

Rifampicin Resistance in Primary Pulmonary Tuberculosis at HMC Hospital Peshawar Department of Pulmonology a Multi Center Study

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ABSTRACT

Background: According to estimates from the World Health Organization, TB afflicted about 12 million people in 2019 and claimed nearly 1.7 million lives. Pakistan is rated fifth worldwide for the prevalence of TB and fourth among developing nations for the emergence of treatment resistance. In Pakistan, there are around 525,000 new cases of TB each year, and 20,000 people develop medication resistance. A high mortality rate is caused by drug resistance. Before treating the patient for medication resistance and for a cure, it should be confirmed with a drug susceptibility test.

Objective: To determine the prevalence of rifampicin resistance in patients with primary pulmonary TB using a drug susceptibility test.

Methodology: In this Multi Center study, all patients who attended the pulmonology department of the HMC Hospital in Peshawar between 2018 and 2020 were included. The study comprised 296 smear-positive TB patients who attended the pulmonology department and had no prior history of ATT consumption. Further testing of the patient's sputum for rifampicin resistance and Mycobacterium TB was done using the PCR-based Gene Expert assay.

Results: In the current study, 296 TB patients in total were included. According to our statistics, there were 200, 205, and 140 TB patients in the most recent three years 2018,19,2020, correspondingly (Figure 2). The study's participant population consisted of 157 men (52%) and 139 women (48%) (Table 1). The ratio of men to women was 01.11:12. 192 (64%) of the population lived in Peshawar, 33 (11%) in Khurram Agency, swat 25 (10%) and 45 (18%) in Charsadda (Figure 3). The findings revealed that Peshawar City was home to the bulk of the TB sufferers. 95 (07%) of the TB patients had extremely excellent socioeconomic standing, followed by 106 (36%) patients with average socioeconomic standing, and 166 (57%) patients with poor socioeconomic standing. Rifampicin resistance was found in 18 (06%) of these 296 TB patients (Table 2). It's important to note that 20 (60%) of the positive rifampicin resistance cases were in men and 13 (40%) were in women (Table 1). Additionally, the data we gathered indicated that rifampicin resistance was stronger in patients with low socioeconomic level (17%) and was lower in patients with high socioeconomic status (3%) for TB patients. Table 2.

Conclusion: This study demonstrates a clear relationship between patient socioeconomic level and rifampicin resistance. Although TB is curable, a patient's chances of being cured are decreased and they become more resistant to other medications when they develop resistance to one or more treatments, particularly rifampicin.

Keywords: Rifampicin, Tuberculosis, GeneXpert assay, drug susceptibility.

INTRODUCTION

Globally, tuberculosis is the most contagious and infectious disease¹. According to estimates from the World Health Organization, 12 million individuals worldwide are predicted to have TB in 2021, of whom about 01.2 million will die from the illness. Of these, 05.9, 4.4, and 01.05 million patients were men, women, and children, respectively⁰¹. According to a World Health Organization (WHO) study, there were 7.5 million new cases in 2018 and 6 million new cases globally. 2 The number of cases reported in [2018] is greater than [2017], according to a WHO report. TB patient cases were shown to have increased significantly between 2018 and 2020. According to the WHO survey report from [2018], the majority of TB cases were found in South-East Asia, Africa, and the Western Pacific (43%), (25%), and (19%), respectively⁰². Other nations with high TB prevalence include South Africa, India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and (09%), (08%), (06%), (06%), (04%), and (03%). 02/03 of the worldwide TB burden is borne by these 8 nations. 3, 4 Pakistan was rated fifth overall for TB burden and fourth for medication resistance. TB is widespread in Pakistan, where there are an estimated [510,000] new cases each year and an estimated 16000 patients acquire drug-resistant TB⁰³. Globally, medication resistance to treatments for TB is a serious issue for public health. Drug resistance develops as a result of poor anti-tuberculosis chemotherapeutic usage, such as the prescribing of incorrect regimens, fake medications, and inability to finish the full course of treatment. In general, medication resistance develops in regions with ineffective TB control initiatives⁰⁴.

For short-term anti-tuberculosis treatment, rifampicin, a bactericidal medication from the rifampicin group, is crucial.

Treatment time increases without rifampicin and is more likely to fail⁰⁵. It works by concentrating on DNA-dependent RNA polymerase and preventing mycobacterial transcription. RpoB gene mutations lead to the development of rifampicin resistance. 7 In the 2018 Global Tuberculosis Report, rifampicin resistance was reported in Primary resistance isolates from new patients were at 04.05% in Pakistan, while retreatment cases were at 15%⁰⁶. According to a study conducted in Quetta, Pakistan, rifampicin primary resistance was 05.02%. 9 A study conducted in Lahore, Pakistan, revealed 4.9% main rifampicin resistance. 10 A second study from the same region found main rifampicin resistance at 15.44%. A key factor in determining how well a therapy works is drug resistance. To find Mycobacterium tuberculosis and medication resistance, many methods are used. Sadly, the techniques used to identify medication resistance to treat TB are not the best. The gold standard for culture and sensitivity testing is sputum, but it takes two to three months. Molecular methods of detection and automated liquid culture-based systems are other techniques. Versatrek and the Mycobacterial Growth Indicator Tube (MGIT) are two components of an automated liquid culture-based system⁰⁷. These techniques are quite costly, involve experienced technical workers, and take roughly two weeks to provide results. The recently released real time PCR Gene Xpert MTB/RIF can quickly and accurately determine if Mycobacterium tuberculosis complex is present and whether it is rifampicin susceptible⁰⁸. Numerous investigations have shown that 89% of isolates with rifampicin resistance also had isoniazid resistance. 14 Rifampicin resistance may thus be used as a stand-in marker for multidrug resistant TB. Studies that are now in the public domain show that Gene Xpert has a pooled sensitivity

of 93% and a pooled specificity of 98%. A combination of medications that the TB bacilli are responsive to is necessary for effective tuberculosis therapy⁹. The likelihood of a cure is decreased and bugs are more likely to develop medication resistance if TB bacilli are resistant to one or more medicines, particularly rifampicin. Therefore, it is crucial to understand the TB bacilli's sensitivity to these medications before beginning therapy. It takes longer to perform standard tests (such as sensitivity and culture on solid and liquid media) (6-12 weeks). If there is resistance in a situation, the delay will be caused by it. The development of new drug resistance, the course of a patient's illness, and the possibility of the illness spreading to others¹⁰. The Gene Xpert MTB/RIF test, which also promptly determines rifampicin resistance, confirms the presence of Mycobacterium TB. The WHO suggests it as a rapid diagnostic test for TB and rifampicin resistance in order to avoid the aforementioned unfavorable outcome. The frequency of rifampicin resistance may vary dramatically across and even within different countries. To better inform treatment, it is essential to do study to discover the area data. No comparable studies in this area have been done, as far as I know¹¹.

MATERIALS AND METHODS

The Department of Pulmonology at the HMC Hospital in Peshawar conducted this Multi Center study from February 2018 to February 28, 2020. The HMC Hospital Peshawar's ethics committee provided their clearance. This study included sputum samples from 296 individuals who were suspected of having TB. These chosen patients were from a variety of areas in KPK, including Peshawar, the Khurram Agency, Charsadda, and the Swat region. Through AFB sputum smear microscopy, these individuals were originally examined for tuberculosis (TB). All suspected TB patients with ongoing clinical symptoms were sent to the TB lab for a GeneXpert MTB/RIF test to confirm the presence of MTB/DR. The pulmonology department of the hmc Peshawar conducted the experimental work for the AFB smear microscopy and GeneXpert MTB/RIF test. Patients were told about the study before specimens were collected, and signed agreement was acquired. The patients were instructed to gather the sputum samples using the prescribed sterile plastic 51-mL Tarson) containers and the normal sputum collection procedure. The AFB sputum smear microscopy was performed on half of the collected sputum specimen, and the GeneXpert MTB/RIF test was performed on the other half. The study was carried out in accordance with the standards established by the study committee of the HMC Hospital in Peshawar. Criteria for inclusion and exclusion Study participants comprised newly diagnosed pulmonary TB patients of either sex older than 13 years and with a positive sputum smear. All instances of extra-pulmonary TB and pulmonary tuberculosis with sputum smear results that were negative were excluded from the study.

Smea microscopy: One drop of sputum sample was applied to a clean glass slide that was labeled with the ID number to create direct smears for microscopic investigation of AFB. The smear was air dried before being heat fixed, then stained using ZN staining techniques. The stained smears were examined with a 100 objective lens under a microscope. Each session of ZN staining included control slides (known positive and known negative) as a procedural check¹⁶.

MTB/RIF test by GeneXpert: The sputum sample was mixed with two milliliters of sample reagent, one milliliter of the sample, and left to liquefy for 20 minutes. 0.2 mL of the mixture was placed into the GeneXpert cartridge using a sterile dropper that was included in the package. The necessary reagents for nucleic acid amplification and RIF drug resistance detection were included in this cartridge. As shown in Figure 1, the infected cartridge was inserted into the GeneXpert device. Within two hours, the GeneXpert machine immediately revealed the results. MTB found; RIF resistance not detected is how the operator can interpret and report the test findings.

Data analysis: Data were analyzed using SPSS version 28. Frequency and percentages were used to depict qualitative characteristics.

RESULTS

In the current study, 296 TB patients in total were included. According to our statistics, there were 200, 205, and 140 TB patients in the most recent three years 2018, 19, 2020, correspondingly (Figure 2). The study's participant population consisted of 157 men (52%) and 139 women (48%) (Table 1). The ratio of men to women was 01.11:12. 192 (64%) of the population lived in Peshawar, 33 (11%) in Khurram Agency, Swat 25 (10%) and 45 (18%) in Charsadda (Figure 3). The findings revealed that Peshawar City was home to the bulk of the TB sufferers. 95 (07%) of the TB patients had extremely excellent socioeconomic standing, followed by 106 (36%) patients with average socioeconomic standing, and 166 (57%) patients with poor socioeconomic standing. Rifampicin resistance was found in 18 (06%) of these 296 TB patients (Table 2). It's important to note that 20 (60%) of the positive rifampicin resistance cases were in men and 13 (40%) were in women (Table 1). Additionally, the data we gathered indicated that rifampicin resistance was stronger in patients with low socioeconomic level (17%) and was lower in patients with high socioeconomic status (3%) for TB patients. Table 2.



Figure 1: Different phases in the Xpert MTB/RIF test procedure.

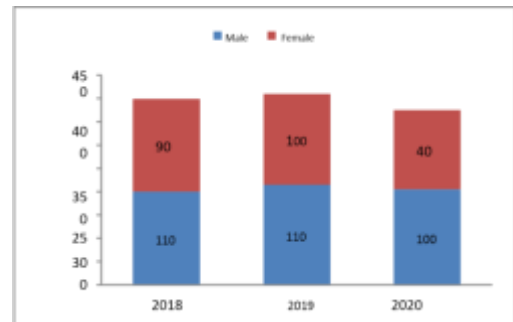


Figure 2: Year and gender wise distribution of TB patients.

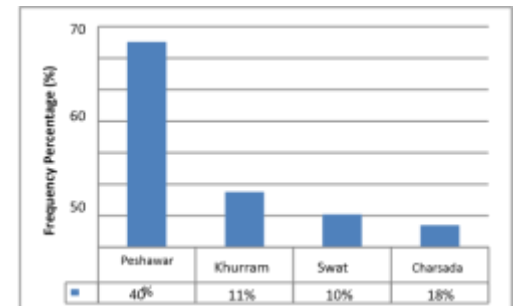


Figure 3: Locality of study subjects' homes is shown in a column chart.

Table 1: Rifampicin resistance and the prevalence of tuberculosis patients among study participants.

Year	Patients	Male	Female
2018	200	110	90
2019	210	110	100
2020	140	100	40
Total	550	320	280
Rifampicin resistance	35	20	13

Table 2: Patients' socioeconomic status

Socio-economic status	Total	Rifampicin resistance
Verygood ^d	45	03
Mediocre	208	10
Poor ⁱⁱⁱ	335	19

DISCUSSION

Drug-resistant M. tuberculosis is a severe problem. Recent study shows that rising nations have more drug-resistant populations, with the greatest rates in densely populated areas¹². In 1967, Salman H. et al. found that 45% of never-treated patients exhibited ant tuberculosis treatment resistance, compared to 86% of newly treated individuals¹³. According to A. Aziz et al. Lahore's population survey, rifampicin was just introduced and had little resistance. 5.2% were treatment-resistant. Rifampicin resistance rates in the same population varied from [02-04%] in Siddique al[1976] study due to the drug's rare usage¹⁴. Rifampicin usage increased, so did resistance. Multiple drug treatment, which does not usually include rifampicin, increased the chance of resistance in previous trials¹⁵. The present study found that ant tuberculosis drug resistance has increased among Peshawar hmc hospital pulmonology patients. Numerous studies have shown high rates of primary drug resistance in adolescents and adults in diverse countries. Medication resistance—primary and acquired—is the main cause of treatment failure. Drug abuse is rampant. Expected public opposition. Rifampicin resistance is common in this study. Rifampicin resistance is rare in other locations, according to several studies¹⁶. The present study demonstrated limited patient rifampicin resistance. In this study, patients were classified as high, medium, or poor. First, high-socioeconomic primary pulmonary TB patients had a reduced rate of rifampicin resistance because they could afford treatment. They're well-off. Primary pulmonary TB patients with low socioeconomic status are more likely to be rifampicin-resistant. They have less money for family needs, thus they have more substandard patients¹⁷. They self-medicate without investigating reasons. Thus, unnecessary medications may cause rifampicin resistance in primary pulmonary TB patients. Primary pulmonary TB is more common in low-socioeconomic patients. Patients can't afford therapy, housing, or food. These variables make these patients more likely to withstand rifampicin. Other studies show the same explanation of increasing and reduced rifampicin-resistant patient frequency. This observation also examined males and women¹⁸. Rifampicin resistance is higher in males (60% vs. 39%). A. Alemuet al. 29 reported 56% rifampicin resistance in men. Male self-medication causes their predominance. TB patient starts cough and sickness medicines. It increases rifampicin resistance. This study highlights the nationwide problem of drug resistance, which hinders TB therapy. This causes population mortality. Drug resistance is more widespread and severe in underdeveloped countries. Address TB treatment resistance concerns. Tuberculosis programs in developing countries may overcome these obstacles by educating patients and medical and paramedical staff on diagnosis and treatment. Drug susceptibility requires precise laboratory facilities¹⁹. TB patients need primary and secondary drugs. A knowledgeable doctor who examined the patient should also recommend TB medication²⁰.

CONCLUSION

This study demonstrates a clear relationship between patient socioeconomic level and rifampicin resistance. Although TB is

curable, a patient's chances of being cured are decreased and they become more resistant to other medications when they develop resistance to one or more treatments, particularly rifampicin.

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