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Risk factors of multidrug resistant tuberculosis among patients with tuberculosis at selected multidrug resistance treatment initiative centres in southern Ethiopia: a case-control study

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ABSTRACT

Objective To identify the risk factors for multidrug resistant tuberculosis (MDR-TB) among patients with TB at selected MDR-TB treatment initiative centres, southern Ethiopia, 2021.

Design An unmatched case-control study was employed.

Setting Multidrug resistance treatment initiative centres in southern Ethiopia (Nigist Elen Mohamed Memorial Comprehensive Specialized Hospital and Butajira General Hospital).

Participants A total sample size of 392 (79 cases and 313 controls) were selected by the systematic sampling technique. Cases *were all patients with TB with culture proven or line probe assay confirmed Mycobacterium tuberculosis resistant to at least both isoniazid and rifampicin and registered on second-line TB treatment. Controls were all patients with bacteriological (molecular) proven drug-susceptible TB strains and whose recent smear results were turned to negative and registered as cured*. Both bivariate and multivariable logistic regression analysis was used to identify risk factors of MDR-TB infections.

Main outcome measure Identifying the risk factors for MDR-TB.

Results A total of 392 participants (79 cases and 313 controls) were interviewed. Multivariable analysis showed that direct contact with known patients with TB (AOR =4.35; 95% CI: 1.45 to 9.81), history of previous TB treatment (AOR=2.51; 95% CI: 1.50 to 8.24), history of cigarette smoking (AOR=3.24; 95% CI :2.17 to 6.91) and living in rural area (AOR=4.71; 95% CI :3.13 to 9.58) were identified risk factors for MDR-TB infections.

Conclusions The study findings revealed that direct contact with known patients with TB, previous history of TB treatment, history of cigarette smoking and rural residence were potential risk factors for the occurrence of MDR-TB. In order to reduce the burden of drug resistance, strategies of controlling MDR-TB in the study area should emphasise on enhancing public health education and reducing treatment interruptions of patients with TB and drug-resistant TB.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Data were collected from a multicentre multidrug-resistant tuberculosis (MDR-TB) treatment initiative and several risk factors of MDR-TB were identified.
⇒ Due to the small number of patients with MDR-TB undergoing anti-TB treatment at both hospitals, several factors, such as HIV status and drinking alcohol, which are known to be associated with the occurrence of MDR TB, were not identified.
⇒ However, other aspects such as the treatment outcome and adverse reactions of drugs used to treat patients with MDR-TB was out of the range of this study; future studies will be undertaken to explore this aspect further.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* which is a major public health problem throughout the world.[1] Similarly, forms of TB resistant to first-line and second-line TB medicines present a major challenge for patients, healthcare workers and healthcare services.[2]

Drug-resistant TB is a major global health threat, driving the ongoing TB epidemic and increasing morbidity and mortality due to TB worldwide.[3 4]Resistance to isoniazid and rifampicin is defined as multidrug-resistant TB (MDR-TB). MDR-TB is caused by *M. tuberculosis* strains that are resistant to at least isoniazid and rifampicin, two first-line medicines used to treat TB.[4 5] Both MDR-TB and rifampicin-resistant TB (RR-TB) require treatment with second-line drugs. Although WHO has made efforts to expand treatment access for TB treatment, MDR-TB—which is resistant to at least isoniazid and rifampicin, the two most potent TB drugs[6]—remains a major public health problem.[7]

Table 1 Sociodemographic characteristics of patients with multidrug-resistant tuberculosis (TB) at selected multidrug-resistant TB treatment initiative centres, southern Ethiopia, 2021.

Variables	Cases N (%)	Controls N (%)
Age, years		
19–30	13 (16.46)	23 (7.35)
30–40	45 (56.96)	176 (56.23)
≥41	21 (26.58)	114 (36.42)
Gender		
Male	44 (55.69)	172 (54.95)
Female	35 (44.31)	141 (45.05)
Marital status		
Single	29 (36.71)	124 (39.62)
Married	50 (62.29)	189 (60.38)
Educational level		
No formal education	46 (58.23)	160 (51.11)
Primary education	18 (22.78)	68 (21.72)
Secondary and above education	15 (18.99)	85 (27.15)
Religion		
Protestant	23 (29.11)	124 (39.80)
Orthodox	31 (39.24)	82 (26.11)
Muslim	19 (24.05)	96 (30.60)
Others	6 (7.61)	11 (3.52)
Occupation		
Farmer	15 (18.89)	45 (14.38)
Housewife	8 (10.12)	40 (12.78)
Merchant	19 (24.05)	53 (16.93)
Government employee	21 (26.58)	104 (33.22)
Student	12 (15.19)	64 (20.45)
Others	4 (5.06)	7 (2.23)
Place of residence		
Rural	43 (54.43)	116 (36.94)
Urban	36 (45.57)	198 (63.06)

Drug resistance has mainly happened due to poor treatment outcomes, poor treatment adherence, poor quality of drugs and poor infection control practices. Currently, TB control mostly faces the emergence of drug resistance to more anti-TB drugs resulting in MDR, pre-extensively drug-resistant TB and extensively drug-resistant TB.[8]

Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 were cases of MDR/RR-TB.[9] Additionally, despite recent advances in treatment, the global average of MDR/RR-TB treatment success rate has been around 59%.[10]

Ethiopia is one the of high burden TB/MDR-TB burden countries around the world,[11 12] with 1.03% among newly confirmed and 6.52% among previously treated patients with TB. The RR/MDR-TB treatment success rate was 75.1% in 2020 indicating one of the highest among high-burden countries. Among nationally notified persons with RR/MDR-TB, 98% have bacteriologically confirmed pulmonary and/or extrapulmonary TB (EPTB), while 58% have a history of past TB treatment.[13]

M. tuberculosis infection is associated with factors such as smoking, occupation, alcoholism and TB-HIV co-infection.[14] Previous TB treatment and history of contact with known patients with TB and interruption of treatment is the strongest risk factor to the development of drug resistance.[11 13 15]

However, there is little evidence about risk factors that are responsible for the development of MDR-TB in patients undergoing anti-TB treatment in the areas under study. Therefore, understanding the risk factors that contribute to MDR-TB is important to design effective prevention and control strategies against its transmission and development of resistance to more anti-TB drugs, and determining how to secure resources and monitor the progress of TB detection and treatments.

MATERIALS AND METHODS

Study population and design

An unmatched case-control study was conducted at Nigist Elen Mohamed Memorial Comprehensive Specialized Hospital (NEMMCSH) and Butajira General Hospital from 1 June to 30 July 2021. Currently, a total of four MDR-TB treatments initiative centres are available in the southern region, of which two randomly selected MDR-TB treatment initiative centres, namely NEMMCSH and Butajira General Hospital, were included in this study. The source population included all patients with TB with culture-proven or line probe assay *confirmed M. tuberculosis resistant to at least both isoniazid and rifampicin and registered on second-line TB treatment (as cases) and all patients with bacteriological (molecular) proven drug-susceptible TB strains and whose recent smear results were turned to negative and registered as cured (as controls)* at NEMMCSH and Butajira General Hospital undergoing anti-TB treatment during the study period. The study population included all the cases and controls who were accessible for sampling during the study period.

Patients with MDR-TB and non-MDR-TB who were under treatment follow-up during the study period were included in the study. Patients were confirmed by culture and sensitivity testing considered as MDR-TB and patients were either newly or previously treated patients with TB who had smear microscopy that was positive for acid-fast bacilli or had clinical and/or radiological evidence of disease were included considered as TB. However, patients with EPTB or extensively drug-resistant TB were excluded from the study.

Sample size determination and sampling procedures

The sample size was calculated using Epi Info V.7.2 statistical software based on the following parameter

Table 2 Clinical characteristics of patients with tuberculosis (TB) at selected multidrug-resistant TB treatment initiative centres, southern Ethiopia, 2021.

Variables	Cases N (%)	Controls N (%)
History of contact with a TB patient		
Yes	31 (39.24)	58 (18.53)
No	48 (60.76)	255 (81.47)
History of previous TB treatment		
Yes	70 (88.61)	105 (33.55)
No	9 (11.39)	208 (66.45)
Previous TB treatment outcome		
Failure	49 (62.03)	72 (23.00)
Completed or cured	30 (37.97)	241 (76.00)
HIV infection		
Yes	10 (12.66)	12 (3.83)
No	69 (87.34)	301 (96.17)
Adverse effect		
Yes	15 (18.98)	45 (14.38)
No	64 (81.02)	268 (85.52)
History of hospital admission		
Yes	33 (41.77)	80 (25.56)
No	46 (58.23)	233 (74.44)

assumptions that considered a 39.7% proportion of direct contact to known patients with TB among controls as the exposure variable and 2.1 OR from a study conducted in the Amhara region of Ethiopia,[16] 95% confidence level, 80% power of the study, 1:4 cases and controls ratio that included 79 cases and 313 controls, and the total sample size was 392.

All cases and controls fulfilling the inclusion criteria were selected using systematic random sampling until the sample size was achieved. Sampling frames were prepared for cases and controls separately. Accordingly, a total of 392 study respondents were included (49 cases and 199 controls from NEMMCSH and 30 cases and 114 controls from Butajira General Hospital).

Table 3 Environmental and behavioural characteristics of patients with tuberculosis (TB) at selected multidrug-resistant TB treatment initiative centres, southern Ethiopia, 2021.

Variables	Cases N (%)	Controls N (%)
History of cigarette smoking		
Yes	20 (25.32)	28 (8.95)
No	59 (74.68)	285 (91.05)
History of prison		
Yes	7 (8.86)	10 (3.20)
No	72 (91.14)	303 (96.80)
History of drinking alcohol		
Yes	21 (26.58)	49 (15.65)
No	58 (73.42)	264 (84.35)
History of migration		
Yes	16 (20.25)	34 (10.86)
No	63 (79.75)	279 (89.14)
Knowledge of TB symptoms		
Yes	18 (22.78)	127 (40.57)
No	61 (77.22)	186 (59.43)

Data collection procedures and quality assurance

A structured questionnaire was used to collect information from study respondents. After obtaining informed consent, a face-to-face interview was conducted to collect information on risk factors including gender, age, ethnicity, occupation, education, cigarette smoking, alcohol drinking, history of previous treatment, adverse effects of anti-TB medication and knowledge of TB symptoms. Others information such as height, weight, clinical diagnosis and drug susceptibility testing results were obtained directly from the medical records by using checklists. Data collectors and supervisors were trained to ensure quality of data. The questionnaires were pretested to identify potential problems of the questionnaires and unanticipated interpretations. Based on the pretest results, the questionnaires were additionally adjusted contextually and terminologically, reliability analysis was done and 0.73 Cronbach's α was obtained, and finally data were collected from the whole sample.

Statistical analysis

Data were cleaned and entered into the computer using EpiData V.3.1 and analyses were done using Statistical Package for Social Sciences (SPSS) V.25.0. Descriptive statistical were used to obtain summary measures for cases and controls separately. Bivariate analysis was performed to identify the crude association between dependent and independent variables. All variables with a value of $p \leq 0.25$ in the bivariate analysis were included in the multivariable logistic regression analysis to identify independent MDR-TB risk factors. The adjusted OR (AOR) and 95% CI were used to evaluate the magnitude of association between risk factors and MDR-TB. A value of $p<0.05$ in the multivariable logistic regression model was the cut-off point to declare statistical significance.

Patient and public involvement

No patient or the public was involved in the development of research questions and design of the study. The results of this research will be disseminated to stakeholders such as the zonal and regional health bureaus and Wachemo University after being published in a scientific journal.

RESULTS

Sociodemographic characteristic

A total of 392 study respondents including 79 cases and 313 controls were interviewed. More than half of the respondents were male (55.12% of cases and 55.27% of controls). The mean age of the patients in the cases group was 30.73 years and in the controls group was 30.69 years and the minimum age of the respondents was 19 years.

Table 4 Bivariate and multivariable logistic regression analysis of patients with tuberculosis (TB) at selected multidrug-resistant TB treatment initiative centres, southern Ethiopia, 2021.

Variables	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	P value
Place of residence					
Rural	43 (54.43)	116 (36.94)	2.00 (1.20 to 6.28)	4.71 (3.13 to 9.58)	0.032
Urban	36 (45.57)	198 (63.06)	1	1	
History of cigarette smoking					
Yes	20 (25.32)	28 (8.95)	3.28 (3.58 to 11.73)	3.24 (2.17 to 6.91)	0.001
No	59 (74.68)	285 (91.05)	1	1	
Direct contact of TB patients					
Yes	31 (39.24)	58 (18.53)	2.75 (1.17 to 9.06)	4.35 (2.45 to 9.81)	0.012
No	48 (60.76)	255 (81.47)	1	1	
Previous TB treatment					
Yes	70 (88.61)	105 (33.55)	17.33 (5.69 to 26.27)	2.51 (1.50 to 8.24)	0.015
No	9 (11.39)	208 (66.45)	1	1	
Previous TB treatment outcome					
Failure or default	49 (62.03)	72 (23.00)	5.36 (3.56 to 10.21)	2.45 (0.35 to 8.14)	0.051
Completed or cured	30 (37.97)	241 (76.00)	1		

Most of the respondents were married (62.29% of cases and 60.38% of controls). More than half of the respondents had no formal education (58.23% of cases and 51.11% of controls). Forty-two (53.85%) of the cases were living in a rural area, while 198 (63.06%) of the controls were living in an urban area (table 1).

Clinical characteristics of study respondents

Among the study respondents, 31 (39.24% of cases) and 58 (18.53% of controls) had a history of contact with known patients with TB, 70 (88.61% of cases) and 105 (33.55% of controls) had a history of previous TB treatment, and 49 (62.03% of cases) and 72 (23% of controls) had a history of TB treatment failure (table 2).

Environmental and behavioural characteristics

Among the study respondents, 20 (25.32% of cases) and 28 (8.95% of controls) had history of cigarette smoking, 21 (26.58% of cases) and 49 (15.65% of controls) had history of drinking alcohol, and 16 (20.25% of cases) and 34 (10.86% of controls) had a history of migration (table 3).

Risk factors of MDR-TB

In multivariable logistic regression analysis, four variables were found to be significantly independent risk factors for the occurrence of MDR-TB: direct contact with known patients with TB (AOR=4.35; 95% CI 2.45 to 9.81), history of previous TB treatment (AOR=2.51; 95% CI 1.50 to 8.24), history of cigarette smoking (AOR=3.24; 95% CI 2.17 to 6.91) and living in a rural area (AOR=4.71; 95% CI 3.13 to 9.58) were identified risk factors of MDR-TB infection (table 4).

DISCUSSIONS

This study attempted to identify risk factors of MDR-TB at selected MDR-TB treatment initiative centres, southern Ethiopia. Factors such as history of contact with known TB patient, previous history of TB treatment, rural residence and history of cigarette smoking were found to be statistically associated with the occurrence of MDR-TB infections. However, variables like age, sex, educational status, adverse effects, knowledge of TB symptoms, history of prison and TB treatment outcome were not statistically associated with MDR-TB in this study. The non-existence of a statistical association between these factors and MDR-TB in this study does not mean that they are not significant factors affecting the occurrence of MDR-TB. These findings might be due to possible variations in the epidemiology of the disease and the socioeconomic status and health status of the community. Therefore, it is important to mention that the current findings do not mean that these factors are not related to MDR-TB. However, the authors decided to focus the following discussion on those variables that were found to be statistically associated with the occurrence of MDR-TB in the studied areas.

In this study, patients who had a history of contact with known patients with TB were at higher risk of developing MDR-TB than their counterparts. This finding was supported by a study done in Oromia region, Ethiopia, Burundi, Mali, Nepal.[7 11 17 18] This could be because contacts of patients with TB are at a greater risk of contracting either TB infection or TB disease, depending on factors such as type of contact infectiousness of source case and environmental characteristics. Besides, patient-related factors (increased age and immunological suppression) could aggravate the occurrence of MDR-TB.

Meanwhile, either the transmission of MDR strains or the selection of single drug-resistant strains may have contributed to the occurrence of MDR-TB.[19]

In the present study, patients with a previous history of TB treatment were at a higher risk of contracting MDR-TB as compared with those without a history of TB treatment. This finding was consistent with a study done in Shoa, Addis Ababa, Ethiopia, Sudan, Malaysia, Bhutan, Thailand, Minas Gerais, Brazil.[11 20–25] The acquired drug resistance of *M. tuberculosis* to anti-TB drugs can occur when there is a history of incomplete or inappropriate TB treatment regimens lasting at least 1 month.[26] This might be because prior inadequate anti-TB treatment only suppresses the growth of susceptible bacilli and does not affect other resistant strains, leading to suitable conditions for the dominant multiplication of pre-existing drug-resistant mutants, which is a rise and fall phenomenon. In a similar manner, patients with MDR-TB in this study may have experienced similar conditions of previous inadequate treatment that led to the occurrence of MDR-TB. Additionally, patients with poor adherence and treatment discontinuation may increase the risk of TB recurrence and the probability of acquired drugs resistance.**26 27**

In this study, patients who had a history of cigarette smoking were at a higher risk of contracting MDR-TB. This finding was inconsistent with a study conducted in Shoe, Ethiopia.[11] But, this finding was consistent with a study conducted in Burundi,[7] Nepal, Belarus, Brazil, China.[28–31] Several studies have indicated that cigarette smoking increases the risk of TB infection by suppressing the immune system of infected individuals.[32] Therefore cigarette smoking was strongly associated with an increased risk of TB, and with the recurrence and severity of pulmonary TB.[33]

In the current study, patients living in rural areas were at a higher risk of developing MDR-TB as compared with urban dwellers. This finding was comparable to a study done in Oromia region, Ethiopia,[11] Sudan,[34] Abu-Anga, Sudan.[35] In contrast, living in a rural area was not significantly associated with MDR-TB in a study done in Amhara region, Ethiopia, Yemen, Bhutan.[23 36 37] This difference might be because rural inhabitants do not have accessibility to healthcare facilities and lack proper counselling and education at the time of prescribing drugs as compared with their urban counterparts.

CONCLUSIONS

The findings of this study identified that history of contact with patients with TB, previous history of TB treatment, history of cigarette smoking and rural residence were statistically associated with occurrence of MDR-TB. Additionally, further studies should be conducted to clearly establish the epidemiological link and causal relationships between living in a rural setting, and cigarette smoking and the development of MDR-TB. In order to reduce the burden of drug resistance, strategies of controlling MDR-TB in the study area should emphasize on enhancing public health education and reducing treatment interruptions of tuberculosis and drug-resistant tuberculosis (TB/DR-TB) patients.

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Collaborators No.

Contributors FA designed the study, participated in data collection, analysed the data and drafted the manuscript. EA participated in data collection, statistical analysis and responsible for the overall content as guarantor. AG, TS and TG critically revised the manuscript for methodological and intellectual content. All authors read and approved the final version of the manuscript.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethical review board of Wachemo University (reference number 114/2021). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author on reasonable request.

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