

Sociodemographic Profile of Mono Rifampicin-Resistant (RR) Cases among Pulmonary Tuberculosis Patients, Erbil, Iraq, 2015–2020

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Abstract

Background: Rifampicin-resistant pulmonary tuberculosis (RR-PTB) remains a global health burden. The spread of RR *Mycobacterium tuberculosis* is a threat to treatment and control of tuberculosis. **Objective:** This study aimed to assess the rate of RR-PTB and further determine the factors associated with it. **Materials and Methods:** This study was achieved in April and May 2022. Data were collected, reviewed, and analyzed from archived records of patients who had been tested using Xpert MTB/RIF assay at the Chest and Respiratory Disease Specialized Centre in Erbil City from January 1, 2015 to December 31, 2020. **Results:** A total of 1236 medical records of patients who tested for drug resistance using GeneXpert were included in this retrospective data analysis study. Overall, GeneXpert positive results were reported in 196 cases (15.9%) which denote confirmed cases of tuberculosis by the GeneXpert test in the period 2015–2020. From the total confirmed patients, twenty-one cases (21,10.7%) were found to be RR-PTB. The highest prevalence of RR-PTB according to gender, age range, category of patients, and prevalence of HIV status was as follows: male (11; 52.4%), 18–28 years (9; 42.9%), relapse (13; 61.9%), and HIV positivity (12; 57.1%), respectively. The differences in distribution of the rifampicin resistance concerning the aforementioned demography were as follows: gender: nonsignificant, age range: not significant, relapse: significant ($P \leq 0.05$), HIV positivity: highly significant ($P \leq 0.01$). **Conclusion:** This study reported the prevalence rate of rifampicin-resistant *M. tuberculosis* was 10.7% among confirmed TB patients. HIV-positive and previous TB treatment history were significantly associated with high RR-PTB. This result showed that GeneXpert assay is a convenient tool for the early diagnosis of rifampicin-resistant *M. tuberculosis*.

Keywords: Erbil, rifampicin-resistant tuberculosis, socio-demographic variables, tuberculosis, Xpert® MTB/RIF assay

INTRODUCTION

Tuberculosis (TB) is one of the most contagious bacterial diseases that poses a public health risk.^[1] It is estimated that 10.0 million new cases of tuberculosis occurred in 2019 at a rate of 132 per 100,000 population, with high mortality, resulting in 1.2 million (16 per 100,000 population) deaths globally.^[2] According to the World Health Organization (WHO), the Middle East has 810,000 cases of tuberculosis at a rate of 115 per 100,000 people, and Iraq has 16 000 cases at a rate of 42 per 100,000 people.^[3] Currently, the standard TB treatment regimen combines four first-line antibiotics, isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB), which render a patient noncontagious when

properly administered.^[4] Drug-resistant *Mycobacterium tuberculosis* (TB), notably multidrug-resistant tuberculosis (MDR-TB) and, more recently, extensively drug-resistant tuberculosis (XDR-TB), has emerged as a serious public health issue, posing a danger to global TB control efforts.^[5] MDR-TB is defined as a disease caused by strains of *M. tuberculosis* that are resistant to treatment with at least isoniazid (INH) and rifampicin

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Submission: 23-May-2022 **Accepted:** 14-Jun-2022 **Published:** 29-Sep-2022

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How to cite this article: Abdullah SQ. Sociodemographic profile of mono rifampicin-resistant (RR) cases among pulmonary tuberculosis patients, Erbil, Iraq, 2015–2020. Med J Babylon 2022;19:441-7.

Access this article online

Quick Response Code:



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DOI:
10.4103/MJBL.MJBL_75_22

(RIF).^[6] According to the WHO, 465,000 TB cases in 2019 had rifampicin resistance, with 78% of being confirmed as multidrug-resistant TB (MDR-TB), with TB strains resistant to rifampicin and isoniazid.^[7] INH resistance is also linked to worse treatment outcomes when compared to drug-sensitive TB. Although RIF and INH resistance frequently coexist, as in MDR-TB strains, resistance to each of these agents develops independently of the other, and resistance to one can occur without resistance to the other.^[2,8] Drug resistance tuberculosis (DR-TB) can be detected quickly and accurately and it is the basis for relevant TB control interventions, as well as allowing clinicians to tailor effective TB treatment strategies.^[9] The WHO identifies a number of social determinants that influence the likelihood of developing resistance. Poverty, poor living conditions, various causes of social vulnerability, and limited access to and availability of health services all received special attention. Furthermore, the need for a better understanding of the factors influencing behavior (at both the individual and community levels) is stated.^[10,11] Therefore, this study was conducted to determine the sociodemographic and clinical-epidemiological profile associated with the prevalence of rifampicin resistance TB alone (RR-TB) among GeneXpert test confirmed pulmonary tuberculosis (PTB) patients in order to provide evidence for the planning of the targeted programmatic interventions to reduce the burden of multidrug-resistant tuberculosis in Erbil governorate.

MATERIALS AND METHODS

Setting

Data from January 1, 2015 to December 31, 2020 were reviewed retrospectively from archived results for specimens received and tested using the Xpert MTB/RIF assay at the Chest and Respiratory Disease Specialized Centre in Erbil City.

This specialized center is a nationally accredited reference laboratory that offers a variety of services, including diagnostic testing with the Xpert® MTB/RIF assay.

Data from archived logbooks and databases were reviewed in retrospect.

The assay was carried out using the Xpert MTB/RIF assay (Cepheid, Sunnyvale, California). For patients with RR-TB results, sociodemographic and clinical data were examined. The database was used to get important information.

Inclusion criteria

This study included all PTB patients who had visited the Chest and Respiratory Disease Specialized Centre and had complete records of age, gender, Xpert MTB/RIF results, HIV status, and TB treatment history.

Exclusion criteria

GeneXpert results which are negative. Data sets that lack sociodemographic information. Patients under the age of 15 and immigrants were barred.

Sample and diagnostic procedures

Patients who met the clinical eligibility requirements were asked to provide three sputum specimens: two spot samples and one obtained in the morning.

AFB and culture

Collected samples were processed in a TB center's special laboratory, then two of the three samples were chosen at random and treated with N-acetylcysteine and sodium hydroxide before centrifugation. The samples were resuspended in 1.5 mL of sample buffer, microscopically examined using Ziehl-Neelsen staining, and cultured on solid medium (Löwenstein-Jensen, bioMérieux, France). The third sputum sample was directly tested using the GeneXpert test. After 42 days of incubation, solid cultures were deemed negative due to the absence of any *Mycobacteria* isolation.^[12]

GeneXpert assay

As previously stated, the GeneXpert assay was used.^[13,14] The patient was told to inhale deeply two to three times, breathe out each time, cough deeply from the chest, and collect the specimen with the open container close to the mouth. Sputum was an appropriate specimen for Xpert, with a minimum of 1 mL without food particles and a maximum storage time of 10 days at 40°C. Briefly, the provided buffer was added to clinical samples in a 3:1 ratio. Before 2 mL of the inactivated material was transferred to the test cartridge, the tubes were manually mixed twice at room temperature over a 15-min period. The cartridge was then inserted into the test platform, and the hands-on work came to an end. The machine then filtered, washed, and ultrasonically lysed the DNA. Amplification and detection of real-time PCR were carried out in an integrated reaction tube. The following primers were used for this assay: (CGTGGAGGCGATCACACCGCAGAC) and reverse:

(AGCTCCAGCCCCGGCAGCTCACGT) (Applied Biosystems). After one hour and 45 minutes, the results were finally read, and the fluorescent signal was automatically measured. The report's findings were as follows:

MTB found, MTB not found, RIF resistance found, RIF resistance not found, RIF resistance indeterminate, and Error/invalid. Based on the detection of mutations in the *rpoB* gene (MTB-RIF Instructions), patients are classified as susceptible or resistant to rifampin.^[15]

Ethical Consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of

Helsinki. The study protocol and the subject information and consent form were reviewed and approved by Health Directorate Ethics Committee according to the document number P14 24/4/2022.

Statistical analysis

Descriptive statistics, such as frequency and frequency percentage, were used to analyze the data. The chi-square test was used to make comparisons. The acceptable level of significance was set at $P \leq 0.05$ or $P \leq 0.01$ for the results.

RESULTS

A total of 1236 medical records of suspected DR-TB patients who tested for drug resistance using GeneXpert were included in this retrospective study. Overall, GeneXpert positive results were reported in 196 cases (15.9%) which denote confirmed cases of tuberculosis by the GeneXpert test in the period 2015–2020. From the total confirmed cases, twenty-one cases (21; 10.7%) were found to be RR-PTB. Table 1 shows the prevalence of RR-PTB among confirmed tuberculosis patients according to age and gender. The highest prevalence according to gender and age was as follows: male (11; 52.4%) and 18–28 years (9; 42.9%), respectively. The male-to-female ratio was 1.1. Statistically, the differences of distribution of the MTB/RR in concerning to gender and age were non-significant. Table 2 shows the distribution of RR-PTB according to patients' category. Higher rifampicin resistance was noted in the relapse cases (13; 61.1%) in comparison to eight new cases (8; 38.9%) with confirmed rifampicin resistance. The difference in the distribution of RR between both groups was significant ($P \leq 0.05$). Table 3 shows the distribution of RR-PTB according to HIV status. Higher rifampicin resistance was noted in HIV-positive cases (12; 57.1%) in comparison to nine cases (9; 42.9%) who were HIV negative. The difference in the distribution of RR between both groups was highly significant ($P \leq 0.01$).

Table 1: Prevalence of RR-PTB among confirmed TB patients according to gender, age

Parameter	RR- (sensitive)		RR+ (resistant)		T
	N	%	N	%	
Gender					
Male	90	51.4	11	52.4	101
Female	85	48.6	10	47.6	95
Total	175	100	21	100	196
df = 1 NS					
Age					
18–28	55	31.4	9	42.9	64
28–38	51	29.1	7	33.3	58
38–48	55	22.9	4	19	44
>48	29	16.6	1	4.8	30
Total	175	100	21	100	196
df = 3 NS					

DISCUSSION

To the best of our knowledge, there are no published data on the prevalence of rifampicin resistance among confirmed tuberculosis patients in Erbil governorate, so this study can be considered the first of its kind to look into the prevalence, demography, and profile of these patients. The spread of rifampicin-resistant *M. tuberculosis* poses a threat to tuberculosis treatment and control. As a result, early detection is critical for disease management and transmission prevention.^[16]

This study clarified that the prevalence of RR-PTB was 10.6% among GeneXpert confirmed patients. This finding is lower than that obtained by the study of Al-Mussawi *et al.*^[17] in Basrah, Iraq in which the prevalence of RR-PTB was 7.5%. Al-Obaidey^[5] in Baghdad had reported that 14.3% of tuberculosis patients were in rifampicin resistance. A study by Ahmed^[8] Nineveh, IRAQ concluded that the prevalence of RIF resistance was 14.2% out of the total positive TB cases. Studies conducted around the world, using different methodologies and at different times, yielded different figures for this resistance.^[18] Al-Hayani^[19] proclaimed that RIF resistance was found to be of 2.5% prevalent in a study conducted in Makkah, Saudi Arabia. Another study was conducted in Riyadh, Saudi Arabia, by Singla *et al.*^[20] announced that 6% of approved TB was resistance to rifampicin. Bahraminia *et al.*^[21] from Iran reported that the frequency of RIF resistance among patients with TB was 8%. Selfegna and Alelign in Ethiopia^[18] stated that 15.8% of the proven TB cases were recognized to be resistant to rifampicin (RR). The prevalence of RIF resistance accomplished by studies in other parts of Africa were as follows: Kenya 3.7%^[22] and Zambia 5.9%.^[23] RR-TB was also observed

Table 2: Prevalence of RR-PTB among confirmed TB patients according to patients category (new and relapse)

Patients category	RR-(sensitive)		RR+ (resistant)		T
	N	%	N	%	
New	110	62.9	8	38.1	118
Relapse	65	37.1	13	61.9	78
Total	175	100	21	100	196
$\chi^2 = 4.7985$, df = 1, Significant ($P \leq 0.05$)					

Table 3: Prevalence of RR-PTB among confirmed TB patients according to HIV status

Parameter	RR- (sensitive)		RR+ (resistant)		T
	N	%	N	%	
HIV					
Positive	29	16.8	12	57.1	41
Negative	146	83.2	9	42.9	155
Total	175	100	21	100	196
$\chi^2 = 18.6569$, df = 1, HS ($P \leq 0.01$)					

in other parts of Ethiopia such as Adigrat General Hospital 9.1%,^[24] Debre Markos Referral Hospital 10.3%,^[25] Felege Hiwot Referral Hospital, and Debre Tabor Hospital 9.3%.^[26] The present finding was lower than previous studies conducted in South Gondar 18%,^[27] Congo 42.2%,^[28] and China 17.6%.^[29] Diversified global studies have deduced that dissimilarities in the announced prevalence, even within the homeland itself, can be correlated to divergences in sample size, geographical variation, methodology (sample size), method of drug resistance diagnosis, availability of health care facilities, and the validation of TB control programs.^[2,18,30,31] As more than 90% of rifampicin-resistant strain are likewise reluctance to Isoniazid, rifampicin resistance can also be utilized as a beneficial replacement sign for MDR-TB.^[7] Subsequently, emanation of rifampicin resistance is considered to be dangerous because it will ultimately procure to isoniazid resistance also, which will restrain the treatment and entanglement the endeavors to govern the dispersal of the ailment.^[24] Molecular tests such as GeneXpert are modifying the landscape of the diagnosis and management of drug-resistant TB and may confirm to be an efficient and felicitous solution to this dilemma.^[17] Routine DST of *M. tuberculosis* is difficult and time-consuming. Thus, tardiness in diagnosis and commence of treatment has negative leverage on TB control programs. The yield of Xpert MTB/RIF for the diagnosis of RIF in *M. tuberculosis* was studied formerly, and the sensitivity of the Xpert MTB/RIF test for detecting RIF resistance was reported to be 94.4%–100%, with a specificity of 98.3%–100%.^[8,28,32]

Regardless of the noted divergence in the rate of RR-PTB, none of age and gender were found to be correlated with anti-TB drug resistance. This observation is propped by other studies in Ethiopia^[26,27] and Zambia.^[23] In regarding to gender, Masenga *et al.*^[23] concluded in their study which was conducted at Livingstone Central Hospital (LCH), Livingstone, Zambia, gender was not a factor assumed to be linked to rifampicin resistance. This is similar to a study that was achieved in India^[33] where it was recorded that danger of rifampicin resistance among genders was similar. This could have been a consequence of the verity that men and women are confronting evenly to factors that produce rifampicin resistance.^[23,33] However, other studies^[34,35] had mentioned more RR-PTB among females in comparison to males. In contrast, other studies had documented more RR-MTB infection among males.^[36,37] Males have a higher prevalence of RIF, which could be elucidated by the fact that there is a: (i) paramount intrinsic predisposition to tuberculosis, (ii) increased tuberculosis risk due to occupations such as mining and blasting, which expose them to *M. tuberculosis* (iii) because of their occupation, they are more likely to be relocated to another area, increasing the risk of treatment hindering, (iv) Finally, men smoke and use narcotics more

than women; these two factors are independent of one another.^[8,16,30,38] Dejene *et al.*^[39] mentioned that the higher prevalence of RR-MTB in females reported in their study could be linked to females' lack of knowledge about TB transmission and control, poor health-seeking behavior, and thus delay in detection in females.

This study had shown that age groups of 18–28 years were more likely to be infected by RR-PTB with no significant association of age with rifampicin resistance. The aforementioned result is in accordance with the conclusions delineated by many other studies.^[7,10,34] Other studies concluded a significant correlation between age and prevalence of RR-PTB.^[40,41] According to a study conducted in Pakistan, young age (between the ages of 10 and 25) was a significant risk factor for the development of drug resistance among TB patients.^[42] The age variation in the reported drug resistance rates could be due to localized socioeconomic factors related to exposure opportunity and resistance development. Furthermore, it could be due to a difference in sample size and cut-off points for age groups.^[2,11,34] In this study, 61.9% of RIF-PTB cases reported having received TB treatment in the past. According to this finding, participants who had a previous history of anti-TB drug treatment were more likely to develop TB resistance than participants who had no prior TB treatment history. This finding is in line with the proclamations of many other studies, which had reported that a history of prior anti-TB treatment was the most significant factor correlated with the prevalence of RR-PTB. Admassu *et al.*^[2] deduced that patients who had a past history such as treatment failures, defaulters, or relapse cases are at more risk of developing drug-resistant TB. In a study of tuberculosis-infected Cameroonian patients, researchers^[9] disclosed that the prevalence of RIF resistance was almost ten times higher in relapse cases than in new cases. Nasiri *et al.*,^[43] Iran, revealed that 23% of new cases and 65.6% of previously treated TB cases were resistant to at least one drug. It is recognized that drug-resistant tuberculosis can be the consequence of either being infected by a drug-resistant TB, or drug-susceptible TB strains can obtain resistance to anti-TB drugs resulting in gained drug resistance.^[2,8,24] Drug-resistant TB is predominately the sequel of human faults as a result of bad supply management and quality of anti-TB drugs and inappropriate or erroneous treatment.^[7,9,11] Researches had declared that retreatment tuberculosis cases possibly contain strains with full or partial drug resistance for drugs used in prior treatment so that acquired drug resistance is mostly detected among them.^[39,44] A population-based survey that analyzed data from 11 countries found that the likelihood of developing resistant tuberculosis increased with the length of treatment as a result of treatment failure.^[45] The high TB prevalence in the previously treated patients may elucidate a high TB spread in the society and in the case of relapse, the lack of TB treatment monitoring

and control.^[24,32] These findings highlight the importance of paying close attention to treatment completion rates in new cases, as well as increased drug resistance monitoring in those who have previously received TB treatment.^[19,34] Rifampicin resistance in *M. tuberculosis* has been linked to a mutation in the RNA polymerase *rpoB*, which reduces rifampicin affinity. Some studies have been able to pinpoint specific codons that, when mutated, can result in rifampicin resistance.

A missense mutation and nucleotide substitution at codons 526 and 531 of *rpoB* are found in the majority of RR isolates.^[17,24,27]

RR tuberculosis co-infected patients had a higher prevalence of HIV infections, according to this study (57.1%). Drug-resistant TB is more common in TB/HIV coinfecting patients than in HIV-negative patients, according to studies. A study achieved by Araya *et al.*^[6] showed that rifampicin resistance was higher (12.5%) in HIV-positive tuberculosis patients than in seronegative tuberculosis patients (7.2%) ($P = 0.032$).

A meta-analysis of 10,000 adult TB-resistant patient records revealed that HIV-positive people had a 2.5 times higher risk of death than HIV-negative people.^[30] Abay and Abraha^[24] in Ethiopia discovered that 15.2% (26/171) of the total TB-HIV coinfecting patients had rifampicin resistance and both the sensitivity and resistance of rifampicin results were statistically related to HIV status. Other findings, on the other hand, indicated that HIV status was not a significant factor in rifampicin resistance.^[46-48] This discrepancy in results could be due to differences in design and sample size, as well as the fact that results were rarely adjusted for potential confounding.

Several biological mechanisms have been proposed to link drug-resistant tuberculosis to HIV infection. Drug malabsorption in HIV patients, especially with rifampin and ethambutol, can lead to drug resistance and treatment failure.^[13] The link between HIV infection and DR-TB may be decomposed by risk factors shared by both, such as injection drug use, incarceration, socioeconomic status, alcohol use, and hospitalization.^[6,13] Patients with HIV and MDR-TB are more likely to be admitted to hospitals than HIV-negative patients. Patients who are infected with HIV may be more likely to be exposed to patients who have drug-resistant isolates, and thus infected or re-infected with a resistant isolate.^[13,24,30]

The detection of *M. tuberculosis* and rifampicin resistance in adults using the Xpert MTB/RIF assay from a large sample size using respiratory specimens was the study's main strength. There were some limitations to our research. Extrapulmonary cases were excluded from the study. This retrospective study only collected data from a single governorate's TB/pulmonary disease specialized hospital, so it cannot represent national prevalence.

This dataset only included people who had their testing confirmed, excluding presumptive cases. The study participants' MDR-TB and TB contact histories, living conditions, smoking habits, and education levels were not obtained.

Our findings, however, highlight the importance of careful management and monitoring of tuberculosis patients. Despite these flaws, the study has provided useful information about the current situation.

CONCLUSIONS

According to this study, the prevalence of rifampicin-resistant *M. tuberculosis* among confirmed TB patients was 10.7%. HIV positivity and a history of previous TB treatment were both associated with a high RR-PTB. This finding showed that the GeneXpert assay is a useful tool for the early detection of rifampicin-resistant *M. tuberculosis*. According to the findings, there is an urgent need for appropriate intervention measures to reduce PTB transmission and the development of anti-TB drug resistance in the study area. Early detection of drug-resistant *M. tuberculosis* should be prioritized in order to improve tuberculosis case management, improve direct observation therapy short-course, and eventually reduce the spread of rifampicin-resistant tuberculosis strains in the community.

Acknowledgement

The authors express their gratitude to Erbil's Health Directorate for allowing them to conduct the research. We also appreciate the cooperation and support of the senior staff and colleagues in the Department of Microbiology at the Erbil City-based Chest and Respiratory Disease Specialized Centre.

Financial support and sponsorship

Not applicable.

Conflicts of interest

There are no conflicts of interest.

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