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Magnitude, predictors, and trends of multidrug-resistant tuberculosis among tuberculosis patients at Debre Markos, Northwest, Ethiopia: a five-year retrospective study

Aytenew Atnaf [1]*, Mekuanenit Kibret[2], Bekele Tesfaye[3] and Desalegn Abebaw[1]

[1]Department of Medical Laboratory Sciences, Debre Markos University, PO. Box 269, Debre Markos, Ethiopia; [2]School of Medicine, Debre Markos University, PO. Box 269, Debre Markos, Ethiopia; [3]Department of Nursing, Debre Markos University, PO. Box 269, Debre Markos, Ethiopia

*Corresponding author. E-mail: atnafnew5@gmail.com

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Background: The emergence of multidrug-resistant tuberculosis (MDR-TB) is a threat to the people of resource-limited countries, such as Ethiopia. This study aimed to assess the magnitude, predictors and trends of multidrug-resistant tuberculosis among patients with pulmonary tuberculosis (TB) at Debre Markos Comprehensive and Specialized Hospital (DMCSH), Northwest Ethiopia.

Materials and Methods: A retrospective cross-sectional study was conducted among patients with TB treated at the directly observed treatment short course (DOTS) clinic at DMCSH from 1 June 2016 to 1 June 2020. Data from 1509 patients with TB registered in the clinic were retrieved from medical records. Statistical analysis was performed using SPSS v.24. The frequency of variables is presented via tables and figures. Logistic regression was fitted to predictors of MDR-TB, and a P value < 0.05 was considered statistically significant.

Results: Overall, data from 1509 patients with pulmonary TB were retrieved during the study. The overall prevalence of MDR-TB was 4.1%. Variables such as sex, human immunodeficiency virus (HIV) status, lesion on chest X-ray, and a history of anti-TB treatment were significantly associated with MDR-TB. The trend of MDR-TB decreased by 40% in 2017, 29% in 2018, and 10% in 2019, but increased by 21% in 2020.

Conclusions and recommendations: The prevalence of MDR-TB among patients with pulmonary TB was comparable to the national rate. Key risk factors for MDR-TB included male sex, prior TB treatment, HIV infection, and chest X-ray abnormalities. The increasing trend in 2020 highlights the need for strengthened TB treatment adherence counselling and further prospective studies to explore additional predictors of MDR-TB.

Background

Multidrug-resistant tuberculosis (MDR-TB) is a type of tuberculosis caused by *Mycobacterium*, which are resistant to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs.[1] Resistance to isoniazid is due to mutations at one of two main sites in either the *katG* or *inhA* genes,[2] whereas resistance to rifampicin is due to mutations in the *rpoB* gene.[3]

The World Health Organization (WHO) 'End TB' strategy set milestones in 2015 to reduce the number of deaths and incidence rate of TB cases by 35% and 20%, respectively, in the year 2020.[4] However, it is impossible to meet the target.[5]

The emergence of drug-resistant tuberculosis has become a serious public health threat in several countries.[6] The largest single risk factor for the presence of MDR-TB is attributable to previous drug treatment.[7]

The largest survey conducted by the WHO in >80 countries from 2002 to 2007 estimated that the spread of MDR-TB may increase at an alarming rate from 1.6% to 3.1% in new cases and 11.7% to 19.3% in previously treated TB cases, despite the implementation of the directly observed therapy strategy (DOTS) since the 1990s.[8,9]

According to the 2019 WHO report, an estimated 3.4% of new cases and 18% of previously treated cases had

multidrug-resistant (MDR)/rifampicin-resistant (RR)-TB, with an incidence of 484 in 1000 people.[10] The prevalence of MDR tuberculosis was 2.3% in Australia[11] and 2.1% in new cases in sub-Saharan Africa.[12] The prevalence was higher in children (8.8%), and the burden was more pronounced in HIV-infected children.[13]

The development of multidrug-resistant tuberculosis (MDR-TB) is influenced by clinical, biological and microbiological factors. These arise from factors such as patient nonadherence to treatment, physician errors in managing therapy, the complexity and poor vascularization of granulomatous lesions, the intrinsic drug resistance of tubercle bacilli, the formation of nonreplicating, drug-tolerant bacilli within granulomas and the emergence of mutations in *Mycobacterium* genes. Among these, mutations in *Mycobacterium* genes are considered the most critical molecular mechanisms underlying resistance.[14] Another study indicated that the most significant factors for single or multiple drug-resistant tuberculosis were being male, having a history of TB and previous or current treatment for >4 weeks, having advanced disease with cavitation and having a history of imprisonment.[15]

In Ethiopia, the prevalence of MDR-TB is 7.24%: 2.18% in newly diagnosed TB patients and 21.07% in previously treated TB patients.[16] In the Amhara region, it accounts for 6.3% of cases.[17]

However, there is a paucity of information available regarding the burden, associated factors and trends of MDR-TB in the East Gojjam Zone. Therefore, this study aimed to determine the burden, associated factors and trends of MDR-TB among previously treated pulmonary patients. This study provides the burden, associated factors and trends of MDR-TB cases at DMCSH to clinicians for better management of treatment adherence and for higher officials and voluntary organizations to collaborate in prevention and control strategies.

Materials and methods

Study design, setting and period

An institution-based retrospective cross-sectional study design was conducted among 1509 patients with pulmonary tuberculosis (PTB) who were treated and registered from 1 June 2016 to 1 June 2020 at the DMCSH anti-TB clinic. The DMCSH anti-TB clinic run under the Department of Internal Medicine was established in March 2014 under the National Tuberculosis and Leprosy Programme and serves as a TB and MDR-TB treatment centre in Ethiopia. The hospital is located in Debre Markos city and is dedicated to provide comprehensive medical services and specialized care, addressing a wide array of health challenges faced by the local population. It is the only specialized hospital that has different clinics, such as an ART clinic, anti-TB clinic, diabetic clinic and so on, in the East Gojjam Zone, Ethiopia. We selected the hospital to gather data from records of patients with PTB visiting anti-TB clinic for the last 5 years from 2016 to 2020 since there are no anti-TB clinics in the area. Data were retrieved from the registration from 1–15 July 2020.

Population

Study population

The study population was formed of patients with PTB who attended an anti-TB clinic at DMCSH in the last 5 years from 1 June 2016 to 1 June 2020.

Inclusion and exclusion criteria

Inclusion

PTB patients who had complete information on their medical records and treatment chart registration in the specified study period were included in the study.

Exclusion

We excluded PTB patients <15 years old and patients with extra PTB.

Sample size determination and sampling procedures

Five years of data were retrieved retrospectively from the registration log books and patient records from 1 June 2016–2020. A total of 1585 TB patients were registered on the TB follow-up log book for the specified periods. We found 76 incomplete data points and so we excluded these from the study. The remaining 1509 TB patients' data (95.2%) were included in the study consecutively based on the order of their registries. Therefore, the total sample size was 1509.

Data collection tool and procedure and quality assurance

Ethical approval was obtained from Debre Markos University, School of Medicine, and a support letter was obtained from DMCSH before data collection. Then, permission was given by Debre DMCSH anti-TB clinic.

Data were extracted retrospectively from 1 June 2016 to 1 June 2020 by reviewing all the necessary registration formats from medical records and treatment charts related to TB results at DMCSH, an anti-TB clinic. The sociodemographic factors together with the clinical profiles of the patients were extracted from medical records and treatment charts from the hospital TB database consecutively via a predesigned checklist. The data collected were checked for completeness and cleaned on a daily basis. Seventy-six incomplete data points were excluded from the total registration, and 1509 patients' data points were obtained from 1 June 2016–2020.

Data processing and analysis

The data were entered into Epi-Data version 4.2, exported to the Statistical Package for Social Science (SPSS) version 24 and analysed. The frequencies of the outcome variables, predictor variables and/or sociodemographic factors are presented in the tables and figures. The odds ratio was calculated via binary logistic regression analysis, and a P value <0.25 was used for selecting candidate variables for multinomial logistic regression analysis. Crude odds ratio (COR) and adjusted odds ratio (AOR) were calculated with their 95% confidence interval (CI). A P value <0.05 was considered statistically significant.

Ethics approval

An ethical approval letter from the Research Ethical Review Committee of Debre Markos University, School of Medicine, with the reference letter SCM/154/02/20 was obtained. Moreover, a permission letter was obtained from the administrative bodies of DMCSH to retrieve recorded data on PTB from an anti-TB clinic. We did not directly collect data or samples from the study participants (TB patients); rather, we retrieved previously collected data stored at the hospital. Therefore, obtaining written consent was difficult from the study participants because we could not contact them. However, we used written informed consent from the study participants previously used by the DMCSH and filed the data with patient records to obtain sputum samples and receive anti-TB treatments in the DOT clinic of the DMCSH. Confidentiality was maintained by not recording the identity (name and unique medical registration number) that described the participants.

Results

Sociodemographic characteristics and clinical factors

The study found that 68% of patients with PTB were male, with a similar prevalence of multidrug-resistant TB (MDR-TB) among males [2.1% (32/1509)] and females [2.0% (30/1509)]. The majority (63%) of MDR-TB patients were aged 15–45 years, and MDR-TB was found in nearly equal proportions in urban (2.1%) and rural (2.0%) populations. Among TB patients, MDR-TB was detected in 2.7% of new cases, 10.1% of relapse cases, 8.0% of those lost to follow up, 5.7% of first treatment failures and 9.3% of retreatment failures.

MDR-TB was detected in 18.7% of HIV-positive patients and 4.4% of HIV-negative patients. Among patients with a history of close contact with MDR-TB patients, 4.9% developed MDR-TB, compared to 3.8% of those without contact history. Regarding lung conditions, MDR-TB was most prevalent in patients with pleural effusion (7.7%), followed by lung cavitation (5.6%) and consolidation (3.9%). Patients with a history of TB treatment had a higher MDR-TB prevalence (8.6%) compared to those with no previous treatment (2.7%).

In terms of treatment outcomes, among 62 MDR-TB patients, 34 were cured, 19 completed treatment, five died, one experienced treatment failure and three were lost to follow up. The treatment success rate was 85.5% (53/62), while the treatment failure rate was 14.5% (9/62) (Table 1).

Multidrug resistance pattern of PTB and its predictors

The binary logistic regression analysis revealed that variables such as sex, TB group, HIV status, lesions identified on chest X-ray and previous history of anti-TB treatment were associated with MDR-TB. All the variables in the binary logistic regression were candidate variables for multivariable logistic regression analysis since the *P* value was <0.25. The multivariable logistic regression results revealed that being male [AOR = 0.5, 95% CI (0.3, 0.9), *P* = 0.02] and having infiltration lesions identified via chest X-ray [AOR = 0.1, 95% CI (0.02, 0.9), *P* = 0.04)] were protective

Table 1. Sociodemographic characteristics and clinical factors associated with MDR-TB among patients with PTB at DMCSH from 2016 to 2020

		MDR		
Variables	Categories	Positives *N* (%)	Negatives *N* (%)	Total *N* (%)
Sex	Male	32 (3.1)	994 (96.9)	1026 (68.0)
	Female	30 (6.2)	453 (93.8)	483 (32.0)
Age	15–30	18 (4.7)	369 (95.3)	387 (25.6)
	31–45	21 (4.2)	474 (95.8)	495 (32.8)
	46–60	14 (5.2)	256 (94.8)	270 (17.9)
	>60	9 (2.5)	348 (97.5)	357 (23.7)
Residence	Urban	32 (4.7)	650 (95.3)	682 (45.2)
	Rural	30 (3.6)	797 (96.4)	827 (54.8)
Anti-TB treatment category	New	31 (2.7)	1117 (97.3)	1148 (76.1)
	Relapse	13 (10.1)	116 (89.9)	129 (8.5)
	After loss to follow up	7 (8.0)	80 (92)	87 (5.8)
	After the failure of the first Rx	4 (5.7)	66 (94.3)	70 (4.6)
	After the failure of retreatment	7 (9.3)	68 (90.7)	75 (5.0)
HIV status	Positive	23 (18.7)	100 (81.3)	123 (8.2)
	Negative	39 (2.8)	1347 (97.2)	1386 (91.8)
History of close contact with MDR-TB patients	Yes	22 (4.9)	425 (95.1)	467 (4.1)
	No	40 (3.8)	1022 (96.2)	1062 (95.9)
Lesions identified on CXR	Cavitation	41 (5.6)	693 (94.4)	734 (48.6)
	Consolidation	10 (3.9)	249 (96.1)	259 (17.2)
	Infiltrations	2 (0.7)	267 (99.3)	269 (17.8)
	Miliary	5 (2.6)	190 (97.4)	195 (12.9)
	Pleural effusion	4 (7.7)	48 (92.3)	52 (3.4)
Previous anti-TB Rx history	Yes	31 (8.6)	330 (91.4)	361 (23.9)
	No	31 (2.7)	1117 (97.3)	1148 (76.1)
Treatment Outcome	Cured	34 (4.1)	799 (95.9)	833 (55.2)
	Completed	19 (3.7)	488 (96.3)	507 (33.6)
	Died	5 (5.4)	88 (94.6)	93 (6.2)
	Failed	1 (20)	4 (80)	5 (0.3)
	Lost to follow up	3 (4.2)	68 (95.8)	71 (4.7)

Hx, history; Rx, treatment; NA, not applicable; CXR, chest X-ray.

Table 2. Magnitude of MDR-TB and its associated factors at DMCSH, 2016–2020

Variables	Categories	MDR-TB					
		Positives	Negatives	COR (95%CI)	*P* value	AOR (95%CI)	*P* value
Sex	Male	32 (3.1)	994 (96.9)	0.5 (0.3, 0.9)	0.0134	0.5 (0.3, 0.9)	**0.02**[a]
	Female	30 (6.2)	453 (93.8)	1			
Age group	15–30	18 (4.7)	369 (95.3)	1			
	31–45	21 (4.2)	474 (95.8)	1.0 (0.5, 1.9)	1.000	1.1 (0.5, 2.4)	0.74
	46–60	14 (5.2)	256 (94.8)	1.4 (0.7, 1.6)	0.1106	2.2 (0.8, 5.9)	0.11
	>60	9 (2.5)	348 (97.5)	0.7 (0.3, 1.6)	0.4036	0.8 (0.3, 1.9)	0.60
Residence	Urban	32 (4.7)	650 (95.3)	1			
	Rural	30 (3.6)	797 (96.4)	0.8 (0.5, 1.3)	0.3600	0.6 (0.3, 1.1)	0.1
Anti-TB treatment category	New	31 (2.7)	1117 (97.3)	1			
	Relapse	13 (10.1)	116 (89.9)	4.0 (2.1, 7.9)	0.077	2.7 (1.3, 5.7)	**0.007**[a]
	After loss to follow up	7 (8.0)	80 (92)	3.2 (1.3, 7.4)	0.673	2.8 (1.1, 7.3)	**0.04**[a]
	After failure of the first Rx	4 (5.7)	66 (94.3)	2.2 (0.7, 6.4)	0.179	1.8 (0.6, 5.8)	0.30
	After failure of retreatment	7 (9.3)	68 (90.7)	3.7 (1.6, 8.7)	—	2.2 (0.8, 5.9)	0.12
HIV status	Positive	23 (18.7)	100 (81.3)	7.9 (4.6, 13.8)	<0.0001	6.7 (3.8, 12.1)	**<0.01**[a]
	Negative	39 (4.4)	1347 (95.6)	1			
Hx of close contact with MDR-TB patients	Yes	22 (4.9)	425 (95.1)	1.3 (0.8, 2.3)	0.54	1.0 (0.5, 1.9)	0.98
	No	40 (3.8)	1022 (96.2)	1			
Lesions identified on CXR	Cavitation	41 (5.6)	693 (94.4)	0.7 (0.2, 2.1)	0.0001	1.3 (0.3, 5.6)	0.7
	Consolidation	10 (3.9)	249 (96.1)	0.5 (0.1, 1.6)	0.0049	0.6 (0.1, 2.7)	0.5
	Infiltrations	2 (0.7)	267 (99.3)	0.1 (0.02, 0.5)	0.7295	0.1 (0.02, 0.9)	**0.04**[a]
	Miliary	5 (2.6)	190 (97.4)	0.3 (0.1, 1.2)	0.2020	0.5 (0.09, 2.5)	0.36
	Pleural effusion	4 (7.7)	48 (92.3)	1		1	
Previous anti-TB Rx history	Yes	31 (8.6)	330 (91.4)	3.4 (2.0, 5.6)	<0.0001	2.6 (1.5, 4.5)	**<0.01**[a]
	No	31 (2.7)	1117 (97.3)	1			
Treatment outcomes	Cured	34 (4.1)	799 (95.9)	1			
	Completed	19 (3.7)	488 (96.3)	0.9 (0.5, 1.6)	0.289	NA	
	Died	5 (5.4)	88 (94.6)	1.3 (0.5, 3.5)	0.989	NA	
	Failure	1 (20)	4 (80)	5.9 (0.6, 54)	—	NA	
	Lost to follow up	3 (4.2)	68 (95.8)	1.0 (0.3, 3.5)	0.996	NA	

Hx, history; Rx, treatment; NA, not applicable; CXR, chest X-ray.
[a](bold values) indicated $P < 0.05$ (significant association).

for MDR-TB by 50% and 90%, respectively. However, the odds of having MDR-TB among patients with relapse was 2.7 times more likely than the new anti-TB treatment category [AOR = 2.7, 95% CI (2.1, 7.9), $P = 0.007$]. Similarly, patients receiving treatment after being lost to follow up were 2.8 times more likely to have MDR-TB than the new anti-TB treatment patients [AOR = 2.8, 95% CI (1.1, 7.3), $P = 0.04$]. Regarding MDR-TB and HIV association, our result revealed that the odds of having MDR-TB among HIV positives is 6.7 times more likely to happen than HIV negatives [AOR = 6.7, 95% CI (3.8, 12.1), $P < 0.01$]. Having a previous history of anti-TB treatment is linked to an increased likelihood of developing multidrug-resistant tuberculosis (MDR-TB). Individuals with such a history are 2.6 times more likely to have MDR-TB compared to those without any prior treatment [AOR = 2.6, 95% CI (1.5, 4.5), $P < 0.01$] (Table 2).

Trends of MDR-TB in the 5 years

The annual prevalence of MDR-TB decreased from 4.8% in 2016 to 2.9% in 2017 but increased to 3.4% in 2018, 4.3% in 2019 and 5.8% in 2020. However, the trend decreased by 40% in 2017, 29% in 2018 and 10% in 2019 but increased by 21% in 2020 compared with 2016 (Figure 1).

The trend analysis of MDR-TB was performed via a linear regression model and indicated that a 1-year increase caused a 0.5% increase in the incidence of MD-TB, but this variation was not statistically significant ($P > 0.05$) (Table 3).

Discussion

MDR-TB affects both developed and developing countries worldwide. The global trend of MDR-TB decreased from 2015 to 2020 and was constant from 2020 to 2022.[18] Even if Ethiopia was not mentioned in the 30 countries with high MDR-TB after 2015, the prevalence of MDR-TB has increased from time to time.

The overall prevalence of MDR-TB in our study was 4.1% (3.1%–5.1%) which was in line with the 4.6% national prevalence in Ethiopia reported in 2017.[19] However, it was lower than the national prevalence, which was 10.78% in Ethiopia in 2022,[20] 10.5% in Nigeria,[21] 5.4% in India from 2013 to 2018,[22] 7.4% in

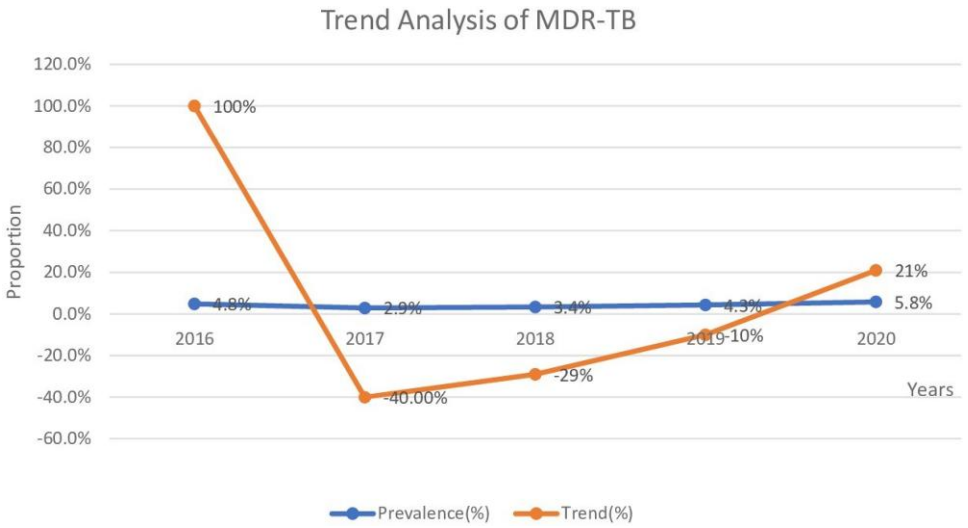

Figure 1. Trends of MDR-TB among patients with TB from 2016 to 2020.

Table 3. Linear regression analysis for trends in MDR-TB

Model 1	MDR			*P* value	95%CI	
	Unstandardized Beta(β)	Standard error of β	t test		lower	Upper
Y-intercept	−9.3	7.99	−1.17	0.24	−24.997	6.366
Years	0.005	0.004	1.17	0.24	−0.003	0.012

Malaysia,[23] 12.2% in China[24] and 10.1% in another study in China.[25] However, it was higher than 2.7% in Haiti.[26] This variation may be due to the difference in the time of the study, the small sample size used and the lower-precision diagnostic methods used in the previous study.[27] The other possible reason is the global 'End TB Strategy' implementation by 2015 to end TB by 2030 with no public health threat that has been accepted and implemented in Ethiopia. Ethiopia has developed a national guideline entitled 'The National End TB Strategy', which is a comprehensive approach to end TB in Ethiopia. The strategy aims to reduce TB-related deaths by 95% and to cut incident TB cases by 90% between 2015 and 2035. The strategy also aims to ensure that no family is burdened with catastrophic expenses due to TB. To achieve these goals, the strategy calls for the use of robust TB case-finding strategies and rapid diagnostic technologies to address the gap in finding missed TB cases and the threat of drug-resistant TB.[28] These implementations may decrease the MDR prevalence.[29]

In the current study, the prevalence of MDR-TB was almost similar in both sex (male = 2.1% versus female 2.0%), residences (urban = 2.1% versus rural 2.0%), new cases (2.1%) and previously treated patients (2.1%). Being male was negatively associated with MDR-TB, which is supported by the study done in Ethiopia[30] and Nigeria.[31] The prevalence of MDR-TB among new cases was 2.1% (1.37–2.82), which was in line with 2% in Ethiopia,[19] 2.64% in Ethiopia[20] and 2.4% in Iraq[32] but <3.5% in Nigeria[21] whereas its prevalence among previously treated patients was 2.1%, <15% in Ethiopia,[19] 7% in Nigeria[21] and 20.3% in Iraq.[32] Nearly 63% (51%–75%) of the MDR-TB was prevalent in patients with PTB with the age range 15–45 years, which was in line to 57% in Pakistan[33] but our finding was not statistically significant with age group. About 2.7% of the new cases had MDR-TB detected, consistent with the finding reported in Ethiopia.[20]

TB patients who had TB treatment group 'relapse' were 2.7 times more likely to develop MDR than newly diagnosed TB patients (AOR = 2.7, $P = 0.007$) whereas TB patients grouped lost to follow up were 2.8 times more likely to have MDR-TB compared to newly diagnosed cases (AOR = 2.8, $P = 0.04$). These findings confirmed that newly diagnosed TB cases had low risk for MDR-TB, which is supported by the National Guideline.[28]

The prevalence of MDR-TB/HIV co-infections was 1.5%. From HIV-positive patients, 18.7% had developed MDR-TB which is higher than the study done in Iran.[34] The odds of having MDR-TB was 6.7 times more likely in HIV-positive than HIV-negative patients (AOR = 6.7, $P < 0.01$). MDR-TB was detected among 4.9% of TB patients who had history of contact with MDR-TB patients and 3.8% of TB patients without any history of contact. However, in this study, history of contact with MDR-TB patients has no effect on MDR-TB infection (AOR = 1, $P = 0.98$). The chest X-ray radiological result indicated only infiltration was significantly associated with MDR-TB infections but it was protective compared to pleural effusion (AOR = 0.1 and $P = 0.04$). HIV/TB co-infections affect the middle and lower lung and result in lymphadenopathy and pleural effusions, or a miliary pattern and absence of cavitations.[35]

About 8.6% of the TB patients who had a history of anti-TB treatment were MDR positives. TB patients who had a history of anti-TB treatment were 2.6 times more likely to have MDR-TB compared to TB patients who did not have (AOR = 2.6(1.5, 4.5), $P < 0.01$) and this finding was supported by a study done in Nepal.[15]

The trend of MDR-TB in the current study decreased from 4.8% in 2016 by 40% in 2017, 29% in 2018, 10% in 2019, but increased by 21% in 2020. However, the annual prevalence of MDR-TB increased from 2017 to 2020. Our finding indicated that a 1-year increase may cause a 0.5% increase in the trend of MDR-TB. When the prevalence of MDR-TB is increasing in this pattern, the impact of its transmission will be exacerbated as projected in South Africa (5%–15%), and Vietnam (14%–41%) in 2040.[36]

Limitations of this study

The limitations of this study are the retrospective nature of the study and the difficulty in identifying important potential risk factors for MDR-TB, such as alcohol consumption, smoking, blood transfusion history, and occupational status. Additionally, owing to the cross-sectional nature of the study, it was difficult to study exposure and outcomes at different times. Therefore, a prospective follow-up study is recommended to investigate the factors associated with increased MDR-TB.

Conclusions and recommendations

The overall prevalence of MDR-TB in our study was comparable with the national prevalence. The prevalence of MDR-TB was similar in both newly diagnosed and previously treated TB patients. Male sex, a history of previous TB treatment, HIV infection, infiltration on chest X-ray and a history of anti-TB treatment were significantly associated with MDR-TB. The trend of MDR-TB was increasing in 2020. Counselling related to anti-TB drug adherence during the TB treatment is mandatory to decrease MDR-TB. A further prospective study is needed to obtain more updated information about MDR-TB in the study area.

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Transparency declarations

The author and co-authors declare that they have no competing interests.

Authors' contributions

A.A.: conception of the research idea, study design, data curation, analysis and interpretation, manuscript writing, and revision. M.K.: conception of the research idea; data curation, analysis and interpretation; manuscript preparation and revision. B.T.: conception of the research idea; data curation, analysis and interpretation; manuscript preparation and revision. D.A.: supervision, data analysis, manuscript preparation and revision. All authors have read and approved the final manuscript.

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