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Research Article

Risk factors associated with morbidity and unfavorable treatment outcome in drug-resistant pulmonary tuberculosis: a case-control study

Changshu Li,[1,‡] Shufan Liang,[1,‡] Xue Wang,[1] Su Lui ,[2,*] Chengdi Wang[1,*]

[1]Department of Pulmonary and Critical Care Medicine, Targeted Tracer Research and Development Laboratory, Frontiers Science Center for Disease-Related Molecular Network, State Key Laboratory of Respiratory Health and Multimorbidity, West China Hospital, West China School of Medicine, Sichuan University, Chengdu 610041, China

[2]Department of Radiology, and Functional and Molecular Imaging Key Laboratory of Sichuan Province, Huaxi MR Research Center (HMRRC), Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, West China Hospital, West China School of Medicine, Sichuan University, Chengdu 610041, China

*Corresponding authors: Chengdi Wang, chengdi_wang@scu.edu.cn; Su Lui, lusuwcums@hotmail.com

‡Changshu Li and Shufan Liang contributed equally to this work.

Abstract

Objectives: To investigate the risk factors in patients with drug-resistant tuberculosis (DR-TB) and clinical characteristics related to unfavorable anti-TB treatment outcomes.

Methods: A total of 961 pulmonary tuberculosis (TB) patients were included at West China Hospital of Sichuan University from January 2008 to November 2023. We analyzed the differences of clinical characteristics between DR-TB and drug-sensitive tuberculosis (DS-TB), and then compared these features in DR-TB patients with different outcomes. Multivariable logistic regression models were employed to quantify risk factors associated with DR-TB and adverse treatment outcomes.

Results: Among 961 pulmonary TB patients, a history of anti-TB treatment [odds ratio (OR), 3.289; 95% confidence interval (CI), 2.359–4.604] and CT-scan cavities (OR, 1.512; 95% CI, 1.052–2.168) increased DR-TB risk. A total of 214 DR-TB patients were followed for a median of 24.5 months. Among them, 116/214 (54.2%) patients achieved favorable outcomes. Prior anti-TB treatment (OR, 1.927; 95% CI, 1.033–3.640), multidrug-resistant tuberculosis (MDR-TB) (OR, 2.558; 95% CI, 1.272–5.252), positive sputum bacteriology (OR, 2.116; 95% CI, 1.100–4.134), and pleural effusion (OR, 2.097; 95% CI, 1.093–4.082) were associated with unfavorable outcomes, while isoniazid-resistant TB patients showed better outcomes (OR, 0.401; 95% CI, 0.181–0.853). The clinical model for unfavorable outcome prediction of DR-TB achieved an area under the curve (AUC) of 0.754 (95% CI, 0.690–0.818).

Conclusions: Treatment history of anti-TB not only increases the risk of the emergence of DR-TB, but also potentially leads to treatment failure during re-treatment in DR-TB patients. Drug resistance subtypes, radiological characteristics, and the results of sputum smear or culture may affect the treatment outcome of DR-TB.

Keywords: drug-resistant tuberculosis; multidrug-resistant tuberculosis; anti-TB treatment; clinical characteristics; risk factors; treatment outcome

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* infection with predominant pulmonary involvement remains the leading cause of infection-related mortality, resulting in 10.8 million new cases and 1.25 million deaths worldwide annually [1–4]. Additionally, it has been reported that the lengthy treatment courses for TB may induce chronic inflammation and impaired lung function, ultimately significantly increasing the risk of developing chronic lung diseases [5–7]. Drug-resistant tuberculosis (DR-TB) refers to resistance to at least one anti-TB drug confirmed by drug susceptibility testing (DST), serving as the major reason for death due to antimicrobial resistance [8–11]. It is estimated by the World Health Organization (WHO) that 400 000 patients developed multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) in 2023 and 56% were untreated. Worse yet, the treatment success rate of MDR/RR-TB is lower than that of susceptible patients (68% vs. 88%) [1]. The diagnostic challenges inherent in TB also contribute, to a significant extent, to the relatively low treatment success rates observed in clinical practice [12]. China ranks the third among the high-TB burden countries and the number of TB cases in China accounted for 6.8% of the world total [1, 13–15]. In addition, with a serious DR-TB epidemic, the global proportion of MDR/RR-TB in China also reached >7.3%, leaving an inadequately addressed concern for public hygiene [1]. Besides, despite the emergence of novel antimicrobial peptides and renewed interest in developing TB treatment regimens over the past years, which have yielded impressive achievements and saved millions of lives [16–21], TB remains the primary killer among single infectious pathogens.

DR-TB persists as a severe public health crisis and continuous surveillance of its burden is crucial for formulating and implementing an effective intervention strategy [22]. Early identification of patients at high risk of DR-TB, enhanced treatment enrollment, and optimal treatment regimens are essential for

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effectively controlling DR-TB. This not only helps in reducing the spread of DR strains but also improves the prognosis for affected individuals, ultimately contributing to the overall goal of curbing the global TB epidemic. Previous studies have explored hazardous factors of DR-TB, such as demographics, bacterial load, and radiological characteristics [23–25]. However, such studies mostly focused on certain subtypes, especially for MDR-TB and extensively drug-resistant tuberculosis (XDR-TB) [26–29]; moreover, limited research on predicting unfavorable outcomes in DR-TB restricts the comprehensiveness of the studies. Therefore, in this study, we comprehensively compared demographics, anti-TB treatment history, comorbidities, clinical symptoms, and radiological manifestations between DR-TB and drug-sensitive tuberculosis (DS-TB) to identify the risk factors of DR-TB. Furthermore, additional information, including drug resistance profiles, subtypes, and therapeutic schemes, was included to analyze the clinical discrepancies of different treatment outcomes in patients with DR-TB, along with the construction of multivariable logistic regression models for DR-TB and unfavorable treatment outcome prediction in a manner simulating clinical decision-making process, with the aim of improving vigilance in clinic settings and optimizing management planning.

Materials and methods

Study participants

Patients with pulmonary TB who visited West China Hospital of Sichuan University between January 2008 and November 2023 were randomly enrolled in the retrospective research. Based on the inclusion and exclusion criteria in our previously published work [30], we selected participants with completed information. The inclusion criteria were as follows: (i) patients diagnosed with TB through pathogenic detection (microscopy or culture of *M. tuberculosis*) or clinical confirmation via a comprehensive analysis of radiology, symptoms, and laboratory tests; (ii) availability of DST, GeneXpert MTB/RIF results, or gene testing for drug resistance detection for DR-TB, and the results or follow-up information for DS-TB; and (iii) patients aged between 18 and 90 years. The exclusion criteria were: (i) unavailability of CT images obtained within 3 months of diagnosis; (ii) incomplete CT images; and (iii) presence of other severe lung diseases that can cause confusion on CT volumes, such as severe pneumonia, pulmonary abscess, lung cancer, pulmonary fibrosis, sarcoidosis, etc. Finally, 961 patients were involved, comprising 214 and 747 patients with DR-TB and DS-TB, respectively. The study was approved by the Institutional Review Board (IRB)/Ethics Committee of West China Hospital of Sichuan University (No. 2023.2286).

Definitions of drug resistance and outcomes

Patients with isoniazid-resistant tuberculosis (HR-TB) and RR-TB were defined as resistant to isoniazid (INH) or rifampin (RIF) confirmed by phenotypic or genotypic DST. Cases exhibiting concurrent resistance to both INH and RIF were classified as MDR-TB. If resistance to any fluoroquinolones (FQs) and at least one of the second-line injectable drugs (amikacin, capreomycin, or kanamycin), plus MDR-TB were confirmed, the patients would be grouped into XDR-TB. We investigated the outcomes of patients with DR-TB through medical records or telephone follow-ups from 10 April 2024 to 19 July 2024. According to the WHO treatment outcome definitions updated in 2021, the favorable outcome group was described as cured or treatment completed, while patients who were treatment failed, died, lost to follow-up, and unevaluated were in the unfavorable group [31].

Data collection

General characteristics including demographics, smoking, and alcohol use were included. We analyzed anti-TB treatment history, comorbidities including diabetes, hepatitis B, human immunodeficiency virus (HIV) infection, and syphilis, as well as clinical symptoms consisting of cough, expectoration, hemoptysis, fever, chest pain, dyspnea, short breath, night sweating, chest distress, and fatigue. Next, radiological manifestations, including lobar involvement numbers, lesion location, nodule, patchy shadow, cavity, consolidation, bronchiectasis, pleural effusion, miliary nodule, ground-glass opacity (GGO), and mass, were recorded. For patients with DR-TB, we recorded drug resistance profiles and treatment-associated information consisting of the numbers and specific types of anti-TB drugs.

Statistical analysis

GraphPad Prism version 9.5.0 was utilized for data analysis. We used median (interquartile range, IQR) and numbers (%) to express continuous and categorical variables, respectively. Data comparison was calculated by chi-square test or Fisher exact test, and $P < 0.05$ was considered statistically significant. Then, we selected the variables with significant differences to construct two clinical models respectively for diagnosis of DR-TB and prediction of unfavorable outcomes. Odds ratio (OR) was calculated by multivariable logistic regression to interpret the prediction implication of the clinical parameters. Receiver operating characteristic curves (ROCs), area under the curve (AUC), and Hosmer–Lemeshow goodness-of-fit test were utilized to assess the model performance.

Results

Clinical characteristics of the included patients

In this study, we analyzed the clinical and radiological characteristics of 961 pulmonary TB patients, comprising 214 with DR-TB and 747 with DS-TB. The overall workflow of this study is depicted in Fig. S1 (see online supplementary material). Key findings revealed that DR-TB patients were significantly more likely to have a history of prior anti-TB treatment (58.4% vs. 28.1%, $P < 0.0001$), cigarette smoking history (42.1% vs. 32.8%, $P = 0.0122$), and clinical symptoms such as cough (79.4% vs. 65.9%, $P = 0.0002$), expectoration (65.9% vs. 51.7%, $P = 0.0002$), hemoptysis (22.9% vs. 14.2%, $P = 0.0023$), and night sweats (23.8% vs. 17.3%, $P = 0.03$). Radiologically, DR-TB was associated with whole-lung involvement (72.0% vs. 60.6%, $P = 0.0025$), cavity formation (48.6% vs. 27.0%, $P < 0.0001$), and higher prevalence of bronchiectasis (32.7% vs. 19.7%, $P < 0.0001$) and GGO (8.4% vs. 4.8%, $P = 0.0443$). Conversely, pleural effusion was more common in DS-TB (41.0% vs. 32.2%, $P = 0.0211$). These findings highlight the distinct clinical and radiological profiles between DR-TB and DS-TB (Table 1).

Risk factors and clinical prediction model of DR-TB

In the multivariable analysis, significantly increased risk of DR-TB was observed in patients with prior anti-TB treatment [OR, 3.289; 95% confidence interval (CI), 2.359–4.604]. Additionally,

Table 1. Clinical characteristics of the included patients.

Characteristics	DS-TB (*n* = 747)	DR-TB (*n* = 214)	*P* value	Adjusted OR (95% CI)
Age (years) — no. (%)				
18–44	370 (49.5)	117 (54.7)	0.1847	-
45–90	377 (50.5)	97 (45.3)		
Gender-male — no. (%)	427 (57.2)	134 (62.6)	0.1535	-
Smoking — no. (%)	245 (32.8)	90 (42.1)	0.0122	1.226 (0.868–1.726)
Alcohol use — no. (%)	208 (27.8)	70 (32.7)	0.1664	-
History of anti-TB treatment — no. (%)	210 (28.1)	125 (58.4)	<0.0001	3.289 (2.359–4.604)
Extra-pulmonary tuberculosis — no. (%)	125 (16.7)	38 (17.8)	0.7251	-
Diabetes — no. (%)	84 (11.2)	31 (14.5)	0.1978	-
Hepatitis B — no. (%)	48 (6.4)	11 (5.1)	0.5083	-
HIV positive — no. (%)	5 (0.7)	2 (0.9)	0.9572	-
Syphilis — no. (%)	9 (1.2)	4 (1.9)	0.6846	-
Symptom — no. (%)				
Cough	492 (65.9)	170 (79.4)	0.0002	1.606 (0.926–2.775)
Expectoration	386 (51.7)	141 (65.9)	0.0002	1.113 (0.695–1.813)
Hemoptysis	106 (14.2)	49 (22.9)	0.0023	1.003 (0.647–1.536)
Fever	296 (39.6)	85 (39.7)	0.9801	-
Chest pain	157 (21.0)	37 (17.3)	0.2310	-
Dyspnea	49 (6.6)	10 (4.7)	0.3107	-
Short breath	211 (28.2)	65 (30.4)	0.5442	-
Night sweating	129 (17.3)	51 (23.8)	0.0300	1.282 (0.858–1.897)
Chest distress	83 (11.1)	17 (7.9)	0.1810	-
Fatigue	124 (16.6)	30 (14.0)	0.3642	-
Whole-lung involvement — no. (%)	453 (60.6)	154 (72.0)	0.0025	1.322 (0.790–2.289)
Lesion location — no. (%)				
LUL	622 (83.3)	187 (87.4)	0.1456	-
LLL	597 (79.9)	181 (84.6)	0.1259	-
RUL	625 (83.7)	187 (87.4)	0.1856	-
RML	561 (75.1)	176 (82.2)	0.0293	1.027 (0.550–1.883)
RLL	615 (82.3)	183 (85.5)	0.2738	-
Pulmonary abnormality — no. (%)				
Nodule	612 (81.9)	187 (87.4)	0.0602	-
Patchy shadow	525 (70.3)	168 (78.5)	0.0180	1.217 (0.824–1.820)
Cavity	202 (27.0)	104 (48.6)	<0.0001	1.512 (1.052–2.168)
Consolidation	267 (35.7)	96 (44.9)	0.0153	1.292 (0.911–1.830)
Bronchiectasis	147 (19.7)	70 (32.7)	<0.0001	1.253 (0.857–1.819)
Calcification	188 (25.2)	51 (23.8)	0.6903	-
Pleural effusion	306 (41.0)	69 (32.2)	0.0211	0.596 (0.410–0.860)
Miliary nodule	81 (10.8)	24 (11.2)	0.8779	-
GGO	36 (4.8)	18 (8.4)	0.0443	1.745 (0.905–3.273)
Mass	54 (7.2)	9 (4.2)	0.1152	-

Data are no. (%). CI, confidence interval; DR-TB, drug-resistant tuberculosis; DS-TB, drug-sensitive tuberculosis; HIV, human immunodeficiencpy virus; GGO, ground-glass opacity; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

those with radiological abnormality of cavity on the CT volumes also had an increased risk (OR, 1.512; 95% CI, 1.052–2.168) (Fig. 1A, Table 1), while pleural effusion served as a protective factor (OR, 0.596; 95% CI, 0.410–0.860). Subsequently, we constructed a clinical model to predict the likelihood of DR-TB, showing an AUC of 0.73 (95% CI, 0.692–0.768) (Fig. 1B). The predicted probability of DR-TB was obviously higher than DS-TB, indicating the potential of the model to discriminate across the two cohorts (Fig. 1C).

Drug resistance profiles and treatment regimens of DR-TB

Regarding the drug resistance detection approaches, 49 (22.9%) patients and 165 (77.1%) patients were confirmed by phenotypic and genotypic DST, respectively. Additionally, 58 (27.1%), 60 (28.1%), 66 (30.8%), 7 (3.3%), and 23 (10.7%) patients were diagnosed as HR-TB, RR-TB, MDR-TB, XDR-TB, and others (referring to drug resistance other than the previous four subtypes). RIF and INH held the highest resistance rates, which respectively implicated 133 (62.1%) and 131 (61.2%) patients, while resistance to streptomycin (SM) and ethambutol (EMB) was also commonly detected, followed by capreomycin (CM) and fluoroquinolones (FQs). Resistance against para-aminosalicylic acid (PAS), amikacin (AM), clofazimine (CFZ), and pyrazinamide (PZA) was less observed (Fig. 2A, Table 2). In terms of treatment, the six most frequently used agents were FQs (79.9%), EMB (53.3%), PZA (43%), prothionamide (PTO) (39.3%), INH (38.3%), and AM (36.4%) (Fig. 2B, Table S1, see online supplementary material).

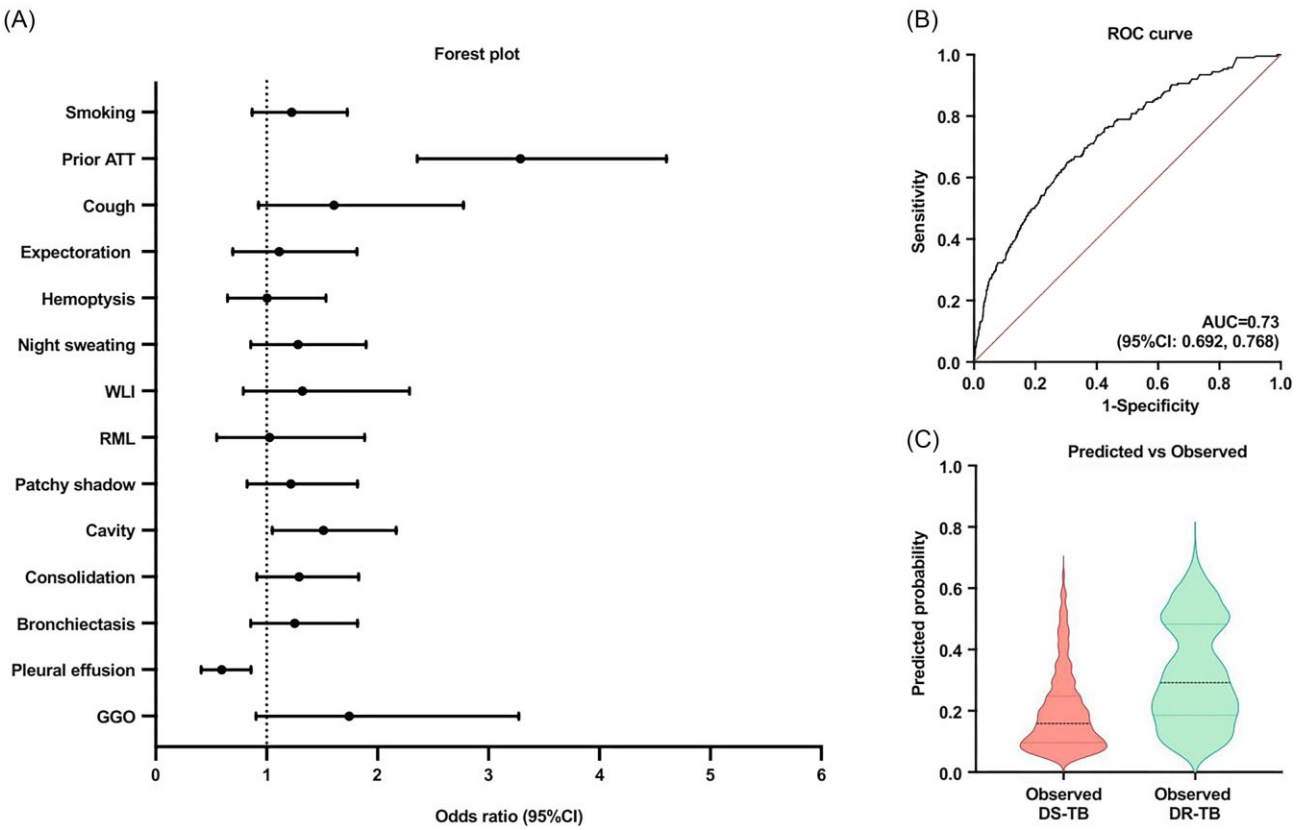

Figure 1. Multivariable analysis of drug-resistant tuberculosis (DR-TB) and the prediction performance of the clinical model. (**A**) Forest plot demonstrating the odds ratio (OR) of significant parameters in univariable analysis between DS-TB and DR-TB. (**B**) Receiver operating characteristic (ROC) curve of the clinical model in DR-TB prediction. (**C**) Comparison between the predicted probability of DS-TB and DR-TB, respectively. ATT, anti-TB treatment; DR-TB, drug-resistant tuberculosis; DS-TB, drug-sensitive tuberculosis; GGO, ground-glass opacity; RML, right middle lobe; ROC, receiver operating characteristic curve; WLI, whole-lung involvement.

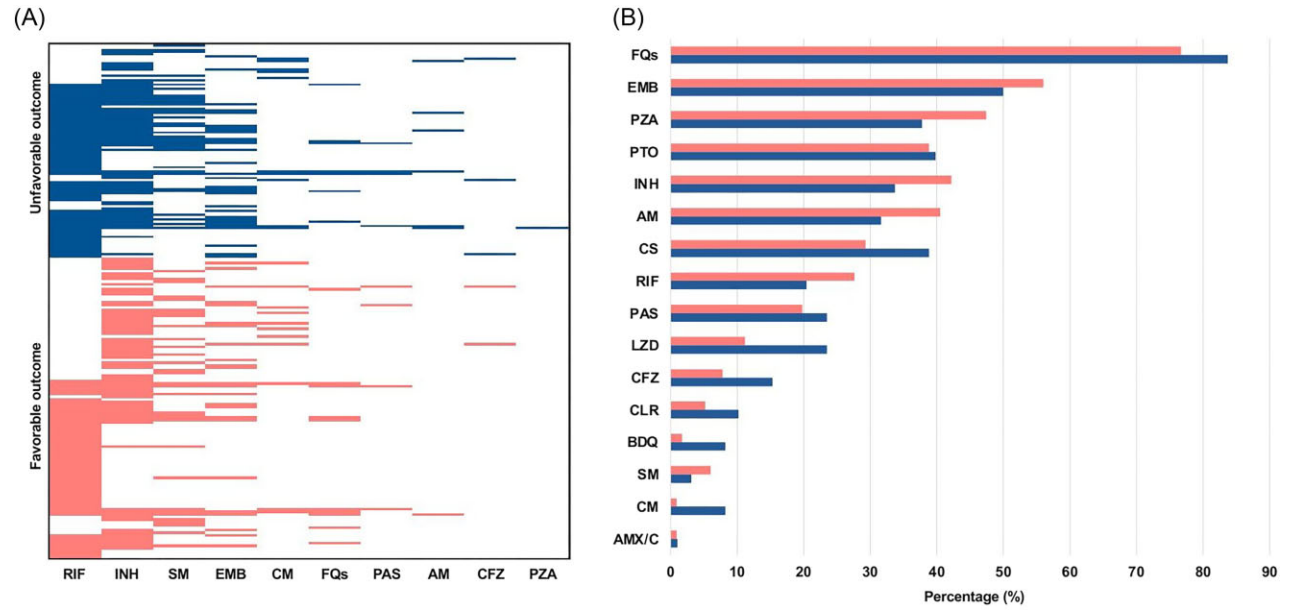

Figure 2. Analysis of drug resistance profiles and treatment regimens of drug-resistant tuberculosis (DR-TB). (**A**) Resistance to different drugs in the included patients with DR-TB. (**B**) Utilization frequency of different anti-TB drugs. The orange column represents the favorable outcome group, while the blue represents the unfavorable outcome group. AM, amikacin; AMX/C, amoxicillin/clavulanate; BDQ, bedaquiline; CFZ, clofazimine; CLR, clarithromycin; CM, capreomycin; CS, cycloserine; EMB, ethambutol; FQs, fluoroquinolones; INH, isoniazid; LZD, linezolid; PAS, para-aminosalicylic acid; PTO, prothionamide; PZA, pyrazinamide; RIF, rifampin; SM, streptomycin.

Table 2. Drug resistance profiles of patients with DR-TB.

Drug	Total (n = 214)	Favorable outcome (n = 116)	Unfavorable outcome (n = 98)
RIF — no. (%)	133 (62.1)	60 (51.7)	73 (74.5)
INH — no. (%)	131 (61.2)	68 (58.6)	63 (64.3)
SM — no. (%)	67 (31.3)	32 (27.6)	35 (35.7)
EMB — no. (%)	55 (25.7)	24 (20.7)	31 (31.6)
CM — no. (%)	21 (9.8)	11 (9.5)	10 (10.2)
FQs — no. (%)	17 (7.9)	10 (8.6)	7 (7.1)
PAS — no. (%)	8 (3.7)	4 (3.4)	4 (4.1)
AM — no. (%)	7 (3.3)	1 (0.9)	6 (6.1)
CFZ — no. (%)	5 (2.3)	2 (1.7)	3 (3.1)
PZA — no. (%)	1 (0.5)	0 (0.0)	1 (1.0)

Data are no. (%). AM, amikacin; CFZ, clofazimine; CM, capreomycin; EMB, ethambutol; FQs, fluoroquinolones; INH, isoniazid; PAS, para-aminosalicylic acid; PZA, pyrazinamide; RIF, rifampin; SM, streptomycin.

Clinical characteristics of DR-TB with different outcomes

The median follow-up duration for the DR-TB cohort was 24.5 months (IQR, 16.5–55.5 months), with the longest duration of >13 years. A total of 116 (54.2%) patients were observed to have favorable outcomes. Patients with unfavorable outcomes had a higher proportion of smoking history (51% vs. 34.5%, $P = 0.0146$), alcohol consumption (39.8% vs. 26.7%, $P = 0.0423$), and a history of previous anti-TB treatment (68.4% vs. 50.0%, $P = 0.0066$). The subtype of HR-TB (15.3% vs. 37.1%, $P = 0.0004$) was more observed in patients with favorable outcomes while MDR-TB (18.1% vs. 45.9%, $P < 0.0001$) appeared more often in the unfavorable outcome group. Moreover, patients with positive sputum smear or culture results tend to experience unfavorable outcomes (64.3% vs. 44.0%, $P = 0.003$). No significance was observed in other drug resistance types, extra-pulmonary TB, comorbidities, and clinical symptoms. Regarding radiological characteristics, patients with unfavorable outcomes were more likely to have the manifestations of cavity (57.1% vs. 41.4%, $P = 0.0215$) and pleural effusion (40.8% vs. 25.0%, $P = 0.0137$) (Table 3).

Risk factors associated with unfavorable outcome of DR-TB and clinical prediction model

In the multivariable logistic analysis, we identified four independent predictors of unfavorable outcomes: previous anti-TB treatment (OR, 1.927; 95% CI, 1.033–3.64), MDR-TB (OR, 2.558; 95% CI, 1.272–5.252), positive bacteriology (OR, 2.116; 95% CI, 1.1–4.134), and pleural effusion (OR, 2.097; 95% CI, 1.093–4.082). Conversely, HR-TB suffering probably served as the protective factor of treatment outcome in DR-TB (OR, 0.401; 95% CI, 0.181–0.853) (Fig. 3A, Table 3). The clinical model demonstrated an AUC of 0.754 (95% CI, 0.69–0.818), along with a higher predicted probability in the unfavorable outcome group (Fig. 3B and C).

Discussion

This study aimed to provide scientific evidence for the clinical management of DR-TB by comprehensively analyzing the clinical characteristics and risk factors associated with treatment outcomes in DR-TB patients, and constructing prediction models. The identification of prior anti-TB treatment as a dual-risk factor (OR = 3.289 for DR-TB incidence; OR = 1.927 for unfavorable outcome) underscores the imperative for optimized initial treatment protocal and enhanced antimicrobial stewardship. Notably, the distinct prognostic divergence between HR-TB (OR = 0.401) and MDR-TB (OR = 2.558) subgroups reveals subtype-specific pathophysiological trajectories, suggesting tailored management strategies could improve therapeutic efficacy. Our findings revealed that DR-TB patients exhibited higher rates of smoking, prior anti-TB treatment, and clinical symptoms such as cough, expectoration, hemoptysis, and night sweats compared to DS-TB patients. Although previous studies have explored differences between DS-TB and DR-TB, this study systematically analyzed symptomatological features for the first time, suggesting that clinicians should promptly perform DST for patients presenting with these symptoms [32, 33].

In the DR-TB cohort, RIF and INH emerged as the top two most frequently observed resistant drugs, and FQs were the most frequently used agent. As the all-oral shorter regimens including bedaquiline and linezolid have been proposed in recent years [34], research in a fresher cohort to keep up with this trend is needed. For outcome analysis, 116/214 (54.2%) patients achieved treatment success, align with previous research [17, 35]. However, most of those studies focused on a particular drug resistance subtype [36–38]. We conducted a more comprehensive analysis including four subtypes, along with developing a clinical prediction model for treatment outcome prediction of DR-TB. As a result, the varying treatment outcomes among subtypes provided some evidence that patients with HR-TB were apt to develop a better prognosis, while MDR-TB patients may undergo disease progression. The superior prognosis of HR-TB arises from its narrow resistance spectrum, maintaining sensitivity to first-line RIF and EMB, with WHO-recommended 9-month regimens yielding favorable outcomes [39]. In contrast, MDR-TB exhibits worse prognosis due to broader resistance and complex therapies. Mechanistically, INH inhibits mycobacterial cell wall synthesis without impairing replication, allowing post-resistance control by other drugs like RIF [40, 41]. However, untreated HR-TB may progress to MDR-TB, underscoring the need for early diagnosis and tailored treatment. Previous research has found that the treatment success rate of XDR-TB is lower [37, 42–44]. Nevertheless, due to the small amount of XDR-TB in this study, we did not find an association between outcome and XDR-TB, and the data needs to be expanded in the future to optimize our research.

According to the latest data released by the WHO, the proportion of MDR/RR-TB in new TB cases is 3.2%, while the ratio in previously treated patients is 16% [1], and the proportion in our study lay between these values. Re-treatment of TB has been identified as a strong risk factor for DR-TB and worse outcomes [32, 35]. Our results also illustrate this point. *Mycobacterium tuberculosis* resistance to anti-TB drugs arises through multiple mechanisms, including target gene mutations, drug efflux pumps, and epigenetic remodeling [45]. Target mutations, such as those in *katG* [46] (INH

Table 3. Clinical characteristics of the DR-TB patients with different outcomes.

Characteristics	Favorable outcome (*n* = 116)	Unfavorable outcome (*n* = 98)	*P* value	Adjusted OR (95% CI)
Age (years) — no. (%)[a]				
18–42	58 (50.0)	48 (49.0)	0.8818	-
43–90	58 (50.0)	50 (51.0)		
Gender-male — no. (%)	67 (57.8)	67 (68.4)	0.1100	-
Smoking — no. (%)	40 (34.5)	50 (51.0)	0.0146	1.268 (0.569–2.832)
Alcohol use — no. (%)	31 (26.7)	39 (39.8)	0.0423	1.316 (0.568–3.024)
History of anti-TB treatment — no. (%)	58 (50.0)	67 (68.4)	0.0066	1.927 (1.033–3.640)
Drug-resistance types — no. (%)				
HR-TB	43 (37.1)	15 (15.3)	0.0004	0.401 (0.181–0.853)
RR-TB	35 (30.2)	25 (25.5)	0.4494	-
MDR-TB	21 (18.1)	45 (45.9)	<0.0001	2.558 (1.272–5.252)
XDR-TB	4 (3.4)	3 (3.1)	0.8204	-
Others	13 (11.2)	10 (10.2)	0.8134	-
Bacteriologically positive — no. (%)[b]	51 (44.0)	63 (64.3)	0.0030	2.116 (1.100–4.134)
Extra-pulmonary TB — no. (%)	20 (17.2)	18 (18.4)	0.8300	-
Diabetes — no. (%)	16 (13.8)	15 (15.3)	0.754	-
Hepatitis B — no. (%)	7 (6.0)	6 (6.1)	0.9786	-
HIV positive — no. (%)	0 (0.0)	2 (2.0)	0.2085	-
Syphilis — no. (%)	2 (1.7)	2 (2.0)	0.7368	-
Symptom — no. (%)				
Cough	91 (78.4)	79 (80.6)	0.6963	-
Expectoration	75 (64.7)	66 (67.3)	0.6790	-
Hemoptysis	27 (23.3)	22 (22.4)	0.8859	-
Fever	47 (40.5)	38 (38.8)	0.7953	-
Chest pain	15 (12.9)	22 (22.4)	0.0666	-
Dyspnea	2 (1.7)	8 (8.2)	0.0576	-
Short breath	30 (25.9)	35 (35.7)	0.1184	-
Night sweating	31 (26.7)	20 (20.4)	0.2799	-
Chest distress	7 (6.0)	10 (10.2)	0.2611	-
Fatigue	14 (12.1)	16 (16.3)	0.3714	-
Whole-lung involvement — no. (%)	79 (68.1)	75 (76.5)	0.1715	-
Lesion location — no. (%)				
LUL	100 (86.2)	87 (88.8)	0.5729	-
LLL	95 (81.9)	86 (87.8)	0.2371	-
RUL	101 (87.1)	86 (87.8)	0.8803	-
RML	92 (79.3)	84 (85.7)	0.2219	-
RLL	97 (83.6)	86 (87.8)	0.3919	-
Pulmonary abnormality — no. (%)				
Nodule	102 (87.9)	85 (86.7)	0.7929	-
Patchy shadow	88 (75.9)	80 (81.6)	0.3059	-
Cavity	48 (41.4)	56 (57.1)	0.0215	1.163 (0.594–2.256)
Consolidation	53 (45.7)	43 (43.9)	0.7906	-
Bronchiectasis	38 (32.8)	32 (32.7)	0.9869	-
Calcification	29 (25.0)	22 (22.4)	0.6625	-
Pleural effusion	29 (25.0)	40 (40.8)	0.0137	2.097 (1.093–4.082)
Miliary nodule	13 (11.2)	11 (11.2)	0.9968	-
GGO	7 (6.0)	11 (11.2)	0.1729	-
Mass	6 (5.2)	3 (3.1)	0.6710	-

Data are no. (%). HIV, human immunodeficiencpy virus; GGO, ground-glass opacity; LLL, Left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.
[a]Patients were grouped by the median age of 42 (IQR, 27.5–51) years in the DR-TB cohort.
[b]Sputum smear or culture.

resistance) or *rpoB* [47] (RIF resistance), alter drug binding sites or enzymatic activity. Drug efflux pumps, like MmpL5, EfpA, or AcrB, reduce intracellular drug accumulation by expelling compounds [48–51]. Epigenetic modifications, including histone acetylation or DNA methylation, regulate gene expression to adapt to drug pressure [52]. In addition, ubiquitin enzyme-induced autophagy is also a source of drug resistance [53]. Understanding these pathways is critical for developing novel diagnostics and therapies to combat DR-TB. As for clinical management, strengthened combination therapy decision-making by physicians in the initial regimens, close monitoring of dynamic condition changes, and good compliance of patients during treatment are stressed in concerted efforts to lessen the burden of drug resistance.

The bacteriological response is a crucial indicator for treatment outcome evaluation in TB, and the standard, especially "cured", for DR-TB is more stringent than for DS-TB, which usually requires consecutive negative results in cultures at least 7 days apart [31]. However, it may be quite difficult to request each patient to attend a subsequent visit after one bacteriological conversion in time, and our "favorable group" mostly contained patients with

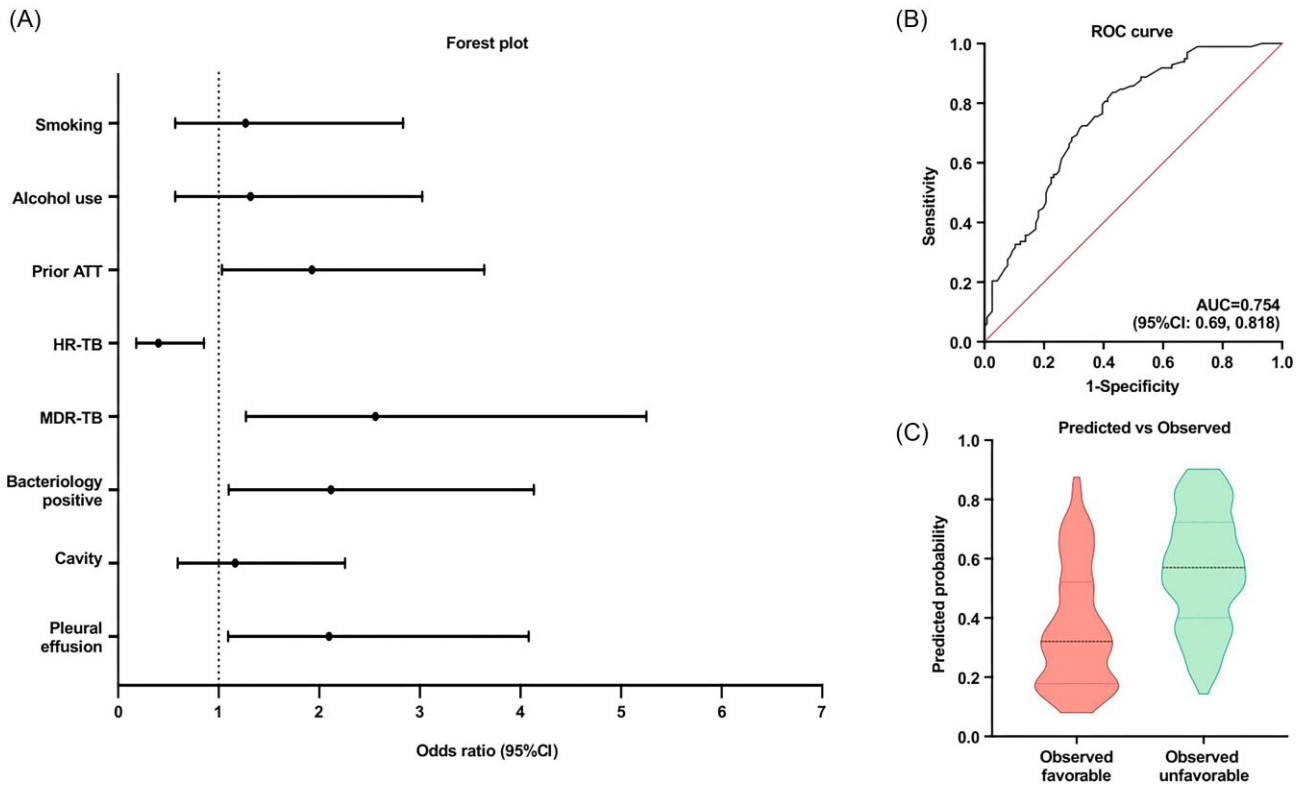

Figure 3. Multivariable analysis of treatment outcome in DR-TB patients and the prediction performance of the clinical model. (**A**) Forest plot demonstrating the ORs of significant parameters in univariable analysis. (**B**) ROC curve of the clinical model in prediction of unfavorable treatment outcome in DR-TB. (**C**) Comparison of the predicted probability generated by the model between favorable and unfavorable outcomes. ATT, Anti-TB treatment; HR-TB, isoniazid-resistant tuberculosis; MDR-TB, multidrug-resistant tuberculosis, ROC, Receiver operating characteristic curve.

"treatment completed". For bacteriology comparison, the unfavorable group had a significantly higher incidence of positive sputum smear or culture, implying the warning role of bacteriologically positive results for adverse outcome prediction, with expanded infectiousness observed among the patients with poor outcomes.

In radiology, emerging studies have explored the utility of chest CT for differentiating DR-TB from DS-TB, revealing that DR-TB patients more frequently exhibited thoracic abnormalities such as pan-pulmonary involvement, bronchiectasis, and cavitary lesions [54, 55], which align closely with our observations. Notably, we identified a higher prevalence of right middle lobe (RML) lesions, patchy infiltrates, and GGOs in DR-TB cohorts. Whereas classic TB lesions typically localize to the upper and lower lobes [56], the increased involvement of the RML in DR-TB suggested a more aggressive disease phenotype, corroborating the notion of extensive pulmonary parenchymal damage in drug-resistant cases. Cavity formation emerged as a shared risk factor for both DR-TB development and unfavorable treatment outcomes in our analysis, consistent with previous reports [32, 57]. Pleural effusion exhibited divergent effects on the two clinical contexts. Specifically, this radiographic finding demonstrated a protective association against DR-TB development while emerging as a risk factor for unfavorable treatment outcomes, evidenced by its significantly lower prevalence in DR-TB patients versus DS-TB, and higher frequency in the unfavorable outcome cohort compared to successfully treated DR-TB patients. We speculated that the rationale behind this finding was probably due to that TB patients with pleural effusion might receive more intense comprehensive treatment and subsequently follow regular treatment, whereas when DR-TB patients develop pleural effusion the body condition may be too serious to reach complete healing.

This study has several limitations. First, the patients were retrospectively involved and from a single hospital, which may lead to potential biases and insufficient explanations for the general population. Involving more institutions and prospective validation of the results is warranted in the future. Second, since the usage of second-line injectables demonstrates a decreasing trend compared to bedaquiline and linezolid, to better assist therapeutic regimen development, the WHO has implemented a new definition of XDR-TB as resistance to RIF, bedaquiline or linezolid, and any kind of FQ from 2021 [58]. Nevertheless, we still employed the previous definitions due to the retrospective nature of the study and the limited availability of phenotypic or genotypic testing for bedaquiline/linezolid resistance at the time of data collection. Thus, in order to closely keep up with the updated status of DR-TB supervision, overall coordination of laboratory systems and the clinic is urgently needed. Thus, the prediction models may only serve as reference tools for diagnosis and risk assessment, while accurate evaluation still requires comprehensive consideration of molecular tests and real body conditions. In addition, scanning for resistance-related mutations and evolutionary analysis based on genomic sequences have also enhanced our understanding of DR-TB [59–62]. Subsequently, biological analyses integrating genomics and transcriptomics are to be considered. Only then would it be possible to fully discuss the risk factors of DR pulmonary TB at the molecular and clinical levels.

In clinical practice, the differential diagnosis between primary pulmonary TB and extrapulmonary TB such as abdominal TB has always been a challenging problem. Recently, researchers have integrated CT images and clinical data to construct a highly accurate differential diagnosis model, which successfully enables the accurate differentiation between extrapulmonary manifestations of pulmonary TB and lesions of abdominal lymph nodes [63]. This research achievement has pointed out the direction for subsequent studies: we can further explore a multimodal deep learning model based on radiomics and clinical data to accurately identify different drug-resistant types of pulmonary TB, thus providing a more targeted decision-making basis for the diagnosis and treatment of TB.

In line with previous research on the precise identification and prediction of pulmonary infections [64, 65], we aim to include more DR-TB cases from diverse regions, cohorts, and types, systematically summarize their clinical indicators and molecular changes, and ultimately develop an integrated model for diagnosis, treatment, and prognosis. This model would enable accurate identification of DR-TB and its subtypes while providing valuable references for subsequent treatment decisions.

Conclusion

We discussed the risk factors that contribute to DR-TB and unfavorable treatment outcomes, and provide a potential clinical strategy for patient recognition, which could be useful for physicians before DST results are available and provide support for intervention planning. Our findings suggest that giving consideration to anti-TB history, radiological manifestations, and drug resistance subtypes of patients with DR-TB may play a part in their overall management. Moreover, how to bridge the gap between DR-TB diagnosis and treatment deserves deep reflection.

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Author contributions

Changshu Li (Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing), Shufan Liang (Data curation, Formal analysis, Investigation, Writing – original draft), Xue Wang (Data curation), Su Lui (Project administration, Writing – review & editing), and Chengdi Wang (Funding acquisition, Resources, Supervision).

Supplementary data

Supplementary data are available at *PCMEDI Journal* online.

Conflict of interest

None declared.

Ethics statement

This study was conducted in strict accordance with the principles of the Declaration of Helsinki, ensuring ethical integrity and participant rights. Written informed consent was obtained from all participants prior to sample collection, following standard ethical guidelines. The study protocol was approved by the Institutional Review Board of West China Hospital, Sichuan University (Approval No. 2023.2286). Informed consent, either verbal or written, was obtained as per local regulatory requirements, except in cases where waivers or exemptions were granted by the respective ethics committee.

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