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National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective cohort study

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Abstract

Objectives: Treatment success in patients treated for multidrug-resistant tuberculosis (MDR-TB) is low, but predictors of death and treatment failure have understudied. Thus, we aimed to estimate the national proportion of treatment outcomes in past 10 years and factors that predict duration from treatment initiation to death and treatment failure in MDR-TB patients in Ethiopia.

Setting: A retrospective cohort study with 10 years follow up period was conducted in 42 treatment centers in Ethiopia.

Participants: A total of 3,553 adult MDR-TB patients who had final treatment outcome and treated under nation TB programme were included. Data was collected from clinical charts, registration books and laboratory result reports. Competing risk survival analysis model with robust standard error was used to determine predictors of duration from treatment initiation to death and treatment failure.

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

Results: The proportion of treatment success was 75.7%, while death 12.8%, treatment failure 1.7% and lost to follow up 9.7%. Older age (Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); $p < 0.001$), being HIV sero-reactive (AHR = 2.0; 95% CI (1.6–2.4); $p < 0.001$) and presence of any grade of anemia (AHR = 1.7; 95% CI (1.4–2.0); $p < 0.001$) were significantly predicted duration from treatment initiation to death. However, all variables included to multivariable model were not significantly associated with duration from treatment initiation to treatment failure.

Conclusion: In past ten years, MDR-TB treatment success in Ethiopia is well achieved. However, the proportion of patients who died is considerable. Death could be reduced through providing special attention to old age, HIV-infected and anemic patients. Further prospective cohort study is necessary to explore predictors of duration from treatment initiation to death and treatment failure.

Keywords: Tuberculosis, Multidrug resistance, Refampin resistance, Treatment outcome

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Strengths and Limitations of this study

- ❖ National multidrug resistance tuberculosis (MDR-TB) treatment outcomes proportions in past ten years were estimated using MDR-TB treatment programme data.
- ❖ Although MDR-TB treatment outcome is low across the world, predictors of time to death and treatment failure have underreported.
- ❖ This study was determined the predictors of duration from treatment initiation to death and treatment failure using competing risk survival analysis model with robust standard error.
- ❖ 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.

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Background

The emergency of drug resistance tuberculosis (TB) has been undermining the global TB control programme and continues to cause severe morbidity and mortality among millions across the world. World health organization (WHO) estimated that nearly half a million rifampin-resistant new TB cases occurred in 2018 across the world.[1] The treatment of multidrug resistance (MDR) and extensively drug resistance (XDR) TB has been challenging the global TB control efforts due to difficulty related to diagnosis, long duration treatment, less effective and toxic drugs used for the treatment, and limitation they impose on the available treatment options.[2–4] MDR-TB is defined as a *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin, whereas XDR-TB is refers to a *Mycobacterium tuberculosis* resistance at least to rifampin and isoniazid plus resistance to any fluoroquinolone and at least one of the three injectable anti-TB drugs (capreomycin, kanamycin or amikacin).[5]

The current MDR-TB treatment success rate (the sum of cured and treatment completed) is considerably low.[1,3,6] The WHO recent global estimation indicates that only 56% of MDR-TB patients were successfully treated in 2018.[1] This indicates that nearly half of MDR-TB patients who were diagnosed and treated have succumbed unsuccessful treatment outcome which is the main obstacle to achieve WHO End TB treatment success target of ≥ 90% at 2035.[1] According to more recent studies, the treatment success rate of MDR-TB is 54% in Russia[6], 53.4% in Morocco[7] and 60% in India.[8] In contrast, a recent studies indicated that, relatively high treatment success rates in certain settings.[9–12] For example, 82.4% of MDR-TB patients treated successfully in Taiwan[9], and 75.7% in Tanzania.[10] Moreover, 78.8% of MDR-TB patients are successfully treated in Ethiopia[11], and 75.8% in Pakistan.[12] A review studies are also indicated that about 60%[13,14] of MDR-TB patients treated successfully.

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Heterogeneous and interrelated factors are associated with poor MDR-TB treatment outcome. Infection with Human immunodeficiency Virus (HIV)[15–21], diabetes mellitus[19,22,23], malnutrition[24,25], anemia[19,21,26] are co-morbidities that associated with poor treatment outcome in patients treated for MDR-TB. Moreover, treatment interruption[21,27,28], medication regimens[29], Antiretroviral therapy (ART) timing[30], time to MDR-TB treatment initiation after diagnosis[31] and previous TB treatment history[15,25,32] are treatment related factors that associated with poor treatment outcome in MDR-TB patients. Being smear positive at diagnosis[15,25], occurrence of XDR-TB[12,18,25,32], socioeconomic factors[26,33], presence of cavity on chest X-ray[10,16,30] and lack of Directly Observed Therapy (DOT) programme[34] are also among factors that associated with poor treatment outcome in MDR-TB patients.

Ethiopia is among the 30 high TB and MDR-TB prevalent countries with an estimated TB incidence of 165 per 100,000 population in 2018.[1] Despite an improving TB control programme and treatment success rate, the burden of MDR-TB in Ethiopia remains high which accounts 2.2% in new and 21.1% in previously treated TB cases.[35] However, WHO recent estimate indicated that 0.71% of MDR-TB in new cases and 16% in previously treated cases were developed in 2018 in Ethiopia.[1] Although there is no national level report on MDR-TB treatment outcome, studies reported from local data indicated variable treatment success which ranges from 63%–78.8% in Ethiopia[11,16,26]

Although evidence indicates low treatment success rate among MDR-TB patients, there is less information on the factors that predicting duration from treatment initiation to death and treatment failure in different setups. Beside evidence limitation, available studies are focused in the determination of predictors of unsuccessful treatment outcome which comprises the sum of death, treatment failure and lost to follow up in one category. Categorization of death, treatment

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failure and lost to follow up in one category could cover 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 robust standard competing risk survival analysis model. Ethiopia is among the countries lack such evidence at national level to plan effective intervention that could decrease death and treatment failure in MDR-TB patients. Thus, we aimed to estimate the national level treatment outcome rate in past 10 years and factors that predict duration from treatment initiation to death and treatment failure in MDR-TB patients in Ethiopia.

Materials and methods

Study setting, population and design

We conducted a retrospective cohort study on adult patients aged ≥ 15 years old, diagnosed either biologically or clinically for both pulmonary and extra-pulmonary TB, and enrolled to MDR-TB treatment at 42 treatment initiating centers (TICs) in Ethiopia from February 2009–February 2019. MDR-TB treatment was started in February 2009 in one hospital in Addis Ababa, Ethiopia.[16] During this study period there were a total of 53 TICs and several treatment follow up centers (TFCs) in the country. The majority of MDR-TB patients initiate their treatments in TICs while stable patients follow the treatment under directly observed therapy (DOT) 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 to this study, due to the remaining 11 TICs had no patients who completed their treatment during the study period.

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Inclusion and exclusion criteria

We included all adult patients who were aged 15 years and older, diagnosed either bacteriologically or clinically for MDR-TB and enrolled to the treatment from February 2009. However, 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 and national TB programme recommendations in quality assurance TB laboratories.[36,37] Culture tests were carried out with solid (Löwenstein-Jensen (LJ)) and a fluorometric BACTEC MGIT960 at one national TB reference laboratory and nine regional laboratories. In addition, Xpert MTB/RIF assay is a rapid, sensitive and specific technique that has been widely using to detect *M. tuberculosis* and rifampin resistant at each level in the national health system. Drug susceptibility test (DST) for first-line drugs was performed by indirect proportional method based on WHO recommended critical concentrations, for rifampicin (1.0 μg/ml), isoniazid (0.1 μg/ ml), streptomycin (1.0 μg/ml), ethambutol (5μg/ml) and pyrazinamide (100 μg/ml). DST for second-line has been recently started in the country and rarely performed. Data on second-line DST not included to this study because very few DST results for SLDs obtained in the records. Quality assurance for DST was regularly performed by Milan WHO's Supranational Reference Laboratory in Rome, Italy.

Treatment

Previously, all MDR-TB patients were treated as inpatient model of care for the first few months at treatment centers until the patient become clinically stable and *M. tuberculosis* culture conversion. However, according to the recent edition of national TB treatment guideline, all

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patients with MDR-TB need to be treated under clinic-based ambulatory model of care, unless the patient unstable or developed sever adverse drug reaction during the course of treatment. Patients either with serious medical or social conditions could be admitted with the decision of the treatment panel. Standardized long treatment regimens were used to treat MDR-TB patients in Ethiopia. The long treatment regimen contained at least four oral drugs which used daily during full course of treatment and one injectable drug until *M. tuberculosis* culture conversion. Treatment with injectable drugs continues at least for eight months based on clinical, microbiological and radiographic examination results. The minimum treatment duration was 20 months for long regimen which is at least 18 months after bacteriological conversion, whereas nine to 11 months for short treatment regimen.[37] All patients included to this study were on long treatment regimens. 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 extra-pulmonary TB patients. MDR-TB treatment is free of any const in Ethiopia and there is full access to all categories of drugs to treat MDR-TB patients.

Data collection

We collected data on socio-demographic 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 (RR vs MDR), previous treatment (new vs previously treated), diagnosis method (bacteriologically vs clinically), HIV sero-status (reactive vs non-reactive) and Antiretroviral Therapy (ART) status (on ART vs not applicable vs not on ART). In addition, we collected information on bacteriological status (smear, Xpert MTB/RIF, culture or first-line drugs DST

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results) at treatment initiation. All data were extracted from patients' clinical charts, registration books and laboratory result reports. Data were collected by health professionals familiar with MDR-TB treatment after two days practical training on data collection tool.

Definitions

In this study, we used standard WHO and national treatment guidelines definitions for laboratory confirmations, patient categories and treatment outcomes.[36,37] Clinically diagnosed MDR-TB refers to those cases with no documented drug susceptibility test (DST) results but treated empirically with a course of treatment including SLDs based on clinical criteria and contact history.[37] However, bacteriologically confirmed MDR-TB refers to those cases with documented DST results. All patients were categorized into new patients (never treated for TB or has treated for less than one month) and patients previously treated for tuberculosis. The final treatment outcomes of MDR-TB were cured, treatment completed, death, treatment failed and lost to follow up. Cured is 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 are 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 categorized as treatment failure. Lost to follow up is also refers to a patient whose treatment is interrupted for two 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.

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Data analysis

We entered data into CSPro software version 6.1 and analyzed by STATA version 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 30, 2009–February 30, 2019 in each TIC.

We used a competing risk survival analysis model with robust standard error to assess the effects of different variables on the duration from treatment initiation to death and treatment failure. Effect levels were reported by Hazard Ratio (HR) with 95% Confidence Intervals (CIs). We included variables scored p-values less than or equal to 0.2 during Univariate analysis and clinically or epidemiologically relevant. We considered death as failure event to estimate the effects of different variables on duration from treatment initiation to death, while treatment failure and success 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 considered as competing risks. Lost to follow up was considered as 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.

Results

Participants' characteristics

A total of 4,419 patients were enrolled to MDR-TB treatment in 42 of 53 (79.2%) treatment initiating centers (TICs) in Ethiopia from February, 2009 to February, 20019 [Fig 1]. Of 4,419

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patients, 3,395 (76.8%) were fulfilled our inclusion criteria and enrolled to this study analysis [Fig 1].

The highest proportion of patients was enrolled into the treatment in 2015 (667 patients), while the lowest number of patients registered in 2019 (only 4 patients) [Fig 2].

Of 3,395 patients included to this study analysis 1,870 (55.1%) were male, and the mean age was 31.6 (SD ± 11.7) years with the age range of 15 to 85 years. Seventy two percent of the patients were in the age category of 15 to 35 years [Table 1]. More than 50% of the patients were infected with TB bacilli resistant to rifampin (isonizid susceptibility status unknown), and 3,171 (93.4%) were pulmonary TB patients [Table 1]. Eighty six percent of patients had previous TB treatment history and drug resistance status of 3,242 (95.5) isolates were bacteriologically confirmed at treatment enrolment [Table 1]. The main drug resistant diagnosis method was GeneXpert MTB/RIF (57.9%) and 1,421 (41.9%) patients had previous exposure to second line drugs [Table 1]. Of the 3,395 patients, 767 (22.6%) were HIV infected [Table 1], and of 767 patients whose HIV sero-status were known, 686 (89.4%) were on ART. Only 6.0% of the patients had previous MDR-TB patient contact history and 1,831 (53.9%) of patients were hospitalized at the treatment initiation [Table 1]. Of the patients who were hospitalized at the treatment initiation the mean duration of hospitalization was 81.7 (±47.4) days.

Table 1: Demographic and clinical characteristics of the patients (n = 3,395)

Variable		n (%)
Sex	Male	1,870 (55.1)
	Female	1,525 (44.9)
Age (in year)	15–25	1,268 (37.3)
	26 –35	1,186 (34.9)
	36 –45	529 (15.6)
	≥ 46	412 (12.1)
Drug resistance type	RR/INH status unknown	1,810 (53.3)
	MDR-TB	1,585 (46.7)
Anatomical site of TB	Pulmonary	3,171 (93.4)
	Extra pulmonary	224 (6.6)
Previous TB treatment	New	462 (13.6)

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	Previously treated	2,933 (86.4)
Previous exposure to SLDs	Yes	1,421 (41.9)
	No	1,842 (54.3)
	Unknown	132 (3.9)
Drug resistance identification method	GeneXpert MTB/RIF	1,967 (57.9)
	Culture/LPA	1,275 (37.6)
	Clinical	153 (4.5)
Diagnosis method	Bacteriological	3,242 (95.5)
	Clinical	153 (4.5)
HIV sero-status	Non-reactive	2,554 (75.2)
	Sero-reactive	767 (22.6)
	Unknown	74 (2.2)
ART status	Not applicable	2,556 (75.3)
	On ART	686 (20.2)
	HIV sero-status known but, ART status unknown	79 (2.3)
	Both ART and HIV sero- statuses unknown	74 (2.2)
MDR-TB patient contact history	Yes	204 (6.0)
	No	1,511 (44.5)
	Unknown	1,680 (49.5)
Hospitalization history at treatment initiation	Hospitalized	1,831 (53.9)
	Not hospitalized	487 (14.3)
	Unknown	1,077 (31.7)
Treatment interruption	Never interrupted/interruption status unknown	3,192 (94.0)
	At least one day interrupted	203 (6.0)

TB-tuberculosis, ART-Antiretroviral therapy, SLDs-Second line drugs, HIV-Human immunodeficiency virus, MDR-Multidrug resistant, LPA-Line probe Assay

Table 2 depicts the sociodemographic and clinical characteristics distribution of treatment outcome categories. Of 1,810 patients whose isolates were resistant to rifampin, 1,052 (58.1%) were cured, 251 (13.9%) died and the treatment of 42 (2.3) patients were failed. Of patients whose isolates were resistant to rifampin and isoniazed (MDR-TB), 793 (50.0%) cured, while 180 (11.4%) died and the treatment of 24 (1.5) patients were failed. Treatment failure was five times higher in the patients who had previous TB treatment history (21.7%), than those who never treated (2.2%). Mortality was two times higher in the patients who were HIV sero-reactive (21.3%), than those who HIV non-reactive (10.2%).

Table 2: Demographic and clinical characteristics distribution of treatment outcome

		Treatment outcome n (%)					
Variables		**Cured**	**Completed**	**Failed**	**Death**	**LTFU**	**P-value**
Sex	Male	1,006 (53.8)	376 (20.1)	40 (2.1)	245 (13.1)	203 (10.9)	
	Female	839 (55.0)	344 (22.6)	26 (1.7)	186 (12.2)	130 (8.5)	0.071
Resistance type	RR/INH status	1,052 (58.1)	274 (15.1)	42 (2.3)	251 (13.9)	191 (10.6)	

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	unknown						
	MDR	793 (50.0)	446 (28.1)	24 (1.5)	180 (11.4)	142 (9.0)	< 0.001
Anatomical site	EPTB	50 (22.3)	125 (55.8)	4 (1.8)	20 (8.9)	25 (11.2)	
	PTB	1,795 (56.6)	595 (18.8)	62 (2.0)	411 (13.0)	308 (9.7)	< 0.001
Previous TB treatment	New	243 (52.6)	83 (18.0)	10 (2.2)	75 (16.2)	51 (11.0)	
	Previously treated	1,602 (54.6)	637 (21.7)	56 (21.7)	356 (12.1)	282 (9.6)	0.057
Diagnosis method	Bacteriological	1,771 (54.6)	686 (21.2)	64 (2.0)	409 (12.6)	313 (9.7)	
	Clinical	74 (48.7)	34 (22.4)	2 (1.3)	22 (14.5)	20 (13.2)	0.466
HIV-sero-status	Non-reactive	1,429 (56.0)	561 (22.0)	48 (1.9)	261 (10.2)	255 (10.0)	
	Reactive	378 (49.3)	141 (18.4)	17 (2.2)	163 (21.3)	68 (8.9)	< 0.001
Anemia	None anemic	880 (55.0)	380 (23.8)	29 (1.8)	150 (9.4)	161 (10.1)	
	Any grade of anemia present	965 (53.8)	340 (18.9)	37 (2.1)	281 (15.7)	172 (9.6)	< 0.001

Treatment outcome

Of 3,395 patients included to this study 1,845 (40.0%) were cured, 720 (35.7%) were completed the treatment, 431 (12.8%) died, 333 (9.7%) lost to follow up and the treatment of 66 (1.7%) patients were failed [Fig 3]. The overall treatment success (cured plus treatment completed) was 2,565 (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 duration from treatment initiation to death and treatment failed

Univariate analysis

The proportions of failure events were: death 431 (12.8%), treatment failure 66 (1.7%) and treatment success 2,565 (75.7%). The proportion of censored as a result of lost to follow up was 333 (9.7%). In the Univariate competing risk survival analysis model old age (*Unadjusted hazard ratio* (*UHR) = 1.03; 95% CI (1.04–1.05); p < 0.001)*, had rifampin resistant bacilli (*UHR = 1.3; 95% CI (1.03–1.5); p = 0.022*), HIV sero-reactive (*UHR = 2.2; 95% CI (1.8–2.7); p < 0.001*) and presence of any grade of anemia (*UHR = 1.7; 95% CI (1.4–2.1); p < 0.001*) were significantly decreased duration from treatment initiation to death [Table 3]. Having previous TB treatment history (*UHR = 0.71; 95% CI (0.56–0.92); p = 0.009*) was significantly increased duration from treatment starting to death [Table 3]. However, none of variables assessed were

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shown significant association with duration from treatment initiation to treatment failure [Table 3].

Table 3: Predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia, 2009-2019 (Unavailable model)

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

TB-tuberculosis, HIV-Human immunodeficiency virus, UHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Multivariable analysis

In multivariable analysis older age (*Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); p < 0.001*), being HIV sero-reactive (*AHR = 2.0; 95% CI (1.6–2.4); p < 0.001*) and presence of any grade anemia (*AHR = 1.7; 95% CI (1.4–2.0); p < 0.001*) were able to significantly decrease duration from treatment initiation to death [Table 4]. All variables included into multivariable competing risk survival analysis model were not significantly predicted duration from treatment initiation to treatment failure [Table 4].

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

		Death		Treatment failure	
Variable		**AHR (95%CI)**	**P-value**	**AHR(95% CI)**	**P-value**
Sex	Female	1.00		1.00	
	Male	0.92 (0.75–1.1)	0.397	1.3 (0.82–2.2)	0.248
Age (year)		1.04 (1.03–1.05)	< 0.001	0.98 (0.96–1.0)	0.077
Anatomical sit	Extra-pulmonary TB	1.00		1.00	
	Pulmonary TB	1.4 (0.91–2.2)	0.126	1.1 (0.39–3.0)	0.878

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Drug resistance type	MDR	1.00		1.00	
	RR/INH status unknown	1.2 (0.98–1.5)	0.083	1.7 (0.98–2.8)	0.060
Previous treatment	New	1.00		1.00	
	Previously treated	0.79 (0.61–1.0)	0.083	0.98 (0.49–1.9)	0.947
HIV sero-status	Non-reactive	1.00		1.00	
	Reactive	2.0 (1.6–2.4)	< 0.001	1.3 (0.72–2.2)	0.425
Anemia status	Absent	1.00		1.00	
	Anemia present	1.7 (1.4–2.0)	< 0.001	1.1 (0.66–1.8)	0.767

TB-tuberculosis, HIV-Human immunodeficiency virus, AHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Drug resistance status at treatment initiation

Drug susceptibility testing was done for four first-line drugs such as rifampin, isonized, ethambutol and streptomycin [Table 5]. Rifampcin susceptibility test was performed on isolates of all patients included to this study, and 99.3% of isolates were demonstrated resistance to the therapy [Table 5].

Table 5: Anti-tuberculosis drug susceptibility test results

Anti-tuberculosis drug	**Susceptibility test results**	**n (%)**
Rifampicin	Resistant	3,371 (99.3)
	Susceptible	24 (0.7)
Isonized (n = 1,313)	Resistant	1,241 (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)

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Discussion

The current study aimed to determine the proportion of national treatment outcomes and predictors of duration from treatment initiation to death and treatment failure in patients treated for MDR-TB in Ethiopia in past ten years. It was indicated that 75.7% of MDR-TB patients were successfully treated, whereas 12.8% died, 9.7% lost to follow up and the treatment of 1.7% patients were failed. The proportion of the patients registered for MDR-TB treatment was shown increasing trend from 2009 and the maximum proportion (19.6%) was registered in 2015. However, the proportion of the patients registered for the treatment was decreased after 2015 and the minimum patients were registered in 2019. Old age, being HIV sero-reactive and presence of any grade of anemia were significantly predicted duration from treatment initiation to death in patients treated for MDR-TB in present study. However, none of variables included to multivariable model was significantly predicted duration from treatment initiation to treatment failure.

The present study findings indicated that the proportion of treatment enrolment after 2015 was decreased and the lowest cases were recorded in 2019. This might be due to the burden of MDR-TB is decreasing in the country or case registration related problems as the result of treatment centers decentralization to the periphery. Moreover, the decreasing trend in patients enrolment into the treatment after 2015 could be due to the patients included to this study were those who had final treatment outcome results. Thus, this analysis is missed the patients who were registered in 2018 and 2019, but still on treatment during data collection period.

In the current study, treatment success proportion in MDR-TB patients who received a standardized long regimen was higher than the treatment success rate previously reported from other settings including from Ethiopia.[7,26,27] For instance, a study reported from Morocco

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indicated that only 53.4% of MDR-TB patients treated successfully.[7] In addition, a study reported from Armenia shows that less than 50% of MDR-TB patients are successfully treated.[27] A recent review study that pooled data from different settings have also shown lower treatment success than our finding.[13] These differences most likely due to the differences in quality of TB control programme, sample size, severity of the disease at diagnosis, TB/HIV co-infection burden and treatment regimens. A previous study conducted in Ethiopia in two treatment initiation centers[16] reported similar treatment success proportion with our finding (78.6% Vs 75.6%).

The proportion of death in the current study was considerable and it was similar with previously reported findings.[16,26] In contrast, the proportion of patients who died in our study was more than double to the mortality proportion reported from Morocco (5% vs 12.7%).[7] This difference is most probably due to difference in the study period, quality of care and case registration, treatment regimens, severity of the disease during treatment initiation and nutritional status of the patients.

It is well documented that incidence and mortality is higher in TB patients in older age group.[38] Thus, particular attention has to be given to old patients to avert mortality related to TB. Our study finding confirms that older age significantly associated with the duration from treatment initiation to death. This is in line with the results from previous studies[39,40] in which older age significantly associated with death in MDR-TB patients. In contrast to current study, previous study shown that younger age is significantly associated with poor treatment outcome than older age.[8] This difference most probably happens due to the age variation in the included patients and the difference in the severity of the disease at treatment initiation.

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In the current study, as in several previous studies[8,15,16,26,35], HIV sero-reactive was significantly associated with time from treatment initiation to death. Despite proportion of patients who were not on antiretroviral therapy (ART) were low (of HIV sero-reactive patients only 4.5 %), the hazard of death was 2.0 times higher in the patients HIV sero-reactive than non-reactive. However, previous study indicated that a combined anti-TB and anti-HIV treatment has been proven to improve treatment success in co-infected patients.[41] The possible explanation on the significant effect of HIV sero-reactivity 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. Since data on CD4 count, HIV viral load level and disease severity status at enrolment were not registered in our data sources, we could not assess their effects on MDR-TB treatment outcome.

In the present study the presence of any grade of anemia was significantly associated with the duration from treatment initiation to death. The current result was similar with the previous study reported from Ethiopia in which the hazard of poor treatment outcome was 4.2 times higher in the patients had any grade of anemia at treatment initiation than those who were non-anemic. The presence of anemia at the treatment initiation might be due to parasitic infection and some other chronic diseases. This finding tried to attract attention to the importance of hemoglobin monitoring in MDR-TB patients on treatment to increase treatment success and decrease mortality.

In the present study none of variables included to the models were significantly associated with duration from treatment initiation to treatment failure. The absence of significant association between the variables and duration from the treatment initiation to treatment failure could be due to the number of failure event (treatment failure) was very smaller than the competing risks (death and treatment success).

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The main limitation of this study was the retrospective nature of the study design. Data on sociodemographic, behavioural, adverse drug reactions, key laboratory variables and treatment adherence status were missing for majorities of the patients, and these variables were excluded from the analysis. These limited us to explore further the predictors of duration from treatment initiation to death and treatment failure. Thus, the predictors of duration from treatment initiation to 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 different variables in the model on the duration from treatment initiation to death and treatment failure. Prospective study that could capture all potential variables is important to determine predictors of duration from treatment initiation to death and treatment failure.

The findings of the present study have shown clear message for TB control programme efforts. Although treatment success rate is well achieved, mortality in the current study is considerable to be addressed by TB programme. Old age is one of the main predictors of death in MDR-TB patients on treatment. Thus, early diagnosis and commencement of treatment in old patients could increase cure rate. HIV sero-reactive is also one of strong predictors of duration from treatment initiation to death in MDR-TB patients. Taking in consideration the sero-status of MDR-TB patients and immediate commencement of anti-TB treatment together with ART is the mechanism to improve treatment success in MDR-TB patients who co-infected with HIV. Moreover, our result indicates that special attention should be paid to patients who have anemia at treatment initiation in order to improve their treatment outcome. Strengthen and standardizing of information registration on MDR-TB treatment is crucial to facilitate further data analysis which is important to monitor the status of treatment outcome.

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Conclusion

In past ten years, MDR-TB treatment success in Ethiopia is well achieved. However, the proportion of patients who died is considerable, and it could be reduced through providing special attention to old, HIV-infected and anemic patients. Further prospective cohort study is required to explore predictors of duration from treatment initiation to death and treatment failure.

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Author contributions: HHT and KH conceived and designed the study; HHT, DFG, ET and ZM collected data; HHT, MAM and MY analyzed and interpreted the data; HHT drafted the manuscript. All authors have critically reviewed and approved the manuscript for submission.

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Competing interests: None declared.

Ethics consideration: This study was approved by the research Ethics Review Board of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1396.4287), Ethiopian Public Health Institute (EPHI-IRB-065-2017), St. Peter's Specialized Hospital (V81622018) and Armouer Hansen Research Institute (PO13/18). We also obtained a waiver of informed consent from each

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review board. To maintain confidentiality sensitive information that could identify participants was not reported in this study.

Data availability statement: Data used in this study is available in the corresponding authors and can be accessed on reasonable request.

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Figure legend

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

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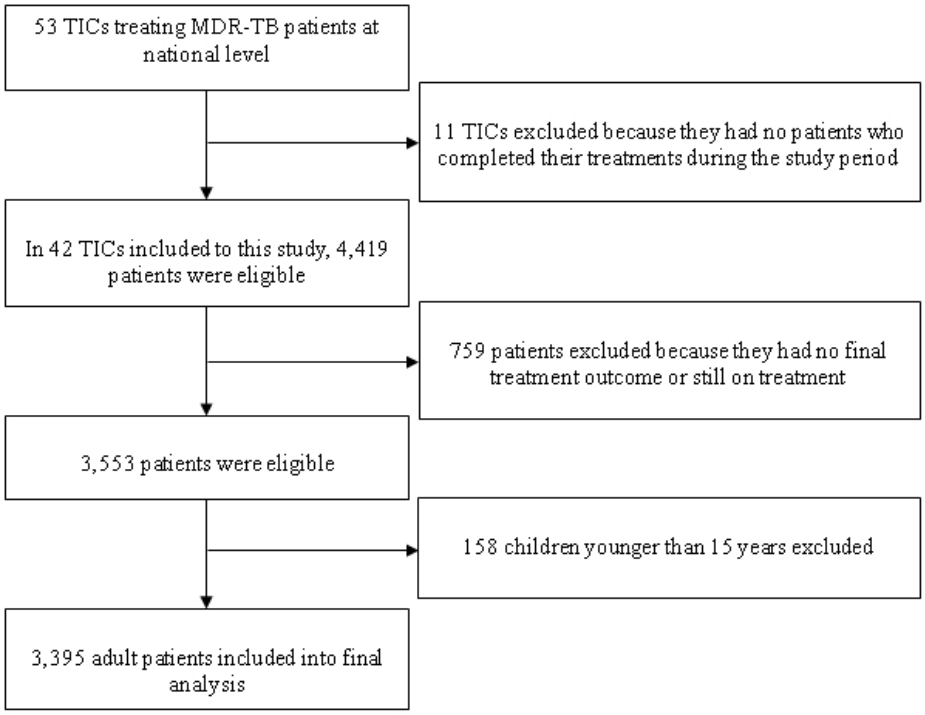

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

171x132mm (96 x 96 DPI)

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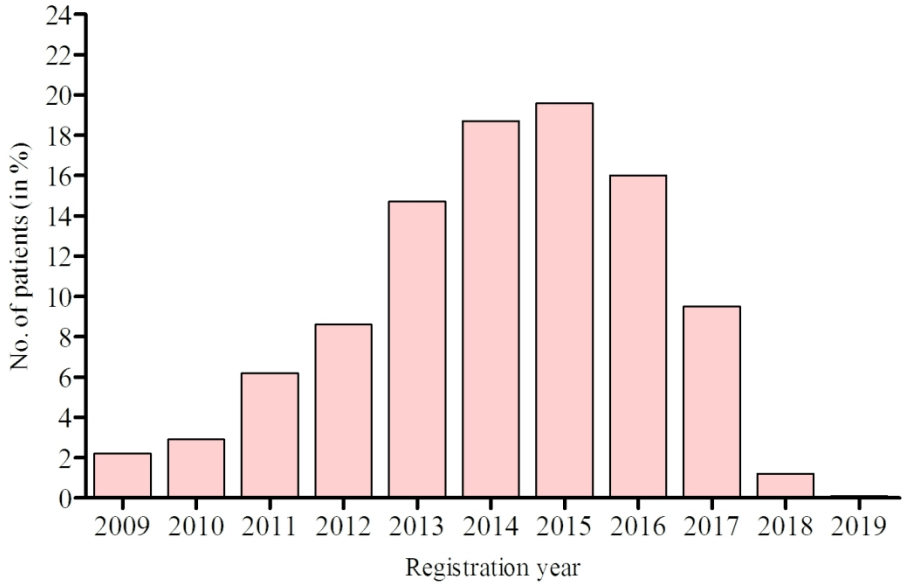

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

137x88mm (300 x 300 DPI)

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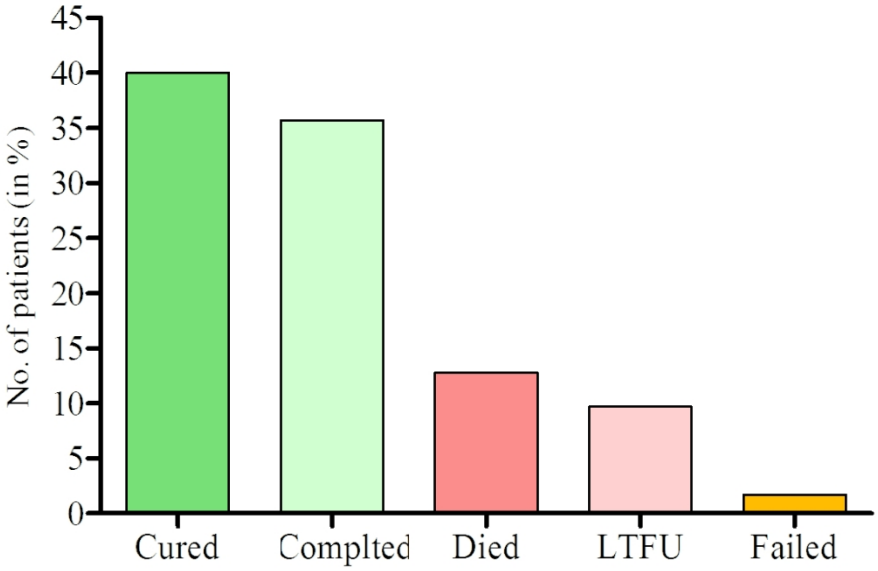

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

110x71mm (300 x 300 DPI)

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National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective cohort study

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National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years 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 underreported. Thus, we aimed to determine the national proportion of treatment success in the past 10 years and factors that predict treatment failure and death in MDR-TB patients in Ethiopia.

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

Participants: A total of 3,395 adult MDR-TB patients who had final treatment outcome and who were treated under national TB programme were included. Data was collected from clinical charts, registration books and laboratory reports. Competing risk survival analysis model with robust standard error was used to determine 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 was 12.8%, treatment failure was 1.7% and lost to follow up 9.7%. The significant predictors of death were older age (adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); $p < 0.001$), HIV sero-reactive (AHR = 2.0; 95% CI (1.6–2.4); $p < 0.001$) and presence of any grade of anemia (AHR = 1.7; 95% CI (1.4–2.0); $p < 0.001$). Unlike the predictors of death, all variables included into multivariable model were not significantly associated with treatment failure.

Conclusion: In the past ten years, although MDR-TB treatment success in Ethiopia is well achieved, the proportion of patients who died is still considerable. Death could be reduced by providing special attention to old age, HIV-infected and anemic patients. Further prospective cohort study is necessary to explore the predictors of treatment failure.

Keywords: Tuberculosis, Multidrug resistance, Refampin resistance, Treatment outcome

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Strengths and Limitations of this study

- ❖ National multidrug resistance tuberculosis (MDR-TB) treatment success rate in the past ten years was determined using MDR-TB treatment programme data.
- ❖ Although MDR-TB mortality is high, predictors of death and treatment failure are underreported.
- ❖ This study determined the predictors of treatment failure and death using competing risk survival analysis model with robust standard error.
- ❖ 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.
- ❖ Short MDR-TB treatment regimen is recently introduced in Ethiopia, therefore patients treated by long regimen only were enrolled in this study.

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Background

The emergence of drug resistance tuberculosis (TB) has been undermining the efforts to control TB and continues to cause severe morbidity and mortality among millions across the world. The World Health Organization (WHO) estimated that nearly half a million rifampin-resistant new TB cases occurred in 2018 across the world.[1] Multidrug resistance (MDR) TB is defined as a *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin, whereas extensively drug resistance (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 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.[2–4]

The current MDR-TB treatment success rate (the sum of cured and treatment completed) is considerably low.[1,3,6] The WHO's recent global estimation indicates that only 56% of MDR-TB patients were successfully treated in 2018.[1] This indicates that nearly half of MDR-TB patients who were diagnosed and treated have succumbed to unsuccessful treatment outcome which is the main obstacle in achieving the WHO End TB treatment success target of ≥ 90% by 2035.[1] Countries with low treatment success rate of MDR-TB include Russia (54%)[6], Morocco (53.4%).[7] and India (60%)[8]. In contrast, recent studies indicated relatively higher treatment success rates in certain settings.[9–12] For example, 82.4% of MDR-TB patients were treated successfully in Taiwan[9], 75.8% in Pakistan[12] and 75.7% in Tanzania.[10]In Ethiopia, 78.8% of MDR-TB patients were treated successfully.[11]

Heterogeneous and interrelated factors are associated with poor MDR-TB treatment outcome. Infection with Human Immunodeficiency Virus (HIV)[13–16], diabetes mellitus[14,17,18], malnutrition

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[19,20], and anemia[14,16,21] are co-morbidities that are associated with poor treatment outcome in patients treated for MDR-TB. Moreover, treatment interruption[16,22,23], medication regimens[24], antiretroviral therapy (ART) timing[25], time to MDR-TB treatment initiation after diagnosis[26] and previous TB treatment history[20,27] are treatment related factors that are associated with poor treatment outcome in MDR-TB patients.

Ethiopia is among the 30 high TB and MDR-TB prevalent countries with an estimated TB incidence of 165 per 100,000 population in 2018.[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 and 21.1% in previously treated TB cases[28]. However, WHO's recent estimate in Ethiopia indicated a lower prevalence of 0.71% of MDR-TB in new cases and 16% in previously treated cases in 2018.[1] Although there is no national level report on MDR-TB treatment outcome, studies reported from local data indicated variable treatment success ranging between 63% – 78.8% in Ethiopia.[11,21,29]

Although evidence indicates a low treatment success rate among MDR-TB patients, there is less information on the factors that are associated with treatment failure and death in different setups. Beside evidence limitation, 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, merging of death, treatment failure and lost to follow up in one category 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 robust standard competing risk survival analysis model. Ethiopia is among the countries which lack such evidence at national level to plan effective intervention that could decrease treatment failure and reduce death in MDR-TB patients. Thus, we aimed to determine the national level treatment

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success rate in the past 10 years and factors that could predict treatment failure and death in MDR-TB patients in Ethiopia.

Materials and methods

Study setting, population and design

We conducted a retrospective cohort study on adult patients aged ≥ 15 years old, diagnosed either biologically or clinically for both pulmonary and extra-pulmonary TB, and enrolled to MDR-TB treatment at 42 treatment initiating centers (TICs) in Ethiopia from February 2009–February 2019. MDR-TB treatment was started in February 2009 in one hospital in Addis Ababa, Ethiopia.[29] During this study period there were a total of 53 TICs and several treatment follow up centers (TFCs) in the country. The majority of MDR-TB patients initiate their treatments in TICs while stable patients follow the treatment under directly observed therapy (DOT) 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 to this study, due to 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 and older, diagnosed either bacteriologically or clinically for MDR-TB and enrolled to the treatment from February 2009. Children less than 15 years old were excluded from this study, because their treatment guideline is different from the adults. However, we excluded patients who had no final treatment outcome (transferred out or still on treatment or treatment outcome missed from data sources).

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Laboratory test

All laboratory tests were performed according to WHO recommendation and national TB laboratory algorithm in quality assured TB laboratories[30,31]. Culture tests were carried out with solid (Löwenstein-Jensen (LJ)) and a fluorometric BACTEC MGIT960 at one national TB reference laboratory and nine regional laboratories. In addition, Xpert MTB/RIF assay is a rapid, sensitive and specific technique that has been widely using to detect *M. tuberculosis* and rifampin resistant 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 μg/ml), isoniazid (0.1 μg/ ml), streptomycin (1.0 μg/ml), ethambutol (5μg/ml) and pyrazinamide (100 μg/ml). DST for second-line has been recently started in the country and rarely performed. Data on second-line DST was not included to this study because very few DST results for SLDs 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 MDR-TB patients were treated as inpatient model of care for the first few months at treatment centers until the patient become clinically stable and *M. tuberculosis* culture conversion. However, according to the recent edition of national TB treatment guideline, all patients with MDR-TB need to be treated under clinic-based ambulatory model of care since 2018, unless the patient unstable or developed severe adverse drug reaction during the course of treatment. Patients either with serious medical or social conditions could be admitted with the decision of the treatment panel. Standardized long treatment regimens were used to treat MDR-TB patients in Ethiopia. The long treatment regimen contained at least four oral drugs which

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used daily during full course of treatment and one injectable drug until *M. tuberculosis* culture conversion. Treatment with injectable drugs continues at least for eight months based on clinical, microbiological and radiographic examination results. The minimum treatment duration was 20 months for long regimen which is at least 18 months after bacteriological conversion, whereas nine to 11 months for short treatment regimen.[31] The second line drugs used to treat MDR-TB in Ethioia are levofloxacin, ethionamide, cycloserine, para-aminosalicyclic acid (PAS), pyrazinamide, prothionamide, linezolid, clofazimine and injectable drugs such as amikacin, kanamycin and capreomycin.[31] All the patients enrolled into this study were treated by a standardized long term regimen consists capreomycin, levofloxacin, prothionamide, cycloserine and high dose isoniazid during the intensive phase.[31] During the continuation phase, levofloxacin, prothionamide, cycloserine and high dose isoniazid were used.[31] 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 extra-pulmonary TB patients. MDR-TB treatment is free of any const in Ethiopia and there is full access to all categories of drugs to treat MDR-TB patients.

Data collection

We collected data on socio-demographic 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 (RR vs MDR), previous treatment (new vs previously treated), diagnosis method (bacteriologically vs clinically), HIV sero-status (reactive vs non-reactive) and antiretroviral therapy (ART) status (on ART vs not applicable vs not on ART). In addition, we collected

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information on bacteriological status (smear, Xpert 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 two days practical training on data collection tool.

Definitions

In this study, we used standard WHO and national treatment guidelines definitions for laboratory confirmations, patient categories and treatment outcomes.[30,31] Clinically diagnosed MDR-TB refers to those cases with no documented drug susceptibility test (DST) results but treated empirically with a course of treatment including SLDs based on clinical criteria and contact history.[31] However, bacteriologically confirmed MDR-TB refers to those cases with documented DST results. All patients were categorized into new patients (never treated for TB or has treated for less than one month) and patients previously treated for tuberculosis. The final treatment outcomes of MDR-TB were cured, treatment completed, death, treatment failed and lost to follow up. Cured is 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 are 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 categorized as treatment failure. Lost to follow up is also refers to a patient whose treatment is interrupted for two 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.

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Data analysis

We entered data into CSPro software version 6.1 and analyzed by STATA version 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 30, 2009–February 30, 2019 in each TIC.

We used a competing risk survival analysis model with robust standard error to assess the effects of different variables on the treatment failure and death. Effect levels were reported by Hazard Ratio (HR) with 95% Confidence Intervals (CIs). We included variables scored p-values less than or equal to 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 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 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.

Results

Participants' characteristics

A total of 4,419 patients were enrolled to MDR-TB treatment in 42 of 53 (79.2%) treatment initiating centers (TICs) in Ethiopia from February, 2009 to February, 2019 [Fig 1]. Of the 4,419 patients, 3,395 (76.8%) fulfilled our inclusion criteria and enrolled to this study [Fig 1].

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The highest number of patients enrolled into the treatment were in 2015 (667 patients), while the lowest number of patients were registered in 2019 (only 4 patients) [Fig 2].

Of the 3,395 patients included into this study, 1,870 (55.1%) were male, and the mean age was 31.6 (SD ± 11.7) years with the age range of 15 to 85 years. Seventy two percent of the patients were in the age category of 15 to 35 years [Table 1]. Ninety three percent of the participants were pulmonary TB patients [Table 1]. Eighty six percent of patients had previous TB treatment history. Drug resistance status of 3,242 (95.5%) isolates were bacteriologically confirmed at the initiation of treatment [Table 1]. The main drug resistance diagnosis method was GeneXpert MTB/RIF (57.9%). Of the 3,395 patients, 1,421 (41.9%) had previous exposure to second line drugs and 767 (22.6%) were HIV infected [Table 1] of which686 (89.4%) were on ART. Only 6.0% of the patients had previous MDR-TB patient contact history and 1,831 (53.9%) of patients were hospitalized at the treatment initiation [Table 1]with mean duration of hospitalization 81.7 (±47.4) days.

Table 1: Demographic and clinical characteristics of the patients (n = 3,395)

Variable		n (%)
Sex	Male	1,870 (55.1)
	Female	1,525 (44.9)
Age (in year)	15–25	1,268 (37.3)
	26 –35	1,186 (34.9)
	36 –45	529 (15.6)
	≥ 46	412 (12.1)
Drug resistance type	RR/INH status unknown	1,810 (53.3)
	MDR-TB	1,585 (46.7)
Anatomical site of TB	Pulmonary	3,171 (93.4)
	Extra pulmonary	224 (6.6)
Previous TB treatment	New	462 (13.6)
	Previously treated	2,933 (86.4)
Previous exposure to SLDs	Yes	1,421 (41.9)
	No	1,842 (54.3)
	Unknown	132 (3.9)
Drug resistance identification method	GeneXpert MTB/RIF	1,967 (57.9)
	Culture/LPA	1,275 (37.6)
	Clinical	153 (4.5)
Diagnosis method	Bacteriological	3,242 (95.5)
	Clinical	153 (4.5)
HIV sero-status	Non-reactive	2,554 (75.2)

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	Sero-reactive	767 (22.6)
	Unknown	74 (2.2)
ART status	Not applicable	2,556 (75.3)
	On ART	686 (20.2)
	HIV sero-status known but, ART status unknown	79 (2.3)
	Both ART and HIV sero- statuses unknown	74 (2.2)
MDR-TB patient contact history	Yes	204 (6.0)
	No	1,511 (44.5)
	Unknown	1,680 (49.5)
Hospitalization history at treatment initiation	Hospitalized	1,831 (53.9)
	Not hospitalized	487 (14.3)
	Unknown	1,077 (31.7)
Treatment interruption	Never interrupted/interruption status unknown	3,192 (94.0)
	At least one day interrupted	203 (6.0)

TB-tuberculosis, ART-Antiretroviral therapy, SLDs-Second line drugs, HIV-Human immunodeficiency virus, MDR-Multidrug resistant, LPA-Line probe Assay

Drug resistance status at treatment initiation

Drug susceptibility testing was performed for four first-line drugs which are rifampin, isoniazed, ethambutol and streptomycin [Table 2]. Rifampin susceptibility test was performed on isolates of all patients included into this studyand 99.3% of isolates demonstrated resistance to the therapy [Table 2].

Table 2: Anti-tuberculosis drug susceptibility test results

Anti-tuberculosis drug	**Susceptibility test results**	**n (%)**
Rifampin (n=3,395)	Resistant	3,371 (99.3)
	Susceptible	24 (0.7)
Isoniazed (n = 1,313)	Resistant	1,241 (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)

Table 3 depicts the distribution of treatment outcome categories by sociodemographic and clinical characteristics. Of 1,585 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

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were failed. Treatment failure was almost ten times higher in patients who had previous TB treatment history (21.7%), than those who were never treated (2.2%). Moreover, mortality was two times higher in patients who were HIV sero-reactive (21.3%), than those who were HIV non-reactive (10.2%).

Table 3: Demographic and clinical characteristics distribution of treatment outcome

Variables		Treatment outcome n (%)						
		Cured	Completed	Treatment success	Failed	Death	LTFU	P-value
Sex	Male	1,006 (53.8)	376 (20.1)	1,382 (73.9)	40 (2.1)	245 (13.1)	203 (10.9)	
	Female	839 (55.0)	344 (22.6)	1,183 (77.6)	26 (1.7)	186 (12.2)	130 (8.5)	0.071
Resistance type	RR/INH status unknown	1,052 (58.1)	274 (15.1)	1,326 (73.2)	42 (2.3)	251 (13.9)	191 (10.6)	
	MDR	793 (50.0)	446 (28.1)	1,239 (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	1,795 (56.6)	595 (18.8)	2,390 (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	1,602 (54.6)	637 (21.7)	2,239 (76.3)	56 (21.7)	356 (12.1)	282 (9.6)	0.057
Diagnosis method	Bacteriological	1,771 (54.6)	686 (21.2)	5,457 (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-sero-status	Non-reactive	1,429 (56.0)	561 (22.0)	1,990 (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
Anemia	None anemic	880 (55.0)	380 (23.8)	1,260 (78.8)	29 (1.8)	150 (9.4)	161 (10.1)	
	Any grade of anemia present	965 (53.8)	340 (18.9)	1,305 (72.7)	37 (2.1)	281 (15.7)	172 (9.6)	< 0.001

Treatment outcome

Of the 3,395 patients enrolled into this study, 1,845 (40.0%) were cured, 720 (35.7%) completed the treatment, 431 (12.8%) have died, 333 (9.7%) were lost to follow up and the treatment of 66 (1.7%) patients failed [Fig 3]. The overall treatment success (cured plus treatment completed) was 2,565 (75.7%), whereas the overall unsuccessful treatment outcome (the sum of lost to follow up, treatment failed and death) was 830 (24.3%).

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Predictors of treatment failure and death

Bivariate analysis

In the current competing risk survival analysis model, failure events were treatment success (2,565), treatment failure (66) and death 431 (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 (1.04–1.05); p < 0.001), HIV sero-reactive (UHR = 2.2; 95% CI (1.8–2.7); p < 0.001) and presence of any grade of anemia (UHR = 1.7; 95% CI (1.4–2.1); p < 0.001) were significantly associated with death [Table 4]. Moreover, having previous TB treatment history (UHR = 0.71; 95% CI (0.56–0.92); p = 0.009) and presence of rifampin resistant bacilli (UHR = 1.3; 95% CI (1.03–1.5); 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].

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)

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

TB-tuberculosis, HIV-Human immunodeficiency virus, UHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

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Multivariable analysis

In multivariable analysis, older age (Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); p < 0.001), HIV sero-reactive (AHR = 2.0; 95% CI (1.6–2.4); p < 0.001) and presence of any grade anemia (AHR = 1.7; 95% CI (1.4–2.0); 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 presence of rifampin resistant bacilli and having previous TB treatment history were significantly associated with death in the unadjusted analysis, they failed to significantly associate in the adjusted analysis.

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)

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

TB-tuberculosis, HIV-Human immunodeficiency virus, AHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Discussion

The current 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 ten years. We have found that 75.7% of MDR-TB patients 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

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maximum proportion (19.6%) was registered in 2015. However, the proportion of the patients registered for the treatment has decreased after 2015 and the minimum patients were registered in 2019. Old age, being HIV sero-reactive and presence of any grade of anemia had significantly predicted death in patients treated for MDR-TB in the present study. However, none of the variables included into the multivariable model were able to significantly predict treatment failure.

The present study indicates that the proportion of treatment enrolment after 2015 has decreased and the lowest cases were recorded in 2019. This might be due to the burden of MDR-TB decreasing in the country or case registration related problems as the result of treatment centers were decentralized to the periphery. 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 the current study, treatment success proportion in MDR-TB patients who received a standardized long regimen was higher than the treatment success rate previously reported from other settings including from Ethiopia.[8,21,22] For instance, a study reported from Morocco indicated that only 53.4% of MDR-TB patients were treated successfully.[8] In addition, a study reported from Armenia shows that less than 50% of MDR-TB patients were successfully treated.[22] A recent review study that pooled data from different settings have also shown lower treatment success rate than our findings.[32] These differences originate most likely due to the differences in the quality of TB control programme, sample size, severity of the disease at diagnosis, TB/HIV co-infection burden and treatment regimens. A previous study conducted in Ethiopia in two treatment initiation centers[29] reported very similar treatment success proportion with our finding (78.6% Vs 75.7%).

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The proportion of death in the current study was considerably higher and it was similar with previously reported findings.[21,29] Case in point, the proportion of patients who died in our study was more than double compared to the mortality proportion reported from Morocco (5% vs 12.7%).[8] This difference is most probably due to 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 findings, it is well documented that MDR-TB mortality is higher in older age group.[33–35] Thus, particular attention has to be given to older patients to avert mortality related to TB. A previous study has shown that younger age is significantly associated with poor treatment outcome than older age.[7] 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 the current study, as in several previous studies[7,21,27–29], HIV sero-reactive was significantly associated with death. Despite the proportion of patients who were not on antiretroviral therapy (ART) were low (of HIV sero-reactive patients only 4.5 %), the hazard of death was 2.0 times higher in sero-reactive HIV patients. The possible explanation for the significant effect of HIV sero-reactivity 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 indicated that a combined anti-TB and anti-HIV treatment has been proven to improve treatment success in co-infected patients.[36]

In the present study, the presence of any grade of anemia was significantly associated with death due to MDR-TB. This finding is similar with a previous study reported from Ethiopia in which

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the hazard of poor treatment outcome was 4.2 times higher in the patients who had any grade of anemia at treatment initiation than those who were non-anemic.[21] The presence of anemia at the treatment initiation might be due to parasitic infections and some other chronic diseases. This finding highlights the importance of hemoglobin monitoring in MDR-TB patients on treatment to increase treatment success and decrease mortality.

In the present 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 were very smaller than the competing risks i.e. 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 history etc on treatment failure and death.. A prospective study that could capture all these uninvestigated variables is important to determine predictors of treatment failure and death..

The findings of the present study have clearly indicated the message for TB control programme efforts. Although treatment success rate is well achieved, mortality in the current study is considerably high and hence should be addressed by the TB programme. Old age is one of the main predictors of death in MDR-TB patients on treatment. Thus, early diagnosis and

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commencement of treatment in old patients could increase the cure rate. HIV sero-reactive is also one of strong predictors of death in MDR-TB patients. Taking in consideration the sero-status of MDR-TB patients and immediate commencement of anti-TB treatment together with ART is the mechanism to improve treatment success in MDR-TB patients with HIV co-infection.. Moreover, our result indicates that special attention should be paid to patients who have anemia at treatment initiation in order to improve their treatment outcome. Strengthen and standardizing 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 past ten years, MDR-TB treatment success in Ethiopia is well achieved. However, the proportion of patients who died is considerably high, and it could be reduced through providing special attention to old, HIV-infected and anemic patients. Further prospective cohort study is required to explore other predictors of treatment failure and death.

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Author contributions: HHT and KH conceived and designed the study; HHT, DFG, ET, ZM and MMS collected the data; HHT, MAM and MY analyzed and interpreted the data; HHT

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drafted the manuscript. All authors have critically reviewed and approved the manuscript for submission.

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Competing interests: None declared.

Ethics consideration: This study was approved by the research Ethics Review Board of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1396.4287), Ethiopian Public Health Institute (EPHI-IRB-065-2017), St. Peter's Specialized Hospital (V81622018) and Armauer Hansen Research Institute (PO13/18). We also obtained a waiver of informed consent from each review board. To maintain confidentiality, sensitive information that could identify participants was not reported in this study.

Data availability statement: Data used in this study is available from the corresponding authors and accessible upon reasonable request.

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Figure legend

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

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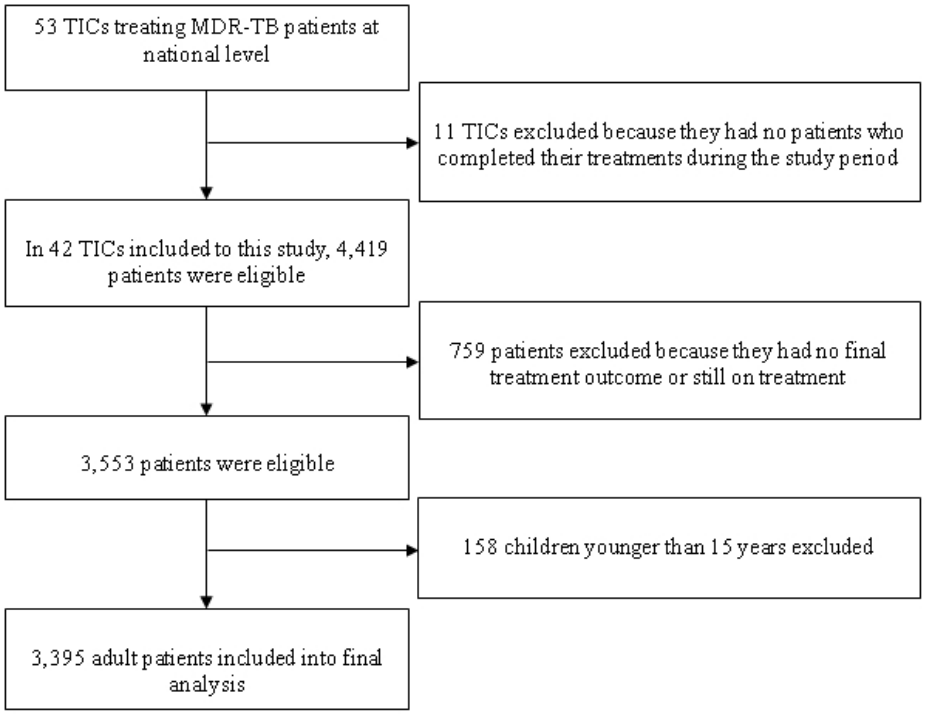

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

171x132mm (96 x 96 DPI)

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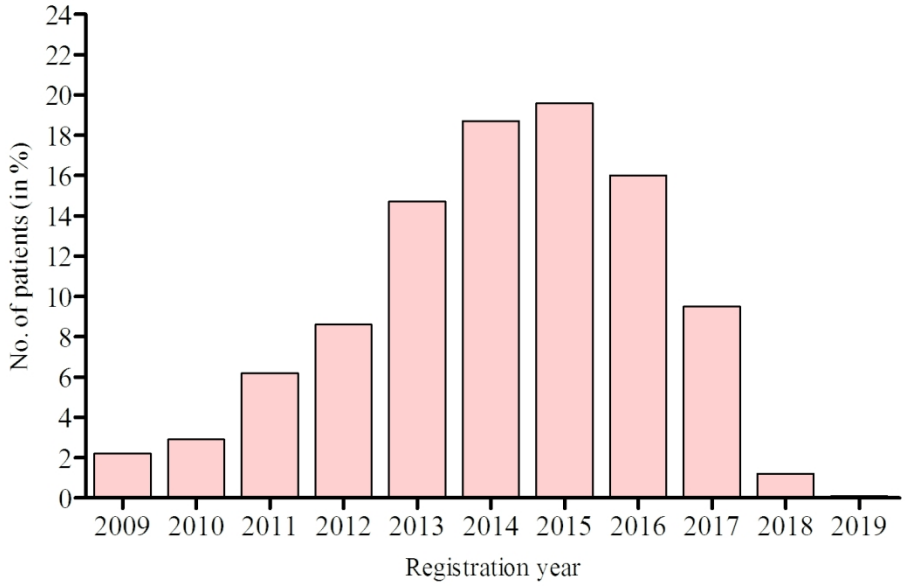

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

137x88mm (300 x 300 DPI)

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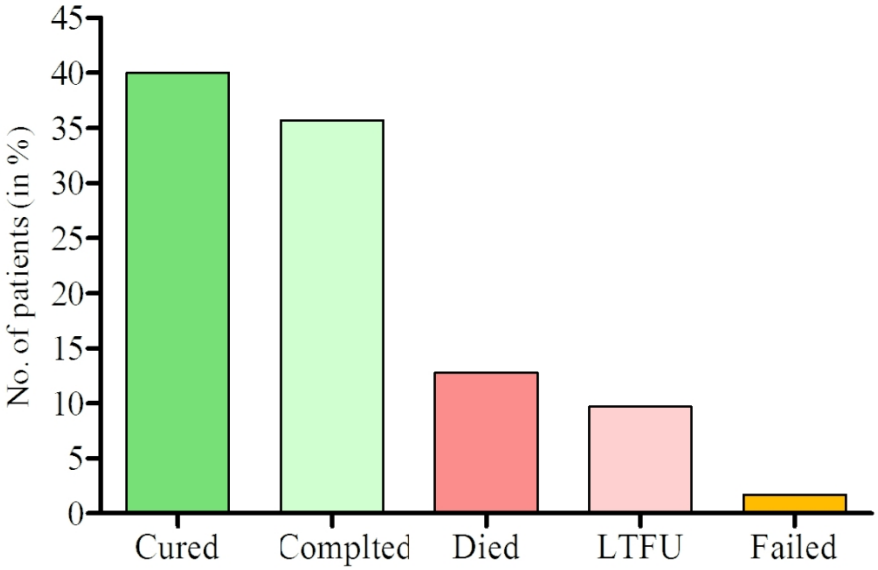

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

110x71mm (300 x 300 DPI)

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 - 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-13
		(b) Indicate number of participants with missing data for each variable of interest	Fig 1
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	15

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15-16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective cohort study

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National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years 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 underreported. 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 MDR-TB patients in Ethiopia.

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

Participants: A total of 3,395 adult MDR-TB patients who had final treatment outcome and who were treated under national TB programme were included. Data was collected from clinical charts, registration books and laboratory reports. Competing risk survival analysis model with robust standard error was used to determine 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 9.7%. The significant predictors of death were older age (adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); $p < 0.001$), HIV infection (AHR = 2.0; 95% CI (1.6–2.4); $p < 0.001$) and presence of any grade of anemia (AHR = 1.7; 95% CI (1.4–2.0); $p < 0.001$). Unlike the predictors of death, all variables included into multivariable model were not significantly associated with treatment failure.

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

Keywords: Tuberculosis, Multidrug resistance, Rifampin resistance, Treatment outcome

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Strengths and Limitations of this study

- ❖ National multidrug resistance tuberculosis (MDR-TB) treatment success rate in the past ten years was determined using MDR-TB treatment programme data.
- ❖ Although MDR-TB mortality is high, predictors of death and treatment failure are underreported.
- ❖ This study determined the predictors of treatment failure and death using competing risk survival analysis model with robust standard error.
- ❖ 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 only were enrolled into this study.

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Background

The emergence of drug resistance tuberculosis (TB) has been undermining the efforts to control TB and continues to cause severe morbidity and mortality among millions across the world. The World Health Organization (WHO) estimated that nearly half a million rifampin-resistant new TB cases occurred in 2019 across the world.[1] Multidrug resistance (MDR) TB is defined as a *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin, whereas extensively drug resistance (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 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) is considerably low.[1,3,6] The WHO's recent global estimation indicates that only 57% of MDR-TB patients were successfully treated in 2017.[1] Moreover, a recently published -individual patient data meta-analysis study indicated that 61% of MDR-TB patients treated successfully.[6] However, recent studies indicated relatively higher treatment success rates in certain settings.[7–10] For example, 82.4% of MDR-TB patients were treated successfully in Taiwan[7], 75.8% in Pakistan[10] and 75.7% in Tanzania.[8]

Heterogeneous and interrelated factors are associated with poor MDR-TB treatment outcome. Infection with Human Immunodeficiency Virus (HIV)[11–14], diabetes mellitus[12,15,16], malnutrition [17,18], and anemia[12,14,19] are co-morbidities 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

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previous TB treatment history[18,25] are treatment related factors that are associated with poor treatment outcome in MDR-TB patients.

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 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%–78.8%.[9,19,27]

The global treatment success rate of MDR-TB is low and there is evidence limitation on the factors that 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 standard error. Ethiopia is among the countries which lack such evidence at national level to plan effective intervention that could decrease treatment failure and reduce death in MDR-TB patients. 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 MDR-TB patients in Ethiopia.

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Materials and methods

Study setting, population and design

We conducted a retrospective cohort study on adult patients aged ≥ 15 years old, diagnosed either biologically or clinically for both pulmonary and extra-pulmonary TB, and enrolled to MDR-TB treatment at 42 treatment initiating centers (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 centers (TFCs) in the country. The majority of MDR-TB patients initiate their treatments in TICs while stable patients follow the treatment under directly observed therapy (DOT) 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 and older, diagnosed either bacteriologically or clinically for MDR-TB and enrolled to the treatment from February 2009. Children less than 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 (LJ)) and a fluorometric BACTEC

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MGIT960 at one national TB reference laboratory and nine regional laboratories. In addition, GeneXpert 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 μg/ml), isoniazid (0.1 μg/ml), streptomycin (1.0 μg/ml), ethambutol (5μg/ml) and pyrazinamide (100 μg/ml). DST for second-line drugs has been recently started in the country and rarely performed. Data on second-line DST was 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 MDR-TB patients were treated as inpatient model of care for the first few months at treatment centers until the patient 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 clinic-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. Standardized long treatment regimens were used to treat MDR-TB patients 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 eight months based on clinical, microbiological and radiographic examination results. The minimum treatment duration was 20 months -at least 18 months after

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bacteriological conversion. The 9–11 months (short treatment regimen) was not used.[29] The second line drugs used to treat MDR-TB in Ethiopia are levofloxacin, ethionamide, cycloserine, para-aminosalicyclic acid (PAS), 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 standardized 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 extra-pulmonary TB patients. MDR-TB treatment is free of any cost in Ethiopia and there is full access to all categories of drugs to treat MDR-TB patients.

Data collection

We collected data on socio-demographic 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 (RR vs MDR), previous treatment (new vs previously treated), diagnosis method (bacteriologically vs clinically), HIV status (HIV-infected vs not infected) and antiretroviral therapy (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 two days practical training on data management.

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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 drug susceptibility test (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 documented DST results. All patients were categorized into new patients (never treated for TB or for less than one 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 is 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 categorized as treatment failure. Lost to follow up also refers to a patient whose treatment is interrupted for two 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 version 6.1 and analyzed by STATA version 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

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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 standard error to assess the effects of different variables on the treatment failure and death. Effect levels were reported by Hazard Ratio (HR) with 95% Confidence Intervals (CIs). We included variables scored p-values less than or equal to 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.

Results

Participants' characteristics

A total of 4,419 patients were enrolled to MDR-TB treatment in 42 of 53 (79.2%) treatment initiating centers (TICs) in Ethiopia from February, 2009 to February, 2019 [Fig 1]. Of the 4,419 patients, 3,395 (76.8%) fulfilled our inclusion criteria and enrolled to this study [Fig 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) [Fig 2].

Of the 3,395 patients included into this study, 1,870 (55.1%) were male, and the mean age was 31.6 (SD ± 11.7) years with the age range of 15 to 85 years. Seventy two percent of the patients

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were in the age category of 15 to 35 years [Table 1]. Ninety three percent of the participants were pulmonary TB patients [Table 1]. Eighty six percent of patients had previous TB treatment history. Drug resistance status of 3,242 (95.5%) isolates were bacteriologically confirmed at the initiation of treatment [Table 1]. The main drug resistance diagnosis method was GeneXpert MTB/RIF (57.9%). Of the 3,395 patients, 1,421 (41.9%) had previous exposure to second line drugs and 767 (22.6%) were HIV infected [Table 1] of which 686 (89.4%) were on ART. Only 6.0% of the patients had previous MDR-TB patient contact history and 1,831 (53.9%) of patients were hospitalized at the treatment initiation [Table 1] with mean duration of hospitalization 81.7 (±47.4) days.

Table 1: Demographic and clinical characteristics of the patients (n = 3,395)

Variable		n (%)
Sex	Male	1,870 (55.1)
	Female	1,525 (44.9)
Age (in year)	15–25	1,268 (37.3)
	26 –35	1,186 (34.9)
	36 –45	529 (15.6)
	≥ 46	412 (12.1)
Drug resistance type	RR/INH status unknown	1,810 (53.3)
	MDR-TB	1,585 (46.7)
Anatomical site of TB	Pulmonary	3,171 (93.4)
	Extra pulmonary	224 (6.6)
Previous TB treatment	New	462 (13.6)
	Previously treated	2,933 (86.4)
Previous exposure to SLDs	Yes	1,421 (41.9)
	No	1,842 (54.3)
	Unknown	132 (3.9)
Drug resistance identification method	GeneXpert MTB/RIF	1,967 (57.9)
	Culture/LPA	1,275 (37.6)
	Clinical	153 (4.5)
Diagnosis method	Bacteriological	3,242 (95.5)
	Clinical	153 (4.5)
HIV infection	Not infected	2,554 (75.2)
	Infected	767 (22.6)
	Unknown	74 (2.2)
ART status	Not applicable	2,556 (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)
MDR-TB patient contact history	Yes	204 (6.0)
	No	1,511 (44.5)
	Unknown	1,680 (49.5)

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Hospitalization history at treatment initiation	Hospitalized	1,831 (53.9)
	Not hospitalized	487 (14.3)
	Unknown	1,077 (31.7)
Treatment interruption	Never interrupted/interruption status unknown	3,192 (94.0)
	At least one day interrupted	203 (6.0)

TB-tuberculosis, ART-Antiretroviral therapy, SLDs-Second line drugs, HIV-Human immunodeficiency virus, MDR-Multidrug resistant, LPA-Line probe Assay

Drug resistance status at treatment initiation

Drug susceptibility testing was performed for four first-line drugs which are rifampin, isoniazed, ethambutol and streptomycin [Table 2]. Rifampin susceptibility test was performed on isolates of all patients included into this study and 99.3% of isolates demonstrated resistance to the therapy [Table 2].

Table 2: Anti-tuberculosis drug susceptibility test results

Anti-tuberculosis drug	**Susceptibility test results**	**n (%)**
Rifampin (n=3,395)	Resistant	3,371 (99.3)
	Susceptible	24 (0.7)
Isoniazid (n = 1,313)	Resistant	1,241 (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)

Table 3 depicts the distribution of treatment outcome categories by sociodemographic and clinical characteristics. Of 1,585 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 ten times higher in patients who had previous TB treatment history (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%).

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Table 3: Demographic and clinical characteristics distribution of treatment outcome

Variables		Treatment outcome n (%)						
		Cured	Completed	Treatment success	Failed	Death	LTFU	P-value
Sex	Male	1,006 (53.8)	376 (20.1)	1,382 (73.9)	40 (2.1)	245 (13.1)	203 (10.9)	
	Female	839 (55.0)	344 (22.6)	1,183 (77.6)	26 (1.7)	186 (12.2)	130 (8.5)	0.071
Resistance type	RR/INH status unknown	1,052 (58.1)	274 (15.1)	1,326 (73.2)	42 (2.3)	251 (13.9)	191 (10.6)	
	MDR	793 (50.0)	446 (28.1)	1,239 (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	1,795 (56.6)	595 (18.8)	2,390 (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	1,602 (54.6)	637 (21.7)	2,239 (76.3)	56 (21.7)	356 (12.1)	282 (9.6)	0.057
Diagnosis method	Bacteriological	1,771 (54.6)	686 (21.2)	5,457 (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	1,429 (56.0)	561 (22.0)	1,990 (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
Anemia	None anemic	880 (55.0)	380 (23.8)	1,260 (78.8)	29 (1.8)	150 (9.4)	161 (10.1)	
	Any grade of anemia present	965 (53.8)	340 (18.9)	1,305 (72.7)	37 (2.1)	281 (15.7)	172 (9.6)	< 0.001

Treatment outcome

Of the 3,395 patients enrolled into this study, 1,845 (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 [Fig 3]. The overall treatment success (cured plus treatment completed) was 2,565 (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 (2,565), treatment failure (66) and death 431 (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 (1.04–1.05); $p < 0.001$), HIV infection (UHR = 2.2; 95% CI (1.8–2.7); $p < 0.001$) and presence of any grade of anemia (UHR = 1.7; 95% CI

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(1.4–2.1); p < 0.001) were significantly associated with death [Table 4]. Moreover, having previous TB treatment history (UHR = 0.71; 95% CI (0.56–0.92); p = 0.009) and presence of rifampin resistant bacilli (UHR = 1.3; 95% CI (1.03–1.5); 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].

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)

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

TB-tuberculosis, HIV-Human immunodeficiency virus, UHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Multivariable analysis

In multivariable analysis, older age (Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); p < 0.001), HIV infection (AHR = 2.0; 95% CI (1.6–2.4); p < 0.001) and presence of any grade anemia (AHR = 1.7; 95% CI (1.4–2.0); 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 presence of rifampin resistant bacilli and having previous TB treatment history were significantly associated with death in the unadjusted analysis, they failed to significantly associate in the adjusted analysis.

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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)

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

TB-tuberculosis, HIV-Human immunodeficiency virus, AHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Discussion

The current 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 ten years. We have found that 75.7% of MDR-TB patients 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 anemia were significant predictors of death in patients treated for MDR-TB in the present study. However, none of the variables included into the multivariable model were able to significantly predict treatment failure.

The present study indicates that the proportion of treatment enrolment after 2015 has decreased and the lowest 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 decentralization of TB care to the communities. As patients

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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 the current study, treatment success proportion in MDR-TB patients who received a standardized 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 MDR-TB patients were treated successfully.[30] In addition, a study reported from Armenia shows that less than 50% of MDR-TB patients were successfully treated.[20] A recent review study 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 treatment initiation centers[27] reported very similar treatment success rate with our finding (78.6% vs 75.7%).

The proportion of death in the current 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 to the mortality proportion reported from Morocco (5% vs 12.7%).[30] This difference is most probably due to 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 findings, 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

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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 the current 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 antiretroviral therapy (ART) were 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 indicated that a combined anti-TB and anti-HIV treatment has been proven to improve treatment success in co-infected patients.[36]

In the present study, the presence of any grade of anemia 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 anemia at treatment initiation than those who were non-anemic.[19] The presence of anemia at the treatment initiation might be due to parasitic infections and some other chronic diseases. This finding highlights the importance of hemoglobin monitoring in MDR-TB patients on treatment to increase treatment success and decrease mortality.

In the current 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 i.e. death and treatment success.

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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 history etc on treatment failure and death. A prospective study that could capture all these uninvestigated variables is important to determine predictors of treatment failure and death.

The findings of the present study have clearly indicated the message for TB control programme efforts. Although treatment success rate is well achieved, mortality in the current study is considerable and hence should be addressed by the TB programme. HIV infection is one of strong predictors of death in MDR-TB patients. Taking in consideration of HIV infected MDR-TB patients and immediate commencement of anti-TB treatment together with ART is the mechanism to improve treatment success in MDR-TB patients. Moreover, our result indicates that special attention should be given to patients who have anemia at treatment initiation in order to improve their treatment outcome. Strengthening and standardizing 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 ten 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

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special attention to HIV-infected and anemic patients. Further prospective cohort study is required to explore other predictors of treatment failure and death.

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Author contributions: HHT and KH conceived and designed the study; HHT, DFG, ET, ZM and MMS collected the data; HHT, MAM and MY analyzed and interpreted the data; HHT drafted the manuscript. All authors have critically reviewed and approved the manuscript for submission.

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Competing interests: None declared.

Ethics consideration: This study was approved by the research Ethics Review Board of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1396.4287), Ethiopian Public Health Institute (EPHI-IRB-065-2017), St. Peter's Specialized Hospital (V81622018) and Armauer Hansen Research Institute (PO13/18). We also obtained a waiver of informed consent from each review board. To maintain confidentiality, sensitive information that could identify participants was not reported in this study.

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Data availability statement: Data used in this study is available from the corresponding authors and accessible upon reasonable request.

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Figure legend

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

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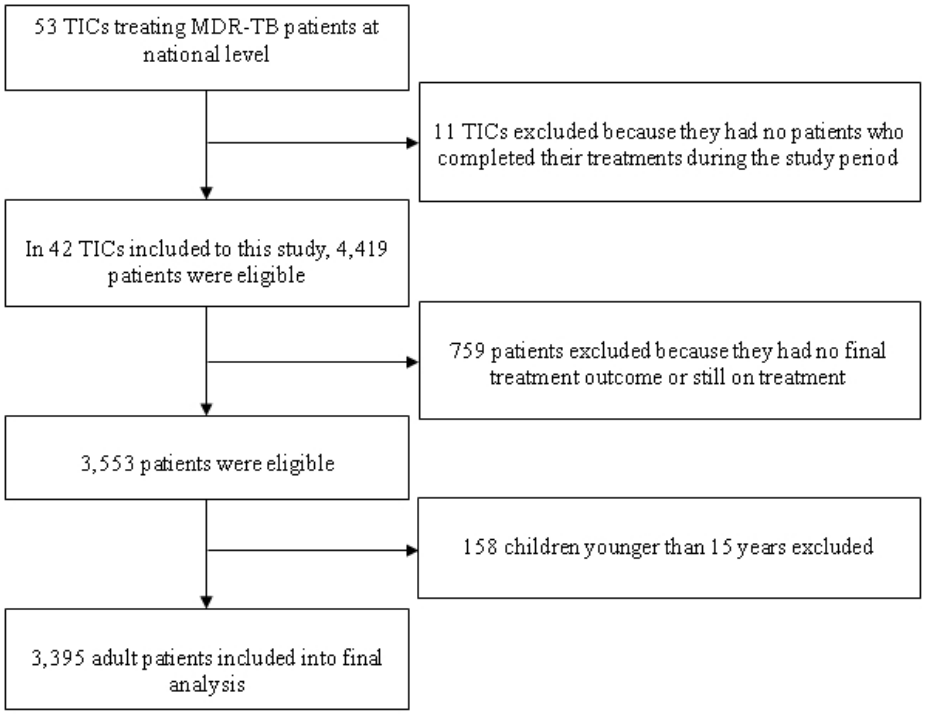

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

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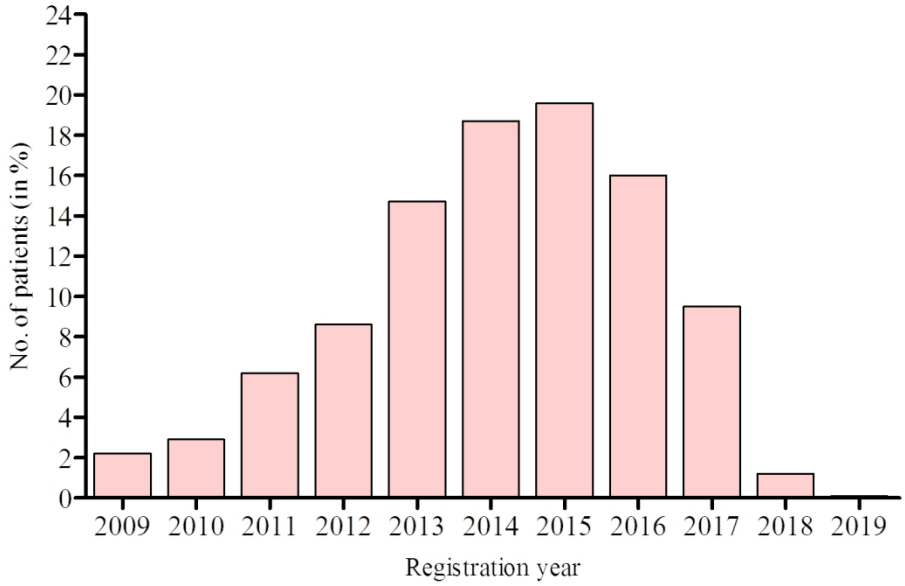

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

137x88mm (300 x 300 DPI)

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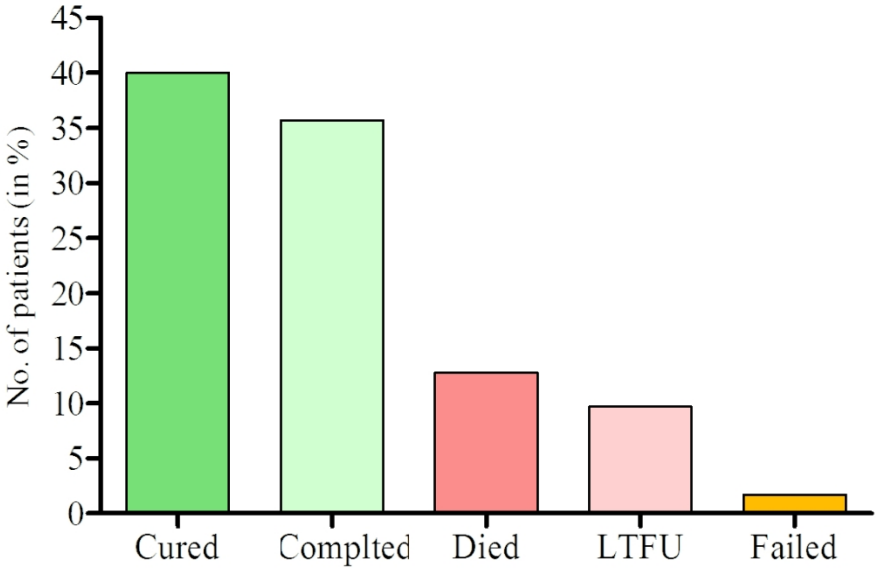

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

110x71mm (300 x 300 DPI)

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 - 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-13
		(b) Indicate number of participants with missing data for each variable of interest	Fig 1
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	15

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15-16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years retrospective cohort study

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National treatment outcome and predictors of death and treatment failure in multidrug resistant tuberculosis in Ethiopia: A ten years 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 underreported. 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 MDR-TB patients in Ethiopia.

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

Participants: A total of 3,395 adult MDR-TB patients who had final treatment outcome and who were treated under national TB programme were included. Data was collected from clinical charts, registration books and laboratory reports. Competing risk survival analysis model with robust standard error was used to determine 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 9.7%. The significant predictors of death were older age (adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); $p < 0.001$), HIV infection (AHR = 2.0; 95% CI (1.6–2.4); $p < 0.001$) and presence of any grade of anemia (AHR = 1.7; 95% CI (1.4–2.0); $p < 0.001$). Unlike the predictors of death, all variables included into multivariable model were not significantly associated with treatment failure.

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

Keywords: Tuberculosis, Multidrug resistance, Rifampin resistance, Treatment outcome

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Strengths and Limitations of this study

- ❖ National multidrug resistance tuberculosis (MDR-TB) treatment success rate in the past ten years was determined using MDR-TB treatment programme data.
- ❖ Although MDR-TB mortality is high, predictors of death and treatment failure are underreported.
- ❖ This study determined the predictors of treatment failure and death using competing risk survival analysis model with robust standard error.
- ❖ 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 only were enrolled into this study.

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Background

The emergence of drug resistance tuberculosis (TB) has been undermining the efforts to control TB and continues to cause severe morbidity and mortality among millions across the world. The World Health Organization (WHO) estimated that nearly half a million rifampin-resistant new TB cases occurred in 2019 across the world.[1] Multidrug resistance (MDR) TB is defined as a *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin, whereas extensively drug resistance (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 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) is considerably low.[1,3,6] The WHO's recent global estimation indicates that only 57% of MDR-TB patients were successfully treated in 2017.[1] Moreover, a recently published -individual patient data meta-analysis study indicated that 61% of MDR-TB patients were treated successfully.[6] However, recent studies indicated relatively higher treatment success rates in certain settings.[7–10] For example, 82.4% of MDR-TB patients were treated successfully in Taiwan[7], 75.8% in Pakistan[10] and 75.7% in Tanzania.[8]

Heterogeneous and interrelated factors are associated with poor MDR-TB treatment outcome. Infection with Human Immunodeficiency Virus (HIV)[11–14], diabetes mellitus[12,15,16], malnutrition [17,18], and anemia[12,14,19] are co-morbidities 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

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previous TB treatment history[18,25] are treatment related factors that are associated with poor treatment outcome in MDR-TB patients.

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 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%–78.8%.[9,19,27]

The global treatment success rate of MDR-TB is low and there is evidence limitation on the factors that 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 standard error. Ethiopia is among the countries which lack such evidence at national level to plan effective intervention that could decrease treatment failure and reduce death in MDR-TB patients. 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 MDR-TB patients in Ethiopia.

Materials and methods

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Study setting, population and design

We conducted a retrospective cohort study on adult patients aged ≥ 15 years old, diagnosed either biologically or clinically for both pulmonary and extra-pulmonary TB, and enrolled to MDR-TB treatment at 42 treatment initiating centers (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 centers (TFCs) in the country. The majority of MDR-TB patients initiate their treatments in TICs while stable patients follow the treatment under directly observed therapy (DOT) 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 and older, diagnosed either bacteriologically or clinically for MDR-TB and enrolled to the treatment from February 2009. Children less than 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 (LJ)) and a fluorometric BACTEC MGIT960 at one national TB reference laboratory and nine regional laboratories. In addition,

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GeneXpert 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 μg/ml), isoniazid (0.1 μg/ml), streptomycin (1.0 μg/ml), ethambutol (5μg/ml) and pyrazinamide (100 μg/ml). DST for second-line drugs has been recently started in the country and rarely performed. Data on second-line DST was 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 MDR-TB patients were treated as inpatient model of care for the first few months at treatment centers until the patient 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 clinic-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. Standardized long treatment regimens were used to treat MDR-TB patients 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 eight months based on clinical, microbiological and radiographic examination results. The minimum treatment duration was 20 months -at least 18 months after bacteriological conversion. The 9–11 months (short treatment regimen) was not used.[29] The second line drugs used to treat

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MDR-TB in Ethiopia are levofloxacin, ethionamide, cycloserine, para-aminosalicyclic acid (PAS), 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 standardized 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 extra-pulmonary TB patients. MDR-TB treatment is free of any cost in Ethiopia and there is full access to all categories of drugs to treat MDR-TB patients.

Data collection

We collected data on socio-demographic 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 (RR vs MDR), previous treatment (new vs previously treated), diagnosis method (bacteriologically vs clinically), HIV status (HIV-infected vs not infected) and antiretroviral therapy (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 two days practical training on data management.

Definitions

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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 drug susceptibility test (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 documented DST results. All patients were categorized into new patients (never treated for TB or for less than one 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 is 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 categorized as treatment failure. Lost to follow up also refers to a patient whose treatment is interrupted for two 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 version 6.1 and analyzed by STATA version 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

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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 standard error to assess the effects of different variables on the treatment failure and death. Effect levels were reported by Hazard Ratio (HR) with 95% Confidence Intervals (CIs). We included variables scored p-values less than or equal to 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.

Results

Participants' characteristics

A total of 4,419 patients were enrolled to MDR-TB treatment in 42 of 53 (79.2%) treatment initiating centers (TICs) in Ethiopia from February, 2009 to February, 2019 [Fig 1]. Of the 4,419 patients, 3,395 (76.8%) fulfilled our inclusion criteria and enrolled to this study [Fig 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) [Fig 2].

Of the 3,395 patients included into this study, 1,870 (55.1%) were male, and the mean age was 31.6 (SD ± 11.7) years with the age range of 15 to 85 years. Seventy two percent of the patients were in the age category of 15 to 35 years [Table 1]. Ninety three percent of the participants were

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pulmonary TB patients [Table 1]. Eighty six percent of patients had previous TB treatment history. Drug resistance status of 3,242 (95.5%) isolates were bacteriologically confirmed at the initiation of treatment [Table 1]. The main drug resistance diagnosis method was GeneXpert MTB/RIF (57.9%). Of the 3,395 patients, 1,421 (41.9%) had previous exposure to second line drugs and 767 (22.6%) were HIV infected [Table 1] of which 686 (89.4%) were on ART. Only 6.0% of the patients had previous MDR-TB patient contact history and 1,831 (53.9%) of patients were hospitalized at the treatment initiation [Table 1] with mean duration of hospitalization 81.7 (±47.4) days.

Table 1: Demographic and clinical characteristics of the patients (n = 3,395)

Variable		n (%)
Sex	Male	1,870 (55.1)
	Female	1,525 (44.9)
Age (in year)	15–25	1,268 (37.3)
	26 –35	1,186 (34.9)
	36 –45	529 (15.6)
	≥ 46	412 (12.1)
Drug resistance type	RR/INH status unknown	1,810 (53.3)
	MDR-TB	1,585 (46.7)
Anatomical site of TB	Pulmonary	3,171 (93.4)
	Extra pulmonary	224 (6.6)
Previous TB treatment	New	462 (13.6)
	Previously treated	2,933 (86.4)
Previous exposure to SLDs	Yes	1,421 (41.9)
	No	1,842 (54.3)
	Unknown	132 (3.9)
Drug resistance identification method	GeneXpert MTB/RIF	1,967 (57.9)
	Culture/LPA	1,275 (37.6)
	Clinical	153 (4.5)
Diagnosis method	Bacteriological	3,242 (95.5)
	Clinical	153 (4.5)
HIV infection	Not infected	2,554 (75.2)
	Infected	767 (22.6)
	Unknown	74 (2.2)
ART status	Not applicable	2,556 (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)
MDR-TB patient contact history	Yes	204 (6.0)
	No	1,511 (44.5)
	Unknown	1,680 (49.5)
Hospitalization history at treatment initiation	Hospitalized	1,831 (53.9)
	Not hospitalized	487 (14.3)

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	Unknown	1,077 (31.7)
Treatment interruption	Never interrupted/interruption status unknown	3,192 (94.0)
	At least one day interrupted	203 (6.0)

TB-tuberculosis, ART-Antiretroviral therapy, SLDs-Second line drugs, HIV-Human immunodeficiency virus, MDR-Multidrug resistant, LPA-Line probe Assay

Drug resistance status at treatment initiation

Drug susceptibility testing was performed for four first-line drugs which are rifampin, isoniazed, ethambutol and streptomycin [Table 2]. Rifampin susceptibility test was performed on isolates of all patients included into this study and 99.3% of isolates demonstrated resistance to the therapy [Table 2].

Table 2: Anti-tuberculosis drug susceptibility test results

Anti-tuberculosis drug	Susceptibility test results	n (%)
Rifampin (n=3,395)	Resistant	3,371 (99.3)
	Susceptible	24 (0.7)
Isoniazid (n = 1,313)	Resistant	1,241 (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)

Table 3 depicts the distribution of treatment outcome categories by sociodemographic and clinical characteristics. Of 1,585 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 ten times higher in patients who had previous TB treatment history (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%).

Table 3: Demographic and clinical characteristics distribution of treatment outcome

		Treatment outcome n (%)

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Variables		Cured	Completed	Treatment success	Failed	Death	LTFU	P-value
Sex	Male	1,006 (53.8)	376 (20.1)	1,382 (73.9)	40 (2.1)	245 (13.1)	203 (10.9)	
	Female	839 (55.0)	344 (22.6)	1,183 (77.6)	26 (1.7)	186 (12.2)	130 (8.5)	0.071
Resistance type	RR/INH status unknown	1,052 (58.1)	274 (15.1)	1,326 (73.2)	42 (2.3)	251 (13.9)	191 (10.6)	
	MDR	793 (50.0)	446 (28.1)	1,239 (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	1,795 (56.6)	595 (18.8)	2,390 (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	1,602 (54.6)	637 (21.7)	2,239 (76.3)	56 (21.7)	356 (12.1)	282 (9.6)	0.057
Diagnosis method	Bacteriological	1,771 (54.6)	686 (21.2)	5,457 (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	1,429 (56.0)	561 (22.0)	1,990 (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
Anemia	None anemic	880 (55.0)	380 (23.8)	1,260 (78.8)	29 (1.8)	150 (9.4)	161 (10.1)	
	Any grade of anemia present	965 (53.8)	340 (18.9)	1,305 (72.7)	37 (2.1)	281 (15.7)	172 (9.6)	< 0.001

Treatment outcome

Of the 3,395 patients enrolled into this study, 1,845 (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 [Fig 3]. The overall treatment success (cured plus treatment completed) was 2,565 (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 (2,565), treatment failure (66) and death 431 (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 (1.04–1.05); $p < 0.001$), HIV infection (UHR = 2.2; 95% CI (1.8–2.7); $p < 0.001$) and presence of any grade of anemia (UHR = 1.7; 95% CI (1.4–2.1); $p < 0.001$) were significantly associated with death [Table 4]. Moreover, having previous TB

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treatment history (UHR = 0.71; 95% CI (0.56–0.92); p = 0.009) and presence of rifampin resistant bacilli (UHR = 1.3; 95% CI (1.03–1.5); 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].

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)

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

TB-tuberculosis, HIV-Human immunodeficiency virus, UHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Multivariable analysis

In multivariable analysis, older age (Adjusted hazard ratio (AHR) = 1.03; 95% CI (1.03–1.05); p < 0.001), HIV infection (AHR = 2.0; 95% CI (1.6–2.4); p < 0.001) and presence of any grade anemia (AHR = 1.7; 95% CI (1.4–2.0); 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 presence of rifampin resistant bacilli and having previous TB treatment history were significantly associated with death in the unadjusted analysis, they failed to significantly associate in the adjusted analysis.

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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)

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

TB-tuberculosis, HIV-Human immunodeficiency virus, AHR- Unadjusted hazard ratio, CI-Confidence interval, MDR-Multidrug resistant

Discussion

The current 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 ten years. We have found that 75.7% of MDR-TB patients 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 anemia were significant predictors of death in patients treated for MDR-TB in the present study. However, none of the variables included into the multivariable model were able to significantly predict treatment failure.

The present study indicates that the proportion of treatment enrolment after 2015 has decreased and the lowest 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 decentralization of TB care to the communities. As patients

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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 the current study, treatment success proportion in MDR-TB patients who received a standardized 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 MDR-TB patients were treated successfully.[30] In addition, a study reported from Armenia shows that less than 50% of MDR-TB patients were successfully treated.[20] A recent review study 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 treatment initiation centers[27] reported very similar treatment success rate with our finding (78.6% vs 75.7%).

The proportion of death in the current 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 to the mortality proportion reported from Morocco (5% vs 12.7%).[30] This difference is most probably due to 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 findings, 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

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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 the current 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 antiretroviral therapy (ART) were 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 indicated that a combined anti-TB and anti-HIV treatment has been proven to improve treatment success in co-infected patients.[36]

In the present study, the presence of any grade of anemia 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 anemia at treatment initiation than those who were non-anemic.[19] The presence of anemia at the treatment initiation might be due to parasitic infections and some other chronic diseases. This finding highlights the importance of hemoglobin monitoring in MDR-TB patients on treatment to increase treatment success and decrease mortality.

In the current 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 i.e. death and treatment success.

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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 history etc on 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 be overestimated the treatment success rate in the current study. A prospective study that could capture all these uninvestigated variables is important to determine predictors of treatment failure and death.

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

Conclusion

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In the past ten 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 anemic patients. Further prospective cohort study is required to explore other predictors of treatment failure and death.

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Author contributions: HHT and KH conceived and designed the study; HHT, DFG, ET, ZM and MMS collected the data; HHT, MAM and MY analyzed and interpreted the data; HHT drafted the manuscript. All authors have critically reviewed and approved the manuscript for submission.

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Competing interests: None declared.

Ethics consideration: This study was approved by the research Ethics Review Board of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1396.4287), Ethiopian Public Health Institute (EPHI-IRB-065-2017), St. Peter's Specialized Hospital (V81622018) and Armauer Hansen Research Institute (PO13/18). We also obtained a waiver of informed consent from each review board. To maintain confidentiality, sensitive information that could identify participants was not reported in this study.

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Data availability statement: Data used in this study is available from the corresponding authors and accessible upon reasonable request.

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Figure legend

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

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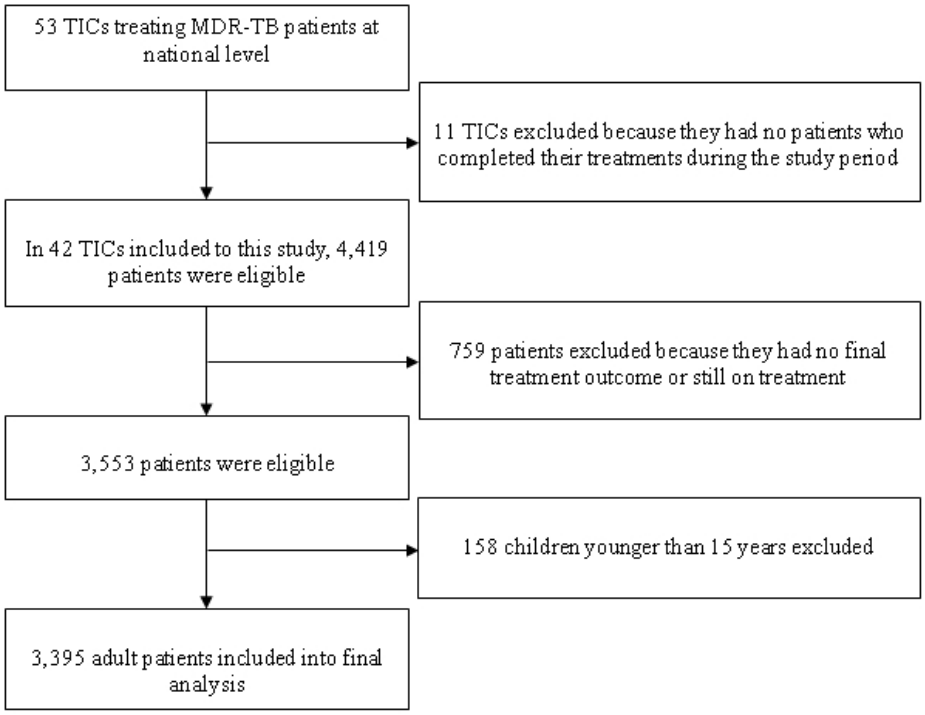

Figure 1: Treatment initiation centers and patients inclusion flow diagram (TICs- Treatment initiating centers)

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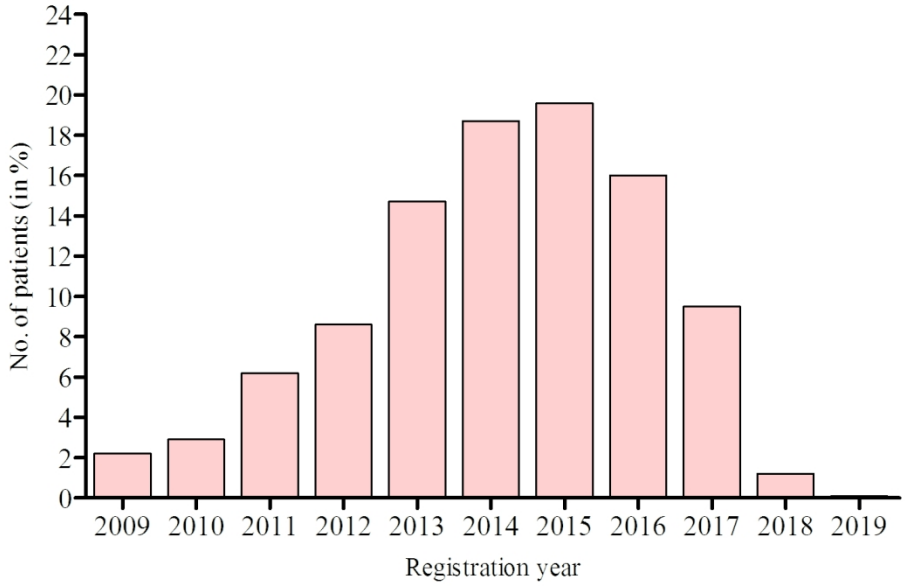

Figure 2: Patient enrolment into MDR-TB treatment in past ten years in Ethiopia (From 2009–2019)

137x88mm (300 x 300 DPI)

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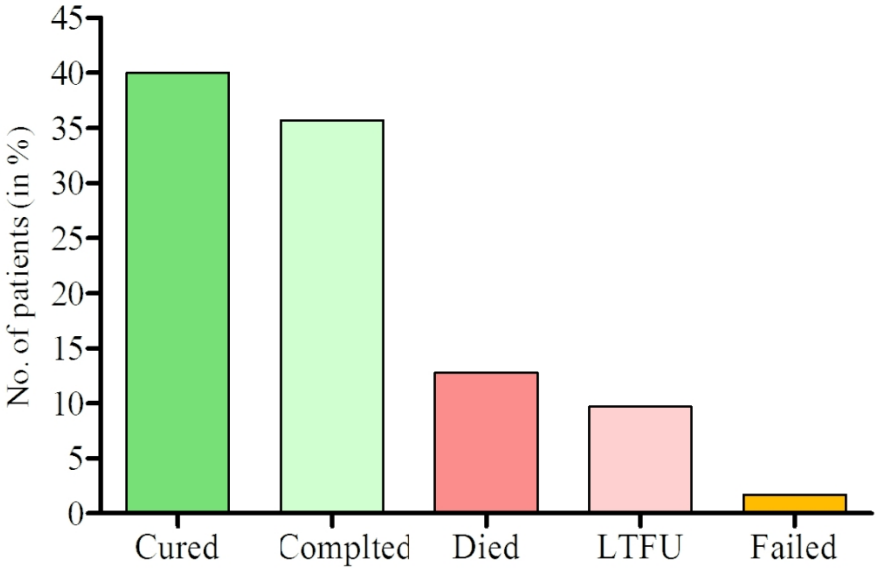

Figure 3: MDR-TB treatment outcomes in past ten years in Ethiopia (2009 to 2019)

110x71mm (300 x 300 DPI)

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 - 7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-13
		(b) Indicate number of participants with missing data for each variable of interest	Fig 1
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	15

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15-16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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