Risk factors associated with drug-resistant tuberculosis in Ethiopia: A systematic review and meta-analysis

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Abstract

The emergence of drug-resistant tuberculosis (DR-TB) is becoming a challenge to the national TB control programs including Ethiopia. Different risk factors are associated with the emergence of DR-TB. Identifying these risk factors in a local setting is important to strengthen the effort to prevent and control DR-TB. Thus, this study aimed to assess the risk factors associated with drug-resistant TB in Ethiopia. The Preferred Reporting Items for Systematic Reviews and Meta-analysis checklist was followed to conduct this study. We systematically searched the articles from electronic databases and gray literature sources. We used the Joanna Briggs Institute Critical Appraisal tools to assess the quality of studies. Data were analyzed using STATA version 15. We estimated the pooled OR along with 95%CI for each risk factor. The heterogeneity of the studies was assessed using the forest plot and I^2 heterogeneity test. Besides, we explored the presence of publication bias through visual inspection of the funnel plot and Egger's regression test. After intense searching, we found 2238 articles, and 27 eligible studies were included in the final analysis. Based on the pooled analysis of the odds ratio, unemployment (OR; 2.71, 95% CI; 1.64, 3.78), having a history of the previous TB (OR; 4.83, 95% CI; 3.02, 6.64), having contact with a known TB patient (OR; 1.72, 95% CI; 1.05, 2.40), having contact with a known MDR-TB patient (OR; 2.54, 95% CI; 1.46, 3.63), and having pulmonary TB (OR; 1.80, 95% CI; 1.14, 2.45) were found to be the risk factors of drug-resistant TB. While older age TB patients (OR; 0.77, 95% CI; 0.60, 0.95) including age above 45 years OR; (0.76, 95% CI; 0.55, 0.97), and males (OR; 0.86, 95% CI; 0.76, 0.97) were found to had lower risk of DR-TB compared to their counterparts. A previous history of TB treatment is a major risk factor for acquiring DR-TB in Ethiopia that might be due to poor adherence during the first-line anti TB treatment. Besides, having contact with a known TB patient, having contact with a known MDR-TB patient, having pulmonary TB, and being unemployed were the risk factors of DR-TB in Ethiopia. Thus, active screening of TB contacts for DR-TB might help to detect DR-TB cases as early as possible and could help to mitigate its further transmission across the community.

Title page

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Abstract

The emergence of drug-resistant tuberculosis (DR-TB) is becoming a challenge to the national TB control programs including Ethiopia. Different risk factors are associated with the emergence of DR-TB. Identifying these risk factors in a local setting is important to strengthen the effort to prevent and control DR-TB. Thus, this study aimed to assess the risk factors associated with drug-resistant TB in Ethiopia. The Preferred Reporting Items for Systematic Reviews and Meta-analysis checklist was followed to conduct this study. We systematically searched the articles from electronic databases and gray literature sources. We used the Joanna Briggs Institute Critical Appraisal tools to assess the quality of studies. Data were analyzed using STATA version 15. We estimated the pooled OR along with 95%CI for each risk factor. The heterogeneity of the studies was assessed using the forest plot and I^2 heterogeneity test. Besides, we explored the presence of publication bias through visual inspection of the funnel plot and Egger's regression test. After intense searching, we found 2238 articles, and 27 eligible studies were included in the final analysis. Based on the pooled analysis of the odds ratio, unemployment (OR; 2.71, 95% CI; 1.64, 3.78), having a history of the previous TB (OR; 4.83, 95% CI; 3.02, 6.64), having contact with a known TB patient (OR; 1.72, 95% CI; 1.05, 2.40), having contact with a known MDR-TB patient (OR; 2.54, 95% CI; 1.46, 3.63), and having pulmonary TB (OR; 1.80, 95% CI; 1.14, 2.45) were found to be the risk factors of drug-resistant TB. While older age TB patients (OR; 0.77, 95% CI; 0.60, 0.95) including age above 45 years OR; (0.76, 95% CI; 0.55, 0.97), and males (OR; 0.86, 95% CI; 0.76, 0.97) were found to had lower risk of DR-TB compared to their counterparts. A previous history of TB treatment is a major risk factor for acquiring DR-TB in Ethiopia that might be due to poor adherence during the first-line anti TB treatment. Besides, having contact with a known TB patient, having contact with a known MDR-TB patient, having pulmonary TB, and being unemployed were the risk factors of DR-TB in Ethiopia. Thus, active screening of TB contacts for DR-TB might help to detect DR-TB cases as early as possible and could help to mitigate its further transmission across the community.

Keywords: Risk factors, Determinants, Drug-resistant tuberculosis, Ethiopia

INTRODUCTION

National tuberculosis (TB) control programs are challenged by the emergence of drug-resistance to more anti-TB drugs resulting in multi-drug resistant tuberculosis (MDR-TB), pre-extensively drug-resistant TB (pre-XDR-TB), and extensively drug-resistant TB (XDR-TB). Globally, about 465, 000 population have rifampicin-resistant TB (RR/TB) (78% MDR-TB), were about 3.5% among new cases and 18% among previously treated cases developed RR/MDR-TB. In addition, about 9% of RR/MDR-TB patients develop XDR-TB (WHO, 2020). The problem is also worse high burden countries including Ethiopia. In Ethiopia, based on the 2019 global TB report there were about 1600 RR/MDR-TB estimated cases where only 741 were laboratory confirmed, and 747 enrolled in treatment (WHO, 2019). In the country, about 12% among previously treated and 0.71% among the new TB cases are estimated to have RR/MDR-TB (WHO, 2020).

The poor treatment adherence during anti-TB treatment such that not taking TB drugs regularly or not taking the full dose of TB drugs result in the emergence of DR-TB. During anti-TB treatment, if there is a poor treatment adherence there is a selective pressure where the drug only kills the drug-susceptible *Mycobacterial* strain is leaving the resistant ones that could cause a DR-TB onwards (Petrini et al., 1999). The other major mechanism of acquiring DR-TB is through the transmission of drug-resistant *Mycobacterial* strains among the community. Someone who had contact with a person with DR-TB becomes easily got the disease (WHO, 2012). However, the transmission of DR-TB among the community can be favored by different factors such as demographic, behavioral, clinical, and environmental factors (Li et al., 2015). These risk factors vary from setting to setting and from community to community. Therefore, assessing the major associated risk factors contributing to the emergence of DR-TB based on data-driven from the local setting is important to take appropriate action. Even though there are individual studies that assessed the risk factors of DR-TB in different settings in Ethiopia, their finding is inconclusive and there is limited information that addressed the risk factors of DR-TB at the national level. However, identifying these factors at the national level would be an important input to aid the national TB control program in preventing and controlling the emergence of DR-TB in the country. Thus, this study aimed to assess the risk factors associated with

DR-TB in Ethiopia by performing a pooled estimate from individual studies.

METHODS

Search strategy

The study was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist designed for systematic review and meta-analysis studies (Hutton et al., 2015; Knobloch et al., 2011) **(Additional file 1).** A systematic article searching was conducted using an electronic database (PubMed). The search was also performed using the gray literature sources such that WorldCat, Google Scholar and Google. The search was conducted regardless of the publication year. The searching was conducted up to 20 August 2021. Predictors, determinates, risk factors, drug-resistant, multi-drug resistant, rifampicin-resistant, extensively drug-resistant, tuberculosis, and Ethiopia were the keywords used during the searching process. The Boolean operators AND and OR were used accordingly. The search string of the PubMed was (((((((determinants) OR (Predictors)) OR ("Risk Factors" [Mesh])) AND ("Drug Resistance" [Mesh] OR "Tuberculosis, Multidrug-Resistant" [Mesh])) OR (rifampicin resistant)) AND ("Tuberculosis" [Mesh])) OR (TB) AND ("Ethiopia" [Mesh]) **(Additional file 2).** Two authors (AA, GD) who have previous experience in conducting a systematic review and meta-analysis studies performed the article searching independently under the guidance of a senior librarian at the Ethiopian Public Health Institute. The inconsistencies that arose between two authors were resolved by the third author (ZWB).

Study selection procedure

In the current study, original studies that assessed the risk factors/determinates/predictors of drug-resistant TB at different settings of Ethiopia that are published in the English language were included. Drug-resistant TB in the current study includes either resistance to any of the anti-TB drugs or rifampicin-resistant TB or MDR-TB. While articles that did not reported the risk factors in mixed TB patients both drug-suceptible and drug-resistant TB, incomplete outcomes, commentaris, and without full–text were excluded from the present study. After conducting intense article searching in the available databases and gray literature sources, article screening was conducted through different stages. Primarily the duplicates were removed using the Endnote 8 citation manager. In the second stage, we assessed the articles by title and abstract, and in the third stage, those articles that passed screening by title and abstract were assessed for full-text review. Finally, the eligibility of the individual studies to be included in the final analysis was performed by two independent authors (AA, GD), and the inconsistencies were resolved by the third author (ZWB) through discussion **(Figure 1).** The PICOS criteria (participants, interventions, comparison, outcome, and study setting) were used to assess the eligibility of the individual studies.

PICOS criteria

Participants: Tuberculosis patients

Interventions: Drug-*resistant tuberculosis*

Comparators: drug-susceptible tuberculosis

Outcomes: Risk factors of drug-resistant tuberculosis

Study type: Cross-sectional and case-control studies.

Study setting: Any setting in Ethiopia

Data extraction

Independent data extraction was performed by two authors (AA, ZWB), and the inconsistencies were resolved by the third author (GD). The extracted data includes; study characteristics (author, publication year, study area per regional state, study setting, data collection period), study age-group, the type of drug-resistant-TB (any drug-resistant TB, RR-TB, MDR-TB), the sample size (cases, controls), and different risk factors of

DR-TB using the odds ratio along with the 95% CI. We summarized the extracted data using Microsoft Excel 2016

(Table 1).

Quality assessment

We assessed the quality of studies using the Joanna Briggs Institute Critical Appraisal (JBI) tools designed for cross-sectional and case-control studies (Moola et al., 2020). The critical appraisal checklist for the cross-sectional and case-control studies contains eight and ten questions respectively. Each question was scored out of 100% and finally, the sum of all questions was turned into 100%. The quality score was graded as low if $<$ 60%, medium if 60–80% and high if $>$ 80% (Porritt et al., 2014; Munn et al., 2019). Two authors (AA, GD) independently assessed the quality of the studies and the third author (ZWB) resolved the inconsistencies through discussion **(Additional file 3)** .

Outcomes

The primary outcome of this systematic review and meta-analysis study was drug-resistant TB. Whereas, the risk factors associated with DR-TB were the secondary outcomes. The pooled odds ratio along with their 95% CIs were estimated to assess the risk factors associated with DR-TB in Ethiopia.

Data analysis

Data that were summarized in Microsoft Excel 16 spreadsheet were exported to STATA version 15 for statistical analysis. The pooled OR with 95%CI of each risk factor was estimated by assuming the true effect size varies between studies. We presented the pooled results using a forest plot. We used the forest plot and I ^{2}heterogeneity test to assess the heterogeneity among the studies**.** The I^2 values of 25%, 50%, and 75% were interpreted as the presence of the low, medium, and high heterogeneity, **respectively (Sterne and Egger, 2001; Riley et al., 2011). In this study, we used a random-effects model for all risk factors to perform the analysis by considering substantial variability among the studies (Riley et al., 2011). We explored the** presence of publication bias through visual inspection of the funnel plot and statistical significance of Egger's regression test.

RESULTS

Study characteristics

After the systematic article searching in the available databases and other literature sources, we identified 2238 articles. After removing 244 duplicates, 1994 articles were screened by title and abstract. Then, full-text screening was conducted for 43 articles. Finally, after the full-text screening, 27 eligible articles were included in the study (Abay et al., 2020; Abdella et al., 2015; Adane et al., 2015; Alene et al., 2019; Arega et al., 2019; Assefa et al., 2017; Babure et al., 2019; Bedewi et al., 2017; Biru et al., 2020; Deressa et al., 2014; Desissa et al., 2018; Dessalegn et al., 2016; Fikre et al., 2019; Gobena et al., 2018; Hamusse et al., 2016; Hirpaet al., 2013; Jaleta et al., 2017; Mehari et al., 2019; Mekonnen et al., 2015; Mesfin etal., 2018; Mulisa et al., 2015; Mulu et al., 2015; Seyoum et al., 2014; Tadesse et al., 2015; Tesfay et al., 2016; Tsega et al., 2017; Welekidan et al., 2020). We presented the detail using the PRISMA flow diagram **(Figure 1).** The studies were conducted in different administrative regions across the country with the most frequent studies were from Addis Ababa (7 studies) followed by the Amhara region (6 studies), the Oromia region (5 studies), and the Tigray region (4 studies). However, the studies were reported from the majority of the regional administrative states. The studies were based on data collected from TB patients in health care facilities. The study period for these studies ranges from 2008 (Tadesse et al., 2015) to 2019 (Welekidan et al., 2020). Based on the study designs, 15 studies were cross-sectional studies while the remaining 12 studies used a case-control study design. The majority of the studies included all the age group categories while three studies and two studies included TB patients above 15 and 18 years of age respectively. The studies assessed the risk factors/determinates of either MDR-TB (18 studies), RR-TB (3 studies), or any type of

drug resistance (6 studies). The sample size of individual studies ranges from 65 in a study conducted by Babure et al. (2019) to 1876 in a study done by Arega et al. (2019) **(Table 1).**

Risk factors of drug-resistant tuberculosis

In the current study, we extracted data to assess the risk factors of drug-resistant TB in the Ethiopian setting. The risk factors include; socio-demographic characteristics (age, sex, marital status, residence, occupation, and family size), behavioral characteristics (smoking status, alcohol consumption, and khat chewing), and clinical characteristics (HIV serostatus, DM co-occurrence, contact history, imprisonment, previous TB treatment, number of TB episodes, and site of TB infection). We performed a pooled analysis for each variable using a random effect model by considering substantial variability among the individual studies. Based on the pooled analysis of the odds ratio, unemployment (OR; 2.71, 95% CI; 1.64, 3.78, I^2; 0.0%) **(Figure 2)** , having a history of previous TB (OR; 4.83, 95% CI; 3.02, 6.64, I^2; 69.6%) **(Figure 3)** , having contact with a known TB patient (OR; 1.72, 95% CI; 1.05, 2.40, I^2; 73.8%) **(Figure 4)** , having contact with a known MDR-TB patient (OR; 2.54, 95% CI; 1.46, 3.63, I^2; 0.0%) **(Figure 5)** , and having pulmonary TB (OR; 1.80, 95% CI; 1.14, 2.45, I^2; 71.4%)**(Figure 6)** were found to be the risk factors associated with drug-resistant TB in Ethiopia. While, old age individuals (OR; 0.77, 95% CI; 0.60, 0.95, I^2; 47.2%) **(Figure 7)**including above 45 years of age (OR; 0.76, 95% CI; 0.55, 0.97, I^2; 47.6%) **(Figure 8)** , and males (OR; 0.86, 95% CI; 0.76, 0.97, I^2; 19.0%) **(Figure 9)**had lower risk of DR-TB compared to their counterparts **(Table 2)** .

However, statistically significant association was not found for the following variables; urban residence (OR; 0.86, 95% CI; 0.58, 1.15, I^2; 75.2%), being single (OR; 1.12, 95% CI; 0.84, 1.40, I^2; 46.0%), being a house wife (OR; 0.86, 95% CI; 0.50, 1.21, I^2; 0.0%), being a farmer (OR; 0.81, 95% CI; 0.42, 1.19, I^2; 48.0%), being a daily laborer (OR; 0.97, 95% CI; 0.16, 1.78, I^2; 33.4%), family size above three members (OR; 0.87, 95% CI; 0.61, 1.14, I^2; 0.0%), alcohol consumption (OR; 0.96, 95% CI; 0.53, 1.38, I^2; 70.01%), khat chewing (OR; 1.01, 95% CI; 0.63, 1.38, I^2; 0.0%), smoking (OR; 0.75, 95% CI; 0.34, 1.16, I^2; 58.3%), imprisoned (OR; 1.00, 95% CI; 0.43, 1.56, I^2; 0.0%), being *HIV* positive (OR; 1.35, 95% CI; 0.95, 1.74, I^2; 73.6%), having DM (OR; 0.85, 95% CI; -0.85, 1.93, I^2; 0.0%), and having two or more number of TB episodes (OR; 1.03, 95% CI; -0.03, 2.99, I^2; 79.2%) **(Table 2) (Supplementary figure 1)** .

Accordingly, those individuals who were unemployed had 2.71 times the odds to develop DR-TB compared to the employed ones. Likewise, those individuals who had a history of previous TB had 4.83 times the odds to develop DR-TB compared to new TB patients. Similarly, those who had a contact history with a known TB patient had 1.72 times the odds to develop DR-TB compared to their counterparts. Also, those who had a contact history with a known MDR-TB patient had 2.54 times the odds to develop DR-TB compared to individuals who didn't have a contact history with a known MDR-TB patient. Besides, individuals with pulmonary TB had1.80 times the odds to develop DR-TB compared with patients with extrapulmonary TB. While the risk of DR-TB decreased by 23% among older age groups, i.e. individuals who were above 45 years had a 24% decreased risk of DR-TB compared to individuals below 45 years of age. Likewise, the risk of DR-TB decreased by 14% among males compared to females **(Table 2)** .

Publication bias assessment

Based on the funnel plot and the Egger's regression test publication bias was detected for older age (P<0.001), above 45 years age (P<0.001), male sex (P=0.0047), being single (P=0.0036), being farmer (P<0.0299), urban residence (P<0.001), HIV seropositive (P<0.001), smoking (P<0.001), alcohol consumption (P<0.001), previous TB history (P<0.001), having two or more TB episodes (P<0.001), and contact with known TB patient (P=0.001). While publication bias was not detected for age above 40 years (P=0.0608), family size above three members (P=0.7071), being a daily laborer (P=0.7341), being a house wife (P=0.3798), unemployed (P=0.8805), imprisoned (P=0.3692), having contact with known MDR-TB patient (P=0.3425), khat consumption (P=0.2586), having DM (P=0.3082), and having pulmonary TB (P=0.0622)

DISCUSSION

In the current study, we explored in detail the risk factors associated with drug-resistant TB in Ethiopia using 27 eligible articles. After performing a pooled analysis for 18 variables extracted from individual studies, we found that five variables such that unemployment, having a history of previous TB, having contact with a known TB patient, having contact with a known MDR-TB patient, and having pulmonary TB were the risk factors associated with drug-resistant TB in Ethiopia. However, older age and male individuals had a lower risk compared to their counterparts.

The current study revealed that those individuals who were unemployed had 2.71 times the odds to develop DR-TB compared to the employed ones. It was also supported in a global pooled estimate performed by Pradipa et al. (2018). The poor living condition of unemployed individuals that leads them to pathological changes might be the possible cause (Przybylski et al., 2014). The present study also revealed that previous history of TB treatment is a major risk factor associated with DR-TB in Ethiopia, such that those individuals who had a history of previous TB treatment had 4.83 times the odds to develop DR-TB compared to their counterparts. In line with this study, pooled estimates conducted at different countries across the globe reported a statistically significant association of previous TB treatment with DR-TB (Pradipta et al., 2018; Lukoye et al., 2015; Jimma et al., 2017; Faustini et al., 2006; Zhao et al., 2012). Studies reported that poor treatment adherence during anti-TB treatment results in the subsequent emergence of drug resistance (Zhao et al., 2012).

The other risk factor identified based on the pooled estimates in this study was having contact with a known TB patient whether with an MDR-TB patient specifically or with a TB patient as a general. Our study revealed that those individuals who had a contact history with a known TB patient had 1.72 times the odds to develop DR-TB compared to their counterparts. The risk becomes higher among individuals who had contact with an MDR-TB patient. Such that those who had a contact history with a known MDR-TB patient had 2.54 times the odds to develop DR-TB compared to individuals who did not have a contact history with a known MDR-TB patient. Studies from Burkina Faso and Bangladesh also supported it (Flora et al., 2013; Diande´ et al., 2009). Screening contacts could help to early detect DR-TB cases before disseminated across the population. Besides, the present study revealed that the site of infection was associated with DR-TB. Based on the pooled estimate in this study, individuals with pulmonary TB had 1.80 times the odds to develop DR-TB compared with individuals with extrapulmonary TB. A higher risk of DR-TB among PTB cases was also reported from India in a study based on a 13 years retrospective hospital-based analysis (Raveendran et al., 2015). Another study also supported this (Peto et al., 2009). Difficulties in detecting EPTB cases with lower bacterial loads might be the reason. The mycobacterial strains circulating in the country might be also a reason. For example, a study from China revealed that the DR-TB is higher among extrapulmonary TB cases compared to pulmonary TB cases due to the high prevalence of the Beijing strain (Pang et al., 2019).

The present study also revealed that older individuals had a lower risk to develop DR-TB. The pooled estimate revealed that individuals who were above 45 years had a 24% decreased risk of DR-TB compared to individuals below 45 years of age. Such that those productive age groups are at high risk of DR-TB in Ethiopia. Likewise, a pooled estimate in Jimma et al's. (2017) study based on a systematic review and meta-analysis conducted in Iran and its neighboring countries revealed that individuals below 45 years of age had 1.57 times the odds to develop MDR-TB compared with those individuals above 45 years old. Higher pooled odds of MDR-TB among individuals below the age of 65 was also reported from a systematic review performed in Europe (Faustini et al., 2006). Besides, a study conducted at Northeastern China reported that those individuals between 28-54 years of age had double odds of MDR-TB when compared with those 65 years or older (Liu et al., 2013). The treatment adherence in the productive age group and the working style of these groups who have a higher contact chance to DR-TB patients might also contribute. The findings of the present study revealed that males had a lower risk of DR-TB compared to females. The risk of DR-TB decreases by 14% in males compared to females. Likewise, individual studies also reported a higher risk of DR-TB among females (Lomtadze et al., 2009; Shivekar et al., 2020). However, the reason behind it should be explored in detail in future works. In the end, this study was based on studies published in the English language that might affect the true estimates. Besides, publication bias was confirmed by the Egger's

regression test for about half of the study variables that might bias the true estimates.

In conclusion, a previous history of TB treatment is a major risk factor for acquiring DR-TB in Ethiopia that might be due to poor adherence during the first-line anti TB treatment. Besides, having contact with a known TB patient, having contact with a known MDR-TB patient, having pulmonary TB, and being unemployed were the risk factors of DR-TB in Ethiopia. Thus, active screening of TB contacts for DR-TB might help to detect DR-TB cases as early as possible and could help to decrease its transmission across the population.

Abbreviations

DM: Diabetes Mellitus, DR-TB: Drug-Resistant Tuberculosis, EPTB: Extrapulmonary Tuberculosis, HIV: Human Immunodeficiency Virus, MDR-TB: Multi-Drug-Resistant Tuberculosis, OR: Odds Ratio, Pre-XDR-TB: Pre-Extensively Drug-Resistant Tuberculosis, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis, PTB: Pulmonary Tuberculosis, RR-TB: Rifampicin-Resistant Tuberculosis, TB: Tuberculosis, XDR-TB: Extensively Drug-Resistant Tuberculosis

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Author contributions

AA conceptualized, designed, and drafted the manuscript. AA, GD, and ZWB performed article searching, data extraction, quality assessment, data analysis and wrote the manuscript. BG reviewed the final manuscript. All authors read, reviewed, and approved the final manuscript.

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Availability of data and materials

All relevant data are available from the corresponding author upon request.

Ethics approval and consent to participate

Since it is based on published studies, it doesnot require ethical approval.

Consent for publication

Not applicable.

Competing interests

The authors have declared that they do not have any competing interests.

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Table 1: Characteristics of individual studies on the determinants of drug-resistant tuberculosis in Ethiopia, included in this systematic review and meta-analysis.

Author, Year	Regional state covered	Study setting	Study desig
Abay et al., 2020	Tigray	Adigrat General Hospital	Cross-section
Abdella et al., 2015	Southwest Ethiopia	Southwest Ethiopia	Cross-section
Adane et al., 2015	Amhara	Debre Markos and Mota District hospitals	Cross-section

Author, Year	Regional state covered	Study setting	Study desig
Alene et al., 2019	Amhara	Gondar University Hospital	Case-control
Arega et al., 2019	Addis Ababa	Three referral hospitals and regional laboratory	Cross-section
Assefa et al., 2017	Addis Ababa	St Peter, and ALERT hospitals	Case-control
Babure et al., 2019	Oromia	Nekemte Hosp	Case-control
Bedewi et al., 2017	Central Ethiopia	Health facilities in Central Ethiopia	Cross-section
Biru et al., 2020	SNNP	Yirgalem and Butajira Hospitals	Case-control
Deressa et al., 2014	Addis Ababa	10 health facilities	Case-control
Desissa et al., 2018	Oromia	Bishoftu & Adama Hospitals	Case-control
Dessalegn et al., 2016	Addis Ababa	St Peter Hosp	Case control
Fikre et al., 2019	SNNP	Six hospitals	Case-control
Gobena et al., 2018	Oromia	Shenen Gibe Hospital	Case-control
Hamusse et al., 2016	Oromia	Hitossa District of Arsi Zone	Cross-section
Hirpa et al., 2013	Addis Ababa	St. Peter Hospital and five health centers	Case-control
Jaleta et al., 2017	Amhara	Gondar Hospital	Cross-section
Mehari et al., 2018	Tigray	Health facilities in all zones	Cross section
Mekonnen et al., 2015	Amhara	Metema & west armachiho	Cross section
Mesfin et al., 2018	Addis Ababa	Different health facilities	Cross-section
Mulisa et al., 2015	Oromia	Different health facilities	Case-control
Mulu et al., 2015	Amhara	Gondar University specialized and Borumeda Hospital	Case-control
Seyoum et al., 2014	Eastern Ethiopia	Five health facilities in Dire Dawa, Harar, and Jigjiga	Cross-section
Tadesse et al., 2015	Addis Ababa	26 public health centers	Cross-section
Tesfay et al., 2016	Tigray	Tigray regional TB Lboratory	Cross-section
Tsega et al., 2017	Amhara	Debre Markos Hosp	Cross-section
Welekidan et al., 2020	Tigray	Six hospitals in Tigray	Cross-section

Table 2: The summary of the pooled estimates of the OR per associated risk factors of drug-resistant tuberculosis in Ethiopia.

Variable	Odds ratio	Odds ratio	Odds ratio	Odds ratio
	Number of studies	Estimate, 95% CI	Heterogeneity I^2	Heterogeneity P-value
Older age	23	0.77 (0.60, 0.95)	47.2%	0.007
Age > 40 years	4	0.83 (0.54, 1.13)	34.2%	0.207
Age > 45 years	19	0.76 (0.55, 0.97)	47.6%	0.011
Being male	24	0.86 (0.76, 0.97)	19.0%	0.202
Urban residence	17	0.86 (0.58, 1.15)	75.2%	<0.001
Single	11	1.12 (0.84, 1.40)	46.0%	0.047
Being a house wife	7	0.86 (0.50, 1.21)	0.0%	<0.875
Being a farmer	8	0.81 (0.42, 1.19)	48.0%	0.061
Being a daily laborer	4	0.97 (0.16, 1.78)	33.4%	0.212
Unemployed	4	2.71 (1.64, 3.78)	0.0%	0.556
Family size > 3 members	6	0.87 (0.61, 1.14)	0.0%	0.760
Alcohol consumption	12	0.96 (0.53, 1.38)	70.01%	<0.001
Khat chewing	6	1.01 (0.63, 1.38)	0.0%	0.440
Smoker	11	0.75 (0.34, 1.16)	58.3%	0.08
Imprisonment	8	1.00 (0.43, 1.56)	0.0%	0.954
Being HIV positive	21	1.35 (0.95, 1.74)	73.6%	<0.001
Have DM	4	0.85 (-0.22, 1.93)	0.0%	0.838
MDR-TB contact	4	2.54 (1.46, 3,63)	0.0%	0.621

Variable	Odds ratio	Odds ratio	Odds ratio	Odds ratio
TB contact	11	1.72 (1.05, 2.40)	73.8%	<0.001
History of previous TB treatment	20	4.83 (3.02, 6.64)	69.6%	<0.001
History of two or more TB episodes	7	1.03 (-0.03, 2.99)	79.2%	<0.001
Having pulmonary TB	8	1.80 (1.14, 2.45)	0.0%	0.487

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