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Risk factors for poor outcomes in patients with drug-resistant tuberculosis: a 6-year multicenter prospective study in Zhejiang, China

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Abstract

Background At present, the disease burden of drug-resistant tuberculosis (DR-TB) is still heavy in the world. In this study, we aimed to evaluate the success rate of DR-TB patients after standardized treatment and to analyze the risk factors for poor outcomes in Zhejiang, China.

Methods From 2017 to 2021, all culture-confirmed tuberculosis (TB) patients were prospectively enrolled from three designated TB hospitals in Zhejiang, China. Demographic surveys were conducted in all patients, and drug susceptibility of TB strains was tested by fluorescent polymerase chain reaction probe melting curve analysis (MeltPro). DR-TB patients were treated with WHO recommended standardized treatment according to the type of drug resistance, and the outcomes were thoroughly monitored and tracked until June 2023. Binary logistic regression model was used to analyze the related risk factors of poor outcomes in patients with DR-TB. The patients' socio-demographic information, comorbidities, fever, antibiotic use, laboratory test results, lung imaging characteristics and drug resistance characteristics were included in the analysis. A simple TB severity score was developed according to the WHO definition and applied to the analysis.

Results Among 1013 patients with confirmed TB, 779 were sensitive to all of the tested drugs (rifampicin, isoniazid, ethambutol, streptomycin and fluoroquinolones), and 234 were resistant to at least one tested drug.

Among the 234 DR-TB patients in the study, 50 patients had poor outcomes (23 cases of failure, 13 cases of death, and 14 patients lost to follow-up), 158 patients were successfully treated (125 cases were cured and 33 cases completed treatment), and 26 were referred to other provinces. The overall treatment success rate was 76.0% (158/208).

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Multivariate analysis showed that age (AOR 1.03; 95%CI 1.01—1.05), previous TB treatment history (AOR 5.03; 95%CI 1.33—18.99), higher TB severity score (AOR 1.48; 95%CI 1.09—2.03), MDR/RR-TB (AOR 8.34; 95%CI 2.99—23.24) and pre-XDR-TB (AOR 9.50; 95%CI 2.24—40.26) were independent risk factors for poor outcomes in DR-TB patients.

Conclusions The treatment success rate of DR-TB patients in this study reached that of the WHO standard treatment (75%).

Physicians should be alert to the possibility of poor outcomes in DR-TB patients with old age, previous TB treatment history, higher TB severity score, MDR/RR-TB or pre-XDR-TB.

Keywords Drug-resistant tuberculosis, Prospective multicenter study, Outcomes, Risk factors, Standardized treatment, Drug-susceptibility test, Tuberculosis severity score

Background

Tuberculosis (TB) is a respiratory infectious disease caused by *Mycobacterium tuberculosis* (*M.tb*). TB had ravaged humans for thousands of years before its causative agent was discovered by Robert Koch in 1882. [1] At present, the disease burden of TB is still high worldwide. According to WHO, about 10.8 million people suffered and 1.25 million people died from TB in 2023. [2].

The emergence of drug-resistant strains has had a major impact on the spread of *M.tb* and is a major obstacle to TB control and eradication. [3, 4] In 2023, there were an estimated 400 000 cases of multidrug-resistant/ rifampicin-resistant TB (MDR/RR-TB) and 150 000 deaths from MDR/RR-TB in the world, which seriously affected the global TB prevention and control. [2] Although the estimated TB incidence rate in China has decreased in the past decade (52/100 000 in 2023), there were still 29 000 people suffering from MDR/RR-TB in 2023, which is a heavy burden to public health in China. [2, 5].

TB is one of the three major infectious diseases, and also one of the key infectious diseases to be managed in China. In this study, we performed rapid drug-susceptibility testing in all patients with culture-confirmed TB who presented to three medical centers (The First Affiliated Hospital of Zhejiang University, Affiliated Dongyang Hospital of Wenzhou Medical University, and Taizhou Enze Medical Center) from 2017 to 2021, implemented standardized TB treatment on all drug-resistant tuberculosis (DR-TB) patients, and analyzed their clinical information and outcomes. This study evaluated the treatment outcomes of DR-TB patients and explored the risk factors for poor outcomes, aiming to provide recommendations for clinical TB treatment and follow-up.

Methods

Study aims

To evaluate the success rate of DR-TB patients after standardized treatment and to analyze the risk factors for poor outcomes in Zhejiang, China.

Study design

This prospective observational study was conducted in three tertiary general public hospitals in Zhejiang, China. The First Affiliated Hospital of Zhejiang University, Affiliated Dongyang Hospital of Wenzhou Medical University, and Taizhou Enze Medical Center are three teaching and designated TB hospitals. All of the medical centers were fully equipped with TB testing facilities and wards, staffed by doctors, nurses, data maintainers, disease control personnel, laboratory staff and other professionals who provided medical and scientific support. Patients with culture-confirmed TB admitted to the three medical centers from 2017 to 2021 were included in this study. The follow-up for outcomes was conducted for all patients until June 2023.

Data collection and eligibility criteria

The patients' basic information, comorbidities, and clinical characteristics were collected at the TB diagnosis. Pre-treatment investigations included complete blood count, liver and kidney function, blood IGRA, acid-fast smear, drug sensitivity of TB, pulmonary CT examinations.

Cases with the following conditions were excluded: sensitive TB detected by MeltPro, pregnancy, or referred to other provinces during treatment (Fig. 1).

Drug susceptibility testing

In case of a high suspicion of tuberculosis, acid-fast bacilli (AFB) smears, cultures of *M.tb*, and drug-susceptibility testing (DST) were performed in all patients as soon as possible. All TB samples were collected and preprocessed under the supervision of local CDCs. All TB-related tests were performed in the approved biosafety laboratory.

We used fluorescent polymerase chain reaction (PCR) probe melting curve (MeltPro) for DST. [6–10] Drug susceptibility kits were from Zeesan Biotecheh (Xiamen, China), including MTB/RIF Test Kit (MMCA), MTB/INH Test Kit (MMCA), MTB/EMB Test Kit

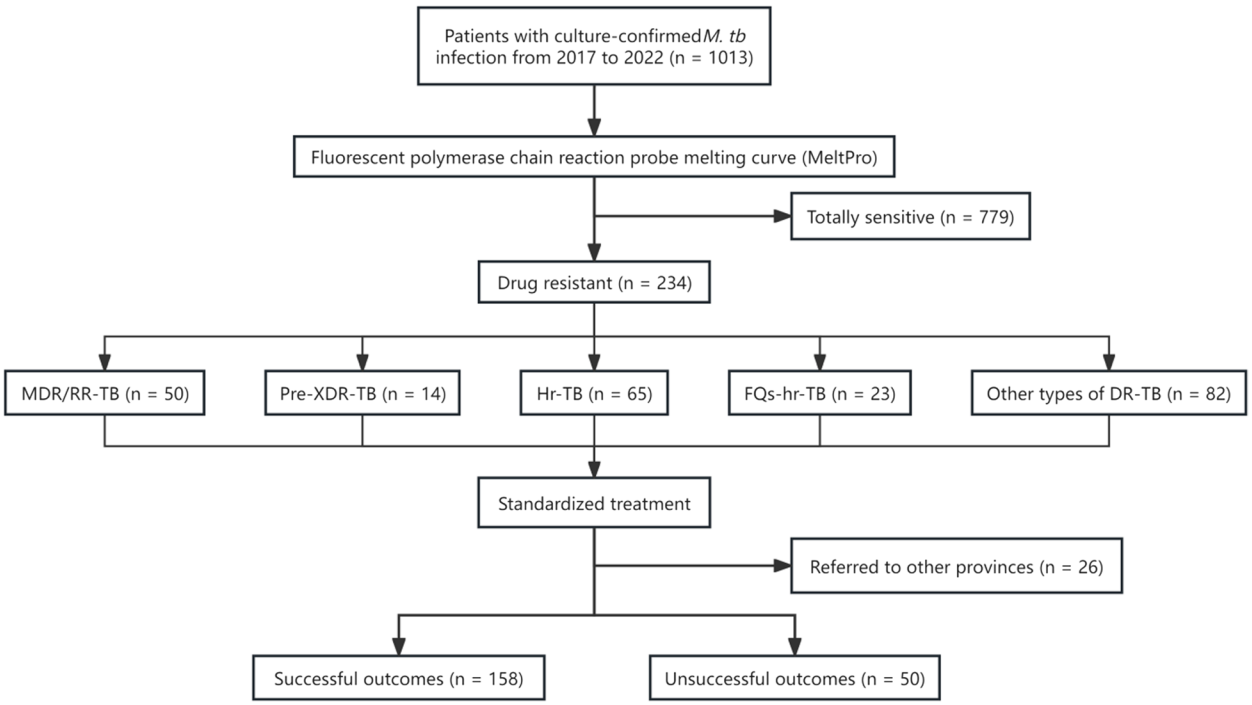

Fig. 1 Patients involved in the study. *M.tb*: *Mycobacterium tuberculosis*. MDR/RR-TB: multidrug-resistant TB (MDR-TB, defined as resistance to both rifampicin and isoniazid) or rifampicin-resistant TB (RR-TB). Pre-XDR-TB: pre-extensively drug-resistant TB, defined as TB that is resistant to rifampicin and any fluoroquinolones. Hr-TB: isoniazid-resistant but rifampicin-susceptible TB. FQs-hr-TB: fluoroquinolones-resistant TB, but susceptible to rifampicin and isoniazid

(MMCA), MTB/STR Test Kit (MMCA), and MTB/FQ Test Kit (MMCA), which could detect the common drug resistance sites of rifampicin, isoniazid, ethambutol, streptomycin and fluoroquinolones. SLAN®−96S Real-Time PCR System (Shanghai Hongshi Medical Technology Co Ltd, China) was used for fluorescent PCR amplification, and the drug resistance information was interpreted by SLAN®−96S automatic medical PCR analysis system 8.2.2. Phenotypic drug susceptibility testing was not performed in all cases because of the availability of molecular drug-susceptibility test.

Treatment protocol

According to WHO recommendations, all TB patients were reported to local CDCs as soon as diagnosed. [11] All DR-TB patients determined by MeltPro were reported as cases of DR-TB, and treatments for DR-TB were started immediately according to the WHO guidelines on drug resistant TB. [12] In March 2019, WHO recommended bedaquiline containing all-oral regimens for 9–18 months for DR-TB treatment, which is adpoted in this study. According to the WHO guidelines and clinical experience, we used standardized treatment regimens for different types of DR-TB patients (Table 1).

TB severity score

We developed a simplified scoring scale to estimate the severity of TB disease (Table 2). The scoring scale was based on the WHO definitions of extensive (or advanced) TB disease and severe extrapulmonary TB, and incorporated the description of TB imaging in previous studies [12].

Definitions of outcomes

According to the WHO definition, the treatment outcomes of TB patients were divided into "unsuccessful outcomes" and “successful outcomes” groups. [12] “Successful outcomes” included “cured” and “treatment completed”. "Unsuccessful outcomes" included “failure”, “died” and “lost to follow up”. [13].

Data analysis

Categorical variables were described as count and percentages, and continuous variables were described as median (P25—P75). Univariate logistic analysis was used to identify potential influencing factors associated with outcome of DR-TB. Factors with $P < 0.05$ were included in multivariate logistic analysis. OR values and 95% CIs were calculated. All statistical analysis was performed

Table 1 Standardized treatment regimens for DR-TB patients

Classification of drug resistance	Treatment regimens
MDR/RR-TB[a] or pre-XDR-TB [b]	**An all-oral regimen containing bedaquiline for 9–18 months**
Hr-TB[c]	
Susceptible to ethambutol and fluoroquinolones	6 (H) REZ-Lfx[f]
Resistant to ethambutol or fluoroquinolones	6(H)RZ-Lfx or 6(H)REZ, with a second-line drug (amikacin or cycloserine) added during the intensive phase
Resistant to ethambutol and fluoroquinolones	6(H)RZ, with two second-line drugs (cycloserine and linezolid) during the intensive phase
FQs-hr-TB[d]	
Susceptible to ethambutol	4HRZE/2HR
Resistant to ethambutol	4HRZ and at least one other second-line drug (typically linezolid) /2HR
hr-TB[e]	
Resistant to ethambutol	4HRZ-Lfx (Mfx) /2HR[g]
Resistant to streptomycin	4HRZE/2HR

[a] MDR/RR-TB: multidrug-resistant TB (MDR-TB, defined as resistance to both rifampicin and isoniazid) or rifampicin-resistant TB (RR-TB)

[b] Pre-XDR-TB: pre-extensively drug-resistant TB, defined as TB that is resistant to rifampicin and any fluoroquinolones

[c] Hr-TB: isoniazid-resistant but rifampicin-susceptible tuberculosis

[d] FQs-hr-TB: fluoroquinolones-resistant TB, but susceptible to rifampicin and isoniazid

[e] hr-TB: both isoniazid and rifampicin-susceptible TB

[f] H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; Lfx: levofloxacin

[g] Mfx: Moxifloxacin

Table 2 Parameters used for estimating the severity of TB

Parameters		Points assigned [c]
Active pulmonary TB range[a]		
	Each lobe of lung[b]	1
Pulmonary cavities[c]		
	The sum of cavities diameters < 3 cm[d]	1
	The sum of cavities diameters ≥ 3 cm and < 5 cm	2
	The sum of cavities diameters ≥ 5 cm	3
Extrapulmonary forms of TB		
	Extrapulmonary TB disease other than miliary TB or TB meningitis (except mediastinal mass)	2
	Miliary TB or TB meningitis	5[e]

[a] Active pulmonary TB range: under the discretion of licensed medical imaging physicians, including nodule, pneumonia, effusion, mass, and other pulmonary lesions suggestive of active pulmonary tuberculosis

[b] Each lobe of lung: the lung lobes were classified based on anatomical structure, with 3 right lobes and 2 left lobes. Each lobe with active TB lesions scored 1 point, with a maximum of 5 points

[c] Pulmonary cavities: cavities caused by tuberculosis infection. When the patient had other diseases that can cause pulmonary cavities at the same time, we would compare the CT images before and after the diagnosis of TB, and conduct PET-CT and fiberoptic bronchoscopy sampling for identification

[d] The sum of cavities diameters: sum of the internal diameters of all pulmonary TB cavities

[e] Miliary TB and TB meningitis are very serious extrapulmonary TB diseases, thus we scored them as 5 points. The final score was the sum of the scores of the three parameters, ranging from 0 (representing no TB infection) to 15. Higher scores represented more severe TB diseases

using IBM SPSS Statistics (version 22.0, IBM Corp., Armonk, N.Y., USA). The significance level for statistical tests was set at 0.05 (two-sided).

Results

Socio-demographic and clinical characteristics of DR-TB patients

Among the 234 DR-TB patients, 26 were referred to other provinces, and 208 patients were finally included in the analysis (Fig. 1). Among the 208 cases, the median follow-up period was 356 days, 61.5% cases were male and 38.5% were female. The median age of all cases was 52.0 years old (Table 3).

23.6% cases had a history of smoking (including cigarettes and hand-rolled cigarettes) within 30 days prior to the diagnosis of tuberculosis. Additionally, 22.1% cases had a drinking habit (consuming at least the equivalent of 25g of 50% ABV spirits or more in alcoholic beverages per month) in the year prior to diagnosis. The median BMI of all the patients was within the normal weight range ($20.4kg/m^2$). 39.4% of the patients had comorbidities.

The main TB type was type-III secondary pulmonary tuberculosis (93.8%). 32.7% of the patients had fever at the time of diagnosis. 50.0% of the patients had received antibiotics before the initiation of TB treatment. 7.7% of the patients had received previous TB treatment.

AFB was positive in 57.2% of the patients, and blood interferon gamma release assays (IGRA) were positive in 90.9% of the patients.

In general laboratory tests, 21.6% of the patients' white blood cell count lower than $4*10^9/L$ or higher than $10*10^9/L$, 68.8% had an increase in erythrocyte sedimentation rate, and 74.5% had an increase in C-reactive protein (CRP). 29.3% of the patients had anemia, and 34.6% had a plasma albumin level of lower than 35g/L.

Lung CT images showed bilateral pulmonary lesions in 74.5% of the patients. Bilateral pulmonary cavities (6.3%) accounted for 20.3% (13/64) of patients with pulmonary cavities (30.8%). Only 2.9% of the patients had extensive parenchymal damage, and 3.4% had miliary TB or TB meningitis. Extrapulmonary TB diseases other than miliary TB or TB meningitis (except mediastinal mass) accounted for 35.1% of all DR-TB patients. The TB severity score ranged from 1—13 in all DR-TB cases, with median score at 5.0 (IQR 3.0—7.0).

Drug susceptibility

With the use of Meltpro for molecular DST, it showed that the overall drug resistance rate of all tested TB cases was 23.1% (234/1013), 6.3% (64/1013) cases were resistant to rifampicin, 11.4% (115/1013) were resistant to isoniazid, 3.3% (33/1013) were resistant to ethambutol, 14.0% (142/1013) were resistant to streptomycin, and 4.1% (42/1013) were resistant to fluoroquinolones.

Among the 208 DR-TB patients included in final analysis, 42(20.2%) cases were MDR/RR-TB, 13(6.3%) were pre-XDR-TB, 58(27.9%) were Hr-TB and 21(10.1%) were FQs-hr-TB. MDR-TB accounted for 73.8%(31/42)

Table 3 Socio-demographic and clinical characteristics of DR-TB patients ($n = 208$)

Characteristics		Patients, N (%)
Follow-up period(Median, IQR(days))		356 (216.5—398.5)
Gender		
	Male	128 (61.5)
	Female	80 (38.5)
Age(Median, IQR(years old))		52.0 (32.0—67.0)
Smoking		49 (23.6)
Alcohol drinking		46 (22.1)
BMI(Median, IQR(Kg/m^2))		20.4 (18.1—22.5)
Comorbidities		82 (39.4)
	Diabetes	21 (10.1)
	Chronic lung diseases	38 (18.3)
	HIV	4 (1.9)
	Autoimmune diseases	7 (3.4)
	Malignant tumor	25 (12.0)
	Liver cirrhosis	7 (3.4)
	Use of immunosuppressive agents	17 (8.2)
Fever		68 (32.7)
Antibiotic use before treatment		104 (50.0)
Previous TB treatment history		16 (7.7)
Tuberculosis types		
	Type-I primary pulmonary tuberculosis	0 (0.0)
	Type-II hematogenous disseminated pulmonary tuberculosis	2 (1.0)
	Type-III secondary pulmonary tuberculosis	195 (93.8)
	Type-IV tuberculous pleurisy	7 (3.4)
	Type-V other extra-pulmonary tuberculosis	20 (9.6)
Acid-fast bacilli (smear)[b]		
	Positive	119 (57.2)
	Negative	89 (42.8)
Blood interferon gamma release assay(IGRA)		
	Positive	189 (90.9)
	Negative	19 (9.1)
Laboratory tests		
	White blood cells increase or decrease [c]	45 (21.6)
	Erythrocyte sedimentation rate increase [d]	143 (68.8)
	C-reactive protein increase[e]	155 (74.5)
	Anemia [f]	61 (29.3)
	Hypoalbuminemia [g]	72 (34.6)
Pulmonary CT features		
	Bilateral pulmonary lesions	155 (74.5)
	Pulmonary cavities	64 (30.8)
	Extensive (or advanced) TB disease	16 (7.7)
	Severe extrapulmonary TB	7 (3.4)
TB severity score(Median, IQR)		5.0 (3.0—7.0)

[a] In this study, the age of patients ranged from 16 to 97 years old

[b] Acid-fast bacilli smear: including sputum smears, bronchoalveolar lavage fluid smears, pus smears and pleural effusion smears

[c] White blood cells increase or decrease: white blood cell count lower than $4*10^9$/L or higher than $10*10^9$/L

[d] Erythrocyte sedimentation rate increase: erythrocyte sedimentation rate > 15mm/h for men and > 20mm/h for women

[e] C-reactive protein increase: C-reactive protein > 10mg/L

[f] Anemia: hemoglobin < 120g/L for men, and < 110g/L for women and children

[g] Hypoalbuminemia: albumin < 35g/L

of MDR/RR-TB. 84.6%(11/13) pre-XDR-TB cases were resistant to isoniazid. 8.6%(5/58) Hr-TB cases were resistant to fluoroquinolones (Table 4).

Treatment outcomes

Among 208 DR-TB cases, the overall successful outcome rate was 76.0% (158/208). 5.8% (12/208) of DR-TB patients were lost to follow up (Table 5).

Of the successful outcome rates for the 5 types of DR-TB, other types of DR-TB (including Ethambutol resistance and Streptomycin resistance) was the highest (86.5%, 64/74). The successful outcome rate of MDR/RR-TB (59.5%, 25/42) was higher than that of

Table 5 Treatment outcomes in DR-TB patients ($n = 208$)

TB Outcomes [a]		Total, N(%)
Successful outcomes		158 (76.0)
	Cured	125 (60.1)
	Treatment completed	33 (15.9)
Unsuccessful outcomes		50 (24.0)
	Failure	24 (11.5)
	Died	14 (6.7)
	Lost to follow up	12 (5.8)
Total		208 (100.0)

[a] All outcomes of DR-TB patients were followed until June 30, 2023

Table 4 Classifications of DR-TB patients ($n = 208$)

Classifications of drug resistance		Patients, N(%)	Successful Outcomes, N(%)	Unsuccessful Outcomes, N(%)
MDR/RR-TB [a]		**42 (20.2)**	**25 (12.0)**	**17 (8.2)**
	Rifampicin resistance	8 (3.8)	8 (3.8)	0 (0.0)
	Rifampicin + Streptomycin resistance	3 (1.4)	1 (0.5)	2 (1.0)
	Rifampicin + Isoniazid resistance	10 (4.8)	6 (2.9)	4 (1.9)
	Rifampicin + Isoniazid + Ethambutol resistance	1 (0.5)	1 (0.5)	0 (0.0)
	Rifampicin + Isoniazid + Streptomycin resistance	11 (5.3)	6 (2.9)	5 (2.4)
	Rifampicin + Isoniazid + Ethambutol + Streptomycin resistance	9 (4.3)	3 (1.4)	6 (2.9)
Pre-XDR-TB[b]		13 (6.3)	5 (2.4)	8 (3.8)
	Rifampicin + Isoniazid + Fluoroquinolones resistance	1 (0.5)	1 (0.5)	0 (0.0)
	Rifampicin + Isoniazid + Ethambutol + Fluoroquinolones resistance	2 (1.0)	0 (0.0)	2 (1.0)
	Rifampicin + Isoniazid + Streptomycin + Fluoroquinolones resistance	3 (1.4)	0 (0.0)	3 (1.4)
	Rifampicin + Isoniazid + Ethambutol + Streptomycin + Fluoroquinolones resistance	5 (2.4)	3 (1.4)	2 (1.0)
	Rifampicin + Fluoroquinolones resistance	1 (0.5)	1 (0.5)	0 (0.0)
	Rifampicin + Ethambutol + Fluoroquinolones resistance	1 (0.5)	0 (0.0)	1 (0.5)
Hr-TB[c]		58 (27.9)	50 (24.0)	8 (3.8)
	Isoniazid resistance	33 (15.9)	27 (13.0)	6 (2.9)
	Isoniazid + Streptomycin resistance	20 (9.6)	18 (8.7)	2 (1.0)
	Isoniazid + Fluoroquinolones resistance	1 (0.5)	1 (0.5)	0 (0.0)
	Isoniazid + Fluoroquinolones + Streptomycin resistance	2 (1.0)	2 (1.0)	0 (0.0)
	Isoniazid + Fluoroquinolones + Ethambutol + Streptomycin resistance	2 (1.0)	2 (1.0)	0 (0.0)
FQs-hr-TB[d]		21 (10.1)	14 (6.7)	7 (3.4)
	Fluoroquinolones resistance	18 (8.7)	12 (5.8)	6 (2.9)
	Fluoroquinolones + Streptomycin resistance	2 (1.0)	1 (0.5)	1 (0.5)
	Fluoroquinolones + Ethambutol + Streptomycin resistance	1 (0.5)	1 (0.5)	0 (0.0)
Other types of DR-TB		74 (35.6)	64 (30.8)	10 (4.8)
	Ethambutol resistance	5 (2.4)	4 (1.9)	1 (0.5)
	Streptomycin resistance	69 (33.2)	60 (28.8)	9 (4.3)

[a] MDR/RR-TB: rifampicin-resistant TB (RR-TB) or multidrug-resistant TB (MDR-TB, defined as resistance to both rifampicin and isoniazid)

[b] Pre-XDR-TB: pre-extensively drug-resistant TB, defined as TB that is resistant to rifampicin and any fluoroquinolones

[c] Hr-TB: isoniazid-resistant but rifampicin-susceptible TB

[d] FQs-hr-TB: fluoroquinolones-resistant TB, but susceptible to rifampicin and isoniazid

pre-XDR-TB (38.5%, 5/13), which had the lowest successful outcome rate (Table 4).

Risk factors for poor outcomes

Multivariate logistic analysis showed that old age (AOR 1.03; 95%CI 1.01—1.05), previous TB treatment history (AOR 5.03; 95%CI 1.33—18.99), higher TB severity score (AOR 1.48; 95%CI 1.09—2.03), MDR/RR-TB (AOR 8.34; 95%CI 2.99—23.24) and pre-XDR-TB (AOR 9.50; 95%CI 2.24—40.26) were independent risk factors for unsuccessful outcomes (Table 6).

Discussion

In this prospective study, we analyzed 208 DR-TB cases after standardized treatment in three designated TB hospitals from 2017—2021 in Zhejiang Province, China, in order to evaluate the treatment outcomes of DR-TB and identify the risk factors for poor outcomes. The overall successful outcomes rate (76.0%) in this study achieved the WHO target (>75%), and higher than that reported in Pakistan (63.9%), Ethiopia (63.8%), Brazil (63.4%), and Morocco (53.5%) [14–17]. It is worth mentioning that compared with the results of Jiang et al. [18], this study found that the overall treatment success rate of DR-TB patients in Zhejiang, China from 2017 to 2021 (76.0%) was higher than that in 2015 (73.5%) and 2016 (69.2%) [18]. For MDR/RR-TB, the treatment success rate in this study (59.5%, 25/42) was higher than the data reported by WHO in China (55.9%, 30 388/54 365) from 2017 to 2022, and it was higher than that reported in the pooled cure rate in a meta-analysis (55.6%), Colombia (49.9%), Armenia and Abkhazia (43.5%), India (38.6%) and Ukraine (18.1%), but lower than that reported in Sudan (63.5%) [2, 19–24].

It was shown that age (AOR 1.03) was an independent risk factor for poor outcomes. A retrospective study from Uzbekistan from 2013 to 2018 suggested that DR-TB patients aged > 30 years had approximately twofold risk for unsuccessful treatment outcomes (ARR 1.9–2.2), and those aged > 50 years had an ARR of 2.2 [25]. Age over 60 years old was also confirmed as a risk factor of poor outcomes, and was mentioned in a retrospective study of DR-TB from Pakistan (AOR: 3.34) and another study of MDR/XDR-TB in China (OR, 9.053) [26, 27]. Previous studies have shown increased rates of diabetes, alcohol abuse and chronic lung disease in people over 40, may affect TB treatment outcomes [28]. An analysis of the incidence and mortality of TB in China from 2004 to 2019 also showed that patients over 60 years had a higher risk of TB death [29].

Previous TB treatment history (AOR 5.03) was one of the most important epidemiological features in TB patients, as it refers to TB patients who have failed initial treatment or relapsed, or who have been treated irregularly for more than a month [30]. It has been shown that previous TB treatment was associated with TB resistance and increased the risk of poor outcomes [31, 32]. The factors leading to previous TB treatment included complexity of disease conditions, poor economic conditions, and difficulty in tolerating side effects of drugs. These patients were also more likely to have unsuccessful treatment outcomes again and need more attention.

Higher TB severity score (AOR 1.48) was another independent risk factor for DR-TB patients' poor outcomes. WHO defined extensive (or advanced) TB disease and severe extrapulmonary TB emphatically, bilateral cavitary disease, extensive parenchymal damage, miliary TB or TB meningitis could cause death and other undesired results [12]. The study by Lytvynenko suggested that pulmonary cavities are a risk factor for poor outcomes in MDR-TB and XDR-TB [33]. A study from Ethiopia showed that DR-TB patients with bilateral lung cavities on baseline chest X-rays were at a high risk (AOR 12.08) for unfavorable outcomes [34]. A 10-year study from the Netherlands showed that miliary and central nervous system TB (OR 15.60) might also be a predictor of TB mortality [35]. However, when these factors were analyzed separately in this study, no significant difference between the two groups was found. Therefore, we developed a scoring system for the severity of DR-TB, and after integrating the factors mentioned by the WHO and other studies, it was found that patients in the poor outcome group had more severe TB. There were also some studies with detailed chest radiography scores for pulmonary TB, but we preferred a clinical assessment of the disease [36, 37]. This simple scoring system helped us to integrate a portion of the influencing factors when the sample size was small, and we would be interested in refining it further in future studies.

MDR/RR-TB (AOR 8.34) and pre-XDR-TB (AOR 9.50) had the highest risk for poor outcomes, which was enough for clinicians to pay attention to. The negative impact of MDR/RR-TB and pre-XDR-TB on the treatment of TB patients was clear, as they directly led to the failure of the bactericidal action of rifampicin, isoniazid and fluoroquinolones, and have been proven to be associated with poor treatment outcomes [12]. MDR/RR-TB and pre-XDR-TB patients also need to take at least two alternative second-line drugs, which may increase the financial burden of patients, as well as unexpected side effects, increasing the rate of unsuccessful treatment.

There are certain limitations in this study. Firstly, the study was conducted in only three medical centers, and the sample size was not large enough to allow for more detailed stratified analysis — which may be prone to bias and unstable results. Secondly, in the latest WHO

Table 6 Analysis of risk factors for poor outcomes in DR-TB patients (n = 208)

Characteristics		Successful Outcomes (n = 158), N(%)	Unsuccessful Outcomes (n = 50), N(%)	COR (95% CI)	AOR (95% CI)
Gender					
	Male	96 (60.8)	32 (64.0)	1.15 (0.59—2.22)	-[b]
	Female	62 (39.2)	18 (36.0)	Referent [a]	-
Age(Median, IQR(years old))		50.0 (31.5—66.0)	56.0 (43.5—69.5)	1.02 (1.00—1.03)*	1.03 (1.01—1.05)*
Smoking		42 (26.6)	6 (12.0)	0.40 (0.13—1.24)	-
Alcohol drinking		37 (23.4)	8 (16.0)	0.62 (0.22—1.76)	-
BMI(Median, IQR(Kg/m^2))		20.4 (18.3—22.5)	20.2 (17.2—23.6)	1.01 (0.88—1.17)	-
Comorbidities		57 (36.1)	26 (52.0)	1.85 (0.95—3.64)	-
	Diabetes	14 (8.9)	7 (14.0)	1.59 (0.57—4.45)	-
	Chronic lung diseases	26 (16.5)	12 (24.0)	1.66 (0.74—3.72)	-
	HIV	2 (1.3)	2 (4.0)	3.37 (0.46—24.65)	-
	Autoimmune diseases	2 (1.3)	4 (8.0)	7.07 (1.25—40.00)*	6.44 (0.60—68.86)
	Malignant tumor	18 (11.4)	7 (14.0)	1.18 (0.43—3.19)	-
	Liver cirrhosis	4 (2.5)	2 (4.0)	1.66 (0.29—9.39)	-
	Use of immunosuppressive agents	12 (7.6)	6 (12.0)	1.55 (0.51—4.71)	-
Fever		54 (34.2)	14 (28.0)	0.79 (0.38—1.63)	-
Antibiotic use before treatment		84 (53.2)	19 (38.0)	0.54 (0.24—1.25)	-
Previous TB treatment history		7 (4.4)	9 (18.0)	4.85 (1.70—13.83)**	5.03 (1.33—18.99)*
Tuberculosis types					
	Type-I primary pulmonary tuberculosis	0 (0.0)	0 (0.0)	Not included[d]	-
	Type-II hematogenous disseminated pulmonary tuberculosis	2 (1.3)	0 (0.0)	Not included[e]	-
	Type-III secondary pulmonary tuberculosis	150 (94.9)	45 (90.0)	0.48 (0.15—1.54)	-
	Type-IV tuberculous pleurisy	6 (3.8)	1 (2.0)	0.52 (0.05—4.40)	-
	Type-V other extra-pulmonary tuberculosis	12 (7.6)	8 (16.0)	2.32 (0.89—6.04)	-
Acid-fast bacilli smear					
	Positive	84 (53.2)	35 (70.0)	2.10 (1.02—4.35)*	2.02 (0.78—5.24)
	Negative	74 (46.8)	15 (30.0)	Referent	Referent
Blood interferon gamma release assay(IGRA)					
	Positive	142 (89.9)	48 (96.0)	2.19 (0.47—10.13)	-
	Negative	16 (10.1)	2 (4.0)	Referent	-
Laboratory tests					
	White blood cell increase or decrease	33 (20.9)	13 (26.0)	1.28 (0.58—2.83)	-
	Erythrocyte sedimentation rate increase	105 (66.5)	39 (78.0)	1.71 (0.68—4.34)	-
	C-reactive protein increase	113 (71.5)	43 (86.0)	2.31 (0.83—6.44)	-
	Anemia	38 (24.1)	23 (46.0)	2.60 (1.28—5.27)**	1.60 (0.62—4.17)
	Hypoalbuminemia	50 (31.6)	22 (44.0)	1.71 (0.85—3.44)	-
Pulmonary CT features					
	Bilateral pulmonary lesions	119 (75.3)	36 (72.0)	0.84 (0.39—1.81)	-
	Pulmonary cavities	44 (27.8)	21 (42.0)	1.87 (0.92—3.79)	-
	Extensive (or advanced) TB disease	11 (7.0)	5 (10.0)	1.89 (0.60—5.99)	-
	Severe extrapulmonary TB	5 (3.2)	2 (4.0)	1.64 (0.29—9.27)	-

Table 6 (continued)

Characteristics		Successful Outcomes (n = 158), N(%)	Unsuccessful Outcomes (n = 50), N(%)	COR (95% CI)	AOR (95% CI)
Gender					
TB severity score(Median, IQR)		4.0 (2.0—5.0)	5.0 (3.0—7.3)	1.30 (1.02—1.67)*	1.48 (1.09—2.03)*
Classifications of DR-TB[f]					
	MDR/RR-TB	25 (15.8)	17 (34.0)	2.74 (1.33—5.66)**	8.34 (2.99—23.24)**
	Pre-XDR-TB	5 (3.2)	8 (16.0)	5.83 (1.81—18.75)**	9.50 (2.24—40.26)**
	Hr-TB	50 (31.6)	8 (16.0)	0.41 (0.18—0.94)*	0.85 (0.25—2.87)
	FQs-hr-TB	14 (8.9)	7 (14.0)	1.67 (0.64—4.41)	-

* $P < 0.05$

** $P < 0.01$

[a] Referent: In SPSS 22.0 software, binary variables were assigned values of 1 and 0 when performing binary logistics regression, and 0 was the reference value

[b] -: Variables with P ≥ 0.05 in univariate analysis were not included in multivariate analysis, and there was no AOR.

[c] Variables used as reference values in the four categorical variables. Meanwhile, no significance was found for the other variables when used separately as reference values

[d] Both groups of variables were 0 (0.0%), so they were not included in the analysis

[e] The P value of binary logistics regression analysis was > 0.99, and the COR value was not obtained, so this variable was not included in the analysis

[f] MDR/RR-TB: multidrug-resistant TB (MDR-TB, defined as resistance to both rifampicin and isoniazid) or rifampicin-resistant TB (RR-TB); pre-XDR-TB: pre-extensively drug-resistant TB, defined as TB that is resistant to rifampicin and any fluoroquinolones; Hr-TB: isoniazid-resistant but rifampicin-susceptible TB; FQs-hr-TB: fluoroquinolones-resistant TB, but susceptible to rifampicin and isoniazid

guidelines (2021), MeltPro® XDR-TB (MeltPro, Xiamen Zeesan Biotech Co., Ltd., China) was considered to have insufficient evidence and lacked independent evaluations, which resulted in MeltPro not being approved by WHO for routine TB DST [38]. Although increasing evidence in recent years has shown that the MeltPro TB assay may serve as an effective alternative to rapid DST of TB, this method may still yield results inconsistent with phenotypic DST, potentially leading to incorrect grouping and clinical decision-making of some cases [39–41]. Finally, we did not test enough types of drugs to assess whether resistance to other drugs such as pyrazinamide and second-line drugs was responsible for the poor outcomes, nor were the XDR-TB cases classified. We will strive to overcome the above limitations in future studies.

Conclusions

The treatment success rate of DR-TB patients in this study reached that of WHO standard (75%). Physicians should be alert to the possibility of poor outcomes in DR-TB patients with old age, previous TB treatment history, high TB severity score, and MDR/RR-TB or pre-XDR-TB.

Abbreviations

TB	Tuberculosis
M.tb	Mycobacterium tuberculosis
DR-TB	Drug-resistant tuberculosis
MDR/RR-TB	Multidrug-resistant/ rifampicin-resistant tuberculosis
Pre-XDR-TB	Pre-extensively drug-resistant TB
Hr-TB	Isoniazid-resistant but rifampicin-susceptible TB
FQs-hr-TB	Fluoroquinolones-resistant TB, but susceptible to rifampicin and isoniazid
AFB	Acid-fast bacilli smears
DST	Drug-susceptibility testing
MeltPro	Fluorescent polymerase chain reaction probe melting curve
IGRA	Blood interferon gamma release assay
CRP	C-reactive protein

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Authors' contributions

Xuewen Feng and Li Hong wrote the first draft of the manuscript. Xuewen Feng, Li Hong, Yanwan Shangguan, Songhua Chen, Zebao He were responsible for collection of clinical data. Wanru Guo was responsible for data curation. Xuewen Feng and Cheng Ding were responsible for statistical analysis and the figure preparation. Zhongkang Ji was responsible for drug susceptibility testing. Kaijin Xu was responsible for study design and monitoring. Ying Zhang and Bing Ruan supervised the study and gave scientific guidance. Xuewen Feng, Kaijin Xu, and Ying Zhang made revisions to the manuscript. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Declarations

Ethics approval and consent to participate

This work was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the First Affiliated Hospital, School of Medicine, Zhejiang University (Approval No. 20160511B). All adult participants provided written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Cambau E, Drancourt M. Steps towards the discovery of Mycobacterium tuberculosis by Robert Koch, 1882. Clin Microbiol Infect. 2014;20(3):196–201.
2. World Health Organization. Global Tuberculosis Report 2024. 2024. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024
3. Macgowan AP, Surveillance BWPoR. Clinical implications of antimicrobial resistance for therapy. J Antimicrob Chemother. 2008;62(Suppl 2):ii105-14.
4. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013;13(12):1057–98.
5. Ding C, Wang S, Shangguan Y, Feng X, Guo W, Shi P, et al. Epidemic Trends of Tuberculosis in China from 1990 to 2017: Evidence from the Global Burden of Disease Study. Infect Drug Resist. 2020;13:1663–72.
6. Hu S, Li G, Li H, Liu X, Niu J, Quan S, et al. Rapid detection of isoniazid resistance in Mycobacterium tuberculosis isolates by use of real-time-PCR-based melting curve analysis. J Clin Microbiol. 2014;52(5):1644–52.
7. Wang J, Zhao W, Liu R, Huo F, Dong L, Xue Y, et al. Rapid Detection of Ethambutol-Resistant Mycobacterium tuberculosis from Sputum by High-Resolution Melting Analysis in Beijing. China Infect Drug Resist. 2020;13:3707–13.
8. Huo F, Ma Y, Li S, Xue Y, Shang Y, Dong L, et al. Specific gyrA Gene Mutations Correlate with High Prevalence of Discordant Levofloxacin Resistance in Mycobacterium tuberculosis Isolates from Beijing. China J Mol Diagn. 2020;22(9):1199–204.
9. Song Y, Wang G, Li Q, Liu R, Ma L, Li Q, et al. The Value of the inhA Mutation Detection in Predicting Ethionamide Resistance Using Melting Curve Technology. Infect Drug Resist. 2021;14:329–34.
10. Pang Y, Dong H, Tan Y, Deng Y, Cai X, Jing H, et al. Rapid diagnosis of MDR and XDR tuberculosis with the MeltPro TB assay in China. Sci Rep. 2016;6:25330.
11. World Health Organization. WHO operational handbook on tuberculosis: module 2: screening systematic screening for tuberculosis disease. 2021. https://www.who.int/publications/i/item/9789240022676.
12. World Health Organization. WHO operational handbook on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment. 2020. https://www.who.int/publications/i/item/9789240006997.
13. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision: updated December 2014 and January 2020. 2013. https://www.who.int/publications/i/item/9789241505345.
14. El Hamdouni M, Bourkadi JE, Benamor J, Hassar M, Cherrah Y, Ahid S. Treatment outcomes of drug resistant tuberculosis patients in Morocco: multi-centric prospective study. BMC Infect Dis. 2019;19(1):316.
15. Alemu A, Bitew ZW, Worku T. Poor treatment outcome and its predictors among drug-resistant tuberculosis patients in Ethiopia: A systematic review and meta-analysis. Int J Infect Dis. 2020;98:420–39.
16. Bartholomay P, Pinheiro RS, Dockhorn F, Pelissari DM, de Araujo WN. Brazilian cohort study of risk factors associated with unsuccessful outcomes of drug resistant tuberculosis. BMC Infect Dis. 2021;21(1):1049.
17. Khan FU, Rehman AU, Khan FU, Hayat K, Khan A, Ahmad N, et al. Assessment of factors associated with unfavorable outcomes among drug-resistant TB patients: a 6-year retrospective study from Pakistan. Int J Environ Res Public Health. 2022;19(3):1574.
18. Jiang W, Peng Y, Wang X, Elbers C, Tang S, Huang F, et al. Policy changes and the screening, diagnosis and treatment of drug-resistant tuberculosis patients from 2015 to 2018 in Zhejiang Province, China: a retrospective cohort study. BMJ Open. 2021;11(4): e047023.
19. Ali MH, Alrasheedy AA, Kibuule D, Godman B, Hassali MA, Ali HMH. Assessment of multidrug-resistant tuberculosis (MDR-TB) treatment outcomes in Sudan; findings and implications. Expert Rev Anti Infect Ther. 2019;17(11):927–37.
20. Bastard M, Sanchez-Padilla E, Hewison C, Hayrapetyan A, Khurkhumal S, Varaine F, et al. Effects of treatment interruption patterns on treatment success among patients with multidrug-resistant tuberculosis in Armenia and Abkhazia. J Infect Dis. 2015;211(10):1607–15.
21. Patel SV, Nimavat KB, Alpesh PB, Shukla LK, Shringarpure KS, Mehta KG, et al. Treatment outcome among cases of multidrug-resistant tuberculosis (MDR TB) in Western India: A prospective study. J Infect Public Health. 2016;9(4):478–84.
22. Aibana O, Bachmaha M, Krasiuk V, Rybak N, Flanigan TP, Petrenko V, et al. Risk factors for poor multidrug-resistant tuberculosis treatment outcomes in Kyiv Oblast, Ukraine. BMC Infect Dis. 2017;17(1):129.
23. Kibret KT, Moges Y, Memiah P, Biadgilign S. Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: a systematic review and meta-analysis of published studies. Infect Dis Poverty. 2017;6(1):7.
24. Chaves-Torres NM, Fadul S, Patino J, Netto E. Factors associated with unfavorable treatment outcomes in patients with rifampicin-resistant tuberculosis in Colombia 2013–2015: A retrospective cohort study. PLoS ONE. 2021;16(4): e0249565.
25. Safaev K, Parpieva N, Liverko I, Yuldashev S, Dumchev K, Gadoev J, et al. Trends, characteristics and treatment outcomes of patients with drug-resistant tuberculosis in Uzbekistan: 2013–2018. Int J Environ Res Public Health. 2021;18(9):4663.
26. Mitchell GH, Hadley TJ, McGinniss MH, Klotz FW, Miller LH. Invasion of erythrocytes by Plasmodium falciparum malaria parasites: evidence for receptor heterogeneity and two receptors. Blood. 1986;67(5):1519–21.
27. Zhang MW, Zhou L, Zhang Y, Chen B, Peng Y, Wang F, et al. Treatment outcomes of patients with multidrug and extensively drug-resistant tuberculosis in Zhejiang, China. Eur J Med Res. 2021;26(1):31.
28. Echazarreta A, Zerbini E, De Sandro J, Sáenz C, Yessi L, Saad R, et al. Tuberculosis and comorbidities in urban areas in Argentina. A gender and age perspective Biomedica. 2018;38(2):180–8.
29. Wang L, Wang W. Temporal trends in notification and mortality of tuberculosis in China, 2004–2019: a joinpoint and age-period-cohort analysis. Int J Environ Res Public Health. 2021;18(11):5607.
30. Ullah I, Javaid A, Tahir Z, Ullah O, Shah AA, Hasan F, et al. Pattern of Drug Resistance and Risk Factors Associated with Development of Drug Resistant Mycobacterium tuberculosis in Pakistan. PLoS ONE. 2016;11(1): e0147529.
31. Tembo BP, Malangu NG. Prevalence and factors associated with multi-drug/rifampicin resistant tuberculosis among suspected drug resistant tuberculosis patients in Botswana. BMC Infect Dis. 2019;19(1):779.
32. Gegia M, Cohen T, Kalandadze I, Vashakidze L, Furin J. Outcomes among tuberculosis patients with isoniazid resistance in Georgia, 2007–2009. Int J Tuberc Lung Dis. 2012;16(6):812–6.

33. Lytvynenko N, Cherenko S, Feschenko Y, Pogrebna M, Senko Y, Barbova A, et al. Management of multi- and extensively drug-resistant tuberculosis in Ukraine: how well are we doing? Public Health Action. 2014;4(Suppl 2):S67-72.
34. Gamachu M, Deressa A, Birhanu A, Ayana GM, Raru TB, Negash B, et al. Sputum smear conversion and treatment outcomes among drug-resistant pulmonary tuberculosis patients in eastern Ethiopia: A 9-years data analysis. Front Med (Lausanne). 2022;9:1007757.
35. Pradipta IS, Van't Boveneind-Vrubleuskaya N, Akkerman OW, Alffenaar JC, Hak E. Treatment outcomes of drug-resistant tuberculosis in the Netherlands, 2005–2015. Antimicrob Resist Infect Control. 2019;8:115.
36. Rao Y, Cao W, Qu J, Zhang X, Wang J, Wang J, et al. More severe lung lesions in smoker patients with active pulmonary tuberculosis were associated with peripheral NK cell subsets. Tuberculosis (Edinb). 2023;138:102293.
37. Ralph AP, Ardian M, Wiguna A, Maguire GP, Becker NG, Drogumuller G, et al. A simple, valid, numerical score for grading chest x-ray severity in adult smear-positive pulmonary tuberculosis. Thorax. 2010;65(10):863–9.
38. World Health Organization. (2021). WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update. World Health Organization. https://iris.who.int/handle/10665/342331.
39. Hu Y, Chi YQ, Feng X, Li HR, Shang YY, Pan JH, et al. Comparison of the Diagnostic Performance of MeltPro and Next-Generation Sequencing in Determining Fluoroquinolone Resistance in Multidrug-Resistant Tuberculosis Isolates. J Mol Diagn. 2023;25(6):342–51.
40. Liu ZB, Cheng LP, Pan HQ, Wu XC, Lu FH, Cao J, et al. Performance of the MeltPro TB assay as initial test for diagnosis of pulmonary tuberculosis with drug-resistance detection. Mol Med. 2023;29(1):153.
41. Hu Y, Yu M, You GQ, Fan J, Zheng HW. Evaluation of MeltPro Assay in Identification of Second-Line Injectable Drug Resistance in Multidrug-Resistant Tuberculosis Isolates. Infect Drug Resist. 2024;17:2069–76.

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