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ORIGINAL RESEARCH

Treatment Outcomes and Risk Factors of Multidrug-Resistant Tuberculosis Patients in Xi'an China, a Retrospective Cohort Study

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Background: Long-term regimens are widely used for multidrug-resistant tuberculosis (MDR-TB) in North-West China; however, risk factors associated with the treatment outcomes are not well known.

Methods: This was a retrospective cohort study of MDR-TB patients treated with longer regimen in Xi'an from 2017 to 2019. Risk factors associated with the treatment outcome were analyzed using multiple logistic regression.

Results: Of the 446 patients with MDR-TB included, 215 were cured, 84 completed treatment, 23 failed treatment, 108 were lost to follow-up, and 16 died. Unfavorable outcome risk factors were age >40 years (OR = 3.25, 95% CI = 2.12–4.98), male sex (OR = 2.53, 95% CI = 1.52–4.22), and re-treated tuberculosis (OR = 1.70, 95% CI = 1.11–2.61), whereas poor treatment outcome risk factors were age >40 years (OR = 5.51, 95% CI = 2.52–12.07), fluoroquinolones not used in the regimen (OR = 3.31, 95% CI = 1.45–7.51), and smear-positive (OR = 4.0, 95% CI = 1.47–10.8).

Conclusion: In Xi'an, MDR-TB treatments with long-term regimens had low success rates, and age, sex, and tuberculosis treatment history were risk factors of MDR-TB treatment outcomes.

Keywords: tuberculosis, multidrug-resistant, treatment outcomes, risk factors, China

Introduction

Tuberculosis has become a major epidemic infectious disease worldwide. Annually, 10 million new tuberculosis cases and 1.5 million deaths are reported.[1] The World Health Organization (WHO) proposed a strategy of End-TB to reduce incidence and mortality rates to 90% and 95% before 2035, respectively; however, several issues need to be addressed to achieve this goal, the most important being drug resistance.[2] Owing to the high cost, long duration, and associated adverse effects, the treatment of multi-drug-resistant tuberculosis (MDR-TB) is challenging and results in a wide-scale spread of tuberculosis.[3–5]

China has a high burden for MDR-TB, albeit with a low treatment success rate of 54% in 2018, which only reached the global average rate.[1] The MDR-TB incidence rate in North-West China is particularly high; however, the low economic conditions[6] may further reduce the treatment success rate. Studies evaluating MDR-TB treatment success rate and associated factors in North-West China are few. Although WHO has regrouped the MDR-TB therapeutic drugs in 2019, the short-term and oral regimens suggested for treating MDR-TB[7] cannot be effectively used in North-West China owing to the high resistance to fluoroquinolone and the high price of bedaquiline.[8] The long-term regimen is widely used to treat MDR-TB; thus, understanding the treatment outcomes of MDR-TB and associated factors will benefit treatment success. However, to the best of our knowledge, no study has assessed risk factors associated with MDR-TB treatment outcomes in North-West China.

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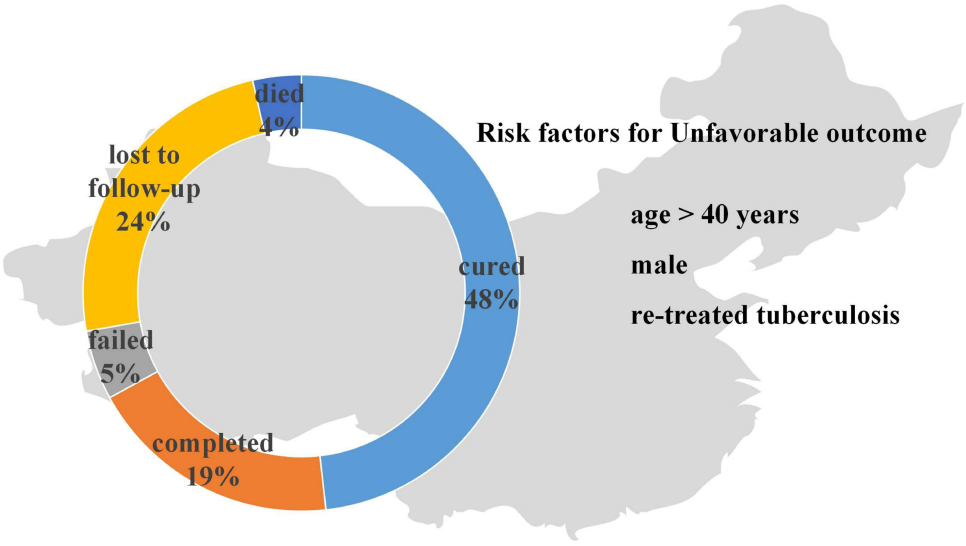
Graphical Abstract



In the present retrospective study, we examined patients with MDR-TB in Xi'an, North-West China. We used data from the diagnosis and treatment database of patients with MDR-TB established by us in Xi'an Chest Hospital since 2017. All patients were followed up every month according to the treatment plan developed by a therapy group (Table S1). DOTs were performed by professional health workers to ensure that each patient was being followed as required by the follow-up plan. In the present study, we aimed to examine treatment outcomes and risk factors for MDR-TB in Xi'an, China.

Methods

Study Population and Procedures

Xi'an is the capital and largest city of Shaanxi Province and is the largest city in North-West China. It has 12.9 million residents and is divided into 11 districts and two counties. The largest TB specialty hospital in this area, Xi'an Chest Hospital, is dedicated to treating drug-resistant TB patients. We included patients with MDR-TB between January 2017 and December 2019 in the study. The inclusion criteria were (1) *Mycobacterium tuberculosis* culture-positive or PCR positive in sputum or bronchoalveolar lavage fluid (BALF); (2) rifampin resistant, including mono-rifampin-resistant, MDR-TB, and XDR-TB confirmed via drug sensitivity test (DST) or GeneXpert RIF; and (3) presence of pneumonia confirmed by CT scan. Exclusion criteria were (1) patients with MDR-TB who had died before an MDR treatment started; (2) patients who received an incorrect regimen (enough core medication); (3) Patients co-infected with non-tuberculosis *Mycobacterium* sp. (nontuberculous mycobacteria may influence identifying of outcome); and (4) patients who received a short-term regimen.

Treatment regimens were prescribed according to treatment guidelines for drug-resistant tuberculosis, 2016 update guidelines,[9] and other factors like DST result, history of treatment, economics, and potential drug side effects were also concurrently considered by the therapy group. During the intensive phase, the regimen includes pyrazinamide and four core second-line TB medications, and in subsequent phases, the regimen includes four TB medications. The essential second-line TB medications were selected in the order of Group "ABCD",[9](Table S2). Treatment lasts 18–24 months, depending on clinical improvement and follow-up culture results.

EpiData was used for data management, and data were entered by personnel, and an attending doctor checked the entered data and outcome. All data were collected from the Electronic Medical Record System, including baseline

characteristics like sex, age, height, weight, marriage, address, co morbidities (diabetes and HIV), testing results (sputum smear test, DST, and cavity on CT), and treatment regimen.

Definitions

Mono-rifampin-resistant TB and MDR-TB were defined as tuberculosis resistant to rifampin and to both isoniazid and rifampin, respectively. Initial treatment tuberculosis was defined as tuberculosis that has never been treated with an anti-tuberculosis drug or has been treated for less than 1 month; re-treated tuberculosis includes tuberculosis that has been treated for >1 month, relapse, and failure to respond to initial treatment. Treatment outcomes were classified into six categories as follows:[10] (1) Outcome was classified as cured when patients completed the treatment regimen, and three consecutive negative cultures were collected separately at least 30 days after the intensive phase; (2) Treatment completed indicated patients who completed the treatment regimen lack three consecutive negative cultures and showed no evidence for failure; (3) Treatment failure occurred when treatment was discontinued, or regimen was changed by at least two drugs owing to adverse reactions, culture remained positive at the end of the intensive phase, or culture reverted in the continuation phase after conversion to negative, or acquired resistance to fluoroquinolones, or second-line injections was confirmed. (4) Outcome was classified as lost when treatment was interrupted for more than 2 months (5) Death was defined as death from any cause, including treatment. (6) Transferred indicated patients who were transferred to another hospital during treatment. Outcomes were reclassified as treatment success (cured and treatment completed), unfavorable outcome (treatment failure, loss to follow-up, and death), and poor treatment outcome (treatment failure and death).

Laboratory Cultures and Antibiotics Sensitivity Test

The BACTEC MGIT 960 culture system (Becton, Dickinson and Company, America) was used for Mycobacterium culture. For positive results, strain identification was undertaken by Mpb64 (Hangzhou Genesis Biodetecton & Biocontrol Ltd, China) monoclonal antibody. First-line drug sensitivity was tested with BACTEC MGIT 960 system, and second-line drug sensitivity was tested with the absolute concentration method. Drug concentrations for isoniazid, rifampin, levofloxacin, moxifloxacin, amikacin, Capreomycin were 0.1, 1.0, 2.0, 1.0, 30, 40 μg/mL.[11] The Ziehl-Neelsen acid-fast staining was used for the smear test.

Data Analysis

First, we used descriptive analyses to show the baseline characteristics, treatment regimen, and outcomes, calculating means with standard deviations (SD) for normally distributed continuous variables, medians with an interquartile range (IQR) for non-normally distributed continuous variables, and percentages for categorical variables. To investigate factors associated with unfavorable outcomes, univariate and multivariate logistic regression analyses were performed. Taking it into consideration that the loss of follow-up may lead to an uncertain result, poor treatment outcome (including failure and death) was carried out, and also univariate and multivariate logistic regression analyses were conducted to analyze factors associated with poor treatment outcome. Twenty-four cases missing data of Fluoroquinolones and second-line injections DST result was filled up according to resistant rate and characteristics of patients (age and treatment history). Statistical analysis was conducted by SPSS 23.0, and $P < 0.05$ indicated statistical significance.

Result

Figure 1 shows that 543 patients with MDR-TB conformed to the inclusion criteria from January 2017 to December 2019, and 446 cases were finally included in this study. Of the 446 cases, 215 were cured, 84 had their treatment completed, 23 showed treatment failure, 108 were lost to follow-up, and 16 died. Treatment success and unfavorable outcome rates were 67.0% (299/446) and 33.0% (147/446), respectively.

Furthermore, of the 446 patients (312 men and 134 women; age, 8–82 years, SD = 38.0 ± 14.9 years), 236 and 210 were diagnosed with initial treatment and re-treated tuberculosis. Additionally, 70 patients had diabetes and 2 had tested positive for HIV. Characteristics of 446 participants are shown in Table 1.

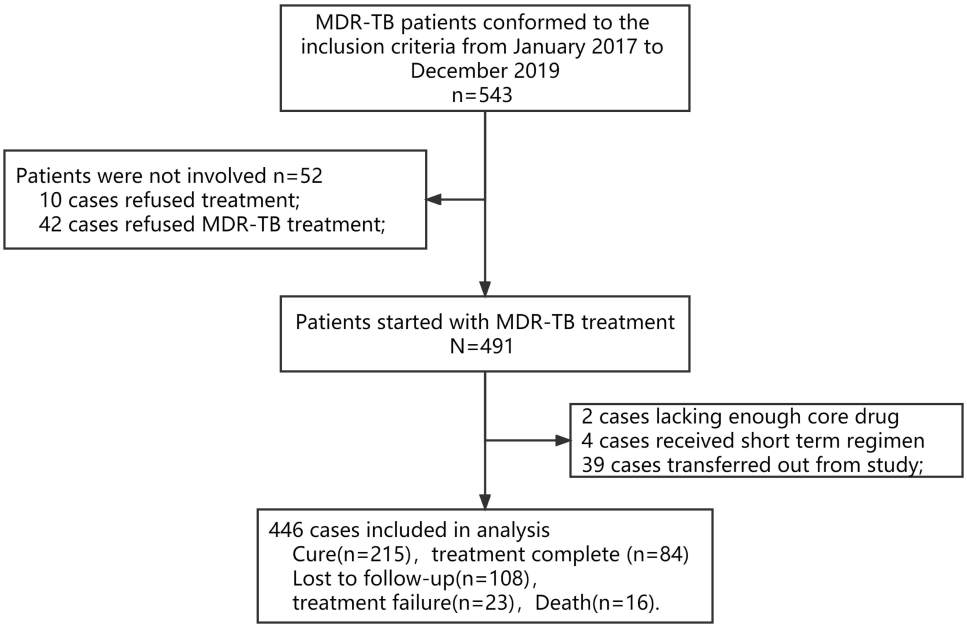


Figure 1 Flow chart study participants.
Abbreviation: MDR-TB, multidrug resistance tuberculosis.

Multiple Logistic Regression of Unfavorable and Poor Treatment Outcomes

As shown in Table 2, univariate analysis revealed that male sex, age >40 years, unmarried, retreat tuberculosis, diabetes, and smear-positive were risk factors for unfavorable outcomes; furthermore, all of these factors were included in the multiple logistic regression, which revealed that age >40 years was the highest factor increasing the unfavorable outcome with RR = 3.25. Men had a 2.53 fold higher risk of unfavorable outcomes than women and retreated tuberculosis had 1.70 fold higher odds of unfavorable outcomes than initial treatment tuberculosis.

When analyzing poor treatment outcomes, we treated lost follow-up outcomes as missing data and excluded them from the analysis. As illustrated in Table 3, univariate analysis revealed that factors such as male gender, age >40 years, unmarried status, smear positivity, Fluoroquinolones used in the regimen, clofazimine, and Prothionamide were associated with poor treatment outcomes. and factors such as sex, treatment history, and the use of Linezolid in the regimen were also included in the multiple logistic regression. It was discovered that age >40 years was still the highest factor increasing the poor treatment outcome, and Fluoroquinolones not used in the regimen had a 3.31 fold higher odds of poor treatment outcome, and smear-positive had a 4.0 fold higher odds of poor treatment outcome.

Discussion

In our study, the MDR-TB treatment success rate was 67.0% in Xi'an, China, higher than the rate of 54% reported by WHO.[1] The success rate is also higher than what was reported in other studies: 57% in Hunan China,[12] 53.3% in India,[13] 60% in Brazil,[14] and 61% in a meta-analysis.[15] Some studies have a higher success rate than our study: 69.6% in Zhejiang, China,[16] 75.6% in Hangzhou, China,[17] and 86% in Netherland.[18] The low success rate was related to the high rate of loss to follow-up compared with the studies mentioned above. The rate of lost follow-up in these studies was 4.8%–10.3%.[16–18] A meta-analysis of 14 observation studies showed an average loss to follow-up rate of 14%,[19] so any measurement that can reduce the loss to follow-up is needed to achieve a higher success rate.

Males had 2.53 times the odds of an unfavorable outcome as females in our study, age >40 years had 3.25 times the odds of an unfavorable outcome as age 40 years, and retreated tuberculosis had 1.70 times the odds of an unfavorable outcome as initial treatment tuberculosis. Age >40 years, non-use of Fluoroquinolones in the regimen, and smear positivity were all independent risk factors for poor treatment outcomes. Males are well known to be a risk factor for developing tuberculosis and MDR-TB; however, in this study, the male was an independent risk factor for an unfavorable outcome. The same result was found in other

Table 1 Characteristics of Patients with MDR-TB (n = 446)

Characteristics	Descriptive Analyses (n = 446), n (%)
Sex	
Male	312 (70.0)
Female	134 (30.0)
Age (years)	
≤20	39 (8.7)
20–40	227 (50.9)
>40	180 (40.4)
BMI (kg/m^2)	
<18.5	127 (28.5)
≥18.5	319 (71.5)
Marriage	
Married	292 (65.5)
Single	139 (31.2)
Divorced	13 (2.9)
Widowed	2 (0.4)
Address	
Xi'an	189 (42.4)
Other regions	257 (57.6)
Treatment history	
Initial treatment tuberculosis	236 (52.9)
Retreat tuberculosis	210 (47.1)
Diabetes mellitus	70 (15.7)
Sputum/BALF smear	
0	182 (40.8)
1+	106 (23.8)
2+	53 (11.9)
3+	49 (11.0)
4+	56 (12.5)
Drug sensitivity test	
Fluoroquinolones	
Not done	24 (5.4)
Sensitive	320 (71.7)
Resistant	102 (22.9)
Second-line injections	
Not done	24 (5.4)
Sensitive	407 (91.3)
Resistant	15 (3.3)
Cavity	161 (36.1)
Drugs used in the regimen	
Fluoroquinolones	373 (83.6)
Second-line injections	431 (96.6)
Linezolid	113 (25.3)
Clofazimine	36 (8.1)
Cycloserine	332 (74.4)
Ethambutol	181 (40.6)
Pyrazinamid	439 (98.4)
Prothionamide	406 (91.0)
P-aminosalicylate	30 (6.7)

studies.[13,20] However, in this study, the male was not a risk factor for poor treatment outcomes, so the reason why males had a high risk of unfavorable outcomes was due to a high loss to follow-up rate. To reduce loss to follow-up in male patients, measures should be taken to improve their knowledge of tuberculosis, as well as improve family and economic support.[21,22]

Table 2 Univariate and Multiple Analyses of Factors Associated with Unfavorable Outcome

Characteristics	Unfavorable Outcome (Failure, Died, Lost to Follow-Up) N = 446				
	n (%)	OR (95%CI)	P value	Adj OR (95%CI)	P value
Sex					
Female	25 (18.7)	Reference	<0.001	Reference	<0.001
Male	122 (39.1)	2.80 (1.71–4.57)		2.53 (1.52–4.22)	
Age (years)					
≤40	57 (21.4)	Reference	<0.001	Reference	<0.001
>40	90 (50.0)	3.67 (2.42–5.55)		3.25 (2.12–4.98)	
BMI (Kg/m^2)					
≤18.5	48 (37.8)	Reference	0.170	–	
>18.5	99 (31.0)	0.74 (0.48–1.14)		–	
Marriage					
Married	107 (36.6)	Reference	0.023	–	
Unmarried	40 (26.0)	0.61 (0.39–0.93)		–	
Address					
Xi'an	65 (34.4)	Reference	0.581	–	
Other regions	82 (31.9)	0.89 (0.60–1.33)		–	
Treatment history					
Initial treatment tuberculosis	60 (25.4)	Reference	<0.001	Reference	0.014
Retreat tuberculosis	87 (41.4)	2.08 (1.39–3.10)		1.70 (1.11–2.61)	
Diabetes					
No	112 (29.8)	Reference	0.001	–	
Yes	35 (50.0)	2.36 (1.40–3.96)		–	
Sputum or BALF smear					
Negative	45 (24.8)	Reference	0.002	–	
Positive	102 (38.6)	1.92 (1.26–2.91)		–	
Drug sensitivity test					
Fluoroquinolones					
Sensitive	107 (31.8)	Reference	0.382	–	
Resistant	40 (36.4)	1.22 (0.78–1.92)		–	
Second-line injections					
Sensitive	141 (32.8)	Reference	0.694	–	
Resistant	6 (37.5)	1.23 (0.44–3.45)		–	
Cavity					
Yes	57 (35.4)	Reference	0.409	–	
No	90 (31.6)	0.84 (0.56–1.27)		–	
Drugs used in the regimen					
Fluoroquinolones					
Yes	118 (31.6)	Reference	0.179	–	
NO	29 (39.7)	1.42 (0.85–2.39)		–	
Second-line injections					
Yes	141 (32.7)	Reference	0.555	–	
NO	6 (40.0)	1.37 (0.48–3.93)		–	
Linezolid					
Yes	39 (34.5)	Reference	0.684	–	
NO	108 (32.4)	0.91 (0.58–1.43)		–	
Clofazimine					
Yes	14 (38.9)	Reference	0.430	–	
NO	133 (32.4)	0.76 (0.37–1.52)		–	
Cycloserine					
Yes	104 (31.3)	Reference	0.210	–	
NO	43 (37.7)	1.33 (0.85–2.07)		–	

(*Continued*)

Table 2 (Continued).

Characteristics	Unfavorable Outcome (Failure, Died, Lost to Follow-Up) N = 446				
	n (%)	OR (95%CI)	P value	Adj OR (95%CI)	P value
Ethambutol					
Yes	57 (31.5)	Reference	0.586	–	
NO	90 (34.0)	1.12 (0.75–1.68)		–	
Pyrazinamide					
Yes	145 (33.0)	Reference	0.803	–	
NO	2 (28.6)	0.81 (0.16–4.23)		–	
Prothionamid					
Yes	135 (33.3)	Reference	0.676	–	
NO	12 (30.0)	0.86 (0.42–1.75)		–	
P-aminosalicylate					
Yes	14 (46.7)	Reference	0.098	–	
NO	133 (32.0)	0.54 (0.26–1.13)		–	

Table 3 Univariate and Multiple Analyses of Factors Associated with Poor Treatment Outcome

Characteristics	Poor Treatment Outcome (Failure, Died) N = 338				
	n (%)	OR (95%CI)	P value	Adj OR (95%CI)	P value
Sex					
Female	8 (6.8)	Reference	0.049	–	
Male	31 (14.0)	2.22 (0.99–5.01)		–	
Age (years)					
≤40	11 (5.0)	Reference	<0.001	Reference	<0.001
>40	28 (23.7)	5.91 (2.82–12.39)		5.51 (2.52–12.07)	
BMI (Kg/m^2)					
≤18.5	14 (15.1)	Reference	0.213	–	
>18.5	25 (10.2)	0.64 (0.32–1.30)		–	
Marriage					
Married	33 (15.1)	Reference	0.005	–	
Unmarried	6 (5.0)	0.30 (0.12–0.73)		–	
Address					
Xi'an	17 (12.1)	Reference	0.801	–	
Other regions	22 (11.2)	0.92 (0.47–1.80)		–	
Treatment history					
Initial treatment tuberculosis	17 (8.8)	Reference	0.070	–	
Retreat tuberculosis	22 (15.2)	1.85 (0.94–3.63)		–	
Diabetes					
No	7 (16.7)	Reference	0.266	–	
Yes	32 (10.8)	1.65 (0.68–4.02)		–	
Sputum or BALF smear					
Negative	5 (3.5)	Reference	<0.001	Reference	0.007
Positive	34 (17.3)	5.75 (2.19–15.11)		4.0 (1.47–10.8)	
Drug sensitivity test					
Fluoroquinolones					
Sensitive	27 (10.5)	Reference	0.313	–	
Resistant	12 (14.6)	1.45 (0.70–3.02)		–	
Second-line injections					
Sensitive	38 (11.6)	Reference	0.796	–	
Resistant	1 (9.1)	0.76 (0.10–6.11)		–	

(*Continued*)

Table 3 (Continued).

Characteristics	Poor Treatment Outcome (Failure, Died) N = 338				
	n (%)	OR (95%CI)	P value	Adj OR (95%CI)	P value
Cavity					
Yes	15 (12.6)	Reference	0.651	–	
No	24 (11.0)	0.85 (0.43–1.70)		–	
Drugs used in the regimen					
Fluoroquinolones					
Yes	26 (9.3)	Reference	0.003	Reference	0.004
NO	13 (22.8)	2.90 (1.38–6.07)		3.31 (1.45–7.51)	
Second-line injections					
Yes	37 (11.3)	Reference	0.483	–	
NO	2 (18.2)	1.74 (0.36–8.37)		–	
Linezolid					
Yes	15 (16.9)	Reference	0.067	-	
NO	24 (9.6)	0.53 (0.26–1.06)		-	
Clofazimine					
Yes	8 (26.7)	Reference	0.007	–	
NO	31 (10.1)	0.31 (0.13–0.75)		–	
Cycloserine					
Yes	27 (10.6)	Reference	0.338	–	
NO	12 (14.5)	1.43 (0.69–2.96)		–	
Ethambutol					
Yes	17 (12.1)	Reference	0.801	–	
NO	22 (11.2)	0.92 (0.47–1.80)		–	
Pyrazinamide					
Yes	39 (11.7)	Reference	0.416	–	
NO	0 (0)	0.88 (0.85–0.92)		–	
Prothionamid					
Yes	31 (10.3)	Reference	0.034	–	
NO	8 (22.2)	2.50 (1.05–5.96)		–	
P-aminosalicylate					
Yes	5 (23.8)	Reference	0.069	–	
NO	34 (10.7)	0.38 (0.13–1.12)		–	

It was reported in many studies that aging was a risk factor for an unfavorable outcome of MDR-TB treatment;[13,16,21,23] it is due to older people may combine other diseases and suffer more from drug side effects or death.[24] In this study, 40% of the patients were older than 40 years old, indicating that a considerable number of patients are at risk of unfavorable outcomes. It is important to deal with complications and formulate individualized treatments for older patients. In this study, retreatment tuberculosis was a risk factor for an unfavorable outcome; it was also reported in previous studies.[14,16,23] When it came to poor treatment outcomes, retreatment tuberculosis was not a risk factor anymore. Studies had shown that retreated patients with a history of drug-resistant tuberculosis treatment had a higher risk of poor treatment outcomes,[14,16,25] But this study did not further analyze the previous treatment, which may be the reason for the low odds ratio of this study and the failure to conclude when analyzing the influencing factors of poor treatment outcomes. Therefore, treatment history and drugs ever used should be acquired before starting treatment. Smear-positive was associated with poor treatment outcomes; high-grade smear and cavity were found to be risk factors for poor treatment outcomes.[16,23] Smear-positive patients may be more infective and serious; hence, the regimen of these patients may be strengthened during the intensive phase.

The benefit of our study was that Fluoroquinolones and second-line injections produced DST results in 95% of patients. Second-line injection resistance was only 3.3%, and 96.6% of patients used second-line injection (including Am and Cm) during the intensive period. We found no unfavorable outcomes associated with the use of second-line injection. Therefore, second-line injections can still be used when bedaquiline cannot be used. Fluoroquinolones are important anti-tuberculosis drugs; we found that non-use of Fluoroquinolones was a risk factor for poor treatment outcomes. Although, like other studies, the Fluoroquinolones resistance rate in this study was as high as 22.9%,[8,26] 86% of patients still used Fluoroquinolones. Previous research has found that Fluoroquinolones can significantly improve treatment success rates and that levofloxacin and moxifloxacin can still improve treatment success rates in ofloxacin-resistant patients.[15] As a result, unless resistance is confirmed, Fluoroquinolones should be used in the anti-tuberculosis strategy.

Pyrazinamide was another commonly used drug in our study, with 98% of patients taking it. We had not tested the sensitivity of pyrazinamide because of a lack of an accurate test method; however, studies had shown that MDR-TB had a high pyrazinamide resistance rate of 30–62% in China.[27,28] Another study found that even though 31.5% of patients were resistant to pyrazinamide, the treatment outcome was unaffected.[29] However, some studies have shown that when pyrazinamide is sensitive, it can help with early smear conversion and improve treatment success rates.[30,31] As a result, if enough core drugs from Groups A and B were not selected, pyrazinamide can be used.

There were also some limitations in our study. Some studies showed that smoking and drinking were risk factors for unfavorable outcomes,[21,22,32] but we did not involve these factors. China is a country with a high burden of tuberculosis and HIV, but there were only 2 HIV-positive cases in our study. It is mainly because HIV co-infected patients were admitted to another hospital. The co-infection of HIV may be underestimated. Regimens used in our study were long-term regimens, and injections were widely used, it disagree with the new recommendation of WHO. Moreover, data used in this study were clinical records, so some socioeconomic variables could not be obtained.

Despite some limitations, it was the first study on MDR-TB treatment outcomes in Xi'an, China, to our knowledge. Our research found that aging, male gender, and retreat tuberculosis is all independent risk factors for poor outcomes. In our study, the rate of loss to follow-up was high; therefore, steps should be taken to prevent patients from becoming lost. Fluoroquinolones and second-line injections, as well as pyrazinamide, can still be used in long-term regimens.

Conclusion

Patients with MDR-TB had a low treatment success rate in Xi'an, China, and age, sex, tuberculosis treatment history can be used as risk factors for multidrug-resistant tuberculosis treatment outcomes.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was reviewed and approved by the ethics committees of Xi'an Chest Hospital in April 2020 (NO. S2020-0020), which granted permission for the use of the identified data for the study. The study was in Accordance with Declaration of Helsinki. To protect patient confidentiality, only one investigator (ELM) had access to identified and de-identified codes; she prepared the anonymous database used herein.

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Author Contributions

All authors made a significant contribution to the work reported. All authors contributed to conception, study design; acquisition of data, analysis and interpretation of data; took part in, revising or critically reviewing the article; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. The corresponding author ensured all listed authors meet authorship.

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Disclosure

The authors declare that they have no competing interests.

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