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National treatment outcome and predictors of death and treatment failure in multidrug-resistant tuberculosis in Ethiopia: a 10-year retrospective cohort study

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ABSTRACT

Objectives Treatment success rate in patients treated for multidrug-resistant tuberculosis (MDR-TB) is low, but predictors of treatment failure and death have been under-reported. Thus, we aimed to determine the national proportion of treatment success rate in the past 10 years and factors that predict treatment failure and death in patients with MDR-TB in Ethiopia.

Setting A retrospective cohort study with a 10-years follow-up period was conducted in 42 MDR-TB treatment-initiating centres in Ethiopia.

Participants A total of 3395 adult patients with MDR-TB who had final treatment outcome and who were treated under national TB programme were included. Data were collected from clinical charts, registration books and laboratory reports. Competing risk survival analysis model with robust standard errors (SE) was used to determine the predictors of treatment failure and death.

Primary and secondary outcomes Treatment outcome was a primary outcome whereas predictors of treatment failure and death were a secondary outcome.

Results The proportion of treatment success was 75.7%, death rate was 12.8%, treatment failure was 1.7% and lost to follow-up was 9.7%. The significant predictors of death were older age (adjusted hazard ratio (AHR)=1.03; 95% CI 1.03 to 1.05; p<0.001), HIV infection (AHR=2.0; 95% CI 1.6 to 2.4; p<0.001) and presence of any grade of anaemia (AHR=1.7; 95% CI 1.4 to 2.0; p<0.001). Unlike the predictors of death, all variables included into multivariable model were not significantly associated with treatment failure.

Conclusion In the past 10 years, although MDR-TB treatment success in Ethiopia has been consistently favourable, the proportion of patients who died is still considerable. Death could be attributed to advanced age, HIV infection and anaemia. Prospective cohort studies are necessary to further explore the potentially modifiable predictors of treatment failure.

Strengths and limitations of this study

► National multidrug-resistant tuberculosis (MDR-TB) treatment success rate in the past 10 years was determined using MDR-TB treatment programme data.
► Although MDR-TB mortality is high, predictors of death and treatment failure are under-reported.
► This study determined the predictors of treatment failure and death using competing risk survival analysis model with a robust SE.
► Retrospective nature of the study design leads to key variables such as sociodemographic, behavioural, adverse drug reactions, key laboratory variables and treatment adherence status missing.
► A short MDR-TB treatment regimen is recently introduced in Ethiopia; therefore, patients treated by long regimen alone were enrolled into this study.

to control TB and continues to cause severe morbidity and mortality among millions across the world. The WHO estimated that nearly half a million rifampin-resistant new TB cases occurred in 2019 across the world.[1] Multidrug-resistant (MDR)-TB is defined as a *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin; whereas, extensively drug-resistant (XDR)-TB refers to a *M. tuberculosis* resistance to at least rifampin and isoniazid as well as resistance to any fluoroquinolone and at least one of the three injectable anti-TB drugs (capreomycin, kanamycin or amikacin).[2] The treatment of MDR-TB and XDR-TB has been largely unsuccessful due to the difficulty of the diagnosis, long duration of the treatment, the less effective and toxic drugs used for the treatment and unavailability of drug options.[3–5]

The current MDR-TB treatment success rate (the sum of cured and treatment completed)

BACKGROUND

The emergence of drug-resistant tuberculosis (TB) has been undermining the efforts

is considerably low.[1 3 6] The WHO's recent global estimation indicates that only 57% of patients with MDR-TB were successfully treated in 2017.[1] Moreover, a recently published individual patient data meta-analysis study indicated that 61% of patients with MDR-TB were treated successfully.[6] However, recent studies indicated relatively higher treatment success rates in certain settings.[7–10] For example, 82.4% of patients with MDR-TB were treated successfully in Taiwan,[7] 75.8% in Pakistan[10] and 75.7% in Tanzania.[8]

Heterogeneous and inter-related factors are associated with poor MDR-TB treatment outcome. Infection with HIV,[11–14] diabetes mellitus,[12 15 16] malnutrition[17 18] and anaemia[12 14 19] are comorbidities that are associated with poor treatment outcome in patients treated for MDR-TB. Moreover, treatment interruption,[14 20 21] medication regimens,[22] antiretroviral therapy (ART) timing,[23] time to MDR-TB treatment initiation after diagnosis[24] and previous TB treatment[18 25] are the treatment-related factors that are associated with poor treatment outcome in the patients with MDR-TB.

Ethiopia is among the 30 high-TB and MDR-TB prevalent countries with an estimated TB incidence of 140 per 100 000 population in 2019.[1] Despite an improving TB control programme and relative treatment success rate, the prevalence of MDR-TB in Ethiopia remains high with 2.2% in new TB cases and 21.1% in previously treated TB cases.[26] However, WHO's recent estimate in Ethiopia indicated a lower prevalence of 0.71% of MDR-TB in new cases and 12% in previously treated cases in 2019.[1] Although there is no national level report on MDR-TB treatment outcome in Ethiopia, studies reported from local data indicated variable treatment success that ranges between 63% and 78.8%.[9 19 27]

The global treatment success rate of MDR-TB is low and there is limited evidence on the factors that are associated with poor treatment outcome. Furthermore, available studies are focused in the determination of predictors of unsuccessful treatment outcome by merging death, treatment failure and lost to follow-up in one category. However, this could conceal the actual predictors of death and treatment failure. To that extent, there is no study that reported the predictors of death and treatment failure separately using competing risk survival analysis model with robust SE. Ethiopia is among the countries which lack such evidence at national level to plan an effective intervention that could decrease treatment failure and reduce death in patients with MDR-TB. Thus, we aimed to determine the national level treatment success rate in the past 10 years and factors that could predict treatment failure and death in patients with MDR-TB in Ethiopia.

MATERIALS AND METHODS
Study setting, population and design
We conducted a retrospective cohort study on adult patients aged ≥15 years, diagnosed either biologically or clinically for both pulmonary and extra-pulmonary TB and enrolled to MDR-TB treatment at 42 treatment-initiating centres (TICs) in Ethiopia from February 2009 to February 2019. MDR-TB treatment was started in February 2009 in one hospital in Addis Ababa, Ethiopia.[27] During this study period, there were a total of 53 TICs and several treatment follow-up centres (TFCs) in the country. The majority of the patients with MDR-TB initiate their treatments in TICs while stable patients follow the treatment under directly observed therapy programme in nearby TICs or TFCs as ambulatory outpatients. However, all information on the patients registered for MDR-TB treatment has been documented at TICs where the patient started the treatment. We included a total of 42 TICs into this study; the remaining 11 TICs had no patients who completed their treatment during the study period.

Inclusion and exclusion criteria
We included all adult patients who were aged ≥15 years, diagnosed either bacteriologically or clinically for MDR-TB and enrolled to the treatment from February 2009. Children <15 years old were excluded from this study, because their treatment guideline is different from the adults. Moreover, we excluded patients who had no final treatment outcome (transferred out or still on treatment or treatment outcome missed from data sources).

Laboratory test
All laboratory tests were performed according to WHO recommendation and national TB laboratory algorithm in quality-assured TB laboratories.[28 29] To detect drug-resistant TB, culture tests were carried out with solid media (Löwenstein-Jensen) and a fluorometric BACTEC MGIT960 at one national TB reference laboratory and nine regional laboratories. In addition, GeneXpert *Mycobactgerium tuberculosisr*/resistance to rifampin (MTB/RIF) assay was used to detect rifampin-resistant TB. This assay is a rapid, sensitive and specific technique that is widely used to detect *M. tuberculosis* and rifampin resistance at each level in the national health system. Drug susceptibility test (DST) for first-line drugs was performed by BACTEC MGIT960 system based on WHO-recommended critical concentrations for rifampin (1.0 g/mL), isoniazid (0.1 g/mL), streptomycin (1.0 g/mL), ethambutol (5 g/mL) and pyrazinamide (100 g/mL). DST for second-line drugs (SLDs) has been recently started in the country and rarely performed. Data on second-line DST were not included to this study because very few DST results for SLDs were obtained in the records. Quality assurance for DST was regularly performed by Milan supranational reference laboratory in Italy and demonstrated constant proficiency.

Treatment
Previously, all patients with MDR-TB were treated as inpatient model of care for the first few months at treatment centres until the patients were clinically stable with culture conversion. However, according to the recent

edition of National TB Treatment guideline (2018), all patients with MDR-TB need to be treated under clinical-based ambulatory model of care,[29] unless the patients are clinically unstable or developed severe adverse drug reaction. Patients either with serious medical or social conditions could be admitted with the decision of the treatment panel. Standardised long-treatment regimens were used to treat the patients with MDR-TB in Ethiopia. The long-treatment regimen contained at least four oral drugs used daily during full course of treatment and one injectable drug until *M. tuberculosis* culture conversion. Treatment with injectable drugs continues at least for 8 months based on clinical, microbiological and radiographic examination results. The minimum treatment duration was 20 months—at least 18 months after bacteriological conversion. The treatment duration of 9–11 months (short-treatment regimen) was not used.[29] The SLDs used to treat MDR-TB in Ethiopia are levofloxacin, ethionamide, cycloserine, para-aminosalicyclic acid, pyrazinamide, prothionamide, linezolid, clofazimine and injectable drugs such as amikacin, kanamycin and capreomycin.[29] All the patients enrolled into this study were treated by a standardised long-term regimen consisting of capreomycin, levofloxacin, prothionamide, cycloserine and high-dose isoniazid during the intensive phase.[29] During the continuation phase, levofloxacin, prothionamide, cycloserine and high-dose isoniazid were used.[29] Laboratory tests, chest X-ray and clinical investigations are used to monitor response to the treatment and to identify treatment-related complications in patients on MDR-TB treatment in Ethiopia. Clinical investigations only are used to monitor response to the treatment, while laboratory tests are used to identify treatment-related complications for patients with extra-pulmonary TB. MDR-TB treatment is free of any cost in Ethiopia and there is full access to all categories of drugs to treat patients with MDR-TB.

Data collection

We collected data on sociodemographic variables such as sex, age and regional state. We also collected TB-related data such as anatomical site of TB (pulmonary vs extra-pulmonary), drug resistance type (rifampin resistance (RR) vs MDR), previous treatment (new vs previously treated), diagnosis method (bacteriologically vs clinically), HIV status (HIV-infected vs not infected) and ART status (on ART vs not on ART vs not applicable). In addition, we collected information on bacteriological status (smear, GeneXpert MTB/RIF, culture or first-line drugs DST results) at treatment initiation. All data were extracted from patients' clinical charts, registration books and laboratory reports. Data were collected by health professionals familiar with MDR-TB treatment after 2 days of practical training on data management.

Definitions

In this study, we used standard WHO and national treatment guidelines definitions for laboratory confirmations,

patient categories and treatment outcomes.[28 29] Clinically diagnosed MDR-TB refers to those cases with no documented DST results but treated empirically with a course of treatment including SLDs based on clinical criteria and contact history.[29] However, bacteriologically confirmed MDR-TB refers to those cases with the documented DST results. All patients were categorised into new patients (never treated for TB or for <1 month) and patients previously treated for TB. The final treatment outcomes of MDR-TB were cured, treatment completed, death, treatment failed and lost to follow-up. Cured refers to a patient initially bacteriologically confirmed and completed the treatment without the evidence of treatment failure and three or more consecutive cultures taken at least 30 days apart being negative after the intensive phase. Treatment completed is defined as a patient who completed the treatment without the evidence of treatment failure but there is no record that indicates three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. A patient whose treatment is terminated or need for permanent regimen change of at least two anti-TB drugs is categorised as treatment failure. Lost to follow-up also refers to a patient whose treatment is interrupted for 2 consecutive months or more. Successful treatment outcome was the sum of cured and treatment completed, whereas unsuccessful was the combination of death, treatment failed and lost to follow-up.

Data analysis

We entered data into CSPro software V.6.1 and analysed using STATA V.14 (StataCorp, College Station, TX, USA). The data were confirmed from each data source and cleaned for errors before main analysis. We described participants' demographic and clinical characteristics using descriptive statistics. The proportions of MDR-TB treatment outcomes were frequency weighed by the total number of patients registered from February 2009 to February 2019 in each TIC.

We used a competing risk survival analysis model with robust SE to assess the effects of different variables on the treatment failure and death. Effect levels were reported by HR with 95% CIs. We included variables scored p values ≤0.2 during bivariate analysis and clinically or epidemiologically relevant. We considered death as failure event to estimate the effects of different variables on death, while treatment failure and success were considered as competing risks. Similarly, we considered treatment failure as failure event to estimate the effects of different variables on the duration from treatment enrolment to treatment failure, whereas death and treatment success were considered as competing risks. Lost to follow-up was considered as a censored across the fitted models. Level of significance was set at 5% for all analysis.

Patient and public involvement

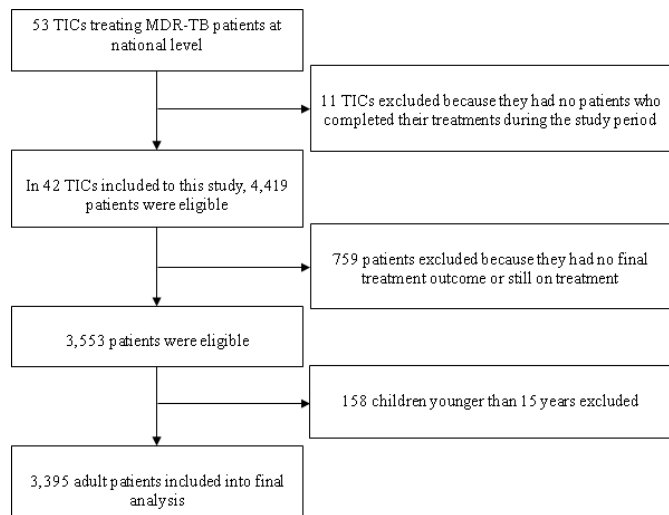Both patient and public were not involved in this study.

Figure 1 TICs and patients' inclusion flow diagram. MDR-TB, multidrug-resistant tuberculosis; TICs, treatment-initiating centres.

RESULTS
Participants' characteristics

A total of 4419 patients were enrolled to MDR-TB treatment in 42 of 53 (79.2%) TICs in Ethiopia from February 2009 to February 2019 (figure 1). Of the 4419 patients, 3395 (76.8%) fulfilled our inclusion criteria and enrolled to this study (figure 1).

The highest number of patients enrolled into the treatment was in 2015 (667 patients), while in 2019 the smallest number of patients were registered (only 4 patients; figure 2).

Of the 3395 patients included into this study, 1870 (55.1%) were male and the mean age was 31.6 (SD ±11.7) years with the age range of 15–85 years. Seventy-two per cent of the patients were in the age category of 15–35 years (table 1). Ninety-three per cent of the participants were patients with pulmonary TB (table 1). Eighty-six per cent of the patients had previous TB treatment. Drug resistance status of 3242 (95.5%) isolates were bacteriologically confirmed at the initiation of treatment (table 1).
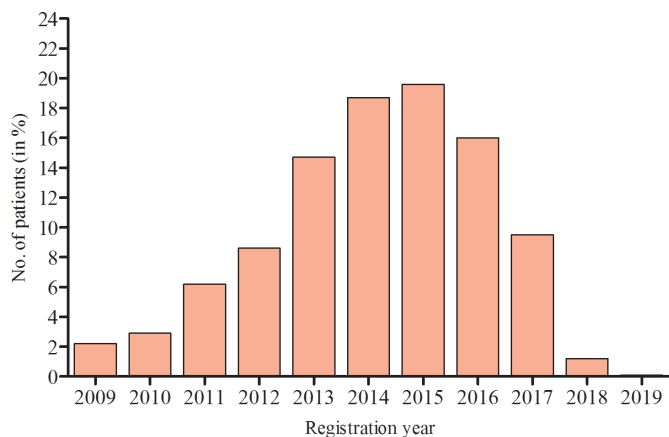

Figure 2 Patient enrolment into MDR-TB treatment in past 10 years in Ethiopia (2009–2019). MDR-TB, multidrug-resistant tuberculosis.

Table 1 Demographic and clinical characteristics of the patients (n=3395)

Variable		n (%)
Sex	Male	1870 (55.1)
	Female	1525 (44.9)
Age (in years)	15–25	1268 (37.3)
	26–35	1186 (34.9)
	36–45	529 (15.6)
	≥46	412 (12.1)
Drug resistance type	Rifampin/Isoniazid(RIF/INH) status unknown	1810 (53.3)
	MDR-TB	1585 (46.7)
Anatomical site of TB	Pulmonary	3171 (93.4)
	Extra-pulmonary	224 (6.6)
Previous TB treatment	New	462 (13.6)
	Previously treated	2933 (86.4)
Previous exposure to SLDs	Yes	1421 (41.9)
	No	1842 (54.3)
	Unknown	132 (3.9)
Drug resistance identification method	GeneXpert MTB/RIF	1967 (57.9)
	Culture/LPA	1275 (37.6)
	Clinical	153 (4.5)
Diagnosis method	Bacteriological	3242 (95.5)
	Clinical	153 (4.5)
HIV infection	Not infected	2554 (75.2)
	Infected	767 (22.6)
	Unknown	74 (2.2)
ART status	Not applicable	2556 (75.3)
	On ART	686 (20.2)
	HIV status known but, ART status unknown	79 (2.3)
	Both ART and HIV statuses unknown	74 (2.2)
Contact history of patient with MDR-TB	Yes	204 (6.0)
	No	1511 (44.5)
	Unknown	1680 (49.5)
Hospitalisation history at treatment initiation	Hospitalised	1831 (53.9)
	Not hospitalised	487 (14.3)
	Unknown	1077 (31.7)
Treatment interruption	Never interrupted/interruption status unknown	3192 (94.0)
	At least 1 day interrupted	203 (6.0)

ART, antiretroviral therapy; LPA, line probe assay; MDR, multidrug-resistant; SLDs, second-line drugs; TB, tuberculosis.

The main drug resistance diagnosis method was GeneXpert MTB/RIF (57.9%). Of the 3395 patients, 1421 (41.9%) had previous exposure to SLDs and 767 (22.6%) were HIV-infected (table 1) of which 686 (89.4%) were on

Table 2 Antituberculosis drug susceptibility test results

Antituberculosis drug	Susceptibility test results	n (%)
Rifampin (n=3395)	Resistant	3371 (99.3)
	Susceptible	24 (0.7)
Isoniazid (n=1313)	Resistant	1241 (94.5)
	Susceptible	72 (5.5)
Ethambutol (n=427)	Resistant	299 (70.0)
	Susceptible	128 (30.0)
Streptomycin (n=443)	Resistant	337 (76.1)
	Susceptible	106 (23.9)

ART. Only 6.0% of the patients had previous contact with a patient having MDR-TB and 1831 (53.9%) of patients were hospitalised at the treatment initiation (table 1) with mean duration of hospitalisation 81.7 (±47.4) days.

Drug resistance status at treatment initiation
Drug susceptibility testing was performed for four first-line drugs which are rifampin, isoniazid, ethambutol and streptomycin (table 2). Rifampin susceptibility test was performed on isolates of all the patients included into this study and 99.3% of isolates demonstrated resistance to the therapy (table 2).

Table 3 depicts the distribution of treatment outcome categories by sociodemographic and clinical

characteristics. Of 1585 patients whose isolates were resistant to rifampin and isoniazid (MDR-TB), 793 (50.0%) cured, while 180 (11.4%) died and the treatment of 24 (1.5%) patients were failed. Treatment failure was almost 10 times higher in patients who had previous TB treatment (21.7%), than those who were never treated (2.2%). Moreover, mortality was two times higher in patients who were HIV-infected (21.3%) than those who were HIV non-reactive (10.2%).

Treatment outcome
Of the 3395 patients enrolled into this study, 1845 (40.0%) were cured, 720 (35.7%) completed the treatment, 431 (12.8%) died, 333 (9.7%) were lost to follow-up and the treatment of 66 (1.7%) patients failed (figure 3). The overall treatment success (cured plus treatment completed) was 2565 (75.7%), whereas the overall unsuccessful treatment outcome (the sum of lost to follow-up, treatment failed and death) was 830 (24.3%).

Predictors of treatment failure and death
Bivariate analysis
In the current competing risk survival analysis model, failure events were treatment success (2565), treatment failure (66) and death (431). To the contrary, 333 (9.7%) lost to follow-up were considered as censored. In the bivariate competing risk survival analysis model, old age (unadjusted hazard ratio (UHR)=1.03; 95% CI 1.04 to 1.05; p<0.001), HIV infection (UHR=2.2; 95% CI 1.8

Table 3 Demographic and clinical characteristics distribution of treatment outcome

Variables		Cured	Completed	Treatment success	Failed	Death	LTFU	P value
Sex	Male	1006 (53.8)	376 (20.1)	1382 (73.9)	40 (2.1)	245 (13.1)	203 (10.9)	
	Female	839 (55.0)	344 (22.6)	1183 (77.6)	26 (1.7)	186 (12.2)	130 (8.5)	0.071
Resistance type	RR/INH status unknown	1052 (58.1)	274 (15.1)	1326 (73.2)	42 (2.3)	251 (13.9)	191 (10.6)	
	MDR	793 (50.0)	446 (28.1)	1239 (78.1)	24 (1.5)	180 (11.4)	142 (9.0)	<0.001
Anatomical site	EPTB	50 (22.3)	125 (55.8)	173 (78.1)	4 (1.8)	20 (8.9)	25 (11.2)	
	PTB	1795 (56.6)	595 (18.8)	2390 (75.4)	62 (2.0)	411 (13.0)	308 (9.7)	<0.001
Previous TB treatment	New	243 (52.6)	83 (18.0)	326 (70.6)	10 (2.2)	75 (16.2)	51 (11.0)	
	Previously treated	1602 (54.6)	637 (21.7)	2239 (76.3)	56 (21.7)	356 (12.1)	282 (9.6)	0.057
Diagnosis method	Bacteriological	1771 (54.6)	686 (21.2)	5457 (75.8)	64 (2.0)	409 (12.6)	313 (9.7)	
	Clinical	74 (48.7)	34 (22.4)	108 (71.1)	2 (1.3)	22 (14.5)	20 (13.2)	0.466
HIV status	Non-reactive	1429 (56.0)	561 (22.0)	1990 (78.0)	48 (1.9)	261 (10.2)	255 (10.0)	
	Reactive	378 (49.3)	141 (18.4)	519 (67.7)	17 (2.2)	163 (21.3)	68 (8.9)	<0.001
Anaemia	None anaemic	880 (55.0)	380 (23.8)	1260 (78.8)	29 (1.8)	150 (9.4)	161 (10.1)	
	Any grade of anaemia present	965 (53.8)	340 (18.9)	1305 (72.7)	37 (2.1)	281 (15.7)	172 (9.6)	<0.001

EPTB, extra-pulmonary tuberculosis; LFTU, loss to follow-up; MDR, multidrug-resistant; PTB, pulmonary tuberculosis; TB, tuberculosis.
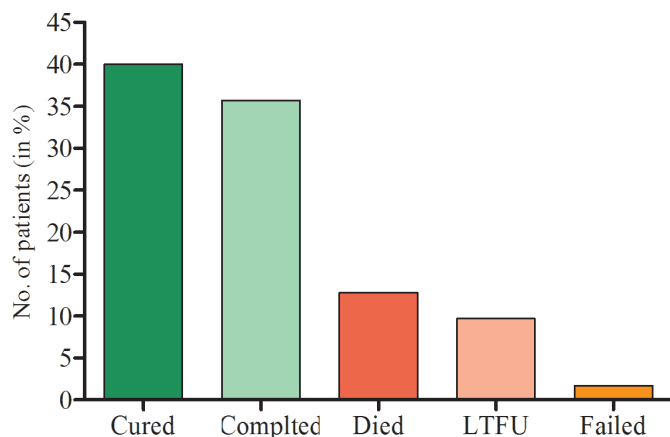
Figure 3 MDR-TB treatment outcomes in past 10 years in Ethiopia (2009–2019). LTFU, loss to follow-up; MDR-TB, multidrug-resistant tuberculosis.

to 2.7; p<0.001) and presence of any grade of anaemia (UHR=1.7; 95% CI 1.4 to 2.1; p<0.001) were significantly associated with death (table 4). Moreover, having previous TB treatment (UHR=0.71; 95% CI 0.56 to 0.92; p=0.009) and presence of rifampin-resistant bacilli (UHR=1.3; 95% CI 1.03 to 1.5; p=0.022) were significantly associated with death (table 4). However, none of the variables assessed had shown significant association with treatment failure (table 4).

Multivariable analysis

In multivariable analysis, older age (adjusted hazard ratio (AHR)=1.03; 95% CI 1.03 to 1.05; p<0.001), HIV infection (AHR=2.0; 95% CI 1.6 to 2.4; p<0.001) and presence of

any grade anaemia (AHR=1.7; 95% CI 1.4 to 2.0; p<0.001) were significantly associated with death (table 5). All variables included into multivariable competing risk survival analysis model were not significantly associated with treatment failure (table 5). Although the presence of rifampin-resistant bacilli and having previous TB treatment were significantly associated with death in the unadjusted analysis, they failed to significantly associate in the adjusted analysis.

DISCUSSION

This study aimed to determine the proportion of national treatment success rate and predictors of treatment failure and death in patients treated for MDR-TB in Ethiopia in the past 10 years. We have found that 75.7% of patients with MDR-TB were successfully treated; whereas, 12.8% died, 9.7% lost to follow-up and the treatment of 1.7% patients failed. The proportion of the patients registered for MDR-TB treatment has shown increasing trend from 2009 and the maximum proportion (19.6%) was registered in 2015. However, the proportion of patients registered for the treatment has decreased after 2015 and the minimum patients were registered in 2019. Old age, HIV infection and any grade of anaemia were significant predictors of death in patients treated for MDR-TB in this study. However, none of the variables included into the multivariable model were able to significantly predict treatment failure.

This study indicates that the proportion of treatment enrolment after 2015 has decreased and the lowest

Table 4 Predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia, 2009–2019 (unavailable model)

Variable		Death		Treatment failure	
		UHR (95% CI)	**P value**	**UHR (95% CI)**	**P value**
Sex	Female	1.00		1.00	
	Male	1.1 (0.89 to 1.3)	0.436	1.3 (0.78 to 2.1)	0.335
Age (year)		1.03 (1.04 to 1.05)	<0.001	0.98 (0.96 to 1.0)	0.122
Anatomical site	Extra-pulmonary	1.00		1.00	
	Pulmonary	1.5 (0.94 to 2.3)	0.094	1.1 (0.40 to 3.0)	
Drug resistance type	MDR	1.00		1.00	
	RR/INH status unknown	1.3 (1.03 to 1.5)	0.022	1.6 (0.95 to 2.6)	0.080
Previous treatment	New	1.00		1.00	
	Previously treated	0.71 (0.56 to 0.92)	0.009	0.86 (0.44 to 1.7)	0.668
Diagnosis method	Bacteriological	1.00		1.00	
	Clinical	1.2 (0.76 to 1.8)	0.468	0.68 (0.17 to 2.8)	0.589
HIV status	Non-reactive	1.00		1.00	
	Reactive	2.2 (1.8 to 2.7)	<0.001	1.2 (0.68 to 2.1)	0.548
Anaemia status	Absent	1.00		1.00	
	Any grade of anaemia present	1.7 (1.4 to 2.1)	<0.001	1.1 (0.70 to 1.9)	0.592

MDR, multidrug-resistant; TB, tuberculosis; UHR, unadjusted hazard ratio.

Table 5 Predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia, 2009–2019 (multivariate model)

Variable		Death		Treatment failure	
		AHR (95% CI)	P value	AHR (95% CI)	P value
Sex	Female	1.00		1.00	
	Male	0.92 (0.75 to 1.1)	0.397	1.3 (0.82 to 2.2)	0.248
Age (year)		1.04 (1.03 to 1.05)	<0.001	0.98 (0.96 to 1.0)	0.077
Anatomical site	Extra-pulmonary TB	1.00		1.00	
	Pulmonary TB	1.4 (0.91 to 2.2)	0.126	1.1 (0.39 to 3.0)	0.878
Drug resistance type	MDR	1.00		1.00	
	RR/INH status unknown	1.2 (0.98 to 1.5)	0.083	1.7 (0.98 to 2.8)	0.060
Previous treatment	New	1.00		1.00	
	Previously treated	0.79 (0.61 to 1.0)	0.083	0.98 (0.49 to 1.9)	0.947
HIV status	Non-reactive	1.00		1.00	
	Reactive	2.0 (1.6 to 2.4)	<0.001	1.3 (0.72 to 2.2)	0.425
Anaemia status	Absent	1.00		1.00	
	Anaemia present	1.7 (1.4 to 2.0)	<0.001	1.1 (0.66 to 1.8)	0.767

AHR, adjusted hazard ratio; MDR, multidrug-resistant; TB, tuberculosis.

number of cases were recorded in 2019. We do not think that the MDR-TB incidence decreased importantly, and we therefore think that there might have been registration-related problems as the result of decentralisation of TB care to the communities. As patients included into this study were those who had final treatment outcome results, enrolment of patients in 2018 and 2019 is expectedly low as they were still on treatment.

In this study, treatment success proportion in patients with MDR-TB who received a standardised long regimen was higher than the treatment success rate previously reported from other settings including from Ethiopia.[19 20 30] For instance, a recent study reported from Morocco indicated that only 53.4% of patients with MDR-TB were treated successfully.[30] In addition, a study reported from Armenia shows that <50% of patients with MDR-TB were successfully treated.[20] A recent review study shows that pooled data from different settings have also shown lower treatment success rate than our findings.[31] These differences originate most likely from the differences in the quality of TB control programme, sample size, severity of the disease at diagnosis, TB/HIV co-infection burden, treatment regimens and study period. A previous study conducted in Ethiopia in two TICs[27] reported very similar treatment success rate with our finding (78.6% vs 75.7%).

The proportion of death in this study was considerably higher and it was similar with previously reported findings.[19 27] Case in point, the proportion of patients who died in our study was more than double compared with the mortality proportion reported from Morocco (5% vs 12.7%).[30] This difference is most probably due to the difference in the study period, quality of care, treatment regimens and severity of the disease during treatment initiation.

Our study finding shows that older age is significantly associated with death from MDR-TB. In agreement with this finding, it is well documented that MDR-TB mortality is higher in older age group.[32–34] Thus, particular attention has to be given to older patients to reduce mortality related to TB. A previous study has shown that younger age is significantly associated with poor treatment outcome than older age.[35] This difference could probably be due to the age variation in the included patients and the difference in the severity of the disease at treatment initiation.

In this study, as in several previous studies,[19 25–27 35] HIV infection was significantly associated with death. Despite the proportion of patients who were not on ART was low (of HIV-infected patients only 4.5 %), the hazard of death was 2.0 times higher in HIV-infected patients. The possible explanation for the significant effect of HIV status on mortality in patients on MDR-TB treatment could be due to low CD4 count, high viral load and severity of the disease at treatment initiation. However, since data on CD4 count, HIV viral load level and disease severity status at enrolment were not registered in our data sources, we were not able to verify their effects on MDR-TB treatment outcome. Furthermore, a previous study indic ated that a combined anti-TB and anti-HIV treatment has been proven to improve treatment success in co-infected patients.[36]

In this study, the presence of any grade of anaemia was significantly associated with death due to MDR-TB. This finding is similar with a previous study reported from Ethiopia in which the hazard of poor treatment outcome

was 4.2 times higher in the patients who had any grade of anaemia at treatment initiation than those who were non-anaemic.[19] The presence of anaemia at the treatment initiation might be due to parasitic infections and some other chronic diseases. This finding highlights the importance of haemoglobin monitoring in patients with MDR-TB on treatment to increase treatment success and decrease mortality.

In this study, none of the variables included into the multivariable model were significantly associated with treatment failure. The absence of significant association between the variables and treatment failure could be due to the number of treatment failure events that was much smaller than the competing risks, that is, death and treatment success.

The main limitation of this study is the retrospective nature of the study design. Data on sociodemographic, behavioural, adverse drug reactions, key laboratory variables and treatment adherence status were missing for the majority of the patients; hence, these variables were excluded from the analysis. This limited us to further explore the predictors of treatment failure and death. Thus, the predictors of death may not be limited to the factors presented in this study. Moreover, lack of important variables could have resulted in an underestimation/overestimation of the effects of the investigated variables in the model such as age, HIV status, previous TB treatment on the treatment failure and death. The final treatment outcome of 759 patients was also not obtained and the patients were excluded from the analysis. This might have overestimated the treatment success rate in this study. A prospective study that could capture all these uninvestigated variables is important to determine predictors of treatment failure and death.

The findings of this study have clearly indicated the message for TB control programme efforts. Although treatment success rate is well achieved, mortality in this study is considerable and hence should be addressed by the TB programme. HIV infection is one of the strong predictors of death in patients with MDR-TB. Taking in consideration of HIV-infected patients with MDR-TB and immediate commencement of anti-TB treatment together with ART is the mechanism to improve the treatment success in patients with MDR-TB. Moreover, our result indicates that special attention should be given to the patients who have anaemia at treatment initiation to improve their treatment outcome. Strengthening and standardising information registration on MDR-TB treatment is crucial to facilitate further data analysis which is important to monitor the status of treatment outcome.

Conclusion

In the past 10 years, MDR-TB treatment in Ethiopia has been successful. However, the proportion of patients who died is considerable, and it could be reduced through providing special attention to HIV-infected and anaemic patients. Further prospective cohort study is required to explore other predictors of treatment failure and death.

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