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Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects

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Abstract

BACKGROUND—Objective of this analysis was to identify predictors of death, failure, and default among MDR-TB patients treated with second-line drugs in DOTS-plus projects in Estonia, Latvia, Philippines, Russia, and Peru, 2000–2004.

METHODS—Risk ratios (RR) with 95% confidence intervals (CI) were calculated using multivariable regression.

RESULTS—Of 1,768 patients, treatment outcomes were: cure/completed – 1,156 (65%), died – 200 (11%), default - 241 (14%), failure - 118 (7%). Independent predictors of death included: age>45 years (RR=1.90 (95%CI 1.29–2.80), HIV infection (RR=4.22 (2.65–6.72)), extrapulmonary disease (RR=1.54 (1.04–2.26)), BMI<18.5 (RR=2.71 (1.91–3.85)), previous use of fluoroquinolones (RR=1.91 (1.31–2.78)), resistance to any thioamide (RR=1.59 (1.14–2.22)), baseline positive smear (RR=2.22 ()1.60–3.10), no culture conversion by 3rd month of treatment (RR=1.69 (1.19–2.41)); failure: cavitary disease (RR=1.73 (1.07–2.80)), resistance to any fluoroquinolone (RR=2.73 (1.71–4.37)) and any thioamide (RR=1.62 (1.12–2.34)), and no culture

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IRB approval. The original study was approved by the U.S. Centers for Disease Control and Prevention (CDC) Institutional Review Board (IRB). Secondary analysis of these data reported in current manuscript received non-research determination by the U.S. Centers for Disease Control and Prevention (CDC) because this activity was considered to be a research but does NOT involve identifiable human subjects (i.e. personal identifiers were stripped from the combined database, and the data were anonymized; the data cannot be linked or re-linked with identifiable human subjects; there was no additional data collection or further interaction with patient medical records).

Disclaimer. The conclusions and interpretations of data presented in this report are solely those of the authors and do not necessarily represent an official position of CDC, USAID, WHO or the governments of the five countries.

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conversion by 3rd month (RR=5.84 (3.02–11.27)); default: unemployment (RR=1.50 (1.12–2.01)), homelessness (RR=1.52 (1.00–2.31)), imprisonment (RR=1.86 (1.42–2.45)), alcohol abuse (RR=1.60 (1.18–2.16)), and baseline positive smear (RR=1.35 (1.07–1.71)).

CONCLUSION—Patients with biomedical risk factors for treatment failure or death should receive heightened medical attention. To prevent treatment default, management of patients who are unemployed, homeless, alcoholic, or have a prison history requires extra measures to insure treatment completion.

Keywords

multidrug-resistant tuberculosis; treatment outcomes; risk factors

Introduction

Modern chemotherapy of drug-susceptible tuberculosis (TB) has >95% efficacy in randomized, controlled clinical trials, and the new World Health Organization (WHO) target for treatment success rates for TB Control programs is 90% by 2015.[1] Treatment of multidrug-resistant (MDR) TB (i.e., TB caused by strains of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin) has far worse outcomes as summarized in two recent systematic reviews and meta-analyses.[2, 3] Treatment of MDR-TB is more expensive, longer, and more toxic compared with standardized short-course chemotherapy for drug-susceptible TB.[4]

In 2000, the Green Light Committee (GLC) was formed to increase access to quality-assured second-line drugs (SLDs) at reduced prices while at the same time preventing the emergence of further drug resistance. From February 1999 to August 2001 the first five DOTS-plus projects approved by the GLC started treating patients, including Estonia; Latvia; Makati Medical Center, Manila, Philippines; the Harvard/Partners in Health Project in northern Lima, Peru; and Tomsk Oblast, Russia.[5, 6] In an effort to improve MDR-TB treatment outcomes we analyzed data from these projects focusing on early predictors of poor treatment outcomes that should trigger timely clinical re-assessment and further action.

Methods

Study Design and Patient Population

This retrospective cohort included adult patients with MDR-TB starting treatment between 01/01/2000–12/31/2003 in five GLC-approved DOTS-Plus programs.[6] The majority of patients in Russia, Latvia, and Estonia were hospitalized, while most patients in Peru and the Philippines received treatment as outpatients. Patients received individualized treatment regimens including 5–7 drugs (typically including a fluoroquinolone and injectable second-line drug) to ensure at least four drugs were effective, in accordance with the GLC-approved protocols.[7] The study was approved by the U.S. Centers for Disease Control and Prevention Institutional Review Board (IRB) and IRBs at all participating sites.

Definitions

Treatment outcomes were programmatically assigned according to each site's criteria. Consensus definitions were developed from 2000–2002 by an international panel of experts including representatives of these five projects and were used in GLC-approved pilot projects before their formal publication in 2005.[8] Positive smear, positive culture, and culture conversion were defined according to WHO guidelines.[4] Baseline drug resistance was determined by drug susceptibility tests (DST) in the local laboratory from sputum collected between 60 days prior to 30 days after MDR-TB treatment initiation. Extensively drug-resistant (XDR) TB and SLDs groups were defined according WHO guidelines.[4]

Data Collection and Statistical Analysis

The database was compiled from existing electronic medical records from five countries. Common variables were identified, common data definitions were operationalized, and disparate data formats were harmonized as previously described[6]. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). Risk ratios (RR) with 95% confidence intervals (CI) for each of the poor outcomes (death, failure, and default) were calculated using log-binomial regression. Factors significant at a value of P≤. 05 in the univariate analysis as well as factors with plausible epidemiological or biological association with each outcome of interest were included in a multivariable log-binomial regression model. Confounding and interaction were assessed. Backward selection was used to choose prognostic variables for final models. A P value of ≤0.05 was considered statistically significant.

Results

A total of 1,768 patients were included in analysis: 663 (37.5%) from Peru, 444 (25.1%) from Latvia, 280 (15.8%) from Estonia, 221 (12.5%) from Russia and 160 (9.1%) from the Philippines. The majority of patients were males (70%), median age was 36 years, and 1.6% were HIV-infected. Socio-demographic and clinical characteristics of this cohort were previously reported by Gammino et al.[6] Pre-treatment isolates were resistant to a median and mean of 5 (interquartile range [IQR] 4–6; range 2–11) first- and second-line anti-TB drugs at the start of treatment. A total of 57 (4.7%) of 1,221 patients with available DST result for at least one injectable SLD and fluoroquinolone had extensively drug resistant tuberculosis at the start of treatment (ranged between sites from 2.9% to 7.9%).

Overall 92.9% (756 of 832 patients with available information) had at least one adverse event reported, with a median of 2 (mean 2.4±1.5; range 0–8) adverse event types per patient (Table 1). The most commonly recorded adverse events of treatment with second-line drugs included nausea (n=540, 65.6%), diarrhea (n=249, 30.3%), and ototoxicity/ hearing disturbances (n=130, 15.8%).

Of 1,768 patients, treatment outcomes were: cure/completed – 1,156 (65.4%), died – 200 (11.3%), failure - 118 (6.7%), default - 241 (13.6%), transferred/unknown - 53 (3.0%). The exact outcome dates were not available, but using the length of microbiological monitoring as a proxy for the length of treatment, patients in whom treatment was successful were on

treatment for median of 21 months (IQR 17–25), patients who died - 8.5 months (IQR 2–16), patients who defaulted treatment – 8 months (IQR 3–15), and those in whom treatment failed – 13 months (IQR 7–23). Of 57 patients with XDR TB, treatment outcomes were: 31 (54.4%) patients had cure/completed treatment, 10 (17.5%) died, 13 (22.8%) failed, and 3 (5.3%) defaulted.

Results of univariate and multivariable analysis of predictors of poor treatment outcomes are shown in Tables 2–4. In multivariable analysis independent risk factors for death included age>45 years (RR=1.90 (95%CI 1.29–2.80), HIV infection (RR=4.22 (2.65–6.72)), extrapulmonary with pulmonary 6 disease (RR=1.54 (1.04–2.26)), BMI<18.5 (RR=2.71 (1.91–3.85)), previous use of fluoroquinolones (RR=1.91 (1.31–2.78)), resistance to any thioamide (RR=1.59 (1.14–2.22)), baseline positive smear (RR=2.22 (1.60–3.10)), and no culture conversion by 3rd month of treatment (RR=1.69 (1.19–2.41)). Patients with prior contact with any TB patient had decreased risk of death (RR=0.10 (0.01–0.68)). Treatment failure was associated in multivariable analysis with cavitary disease (RR=1.73 (1.07–2.80)), resistance to any fluoroquinolone (RR=2.73 (1.71–4.37)) and any thioamide (RR=1.62 (1.12–2.34)), and no culture conversion by 3rd month (RR=5.84 (3.02–11.27)). Independent predictors of default in multivariable analysis included unemployment (RR=1.50 (1.12–2.01)), homelessness (RR=1.52 (1.00–2.31)), imprisonment (RR=1.86 (1.42–2.45)), alcohol abuse (RR=1.60 (1.18–2.16)), and baseline positive smear (RR=1.35 (1.07–1.71)).

Discussion

In summary, despite the use of DOTS-plus to treat this large retrospective cohort of 1,768 patients with drug-resistant tuberculosis, treatment succeeded only in 65% of patients, while 32% had poor treatment outcomes, including death (11%), failure (7%), and default (14%). Treatment outcomes were strikingly similar to the results of two recent meta-analyses and recent surveillance data from 71 countries.[9] Johnston et al[2] reported from 36 studies that 62% of patients achieved successful outcomes, while 11% died, 8% failed, and 13% defaulted. Orenstein et al[3] reported a mean proportion of patients with treatment success in 29 studies of individualized treatment regimens for MDR-TB was 64%, while 11% died, 6% failed, and 12% defaulted treatment. Surveillance data from 71 countries or territories on treatment outcomes for MDR-TB cases showed similar overall treatment success rate (60% after adjustment for clustering by countries) and deaths (8%-13% in new and retreatment cases).[9]

When patients are heading for a poor outcome, prompt action by the physician/program is required. This may include repeating or broadening DST, changing treatment, social/behavioral support, surgery, and further evaluation. Death and treatment failure were associated mainly with biomedical factors, while default from treatment was associated mostly with social factors.

Independent predictors of death and failure, including HIV infection, low body mass index, extensive disease, previous treatment with specific drugs, baseline positive smear, additional resistance to specific drugs, and persistently positive cultures at the 3rd month of treatment

should trigger additional steps and may be amenable to specific interventions. Older age, HIV infection, and extensive TB disease are well-known risk factors for mortality of patients with tuberculosis.[10] Association of prior contact with any TB patient with reduced mortality may be related to earlier diagnosis of MDR TB through contact investigation. Malnutrition, positive baseline smear, and delayed culture conversion were previously demonstrated as risk factors for poor outcomes of MDR-TB treatment.[2, 11] Our findings suggest that fluoroquinolones play an important part in TB treatment, which concurs with previous studies demonstrating that fluoroquinolone resistance was associated with poor MDR-TB treatment outcomes.[2, 12, 13] Regimens for treatment of TB that include fluoroquinolones need to be strong enough not to amplify resistance to fluoroquinolones. Also patients who receive fluoroquinolones for other reasons (e.g. pneumonia) should be screened for TB first. The impact of thioamide resistance on poor outcomes should be further studied.

Socioeconomic factors that increase the risk of default such as unemployment, homelessness, imprisonment, and alcoholism should trigger different types of measures to improve treatment adherence, such as disability stipends, different types of incentives and/or enablers, consultation with a social worker, home visiting, reimbursement of transportation to/from the place of treatment, psychological counseling, legal consulting, etc.[14] Collaboration between TB services and substance abuse services may improve TB treatment adherence, but this needs further research.

Concordantly with previous reports,[15–17] we found that adverse events during MDR TB treatment were very common – 93% of patients had at least one adverse event reported. Gastrointestinal disturbances (nausea and diarrhea) were most often reported side effects. It is important to emphasize that adverse events may have a severe impact on adherence to treatment, so it is crucial to clinically monitor patients for adverse events and timely manage side effects if they occur.[4, 7]

This study has several limitations. The data were retrospective and not originally collected for the purpose of this study; thus there was site-to-site variation in data definitions and recording format. We operationalized the variables for this analysis so they would be consistent across sites. However, not all sites collected data on the same variables; consequently data were missing for individual variables (for up to 30% of observations for certain variables) for some sites; however, we included a category for “missing” results as a dummy variable in the multivariable regression analysis for variables missing more than 7% of data. Data were not available regarding details of treatment, but all sites followed GLC approved treatment protocols consisting of at least four effective drugs, generally treating with aggressive regimens of five to seven drugs. Treatment outcomes at each of the DOTS-plus projects were defined by national norms, but these were generally consistent with international consensus recommendations developed 2000–2002.[8] Generalizability of the study findings may be limited to sites with comparable patient populations, i.e. with low HIV rates, similar drug-resistance epidemiology, and on individualized MDR-TB treatment.

The overall findings of our study corroborate with findings of recent individual patient data (IPD) meta-analysis of 9,153 patients[18] which was used to inform the revision of the WHO

Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (PMDT)[19]. The median duration of treatment of 21 months among those with success outcome in our study was similar to total treatment duration of 18.6–21.5 months associated with increased odds of success in IDP meta-analysis. Similarly to Menzies at al[18], we found an independent association of poor outcomes with fluoroquinolone resistance or use of fluoroquinolone in the past for treatment of TB and thioamide resistance, and no independent association of resistance to injectable agents with poor treatment outcomes. Thus, the findings of our study support current WHO recommendations on including a later generation quinolone and thioamide in treatment regimen and total duration of treatment of at least 21 months.[19] Given gross lack of prospective evaluation of MDR regimens (with and without new drugs), exemplified by the finding that fluoroquinolones resistance was the strongest risk factor for failure, better understanding on how to best combine old drugs with novel drugs in the pipeline is also needed. Randomized clinical trials are urgently needed to determine the optimal treatment regimens for patients with MDR-TB.

In conclusion, patients with identified biomedical risk factors for death or treatment failure should receive targeted medical attention from the beginning of MDR-TB treatment including aggressive treatment with maximum number of effective drugs, adjuvant interventions, including nutritional supplementation and consideration of surgery. To prevent treatment default, management of patients who are unemployed, homeless, alcoholic, or have a history of imprisonment requires extra measures to insure treatment completion. Operations research should be carried out to identify effective interventions for both adherence and treatment outcome improvement in specific settings.

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Table 1

Adverse events on treatment with second-line drugs (N=823)

Adverse event	Number (percent*)
Nausea	540 (65.6)
Diarrhea	249 (30.3)
Ototoxicity (hearing disturbances)	130 (15.8)
Headache	95/602** (11.5)
Hypokalemia	99/221** (14.9)
Peripheral neuropathy	76 (9.2)
Hypothyroidism	40 (4.9)
Seizure	39 (4.7)
Psychosis	35/379** (4.3)
Hepatitis	19 (2.3)
Renal insufficiency (elevated creatinine)	15/602** (1.8)

* Percentage from total 823 unless states otherwise.

** Denominator is number of patients with available data on particular adverse event.

Table 2

Univariate and multivariable analyses of socio-demographic risk factors for death, failure, and default versus successful treatment outcome in patients with MDR-TB

Factor	Died N=200 n (%)	cRR (95% CI) for death	aRR* (95% CI) for death	Failed N=118 n (%)	cRR (95% CI) for failure	aRR* (95% CI) for failure	Defaulted N=241 n (%)	cRR (95% CI) for default	aRR* (95% CI) for default	Success** N=1156 n
Age group¶										
Age <25 years	29 (11.5)	1.00	1.00	11 (4.7)	1.00		29 (11.5)	1.00		565
Age 25–45 years	97 (14.7)	1.27 (0.86–1.88)	1.35 (0.94–1.93)	73 (11.4)	**2.43 (1.31–4.51)**	-	143 (20.2)	**1.76 (1.21–2.55)**	-	314
Age >45 years	64 (16.9)	1.47 (0.98–2.21)	**1.90 (1.29–2.80)**	34 (9.8)	2.08 (1.07–4.02)		65 (17.2)	1.49 (0.99–2.24)		223
Gender										
Male	133 (14.2)	0.89 (0.68–1.17)	-	82 (9.3)	1.00 (0.69–1.46)	-	82 (9.3)	1.00 (0.69–1.46)	-	802
Female	67 (15.9)	1.00		36 (9.2)	1.00		36 (9.2)	1.00		354
Homelessness										
Yes	2 (11.1)	0.77 (0.21–2.89)	-	4 (20.0)	2.16 (0.88–5.29)	-	16 (50.0)	**3.01 (2.08–4.36)**	**1.52 (1.00–2.31)**	16
No	159 (14.3)	1.00		97 (9.3)	1.00		189 (16.6)	1.00	1.00	950
Unknown	39 (17.0)	1.19 (0.86–1.64)		17 (8.2)	0.89 (0.54–1.45)		36 (15.9)	0.96 (0.69–1.33)	1.17 (0.62–2.21)	190
Imprisonment										
Current or history	26 (10.4)	0.87 (0.57–1.33)	-	44 (16.5)	**1.76 (1.21–2.56)**	-	83 (27.1)	**1.82 (1.40–2.38)**	**1.86 (1.42–2.45)**	223
Never	69 (12.0)	1.00		52 (9.4)	1.00		88 (14.9)	1.00	1.00	504
Unknown	105 (19.7)	1.63 (1.23–2.16)		22 (4.9)	0.52 (0.32–0.85)		70 (14.0)	0.94 (0.71–1.26)	1.24 (0.74–2.07)	429
Employment status										
Unemployed	101 (17.2)	**1.57 (1.13–2.17)**	-	55 (10.1)	1.03 (0.70–1.51)	-	139 (22.2)	**1.68 (1.27–2.23)**	**1.50 (1.12–2.01)**	488
Employed or other***	46 (10.9)	1.00		41 (9.9)	1.00		57 (13.2)	1.00	1.00	375
Unknown	53 (15.3)	1.40 (0.97–2.03)		22 (7.0)	0.71 (0.43–1.16)		45 (13.3)	1.01 (0.70–1.45)	0.83 (0.51–1.36)	293
Alcohol abuse										
Yes	44 (13.5)	**1.69 (1.09–2.61)**	-	57 (16.8)	**2.04 (1.36–3.07)**	-	106 (27.3)	**1.95 (1.46–2.61)**	**1.60 (1.18–2.16)**	282
No	31 (8.0)	1.00		32 (8.2)	1.00		58 (14.0)	1.00	1.00	357
Unknown	125 (19.5)	2.44 (1.68–3.54)		29 (5.3)	0.65 (0.40–1.05)		77 (13.0)	0.93 (0.68–1.27)	0.93 (0.64–1.35)	517

Factor	Died N=200 n (%)	cRR (95% CI) for death	aRR* (95% CI) for death	Failed N=118 n (%)	cRR (95% CI) for failure	aRR* (95% CI) for failure	Defaulted N=241 n (%)	cRR (95% CI) for default	aRR* (95% CI) for default	Success** N=1156 n
Smoking										
Yes	22 (9.6)	**0.53 (0.34–0.82)**	-	11 (5.0)	0.95 (0.47–1.93)	-	31 (13.0)	1.01 (0.67–1.52)	-	208
No	87 (18.0)	1.00		22 (5.3)	1.00		58 (12.8)	1.00		395
Unknown	91 (14.1)	0.78 (0.60–1.02)		85 (17.7)	**2.53 (1.61–3.97)**		152 (21.6)	**1.68 (1.27–2.22)**		553
Injecting drug use										
Yes	2 (6.7)	1.01 (0.25–4.04)	-	0 (0)	undefined	-	13 (31.7)	**2.06 (1.25–3.39)**	-	732
No	28 (6.6)	1.00		58 (12.8)	1.00		72 (15.4)	1.00		28
Unknown	170 (30.0)	**2.85 (1.95–4.18)**		60 (13.2)	0.59 (0.42–0.83)		156 (28.3)	1.14 (0.88–1.47)		396

cRR = crude risk ratio (univariate analysis); aRR = adjusted risk ratio (multivariable analysis); CI = confidence interval.

¶68 patients had missing information on age and were not included in multivariable analysis (including 10 patients with death, 4 patients with default and 54 with success outcome).

*Controlling for GLC site.

**Successful treatment outcome is referent group for each poor outcome (death, treatment failure and default).

***Other employment status includes retired, student, disabled. Variables for which aRRs are not shown were not included in the final multivariable model. Risk ratios for predictors significant at P=0.05 are highlighted in bold.

Table 3

Univariate and multivariable analyses of clinical risk factors for death, failure, and default versus successful treatment outcome in patients with MDR-TB

Factor	Died N=200 n (%)	cRR (95% CI) for death	aRR* (95% CI) for death	Failed N=118 n (%)	cRR (95% CI) for failure	aRR* (95% CI) for failure	Defaulted N=241 n (%)	cRR (95% CI) for default	aRR* (95% CI) for default	Success** N=1156 n
HIV status										
Positive	9 (50.0)	**3.82 (2.35–6.22)**	**4.22 (2.65–6.72)**	1 (10.0)	1.20 (0.18–7.77)	-	8 (47.1)	**2.88 (1.71–4.86)**	-	9
Unknown	49 (19.4)	**1.49 (1.11–2.00)**	**1.57 (1.13–2.18)**	31 (13.2)	1.59 (1.08–2.33)		49 (19.4)	1.19 (0.90–1.58)		201
Negative	142 (13.1)	1.00	1.00	86 (8.3)	1.00		184 (16.3)	1.00		944
Diabetes mellitus										
Yes	9 (16.7)	1.24 (0.67–2.30)	-	6 (11.8)	1.39 (0.64–3.04)	-	8 (15.1)	1.02 (0.53–1.96)		45
No	145 (13.4)	1.00		87 (8.5)	1.00		163 (14.8)	1.00		938
Unknown	46 (21.0)	**1.57 (1.16–2.11)**		25 (12.6)	1.49 (0.98–2.26)		70 (28.8)	**1.95 (1.53–2.48)**		173
Body mass index (BMI)										
BMI<18.5	53 (24.3)	**3.36 (2.35–4.79)**	**2.71 (1.91–3.85)**	28 (14.5)	**1.80 (1.18–2.76)**	-	24 (12.0)	0.83 (0.55–1.26)	-	165
BMI>=18.5	50 (7.2)	1.00	1.00	56 (8.0)	1.00		115 (15.2)	1.00		640
Unknown	97 (21.7)	2.99 (2.17–4.11)	**2.01 (1.40–2.88)**	34 (8.8)	1.10 (0.73–1.65)		102 (22.5)	**1.48 (1.16–1.88)**		351
Site of TB										
Pulmonary with EPTB	17 (28.8)	**2.02 (1.32–3.08)**	**1.54 (1.04–2.26)**	4 (8.7)	1.13 (0.44–2.93)		7 (14.30	1.26 (0.63–2.53)	-	42
Pulmonary only	170 (14.3)	1.00	1.00	111 (9.8)	1.00		224 (18.0)	1.00		1020
Unknown	13 (12.2)	0.85 (0.50–1.44)	0.95 (0.29–3.09)	3 (3.1)	0.36 (0.08–1.52)		10 (9.6)	0.67 (0.27–1.66)		94
Cavitary TB disease										
Yes	131 (15.9)	**1.55 (1.08–2.23)**	-	93 (11.8)	**2.33 (1.37–3.95)**	**1.73 (1.07–2.80)**	168 (19.5)	1.31 (0.98–1.75)	-	693
No	32 (10.3)	1.00		15 (5.1)	1.00	1.00	49 (14.9)	1.00		280
Unknown	37 (18.5)	**1.64 (1.06–2.55)**		10 (5.2)	1.02 (0.47–2.22)	1.49 (0.62–3.58)	24 (11.6)	0.78 (0.49–1.23)		183
Outcome of previous treatment of TB under DOTS										
Cure	14 (9.3)	1.77 (0.74–4.27)	-	13 (8.7)	1.46 (0.63–3.42)	1.25 (0.57–2.75)	24 (14.9)	0.88 (0.53–1.46)	-	137
Failure or default	105 (16.1)	**3.07 (1.46–6.46)**		35 (6.0)	1.01 (0.48–2.13)	2.04 (0.98–4.24)	78 (12.4)	0.73 (0.49–1.10)		549
Unknown	74 (17.7)	**3.40 (1.60–7.19)**		62 (15.3)	**2.58 (1.27–5.25)**	**2.86 (1.43–5.74)**	113 (24.8)	1.46 (0.99–2.14)		343

Factor	Died N=200 n (%)	cRR (95% CI) for death	aRR* (95% CI) for death	Failed N=118 n (%)	cRR (95% CI) for failure	aRR* (95% CI) for failure	Defaulted N=241 n (%)	cRR (95% CI) for default	aRR* (95% CI) for default	Success** N=1156 n
New MDR-TB case	7 (5.2)	1.00		8 (5.9)	1.00	1.00	26 (17.0)	1.00		127
History of TB treatment with fluoroquinolones										
Yes	96 (26.1)	**2.48 (1.93–3.18)**	**1.91 (1.31–2.78)**	30 (9.9)	1.10 (0.74–1.63)	-	47 (14.7)	0.82 (0.61–1.10)	-	272
No	104 (10.5)	1.00	1.00	88 (9.1)	1.00		194 (18.0)	1.00		884
History of TB treatment with any injectable SLD										
Yes	99 (20.9)	**1.82 (1.42–2.35)**	-	43 (10.3)	1.17 (0.82–1.68)	-	65 (14.8)	0.80 (0.62–1.04)	-	375
No	101 (11.5)	1.00		75 (8.8)	1.00		176 (18.4)	1.00		781

Note. cRR = crude risk ratio (univariate analysis); aRR = adjusted risk ratio (multivariable analysis); CI = confidence interval; EPTB=Extrapulmonary TB.

*Controlling for GLC site.

**Successful treatment outcome is referent group for each poor outcome (death, treatment failure and default). Variables for which aRRs are not shown were not included in the final multivariable model. Risk ratios for predictors significant at P=0.05 are highlighted in bold.

Table 4

Univariate and multivariable analyses of laboratory predictors for death, failure, and default versus successful treatment outcome in patients with MDR-TB

Factor	Died N=200 n (%)	cRR (95% CI) for death	aRR* (95% CI) for death	Failed N=118 n (%)	cRR (95% CI) for failure	aRR* (95% CI) for failure	Defaulted N=241 n (%)	cRR (95% CI) for default	aRR* (95% CI) for default	Success** N=1156 n
Baseline AFB smear status										
Positive	160 (19.3)	**2.67 (1.90–3.75)**	**2.22 (1.60–3.10)**	89 (11.7)	**2.11 (1.40–3.17)**	-	156 (18.9)	1.27 (0.99–1.62)	**1.35 (1.07–1.71)**	669
Negative	37 (7.2)	1.00		28 (5.6)	1.00		83 (14.9)	1.00	1.00	474
Unknown	3 (18.8)	2.59 (0.89–7.52)	1.67 (0.52–5.38)	1 (7.1)	1.28 (0.19–8.76)		2 (13.3)	0.89 (0.24–3.30)	1.47 (0.39–5.59)	13
Baseline resistance to any fluoroquinolone										
Yes	29 (24.8)	**2.01 (1.40–2.88)**	-	22 (20.0)	**2.75 (1.76–4.30)**	**2.73 (1.71–4.37)**	12 (12.0)	0.79 (0.45–1.37)	-	88
No	106 (12.4)	1.00		59 (7.3)	1.00	1.00	135 (15.2)	1.00		752
Unknown	65 (17.1)	**1.38 (1.04–1.83)**		37 (10.5)	1.44 (0.97–2.13)	0.80 (0.43–1.47)	94 (22.9)	**1.51 (1.19–1.91)**		316
Baseline resistance to any injectable SLD										
Yes	50 (15.5)	1.27 (0.92–1.75)	-	47 (14.7)	**2.22 (1.51–3.25)**	-	41 (13.1)	0.88 (0.63–1.22)	-	272
No	92 (12.2)	1.00		47 (6.6)	1.00		116 (14.9)	1.00		661
Unknown	58 (20.6)	**1.69 (1.25–2.28)**		24 (9.7)	1.46 (0.91–2.34)		84 (27.4)	**1.83 (1.43–2.35)**		223
Baseline resistance to any thioamide										
Yes	58 (19.9)	**1.90 (1.37–2.62)**	**1.59 (1.14–2.22)**	33 (12.4)	**1.93 (1.24–3.01)**	**1.62 (1.12–2.34)**	38 (14.0)	1.01 (0.71–1.44)	-	233
No	65 (10.5)	1.00	1.00	38 (6.4)	1.00	1.00	89 (13.9)	1.00		553
Unknown	77 (17.2)	**1.64 (1.21–2.23)**	1.36 (0.89–2.07)	47 (11.3)	**1.75 (1.16–2.64)**	**2.07 (1.07–3.98)**	114 (23.6)	**1.70 (1.32–2.18)**		370
Baseline XDR										
Yes	10 (24.4)	**1.82 (1.03–3.19)**	-	13 (29.5)	**3.80 (2.28–6.33)**	-	3 (8.8)	0.59 (0.20–1.74)	-	31
No	125 (13.4)	1.00	-	68 (7.8)	1.00	-	143 (15.1)	1.00	-	806
Unknown	65 (16.9)	1.26 (0.96–1.66)	-	37 (10.4)	1.34 (0.91–1.96)	-	95 (22.9)	**1.52 (1.21–1.92)**	-	319
Initial sputum culture conversion within 3 months of treatment* **										
No	77 (26.1)	**2.07 (1.44–2.96)**	**1.69 (1.19–2.41)**	84 (27.8)	**7.20 (3.82–13.58)**	**5.84 (3.02–11.27)**	70 (24.3)	**1.43 (1.04–1.97)**	-	218
Yes	87 (11.2)	0.89 (0.62–1.28)	0.94 (0.66–1.33)	24 (3.4)	0.87 (0.42–1.80)	0.96 (0.46–1.99)	120 (14.8)	0.87 (0.65–1.18)		689

Factor	Died N=200 n (%)	cRR (95% CI) for death	aRR* (95% CI) for death	Failed N=118 n (%)	cRR (95% CI) for failure	aRR* (95% CI) for failure	Defaulted N=241 n (%)	cRR (95% CI) for default	aRR* (95% CI) for default	Success** N=1156 n
Baseline culture negative	36 (12.6)	1.00	1.00	10 (3.9)	1.00	1.00	51 (17.0)	1.00		249

cRR = crude risk ratio (univariate analysis); aRR = adjusted risk ratio (multivariable analysis); CI = confidence interval.

* Controlling for GLC site.

** Successful treatment outcome is referent group for each poor outcome (death, treatment failure and default).

*** Cut point for timing of initial sputum culture conversion was chosen based on median time to conversion at 3 months of treatment (interquartile range [IQR]: 2.0, 5.0). Risk ratios for predictors significant at P=0.05 are highlighted in bold.

Variables for which aRRs are not shown were not included in the final multivariable model.