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Drug resistance of previously treated tuberculosis patients with diabetes mellitus in Shandong, China

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Drug resistance of previously treated tuberculosis patients with diabetes mellitus in Shandong, China

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ABSTRACT

Background: Although the association between diabetes mellitus (DM) and tuberculosis (TB) has been well-documented for centuries, evidence of the link between diabetes and drug resistance among previously treated TB patients remains limited and inconsistent.

Methods: An observational study was performed that involved 1791 retreated TB-no DM patients (refers to TB cases without diabetes) and 93 retreated TB-DM patients (refers to TB cases with diabetes) in Shandong, China from 2004 to 2017. Baseline data including demographic and clinical characteristics, drug susceptibility test (DST) results, and diabetes status were collected. Categorical baseline characteristics were compared by Fisher's exact or Pearson Chi-square test. Univariable analysis and multivariable logistic models were used to estimate the association between diabetes and different drug resistance profiles.

Results: Retreated TB-DM patients have a higher rate of drug resistance than TB-no DM patients (34.41% vs 25.00%, $P < 0.01$). Diabetes co-morbidity was significantly associated with any drug-resistant tuberculosis (DR-TB, odds ratio (OR):1.56, 95% confidence interval (CI): 1.01–2.43), multidrug resistant tuberculosis (MDR-TB, OR: 2.48, 95%CI:1.39–4.41; adjusted OR (aOR):2.94, 95%CI:1.57–5.48), isoniazid-related resistance (OR:1.71, 95%CI:1.04–2.81), rifampin-related resistance (OR:2.56, 0.54, 95%CI: 1.54–4.26; aOR:2.69, 95%CI:1.524–4.74), isoniazid + rifampin resistance (OR: 3.55, 95%CI:1.33–9.44; aOR:4.13, 95%CI:1.46–11.66), any resistance to isoniazid + streptomycin (OR:2.34, 95%CI:1.41–3.89; aOR:2.22, 95%CI:1.26–3.94), and any resistance to rifampin + isoniazid (OR:2.48, 95%CI:1.39–4.41; aOR:2.94, 95%CI: 1.57–5.48), compared with pan susceptible TB cases, $P < 0.05$.

Conclusions: The risk of acquired drug resistance increased significantly among retreated TB-DM patients compared with retreated TB-no DM patients, underlining the necessity of more interventions during the clinical management of TB-DM cases.

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1. Introduction

Resistance to anti-tuberculosis drugs could result in less effective treatment options, poor outcomes of the treatments, the spread of drug-resistant tuberculosis (DR-TB), and higher medical expenses of the healthcare system [1,2].There were two mechanisms for DR-TB: i) acquired (or secondary) resistance: *Mycobacterium tuberculosis* strains develop resistance during TB treatment, usually caused by spontaneous chromosomal mutations or ii) transmitted (or primary) resistance: infection with a drug-resistant strain [3]. According to the World Health Organization (WHO), multidrug resistant tuberculosis (MDR-TB) is a major challenge for tuberculosis (TB) elimination [4]. In 2017, there were an estimated 10.0 million incident cases of TB (range, 9.0–11.1 million), equivalent to 133 cases (range, 120–148) per 100,000 population. 3.5% (95% confidence interval [CI]: 2.5–4.7%) of new cases and 18% (95% CI:6.3–34%) of previously treated cases had MDR/RR-TB [4]. China accounted for 9% of the global total TB cases (only behind India, 27%) and with the largest numbers of MDR/RR-TB cases [4].

Diabetes mellitus (DM) is a major risk factor for tuberculosis infection, and triples the risk of developing active TB disease due to an impaired immune system [5,6], meanwhile it to some extent contributes to DR-TB [7,8]. At present there were nearly 415 million people worldwide living with DM, and approximately 15% of global TB cases can be attributed to DM co-morbidity [9]. The dual burden of TB and DM has became a major global public health problem [5].The global burden of TB-DM overlap is high, with a prevalence of 16% globally, 24% in North America, 23% in Oceania, 17% in Asia, 11% in South America, 7% in Africa, and 6% in Europe [10]. Recent years, there are a growing number of researches centred on the risk of active or latent tuberculosis infection among diabetes patients, and treatment outcomes or rate of smear conversion among TB-DM patients (defined as tuberculosis cases with diabetes) [7,10,11]. However, few previous study [5,7,8] had focused on acquired drug resistance profiles and clinical characteristics among retreated TB-DM patients, most of which were conducted among newly diagnosed TB cases. Considering the widespread of TB and DM, and the higher drug resistant rate of retreated TB patients, it is of great significance to explore the association between DM and acquired - drug resistance among retreated TB patients, especially in China.

The objectives for our study were to:1) compare the clinical characteristics and drug resistance profiles between retreated TB-DM cases and TB-no DM cases (defined as tuberculosis cases without diabetes); 2) investigate the risk factors of acquired drug resistance among retreated TB-DM cases; 3) evaluate the correlations between DM and different subgroups of retreated DR-TB, for instance, mono-resistant tuberculosis (MR-TB), MDR-TB, polydrug resistant tuberculosis (PDR-TB), isoniazid-related resistance, rifampin-related resistance, and isoniazid + rifampin resistance.

2. Methods

2.1. Ethics statement

Ethical approvals of our study were obtained from the Ethics Committee of Shandong Provincial Hospital, affiliated with Shandong University (SPH) and the Ethic Committee of Shandong Provincial Chest Hospital (SPCH), China. Before data analysis and reporting, any personal identifiers of TB patients were removed.

2.2. Setting

Study population were collected from Shandong province, China, located at 36°24′N latitude 118°24′E longitude with an area of 157,100 km^2. Shandong province was consisted by 17 municipalities and 140 counties (districts) with 100 million inhabitants in 2018 [12]. There were approximately 224,480 diagnosed pulmonary TB cases in 6 cities of Shandong, China, during 2005–2017, and 92% were new cases; the prevalence of total pulmonary TB patients had declined from 40.8 to 26.25 per 100,000 during this period [13].The MDR-TB rate of retreated TB cases (8.7%) was higher than the total MDR-TB rate (6.2%) in Shandong during 2007–2014 [14].The total prevalence of diabetes in China was 9.4%, up to 109.6 million diabetes patients (aged between 20 and 79) [15].

2.3. Study population and definitions

We conducted a retrospective observational study of all retreated TB patients (1884 cases) with drug-susceptibility testing (DST) results and information on diabetes status notified to the TB Surveillance System in Shandong, China between 1 January 2004 and 31 December 2017, of which 93 were TB-DM cases, and 1791 were TB-no DM patients. All these retreated TB patients were fully cured at their initial treatment. DST results were available for at least first-line anti-TB drugs (isoniazid, INH; rifampin, RFP; ethambutol, EMB; streptomycin, SM). Two province-level hospitals (SPH and SPCH), 13 municipal-level and 21 county-level local health departments were responsible for the surveillance of DR-TB throughout Shandong, China. Demographic and clinical characteristics on age, sex, body mass index (BMI), drinking, smoking, cavity, and extra-pulmonary TB were also collected. Patients infected with *Nontuberculosis mycobacteria* (NTM), or patients without information on diabetes were excluded (Fig. 1). Acquired resistance was defined as a sensitive DST result for a drug on 1 isolate and a subsequent resistant DST result for the same drug on another [16]. TB-DM cases and TB-no DM cases were defined as TB patients with or without diabetes, respectively [16]. Mono-resistance (MR) refers to resistance to one first-line anti-TB drug only [16]. Polydrug resistance (PDR) refers to resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin [16]. Multidrug resistance (MDR) refers to resistance to at least both isoniazid and rifampicin [16].

2.4. Laboratory diagnosis and drug susceptibility testing

Surveillance sites in Shandong follows the global guidance that at least two sputum samples were collected from eligible patients, and then sent all sputum samples to Katharine Hsu International Research Center of Human Infectious Diseases (KICID) of SPCH for bacteriologic culture, phenotypic DST, and species identification. Isolates were inoculated into tubes of acidified Löwenstein-Jensen (L-J) medium after conventional pretreatment process [17]. Cultures with growing colonies were sent for further identification and DST. Based on previous published protocol, standard traditional biochemical testings including P-nitrobenzoic acid, 2-thiophene carboxylic acid hydrazide testing and 16S rRNA gene sequence analysis (MicroSeq ID Microbial Identification Software (version 2.0); Applied Biosystems, Foster City, CA, USA) were used to differentiate *Mycobacterium tuberculosis* from other *Mycobacteria* spp. [18].

For decades, the diagnosis of diabetes has been based on glucose criteria, either the fasting plasma glucose (FPG) or the 75-g oral glucose tolerance test (OGTT) [19]. The screening and laboratory diagnosis for DM strictly followed national guidelines, and a FPG was examined by venous plasma and biochemical analyser with cut-off thresholds recommended by the WHO [19,20]. Diagnostic criteria include the following: 1) FPG ≥7.0 mmol/L (126 mg/dl); 2) A 2-h plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during OGTT [20].

The reference laboratories routinely performed DST for first-line anti-TB drugs (isoniazid, 0.2 μg/mL; rifampin, 40 μg/mL; streptomycin, 10 μg/mL; ethambutol, 2 μg/mL) on all *Mycobacterium tuberculosis* complex samples using absolute concentration method on L-J media. DST for second-line injectables (amikacin, capreomycin, and kanamycin) and fluoroquinolones (ofloxacin, moxifloxacin, and ciprofloxacin) was performed on rifampin-resistant isolates or at the request of the treating clinician. Two professionally trained investigators were independently responsible for quality assessment and data extraction;

and all laboratories involved in our study regularly accepted external quality assessment of Superior TB National Reference laboratory in SPCH.

2.5. Statistical analysis

Categorical baseline characteristics of retreated TB cases including age (0–14, 15–24, 25–44, 45–64, 65+), sex (male or female), BMI (<18.5, 18.5–24.9, ≥25), drinking (yes/no), smoking (yes/no), cavity (yes/no), patients type (extra-pulmonary TB/pulmonary TB) were compared by diabetes status using Fisher's exact or Pearson Chi-square test. Univariable analysis and Multivariable logistic models were used to estimate the association between diabetes and different drug resistance profiles including DR-TB (total), MR-TB (total), MDR-TB (total), PDR-TB (total). INH-related resistance, RFP-related resistance, SM-related resistance, INH + SM resistance (PDR2), INH + RFP resistance (MDR1), any resistance to INH + SM, any resistance to RFP + INH. Similarly, logistic regression models were applied to explore the risk factors of primary drug resistance among TB-DM cases as well. Covariates adjusted for multivariable models were chosen based on previous studies, including age, sex (male or female), BMI, drinking (yes/no), smoking (yes/no), and cavity (yes/no) [21]. All statistical analyses were performed using SPSS software (version 20.0). A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1. Patient population

A total of 93 retreated TB-DM cases (Group 1, G1) and 1791 retreated TB-no DM patients (Group 2, G2) with susceptibility data from Shandong, China during 2004–2017 were enrolled in our study. More than 95% were aged more than 15 years. The percentage of TB-DM cases aged between 45 and 64 years (44/81, 54.32%) were much higher than that of TB-no DM cases (571/1703, 33.53%)(P < 0.01), but lower among 15–24 years old (G1 vs G2:2.47% vs 17.21%, p < 0.01). Both these two groups had a similar proportion of those aged between 25 and 44 years (G1 vs G2:18.52% vs 22.20%) or >65 years (G1 vs G2:29.63% vs 26.84%), P > 0.10. Most were male (G1 vs G2:86.05 vs 81.04%), P > 0.10. More than two thirds had a BMI between 18.9 and 24.9 (G1 vs G2:67.90% vs 66.67%), P > 0.10. 13.95% of group 1 had a BMI <18.5, which was much less than that of group 2 (29.20%), P < 0.01. In contrast, group 1 had more cases with BMI ≥25 than group 2 (16.05% vs 4.14%), P < 0.01. More than half (58.23%) of TB-DM cases were combined with cavities, while which were less than half among TB-no DM patients (33.82%), P < 0.01. The percentage of smokers and alcohol

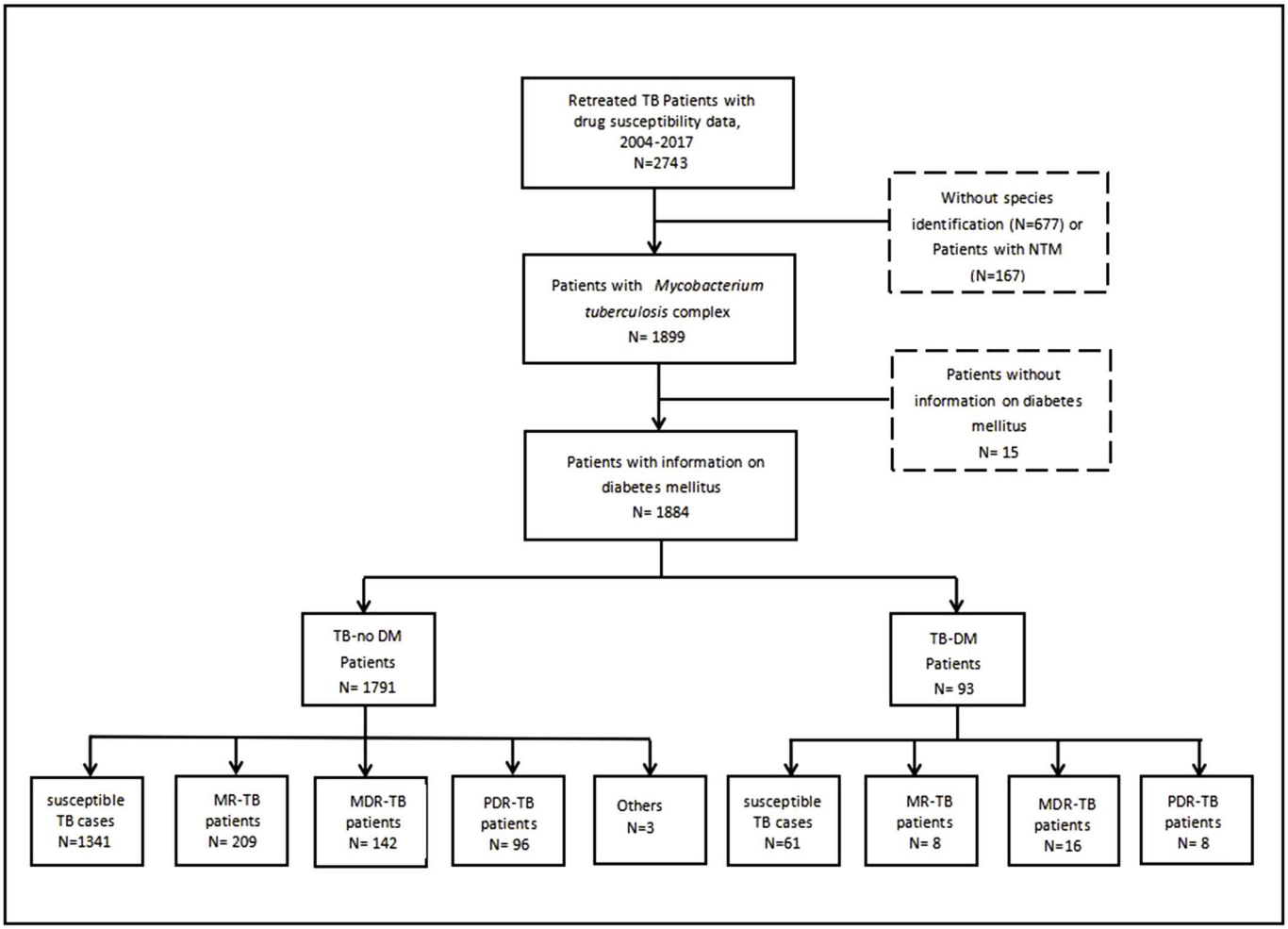

Fig. 1. Retreated TB-DM patients and TB-no DM patients in Shandong, China.
NTM, *nontuberculous mycobacteria*; DR-TB, drug-resistant tuberculosis; MR-TB, mono-resistant tuberculosis; MDR-TB, multidrug resistant tuberculosis; PDR-TB, polydrug resistant tuberculosis;
TB-DM refers to TB patients with diabetes.
TB-no DM refers to TB patients without diabetes.
Others in TB-no DM refers to those which are DR-TB but belong not to MR-TB, MDR-TB, and PDR-TB.

users were 25.67% and 22.22% in group 1, 19.20% and 17.03% in group 2, respectively. There were no statistical differences in comorbidities including asthma (0.00% vs 0.61%), COPD (3.23% vs 1.90%), bronchiectasis (1.08% vs 0.45%), silicosis (0.00% vs 0.22%), cancer (1.08% vs 0.34%) between TB-DM cases and TB-no DM patients, P > 0.10, but TB-DM cases were more likely to be complicated with hypertension than TB-DM cases (9.68% vs 0.84%, P < 0.01). Other patient characteristics are shown in Table 1.

3.2. Acquired drug resistance profile

The percentage of DR-TB among 93 retreated TB-DM cases and 1791 retreated TB-no DM cases were 34.41% (32/93) and 25.13% (447/1791), respectively, P < 0.05 (see Table 2). While divided into different drug resistant subgroups, we found that the rates of MDR were much higher in group 1 (G1 vs G2:17.20% vs 7.94%, p < 0.05) including MDR1 (INH + RFP, G1 vs G2:5.38% vs 1.73%, p < 0.01), MDR2(INH + RFP + EMB + SM, G1 vs G2:2.15% vs 1.57%, P > 0.05), and MDR3 (INH + RFP + SM, G1 vs G2:7.53% vs 3.58%, P > 0.05). There were no significant differences on the rates of total MR-TB cases (G1 vs G2:8.60% vs 11.69%, P > 0.10) and PDR-TB cases (G1 vs G2:8.6% vs 5.37%, P > 0.10) between group 1 and group 2, but with statistical differences on the proportion of MR-TB (RFP) (G1 vs G2:4.3% vs 1.34%, P < 0.05). When considering any resistance to first-line anti-TB drugs, we found that TB-DM cases had higher rates of INH-related resistance (G1 vs G2:24.73% vs 16.50%, p < 0.05) and INH-related resistance (G1 vs G2:23.66% vs 10.57%, p < 0.01) than TB-no DM cases. In addition, the percentage of any resistance to EMB (G1 vs G2:4.30% vs 3.41% P > 0.10) or SM (G1 vs G2:21.51% 16.11%, P > 0.10) were similar in these two groups.

Table 1
Baseline characteristics of 1884 retreated TB patients in Shandong, China, 2004–2017.

Characteristics	TB patients without diabetes n = 1791	TB patients with diabetes n = 93	P value
Age(years) (n = 1703/n = 81)			
0-14	4/1703 (0.235%)	0/81 (0.00%)	1.00
15-24	293/1703 (17.21%)	2/81 (2.47%)	P < 0.001**
25-44	378/1703 (22.20%)	15/81 (18.52%)	0.44
45-64	571/1703 (33.53%)	44/81 (54.32%)	P<0.001**
>65	457/1703 (26.83%)	24/81 (29.63%)	0.58
Sex(n = 1730/n = 86)			
Female	328/1730 (18.96%)	12/86 (13.95%)	0.25
Male	1402/1730 (81.04%)	74/86 (86.05%)	0.25
BMI(n = 1593/n = 81)			
<18.5	465/1593 (29.19%)	13/81 (16.05%)	0.011*
18.5–24.9	1062/1593 (66.67%)	55/81 (67.90%)	0.82
≥25	66/1593 (4.14%)	13/81 (16.05%)	P < 0.001**
Cavity(n = 1635/n = 79)			
No	1082/1635 (66.18%)	33/79 (41.77%)	P < 0.001**
Yes	553/1635 (33.82%)	46/79 (58.23%)	P < 0.001**
smoking(n = 1698/n = 90)			
No	1372/1698 (80.801%)	67/90 (74.44%)	0.14
Yes	326/1698 (19.20%)	23/90 (25.56%)	0.14
Drinking(1691/n = 90)			
No	1403/1691 (82.97%)	70/90 (77.78%)	0.21
Yes	288/1691 (17.03%)	20/90 (22.22%)	0.21
Type(n = 1776/n = 93)			
Extrapulmonary TB	1/1776 (0.06%)	1/93 (1.08%)	0.097
Pulmonary TB	1775/1776 (99.94%)	92/93 (98.92%)	0.097
Comorbidities			
Asthma	11/1791 (0.61%)	0/93 (0.00%)	1.00
COPD	34/1791 (1.90%)	3/93 (3.23%)	0.43
Bronchiectasis	8/1791 (0.45%)	1/93 (1.08%)	0.37
Silicosis	4/1791 (0.22%)	0/93 (0.00%)	1.00
Hypertension	15/1791 (0.84%)	9/93 (9.68%)	P < 0.001**
Cancer	6/1791 (0.34%)	1/93 (1.08%)	0.29

BMI, body mass index; COPD, chronic obstructive pulmonary disease; **P < 0.01; *P < 0.05.

Table 2
Drug-resistant profiles among retreated TB patients with diabetes.

Drug Resistance	DR-TB patients without diabetes (n = 450/1791, 25.13%)	DR-TB patients with diabetes (n = 32/n = 93, 34.41%)	P value
DR-TB (Total)	450 (25.13%)	32 (34.41%)	0.045*
Any resistance to first-line drug			
INH	295 (16.5%)	23 (24.73%)	0.039*
RFP	189 (10.57%)	22 (23.66%)	P < 0.001**
EMB	61 (3.41%)	4 (4.30%)	0.56
SM	288 (16.11%)	20 (21.51%)	0.17
MR-TB (Total)	209 (11.69%)	8 (8.6%)	0.36
INH	80 (4.47%)	1 (1.08%)	0.18
RFP	24 (1.34%)	4 (4.30%)	0.046
EMB	8 (0.45%)	1 (1.08%)	0.37
SM	92 (5.15%)	1 (1.08%)	0.085
Others	5 (0.28%)	1 (1.08%)	0.26
MDR-TB (Total)	142 (7.94%)	16 (17.20%)	0.002**
MDR1:INH + RFP	31 (1.73%)	5 (5.38%)	0.012*
MDR2:INH + RFP + EMB + SM	28 (1.57%)	2 (2.15%)	0.66
MDR3:INH + RFP + SM	64 (3.58%)	7 (7.53%)	0.051
Others	19 (1.06%)	2 (2.15%)	0.28
PDR-TB (Total)	96 (5.37%)	8 (8.60%)	0.18
PDR1:INH + EMB	4 (0.22%)	1 (1.08%)	0.22
PDR2:INH + SM	68 (3.8%)	5 (5.38%)	0.44
PDR3:RFP + SM	15 (0.84%)	2 (2.15%)	0.20
Others	9 (0.5%)	0 (0.00%)	1.00

TB, tuberculosis; DR-TB, drug-resistant tuberculosis; MR-TB, mono-resistant tuberculosis; MDR-TB, multidrug resistant tuberculosis; PDR-TB, polydrug resistant tuberculosis.
EMB, ethambutol; INH, isoniazid; RFP, rifampin; SM, streptomycin. **P < 0.01; *P < 0.05.

3.3. Risk factors of acquired drug resistance among TB-DM cases

As shown in Table 3, while in univariable analysis and multivariable analysis, aged between 45 and 64 years (OR: 2.06, 95%CI: 0.56–7.55; aOR:4.26, 95%CI: 0.68–26.76), higher BMI (≥25) (OR: 1.67, 95%CI: 0.31–9.01; aOR: 1.91, 95%CI: 0.23–15.72), and cavities (OR: 2.17, 95% CI: 0.73–6.46; aOR: 3.576, 95%CI: 0.92–13.89) were risk factors for acquired drug resistance among retreated TB-DM cases. In contrast, ≥65 years old (OR: 0.55, 95%CI: 0.12–2.6; aOR: 0.65, 95%CI: 0.096–4.47), BMI 18.5–24.9 (OR: 0.77, 95%CI: 0.20–2.94; aOR: 0.84, 95%CI: 0.18–3.83), and drinking (OR: 0.35, 95%CI: 0.093–1.33; aOR: 0.20, 95% CI: 0.03–1.38) were protective factors for acquisition of drug resistance. Both male (OR: 0.54, 95%CI: 0.15–1.96; aOR:1.12,95%CI: 0.23–5.89) and smoking (OR: 0.647, 95%CI: 0.21–2.00; aOR: 2.07, 95%CI: 0.427–10.02) were protective factors in univariable analysis but shifted to risk factors in multivariable analysis. However, none of the above were statistically significant, P > 0.05.

3.4. Association between diabetes and acquired drug resistance profile

In univariable analysis and multivariable analysis, acquired drug resistance subgroups including MDR-TB (OR: 2.48, 95%CI: 1.39–4.41; aOR:2.94, 95%CI: 1.57–5.48), RFP-related resistance (OR: 2.56, 0.54, 95%CI: 1.54–4.26; aOR:2.69, 95%CI: 1.524–4.74), INH + RFP

Table 3
Univariable and multivariable analysis of risk factors for drug-resistance among retreated TB-DM patients.

Characteristics	Non-DR n = 61 (%)	DR-TB n = 32 (%)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	P value	OR (95% CI)	P value
Age(years) (n = 81)						
25-44	11 (18.03%)	4 (13.33%)	Reference	Reference	Reference	Reference
45-64	24 (39.34%)	20 (66.67%)	2.06 (0.56–7.55)	0.27	4.26 (0.68–26.76)	0.12
≥65	20 (32.79%)	4 (13.33%)	0.55 (0.12–2.64)	0.46	0.65 (0.096–4.47)	0.67
Sex(n = 86)						
Female	6 (9.84%)	6 (20%)	Reference	Reference	Reference	Reference
Male	49 (80.33%)	23 (76.67%)	0.54 (0.15–1.96)	0.35	1.15 (0.23–5.89)	0.87
BMI(n = 81)						
<18.5	8 (13.11%)	4 (13.33%)	Reference	Reference	Reference	Reference
18.5–24.9	39 (63.93%)	16 (53.33%)	0.77 (0.20–2.94)	0.70	0.84 (0.18–3.83)	0.82
≥25	6 (9.84%)	6 (20.00%)	1.67 (0.31–9.01)	0.55	1.91 (0.23–15.72)	0.55
Cavity(n = 79)						
No	27 (44.26%)	6 (20%)	Reference	Reference	Reference	Reference
Yes	29 (47.54%)	16 (53.33%)	2.17 (0.73–6.46)	0.16	3.58 (0.92–13.89)	0.066
smoking(n = 90)						
No	41 (67.21%)	24 (80%)	Reference	Reference	Reference	Reference
Yes	20 (32.79%)	3 (10.00%)	0.65 (0.21–2.00)	0.45	2.07 (0.43–10.02)	0.37
Drinking(n = 90)						
No	47 (77.05%)	21 (70.00%)	Reference	Reference	Reference	Reference
Yes	14 (22.95%)	6 (20.00%)	0.35 (0.093–1.33)	0.125	0.20 (0.03–1.38)	0.10

OR, odds ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

resistance (OR: 3.55, 95%CI: 1.33–9.44; aOR:4.13, 95%CI: 1.46–11.66), any resistance to INH + SM (OR: 2.34, 95%CI: 1.41–3.89; aOR:2.22, 95%CI: 1.26–3.94), and any resistance to RFP + INH (OR: 2.48, 95%CI: 1.39–4.41; aOR:2.94, 95%CI: 1.57–5.48) had a significant association with diabetes, $P < 0.01$. Diabetes was significantly associated with any DR-TB (OR:1.56, 95%CI: 1.01–2.43) and INH-related resistance (OR:1.71, 95%CI: 1.04–2.81) in univariable analysis, $P < 0.05$, but not in multivariable analysis, $P > 0.10$ (see Table 4).

4. Discussion

In China, a total of fifty-nine published studies found that the rates of DR-TB and MDR-TB among retreated TB cases were 49.8% (46.0%–53.6%; 4155/8291) and 26.3% (23.1%–29.7%; 3125/11589), respectively [22]. Acquisition of drug resistance will lead to fewer treatment options, thus complicating a poor prognosis [23]. It has been widely accepted that inadequate treatment caused by insufficient dosing, unsatisfactory therapy time, substandard therapeutic regimen, poor compliance to directly-observed treatment strategy (DOTS) and so on were the major reasons of acquired drug resistance in TB patients [24]. More and more evidences [7,8] revealed that there was an association between diabetes and drug-resistant TB. However, most of which took primary and acquired drug resistance together into account to a total rate. Few previous [7,8,10] had focused on retreated TB-DM cases and its acquired drug resistance rate separately. This study enrolled 1884 retreated TB cases with DST results and information on diabetes from Shandong, China, 2004–2017 to evaluate the clinical characteristics and drug-resistant profiles of TB-DM group and TB-no DM group, measure the increased risk of acquired drug resistance caused by diabetes, and figure out the risk factors of DR-TB among retreated TB-DM cases.

Table 4
Association between diabetes and anti-tuberculosis drug resistance among retreated TB cases.

Type	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P value	aOR (95%CI)	P value
Any DR-TB	1.56 (1.01–2.43)	0.047*	1.44 (0.88–2.34)	0.14
INH-related resistance*	1.71 (1.04–2.81)	0.034*	1.56 (0.90–2.69)	0.11
RFP-related resistance*	2.56 (1.54–4.26)	P < 0.001**	2.69 (1.52–4.74)	0.001**
SM-related resistance*	1.52 (0.90–2.56)	0.11	1.44 (0.81–2.571)	0.22
INH + SM resistance	1.56 (0.61–4.02)	0.35	1.30 (0.47–3.59)	0.61
INH + RFP resistance	3.55 (1.33–9.44)	0.011*	4.13 (1.46–11.66)	0.007**
Any resistance to INH + SM	2.34 (1.41–3.89)	0.001**	2.22 (1.26–3.94)	0.006**
Any resistance to RFP + INH	2.48 (1.39–4.41)	0.002**	2.80 (1.49–5.27)	0.001**
MR-TB	0.84 (0.40–1.78)	0.65	0.79 (0.35–1.80)	0.58
MDR-TB	2.48 (1.39–4.41)	0.002**	2.94 (1.57–5.48)	0.001**
PDR-TB	1.83 (0.85–3.94)	0.12	1.31 (0.53–3.21)	0.56
Pan susceptible	reference	reference	reference	reference

DR-TB, drug-resistant tuberculosis; MR-TB, mono-resistant tuberculosis; MDR-TB, multidrug resistant tuberculosis; PDR-TB, polydrug resistant tuberculosis; INH, isoniazid; RFP, rifampin; SM, streptomycin; *P < 0.05, **P < 0.01.

We found that retreated TB-DM cases tended to have a much older age, higher BMI, more cavity and more likely to be complicated with hypertension than retreated TB-no DM cases, consistent with the findings of a prospective study conducted in Indonesia, Peru, Romania and South Africa that both older age and higher BMI were risk factors of diabetes among TB cases, $P < 0.05$ [21]. Obesity and hypertension were strongly associated with diabetes in the general population such as metabolic syndrome [25,26], but obesity was not always been identified as a risk factor of TB infection due to the high proportion of malnutrition and weight loss among TB cases, regardless of diabetes status [27]. Similar to our findings, previous studies [28–30] have reported more cavitation among TB-DM patients than TB-no DM patients, for example in Georgia [28](aOR: 2.26), it was interesting that other TB symptoms including cough and hemoptysis were also more serious in those with diabetes [29,30]. There are several explanations for more cavities including impaired immune responses in diabetes patients which could increase the risk of active TB by three-times [10], poor response to anti-tuberculosis treatment [31], a higher possibility of severe TB [31].

Former studies [23,24,32]helped to detect the following possible risk factors of acquired drug resistance: alcoholism, smoking, irregular treatment, and lung cavities, younger than 65 years (OR: 2.53; 95% CI 1.74 to 4.83), male (OR: 1.38; 95% CI 1.16 to 1.65), and HIV positive (OR: 3.52; 95% CI 2.48 to 5.01) [32]. However, the risk factors of acquired drug resistance among previously treated TB-DM patients have not been explored. Our study took most of the above factors into

account, and estimated the OR through univariable analysis and multivariable analysis. Unexpectedly, none was statistically significant. One hypothesis was that the differences of the clinical characteristics between drug-resistant and susceptible TB-DM group might be underestimated due to the coexistence of risk factors for previously diagnosed diabetes including smoking [33,35], alcohol consumption [34], overweight and obesity [33,35], older age [35]. Another potential reason may be the lack of samples, which should be further studied and solved in the future.

Diabetes has been identified as a significant risk for the development of active TB and increases the odds of developing MDR-TB for decades. A meta-analysis of 24 observational studies from 15 different countries revealed that DM has a significant association with MDR-TB (OR = 1.97, 95% CI = 1.58–2.45, I = 38.2%, P value for heterogeneity = 0.031) [36]. Moreover, in Eastern Taiwan, among new patients, diabetes was significantly associated with any resistance to INH excluding MDR-TB (aOR: 1.88, 95%CI:1.07–3.31), but not with MDR-TB (aOR: 0.95, 95% CI: 0.34–2.68) [37]. However, there were still disputes about on whether the retreated TB-DM co-morbidity contributes to the development of MDR-TB and other acquired drug resistance profiles, and few researches were done in this area [7,8,10]. Interestingly, we found that the percentages of DR-TB, MDR-TB, any resistance to INH, any resistance to RFP, MR-TB (RFP), MDR1(INH + RFP) among retreated TB-DM group were much higher than those among retreated TB-no DM group. In addition, diabetes were defined as a risk factor for acquired drug-resistance among retreated TB-DM group including RFP-related resistance, INH + RFP resistance (MDR1), any resistance to INH + SM, any resistance to RFP + INH in both univariable and multivariable analysis, and any DR-TB, INH-related resistance in univariable analysis. Similarly, a study in Taiwan found that among previously treated patients, diabetes was associated with INH resistance (aOR: 6.76, 95% CI:1.53–29.98), but not with MDR-TB (Total) (aOR 1.52, 95%CI 0.59–3.95) [37].

The potential causes of increased risk for acquired drug resistance among retreated TB-DM patients compared with TB-no DM cases are various. First, TB-DM patients may have a poor prognosis. Higher sputum positivity (OR:1.247; 95% CI: 0.539–2.886) at the end of 2-month treatment, more adverse drug reactions (OR:3.578; 95% CI:1.114–11.494, p = 0.032), and poor outcome (OR:1.176; 95% CI: 0.310–4.457) at the completion of treatment compared with TB-no DM cases have been observed [38]. Second, diabetes concurrence might contribute to the dysregulation of the inflammasome and chronic inflammation among TB-DM patients, which was to some extent similar to acquired immunodeficiencies [39]. Third, there might be a negative correlation between blood glucose and drug concentrations. Previous study found that TB-DM patients had lower INH and pyrazinamide (PZA) concentrations, suggesting delayed absorption/faster elimination of INH and PZA in the presence of elevated glucose [40].

Our study have some strengthens. First, identifying that patients with diabetes have an increased risk of acquired drug resistance might indicate the necessity for more intensive clinical management of TB-DM patients. Second, different from most previous researches [7,8] focusing merely on the total rate of MDR-TB, drug resistance profiles in our study including MDR-TB, MDR-TB, PDR-TB had been further divided into more detailed subgroups, and it helps to figure out the association between drug resistance and diabetes more accurately.

There are also some limitations. First, so far DST of second-line anti-TB drugs have not been routinely conducted in China, thus the association between diabetes and second-line drug resistance of TB cases still remains to be explored in future. Second, although we have collected all retreated TB cases with susceptibility data and information on diabetes in Shandong, China, from 2004 to 2017, the sample size was still limited. More appropriate cases need to be enrolled in order to gain a higher validity and reliability of our findings.

5. Conclusions

TB-DM comorbidity results in a higher rate of acquired drug resistance (34.41%) compared with TB-no DM cases (25.13%). Diabetes was a risk factor for various acquired drug resistance including any DR-TB, INH-related resistance, RFP-related resistance, INH + RFP resistance (MDR1), any resistance to INH + SM, any resistance to RFP + INH. These results remain to be validated at the molecular level in near future. Our findings suggest that increased researches into co-morbidity screening programs, especially diabetes, may be necessary for existing TB care frameworks, or in some cases TB screening. This study also underscores the need for more interventions on retreated TB-DM cases to decrease the risk for acquired drug resistance, thus reducing the transmission of drug-resistant *Mycobacterium tuberculosis*.

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Author contributions

H.C.L., W.M.S. and Y.F.L. conceived and designed the study. H.C.L., C.B.Y., M.Z., Q.Q.A., S.Q.L., C.X.Y. and L.G. directed its implementation including the data analysis and writing of the paper. W.M.S. and Y.F.L. analyzed the data; Y.L., Q.Y.Z., J.Y.L, T.T.X, S.J.L. and N.N.T contributed materials/analytic tools; W.M.S., Y.F.L.and H.C.L. wrote and revised the manuscript. All authors reviewed and approved the manuscript.

Declaration of competing interest

The authors declare that they have no competing interest.

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