Clinical Microbiology and Infection xxx (2017) 1–8

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Treatment outcomes of multidrug-resistant tuberculosis patients in Zhejiang, China, 2009–2013

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ARTICLE INFO

Article history:
Received 26 February 2017
Received in revised form
2 July 2017
Accepted 7 July 2017
Available online xxx

Editor: M. Paul

Keywords:
Drug-resistant tuberculosis
MDR-TB
Standardized treatment
Treatment outcomes
Tuberculosis

ABSTRACT

Objectives: To examine treatment outcomes and factors associated with poor outcome of multidrug-resistant (MDR) tuberculosis (TB) in China.

Methods: We conducted a prospective observational cohort study including consecutive patients with MDR-TB between 2009 and 2013 in six regions of Zhejiang province. Patients were prescribed treatments by infectious disease specialists, and treatment outcomes were recorded. Sociodemographic characteristics were obtained through a structured questionnaire. The primary endpoint was poor treatment outcomes, defined as treatment failure based on microbiologic persistence, default (lost to follow-up) or death at 24 months. We assessed risk factors for poor treatment outcomes using a Cox proportional hazards model.

Results: A total of 820 MDR-TB patients were observed, and 537 with known treatment outcomes were included in our study. Overall, the treatment success rate was 40.2 per 100 years (374/537 participants, 69.6%), while treatment failure, death and default rates were 10.0 per 100 years (101 participants, 18.8%), 3.4 per 100 years (36 participants, 6.7%) and 2.7 per 100 years (26 participants, 4.8%) respectively. Independent predictors of poor treatment outcomes included age >60 years (hazard ratio (HR) 2.3, 95% confidence interval (CI) 1.2–4.2), patients registered as experiencing relapse (HR 2.2, 95% CI 1.1–4.4), patients registered as receiving treatment after failure (HR 2.4, 95% CI 1.2–4.9), use of standardized MDR-TB regimens (HR 0.6, 95% CI 0.4–1.0), cavitary disease (HR 4.9, 95% CI 2.8–8.6) and adverse events (HR 2.5, 95% CI 1.2–5.5).

Conclusions: Under well-designed treatment and management scheme, high treatment success rates were achieved in a high-MDR-TB-burden country. Antimicrobial susceptibility testing for all second-line drugs should be conducted to further assist in the treatment of MDR-TB. **L. Zhang, Clin Microbiol Infect 2017;▪:1**

Introduction

The emergence of multidrug-resistant (MDR) tuberculosis (TB) and extensively drug-resistant (XDR) TB continue to pose a great threat to the elimination of TB, with estimates of 3.9% of new and 21% of previously treated TB cases being MDR-TB and 0.25 million people dying from MDR-TB worldwide [1]. MDR-TB develops with poor management or as a result of previous exposure to anti-TB drugs [2,3].

To achieve the global target of ending the TB epidemic by 2030, providing high-quality disease management to improve treatment outcome is one of the key strategies [4]. To date the treatment

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http://dx.doi.org/10.1016/j.cmi.2017.07.008
1198-743X/

success rate of MDR-TB patients has been described as being only 52% globally [5]. However, this was mainly based on a small cohort and was also confounded by hospital admission bias. Different MDR-TB treatment regimens were prescribed to patients according to their medical conditions and registration group because there is little evidence for management based on randomized controlled trials. Apart from treatment regimen, there are many other factors affecting treatment outcomes, including gender, hospitalization, previous treatment [6], residence, acid-fast bacilli (AFB) result at baseline [7] and HIV status [8]. Factors associated with MDR-TB treatment outcomes vary largely from setting to setting.

China is among the 30 high-MDR-TB-burden countries worldwide. A national TB resistance survey found that 5.7% and 25.6% of new and previously treated cases were MDR-TB [9], 1.55 and 1.28 times higher than the global average respectively. However, China has few reports regarding treatment outcomes of MDR-TB, and all studies were conducted in hospitals [10,11]. To investigate treatment outcomes and factors associated with poor outcomes in China, we conducted this population-based study which intended to further support TB control and management.

Methods

Study population and procedures

We performed a prospective observational cohort study from July 2009 to July 2013 in six regions of Zhejiang province: Hangzhou, Huzhou, Jiaxing, Lishui, Quzhou and Shaoxing, initiated by the Zhejiang Disease Control and Prevention Center and the Global Fund MDR-TB Project. Zhejiang has set up routine drug resistance monitoring since 1999, and details can be found in our previous studies [12].

All MDR-TB patients involved in the study met the inclusion criteria: MDR-TB was confirmed by antimicrobial susceptibility testing (AST) from a regional reference laboratory; patients were sputum smear positive for AFB and culture positive for *Mycobacterium tuberculosis;* and patients were receiving treatment. As a result of the delay in receiving AST results, before patients switched to the definitive MDR-TB treatment, all newly diagnosed TB patients received the national standard 'new patient regimen': 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin (2HRZE/4HR) and retreatment patients received the 'retreatment regimen'—2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin (2HRZES/6HRE). We classified patients' definitive MDR-TB treatments into five types of standard regimens, each including four to five drugs that patients' disease was sensitive to according to the AST results. Four standard regimens were provided for 24 months and one for 36 months (Supplementary Table S1). The doses of all anti-TB drugs are described in Supplementary Table S2. If treated differently, patients were classified as receiving an individualized regimen. This individualized regimen was based on AST and TB treatment history. Treatments were prescribed by infectious disease specialists.

Patients were followed daily until the end of follow-up or until the outcome event had been reached, and drugs were provided under direct observation. We examined sputum smear, sputum culture, liver function, body weight and blood routine examination periodically to prevent adverse events. Additionally, 70 renminbi (the currency of China) nutritional subsidies and 70 renminbi traffic subsidies were given to impoverished patients every month. Those with poor mental health status received two free psychological consultations, and health education was also provided.

Information on sociodemographic characteristics (age, sex, occupation and household), MDR-TB-related characteristics (registration group, treatment history, hospitalization, treatment regimen and baseline resistance pattern) and indicators of severity (haemoptysis, cavitary disease and adverse events) were collected through questionnaires and medical records by trained health workers. Treatment outcomes, sputum culture and smear conversion, and chest radiographs were monitored periodically.

Approval of the study was obtained from the ethics committees at the Zhejiang Disease Control and Prevention Center. Written informed consent was obtained from all participants.

Definitions

MDR-TB and XDR-TB were defined according to World Health Organization (WHO) guidelines [7]. Pre-XDR-TB was defined as TB with resistance to both isoniazid and rifampicin, and either a fluoroquinolone (ofloxacin) or a second-line injectable drug (kanamycin).

Treatment outcomes were categorized according to the Global Fund MDR-TB Project. Cure was defined as a patient who completed treatment, and at least five final consecutive cultures of his or her sputum during the final 12 months of treatment were negative; or if one culture was positive, then at least three of its following consecutive cultures had to be negative. Treatment completed was defined as patients who had completed their treatments without evidence of failure but with inadequate bacteriologic records to be defined as cure. Treatment failure was defined when there were two or more positive sputum cultures of the five final cultures, or one positive culture of the final three cultures during the final 12 months of treatment. Death was defined as patients who died of any cause during treatment. Lost to follow-up (default) was defined as patients whose treatment was interrupted for two or more consecutive months against their clinician's advice.

Treatment success was defined as cure or completed treatment, whereas poor treatment outcome was defined as treatment failure, default or death.

Laboratory cultures and AST

Sputum smear microscopy was performed directly at the tuberculosis bacterium laboratory of each region, where direct AFB smear microscopy and AFB culture on Löwenstein-Jensen solid medium were applied. The identification of *M. tuberculosis* and AST was performed at a provincial reference laboratory. AST of four first-line drugs (isoniazid, rifampin, streptomycin, ethambutol) and two second-line drugs (ofloxacin, kanamycin) was performed for sputum culture–positive stains by the proportion method [13], and results were compared to standardized strains. Drug concentrations for rifampin, isoniazid, ethambutol, streptomycin, ofloxacin and kanamycin were 40.0, 0.2, 2.0, 4.0, 2.0 and 30.0 μg/mL respectively.

Statistical analysis

Sociodemographic, MDR-TB-related characteristics and indicators of severity were described as percentages stratified by regions. To investigate risk factors for poor outcomes, we conducted univariate and multivariate Cox regression analyses (stratified by region to control for setting-associated confounding). We also developed a sensitivity analysis excluding patients whose treatment were unrecorded to examine our findings. Hazard ratios and 95% confidence intervals were calculated to demonstrate the risks for poor outcomes. We also used the Kaplan-Meier method with the log-rank test to compare survival curves of time to poor

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outcomes by baseline resistance patterns. Statistical analysis was conducted by R 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/), and $P < 0.05$ indicated statistical significance.

Results

Study cohort and characteristics of participants

From 1 July 2009 to 13 July 2013, a total of 820 patients were diagnosed with sputum smear–positive MDR-TB in six regions of Zhejiang province. A total of 204 MDR-TB cases were not treated because of patient refusal to receive treatment, death or default before treatment, no effective treatment regimen, moving away and an having underlying medical conditions (not suitable for chemotherapy or could not receive treatment at the present time) (Fig. 1). Among 616 patients receiving treatment, 79 patients had incomplete outcome records. Overall, 537 patients were involved in our analysis. Basic characteristics stratified by region are shown in Table 1.

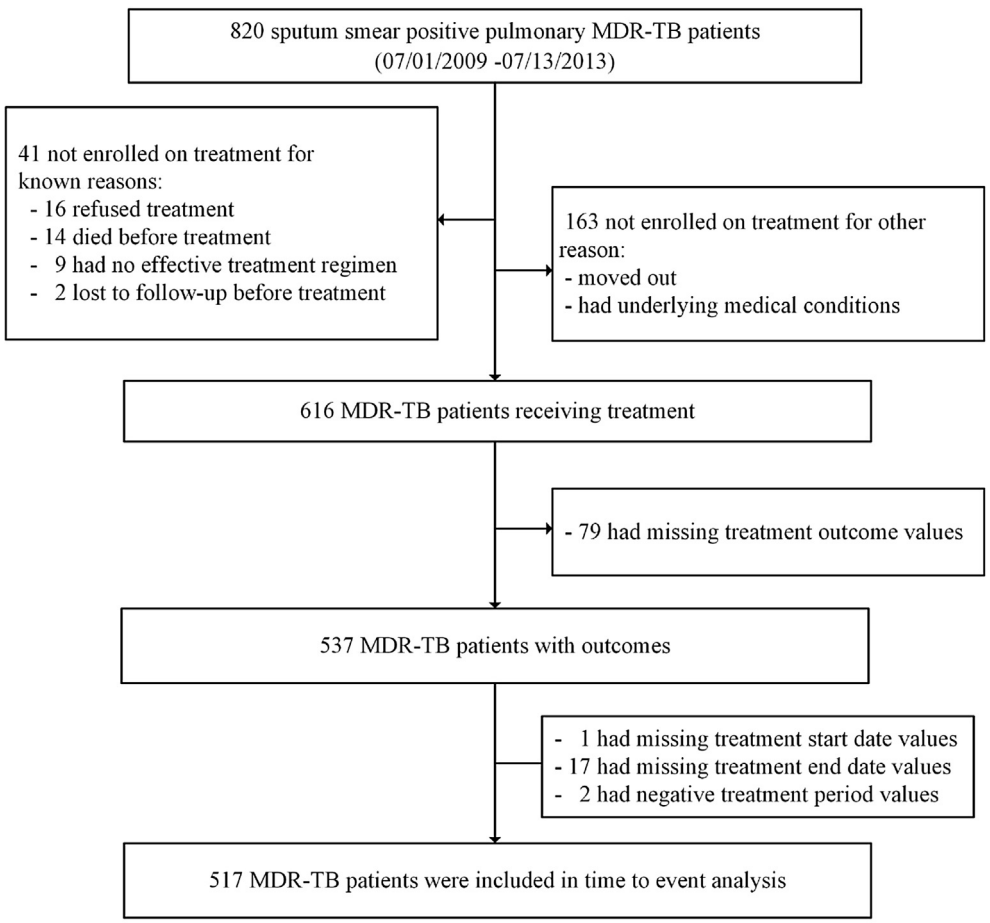
Of all 537 individuals, 382 were male, with mean age of 47 years (SD 16.0), while female subjects were younger on average, at 41 years (SD 15.1). The delay in starting appropriate MDR-TB treatment after TB diagnosis was a median of 88 days (interquartile range 17–163 days). AST for second-line drugs was conducted for 159 patients. The majority of MDR-TB patients had disease resistant only to first-line drugs (71.1%, 113/159). Pre-XDR-TB was seen in 27 MDR-TB patients (17.0%), of whom 26 had disease resistant to fluoroquinolones, and one had disease resistant to second-line injectable drugs. XDR-TB was seen in 19 patients (11.9%, Fig. 2).

Treatment outcomes

MDR-TB patients were followed for a mean of 20 months after treatment initiation. During 917.3 person-years of follow-up, the treatment success rate was 40.2 per 100 person-years (369/917.3 person-years), while the treatment failure, death and default rates were 10.0 per 100 person-years (92/917.3 person-years), 3.4 per 100 person-years (31/917.3 person-years) and 2.7 per 100 person-years (25/917.3 person-years) respectively (Table 2). The number of participants with success, failure, death and default outcomes out of 537 participants were 374 (69.6%), 101 (18.8%), 36 (6.7%) and 26 (4.8%) respectively (Supplementary Table S3). Newly diagnosed patients had the highest treatment success rate (82.3%, 65/79). The success rate of relapsed patients (65.3%, 128/196) was lower than patients registered as receiving treatment after failure (71%, 169/238) and patients registered as receiving treatment after default (71.4%, 5/7).

Risk factors for poor treatment outcome

In our multivariable Cox model (Table 3), being older than 60 was associated with a greater likelihood of poor outcomes compared to patients under 30 (hazard ratio (HR) 2.3, 95%



Abbreviation: MDR-TB, multidrug resistance tuberculosis.

Fig. 1. Inclusion of MDR-TB patients in analysis. MDR-TB, multidrug-resistant tuberculosis.

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Table 1
Characteristics of MDR-TB cases stratified by county, Zhejiang province, China, 2009–2013

Characteristic	Overall	Region					
		Hangzhou	Huzhou	Jiaxing	Lishui	Quzhou	Shaoxing
Total	537	323	41	8	46	39	80
Age group							
≤30 years	124 (23.1)	94 (29.1)	5 (12.2)	1 (12.5)	5 (10.9)	5 (12.8)	14 (17.5)
30–60 years	300 (55.9)	180 (55.7)	28 (68.3)	7 (87.5)	19 (41.3)	21 (53.8)	45 (56.2)
>60 years	113 (21.0)	49 (15.2)	8 (19.5)	0 (0.0)	22 (47.8)	13 (33.3)	21 (26.2)
Gender							
Female	155 (28.9)	92 (28.5)	13 (31.7)	2 (25.0)	10 (21.7)	15 (38.5)	23 (28.7)
Male	382 (71.1)	231 (71.5)	28 (68.3)	6 (75.0)	36 (78.3)	24 (61.5)	57 (71.2)
Occupation							
Farmer	287 (53.4)	140 (43.3)	17 (41.5)	4 (50.0)	34 (73.9)	24 (61.5)	68 (85.0)
Other	250 (46.6)	183 (56.7)	24 (58.5)	4 (50.0)	12 (26.1)	15 (38.5)	12 (15.0)
Household registration[a]							
Floating	268 (49.9)	226 (70.0)	16 (39.0)	8 (100.0)	8 (17.4)	1 (2.6)	9 (11.2)
Local	269 (50.1)	97 (30.0)	25 (61.0)	0 (0.0)	38 (82.6)	38 (97.4)	71 (88.8)
Patient registration group							
Newly diagnosed patients	79 (14.7)	34 (10.5)	4 (9.8)	2 (25.0)	11 (23.9)	6 (15.4)	22 (27.5)
Relapse patients	196 (36.5)	97 (30.0)	7 (17.1)	3 (37.5)	18 (39.1)	23 (59.0)	48 (60.0)
Treatment after failure patients	238 (44.3)	173 (53.6)	29 (70.7)	3 (37.5)	13 (28.3)	10 (25.6)	10 (12.5)
Treatment after default patients	7 (1.3)	5 (1.5)	1 (2.4)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Other previously treated patients	17 (3.2)	14 (4.3)	0 (0.0)	0 (0.0)	3 (6.5)	0 (0.0)	0 (0.0)
Previous treatment history							
None	22 (4.1)	6 (1.9)	1 (2.4)	0 (0.0)	11 (23.9)	2 (5.1)	2 (2.5)
First-line drugs only	351 (65.3)	210 (65.0)	16 (39.0)	7 (87.5)	28 (60.9)	32 (82.1)	58 (72.5)
Second-line drugs	164 (30.5)	107 (33.1)	24 (58.5)	1 (12.5)	7 (15.2)	5 (12.8)	20 (25.0)
Hospitalization							
Yes	91 (16.9)	30 (9.3)	20 (48.8)	8 (100.0)	0 (0.0)	28 (71.8)	5 (6.2)
No	446 (83.1)	293 (90.7)	21 (51.2)	0 (0.0)	46 (100.0)	11 (28.2)	75 (93.8)
Treatment regimen							
Individualized	94 (17.5)	25 (7.7)	4 (9.8)	6 (75.0)	0 (0.0)	9 (23.1)	50 (62.5)
Standardized	340 (63.3)	213 (65.9)	36 (87.8)	2 (25.0)	46 (100.0)	28 (71.8)	15 (18.8)
Unknown	103 (19.2)	85 (26.3)	1 (2.4)	0 (0.0)	0 (0.0)	2 (5.1)	15 (18.8)
MDR-TB baseline resistance pattern							
MDR-FL	117 (21.8)	19 (5.9)	36 (87.8)	0 (0.0)	0 (0.0)	20 (51.3)	42 (52.5)
Pre-XDR	29 (5.4)	6 (1.9)	5 (12.2)	0 (0.0)	0 (0.0)	18 (46.2)	0 (0.0)
XDR	19 (3.5)	17 (5.3)	0 (0.0)	0 (0.0)	1 (2.2)	1 (2.6)	0 (0.0)
Unknown	372 (69.3)	281 (87.0)	0 (0.0)	8 (100.0)	45 (97.8)	0 (0.0)	38 (47.5)
Haemoptysis at diagnosis							
No	283 (52.7)	96 (29.7)	34 (82.9)	6 (75.0)	42 (91.3)	31 (79.5)	74 (92.5)
Yes	254 (47.3)	227 (70.3)	7 (17.1)	2 (25.0)	4 (8.7)	8 (20.5)	6 (7.5)
Cavity on chest							
No	186 (34.6)	71 (22.0)	20 (48.8)	4 (50.0)	44 (95.7)	21 (53.8)	26 (32.5)
Yes	235 (43.8)	161 (49.8)	19 (46.3)	4 (50.0)	2 (4.3)	18 (46.2)	31 (38.8)
Unknown	116 (21.6)	91 (28.2)	2 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	23 (28.7)
Adverse events							
No	62 (11.5)	0 (0.0)	22 (53.7)	2 (25.0)	3 (6.5)	11 (28.2)	24 (30.0)
Yes	230 (42.8)	104 (32.2)	15 (36.6)	6 (75.0)	42 (91.3)	28 (71.8)	35 (43.8)
Unknown	245 (45.6)	219 (67.8)	4 (9.8)	0 (0.0)	1 (2.2)	0 (0.0)	21 (26.2)

MDR, multidrug resistant; MDR-FL, TB with resistance to isoniazid and rifampin, but not any second-line drugs; pre-XDR-TB, TB with resistance to isoniazid, rifampin, and either ofloxacin or kanamycin; TB, tuberculosis; XDR, extensively drug resistant (TB with resistance to isoniazid, rifampin, and both ofloxacin and kanamycin).

[a] People who keep their *hukou* (a record in a government system of household registration determining where citizens are allowed to live in China) in their hometown but reside in other areas for various reasons.

confidence interval (CI) 1.2–4.2). Compared to newly diagnosed patients, those registered as experiencing relapse and those receiving treatment after failure were both at increased risk of poor outcomes (HR 2.2, 95% CI 1.1–4.4; HR 2.4, 95% CI 1.2–4.9), while the risk for patients registered as receiving treatment after default was not significant. Standardized treatment regimens were associated with a lower risk of poor outcomes (HR 0.6, 95% CI 0.4–1.0), though the result was not significant in a sensitivity analysis restricted to patients whose treatment regimen was available (n = 415, Supplementary Table S4). Having a cavity on chest radiograph was a strong predictor for poor outcomes (HR 4.9, 95% CI 2.8–8.6). Experiencing adverse events increased the risk of poor outcomes by 2.5 times (HR 2.5, 95% CI 1.2–5.5).

Survival curves stratified by resistance pattern

Survival days to poor outcomes between different resistance pattern are shown in Fig. 3. Pre-XDR-TB and XDR-TB patients reached poor outcomes more rapidly than MDR-TB first-line patients. Poor outcomes increased with levels of resistance patterns (MDR-TB first-line, pre-XDR-TB, XDR-TB), and the log-rank test for trend of survival functions was significant ($P = 0.0018$).

Discussion

In our prospective study, the treatment success rate of MDR-TB reached 69.6% (374/537). We identified significant risk factors for poor treatment outcomes: age group, patient registration group, cavity on baseline chest radiograph, treatment regimen and occurrence of adverse events. The treatment success rate in our cohort was much higher than the national average (55%), the global average (52%) and the WHO Western Pacific average (57%) [1]. Preplanned standardized regimens based on local susceptibility patterns, individualized regimens based on personal AST results and adequate supplementary measures may have played

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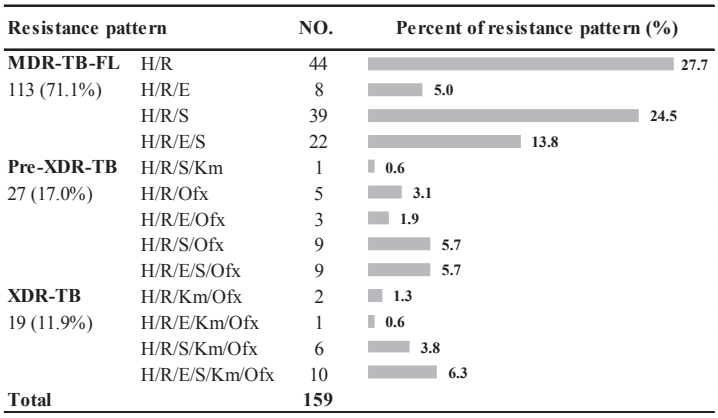

Fig. 2. Drug resistance among 159 MDR-TB patients whose second-line drug-susceptibility testing results were available. E, ethambutol; H, isoniazid; Km, kanamycin; MDR, multidrug resistance; MDR-FL, TB with resistance to isoniazid and rifampin, but not any second-line drugs; MDR-TB, multidrug-resistant tuberculosis; Ofx, ofloxacin; pre-XDR-TB, TB with resistance to isoniazid, rifampin and either ofloxacin or kanamycin; R, rifampicin; S, streptomycin; TB, tuberculosis; XDR, extensively drug resistant (TB with resistance to isoniazid, rifampin, and both ofloxacin and kanamycin).

important roles. These measures included incentives for both Directly Observed Treatment-performing clinicians and patients, help with nutrition and emotional support. Offering free diagnoses and drugs may have ensured adherence.

Our supplementary measures might have produced a positive effect on compliance, with default rates of only 4.8%, much lower than the global average (15%). Worldwide, most cohorts have reported >10% default rates: 17% in Estonia [7], 26% in Latvia [14], 20.9% in South Africa [15] and 10.0% in Peru [16]. In China the default rate was significantly lower: 12.5% in Shenzhen [17], 6% in Guangzhou [18] and 4% in a meta-analysis [19].

However, this success rate was far below the global target of 75% [20]. The rate was lower than Korea, Kenya, Myanmar, Nigeria and Somalia, which were also among the 30 high-MDR-TB-burden countries reporting treatment success rates of >75% [1]. The high success rates in these countries were probably due to application of new drugs [21] and broader access to second-line drug-susceptibility testing. WHO treatment guidelines for drug-resistant TB recommend prescribing at least five effective TB drugs [22]. However, as a result of financial constraints, China has not ensured universal access to second-line drug-susceptibility testing, so there remain many MDR-TB patients treated with an inadequate number of effective drugs. Improving diagnostic capacity can result in better MDR-TB treatment, and can reduce MDR-TB transmission and further drug resistance in China.

We found that patients older than 60 were at risk for poor outcomes, which is consistent with previous studies [23–25]. This result may be because of the adverse events of anti-TB drugs and the economic status of older people. Adverse events caused by anti-TB drugs were reported to be age related [26,27], and some second-line drugs are not free in China.

Not surprisingly, our study demonstrated that re-treated patients were at higher risks of poor outcomes than newly diagnosed patients, which is consistent with published studies [14,28,29]. We divided re-treated patients into four groups, which have not been normally analysed in other studies. We found it was patients registered as receiving treatment after failure among re-treated patients that contributed to the higher risk of poor outcome. This implies that we should provide better treatment and management to re-treated patients registered as receiving treatment after failure.

Standardized treatment regimens were a protective factor for poor outcomes. However, this result is subject to selection bias, though we adjusted for indicators of severity; also, this factor was not significant in our sensitivity analysis. A well-designed standard regimen is highly cost-effective and may achieve high treatment success rates, especially in low- and middle-income settings. Nonetheless, it is important to underline that the clinical effectiveness of a drug cannot be predicted by AST with 100% certainty [30]. Treating MDR-TB patients with a standard regimen would reduce expenses and human resources in China.

Cavitary disease was significantly associated with poor outcomes. Bilateral cavitation was found to be linked to poor outcomes in some studies [31]. Adverse events were also a strong predictor for poor outcomes, which may lead to poor compliance and inadequate treatment.

In our study, pre-XDR-TB patients were not associated with poor outcomes, which is inconsistent with published studies. This was due to a high proportion of unknown second-line drug-susceptibility testing results. In fact, AST for second-line drugs was conducted for all patients in two regions (Huzhou and Quzhou) but was not conducted in Jiaxing and Lishui. In Hangzhou and Shaoxing, the testing was conducted for 13% and 52.2% of patients respectively. The implementation of second-line drug-susceptibility testing was based on the results of individual's smear sputum and the local capacity of laboratory testing. Our analysis of 159 patients with AST results showed that the risk of poor outcome increased with baseline resistance pattern (TB with resistance to isoniazid and rifampin, pre-XDR, XDR). Pre-XDR-TB patients should receive careful management and treatment in case their condition progresses.

Table 2
Treatment outcome of multidrug-resistant tuberculosis in Zhejiang province, China, 2009–2013

Treatment outcome	Total	No. of patients included in time-to-event analysis	Rate (per 100 person-years) (95% confidence interval)
Total	537	517	917.3 person-years
No event (success)	374 (69.6%)	369 (71%)	40.2 (35.5–45.7)
Failure	101 (18.8%)	92 (18%)	10.0 (8.2–12.3)
Death	36 (6.7%)	31 (6%)	3.4 (2.4–4.8)
Default	26 (4.8%)	25 (5%)	2.7 (1.8–4)

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Table 3
Multivariable analysis of factors associated with poor treatment outcomes in patients with MDR-TB, Zhejiang province, China, 1999–2013

Characteristic	Predictor	Events/patients[a]	Person-years	Rate (95% CI) per 100 person-years	uHR (95% CI)	aHR (95% CI)
Sociodemographic characteristic	Age group					
	≤30 years	21/124	243.65	8.62 (5.62–13.22)	Reference	Reference
	30–60 years	80/300	513.63	15.58 (12.51–19.39)	1.7 (1.1, 2.8)	1.3 (0.8, 2.2)
	>60 years	47/113	159.98	29.38 (22.07–39.10)	3.1 (1.8, 5.2)	2.3 (1.2, 4.2)
	Gender					
	Female	43/155	264.44	16.26 (12.06–21.93)	Reference	Reference
	Male	105/382	652.83	16.08 (13.28–19.47)	0.9 (0.7, 1.3)	0.8 (0.6, 1.2)
	Occupation					
	Farmer	92/287	478.05	19.24 (15.69–23.61)	Reference	Reference
	Other	56/250	439.22	12.75 (9.81–16.57)	0.7 (0.5, 1.0)	0.9 (0.6, 1.4)
	Household registration[b]					
	Floating	63/268	474.24	13.28 (10.38–17.01)	Reference	Reference
	Local	85/269	443.02	19.19 (15.51–23.73)	1.4 (1.0, 1.9)	1.2 (0.8, 1.9)
MDR-TB characteristic	Patient registration group					
	Newly diagnosed patients	12/79	149.27	8.04 (4.57–14.16)	Reference	Reference
	Relapse patients	60/196	326.38	18.38 (14.27–23.68)	2.4 (1.3, 4.5)	2.2 (1.1, 4.4)
	Treatment after failure patients	67238	405.74	16.51 (13–20.98)	2.4 (1.3, 4.6)	2.4 (1.2, 4.9)
	Treatment after default patients	2/7	11.52	17.36 (4.34–69.43)	3.0 (0.7, 13.4)	3.3 (0.7, 15.6)
	Other previously treated patients	7/17	24.36	28.74 (13.7–60.28)	4.1 (1.6, 10.4)	3.5 (1.2, 9.8)
	Previous treatment					
	First-line drugs only	92/351	599.94	15.33 (12.5–18.81)	Reference	Reference
	Second-line drugs	50/164	283.25	17.65 (13.38–23.29)	1.2 (0.8, 1.6)	1.2 (0.8, 1.8)
	None	6/22	34.07	17.61 (7.91–39.2)	1.0 (0.4, 2.4)	1.7 (0.7, 4.2)
	Hospitalization					
	Yes	26/91	155.11	16.76 (11.41–24.62)	Reference	Reference
	No	122/446	762.15	16.01 (13.4–19.12)	1.0 (0.6, 1.5)	1.2 (0.7, 2.1)
	Treatment regimen					
	Individualized	32/94	152.14	21.03 (14.87–29.74)	Reference	Reference
	Standardized	100/340	557.44	17.94 (14.75–21.82)	1.0 (0.7, 1.5)	0.6 (0.4, 1.0)
	Unknown	16/103	207.69	7.70 (4.72–12.57)	0.4 (0.2, 0.7)	0.2 (0.1, 0.5)
	MDR-TB baseline resistance pattern					
	MDR-FL	35/117	194.8	17.97 (12.9–25.02)	Reference	Reference
	Pre-XDR	10/29	44	22.73 (12.23–42.24)	1.3 (0.6, 2.6)	0.7 (0.3, 1.7)
	XDR	13/19	29.61	43.91 (25.5–75.62)	2.7 (1.4, 5.2)	1.0 (0.4, 2.3)
	Unknown	90/372	648.87	13.87 (11.28–17.05)	0.8 (0.5, 1.2)	0.6 (0.3, 1.1)
Indicator of severity	Haemoptysis at diagnosis					
	No	69/283	485.93	14.2 (11.22–17.98)	Reference	Reference
	Yes	79/254	431.34	18.32 (14.69–22.83)	1.5 (1.1, 2.1)	1.2 (0.7, 2.3)
	Cavity on chest					
	No	30/186	319.37	9.39 (6.57–13.43)	Reference	Reference
	Yes	96/235	377	25.46 (20.85–31.1)	2.8 (1.8, 4.2)	4.9 (2.8, 8.6)
	Unknown	22/116	220.9	9.96 (6.56–15.13)	1.0 (0.6, 1.7)	5.0 (1.7, 14.8)
	Adverse events					
	No	10/62	113.91	8.78 (4.72–16.32)	Reference	Reference
	Yes	65/230	372.56	17.45 (13.68–22.25)	2.0 (1.0, 3.8)	2.5 (1.2, 5.5)
	Unknown	73/245	430.8	16.95 (13.47–21.31)	2.0 (1.0, 3.7)	5.6 (2.3, 13.5)

aHR, adjusted hazard ratio; CI, confidence interval; MDR, multidrug resistant; MDR-FL, TB with resistance to isoniazid and rifampin, but not any second-line drugs; pre-XDR-TB, TB with resistance to isoniazid, rifampin, and either ofloxacin or kanamycin; TB, tuberculosis; uHR, unadjusted hazard ratio; XDR, extensively drug resistant (TB with resistance to isoniazid, rifampin, and both ofloxacin and kanamycin).

[a] Events/patients refers to no. of patients with poor treatment outcomes/no. of patients evaluated.

[b] People who keep their *hukou* (a record in a government system of household registration determining where citizens are allowed to live in China) in their hometown but reside in other areas for various reasons.

The current study has several limitations. Firstly, many MDR-TB patients were not enrolled to receive treatment as a result of physical conditions, and there were also a few patients with unknown treatment outcomes, which were the result of missing data and incorrect documentation. This may overestimate our treatment success rates. Secondly, our study was an observational study, and although we adjusted carefully for indicators of disease severity, residual confounding may still be possible. For example, in our MDR-TB program, HIV status was only available for 7% (59/820) patients, and they were all HIV negative. The mean incidence of HIV in Zhejiang province is 1.27 per 100 000 population over the study period. This uncontrolled confounding may have biased our results. Thirdly, second-line drug-susceptibility testing was only performed for 159 patients, which may lead to bias in the measurement of association between drug resistance pattern and poor outcomes. Fourthly, the treatment outcomes were defined mainly by microbiologic response; there might be some differences in clinical response among patients in the same treatment outcome group. Fifthly, we did not test the susceptibilities of all second-line drugs used in our treatment, only ofloxacin of fluoroquinolones and kanamycin of injectable drugs. We may underestimate the proportion of pre-XDR-TB and XDR-TB patients.

In spite of these limitations, to our knowledge, our study is the first population-based study to investigate treatment outcomes and factors associated with poor treatment outcome of MDR-TB patients in China. Our study indicated that aging, cavitary disease, occurrence of adverse events, standardized regimen, retreatment and relapsed disease are independent risk factors for poor outcomes. Rapid diagnostics and universal access to AST should be emphasized in current MDR-TB control policy. In addition, AST for all second-line drugs should be ensured to further assist the treatment and control of MDR-TB.

Please cite this article in press as: Zhang L, et al., Treatment outcomes of multidrug-resistant tuberculosis patients in Zhejiang, China, 2009–2013, Clinical Microbiology and Infection (2017), http://dx.doi.org/10.1016/j.cmi.2017.07.008

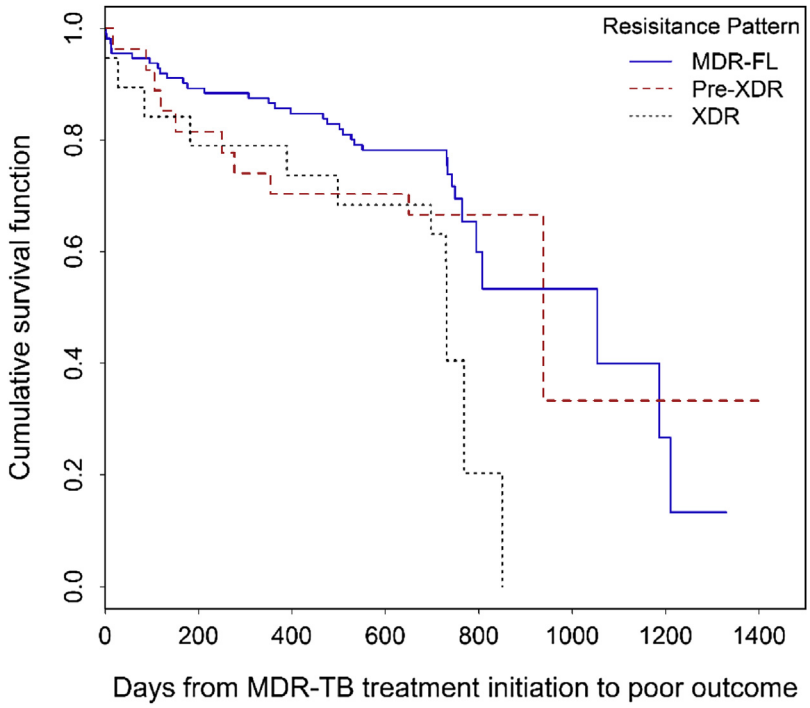

Fig. 3. Time to poor treatment outcome of MDR-TB by drug resistance pattern. Poor treatment outcome was defined as treatment failure, death or death. Log-rank test p value for trend of survivor functions = 0.0018. MDR, multidrug resistant; MDR-FL, TB with resistance to isoniazid and rifampin, but not any second-line drugs; pre-XDR-TB, TB with resistance to isoniazid, rifampin and either ofloxacin or kanamycin; TB, tuberculosis; XDR, extensively drug resistant (TB with resistance to isoniazid, rifampin, and both ofloxacin and kanamycin).

Transparency declaration

Supported by National Natural Science Foundation in China (U1611264 and 61571001). All authors report no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2017.07.008.

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