BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044349
Article Type:	Original research
Date Submitted by the Author:	07-Sep-2020
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Keywords:	EPIDEMIOLOGY, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Tuberculosis < INFECTIOUS DISEASES

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The association between drug resistant tuberculosis and comorbidity status

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Abstract:

Objectives: This study was designed to identify the association of comorbidity and drug-resistance among retreated pulmonary tuberculosis (PTB).

Design: A retrospective study.

Setting: All the 36 monitoring sites in Shandong Province were included. TB Surveillance System were searched.

Participants: A total of 10,975 PTB patients were recorded during 2004-2019. Finally 1924 retreated PTB were included.

Results: Among 1924 retreated PTB, 26.2% were DR-TB, 12.5% had comorbidity. Smoking (adjusted odds ratio (aOR): 1.69, 95% confidence interval (CI): 1.19-2.39), cavity (aOR: 1.55, 95%CI: 1.22-1.97), comorbidity (aOR: 1.44, 95%CI: 1.02-2.02) were risk factors for DR-TB. Of 504 DR-TB, 9.5% had diabetes mellitus (DM), followed by hypertension 2.0% and chronic obstructive pulmonary disease (COPD) 1.8%. Retreated PTB with comorbidity were more likely to be older, to have more bad habits (smoking, alcohol abuse) and clinical symptoms (expectoration, hemoptysis, weight loss). Comorbidity was significantly associated with DR-TB (aOR: 1.44, 95%CI: 1.02-2.02), overall rifampin

(RFP) resistance (aOR: 2.17, 95%CI: 1.41-3.36), overall streptomycin (SM) resistance (aOR: 1.51, 95%CI: 1.00-2.27), and multidrug resistance (MDR) (aOR: 1.96, 95%CI: 1.17-3.27) compared with pan-susceptible patients (P<0.05).

Conclusion: This study demonstrated that comorbidity was a risk factor for DR and MDR of retreated PTB patients. The strategies to improve host health including smoking cessation, screening and treatment of comorbidity might contribute to the control of TB, especially DR-TB in China.

Strengths and limitations of this study:

This seems to be one of the largest retrospective studies from the aspect of time span (16-years) to describe the association between comorbidity status and DR-TB among retreated PTB patients in Shandong province, China.

This study detailed the relationships between comorbidity and DR-TB by specifying different DR types.

DST for second-line anti-TB drugs were not routinely conducted in China, thus only DR for first-line anti-TB drugs were included.

All comorbidities were calculated as a whole factor in this study.

Keywords: drug resistance, retreated pulmonary tuberculosis, comorbidity, risk factor

Introduction:

With the changing of demographic and lifestyle, the spectrum of disease has been transformed from infectious diseases to noncommunicable diseases (NCDs) [1]. However, people from developing country suffered from double burden of infectious diseases and NCDs [2]. As an infectious disease, tuberculosis (TB) can be prevented and well treated. Although the control of TB achieved considerable progress in the past decades, the work seems to reach its bottleneck recently with 1.45 million death caused by TB which ranks the topmost cause of death among infectious agents [3]. The overlapping TB and comorbidities amplify the risk and mortality of the other [1]. Bidirectional deleterious correlation between TB and coexisting disease might open up a new direction for future TB control.

Drug-resistance is a intractable public problem and a crucial obstacle to the control of TB. According to the 2019 global TB report, about 1/2 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, it also resulted in fewer effective drugs to choose, higher expenses to pay, the spreading and amplifying of DR-TB [4, 5]. Patients with previously anti-TB treatment history were at high risk to develop DR-TB. Compared with newly treated TB cases (3.4%), the rate of MDR/RR-TB were 18% among retreated cases [3]. The control of DR-TB especially those among retreated patients are imperative.

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

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

Methods:

Ethics statement

Ethical approvals of this study were obtained from the Ethics Committee of Shandong Provincial Hospital, affiliated with Shandong University, Shandong, China. Before analysis and reporting, patient records were anonymized and de-identified. The Ethics Committee waived the necessity of informed consent because the retrospective nature of this study.

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^2 in Shandong province, which 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, two province-level and 21 county-level hospitals which were responsible for the quality assessment in surveillance of TB. We searched the TB Surveillance System in Shandong and collected information for PTB patients with full data on comorbidity status and drug-susceptibility testing (DST) results (at least for all the four first-line anti-TB drugs) during 2004-2019. We ruled out those patients who without information on comorbidity status, with extra-pulmonary TB or *Nontuberculosis mycobacteria* (NTM) infection (Fig. 1). A total of 9,051 newly treated and 1,924 retreated PTB cases were detected. Of all the retreated PTB patients

with *mycobacterium tuberculosis* (MTB) infection, 1,683 had no comorbidity, and 241 had at least one comorbidity. Demographic information (age, sex) and clinical information (BMI, smoking, alcohol abuse, cavity, and symptoms) were collected.

Laboratory diagnosis and drug susceptibility testing

All samples available from suspicious patients were collected by specialist at each surveillance site. One patient should offer at least two sputum samples for the examinations of bacteriologic culture, species identification, and DST. The smear microscopy with ZiehlNeelsen staining was performed to identify acid-fast bacilli. Each sample was inoculated into tubes with acidified Löwenstein-Jensen medium for further culture [18]. Subsequently, the samples with growing colonies were tested for strain identification and DST. The distinguish of MTB from other *Mycobacteria spp* were comprehensive considerations of growth characteristics, morphologic characteristics of the colony, inhibition by p-nitrobenzoic acid, ect [19].

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 the patients' option which was non-routinely.

Quality Control

All procedures during TB surveillance were carried out according to WHO guidelines. External quality assessment (EQA) for all laboratory tests including smear, culture, and DST was supervise by Superior TB National Reference laboratory in Katharine Hsu Center of Shandong Province [18]. The quality assessment and data extraction were accomplished by at least two researchers who were trained professionally.

Definitions

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

The comorbidity information 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. The confirmation of comorbidity status mainly from two ways: 1) self-reported by the patient with a previously diagnosis certificate; 2) new identified cases according to associated diagnostic consensus unified globally.

Statistical analysis

Continuous variables such as age were summarized with mean and standard deviation (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), comorbidities (silicosis, asthma, COPD, bronchiectasia, lung cancer, DM, hypertension, gastrointestinal cancer, hepatitis, renal failure, CTD, other malignancy) were summarized as proportions. Univariable analysis and multivariable logistic models were applied to identify the risk factors of drug-resistance among newly treated or retreated PTB cases. Demographic characteristics, clinical traits and DR types were compared according to the comorbidity status using Fisher's exact or Pearson χ^2 test. Multivariable logistic models were also used to estimated the influence of comorbidity on different DR types with the covariates adjusted by age, sex, BMI, drinking history, smoking history, and cavity according to published researches. A two-sided $P<0.05$ was considered to be significant. All statistical analyses were calculated by using SPSS software, version 20.0.

Results:

Case estimates and risk factors of DR-TB

Baseline characteristics of the study populations were demonstrated in Table 1. A total of 10,975 PTB patients aged 49.8±19.7 were reported in

Shandong, China, 2004-2019, of which 9,051 (82.5%) cases were newly treated and 1,924 (17.5%) cases were retreated PTB. Among these retreated PTB cases, 26.2% were DR cases, 82.7% males, 18.5% drinker, 25.2% smoker, 46.4% with baseline cavity and 16.3% had comorbidity.

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

Demographic and clinical characteristics of retreated PTB

A total of 241 (12.5%) retreated PTB patients with comorbidity (Group A, A) and 1,683 (87.5%) with no comorbidity (Group B, B) were enrolled in this study. According to Pearson χ^2 test, retreated PTB patients 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 smoker (A vs B: 30.0% vs 19.5%, $p < 0.001$), to had cavity (A vs B: 52.5% vs 35.1%, $p < 0.001$), and to had more symptoms including expectoration (A vs B: 85.1% vs 77.2%, $p = 0.006$), hemoptysis (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) retreated PTB patients with comorbidity and 25.1% (422) without comorbidity were DR-TB, P = 0.003. After further dividing into different DR subgroups, it showed that the rate 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 group B. No significant differences on the rates of other DR subgroups between group A and group B were identified (p > 0.05). (Table 3)

Comorbidities detected among retreated PTB

Among 241 (12.5%) retreated PTB patients with comorbidity, extra-pulmonary comorbidity accounted for 77.6% (187), pulmonary comorbidity 27.4% (66), both pulmonary and extra-pulmonary comorbidity 5.0% (12), DM 51.5% (124), COPD 16.6% (40). Among 504 retreated PTB patients with drug-resistance, 16.3% had comorbidity, 13.7% had extra-pulmonary 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 retreated PTB patients with DR and baseline comorbidity, 87.8% (72) had only one kind

comorbidity, 15.9% (13) had pulmonary comorbidity alone, 79.3% (65) had extra-pulmonary comorbidity alone, and 4.9% (4) had both pulmonary and extra-pulmonary comorbidity. (Table 4)

Association between comorbidity status and DR profiles of retreated PTB

According to the univariable analysis and multivariable analysis, overall DR (OR: 1.54, 95%CI: 1.16-2.06; aOR:1.44, 95%CI: 1.02-2.02), overall RFP resistance (OR: 2.05, 95%CI: 1.43-2.94; aOR:2.17, 95%CI: 1.41-3.36), overall SM resistance (OR: 1.48, 95%CI: 1.05-2.08; aOR:1.51, 95%CI: 1.00-2.27), and MDR (OR: 1.91, 95%CI: 1.25-2.92; aOR:1.96, 95%CI: 1.17–3.27) had a significant association with comorbidity, $P < 0.05$. Comorbidity was significantly associated with overall INH (OR:1.62, 95%CI: 1.16-2.26) and PDR (OR:1.74, 95%CI: 1.05-2.87) in univariable analysis, $P < 0.05$, but not in multivariable analysis, $P > 0.05$. (Table 5)

Discussion:

This retrospective cohort study of PTB patients in Shandong province of China illustrates the risk factors of retreated PTB and the association between comorbidity status and DR profiles among these patients during the past 16-years. This study achieves several findings including: 1) among 1924 retreated PTB cases, 26.2% were DR-TB, 12.5% had comorbidity; 2) smoking/cavity/comorbidity were risk factors for DR among retreated PTB; 3) among 241 retreated PTB patients with comorbidity, DM had the

highest percentage (51.5%), followed by COPD (16.6%); 4) retreated PTB with comorbidity were more likely to be male, to be older, with BMI ≥25, to abuse cigarette/alcohol, to have clinical symptoms (expectoration, hemoptysis, weight loss), and to be DR-TB; 5) with comorbidity also was a risk factor for overall RFP resistance, overall SM resistance, and MDR of retreated PTB.

Globally, the number of TB has been relatively stable which maintained at ≈10.0 million in recent years. Only 6.3% reduction of TB incidence and 11% of TB deaths occurred during 2015-2018, far away from the goal of 20% and 35% reduction of TB incidence and death in End TB Strategy from 2015 to 2020 [3]. As a major obstacle of TB control, the prevention and treatment of DR-TB are intractable and urgent. Followed after India (27%), China had the second largest number of MDR/RR-TB about 66,000 (50,000-85,000) cases which accounted for 14% of global burden. The rate of MDR/RR-TB is more seriously among retreated patients (21%) which amounts to three times of newly treated patients (7.1%) in China [3]. Even terribly, only 1/3 of these MDR/RR-TB patients enrolled in the treatment, and China along with India contributed to nearly half (43%) of these gap between estimated and treatment cases [3]. In this study, 17.5% patients were retreated PTB, among which 26.2% were DR-TB and 20.2% were MDR/RR-TB. With limitted drugs effective, the treatment of DR-TB, especially MDR-TB and extensively drug-resistant TB (XDR-TB) are

costly, complicated, and more likely to have poor treatment outcomes [20, 21]. The control of DR-TB especially among those with treatment history is vital to the eradication of TB.

The improvement of health-associated risk factors (e.g. smoking, DM, HIV infection) can mitigate the development and mortality of TB [3]. In this study, 18% of retreated PTB abuse alcohol, 20.9% were smoker, 12.5% had comorbidity. Moreover, smoking and comorbidity were risk factors for the drug-resistance among retreated PTB patients. Based on real world researches, TB, smoking, COPD and HIV have deleterious and synergistic relationship [22]. There's reason to believe that special attention on the population who were at high risk to development TB especially DR-TB can reduce the rate of missed diagnosis and contribute to the control of TB. However, traditional disease-specific health-care strategy may be less effective, multidisciplinary co-operation and integrated therapies towards high-risk population are urgently needed.

The correlations between TB and overlapping comorbid diseases are well recognized previously. On one hand, comorbidity can increase TB incidence and mortality. Extra-pulmonary comorbidity (e.g. HIV infection, DM, CKD) can facilitate the development of TB by impairing immune function, increasing bacterial loads [23-25]. While pulmonary comorbidity such as COPD can promote the process of TB by damaging innate lung defence, impairing lung function, and changing lung structure [26, 27]. In

this study, 12.5% retreated PTB had comorbidity, among which DM (51.5%) accounted for a half, followed by COPD (16.6%). DM is one confirmed risk factor for TB which account for 6-24% of TB burden according to geography disparity [28]. DM and COPD can increase the risk of TB by 3.11 (95% CI: 2.27-4.26) and 2.47 (95% CI: 2.21-2.76) compared to control group [11, 29]. What's more, previous studies revealed that TB and COPD played bi-directional roles by acting as an independent risk factor for the other [30]. TB patients with comorbidity are at increased risk to be aggravated and die [31, 32]; even some patients who have a latent TB infection and other patients that complete the treatment or are cured could further impede TB control by reactivating or relapsing [11, 31].

On the other hand, comorbidity can facilitate the development of DR among TB patients. One study in Mexican demonstrated that the proportion of DM among TB patients with and without MDR were significantly different (47.2 vs. 28.1%; $p < 0.05$) [16]. TB patients with COPD were 2 times higher to be death [31] and 2.5 times higher to have MDR-TB [6] than those without COPD. However, previous studies of correlations between TB and coexisting disease mainly focused on the specific DR type (MDR) and view all TB patients as a whole. So far, studies of these correlations on other DR types among retreated PTB patients were very limited. 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 retreated PTB patients.

Similarly with previous researches that TB and coexisting disease shared risk factors: age, BMI, cigarette abuse [30, 33]. This study showed that retreated PTB with comorbidity were more likely to be male, to be older, with BMI ≥25, and to abuse cigarette/alcohol than those without comorbidity. Moreover, the higher proportion of expectoration and haemoptysis among retreated PTB patients with comorbidity may be attributed to coexisting pulmonary disease.

Conclusion:

In summary, this study elaborates that retreated PTB patients with comorbidity are more likely to be older, with higher proportion of symptoms and to be DR-TB compared to those without comorbidity in Shandong Province, China. Comorbidity is a risk factor for DR (overall DR, overall RFP resistance, overall SM resistance, MDR) among retreated PTB patients. 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; 3) attention on the DR surveillance among TB patients, especially among who had comorbidity were imperative.

Conflict of interests

The authors state that they have no conflicts of interest.

Funding statement

This work was supported by Department of Science & Technology of Shandong Province (CN) (No.2007GG30002033; 2015GSF121052; No.2017GSF218052) and Jinan Science and Technology Bureau (CN) (No.201704100).

Authors' contributions

NNT, YFL and HCL designed this study and drafted the initial manuscript. SSW, JYL, QYZ and TTX collected and analyzed the data. SJL, QQA and SQL coordinated and supervised data collection, constructed the figures and tables.

Patient and Public Involvement

Not appropriate.

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

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

Characteristics	New 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 (0.993-0.998)	0.001	0.994 (0.991-0.998)	0.001	51.0±19.8	48.7±18.6	0.994 (0.989-0.999)	0.021	0.986 (0.980-0.993)	<0.001	49.8±19.7
Sex (male)	6098/7348 (83.0)	1460/1703 (85.7)		0.006	1.249 (1.033-1.510)	0.022	1155/1420 (81.3)	417/1420 (82.7)	1.100 (0.842-1.436)	0.485	1.202 (0.865-1.670)	0.273	9130/10975 (83.2)
BMI													
<18.5	1550/6627 (23.4)	352/1548 (22.7)	0.949 (0.723-1.247)	0.708	0.917 (0.675-1.246)	0.581	354/1309 (27.0)	135/468 (28.8)	0.554 (0.336-0.911)	0.020	0.557 (0.316-0.983)	0.044	2391/9952 (24.0)
18.5-24.9	4751/6627 (71.17)	1118/1548 (72.2)	0.984 (0.762-1.270)	0.899	0.981 (0.690-1.223)	0.560	910/1309 (69.5)	320/468 (64.5)	0.482 (0.299-0.775)	0.003	0.448 (0.260-0.774)	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 (0.979-1.325)	0.092	0.868 (0.707-1.067)	0.179	242/1355 (17.9)	85/459 (18.5)	1.045 (0.795-1.374)	0.751	0.820 (0.568-1.185)	0.291	1824/8884 (20.5)
Smoking	1475/5822 (25.3)	318/1299 (24.5)	1.047 (0.910-1.204)	0.521	1.033 (0.851-1.255)	0.741	264/1360 (19.4)	116/461 (25.2)	1.396 (1.088-1.792)	0.009	1.687 (1.191-2.388)	0.003	2173/8942 (24.3)
Cavity	2765/6201 (44.6)	689/1452 (47.5)	0.891 (0.795-0.999)	0.049	1.152 (1.012-1.312)	0.033	444/1299 (34.2)	205/442 (46.4)	1.666 (1.338-2.074)	<0.001	1.550 (1.219-1.971)	<0.001	4103/9394 (43.7)
Comorbidity	1032/7348 (14)	246/1703 (14.4)	1.033 (0.889-1.201	0.669	1.079 (0.901-1.293)	0.408	159/1420 (11.2)	82/504 (16.3)	1.541 (1.155-2.056)	0.003	1.436 (1.020-2.022)	0.038	1519/10975 (13.8)

aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; DR, drug-resistant; PTB, pulmonary tuberculosis.

Table 2. Demographic and clinical characteristics of 1924 retreated PTB patients.

Characteristics	Total N=1924	PTB patients with comorbidity N=241	PTB patients 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
BMI (N=1777/230/1547)				
<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
Symptom				
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
TB 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.

Table 3. Drug-resistant profiles among retreated PTB patients.

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
Mono-resistant tuberculosis	85 (4.4)	10 (4.1)	75 (4.5)	0.828
INH	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	1 (0.1)	1 (0.4)	0 (0)	0.125
INH + EMB	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)	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, drug-resistant; EMB, ethambutol; INH, isoniazid; MDR, multidrug-resistant; PTB, pulmonary tuberculosis; RFP, rifampicin; SM, streptomycin; TB, tuberculosis.

Table 4. Comorbidities detected among retreated PTB patients.

Comorbidity	INH N=324	RFP N=229	MDR N=160	DR N=504	Susceptible N=1420	Total N=1924
Extra-pulmonary 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 9 (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)
Extra-pulmonary 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; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis.

Table 5. Association between comorbidity and anti-tuberculosis drug resistance among retreated PTB patients.

Type	Univariable		Multivariable	
	OR (95%CI)	p value	aOR (95%CI)	p value
DR-TB	1.541 (1.155-2.056)	0.003	1.436 (1.020-2.022)	0.038
Any resistance to first-line drugs				
INH	1.622 (1.162-2.264)	0.005	1.488 (0.997-2.221)	0.052
RFP	2.048 (1.428-2.937)	<0.001	2.173 (1.408-3.355)	<0.001
EMB	1.866 (0.974-3.575)	0.06	1.643 (0.712-3.790)	0.244
SM	1.476 (1.049-2.077)	0.025	1.511 (1.004-2.272)	0.048
Mono-resistant tuberculosis	1.208 (0.795-1.835)	0.376	1.144 (0.703-1.861)	0.587
Polydrug resistant tuberculosis	1.735 (1.052-2.861)	0.031	1.546 (0.811-2.944)	0.185
MDR-TB	1.906 (1.246-2.916)	0.003	1.956 (1.171-3.265)	0.01
Pan susceptible	reference	reference	reference	reference

aOR, adjusted odds ratio; CI, confidence interval; DR, drug-resistant; EMB, ethambutol; INH, isoniazid; MDR, multidrug-resistant; OR, odds ratio; PTB, pulmonary tuberculosis; RFP, rifampicin; SM, streptomycin; TB, tuberculosis.

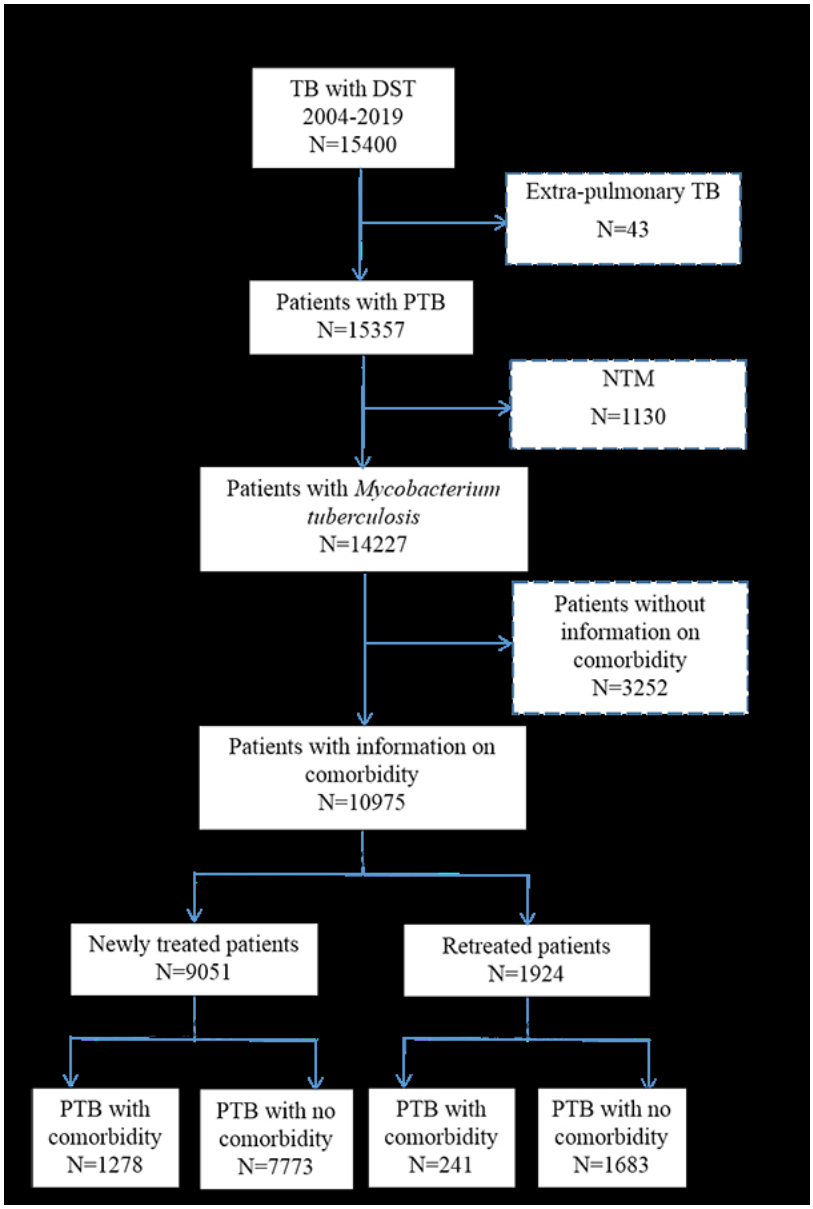

Figure 1. TB cases in Shandong, China. DST, drug-susceptibility testing; NTM, nontuberculous mycobacteria; PTB, pulmonary tuberculosis.

51x76mm (300 x 300 DPI)

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044349.R1
Article Type:	Original research
Date Submitted by the Author:	28-Dec-2020
Complete List of Authors:	Tao, Ning; Shandong Provincial Hospital, Department of Respiratory and Critical Care Medicine Li, Yi-fan ; Shandong Provincial Hospital Song, Wan-mei ; Shandong Provincial Hospital Liu, Jin-yue ; Shandong Provincial Third Hospital Zhang, Qian-yun ; Shandong Provincial Hospital Xu, Ting-ting ; Shandong Provincial Hospital Li, Shi-jin ; Shandong Provincial Hospital An, Qi-qi ; Shandong Provincial Hospital Liu, Si-qi ; Shandong Provincial Hospital Li, Huai-chen ; Shandong Provincial Hospital
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Public health, Respiratory medicine
Keywords:	EPIDEMIOLOGY, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Tuberculosis < INFECTIOUS DISEASES

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The risk factors of drug resistant tuberculosis, the association between comorbidity status and drug resistant patterns: a retrospective study from previously treated pulmonary tuberculosis in Shandong, China, during 2004-2019

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Abstract:

Objectives: This study was designed to identify the risk factors of drug resistant tuberculosis (DR-TB), the association of 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 TB Surveillance System. Categorical variables were compared by Fisher's exact or Pearson Chi-square test. The risk factors of DR were identified using univariable analysis and multivariable logistic models. The influences of comorbidity on different DR types were 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 PTB patients were recorded during 2004-2019. Finally 1,924 retreated PTB were included. Among retreated PTB, 26.2% were DR-TB, 12.5% had comorbidity. Smoking (adjusted odds ratio (aOR): 1.69, 95% confidence interval (CI): 1.19-2.39), cavity (aOR: 1.55, 95%CI:

1.22-1.97), comorbidity (aOR: 1.44, 95%CI: 1.02-2.02) were risk factors for DR-TB. Of 504 DR-TB, 9.5% had diabetes mellitus (DM), followed by hypertension 2.0% and chronic obstructive pulmonary disease (COPD) 1.8%. Retreated PTB with comorbidity were more likely to be older, to have more bad habits (smoking, alcohol abuse) and clinical symptoms (expectoration, hemoptysis, weight loss). Comorbidity was significantly associated with DR-TB (aOR: 1.44, 95%CI: 1.02-2.02), overall rifampin (RFP) resistance (aOR: 2.17, 95%CI: 1.41-3.36), overall streptomycin (SM) resistance (aOR: 1.51, 95%CI: 1.00-2.27), and multidrug resistance (MDR) (aOR: 1.96, 95%CI: 1.17-3.27) compared with pan-susceptible patients (P<0.05).

Conclusion: Smoking, cavity, and comorbidity lead to an increased risk of DR among retreated PTB. The strategies to improve host health including smoking cessation, screening and treatment of comorbidity might contribute to the control of TB, especially DR-TB in China.

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 DR-TB among retreated PTB patients in Shandong province, China is representative.

The diversities in diagnostic and therapeutic level from different TB monitoring sites may lead to bias.

The diagnosis of TB based on microscopy inevitably underestimated the burden of TB.

Keywords: drug resistance, retreated pulmonary tuberculosis, comorbidity, risk factor

Introduction:

With the changing of demographic and lifestyle, the spectrum of disease has been transformed from infectious diseases to noncommunicable diseases (NCDs) [1]. However, people from developing country suffered from double burden of infectious diseases and NCDs [2]. As an infectious disease, tuberculosis (TB) can be prevented and well treated. Although the control of TB achieved considerable progress in the past decades, the work seems to reach its bottleneck recently with 1.45 million death caused by TB which ranks the topmost cause of death among infectious agents [3]. The overlapping TB and comorbidities amplify the risk and mortality of the other [1]. Bidirectional deleterious correlation between TB and coexisting disease might open up a new direction for future TB control.

Drug-resistance is a intractable public problem and a crucial obstacle to the control of TB. According to the 2019 global TB report, about 1/2 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, it also resulted in fewer effective drugs to

choose, higher expenses to pay, the spreading and amplifying of DR-TB [4, 5]. Patients with previously anti-TB treatment history were at high risk to develop DR-TB. Compared with newly treated TB cases (3.4%), the rate of MDR/RR-TB were 18% among retreated cases [3]. The control of DR-TB especially those among retreated patients are imperative.

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

Although China is a upper middle income country with half population resided in urban area, the burden of DR-TB (only followed behind India) and NCDs are very serious. This study aims to summarize the characteristics of host status, DR types of retreated pulmonary TB (PTB),

to identify the risk factor for drug-resistance of these patients, and to evaluate the contribution of comorbidity to different DR types among retreated PTB in Shandong Province, China, during 2004-2019.

Methods:

Ethics statement

Ethical approvals of this study were obtained from the Ethics Committee of Shandong Provincial Hospital, affiliated with Shandong University, Shandong, China. Before analysis and reporting, patient records were anonymized and de-identified. The Ethics Committee waived the necessity of informed consent because the retrospective nature of this study.

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^2 in Shandong province, which 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, two province-level and 21 county-level hospitals which were responsible for the quality assessment in surveillance of TB. We searched the TB Surveillance System in Shandong and collected information for PTB patients with full data on comorbidity status and drug-susceptibility

testing (DST) results (at least for all the four first-line anti-TB drugs) during 2004-2019. We ruled out those patients who without information on comorbidity status, with extra-pulmonary TB or *Nontuberculosis mycobacteria* (NTM) infection (Fig. 1). A total of 9,051 newly treated and 1,924 retreated PTB cases were detected. Of all the retreated PTB patients with *mycobacterium tuberculosis* (MTB) infection, 1,683 had no comorbidity, and 241 had at least one comorbidity. Demographic information (age, sex) and clinical information (BMI, smoking, alcohol abuse, cavity, and symptoms) were collected.

Laboratory diagnosis and drug susceptibility testing

All samples available from suspicious patients were collected by specialist at each surveillance site. One patient should offer at least two sputum samples for the examinations of bacteriologic culture, species identification, and DST. The smear microscopy with ZiehlNeelsen staining was performed to identify acid-fast bacilli. Each sample was inoculated into tubes with acidified Löwenstein-Jensen medium for further culture [18]. Subsequently, the samples with growing colonies were tested for strain identification and DST. The identification of *M. tuberculosis* were comprehensive considerations of results according to p-nitrobenzoic acid, 2-thiophene carboxylic acid hydrazide testing and 16S rRNA gene sequence analysis [19].

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 the patients' option which was non-routinely.

Quality Control

All procedures during TB surveillance were carried out according to WHO guidelines. External quality assessment (EQA) for all laboratory tests including smear, culture, and DST was supervised by Superior TB National Reference laboratory in Katharine Hsu Center of Shandong Province [18]. The quality assessment and data extraction were accomplished by at least two researchers who were trained professionally.

Definitions

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

The comorbidity information 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. The confirmation of comorbidity status mainly from two ways: 1) self-reported by the patient with a previously diagnosis certificate; 2) new identified cases according to associated diagnostic consensus unified globally.

Statistical analysis

Continuous variables such as age were summarized with mean and standard deviation (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), comorbidities (silicosis, asthma, COPD, bronchiectasia, lung cancer, DM, hypertension, gastrointestinal cancer, hepatitis, renal failure, CTD, other malignancy) were summarized as proportions. Univariable analysis and multivariable logistic models were applied to identify the risk factors of drug-resistance among newly treated or retreated PTB cases. Demographic characteristics, clinical traits and DR types were compared according to the comorbidity status using Fisher's exact or Pearson χ^2 test. Multivariable logistic models were also used to estimate the influence of comorbidity on different DR types with the covariates adjusted by age, sex, BMI, drinking history, smoking history, and cavity according to published researches. A two-sided $P<0.05$ was considered to be significant. All statistical analyses were calculated by

using SPSS software, version 20.0.

Results:

Case estimates and risk factors of DR-TB

Baseline characteristics of the study populations were demonstrated in Table 1. A total of 10,975 PTB patients aged 49.8±19.7 were reported in Shandong, China, 2004-2019, of which 9,051 (82.5%) cases were newly treated and 1,924 (17.5%) cases were retreated PTB. Among these retreated PTB cases, 26.2% were DR cases, 82.7% males, 18.5% drinker, 25.2% smoker, 46.4% with baseline cavity and 16.3% had comorbidity.

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

Demographic and clinical characteristics of retreated PTB

A total of 241 (12.5%) retreated PTB patients with comorbidity (Group A, A) and 1,683 (87.5%) with no comorbidity (Group B, B) were enrolled in this study. According to Pearson χ^2 test, retreated PTB patients 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 smoker (A vs B: 30.0% vs 19.5%, p < 0.001), to had cavity (A vs B: 52.5% vs 35.1%, p < 0.001), and to had more symptoms including expectoration (A vs B: 85.1% vs 77.2%, p = 0.006), hemoptysis (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) retreated PTB patients with comorbidity and 25.1% (422) without comorbidity were DR-TB, P = 0.003. After further dividing into different DR subgroups, it showed that the rate 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 group B. No significant differences on the rates of other DR subgroups between group A and group B were identified (p > 0.05). (Table 3)

Comorbidities detected among retreated PTB

Among 241 (12.5%) retreated PTB patients with comorbidity, extra-pulmonary comorbidity accounted for 77.6% (187), pulmonary comorbidity 27.4% (66), both pulmonary and extra-pulmonary comorbidity 5.0% (12), DM 51.5% (124), COPD 16.6% (40). Among 504

retreated PTB patients with drug-resistance, 16.3% had comorbidity, 13.7% had extra-pulmonary 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 retreated PTB patients with DR and baseline comorbidity, 87.8% (72) had only one kind comorbidity, 15.9% (13) had pulmonary comorbidity alone, 79.3% (65) had extra-pulmonary comorbidity alone, and 4.9% (4) had both pulmonary and extra-pulmonary comorbidity. (Table 4)

Association between comorbidity status and DR profiles of retreated PTB

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

Discussion:

This retrospective cohort study of PTB patients in Shandong province of China illustrates the risk factors of retreated PTB and the association between comorbidity status and DR profiles among these patients during

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

Previous findings on the risk factors of DR-TB may vary in ethnicity, geographic region, and study design. In this study, smoking, cavity and comorbidity were risk factors for DR among retreated PTB patients. Similarly, these factors have been reported to increased the risk of DR-TB [17, 20-22]. Having TB treatment history was acknowledged as the strongest and most crucial determinant of DR-TB. While the majority studies indicated that comorbidity (DM, HIV, COPD) and tobacco smoking were associated with DR-TB, still other found no significant relationship between them [14, 16, 23-26]. Based on a real world study, TB, smoking, COPD and HIV had deleterious and synergistic relationship [27]. The coexisting of TB and baseline disease may favor the progression of disease and increase the probability of drug-drug interactions or side

effects. The improvement of health-associated risk factors (e.g. smoking, DM, HIV infection) was reported to mitigate the development and mortality of TB [3]. In this study, 17.5% cases were retreated PTB, among which 18% abuse alcohol, 20.9% were smoker, 37.3% had cavity, 12.5% had comorbidity. The high proportion of those 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 retreated PTB in this study. Extra-pulmonary comorbidity (e.g. HIV infection, DM, CKD) can facilitate the development of TB by impairing immune function, increasing bacterial loads [28-30]. While, pulmonary comorbidity such as COPD can promote the process of TB by damaging innate lung defence, impairing lung function, and changing lung structure [31, 32]. As reported, DM and COPD can increase the risk of TB by 3.11 (95% CI: 2.27-4.26) and 2.47 (95% CI: 2.21-2.76) compared to control group [11, 33]. DM is one confirmed risk factor for TB which account for 6-24% of TB burden according to geography disparity [34]. DM not only increase the bacillary load of active TB patients but also change the absorption and clearance of drugs. Thus it prolonged the duration of culture conversion and treatment. Similarly, TB and COPD played bi-directional roles by acting as an independent risk factor for the other [24]. 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 retreated PTB patients. Previous study demonstrated that the proportion of DM among TB patients with and without MDR were significantly different (47.2 vs. 28.1%; $p < 0.05$) [16]. TB patients with COPD were 2 times higher to die [23] and 2.5 times higher to have MDR-TB [6] than those without COPD. However, the studies of correlations between TB and coexisting disease mainly focused on the specific DR type (MDR) and viewed all TB patients as a whole. Studies of these correlations on other DR types among retreated PTB patients were very limited. This study found that retreated PTB patients with comorbidity were more likely to develop DR (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 country [3, 30]. With 95,549 new HIV patients and 15,467 HIV-related deaths in 2018, China still confronted with arduous challenges in controlling HIV [35]. However, five of all 31 provinces accounted for approximately the whole burden of HIV in China [36]. Moreover, both the incidence and HIV-related deaths in Shangdong province ranked last but one of all 31 provinces during 2004-2017 [35]. In this study, only three (0.2%) of retreated PTB patients were co-infected with HIV. Accordingly, HIV infection may not be the major factor of TB transmission in Shandong.

Similarly with previous researches that TB and coexisting disease shared risk factors: age, BMI, cigarette abuse [24, 37]. This study showed that

retreated PTB with comorbidity were more likely to be male, to be older, with BMI ≥25, and to abuse cigarette/alcohol than those without comorbidity. As the condition of retreated PTB patients, especially those with comorbidity are complex, traditional disease-specific health-care strategy may be less effective, multidisciplinary co-operation and integrated therapies towards high-risk population are urgently needed.

Some information, such as DST for second-line anti-TB drugs, contact history and previous therapeutic regimen were 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 comorbidity inconsistently. Thus, more detailed and perspective investigations both epidemiological and cellularly/molecularly were 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 DR among retreated PTB in Shandong Province, China. Retreated PTB patients with comorbidity are more likely to be older, with higher proportion of symptoms compared to those without comorbidity. Comorbidity also is a risk factor for overall RFP resistance, overall SM resistance, MDR among retreated PTB patients. 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; 3) attention on the DR surveillance among TB patients, especially among who had comorbidity were imperative.

Conflict of interests

The authors state that they have no conflicts of interest.

Funding statement

This work was supported by Department of Science & Technology of Shandong Province (CN) (No.2007GG30002033; 2015GSF121052; No.2017GSF218052) and Jinan Science and Technology Bureau (CN) (No.201704100).

Authors' contributions

NNT, YFL and HCL designed this study and drafted the initial manuscript. WMS, JYL, QYZ and TTX collected and analyzed the data. SJL, QQA and SQL coordinated and supervised data collection, constructed the figures and tables.

Patient and Public Involvement

Not appropriate.

Data sharing statement

No additional data are available.

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

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

Characteristics	New 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 (0.993-0.998)	0.001	0.994 (0.991-0.998)	0.001	51.0±19.8	48.7±18.6	0.994 (0.989-0.999)	0.021	0.986 (0.980-0.993)	<0.001	49.8±19.7
Sex (male)	6098/7348 (83.0)	1460/1703 (85.7)		0.006	1.249 (1.033-1.510)	0.022	1155/1420 (81.3)	417/1420 (82.7)	1.100 (0.842-1.436)	0.485	1.202 (0.865-1.670)	0.273	9130/10975 (83.2)
BMI													
<18.5	1550/6627 (23.4)	352/1548 (22.7)	0.949 (0.723-1.247)	0.708	0.917 (0.675-1.246)	0.581	354/1309 (27.0)	135/468 (28.8)	0.554 (0.336-0.911)	0.020	0.557 (0.316-0.983)	0.044	2391/9952 (24.0)
18.5-24.9	4751/6627 (71.17)	1118/1548 (72.2)	0.984 (0.762-1.270)	0.899	0.981 (0.690-1.223)	0.560	910/1309 (69.5)	320/468 (64.5)	0.482 (0.299-0.775)	0.003	0.448 (0.260-0.774)	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 (0.979-1.325)	0.092	0.868 (0.707-1.067)	0.179	242/1355 (17.9)	85/459 (18.5)	1.045 (0.795-1.374)	0.751	0.820 (0.568-1.185)	0.291	1824/8884 (20.5)
Smoking	1475/5822 (25.3)	318/1299 (24.5)	1.047 (0.910-1.204)	0.521	1.033 (0.851-1.255)	0.741	264/1360 (19.4)	116/461 (25.2)	1.396 (1.088-1.792)	0.009	1.687 (1.191-2.388)	0.003	2173/8942 (24.3)
Cavity	2765/6201 (44.6)	689/1452 (47.5)	0.891 (0.795-0.999)	0.049	1.152 (1.012-1.312)	0.033	444/1299 (34.2)	205/442 (46.4)	1.666 (1.338-2.074)	<0.001	1.550 (1.219-1.971)	<0.001	4103/9394 (43.7)
Comorbidity	1032/7348 (14)	246/1703 (14.4)	1.033 (0.889-1.201	0.669	1.079 (0.901-1.293)	0.408	159/1420 (11.2)	82/504 (16.3)	1.541 (1.155-2.056)	0.003	1.436 (1.020-2.022)	0.038	1519/10975 (13.8)

aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; DR, drug-resistant; PTB, pulmonary tuberculosis.

Table 2. Demographic and clinical characteristics of 1924 retreated PTB patients.

Characteristics	Total N=1924	PTB patients with comorbidity N=241	PTB patients 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
BMI (N=1777/230/1547)				
<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
Symptom				
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
TB 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.

Table 3. Drug-resistant profiles among retreated PTB patients.

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
Mono-resistant tuberculosis	85 (4.4)	10 (4.1)	75 (4.5)	0.828
INH	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	1 (0.1)	1 (0.4)	0 (0)	0.125
INH + EMB	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)	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, drug-resistant; EMB, ethambutol; INH, isoniazid; MDR, multidrug-resistant; PTB, pulmonary tuberculosis; RFP, rifampicin; SM, streptomycin; TB, tuberculosis.

Table 4. Comorbidities detected among retreated PTB patients.

Comorbidity	INH N=324	RFP N=229	MDR N=160	DR N=504	Susceptible N=1420	Total N=1924
Extra-pulmonary 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 9 (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)
Extra-pulmonary 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; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis.

Table 5. Association between comorbidity and anti-tuberculosis drug resistance among retreated PTB patients.

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

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

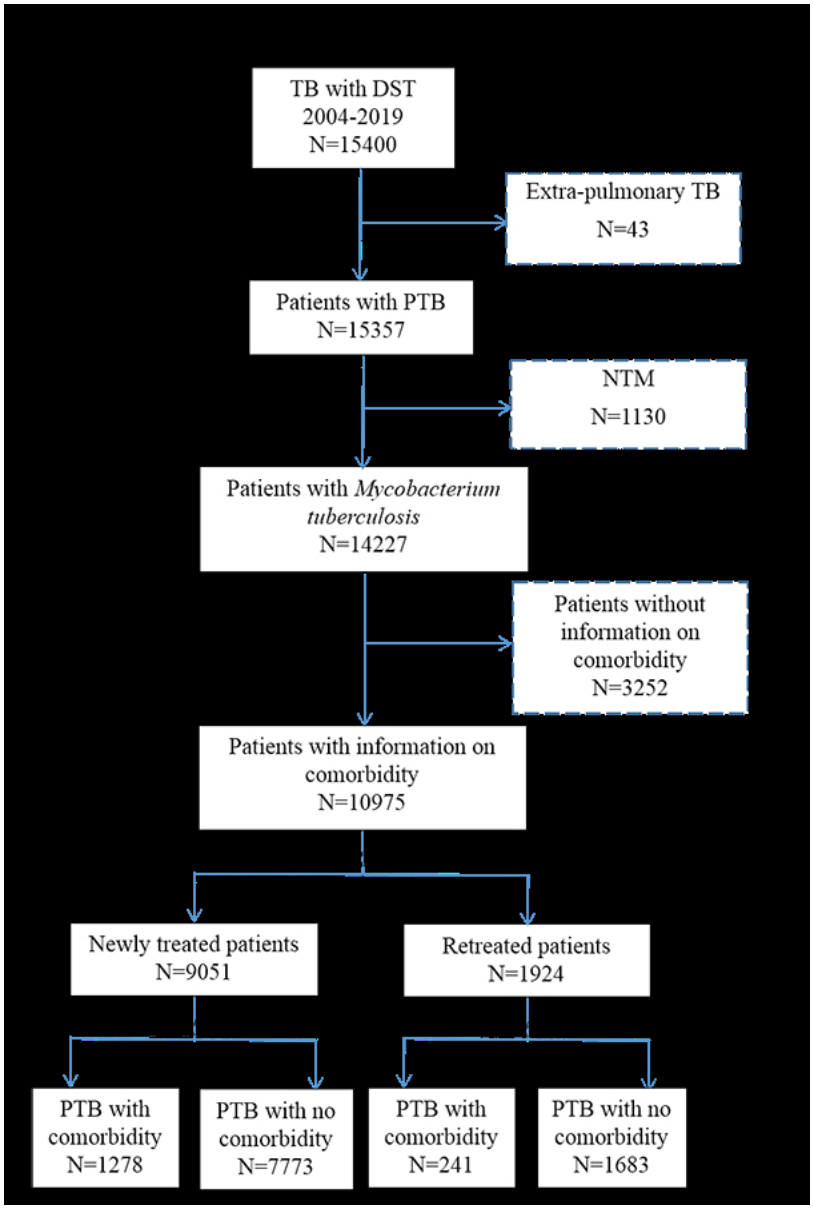

Figure 1. TB cases in Shandong, China. DST, drug-susceptibility testing; NTM, nontuberculous mycobacteria; PTB, pulmonary tuberculosis.

51x76mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			**4-6**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			**6-9**
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*
Bias	9	Describe any efforts to address potential sources of bias	9

Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	9
		(*e*) Describe any sensitivity analyses	9
Results			10-12
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12

		(*b*) Report category boundaries when continuous variables were categorized	10-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			12-16
Key results	18	Summarise key results with reference to study objectives	12-16
Limitations			3,16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-17
Other information			17-25
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.