Preplanned Studies

Predictors for Treatment Outcomes in Patients with Multi-drug Resistant Tuberculosis — China, 2018–2020

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Summary

What is already known about this topic?

Multi-drug resistant tuberculosis (MDR-TB) is a critical global public health problem.

What is added by this report?

Sputum cultures and lung images show a strong association with treatment outcomes, serving as a multi-dimensional approach to identify MDR-TB patients with poor outcomes.

What are the implications for public health practice?

The results imply that funds and policy investments should be increased by early monitoring of MDR-TB patients, especially regarding imaging and sputum bacterium. By informing physicians on changes to the therapeutic schedule, treatment outcomes can be improved.

Multi-drug resistant tuberculosis (MDR-TB) is caused by the *Mycobacterium tuberculosis* that is resistant to rifampicin and isoniazid (*1*). MDR-TB has become a global public health concern, which seriously threatens the realization of the goal of "stopping the tuberculosis (TB) epidemic" by 2035 (*1*–*3*). China is a country with a high burden of MDR-TB (*1*). The coronavirus disease 2019 (COVID-19) pandemic poses significant challenges to control MDR-TB in China (*1*,*4*–*5*). Therefore, a model based on multi-modal data may predict the treatment outcome in the early treatment phase. The results of the study suggest that physicians should pay special attention to dynamic changes of the sputum bacterium and lung images at the intensive stage, and it may help physicians adapt the therapeutic schedule to improve the cure rate.

A multi-center retrospective study was conducted in twenty-three sentinel hospitals selected from sixteen provincial level administration divisions (PLADs) in China. There were 6 hospitals in the east, 3 hospitals in the west, 5 hospitals in the south, 4 hospitals in the north and 5 hospitals in the middle region of China. Among them, there were 8 tertiary hospitals, 10 second-grade hospitals, and 5 community hospitals.

These treatment outcomes were based on World Health Organization (WHO) recommendations, defined as follows: 1) 'Cured' meant the course of treatment was completed according to the national guidelines without evidence of treatment failure, and the sputum culture was negative for 3 consecutive times or more at least 30 days after the enhancement period. 2) 'Treatment failure' was defined as treatment terminated due to the following reasons: at least two anti-TB drugs in the treatment protocol needed to be permanently changed, no negative conversion after the enhancement period, reversed bacteriological test results in the continuing period after negative conversion, evidence indicating acquired drug resistance to fluoroquinolones or second-line injections, adverse drug reactions, or death directly associated with MDR-TB (*2*).

All patients with MDR-TB who visited one of the 23 sentinel hospitals between January 2018 and December 2020 were considered as possible subjects. Patients who met the following inclusion criteria were considered: 1) MDR-TB patients, with the definition of MDR-TB as presented by the WHO was used (*2*). 2) Signed informed consent. Exclusion criteria included the following: 1) Patients with other serious diseases (mental diseases, various cancers, hepatitis patients, serious skin diseases, severe metabolic disease, human immunodeficiency virus/acquired immunodeficiency syndrome, etc). 2) Pregnant or lactating patients and patients with pneumonia, pneumoconiosis or other lung diseases.

MDR-TB treatment was defined as receiving recommended regimen in the national MDR-TB control program (*2*–*3*). For each MDR-TB case, sputum smear, sputum culture, drug sensitivity test (DST), physical examination and routine blood counts, biochemical tests, and urinalyses were recorded through monthly examinations. Chest-computed tomography (CT) was performed during the intensive phase and continuation phase to all patients according

to the National TB Program (NTP) of China. Sputum specimens were collected and examined through direct smear microscopy for the presence of acid-fast bacilli (AFB) using Ziehl-Neelsen staining. A conventional DST was performed using the agar proportion method on enriched Middle-Brook 7H10 medium against first-line anti-TB drugs (FLDs). The rapid DST (Xpert MTB/RIF®) assay was performed to detect rifampicin resistance (RR) in smear-positive sputum samples. Second-line anti-TB drugs (SLDs) (*1*), such as Ethambutol, Streptomycin, Kanamycin, Ofloxacin, P-aminosalicylic acid, and Pyrazinamide, were also included. All positive cultures were submitted to the upper-level laboratory in the prefectural Center for Disease Control and Prevention (CDC).

As to all-round utilization of our clinical data, electronic medical record systems and questionnaires with telephone surveys, and underlying prognostic variables were collected with structured questionnaire using REDCap (version 10.0, Vanderbilt University, Nashville, USA). The questionnaire involved socio-demographic characteristics, risk factors, MDR-TB diagnosis and a history of TB, comorbidities, clinical laboratory indicators, and drug resistance at month zero. Data were cleaned in Microsoft Office Excel (version 2020, Microsoft Corp, Washington, USA) and analyzed with SAS (version 9.4, SAS Institute Inc, Cary, USA). Univariable analysis was done for computing odds ratios (ORs) and their 95% confidence intervals (CIs). The level of significance was assessed by the Wald χ^2 test. Variables with $P<0.05$ were entered into a multivariable logistic regression model to examine their independent effects through stepwise deletion of variables. $P<0.05$ was considered significant using a two-tailed test.

A total of 556 patients completed the therapeutic process, including cured patients (n=389) and patients with treatment failure (n=167). The average age of cured patients was lower than that of treatment failure patients (37.1, 40.2, $Z=-3.844$, $P<0.001$). The number of lobes involved in the pulmonary lobe in month 0 of the cured patients were less than that of non-cured patients (3, 5, $Z=-6.695$, $P<0.001$). Furthermore, the cavity count in the initial month in cured patients was lower compared to that in failure patients (1, 2, $Z=-4.689$, $P<0.001$).

Single factor analysis showed that variables related to the negative prognosis of MDR-TB patients included age, marriage, irregular treatment, lesions involving lung lobes in month zero, cavities counts in month zero, time from TB diagnosis to MDR-TB diagnosis, time from MDR-TB diagnosis to treatment, time from TB diagnosis to MDR-TB treatment, leukocytes, platelets, erythrocytes, sedimentation rate, streptomycin resistance, Ofloxacin resistance, Para-aminosalicylic acid treatment, Pyrazinamide treatment, Moxifloxacin treatment, and Kanamycin treatment (Table 1). In addition, sputum culture results and lung images (lesion absorption, cavity closure) were associated with unsuccessful treatment outcomes, including a sputum culture at month 1, a sputum culture at month 2, a sputum culture at month 3, a sputum culture at month 6, lesion absorption at month 6, and cavity closure at month 6 (Table 1). Finally, age, irregular treatment, time from MDR-TB diagnosis to treatment, erythrocyte sedimentation rate, Ofloxacin resistance, sputum culture month 3, lesions in the pulmonary lobe month zero, cavity count month zero, and cavity closure month 6 were associated with treatment outcome (Table 2).

TABLE 1. Predictors for MDR-TB treatment outcome using univariate analysis.

Predictor	Subgroup	Failure n=167 n (%)	Cured n=389 n (%)	χ^2	*P*	OR (95% CI)
Socio-demographic characteristics						
Age (year)	≥50 years (n=109)	47 (28.1)	62 (15.9)	11.044	0.001	0.484 (0.314, 0.746)
Gender	Female (n=182)	52 (31.1)	130 (33.4)	0.276	0.599	1.110 (0.752, 1.639)
Residential area	Urban (n=236)	70 (41.9)	166 (42.7)	0.027	0.868	1.032 (0.715, 1.489)
Marriage	Alone (n=166)	39 (23.4)	127 (32.6)	4.821	0.028	0.629 (0.415, 0.953)
Occupation	Farmer (n=240)	75 (44.9)	165 (42.4)	0.296	0.586	1.665 (1.156, 2.400)
Education	≥ High school (n=214)	58 (34.7)	156 (40.1)	1.424	0.233	1.258 (0.863, 1.836)
MDR-TB risk factors						
Smoking	Yes (n=213)	67 (40.1)	146 (37.5)	0.331	0.565	0.897 (0.619, 1.300)
Alcohol addiction	Yes (n=242)	77 (46.1)	165 (42.4)	0.648	0.421	0.861 (0.598, 1.240)
History of TB disease	Retreatment (n=406)	121 (72.5)	285 (73.3)	0.039	0.844	1.042 (0.693, 1.565)
Medical insurance	Yes (n=544)	161 (96.4)	383 (98.5)	2.326	0.127	2.379 (0.756, 7.487)

TABLE 1. (Continued)

Predictor	Subgroup	Failure n=167 n (%)	Cured n=389 n (%)	χ^2	*P*	OR (95% CI)
Current MDR-TB diagnosis and history of TB disease						
Liver protective drugs	Yes (n=178)	62 (37.1)	116 (29.8)	2.865	0.091	0.731 (0.499, 1.073)
Irregular treatment	Yes (n=116)	59 (35.3)	57 (14.7)	30.254	<0.001	0.314 (0.206, 0.480)
AFB smear month 0 (sputum grading)	High (>+++, n=192)	67 (40.1)	125 (32.1)	3.296	0.069	0.707 (0.485, 1.029)
Lesions in the pulmonary lobe month 0	≥3 (n=395)	140 (83.8)	255 (65.6)	18.978	<0.001	0.367 (0.231, 0.583)
Cavities month 0	Yes (n=321)	114 (68.3)	207 (53.2)	10.845	0.001	0.529(0.361, 0.775)
Time from TB diagnosis to MDR-TB diagnosis	≥1 year (n=271)	93 (55.7)	178 (45.8)	4.612	0.032	0.671 (0.466, 0.967)
Time from MDR-TB diagnosis to treatment	≥1 year (n=64)	38 (22.8)	26 (6.7)	29.625	<0.001	0.243 (0.142, 0.416)
Time from TB diagnosis to MDR-TB diagnosis	≥1 year (n=302)	108 (64.7)	194 (49.9)	10.313	0.001	0.544 (0.374, 0.790)
Comorbidities						
Diabetes	Yes (n=16)	7 (4.2)	9 (2.3)	1.474	0.224	0.541 (0.198, 1.478)
Hypertension	Yes (n=80)	28 (16.8)	52 (13.4)	1.131	0.288	0.766 (0.465, 1.263)
COPD	Yes (n=36)	12 (7.2)	24 (6.2)	0.199	0.655	0.849 (0.414, 1.741)
Malignancy	Yes (n=4)	3 (1.2)	2 (0.5)	0.764	0.382	0.283 (0.049, 1.707)
Clinical laboratory indicators at the beginning of treatment for MDR-TB cases						
Leukocytes	Above normal (n=45)	22 (13.2)	23 (5.9)	8.281	0.004	0.414 (0.224, 0.766)
Platelets	Below normal (n=122)	46 (27.5)	76 (19.5)	4.375	0.036	0.639 (0.419, 0.974)
Red blood cells	Below normal (n=14)	2 (1.2)	12 (3.1)	1.695	0.193	2.626 (0.581, 11.865)
Urinary protein	Above normal (n=61)	20 (12.0)	41 (10.5)	0.247	0.619	0.866 (0.491, 1.529)
Erythrocyte sedimentation rate	Above normal (n=266)	116 (69.5)	150 (38.6)	44.709	<0.001	0.276 (0.187, 0.770)
Drug resistance at the beginning of treatment for MDR-TB cases						
Ethambutol resistance	Yes (n=161)	53 (31.7)	108 (27.8)	0.897	0.344	0.827 (0.557, 1.226)
Streptomycin resistance	Yes (n=301)	101 (60.5)	200 (51.4)	3.867	0.049	0.692 (0.478, 0.999)
Pyrazinamide resistance	Yes (n=254)	73 (43.7)	181 (46.5)	0.374	0.551	1.121 (0.778, 1.614)
Kanamycin resistance	Yes (n=30)	10 (6.0)	20 (5.1)	0.164	0.684	3.095 (1.433, 6.686)
Ofloxacin resistance	Yes (n=89)	46 (27.5)	43 (11.1)	23.633	<0.001	0.327 (0.206, 0.521)
Sputum bacteria and imaging indicators in intensive phase of the treatment						
Sputum culture month 1	Positive (n=381)	144 (86.2)	237 (60.9)	34.681	<0.001	0.716 (0.650, 0.789)
Sputum culture month 2	Positive (n=315)	125 (74.9)	190 (48.8)	80.478	<0.001	0.731 (0.657, 0.813)
Sputum culture month 3	Positive (n=295)	137 (82.0)	158 (40.6)	7.302	0.007	0.605 (0.540, 0.679)
Sputum culture month 6	Positive (n=215)	102 (61.1)	113 (29.0)	16.085	<0.001	0.649 (0.566, 0.775)
Lesion absorption month 6	Absorbed (n=296)	75 (44.9)	221 (56.8)	6.649	0.011	1.156 (1.033, 1.292)
Cavity closure month 6	Absorbed (n=214)	53 (31.7)	161 (41.4)	4.597	0.032	1.129 (1.014, 1.256)
Drugs used during treatment procession						
Ofloxacin	Yes (n=393)	103 (61.7)	290 (74.6)	9.344	0.002	1.820 (1.237, 2.679)
Para-aminosalicylic acid	Yes (n=283)	72 (43.1)	211 (54.2)	5.789	0.016	1.564 (1.085, 2.254)
Pyrazinamide	Yes (n=469)	133 (79.6)	336 (86.4)	4.015	0.045	1.621 (1.008, 2.607)
Moxifloxacin	Yes (n=105)	41 (24.6)	64 (16.5)	5.002	0.025	0.605 (0.389, 0.942)
Kanamycin	Yes (n=8)	5 (3.0)	3 (0.8)	4.071	0.044	0.252 (0.060, 1.066)
Ethionamide	Yes (n=10)	4 (2.4)	6 (1.5)	0.481	0.488	0.638 (0.178, 2.292)
Clofazimine	Yes (n=7)	2 (1.2)	5 (1.3)	0.007	0.932	1.074 (0.206, 5.592)
Isoniazid	Yes (n=79)	20 (12.0)	59 (15.2)	0.976	0.323	1.314 (0.763, 2.262)
Clarithromycin	Yes (n=27)	9 (5.4)	18 (4.6)	0.147	0.702	0.852 (0.375, 1.937)
Rifapentine	Yes (n=45)	9 (5.4)	36 (9.3)	2.347	0.126	1.790 (0.842, 3.806)
Pasniazid	Yes (n=3)	1 (0.6)	2 (0.5)	0.016	0.901	0.858 (0.077, 9.527)

Abbreviation: MDR-TB=multi-drug resistant tuberculosis; TB=tuberculosis; AFB=acid-fast bacilli; COPD=chronic obstructive pulmonary disease; CI=confidence interval; OR=odds ratio.

TABLE 2. Predictors for favorable MDR-TB treatment outcome using multivariate analysis.

Variable	β	SE	Wald χ^2	df	P	OR (95% CI)
Age	−0.589	0.279	4.470	1	0.034	0.555 (0.321, 0.958)
Irregular treatment	−0.928	0.271	11.698	1	0.001	0.395 (0.232, 0.673)
Time of MDR-TB diagnosis to treatment	−1.168	0.341	11.719	1	0.001	0.311 (0.159, 0.607)
Erythrocyte sedimentation rate	−1.215	0.247	24.286	1	<0.001	0.297 (0.183, 0.481)
Ofloxacin resistance	−1.117	0.295	14.324	1	<0.001	0.327 (0.184, 0.584)
Sputum culture month 3	−1.894	0.268	50.091	1	<0.001	0.151 (0.089, 0.254)
Lesion in the pulmonary lobe month 0	−0.588	0.295	3.967	1	0.046	0.556 (0.312, 0.991)
Cavity count month 0	−1.697	0.324	27.384	1	<0.001	0.183 (0.097, 0.346)
Cavity closure month 6	1.649	0.315	27.347	1	<0.001	5.202 (2.804, 9.652)

Abbreviation: MDR-TB=multi-drug resistant tuberculosis; SE=standard error; df=degree of freedom; CI=confidence interval; OR=odds ratio.

DISCUSSION

The findings of the study indicated that a range of risk factors were associated with poor treatment outcomes in 23 sentinel hospitals in China. Risk factors in the intensive treatment phase involved irregular treatment, pulmonary cavity and a persistent positive culture in month 6. Patients at high risk need to be given more attention by physicians to help identify patients with poor responses to treatment, so physicians can adjust the treatment plan to improve cure rates.

Etiological examination has always been the primary means of evaluating the MDR-TB treatment outcome (*4*–*5*). Sputum negative conversion is considered a reliable indicator of the loss of bacterial infectivity. Bacterial changes (change to be negative) in the sputum during treatment are a critical indicator for find patients with poor outcomes in an early stage. In addition, dynamic changes in CT findings have shown that cavities non-closure on chest CT performed at month 6 of treatment was highly predictive of treatment failure. These findings were consistent with evidence that the presence and extent of cavities at initiation were a risk factor for unfavorable treatment outcomes (*5*).

This study was subject to some limitations: 1) Some biomarkers (specific proteins and genes related to the prognosis of MDR-TB) were not included. 2) We estimated only some lung features, whereas the pathological location of the lesion, ground glass shadows, and nodules may give additional clinical significance. Hence, a large-scale multi-centers prospective cohort study based on multi-dimensional information should be conducted in future.

In conclusion, our findings showed that the first 6 months are critical in reducing an unfavorable treatment outcome. The findings implied that physicians should pay special attention to the dynamic changes of the disease at the intensive stage. Regular testing of bacteria in sputum should be performed every month in the first six months at the CDC or a designated hospital, and a CT examination should be carried out to evaluate the therapeutic effects in the early stage. These steps can optimize the treatment plans to improve the outcomes for MDR-TB patients.

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