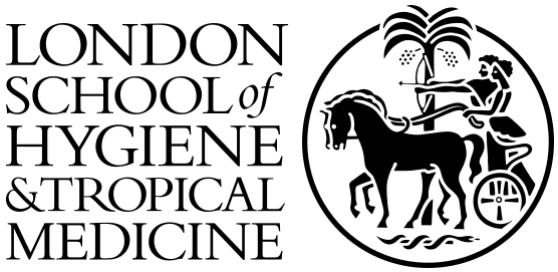

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Treatment responses in multidrug-resistant tuberculosis in Germany

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Abstract (200)

Recently, excellent treatment outcomes have been reported for patients with multidrug/extensively drug-resistant tuberculosis (M/XDR-TB) in settings where optimal resources for individualized therapy are available. We ascertained whether differences in treatment responses still exist in patients with M/XDR-TB compared to patients with non-M/XDR-TB.

Patients with tuberculosis were prospectively enrolled between March 2013 and March 2016 at five hospitals in Germany. Treatment was conducted following current guidelines and individualized on the basis of comprehensive drug-resistance testing. Two-months and 6-months sputum-smear and sputum-culture conversion rates were assessed. A clinical and a radiological score were used to assess the response to anti-tuberculosis therapy.

Non-M/XDR-TB (n=29) and M/XDR-TB (n=46) patients showed similar rates of microbiological conversion (2-months smear-conversion-rate 90% vs. 78% and culture-conversion-rate 67% versus 61%, respectively; time-to-smear/culture-conversion 19 (IQR10-32) vs. 31 (IQR14-56) (p=0.066), and 39 (IQR17-67) vs. 39 (IQR6-85) days (p=0.191), respectively). Both clinical and radiological scores declined after the introduction of anti-tuberculosis therapy. There were no significant differences of scores between the groups until 6 months of therapy.

Under optimal clinical conditions with availability of novel diagnostics and a wide range of therapeutic options for individualized therapy, patients with M/XDR-TB achieve 6 month culture conversion rates that are compatible to patients with non-M/XDR-TB.

Introduction

Tuberculosis (TB) is the leading cause of mortality attributed to a single microbial pathogen worldwide (1, 2). The World Health Organization (WHO) estimates that more than 10 million people developed active TB in 2016, the highest ever-estimated number of affected patients in history. The emergence of multidrug-resistant (MDR; defined by bacillary resistance against rifampicin and isoniazid) and extensively drug-resistant (XDR; MDR plus resistance against at least one fluoroquinolone and one second-line injectable drug) TB is especially worrisome. M/XDR-TB has been related to high treatment costs, increased frequency of adverse drug-events, and poor therapy outcomes (1, 3-7). At the recent meeting of the G20 leaders in Hamburg, Germany, combatting antimicrobial resistance, including drug-resistant TB, has been identified as a global priority (8).

Currently, the World Health Organization (WHO) recommends a therapy duration for M/XDR-TB patients of at least 20 months unless specific criteria allow for a standardized short course MDR-TB regimen over 9-12 months (3, 9-13). Only approximately 50% of M/XDR-TB patients in Europe attain favorable outcomes. In contrast, in settings where individualized treatment can be provided, successful treatment outcomes are usually observed (3, 4, 14-16). The concept of individualized therapy targets the special demands of every host and pathogen leading to tailored treatment in every patient (17). Currently, new diagnostic methods and novel drugs have been introduced that may improve treatment outcomes (17-20).

Based on these observations, we aimed to compare 6-months culture conversion, as early indicators of treatment outcomes, in M/XDR-TB and non-M/XDR-TB patients from settings where optimal resources are available. Additionally, we evaluated a clinical and a radiological scoring system (21).

Study population and methods

Between March 2013 and March 2016 patients with TB identified by sputum GeneXpert MTB/RIF test (Cepheid, Sunnyvale, USA) were prospectively enrolled at the Medical Clinic, Research Center Borstel; Karl-Hansen-Klinik, Bad Lippspringe; Sankt Katharinen-Krankenhaus, Frankfurt; Thoraxklinik-Heidelberg, Heidelberg; Asklepios Fachkliniken München-Gauting, Munich in Germany. Patients with M/XDR-TB were enrolled consecutively at all centers after satisfying in- and exclusion criteria, and providing written informed consent. Patients with non-MDR-TB were also recruited if inclusion criteria were met or exclusion criteria were not met and they agreed with participation. Athough patients with non-MDR-TB were not strictly recruited consecutively at all centers, selection was not based on patients characteristics but depended on staff availability. Individuals were excluded if they were less than 18 years of age, not legally able to provide consent or if they were infected with HIV. All patients gave written informed consent. Following approval at the Ethics Committee of the University of Lübeck (AZ 12-233), Germany, the study protocol was approved at the local Ethic Committees of all participating centers.

Following rapid molecular identification of rifampicin resistance by GeneXpert, sputum samples underwent second-line molecular drug resistance testing of *M. tuberculosis* by line-probe-assays (GenoType MTBDR*plus* and MTBDR*sl* Hain Lifesciences, Nehren, Germany).

Sputum samples also underwent phenotypic drug susceptibility testing according to WHO recommendations at a certified and quality controlled microbiology laboratory (WHO Supranational Reference Laboratory Network). During the in-patient period, sputum samples were collected for smear microscopy and culture on a weekly basis. After discharge, sputum was collected as part of routine follow-up visits. Demographic information was collected on study enrolment.

A novel clinical score consisting of self-reported and objectively observed items (maximum score of 30 points), which is based on a published scoring system (22), was recorded by a physician during the clinical visits. Self-reported items were cough, hemoptysis, dyspnea, thoracic pain, night sweats, loss of weight, and inability to walk (each one point). The examined score items (if not indicated differently, one point each) consisted of axillary body temperature (>37°= one point, >38°= two points), impaired consciousness, focal neurologic deficits, body mass index (kg/m^2; <20= one point, <18= two points, <16= three points), middle upper arm circumference (mm; <220= one point, <200= two points), capillary filling time >2 sec., cyanosis, tachycardia (beats per minute; >100= one point, >120=two points), blood pressure <90 mmHg systolic or <60 mmHg diastolic, lung crackles, tachypnea (per minute; >20= one point, >25= two points, >30= three points), oxygen saturation (%; <90= one point, < 87= 2 points), and age above 65 (one point).

Chest X-rays were performed at clinically relevant time-points during the course of treatment. The extent of pulmonary TB was assessed by a validated scoring system (21). In brief, the percentage of TB-associated infiltrations in chest X-rays was assessed and 40

points were added to the score if cavities were present (max. 140 points). An experienced chest physician scored the chest X-rays.

Time to sputum culture conversion (TCC) and smear conversion (TSC) were defined as the time (in days) from the initiation of effective anti-TB therapy to the date of the first negative culture or sputum smear (date of collection). Therapy was deemed effective according to DST results.

Individualized anti-TB drug regimens for patients with M/XDR-TB were designed using current therapy recommendations, and results of molecular and phenotypic drug susceptibility testing (10, 11, 23, 24). Patients with non-M/XDR TB were treated following national TB guidelines (25).

Smear and culture conversion for the first six months after treatment initiation were evaluated using survival analysis, and compared with survival curves for the two cohorts by a logrank test. Kaplan-Meier estimates derived from the survival curves for smear and culture conversion at month 2 and month 6, and the medium time to smear or culture conversion are reported. Measured clinical score and change in radiological score were assessed by mean and 95% confidence interval at *a priori* time points. All statistical tests used a two-sided alpha-value of 0.05 to assess statistical significance. Analyses were performed using STATA (Version 14, StataCorp LLC, College Station, Texas, USA).

Results

Seventy-five patients were enrolled, of whom 46 were infected with non-M/XDR and 29 with M/XDR-TB strains. Patients´ characteristics are displayed in **table 1**. Of the 29 patients with M/XDR-TB, eight patients were infected with an XDR strain of *M. tuberculosis*. Median age was higher in patients with non-M/XDR-TB compared to M/XDR-TB patients (43.0 years (IQR 31.0 – 58.0) vs. 36.0 years (IQR 30.0 – 41.0)). Sex distribution (non-M/XDR-TB: males 30 (65.2%) vs. M/XDR-TB: males 16 (62.1%)) and median BMI values (non-M/XDR-TB: 21.1 kg/m^2 (IQR 18.1 – 24.8 vs. M/XDR-TB: 21.7 kg/m^2 (19.4 - 25.4)) were similar in both patient groups.

The results of available DST results are shown in **table 2**. Among the 46 patients with non-M/XDR-TB two patients had isoniazid mono-resistance. No further drug-resistances to first-line drugs (ethambutol and pyrazinamide tested in 44 strains) nor second-line drugs (prothionamide, ofloxacin, and capreomycin tested in 11 strains) were detected in this group. Strains from patients with M/XDR-TB showed high frequencies of first-line drug resistance; 18/27 (66.7%) for ethambutol, 22/27 (81.5%) pyrazinamide. Additionally, resistance was present in M/XDR-TB strains to capreomycin 10/29 (34.5%), amikacin 7/29 (24.1%), ofloxacin 9/27 (33.3%), prothionamide 14/27 (51.9%), para-amino-salicylic acid 1/27 (3.7%) and linezolid 1/27 (3.7%). None of the M/XDR-TB strains were resistant to terizidone/cycloserin.

The starting therapy regimens are shown in **table 3**. Most M/XDR-TB patients receiving fluoroquinolones were treated with moxifloxacin 18/22 (81.8%) and only 4/22 (18.2%) received levofloxacin. Of 21/29 (72.4%) M/XDR-TB patients who were treated with second-line injectable drugs 14/21 (66.7%) patients were given capreomycin and 7/21 (33.3%)

amikacin. Only 3/29 (10.4%) M/XDR-TB patients were treated with regimens containing bedaquiline or delamanid.

Patients with M/XDR-TB had a slightly lower Kaplan-Meier estimate for smear conversion compared to patients with non-M/XDR-TB at month two (78% versus 90%, respectively), and at month six (93% and 96%, respectively, p=0.004; **table 4** and **figure 1A**). Such a difference was not seen for culture conversion (**figure 1B** and **table 4**), where Kaplan-Meier estimates were 61% and 67%, respectively at month two, and 95% and 97%, respectively, at month six (p = 0.191). The median time to smear conversion was 31 days (IQR: 14-56) and 19 days (IQR: 10-32) for patient with non-M/XDR-TB and M/XDR-TB respectively. Time to culture conversion was with 39 days, identical in both groups.

The mean clinical scores before treatment initiation were higher in patients with non-M/XDR-TB TB than in patients with M/XDR-TB (5.8 (95%CI 3.5–7.4) vs. 4.8 (95%CI 3.6–5.6)) with a decline of mean scores in both cohorts after therapy initiation (**online appendix table 1** and **figure 2**). There were no obvious differences in the development of the clinical score between treatment initiation and month 6.

The radiological extent of disease evaluated using the Ralph score at baseline showed similar values in both groups (mean 58.8 vs. 52.1 points; **online appendix table 1** and **figure 3**). Although there was a slight increase of pulmonary infiltrations in the non-M/XDR-TB cohort after treatment start, the score values declined over the time of treatment. Here, the radiological scores of patients with M/XDR-TB remained at higher values, which was mainly explained by a higher frequency of the persistence of cavitary lesions in the chest X-rays. A higher proportion of patients with M/XDR-TB previously had TB and thus prior lung damage, which would explain more extensive infiltrations.

Discussion

We compared early treatment response in a prospective cohort of patients with M/XDR-TB and patients with non-M/XDR-TB in Germany, a country where unrestricted diagnostic and therapeutic resources for the management of patients with M/XDR-TB are available. Six-months culture conversion was similar for patients with non-MDR-TB and M/XDR-TB, which could suggest a high chance of cure for patients with M/XDR-TB.

Our findings are in line with published data showing that the 6-months culture conversion status is indicative for sustained treatment response in patients with M/XDR-TB (14, 26). Using 6-months culture conversion status and a one-year follow-up after therapy completion as markers for therapy outcome has also been suggested in a recently published study (14). Although the 2-months culture conversion status has been evaluated as a surrogate for treatment response in clinical trials evaluating novel anti-TB drugs, such as bedaquiline and delamanid (27, 28), treatment outcomes are better correlated to the 6-months culture conversion status (29). Six-months culture-conversion status was similar in both groups (table 4). In the present study, the 2-months culture conversion rates of our M/XDR-TB patients undergoing tailored treatment regimens on the basis of comprehensive drug susceptibility testing exceeded the rates from trials presenting promising novel drugs with excellent therapy results (27, 28, 30).

Standardized therapy regimens as presented by the “Bangladesh” regimen have yielded excellent outcomes in specific settings with low frequencies of second-line drug resistance (30). Based on these results the WHO made a conditional recommendation for a “shorter course regimen” for the treatment of MDR-TB (9). However, only very few patients from the European region may be eligible for this regimen due to high frequencies of second-line drug

resistance (13, 31, 32), which may lead to treatment failure and acquisition of additional drug resistance (33). The low eligibility of patients from this setting is also reflected by our study where high frequencies of first and second-line drug resistance were identified. This strongly indicates that standard treatment regimens could lead to the emergence of additional drug resistance due to inadequate therapy.

This study also showed that tailored treatment regimens in our study were highly variable. In fact, such individualized therapy regimens were shown to lead to very high frequencies of favorable treatment outcomes in an Austrian cohort (15). In contrast to patients who received standardized treatment regimens, higher frequencies of cure for patients with MDR-TB from the European region were found with individualized treatment regimens in a large European multicenter cohort (Günther et al. submitted). Higher frequencies of treatment success in patients receiving individualized therapy were also shown by large meta-analyses comparing treatment results of patients with MDR-TB under standardized or individualized regimens (16, 34).

We also evaluated the performance of an existing radiological score using chest X-rays and a novel clinical score to further characterize the effect of treatment on an individual basis (21, 35). The items included in the clinical score were based on a published scoring system, which was shown to predict mortality and treatment response in African cohorts (22, 36, 37). Although we were able to show declining clinical and radiological scores after therapy initiation (figure 3 and 4, online appendix table 1), our intention to correlate the scores' trajectories with the established markers such as time to culture or to smear conversion, and 2- or 6 month culture conversion status failed, given the almost uniformly high frequency of conversion in a relatively small cohort. Unfortunately, the small number of patients

precluded data reduction strategies like principal component analysis to evaluate the clinical score. The decline in radiological score observed in our study was slow probably due to persistence of cavitary lesions, which are slower to resolve, and in the presence of an adequate clinical and microbiological response. Nevertheless, these or other clinically derived scores may serve as alternative end-points for future biomarker validation and should be reconsidered in future studies (38).

Although the relatively low number of patients evaluated limits our study, a very close microbiological and clinical monitoring and the observations from clinical and radiological scores strengthens our findings.

In conclusion, under optimal clinical conditions with availability of novel diagnostics and individualized therapy, patients with M/XDR-TB can achieve 6-months culture conversion, the frequency of which is similar to that of to patients with non-M/XDR-TB. This personalized approach to therapy may have the potential to yield high frequencies of cure. The clinical and radiological scores should be further evaluated with the aim to identify and validate markers to individualize the duration of therapy.

Acknowledgements

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TABLES

Table 1. Clinical characteristics of patients with non-MDR-TB and M/XDR-TB.

	Non-M/XDR*		M/XDR		Total	
	N = 46		N = 29		N = 75	
	n	%	n	%	n	%
Sex						
Male	30	65.2	18	62.1	48	64.0
Age, median (IQR)	43.0	31.0 – 58.0	36.0	30.0 – 41.0	39.0	31.0 – 56.0
BMI, median (IQR)	21.1	18.1 – 24.8	21.7	19.4 - 25.4	21.2	18.3 – 25.4
TB contact						
No	21	45.7	9	31.0	30	40.0
Yes	6	13.0	4	13.8	10	13.3
missing	19	41.3	16	55.2	35	46.7
BCG						
Yes	13	28.3	16	55.2	29	38.7
missing	28	60.9	12	41.4	40	53.3
TB type						
not previously treated for TB	35	76.1	18	62.1	53	70.7
Relapse	6	13.0	6	20.7	12	16.0
Failure	0	0.0	1	3.4	1	1.3
Return from default	1	2.2	1	3.4	2	2.7
missing	4	8.7	3	10.3	7	9.3
Previous TB						
Yes	7	15.2	10	34.5	17	22.7
missing	14	30.4	4	13.8	18	24.0
Diabetes						
Yes	4	8.7	2	6.9	6	8.0
missing	19	41.3	5	17.2	24	32.0
Hepatitis B						
Yes	3	6.5	1	3.4	4	5.3
missing	25	54.3	12	41.4	37	49.3
Hepatitis C						
Yes	2	4.3	3	10.3	5	6.7
missing	25	54.3	11	37.9	36	48.0

*44 patients with pan-drug susceptible TB and 2 patients with isoniazid mono-resistance

Table 2. Results of *Mycobacterium tuberculosis* phenotypic drug susceptibility testing from patients with non-M/XDR and M/XDR.

	Non M/XDR*				M/XDR			
	N = 46				N = 29			
Drug	Tested		Resistant		Tested		Resistant	
	N	%	N	%	N	%	N	%
H	45	97.8	2	4.4	27	93.1	27	100
R	46	100	0	0.0	29	100	29	100
E	44	95.7	0	0.0	27	93.1	18	66.7
Z	44	95.7			27	93.1	22	81.5
L					10	34.5	9	90.0
M					16	55.2	9	56.3
O	11	23.9	0	0.0	27	93.1	9	33.3
S					16	55.2	12	75.0
A					29	100	7	24.1
C	11	23.9	0	0.0	29	100	10	34.5
K					8	27.6	2	25.0
P	11	23.9	0	0.0	27	93.1	14	51.9
T					26	89.7	0	0.0
c					1	3.4	1	100
l					27	93.1	1	3.7
p					27	93.1	1	3.7
m					1	3.4	1	100
a					1	3.4	1	100

*44 patients with pan-drug susceptible TB and 2 patients with isoniazid mono-resistance

H: isoniazid; R: rifampicin; Z: pyrazinamid; E: ethambutol; O: ofloxacin; M: moxifloxacin; L: levofloxacin; S: streptomycin; C: capreomycin; A: amikacin; K: kanamycin; P: protionamide; T: terizidone/cycloserin; l: linezolid; c: clofazamin; p: para-amino-salicylic acid; m: meropenem; a: amoxicillin/clavulanic acid.

Table 3. Starting regimens in patients with non-MDR-TB and M/XDR-TB.

Drugs	Non-M/XDR*	M/XDR
HRZE – OML – SCAK – PTlc – BD - pma		
XXXX – ... – .... – .... – .. – ...	34	0
XXXX – ... – .... – ..X. – .. – X..	1	0
XXX. – ... – .... – .... – .. – ...	6	0
XX.X – ... – X... – .... – .. – ...	2	0
XX.X – ... – .... – .... – .. – ...	1	0
X..X – ... – .... – .... – .. – ...	1	0
.XXX – .X. – .... – .... – .. – ...	1	0
.X.. – .X. – .X.. – XX.. – .. – ...	0	1
..XX – .X. – .X.. – XX.. – .. – ...	0	1
..XX – .X. – .X.. – XX.. – .. – ...	0	1
..XX – .X. – ..X. – XX.. – .. – ...	0	1
..XX – ..X – ..X. – .XX. – .. – ...	0	1
..X. – .X. – .X.. – XXX. – .. – ...	0	1
..X. – .X. – .X.. – XX.. – .. – ...	0	2
..X. – .X. – .X.. – .X.. – .. – ...	0	1
..X. – .X. – ..X. – ..XX – .. – ...	0	1
..X. – ..X – ..X. – .XXX – .. – ...	0	1
..X. – ... – .X.. – .XX. – .. – ...	0	1
..X. – ... – ..X. – .X.X – .. – XXX	0	1
..X. – ... – .... – .X.X – .. – XXX	0	1
...X – .X. – .X.. – XX.X – .. – ...	0	1
...X – .X. – .X.. – XX.. – .. – ...	0	1
...X – .X. – .X.. – X... – .. – ...	0	1
...X – ..X – .... – XXX. – .. – ...	0	1
.... – .X. – .X.. – .XXX – .. – X..	0	1
...X – ... – ..X. – .XX. – X. – ...	0	1
.... – .X. – .X.. – .XX. – .. – X..	0	1
.... – .X. – .X.. – .X.. – .. – X..	0	1
.... – .X. – ..X. – .XX. – .. – X..	0	1
.... – .X. – .... – XXXX – .. – ...	0	1
.... – ..X – .... – .XX. – X. – ...	0	1
.... – ... – .... – .XXX – X. – .XX	0	2
.... – ... – .... – .XXX – .. – XXX	0	1
.... – ... – .... – .XX. – .. – ...	0	1

*44 patients with pan-drug susceptible TB and 2 patients with isoniazid mono-resistance

"." indicates if drug was not used and "X" if drug was used; H: isoniazid; R: rifampicin; Z: pyrazinamid; E: ethambutol; O: ofloxacin; M: moxifloxacin; L: levofloxacin; S: streptomycin; C: capreomycin; A: amikacin; K: kanamycin; P: protionamide; T: terizidone/cycloserin; l: linezolid; c: clofazamin; B: bedaquiline; D: delamanid; p: PAS; m: meropenem; a: amoxicillin/clavulanic acid.

Table 4. Percentage of patients with *M. tuberculosis* culture and smear conversion at month 2 and 6 after therapy initiation and median time to conversion with interquartile range for patients with non-M/XDR-TB and M/XDR-TB.

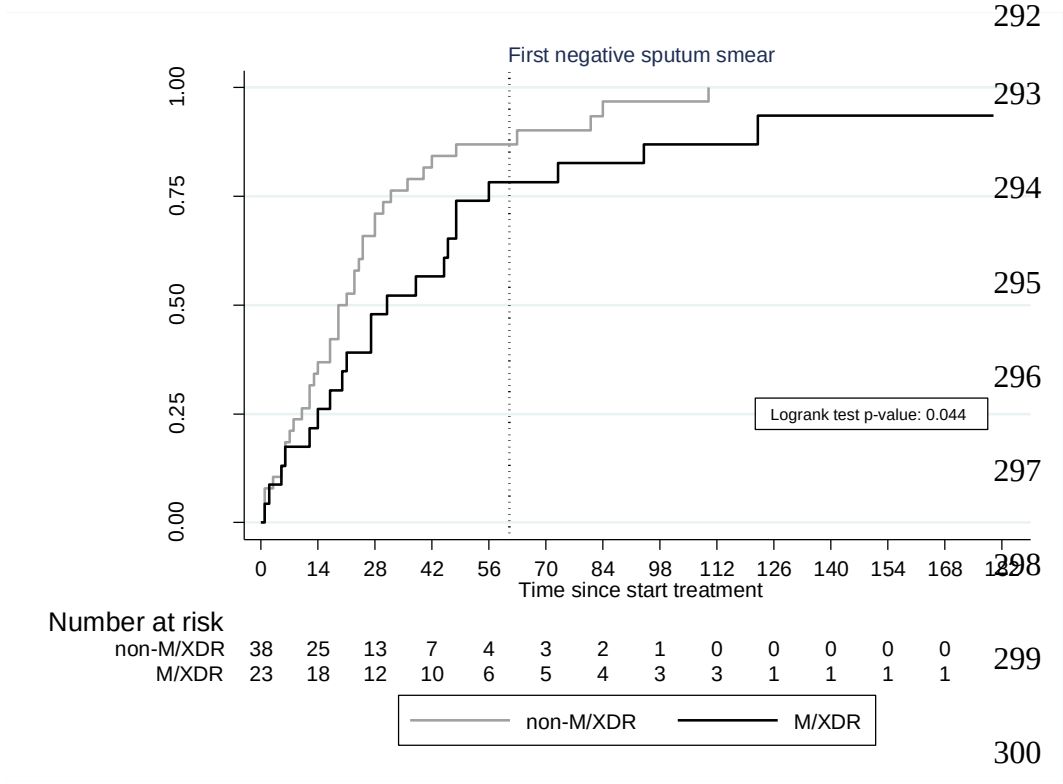
	Non-M/XDR*				M/XDR				p-value#
	KM estimate (%)		Time to conversion		KM estimate (%)		Time to conversion		
	Month 2	Month 6	Median	IQR	Month 2	Month 6	Median	IQR	
	%	%	Days	Days	%	%	Days	Days	
Smear conversion	90	96	19	10 - 32	78	93	31	14 - 56	0.044
Culture conversion	67	97	39	17 - 67	61	95	39	6 - 85	0.191

*44 patients with pan-drug susceptible TB and 2 patients with isoniazid mono-resistance

#Derived from Log-rank test.

FIGURES

A


First negative sputum smear
1.00
0.75
0.50
0.25
0.00
Logrank test p-value: 0.044
0 14 28 42 56 70 84 98 112 126 140 154 168 182
Time since start treatment
Number at risk
non-M/XDR 38 25 13 7 4 3 2 1 0 0 0 0 0
M/XDR 23 18 12 10 6 5 4 3 3 1 1 1 1
non-M/XDR
M/XDR

B

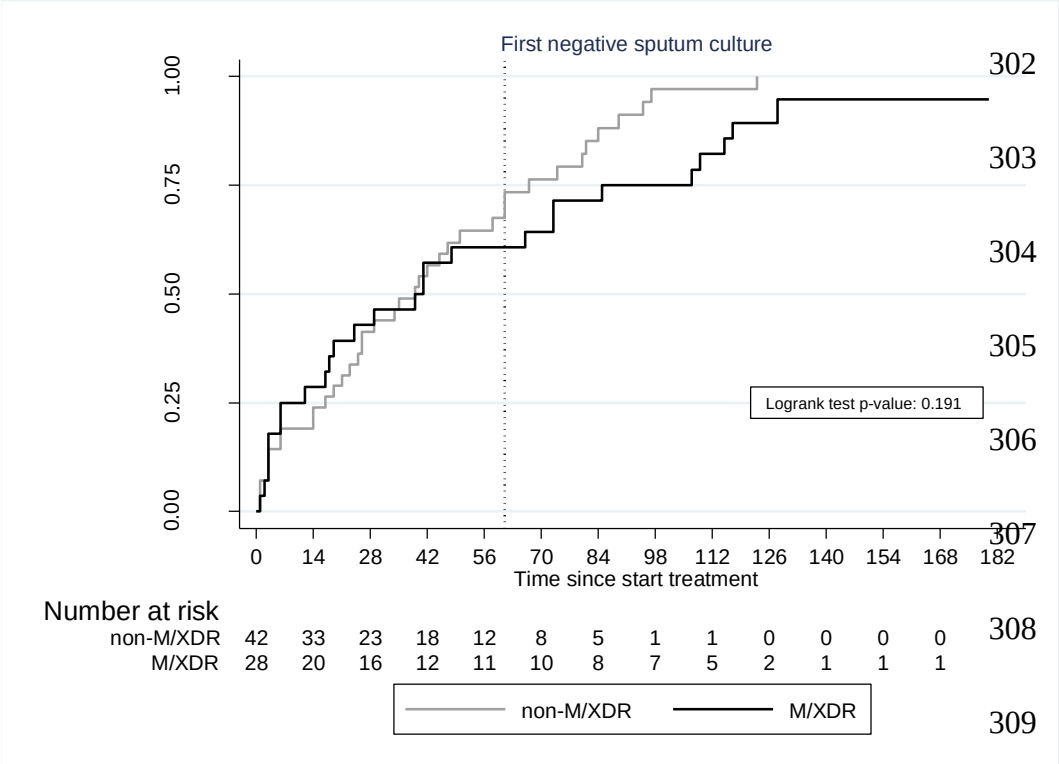

First negative sputum culture
1.00
0.75
0.50
0.25
0.00
Logrank test p-value: 0.191
0 14 28 42 56 70 84 98 112 126 140 154 168 182
Time since start treatment
Number at risk
non-M/XDR 42 33 23 18 12 8 5 1 1 0 0 0 0
M/XDR 28 20 16 12 11 10 8 7 5 2 1 1 1
non-M/XDR
M/XDR

Figure 1A and 1B.

A. Kaplan-Meier estimates for the first negative sputum smear microscopy in patients with non-M/XDR-TB (grey line) and M/XDR-TB (black line) after therapy initiation. Below the X-axis, the number at risk is shown. **B.** Kaplan-Meier estimates for the first negative sputum culture (liquid and solid) in patients with non-M/XDR-TB (grey line) and M/XDR-TB (black line) after therapy initiation. Below the X-axis, the number at risk is shown.

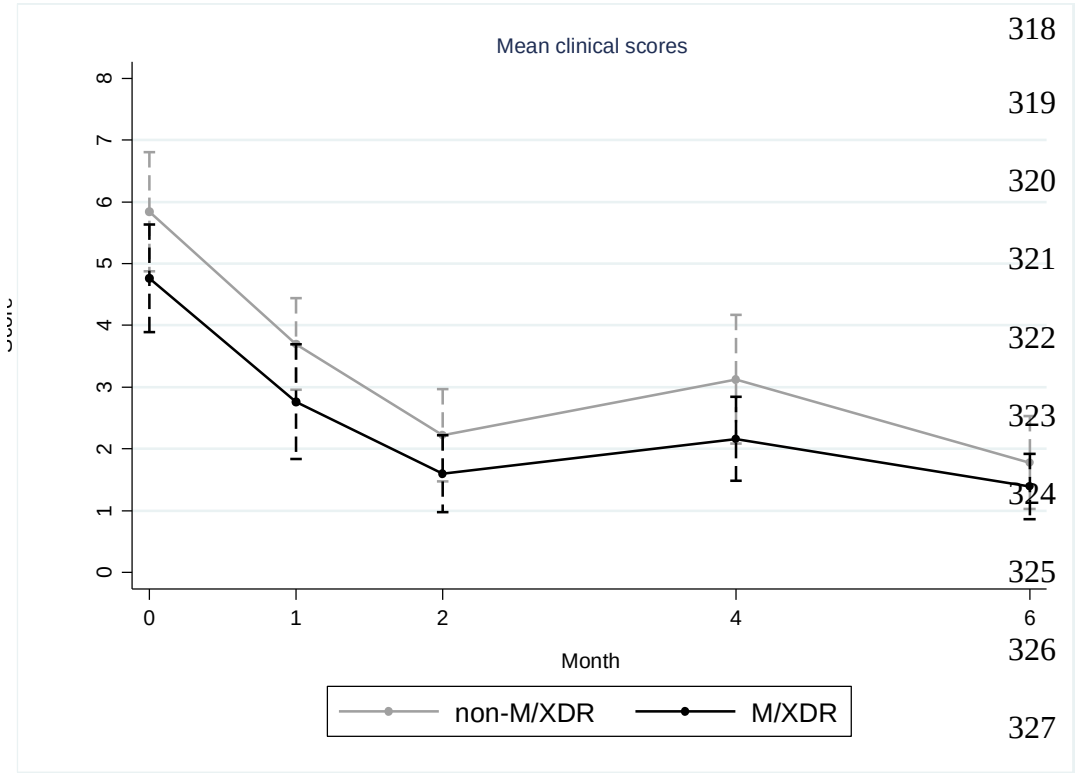


Figure 2. Mean clinical scores (Y-axis) during the course of therapy (X-axis, months) for patients with susceptible (gray line) and M/XDR-TB (black line) with 95% confidence interval (dashed lines).

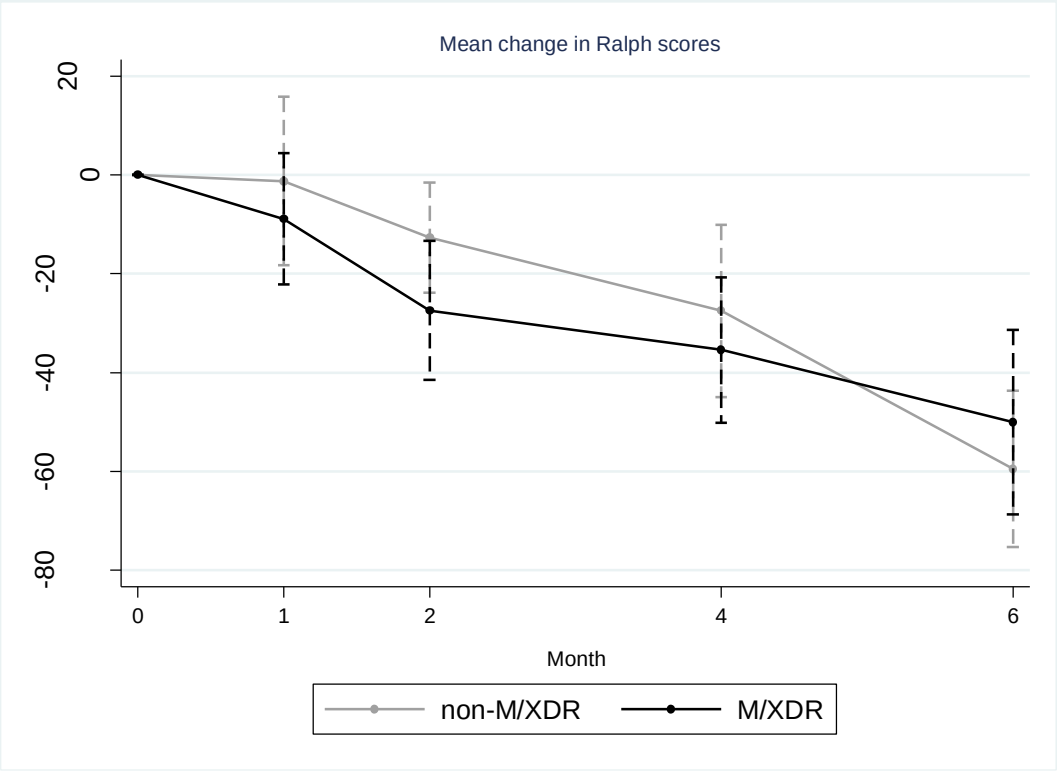


Figure 3. Mean change of radiological (Ralph) scores (Y-axis, %) in the course of therapy (X-axis, months) for patients with susceptible (grey line) and M/XDR-TB (black line) with 95% confidence interval (dashed lines).

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