM for TB outcomes has been determined. The size of effect is a comprehensive view to weigh the clinical effect of a factor, in our case T2DM. Namely, we found effect sizes of 69% for drug resistance, 43% for treatment failure and 35% for relapses. These data show the clinical relevance of T2DM on the evolution of TB and presence of MDR-TB.

The patients with TB-T2DM were 10 years older than those with TB only. This difference can be explained by the parallel increase of the prevalence of T2DM with age, as has been previously reported (Delgado-Sanchez et al., 2015; Hongguang et al., 2015; Perez-Navarro et al., 2015; Raghuraman, Vasudevan, Govindarajan, Chinnakali, & Panigrahi, 2014). Our study supports the concept that family history of diabetes (reported in 68% of patients with TB-T2DM, OR 5.04, IC 95% 3.4, 7.4, $p< 0.001$) is a risk factor for development of TB (Ogbera et al., 2015; Perez-Navarro et al., 2015; Chittoor et al., 2013).

Even though malnutrition or underweight are traditional risk factors for developing TB (Leung et al., 2007), only 18% of TB patients had BMI ≤18.5. Low BMI was less frequent in TB-T2DM and consistent with findings from other researchers where BMI >25 is more likely among TB-T2DM (Magee et al., 2013; Perez-Navarro et al., 2011). This can have clinical implications because according to the management guidelines for TB control, drug therapy should be adjusted when the BMI ≥ 25 (WHO, 2015). However, overweight and obesity is not routinely taken into account for drug adjustment during TB treatment. Thus, it is possible that TB-2DM patients who are overweight are receiving suboptimal doses of TB medications, and could be contributing to

their reported lower plasma levels (Babalik et al., 2013; Nijland et al., 2006; Ruslami et al., 2007). In these studies, suboptimal levels of TB medications have been attributed to chronic hyperglycemia or to a possible interaction between drugs for the management of DM and TB (Baker et al., 2011; Ruslami et al., 2010). Our findings suggest that overweight should be an additional consideration in such cases.

At the time of TB diagnosis, TB-T2DM patients were more likely to have fever, more hemoptysis, more likely to be smear-positive, and after two months of treatment higher odds for persistence of positive smear. Smear positivity and delayed bacterial clearance from sputum during treatment are reported in most other studies on TB-T2DM (Alisjahbana et al., 2007; Dooley & Chaisson, 2009; Jimenez-Corona et al., 2013; Wu et al., 2016). Together, these findings reflect higher bacillary load at diagnosis that takes longer to clear during treatment, which should favor TB transmission to nearby contacts (Carrion-Torres et al., 2015). Thus, T2DM co-morbidity is not only a problem for the patient with TB, but a comorbidity that challenges TB control in the community.

The delay in smear conversion during treatment may also be due to primary drug resistance that is not detected at the time of TB diagnosis, but rather, until after of three months of treatment and the patients persisting whit smear positive. This delay in DR testing is due to funding limitations, and it is not just a particular situation in Mexico, but for most of the developing countries where TB and T2DM are prevalent. Thus, we find higher number of cases of MDR-TB among TB-T2DM patients, as reported in some studies (Bashar, Alcabes, Rom, & Condos, 2001; Chang et al., 2011; Chiang et al., 2015; Garcia-Garcia et al., 2001), but we cannot distinguish primary from secondary drug resistance cases in TB-T2DM patients. This is a serious limitation that calls for changes.

We found that subjects with TB-T2DM are prone to TB drug resistance which is known to occur by the occurrence of mutations in the bacterial genome, after selective pressure by TB drugs (Fujino, Hasegawa, Satou, Komatsu, & Kawada, 1998). Our finding of higher odds of drug resistance for isoniazid, rifampicin and pyrazinamide in TB-T2DM patients is consistent with previous reports (Dooley & Chaisson, 2009; Fisher-Hoch et al., 2008; Garcia-Garcia et al., 2001; Jimenez-Corona et al., 2013; Magee et al., 2013), but not others (Chang et al., 2011; Chiang et al., 2015; Jimenez-Corona et al., 2013; Singla et al., 2006; Syed Suleiman, Ishaq Aweis,

Mohamed, Razakmuttalif, & Moussa, 2012). One explanation could be due to differences in the host immune response resulting from the diverse genetic background of different populations, or differences in the management of the disease by the TB programs worldwide due to availability of resources. For example, testing for DR is not available for all newly-diagnosed TB patients in Mexico or many other countries worldwide. Under these circumstances, our findings highlight the importance of prioritizing the use of limited resources for DR testing among newly-diagnosed TB patients with T2DM.

In our study we could not distinguish primary versus acquired drug resistance, given that testing was only conducted three months after the beginning of treatment in the patients persisting with smear positive. A previous study suggested mainly the occurrence of primary MDR-TB in T2DM patients (Fisher-Hoch et al., 2008), but overall, data is scanty in the literature. Acquired drug resistance could be favored by the apparently lower serum concentrations of anti-tuberculosis drugs in TB-T2DM patients. Possible explanations for these pharmacokinetic alterations are related with the interactions between drugs for TB and T2DM, reduced absorption or defective liver function in T2DM patients.(Babalik et al., 2013; Baker et al., 2011; Nijland et al., 2006; Ruslami et al., 2010; Ruslami et al., 2007).

We further found that stratification by T2DM status of individuals with positive smear at two months, further defined a higher risk group, with nearly 3-fold higher odds of DR and a similar risk for TB relapses, when compared to TB-no T2DM with smear positivity at two months. Together, our findings on higher risk of adverse TB treatment outcomes points to the need for clinical trials that evaluate modifications to current TB treatment regimens in T2DM, such as extended time for the first phase of treatment, modification to higher doses of anti-TB medications, and treatment for 9 months (DOT) versus 6 months (DOTS).

T2DM may favor the development and adverse treatment outcomes of TB due to the presence of hyperglycemia (Dooley & Chaisson, 2009; Ruslami et al., 2010; Singla et al., 2006), compromising the immune response of the host against Mycobacterium by dysregulation of interleukin IL1β, TNF-α and IL-6, IFN-γ, IL-18, IL-10 and IL-12, (Delamaire et al., 1997; Tsukaguchi et al., 2002), reducing or delaying phagocytosis and initiation of innate immune responses in TB naïve or latent tuberculosis infection-positive individuals, and an exaggerated Th1 and Th17 response once TB infection has developed (Bashar et al., 2001; Restrepo,

Twahirwa, Rahbar, & Schlesinger, 2014; van Crevel, Dockrell, & Consortium, 2014). Future studies should address the impact of the increase of T2DM prevalence on TB. The International Diabetes Federation predicts that the prevalence of diabetes will be 642 million in 2040 (IDF, 2015), so it should be a priority for the development of deeper binomial studies, and pharmacological management in order to reduce the social and economic impact in society. (Dye, Bourdin Trunz, Lonnroth, Roglic, & Williams, 2011; Jeon & Murray, 2008; Perez-Navarro et al., 2015; Riza et al., 2014).

In conclusion our findings suggest that T2DM has an important effect on the presence of TB adverse events, such as drug resistance, smear persistence, treatment failure and relapse. Thus, prompt identification of T2DM patients among the newly diagnosed TB patients diabetes should help flag patients. Thus, resources to expand diabetes testing will help improve TB outcomes. A coordinated approach to understanding both pathologies is necessary for as reducing the risk of local, regional and global spread, related to these co-morbid conditions in order to achieve the desired goal of TB elimination by 2050.

Acknowledgements

Non

6. **Literature cited**

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FIGURE LEGENDS

Figure 1. Time elapsed from diagnosis of TB to the detection of drug resistance by T2DM status. Newly-diagnosed TB patients were followed during the course of treatment and Cox Proportional hazards ratio was estimated for detection of drug resitance to either isoniazid, rifampin, ethambutol, pyrazinamide or streptomycin, by T2DM status.

Figure 2. Time elapsed from diagnosis to death among TB patients by T2DM status. Newly-diagnosed TB patients were followed for death of any cause during the course of treatment and Cox Proportional hazards ratio was estimated by T2DM status.

Figure 3. Time elapsed from TB diagnosis to detection of treatment failure treatment by T2DM status. Persistence of culture-confirmed bacilli in the sputum or other specimens at the end of treatment or after a period of defaulting from treatment disappearance during treatment, and Cox Proportional hazards ratio estimated by T2DM status.

Figure 4. Time elapsed since the completion of TB treatment and diagnosis of TB relapse by T2DM status. TB patients were followed for 35±24 months after successful completion of treatment (smear negative), and relapses after at least 3 months of treatment completion were analyzed by Cox Proportional Hazards ratio by T2DM status.

Table 1. Socio-demographic and clinical characteristics of TB patients by T2DM status

Variable		Total *n*= 507 (%)	TB *n*=324 (%)	TB-T2DM *n*=183 (%)	*p*
Sex	Male	337 (67)	219 (68)	118 (64)	0.53
	Female	170 (33)	105 (32)	65 (36)	
Age (years)	Mean ±SD	42.65±16.4	38.6±17.4	49.7±11.4	*<0.005*
	≥ 35	332 (66)	170 (53)	162 (88)	*<0.005*
	< 35	175 (34)	154 (47)	21 (12)	
Illiteracy	Yes	85 (17)	49 (15)	36 (20)	0.23
	No	422 (83)	275 (85)	147 (80)	
Place of residence	Rural	149 (29)	90 (28)	59 (32)	0.33
	Urban	358 (71)	234 (72)	124 (68)	
Overcrowding	Yes	190 (38)	111 (34)	79 (43)	*0.05*
	No	317 (62)	213 (66)	104 (57)	
Ethnic group	Yes	30 (6)	14 (4)	16 (9)	0.06
	No	477 (94)	310 (96)	167 (91)	
Socio-economic status	Low	191 (38)	126 (39)	65 (36)	0.51
	Medium-High	316 (62)	198 (61)	118 (64)	
Smoking	Yes	194 (38)	140 (43)	54 (30)	*<0.005*
	No	313 (62)	184 (57)	129 (70)	
Alcoholism	Yes	259 (51)	170 (53)	89 (49)	0.46
	No	248 (49)	154 (47)	94 (51)	
Previous TB contact	Yes	133 (26)	81 (33)	52 (40)	0.26
	No	374 (74)	243 (77)	131 (60)	
T2DM family history	Yes	222 (44)	97 (30)	125 (68)	*<0.005*
	No	285 (56)	227 (70)	58 (32)	
Sedentary lifestyle	Yes	426 (84)	270 (83)	156 (85)	0.66
	No	81 (16)	54 (17)	27 (15)	
TB diagnosis by:	Positive smear	464 (91.5)	292 (90)	172 (94)	0.18
	Chest Ray X	42 (8)	31(9.5)	11 (6)	0.22
	TAC	1(0.5)	1 (0.5)	0	
Smear at baseline	No bacillus	17 (4)	16 (6)	1 (1)	*0.01*
	< 1	187 (40)	122 (42)	65 (38)	0.47
	1-10	121 (26)	70 (24)	51 (29)	0.20
	> 10	139 (30)	84 (29)	55 (32)	0.51
BMI (kg/m^2)	< 18.5	78 (18)	68(25)	10 (7)	*<0.005*
	18.6-24.9	256 (61)	162 (60)	94 (62)	*0.69*
	≥25	88 (21)	41 (15)	47 (31)	*<0.005*

BMI: Body mass index determined at the time of TB diagnosis.
TB: Tuberculosis
T2DM: Type 2 diabetes mellitus
TAC: Computed axial tomography
p: Proportions were compared by z-test, and mean with standard deviations with square Chi

Table 2. Clinical signs and symptoms observed in patients TB and TB-T2DM

Variable		Total n=507 (%)	TB n=324 (%)	TB-T2DM n=183 (%)	*d°*	*OR**	*IC 95%*	*p*
Cough	Yes	457 (93)	286 (92)	171 (95)	0.29	1.7	0.73-3.9	0.21
	No	35 (7)	26 (8)	9 (5)				
Fever	Yes	492 (65)	189 (61)	130 (72)	***0.32***	***1.8***	***1.2-2.9***	***0.004***
	No	173 (35)	123 (39)	50 (28)				
Hemoptysis	Yes	115 (23)	66 (21)	49 (27)	0.22	1.5	0.95-2.4	0.07
	No	377 (77)	246 (79)	131 (73)				
Diaphoresis	Yes	422 (86)	42 (14)	28 (16)	0.05	1.1	0.63-1.9	0.71
	No	70 (14)	270 (87)	152 (84)				
Weakness	Yes	249 (51)	152 (49)	97 (54)	0.1	1.2	0.8-1.8	0.35
	No	243 (49)	160 (51)	83 (46)				
Fatigue	Yes	265 (54)	162 (52)	103 (57)	0.1	1.2	0.8-1.8	0.31
	No	227 (46)	150 (48)	77 (43)				
Anorexy	Yes	85 (17)	56 (18)	29 (16)	-	0.9	0.53-1.5	0.75
	No	407 (83)	256 (82)	151 (84)	0.05			
Weight loss	Yes	334 (68)	217 (70)	117 (65)	-	0.8	0.57-1.3	0.56
	No	158 (32)	95 (30)	63 (35)	0.11			
Hospitalization	Yes	72 (14)	41 (13)	31 (17)	***0.32***	***1.8***	***1.04-3.3***	***0.03***
	No	435 (86)	283 (87)	152 (83)				

* OR adjusted by age, sex, smoking and overcrowding, ° Size effect by Cohen *d.*

Table 3. Drug resistance in tuberculosis in patients with and without type 2 diabetes mellitus

Variable		**Total n=507 (%)**	**TB n=324 (%)**	**TB-T2DM n=183 (%)**	***d°***	***OR****	***95% CI***	***p***
Smear + at 2 months	Yes	149 (29)	77 (24)	72 (39)	0.38	**2.01**	**1.3-3.1**	**<0.005**
of treatment	No	358 (71)	247 (76)	111 (61)				
Resistance	Yes	57 (11)	22 (7)	35 (19)	0.69	**3.5**	**1.8-6.7**	**<0.005**
to 1≥ drugs	No	450(89)	302 (93)	148 (81)				
MDR	Yes	42 (8)	16 (5)	26 (14)	0.69	**3.5**	**1.6-7.1**	**<0.005**
	No	465 (92)	308 (90)	157 (86)				
Isoniazid	Yes	52 (10)	19 (6)	33 (18)	0.75	**3.9**	**2.01-7.9**	**<0.005**
	No	455 (90)	305 (94)	150 (82)				
Rifampicin	Yes	41 (8)	16 (5)	25 (14)	0.67	**3.4**	**1.6-7.2**	**<0.005**
	No	466 (92)	308 (95)	158 (86)				
Pyrazinamide	Yes	23 (5)	6 (2)	17 (9)	1.17	**9.4**	**2.8-25.6**	**<0.005**
	No	484 (95)	318 (98)	166 (91)				
Streptomycin	Yes	34 (7)	17 (5)	17 (9)	0.29	1.7	0.81-3.8	0.14
	No	473 (93)	307 (95)	166 (91)				
Ethambutol	Yes	22 (4)	13 (4)	26 (14)	0.10	1.2	0.46-3.2	0.69
	No	485 (96)	311 (96)	157 (86)				

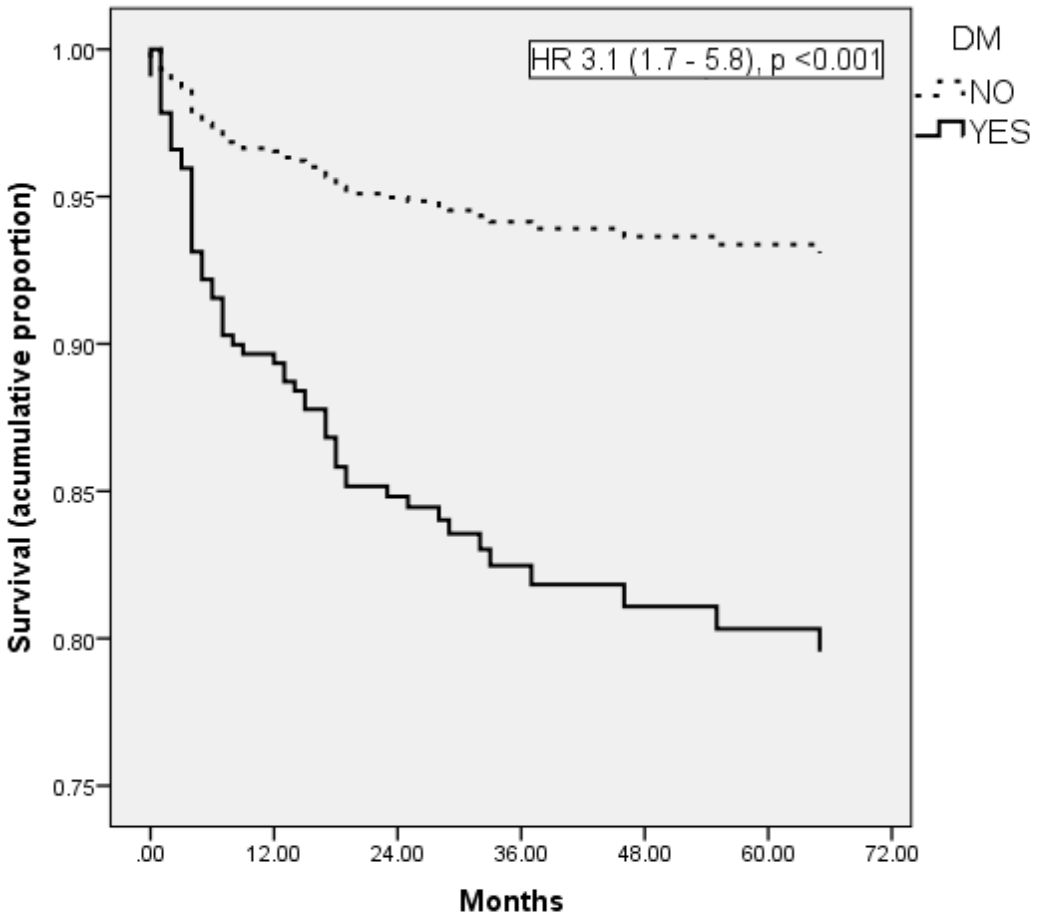
* OR adjusted by age, sex, smoking and overcrowding, ° Size effect by Cohen-*d.*

Table 4. Drug resistance and treatment outcomes by T2DM and smear positivity at two months

	TB-T2DM (*n*=183)		**TB (*n*=324)**					
Smear results at two months of treatment:	**+ n= 72 (39%)**	**- n=111 (61%)**	**+ n= 77 (24%)**	**- n=247 (75%)**	***d*°**	**OR***	**IC 95%**	***p***
Drug resistance	21(29)	14(13)	16 (21)	6 (2)	0.48	2.4	1.09 – 5.2	0.02
Failure	14 (19)	10 (9)	17 (22)	6 (2)	0.40	2.07	0.84-5.8	0.11
Relapse	21(29)	13 (12)	10 (13)	22 (9)	0.54	2.7	1.2-6.1	0.01
Death	5 (7)	5 (5)	4 (5)	9 (4)	0.25	1.6	0.4-6.5	0.46

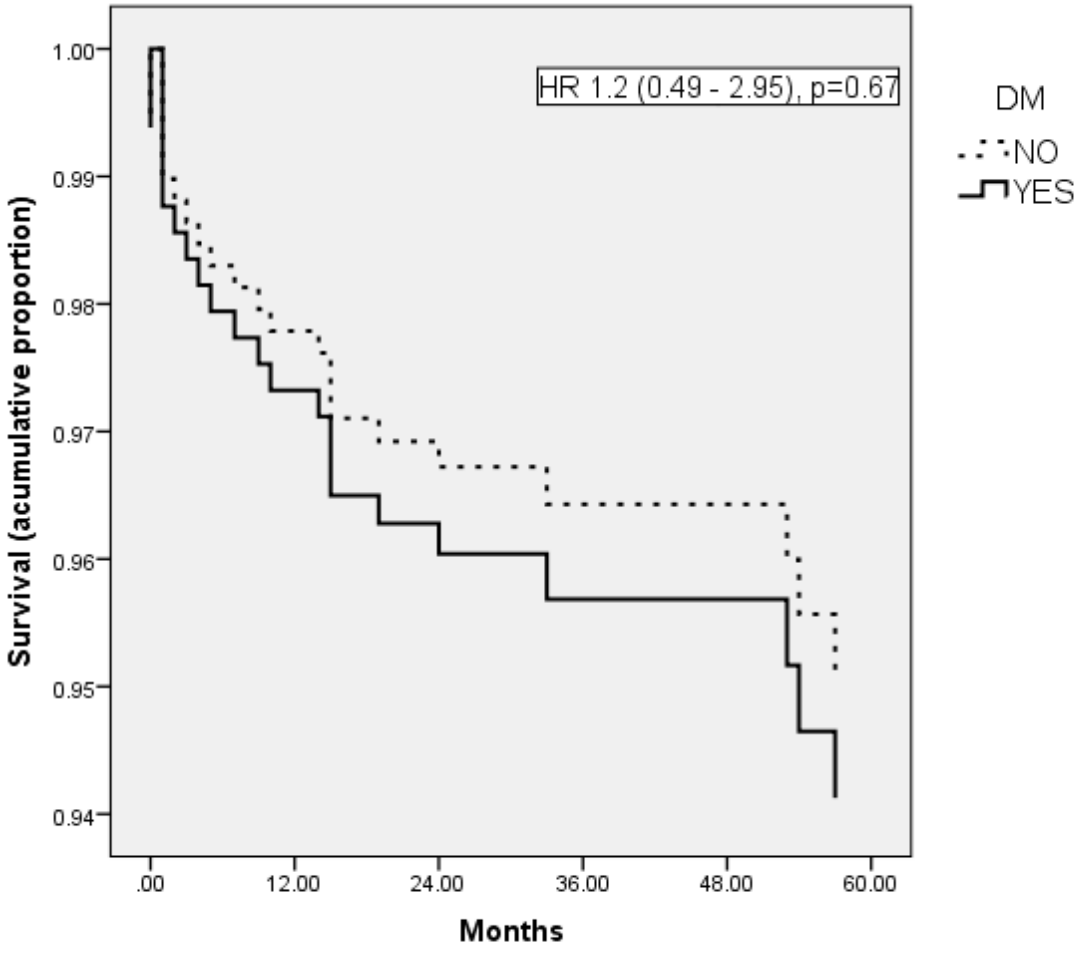
* OR adjusted by age, sex, smoking and overcrowding, ° Size effect by Cohen *d*

Figure 1. Time elapsed from diagnosis of TB to the detection of drug resistance by T2DM status



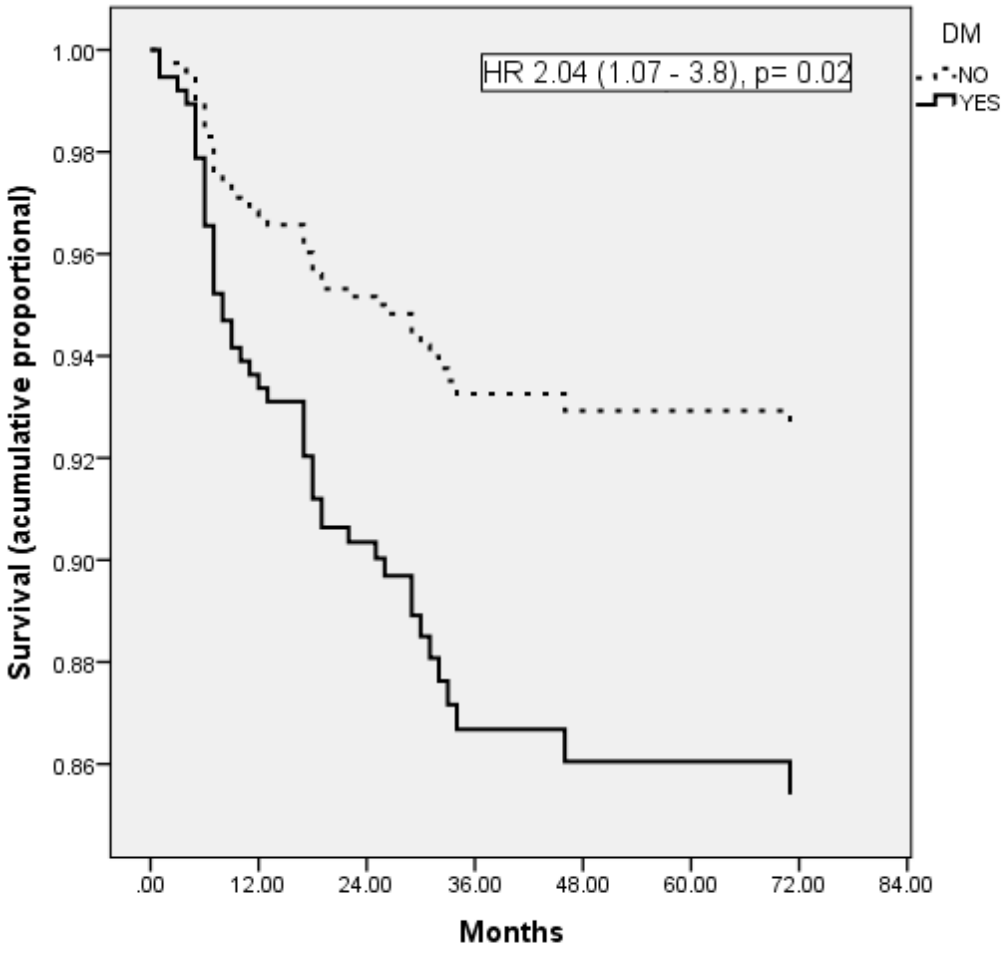
*HR,Cox regression,adjusted by age,sex,smoking,overcrowding,effect size Cohen's d=0.62

Figure 2. Time elapsed from diagnosis to death among TB patients by T2DM status



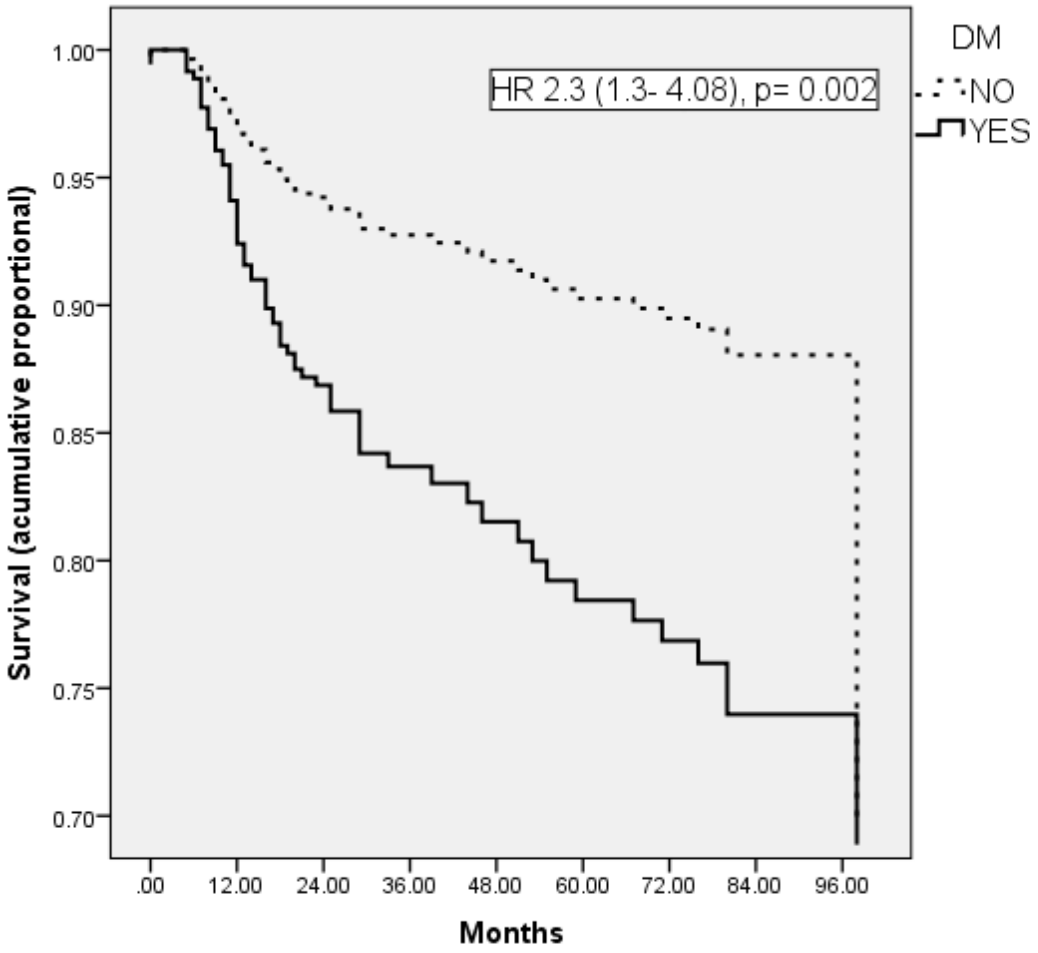
*HR, Cox regression, adjusted by age, sex, smoking and overcrowding, effect size Cohen's d= 0.1

Figure 3. Time elapsed from TB diagnosis to detection of treatment failure treatment by T2DM status



HR*, Cox regression, adjusted by age, sex, smoking and overcrowding, effect size Cohen's d= 0.39

Figure 4. Time elapsed since the completion of TB treatment and diagnosis of TB relapse by T2DM status



HR*, Cox regression, adjusted by age, sex, smoking and overcrowding, effect size Cohen's d= 0.45