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ORIGINAL RESEARCH

Unfavorable Treatment Outcome and Its Predictors Among Patients with Multidrug-Resistance Tuberculosis in Southern Ethiopia in 2014 to 2019: A Multi-Center Retrospective Follow-Up Study

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Lemlem Bogale[1]
Tewodros Tsegaye[1]
Mohamed Abdulkadir[1]
Temesgen Yihunie Akalu[2]

[1]Department of Internal Medicine, School of Medicine, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia; [2]Department of Epidemiology and Biostatistics, Institute of Public Health, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

Background: According to the 2017 global report, Ethiopia is among the top 30 high tuberculosis (TB) and multidrug-resistant tuberculosis (MDR-TB) burden countries. However, studies on MDR-TB treatment outcomes in Southern Ethiopia was very limited. Therefore, the study was aimed at determining the unfavorable treatment outcome and its predictors among patients with multidrug-resistant tuberculosis in Southern Ethiopia MDR-TB treatment centers.

Subjects and Methods: A retrospective follow-up study was conducted in Southern Ethiopia MDR-TB treatment initiating centers. Three hundred sixty-three patients were included in the study. Kaplan–Meier failure curve, median time, and Log rank test were used to present the descriptive findings. Then, a Cox regression analysis was used to identify predictors of unfavorable treatment outcome. The strength of the association was reported using an adjusted hazard ratio (AHR) and a 95% confidence interval (CI). Finally, the Cox Snell residual test was used to check the goodness of fit.

Results: For the entire cohort, the unfavorable treatment outcome was 23.68% (19.29, 28.09). Hospitalization for care (AHR = 2.07; 95% CI = 1.21, 3.63), male sex (AHR = 1.85; 95% CI = 1.002, 3.42), attending tertiary education (AHR = 0.31; 95% CI = 0.11, 0.91), and those with low hemoglobin (AHR = 2.89; 95% CI = 1.55, 5.38) were predictors for unfavorable treatment outcome.

Conclusion: The unfavorable treatment outcome was higher compared with the national goal of END-TB by 2020. Hospitalizations for care, male sex, and low hemoglobin level increased the hazard of the unfavorable treatment outcome. On the other hand, attending territory education decreased the hazard of the unfavorable treatment outcome.

Keywords: multidrug-resistant tuberculosis, unfavorable treatment outcome, Southern Ethiopia

Correspondence: Temesgen Yihunie Akalu
Department of Epidemiology and Biostatistics, Institute of Public Health, College of Medicine and Health Sciences, University of Gondar, Po Box 196, Gondar, Ethiopia
Tel +251 929390709
Email temesgenyihunie@gmail.com

Background

Multidrug-resistant tuberculosis, defined as tuberculosis (TB) resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs. It results from either primary infection or may develop in the course of a patient's treatment.[1] The treatment outcome of MDR-TB could be cured, completed, treatment failure, lost to follow-up (LTFU), died, and extensively drug-resistant tuberculosis (XDR-TB).

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Treatment failure, death, and LTFU were considered unfavorable treatment outcomes.[2]

According to the 2017 global report, 558,000 people developed active TB. Of these, 3.6% of new cases and 17% of previously treated cases developed MDR-TB. Nearly half of the global MDR/RR-TB cases were from the three countries: India (24%), China (13%), and the Russian Federation (10%).[1] Ethiopia is one of the 30 high TB and MDR-TB burden countries. It has an annual incident of 5500 MDR/RR-TB cases in 2017. Of these, an estimated 2.7% and 14% of MDR/RR-TB cases were new and previously treated, respectively.[3] In Ethiopia, the treatment success rate of MDR/RR-TB cases was 75% in 2015. However, the national TB strategic plan towards achieving the END-TB 90–90-90 targets set for 2020 is to reduce the unfavorable treatment outcome to <10%.[1,4]

The unfavorable treatment outcome would result in transmitting a drug-resistant form of TB to the community, which increases the burden of TB. Also, it increases the risk of acquiring additional resistance, cost of TB treatment, and loss of productivity.[5] The presence of medical complications, drug side effects, human immunodeficiency virus (HIV) co-infection, underweight, presence of anemia, being a farmer, older age, treatment delay, male gender, abuse of alcohol, and smear positivity at diagnosis were significantly affect the unfavorable treatment outcome among MDR-TB patients.[6–15] Non-governmental organizations and the Federal Ministry of Health did in collaboration to improve a good treatment outcome. However, the end TB 90–90-90 target is still not achieved. Hence, the current study was aimed at determining the unfavorable treatment outcome and its predictors in Southern Ethiopia.

Subjects and Methods

Study Design and Setting

A retrospective follow-up study design was conducted between September 2014 and September 2019. Multidrug-resistant TB treatment was started at Saint Peter TB Specialized Hospital by the end of 2009. Then the service was expanded to selected regional referral hospitals. Eight public Hospitals are providing MDR-TB treatment in Southern nation: Arbaminch, Yirgalem, Hosanna, Butajira, Mizan Tepi, Jinka, Dilla, and Sawla Hospitals. About 427 MDR-TB patients were enrolled from the inauguration. Of all, more than 95% were enrolled in Yirgalem General Hospital, Wachamo University Queen Elleni Mohamed Memorial Referral Hospital, Butajira General Hospital, and Dilla University Specialized Referral Hospital.

Yirgalem General Hospital and Wachamo University Queen Elleni Mohamed Memorial Referral Hospital initiated treatment for MDR-TB at the end of 2013. Then Butajira General Hospital and Dilla University Specialized Referral Hospital initiated MDR-TB treatment in 2017 and 2018, respectively.

Population and Sample

All MDR-TB patients who initiated treatment at the four treatment initiating centers (TICs) found in Southern Ethiopia were the source population. All MDR-TB patients who were found in the four TICs and enrolled between September 2014 and September 2019 were the study population. All MDR-TB patients enrolled in the Southern nation and nationality peoples' region (SNNPR) between September 2014 and September 2019 were included in the study. Patients with an incomplete date of entry, exit, and treatment outcome were excluded. The sample size was estimated using Stata 14.1. The following assumptions; 80% Power, 5% significant level, effect size (Hazzard ratio), and 10% lost to follow-up were used (Table 1).

Variables of the Study

The dependent variable, unfavorable treatment outcome, was defined as a patient who is died, lost to follow-up, and/or treatment failure during the treatment course. Time to unfavorable treatment outcome: measured in months from the start of MDR-TB treatment to the occurrence of the unfavorable treatment outcome. Independent variables including socio-demographic characteristics: TIC, baseline age, sex, residence, occupation, marital status, and educational status, behavioral characteristics: baseline alcohol drinking, smoking, and chat chewing history, clinical characteristics: duration of illness before diagnosis, treatment delay, body mass index (BMI), previous TB treatment, diagnosis methods, site of MDR-TB, HIV status, other comorbidities, baseline sputum smear/culture grade, presence of CXR finding, baseline hemoglobin, creatinine, alanine transaminase (ALT), aspartate transaminase (AST), serum potassium (K), thyroid-stimulating hormone (TSH), treatment regimen, adverse drug reaction, types of drug resistance, treatment support, and adherence.

Table 1 Estimated Sample Size for Treatment Outcomes and Its Predictors at TIC in Southern Ethiopia, 2014 to 2019

Outcome	Proportions	Withdrawal Probability	Power	Final Sample Size
Unfavorable outcome	0.214	0.1	80%	374
Predictors	**Assumptions** Power=80% 1:1 (ratio), wdprob=5% Π =0.5, p = 0.26, Withdrawal = 10%	**Proportion**	**CHR**	**Final Sample**
Being farmer	80%	1:1	2.7	150
Low hemoglobin	80%	1:1	2.6	162

Good adherence: was defined as a patient taking the drug according to instructions given by the providers and an estimated adherence level of ≥ 85%. A major adverse drug event: was defined as when a patient developed at least one (nephrotoxicity, hepatotoxicity, hypokalemia, hypothyroidism, and hematologic abnormalities). Hepatotoxicity: was defined as an elevation of serum transaminases >3 times the normal upper limit with symptoms or elevation of serum bilirubin >2 times the normal upper limit with symptoms or elevation of serum transaminases or serum bilirubin >5 times of the normal upper limit with or without symptoms. Anemia: was defined as when hemoglobin level was <11g/dl. Hypokalemia: was defined as when a patient had at least one serum potassium value < 3.5 mmol/l. Hypothyroidism: was defined as when a patient had at least one measure of serum thyroid-stimulating hormone greater than 5.0 mIU/L. Nephrotoxicity: was defined as when a patient had an elevation of at least one serum creatinine value greater than 133 mmol/l. Censored: was defined as when a patient does not develop an event (cured, completed, and transfer out). Cured: was defined as when a patient completed treatment according to the national recommendation without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. Death: was defined when a patient dies for any reason during TB treatment. Duration of illness before diagnosis: was defined from the date of a patient having symptoms (duration of complaint in association with TB) plus a duration of a patient diagnosed with MDR after seeking medical care (the days between the date of seeking care and MDR-TB confirmation). Lost to follow up: was defined when a patient started anti-TB treatment and interrupted for 2 or more consecutive months. Previous TB treatment: was defined as a patient who was treated for TB at least for one month. Sputum smear grade: Negative (no AFB/100 high-power fields [HPF]), scanty (1–9 AFB/100 HPF), 1+ (10–99 AFB/100 HPF), 2+ (1–9 AFB/HPF), and 3+ (>9 AFB/HPF). Treatment completed: Treatment completed according to national recommendation without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. Treatment delay: was defined as the median time from the duration in days between the date of MDR-TB confirmation and the date of treatment initiation. Treatment failure: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of lack of conversion by the end of the intensive phase, or bacteriological reversion in the continuation phase after conversion to negative after intensive phase, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions.

Sputum culture grade: No growth (none), record actual number (1–9 colonies), 1+ (10–100 colonies), 2+ (>100–-200 colonies), 3+ (>200 colonies), positive for other mycobacteria (other mycobacterial growth), contaminated (contaminated), and positive for MTB and contamination. Successful treatment outcome: was defined when a patient became cured or completed the treatment.

Data Collection Tools and Procedures

Data was collected using a structured checklist from patient medical charts and registration books. One supervisor (senior BSc nurse) and two data collectors (BSc nurses) were enrolled for each selected TIC in the data

collection process. Patient information including socio-demographic characteristics such as age, sex, residence, education, and occupation; behavioral characteristics such as baseline smoking, alcohol drinking and chat chewing history; clinical variables such as duration of illness before diagnosis, treatment delay, BMI, treatment outcomes, duration of therapy, previous TB treatment history, way of diagnosis, site of MDR, smear and culture results, HIV status, other comorbidities, CXR finding, adverse drug event, drug regimen, types of DR, and laboratory investigations; as well as adherence, treatment support and mode of care were obtained from MDR-TB medical records and the registration book. Body mass index is measured by using patient weight (kg) and height (M), then dividing weight by height square. Hemoglobin is measured as total hemoglobin and the result is expressed in grams (gm) per deciliter (dl) of whole blood, a deciliter being 100 milliliters.

Data Quality Control

Appropriate training and supervision of data collectors were given to ensure the data quality. A two days training on how to extract data from patient medical charts and registration books was given to data collectors and supervisors. The principal investigator made the overall supervision. The pre-test was done on 5% of the sample in Yirgalem General Hospital and Wachamo University Queen Elleni Mohamed Memorial Referral Hospital.

Data Processing and Analysis

Data was entered into Epi-data version 3.1 and exported to Stata 14 for analysis. Data cleaning, coding, and recoding were made. Descriptive findings were summarized using counts and percentages. The presence of influential outliers, multicollinearity, and the proportional hazard assumption were checked. The median time with Interquartile range (IQR) was used to present the continuous variables. Life table was constructed to estimate the probability of unfavorable treatment outcome at different time intervals. Kaplan–Meier's failure curve was used to compare the different groups. Besides, a Log rank test was used to test the presence of differences in the incidence of unfavorable treatment outcome among the groups. A bivariate Cox regression model was used at p-value <0.2 and variables significant in the bivariate analysis were entered in the final multivariable Cox regression model.

The Cox proportional hazard assumption was assessed graphically using log-log survival curves and Schoenfeld residual statistical tests. The goodness of fit of the final model was checked by Nelson Aalen's cumulative hazard function against the Cox-Snell residual. The finding was presented using the adjusted hazard ratio (AHR) and the 95% confidence interval (CI).

Results

Socio-Demographic Characteristics of MDR-TB Patients

A total of 381 patients were registered from September 2014 to September 2019. Among these, 18 (4.72%) were excluded from the study due to incomplete records on the date of treatment outcome and unknown outcome status. Thus, a total of 363 (95.28%) participants were included in the study. Of all, 220 (60.61%) participants were male. About one-third (36.91%) participants were from the Sidama region. About a quarter (24.53%) participants were students (Table 2).

Behavioral Characteristics of MDR-TB Patients

Three-hundred-fifty-three (97.25%) patients had no baseline smoking history. Nearly 13% patients had a history of alcohol drinking (Table 3).

Clinical Characteristics of MDR-TB Patients

The median duration of illness among MDR-TB patients before the diagnosis was 91 (51–161) days. Almost all, 98.35% of MDR-TB patients had pulmonary tuberculosis. Baseline sputum culture and smear were positive for 69.97% and 71.35% patients, respectively. The majority, 93.9% of patients were diagnosed by gene-expert. Most of the patients, 80.44% were put on a long-term drug regimen. About a quarter, 27 (7.44%) of MDR-TB patients were reactive for HIV. Nineteen (5.33%) of MDR-TB patients had other co-morbidities. About 15.43% of MDR-TB patients had developed adverse drug events. Of these, had a hematologic disorder (41.07%), nephrotoxicity (26.78%), hypokalemia (23.21%), hepatotoxicity (7.14%), and hypokalemia (1.78%) (Table 4).

Treatment Outcome of MDR-TB Patients

The overall median time was 19.23 (IQR: 9.53 to 20.73) months with a total of 5511.39 person-months observation.

Table 2 Sociodemographic Characteristics of Patients with Multidrug-Resistance Tuberculosis in Southern Ethiopia, from 2014 to 2019

Variable	Frequency	Percentages
Gender		
Female	143	39.39
Male	220	60.61
Residence		
Sidama	134	36.91
Guraghe	61	16.8
Hadiya	48	13.22
Gedeo	39	10.74
Silte	32	8.82
Hawassa	20	5.51
Wolayta	13	3.58
Kambata	8	2.2
Others*	8	2.2
Marital status		
Single	168	46.28
Married	167	46.01
Separated	6	1.65
Widowed	15	4.13
Divorced	7	1.93
Occupational status		
Government	25	6.89
Self-employee	98	27
Farmer	75	20.66
Unemployed	65	17.91
Student	89	24.52
Educational status		
Illiterate	73	20.11
Primary	136	37.47
Secondary	110	30.3
Tertiary	44	12.12

Note: Others* Oromia and Halaba.

Table 3 Behavioral Characteristics of Patients with Multidrug-Resistant in Southern Ethiopia, from 2014 to 2019

Variable	Frequency	Percentages
Baseline smoking history		
Yes	10	2.75
No	353	97.25
Baseline alcohol history		
Yes	47	12.95
No	316	87.05
Baseline chat chewer		
Yes	57	15.7
No	306	84.3

Table 4 Clinical Characteristics of Patients with Multidrug-Resistance Tuberculosis in Southern Ethiopia, from 2014 to 2019

Variable	Frequency	Percentages
Previous TB treatment		
No	87	23.97
Yes	276	76.03
Site of disease		
Pulmonary	357	98.35
Extrapulmonary	6	1.65
Method of diagnosis		
Gene x-pert	339	93.39
Line probe assay	17	4.68
Culture	6	1.65
Clinical	1	0.28
HIV status		
Reactive	27	7.44
Non-reactive	336	92.56
Any other comorbidities		
None recorded	344	94.77
Yes	19	5.33
Congestive heart failure (CHF) and Corpulmonale	11	57.89
Diabetic mellitus (DM)	3	15.79
Deep venus thrombosis (DVT)	3	15.79
Chronic kidney disease (CKD)	2	10.52
Baseline sputum smear grade		
Negative	85	23.42
Positive	259	71.35
Not recorded	19	5.23
Baseline sputum culture grade		
Negative	68	18.73
Positive	254	69.97
Not recorded	41	11.29
Chest x-ray finding		
Not recorded	92	25.34
Infiltration	86	23.69
Cavitary lesion	56	15.43
Chronic fibrotic lesions	40	11.02
Consolidation	31	8.54
Cavitation and infiltration	29	7.99
Others**	29	7.99
Baseline hemoglobin		
Low	188	53.41
Normal	164	46.59
Baseline total white blood cell count		
Low count	7	1.99
Normal count	202	57.39

(*Continued*)

Table 4 (Continued).

Variable	Frequency	Percentages
High count	143	40.63
Baseline creatinine		
Normal	319	95.8
Elevated	14	4.2
Baseline aspartate transaminase		
Normal	284	81.84
Elevated	63	18.16
Baseline alanine transaminase		
Normal	299	86.17
Elevated	48	13.83
Baseline potassium		
Low	54	18.18
Normal	243	81.82
Baseline thyroid-stimulating hormone		
Normal	223	78.52
Elevated	61	21.48
Drug regimen		
Short-term	71	19.56
Long-term	292	80.44
Major adverse drug event		
Not recorded	307	84.57
Yes	56	15.43
Hematologic disorder	23	41.07
Nephrotoxicity	15	26.78
Hypokalemia	13	23.21
Hepatotoxicity	4	7.14
Hypothyroidism	1	1.78
Other adverse drug events		
Not recorded	197	54.27
Yes	166	45.73
Gastrointestinal	74	44.58
Arthralgia	56	33.73
Psychiatric disorder	10	6.02
Peripheral neuropathy	8	4.82
Ototoxicity	8	4.82
Visual disturbance	6	3.61
Dermatologic disorder	2	1.2
CNS disorder	2	1.2
Type of resistance		
Rifapcline resistance (RR)	350	96.69
Multi-drug resistance (MDR)	12	3.31
Mode of care		
Ambulatory	274	75.48
Hospitalized	89	24.52
Treatment support		
Yes	301	82.92
No	62	17.08
Adherence		
Good	306	84.3
Poor	57	15.7

(*Continued*)

Table 4 (Continued).

Notes: Others** was either normal x-ray or pleural effusion or lung collapse or hydro-pneumothorax or military pattern or pleural emphysema.
Abbreviation: IQR*, interquartile range.

Two-hundred-fifty-one (69.15%) of MDR-TB patients had favorable treatment outcome. The remaining 23.68% (19.29%, 28.09%) of MDR-TB patients had unfavorable treatment outcome (Figure 1).

Based on the treatment initiation centers about half (50.14%) of MDR-TB patients were from Yirgalem general hospital (Figure 2).

Survival Status of MDR-TB Patients

The overall cumulative failure of the unfavorable treatment outcome was 8%, 19%, and 27% at the end of 6, 12, and 24 months, respectively (Figure 3).

Hospitalized MDR-TB patients had a higher hazard of unfavorable treatment outcome compared with ambulatory care patients (Figure 4).

Log Rank Test for the Equality of Survival Function

The Log rank test indicates that there is statistically a significant difference in survival experience among groups of smokers at baseline, alcohol drinkers at the baseline, the presence of co-morbidity, other adverse drug events, and model of care at a 5% level of significance (Table 5).

Model Diagnostics and Goodness of Fit of the Final Model

The Schoenfeld residual global test showed that the proportional hazard assumption was met (P-value = 0.098). The hazard function follows the 45 degree line very closely except for large values of the time. It is very common for models with censored data to have some wiggling at large values of the time and it is not something which

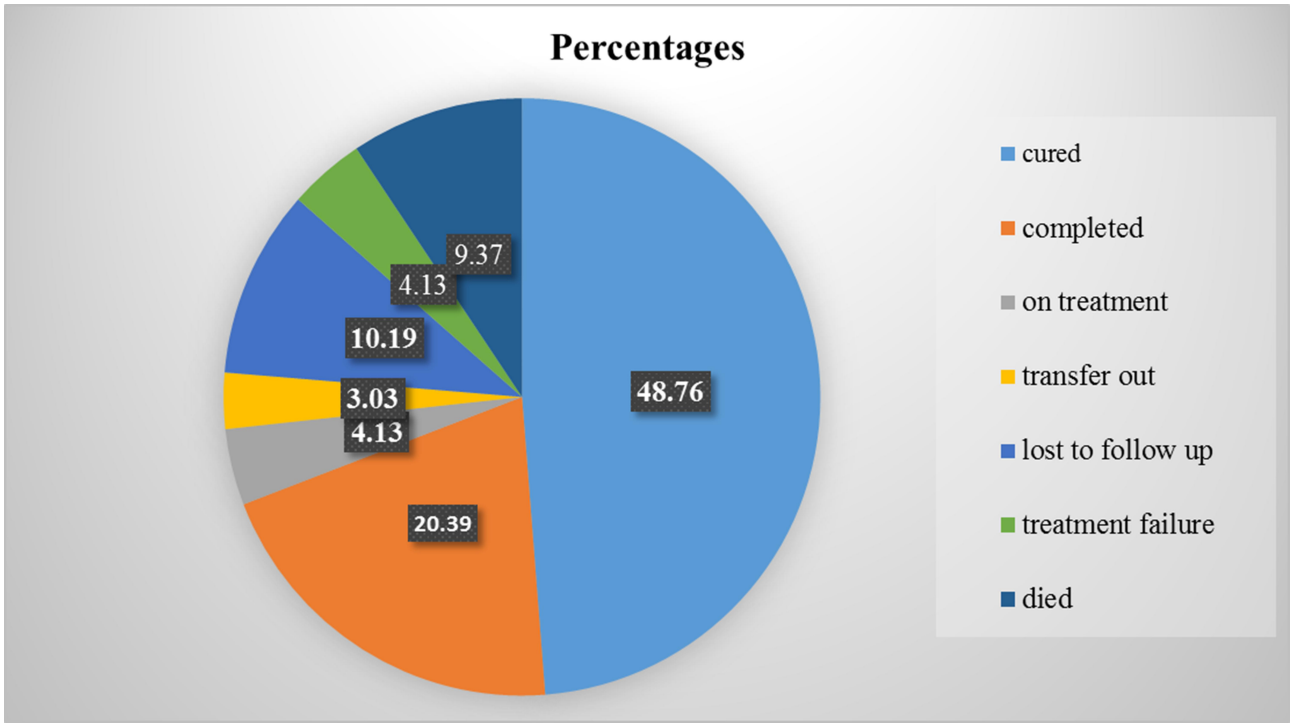

Figure 1 Treatment outcome of patients with multidrug-resistant tuberculosis in Southern Ethiopia, from 2014 to 2019.

should cause much concern. Overall, we could conclude that the final model fits the data very well (Figure 5).

Factors Affecting Unfavorable Treatment Outcome Among MDR-TB Patients

Sex, educational status, baseline smoking history, baseline alcohol drinking history, treatment delay, HIV status, co-morbidity, baseline sputum culture, baseline hemoglobin, baseline creatinine, baseline ALT, baseline potassium, major adverse drug event, other adverse drug events, mode of care and treatment support were fitted in multivariable analysis for unfavorable treatment outcome. Being male, attending tertiary education, low hemoglobin, and hospitalization for MDR-TB were predictors of the unfavorable treatment outcome.

The hazard of developing unfavorable treatment outcome among male MDR-TB patients was 85% higher than

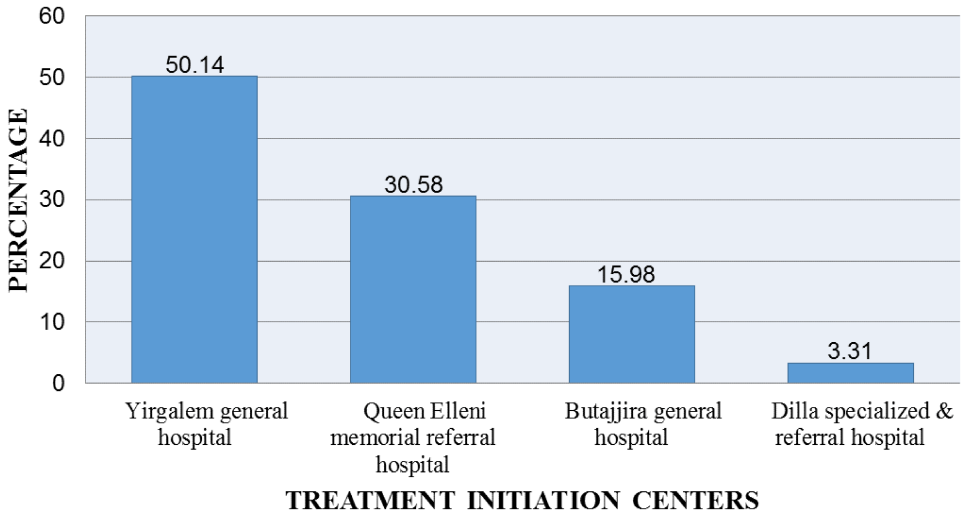

Figure 2 The percentage of multidrug-resistance tuberculosis patients in treatment initiation centers of Southern Ethiopia, from 2014 to 2019.

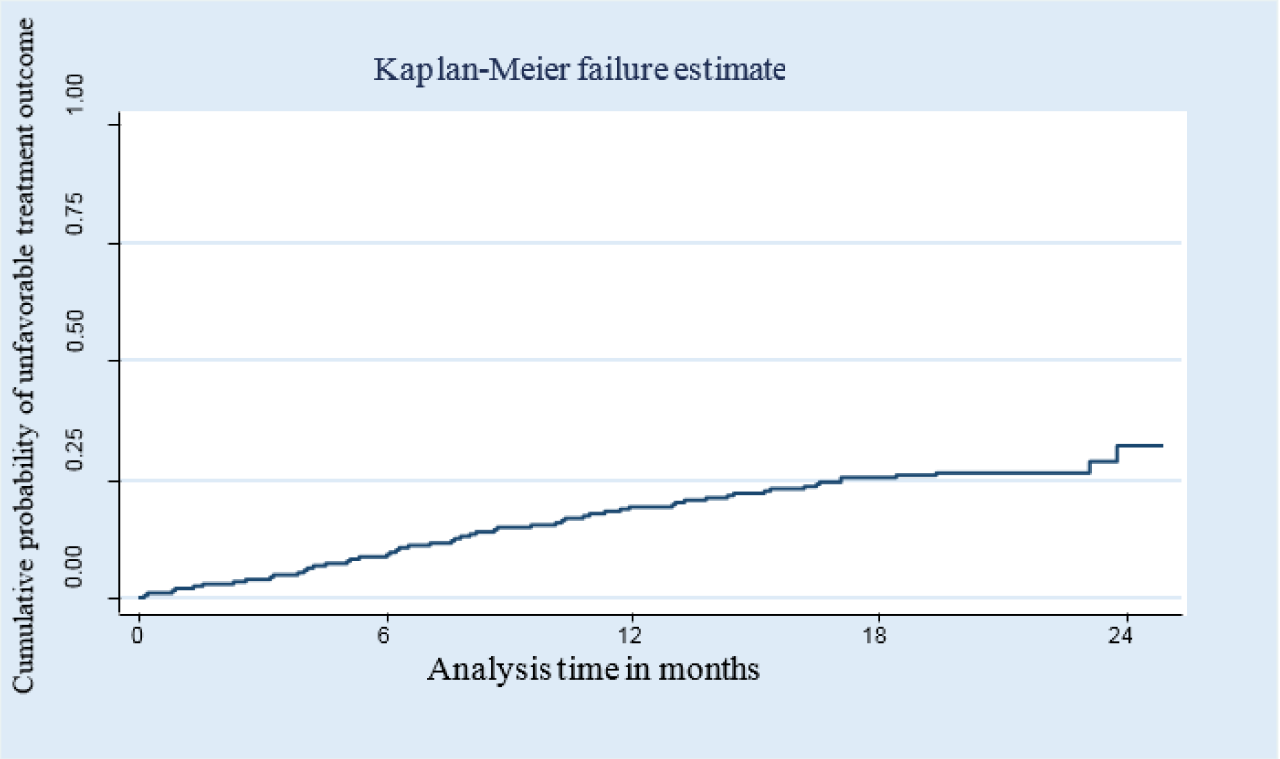

Figure 3 The plot of the overall estimate of the Kaplan–Meier failure function of MDR-TB patients in Southern Ethiopia, from 2014 to 2019.

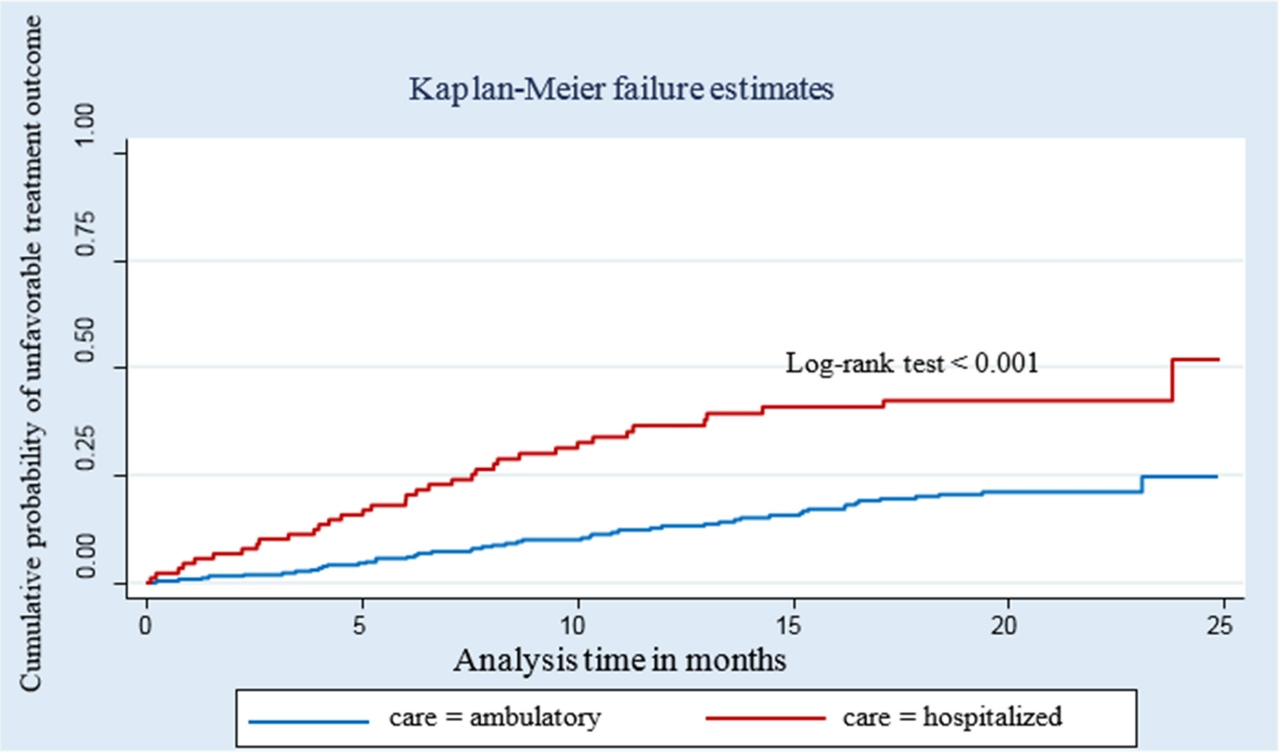

Figure 4 The plot of Kaplan–Meier failure function of MDR-TB patients based on the model of care in Southern Ethiopia, from 2014 to 2019.

Table 5 Results of the Log Rank Test for the Categorical Variables of Patients with Multidrug-Resistance Tuberculosis in Southern Ethiopia, from 2014 to 2019

Covariates	Chi2	P-value
Sex	3.75	0.0529
Baseline smoking history	5.31	0.0212
Baseline alcoholic history	7.24	0.0071
Baseline chat chewer	0.07	0.7845
Previous TB treatment	1.49	0.2219
Site of disease	1.56	0.2117
HIV status	2.38	0.1232
Co-morbidity	16.13	0.0001
Drug regimen	0.12	0.7286
Major adverse drug event	3.76	0.0524
Other adverse drug events	4.84	0.0278
Drug resistance	2.16	0.1418
Mode of care	21.53	0.0000
Treatment support	2.17	0.1406

female MDR-TB patients. Attending tertiary education decreased the hazard of unfavorable treatment outcome by 69% compared to patients' attending primary education. The hazard of an unfavorable treatment outcome among MDR-TB patients with low baseline hemoglobin was 2.89 times that of normal baseline hemoglobin. The hazard of developing unfavorable treatment outcome among hospitalized patients was 2.07 times that of ambulatory patients (Table 6).

Discussion

The objective of this study was to assess unfavorable treatment outcome and its predictors among patients with multidrug-resistant tuberculosis. In this study, 86 (23.69%) of MDR-TB patients had unfavorable treatment outcome. This finding is in line with a study conducted from Shanghai, Pakistan, India, Tanzania, Gabon, and a systematic and meta-analysis study.[1,16–21] Besides, it is in agreement with the studies done in different regions of Ethiopia including the Amhara region, Southern region, and Oromia region.[8,10,22]

Unfavorable treatment outcome is lower compared with studies done in Ukraine, Armenia, Uzbekistan, China, Western India, and Morocco.[7,9,23–25] This could be in the current study there is an improvement of care on MDR-TB treatment. Moreover, the introduction of

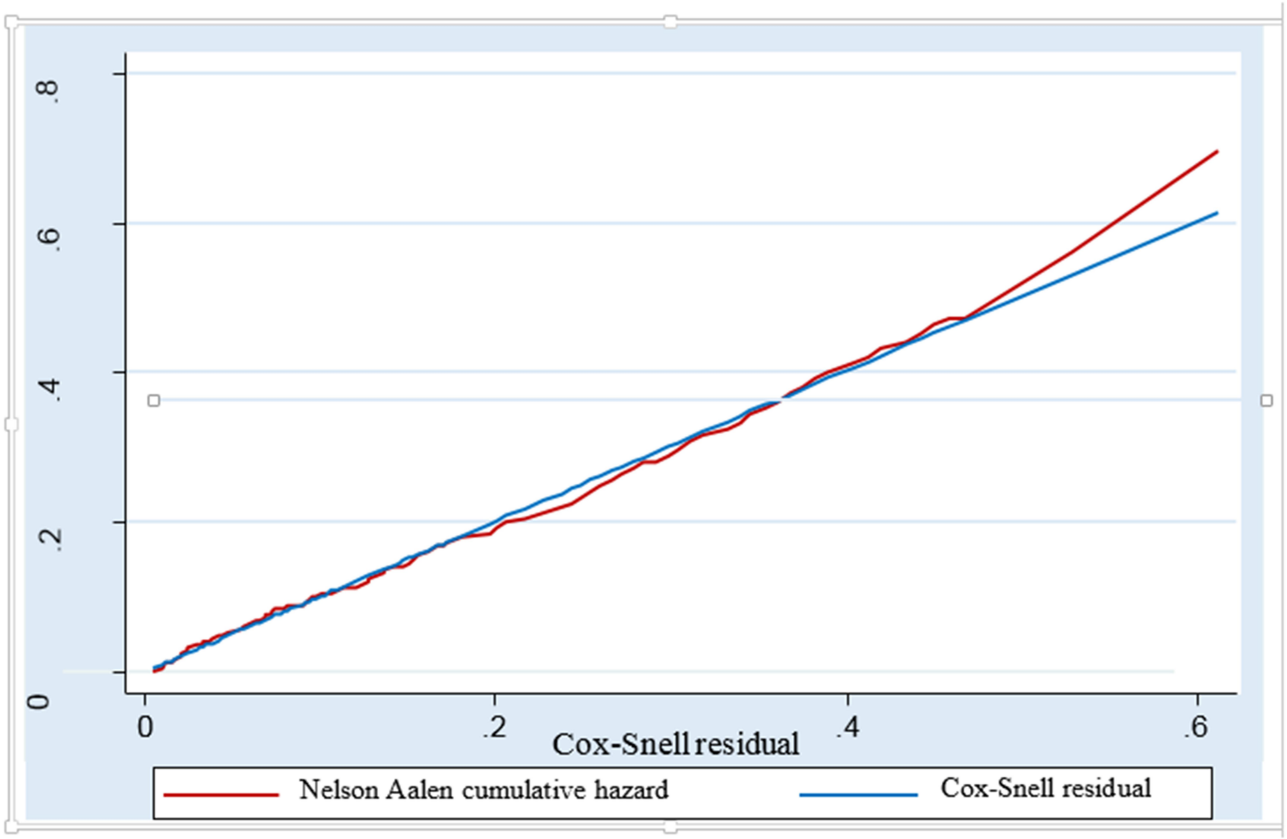

Figure 5 Cumulative hazard plot of the Cox-Snell residuals of the proportional hazard against the Nelson-Aalen cumulative hazard function.

Table 6 Bivariate and Multivariable Cox Proportional Hazards Regression Analysis of Time to Unfavorable Treatment Outcome in Southern Ethiopia, from 2014 to 2019

Variables	Status		CHR 95% CI	AHR 95% CI
	Event	Censored		
Gender				
Female	25	118	1	1
Male	61	159	1.58 (0.99, 2.51)	1.85 (1.002, 3.42)
Educational status				
Illiterate	20	53	0.94 (0.54, 1.63)	0.64 (0.32, 1.29)
Primary	36	100	1	1
Secondary	26	84	0.86 (0.52, 1.43)	0.68 (0.38, 1.24)
Tertiary	4	40	0.31 (0.11, 0.88)	0.31 (0.11, 0.91)
Baseline smoking history				
Yes	5	5	2.77 (1.12, 6.85)	0.98 (0.33, 2.94)
No	81	272	1	1
Baseline alcohol history				
Yes	19	28	1.98 (1.19, 3.30)	1.73 (0.89, 3.36)
No	67	249	1	1
Treatment delay				
Short	43	162	1	1
Long	43	115	1.35 (0.88, 2.06)	1.38 (0.81, 2.34)
HIV status				
Reactive	9	18	1.71 (0.86, 3.41)	2.22 (0.99, 4.92)
Non-reactive	77	259	1	1
Co-morbidity				
No	76	268	1	1
Yes	10	9	3.56 (1.83, 6.91)	1.48 [0.54, 4.08]
Baseline sputum culture				
Negative	19	66	1	1
Positive	63	196	1.16 (0.67, 2.01)	1.50 (0.77, 2.91)
Not recorded	4	15	0.51 (0.19, 1.39)	0.72 (0.22, 2.35)
Baseline hemoglobin				
Low	66	122	3.11 (1.89, 5.14)	2.89 (1.55, 5.38)
Normal	20	144	1	1
Baseline creatinine				
Normal	73	246	1	1
Elevated	6	8	2.65 (1.15, 6.10)	1.33 (0.46, 3.84)
Baseline ALT				
Normal	67	232	1	1
Elevated	16	32	1.69 (0.98, 2.92)	1.48 (0.80, 2.72)
Baseline K				
Normal	58	185	1	1
Low	19	35	1.57 (0.94, 2.64)	1.12 (0.60, 2.07)
Major adverse drug event				
No	67	240	1	1
Yes	19	37	1.65 (0.99, 2.74)	0.82 (0.43, 1.58)

(*Continued*)

Table 6 (Continued).

Variables	Status		CHR 95% CI	AHR 95% CI
	Event	Censored		
Adverse drug event				
No	52	145	1	1
Yes	34	132	0.62 (0.39, 0.95)	0.60 (0.36, 1.02)
Mode of care				
Ambulatory	50	224	1	1
Hospitalized	36	53	2.65 (1.73, 4.07)	2.07 (1.21, 3.53)
Treatment support				
Yes	67	234	1	1
No	19	43	1.46 (0.88, 2.44)	1.03 (0.55, 1.91)

a short-term drug regimen will cause a lower unfavorable treatment outcome in the current study. Furthermore, the addition of Bedaqulline and linezolid which are powerful ant-MDR-TB drugs in the recent study could cause the lower incidence of unfavorable treatment outcome.

On the other hand, this finding was still higher compared with our national target of 2020 which showed only < 10% should have unfavorable treatment outcome.[5] The increasing number of unfavorable treatment outcome could put the community in danger for the transmission of resistant forms of tuberculosis in addition to poverty. The median time to unfavorable treatment outcome was 7.6 months which was similar to the study done in the Oromia region.[22]

In the current study, hospitalization for care increases the hazards of unfavorable treatment outcome. This finding is in line with a study done in Uzbekistan that showed that more favorable treatment outcomes occurred for those on ambulatory care than on hospitalized care.[26] This could be because hospitalized patients were more debilitated, have concomitant infections, and could develop adverse drug events from the MDR-TB treatment or other treatment. Hence, this finding suggested that it is better to provide better attention to hospitalized patients.

In this study being male increased the hazard of developing unfavorable treatment outcome. This finding was in agreement with a study done in India.[19] This could be due to the working behavior of males that may compromise drug compliance and nutrition. As a result, it is highly recommended to give enhanced counseling and provide strict follow-up by health professionals for better treatment outcomes.

Those attending tertiary education decreased the hazard of unfavorable treatment outcome. This finding is similar to the finding in Western India.[7] This could be due to the increased level of education that would cause better nutrition, information to initiate treatment early, and good adherence to treatment. Hence, it is valuable to educate the community to reduce unfavorable treatment outcome.

Low hemoglobin level was a predictor of unfavorable treatment outcome. This finding is comparable to the study done in Northwest Ethiopia.[10] This could be due to poor nutrition, chronicity of illness, and other concomitant infections. Therefore, clinicians need to give better attention to patients with low hemoglobin levels to minimize the burden of unfavorable treatment outcome.

As per our knowledge, it is the first study that was conducted on predictors of unfavorable treatment outcome in Southern Ethiopia. Secondly, it incorporated new variables like duration of illness before diagnosis and drug regimen (short-term or long-term). However, the study has some limitations. Firstly; it was entirely secondary and data on important variables were missing. Secondly, patient-related factors, health system-related factors, and drug-related factors are needed to further analyze the determinants of unfavorable treatment outcome and to reach solid national decisions for a successful treatment outcomes.

This study will be helpful to policy-makers, planners, and decision-makers to provide timely evidence. Besides, the study will be valuable to clinicians in their day to day activities. Finally, the study will be important to researchers as a baseline information.

Conclusion

This study showed that the unfavorable treatment outcome was higher compared with the national goal of END-TB by 2020. Being male, higher education, low hemoglobin, and hospitalization were significant predictors with unfavorable treatment outcome. Hence, it is appropriate to give more attention to patients with low hemoglobin levels and hospitalized patients.

Abbreviation

ART, Antiretroviral Therapy; BMI, Body Mass Index; CD4, A cluster of Differentiation 4; CI, Confidence Interval; CP, Continuation Phase; CXR, Chest X-ray; DM, Diabetes Mellitus; DOT, Directly Observed Therapy; DR, Drug-Resistance; DST, Drug Susceptibility Test; GHC, Global Health Commute; HR, Hazard Ratio; HIV, Human Immunodeficiency Virus; IP, Intensive Phase; IQR, Interquartile Range; IRB, Institutional Review Board; KM, Kaplan–Meier; LTFU, Loss To Follow Up; MDR, Multidrug-Resistant; RR, Rifampicin Resistance; SCC, Sputum Culture Conversion; SHR, Sub Hazard Ratio; SLD, Second Line Drug; SNNPR, Southern Nation, Nationalities, and People's Region; TIC, Treatment Initiation Centers; TB, Tuberculosis; TF, Treatment Failure; TSH, Thyroid Stimulating Hormone; USA, United States of America; WHO, World Health Organization; XDR, Extensively Drug-Resistance.

Data Sharing Statement

Data will be made available from the primary author upon a reasonable request.

Ethical Approval and Consent to Participate

Ethical clearance and permission were obtained from the University of Gondar institutional review board (IRB) with Reference number. SOM/1734/2019 and permission was secured from SNNPR health departments. Informed consent was not taken from the study participants directly as it is entirely secondary but permission was requested for each hospital for their patients. Besides, the information obtained from the patients was waived by the University of Gondar because of inability to collect information directly from the participants. The checklist was de-identified and kept securely in locked cabinets and the database was password protected to keep the confidentiality of the patients. The study was conducted in accordance with the Declaration of Helsinki.

Consent for Publication

Not applicable.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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