


# BMJ Open Risk factors for drug-resistant tuberculosis, the association between comorbidity status and drug-resistant patterns: a retrospective study of previously treated pulmonary tuberculosis in Shandong, China, during 2004–2019

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## ABSTRACT

**Objective** This study was designed to identify the risk factors for drug-resistant tuberculosis (DR-TB) and the association between comorbidity and drug resistance among retreated pulmonary tuberculosis (PTB).

**Design** A retrospective study was conducted among all the 36 monitoring sites in Shandong, China, over a 16-year period. Baseline characteristics were collected from the TB Surveillance System. Categorical variables were compared by Fisher's exact or Pearson's  $\chi^2$  test. The risk factors for drug resistance were identified using univariable analysis and multivariable logistic models. The influence of comorbidity on different types of drug resistance was evaluated by performing multivariable logistic models with the covariates adjusted by age, sex, body mass index, drinking/smoking history and cavity.

**Results** A total of 10 975 patients with PTB were recorded during 2004–2019, and of these 1924 retreated PTB were finally included. Among retreated PTB, 26.2% were DR-TB and 12.5% had comorbidity. Smoking (adjusted OR (aOR): 1.69, 95% CI 1.19 to 2.39), cavity (aOR: 1.55, 95% CI 1.22 to 1.97) and comorbidity (aOR: 1.44, 95% CI 1.02 to 2.02) were risk factors for DR-TB. Of 504 DR-TB, 9.5% had diabetes mellitus, followed by hypertension (2.0%) and chronic obstructive pulmonary disease (1.8%). Patients with retreated PTB with comorbidity were more likely to be older, have more bad habits (smoking, alcohol abuse) and have clinical symptoms (expectoration, haemoptysis, weight loss). Comorbidity was significantly associated with DR-TB (aOR: 1.44, 95% CI 1.02 to 2.02), overall rifampin resistance (aOR: 2.17, 95% CI 1.41 to 3.36), overall streptomycin resistance (aOR: 1.51, 95% CI 1.00 to 2.27) and multidrug resistance (aOR: 1.96, 95% CI 1.17 to 3.27) compared with pan-susceptible patients ( $p < 0.05$ ).

**Conclusion** Smoking, cavity and comorbidity lead to an increased risk of drug resistance among retreated PTB. Strategies to improve the host's health, including smoking cessation, screening and treatment of comorbidity, might

## Strengths and limitations of this study

- This study had a large sample size and long time span.
- The sample on the association between comorbidity status and drug-resistant tuberculosis among patients with retreated pulmonary tuberculosis in Shandong Province, China, is representative.
- The diversity in diagnostic and therapeutic levels from different tuberculosis monitoring sites may lead to bias.
- The diagnosis of tuberculosis based on microscopy inevitably underestimated the burden of tuberculosis.

contribute to the control of tuberculosis, especially DR-TB, in China.

## INTRODUCTION

With the changing of demographics and lifestyle, the spectrum of disease has been transformed from infectious diseases to non-communicable diseases (NCDs).<sup>1</sup> However, people from developing countries suffer the double burden of infectious diseases and NCDs.<sup>2</sup> As an infectious disease, tuberculosis (TB) can be prevented and treated well. Although the control of TB has achieved considerable progress in the past decades, this seems to have reached its bottleneck recently with 1.45 million deaths due to TB, which ranks the topmost cause of death among infectious agents.<sup>3</sup> The overlapping TB and comorbidities exacerbate the risk and mortality of the other.<sup>1</sup> The bidirectional

deleterious correlation between TB and coexisting diseases might open a new direction for future TB control.

Drug resistance is an intractable public problem and a crucial obstacle to TB control. According to a 2019 global TB report, about half a million new cases were rifampicin-resistant TB (RR-TB), among which 78% cases were multidrug-resistant TB (MDR-TB), a kind of resistance to both isoniazid (INH) and rifampicin (RFP). Drug resistance not only was an indicator of poor outcomes, but it also resulted in fewer effective drugs to choose, higher expenses to pay, and the spread and exacerbation of drug-resistant TB (DR-TB).<sup>4 5</sup> Patients with previous anti-TB treatment are at high risk of developing DR-TB. Compared with newly treated TB cases (3.4%), the rate of MDR-TB/RR-TB was 18% among retreated cases.<sup>3</sup> The control of DR-TB especially those among retreated patients is imperative.

Various studies and reviews reported that host factors including smoking, alcohol abuse, low body mass index (BMI), comorbidity (eg, HIV infection, diabetes mellitus (DM), chronic renal failure (CRF), malignancy, chronic obstructive pulmonary disease (COPD), silicosis) can predispose to the development of TB.<sup>6–12</sup> Several of these factors were associated with poor treatment outcomes (eg, alcohol abuse, HIV infection, DM),<sup>13 14</sup> TB relapse (eg, HIV infection, DM)<sup>13 15</sup> and the development of MDR-TB (eg, alcohol abuse, HIV infection, DM, COPD) significantly.<sup>6 16 17</sup> Coexisting diseases are continuously being identified as a vital factor in the control of TB. It is believed that the improvement of the host's health status, both timely identification and effective treatment of comorbidity, may alleviate the development of TB and reduce the spread of DR-TB.

Although China is an upper-middle-income country, with half its population residing in urban areas, the burden of DR-TB (only followed behind by India) and NCDs is very serious. This study aims to summarise the characteristics of host status and types of drug resistance in retreated pulmonary TB (PTB), identify the risk factors for drug resistance of these patients, and evaluate the contribution of comorbidity to different types of drug resistance among retreated PTB in Shandong Province, China, during 2004–2019.

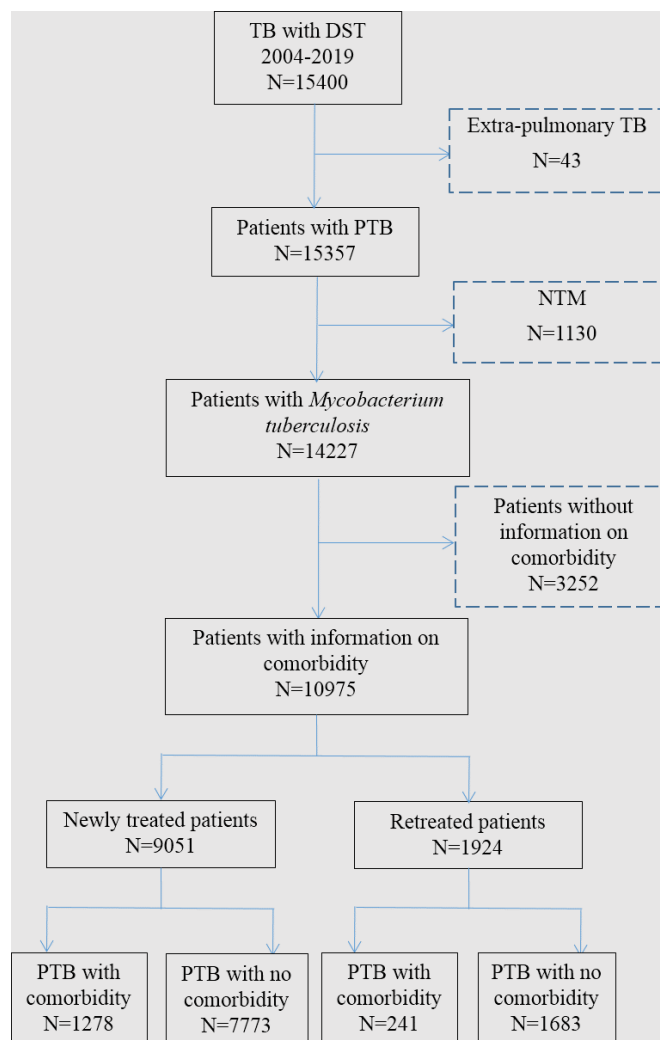
## METHODS

### Setting

This retrospective cohort study was conducted in the second most populous province of China, Shandong Province. In 2019, about 100.47 million populations resided in an area of 157 100 km<sup>2</sup> in Shandong Province, which is located at 36°24'N latitude, 118°24'E longitude, with 17 municipalities and 137 counties (districts) (<http://www.stats-sd.gov.cn/>).

### Study population and data collection

In Shandong Province, there are 13 municipal-level local health departments, 2 province-level and 21 county-level hospitals, which were responsible for quality assessment in



**Figure 1** TB cases in Shandong, China. DST, drug susceptibility testing; NTM, non-tuberculous mycobacteria; PTB, pulmonary tuberculosis TB, tuberculosis.

TB surveillance. We searched the TB Surveillance System in Shandong and collected information on patients with PTB with full data on comorbidity status and drug susceptibility testing (DST) results (at least for all of the four first-line anti-TB drugs) during 2004–2019. We ruled out those patients without information on comorbidity status and those with extrapulmonary TB or non-tuberculosis mycobacteria infection (figure 1). A total of 9051 newly treated and 1924 retreated PTB cases were identified. Of all the patients with retreated PTB with *Mycobacterium tuberculosis* infection, 1683 had no comorbidity and 241 had at least one comorbidity. Demographic information (age and sex) and clinical information (BMI, smoking, alcohol abuse, cavity and symptoms) were collected.

### Laboratory diagnosis and DST

All samples available from suspicious patients were collected by the specialist at each surveillance site. One patient should have at least two sputum samples for examinations of bacteriological culture, species identification and DST. Smear microscopy with Ziehl-Neelsen staining was performed to

identify acid-fast bacilli. Each sample was inoculated into tubes with acidified Löwenstein-Jensen medium for further culture.<sup>18</sup> Subsequently, the samples with growing colonies were tested for strain identification and DST. The identification of *M. tuberculosis* included a comprehensive consideration of the results according to p-nitrobenzoic acid, 2-thiophene carboxylic acid hydrazide testing and 16S rRNA gene sequence analysis.<sup>19</sup>

DST for first-line anti-TB drugs was performed using the proportion method on Löwenstein-Jensen medium with the following drug concentrations: INH (0.2 µg/mL), RFP (40 µg/mL), ethambutol (EMB, 2.0 µg/mL) and streptomycin (SM, 4.0 µg/mL). DST for other anti-TB drugs, such as pyrazinamide, fluoroquinolone and kanamycin, was performed according to patients' choice, which was non-routinely.

### Quality control

All procedures during TB surveillance were carried out according to the WHO guidelines. External quality assessment for all laboratory tests, including smear, culture and DST, was supervised by the Superior TB National Reference Laboratory in Katharine Hsu Center of Shandong Province.<sup>18</sup> Quality assessment and data extraction were accomplished by at least two researchers who were trained professionally.

### Definitions

Drug-susceptible TB was defined as being susceptible to all of the four first-line anti-TB drugs. DR-TB were classified into monoresistance (MR), resistant to only one first-line anti-TB drug; multidrug resistance (MDR), resistant to at least both INH and RFP; and polydrug resistance (PDR), resistant to at least two first-line anti-TB drug, except to both INH and RFP. Retreated TB referred to patients who had accepted 1 month of anti-TB drugs before.

Comorbidity data collected in this study were DM, hypertension, hepatitis, CRF, connective tissue disease (CTD), disability, malignancy, HIV infection, silicosis, asthma, COPD and bronchiectasia co-occurring with TB. Comorbidity status was confirmed mainly in two ways: (1) self-reported by the patient with a previous diagnosis certificate; and (2) newly identified cases according to associated diagnostic consensus unified globally.

### Statistical analysis

Continuous variables such as age were summarised with mean and SD; categorical variables including sex, BMI (<18.5, 18.5–24.9, ≥25), drinking history, smoking history, TB contact history, cavity, symptoms (cough, expectoration, fever, night sweating, fatigue, haemoptysis, weight loss and chest pain) and comorbidities (silicosis, asthma, COPD, bronchiectasia, lung cancer, DM, hypertension, gastrointestinal cancer, hepatitis, renal failure, CTD and other malignancy) were summarised as proportions. Univariable analysis and multivariable logistic models were applied to identify the risk factors for drug resistance among newly treated or retreated PTB cases. Demographic characteristics,

clinical traits and types of drug resistance were compared according to comorbidity status using Fisher's exact or Pearson's  $\chi^2$  test. Multivariable logistic models were also used to estimate the influence of comorbidity on different types of drug resistance with the covariates adjusted by age, sex, BMI, drinking history, smoking history and cavity according to published research. A two-sided  $p < 0.05$  was considered significant. All statistical analyses were calculated using SPSS V.20.0 software.

## RESULTS

### Case estimates and risk factors for DR-TB

The baseline characteristics of the study populations are demonstrated in table 1. A total of 10 975 patients with PTB aged 49.8±19.7 were reported in Shandong, China, in 2004–2019, of whom 9051 (82.5%) cases were newly treated and 1924 (17.5%) were retreated PTB. Among these retreated PTB cases, 26.2% were drug-resistant, 82.7% were male, 18.5% were drinkers, 25.2% were smokers, 46.4% with baseline cavity and 16.3% had comorbidity.

In all retreated PTB cases, the following characteristics were associated with the presence of DR-TB: (1) smoking (adjusted OR (aOR): 1.69, 95% CI 1.19 to 2.39); (2) cavity (aOR: 1.55, 95% CI 1.22 to 1.97); and (3) comorbidity (aOR: 1.44, 95% CI 1.02 to 2.02). In all newly treated PTB cases, male sex (aOR: 1.25, 95% CI 1.03 to 1.51) and cavity (aOR: 1.15, 95% CI 1.01 to 1.31) were associated with the presence of DR-TB.

### Demographic and clinical characteristics of retreated PTB

A total of 241 (12.5%) patients with retreated PTB with comorbidity (group A) and 1683 (87.5%) with no comorbidity (group B) were enrolled in this study. According to Pearson's  $\chi^2$  test, patients with retreated PTB with comorbidity were more likely than those without comorbidity to be older (A vs B: 60.1±15.9 vs 49.1±19.6,  $p < 0.001$ ), to be male (A vs B: 87.1% vs 80.9%,  $p < 0.001$ ), with BMI ≥25 (A vs B: 7.9% vs 3.4%,  $p = 0.02$ ), to abuse alcohol (A vs B: 24.9% vs 17.0%,  $p = 0.003$ ), to be a smoker (A vs B: 30.0% vs 19.5%,  $p < 0.001$ ), to have cavity (A vs B: 52.5% vs 35.1%,  $p < 0.001$ ), and to have more symptoms including expectoration (A vs B: 85.1% vs 77.2%,  $p = 0.006$ ), haemoptysis (A vs B: 22.0% vs 12.7%,  $p < 0.001$ ) and weight loss (A vs B: 19.5% vs 13.5%,  $p = 0.012$ ) (table 2).

### Drug-resistant profiles of retreated PTB

About 34.0% (82) of patients with retreated PTB with comorbidity and 25.1% (422) without comorbidity had DR-TB ( $p = 0.003$ ). After further dividing into different drug-resistant subgroups, it showed that the rates of overall INH resistance (A vs B: 22.8% vs 16.0%,  $p = 0.008$ ), overall RFP resistance (A vs B: 19.5% vs 10.8%,  $p < 0.001$ ), MR to INH (A vs B: 3.7% vs 1.4%,  $p = 0.007$ ), PDR to RFP+SM (A vs B: 1.2% vs 0.2%,  $p = 0.029$ ), MDR (A vs B: 12.9% vs 7.7%,  $p = 0.006$ ) and resistance to INH+RFP+SM (A vs B: 6.6% vs 3.6%,  $p = 0.026$ ) were much higher in group A than in

**Table 1** Characteristics of patients with new and retreated PTB, Shandong, China, 2004–2019

Characteristics	Newly treated PTB (n=9051)				Retreated PTB (n=1924)				Total (N=10975)				
	Susceptible n=7348 (81.2)	DR n=1703 (18.8)	Univariable analysis OR (95% CI)	P value	Multivariable analysis aOR (95% CI)	P value	Susceptible n=1420 (73.8)	DR n=504 (26.2)		Univariable analysis OR (95% CI)	P value	Multivariable analysis aOR (95% CI)	P value
Age	50.0±19.9	48.3±19.1	0.996 (0.993 to 0.998)	0.001	0.994 (0.991 to 0.998)	0.001	51.0±19.8	48.7±18.6	0.994 (0.989 to 0.999)	0.021	0.986 (0.980 to 0.993)	<0.001	49.8±19.7
Sex (male)	6098/7348 (83.0)	1460/1703 (85.7)		0.006	1.249 (1.033 to 1.510)	0.022	1155/1420 (81.3)	417/1420 (82.7)	1.100 (0.842 to 1.436)	0.485	1.202 (0.865 to 1.670)	0.273	9130/10975 (83.2)
BMI													
<18.5	1550/6627 (23.4)	352/1548 (22.7)	0.949 (0.723 to 1.247)	0.708	0.917 (0.675 to 1.246)	0.581	354/1309 (27.0)	135/468 (28.8)	0.554 (0.336 to 0.911)	0.020	0.557 (0.316 to 0.983)	0.044	2391/9952 (24.0)
18.5–24.9	4751/6627 (71.1)	1118/1548 (72.2)	0.984 (0.762 to 1.270)	0.899	0.981 (0.690 to 1.223)	0.560	910/1309 (69.5)	320/468 (64.5)	0.482 (0.299 to 0.775)	0.003	0.448 (0.260 to 0.774)	0.004	7081/9952 (71.2)
≥25	326/6627 (4.9)	78/1548 (5.0)	Reference	Reference	Reference	Reference	45/1309 (3.4)	31/468 (6.6)	Reference	Reference	Reference	Reference	480/9952 (4.8)
Alcohol abuse	1246/5779 (21.6)	251/1291 (19.4)	1.139 (0.979 to 1.325)	0.092	0.868 (0.707 to 1.067)	0.179	242/1355 (17.9)	85/459 (18.5)	1.045 (0.795 to 1.374)	0.751	0.820 (0.568 to 1.185)	0.291	1824/8884 (20.5)
Smoking	1475/5822 (25.3)	318/1299 (24.5)	1.047 (0.910 to 1.204)	0.521	1.033 (0.851 to 1.255)	0.741	264/1360 (19.4)	116/461 (25.2)	1.396 (1.088 to 1.792)	0.009	1.687 (1.191 to 2.388)	0.003	2173/8942 (24.3)
Cavity	2765/6201 (44.6)	689/1452 (47.5)	0.891 (0.795 to 0.999)	0.049	1.152 (1.012 to 1.312)	0.033	444/1299 (34.2)	205/442 (46.4)	1.666 (1.338 to 2.074)	<0.001	1.550 (1.219 to 1.971)	<0.001	4103/9394 (43.7)
Comorbidity	1032/7348 (14)	246/1703 (14.4)	1.033 (0.889 to 1.201)	0.669	1.079 (0.901 to 1.293)	0.408	159/1420 (11.2)	82/504 (16.3)	1.541 (1.155 to 2.056)	0.003	1.436 (1.020 to 2.022)	0.038	1519/10975 (13.8)

aOR, adjusted OR; BMI, body mass index; DR, drug-resistant; PTB, pulmonary tuberculosis.

**Table 2** Demographic and clinical characteristics of 1924 patients with retreated PTB

Characteristics	Total n=1924	Patients with PTB with comorbidity n=241	Patients with PTB without comorbidity n=1683	P value
Age	50.43±19.53	60.05±15.87	49.05±19.62	<0.001
0–14	4 (0.2)	0 (0)	4 (0.2)	1
15–44	737 (38.3)	42 (17.4)	695 (41.3)	<0.001
45–64	661 (34.4)	99 (41.1)	562 (33.4)	0.019
>65	522 (27.1)	100 (41.5)	422 (25.1)	<0.001
Sex (male)	1572 (81.7)	210 (87.1)	1362 (80.9)	0.02
<b>BMI (n=1777/230/1547)</b>				
<18.5	489 (25.4)	56 (23.2)	433 (25.7)	Reference
18.5–24.9	1212 (63.0)	155 (64.3)	1057 (62.8)	0.449
≥25	76 (4.0)	19 (7.9)	57 (3.4)	<0.001
Alcohol abuse (n=1814/233/1581)	327 (18.0)	58 (24.9)	269 (17.0)	0.003
Smoking (n=1821/233/1588)	380 (20.9)	70 (30.0)	310 (19.5)	<0.001
<b>Symptom</b>				
Cough	1840 (95.6)	226 (93.8)	1614 (95.9)	0.131
Expectoration	1504 (78.3)	205 (85.1)	1299 (77.2)	0.006
Fever	901 (46.8)	104 (43.2)	797 (47.4)	0.221
Night sweat	434 (22.6)	45 (18.7)	389 (23.1)	0.123
Fatigue	756 (39.3)	90 (37.3)	666 (39.6)	0.508
Haemoptysis	266 (13.8)	53 (22.0)	213 (12.7)	<0.001
Weight loss	274 (14.2)	47 (19.5)	227 (13.5)	0.012
Chest pain	217 (11.3)	32 (13.3)	185 (11.0)	0.294
Tuberculosis contact (n=720/162/558)	29 (4.0)	7 (4.3)	22 (3.9)	0.829
Cavity (n=1741/219/1522)	649 (37.3)	115 (52.5)	534 (35.1)	<0.001

BMI, body mass index; PTB, pulmonary tuberculosis.

group B. No significant differences in the rates of other drug-resistant subgroups between group A and group B were identified ( $p>0.05$ ) (table 3).

### Comorbidities detected among retreated PTB

Among 241 (12.5%) patients with retreated PTB with comorbidity, extrapulmonary comorbidity accounted for 77.6% (187), pulmonary comorbidity 27.4% (66), both pulmonary and extrapulmonary comorbidity 5.0% (12), DM 51.5% (124) and COPD 16.6% (40). Among 504 patients with retreated PTB with drug resistance, 16.3% had comorbidity, 13.7% had extrapulmonary comorbidity and 3.4% had pulmonary comorbidity. The highest proportion of comorbidity was found for DM (9.5%), followed by hypertension (2.0%) and COPD (1.8%). Of 82 patients with retreated PTB with drug resistance and baseline comorbidity, 87.8% (72) had only one kind of comorbidity, 15.9% (13) had pulmonary comorbidity alone, 79.3% (65) had extrapulmonary comorbidity alone, and 4.9% (4) had both pulmonary and extrapulmonary comorbidity (table 4).

### Association between comorbidity status and drug resistance profiles of retreated PTB

According to univariable and multivariable analyses, overall RFP resistance (OR: 2.05, 95% CI 1.43 to 2.94; aOR: 2.17, 95% CI 1.41 to 3.36), overall SM resistance (OR: 1.48, 95% CI 1.05 to 2.08; aOR: 1.51, 95% CI 1.00 to 2.27) and MDR (OR: 1.91, 95% CI 1.25 to 2.92; aOR: 1.96, 95% CI 1.17 to 3.27) had a significant association with comorbidity ( $p<0.05$ ). Comorbidity was significantly associated with overall INH (OR: 1.62, 95% CI 1.16 to 2.26) and PDR (OR: 1.74, 95% CI 1.05 to 2.87) in univariable analysis ( $p<0.05$ ), but not in multivariable analysis ( $p>0.05$ ) (table 5).

### DISCUSSION

This retrospective cohort study of patients with PTB in Shandong Province in China illustrates the risk factors for retreated PTB and the association between comorbidity status and drug resistance profiles among these patients

**Table 3** Drug-resistant profiles among patients with retreated PTB

Types	Total n=1924	With comorbidity n=241	Without comorbidity n=1683	P value
DR-TB	504 (26.2)	82 (34.0)	422 (25.1)	0.003
Any resistance to first-line drugs				
INH	324 (16.8)	55 (22.8)	269 (16.0)	0.008
RFP	229 (11.9)	47 (19.5)	182 (10.8)	<0.001
EMB	63 (3.3)	12 (5.0)	51 (3.0)	0.112
SM	325 (16.9)	51 (21.2)	274 (16.3)	0.059
Others	227 (11.8)	30 (12.4)	197 (11.7)	0.738
Monoresistant tuberculosis				
INH	85 (4.4)	10 (4.1)	75 (4.5)	0.828
RFP	32 (1.7)	9 (3.7)	23 (1.4)	0.007
RFP	7 (0.4)	1 (0.4)	6 (0.4)	1
EMB	98 (5.1)	9 (3.7)	89 (5.3)	0.305
SM	5 (0.3)	1 (0.4)	4 (0.2)	0.488
Others	117 (6.1)	21 (8.7)	96 (5.7)	0.067
Polydrug-resistant tuberculosis				
INH+EMB	1 (0.1)	1 (0.4)	0 (0)	0.125
INH+SM	72 (3.7)	10 (4.1)	62 (3.7)	0.722
INH+SM	4 (0.2)	1 (0.4)	3 (0.2)	0.415
RFP+EMB	28 (1.5)	6 (2.5)	22 (1.3)	0.151
RFP+SM	6 (0.3)	3 (1.2)	3 (0.2)	0.029
INH+EMB+SM	6 (0.3)	0 (0)	6 (0.4)	1
MDR-TB (total)				
INH+RFP	160 (8.3)	31 (12.9)	129 (7.7)	0.006
INH+RFP	36 (1.9)	7 (2.9)	29 (1.7)	0.206
INH+RFP+EMB	7 (0.4)	1 (0.4)	6 (0.4)	1
INH+RFP+EMB+SM	28 (1.5)	5 (2.1)	23 (1.4)	0.391
INH+RFP+SM	77 (4.0)	16 (6.6)	61 (3.6)	0.026
Others	12 (0.6)	2 (0.8)	10 (0.6)	0.655

DR-TB, drug-resistant tuberculosis; EMB, ethambutol; INH, isoniazid; MDR-TB, multidrug-resistant tuberculosis; PTB, pulmonary tuberculosis; RFP, rifampicin; SM, streptomycin.

during the past 16 years. This study achieves several findings, including the following: (1) among 1924 retreated PTB cases, 26.2% were DR-TB and 12.5% had comorbidity; (2) smoking/cavity/comorbidity were risk factors for drug resistance among retreated PTB; (3) among 241 patients with retreated PTB with comorbidity, DM had the highest percentage (51.5%), followed by COPD (16.6%); (4) patients with retreated PTB with comorbidity were more likely to be male, to be older, with BMI  $\geq 25$ , to abuse cigarette/alcohol, to have clinical symptoms (expectoration, haemoptysis, weight loss) and to have DR-TB; and (5) comorbidity was also a risk factor for overall RFP resistance, overall SM resistance and MDR of retreated PTB.

Previous findings on the risk factors for DR-TB may vary in ethnicity, geographical region and study design. In this study, smoking, cavity and comorbidity were risk factors for drug resistance among patients with retreated PTB. Similarly, these factors have been reported to increase the risk of DR-TB.<sup>17 20–22</sup> Having TB treatment history was acknowledged as the strongest and most crucial

determinant of DR-TB. While majority of the studies indicated that comorbidity (DM, HIV, COPD) and tobacco smoking were associated with DR-TB, others still found no significant relationship between them.<sup>14 16 23–26</sup> Based on a real-world study, TB, smoking, COPD and HIV had deleterious and synergistic relationships.<sup>27</sup> The coexistence of TB and baseline disease may favour progression of the disease and increase the probability of drug–drug interactions or side effects. The improvement of health-associated risk factors (eg, smoking, DM, HIV infection) was reported to mitigate TB development and mortality.<sup>3</sup> In this study, 17.5% of cases were retreated PTB, among which 18% abuse alcohol, 20.9% were smokers, 37.3% had cavity and 12.5% had comorbidity. The high proportion of these risk factors among retreated PTB in Shandong Province deserves more attention.

DM (51.5%) followed by COPD (16.6%) were the most common comorbidities among patients with retreated PTB in this study. Extrapulmonary comorbidity (eg, HIV infection, DM, CKD) can facilitate the development of

**Table 4** Comorbidities detected among patients with retreated PTB

Comorbidity	INH n=324	RFP n=229	MDR n=160	DR n=504	Susceptible n=1420	Total n=1924
Extrapulmonary disease	47 (14.5)	41 (17.9)	28 (17.5)	69 (13.7)	118 (8.3)	187 (9.7)
DM	30 (9.3)	32 (14.0)	21 (13.1)	48 (9.5)	76 (5.4)	124 (6.4)
Hypertension	7 (2.2)	2 (0.9)	1 (0.6)	10 (2.0)	19 (1.3)	29 (1.5)
Gastrointestinal cancer	1 (0.3)	0 (0)	0 (0)	1 (0.2)	4 (0.3)	5 (0.3)
Hepatitis	4 (1.2)	2 (0.9)	2 (1.3)	4 (0.8)	12 (0.9)	16 (0.8)
CRF	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0.1)
CTD	2 (0.6)	1 (0.4)	1 (0.6)	2 (0.4)	2 (0.1)	4 (0.2)
Malignancy	2 (0.6)	0 (0)	0 (0)	3 (0.6)	16 (1.1)	19 (1.0)
Disability	1 (0.3)	0 (0)	0 (0)	1 (0.2)	5 (0.4)	6 (0.3)
HIV infection	1 (0.3)	3 (1.3)	1 (0.6)	3 (0.6)	0 (0)	3 (0.2)
Pulmonary disease	11 (3.4)	9 (3.9)	5 (3.1)	17 (3.4)	49 (3.5)	66 (3.4)
Silicosis	1 (0.3)	1 (0.4)	0 (0)	3 (0.6)	3 (0.2)	6 (0.3)
Asthma	1 (0.3)	0 (0)	0 (0)	1 (0.2)	10 (0.7)	11 (0.6)
COPD	6 (1.9)	7 (3.06)	4 (2.5)	9 (1.8)	31 (2.2)	40 (2.1)
Bronchiectasia	4 (1.2)	1 (0.4)	1 (0.6)	4 (0.8)	8 (0.6)	12 (0.6)
Lung cancer	0 (0)	0 (0)	0 (0)	1 (0.2)	4 (0.3)	5 (0.3)
Others	1 (0.3)	0 (0)	0 (0)	2 (0.4)	2 (0.1)	4 (0.2)
Number of comorbidities	55 (17.0)	47 (20.5)	31 (19.4)	82 (16.3)	159 (11.2)	241 (12.5)
1	48 (14.8)	44 (19.2)	29 (18.1)	72 (14.3)	132 (9.3)	204 (10.6)
2	6 (1.9)	2 (0.9)	2 (1.3)	8 (1.6)	21 (1.5)	29 (1.5)
≥3	1 (0.3)	1 (0.4)	0 (0)	2 (0.4)	6 (0.4)	8 (0.4)
Pulmonary alone	8 (2.5)	6 (2.6)	3 (1.9)	13 (2.6)	41 (2.9)	54 (2.8)
Extrapulmonary alone	44 (13.6)	38 (16.6)	26 (16.3)	65 (12.9)	110 (7.8)	175 (9.1)
Pulmonary+extrapulmonary	3 (0.9)	3 (1.3)	2 (1.3)	4 (0.8)	8 (0.6)	12 (0.6)

COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CTD, connective tissue disease; DM, diabetes mellitus; DR, drug-resistant; INH, isoniazid; MDR, multidrug-resistant; PTB, pulmonary tuberculosis; RFP, rifampicin.

TB by impairing the immune function and increasing bacterial loads,<sup>28–30</sup> while pulmonary comorbidity such as COPD can promote the development of TB by

damaging innate lung defence, impairing lung function and changing lung structure.<sup>31 32</sup> As reported, DM and COPD can increase the risk of TB by 3.11 (95% CI 2.27

**Table 5** Association between comorbidity and antituberculosis drug resistance among patients with retreated PTB

Type	Univariable		Multivariable	
	OR (95% CI)	P value	aOR (95% CI)	P value
Any resistance to first-line drugs				
INH	1.622 (1.162 to 2.264)	0.005	1.488 (0.997 to 2.221)	0.052
RFP	2.048 (1.428 to 2.937)	<0.001	2.173 (1.408 to 3.355)	<0.001
EMB	1.866 (0.974 to 3.575)	0.06	1.643 (0.712 to 3.790)	0.244
SM	1.476 (1.049 to 2.077)	0.025	1.511 (1.004 to 2.272)	0.048
Mono-resistant tuberculosis	1.208 (0.795 to 1.835)	0.376	1.144 (0.703 to 1.861)	0.587
Polydrug-resistant tuberculosis	1.735 (1.052 to 2.861)	0.031	1.546 (0.811 to 2.944)	0.185
MDR-TB	1.906 (1.246 to 2.916)	0.003	1.956 (1.171 to 3.265)	0.01
Pan-susceptible	Reference	Reference	Reference	Reference

aOR, adjusted OR; EMB, ethambutol; INH, isoniazid; MDR-TB, multidrug-resistant tuberculosis; PTB, pulmonary tuberculosis; RFP, rifampicin; SM, streptomycin.

to 4.26) and 2.47 (95% CI 2.21 to 2.76) compared with a control group.<sup>11 33</sup> DM is one confirmed risk factor for TB which accounts for 6%–24% of TB burden according to geographical disparity.<sup>34</sup> DM not only increases the bacillary load of patients with active TB, but also changes the absorption and clearance of drugs. Thus it prolongs the duration of culture conversion and treatment. Similarly, TB and COPD played bidirectional roles by acting as an independent risk factor for the other.<sup>24</sup> In this study, comorbidity not only was a risk factor for DR-TB and MDR-TB, but also contributed to overall RFP resistance and overall SM resistance among patients with retreated PTB. Previous study demonstrated that the proportions of DM among patients with TB with and without MDR were significantly different (47.2% vs 28.1%,  $p < 0.05$ ).<sup>16</sup> Patients with TB with COPD were two times more likely to die<sup>23</sup> and 2.5 times more likely to have MDR-TB<sup>6</sup> than those without COPD. However, studies on the correlation between TB and coexisting diseases mainly focused on a specific type of drug resistance (MDR) and viewed all patients with TB as a whole. Studies of these correlations with other types of drug resistance among patients with retreated PTB are very limited. This study found that patients with retreated PTB with comorbidity were more likely to develop drug resistance (1.44 times), RFP resistance (2.17 times), SM resistance (1.51 times) and MDR (1.96 times) than those without comorbidity.

HIV infection was reported to be a major risk factor for TB and DR-TB in many countries.<sup>3 30</sup> With 95 549 new patients with HIV and 15 467 HIV-related deaths in 2018, China is still confronted with arduous challenges in controlling HIV.<sup>35</sup> However, 5 of all 31 provinces accounted for approximately the whole burden of HIV in China.<sup>36</sup> Moreover, both the incidence and HIV-related deaths in Shandong Province ranked last but one of all 31 provinces during 2004–2017.<sup>35</sup> In this study, only three (0.2%) patients with retreated PTB were coinfecting with HIV. Accordingly, HIV infection may not be the major factor for TB transmission in Shandong.

<sup>24 37</sup> Previous researches showed that TB and coexisting disease shared risk factors including age, BMI and cigarette abuse. Similarly, this study showed that patients with retreated PTB with comorbidity were more likely to be male, to be older, with BMI  $\geq 25$  and to abuse cigarette/alcohol than those without comorbidity. As the conditions of patients with retreated PTB, especially those with comorbidity, are complex, traditional disease-specific healthcare strategy may be less effective and multidisciplinary cooperation and integrated therapies towards high-risk populations are urgently needed.

Some information, such as DST for second-line anti-TB drugs, contact history and previous therapeutic regimen, was not available in this study, which may influence the results. Moreover, we calculated all comorbidities as a whole factor and did not specify the effect of each comorbidity in detail. In fact, previous investigations had concluded on the relationship between TB and different comorbidities inconsistently. Thus, more detailed and perspective investigations,

both epidemiological and at cellular/molecular level, are urgently needed to further elaborate the contribution of comorbidity to TB/DR-TB in China.

## CONCLUSION

In summary, this study finds that smoking, cavity and comorbidity are risk factors for drug resistance among retreated PTB in Shandong Province, China. Patients with retreated PTB with comorbidity are more likely to be older and with higher proportion of symptoms compared with those without comorbidity. Comorbidity is also a risk factor for overall RFP resistance, overall SM resistance and MDR among patients with retreated PTB. This study points out several directions for the control of retreated PTB: (1) the improvement of baseline health should be part of TB control; (2) bidirectional screening and coordinated treatment for both TB and comorbidity should be advocated; and (3) attention to drug resistance surveillance among patients with TB, especially among those who had comorbidity, is imperative.

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