S1 Microbiological laboratory work

Cultures

For the diagnosis of tuberculosis, primary isolation and culture were performed using the BD MGIT960 system according to the manufacturer (BACTEC MGIT 960, Becton Dickinson, Franklin Lakes, NJ, USA). After turning positive, MGIT 960 inoculum was directly used for phenotypic drug susceptibility testing and also inoculated onto Lowenstein-Jensen medium for determination of minimum inhibitory concentration.

Chemicals

All studied drugs were ordered in chemical pure form including: prothionamide (Riemser, Germany), bedaquiline (Janssen, USA), clofazimine (Sigma-Aldrich, Germany), linezolid (Sigma-Aldrich, Germany), moxifloxacin (Bayer Health Care AG, Germany), levofloxacin (Spring Hourse, PA), cycloserine (Sigma-Aldrich, Germany), pyrazinamide (Sigma-Aldrich, Germany) and ethambutol (Sigma-Aldrich, Germany). As manufacturer recommended, all the chemicals were stored at -20℃. Levofloxacin was dissolved in deionized water, while moxifloxacin was in 0.1 M NaOH with subsequent dilutions in deionized water. All stock solutions were sterilized using 0.22 μm-pore sized membrane filtration (Millipore, Bedford, MA) and then stored at -80℃ until use. The frozen solution was used immediately after thawing. The working solution was prepared freshly from the stock solution and the serial dilutions were carried out to achieve the desired concentrations.

Phenotypic drug susceptibility testing (DST)

The inoculum prepared from MGIT tubes was standardized to a 0.5 McFarland standard and 0.5ml of bacterial suspension was inoculated to each drug containing tube. For the drug-free growth control preparation, the *M. tuberculosis* suspension was diluted 1:100 in sterile saline and 0.5ml of dilution was inoculated (proportion testing). Due to specific pH requirements, pyrazinamide (PZA) susceptibility was determined using the BACTEC MGIT 960 PZA susceptibility test, with a pH of 5.9 as previously described (1). Referred to the WHO technical guideline, critical concentrations were used for the classification of strains into resistant or susceptible.

Minimum inhibitory concentration (MIC) determination

MIC determination was performed with MGIT 960 growth supplement in the BACTEC MGIT 960 system (Becton Dickinson) as well. Briefly, the bacterial suspension was prepared from 2- to 3-week fresh subcultures performed on Lowenstein-Jensen medium. A suspension of 1.0 McFarland Standard was prepared and allowed to rest for around 20 min in order for large bacterial clumps to settle. The supernatant was transferred to another sterile tube and allowed to rest for another 15 min before transferring the supernatant to another tube and adjusted to 0.5 mg/ml using M7H9. This suspension was diluted 1:5 in sterile physiological water to be used as MIC inoculum. The drug-free control was inoculated with 0.5 ml of a 1:100 dilution of inoculum representing 1% of the bacterial population. The MIC was determined to be the lowest drug concentration that tested susceptible.

Quality assurance

All these tests were done in duplicates of the studied isolates. In addition, H37Rv reference strains (ATCC 27294) were included in each batch for inter- and intra-run quality control. For internal quality assurance, DST was repeated for 10% of the isolates by the collaborating Jiangsu Province-level reference laboratory who had passed the WHO's external quality control with a consistency of over 98%. For external quality assessment, 5% of isolates were sent to Shanghai Public Health Clinical Centre, serving as WHO collaborating centre for clinical management, training and research on emerging and re-emerging infectious diseases. The consistency between the two rounds was over 95%.

Reference

1. WHO. Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis. 2018. [Available from: https://www.who.int/tb/publications/2018/WHO_technical_drug_susceptibility_testing/en/]

S2 LC-MS/MS methods for measurement of linezolid, bedaquiline, cycloserine and clofazimine

Plasma concentrations of linezolid, bedaquiline, cycloserine and clofazimine were determined using a validated liquid chromatography with tandem mass spectrometry method (LC-MS/MS) in Agilent co-constructed laboratory, department of environment science, Fudan University. The linezolid-d3, bedaquiline-d6, carbamazepine and clofazimine-d7 were used as the internal standards. Chromatographic separations were performed on a 30 mm Polaris C18 column (Agilent Technology) with a gradient elution. Mobile phases consisted of 25% 0.01 M ammonium formate (pH 4) and 75% methanol, with a flow rate of 1.5 ml/min. Positive ionization mode and multiple reaction monitoring were applied for detection of linezolid, bedaquiline, cycloserine and clofazimine with *m/z* of 338.01 → 296.03, 555.2 → 58.0, 335.9 →157.2 and 473.8→431.4, respectively. The analytical ranges for linezolid, bedaquiline, cycloserine and clofazimine were 0.001~30, 0.001~40.0, 0.0033~40.0 and 0.004~40.0 mg/L, respectively, with good linearity of $r^2 > 99.83\%$ for all analyses. The inter- and intra-day variation ranged from 2.3% to 8.5% for all drugs.

S3 Random Forest, Classification and Regression Tree and modified Poisson regression analysis

To control heterogeneity within and between study populations, Random Forest and Classification and Regression Tree (CART) analysis were performed among patients receiving identical Group A-based regimen. A two-step approach was applied for data analysis. Firstly, Random Forest was used to generate relative variable importance ranking scores for each variable in prediction of six-month culture conversion. One thousand trees were conducted with out of bag data for testing. Variable importance was calculated on the basis of the number of times each variable was used for splitting the data. The most important variable was applied as the reference, i.e. a score of 100%, while subsequent variables were scored relative to the first one. Overall, 22 potential predictors were assessed in the model, including $AUC_{0\text{-}24h}$/MIC of levofloxacin, moxifloxacin, linezolid, bedaquiline, cycloserine, clofazimine, prothionamide, pyrazinamide and ethambutol, number of group A, group B and group C drugs, sex, age, weight, current smoking, diabetes mellitus type 2, baseline time to culture positivity, severe disease, extensive pulmonary disease, pulmonary cavity and baseline drug susceptibility profile.

Then, CART analysis was used to identify the key predictors predictive of six-month sputum culture conversion and to determine their cut-off values from the top ten variables identified in Random Forest. As a nonparametric method, CART analysis uses

binary recursive partitioning to assign patients to homogenous groups on the basis of Gini criterion function. The results were presented in the form of intuitive and easy-to-interpret decision trees, which had the advantage of handling missing data by identifying and using surrogate variables to minimize ascertainment bias. The root node, considered as the primary predictor, was applied for splitting nodes. The fully growing trees were pruned to avoid overmatching. The tree within one standard error of minimum was chosen as the optimal one, which is comparable to the minimum cost tree but less complex. We applied receiver operating characteristic (ROC) analysis and 10-fold cross-validation to evaluate the goodness-of-fit for each model.

Finally, given the advantages of numerically stable procedure and no convergence problem, modified Poisson regression model was applied to estimate risk ratio. Subsequently, the Cox proportional hazard regression model was used to calculate hazard ratio for the cut-off values derived from CART analysis. Both these two analyses were adjusted for current smoking, diabetes mellitus type 2, time to culture positivity at baseline and effective drug numbers at the onset of treatment.

Table S1. Demographic and clinical characteristics of patients with multidrug-resistant tuberculosis in different treatment response groups

Characteristics	No. (%) of patients with two-month sputum culture		No. (%) of patients with six-month sputum culture		No. (%) of patients with treatment outcome	
	Positive (n=109)	Negative (n=88)	Positive (n=69)	Negative (n=128)	Unfavourable (n=41)	Successful (n=156)
Age, years [a]	42.2±10.0	41.9±9.9	43.2±10.7	41.4±9.4	44.6±11.8	41.4±9.3
Sex						
Male	75 (53.6)	65 (46.4)	45 (32.1)	95 (67.9)	27 (19.3)	113 (80.7)
Female	34 (59.6)	23 (40.4)	24 (42.1)	33 (57.9)	14 (24.6)	43 (75.4)
Body mass index [a]	21.1±4.8	20.4±4.2	21.5±5.0	20.4±4.3	21.8±5.2	20.5±4.4
Current smoking						
No	43 (47.8)	47 (52.2)	24 (26.7)	66 (73.3) [b]	15 (16.7)	75 (83.3)
Yes	66 (61.7)	41 (38.3)	45 (42.1)	62 (57.9)	26 (24.3)	81 (75.7)
Diabetes type 2						
No	83 (52.9)	74 (47.1)	49 (31.2)	108 (68.8) [b]	29 (18.5)	128 (81.5)
Yes	26 (65.0)	14 (35.0)	20 (50.0)	20 (50.0)	12 (30.0)	28 (70.0)
Severe disease						
No	77 (54.6)	64 (45.4)	48 (34.0)	93 (66.0)	26 (18.4)	115 (81.6)
Yes	32 (57.1)	24 (42.9)	21 (37.5)	35 (62.5)	15 (26.8)	41 (73.2)
Extensive pulmonary disease						
No	85 (53.5)	74 (46.5)	53 (33.3)	106 (66.7)	29 (18.2)	130 (81.8)
Yes	24 (63.2)	14 (36.8)	16 (42.1)	22 (57.9)	12 (31.6)	26 (68.4)
TTP, days [a]	11.2±3.0	12.8±2.7 [b]	10.9±2.8	12.5±2.9 [b]	10.2±2.7	12.4±2.9 [b]
DST profile						
MDR-TB alone	91 (56.9)	69 (43.1)	62 (38.8)	98 (61.2) [b]	34 (21.3)	126 (78.7)
Pre-XDR-TB	18 (48.6)	19 (51.4)	7 (18.9)	30 (81.1)	7 (18.9)	30 (81.1)
Drug intake						
Levofloxacin	45 (57.7)	33 (42.3)	28 (35.9)	50 (64.1)	22 (28.2)	56 (71.8) [b]
Moxifloxacin	45 (57.0)	34 (43.0)	33 (41.8)	46 (58.2)	11 (13.9)	68 (86.1)
Linezolid	88 (52.4)	80 (47.6)	52 (31.0)	116 (69.0) [b]	26 (15.5)	142 (84.5) [b]
Bedaquiline	28 (40.0)	42 (60.0)	19 (27.1)	51 (72.9)	5 (7.1)	65 (92.9) [b]
Clofazimine	72 (52.9)	64 (47.1)	43 (31.6)	93 (68.4)	23 (16.9)	113 (83.1) [b]
Cycloserine	106 (57.0)	80 (43.0)	67 (36.0)	119 (64.0)	40 (21.5)	146 (78.5)
Prothionamide	46 (53.5)	40 (46.5)	30 (34.9)	56 (65.1) [b]	18 (20.9)	68 (79.1)
Pyrazinamide	64 (64.6)	35 (35.4)	42 (42.4)	57 (57.6)	31 (31.3)	68 (68.7) [b]
Ethambutol	71 (57.7)	52 (42.3)	44 (35.8)	79 (64.2)	31 (25.2)	92 (74.8)
Number of drugs in [a]						
Group A	1.9±0.7	2.2±0.6 [b]	1.9±0.7	2.1±0.6	1.6±0.5	2.1±0.6 [b]
Group B	1.6±0.5	1.6±0.5	1.7±0.5	1.6±0.5	1.7±0.5	1.6±0.5
Group C	2.0±1.1	2.1±1.1	2.0±1.0	2.0±1.1	2.0±0.9	2.0±1.1
Effective drugs [a]	5.6±0.6	5.7±0.7	5.7±0.6	5.6±0.7	5.6±0.6	5.7±0.7

DST: drug susceptibility testing; TTP: time to culture positivity recorded by the MGIT 960 system. Group A, B and C drugs were referred to the multidrug-resistant tuberculosis treatment guidelines released by the World Health Organization.

[a]: mean ± standard deviation

[b]: $P<0.05$

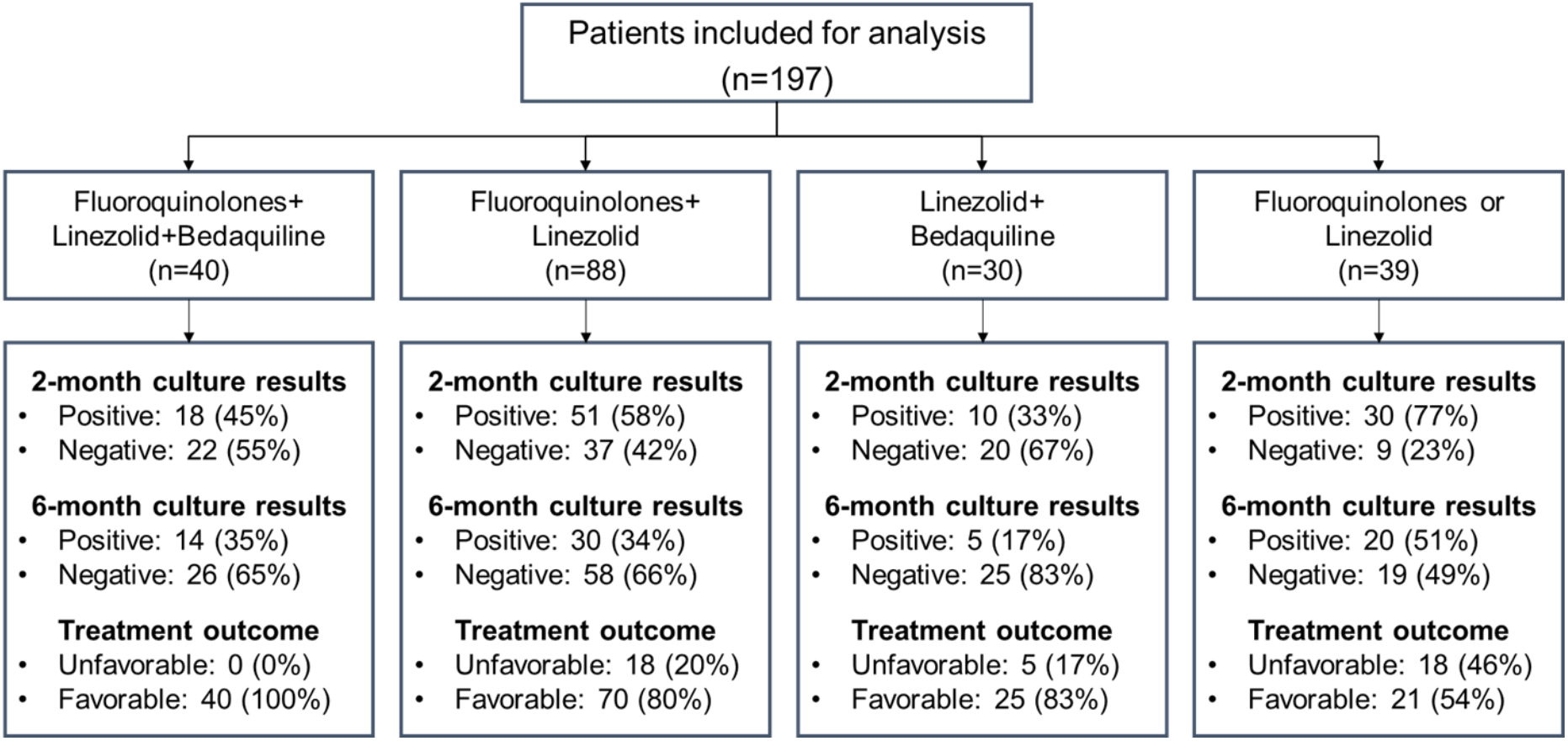

Figure S1. Treatment responses in patients with multidrug-resistant tuberculosis receiving different type and number of Group A drugs

Table S2. Drug change and adverse events during the treatment in correspondence to the treatment categories

	No. (%) of Patients treated with			
	FQs+LZD+BDQ (n=40)	FQs+LZD (n=88)	LZD+BDQ (n=30)	Others (n=39)
Drug change during the treatment				
Group A regimen	3(7.5)	1(1.1)	2(6.7)	0(0.0)
Group B regimen	6(15.0)	4(4.5)	3(10.0)	3(7.7)
Group C regimen	0(0)	1(1.1)	0(0)	1(2.6)
Adverse events [a]				
Gastrointestinal disorders	13(32.5)	31(35.2)	10(33.3)	12(30.8)
Psychiatric disorders	5(12.5)	12(13.6)	6(20.0)	6(15.4)
Central nerve system disorders	1(2.5)	3(3.4)	3(10.0)	3(7.7)
Peripheral neuropathy	3(7.5)	6(6.8)	2(6.7)	1(2.6)
Liver injury	2(5.0)	7(8.0)	2(6.7)	5(12.8)
Kidney injury	1(2.5)	4(4.5)	2(6.7)	0(0.0)
Anaemia	5(12.5)	14(15.9)	5(16.7)	2(5.1)
QTc prolongation	12(30)	3(3.4)	8(26.7)	2(5.1)
Others (pain, skin hyperpigmentation, et al)	5(12.5)	14(15.9)	4(13.3)	6(15.4)

FQs: fluoroquinolones; LZD: linezolid; BDQ: bedaquiline

[a] Adverse events were defined as follows:

Gastrointestinal disorders: presence of nausea, vomiting, abdominal pain, diarrhea, epigastric discomfort, hematemesis, melena, and positive endoscopic findings;

Psychiatric disorders: presence of depression, anxiety, psychosis, suicide, nightmares, and convulsion;

Central nervous system disorders: headache and seizure activity as reported by patient or witness;

Peripheral neuropathy: numbness, weakness, tingling, dizziness, burning/pain in the extremities, diagnosed by physician or electromyography;

Liver injury: alanine transaminase elevations above five times the upper limit of normal (ULN) or above three times the ULN with total bilirubin above 2 times the ULN;

Kidney injury: an abnormal estimated glomerular filtration rate based on serum creatinine using the Modification of Diet in Renal Disease formula;

Anaemia: haemoglobin level below 120 g/L for women and 130 g/L for men;

QTc prolongation: a corrected QT interval with the use of Fridericia's formula of more than 450 msec.

Table S3. Distribution for drug exposure - susceptibility ratio in patients with multidrug-resistant tuberculosis

	Two-month culture conversion			Six-month culture conversion			Treatment outcome		
	Positive (n=109)	Negative (n=88)	*P*	Positive (n=69)	Negative (n=128)	*P*	Unfavourable (n=41)	Successful (n=156)	*P*
Levofloxacin (n=78)									
C_{max}, mg/L	4.8 (4.4, 5.3)	4.6 (4.1, 5.1)	0.36	4.9 (4.4, 5.3)	4.7 (4.1, 5.2)	0.624	4.9 (4.2, 5.1)	4.7 (4.3, 5.3)	0.85
$AUC_{0\text{-}24h}$, mg· h/L	53.2 (44.9, 60.0)	51.6 (39.5, 62.8)	0.915	52.5 (45.1, 56.6)	52.2 (39.6, 62.1)	0.95	51.4 (44.3, 55.8)	53.2 (42.7, 62.4)	0.556
C_{max}/MIC	9.0 (4.9, 10.4)	9.8 (8.6, 22.0)	**0.002**	5.3 (4.5, 10.1)	9.6 (8.6, 11.8)	**<0.001**	5.0 (4.4, 8.1)	9.6 (8.9, 11.7)	**<0.001**
$AUC_{0\text{-}24h}$ /MIC	93.3 (50.6, 114.3)	108.7 (90.0, 249.1)	**0.002**	63.3 (48.7, 107.4)	108.8 (90.1, 136.8)	**<0.001**	52.9 (44.3, 96.6)	108.8 (90.4, 134.0)	**<0.001**
Moxifloxacin (n=79)									
C_{max}, mg/L	3.0 (2.2, 4.0)	3.7 (3.1, 5.0)	**0.01**	2.8 (2.1, 3.9)	3.6 (3.0, 5.3)	**0.007**	3.0 (2.8, 6.5)	3.4 (2.7, 4.8)	0.91
$AUC_{0\text{-}24h}$, mg· h/L	45.8 (24.2, 60.6)	54.8 (47.2, 64.9)	**0.02**	46.4 (23.8, 60.3)	52.3 (44.5, 64.9)	0.054	49.1 (45.8, 88.6)	49.4 (40.0, 60.2)	0.346
C_{max}/MIC	10.8 (4.9, 19.5)	49.1 (38.3, 60.1)	**<0.001**	7.2 (4.6, 13.3)	43.0 (25.0, 57.0)	**<0.001**	9.5 (5.5, 13.5)	28.1 (10.1, 52.0)	**<0.001**
$AUC_{0\text{-}24h}$ /MIC	177.1 (68.5, 268.1)	742.4 (476.9, 871.0)	**<0.001**	119.6 (51.6, 192.7)	624.8 (387.2, 823.9)	**<0.001**	159.0 (91.5, 194.7)	410.6 (155.0, 758.8)	**0.016**
Linezolid (n=168)									
C_{max}, mg/L	7.5 (7.1, 8.7)	7.6 (7.2, 8.6)	0.904	7.4 (6.1, 8.3)	8.0 (7.3, 8.8)	**0.006**	7.3 (5.4, 8.3)	7.6 (7.2, 8.8)	**0.016**
$AUC_{0\text{-}24h}$, mg· h/L	113.0 (92.4, 124.7)	114.5 (101.9, 125.4)	0.542	104.9 (73.9, 122.0)	117.0 (105.2, 126.5)	**0.002**	93.9 (64.9, 122.6)	114.6 (102.2, 125.5)	**0.012**
C_{max}/MIC	32.1 (28.5, 38.7)	33.7 (29.5, 51.9)	**0.038**	29.6 (18.4, 35.0)	34.4 (29.8, 51.9)	**<0.001**	27.3 (10.8, 33.6)	33.1 (29.5, 46.0)	**<0.001**
$AUC_{0\text{-}24h}$ /MIC	472.2 (372.5, 569.7)	492.4 (432.5, 715.4)	**0.039**	429.6 (273.6, 503.1)	497.7 (439.0, 715.4)	**<0.001**	373.4 (129.7, 503.8)	492.4 (433.7, 617.9)	**<0.001**
Bedaquiline (n=70)									
C_{max}, mg/L	2.2 (1.2, 3.9)	2.7 (2.2, 3.9)	0.172	2.0 (1.1, 3.2)	2.7 (2.2, 4.1)	**0.039**	2.4 (1.6, 3.0)	2.6 (1.9, 4)	0.445
$AUC_{0\text{-}24h}$, mg· h/L	34.9 (15.3, 55.1)	44.1 (32.3, 56.5)	0.208	30.5 (13.0, 51.3)	43.7 (32.8, 58.0)	**0.036**	35.7 (21.6, 46.8)	42.1 (28.9, 57)	0.418
C_{max}/MIC	134.1 (75.5, 209.1)	180.7 (134.6, 254.9)	**0.045**	98.4 (64.4, 158.3)	180.2 (135.1, 268.7)	**0.001**	158.3 (104.6, 196.7)	167.8 (110.5, 256.2)	0.707
$AUC_{0\text{-}24h}$ /MIC	2107.5 (914.7, 3275.4)	2901.0 (2103.2, 3765.2)	**0.028**	1527.2 (852.3, 2383.1)	2890.1 (2163.8, 3867.6)	**0.001**	2382 (1441.4, 3120.0)	2383.1 (1627, 3743.4)	0.657
Clofazimine (n=136)									
C_{max}, mg/L	1.0 (0.9, 1.6)	1.0 (0.9, 1.4)	0.711	1.0 (0.7, 1.5)	1.0 (0.9, 1.4)	0.473	1.1 (0.9, 1.6)	1.0 (0.9, 1.4)	0.445
$AUC_{0\text{-}24h}$, mg· h/L	16.3 (13.2, 23.8)	16.3 (12.1, 20.9)	0.456	16.5 (9.4, 22.7)	16.3 (13.3, 22.3)	0.554	18.5 (12.6, 23.9)	15.6 (12.7, 21.6)	0.364

C_{max}/MIC	4.2 (1.9, 9.0)	7.8 (3.4, 15.4)	**0.009**	3.8 (1.9, 8.1)	7.0 (3.2, 15.5)	**0.005**	6.3 (2.0, 12.6)	5.9 (2.5, 15.0)	0.495
$AUC_{0\text{-}24h}$ /MIC	64.4 (30.2, 141.3)	115.7 (45.8, 235.1)	**0.013**	51.7 (26.8, 138.1)	101.1 (45.0, 235.6)	**0.005**	102.7 (34.4, 154.3)	94.8 (36.8, 228.6)	0.548
Cycloserine (n=186)									
C_{max}, mg/L	22.7 (15.4, 42)	27.9 (20.6, 43.0)	0.216	22.8 (11.7, 41.8)	24.1 (18.6, 43.0)	0.189	23.6 (15.8, 42.1)	23.0 (18.3, 42.8)	0.73
$AUC_{0\text{-}24h}$, mg· h/L	465.4 (257.3, 688.9)	563.3 (349.2, 718)	0.274	478 (187.9, 679.7)	478.3 (318.4, 718.3)	0.24	479.3 (263.9, 678.6)	478.2 (313.9, 716.4)	0.683
C_{max}/MIC	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.269	100.0 (93.6, 100.0)	100.0 (100.0, 100.0)	**0.011**	100.0 (95.2, 100.0)	100.0 (100.0, 100.0)	0.073
$AUC_{0\text{-}24h}$ /MIC	86.2 (46.7, 152.4)	130.0 (65.5, 219.3)	**0.004**	79.2 (33.4, 119)	111.0 (65.0, 214.6)	**0.001**	90.7 (33.6, 144.6)	99.4 (59.3, 201.0)	0.048
Prothionamide (n=86)									
C_{max}, mg/L	1.3 (1.1, 1.5)	1.3 (1.2, 1.7)	0.225	1.3 (1.1, 1.5)	1.3 (1.2, 1.6)	0.514	1.2 (1.0, 1.4)	1.3 (1.2, 1.6)	0.08
$AUC_{0\text{-}24h}$, mg· h/L	21.6 (18.8, 25.2)	23.1 (21.0., 28.6)	0.158	20.9 (18.8, 25.5)	22.3 (20.5, 28.3)	0.306	20.2 (18.1, 24.4)	22.6 (20.7, 28.3)	0.06
C_{max}/MIC	2.2 (1.5, 4.5)	3.0 (2.1, 4.4)	0.239	2.2 (1.1, 4.4)	3.0 (2.0, 4.4)	0.186	2.0 (1.0, 4.2)	2.9 (2.0, 4.5)	0.14
$AUC_{0\text{-}24h}$ /MIC	38.0 (28.8, 77.4)	51.4 (37.1, 72.4)	0.25	39.5 (18.7, 75.9)	51.1 (36.0, 73.4)	0.195	37.7 (16.4, 69.5)	51.0 (35.5, 76.0)	0.161
Pyrazinamide (n=99)									
C_{max}, mg/L	15.6 (12.4, 20.2)	16.5 (9.1, 19.2)	0.473	15.9 (12.6, 19.6)	16.3 (10.7, 20.4)	0.821	16.0 (13.2, 19.5)	16.0 (10.9, 20.4)	0.587
$AUC_{0\text{-}24h}$, mg· h/L	253.5 (191.7, 332.4)	253.5 (150.5, 310.5)	0.409	248.3 (195.4, 332.3)	255.1 (169.5, 316.2)	0.605	250.2 (215.7, 332.3)	254.3 (169.6, 323.0)	0.449
C_{max}/MIC	0.3 (0.2, 0.4)	0.5 (0.3, 0.7)	**<0.001**	0.3 (0.2, 0.3)	0.4 (0.2, 0.6)	**0.004**	0.2 (0.2, 0.3)	0.4 (0.2, 0.5)	**0.001**
$AUC_{0\text{-}24h}$ /MIC	4.2 (3.1, 5.6)	7.7 (4.6, 11.9)	**<0.001**	4.1 (3.4, 5.4)	5.9 (3.5, 9.3)	**0.014**	3.9 (3.4, 5.2)	5.6 (3.5, 9.3)	**0.005**
Ethambutol (n=123)									
C_{max}, mg/L	2.1 (1.5, 3.1)	2.7 (1.8, 3.3)	0.097	2.1 (1.5, 3.5)	2.4 (1.8, 3.2)	0.507	2.1 (1.5, 3.8)	2.3 (1.6, 3.2)	0.998
$AUC_{0\text{-}24h}$, mg· h/L	19.4 (13.8, 26.4)	24.3 (15.5, 30.2)	0.132	19.5 (13.8, 37.9)	22.3 (15.4, 28.0)	0.839	19.4 (13.8, 40.3)	21.9 (14.4, 27.9)	0.749
C_{max}/MIC	2.1 (1.4, 2.6)	2.3 (1.6, 3.6)	**0.024**	2.0 (1.4, 2.3)	2.2 (1.5, 3.2)	0.061	2.0 (1.5, 2.3)	2.2 (1.5, 3.2)	0.192
$AUC_{0\text{-}24h}$ /MIC	19.1 (12.7, 23.5)	21.5 (13.9, 31.8)	**0.035**	19.3 (12.9, 23.5)	20.2 (13.5, 27.7)	0.213	19.2 (12.7, 23.1)	20.1 (13.5, 27.6)	0.053

C_{max}: maximum drug concentration; $AUC_{0\text{-}24h}$: area under drug concentration-time curve; MIC: minimum inhibitory concentration. Results are shown median with interquartile range. Mann-Whitney U test was applied for comparison.

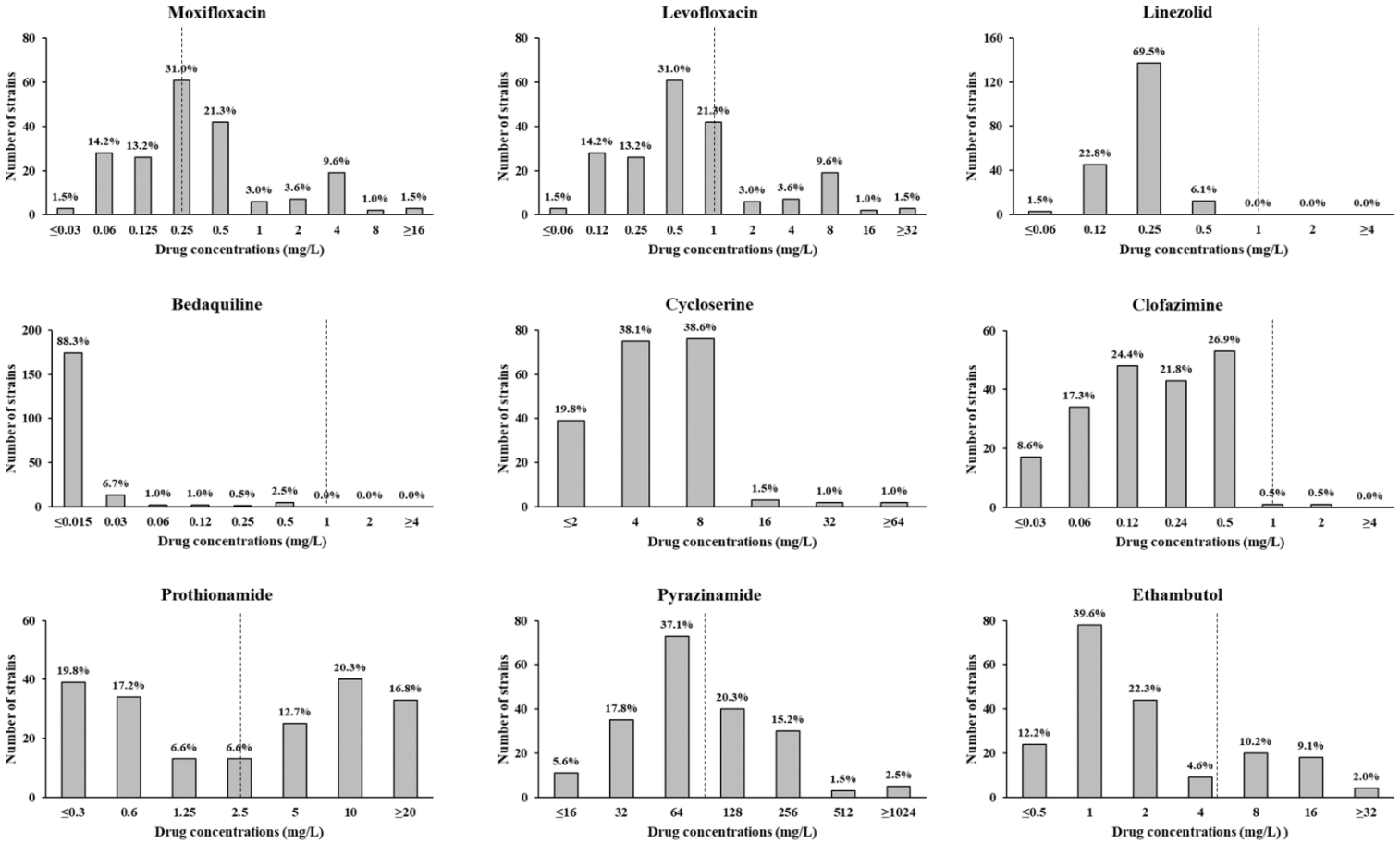

Figure S2. The distribution of minimum inhibitory concentrations for second-line anti-tuberculosis drugs in study patients with multidrug-resistant tuberculosis (n=197). Critical concentrations, recommended by the technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis 2018, were presented as the dotted lines.

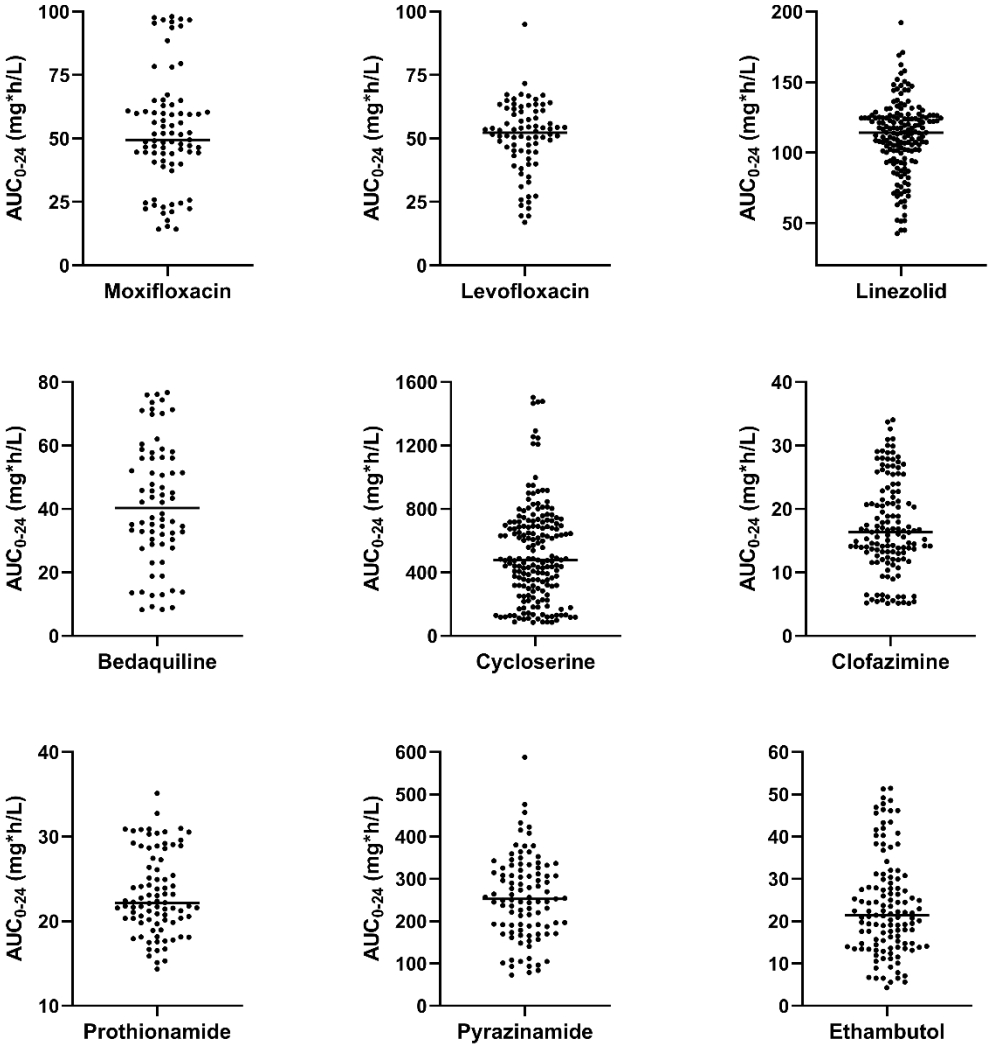

Figure S3. The distribution of area under drug concentration-time curve ($AUC_{0\text{-}24h}$) for second-line anti-tuberculosis drugs in patients with multidrug-resistant tuberculosis

Table S4. Association between CART-derived drug exposure – susceptibility targets and six-month sputum culture conversion

	Modified Poisson regression model			Cox proportional hazards regression model		
	No. of patients with Sputum culture conversion in Month 6 (%)	RR (95%CI)	aRR (95%CI) [a]	Median Time to culture conversion (IQR)	HR (95%CI)	aHR (95%CI) [a]
"Moxifloxacin+Linezolid+/-Bedaquiline" (n=67)						
Moxifloxacin $AUC_{0\text{-}24h}$/MIC≤231	1 (3.8)	1	1	6 (6, 6)	1	1
Moxifloxacin $AUC_{0\text{-}24h}$/MIC>231	40 (97.6)	25.4 (3.7, 173.5)	24.5 (3.4, 176.2)	1 (1, 1)	65.9 (8.8, 493.0)	71.7 (9.3, 550.9)
"Levofloxacin+Linezolid+/-Bedaquiline" (n=61)						
Linezolid $AUC_{0\text{-}24h}$/MIC≤287	1 (10.0)	1	1	6 (6, 6)	1	1
Linezolid $AUC_{0\text{-}24h}$/MIC>287	42 (82.4)	8.2 (1.3, 53.1)	7.8 (1.2, 50.1)	2 (2, 2)	12.9 (1.8, 93.9)	13.4 (1.8, 100.3)

CART: classification and regression tree; IQR: interquartile range; RR: rate ratio; HR: hazard ratio.

[a] adjusted according to smoking, diabetes mellitus type 2, time to culture positivity at baseline and effective drug numbers at the onset of treatment

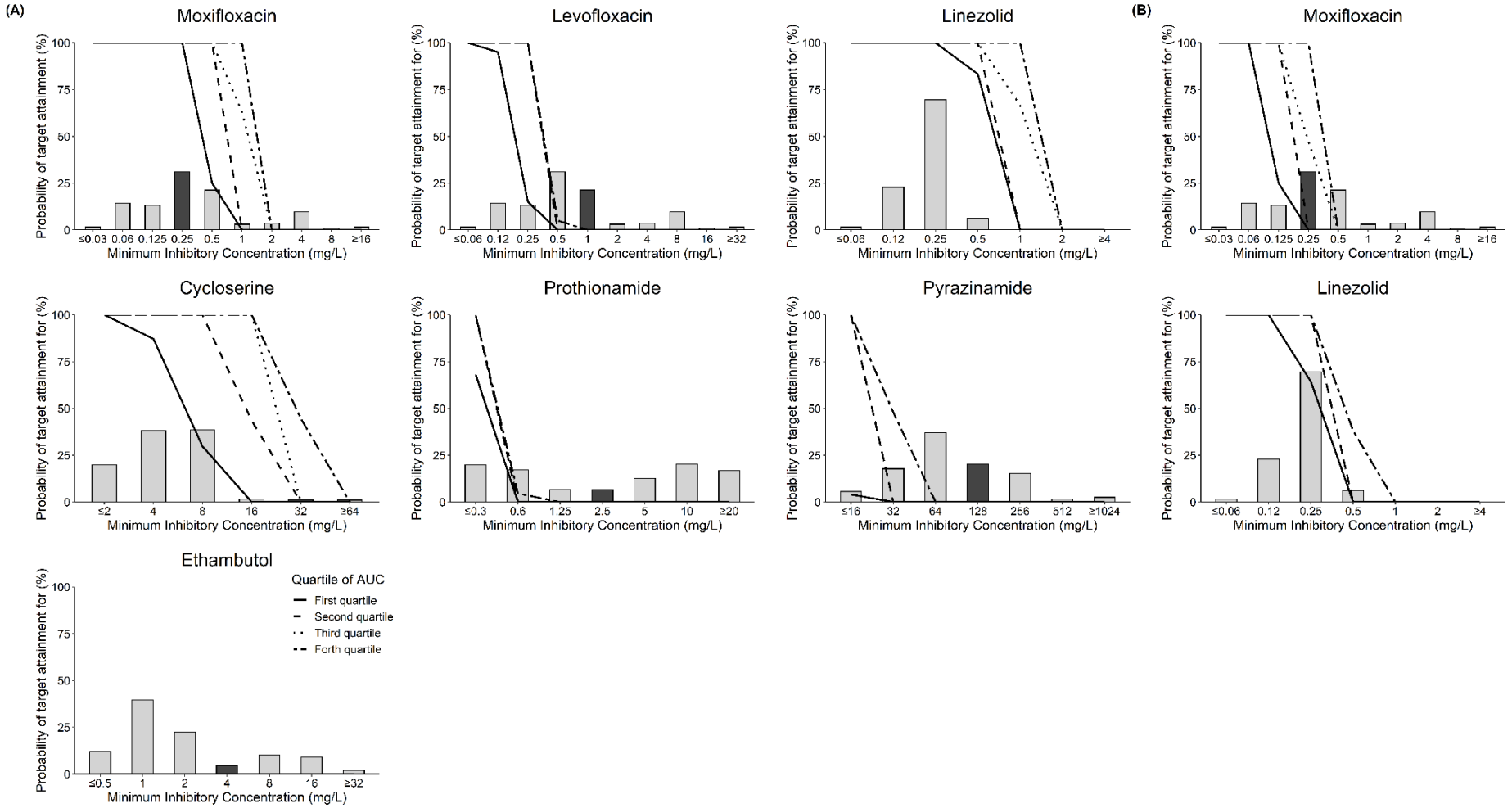

Figure S4. The distribution of minimum inhibitory concentration (MIC) and probability of target attainment for anti-tuberculosis drugs in patients with multidrug-resistant tuberculosis. Patients were divided into four groups according to the quartiles of respective area under drug concentration-

time curve ($AUC_{0\text{-}24h}$). The critical concentrations for moxifloxacin, levofloxacin, linezolid, prothionamide, pyrazinamide and ethambutol were referred as 0.25, 1, 1, 2.5, 100 and 5 mg/L, respectively. No critical concentration was reported for cycloserine. (A) $AUC_{0\text{-}24h}$/MIC ratios of 56, 160, 119, 25.8, 11.3, 56.2 and 119 from *in vitro* studies were applied as the target for moxifloxacin, levofloxacin, linezolid, cycloserine, prothionamide, pyrazinamide and ethambutol, respectively. (B) $AUC_{0\text{-}24h}$/MIC ratios of 231 and 287 from this study were applied as the clinical target for moxifloxacin and linezolid, respectively.