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The association between drug resistant tuberculosis and comorbidity status

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The association between drug resistant tuberculosis and comorbidity status

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9 Email lihuaichen@163.com)
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11
12 **Abstract:**
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14 **Objectives:** This study was designed to identify the association of
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16 comorbidity and drug-resistance among retreated pulmonary tuberculosis
17
18 (PTB).
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22 **Design:** A retrospective study.
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25 **Setting:** All the 36 monitoring sites in Shandong Province were included.
26
27 TB Surveillance System were searched.
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30 **Participants:** A total of 10,975 PTB patients were recorded during 2004-
31
32 2019. Finally 1924 retreated PTB were included.
33

34
35 **Results:** Among 1924 retreated PTB, 26.2% were DR-TB, 12.5% had
36
37 comorbidity. Smoking (adjusted odds ratio (aOR): 1.69, 95% confidence
38
39 interval (CI): 1.19-2.39), cavity (aOR: 1.55, 95%CI: 1.22-1.97),
40
41 comorbidity (aOR: 1.44, 95%CI: 1.02-2.02) were risk factors for DR-TB.
42
43 Of 504 DR-TB, 9.5% had diabetes mellitus (DM), followed by
44
45 hypertension 2.0% and chronic obstructive pulmonary disease (COPD)
46
47 1.8%. Retreated PTB with comorbidity were more likely to be older, to
48
49 have more bad habits (smoking, alcohol abuse) and clinical symptoms
50
51 (expectoration, hemoptysis, weight loss). Comorbidity was significantly
52
53 associated with DR-TB (aOR: 1.44, 95%CI: 1.02-2.02), overall rifampin
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(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:

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4 With the changing of demographic and lifestyle, the spectrum of disease
5
6 has been transformed from infectious diseases to noncommunicable
7
8 diseases (NCDs) [1]. However, people from developing country suffered
9
10 from double burden of infectious diseases and NCDs [2]. As an infectious
11
12 disease, tuberculosis (TB) can be prevented and well treated. Although the
13
14 control of TB achieved considerable progress in the past decades, the work
15
16 seems to reach its bottleneck recently with 1.45 million death caused by
17
18 TB which ranks the topmost cause of death among infectious agents [3].
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20 The overlapping TB and comorbidities amplify the risk and mortality of
21
22 the other [1]. Bidirectional deleterious correlation between TB and
23
24 coexisting disease might open up a new direction for future TB control.
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32 Drug-resistance is a intractable public problem and a crucial obstacle to
33
34 the control of TB. According to the 2019 global TB report, about 1/2
35
36 million new cases were rifampicin resistant TB (RR-TB), among which 78%
37
38 cases were multidrug-resistant TB (MDR-TB), a kind of resistance to both
39
40 isoniazid (INH) and rifampicin (RFP). Drug-resistance not only was an
41
42 indicator of poor outcomes, it also resulted in fewer effective drugs to
43
44 choose, higher expenses to pay, the spreading and amplifying of DR-TB
45
46 [4, 5]. Patients with previously anti-TB treatment history were at high risk
47
48 to develop DR-TB. Compared with newly treated TB cases (3.4%), the rate
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50 of MDR/RR-TB were 18% among retreated cases [3]. The control of DR-
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52 TB especially those among retreated patients are imperative.
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4 Various studies and reviews reported that host factors including smoking,
5 alcohol abuse, low body mass index (BMI), comorbidity (e.g. HIV
6 infection; diabetes mellitus, DM; chronic renal failure, CRF; malignancy,
7 chronic obstructive pulmonary disease, COPD; silicosis) can predispose to
8 the development of TB [6-12]. Several of those factors were associated
9 with poor treatment outcomes (e.g. alcohol abuse, HIV infection, DM) [13,
10 14], TB relapse (e.g. HIV infection, DM) [13, 15] and the development of
11 MDR-TB (e.g. alcohol abuse, HIV infection, DM, COPD) significantly [6,
12 16, 17]. Coexisting disease are continuously being identified as a vital
13 factor for the control of TB. It's believed that the improvement of host
14 health status both timely identification and effective treatment of
15 comorbidity may alleviate the development of TB and decrease the spread
16 of DR-TB.
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37 Although China is a upper middle income country with half population
38 resided in urban area, the burden of DR-TB (only followed behind India)
39 and NCDs are very serious. This study aims to summarize the
40 characteristics of host status, DR types of retreated pulmonary TB (PTB),
41 to identify the risk factor for drug-resistance of these patients, and to
42 evaluate the contribution of comorbidity to different DR types among
43 retreated PTB in Shandong Province, China, during 2004-2019.
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55 **Methods:**

56 **Ethics statement**

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4 Ethical approvals of this study were obtained from the Ethics Committee
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6 of Shandong Provincial Hospital, affiliated with Shandong University,
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8 Shandong, China. Before analysis and reporting, patient records were
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10 anonymized and de-identified. The Ethics Committee waived the necessity
11
12 of informed consent because the retrospective nature of this study.
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14
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16 17 **Setting**

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19 This retrospective cohort study was conducted in the second most
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21 populous province of China, Shandong province. In 2019, about 100.47
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23 million populations resided in an area of 157,100 km² in Shandong
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25 province, which located at 36°24'N latitude 118°24'E longitude with 17
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27 municipalities and 137 counties (districts) (<http://www.stats-sd.gov.cn/>).
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32 33 **Study population and data collection**

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35 In Shandong province, there are 13 municipal-level local health
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37 departments, two province-level and 21 county-level hospitals which were
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39 responsible for the quality assessment in surveillance of TB. We searched
40
41 the TB Surveillance System in Shandong and collected information for
42
43 PTB patients with full data on comorbidity status and drug-susceptibility
44
45 testing (DST) results (at least for all the four first-line anti-TB drugs)
46
47 during 2004-2019. We ruled out those patients who without information
48
49 on comorbidity status, with extra-pulmonary TB or *Nontuberculosis*
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51 *mycobacteria* (NTM) infection (Fig. 1). A total of 9,051 newly treated and
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53 1,924 retreated PTB cases were detected. Of all the retreated PTB patients
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4 with *Mycobacterium tuberculosis* (MTB) infection, 1,683 had no
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6 comorbidity, and 241 had at least one comorbidity. Demographic
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8 information (age, sex) and clinical information (BMI, smoking, alcohol
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10 abuse, cavity, and symptoms) were collected.
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13 14 **Laboratory diagnosis and drug susceptibility testing**

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17 All samples available from suspicious patients were collected by
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19 specialist at each surveillance site. One patient should offer at least two
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21 sputum samples for the examinations of bacteriologic culture, species
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23 identification, and DST. The smear microscopy with Ziehl-Neelsen staining
24
25 was performed to identify acid-fast bacilli. Each sample was inoculated
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27 into tubes with acidified Löwenstein-Jensen medium for further culture
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29
30 into tubes with acidified Löwenstein-Jensen medium for further culture
31
32 [18]. Subsequently, the samples with growing colonies were tested for
33
34 strain identification and DST. The distinguish of MTB from other
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36 *Mycobacteria spp* were comprehensive considerations of growth
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38 characteristics, morphologic characteristics of the colony, inhibition by p-
39
40 nitrobenzoic acid, ect [19].
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46 DST for first-line anti-TB drugs was performed using the proportion
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48 method on Löwenstein-Jensen medium with the following drug
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50 concentrations: INH (0.2 µg/mL), RFP (40 µg/mL), ethambutol (EMB, 2.0
51
52 µg/mL), and streptomycin (SM, 4.0 µg/mL). DST for other anti-TB drugs
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54 such as pyrazinamide, fluoroquinolone, and kanamycin was performed
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56 according to the patients' option which was non-routinely.
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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 referred 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

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4 Shandong, China, 2004-2019, of which 9,051 (82.5%) cases were newly
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6 treated and 1,924 (17.5%) cases were retreated PTB. Among these
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8 retreated PTB cases, 26.2% were DR cases, 82.7% males, 18.5% drinker,
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10 25.2% smoker, 46.4% with baseline cavity and 16.3% had comorbidity.
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14 Of all retreated PTB cases, the following characteristics were
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16 associated with the presence of DR-TB: 1) smoking (adjusted odds ratio
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18 (aOR): 1.69, 95% confidence interval (CI): 1.19-2.39); 2) had cavity (aOR:
19
20 1.55, 95%CI: 1.22-1.97); 3) had comorbidity (aOR: 1.44, 95%CI: 1.02-
21
22 2.02). Of all newly treated PTB cases, male sex (aOR: 1.25, 95%CI: 1.03-
23
24 1.51) and cavity (aOR: 1.15, 95%CI: 1.01-1.31) were associated with the
25
26 presence of DR-TB.
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32 **Demographic and clinical characteristics of retreated PTB**

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34 A total of 241 (12.5%) retreated PTB patients with comorbidity (Group
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36 A, A) and 1,683 (87.5%) with no comorbidity (Group B, B) were enrolled
37
38 in this study. According to Pearson χ^2 test, retreated PTB patients with
39
40 comorbidity were more likely than those without comorbidity to be older
41
42 (A vs B: 60.1±15.9 vs 49.1±19.6, $p < 0.001$), to be male (A vs B: 87.1% vs
43
44 80.9%, $p < 0.001$), with BMI ≥ 25 (A vs B: 7.9% vs 3.4%, $p = 0.02$), to
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46 abuse alcohol (A vs B: 24.9% vs 17.0%, $p = 0.003$), to be smoker (A vs B:
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48 30.0% vs 19.5%, $p < 0.001$), to had cavity (A vs B: 52.5% vs 35.1%, $p <$
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50 0.001), and to had more symptoms including expectoration (A vs B: 85.1%
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52 vs 77.2%, $p = 0.006$), hemoptysis (A vs B: 22.0% vs 12.7%, $p < 0.001$),
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4 and weight loss (A vs B: 19.5% vs 13.5%, $p = 0.012$). (Table 2)
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6 **Drug-resistant profiles of retreated PTB**

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9 About 34.0% (82) retreated PTB patients with comorbidity and 25.1%
10 (422) without comorbidity were DR-TB, $P = 0.003$. After further dividing
11 into different DR subgroups, it showed that the rate of overall INH
12 resistance (A vs B: 22.8% vs 16.0%, $p = 0.008$), overall RFP resistance (A
13 vs B: 19.5% vs 10.8%, $p < 0.001$), MR to INH (A vs B: 3.7% vs 1.4%, $p =$
14 0.007), PDR to RFP+SM (A vs B: 1.2% vs 0.2%, $p = 0.029$), MDR (A vs
15 B: 12.9% vs 7.7%, $p = 0.006$), and resistance to INH + RFP + SM (A vs B:
16 6.6% vs 3.6%, $p = 0.026$) were much higher in group A than group B. No
17 significant differences on the rates of other DR subgroups between group
18 A and group B were identified ($p > 0.05$). (Table 3)
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35 **Comorbidities detected among retreated PTB**

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37 Among 241 (12.5%) retreated PTB patients with comorbidity, extra-
38 pulmonary comorbidity accounted for 77.6% (187), pulmonary
39 comorbidity 27.4% (66), both pulmonary and extra-pulmonary
40 comorbidity 5.0% (12), DM 51.5% (124), COPD 16.6% (40). Among 504
41 retreated PTB patients with drug-resistance, 16.3% had comorbidity, 13.7%
42 had extra-pulmonary comorbidity, and 3.4% had pulmonary comorbidity.
43 The highest proportion of comorbidity was found for DM (9.5%), followed
44 by hypertension (2.0%), and COPD (1.8%). Of 82 retreated PTB patients
45 with DR and baseline comorbidity, 87.8% (72) had only one kind
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4 comorbidity, 15.9% (13) had pulmonary comorbidity alone, 79.3% (65)
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6 had extra-pulmonary comorbidity alone, and 4.9% (4) had both pulmonary
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8 and extra-pulmonary comorbidity. (Table 4)
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11 **Association between comorbidity status and DR profiles of retreated** 12 **PTB** 13 14

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17 According to the univariable analysis and multivariable analysis, overall
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19 DR (OR: 1.54, 95%CI: 1.16-2.06; aOR:1.44, 95%CI: 1.02-2.02), overall
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21 RFP resistance (OR: 2.05, 95%CI: 1.43-2.94; aOR:2.17, 95%CI: 1.41-
22
23 3.36), overall SM resistance (OR: 1.48, 95%CI: 1.05-2.08; aOR:1.51,
24
25 95%CI: 1.00-2.27), and MDR (OR: 1.91, 95%CI: 1.25-2.92; aOR:1.96,
26
27 95%CI: 1.17–3.27) had a significant association with comorbidity, $P < 0.05$.
28
29 Comorbidity was significantly associated with overall INH (OR:1.62,
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31 95%CI: 1.16-2.26) and PDR (OR:1.74, 95%CI: 1.05-2.87) in univariable
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33 analysis, $P < 0.05$, but not in multivariable analysis, $P > 0.05$. (Table 5)
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40 **Discussion:** 41 42

43 This retrospective cohort study of PTB patients in Shandong province of
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45 China illustrates the risk factors of retreated PTB and the association
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47 between comorbidity status and DR profiles among these patients during
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49 the past 16-years. This study achieves several findings including: 1) among
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51 1924 retreated PTB cases, 26.2% were DR-TB, 12.5% had comorbidity; 2)
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53 smoking/cavity/comorbidity were risk factors for DR among retreated PTB;
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56 3) among 241 retreated PTB patients with comorbidity, DM had the
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4 highest percentage (51.5%), followed by COPD (16.6%); 4) retreated PTB
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6 with comorbidity were more likely to be male, to be older, with BMI ≥ 25 ,
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8 to abuse cigarette/alcohol, to have clinical symptoms (expectoration,
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10 hemoptysis, weight loss), and to be DR-TB; 5) with comorbidity also was
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12 a risk factor for overall RFP resistance, overall SM resistance, and MDR
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14 of retreated PTB.
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20 Globally, the number of TB has been relatively stable which maintained
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22 at ≈ 10.0 million in recent years. Only 6.3% reduction of TB incidence and
23
24 11% of TB deaths occurred during 2015-2018, far away from the goal of
25
26 20% and 35% reduction of TB incidence and death in End TB Strategy
27
28 from 2015 to 2020 [3]. As a major obstacle of TB control, the prevention
29
30 and treatment of DR-TB are intractable and urgent. Followed after India
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32 (27%), China had the second largest number of MDR/RR-TB about 66,000
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34 (50,000-85,000) cases which accounted for 14% of global burden. The rate
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36 of MDR/RR-TB is more seriously among retreated patients (21%) which
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38 amounts to three times of newly treated patients (7.1%) in China [3]. Even
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40 terribly, only 1/3 of these MDR/RR-TB patients enrolled in the treatment,
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42 and China along with India contributed to nearly half (43%) of these gap
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44 between estimated and treatment cases [3]. In this study, 17.5% patients
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46 were retreated PTB, among which 26.2% were DR-TB and 20.2% were
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48 MDR/RR-TB. With limited drugs effective, the treatment of DR-TB,
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50 especially MDR-TB and extensively drug-resistant TB (XDR-TB) are
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4 costly, complicated, and more likely to have poor treatment outcomes [20,
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7 21]. The control of DR-TB especially among those with treatment history
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9 is vital to the eradication of TB.

10
11 The improvement of health-associated risk factors (e.g. smoking, DM,
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13 HIV infection) can mitigate the development and mortality of TB [3]. In
14
15 this study, 18% of retreated PTB abuse alcohol, 20.9% were smoker, 12.5%
16
17 had comorbidity. Moreover, smoking and comorbidity were risk factors for
18
19 the drug-resistance among retreated PTB patients. Based on real world
20
21 researches, TB, smoking, COPD and HIV have deleterious and synergistic
22
23 relationship [22]. There's reason to believe that special attention on the
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25 population who were at high risk to development TB especially DR-TB
26
27 can reduce the rate of missed diagnosis and contribute to the control of TB.
28
29 However, traditional disease-specific health-care strategy may be less
30
31 effective, multidisciplinary co-operation and integrated therapies towards
32
33 high-risk population are urgently needed.

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35 The correlations between TB and overlapping comorbid diseases are
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37 well recognized previously. On one hand, comorbidity can increase TB
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39 incidence and mortality. Extra-pulmonary comorbidity (e.g. HIV infection,
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41 DM, CKD) can facilitate the development of TB by impairing immune
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43 function, increasing bacterial loads [23-25]. While pulmonary comorbidity
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45 such as COPD can promote the process of TB by damaging innate lung
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47 defence, impairing lung function, and changing lung structure [26, 27]. In
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4 this study, 12.5% retreated PTB had comorbidity, among which DM
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6 (51.5%) accounted for a half, followed by COPD (16.6%). DM is one
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8 confirmed risk factor for TB which account for 6-24% of TB burden
9
10 according to geography disparity [28]. DM and COPD can increase the risk
11
12 of TB by 3.11 (95% CI: 2.27-4.26) and 2.47 (95% CI: 2.21-2.76) compared
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14 to control group [11, 29]. What's more, previous studies revealed that TB
15
16 and COPD played bi-directional roles by acting as an independent risk
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18 factor for the other [30]. TB patients with comorbidity are at increased risk
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20 to be aggravated and die [31, 32]; even some patients who have a latent TB
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22 infection and other patients that complete the treatment or are cured could
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24 further impede TB control by reactivating or relapsing [11, 31].
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32 On the other hand, comorbidity can facilitate the development of DR
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34 among TB patients. One study in Mexican demonstrated that the proportion
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36 of DM among TB patients with and without MDR were significantly
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38 different (47.2 vs. 28.1%; $p < 0.05$) [16]. TB patients with COPD were 2
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40 times higher to be death [31] and 2.5 times higher to have MDR-TB [6]
41
42 than those without COPD. However, previous studies of correlations
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44 between TB and coexisting disease mainly focused on the specific DR type
45
46 (MDR) and view all TB patients as a whole. So far, studies of these
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48 correlations on other DR types among retreated PTB patients were very
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50 limited. In this study, comorbidity not only was a risk factor for DR-TB
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52 and MDR-TB, but also contributed to overall RFP resistance and overall
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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.

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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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29 **Figure 1.** TB cases in Shandong, China. DST, drug-susceptibility testing; NTM, *nontuberculous mycobacteria*; PTB,
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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 (29.3)	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 (68.5)	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 (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)

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≥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.

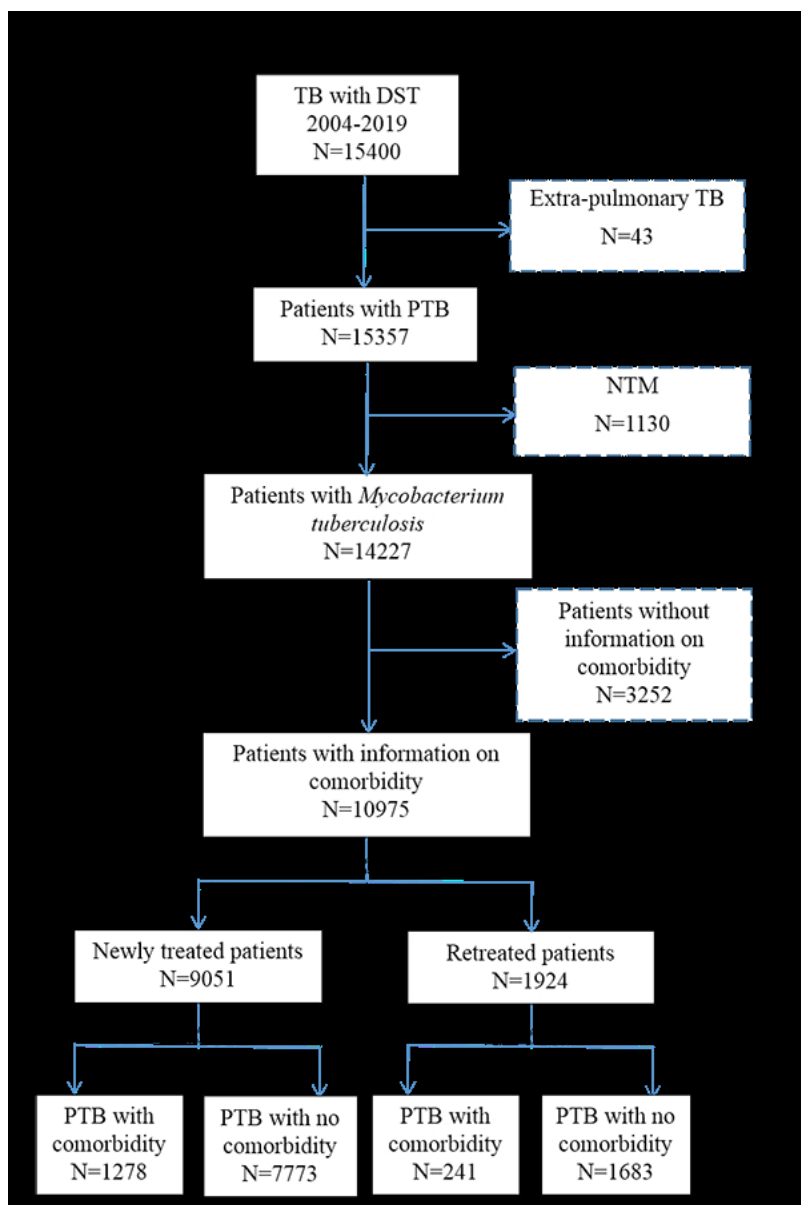


Figure 1. TB cases in Shandong, China. DST, drug-susceptibility testing; NTM, nontuberculous mycobacteria; PTB, pulmonary tuberculosis.

51x76mm (300 x 300 DPI)

BMJ Open

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

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14 27 Email lihuaichen@163.com)

16
17 **Abstract:**

18
19 **Objectives:** This study was designed to identify the risk factors of drug
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22 30 resistant tuberculosis (DR-TB), the association of comorbidity and drug-
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25 31 resistance among retreated pulmonary tuberculosis (PTB).

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27 **Design:** A retrospective study was conducted among all the 36 monitoring
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30 33 sites in Shandong, China, over a 16-year period. Baseline characteristics
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33 34 were collected from TB Surveillance System. Categorical variables were
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36 35 compared by Fisher's exact or Pearson Chi-square test. The risk factors of
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39 36 DR were identified using univariable analysis and multivariable logistic
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42 37 models. The influences of comorbidity on different DR types were
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45 38 evaluated by performing multivariable logistic models with the covariates
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47
48 39 adjusted by age, sex, body mass index, drinking/smoking history, and
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51 40 cavity.

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53 **Results:** A total of 10,975 PTB patients were recorded during 2004-2019.
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56 42 Finally 1,924 retreated PTB were included. Among retreated PTB, 26.2%
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58
59 43 were DR-TB, 12.5% had comorbidity. Smoking (adjusted odds ratio (aOR):
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44 1.69, 95% confidence interval (CI): 1.19-2.39), cavity (aOR: 1.55, 95%CI:

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4 1.22-1.97), comorbidity (aOR: 1.44, 95%CI: 1.02-2.02) were risk factors
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6 for DR-TB. Of 504 DR-TB, 9.5% had diabetes mellitus (DM), followed by
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8 hypertension 2.0% and chronic obstructive pulmonary disease (COPD)
9
10 1.8%. Retreated PTB with comorbidity were more likely to be older, to
11
12 have more bad habits (smoking, alcohol abuse) and clinical symptoms
13
14 (expectoration, hemoptysis, weight loss). Comorbidity was significantly
15
16 associated with DR-TB (aOR: 1.44, 95%CI: 1.02-2.02), overall rifampin
17
18 (RFP) resistance (aOR: 2.17, 95%CI: 1.41-3.36), overall streptomycin (SM)
19
20 resistance (aOR: 1.51, 95%CI: 1.00-2.27), and multidrug resistance (MDR)
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22 (aOR: 1.96, 95%CI: 1.17-3.27) compared with pan-susceptible patients
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24 (P<0.05).
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32 **Conclusion:** Smoking, cavity, and comorbidity lead to an increased risk of
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34 DR among retreated PTB. The strategies to improve host health including
35
36 smoking cessation, screening and treatment of comorbidity might
37
38 contribute to the control of TB, especially DR-TB in China.
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43 **Strengths and limitations of this study:**

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45 This study had a large sample size and long time span.
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48 The sample on the association between comorbidity status and DR-TB
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50 among retreated PTB patients in Shandong province, China is
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52 representative.
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55 The diversities in diagnostic and therapeutic level from different TB
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57 monitoring sites may lead to bias.
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4 67 The diagnosis of TB based on microscopy inevitably underestimated the
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6 68 burden of TB.

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9 69 **Keywords:** drug resistance, retreated pulmonary tuberculosis, comorbidity,
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11 70 risk factor

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14 71 **Introduction:**

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17 72 With the changing of demographic and lifestyle, the spectrum of disease
18
19 73 has been transformed from infectious diseases to noncommunicable
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21 74 diseases (NCDs) [1]. However, people from developing country suffered
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23 75 from double burden of infectious diseases and NCDs [2]. As an infectious
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25 76 disease, tuberculosis (TB) can be prevented and well treated. Although the
26
27 77 control of TB achieved considerable progress in the past decades, the work
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29 78 seems to reach its bottleneck recently with 1.45 million death caused by
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31 79 TB which ranks the topmost cause of death among infectious agents [3].
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33 80 The overlapping TB and comorbidities amplify the risk and mortality of
34
35 81 the other [1]. Bidirectional deleterious correlation between TB and
36
37 82 coexisting disease might open up a new direction for future TB control.

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40 83 Drug-resistance is a intractable public problem and a crucial obstacle to
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42 84 the control of TB. According to the 2019 global TB report, about 1/2
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44 85 million new cases were rifampicin resistant TB (RR-TB), among which 78%
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46 86 cases were multidrug-resistant TB (MDR-TB), a kind of resistance to both
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48 87 isoniazid (INH) and rifampicin (RFP). Drug-resistance not only was an
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50 88 indicator of poor outcomes, it also resulted in fewer effective drugs to
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4 89 choose, higher expenses to pay, the spreading and amplifying of DR-TB
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6 90 [4, 5]. Patients with previously anti-TB treatment history were at high risk
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9 91 to develop DR-TB. Compared with newly treated TB cases (3.4%), the rate
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11 92 of MDR/RR-TB were 18% among retreated cases [3]. The control of DR-
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14 93 TB especially those among retreated patients are imperative.

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17 94 Various studies and reviews reported that host factors including smoking,
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19 95 alcohol abuse, low body mass index (BMI), comorbidity (e.g. HIV
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22 96 infection; diabetes mellitus, DM; chronic renal failure, CRF; malignancy,
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25 97 chronic obstructive pulmonary disease, COPD; silicosis) can predispose to
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27 98 the development of TB [6-12]. Several of those factors were associated
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30 99 with poor treatment outcomes (e.g. alcohol abuse, HIV infection, DM) [13,
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33 100 14], TB relapse (e.g. HIV infection, DM) [13, 15] and the development of
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36 101 MDR-TB (e.g. alcohol abuse, HIV infection, DM, COPD) significantly [6,
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39 102 16, 17]. Coexisting disease are continuously being identified as a vital
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42 103 factor for the control of TB. It's believed that the improvement of host
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45 104 health status both timely identification and effective treatment of
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48 105 comorbidity may alleviate the development of TB and decrease the spread
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51 106 of DR-TB.

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54 107 Although China is a upper middle income country with half population
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57 108 resided in urban area, the burden of DR-TB (only followed behind India)
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60 109 and NCDs are very serious. This study aims to summarize the
110 110 characteristics of host status, DR types of retreated pulmonary TB (PTB),

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4 111 to identify the risk factor for drug-resistance of these patients, and to
5
6 112 evaluate the contribution of comorbidity to different DR types among
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9 113 retreated PTB in Shandong Province, China, during 2004-2019.
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11 114 **Methods:**

12 115 **Ethics statement**

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17 116 Ethical approvals of this study were obtained from the Ethics Committee
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19
20 117 of Shandong Provincial Hospital, affiliated with Shandong University,
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22 118 Shandong, China. Before analysis and reporting, patient records were
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24
25 119 anonymized and de-identified. The Ethics Committee waived the necessity
26
27 120 of informed consent because the retrospective nature of this study.
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29

30 121 **Setting**

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33 122 This retrospective cohort study was conducted in the second most
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35 123 populous province of China, Shandong province. In 2019, about 100.47
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37 124 million populations resided in an area of 157,100 km² in Shandong
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39 125 province, which located at 36°24'N latitude 118°24'E longitude with 17
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42 126 municipalities and 137 counties (districts) (<http://www.stats-sd.gov.cn/>).
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45 127 **Study population and data collection**

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48 128 In Shandong province, there are 13 municipal-level local health
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51 129 departments, two province-level and 21 county-level hospitals which were
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53 130 responsible for the quality assessment in surveillance of TB. We searched
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56 131 the TB Surveillance System in Shandong and collected information for
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58 132 PTB patients with full data on comorbidity status and drug-susceptibility
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4 133 testing (DST) results (at least for all the four first-line anti-TB drugs)
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6 134 during 2004-2019. We ruled out those patients who without information
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9 135 on comorbidity status, with extra-pulmonary TB or *Nontuberculosis*
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11 136 *mycobacteria* (NTM) infection (Fig. 1). A total of 9,051 newly treated and
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13
14 137 1,924 retreated PTB cases were detected. Of all the retreated PTB patients
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17 138 with *mycobacterium tuberculosis* (MTB) infection, 1,683 had no
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19
20 139 comorbidity, and 241 had at least one comorbidity. Demographic
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22 140 information (age, sex) and clinical information (BMI, smoking, alcohol
23
24
25 141 abuse, cavity, and symptoms) were collected.

142 **Laboratory diagnosis and drug susceptibility testing**

143 All samples available from suspicious patients were collected by
144 specialist at each surveillance site. One patient should offer at least two
145 sputum samples for the examinations of bacteriologic culture, species
146 identification, and DST. The smear microscopy with ZiehlNeelsen staining
147 was performed to identify acid-fast bacilli. Each sample was inoculated
148 into tubes with acidified Löwenstein-Jensen medium for further culture
149 [18]. Subsequently, the samples with growing colonies were tested for
150 strain identification and DST. The identification of *M. tuberculosis* were
151 comprehensive considerations of results according to p-nitrobenzoic acid,
152 2-thiophene carboxylic acid hydrazide testing and 16S rRNA gene
153 sequence analysis [19].

154 DST for first-line anti-TB drugs was performed using the proportion

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4 155 method on Löwenstein-Jensen medium with the following drug
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6 156 concentrations: INH (0.2 µg/mL), RFP (40 µg/mL), ethambutol (EMB, 2.0
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8 µg /mL), and streptomycin (SM, 4.0 µg/mL). DST for other anti-TB drugs
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10 157 such as pyrazinamide, fluoroquinolone, and kanamycin was performed
11
12 158 according to the patients' option which was non-routinely.
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14 159

160 **Quality Control**

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

167 **Definitions**

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

175 The comorbidity information collected in this study were DM,
176 hypertension, hepatitis, CRF, connective tissue disease (CTD), disability,

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4 177 malignancy, HIV infection, silicosis, asthma, COPD, and bronchiectasia
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6 178 co-occurring with TB. The confirmation of comorbidity status mainly from
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9 179 two ways: 1) self-reported by the patient with a previously diagnosis
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12 180 certificate; 2) new identified cases according to associated diagnostic
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15 181 consensus unified globally.

17 182 **Statistical analysis**

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19 183 Continuous variables such as age were summarized with mean and
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22 184 standard deviation (SD); categorical variables including sex, BMI (<18.5,
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25 185 18.5-24.9, ≥ 25), drinking history, smoking history, TB contact history,
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28 186 cavity, symptoms (cough, expectoration, fever, night sweating, fatigue,
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31 187 haemoptysis, weight loss, and chest pain), comorbidities (silicosis, asthma,
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34 188 COPD, bronchiectasia, lung cancer, DM, hypertension, gastrointestinal
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37 189 cancer, hepatitis, renal failure, CTD, other malignancy) were summarized
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40 190 as proportions. Univariable analysis and multivariable logistic models
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43 191 were applied to identify the risk factors of drug-resistance among newly
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46 192 treated or retreated PTB cases. Demographic characteristics, clinical traits
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49 193 and DR types were compared according to the comorbidity status using
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52 194 Fisher's exact or Pearson χ^2 test. Multivariable logistic models were also
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55 195 used to estimate the influence of comorbidity on different DR types with
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57
58 196 the covariates adjusted by age, sex, BMI, drinking history, smoking history,
59
60 197 and cavity according to published researches. A two-sided $P < 0.05$ was
198 considered to be significant. All statistical analyses were calculated by

199 using SPSS software, version 20.0.

200 **Results:**

201 **Case estimates and risk factors of DR-TB**

202 Baseline characteristics of the study populations were demonstrated in
203 Table 1. A total of 10,975 PTB patients aged 49.8 ± 19.7 were reported in
204 Shandong, China, 2004-2019, of which 9,051 (82.5%) cases were newly
205 treated and 1,924 (17.5%) cases were retreated PTB. Among these
206 retreated PTB cases, 26.2% were DR cases, 82.7% males, 18.5% drinker,
207 25.2% smoker, 46.4% with baseline cavity and 16.3% had comorbidity.

208 Of all retreated PTB cases, the following characteristics were
209 associated with the presence of DR-TB: 1) smoking (adjusted odds ratio
210 (aOR): 1.69, 95% confidence interval (CI): 1.19-2.39); 2) had cavity (aOR:
211 1.55, 95%CI: 1.22-1.97); 3) had comorbidity (aOR: 1.44, 95%CI: 1.02-
212 2.02). Of all newly treated PTB cases, male sex (aOR: 1.25, 95%CI: 1.03-
213 1.51) and cavity (aOR: 1.15, 95%CI: 1.01-1.31) were associated with the
214 presence of DR-TB.

215 **Demographic and clinical characteristics of retreated PTB**

216 A total of 241 (12.5%) retreated PTB patients with comorbidity (Group
217 A, A) and 1,683 (87.5%) with no comorbidity (Group B, B) were enrolled
218 in this study. According to Pearson χ^2 test, retreated PTB patients with
219 comorbidity were more likely than those without comorbidity to be older
220 (A vs B: 60.1 ± 15.9 vs 49.1 ± 19.6 , $p < 0.001$), to be male (A vs B: 87.1% vs

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4 221 80.9%, $p < 0.001$), with BMI ≥ 25 (A vs B: 7.9% vs 3.4%, $p = 0.02$), to
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6 222 abuse alcohol (A vs B: 24.9% vs 17.0%, $p = 0.003$), to be smoker (A vs B:
7
8 223 30.0% vs 19.5%, $p < 0.001$), to had cavity (A vs B: 52.5% vs 35.1%, $p <$
9
10 224 0.001), and to had more symptoms including expectoration (A vs B: 85.1%
11
12 225 vs 77.2%, $p = 0.006$), hemoptysis (A vs B: 22.0% vs 12.7%, $p < 0.001$),
13
14 226 and weight loss (A vs B: 19.5% vs 13.5%, $p = 0.012$). (Table 2)

227 **Drug-resistant profiles of retreated PTB**

228 About 34.0% (82) retreated PTB patients with comorbidity and 25.1%
229 (422) without comorbidity were DR-TB, $P = 0.003$. After further dividing
230 into different DR subgroups, it showed that the rate of overall INH
231 resistance (A vs B: 22.8% vs 16.0%, $p = 0.008$), overall RFP resistance (A
232 vs B: 19.5% vs 10.8%, $p < 0.001$), MR to INH (A vs B: 3.7% vs 1.4%, $p =$
233 0.007), PDR to RFP+SM (A vs B: 1.2% vs 0.2%, $p = 0.029$), MDR (A vs
234 B: 12.9% vs 7.7%, $p = 0.006$), and resistance to INH + RFP + SM (A vs B:
235 6.6% vs 3.6%, $p = 0.026$) were much higher in group A than group B. No
236 significant differences on the rates of other DR subgroups between group
237 A and group B were identified ($p > 0.05$). (Table 3)

238 **Comorbidities detected among retreated PTB**

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

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4 243 retreated PTB patients with drug-resistance, 16.3% had comorbidity, 13.7%
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7 244 had extra-pulmonary comorbidity, and 3.4% had pulmonary comorbidity.
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9 245 The highest proportion of comorbidity was found for DM (9.5%), followed
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12 246 by hypertension (2.0%), and COPD (1.8%). Of 82 retreated PTB patients
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15 247 with DR and baseline comorbidity, 87.8% (72) had only one kind
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17 248 comorbidity, 15.9% (13) had pulmonary comorbidity alone, 79.3% (65)
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20 249 had extra-pulmonary comorbidity alone, and 4.9% (4) had both pulmonary
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23 250 and extra-pulmonary comorbidity. (Table 4)

251 **Association between comorbidity status and DR profiles of retreated** 252 **PTB**

253 According to the univariable analysis and multivariable analysis, overall
254 RFP resistance (OR: 2.05, 95%CI: 1.43-2.94; aOR:2.17, 95%CI: 1.41-
255 3.36), overall SM resistance (OR: 1.48, 95%CI: 1.05-2.08; aOR:1.51,
256 95%CI: 1.00-2.27), and MDR (OR: 1.91, 95%CI: 1.25-2.92; aOR:1.96,
257 95%CI: 1.17–3.27) had a significant association with comorbidity, $P < 0.05$.
258 Comorbidity was significantly associated with overall INH (OR:1.62,
259 95%CI: 1.16-2.26) and PDR (OR:1.74, 95%CI: 1.05-2.87) in univariable
260 analysis, $P < 0.05$, but not in multivariable analysis, $P > 0.05$. (Table 5)

261 **Discussion:**

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

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4 265 the past 16-years. This study achieves several findings including: 1) among
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6 266 1924 retreated PTB cases, 26.2% were DR-TB, 12.5% had comorbidity; 2)
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9 267 smoking/cavity/comorbidity were risk factors for DR among retreated PTB;
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12 268 3) among 241 retreated PTB patients with comorbidity, DM had the
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14 269 highest percentage (51.5%), followed by COPD (16.6%); 4) retreated PTB
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16 270 with comorbidity were more likely to be male, to be older, with BMI ≥ 25 ,
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18 271 to abuse cigarette/alcohol, to have clinical symptoms (expectoration,
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20 272 hemoptysis, weight loss), and to be DR-TB; 5) with comorbidity also was
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23 273 a risk factor for overall RFP resistance, overall SM resistance, and MDR
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25 274 of retreated PTB.

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30 275 Previous findings on the risk factors of DR-TB may vary in ethnicity,
31
32 276 geographic region, and study design. In this study, smoking, cavity and
33
34 277 comorbidity were risk factors for DR among retreated PTB patients.
35
36 278 Similarly, these factors have been reported to increased the risk of DR-TB
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38 279 [17, 20-22]. Having TB treatment history was acknowledged as the
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40 280 strongest and most crucial determinant of DR-TB. While the majority
41
42 281 studies indicated that comorbidity (DM, HIV, COPD) and tobacco
43
44 282 smoking were associated with DR-TB, still other found no significant
45
46 283 relationship between them [14, 16, 23-26]. Based on a real world study, TB,
47
48 284 smoking, COPD and HIV had deleterious and synergistic relationship [27].
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50 285 The coexisting of TB and baseline disease may favor the progression of
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52 286 disease and increase the probability of drug-drug interactions or side
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4 287 effects. The improvement of health-associated risk factors (e.g. smoking,
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6 288 DM, HIV infection) was reported to mitigate the development and
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9 289 mortality of TB [3]. In this study, 17.5% cases were retreated PTB, among
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11 290 which 18% abuse alcohol, 20.9% were smoker, 37.3% had cavity, 12.5%
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13
14 291 had comorbidity. The high proportion of those risk factors among retreated
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16
17 292 PTB in Shandong province deserves more attention.

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19 293 DM (51.5%), followed by COPD (16.6%) were the most common
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22 294 comorbidities among retreated PTB in this study. Extra-pulmonary
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25 295 comorbidity (e.g. HIV infection, DM, CKD) can facilitate the development
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27
28 296 of TB by impairing immune function, increasing bacterial loads [28-30].
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30 297 While, pulmonary comorbidity such as COPD can promote the process of
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33 298 TB by damaging innate lung defence, impairing lung function, and
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36 299 changing lung structure [31, 32]. As reported, DM and COPD can increase
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38 300 the risk of TB by 3.11 (95% CI: 2.27-4.26) and 2.47 (95% CI: 2.21-2.76)
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41 301 compared to control group [11, 33]. DM is one confirmed risk factor for
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43
44 302 TB which account for 6-24% of TB burden according to geography
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46
47 303 disparity [34]. DM not only increase the bacillary load of active TB patients
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50 304 but also change the absorption and clearance of drugs. Thus it prolonged
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53 305 the duration of culture conversion and treatment. Similarly, TB and COPD
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56 306 played bi-directional roles by acting as an independent risk factor for the
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59 307 other [24]. In this study, comorbidity not only was a risk factor for DR-TB
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308 and MDR-TB, but also contributed to overall RFP resistance and overall

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4 309 SM resistance among retreated PTB patients. Previous study demonstrated
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6 310 that the proportion of DM among TB patients with and without MDR were
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9 311 significantly different (47.2 vs. 28.1%; $p < 0.05$) [16]. TB patients with
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11 312 COPD were 2 times higher to die [23] and 2.5 times higher to have MDR-
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13 313 TB [6] than those without COPD. However, the studies of correlations
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15 314 between TB and coexisting disease mainly focused on the specific DR type
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17 315 (MDR) and viewed all TB patients as a whole. Studies of these correlations
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19 316 on other DR types among retreated PTB patients were very limited. This
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21 317 study found that retreated PTB patients with comorbidity were more likely
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23 318 to develop DR (1.44 times), RFP resistance (2.17 times), SM resistance
24
25 319 (1.51 times), and MDR (1.96 times) than those without comorbidity.

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27 320 HIV infection was reported to be a major risk factor for TB and DR-TB
28
29 321 in many country [3, 30]. With 95,549 new HIV patients and 15,467 HIV-
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31 322 related deaths in 2018, China still confronted with arduous challenges in
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33 323 controlling HIV [35]. However, five of all 31 provinces accounted for
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35 324 approximately the whole burden of HIV in China [36]. Moreover, both the
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37 325 incidence and HIV-related deaths in Shangdong province ranked last but
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39 326 one of all 31 provinces during 2004-2017 [35]. In this study, only three
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41 327 (0.2%) of retreated PTB patients were co-infected with HIV. Accordingly,
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43 328 HIV infection may not be the major factor of TB transmission in Shandong.

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45 329 Similarly with previous researches that TB and coexisting disease shared
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47 330 risk factors: age, BMI, cigarette abuse [24, 37]. This study showed that
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4 331 retreated PTB with comorbidity were more likely to be male, to be older,
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6 332 with BMI ≥ 25 , and to abuse cigarette/alcohol than those without
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9 333 comorbidity. As the condition of retreated PTB patients, especially those
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11 334 with comorbidity are complex, traditional disease-specific health-care
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14 335 strategy may be less effective, multidisciplinary co-operation and
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17 336 integrated therapies towards high-risk population are urgently needed.

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19 337 Some information, such as DST for second-line anti-TB drugs, contact
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22 338 history and previous therapeutic regimen were not available in this study,
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25 339 which may influence the results. Moreover, we calculated all comorbidities
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27 340 as a whole factor and did not specify the effect of each comorbidity in detail.
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30 341 In fact, previous investigations had concluded on the relationship between
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32 342 TB and different comorbidity inconsistently. Thus, more detailed and
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35 343 perspective investigations both epidemiological and cellularly/molecularly
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37 344 were urgently needed to further elaborate the contribution of comorbidity
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40 345 to TB/DR-TB in China.

41 42 43 346 **Conclusion:**

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45 347 In summary, this study finds that smoking, cavity, and comorbidity are
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48 348 risk factors for DR among retreated PTB in Shandong Province, China.
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51 349 Retreated PTB patients with comorbidity are more likely to be older, with
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53 350 higher proportion of symptoms compared to those without comorbidity.
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56 351 Comorbidity also is a risk factor for overall RFP resistance, overall SM
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58 352 resistance, MDR among retreated PTB patients. This study points out
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4 353 several directions for the control of retreated PTB: 1) the improvement of
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6 354 baseline health should be part of TB control; 2) bidirectional screening and
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9 355 coordinated treatment for both TB and comorbidity should be advocated;
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12 356 3) attention on the DR surveillance among TB patients, especially among
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15 357 who had comorbidity were imperative.

16 17 358 **Conflict of interests**

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20 359 The authors state that they have no conflicts of interest.

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34 35 365 **Authors' contributions**

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38 366 NNT, YFL and HCL designed this study and drafted the initial
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40
41 367 manuscript. WMS, JYL, QYZ and TTX collected and analyzed the data.
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44 368 SJL, QQA and SQL coordinated and supervised data collection,
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47 369 constructed the figures and tables.

48 49 370 **Patient and Public Involvement**

50
51 371 Not appropriate.

52 53 372 **Data sharing statement**

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56 373 No additional data are available.

57 58 374 **References**

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

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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 (29.3)	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 (68.5)	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 (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)

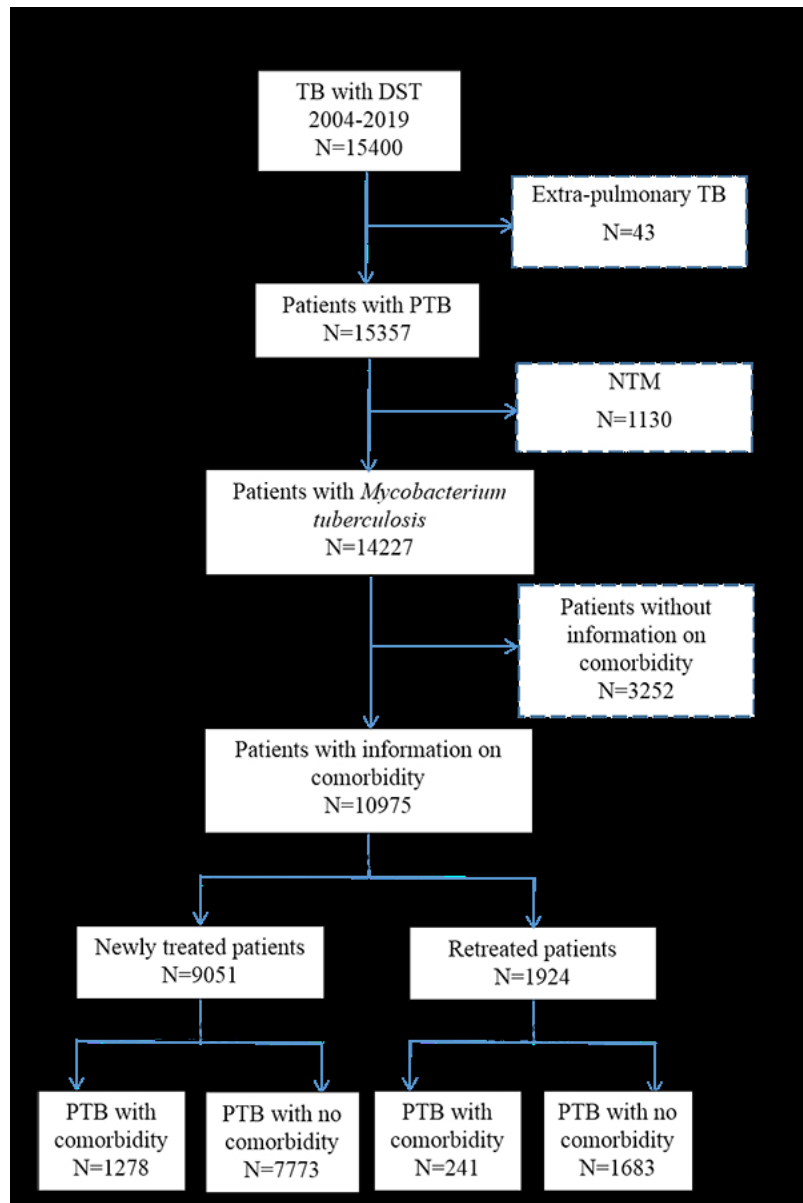
≥3	1 (0.3)	1 (0.4)	0 (0)	2 (0.4)	6 (0.4)	8 (0.4)
Pulmonary alone	8 (2.5)	6 (2.6)	3 (1.9)	13 (2.6)	41 (2.9)	54 (2.8)
Extra-pulmonary alone	44 (13.6)	38 (16.6)	26 (16.3)	65 (12.9)	110 (7.8)	175 (9.1)
Pulmonary+extrapulmonary	3 (0.9)	3 (1.3)	2 (1.3)	4 (0.8)	8 (0.6)	12 (0.6)

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.



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

47 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.