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Original Research Article

Proportion and Associated Factors of Primary Rifampicin Resistance among New Pulmonary TB Patients in Public Hospitals of Gen-Xpert Testing Sites, East Amhara–Ethiopia, 2019

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Abstract

Introduction: The emergence and spreading of Rifampicin-resistance strains of mycobacterium tuberculosis pose significant challenges to tuberculosis control programs in resource-limited countries like Ethiopia. This study aimed to assess the proportion and factors associated with primary rifampicin resistance. ***Methods:*** A facility-based cross-sectional study was conducted from April to November 2019 among 570 new pulmonary tuberculosis patients. A systematic random sampling technique was used to select the study participants from 8 Gene-Xpert testing hospitals. Rifampicin resistance was detected by Gene-Xpert assay from sputum specimens. Data were collected by face-to-face interviews, document review, and laboratory results using a pre-tested structured questionnaire. We developed the questionnaire from different kinds of literature and the World Health Organization resources. Variables with P-value <0.2 in simple binary logistic regression were included in the multiple binary logistic regressions. A statistical test was reported as significant when p-value < 0.05 in multiple variable logistic regressions. Fitness of goodness was checked by using the Hosmer Lemeshow model fitness test. ***Results:*** A total of 570 individuals have participated in this study. Of those, 43 (7.50%) 95% CI: 5-10) were resistant to rifampicin. Persons, have a contact history with known tuberculosis Patients (AOR 2.5 [95% CI: 1.21-5.11]), with human immune virus infection (AOR 2.3 [95% CI: 1.11-4.73]) and being diabetic Mellitus cases (AOR 4.2[95% CI: 1.51-8.78]) were factors significantly associated with rifampicin resistance. ***Conclusions and recommendations*:** The proportion of rifampicin resistance was high. Identified factors significantly associated with rifampicin resistance were persons having contact history with known tuberculosis patients, human immune virus infection, and being diabetic Mellitus cases. Strengthen the prevention of rifampicin resistance tuberculosis transmission, strengthening contact tracing, improve TB/HIV coinfection health care services, and screening tuberculosis patients for diabetic Mellitus is crucial.

Keywords: Tuberculosis, Rifampicin resistance, Gene-Xpert, Eastern Amhara, Ethiopia.

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by a group of bacteria called *Mycobacterium tuberculosis* complex (MTBC) that is spread from person to person through the air [1]. Anti-tuberculosis drug resistance (DR) is a major public health problem that threatens progress made in TB care and control worldwide. Essentially, rifampicin resistance (RR) arises in areas with weak TB control programs and a patient who develops active disease with an (RR-TB) strain can transmit this form of TB to other individuals [2]. Drug resistance (DR) mainly Multidrug-Resistant Tuberculosis (MDR-TB) and Extensively Drug Resistance Tuberculosis(XDR-TB) are caused by a genetic mutation of the *MTB* which renders anti-TB agents ineffective against the mutant tubercle bacilli [3]. But, according to Caminero, suggestions, there are two categories of risk factors for drug-resistant tuberculosis. The first category, he describes as 'those facilitating the selection of resistance in the community and the second as ‘specific conditions that appear to increase some patient’s vulnerability to

resistance [4]. The emergence and spreading of MDR and XDR –MTBC strains pose significant challenges to TB control [5]. According to the World Health Organization/International Union Against Tuberculosis and Lung Disease (WHO/IUATLD) survey of 20 countries with the highest rates of MDR-TB mostly done in previously treated cases [6].

Even though acid-fast staining has very low sensitivity in the detection of MTB, it remains the main diagnostic method in resource-limited settings. On the other hand, culture is the gold standard and the most sensitive method for TB diagnosis and DR; however, its use in clinical practice is limited due to the long turnaround time, biosafety requirements, and high cost [7]. In aware of this fact, WHO introduced the wide use of Xpert MTB/RIF assay; which fully automated diagnostic molecular test using real-time polymerase chain reaction (PCR) technology to simultaneously detect MTB and RR mutations in the rpoB gene [8].

Globally, 3.4% of new TB cases and 18% of previously treated cases had MDR/RR-TB. and, 51% of people with bacteriologically confirmed TB were tested for RR, up from 41%; Coverage of testing was 46% for new and 83% for previously treated TB patients [9]. Drug-resistance surveillance data show that 4.1% of new and 19% of previously treated TB cases in the world were estimated to have RR or MDR-TB. There were an estimated 600 000 new cases of MDR/RR and 240, 000 deaths due to MDR/RR-TB. Most cases and deaths occurred in Asia and also about 6.2% of MDR-TB cases have additional DR and XDR-TB) [10]. Only 55% of the MDR/RR-TB patients who started treatment were successfully treated, while 15% of patients died and treatment failed in 8% of patients. About 8.5% of MDR-TB cases had XDR-TB and treatment success in XDR-TB patients was only 34% [11]. The emergence of DR-TB is a critical threat to TB control and is a major public health concern in several countries. In sub-Saharan Africa (SSA) RR/MDR-TB is emerging as a major clinical and public health challenge [12]. DR-TB in SSA had results for a total of 13,465 new and 1,776 previously treated TB patients through an estimate of any DR-TB prevalence among the new cases was 12.6% (95% CI 10.6-15.0) while for MDR-TB of this was 1.5% (95% CI 1.0-2.3) and among previously treated patients, these were 27.2% (95% CI 21.4-33.8) and 10.3% (95% CI 5.8-17.4%), respectively [13].

Ethiopia is one of the high TB burdened countries in sub-Saharan Africa, which ranks ten among the 30 high TB burden countries in the world [9]. The National Tuberculosis Reference Laboratory together with seven Regional TB laboratories study in Ethiopia showed the proportion of MDR-TB was 4.3% in new patients, while 6.7% in previously treated patients and the overall proportion of MDR-TB was 11.6% [14]. In countries with a high burden of TB, continuous surveillance and regular monitoring of DR based on routine drug susceptibility testing (DST) of TB patients are essential to assess the magnitude and trends of DR-TB [15].

Ethiopia is working towards controlling of transmission dynamics of TB to reduce morbidity and mortality and preventing the emergence and spread of DR in the general population. Despite all these efforts, in Ethiopia, there is limited capacity to perform TB culture and DST [12]. Due to these reasons, there is a lack of study on rifampicin resistance among newly pulmonary TB cases in the eastern part of the Amhara region.

Gene-Xpert offers an opportunity for timely and accurate initiation of TB/DR-TB treatment and shortened time to diagnosis in high burden settings. Detection of RR is very important in resource-limited countries since RR is the strongest proxy marker of MDR-TB. Now a day's TB cases are resistant to rifampicin (RIF) directly treated with second-line anti TB drugs as MDR-TB patients [10]. So, detection of RR in early time is detecting MDR-TB easily and efficiently because there is a limitation of resources to avail culture diagnosis methods like Gene-Xpert in every hospital. In countries with a high burden of TB, rapid detection, continuous surveillance, and regular monitoring of DR- TB is essential for disease management and earlier treatment initiation.

Conducting a study to detect RR on new cases used to estimate the magnitude and associated factors of primary RR, facilitates early detection of RR and also used to prevent primarily RR transmission to others. However, there is a lack of study on the proportion and factors associated with RR-TB among newly pulmonary TB cases. Besides, the available study doesn't show the proportion and factor associated with RR among new pulmonary TB cases in the study area. Therefore, this study aims to determine the proportion and associated factors of RR -TB among M. TB patients in the eastern part of the Amhara Region Ethiopia.

METHODS AND MATERIALS

A facility-based cross-sectional study was conducted from April to November 2019, which is found in the Eastern part of the Amhara Region at eight different Gene-Xpert laboratory testing hospitals, such as Wolidia general hospital, Borumeda district hospital, Dessie referral hospital, Mekane Selam district hospital, Kemissie general hospital, Ataye district hospital, Shoarobit district hospital, and Debrebrehan referral hospital. The Gene-Xpert sites are located in the Northern direction of Addis Ababa in the distance 130 to 581 kilometers far apart and from 250 to751 kilometers from Bahir Dar (the capital city of Amhara Regional state) in the Eastern direction. According to the 2007 Central Statistical Agency report, the study area has an estimated total population of 7,407,286 million people in 2019/20, of which 53.9% were

females. In the study area, there were 27 public hospitals, 339 health centers, 1377 health posts, and 198 private health facilities.

The source population for this study was all new pulmonary TB cases in the Eastern part of the Amhara Region. The study population was all individuals with new pulmonary TB cases at Gene – Xpert site hospitals. All new pulmonary TB cases came to in selected Gene-Xpert sites of hospital laboratories in the Eastern part of the Amhara region were included in the study but persons with new pulmonary TB who were unable to communicate due to severe illness and unable to speak were excluded.

The sample size was determined using a single population proportion for prevalence and two-population proportions formula for factors. But the sample size determined based on the proportion of RR was the maximum sample size, by considering the following assumptions: 5% margin of error, 95% confidence level, and anticipation proportion of RR 3.89% from a previous study which has been conducted at East Gojjam zone –Ethiopia [16] and added a 10% non-response rate, 1.5 design effect. Therefore, the final sample size for this study was 593 among new pulmonary TB patients.

In the Eastern part of the Amhara region, there are twenty functional governments Gene-Xpert site of hospitals from those, eight (40%) Gene-Xpert sites of hospitals were selected randomly using lottery method and the calculated sample size was proportionally allocated to selected Gene-Xpert sites of hospitals based on an average number of new pulmonary TB cases from reviewing survey before the study period was used. A systematic random sampling technique was used to select the study participants from each selected Gene-Xpert laboratory site and a sampling interval was conducted to collect study participants by considering the laboratory flow of MTB cases.

Data were collected by face-to-face interviews, document review, and laboratory results using a pre-tested structured questionnaire. We developed the questionnaire from different kinds of literature to include all possible variables that address the objective of the study and the World Health Organization resources. The data collection tools (questionnaire) were gathered from themes of participants' characteristics, like socio-demographic, clinical related factors housing condition, access to health care service, and behavioral related factors. The data were collected by eight medical laboratory technicians and supervised by eight trained medical laboratory technologists and principal investigators in the data collection process.

A single sputum specimen was recommended for Gene-Xpert MTB/RIF and 2 ml of sputum specimen was collected. Rifampicin resistance was detected by rapid Gene-Xpert assay from sputum specimens. The Gene-Xpert MTB/RIF system is a fully automated nested real-time PCR system, which detects MTB complex DNA in samples. It simultaneously identifies mutations in the rpoB gene, which are associated with RR. The Gene-Xpert MTB/RIF system consists of the instrument, a computer, a barcode scanner, and requires single-use disposable Gene-Xpert MTB/RIF cartridges that contain assay reagents.

Before data collection, the tool/questionnaires were first prepared in English language and then translated to the Amharic version, which is the resident's mother tongue and the national working language to maintain its consistency. The qualities of the data were assured by a properly designed and pre-tested questionnaire, proper training of the interviewers and supervisors. During the data collection time, regular monitoring and supervision of the overall activity were done by supervisors and principal investigators to ensure the quality of data. All the collected data were checked, cleaned, and coded to avoid some inconsistencies and incompleteness before analysis.

The Gene-Xpert System automatically performs internal quality control for each sample. During each test, the system uses one or more of the following controls. Sample-processing control (SPC): Ensures a sample was correctly processed. The sample-processing control is included in the cartridge and is processed with the sample and the DNA is detected by a PCR assay. Internal control (IC)—verifies the performance of the PCR reagents and prevents a false negative result. The internal control PCR assay assesses if there is any inhibition, possibly by components, in the test sample. Internal control is provided in the cartridge and should be positive in a negative sample. Endogenous/inbuilt control (EC): Normalizes targets and ensures a sufficient sample is used in the test. Because of its low variability, the endogenous control can also be used to indicate sample-inhibitor contamination. The endogenous control is taking from the specimen sample.

Data were entered into Epi-data version 3.1 and export to statistical Package for Social Sciences (SPSS) software version 21 for analysis. Descriptive analyses (proportions, frequencies, and averages) were used to determine the socio-demographic, disease-related, and behavioral characteristics.

The possible candidate variables for RR factors have been analyzed first by simple binary logistic regression analysis by using enter method and then variables that have p-value < 0.2 were analyzed in multiple binary logistic regression analysis by incorporate backward logistic regression to control the effects of possible confounding variables. Odds ratio, 95% CI was computed to evaluate the degree of association between dependent and independent

variables to conclude, P-value < 0.05 were considered statistically significant and the goodness of fitness was checked by using Hosmer Lemeshow model of fitness (p-value >0.05).

Operational definitions

- **Patients' involvement:** -in this study patients were involved directly through responding to the questions, providing sputum specimens for laboratory testing and finally they obtain their results for intervention.
- **Public involvement:** - indirect public involvement was observed in this study because data collectors, data entering groups, data editors, and different government officials at each level who permit to conduct the research were parts of the public.
- **New pulmonary TB patients/cases**: - Positive result of MTB patients who were never been treated for TB or received treatment less than one month of therapy.
- **Presumptive/Suspected**: -patients who show signs and symptoms of TB and are suspected by physicians in outpatient departments send to Gene-Xpert laboratory for the diagnosis of TB/RR/MDR-TB at the same time.
- **Primary DR:** - "New Cases "DR in a patient who has never been treated for TB or received less than one month of therapy, implying they were infected with a resistant TB. This reflects the person-to-person transmission of DR- TB bacilli.
- **Presumptive RR/MDR-TB**: - Individuals who have contacted with known TB, MDR/RR-TB, HIV patients, and MTB are positively considered to suspect/presumptive to RR/MDR-TB.
- **Contact:** - defined as people from the same household/dormitory/ sharing common habitation rooms/stay.
- **Rifampicin resistant TB**: - TB caused by strains of M. TB that are resistant to RIF.
- **Non-smokers:** - An adult who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime.
- **Smokers**: - were an adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes
- Khat chewer: - a person who had to chew Khat for at least 5 years with a frequency of at least once a month and a minimum chewing session duration of 3 hours.
- Non- Khat chewers: - a person who had never chewed khat or those who chewed no more than 5 times in their lifetimes.
- **Traditional medicine user**: - person's practices based on the theories, beliefs, and experiences home-grown to different cultures used in the protection of health as well as in the prevention, diagnosis, improvement for their health problem.

RESULTS

Socio-demographic characteristics of new pulmonary tuberculosis patients

A total of 570 new pulmonary TB patients were included in the study with a response rate of 96.30 % of the study sample size. Of those new pulmonary TB patients, 312 (54.7%) of them were males, 380(66.70%) of them were married by marital status. The mean age of new pulmonary TB patients was found to be 38.91 with a standard deviation $\pm$ 16.74 years old. Three hundred forty-seven (60.90%) of them were from rural areas. The educational status of new pulmonary TB patients indicates that 271(47.50%) of them unable to read and write, 171(30%) of them in grades 1-8th plus able to read and write. From new pulmonary TB patients, 193 (33.90%) of them were farmers, and 144(25.30%) of them housewives by occupational status (Table-1).

Table-1: Socio-demographic characteristics of Primary Rifampicin Resistance among new pulmonary TB patients in public Hospitals of Gen-Xpert testing sites , East Amhara–Ethiopia, 2019 (n=570)

Variables	Category	Frequency	Percentage (%)
Sex	Male	312	54.70
	Female	258	45.30
Age	≤30 years	218	38.20
	>30 years	352	61.80
Resident	Urban	223	39.10
	Rural	347	60.90
Marital status	Married	380	66.70
	Single	136	23.90
	Divorced	30	5.30
	Widowed	24	4.20
Education	Illiterate	271	47.50
	Primary	171	30.00
	High school	62	10.90
	Diploma and above	66	11.57

Occupation	Farmer	193	33.90
	Housewife	144	25.30
	Unemployed	116	20.40
	Employed	63	11.10
	Merchant	54	9.50
Family size	Less than five	398	69.80
	Greater than five	172	30.20

Housing condition summary of new pulmonary TB patients

Of the total new pulmonary TB patients, 413(72.50%) of them were living in houses having two and above rooms, 459 (80.50%) of them live in houses having one and above windows and 352(61.80%) in houses having made of mud.

Access to health care services profile of new pulmonary TB patients

Of the total new pulmonary TB patients, 387(67.90%) of them can access health care services in less than two hours' journey and 406(71.20%) of them have got TB laboratory services in the nearby living area.

Clinical profile of new pulmonary TB patients

Ninety-four (16.50%) of new pulmonary TB patients were asthmatic cases, 89 (15.60%) of them have HIV infection in their blood, and 39 (6.80%) were diabetic (Table-2).

Table-2: Clinical characteristics of Primary Rifampicin Resistance among new pulmonary TB patients in public Hospitals of Gen-Xpert testing sites, East Amhara–Ethiopia, 2019 (n=570)

Variables	Category	Frequency (N)	Percentage (%)
Asthmatic case	No	476	83.50
	Yes	94	16.50
Have HIV status	Negative	481	84.40
	Positive	89	15.60
Diabetic mellitus	No	531	93.20
	Yes	39	6.80
Contact history with known TB patients	No	476	83.50
	Yes	94	16.50

HIV: Human immune deficiency virus, PT: pulmonary TB, DR: drug resistance, TB: Tuberculosis

Behavioral assessment of new pulmonary TB patients

Fifty-four (9.50%) of new pulmonary TB patients have imprisoned history, 163 (28.60%) have chat chewing habits, 87(15.30%) take traditional medicines and 55 (9.60%) have a history of living in a refugee camp (Table-3).

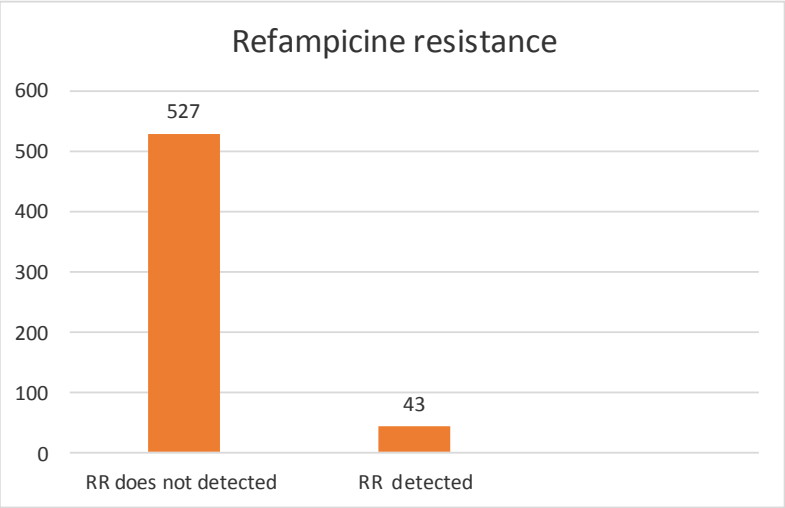

Figure-1: Primary Rifampicin Resistance among new pulmonary TB patients in public Hospitals of Gen-Xpert testing sites, East Amhara–Ethiopia, 2019

Table-3: Behavioral characteristics of Primary Rifampicin Resistance among new pulmonary TB patients in public Hospitals of Gen-Xpert testing sites, East Amhara–Ethiopia, 2019 (n=570)

Variables	Category	Frequency	Percentage (%)
Imprisons history	Yes	516	90.50
	No	54	9.50
Khat chewing	Yes	407	71.40
	No	163	28.60
Smoking	Yes	531	93.20
	No	39	6.80
Taking a sleeping pill	Yes	536	94.00
	No	34	6.00
Taking traditional medicine use	No	483	84.70
	Yes	87	15.30
Refugee camp history	No	515	90.40
	Yes	55	9.60
Time of health facility visit after developing sign and symptom of TB	Less 3 weeks	429	75.30
	After 3 weeks	141	24.70

RR status among new pulmonary TB patients and by their socio-demographic characteristics

From RR-MTB confirmed cases 26 (60.40%) of them were females, 23 (53.50%) age greater than 30 years old and 30 (69.80%) of them were from the rural area. The proportion of RR was higher in married individuals, 28(65%) and with an educational status who are unable to read and write 23 (53.50 %) (Table-4).

Table-4: Status of RR by their socio-demographic characteristics among new pulmonary TB patients in public Hospitals of Gen-Xpert testing sites, East Amhara–Ethiopia, 2019 (n=570)

Variables	Category	Rifampicin status			
		RR not detected		RR detected	
		N	(%)	N	(%)
Sex	Male	295	56.00	17	39.50
	Female	232	44.00	26	60.40
Age	≤30 years age	198	37.60	20	46.50
	≥31 years age	329	62.40	23	53.50
Address	Urban	210	39.80	13	30.20
	Rural	317	60.20	30	69.80
Marital status	Married	352	66.20	28	65.10
	Single	175	33.20	15	34.90
Education	Illiterate	248	47.10	23	53.00
	Primary	161	30.60	10	23.30
	High school	54	10.20	8	19.00
	Diploma and above	64	12.10	2	5.00
Occupation	Farmer	185	35.10	8	18.60
	Housewife	126	23.90	18	41.90
	Unemployed	107	20.30	9	20.00
	Employed	61	11.60	2	5.00
	Merchant	48	9.10	6	13.90
Family size	< five members	368	69.80	30	69.80
	>= five members	159	30.20	13	30.20

Status of RR by clinical characteristics among new pulmonary TB patients

The status of RR by clinical characteristics of the study participants indicates that being HIV positives accounted for 14 (32.60%) and 9(20.90%) have diabetes mellitus. Similarly, of the total confirmed RR cases, 15(34.90%) of them have a history of contact with known TB in the last year (Table-5).

Table-5: Status of RR by Clinical history characteristics among new pulmonary TB patients in public Hospitals of Gen-Xpert testing sites, East Amhara–Ethiopia, 2019 (n=570)

Variables	Category	Rifampicin Status			
		RR not detected		RR detected	
		N	(%)	N	(%)
Asthmatic case	No	442	83.90	34	79.10
	Yes	85	16.10	9	20.90
HIV/AIDS status	Negative	452	85.80	29	67.40
	Positive	75	14.20	14	32.60
Diabetic disease	No	497	94.00	34	79.10
	Yes	30	6.00	9	20.90
Contact history with TB patients	No	448	85.00	28	65.10
	Yes	79	15.00	15	34.90

Factors associated with primary Rifampicin Resistance

In the first bivariate regression model sex, contact history with known TB, HIV status, diabetic's Mellitus status, refugee camp history, number of windows present in the houses were identified as determinants associated with Rifampicin Resistance of study participants.

However, in a multivariable logistic regression analysis, persons who have contact history with known TB patients, Persons who have HIV infection in their blood, and persons who have diabetes mellitus disease were identified as a factor associated with RR-TB were the only independent variables associated with RR-TB (Table-7). There were no significant association between other socio-demographic and household character, clinical conditions, and behavioral related variables with rifampicin resistance (Table-6).

The results revealed that persons who have a contact history with known TB patients was significantly associated with rifampicin resistance. As a result, persons who have a contact history with known TB patients were 2.5 times more likely to have rifampicin resistance than persons who have no contact history with known TB patients (AOR = 2.5; 95% CI: (1.21-5.11)) (Table-6).

The odds of RR among newly confirmed MTB cases with the persons who have HIV infection in their blood were 2.3 times (AOR 2.3 [95% CI: 1.11-4.73]) higher than from those who have no HIV infection in their blood. The odds of RR among newly confirmed MTB cases with persons who have diabetes mellitus disease also were found to be 3.6 times (AOR 3.6 [95% CI: 1.51-8.78]) higher than from those who have no diabetic Mellitus (Table-6).

Table-6: Factors associated with Primary Rifampicin Resistance among new pulmonary TB patients in public Hospitals of Gen-Xpert testing sites, East Amhara–Ethiopia, 2019 (n=570)

Variables	Category	Rifampicin Resistance		COR [95%CI]	AOR [95% CI]	p-value
		Yes	No			
Sex	Female	26	232	1.94(1.03-3.67)	1.78(0.92-3.44)	
	Male	17	295	1	1	
Number of windows in the house	No	13	98	1.89 (0.96-3.77)	1.76(0.85-3.63)	
	Yes	30	429	1	1	
Contact history with Known TB Patients	Yes	15	79	3.04(1.55-5.94)	2.49(1.21-5.11)*	
	No	28	448	1	1	
HIV/AIDS status	Positive	14	75	2.91(1.47-5.76)	2.29(1.11-4.73)*	
	Negative	29	452	1	1	
Diabetic mellitus	Yes	9	30	4.39(1.93-9.98)	3.64(1.51-8.78)*	
	No	34	497	1	1	
Refugee camp history	yes	9	46	2.77(1.25-6.13)	2.36(0.99-5.58)	
	No	34	481	1	1	

DISCUSSION

This study was aimed, assessed the proportion and associated factors of primary Rifampicin Resistance among new pulmonary TB patients in public Hospitals of Gen-Xpert testing sites, East Amhara–Ethiopia.

As the outcome, the proportion of RR/MDR-TB in the study area was found to be 7.50% (95% CI: 5-10). it is comparable with the study done in Debremarkos referral hospital 6.7% [17], in Addis

Ababa-Ethiopia 7.6% [18] and Uttar Pradesh 7.6% [19]. But it is higher than findings conducted in Ambo town which was1.2% [20], Ethiopia national survey in 2016 4.3% [14], in Cameroon 1.6% [21], in Peru 2.3% [22], and global report 3.4% [9]. This higher proportion might be due to the existence of active person-to-person transmission in this area, the launching of Gene-Xpert diagnosis modality which strengthens the detection of RR/DR/ bacteria and a strong disease surveillance system. Also, the study was conducted from eight different hospitals, the lifestyle of the population and geographical difference of study areas which makes to higher.

On the other hand, the finding of the present study is lower compared to the study conducted in Hitossa district, Ethiopia, which was 15.3% [23], Dirie Dawa 23% [24], in Addis Ababa 8.7% [25], in University of Gondar hospital 13% [26], Debremarkos referral hospital 10.7% [17] and in South Africa 8.8% [27]. This might be the result of the time of study conducted, diagnostic modality, and since this study have been conducted facility-based it depends on clients only who visit hospitals. This can be related to low awareness about the RR-TB and poor access to TB diagnostic facilities. In individuals who live houses having floor made of mud 32 (74.4%). It is a similar indication of study in the Amhara region [28]. This might be due to poor living status or indoor air pollution with aerosols that contain drug resistant bacteria. The proportion of RR-TB was also higher in females 26(60.4%) than males. This agrees with the study in Addis Ababa [18]. This because females are the ones that provide care for the sick of their family members which might make them exposed to the TB illness.

In this study person having a contact history with known TB patients (AOR 2.5 [95% CI: 1.21-5.11]) was identified as a factor associated with RR- M.TB and this finding are consistent with the study conducted in Sudan [29], in Dubit Hospital Afar Region [30], East shoa Bisheftu and Adama Hospitals [31], in Amhara region [28]. This might be due to the source patients have DR-TB and associated with the direct person-to-person transmission of primary RR/ DR-TB. Since the spread of TB, as well as DR-TB, occurs mainly in settings where prolonged contact between people promotes the transmission from an infectious 'source case' with TB disease to one or several 'contacts [32]. Being HIV positive (AOR 2.3 [95% CI: 1.11-4.73]) was also the second identified factor for having RR-MTB. This finding was in line with the study done in Peru [22], Eastern Ethiopia Dire Dawa, Jigjiga [24] and Jimma [33]. This might be due to a person with HIV infection have suppressed immunity status that can make them be easily affected by RR-TB. Similarly, diabetic Mellitus cases (AOR 3.6 [95% CI: 1.51-8.78]) were identified as a factor for developing RR-TB. This finding was in line with the study finding of south India [34], China [35, 36], Harar Ethiopia [37]. A reasonable explanation for primary RR-TB in diabetes patients might be, due to their impaired immune system and poor glucose control which is often associated with dysfunction of phagocytosis, and T cell reaction that can increase their vulnerability for RR-M.TB [38]. This study confirms the proportion and factors associated with primary RR-TB among newly diagnosed pulmonary TB patients through Gene-Xpert MTB/RIF diagnostic system/ fully automated molecular technique real-time PCR machine. But as the study was facility-based it depends on clients who visited the health facilities so, the situation of RR in the community might differ and this study might underestimate the real value of RR-TB in the study area.

LIMITATION

There are limitations in this study, it was facility-based so, the situation of RR in the community might differ and this study might under estimate the real value of RR-TB in the study area.

CONCLUSIONS AND RECOMMENDATIONS

The proportion of RR/MDR- TB is higher in the study area than the global and national proportion of RR/MDR- TBs. The high prevalence of RR-TB among new TB cases in the current study implies the existence of active person-to-person transmission or the existence of undiagnosed primary and new RR-TB cases. Persons who have HIV infection, diabetic Mellitus disease, and persons who have contact history with known TB patients were identified factors associated with RR/MDR-M.TB. Based on the study finding the following recommendation is forwarded to Amhara Regional Health Beauro, Hospitals as well as concerned bodies. Prevention and control strategy of RR /primary DR-TB/ transmission should be strengthening in the study area, strengthen the TB-HIV co-infection health care service program in all level health facilities, screening TB patients for diabetic Mellitus should be conducted to help for proper management of diabetic Mellitus and prevention of developing DR-TB and strengthen contact tracing and investigating them should be the main concern because it is an important component of timely case detection of individuals with DR-TB and increases the chance of reducing DR-TB transmission in the community.

Abbreviations

AOR: Adjusted Odds Ratio; BP: Base Pair; CDC: Communicable Disease Control; CI: Confidence Interval; CO: Crude Odds Ratio; DM: Diabetic Mellitus; DNA: Deoxyribonucleic Acid; DR: Drug resistance; DST: Drug Susceptibility Test; EMB/E: Ethambutol; HIV: Human Immune Virus; IC: Internal control; INH/H: Isoniazid; IUATLD: International Union Against Tuberculosis and Leprosy Disease; LiP: Line Probe Assay; LJM: Lowenstein-Jensen Medium; MDR: Multi-Drug Resistance; MLS: Medical

Laboratory Sciences; MTB: Mycobacterium Tuberculosis; Mycobacterium Tuberculosis Complex OR: Odds ratio; PCC: Probe Cell Control; PCR: Polymerase Chain Reaction; RIF: Rifampicin; RR: Rifampicin Resistance; SM: Streptomycin; SPC: Sample Processing Control; SSA: Sub Saharan Africa; TB: Tuberculosis; UK: United Kingdom; USA: United States of America; WHO: World Health Organization; XDR-TB: Extensive Drug Resistance Tuberculosis

DECLARATIONS

Ethical Considerations

Ethical clearance was obtained from the Institutional Review Board of the School of Public Health, College of Medicine and Health Sciences, Bahir Dar University. Co-operation and permission letters were taken from the concerned organization. Verbal consent was obtained from each individual after the purpose of the study was explained. Anyone who refuses to participate in the study was told as he/she had full right not to participate. Participants were also informed that all the data obtained from them were kept confidential using codes instead of any personal identifiers and locks in a file cabinet. Any study participants who were positive for M. TB and RR were linked to TB clinics and treatment initiative centers respectively for further follow.

Consent for publication

Consent to publish is not applicable for this manuscript because there are no individual data details like images or videos.

Availability of data and materials

The finding of this study is generated from the data collected and analyzed based on the stated methods and materials. All the data are already found in the manuscript and there are no supplementary files. The original data supporting this finding will be available at any time upon request.

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Authors' Contributions

Abtew Abera has conceived the study, carried out the overall design, analysed, interpreted the data. Drafted the manuscript, and revised it critically for important intellectual content. Zelalem Mehari, Getachew Hailu, and Seid Legesse have revised the design of the study, data collection techniques and helped in statistical analysis, assisted with the development of the questionnaire and has drafted the manuscript. Dr. Mahteme Haile also has great support to revise the overall manuscript all authors read and approved the final manuscript.

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