BMC Infectious Diseases

RESEARCH

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Prevalence of drug-resistant *Mycobacterium tuberculosis* and its associated factors among tuberculosis patients attending Dilla university referral hospital, Ethiopia

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Abstract

Background Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) and is the second leading cause of death from contagious diseases worldwide. Ethiopia is among the 30 countries with the highest burden of TB and TB/HIV co-infection. The emergence and spread of drug-resistant TB present significant challenges to TB care and control efforts, particularly multi-drug-resistant TB, which poses a serious public health issue in low-income countries such as Ethiopia. This study aimed to determine the prevalence of drug-resistant TB and its associated factors among TB patients in Dilla University Referral Hospital (DURH).

Method A prospective cross-sectional study was conducted from March-2024 to May-2024 among 216 pulmonary TB patients attending DURH. Gene Xpert MTB/RIF Ultra and Xpert MTB/XDR assay was used to assess the pattern of drug resistance in TB. The Xpert MTB/RIF Ultra assay was used to detect rifampicin resistance, while the Xpert MTB/XDR assay was employed to identify isoniazid resistance and resistance to second-line anti-TB drugs when rifampicin resistance was detected. Data were analyzed by using the Statistical Package for Social Sciences (SPSS) version 25.

Result In this study, out of 216 confirmed MTB cases, 5 (2.3%) were identified as drug-resistant TB (DR-TB), with mono-resistance to rifampicin and isoniazid at 1.4% and 0.9%, respectively. The statistical analysis revealed a significant difference in DR-TB prevalence between those with and without a history of anti-TB treatment ($p=0.001$). Notably, isoniazid mono-resistant TB was more prevalent among individuals with diabetes mellitus and those with a history of previous treatment, showing p-values of 0.018 and 0.015, respectively.

Conclusion Among the 216 confirmed TB cases, 5 cases of DR-TB were identified, accounting for 2.3%. DR-TB was more prevalent in patients with a history of anti-TB treatment, highlighting the urgent need for enhanced early detection and improved treatment monitoring. Additionally, isoniazid mono-resistant TB was notably prevalent in individuals with diabetes mellitus and prior treatment history, with p-values of 0.018 and 0.015, respectively. Targeted interventions for these high-risk groups are essential to address drug resistance in TB, enabling us to effectively tackle the emergence of drug-resistant TB at both local and national levels.

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Keywords Drug-resistance, *Mycobacterium tuberculosis*, Associated factors, Gedo, Ethiopia

Background

Tuberculosis (TB) is a preventable and usually curable disease [1]. However, in 2023, it likely became the leading cause of death from a single infectious agent again, surpassing COVID-19, and resulting in nearly twice as many deaths as HIV/AIDS. The Global TB Report 2024 indicates that about 10.8 million people developed active TB disease worldwide in 2023, an increase from 10.7 million in 2022. In the same year, there were 1.25 million TB-related deaths, and an estimated 400,000 people developed drug-resistant TB (DR-TB) [2].

Drug-resistant strains of *Mycobacterium tuberculosis* (MTB) emerge due to spontaneous chromosomal mutations occurring at a low frequency. However, studies have shown that selection pressure from the inappropriate use of anti-TB drugs leads to the development of DR-TB [3]. Resistance to both first- and second-line anti-TB drugs is associated with specific genetic mutations: KatG and inhA for isoniazid resistance; rpoB for rifampicin resistance; gyrA and less frequent gyrB for fluoroquinolone (FLQ) resistance; rrs and the eis promoter region for aminoglycosides (amikacin/kanamycin); rrs and tlyA for capreomycin resistance. A person can get DR-TB through primary direct transmission and secondary due to inadequate TB treatment for extended duration of time [4].

The World Health Organization (WHO) classifies DR-TB cases into five categories: isoniazid-resistant tuberculosis, TB that is resistant to rifampicin (RR-TB), multi-drug resistant TB (MDR-TB), pre-extensively drug-resistant TB (pre-XDR-TB), and extensively drug-resistant TB (XDR-TB) [5]. MDR-TB is caused by MTB strains resistant to isoniazid and rifampicin, the two most effective TB drugs [6]. In 2021, an estimated 3.6% of new TB cases and 18% of previously treated cases were MDR/RR-TB globally [7].

Despite comprising only 15% of the global population, TB poses a significant public health challenge in the WHO African region, accounting for 23% of new TB cases and 31% of TB-related deaths. DR-TB, including RR and MDR-TB, is increasingly problematic, affecting 77,000 individuals in the area [7]. In 2020, of 14 countries listed by WHO that have had the highest triple burden of TB, HIV, and MDR-TB, eight are in sub-Saharan Africa [8]. Ethiopia remained among the 30 countries with a high burden of TB and TB/HIV while transitioning out of the list of MDR/RR-TB for 2021–2025 [7]. According to the 2024 WHO global TB report, the country has an annual TB incidence rate of 146 cases per 100,000 people, with 1.1% of newly diagnosed and 12% of previously treated TB cases classified as MDR/RR-TB [2]. The magnitude and extent of drug resistance in TB is being monitored in Ethiopia through periodic drug resistance surveys (DRS). The third national DRS completed in 2019 revealed a 1.1% prevalence of RR-TB among new cases and 7.5% among previously treated cases [9].

Several factors contribute to the development and transmission of DR-TB [10]. The situation is worsening in developing countries like Ethiopia, where high HIV prevalence, low socioeconomic status, and inadequate diagnostic and treatment facilities exacerbate the impact of MDR-TB. In high-burden countries such as Ethiopia, individuals with TB and MDR-TB often remain undiagnosed and untreated for long periods, increasing the risk of treatment failure and facilitating the spread of the disease within the community [11]. Studies conducted in Ethiopia and China have identified major risk factors for MDR-TB spread, including cigarette smoking, alcohol consumption, overcrowding, and weak DOTS (Directly Observed Treatment Short-course) programs [3]. DOTS is designed to promote adherence to the full course of drug therapy, improving patient outcomes and preventing the development of drug resistance [12]. However, incomplete adherence to the therapeutic regimen and premature treatment termination can lead to clinical unresponsiveness and the emergence of drug-resistant strains [13].

Finding the missing TB and DR-TB cases and closing the incidence-to-case notification gaps remain the top priorities in Ethiopia. In 2020, the country missed 29% of incident TB cases and 59% of RR/MDR-TB cases [9]. Studies indicate that these diagnostic gaps can lead to resistant strains circulating in populations [14]. Ethiopia has also adopted the global End TB strategy, which aims to end the TB epidemic by 2035 [9]. The emergence of TB resistant to key TB medications, such as isoniazid and rifampicin, has hindered the progress being made in controlling the TB epidemic. Additional resistance to core second-line drugs, i.e., fluoroquinolone (FLQ), has been a recent phenomenon in Ethiopia, requiring treatment with new and repurposed TB drugs, however the actual prevalence is not yet well known [15]. Therefore, this study aims to determine the prevalence of DR-TB and its associated factors among TB patients.

Methods

Study design, period, and setting

A hospital-based cross-sectional study was conducted in Dilla University Referral Hospital (DURH), Gedeo zone, South Ethiopia, from March 2024 to May 2024. The hospital is located in Dilla Town, the capital of the Gedeo Zone administration, and it is 90 km from Hawassa and 365 km from Addis Ababa, the capital city of Ethiopia.

The hospital serves as a referral center for patients from health centers, district hospitals, and other private health facilities in the Gedeo Zone and patients from the neighboring Sidama and Oromia Regions. It has a TB clinic where patients with TB are registered and treated based on the DOTS strategy, according to the national TB case treatment recommendation.

Source population and study populations

All presumptive pulmonary TB cases who visited DURH during the study period were the source population. The study population was all pulmonary TB-positive patients (both new and previously treated) who tested positive by Gene Xpert MTB/RIF Ultra at the DURH microbiology laboratory during the study period. Presumptive TB cases were initially diagnosed at the hospital's outpatient departments and referred to the laboratory for GeneXpert testing. Those who tested positive were then sent to the TB clinic for treatment.

Eligibility criteria

The inclusion criteria specified that all pulmonary TB positive patients who were newly diagnosed pulmonary TB patients during the study period and could provide written informed consent were included. Conversely, patients who were seriously ill and unable to produce sputum were excluded.

Sample size and sampling technique

Considering a 16.7% prevalence of DR-TB from a previous study conducted in Ethiopia [10], 5% precision (d = 0.05), and a 95% level of confidence (z = 1.96), the sample size was calculated using the single population proportion formula: n = (1.96/0.05) 2 ∗ 0.167 (1–0.167) = 213. Consequently, the study included 216 consecutive TB-positive patients visiting the DURH microbiology laboratory during the study period.

Data collection

After receiving written informed consent from all study participants, a structured questionnaire adapted from previously conducted studies and national guidelines for TB, DR-TB, and leprosy was used to collect the sociodemographic, behavioral, and clinical data [10, 15–17]. The questions were presented to study participants by face-to-face interview using patient language.

Laboratory methods

Specimen collection

Participants were instructed to provide a sputum specimen (2–4 mL) in a sterile 50 mL Falcon tube specifically prepared for this purpose. Sputum samples were collected by laboratory staff according to federal ministry of health (FMoH) recommendations and were shared between the diagnostic and research teams. The specimens were examined on the same day using both the Xpert MTB/RIF Ultra and Xpert MTB/XDR assays, conducted by a health facility laboratory technologist on-site. The Xpert MTB/RIF Ultra assay was used to detect rifampicin resistance, while the Xpert MTB/XDR assay was employed to identify isoniazid resistance and resistance to second-line anti-TB drugs when rifampicin resistance was detected.

Xpert MTB/RIF ultra assay

The sputum specimens were examined for MTB and RR-TB using the Xpert MTB/RIF Ultra assay (Cepheid, Sunnyvale, USA). Briefly, 2 ml of sample reagent buffer was added to 1 ml of sputum specimen using a sterile pipette. Followed by incubation at room temperature for 15 min. 2 ml of the incubated sample was then transferred to the GeneXpert MTB/Ultra cartridge (Cepheid, Sunnyvale, CA), and the cartridge was then loaded into the GeneXpert device. The results were generated within 90 min, reported as both *M. tuberculosis* negative or positive, and whether those positive were RIF susceptible or resistant.

Xpert MTB/XDR assay Samples that were found to be rifampicin resistant with the Xpert MTB/RIF Ultra test were subjected to the Xpert MTB/XDR assay (Cepheid, Sunnyvale, USA) to determine the susceptibility for INH, FLQs and second-line injectable drugs. Additionally, rifampicin-susceptible MTB cases that remained positive after two months of anti-TB treatment were also tested with the Xpert MTB/XDR assay to determine susceptibility for Isoniazid monoresistance. The sample processing procedure and cartridge handling are the same as for Xpert Ultra; however, the Xpert MTB/XDR runs on a 10-color optics GeneXpert instrument [18].

Data processing and analysis

The collected data was checked for its completeness before entering for analysis. Then, it was exported to SPSS version 25 for analysis. The chi-square tests (continuity correction tests) were used to analyze the associated risk factors of DR-TB, and factors with a P-value ≤ 0.05 were taken as statistically significant.

Standard definitions

Rifampicin mono-resistant TB TB that is resistant to rifampicin only [7].

Isoniazid resistant TB TB that is resistant to isoniazid but susceptible to rifampicin [7].

Multi-drug resistant TB TB that is resistant to both isoniazid and rifampicin [7].

Table 1 Socio-demographic and other characteristics among pulmonary TB patients visiting TB clinic at DURH, South ethiopia, 2024. (*N* = 216)

Variables	Categories	Frequency	Percentage
Gender	Male	138	63.9
	Female	78	36.1
Age	≤ 14	3	1.4
	15–34	153	70.8
	35–44	25	11.6
	45–54	21	9.7
	≥ 55	14	6.5
Monthly Income	≤ 500	10	4.6
	501–1999	92	42.6
	2000–10,000	114	52.8
Residence	Rural	136	63.0
	Urban	80	37.0
Family size	≤ 5	58	26.9
	> 5	158	73.1
History of alcohol consumption	Yes	119	55.1
	No	97	44.9
Cigarette smoking habit	Yes	7	3.2
	No	209	96.8
History of imprisonment	Yes	15	6.9
	No	201	93.1
BMI Kg/M2	< 18.5	22	10.2
	≥ 18.5	194	89.8
TB contact history	Yes	70	32.4
	No	146	67.6
Previous treatment history	Yes	33	15.3
	No	183	84.7
History of diabetes mellitus	Yes	4	1.9
	No	212	98.1
HIV status	Positive	2	0.9
	Negative	101	46.8
	Unknown	113	52.3

Pre-XDR-TB TB that is resistant to rifampicin and any fluoroquinolone (a class of second-line anti-TB drugs) [7].

New case of TB patients have never been treated for TB or have taken anti-TB drugs for less than one month [9].

Previously treated TB patients who have received anti-TB drugs for one or more months in the past and again diagnosed with Tuberculosis [9].

Results

Socio-demographic and other characteristics

A total of 216 GeneXpert-positive samples were collected from 1,667 presumptive pulmonary TB patients who attended DURH during the study period. The median age of the study participants was 25 years [IQR: 20–35]. Among all the study participants, males account for 63.9% (138/216), and 63% (136/216) were rural residents. The average income of the study participants ranges from 400 to 10,000 Ethiopian Birr (ETB) per month, with a median of 2000 [IQR: 1000–2500]. More than half of the patients had an alcohol consumption history (55.1%) and the majority of the participants had a family size greater than 5 (73.1%) (Table 1).

Table 2 Drug resistant to INH and RIF among pulmonary TB patients visiting a TB clinic at DURH, South ethiopia, 2024

Resistance status	New cases (*n* = 183)	Previously treated cases (*n* = 33)	Total (*n* = 216)
Susceptible	182(99.4%)	29(87.9%)	211(97.7%)
Any resistant	1(0.5%)	4(12.1%)	5(2.3%)
Mono resistant			
• RIF	1(0.5%)	2(6.06%)	3(1.4%)
• INH	0	2(6.06%)	2(6.06%)
MDR-TB (RIF + INH)	0	0	0
Pre-extensively and extensively drug resistant TB	0	0	0
Total	183	33	216

INH: *Isoniazid; RIF*: Rifampicin

Magnitude of DR-TB

Of the 216 TB confirmed cases, the prevalence of any resistance to rifampicin or INH was 2.3% (5/216). There was 1.4% (3/216) mono-resistance to rifampicin, and about 0.9% (2/216) of the total were resistant to INH alone. There was no MDR-TB detected in this study. Additionally, the 3 cases of rifampicin resistance identified with the Xpert MTB/RIF Ultra test were subjected to the Xpert MTB/XDR assay (Cepheid, Sunnyvale, USA) to determine the susceptibility for FLQs and second-line injectable drugs, and none of the RR cases showed resistance to the tested drugs (Table 2).

Factors associated with drug resistant TB

Among the various factors assessed in this study, prior treatment with anti-TB drugs was statistically associated with the prevalence of mono-drug-resistant TB, with a p-value of 0.001 (Table 3). The study also found a statistically significant association of INH-resistant TB among patients with diabetes mellitus and a history of previous treatment, with p-values of 0.018 and 0.015, respectively (Table 4). However, no statistically significant association was found between sociodemographic or clinical characteristics and the development of RR-resistant TB ($p > 0.05$).

Discussion

Studies around the world have reported a diverse magnitude of DR-TB infections. This study revealed an overall 2.3% (95% CI: 2.3–5.3) prevalence of any resistance to RIF or INH among TB patients. Which is lower than the reports of earlier studies, that ranging from 6.8 to 18.4%

Table 3 Drug-resistant TB and its associated factors among pulmonary TB patients visiting a TB clinic at DURH, South Ethiopia, 2024

Factors	Category	any drug-resistant TB		*P*-value*
		Yes	No	
Another house member with TB	Yes	5(3.4%)	143 (96.6%)	0.295
	No	0(0%)	68 (100%)	
Alcohol consumption	Yes	4 (4.6%)	83 (95.4%)	0.170
	No	1 (0.8%)	128 (99.2%)	
History of hospitalization	Yes	2 (8.3%)	22 (91.7%)	0.624
	No	3 (30%)	7 (70%)	
Previous treatment history	Yes	4 (12.1%)	29 (87.9%)	< 0.0001*
	No	1 (0.5%)	182 (99.5%)	
Diabetes mellitus	Yes	1 (25%)	3 (75%)	0.172
	No	4 (1.9%)	208 (98.1%)	
Cigarette smoking	Yes	0 (0%)	4 (100%)	0.756
	No	5 (2.4%)	207 (97.6%)	
MTB contact history	Yes	2 (2.9%)	68 (97.1%)	1.000
	No	3 (2.1%)	143 (97.9%)	
HIV/AIDS	Yes	0 (0.0%)	2 (100%)	0.824
	No	3 (3%)	98 (97%)	
	Unknown	2 (1.8%)	111 (98.2%)	

*: X^2 test unless otherwise stated

Table 4 INH-Resistant TB and its associated factors among pulmonary TB patients visiting a TB clinic at DURH, South Ethiopia, 2024

Factors	Category	INH resistance		*P*-value
		Yes	No	
Another household member with TB	Yes	2(1.4%)	146 (98.6%)	0.843
	No	0(0%)	68 (100%)	
Family size	≤ 5	2 (3.4%)	56 (96.6%)	0.123
	> 5	0 (0%)	158 (100%)	
MTB contact history	Yes	2 (2.9%)	68 (97.1%)	0.196
	No	0 (0%)	146 (100%)	
Previous treatment history	Yes	2 (6.1%)	31 (93.9%)	0.018*
	No	0 (0%)	183 (100%)	
Diabetes mellitus	Yes	1 (25%)	3 (75%)	0.015*
	No	1 (0.5%)	211 (99.5%)	

in different study settings [19–21]. In contrast, this estimate is higher compared to the previous reports of 1.8% in Oromia [22] and 1.5% in Kenya [23]. This discrepancy in the prevalence of DR-TB could be explained by the difference in geographical variation, methods of diagnosis (GeneXpert, and culture), study setting, or sample size.

The prevalence of RR-TB was 1.4% (95% CI: 0.3-4), which is lower than results from previous studies in various regions of Ethiopia and other countries: 9.8% in Adis Ababa [24], 8.3% in Amhara [25], 4.1% in Southern Ethiopia [26], and 5.1% in Gedeo, Southern part of Ethiopia [27]. In comparison to other African countries, it is lower than the reports from Banadir, Somalia, which indicated 10.6% [28] and 11% in Congo [29]. In this study, the prevalence of RR-TB was found to be 0.5% among newly diagnosed TB patients and 6.1% among those who had been previously treated. This is relatively lower than those reported in the third National DRS of Ethiopia, which indicated a prevalence of 1.1% in new cases and 7.5% in previously treated cases [9]. The lower prevalence of RR-TB may be attributed to geographical and demographic variations in the study population, accessibility to healthcare, sample size, study duration, and a general decline in TB incidence. However, the prevalence of RR-TB found in this study was in line with 0.9% in Tigray [10] and 0.3% in Lebanon [30]. A lower prevalence of RR-TB was also observed in other parts of Ethiopia, such as Jigjiga [21] and eastern Ethiopia [31], where no RR mono-resistant TB was detected.

The prevalence of INH mono-resistant TB was 0.9% (95% CI: 0.1–3.3), which is lower than 8.2% in Jigjiga [21], 4.3% in Tigray [32], 3.4% in Zambia [33], and 3.7% in South Africa [34]. But it is in line with Tigray's 1.3% [10], 2.5% in eastern Ethiopia [31], and 1.6% in other studies in the country [11].

The findings of the current study demonstrated that none of the MTB cases were found to be MDR, and all rifampicin mono-resistant cases were susceptible to the tested second-line anti-TB drugs, including fluoroquinolone. However, previous studies have reported a statistically significant proportion of MDR and Pre-XDR-TB, with prevalences of 61.9% in the selected TIC centers in Ethiopia [32], 16.7% in Tigray [10], 3.8% in the eastern Amhara region [31], 15% in a multicenter study conducted in Ethiopia [11], 5.7% in Amhara [4], and 1.7% in Zambia [33], respectively. The absence of resistance to second-line anti-TB drugs in this study may be related to the small sample size used and the absence of phenotypic DST availability at the study site.

In this study, 12.1% of participants with a history of TB treatment were positive for any of the RIF- or INH-resistant TB. The prevalence of DR-TB observed among study participants with a history of TB treatment shows a statistically significant difference from those without such a history ($p < 0.001$). The prevalence of DR-TB was higher among participants with a history of TB treatment. A similar pattern of results was obtained in the study conducted in other parts of Ethiopia: the eastern Amhara region, Oromia, and the southern and southwestern parts of Ethiopia [22, 25, 26, 35]. Studies conducted in other countries also reported the high prevalence of DR-TB among those who have a previous treatment history [36–38]. This high risk of acquisition of DR-TB among previously treated cases might be due to treatment interruption or non-adherence that made the bacteria mutate and develop resistance to the drug. During anti-TB treatment, if there is poor treatment adherence, there is a selective pressure where the drug only kills the drug-susceptible Mycobacterial strain, leaving the resistant ones that could cause DR-TB onwards [39].

Furthermore, the majority of the DR-TB cases (60%) (3/5) were in the age group of 14–34 years, which is within the productive age group. This is consistent with previous reports in Ethiopia [38, 39]. This might be due to more exposure to the outer environment, the wide range of mobility of young people to acquire TB bacilli, and additional risk factors correlated with age, such as substance use [40–42]. In this study, the detection rate of DR-TB was significantly higher in males (60%) than females (40%). Likewise, reports from WHO [7], Ethiopia, eastern Amhara [25], Cameroon [43], and Zambia [33] support this finding. The reason for this might be due to disparities in access to high-quality TB care, health-seeking behavior differences, and the higher occupational exposure of males to smoking and alcoholism [41].

Even though this study revealed that only history of treatment was statistically associated with DR-TB, several studies have reported that factors including HIV/AIDS, smoking, and TB contact history were the potential risk factors for the acquisition of DR-TB infection [10, 14, 38, 44].

Limitations of the study

This study had two limitations. First, this study lacks additional drug susceptibility tests, such as phenotypic DST (culture); as a result, there was no bacteriological confirmation to verify the findings from the GeneXpert assay. Second, since all study participants were TB patients seeking health services at the hospital, the reported findings may not accurately reflect the true burden of the issue at the community level. Despite these limitations, the study provides baseline information on drug-resistant TB concerning first-line and second-line anti-TB drugs and assesses various risk factors associated with DR-TB cases in the study area.

Conclusion and recommendation

The prevalence of any drug-resistant TB among the confirmed TB cases was 5/216 (2.3%). The proportions of RR-TB and INH mono-resistant TB were 1.4% and 0.9%, respectively. Moreover, the prevalence of DR-TB was statistically significant among participants with a history of anti-TB treatment compared to those without such a history. Additionally, isoniazid mono-resistant TB was notably prevalent in individuals with diabetes mellitus and prior treatment history, with p-values of 0.018 and 0.015, respectively. These findings highlight the need for improved monitoring of treatment practices to reduce the emergence of DR-TB. Therefore, it is essential to strengthen efforts for the early detection of DR-TB to prevent treatment failures and minimize disease transmission both in the study area and across the nation. Additionally, further research on the drug susceptibility patterns of first- and second-line anti-TB medications will help to gain a comprehensive understanding of the extent of DR-TB and explore the factors contributing to its prevalence in the study area.

Abbreviations

DR-TB	Drug-Resistant Tuberculosis
DURH	Dilla University Referral Hospital
MDR-TB	Multi-Drug-Resistant Tuberculosis
RR-TB	Rifampicin Resistant Tuberculosis
TB	Tuberculosis
XDR-TB	Extensively Drug-Resistant Tuberculosis

Acknowledgements

The authors express their gratitude to the Hawassa University School of Medicine and Health Sciences for the opportunity and support provided during this research. We also thank the laboratory staff and health professionals at Dilla University Referral Hospital for their collaboration in data collection and laboratory work. Lastly, we sincerely appreciate the study participants in the area, without whom this study would not have been possible.

Author contributions

M.H: Participated in designing the study, Writing-original draft, data collection and date analysis. Y.M: Participated in designing the study, Writing-review and editing and supervision. A.M: Participated in designing the study, Data collection, F.B: Date analysis, interpretation, and review M.M.A: Participated in, designing the study, Writing-review and editing and supervision. All authors read and approved the final version of the manuscript.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Hawassa University College of Medicine and Health Science with protocol approval number IRB/163/16. All participants agreed to participate in the study after detail information is provided. All methods were conducted in compliance with the relevant guidelines and regulations outlined in the Declaration of Helsinki.

Consent for publication

All participants consented to the publication of the data collected from them in an anonymous format.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 30 January 2025 / Accepted: 30 May 2025
Published online: 06 June 2025

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