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Research Article

Determinants of Multi-Drug Resistant Tuberculosis among Patients Attending Anti-Tuberculosis Treatment from Peripheral Districts, Southern Ethiopia, 2019: A Case-Control Study

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ABSTRACT

Introduction: The emergence of Multi-Drug Resistant Tuberculosis (MDR-TB) is a challenge for the global prevention and control of tuberculosis. Ethiopia is one of the 30 multi-drug resistant tuberculosis burden countries. There was little research evidence of multi-drug resistant tuberculosis from the peripheral parts of the country.

Objectives: To identify determinants of multi-drug resistant tuberculosis among patients attending anti-tuberculosis treatment from peripheral districts in Southern Ethiopia.

Methods: A facility-based unmatched case-control study was conducted from March to April 2019 in Southern Ethiopia. The cases were confirmed multi-drug resistant tuberculosis patients, while controls were those who declared cured or completed first-line anti-tuberculosis treatment. The study participants were recruited by simple random sampling technique. The data were entered into Epi data version 4.4.3, cleaned, and analyzed by SPSS version 24. Bivariate and multivariable analyses were used to identify the determinants of multi-drug resistant tuberculosis. The determinants with P-value <0.05 were declared as having a significant association with multi-drug resistant tuberculosis and Adjusted Odd Ratio (AOR) with 95% confidence interval was used to measure the degree of association.

Results: A total of 180 study participants: 90 cases and 90 controls were enrolled in this study. Multivariable logistic regression showed that uneducated (AOR: 5.18, 95% CI: 1.69-15.80), rural residents (AOR: 2.60, 95% CI: 1.14-6.88), body mass index <18.5 kg/m^2 (AOR: 3.11, 95% CI: 1.41-6.88), pulmonary tuberculosis (AOR: 3.98, 95% CI: 1.11-14.22), contact history with known tuberculosis patient (AOR: 3.99, 95% CI: 1.75-9.07) and history of previous treatment (AOR: 9.5, 95% CI: 4.08-22) were found independent predictors of multi-drug resistant tuberculosis.

Conclusion: This study revealed that the determinants of multi-drug resistant tuberculosis from the peripheral districts were not different from the main urban centers. We recommend a nationwide future study to assure representativeness and matching cases with controls to identify the determinants of multi-drug resistant tuberculosis from peripheral districts.

Keywords: Determinants; Multi-drug resistant tuberculosis; Case-control

INTRODUCTION

The emergence of Multi-Drug Resistant Tuberculosis (MDR-TB) is a challenge for the global prevention and control of tuberculosis [1]. According to 2018's World Health Organization (WHO) TB report, a total of 160,684 Multi-drug Resistant/Rifampicin Resistant Tuberculosis (MDR/RR-TB) cases were notified in 2017 [2].Moreover, WHO 2019 tuberculosis report revealed that a total of 186,772 cases of MDR-TB were reported in 2018 [3]. There was a gap between the number of cases notified and started the treatment [2, 4].

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A systematic review and meta-analysis in Sub-Saharan countries showed the drug-resistant TB among previously treated tuberculosis patients was highest in East Africa [5]. Furthermore, WHO 2018 global tuberculosis report indicated that Ethiopia is one of the 30 tuberculosis burden countries [2].The report estimated that the incidence of MDR/RR-TB in Ethiopia was 5.2/100000 population in 2017 [2].

Besides, a systematic review and meta-analysis of multi-drug resistant tuberculosis in Ethiopia disclosed that the overall prevalence of MDR-TB was 7.24% [6].This indicated that the prevalence of MDR-TB was higher than the previous review in 2017 [7]. According to a sub-national prevalence survey of tuberculosis in Southern Ethiopia, TB in southern Ethiopia was higher than the national [8].

A global plan to end tuberculosis estimated that the amount for a diagnosis and treatment of MDR-TB increases from US$ 2.0 billion in 2017 to US$ 3.6 billion by 2020 [9]. MDR-TB case management is difficult because case management exposes to further economic and social costs whilst patients seeking help and treatment [10].

HIV/AIDS, under nutrition, smoking, drug and alcohol abuse, history of previous treatment, contact history with the known MDR-TB patient, body mass index below 18.5 Kg/m2, diabetes mellitus, chronic obstructive pulmonary diseases, smear positivity, history of hospitalization for TB, perceived stigma, history of imprisonment and being in a refugee camp were the risk factors identified for MDR-TB [2, 6, 11-13].

The Ethiopian federal ministry of health set the strategic objective that deals with minimizing disparities between groups and regions [14]. The strategic objective was aimed at minimizing disparities in the provision of health care services for the people that are distinguished economically, socially, and geographically [14, 15].

A systematic review and meta-analysis published in 2018 Ethiopia [6] revealed that almost all studies that were conducted in Ethiopia focused on main urban centers. This implies that there was little research evidence from the peripheral districts of the country. Besides, the determinants of MDR-TB have been not explored in the study areas. Therefore, this study was designed to identify the determinants of multi-drug resistant tuberculosis from peripheral districts in Southern Ethiopia.

Socio-demographic determinants of multi-drug resistant tuberculosis

World health organization 2014 tuberculosis report showed that poor socioeconomic background, economic constraints, and poverty were underlying risk factors of drug-resistant TB [10]. A case control study done in Serbia on risk factors of MDR-TB among 124 respondents (31 cases and 93 controls) revealed that monthly income of the family, stigma associated with TB and subjective feeling of sadness were identified risk factors [16]. Other similar case control study in China [17], Nepal [18], Addis Aba [11] and Jimma [13] showed that fearing of disclosure of TB status because of stigma was significant contributor of MDR-TB.

Besides, a systematic review and meta-analysis on prevalence and risk factors for multidrug-resistant tuberculosis in Iran and its neighboring countries depicted that age <45 years and being Malware risk factors to develop MDR-TB [19]. Another case control study in China [17] and cross-sectional study in India [20] identified being male was risk factor for occurrence of MDR-TB. Besides, age group 26-45 in India [20] and age group (18-25 and 26-45) in Bangladesh [21] were risk factors for development of MDR-TB. Other similar finding from Ethiopia [22] divulged that age <26 years was risk factor of MDR-TB. The findings in Serbia [16] and Iran [23] were inconsistent with the finding. In addition to this, the finding of other similar study in Iran [23] identified MDR-TB was related with a sex. A study in South West Nigeria and Equatorial Guinea in Central Africa [24] revealed that age and gender were not significantly associated with drug resistant TB [25].

According to a case control study in three hospitals in Bangladesh [21] among 250 MDR-TB cases and 750 controls to determine risk factors showed that lower level of education was predictor of MDR-TB. The finding is in line with finding in China [17], but finding in Serbia [16] revealed that the level of education did not affect occurrence of MDR-TB.

Finding from case control study in East Shoa in Oromia indicated that those who live in a rural setting acquired MDR-TB than urban residents [12]. This was not in line with the finding in Iran [23] residence did not affect development of MDR-TB.

Behavioral determinants of multi-drug resistant tuberculosis

World health organization 2014 revealed that smoking, drug and alcohol abuse are determinants for drug-resistant TB [10]. A case control study done in Serbia on risk factors of MDR-TB among 124 respondents reported that the use of sedatives was significant independent risk factor to develop MDR-TB [16]. Another study done in Allahabad, India [20] identified that MDR-TB was more common in substance abusers.

A Study in Henan province in China among 287 MDR-TB cases and 291 controls identified that smoking was predictor of multidrug resistant TB [17]. Similar findings were identified in Bangladesh [21], Nepal [21] and Tanzania [26].

According to case control study that was conducted at Amhara regional state in Ethiopia among 153 MDR-TB and equal number of non MDR-TB patient's alcohol consumers more likely developed MDR-TB than non-consumers [22]. Similar finding was identified from case control study in East Shoa in Oromia [12] and in Jimma [13]. But, these findings were inconsistent with other studies in Serbia [16] and Nepal [18] that MDR-TB was not related to consumption of alcohol.

National programmatic management of drug resistant TB in Ethiopia clearly specifies prisoners and refuges are vulnerable groups of people for MDR-TB [27]. But case control study that was conducted in northern Iran among 22 cases and 88 controls on determinant factors of drug resistant tuberculosis revealed that history of imprisonment was not significantly related with development of MDR-TB [23].

A review on Bovine tuberculosis infection in animal and human populations in Ethiopia disclosed that bovine tuberculosis mainly occurs due to drinking raw milk and cervical lymphadenitis form and extra-pulmonary form in close contact [28]. A case report on pet dog in Beijing revealed that the pet dog developed Mycobacterium tuberculosis that was resistant to isoniazid, ethambutol, and streptomycin. The dog was reported as having pre-multidrug-resistant Mycobacterium tuberculosis strain [29]. Besides, a study in Addis Ababa and its surroundings on prevalence of tuberculosis among dairy farm workers divulged that consuming raw animal

products were 4 times more likely to develop tuber than consumers of cooked animal products [30].

Clinical determinants of multi-drug resistant tuberculosis

According to 2014 World health organization report on MDR-TB, immune-compromising conditions such HIV is one of the determinants of drug-resistant TB [10]. A report on drug resistance in the United States from 2010 to 2013 revealed that worsening clinical finding with co-morbidity increases risks of drug-resistant TB [31]. Another case control study in Henan province, China, having an opportunistic infection was the predictor of multidrug resistant TB [17]. A cross-sectional study in India [20] depicted co-morbidity was risk factor of MDR-TB. However, studies from different countries; case control study in Serbia [16], case control study in Iran [23], case control study in Equatorial Guinea in Central Africa [24], case control study in Addis Ababa [11] and case control study in East Shoa [12] reported that MDR-TB was not related with HIV.

The report on drug resistance in the United States from 2010 to 2013 revealed that a previous history of treatment was strong determinant of MDR-TB [31]. A review in Iran and neighboring countries in Iran [19], case control study in Iran [23], cross-sectional study in India [20], case control study in Nepal [18],case control study in China [17],review in Sub Saharan countries [5], retrospective study in Nigeria, Equatorial Guinea in Central Africa [24], case control study in Tanzania [26],case control study in Addis Ababa [11] and case control study in East [12] identified that a previous history of treatment was strong predictor of MDR-TB. However, the finding of case control study in Serbia [16] was inconsistent with previous history of treatment.

The finding on the similar report on drug resistance in the United States from 2010 to 2013 depicted that contact history and exposure to individuals in congregate settings are the most important predictors of drug-resistant TB [31].The similar finding was identified in other studies cross-sectional study in India [20], case control in Equatorial Guinea in Central Africa [24], case control in Tanzania [26],review in Ethiopia [6], case control in Amhara region [22] and case control in East Shoa [12].

A case control study done in Serbia on risk factors of MDR-TB among 124 respondents (31 cases and 93 controls) revealed that defaulting from treatment was identified risk factor [16]. Another case control study in Shenen Gibe hospital, Jimma showed that insufficient instruction on how to take anti-TB drug and missing anti-TB drug were identified predictors of MDR-TB [13]. A similar case control study in Serbia [16] identified COPD was risk factor of MDR-TB. Another case control study done in Bangladesh revealed DM was one of the predictors of MDR-TB [21]. Ethiopia 2015 national wide rapid nutritional assessment report showed, two out of three registered TB patients had low BMI below 18.5 Kg/m2. Another retrospective study in South Korea revealed that underweight status was risk factor for transmission MDR-TB in the community [32]. In addition to this, DM patients are at a higher risk of developing TB. Besides, the patients with diabetes mellitus are more likely to face poor TB treatment outcomes, treatment failure, relapse and even death. Patients with COPD have a three times increased risk of developing active TB compared to the general population [33]. A study in Addis (St. Peter TB Specialized and ALERT) [11] was inconsistent the finding that a patient with DM less likely develop MDR-TB than drug susceptible TB.

A case control study done in St. Peter TB Specialized and ALERT showed that patients who had been hospitalized for TB management were 4 times more likely to have MDR-TB than drug susceptible TB. The study also identified that probability of sputum-smear positivity was found to be higher in the cases than the control [11]. A retrospective study in South Korean patients with multidrug resistant tuberculosis revealed that a positive sputum smear might be risk factor for transmission MDR-TB in the community [32].

MATERIALS AND METHODS

Study design, period and setting

A health-facility based unmatched case-control study design was used from March to April, 2019 in Southern Ethiopia. The study was conducted in the Southern Nation, Nationalities, and peoples region. A region is a higher administrative structure in Ethiopia with a minimum of one nation. According to a population projection figure of 2017, the population of the region was estimated to be 19,170,007 [34]. Since 2014, six public hospitals were serving as MDR-TB Treatment Initiation Center (TIC) in the region. We selected three of these Treatment Initiation Center namely: Yirgalem Hospital, Queen Elen Memorial Hospital, and Butajira Hospital as the study sites. The study hospitals were selected purposively because the majority of MDR-TB cases are managed in the hospitals. The hospitals serve 60% of population in the region as the catchment areas. All three hospitals have a Directly Observed Treatment (DOT) center and separate MDR/TB treatment initiation centers to manage drug-susceptible tuberculosis and MDR-TB patents respectively. A diagnosis and treatment of both drug-susceptible and MDR-TB performed according to the guidelines for clinical and programmatic management of Tuberculosis(TB), leprosy, and Tuberculosis/Human Immunodeficiency Virus(TB/HIV) in Ethiopia [35].

Source population

All confirmed multi-drug resistant tuberculosis patients from peripheral districts and drug-susceptible tuberculosis patients completing first-line anti-tuberculosis treatment attending Yirgalem, Butajira, and Queen Elen Memorial hospitals.

Study population

All confirmed multi-drug resistant tuberculosis patients from peripheral districts who were admitted to the hospitals and on follow-up during the data collection period in the study hospitals.

Eligibility criteria

Drug-susceptible tuberculosis patients who declared cured or treatment completed during the data collection period in the study hospitals.

Exclusion

Newly diagnosed/incident cases and the patients from main urban centers were not included in the study.

Sample size determination

The sample size was determined by a double population proportion

formula. Epi-Info version 7.2 was used to calculate the number of study participants. Contact history with known tuberculosis patient in a previous study that was conducted in East Shoa in Oromia [12] was used for the sample size determination based on the following assumptions: 95% confidence level at the power of 80%, with the ratio of 1:1 case to control, percent of control exposed 39.7 and percent of cases exposed 61.6. The final sample size was 180 (90 cases and 90 controls).

Sampling technique

Cases were selected by simple random sampling technique from admitted and follows up patients. Controls were recruited by simple random sampling technique from patients completed first-line anti-tuberculosis drugs.

Sampling procedure

A total of 135 multi-drug resistant tuberculosis patients were from peripheral districts and 105 patients were eligible to complete first line anti-tuberculosis treatment during the study period. A proportional allocation to the size was made by a lottery method for admitted and follow up patients.

Independent and dependent variables

The outcome variable is multi-drug resistant tuberculosis status (cases controls). The independent variables were age, sex, marital status, occupation, educational status, household monthly income, alcohol consumption, tobacco smoking, Khat chewing, imprisonment, staying in a refugee camp, consumption of raw meat and milk, living with cattle or domestic animals, nutritional status, site of tuberculosis, smear status, contact history, the history of previous tuberculosis treatment, hospitalization for tuberculosis, disclosure of tuberculosis status, co-morbidity, and HIV serostatus.

Operational definitions

Cases: Multi-drug resistant tuberculosis confirmed patients by culture and/or drug susceptibility testing and age 15 years and above.

Control: Drug-susceptible tuberculosis patients who declared cured or treatment completed at the end of first-line ant-tuberculosis treatment and age 15 years and above in their respective catchment areas.

Data collection tools

The data were collected by using a pre-tested and structured questionnaire. The data collection tool was adopted from previously locally conducted studies [11-13, 29, 31, 36, 37].

Data quality assurance

The pre-test was carried out in All Africa Leprosy and Tuberculosis Rehabilitation, and Training Center hospital before 1 week of the actual study. The questionnaire prepared in English was translated to Amharic then retranslated to English for consistency. Training on the questionnaire was given for data collectors and supervisors. Six BSc nurses collected the data and 3 supervisors supervised the data collection. After completing the interview session, additional data were collected from the multi-drug resistant and drug-susceptible tuberculosis registers. To maintain the accuracy of the data, regular supervision was made by the supervisors. The trained supervisors checked the completeness of each questionnaire and data accuracy daily.

Data processing and analysis

The data were entered into Epi data 4.4.3, then exported to SPSS version 24 for cleaning and analysis. The variables were described by frequencies, percentages, and presented in tables. Bivariate analysis was done to select the variables for multivariable analysis. The data were analyzed by a logistic regression model. The predictors which were p-value <0.25 in bivariate analysis were entered into multivariable logistic regression for statistical adjustment. The predictors which were candidate for multivariable analysis were checked for multicollinearity before statistical adjustment in multivariable logistic regression. All the predictors pass the test of multi-collinearity; variance inflation factor (1.022 to 1.093). Cigarette smoking was not included in the multivariable analysis because of the small number of observations. A goodness of fit of the model was assessed from the output of the multivariable logistic regression. The overall goodness of fit of the model was assessed by the Hosmer and Lemeshow test. The determinants with P<0.05 was considered as having a significant association with multi-drug resistant tuberculosis and AOR with 95% CI were used to measure a degree of association.

RESULTS

Socio-demographic characteristics of study participants

A total of 180 study participants were recruited (90 cases and 90 controls) participated in this study. More male respondents were found in cases 55(61.1%) as compared to controls 48(53.3%). 43(47.78%) of the cases were in the age group of 26-45 and 51(56.67%) of controls in the same category of age. The median age for cases and controls was 29 and 30.5 years, respectively, as shown below in Table 1.

Distribution of behavioral characteristics of study participants

34(18.89%) of the study participants were alcohol consumers contributing the same count from the cases and controls (Table 2).

Distribution of clinical characteristics of study participants

More than half of the cases 55(61.1%) had body mass index <18.5 kg/m2, whereas nearly one third 32(35.6%) of the control had body mass index <18.5 kg/m2. Eighty five (94.4%) of the cases were pulmonary tuberculosis. Only 4(2.22%) of participants were found HIV positive of those 3(75%) were control (Table 3).

Multivariable analysis

The odds of multi-drug resistant tuberculosis in a previous history of treatment was 10 times higher than not treated tuberculosis previously (P-value: 0.000; 95%CI (AOR: 9.5(4.08-22)). The odds of developing multi-drug resistant tuberculosis in rural respondents was three times than urban residents (P-value-0.029; 95% CI (AOR: 2.6(1.11-6.11)) (Table 4).

Table 1: Distribution of socio-demographic characteristics of case and control respondents, Southern Ethiopia, 2019 (n=180).

Variables	Category	Case (%)	Control (%)	Total (%)	COR (95% CI)	P-value
Sex	Male	55(61.1)	48(53.3)	103(57.22)	1.375(760-2.48)	0.292
	Female	35(38.9)	42(46.7)	77(42.78)	1	
Age	15-25	37(41.1)	30(33.33)	67(37.22)	1.233(0.45-3.35)	0.681
	26-45	43(47.8)	50(55.56)	93(51.67)	0.860(0.32-2.26)	0.76
	≥ 46	10(11.1)	10(11.11)	20(11.11)	1	
Marital status	Never married	34(37.8)	35(38.9)	69(38.33)	1	0.878
	Married	56(62.2)	55(61.1)	111(61.67)	1.048(0.57-1.91)	
Educational level	Uneducated	30(33.3)	15(16.7)	45(25)	3.44(1.47-8.05)	0.004
	Read and write	12(13.3)	15(16.7)	27(15)	1.38(.53-3.56)	0.511
	Primary	30(33.3)	29(32.2)	59(32.78)	1.782(.82-3.86)	0.143
	Secondary and above	18(20.0)	31(34.4)	49 (27.22)	1	
Occupation	Employed	14(15.56)	18(20)	32(17.78)	1	0.437
	Unemployed	76(84.44)	72(80)	148(82.18)	1.357(0.63-2.93)	
Average monthly household income	≤ 500	29(32.2)	27(30.0)	56(31.1)	0.976(0.44-2.17)	0.953
	501-1000	39(43.3)	43(47.8)	82(45.56)	0.825(0.39-1.74)	0.612
	>1000	22(24.4)	20(22.2)	42(23.33)	1	
Residence	Rural	71(78.9)	49(54.4)	120(66.67)	3.127(1.62-6.01)	0.001
	Urban	19(21.1)	41(45.6)	60(33.33)	1	
Separate room for living and sleeping	Yes	33(36.7)	35(38.9)	68(37.78)	1	0.759
	No	57(63.3)	55(61.1)	112(62.22)	0.91(0.50-1.66)	

Note: Values are presented as number (%): CI: Confidence Interval: COR: Crude Odd Ratio.

Table 2: Distribution of behavioral determinants of case and control respondents Southern Ethiopia, 2019 (n=180).

Variables	Category	Cases (%)	Control (%)	Total (%)	COR (95% CI)	P-value
Alcohol consumption	Yes	17(18.9)	17(18.9)	34(17.78)	1.0 (0.47-.109)	1
	No	73(81.1)	73(81.1)	146(82.22)	1	
Smoking cigarette	Yes	9(10)	1(1.1)	10(5.56)	9.9(1.22-79.70)	0.031
	No	81(90)	89(98.9)	170(94.44)	1	
Chewing Khat	Yes	13 (14.4)	12 (13.3)	25 (13.89)	1.1 (0.47-2.55)	0.83
	No	77(86.6)	78(86.7)	155(86.11)	1	
Imprisonment history for any case	Yes	5(5.6)	3(3.3)	8(4.44)	1.7(0.65-4.34)	0.32
	No	85(94.4)	87(96.7)	172(95.56)	1	
History of being a refugee camp	Yes	5(5.55)	8(8.89)	13(7.22)	1	0.39
	No	85(94.45)	82(91.11)	167(92.78)	0.63(0.82-1.90)	
Consuming a raw milk	Not at all	26(28.9)	19(21.1)	45(25)	1	0.23
	Sometimes	64(71.11)	71(78.89)	135(75)	0.66(0.33-1.30)	
Consuming a raw meat	Not at all	21(23.33)	17(18.89)	38(21.11)	1	0.47
	Sometimes	69(76.67)	73(81.11)	142(78.89)	0.76(0.37-1.57)	
Living with cattle/ domestic animals	Yes	39(43.3)	48(53.3)	87(48.33)	1.49(0.83-2.70)	0.18
	No	51(56.7)	42(46.7)	93(51.67)	1	

Note: Values are presented as number (%): CI: Confidence Interval: COR: Crude Odd Ratio.

Table 3: Distribution of clinical characteristics of case and control respondents Southern Ethiopia, 2019 (n=180)..

Variables	Category	Cases (%)	Control (%)	Total (%)	COR (95% CI)	P-value
Body mass index (in Kg/m^2)	<18.5 Kg/m^2	55(61.1)	32(35.6)	87(48.33)	2.85(1.56-5.2)	0.001
	≥ 18.5 Kg/m^2	35(38.9)	58(64.4)	103(51.67)	1	
Site of tuberculosis	Pulmonary	85(94.4)	68(75.6)	153(85)	5.5(1.98-15.28)	0.001
	Extra pulmonary	5(5.6)	22(24.4)	27(15)	1	
Sputum smear	Positive	53(62.4)	42(61.8)	95(62.09)	0.97(0.51-1.88)	0.941
	Negative	32(37.6)	26(38.2)	58(37.91)	1	
Contact with tuberculosis patients	Yes	47(52.2)	23(25.6)	70(38.89)	3.18(1.70-5.97)	0
	No	43(47.8)	67(74.4)	110(61.11)	1	
Previous treatment of tuberculosis	Yes	56(62.2)	17(18.9)	73(40.56)	7.07(3.59-13.9)	0
	No	34(37.8)	73(81.1)	107(59.44)	1	
Hospitalization for previous treatment of tuberculosis (n=73)	Yes	17(30.4)	5(29.4)	22(30.14)	1.04(0.32-3.43)	0.941
	No	39(69.6)	12(70.6)	51(69.86)	1	
Disclosure of tuberculosis status for family/relatives (n=73)	Yes	34(60.7)	11(64.3)	45(61.64)	0.84(0.27-2.6)	0.797
	No	22(39.5)	6(35.7)	28(38.36)	1	

Note: Values are presented as number (%): CI: Confidence Interval: COR: Crude Odd Ratio.

Table 4: DMultivariable logistic regression analysis of case and control respondents, Southern Ethiopia, 2019 (n=180).

Variable	Category	Case (%)	Control (%)	COR (95% CI)	AOR (95% CI)
Educational level	No formal education	30(33.3)	15(16.7)	3.44(1.47-8.05)	5.18(1.7-15.80)**
	Read and write	12(13.3)	15(16.7)	1.38(.53-3.56)	2.03(0.56-7.33)
	Primary	30(33.3)	29(32.2)	1.78(.82-3.86)	1.88(0.66-5.23)
	Secondary and above	18(20.0)	31(34.4)	1	1
Residence	Rural	71(78.9)	49(54.4)	3.13(1.62-6.0)	2.6(1.11-6.11)*
	Urban	19(21.1)	41(45.6)	1	1
Living with domestic animals	Yes	39(43.3)	48(53.3)	1.5(0.83-2.69)	0.55(.248-1.21)
	No	51(56.7)	42(46.7)	1	1
Consuming a raw milk	Sometimes	64(71.1)	71(78.9)	0.66(0.33-1.3)	1.01(0.38-2.67)
	Not all	26(28.9)	19(21.1)	1	1
Nutritional status	BMI <18.5 kg/m^2	55(61.1)	32(35.6)	2.85(1.5-5.2)	3.11(1.41-6.68)**
	BMI ≥ 18.5 kg/m^2	35(38.9)	58(64.4	1	1
Site of tuberculosis	Pulmonary	85(94.4)	68(75.6)	5.5(1.98-15.28)	3.98(1.1-14.22)*
	Extra pulmonary	5(5.6)	22(24.4)	1	1
Contact history tuberculosis patient	Yes	47(52.2)	23(25.6)	3.18(1.70-5.97)	3.99(1.75-9.10)**
	No	43(47.8)	67(74.4)	1	1
History previous treatment of tuberculosis	Yes	56(62.2)	17(18.9)	7.07(3.6-13.9)	9.5(4.08-22)***
	No	34(37.8)	73(81.1)	1	1

Note: AOR: Adjusted Odd Ratio: CI: Confidence Interval: COR: Crude Odd Ratio.
*P-value<0.05, **P-value<0.01, ***P-value<0.001

DISCUSSION

This unmatched case-control study that was conducted on 180 respondents (90 cases and controls) to identify determinants of multi-drug resistant tuberculosis from the patients who peripheral districts revealed that uneducated, rural residence, body mass index less than 18.5 kg/m2, pulmonary tuberculosis, contact history and previous treatment were found independent predictors of multi-drug resistant tuberculosis. The study addressed several possible determinants of multi-drug resistant tuberculosis but only the mentioned were found independent predictors. This might be due to the small number of observations in different predictors related to the small sample size. Therefore, the predictors which were found independent will be discussed as follow.

This study indicated that the odds of developing multi-drug resistant tuberculosis were five times (AOR: 5.18) higher in uneducated than who had an education level of secondary and above. The finding was in agreement with a study from Bangladesh [21]. In contrast, according to a finding of Addis Ababa [11], having an educational level of secondary and above had a signification association with multi-drug resistant tuberculosis. However, studies in East Shoa [12] and Jimma [13], being uneducated were not associated with the occurrence of multi-drug resistant tuberculosis. According to a study from Serbia [16], a level of education did not affect the development of multi-drug resistant tuberculosis. This may be due to this study recruited the participants from peripheral districts and the majority of the respondents were rural dwellers that might have poor access to education and low health literacy.

The current study revealed that rural residents had three times (AOR: 2.6) higher risk of multi-drug resistant tuberculosis than urban. This was in line with the study that was conducted in East Shoa [12]. However, multi-drug resistant tuberculosis was not associated with residence according to the study reports from Ethiopia [13], China [17], and Iran [23]. This difference might be due to access to tuberculosis services nearby and low knowledge of tuberculosis for drug adherence, transportation problem, inadequate social support, and fear of stigma to complete anti-tuberculosis drugs.

The odds of being body mass index less than 18.5 kg/m2 were 3 times (AOR: 3.11) higher in cases than controls. The finding was in line with other findings [2, 9]. A poor nutritional status decreases a probability of treatment success (response), increases recurrence, decreases smear conversion rate, reduces hosts immunity by enhancing Bacilli development and resistance, and malnutrition is highly common in multi-drug resistant tuberculosis patients and one of the risk factors for the development of multi-drug resistant tuberculosis [9, 14, 38, 39].

The respondents with pulmonary tuberculosis four times (AOR: 3.98) more likely developed multi-drug resistant tuberculosis than extra-pulmonary tuberculosis. The finding was in line with a study in East Shoa [12], Addis Ababa [40], South Korea [32]. However, in the study in Jimma [13], pulmonary tuberculosis had no association with multi-drug resistant tuberculosis. The possible explanation for this could be a higher risk of recurrence of drug-resistant dormant Bacilli which is suppressed by previous tuberculosis drug exposure when host's immunity gets weakened. The patients with a pulmonary tuberculosis have a higher bacterial load which may not respond to first-line anti-tuberculosis drugs in a short period. This affects the adherence of patients [41].

Having a contact history with a known tuberculosis patient had four times (AOR: 3.99) higher odds of multi-drug resistant tuberculosis than non-contact. The similar finding from the studies in East Shoa [12], Amhara regional state [22], Addis Ababa [11], systematic review and meta-analysis in Ethiopia [6], Tanzania [26], Equatorial Guinea [24],Bangladesh [42],India [20],United States of America (USA) [31]. This is supported by [9, 15] having contact is high-risk group to develop multi-drug resistant tuberculosis. A higher chance of acquiring a drug-resistant strain by droplets and aerosol from individuals infected with multi-drug resistant strain [4, 43]. However, a contact history in Iran [23] had no association with multi-drug resistant tuberculosis. This could be due to a small number of cases in Iran that lack adequate power to identify the association with multi-drug resistant tuberculosis.

The current study showed that the odds of multi-drug resistant tuberculosis in previously treated respondents were ten times (AOR: 9.5) higher than treatment naïve respondents. And the previous treatment was a major predictor of multi-drug resistant tuberculosis in this study. Similar findings were found in a number of studies from different countries including the Ethiopia, East Shoa [12], Amhara regional state [22], Addis Ababa [11], Iran and neighboring countries [19], Iran [23], Nepal [18], China [17], Sub-Saharan countries review [9], retrospective study in Nigeria [25], Equatorial Guinea [24], Tanzania [26], USA [31]. Systematic review and meta-analysis in Ethiopia [6] revealed previous treatment was a major determinant of multi-drug resistant tuberculosis, systematic review in Europe [44]. This is supported by the WHO report previously treated patients are at higher risk of drug resistance and had non-adherence [38, 45]. The resistance in a history of previous treatment might be due to multiple exposures to first-line anti-TB drugs and incorrect methods of taking the treatment regimen that facilitate mutation of bacteria and development of resistance [9]. However, the study in Serbia [16]: A history of previous treatment had no association with multi-drug resistant tuberculosis. This difference might be due to the difference in adherence level, the small sample size in Serbia and difference in a study setting.

CONCLUSION

Uneducated, rural residence, body mass index <18.5 kg/m2,pulmonary tuberculosis, contact history with known tuberculosis patient, and history of previous treatment were associated with multi-drug resistant tuberculosis from the patients from peripheral districts. This study revealed that the determinants of multi-drug resistant tuberculosis from the peripheral districts were not different from the other main urban centers.

This study is not without limitation; the study was conducted on small sample size and the controls were not matched with the cases. We suggest a nationwide future study to assure representativeness and matching cases with controls to identify the determinants of multi-drug resistant tuberculosis from peripheral districts.

ETHICS APPROVAL AND INFORMED CONSENT

The study was approved by the Institutional Review Board of Addis Ababa University, College of Health Sciences, School of Nursing and Midwifery with the protocol number of 022/19/SNM. The purpose of the study were explained to each study participant before the data collection. Written informed consent was taken. For those who were age under 16 years, a written guardian or

parental consent was obtained. Only those who gave consent to participate in the study were included in the study. The study participants were coded anonymously and confidentiality of the information was maintained.

DATA AVAILABILITY

The datasets used and analyzed are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

There is no conflict of interest.

FUNDING STATEMENT

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AUTHOR'S CONTRIBUTIONS

LE wrote the proposal, participated in data collection, analyzed the data and prepared the manuscript. ET reviewed, participated in data analysis and subsequent revision of draft of the paper and writing the draft of the manuscript. AH reviewed, participated in data analysis and subsequent revision of draft of the paper. All authors read and approved the final manuscript.

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