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Predictors of early and interim culture un-conversion in multidrug-resistant/rifampicin-resistant tuberculosis: a retrospective multi-center cohort study in China

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Abstract

Background We aimed to evaluate the predictors for early and interim culture conversion within 2 months and 6 months of treatment in multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) patients in China.

Methods This study included adult MDR/RR-TB patients with a positive baseline sputum culture from 8 institutions located in different cities in China from May 2018 to January 2022. We mainly used logistic regression model to derive possible predictors of early and interim culture conversion.

Results A total of 813 patients were enrolled and 28.5% of them received multidrug-resistant treatment regimens containing bedaquiline. Of these, 362 (44.5%) patients experienced culture conversion within 2 months of treatment, and 649 (79.8%) within 6 months. The results of the multivariable logistic regression analysis revealed that acid-fast bacilli smear positive (adjusted odds ratio [aOR] = 1.637, 95% confidence interval [CI] = 1.197–2.238), cavities (aOR = 1.539, 95% CI = 1.132–2.092), bilateral disease (aOR = 1.638, 95% CI = 1.183–2.269), and viral hepatitis (aOR = 2.585, 95% CI = 1.189–5.622) were identified as risk factors for early culture un-conversion within 2 months of treatment. Additionally, smoking history (aOR = 2.197, 95% CI = 1.475–3.273), previous treatment for tuberculosis (aOR = 1.909, 95% CI = 1.282–2.844), bilateral disease (aOR = 2.201, 95% CI = 1.369–3.537), viral hepatitis (aOR = 2.329, 95% CI = 1.094–4.962) were identified as risk factors for interim culture un-conversion within 6 months of treatment, while patients with regimen containing bedaquiline (aOR = 0.310, 95% CI = 0.191–0.502) was a protective factor.

Conclusions A history of smoking, a baseline sputum AFB smear positive, lung cavities, bilateral disease, previous anti-tuberculosis treatment, or a comorbidity of viral hepatitis can be used as the predictors for early and interim culture un-conversion in MDR/RR-TB patients, while bedaquiline was a protective factor .

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Keywords Drug-resistant tuberculosis, Bedaquiline, Culture conversion, Risk factor, China

Introduction

In 2022, tuberculosis (TB) was the world's second leading cause of death from a single infectious agent, after coronavirus disease (COVID-19). In 2022, there were approximately 10.6 million cases developed TB worldwide, leading to an estimated 1.3 million deaths [1]. Globally, about 410 thousand individuals were diagnosed with multidrug-resistant/ rifampin-resistant tuberculosis (MDR/RR-TB) [1]. The treatment success rate for MDR/RR-TB cases was only 63% [1]. China specifically accounted for 7.1% of the global TB burden with 12.4 thousand confirmed cases of MDR/RR-TB and a treatment success rate of 51% [1]. MDR/RR-TB continues to be a significant public health concern in China. Notably, due to the impact of COVID-19, China was among the ten countries responsible for approximately 70% of the global gap between the estimated number of MDR/RR-TB cases and the number of individuals receiving treatment in 2022 [1]. Therefore, MDR/RR-TB remains a catastrophic issue for patients, society, and the health system, particularly in high TB burden countries like China. It is crucial to increase treatment success rate for MDR/RR-TB in order to optimize TB prevention and control in China.

Previous studies showed that achieving culture conversion within the initial 2 or 6 months of treatment were associated with treatment success in MDR-TB patients [2–7], and the overall association was substantially greater at 6 months [2, 7]. Despite the importance of sputum culture conversion in the management of MDR/RR-TB, no sufficient studies of MDR/RR-TB have reported on predictors of early and interim sputum culture un-conversion in China.

Several studies have investigated possible independent risk factors associated with culture conversion or treatment outcomes. However, there is limited research on predictors of early and interim culture conversion in MDR-TB patients. In a multicountry study, it was found that MDR/RR-TB patients with HIV, cavitary disease, and highly positive sputum smear had a lower probability of conversion within 6 months of treatment [8]. Male, cavitary disease, uncontrolled diabetes mellitus (DM), resistance to ofloxacin were found to be significant risk factors for 2-month sputum culture un-conversion [9–12] (Only 3.8 ~ 5.9% [10–12] of the patients were MDR-TB). The majority of studies have focused on identifying risk factors that influence the conversion time or rates of the entire treatment, as well as poor outcomes in patients with MDR-TB. Previous TB treatment, a baseline positive smear, bilateral disease, cavitation, resistance to ofloxacin or fluoroquinolones (FQs), XDR-TB, low body mass index (BMI), smoking, alcoholism or alcohol use, and surgical resection, were found to be associated with a longer sputum culture conversion time, lower conversion rate, or poor treatment outcome in patients with MDR/RR/XDR-TB [3, 7, 13–21]. On the contrary, a treatment regimen containing bedaquiline (BDQ) could achieve early culture conversion [22] or increase conversion rate [23–25], and a systematic review suggested that the BDQ-containing regimen reduced the rate of culture-positive compared to the no-BDQ-containing regimens [26]. These risk factors could also potentially influence early and interim culture conversion in MDR/RR-TB patients.

The ability to achieve culture conversion in a short term is crucial for reducing transmission of MDR/RR-TB and increasing treatment success. It is also beneficial to explore the factors that are effective in shortening the treatment duration of MDR/RR-TB patients. Therefore, the objective of this study was to evaluate the predictors linked to early and interim culture un-conversion among multicenters of MDR/RR-TB patients in China.

Methods

Study design and participants

This study was a multi-center retrospective cohort study. The participants for this study were recruited from 8 institutions located in different cities in China, namely Chengdu, Beijing, Wuhan, Suzhou, Anqing, Nanning, Chongqing and Harbin. The study included adults (≥18 years old) who were diagnosed with multidrug-resistant/ rifampicin-resistant/pre-extensively-drug resistant tuberculosis (MDR/RR/pre-XDR-TB) based on the guidelines of the World Health Organization (WHO) and China [27, 28]. The patients enrolled received the initial treatment regimen for MDR/RR/pre-XDR-TB between May 2018 and January 2022. Patients with a negative baseline sputum culture and unknown culture status were excluded from the study.

Ethical approval and consent to participate

This was an observational analysis of de-identified medical records. Individual informed consent was not obtained. Given that the medical information of inpatients was recorded anonymously by case history and would not bring any risk to the participants, the ethics committee of the Chengdu Public Health Clinical Center approved this study (YJ-K2022-81-01). The anonymity and confidentiality of the participants were guaranteed.

Early and interim culture conversion outcome

The main outcome of this study was sputum culture conversion within the initial 6 months of treatment, which was a commonly used interim endpoint in studies investigating MDR-TB treatment [22, 29–31]. It was also closely related to the final treatment outcomes [2, 7]. We also observed the secondary outcome of sputum culture conversion within the first 2 months of treatment, which was important for early prevention and control measures of tuberculosis, and it was also correlated with final treatment outcomes [2–7].

Definitions of culture conversion

Culture conversion was defined as two or more consecutive negative cultures at least 30 days apart in a patient with a positive initial culture.

Definition of drug resistance

According to WHO [27], MDR/RR-TB referred to multidrug-resistant tuberculosis (resistant to both rifampicin and isoniazid) or rifampicin-resistant tuberculosis. Pre-XDR-TB referred to tuberculosis resistant to rifampicin (and possibly isoniazid) and at least one fluoroquinolone. Resistance categories were determined based on the results of drug susceptibility testing, using either molecular or genotypic techniques to identify mutations that confer resistance, or using phenotypic methods to assess susceptibility to anti-tuberculosis drugs.

Data collection

Epidemiological and clinical data, laboratory tests, baseline anti-tuberculosis treatment regimens, adverse effects, and sputum culture conversion status (culture conversion was described in the *Definitions of culture conversion*) at 2, 6, and 24 months of treatment, were collected from the medical records of eight institutions. Two physicians, QC and XZT, reviewed all the data, and any discrepancies in interpretation between the two primary reviewers were assessed by a third researcher, LPZ.

Laboratory examination

Baseline HIV infection, diabetes mellitus (DM), viral hepatitis (including hepatitis B and C), and anemia (defined as hemoglobin levels below 130 g/L in adult males and 120 g/L in adult females) were assessed through laboratory testing. Sputa samples were collected and analyzed for GeneXpert MTB/rifampin (RIF) (Xpert) as well as examined under smear microscopy for AFB. The BACTEC MGIT960 system (Becton Dickinson & Co., Franklin Lakes, NJ, USA) was used for MTB culture. All patients enrolled were tested for drug susceptibility. Molecular (Xpert) or genotypic techniques (targeted next-generation sequencing) were used to identify mutations with drug resistance, or phenotypic methods were used to assess susceptibility to anti-tuberculosis drugs.

Anti-tuberculosis treatment

The anti-tuberculosis treatment regimens in this study were primarily individualized and managed by qualified physicians, in accordance with the guidelines of WHO [32–34] and China [28]. The treatment regimens were classified into two categories for this study: regimen containing BDQ and regimen without BDQ. Patients who received anti-tuberculosis regimen containing BDQ in this study were administered 400 mg of BDQ once daily for the initial 2 weeks, followed by 200 mg three times a week for the subsequent 22 weeks. The duration of BDQ use should be at least 24 weeks.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation, and other variables were expressed as medians (Q1, Q3). Categorical variables were expressed as n (%). Predictors of early and interim culture conversion were selected based on the baseline epidemiological data, clinical characteristics, laboratory testing, and treatment regimen. We compared characteristics using Chi-square test, T/T' test and Mann-Whitney U test. An initial univariate logistic regression was performed. Multivariable logistic regression was performed by including variables that were significant at $P<0.05$ in univariable logistic regression. Each multivariate model included relevant variables from the univariable logistic regressions pertaining to culture unconversion within 2 months and 6 months of treatment in MDR/RR-TB patients. Collinearity analysis estimated the correlation between predictor variables.

In the secondary analyses, patients were categorized into subgroups based on gender, age, BMI, smoking, alcohol use, treatment history for TB, comorbidity of DM, anemia, viral hepatitis, sputum smear, the presence of cavities on chest radiograph, pulmonary lesion area (bilateral or unilateral), drug-resistant pattern, and baseline treatment regimen (regimen with or without BDQ). The Kaplan-Meier curve was used to represent the time of culture conversion within 24 months for each subgroup. Differences in each subgroup was analyzed using the log-rank test.

Statistically significant results were considered for two-sided p values less than 0.05. All statistical analyzes were performed using SPSS version 24.0 (SPSS Inc, Chicago, IL, USA).

Results

Overview

A total of 1416 patients with RR/MDR/Pre-XDR-TB were screened and 813 patients were enrolled in this study (Fig. 1). The 813 included patients were treated at 8 different institutions in various regions of China: the East (Suzhou and Anqing: 106 patients, 13.0%), West (Chengdu and Chongqing: 332 patients, 40.8%), South (Nanning: 33 patients, 4.1%), North (Beijing and Harbin: 144 patients, 17.7%), and Central region (Wuhan: 198 patients, 24.4%). The 813 patients received individual multidrug regimens including BDQ-containing regimens (28.5%) and regimens without BDQ(71.5%). Among the patients, 455 (55.9%) had MDR-TB, 125 (15.3%) had RR-TB, and 233 (28.7%) had Pre-XDR TB. The median age of the patients was 37.00 (27.00, 52.00) years, with 67.5% of them being male. The median BMI was 20.31 (18.17, 22.28) kg/m^2, and 28.4% of the patients were underweight. Only one patient had acquired immune deficiency syndrome (AIDS) with a normal CD_4^+ T cell count. The most common comorbidity was anemia (29.2%), followed by DM (15.1%). Approximately 33.5% of the patients had history of alcohol use, and 21.3% had a history of smoking. More than half of the patients (59.7%) had been previously treated for TB. Out of the total patients, 524 (64.5%) had a positive AFB of sputum smears. Chest images showed that 514 patients (63.2%) had cavities and 589 patients (71.0%)

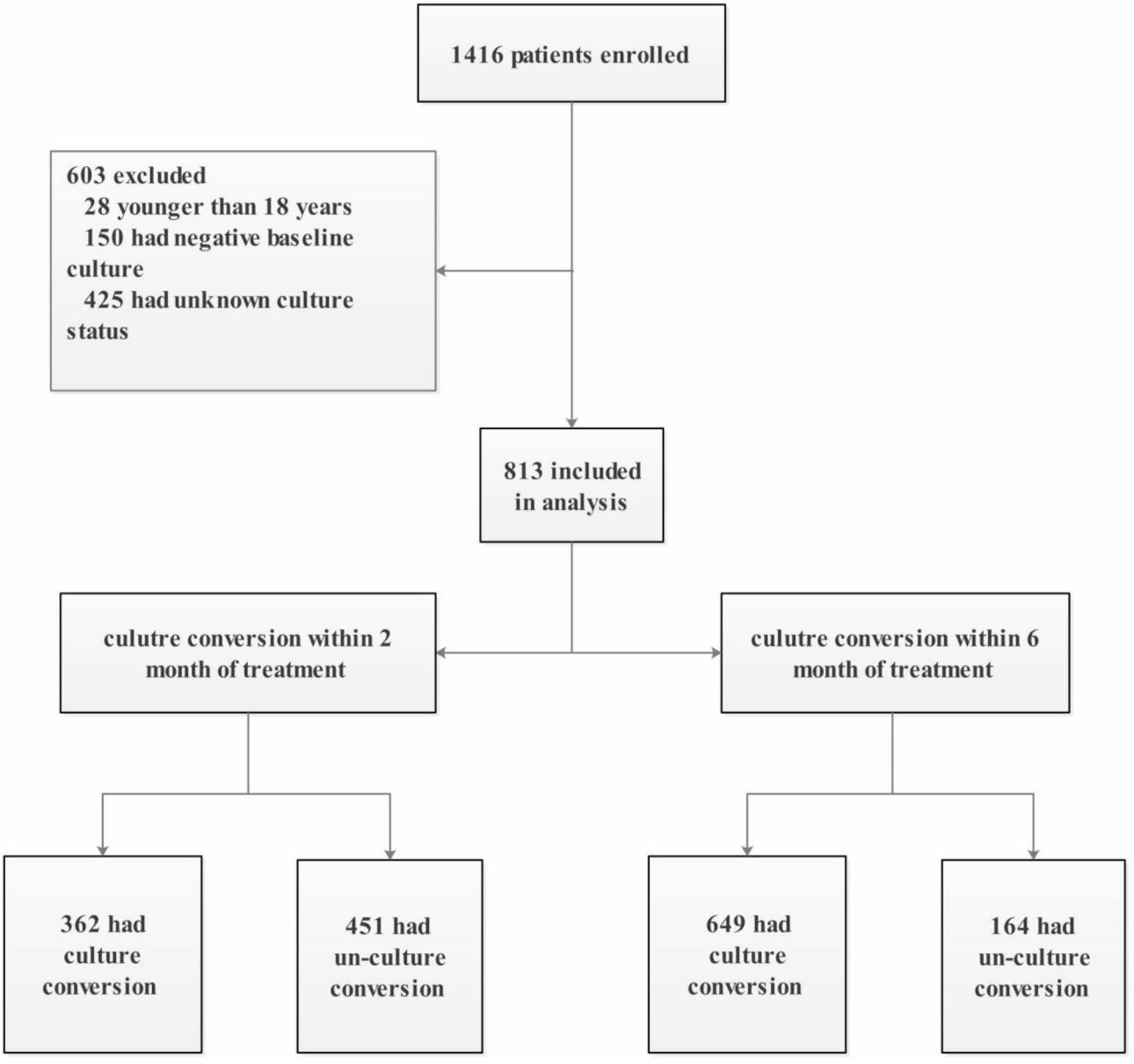

Fig. 1 Overview of the analysis cohort

had bilateral disease. The most common clinical symptoms reported were cough (86.7%) and sputum (76.8%) (Table 1). Besides, only three patients received surgical therapy before 6 months of treatment.

Early and interim sputum culture conversion

Among the 813 patients, 362 patients (44.5%) achieved sputum culture conversion within 2 months of treatment, while 649 patients (79.8%) achieved conversion within 6 months. Median time to culture conversion among those who converted within 6 months was 2.00

Table 1 Predictors for early and interim sputum culture conversion in MDR/RR-TB patients

Predictor	overall	Sputum culture conversion within 2 months of treatment			Sputum culture conversion within 6 months of treatment		
		Yes	No	*P* value	Yes	No	*P* value
Patients	813	362(44.5%)	451(55.5%)	-	649(79.8%)	164(20.2%)	-
Socio-demographic characteristics							
Male	549(67.5%)	236(65.2%)	313(69.4%)	0.203	420(64.7%)	129(78.7%)	0.001
Age, median (Q1, Q3) (year)	37.00(27.00, 52.00)	36.00(27.00, 52.00)	38.00(27.00, 52.00)	0.564	36.00(27.00, 51.00)	43.50(28.00, 56.75)	0.003
>60 years	102(12.5%)	47(13.0%)	55(12.2%)	0.736	72(11.1%)	30(18.3%)	0.013
BMI (Q1, Q3) (kg/m^2)*	20.31(18.17, 22.28)	20.53(18.52, 22.31)	20.05(17.96, 22.28)	0.057	20.51(18.36, 22.48)	19.75(17.44, 21.45)	0.001
<18.5 kg/m^2 (underweight)	228(28.4%)	88(24.6%)	140(31.5%)	0.030	167(26.0%)	61(38.1%)	0.002
Rural	393(48.3%)	169(46.7%)	224(49.7%)	0.398	316(48.7%)	77(47.0%)	0.690
Farmer	139(17.1%)	60(16.6%)	79(17.5%)	0.723	119(18.3%)	20(12.2%)	0.062
MDR/RR-TB risk facters							
Ever smoker	173(21.3%)	62(17.1%)	111(24.6%)	0.010	117(18.0%)	56(34.1%)	<0.001
Alcohol history	272(33.5%)	106(29.3%)	166(36.8%)	0.024	196(30.2%)	76(46.3%)	<0.001
Previously treated for TB	485(59.7%)	195(53.9%)	290(64.3%)	0.003	367(56.5%)	118(72.0%)	<0.001
TB-related characteristics							
AFB smear positive	524(64.5%)	201(55.5%)	323(71.6%)	<0.001	408(62.9%)	116(70.7%)	0.060
Cavitary disease	514(63.2%)	200(55.2%)	314(69.6%)	<0.001	396(61.0%)	118(72.0%)	0.009
Bilateral disease	589(72.4%)	236(65.2%)	353(78.3%)	<0.001	450(69.3%)	139(84.8%)	<0.001
Comorbidities							
Anemia	237(29.2%)	90(24.9%)	147(32.6%)	0.016	180(27.7%)	57(34.8%)	0.077
DM	123(15.1%)	45(12.4%)	78(17.3%)	0.054	94(14.5%)	29(17.7%)	0.307
Hypertension	41(5.0%)	14(3.9%)	27(6.0%)	0.170	29(4.5%)	12(7.3%)	0.136
Viral hepatitis	39(4.8%)	10(2.8%)	29(6.4%)	0.015	26(4.0%)	13(7.9%)	0.036
Clinical symptoms							
Cough	705(86.7%)	301(83.1%)	404(89.6%)	0.007	557(85.8%)	148(90.2%)	0.136
Sputum	624(76.8%)	258(71.3%)	366(81.2%)	0.001	489(75.3%)	135(82.3%)	0.059
Fever	217(26.7%)	97(26.8%)	120(26.8%)	0.952	183(28.2%)	34(20.7%)	0.053
Hemoptysis	184(22.6%)	84(23.2%)	100(22.2%)	0.727	147(22.7%)	37(22.6%)	0.981
Night sweat	167(20.5%)	59(16.3%)	108(23.9%)	0.007	120(18.5%)	47(28.7%)	0.004
Fatigue	219(26.9%)	97(26.8%)	122(27.1%)	0.935	170(26.2%)	49(29.9%)	0.342
Weight loss	195(24.0%)	54(14.9%)	141(31.3%)	<0.001	132(20.3%)	63(38.4%)	<0.001
Chest pain	157(19.3%)	53(14.6%)	104(23.1%)	0.003	102(15.7%)	55(33.5%)	<0.001
Dyspnea	187(23.0%)	53(14.6%)	134(29.7%)	<0.001	123(19.0%)	64(39.0%)	<0.001
DST pattern				0.094			0.053
MDR/RR-TB	580(71.3%)	269(74.3%)	311(69.0%)		473(72.9%)	107(65.2%)	
pre-XDR-TB	233(28.7%)	93(25.7%)	140(31.0%)		176(27.1%)	57(34.8%)	
Baseline treatment regimen				0.174			<0.001
Regimen containing BDQ	232(28.5%)	112(30.9%)	120(26.6%)		206(31.7%)	26(15.9%)	
Regimen without BDQ	581(71.5%)	250(69.1%)	331(73.4%)		443(68.3%)	138(84.1%)	

Abbreviations: AFB, acid-fast bacilli; BDQ, bedaquiline; BMI, body mass index; DM, diabetes mellitus; DST, drug susceptibility test; MDR/RR-TB, multidrug-resistant/rifampicin-resistant tuberculosis; pre-XDR-TB, pre-extensive drug-resistant tuberculosis

* Eleven cases had no BMI data, **Continuous calibration of chi-square test

(1.50, 3.00) month. In the group of patients who had a positive sputum culture within 2 months of treatment, we observed significantly higher proportions of certain factors compared to the culture conversion group. These factors included BMI<18.5 kg/m^2, smoking, alcohol use, previous treatment for TB, AFB smear positive, presence of cavities, bilateral disease, anemia, viral hepatitis, cough, sputum, night sweat, weight loss, chest pain, and dyspnea (all P<0.05). Furthermore, in the group of patients who had sputum culture un-conversion within 6 months of treatment, we also observed significant differences in the proportions of certain factors compared to the culture conversion group. Factors that had higher proportions in the un-conversion group included male, age, BMI<18.5 kg/m^2, smoking, alcohol use, previous treatment for TB, presence of cavities, bilateral disease, viral hepatitis, night sweats, weight loss, chest pain, and dyspnea. On the other hand, the culture conversion group had a higher proportion of patients with a baseline regimen including BDQ compared to the un-conversion group (all P<0.05) (Table 1).

Predictors of early and interim culture un-conversion

The results of the multivariable logistic regression analysis revealed several predictors for early and interim culture un-conversion during tuberculosis treatment. AFB smear positive (adjusted odds ratio [aOR]=1.637, 95% confidence interval [CI]=1.197–2.238), cavities (aOR=1.539, 95% CI=1.132–2.092), bilateral disease (aOR=1.638, 95% CI=1.183–2.269), and viral hepatitis (aOR=2.585, 95% CI=1.189–5.622) were identified as independent risk factors for early culture un-conversion within 2 months of treatment (Table 2). Additionally, smoking (aOR=2.197, 95% CI=1.475–3.273), previous treatment for TB (aOR=1.909, 95% CI=1.282–2.844), bilateral disease (aOR=2.201, 95% CI=1.369–3.537), and viral hepatitis (aOR=2.329, 95% CI=1.094–4.962) were identified as independent risk factors for interim culture un-conversion within 6 months of treatment, while patients with regimen containing BDQ (aOR=0.310, 95% CI=0.191–0.502) was protective factor (Table 3).

Kaplan-Meier estimates of culture conversion within 24 months among subgroups

In this study, 737 out of 813 patients (90.6%) had culture conversion within 24 months of treatment. The Kaplan-Meier survival curve demonstrated that several factors were associated with culture conversion time within 24 months of treatment among subgroups. These factors included gender, age, BMI, smoking, alcohol use, previous treatment for TB, DM, anemia, baseline AFB smear, cavities, bilateral disease, and regimen with BDQ (all P<0.05) (Fig. 2).

Discussion

Faster sputum cultures could simplify patient care and increase cost-effectiveness. Shortening the processing time of sputum cultures is important from a public health perspective, as MDR/RR-TB patients with positive sputum cultures are contagious and may spread the disease to contacts. It is crucial to investigate the factors that predict early and interim sputum culture un-conversion in a high TB burden country like China.

This study was conducted in eight institutions located in various regions of China, including the East, West, South, North, and Central region. This geographical diversity was beneficial in minimizing any imbalances in demographic characteristics. The study conducted a multivariable analysis to collect common risk factors associated with culture conversion and treatment outcomes

Table 2 Factors associated with risk of culture un-conversion within 2 months of treatment in MDR/RR-TB patients

Predictor	Sputum culture un-conversion within 2 months of univariate analysis		Sputum culture un-conversion within 2 months of multivariate analysis	
	Odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Male	1.211(0.902–1.626)	0.203	-	0.500
Age	1.001(0.992–1.011)	0.757	-	0.628
BMI<18.5 kg/m^2	1.413 (1.033–1.932)	0.030	-	0.172
Ever smoker	1.580 (1.116–2.236)	0.010	-	0.058
Alcohol history	1.407 (1.046–1.892)	0.024	-	0.187
Previously treated for TB	1.543 (1.163–2.046)	0.003	-	0.083
AFB smear positive	2.021 (1.510–2.705)	<0.001	1.637 (1.197–2.238)	0.002
Cavitary disease	1.856 (1.391–2.477)	<0.001	1.539 (1.132–2.092)	0.006
Bilateral disease	1.923 (1.409–2.625)	<0.001	1.638 (1.183–2.269)	0.003
Anemia	1.461 (1.073–1.991)	0.016	-	0.105
Viral hepatitis	2.419 (1.163–5.032)	0.018	2.585 (1.189–5.622)	0.017
Regimen containing BDQ	0.809(0.596–1.098)	0.174	-	0.072

Abbreviations: AFB, acid-fast bacilli; BDQ, bedaquiline; BMI, body mass index; CI, confidence interval; MDR/RR-TB, multidrug-resistant/ rifampin-resistant tuberculosis; TB, tuberculosis

Table 3 Factors associated with risk of culture un-conversion within 6 months of treatment in all patients

Predictor	Sputum culture un-conversion within 6 months of treatment in univariate analysis		Sputum culture un-conversion within 6 months of treatment in multivariate analysis	
	Odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Male	2.010 (1.338–3.018)	0.001	-	0.068
Age	1.018 (1.006–1.029)	0.002	-	0.447
BMI<18.5 kg/m^2	1.753 (1.217–2.523)	0.003	-	0.056
Ever smoker	2.358 (1.613–3.447)	<0.001	2.197 (1.475–3.273)	<0.001
Alcohol history	1.996 (1.407–2.832)	<0.001	-	0.218
Previously treated for TB	1.971 (1.356–2.866)	<0.001	1.909 (1.282–2.844)	0.001
AFB smear positive	1.427(0.984–1.427)	0.061	-	0.695
Cavitary disease	1.639 (1.126–2.386)	0.010	-	0.212
Bilateral disease	2.459 (1.556–3.884)	<0.001	2.201 (1.369–3.537)	0.001
Anemia	1.388(0.964–1.998)	0.078	-	0.269
Viral hepatitis	2.063 (1.036–4.109)	0.039	2.329 (1.094–4.962)	0.028
Regimen containing BDQ	0.405 (0.258–0.636)	<0.001	0.310 (0.191–0.502)	<0.001

Abbreviations: BDQ, bedaquiline; CI, confidence interval; MDR/RR-TB, multidrug-resistant/ rifampin-resistant tuberculosis; TB, tuberculosis

which covering various aspects including socio-demographic characteristics, epidemiology, clinical features, comorbidities, DST patterns, and treatment regimens from previous studies [8–26] to reduce the impact of confounding factors. Additionally, the study collected retrospective clinical data from 2018 to 2022, coinciding with the introduction of BDQ to China under the New Drug Introduction & Protection project. The findings from this study can help identify possible predictors for early and interim culture un-conversion and contribute to the future implementation of BDQ-containing regimens and related short-course regimens (such as the 6-month BPaLM regimen or the 9-month all-oral regimen [27]) in China.

In this study, 44.5% of the overall MDR/RR-TB patients achieved culture conversion within 2 months, in line with the previous studies of MDR-TB (ranging from 30%~57.4% [3, 5, 9, 35]). About 79.8% (649/813) patients achieved culture conversion within 6 months of treatment, consistent with previous studies (ranging from 70%~90%) [8, 22, 29, 35–37]. The median time for conversion was 2.00 (1.50, 3.00) months within 6 months of treatment, which falls within the duration reported in previous studies (31 days to 91.5 days [3, 6–7, 13, 15–16, 39–41]).

Through a multivariate analysis, we discovered various factors that independently predicted early and interim culture un-conversion. Patients who had a positive AFB smear, cavities, bilateral disease, and viral hepatitis were found to have a higher probability of experiencing culture un-conversion within 2 months of treatment. Additionally, male patients with a history of smoking, previous treatment for TB, bilateral disease, viral hepatitis, and those who received a regimen without BDQ were more likely to experience culture un-conversion within 6 months of treatment. Part of the predictors of early and interim culture un-conversion were overlapped. Notably, the relationship between sputum culture conversion and a successful outcome was found to be significantly stronger at 6 months compared to 2 months [2]. As a result, it is important to give more consideration to the independent risk factors that influence the interim sputum culture conversion.

The presence of an initial positive or a high grade AFB smear, which indicated a relatively high bacillary burden, was a known predictor of a longer time for sputum conversion in patients with pulmonary tuberculosis [8, 13, 15, 38, 39], and a single center study in Korea found that an initial positive AFB smear was associated with culture un-conversion within 3 months of treatment [40]. These findings are consistent with our study. Notably, a positive AFB smear might had a greater influence on early culture conversion compared to interim in our study.

Historically, patients with MDR-TB [9] and drug-susceptible tuberculosis (DS-TB) [10] who had cavities have been found to have a higher risk of culture un-conversion within 2 months of treatment compared to patients without cavities, which was consistent with the findings of our study. Cavities have long been recognized as a risk factor for delayed culture conversion and treatment failure in TB [4, 6–8, 16, 38, 39, 41–43]. The presence of cavities might hinder the penetration of drugs and consequently reduce the effectiveness of antimicrobial agents [21].

In a prospective cohort study on MDR-TB in America, it was found that bilateral disease (OR 1.90, 95% CI 1.20–3.01) was identified as an independent risk factor for a poor treatment outcome [17]. Our study also found a similar association between bilateral disease and early /interim culture un-conversion. Patients with more extensive lung lesions may experience a longer duration

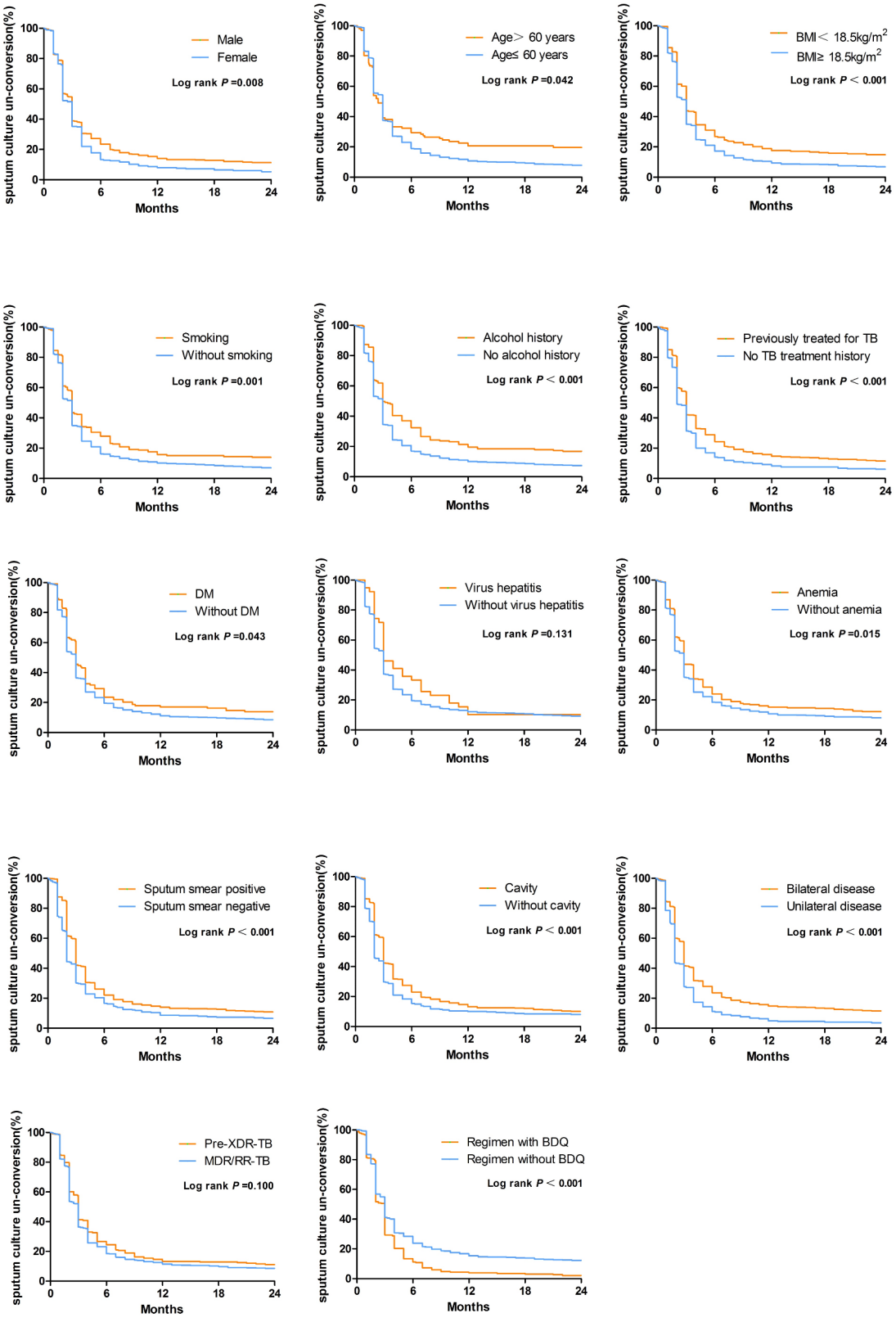

Fig. 2 Kaplan-Meier estimates of culture conversion within 24 months of treatment among subgroups in patients with MDR/RR-TB
Abbreviations: BDQ, bedaquiline; BMI, body mass index; DM, diabetes mellitus; RR-TB, rifampicin-resistant tuberculosis; LZD, linezolid; MDR-TB, multidrug-resistant tuberculosis; pre-XDR-TB, pre-extensive drug-resistant tuberculosis

for culture conversion. It is important to note that while bilateral cavitations have often been considered as a potential risk factor for poor treatment outcomes or culture conversion [4, 6], our study separated the lesion scope and cavity, reducing the mutual influence of objective predictors.

Viral hepatitis was identified as an independent predictor for culture un-conversion within early and interim treatment in patients with MDR/RR-TB. This finding was consistent with a study in Armenia and Georgia, which showed that co-infection with hepatitis C virus (aOR 4.45, 95%CI 1.23–16.13) was associated with unsuccessful outcomes in MDR-TB patients who received BDQ through compassionate use [44]. However, the endTB observational study found no association between hepatitis C infection and conversion [8]. This lack of association could be attributed to differences in sample size, race, treatment regimen, and other factors. Notably, HCV co-infection was found to be linked with higher levels of drug-induced liver injury (DILI) in MDR-TB patients [45, 46]. Although we assessed the proportion of adverse effects in our study, we were unable to analyze the relationship between viral hepatitis and DILI due to the retrospective nature of the study and the lack of information on the timing of adverse effects occurrence, the specific type of viral hepatitis, and the antiviral treatment status. Additionally, there is currently no published data available on the effects of new treatments for HCV infection with direct-acting antivirals on mortality and hepatotoxicity in co-infected MDR-TB patients [44].

Substantial evidence exists suggesting that smoking delays culture conversion or associated with culture un-conversion in MDR-TB patients [15, 16, 47], consistent with our finding that smoking was an independent risk factor for interim culture un-conversion. Smoking has been linked to compromised immune mechanisms, such as a reduction in the phagocytic function of alveolar macrophages [48]. Therefore, in a country with a high burden of MDR-TB like China, it is suggested that a new approach to TB control should include a smoking cessation program to potentially reduce the time for culture conversion. The history of previous tuberculosis treatment has been identified as an independent predictor for delayed culture conversion [14] and poor treatment outcome [6, 17] in patients with MDR-TB. This finding aligns with our findings, which showed that previous treatment for tuberculosis was independently associated with interim culture un-conversion.

According to the guideline of WHO [32] and the consensus of China [28] in 2018 and 2019 respectively, BDQ has been designated as a Group A drug for the treatment of MDR/RR/XDR-TB. Regimens containing BDQ have shown potential in achieving early culture conversion [22] or increasing the conversion rate [23–26]. Since the use of BDQ is still limited in China, part of this study objective to determine whether a regimen containing BDQ can facilitate early and interim culture conversion. Our study found that regimens containing BDQ were an independent predictor for interim culture conversion, similar to previous studies [22–26]. In a study conducted in China, MDR-TB patients who received a BDQ-containing regimen achieved a culture conversion rate of 80.6% (108/134) at the 8th week and 96.8% (120/124) at the 24th week [49]. The culture conversion rate at the 24th week in this study was similar to our study (88.8% for patients who received BDQ-containing regimen within 6 months), suggesting that BDQ has the potential to achieve early culture conversion. In this study, only 5.6% (13/232) of patients who received a BDQ-containing regimen experienced a QTcF prolongation exceeding 500 ms. This suggested that BDQ-containing regimens have an acceptable level of cardiotoxicity. However, short-course regimens such as the 6-month BPaLM/BPaL regimen have not been utilized in China due to the unavailability of pretomanid. Additionally, the 9-month all-oral regimen containing BDQ has not been widely adopted. Therefore, it is crucial to promote the use of BDQ-containing regimens and encourage the adoption of shorter treatment regimens in China.

In addition to the independent predictors mentioned above, our study also identified several factors that were significantly associated with early or interim culture un-conversion. These factors included male, age, BMI<18.5 kg/m^2, alcohol use, and anemia. These associations were observed in the univariate analysis. Two previous studies have shown that being male is an independent risk factor for 2-month sputum culture un-conversion [10, 12]. However, our study differs from these previous ones as they mainly focused on DS-TB, with only 3.8%~5.9% of the patients being MDR-TB [10, 12], and elderly patients with a mean age of 64.7±19.2 years [12]. Additionally, age was found to be significantly associated with sputum smear conversion time in patients with new DS-TB [42]. Alcoholism [13] or drinking [15] were independent predictors of less likely conversion in MDR-TB patients. Baseline anemia was reported to be associated with an unfavorable treatment outcome [50, 51]. However, gender, age, alcohol use, and baseline anemia alone were not sufficient to be considered independent risk factors for early and interim culture conversion in MDR/RR-TB patients.

Notably, a single-center study conducted in Korea revealed that failure to achieve sputum culture conversion within 3 months was independently associated with a low BMI(<18.5 kg/m^2) [42] in MDR-TB patients, which contrasts with our finding. Additionally, we found that the comorbidity of DM was not a risk factor for culture un-conversion within 2 and 6 months of treatment

in multivariate analysis, consistent with another cohort study conducted in China [49]. However, a study conducted in Korea reported that uncontrolled diabetes was identified as an independent risk factor for a positive sputum culture after 2 months of treatment (aOR, 2.11; $P=0.042$) in multivariable analysis [6], which differs from our study. These discrepancies above may be attributed to the fact that we did not collect information on the management of DM in our study, as well as differences in race, age, and sample size between the studies.

In our study, pre-XDR-TB was not a predictor of culture un-conversion at 2 and 6 months of treatment. A total of 233 patients had pre-XDR-TB in this study, all of whom exhibited resistance to FQs. However, according to previous studies, resistance to FQs or ofloxacin has been identified as an independent predictor of less likely conversion [13] or an extended time to conversion [7, 15] in patients with MDR-TB. Additionally, one study conducted in Pakistan [9] found that resistance to ofloxacin had a statistically significant negative association with culture conversion at two months. The inconsistency in results may be attributed to the fact that those studies did not include anti-TB treatment regimens in their analyses, and patients received treatment prior to 2014, which did not include Group A drugs other than FQs (such as BDQ or linezolid). Consequently, MDR-TB patients resistant to FQs had fewer treatment options, making it more challenging to achieve sputum culture conversion. In contrast, approximately 42.5% (99/233) of patients with pre-XDR-TB in our study received BDQ-containing regimens, which was higher than the proportion of patients with MDR/RR-TB (22.9%, 133/580). The selection of more effective drugs (such as bedaquiline, linezolid, delamanid, and pretomanid) may mitigate the impact of drug resistance types, such as pre-XDR-TB, on early and interim culture conversion.

Furthermore, we utilized the Kaplan-Meier survival curve to analyze the relationship between culture conversion time within 24 months of treatment and possible high-risk factors. Our findings revealed that virus hepatitis may have a more significant impact on early and interim culture un-conversion, rather than in subsequent treatment (Fig. 2). On the other hand, factors such as gender, age, BMI, alcohol use, and anemia may have a greater impact on culture un-conversion during the later stages of treatment. However, due to the limited data available on the occurrence time and frequency of adverse effects during treatment, as well as the specific timing of drug interruption and regimen change, only a brief discussion was provided in this study. Therefore, these hypotheses require further investigation.

These findings suggested that the aforementioned objective independent predictors can often be identified before the diagnosis or early treatment of MDR/RR-TB, offering clinicians an opportunity to identify patients who may benefit from targeted management. This may involve the use of improved initial regimens that include BDQ, and increased medical attention to high risk populations. In low-resource settings where sputum cultures are not regularly conducted, more frequent monitoring of sputum cultures in high-risk patients can enable earlier detection of those who do not experience conversion.

This study has several limitations. Firstly, it should be noted that MDR/RR-TB patients in China are recommended to undergo monthly sputum culture tests. However, not all patients were able to complete these tests monthly after 6 months of treatment. As a result, we have utilized the available data to develop a logistic multivariable model instead of Cox regression. This model helped identify certain predictors for early and interim un-conversion. We were only able to present the conversion time within 24 months in different subgroups based on the available data, but it is not possible to compare predictors associated with culture conversion in the early, interim and whole course. Additionally, this study did not collect the occurrence time of adverse effects and changes in treatment regimen throughout the entire duration of the treatment. Therefore, only the initial regimens were considered in the multivariate analysis, and the adverse effects were not taken into consideration. Furthermore, the study did not differentiate between viral hepatitis caused by hepatitis B and hepatitis C, and it did not collect data on the glycemic control status of patients with diabetes mellitus. Moreover, based on the medical records, patients generally reported regular medication usage; therefore, treatment adherence was not included in this study. However, it is important to note that some patients may exhibit poor treatment adherence outside the outpatient clinic, which is not captured in the records. Lastly, the study did not assess the cost-effectiveness of MDR-TB treatment in terms of catastrophic health expenditures.

Conclusions

This study identified specific predictors for early and interim sputum culture conversion for MDR/RR-TB in China. A history of smoking, a baseline sputum AFB smear positive, lung cavities, bilateral disease, previous anti-tuberculosis treatment, or a comorbidity of viral hepatitis requires increased medical attention to achieve faster culture conversion can be used as the predictors for early and interim culture un-conversion in MDR/RR-TB patients, while BDQ was a protective factor. Optimizing the management of MDR/RR-TB patients should be prioritized by considering these predictors and vulnerable subgroups. Furthermore, treatment regimens for MDR/RR-TB should incorporate new anti-tuberculosis drugs like BDQ, whenever feasible.

Adverse effects

The study found that the most common adverse effect was liver injury (47.1%), followed by anemia (36.5%), peripheral neuritis (24.5%), leukopenia (19.4%), optic neuritis (12.8%), thrombopenia (12.7%), acute renal injury (defined according to the Kidney Disease: Improving Global Outcomes clinical practice guidelines [52]) (5.8%), and prolonged Fridericia-corrected QT (QTcF) interval (≥500ms) (2.2%).

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Author contributions
QC, WH, GHW, and SJT had the idea for and designed the study and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. QC and SJT drafted the paper. QC, WH, LPZ, XZT, GHW, and SJT did the analysis. QC, WH, JD, WLK, LPZ, XZT, PJT, CHG, QP, QDZ, SY and ZLG collected the data and did the follow up. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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