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ORIGINAL RESEARCH

Treatment Outcomes and Associated Influencing Factors Among Patients with Rifampicin-Resistant Tuberculosis: A Multicenter, Retrospective, Cohort Study in China

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Objective: Rifampin-resistant tuberculosis (RR-TB) remains a serious global public health concern. We assessed treatment outcomes and associated influencing factors among RR-TB patients in China.

Methods: This research enrolled 1339 patients who started RR-TB treatment between May 2018 and April 2020 in China retrospectively. Data were collected from the electronic medical records. Multivariable logistic regression analysis was used to identify the influencing factors related to unfavorable outcomes.

Results: Of the 1339 RR-TB patients, 78.8% (1055/1339) achieved treatment success (cured or treatment completed), 5.1% (68/1339) experienced treatment failure, 1.1% (15/1339) died during treatment, 10.1% (135/1339) were lost to follow-up, and 4.9% (66/1339) were not evaluated. About 67.7% (907/1339) of patients experienced at least one adverse event (AE). The most common AE was hypohepatia (507/1339, 37.9%), followed by hyperuricemia (429/1339, 32.0%), anemia (368/1339, 27.5%), electrolyte disturbance (318/1339, 23.7%), peripheral neuritis (245/1339, 18.3%), and gastrointestinal reactions (203/1339, 15.2%). Multivariate analysis showed that age ≥60 years [adjusted odds ratio (aOR): 1.96, 95% confidence interval (CI): 1.39–2.77], national minority (aOR: 2.36, 95% CI: 1.42–3.93), smoking (aOR: 1.50, 95% CI: 1.10–2.04), cardiopathy (aOR: 2.90, 95% CI: 1.33–6.31), tumors (aOR: 9.84, 95% CI: 2.27–42.67), immunocompromise (aOR: 2.17, 95% CI: 1.21–3.91), re-treated TB (aOR: 1.46, 95% CI: 1.08–1.97), and experienced gastrointestinal reactions (aOR: 2.27, 95% CI: 1.52–3.40) were associated with unfavorable outcomes. Body mass index (BMI) ≥18.5 kg/m^{2,} regimens containing bedaquiline and experienced adverse events (AEs) such as hypohepatia, leukopenia, peripheral neuritis, and optic neuritis were associated with favorable outcomes.

Conclusion: High rates of treatment success were achieved for RR-TB patients at tertiary tuberculosis hospitals in China. Age ≥60 years, national minority, smoking status, comorbidities, re-treated TB, and experienced gastrointestinal reactions were independent prognostic factors for unfavorable treatment outcomes.

Keywords: RR-TB, treatment outcomes, influencing factors, China

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Introduction

Tuberculosis (TB) is still one of the major epidemic and important infectious diseases, causing illness and even death on a global scale.[1] The World Health Organization (WHO) 's End TB Strategy goal is to reduce the TB incidence and mortality rates by 90% and 95% compared with 2015, respectively, before 2035,[2] but rifampin-resistant TB and multidrug-resistant TB (MDR/RR-TB) seriously threatens the realization of this goal. Owing to the long course of treatment, high treatment costs, significant adverse drug events, scarcity and accessibility of second-line anti-TB drugs, the optimal clinical treatment of RR-TB faces a serious challenge. An estimated 410000 people developed RR-TB in 2022 worldwide, but only about 43% of them received treatment.[1] Despite treatment success rates for RR-TB have improved in recent years, only 63% have been reported in the most recent available patient cohort. As a respiratory transmitted disease, in the absence of effective protection measures, untreated MDR/RR-TB patients, serving as a source of infection, will cause the prevalence of MDR/RR-TB in the crowd.

China remains a high-burden country for RR-TB in 2022, with 30,000 cases, accounting for 7.3% of the total number of RR-TB cases reported globally. Even more alarming is that the recent treatment success rate for RR-TB in China is only 51%, significantly lower than the global average.[1] There is an urgent need to take measures to improve the treatment success rate for RR-TB, including expanding treatment coverage, standardizing treatment regimens, and identifying and avoiding factors that lead to poor treatment outcomes. Previous studies have identified several factors associated with poor prognosis in RR-TB patients, including older age,[3] male gender,[4] HIV infection,[3] Low Body Mass Index (BMI),[5] prior TB treatment,[6] and so on. However, some other studies also have reported contradictory results.[7,8] This discrepancy may be related to factors such as countries, regions, timing, sample size and included variables.

In our study, we reviewed the clinical data of RR-TB patients in China between May 2018 and April 2020 by conducting a multicenter cohort study, in order to describe the characteristics, evaluate treatment outcomes, and related influencing factors among RR-TB patients in China. This will help to facilitate the development of strategies and informed decisions on RR-TB management, and contribute to the promotion of efficient and effective treatment for RR-TB.

Methods

Study Subjects

This retrospective cohort study was performed at eight hospitals in eight provinces of China, including seven specialized tuberculosis hospitals, and all of them were tertiary hospitals.

The patients with laboratory-confirmed RR-TB who started their treatment between May 2018 and April 2020 were enrolled in this study, containing RR-TB, MDR-TB, extensively drug-resistant TB (XDR-TB) and pre-extensively drug-resistant TB (Pre-XDR-TB). The inclusion criteria were as follows: (1) laboratory-confirmed RR-TB tested by rapid molecular, genotypic techniques or phenotypic drug susceptibility testing (DST); (2) At least 15 years old; and (3) Pulmonary lesions indicated by Chest Radiography or CT. The exclusion criteria were as follows: (1) patients with RR-TB who had died before treatment started or did not accept treatment, and (2) patients with incomplete medical records.

RR-TB treatment regimens were developed according to WHO and Chinese guidelines,[9–11] as well as other factors, such as DST results, history of anti-TB treatment, economic considerations, and tolerability of anti-TB drugs. Each treatment regimen, which might be standardized or individualized, included at least four effective anti-TB drugs, primarily consisting of bedaquiline, linezolid, fluoroquinolones (levofloxacin or moxifloxacin), cycloserine, clofazimine, prothionamide, para-aminosalicylic acid, injectable agents (amikacin or capreomycin), and pyrazinamide. The duration of RR-TB treatment usually lasted 9–24 months, based on the improvement of clinical symptoms, radiological resolution, and follow-up sputum bacteriological conversion. Each patient received direct observation therapy (DOT) throughout the treatment.

Definitions

RR-TB is defined as tuberculosis resistant to rifampin. MDR-TB is defined as tuberculosis resistant to both rifampin and isoniazid. MDR/RR-TB refers to either MDR-TB or RR-TB cases. Pre-XDR-TB is resistant to rifampicin (and may be

resistant or susceptible to isoniazid) and to at least one fluoroquinolone (moxifloxacin or levofloxacin). XDR-TB is on the basis of meeting the definition of pre-XDR-TB and resistant to at least one other "Group A" drug (linezolid or bedaquiline) simultaneously.[12]

Initial treatment TB is defined as tuberculosis that has never received anti-TB drugs or has received anti-TB drugs for less than 1 month or is receiving standard anti-TB regimen treatment but has not yet completed the course of treatment. Re-treated TB involves tuberculosis that has been treated for 1 month or more irregularly or nonstandardly, failure of initial treatment, and relapse.

Immunocompromised patients included those with AIDS/HIV, autoimmune system diseases, solid organ transplant recipients, and others who experienced weakened immunity.

TB treatment outcomes were defined as follows according to the WHO guidelines:[13,14] (1) Cured was defined as a TB patient confirmed by bacteriology at the beginning of treatment, with evidence of bacteriological response and no evidence of failure after completing treatment; (2) treatment failure was patient whose treatment regimen had to be suspended or changed to a new treatment strategy or regimen permanently; (3) treatment completed was patient who completed the treatment but not meet the definition for cure and also without evidence of failure; (4) lost to follow-up was defined as a patient whose treatment was discontinued for more than two consecutive months, or who did not initiate therapy; (5) death was TB patient who died before the initiation of treatment or during the treatment; and (6) Not evaluated was TB patient whose treatment outcome was unknown. In our study, cure and treatment completed were classified as "treatment success", while other treatment outcomes were classified as "unfavorable outcomes".

Data Management and Statistical Analysis

All data were extracted from electronic medical records, including epidemiological, demographic, and clinical data, such as gender, age, BMI, nationality, residential area, alcohol use, smoking, treatment history, comorbidities, sputum smear and culture test, DST, imaging manifestations, and adverse effects. The data were entered by health professionals who accepted the standardized training of the research staff.

Qualitative variables were reported as numbers and percentages. Pearson's chi-square test was performed to compare the categorical variables. Univariate and multivariate logistic regression analyses were used to explore the factors associated with unfavorable outcomes. Variables with a p-value <0.05 during the univariate analysis were taken to the multivariate logistic regression analysis. Statistical analysis was performed using SPSS software version 23 (IBM Corporation, Armonk, NY, USA), and a p-value of 0.05 was considered as statistically significant.

Results

Clinical Characteristics

Data on 1416 RR-TB patients with treatment outcomes were collected. After excluding 77 patients with incomplete medical records, 1339 RR-TB patients were enrolled, including Anhui (50 cases, 3.7%), Beijing (170 cases, 12.7%), Sichuan (367 cases, 27.4%), Chongqing (27 cases, 2.0%), Heilongjiang (384 cases, 28.7%), Guangxi (35 cases, 2.6%), Jiangsu (79 cases, 5.9%), and Hubei (227 cases, 17.0%).

The demographic and clinical characteristics of the RR-TB patients are shown in Table 1. Among the 1339 RR-TB patients, 939 (70.1%) were male, 223 (16.7%) were elderly (≥60 years), 332 (24.8%) had a BMI <18.5 kg/m^2, 1255 (93.7%) were of Han ethnicity, 808 (60.3%) were from urban districts, 684 (51.1%) were re-treated, and 655 (48.9%) were initially

Table 1 Baseline Demographic and Clinical Characteristics in 1339 Patients with RR-TB

Variable	n	%
Gender		
Male	939	70.1
Female	400	29.9

(*Continued*)

Table 1 (Continued).

Variable	n	%
Age (years)		
15–59	1116	83.3
≥60	223	16.7
BMI (kg / m^2)		
<18.5	332	24.8
≥18.5	1007	75.2
Nationality		
Han	1255	93.7
National minority	84	6.3
Residential area		
Rural	531	39.7
Urban	808	60.3
TB contact history	122	9.1
Alcohol use	256	19.1
Smoking	388	29.0
Comorbidities		
Diabetes	236	17.6
Immunocompromise	65	4.9
Viral hepatitis or carrier	53	4.0
Cardiopathy	31	2.3
Tumour	11	0.8
TB treatment history		
Initial treatment	655	48.9
Re-treated	684	51.1
Resistance pattern		
RR-TB	383	28.6
MDR-TB	685	51.2
Pre-XDR-TB	269	20.1
XDR-TB	2	0.1
Time from onset of symptoms to treatment		
<6 months	655	48.9
≥6 months	684	51.1
Sputum smear positive	758	56.6
Sputum culture positive	1234	92.2
Lesions involve the lung fields		
Unilateral lung	345	25.8
Bilateral lung	994	74.2
Pulmonary cavities	834	62.3
Clinical symptoms		
Cough	1169	87.3
Expectoration	1068	79.8
Fatigue	508	37.9
Pant	479	35.8
Loss of weight	458	34.2
Night sweat	427	31.9
Thoracalgia	403	30.1
Fever	326	24.3
Hemoptysis	255	19.0
Treatment regimens		
Bedaquiline-containing regimens	265	19.8
Linezolid-containing regimens	872	65.1
Regimens without linezolid and bedaquiline	444	33.2

treated. Additionally, 388 (29.0%) had a history of smoking and 256 (19.1%) had a history of alcohol consumption. Among the 1339 patients, the highest proportion was MDR-TB, accounting for 51.2% (685/1339), followed by RR-TB, pre-XDR-TB, and XDR-TB, accounting for 28.6% (383/1339), 20.1% (269/1339), and 0.1% (2/1339), respectively. The most common comorbidity was diabetes (236/1339, 17.6%), followed by immunocompromise (65/1339, 4.9%), viral hepatitis or carrier (53/1339, 4.0%), cardiopathy (31/1339, 2.3%), and tumors (11/1339, 0.8%). A total of 655 (48.9%) patients had a course of <6 months, and 684 (51.1%) had a course of ≥6 months. In sputum bacteriology and radiographic examinations, there were 1234 (92.2%) cases with positive sputum cultures and 758 (56.6%) cases with positive sputum smears. All cases were diagnosed as pulmonary TB (100%); unilateral lung lesions were observed in 345 (25.8%) cases, and bilateral lung lesions were observed in 994 (74.2%) cases. Additionally, 834 (62.3%) cases presented with pulmonary cavities. The most common clinical symptom was cough (1169/1339, 87.3%), followed by expectoration (1068/1339, 79.8%), fatigue (508/1339, 37.9%), Pant (479/1339, 35.8%), and loss of weight (458/1339, 34.2%). Of the 1339 patients, 265 (19.8%) were treated with a regimen containing bedaquiline, 872 (65.1%) were treated with a regimen containing linezolid, and 444 (33.2%) did not use either bedaquiline or linezolid.

Treatment Outcomes

As shown in Table 2, of the 1339 cases, the number and proportion of cured, treatment completed, treatment failure, died, lost to follow up and not evaluated were 498 (37.2%), 557 (41.6%), 68 (5.1%), 15 (1.1%), 135 (10.1%), and 66 (4.9%), respectively. Treatment success was 78.8% (1055/1399) and unfavorable outcome was 21.2% (284/1339). The treatment success rates were similar between the MDR/RR-TB group and pre-XDR/XDR-TB group (79.8% vs 74.9%, P = 0.080).

Adverse Events (AEs) During Treatment

A total of 907 patients (67.7%) suffered at least one adverse event during the RR-TB treatment. The most common AE was hypohepatia (507/1339, 37.9%), followed by hyperuricemia (429/1339, 32.0%), anemia (368/1339, 27.5%), electrolyte disturbance (318/1339, 23.7%), peripheral neuritis (245/1339, 18.3%), and gastrointestinal reactions (203/1339, 15.2%) (Figure 1). Hypohepatia was defined as an increase in alanine aminotransferase, aspartate aminotransferase, or bilirubin above normal values during RR-TB treatment. Gastrointestinal reaction was defined as vomiting, bloating, abdominal pain and other gastrointestinal symptoms on the gastrointestinal tract during RR-TB treatment.

Univariate and Multiple Logistic Regression of Unfavorable Outcomes

The associations between characteristics and unfavorable outcomes of RR-TB patients are presented in Table 3. It showed that variables related to unfavorable outcomes in univariate logistic regression analysis included age, BMI, nationality, alcohol use, smoking, comorbidities (cardiopathy, immunocompromise status, and tumor), history of TB treatment, lesions involving the lung fields, certain clinical symptoms (loss of weight, thoracalgia, and Pant), anti-TB treatment regimen, and some AEs (P < 0.05). Moreover, all the above factors were enrolled in the stepwise multiple regression analysis. The results showed that age ≥60 years [adjusted odds ratio (aOR): 1.96, 95% confidence interval

Table 2 The Treatment Outcomes in 1339 Patients with RR-TB in China

Treatment Outcomes	n	%
Treatment success	1055	78.8
Cured	498	37.2
Treatment completed	557	41.6
Unfavorable outcomes	284	21.2
Treatment failure	68	5.1
Died	15	1.1
Lost to follow up	135	10.1
Not evaluated	66	4.9

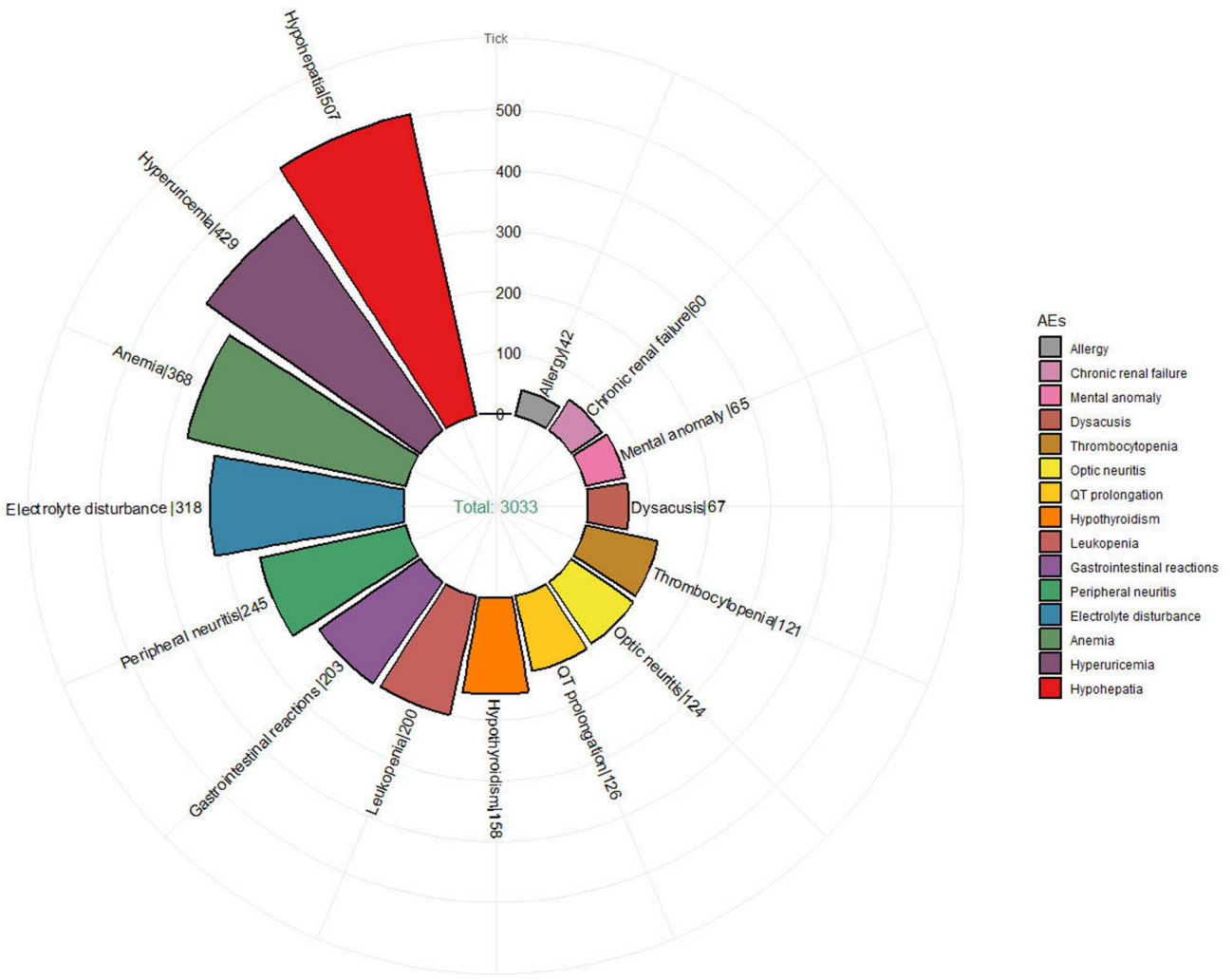

Figure 1 AEs in 1339 patients with RR-TB.

(CI): 1.39–2.77, P < 0.001], national minorities (aOR: 2.36, 95% CI: 1.42–3.93, P = 0.001), smoking (aOR: 1.50, 95% CI: 1.10–2.04, P = 0.01), cardiopathy (aOR: 2.90, 95% CI: 1.33–6.31, P = 0.008), tumors (aOR: 9.84, 95% CI: 2.27–42.67, P = 0.002), immunocompromise (aOR: 2.17, 95% CI: 1.21–3.91, P = 0.01), re-treated TB (aOR: 1.46, 95% CI: 1.08–1.97, P = 0.013), and gastrointestinal reactions (aOR: 2.27, 95% CI: 1.52–3.40, P < 0.001) were factors with increased unfavorable treatment outcomes, whereas BMI ≥18.5 kg/m^2 (aOR: 0.45, 95% CI: 0.33–0.61, P < 0.001), treatment regimens containing bedaquiline (aOR: 0.50, 95% CI: 0.32–0.79, P = 0.003), experiencing AEs containing abnormal liver function (aOR: 0.66, 95% CI: 0.47–0.93, P = 0.017), leukopenia (aOR: 0.44, 95% CI: 0.26–0.74, P = 0.002), peripheral neuritis (aOR: 0.49, 95% CI: 0.30–0.80, P = 0.004) and optic neuritis (aOR: 0.51, 95% CI: 0.28–0.94, P = 0.03) were associated with favorable treatment outcomes (Figure 2).

Discussion

Our study showed that the treatment success rate for RR-TB patients who began treatment in China between May 2018 and April 2020 was 78.8%. This was higher than the global average of 63% and the national average of 51% in China, which was recently reported by WHO.[1] The treatment success rates for RR-TB had generally been reported in the range of 50%–90% across the world (Table 4),[3,4,7,8,15–23] and the treatment success rate of RR-TB in China also varied by region and time, ranging from 59% (Chongqing, 2010–2017) to 76% (Hangzhou, 2010–2015),[4,7,17–19] which were lower than those in our study. The possible reason might be that five of the hospitals in this study participated in the "New anti-

Table 3 Factors Associated with Unfavorable Outcomes Among RR-TB Patients in Univariate Analyses

Variable	Treatment Success* n=1055	Unfavorable Outcome† n=284	Unadjusted OR	P value
Gender				
Male	732 (78.0)	207 (22.0)	Reference	
Female	323 (80.8)	77 (19.3)	0.843 (0.629, 1.129)	0.253
Age				
15–59 years	912 (81.7)	204 (18.3)	Reference	
≥60 years	143 (64.1)	80 (35.9)	2.501 (1.829, 3.420)	<0.001
BMI (kg / m^2)				
<18.5	224 (67.5)	108 (32.5)	Reference	
≥18.5	831 (82.5)	176 (17.5)	0.439 (0.332, 0.582)	<0.001
Nationality				
Han	1005 (80.1)	250 (19.9)	Reference	
National minority	50 (59.5)	34 (40.5)	2.734 (1.731, 4.318)	<0.001
Residential area				
Rural	406 (76.5)	125 (23.5)	Reference	
Urban	649 (80.3)	159 (19.7)	0.796 (0.610, 1.037)	0.091
TB contact history	94 (77.0)	28 (23.0)	1.118 (0.717, 1.743)	0.622
Alcohol use	188 (73.4)	68 (26.6)	1.452 (1.060, 1.989)	0.020
Smoking	289 (74.5)	99 (25.5)	1.418 (1.073, 1.875)	0.014
With comorbidity				
Diabetes	176 (74.6)	60 (25.4)	1.338 (0.964, 1.856)	0.082
Cardiopathy	14 (45.2)	17 (54.8)	4.734 (2.304, 9.727)	<0.001
Tumour	4 (36.4)	7 (63.6)	6.640 (1.930, 22.844)	0.003
Immunocompromise	40 (61.5)	25 (38.5)	2.449 (1.459, 4.112)	0.001
Viral hepatitis or carrier	43 (81.1)	10 (18.9)	0.859 (0.426, 1.731)	0.671
TB treatment history				
Initial treatment	474 (83.5)	94 (16.5)	Reference	
Re-treated	581 (75.4)	190 (24.6)	1.649 (1.252, 2.172)	<0.001
Time from onset of symptoms to treatment				
<6 months	505 (77.1)	150 (22.9)	Reference	
≥6 months	550 (80.4)	134 (19.6)	0.818 (0.634, 1.055)	0.122
Sputum smear positive	586 (77.3)	172 (22.7)	1.229 (0.941, 1.606)	0.130
Sputum culture positive	975 (79.0)	259 (21.0)	0.850 (0.532, 1.359)	0.498
Radiographic characteristics				
Bilateral lung	766 (77.1)	228 (22.9)	1.536 (1.113, 2.120)	0.009
Pulmonary cavities	665 (79.7)	169 (20.3)	0.862 (0.659, 1.127)	0.277
Resistance pattern				
RR-TB	311 (81.2)	72 (18.8)	Reference	
MDR/Pre-XDR/XDR-TB	744 (77.8)	212(22.2)	0.812 (0.603, 1.095)	0.172
Clinical symptoms				
Cough	916 (78.4)	253 (21.6)	1.238 (0.819, 1.873)	0.311
Expectoration	835 (78.2)	233 (21.8)	1.204 (0.859, 1.687)	0.282
Fever	263 (80.7)	63 (19.3)	0.858 (0.628, 1.174)	0.339
Hemoptysis	212 (83.1)	43 (16.9)	0.709 (0.496, 1.015)	0.060
Night sweat	325 (76.1)	102 (23.9)	1.259 (0.956, 1.658)	0.101
Fatigue	397 (78.1)	111 (21.9)	1.063 (0.813, 1.392)	0.654
Loss of weight	335 (73.1)	123 (26.9)	1.642 (1.256, 2.147)	<0.001
Thoracalgia	300 (74.4)	103 (25.6)	1.432 (1.086, 1.888)	0.011
Pant	356 (74.3)	123 (25.7)	1.500 (1.148, 1.959)	0.003

(*Continued*)

Table 3 (Continued).

Variable	Treatment Success* n=1055	Unfavorable Outcome† n=284	Unadjusted OR	P value
Anti-tuberculosis treatment regimen				
Containing linezolid	709 (81.3)	163 (18.7)	0.657 (0.503, 0.859)	0.002
Containing bedaquiline	237 (89.4)	28 (10.6)	0.378 (0.249, 0.572)	<0.001
AEs				
Abnormal liver function	424 (83.6)	83 (16.4)	0.651 (0.463, 0.816)	0.001
Anemia	285 (77.4)	83 (22.6)	1.116 (0.835, 1.490)	0.459
Leukopenia	178 (89.0)	22 (11.0)	0.414 (0.260, 0.658)	<0.001
Thrombocytopenia	91 (75.2)	30 (24.8)	1.251 (0.810, 1.933)	0.313
Allergy	36 (85.7)	6 (14.3)	0.611 (0.255, 1.465)	0.269
Chronic renal failure	45 (75.0)	15 (25.0)	1.252 (0.687, 2.280)	0.269
QT prolongation	105 (83.3)	21 (16.7)	0.722 (0.443, 1.177)	0.192
Mental anomaly	54 (83.1)	11 (16.9)	0.747 (0.385, 1.448)	0.388
Gastrointestinal reactions	145 (71.4)	58 (28.6)	1.611 (1.149, 2.257)	0.006
Peripheral neuritis	221 (90.2)	24 (9.8)	0.348 (0.224, 0.543)	<0.001
Optic neuritis	109 (87.9)	15 (12.1)	0.484 (0.277, 0.844)	0.011
Dysacusis	54 (80.6)	13 (19.4)	0.889 (0.478, 1.653)	0.711
Hyperuricemia	344 (80.2)	85 (19.8)	0.883 (0.664, 1.174)	0.391
Electrolyte disturbance	246 (77.4)	72 (22.6)	1.117 (0.825, 1.512)	0.475
Hypothyroidism	136 (86.1)	22 (13.9)	0.567 (0.354, 0.909)	0.018

Notes: *Treatment success (treatment completed and cured). †Unfavorable outcome (treatment failure, death, loss to follow-up, and not evaluated).

TB Drugs Introduction and Protection Program" which could access to new anti-TB drug bedaquiline in 2018 in China. As bedaquiline is a diarylquinoline compound with a novel mechanism against mycobacterium tuberculosis (MTB) by inhibiting mycobacterium adenosine triphosphate (ATP) synthase that can significantly improve outcomes in patients with MDR/RR-TB,[24,25] there were 265 (19.8%) RR-TB patients received treatment with a regimen containing

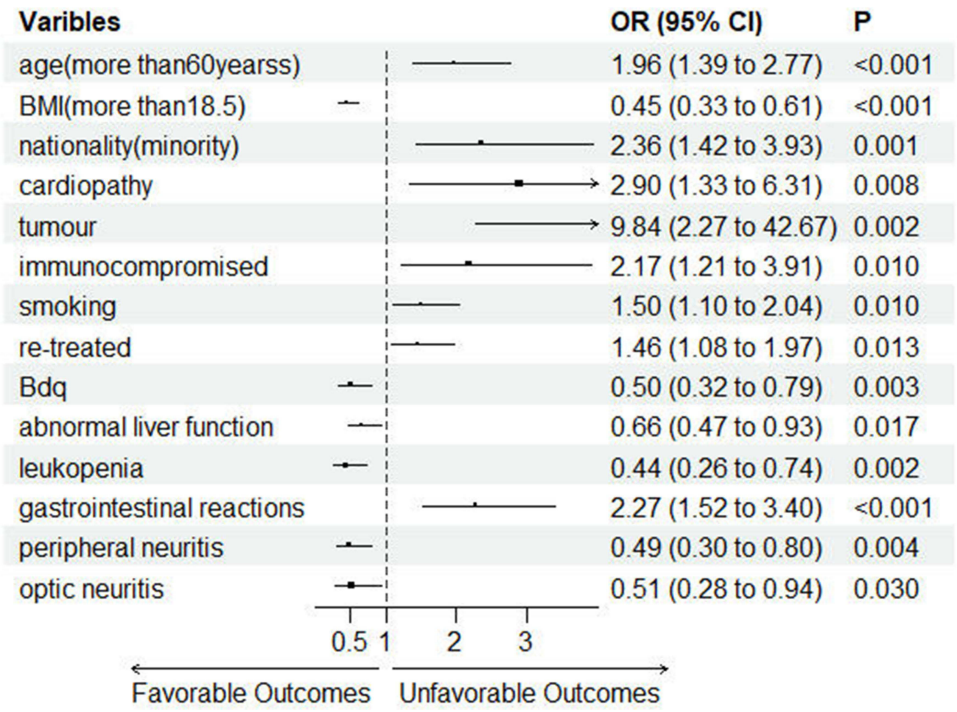

Figure 2 Factors associated with unfavorable outcomes among RR-TB patients in multiple analyses. Bdq: bedaquiline.

Table 4 Reports on the Success Rates of MDR/RR-TB Treatment in Different Times and Regions

Reference	Year of Publication	Country of Study	Number of MDR/RR-TB	Study Duration	Treatment Success Rate
Tola et al[3]	2021	Ethiopia	3395	2009–2019	75.7%
Ma et al[4]	2022	Xi'an, China.	446	2017–2019	67.0%
Lecai et al[7]	2023	Shenzhen, China	261	2010–2015	71.1%
Soeroto et al[8]	2022	West Java, Indonesia	315	2017–2020	64.5%
Chaves-Torres et al[15]	2021	Colombia	511	2013–2015	49.9%
Conradie et al[16]	2020	South Africa	109	2015–2017	90%
Wu et al[17]	2019	Chongqing, China.	618	2010–2017	59%
Li et al[18]	2020	Hangzhou, China	398	2011–2015	76%
Zhang et al[19]	2022	China	556	2018–2020	70%
Sharma et al[20]	2020	Delhi, India	2958	2009–2014	53.3%
Van et al[21]	2020	Ho Chi Minh City, Vietnam	2266	2011–2015	73.3%
Kuaban et al[22]	2021	Yaoundé, Cameroon	242	2013–2019	79.8%
Gualano et al[23]	2019	Italy	74	2008–2016	77%

bedaquiline in our study, and our study also found that regimens containing bedaquiline were associated with favorable treatment outcomes. In addition, the anti-TB drug group and treatment regimens were updated in 2019 according to WHO guidelines. These were possible factors contributing to the increased treatment success rate in the study.

In our study, the main reason of poor treatment outcomes was patient attrition (not evaluated or lost to follow-up), rather than treatment failure or death. Among the 284 RR-TB patients with poor treatment outcomes, 201 cases (70.8%, 201/284) were lost to follow-up or not evaluated during treatment. This finding was similar to a report from Brazil.[26] Therefore, it is necessary to take measures to address the issue of patient adherence to treatment and reduce attrition, such as improving the accessibility of public health facilities, diligently implementing DOTS (Directly Observed Treatment of Short Course), providing psychological support, and offering patient-centered TB services.

In our study, we identified several factors related to the outcomes of RR-TB treatment. Age played a significant role in this study. Compared to younger patients, those aged ≥60 years were more likely to exhibit poor treatment outcomes, which aligned with the findings of previous studies.[15,27] This might be attributed to the decline in physical and immune function, more complex comorbidities, impaired drug metabolism, and suboptimal response to anti-TB therapy observed in older patients.[28] Choosing a safe and effective anti-TB regimen was challenging. Therefore, it was important to manage these complications and to develop individualized treatment regimens for elderly patients.

It was well-known that TB patients beared a significant burden of undernutrition,[29] and TB-related malnutrition would reduce the treatment efficacy and worsen prognostic outcomes.[30] Our study indicated that in RR-TB patients, BMI <18.5 kg/m^2 was an independent factor for unfavorable treatment outcomes, similar to earlier researches.[5,20] Low BMI is an indicator of undernutrition, which adversely affects both adaptive and innate immunity.[31] Malnutrition impacts the function of mucosal barrier, allows translocation of bacterial, and weakens the immune response, particularly cell-mediated immunity, thereby lessens the patient's ability to remove pathogens once they get into the human body.[32] Actually, the relationship between nutrition and TB is reciprocal, since malnutrition can also be caused by the TB disease itself.[33] A low BMI may indicate untreated tuberculosis over a long period and a poor socioeconomic environment. Research has shown that optimized nutritional treatment has a beneficial impact on patient prognosis.[34] Therefore, nutritional screening and nutritional support for malnourished patients may be important measures to improve the treatment outcomes for RR-TB.

In our study, unfavorable treatment outcomes were also common among RR-TB patients who had received treatment previously, which were also observed in cohorts in Xi'an, China,[4] and South Africa.[6] This might be related to the higher drug resistance that had been developed over long-term use in the past. However, some studies had reported that there was only a high risk of adverse outcomes with the use of second-line anti-TB drugs previously and not related to the prior use of first-line anti-TB drugs.[21,27] Unfortunately, we did not collect and further analyze the relationship between previous anti-TB drugs and adverse therapeutic outcomes in this study. Another possible explanation was that TB

survivors usually experience some form of persistent respiratory impairment after the completion of TB treatment, which gradually increased with the frequency of pulmonary TB recurrence,[35,36] and respiratory impairment could increase the risk of death from respiratory.[35]

The results of this research also suggested that smoking was related to poor treatment outcomes. Smoking impacted both innate and adaptive immune responses and had sustained effects on adaptive immunity.[37] Smoking could lead to extensive changes in the lung microenvironment which could affect TB infection and disease progression and might enrich intracellular niches for MTB infection which promoted lung transmission.[38] Compared to non-smoking TB patients, smoking TB patients were more likely to experience severe clinical manifestations and have poor clinical and bacteriological responses to treatment.[39] The implementation of tobacco cessation activities could improve TB treatment outcomes and reduce the relapse rates.[40] In addition, we found that compared with the national minorities, Han individuals were more likely to achieve good treatment outcomes. However, the reason for this discrepancy remains unclear. This may be related to the uneven economic development and the imbalance in accessing medical resources.

Some studies had demonstrated that comorbidities were related to an increased relative risk of unfavorable treatment outcomes in MDR/RR-TB patients, such as those with HIV and diabetes.[22,26] However, in addition to HIV infection and diabetes, findings related to comorbidities were limited. In our study, we analyzed the influence of major comorbidities on treatment outcomes, containing diabetes, immunocompromise, viral hepatitis or carrier status, cardiopathy, and tumors. We found that RR-TB patients with cardiopathy, tumors, or an immunocompromised status (including AIDS/HIV, autoimmune system diseases, and others that experienced weakened immunity) were more likely to experience poor treatment outcomes. However, unlike previous findings, diabetes was not a statistically significant variable in this study, which was similar to the discoveries of another research in China.[19] This discrepancy might stem from differences in sample size, model variations, and the nature of the overall population. The primary reason why these comorbidities were associated with unfavorable treatment outcomes was likely due to the complex medication regimens administered daily for both the comorbid conditions and RR-TB, which might interact with each other and overlap in toxicity, often leading to poor patient compliance. Furthermore, these comorbidities were serious and could lead to adverse outcomes. A study in South Korea analyzed the factors related to non-TB-related death among TB patients, and found that certain comorbidities, containing cardiopathy, were independent risk factors for non-TB-related death.[41] Therefore, addressing comorbidities among patients with RR-TB is essential to ending the TB epidemic.

AEs were common during the RR-TB treatment. In our study, 67.7% of the patients with RR-TB suffered at least one adverse event, which was lower than the 91.6% reported in another study in China.[7] Whether AEs affected treatment outcomes of RR-TB remained controversial. Previous studies showed that experiencing AEs was associated with adverse outcomes, conversely, some other studies reported that experiencing AEs did not affect treatment outcomes, and even the more AEs experienced, the more likely it was to achieve a good outcome.[7,23,42] However, few studies had investigated the relationship between specific AEs and treatment outcomes. In our study, we examined the relationship between specific AEs and treatment outcomes. Interestingly, we discovered that not all AEs could affect treatment outcomes, and only gastrointestinal reactions were associated with unfavorable outcomes. This might be related to the suboptimal absorption of medication caused by gastrointestinal reactions and insufficient effective dosage due to vomiting. Intriguingly, we also found that individuals who experienced AEs during RR-TB treatment, including abnormal liver function, leukopenia, peripheral neuritis, and optic neuritis, were less likely to have poor treatment outcomes. Abnormal liver function was one of the common AEs during anti-tuberculosis treatment, reported in the range of 3.8%–37.9%,[43,44] consistent with our research. The reason why RR-TB patients experienced these AEs such as abnormal liver function were more likely to achieve favorable treatment outcomes was unclear. One possible explanation was the active and frequent monitoring of participants, which increased the chance of detecting AEs and provided timely and appropriate management of AEs in specialized hospitals. Thus, the serious consequences of AEs were avoided. Another plausible reason for this observation could be ascribed to the use of linezolid, which had been recommended as a core second-line medicine in the MDR/RR-TB regimen by WHO and attested to be related to higher treatment success and decreased mortality for MDR/RR-TB,[25] because AEs such as myelosuppression, peripheral neuropathy, and optic neuropathy were mainly caused by linezolid during RR-TB treatment. In our study, univariate analysis also showed that treatment regimens containing linezolid were related to favorable prognosis in RR-TB patients, but this was not demonstrated in multivariate analysis. This discrepancy might be caused by differences in the included variables, or related to the dosage of linezolid used, as

its toxicity was dose-dependent possibly.[45] However, this issue required further investigation. In general, our study results concluded that not all AEs could affect RR-TB treatment outcomes; as long as regular monitoring, timely detection, and appropriate treatment were provided, AEs were not a hindrance for RR-TB patients.

The study also had several limitations. Firstly, this study was retrospective, all of the original records and reports were not prospective designed for research purposes, so that some information that might potentially impact treatment outcomes, such as CD4 count, duration of anti-TB treatment, and anti-TB drugs, might be incomplete. Secondly, the representativeness of this study was relatively limited due to the insufficient number of hospitals and patients participating in the research. Additionally, the RR-TB patients included in this study were all from tertiary hospitals without incorporating patients followed up in other hospitals such as community hospitals and secondary hospitals. Therefore, large-scale multicenter prospective cohort studies based on comprehensive and multi-dimensional information should be carried out in the future.

Conclusion

The proportion of patients with RR-TB achieving favorable treatment outcomes in tertiary tuberculosis hospitals was relatively high in China. Age ≥60 years, national minority, smoking, combined with cardiopathy, tumors or immunocompromised status, re-treated TB, and experiencing gastrointestinal reactions were independent prognostic factors for unfavorable outcomes in RR-TB patients. Meanwhile, BMI ≥18.5 kg/m^2, regimens containing bedaquiline, and experiencing AEs including abnormal liver function, leukopenia, peripheral neuritis, and optic neuritis were associated with favorable outcomes. Hence, to improve treatment outcomes, it is necessary to conduct in-depth research on protective and risk factors related to prognosis. Smoking cessation, nutritional support, use of new anti-tuberculosis drugs, management of comorbidities, active surveillance and appropriate management of AEs, and the development of individualized treatment regimens may improve the success rate of treatment.

Data Sharing Statement

Data used to support the findings of this study will be made available by the corresponding author Guihui Wu.

Ethics Approval and Informed Consent

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Public Health Clinical Center of Chengdu as leading center (No.YJ-K2022-81-01). The present study was a retrospective study, the informed consent was waived signed, and all patient data were analyzed anonymously.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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