The Impact of Alcohol Drinking And Tobacco Smoking On The Drug-Resistance of Newly Diagnosed Tuberculosis

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Research Article

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Abstract

Background: Finding out more predictors of drug-resistant tuberculosis (DR-TB) helps to facilitate TB prevention and control. Previous study had revealed that tobacco smoking and alcohol drinking might be a risk factor for developing drug-resistant tuberculosis. However, few discussed their joint impact on resistance among newly diagnosed TB cases. This study aimed to assess and compare the joint and independent effect of smoking and drinking on TB resistance.

Methods: This was a retrospective study of 7996 newly diagnosed TB patients who were collected from Shandong, China from Jan 1, 2004, to Dec 31, 2020, and all had drug susceptibility results, information about smoking and alcohol consumption. Patients were classified into four groups including smoker only(G_1), drinker only(G_2), smoker+drinker(G_3), non-smoker+non-drinker group(G_0). We described the drug-resistant profiles, clinical factors and also calculated the ORs of different drug-resistance among G_1 , G_2 , G_3 , compared to G_0 .

Results: Of 7996 TB cases enrolled, the proportions of G_1 , G_2 , G_3 , and G_0 were 8.25%, 3.89%, 16.46%, 71.40%, respectively. The rates of DR-TB, mono-resistant (MR)-TB, multidrug resistant (MDR)-TB, polydrug resistant (PDR)-TB in G_1 , G_2 , G_3 and G_0 were 19.24%/16.4%/17.33%/19.08%, 11.52%/8.68%/10.94%/11.63%, 3.03%/2.57%/2.96%/3.66%, 4.7%/4.82%/3.34%/4.08%, respectively. G_3 had a higher risk of MDR1: isoniazid+rifampin (adjusted odds ratio (aOR)=1.913, 95% confidence interval(CI): 1.036-3.532), but had a lower risk of DR-TB (aOR=0.839, 95%CI: 0.712-0.988), rifampin-related resistance (aOR=0.675, 95%CI: 0.492-0.925), streptomycin-related resistance (aOR=0.819, 95%CI: 0.675-0.993), EMB-related resistance (aOR=0.571, 95%CI: 0.342-0.954), MDR3: isoniazid+rifampin+streptomycin (aOR=0.406, 95%CI: 0.194-0.851, any isoniazid+streptomycin resistance (aOR=0.845, 95%CI: 0.714-1). However, there were no significant differences between G_1 and G_0 , G_2 and G_0 in all drug-resistant sub-types. Those who with cavity had a higher risk of DR-TB among G_3 (OR=1.354, 95%CI:1.011-1.814).

Conclusions: Although we did not found a independent impact of alcohol drinking or tobacco smoking on TB drug-resistance respectively, these two habits had a joint effect on TB drug-resistance. We should be alert for the emergence of isoniazid+rifampin resistance among populations with both smoking and drinking habits.

Introduction

Tuberculosis (TB) has become one of the top 10 causes of death for many years, and lead to a global threat of health security, while the development of drug resistance among TB even makes this situation worse[1]. In order to achieve the global TB control targets, more attention should be paid to drug-resistant tuberculosis (DR-TB), especially multidrug resistant (MDR)-TB,, defined as phenotypic resistance to at least isoniazid and rifampin[1]. According to the World Health Organization (WHO) Tuberculosis report, among the estimated 10 million new cases of active TB in 2019, 8.4% were from China (only behind India and Indonesia) and 3.3% were MDR-TB/rifampin-resistant TB (RR-TB)[1]. TB infection has caused to 1.4 million deaths in 2019. The overall success rate of TB treatment was 83%, whereas it was only 54% for MDR-TB/RR-TB and 30% for extensively drug-resistant tuberculosis (XDR-TB)[2]. Recent years, plenty of factors including incomplete treatment, retreated TB, males, TB contact history, human immunodeficiency virus (HIV) and diabetes have been found to be related to the emergence of DR-TB[3, 4]. Nevertheless, determining more clinical predictors of DR-TB will be conducive to the early detection of DR-TB, and it can also guide the empiric selection of anti-TB drugs, especially in low-income areas where were unavailable to drug susceptibility testing (DST)[4].

Both tobacco smoking and alcohol drinking were major public health problems[5, 6]. There were approximately 1.3 billion tobacco users globally, and more than 80% of these population were living in low-income and middle-income countries[5]. The annual global average alcohol consumption among populations older than 15 worldwide increased from 5.5 liters of pure alcohol in 2005 to 6.4 liters in 2016[6]. Globally tobacco and alcohol consumption causes 8 and 2.8 million premature deaths per year respectively[5, 6]. It is estimated that over 20% of adult TB cases may be attributable to smoking, compared with 16% for HIV and 15% for diabetes, while about 10% of the TB cases globally were estimated to be attributable to alcohol[7]. According to previous reports, tobacco smoking doubles the risk of TB infection, and also lead to a twice risk of death during TB therapy[8]. In addition, alcohol drinking contributed to a 35% higher risk of TB infection (relative risk(RR)=1.35, 95% confidence interval(CI):1.09–1.68), accompanied by a lower rate of sputum culture conversion and a worse treatment outcome[9, 10]. Current years, some studies found that smoking (adjusted odds ratio (aOR)=4, 95%CI:1.2-13.2) and alcohol drinking habits (aOR=5.1, 95% CI:1.4-18.7) might be independent predictors for MDR-TB[11]. However, most of these studies had a small sample size, more confounding factors such as retreated TB cases, and few discussed the joint impact of alcohol uses and tobacco smoking on DR-TB[4, 9-11]. It also remains unclear the impact of tobacco smoking and alcohol drinking on various drug-resistant sub-types such as mono-resistant (MR)-TB, MDR-TB, polydrug resistant (PDR)-TB.

In this study, based on the retrospective data of Shandong, China from 2004 to 2020, we aimed to investigate the impact of alcohol drinking and tobacco smoking on the drug-resistance of newly diagnosed tuberculosis in the following aspects: Firstly, we described the clinical features and the drug-resistant profiles of smoker only (G_1), drinker only (G_2), smoker + drinker (G_3), non-smoker + non-drinker group (G_0), respectively. Secondly, the ORs of different drug-resistance among G_1 , G_2 , G_3 compared with G_0 were calculated. Finally, we also explored the risk factors of DR-TB among G_3 and G_0 .

Participants And Methods

2.1 Study design and Settings

This was a retrospective study of baseline data including drug susceptibility test (DST) results, smoking or drinking behavior among newly diagnosed pulmonary TB cases collected from 30 surveillance sites of Shandong, China during between Jan 1, 2004 and Dec 31, 2020. Exclusive criteria: retreated cases; extrapulmonary tuberculosis; without information on DST results, smoking or drinking habits; bacteriological identification as *Nontuberculous mycobacteria* (NTM). Finally, 7996 eligible participants were enrolled.

Shandong is the second most populous province in China, with 100.7 million population in 2019. Although the incidence rate of pulmonary TB in Shandong reduced from 40.8 to 26.25 per 100,000 during 2005 to 2017, the aggravation of bacterial drug resistance makes the epidemic situation of TB still severe[1, 12]. The rates of MR-TB, MDR-TB, PDR-TB in Shandong were 21.38%, 13.35%, 3.73%, 4.30% in 2018, respectively[13].

2.2 Bacterial culture, strain identification, and DST

At least two samples of sputum or bronchoscopy fluid were obtained from each suspected TB cases. Smear microscopy were performed, and then cultures were conducted in solid Lowenstein-Jensen (L-J) medium. All cultures with growing colonies were sent to Reference Laboratory of Katharine Hsu International Research Center of Human Infectious Diseases (KICID) in Shandong Provincial Chest Hospital. Lab technicians identified the strain types by morphology and growth characters of colony, and inhibition of p-nitrobenzoic acid. DST of four first-line anti-TB drugs were routinely performed, including isoniazid (INH 0.2 μ g/mL), rifampicin (RFP, 40 μ g/mL), ethambutol (EMB, 2 μ g/mL), streptomycin (SM, 4 μ g/mL). If the growth rate was higher than 1% compared to the standard reference strain H37Rv, this strain was defined as resistant to the corresponding anti-TB drug. Quality control was assessed by Superior Reference Laboratory.

2.3 Definitions

Definition of smokers and drinkers: **1)** Smokers were defined as subjects who had smoked at least 100 cigarettes in their lifetime and smoked at least once in the past 30 days, and vice versa for non-smokers[14]; **2)** Drinkers for alcohol drinking refers to those who ever consumed any type of alcohol drinking 12 times and at least one alcohol drinking in the past year, and vice versa for non-drinkers[9].

TB drug resistance types[15]: **1)**MR-TB is defined as resistance to one first-line anti-TB drugs in vitro; **2)**MDR-TB is defined as TB infection showing resistance to at least both INH and RFP in vitro; **3)**PDR-TB refers to TB with resistance to at least two first-line anti-TB drugs, other than both INH and RFP in vitro; **4)**DR-TB refers to TB with any resistance to anti-TB drugs in vitro.

2.4 Data analysis

The demographic and clinical characteristics of smoker only(G_1), drinker only(G_2), smoker+drinker(G_3) were compared with non-smoker+non-drinker group(G_0) through Chi-square tests or Fisher's exact test. Drug-resistant profiles of these four groups were also described. In addition, we divided the drug-resistance of TB into many sub-types including DR-TB, MR-TB, MDR-TB, PDR-TB, INH-related resistance, RFP-related resistance, SM-related resistance, EMB-related resistance, MDR1: INH+RFP, MDR2: INH+RFP+EMB+SM, MDR3: INH+RFP+SM, PDR2: INH+SM, PDR3: RFP+SM, Any INH+SM resistance, and then multivariate and univariate logistic regression models were applied to estimate the OR, aOR and its 95% CI of different drug-resistant sub-type among G_1 , G_2 , G_3 compared with G_0 . According to previous studies, covariates such as age, sex, cavity, body mass index (BMI), comorbidity were included in models. Finally, we calculated the risk factors of DR-TB among G_3 . All statistical tests were two-sided with a significance level at 0.05. All above analysis were performed in SPSS statistical software (version 20.0, SPSS Inc., Chicago, USA)

Results

3.1 Patients' Characteristics

A total of 7996 newly diagnosed tuberculosis cases were enrolled (**Table 1**), of which 8.25% (660) were smoker only (G_1), 3.89% (311) were drinker only (G_2), 16.46% (1316) were smoker+drinker (G_3), and 71.40% (5709) were non-smoker+non-drinker group (G_0). Compared with G_0 , G_1 and G_3 were less likely to be aged between 15-24 ($G_1/G_3/G_0$: 7.58%/5.88%/16.75%) and 25-44 ($G_1/G_3/G_0$: 19.85%/20.00%/26.83%) but more likely in 45-64 ($G_1/G_3/G_0$: 35.76%/47.56%/29.69%); G_1 had a higher but G_2 had a lower proportion of >65 age group than G_0 ($G_1/G_2/G_0$: 35.76%/20.39%/26.32%). G_1 , G_2 , G_3 also more likely to be males ($G_1/G_2/G_3/G_0$: 99.09%/99.68%/99.7%/77.54%), and have comorbidities (total) ($G_1/G_2/G_3/G_0$: 18.94%/17.04%/16.87%/11.68%), diabetes ($G_1/G_2/G_3/G_0$: 8.94%/8.36%/10.03%/6.6%). G_1 and G_3 had a higher rate of hypertension than G_0 , but G_2 had a lower rate ($G_1/G_2/G_3/G_0$: 3.33%/0.96%/3.27%/2.05%). Interestingly, we found G_1 were more likely to have chronic obstructive pulmonary disease (COPD, G_1 vs G_0 : 3.79% vs 1.87%), hepatitis (G_1 vs G_0 : 1.82% vs 0.68%). Moreover, The percentage of cavity in G_2 was lower but higher in G_3 ($G_2/G_3/G_0$: 38.25%/47.86%/44.43%). G_2 were more likely to overweight than G_0 (7.95% vs 5.21%). All of the above were of statistical significance, $P < 0.05$).

3.2 Drug resistance patterns

As presented in **Table 2**, the proportions of DR-TB, MR-TB, MDR-TB, PDR-TB in G_1 , G_2 , G_3 and G_0 were 19.24%/16.4%/17.33%/19.08%, 11.52%/8.68%/10.94%/ 11.63%, 3.03%/2.57%/2.96%/3.66%, 4.7%/4.82%/3.34%/4.08%, respectively. Compared with G_0 , G_3 had more MDR1:INH+RFP (1.29% vs 0.65%) but less RFP-related resistance (3.8% vs 5.2%) and MDR3: INH+RFP+SM (0.61% vs 1.56%).

3.3 The impact of alcohol drinking and tobacco smoking on TB drug-resistance

Smoker+drinker(G_3) had a higher risk of MDR1: INH+RFP (OR=2.006, 95%CI: 1.126-3.574, $P=0.018$; aOR=1.913, 95%CI: 1.036-3.532, $P=0.038$), but had a lower risk of DR-TB (aOR=0.839, 95%CI: 0.712-0.988, $P=0.035$), RFP-related resistance (OR=0.72, 95%CI:0.53-0.977, $P=0.035$; aOR=0.675, 95%CI: 0.492-0.925, $P=0.015$), SM-related resistance (aOR=0.819, 95%CI: 0.675-0.993, $P=0.042$), EMB-related resistance (aOR=0.571, 95%CI: 0.342-0.954, $P=0.032$), MDR3: INH+RFP+SM (OR=0.386, 95%CI: 0.187-0.798, $P=0.01$; aOR=0.406, 95%CI: 0.194-0.851, $P=0.017$), Any INH+SM resistance (aOR=0.845, 95%CI: 0.714-1, $P=0.05$). However, there were no significant differences between G_1 and G_0 , G_2 and G_0 in all drug-resistant sub-types (**Table 3**).

3.4 Risk factors for DR-TB

As shown in **Table 4** and **Table 5**, 1) TB cases with alcohol drinking and tobacco smoking habits: Those who with cavity had a higher risk of DR-TB (OR=1.3546, 95%CI:1.011-1.814, $P=0.042$); 2) TB cases without alcohol drinking and tobacco smoking habits: Males (OR=1.238, 95%CI: 1.05-1.46, $P=0.011$; aOR=1.261, 95%CI: 1.067-1.49, $P=0.007$), cavitory disease (OR=1.17, 95%CI:1.016-1.348, $P=0.03$) might evaluate the risk of DR-TB among non-smoker+non-drinker group(G_0). On the contrary, TB cases aged more than 65 were less likely to have DR-TB (OR=0.778, 95%CI: 0.627-0.967, $P=0.023$).

Discussion

Based on 7996 newly diagnosed tuberculosis cases in Shandong, China, we sought to investigate the independent and joint effect of alcohol drinking and tobacco smoking on TB drug-resistance respectively. In short, smoker+drinker(G_3) had a higher risk of MDR1(INH+RFP), but had a lower risk of DR-TB, RFP-related resistance, SM-related resistance, EMB-related resistance, MDR3(INH+RFP+SM), and any INH+SM resistance. However, there were no significant impact of alcohol drinking only or tobacco smoking only on various drug-resistant sub-types ($P > 0.05$). Compared with the control(G_0), whether TB cases belonged to smoker only(G_1), drinker only(G_2), or G_3 , they all had more males, comorbidities (total), and diabetes. Furthermore, males and cavitory diseases were more likely to be DR-TB among non-smoker+non-drinker group(G_0).

According to our study, compared with G_0 , TB cases with both drinking and smoking habits had a different drug-resistant profiles such as an increased risk of MDR1(INH+RFP) but lower risk of DR-TB. Our findings were not identical to a previous meta-analysis which showed that smoking habits was associated with an increased risk of DR-TB (OR=1.57, 95% CI 1.33–1.86), MDR-TB (OR=1.49, 95% CI 1.19–1.86)[16]. Another study found that alcohol abuse (OR=1.3; 95% CI: 1.0-1.8) was risk factor identified for MDR-TB[17]. However, the absence of an correlation between alcohol drinking only, tobacco smoking only with TB resistance in our research was inconsistent with the findings of most previous studies[16, 17].

As we all know, many factors such as incomplete and inadequate treatment, complications of diabetes, direct transmission of drug-resistant strains contribute to the development of DR-TB[4, 17, 18]. Therefore, alcohol drinking and tobacco smoking may also affect the resistance of TB through the above pathways. There may be some explanations for the joint impact of both drinking and smoking habits on TB

resistance: 1) Tobacco smoking and TB resistance: It has been found that tobacco smoking was associated with the evaluated risk of TB infection, the increased TB-related mortality, and the lower treatment compliance[7, 8]. The roles of tobacco smoking in the pathogenesis of TB were that cigarette smoke decreased the mucociliary clearance, reduced the immune response of alveolar macrophage, lead to a lower production of TNF- α and interleukin-12 (IL-12), and impeded granuloma formation, thus creating conditions for the infection and development of TB[8, 19]. Previous studies suggested that mutations associated with TB resistance usually lead to an impaired bacterial growth rate and a decreased virulence which was also known as “fitness cost”[20], presumably, reduced immune function in human body caused by tobacco smoking may contribute to the infection of some drug-resistant TB strains such as MDR1. In addition, TB cases with tobacco smoking had a lower compliance and were less likely to complete anti-TB therapy, which may result in acquired resistance[16, 21]. 2) Alcohol drinking and TB resistance: Similar to smokers, TB cases with alcohol drinking habits also had poorer treatment outcomes including loss to follow-up, death, treatment failure among both sensitive TB (OR=1.99, 95% CI 1.57–2.51) and MDR-TB (OR=2.00, 95% CI 1.73–2.32), while treatment failure were independent a risk factor for acquired resistance[22, 23]. Alcohol use could also lead to weakened immunity, liver damage and nutritional deficiency, which may contribute to both sensitive and resistant TB infection[24]. Interestingly, we found a protective effects of alcohol drinking and tobacco smoking on some resistance, it may also be caused by the altered susceptibility to different TB strains, but more potential mechanisms remained to explored. Finally, our study indicated that the combined effects alcohol drinking and tobacco smoking may be stronger than alone, which may explained the results without statistical significance among drinker-only group and smoker-only group.

People with both smoking and drinking habits were more likely to be males (accounted for 99.7%) and aged between 45-64 (accounted for 47.56%). They also had a higher rate of comorbidities (16.87%) and diabetes (10.03%). The gender difference of smoking and drinking habits is huge, for example, a population-based study in china found that 45% men and 3% women were cigarette smokers, 34% male and 4% female were alcohol drinkers[25]. TB cases also have more males, it was reported that about 6 million adult men and 3.2 million adult women fell ill with TB in 2017[26]. Smoking and drinking had many adverse effects on human health, they could increase the risk of cardiovascular disease, stroke, infection, diabetes and so on[9, 21, 27].

Among TB cases with drinking and smoking habits, those who with cavity had a higher risk of DR-TB, while among TB cases without these habits, both males and cavitory disease were risk factors for DR-TB. So far, studies on the association of gender and TB resistance were still not consistent, some found females were more likely to have MDR-TB than males (aOR=1.315 95% CI: 1.117-1.548, p=0.001), but another found that either sex were at higher risk of MDR/RR-TB[28, 29]. Different gender often means differences in living habits such as smoking and drinking, social pressures, access to health-care services, and exposure to other risk factors[29, 30]. Both males and TB diseases with cavity should be recognized as a vulnerable population to DR-TB, and improve their access to DST and directly-observed treatment strategy (DOTS) may help to reduce the burden of TB in China more effectively, which may also lead to a gender equity in TB therapy and care.

Our study has several strengths. Firstly, although the joint effects of smoking and drinking on TB resistance including many sub-types were rarely discussed in former publications, our study not only explored the combined impact but also investigated the independent effects. Secondly, our study had a great scale and time span, and we collected all newly diagnosed TB cases with DST results, smoking and drinking status in Shandong, China, from 2004 to 2020. Thirdly, our study was conducted among new TB cases after excluding all retreated cases, and which would help to reduce more confounding factors. A disadvantage of our study was that it had not divided smoking and drinking status into more subgroups, and we had to only use the information available because it was a retrospective study. Another limitation was that DST of second-line anti-TB drugs were not routinely conducted in China unless the patient asks for it.

Conclusion

Although we did not found a independent impact of alcohol drinking or tobacco smoking on TB drug-resistance respectively, these two habits had a joint effect on TB drug-resistance. Smoker+drinker(G_3) had a higher risk of MDR1+INH+RFP, but had a lower risk of DR-TB, RFP-related resistance, SM-related resistance, EMB-related resistance, MDR3(INH+RFP+SM), and any INH+SM resistance. TB cases who belonged to smoker only(G_1), drinker only(G_2), or G_3 , were more likely to be males, or combined with comorbidities (total) and diabetes, meanwhile cavitory disease were risk factors for DR-TB among G_3 . In short, considering the joint impact of alcohol drinking or tobacco smoking on TB drug-resistance, we should be alert for the emergence of INH+RFP resistance among these populations.

Abbreviations

TB: tuberculosis; DR-TB: drug-resistant tuberculosis; WHO: world health organization; HIV: human immunodeficiency virus; COPD: chronic obstructive pulmonary disease; BMI: body mass index; RR-TB: rifampin-resistant tuberculosis; MDR-TB: multidrug resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; MR-TB: mono-resistant tuberculosis; PDR-TB: polydrug resistant tuberculosis; aOR: adjusted

odds ratio; OR: odds ratio; CI: confidence interval; INH: isoniazide; RFP: rifampin; EMB: ethambutol; SM: streptomycin; DST: drug susceptibility test; NTM: *non-tuberculous mycobacterium*; DOTS: directly-observed treatment strategy

Declarations

Ethics approval and consent to participate

The protocols applied in this study were approved by the Ethics Committee of Shandong Provincial Hospital, affiliated with Shandong University (SPH) and the Ethic Committee of Shandong Provincial Chest Hospital (SPCH), China. Personal identifiers of TB patients were removed before data analysis and reporting. All methods were performed in accordance with relevant guidelines and regulations. Informed consent for study participation was obtained from all participants and legally authorized representative/guardian of minor participants (age less than 16 years) .

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

H. C.L., W.M.S., J.Y.L. and Y.F.L. conceived and designed the study. H.C.L., C.B.Y., Q.Q.A., S.Q.L., Q.F. and J.H.D. directed its implementation including the data analysis and writing of the paper. W.M.S., J.H.D. 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., J.Y.L. and H.C.L. wrote and revised the manuscript. All authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Availability of data and materials

Data can be available through contact with the corresponding author.

References

1. World Health Organization. Global Tuberculosis Report 2020. [<https://www.who.int/publications/i/item/9789240013131>]
2. World Health Organization. Global Tuberculosis Report 2017. Geneva: WHO; [https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf]
3. Song WM, Shao Y, Liu JY, Tao NN, Liu Y, Zhang QY, Xu TT, Li SJ, Yu CB, Gao L *et al*: **Primary drug resistance among tuberculosis patients with diabetes mellitus: a retrospective study among 7223 cases in China**. *Infection and drug resistance* 2019, **12**:2397-2407.
4. Flores-Treviño S, Rodríguez-Noriega E, Garza-González E, González-Díaz E, Esparza-Ahumada S, Escobedo-Sánchez R, Pérez-Gómez HR, León-Garnica G, Morfín-Otero R: **Clinical predictors of drug-resistant tuberculosis in Mexico**. *PloS one* 2019, **14**(8):e0220946.
5. World Health Organization. Tobacco. 27 May 2020. [<https://www.who.int/news-room/fact-sheets/detail/tobacco>]
6. Hannah Ritchie and Max Roser (2018) - "Alcohol Consumption". Published online at OurWorldInData.org. [<https://ourworldindata.org/alcohol-consumption>]

7. Amere GA, Nayak P, Salindri AD, Narayan KMV, Magee MJ: **Contribution of Smoking to Tuberculosis Incidence and Mortality in High-Tuberculosis-Burden Countries.** *American journal of epidemiology* 2018, **187**(9):1846-1855.
8. Silva DR, Muñoz-Torrico M, Duarte R, Galvão T, Bonini EH, Arbex FF, Arbex MA, Augusto VM, Rabahi MF, Mello FCQ: **Risk factors for tuberculosis: diabetes, smoking, alcohol use, and the use of other drugs.** *Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia* 2018, **44**(2):145-152.
9. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lönnroth K, Rehm J: **Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease.** *The European respiratory journal* 2017, **50**(1).
10. Liu Q, Lu P, Martinez L, Yang H, Lu W, Ding X, Zhu L: **Factors affecting time to sputum culture conversion and treatment outcome of patients with multidrug-resistant tuberculosis in China.** *BMC infectious diseases* 2018, **18**(1):114.
11. Ali MH, Alrasheedy AA, Hassali MA, Kibuule D, Godman B: **Predictors of Multidrug-Resistant Tuberculosis (MDR-TB) in Sudan.** *Antibiotics (Basel, Switzerland)* 2019, **8**(3).
12. Tao NN, Li YF, Wang SS, Liu YX, Liu JY, Song WM, Liu Y, Geng H, Li HC: **Epidemiological characteristics of pulmonary tuberculosis in Shandong, China, 2005-2017: A retrospective study.** *Medicine* 2019, **98**(21):e15778.
13. Song W, Li Y, Ma X, Liu J, Tao N, Liu Y, Zhang Q, Xu T, Li S, Yu C *et al*: **Primary drug resistance of mycobacterium tuberculosis in Shandong, China, 2004-2018.** 2019, **20**(1):223.
14. Jamal A, Phillips E, Gentzke AS, Homa DM, Babb SD, King BA, Neff LJ: **Current Cigarette Smoking Among Adults - United States, 2016.** *MMWR Morbidity and mortality weekly report* 2018, **67**(2):53-59.
15. **World Health Organization. TB drug resistance types** [<https://www.who.int/tb/areas-of-work/drug-resistant-tb/types/en/>]
16. Wang MG, Huang WW, Wang Y, Zhang YX, Zhang MM, Wu SQ, Sandford AJ, He JQ: **Association between tobacco smoking and drug-resistant tuberculosis.** *Infection and drug resistance* 2018, **11**:873-887.
17. Skrahina A, Hurevich H, Zalutskaya A, Sahalchik E, Astrauko A, Hoffner S, Rusovich V, Dadu A, de Colombani P, Dara M *et al*: **Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors.** *Bulletin of the World Health Organization* 2013, **91**(1):36-45.
18. Nsofor CA, Jiang Q, Wu J, Gan M, Liu Q, Zuo T, Zhu G, Gao Q: **Transmission is a Noticeable Cause of Resistance Among Treated Tuberculosis Patients in Shanghai, China.** *Scientific reports* 2017, **7**(1):7691.
19. Strzelak A, Ratajczak A, Adamiec A, Feleszko W: **Tobacco Smoke Induces and Alters Immune Responses in the Lung Triggering Inflammation, Allergy, Asthma and Other Lung Diseases: A Mechanistic Review.** *International journal of environmental research and public health* 2018, **15**(5).
20. Salvatore PP, Becerra MC, Abel zur Wiesch P, Hinkley T, Kaur D, Sloutsky A, Cohen T: **Fitness Costs of Drug Resistance Mutations in Multidrug-Resistant Mycobacterium tuberculosis: A Household-Based Case-Control Study.** *The Journal of infectious diseases* 2016, **213**(1):149-155.
21. Leung CC, Yew WW, Chan CK, Chang KC, Law WS, Lee SN, Tai LB, Leung EC, Au RK, Huang SS *et al*: **Smoking adversely affects treatment response, outcome and relapse in tuberculosis.** *The European respiratory journal* 2015, **45**(3):738-745.
22. Ragan EJ, Kleinman MB, Sweigart B, Gnatenko N, Parry CD, Horsburgh CR, LaValley MP, Myers B, Jacobson KR: **The impact of alcohol use on tuberculosis treatment outcomes: a systematic review and meta-analysis.** *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2020, **24**(1):73-82.
23. Kempker RR, Kipiani M, Mirtskhulava V, Tukvadze N, Magee MJ, Blumberg HM: **Acquired Drug Resistance in Mycobacterium tuberculosis and Poor Outcomes among Patients with Multidrug-Resistant Tuberculosis.** *Emerging infectious diseases* 2015, **21**(6):992-1001.
24. Barr T, Helms C, Grant K, Messaoudi I: **Opposing effects of alcohol on the immune system.** *Progress in neuro-psychopharmacology & biological psychiatry* 2016, **65**:242-251.
25. Liao Y, Chen X, Tang J: **Differences of cigarette smoking and alcohol consumption by sex and region in China: a population-based, multi-stage, cluster sampling survey.** *The Lancet* 2017, **390**, S54
26. **World Health Organization. Tuberculosis and gender** [<https://www.who.int/tb/areas-of-work/population-groups/gender/en/>]
27. Hart CL, Davey Smith G, Gruer L, Watt GC: **The combined effect of smoking tobacco and drinking alcohol on cause-specific mortality: a 30 year cohort study.** *BMC public health* 2010, **10**:789.
28. Shivekar SS, Kaliaperumal V, Bammachary U, Sakkaravarthy A, Raj CKV, Alagappan C, Muthaiah M: **Prevalence and factors associated with multidrug-resistant tuberculosis in South India.** *Scientific reports* 2020, **10**(1):17552.

29. McQuaid CF, Horton KC, Dean AS, Knight GM, White RG: **The risk of multidrug- or rifampicin-resistance in males versus females with tuberculosis.** *The European respiratory journal* 2020, **56**(3).
30. Ek S: **Gender differences in health information behaviour: a Finnish population-based survey.** *Health promotion international* 2015, **30**(3):736-745.

Tables

Table 1
Characteristics of 7996 newly-diagnosed pulmonary tuberculosis

Characteristics	Total (n = 7996)	Subgroups(Group 1–4)				P value		
		G1:Smoker + non-drinker(n = 660, 8.25%)	G2: non-smoker + drinker(n = 311, 3.89%)	G3:Smoker + drinker(n = 1316, 16.46%)	G0:non-smoker + non-drinker(n = 5709, 71.40%)	G1 vs G0	G2 vs G0	G3 vs G0
Age(years) (n = 7962/n = 660/n = 309/n = 1310/n = 5683)								
0–14	24(0.3%)	1(0.15%)	0(0%)	0(0%)	23(0.4%)	0.506	0.629	0.629
15–24	1138(14.29%)	50(7.58%)	59(19.09%)	77(5.88%)	952(16.75%)	P < 0.001***	0.284	P < 0.001***
25–44	2009(25.23%)	131(19.85%)	91(29.45%)	262(20.00%)	1525(26.83%)	P < 0.001***	0.313	P < 0.001***
45–64	2648(33.26%)	242(36.67%)	96(31.07%)	623(47.56%)	1687(29.69%)	P < 0.001***	0.605	P < 0.001***
> 65	2143(26.92%)	236(35.76%)	63(20.39%)	348(26.56%)	1496(26.32%)	P < 0.001***	0.021*	0.859
Sex(n = 7996/n = 660/n = 311/n = 1316/n = 5709)								
Female	1293(16.24%)	6(0.91%)	1(0.32%)	4(0.3%)	1282(22.46%)	P < 0.001***	P < 0.001***	P < 0.001***
Male	6703(84.19%)	654(99.09%)	310(99.68%)	1312(99.7%)	4427(77.54%)	P < 0.001***	P < 0.001***	P < 0.001***
Cavity(n = 7133/n = 622/n = 285/n = 1241/n = 4985)								
No	3921(54.97%)	328(52.73%)	176(61.75%)	647(52.14%)	2770(55.57%)	0.180	0.041*	0.03*
Yes	3212(45.03%)	294(47.27%)	109(38.25%)	594(47.86%)	2215(44.43%)	0.180	0.041*	0.03*
BMI(n = 7733/n = 640/n = 302/n = 1284/n = 5507)								
underweight: <18.5	1846(23.87%)	172(26.88%)	61(20.2%)	315(24.53%)	1298(23.57%)	0.064	0.178	0.465
normal: 18.5 to < 25	5462(70.63%)	434(67.81%)	217(71.85%)	919(71.57%)	3892(70.67%)	0.133	0.661	0.523
overweight : 25.0 to < 30	388(5.02%)	31(4.84%)	24(7.95%)	46(3.58%)	287(5.21%)	0.691	0.040*	0.015
obesity ≥ 30.0	37(0.48%)	3(0.47%)	0(0%)	4(0.31%)	30(0.54%)	1.000	0.404	0.381
Comorbidities(n = 7996/n = 660/n = 311/n = 1316/n = 5709)								

Characteristics	Total (n = 7996)	Subgroups(Group 1–4)				P value		
		G1:Smoker + non-drinker(n = 660, 8.25%)	G2: non-smoker + drinker(n = 311, 3.89%)	G3:Smoker + drinker(n = 1316, 16.46%)	G0:non-smoker + non-drinker(n = 5709, 71.40%)	G1 vs G0	G2 vs G0	G3 vs G0
Total	1067(13.4%)	125(18.94%)	53(17.04%)	222(16.87%)	667(11.68%)	P<0.001***	0.005**	P<0.001***
Diabetes	594(7.46%)	59(8.94%)	26(8.36%)	132(10.03%)	377(6.6%)	0.024*	0.008**	P<0.001***
Hypertension	185(2.32%)	22(3.33%)	3(0.96%)	43(3.27%)	117(2.05%)	0.033*	0.004**	0.008**
COPD	164(2.06%)	25(3.79%)	8(2.57%)	24(1.82%)	107(1.87%)	0.001**	0.226	0.903
Hepatitis	68(0.85%)	12(1.82%)	5(1.61%)	12(0.91%)	39(0.68%)	0.002**	0.827	0.378
Asthma	37(0.46%)	5(0.76%)	4(1.29%)	6(0.46%)	22(0.39%)	0.163	0.338	0.714
Bronchiectasis	35(0.44%)	6(0.91%)	1(0.32%)	3(0.23%)	25(0.44%)	0.100	0.513	0.341
Silicosis	28(0.35%)	2(0.3%)	2(0.64%)	9(0.68%)	15(0.26%)	0.694	0.694	0.018
Cancer	20(0.25%)	3(0.45%)	2(0.64%)	4(0.3%)	11(0.19%)	0.171	0.637	0.503

Notes: TB, tuberculosis; BMI, body mass index; COPD, chronic obstructive pulmonary disease; *P<0.05;**P<0.01;***P<0.001;

Table 2
Drug resistant profiles among TB cases with or without alcohol drinking and tobacco smoking habits

Drug resistance	Total(n = 7966)	Subgroups(Group 1–4)				P value		
		G1:Smoker + non-drinker(n = 660)	G2:non-smoker + drinker(n = 311)	G3:Smoker + drinker(n = 1316)	G0:non-smoker + non-drinker(n = 5709)	G1 vs G0	G2 vs G0	G3 vs G0
DR-TB	1495(18.77%)	127(19.24%)	51(16.4%)	228(17.33%)	1089(19.08%)	0.918	0.241	0.143
Any resistance to first-line drug								
INH	820(10.29%)	74(11.21%)	29(9.32%)	123(9.35%)	594(10.4%)	0.522	0.543	0.253
RFP	389(4.88%)	30(4.55%)	12(3.86%)	50(3.8%)	297(5.2%)	0.469	0.296	0.034*
EMB	145(1.82%)	11(1.67%)	4(1.29%)	18(1.37%)	112(1.96%)	0.602	0.526	0.149
SM	1050(13.18%)	88(13.33%)	38(12.22%)	152(11.55%)	772(13.52%)	0.893	0.512	0.056
MR-TB (Total)	891(11.19%)	76(11.52%)	27(8.68%)	144(10.94%)	664(11.63%)	0.93	0.112	0.480
INH	266(3.34%)	26(3.94%)	7(2.25%)	42(3.19%)	191(3.35%)	0.426	0.292	0.778
RFP	70(0.88%)	7(1.06%)	3(0.96%)	9(0.68%)	51(0.89%)	0.668	0.757	0.457
EMB	20(0.25%)	1(0.15%)	0(0%)	5(0.38%)	20(0.35%)	0.717	0.622	0.871
SM	530(6.65%)	41(6.21%)	15(4.82%)	87(6.61%)	387(6.78%)	0.582	0.179	0.827
Others	5(0.06%)	1(0.15%)	2(0.64%)	1(0.08%)	1(0.02%)	0.197	0.008**	0.340
MDR-TB (Total)	276(3.46%)	20(3.03%)	8(2.57%)	39(2.96%)	209(3.66%)	0.41	0.316	0.217
MDR1: INH + RFP	58(0.73%)	3(0.45%)	1(0.32%)	17(1.29%)	37(0.65%)	0.794	0.721	0.016*
MDR2: INH + RFP + EMB + SM	59(0.74%)	6(0.91%)	3(0.96%)	5(0.38%)	45(0.79%)	0.742	0.737	0.112
MDR3: INH + RFP + SM	110(1.38%)	10(1.52%)	3(0.96%)	8(0.61%)	89(1.56%)	0.931	0.631	0.008**
Others	49(0.62%)	1(0.15%)	1(0.32%)	9(0.68%)	38(0.67%)	0.179	0.721	0.942
PDR-TB (Total)	323(4.05%)	31(4.7%)	15(4.82%)	44(3.34%)	233(4.08%)	0.452	0.521	0.215
PDR1: INH + EMB	9(0.11%)	0(0%)	0(0%)	0(0%)	9(0.16%)	0.611	1.000	0.224
PDR2: INH + SM	257(3.23%)	26(3.94%)	14(4.5%)	41(3.12%)	176(3.08%)	0.235	0.163	0.951
PDR3: RFP + SM	32(0.4%)	1(0.15%)	1(0.32%)	2(0.15%)	28(0.49%)	0.357	1.000	0.102
PDR4: INH + EMB + SM	9(0.11%)	2(0.3%)	0(0%)	0(0%)	7(0.12%)	0.238	1.000	0.361
Others	16(0.2%)	2(0.3%)	0(0%)	1(0.08%)	13(0.23%)	0.664	1.000	0.490

Notes: 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<0.05;

Table 3
Association between alcohol drinking, tobacco smoking and TB drug resistance

The type of drug resistance	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P value	aOR (95%CI)	P value
G1:Smoker + non-drinker vs G0:non-smoker + non-drinker				
DR-TB	1.011(0.824–1.24)	0.918	0.983(0.798–1.212)	0.875
MR-TB	1.024(0.795–1.318)	0.857	1.019(0.787–1.319)	0.888
MDR-TB	0.822(0.516–1.311)	0.411	1.085(0.733–1.605)	0.685
PDR-TB	1.158(0.789–1.7)	0.453	0.799(0.498–1.284)	0.354
INH-related resistance	1.087(0.842–1.405)	0.522	1.011(0.779–1.314)	0.933
RFP-related resistance	0.868(0.591–1.275)	0.469	0.846(0.572–1.252)	0.403
SM-related resistance	0.984(0.776–1.247)	0.893	0.997(0.783–1.271)	0.983
EMB-related resistance	0.847(0.454–1.582)	0.602	0.715(0.38–1.346)	0.299
MDR1: INH + RFP	0.7(0.215–2.277)	0.553	0.669(0.202–2.213)	0.51
MDR2: INH + RFP + EMB + SM	1.155(0.491–2.717)	0.742	0.975(0.407–2.335)	0.954
MDR3: INH + RFP + SM	0.971(0.503–1.877)	0.931	1.026(0.524–2.009)	0.941
PDR2: INH + SM	1.289(0.847–1.962)	0.236	1.247(0.811–1.917)	0.315
PDR3: RFP + SM	0.308(0.042–2.267)	0.247	0.267(0.036–1.997)	0.199
Any INH + SM resistance	0.994(0.805–1.228)	0.956	0.971(0.783–1.204)	0.787
Susceptible	reference	reference	reference	reference
G2:non-smoker + drinker vs G0:non-smoker + non-drinker				
DR-TB	0.832(0.612–1.132)	0.241	0.774(0.567–1.055)	0.105
MR-TB	0.748(0.5–1.119)	0.158	0.718(0.478–1.078)	0.11
MDR-TB	1.191(0.697–2.034)	0.522	0.634(0.308–1.304)	0.216
PDR-TB	0.695(0.34–1.421)	0.319	1.079(0.628–1.854)	0.783
INH-related resistance	0.886(0.599–1.31)	0.543	0.817(0.55–1.213)	0.317
RFP-related resistance	0.731(0.406–1.318)	0.298	0.647(0.357–1.171)	0.15
SM-related resistance	0.89(0.629–1.26)	0.512	0.843(0.593–1.199)	0.342
EMB-related resistance	0.651(0.239–1.777)	0.402	0.575(0.209–1.577)	0.282
MDR1: INH + RFP	0.495(0.068–3.616)	0.488	0.471(0.064–3.477)	0.46
MDR2: INH + RFP + EMB + SM	1.226(0.379–3.967)	0.734	1.099(0.334–3.616)	0.876
MDR3: INH + RFP + SM	0.615(0.194–1.955)	0.41	0.535(0.167–1.714)	0.293
PDR2: INH + SM	1.482(0.849–2.586)	0.166	1.417(0.805–2.494)	0.227
PDR3: RFP + SM	0.654(0.089–4.826)	0.678	0.476(0.064–3.565)	0.47
Any INH + SM resistance	0.801(0.581–1.103)	0.174	0.75(0.543–1.037)	0.082
Susceptible	reference	reference	reference	reference
G3:Smoker + drinker vs G0:non-smoker + non-drinker				
DR-TB	0.889(0.76–1.04)	0.143	0.839(0.712–0.988)	0.035*

The type of drug resistance	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P value	aOR (95%CI)	P value
MR-TB	0.966(0.798–1.17)	0.726	0.935(0.766–1.141)	0.508
MDR-TB	0.804(0.568–1.137)	0.217	0.737(0.525–1.035)	0.078
PDR-TB	0.813(0.586–1.128)	0.216	0.768(0.536–1.099)	0.149
INH-related resistance	0.888(0.724–1.089)	0.253	0.816(0.661–1.009)	0.06
RFP-related resistance	0.72(0.53–0.977)	0.035*	0.675(0.492–0.925)	0.015*
SM-related resistance	0.835(0.694–1.005)	0.057	0.819(0.675–0.993)	0.042*
EMB-related resistance	0.693(0.42–1.144)	0.152	0.571(0.342–0.954)	0.032*
MDR1: INH + RFP	2.006(1.126–3.574)	0.018*	1.913(1.036–3.532)	0.038*
MDR2: INH + RFP + EMB + SM	0.48(0.19–1.212)	0.12	0.401(0.156–1.032)	0.058
MDR3: INH + RFP + SM	0.386(0.187–0.798)	0.01*	0.406(0.194–0.851)	0.017*
PDR2: INH + SM	1.011(0.716–1.428)	0.951	0.944(0.659–1.353)	0.753
PDR3: RFP + SM	0.309(0.073–1.298)	0.109	0.282(0.066–1.214)	0.089
Any INH + SM resistance	0.886(0.754–1.042)	0.142	0.845(0.714–1)	0.05*
Susceptible	reference	reference	reference	reference

Notes: 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; aOR: adjusted odds ratio; OR: odds ratio; CI: confidence interval; *P<0.05;

Table 4
Univariable and multivariable analysis of risk factors for DR-TB in smoker + drinker

Characteristics	non-DR n = 1088(82.67%)	DR-TB n = 228(17.32%)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	P value	aOR (95% CI)	P value
Age(years)(n = 1083/n = 227)						
15–24	65(6%)	12(5.29%)	reference	reference	reference	reference
25–44	217(20.04%)	45(19.82%)	1.123(0.561–2.25)	0.743	1.081(0.537–2.176)	0.827
45–64	508(46.91%)	115(50.66%)	1.226(0.641–2.345)	0.537	1.194(0.621–2.295)	0.596
> 65	293(27.05%)	55(24.23%)	1.017(0.515–2.007)	0.962	1.028(0.517–2.04)	0.938
Sex(n = 1088/n = 228)						
Male	1084(100.09%)	228(100%)	339786504.814(0-.)	0.999	358353335.759(0-.)	0.999
Female	4(0.37%)	0(0%)	reference	reference	reference	reference
Cavity(n = 1021/n = 220)						
Yes	475(43.86%)	119(54.09%)	1.354(1.011–1.814)	0.042*	1.329(0.988–1.788)	0.06
No	546(50.42%)	101(45.91%)	reference	reference	reference	reference
BMI(n = 1060/n = 224)						
underweight: <18.5	258(23.82%)	57(25.45%)	1.081(0.773–1.51)	0.65	1.086(0.773–1.524)	0.634
normal: 18.5 to < 25	763(70.45%)	156(69.64%)	reference	reference	reference	reference
overweight or obesity: ≥25.0	39(3.6%)	11(4.91%)	1.38(0.691–2.753)	0.361	1.305(0.648–2.628)	0.457
Comorbidities(n = 1088/n = 228)						
Yes	180(16.62%)	42(18.42%)	1.139(0.786–1.651)	0.492	1.096(0.751–1.601)	0.634
No	908(83.84%)	186(81.58%)	reference	reference	reference	reference

Notes: DR-TB, drug-resistant tuberculosis; BMI, body mass index; aOR: adjusted odds ratio; OR: odds ratio; CI: confidence interval; *P<0.05;

Table 5
Univariable and multivariable analysis of risk factors for DR-TB in non-smoker + non-drinker

Characteristics	non-DR n = 4620(80.92%)	DR-TB n = 1089(19.08%)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	P value	aOR (95% CI)	P value
Age(years)(n = 4598/n = 1085)						
0–14	20(0.43%)	3(0.28%)	0.622(0.183–2.115)	0.447	0.678(0.198–2.319)	0.536
15–24	767(16.68%)	185(17.05%)	reference	reference	reference	reference
25–44	1207(26.25%)	318(29.31%)	1.092(0.892–1.338)	0.393	1.084(0.884–1.329)	0.44
45–64	1355(29.47%)	332(30.6%)	1.016(0.831–1.241)	0.878	0.96(0.783–1.178)	0.697
> 65	1249(27.16%)	247(22.76%)	0.82(0.664–1.012)	0.065	0.778(0.627–0.967)	0.023*
Sex(n = 4620/n = 1089)						
Male	3551(76.86%)	876(80.44%)	reference	reference	reference	reference
Female	1069(23.14%)	213(19.56%)	1.238(1.05–1.46)	0.011*	1.261(1.067–1.49)	0.007**
Cavity(n = 4033/n = 952)						
Yes	1762(43.69%)	453(47.58%)	1.17(1.016–1.348)	0.03*	1.143(0.991–1.319)	0.067
No	2271(56.31%)	499(52.42%)	reference	reference	reference	reference
BMI(n = 4453/n = 1054)						
underweight: <18.5	1054(23.67%)	244(23.15%)	0.978(0.833–1.148)	0.785	1.012(0.86–1.19)	0.886
normal: 18.5 to < 25	3147(70.67%)	745(70.68%)	reference	reference	reference	reference
overweight : 25.0 to < 30	226(5.08%)	61(5.79%)	1.14(0.85–1.53)	0.382	1.11(0.826–1.492)	0.488
obesity ≥ 30.0	26(0.58%)	4(0.38%)	0.65(0.226–1.868)	0.424	0.624(0.215–1.806)	0.384
Comorbidities(n = 4620/n = 1089)						
Yes	532(11.52%)	954(87.6%)	1.087(0.889–1.33)	0.415	1.15(0.932–1.418)	0.194
No	4088(88.48%)	135(12.4%)	reference	reference	reference	reference

Notes: DR-TB, drug-resistant tuberculosis; BMI, body mass index; aOR: adjusted odds ratio; OR: odds ratio; CI: confidence interval;*P<0.05;**P<0.01;

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