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Unraveling the Complex Landscape of MDR-TB: A Comprehensive Retrospective Study on Treatment History, Demographics, and Drug Resistance Patterns in District Swat

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ABSTRACT

Therapy for tuberculosis (TB) involves the application of first-line medicines (FLDs), such as isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB), and streptomycin (SM). Second-line medications (SLDs) are employed if the first-line therapy fails or the bacteria develop resistance to the FLDs. The present research set out to evaluate the drug-resistant tuberculosis prevalence and determine the drug-resistant patterns in District Swat.
Materials and Methods: This was an observational, hospital-based, retrospective research of previously diagnosed cases of all Drug sensitive TB (DS-TB), MDR-TB, and XDR-TB patients provided by the Programmatic Management of Drug-Resistant TB (PMDT) Saidu Group of Teaching Hospital, Swat from January 2015 to December 2019. There were 15,567 isolates of DS-TB and MDR-TB in all from the research. The data was analyzed applying the statistical software SPSS version 25 (SPSS Inc., Chicago, IL, USA) and Microsoft Excel (Microsoft Office Professional Plus 2016).
Results: According to the results, between January 2014 and December 2019, a total of 15,567 patients were registered from 13 District SWAT centers, comprising 15356 (98.64%) new cases and 211 (1.36%) re-treatment cases with known age and sex. The proportion of TB in the male population (51.9%) was higher than in the female population (48.0 %). Overall treatment success rate (TSR) for PBC cases was (3097) 93.9%.
Conclusion: Finding the baseline susceptibility to first- and second-line medications as soon as possible is necessary to prevent developed drug resistance and unfavorable outcomes, according to the investigation's conclusion

INTRODUCTION

The intracellular bacterium known as Mycobacterium tuberculosis (M. tuberculosis) is responsible for the serious human disease tuberculosis (TB). It is non-motile, non-spore-forming, facultative, obligate-aerobic, and catalase-negative bacilli. The bacteria differ from other microbes in that it has multiple lipids in its cell wall, including Wax-D, cord factor, and mycolic acid Mycobacteria have a lipid bilayer outer membrane (Vohra and Dhaliwal 2020). Declaring tuberculosis (TB) a public health emergency in 1993, the World Health Organization

(WHO) advised the use of Directly Observed Therapy (DOT), which assist in people to use their TB medications under the guidance of medical professionals to support them in their therapy and decrease the caution of developing drug resistance (Rieder 2002).

Resistance to isoniazid (INH) and RIF is the definition of MDR-TB, whereas resistance to any of the second-line injectable medications, including aminoglycoside and fluoroquinolone, is the definition of XDR-TB (WHO 2018). The World Health Organization (WHO) predicted 484,000 (RR/MDR) cases in 2018, of which 378,000 cases were MDR-TB worldwide. By the end of the year, 214 000 persons had lost their lives to RR/MDR-TB. According to a 2019 WHO study, 369,548 confirmed cases of tuberculosis have been found in Pakistan. Compared to 2017, when 368,897 cases were recorded, these numbers show an increase of 651 relatives (WHO 2019). There exists a correlation between smoking and tuberculosis (TB); this correlation can be explained by a number of causes. The risk of tuberculosis sickness is increased by tobacco smoking because it can weaken immune responses or alter the protective function of cilia. A positive sputum culture, coughing, and dyspnea are more common among heavy smokers. Smoking has been linked to mortality and relapses from tuberculosis (Singh, Mynak et al. 2005, Coker, McKee et al. 2006).

In the event that TB bacteria are discovered in a patient's test sample, tuberculosis is diagnosed. A thorough physical examination along with other tests including immunological response testing, histology, microbiology, surgical biopsies, and medical imaging might clearly point to TB as the cause of illness (Steingart, Henry et al. 2006). GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is a molecular diagnostic test that can detect MTB and detect drug rifampicin resistance tuberculosis (RR-TB) at a time with enhanced sensitivity in sputum and other appropriate specimens (Kuhn 2013). The main technique of detecting pulmonary TB is sputum smear microscopy test, which counts the quantity of bacilli in the sputum specimen from patient samples. Smear microscopy is fairly specific even though it is not particularly sensitive (Steingart, Henry et al. 2006). The Mantoux test is less expensive and more suited for low-income areas, whereas the Interferon Gamma Release Assay (IGRA) test offers improved specificities. Nevertheless, specific detection techniques like these are recommended to identify latent TB (Kuhn 2013). A diagnostic evaluation should follow CXR as a triage test to establish a diagnosis.

Therapy for tuberculosis (TB) involves the application of first-line medicines (FLDs), such as isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB), and streptomycin (SM). That being said, second-line medications (SLDs), such as aminoglycosides and fluoroquinolones, are employed if the first-line therapy fails or the bacteria develop resistance to the FLDs. These SLDs are more expensive, more toxic, and more difficult to get (Espinal, Laszlo et al. 2001). Consequently, detecting and treating DS-TB or MDR-TB is important for preventing MDR-TB emergence (Masjedi, Farnia et al. 2006). Delamanid, clofazimine, and bedaquiline are three more new drugs that are now undergoing clinical studies. These drugs are necessary for treating cases of drug-resistant TB, especially those that are severe (Kuhn 2013). Because rifampicin (RIF) resistance is the main problem with TB treatment and a crucial surrogate marker for multidrug resistance, it must be identified early (Heep, Brandstätter et al. 2001, Hillemann, Weizenegger et al. 2005). The present research set out to evaluate the drug-resistant tuberculosis prevalence and determine the drug-resistant patterns in District Swat.

MATERIALS AND METHODS

Study Design

This was an observational, hospital-based, retrospective study of previously diagnosed cases of all Drug sensitive TB (DS-TB), MDR-TB, and XDR-TB patients. Inclusion criteria includes participants that were those who had been previously diagnosed between January 2015 and December 2019 using an Acid-Fast Bacilli (AFB) smear, GeneXpert, culture, and drug susceptibility testing. The patients had to be confirmed cases of DS-TB and MDR-TB over the past five years. The Programmatic Management of Drug-Resistant TB (PMDT) Saidu Group of Teaching Hospital, Swat provided all of the archival data of MDR- and XDR-TB patients that was accessible. After receiving ethical approval from the Coordinator

PMDT of the Saidu Group of Teaching Hospital, Swat, the recruiting procedure and study got underway (IRB Approval no 175-ERB/024).

Inclusion Criteria

The study included all smear-positive patients who were sensitive to anti-TB medications, rifampicin-resistant (RR), and MDR-TB isolates that were available at PTRL archives and were resistant to at least isoniazid and rifampicin (MDR-TB) as determined by the GeneXpert test, drug susceptibility testing, and growth on the Lowenstein-Jensen medium subculture.

Exclusion Criteria

Excluded from the investigation were all TB-negative individuals, non-Rifampicin resistant, non-MDR-TB isolates, and isolates that did not develop on the Lowenstein-Jensen medium cultures and were not RR in the PMDT-STH archives.

Sample Size

Every isolate of DS-TB and DR-TB that met the selection criteria was taken into account. There were 15,567 isolates of DS-TB and MDR-TB in all from the research.

Data Collection

Patient data, such as sample type, age, gender, location, HIV status, anti-TB medications history, etc., were retrieved via the laboratory's "request for examination" forms. All selected TB patients' data were obtained using the TB register and treatment records, as well from the GeneXpert (Cepheid, Sunnyvale, CA, USA) test registers. Microbiological investigations including sputum culture for TB using MGIT 960 (BD Biosciences, Sparks, Md.) or Lowenstein- Jensen medium (BBL™ L-J Medium, BD Biosciences, Sparks, Md) and drug-susceptibility testing (DST) data retrieved at PMDT Saidu teaching hospital for further analysis.

Data Analysis

The information was evaluated by applying the statistical software SPSS version 25 (SPSS Inc., Chicago, IL, USA) and Microsoft Excel (Microsoft Office Professional Plus 2016). The data was then presented in tabular form.

RESULTS

Overall Prevalence of Tuberculosis in The Population of District Swat

Between January 2014 and December 2019, a total of 15,567 patients were registered from 13 District SWAT centers, comprising 15356 (98.64%) new cases and 211 (1.36%) re-treatment cases with known age and sex. Table 1 shows that of the 15,567 TB patients, 3266 (20.9%) had pulmonary bacteria confirmed (PBC), 6136 (39.4%) had pulmonary clinical diagnosis (PCD), and 6165 (39.6%) had extra pulmonary TB (EP). According to Table 3.2, the year 2018 had the highest frequency of instances, while the year 2015 had the lowest frequency. Throughout the research period, there was a noticeable raise in the total number of cases since 2015 (Table 1).

In the present research, the proportion of TB in the male population (51.9%) was more than in the female population (48.0 %). There has been a 3.8% (N=598) increase in male TB-positive cases over females (Table 1). According to data in Table 1, the age of TB patients has been divided into eight groups with ten years' intervals. A high number of cases, 5065 (32.5%), was seen in young adolescents with ages ranging from 4 – 14 years as compared to other age groups. The prevalence rate decreased with increasing age.

Yearly trends in the registration of tuberculosis patients by disease type from January 1, 2015, to the end of 2019 showed that the number of patients with PBC TB cases enrolled for therapy raised from 371 (11.36 %) to 768 (23.52 %) per year. The total number of PCD tuberculosis patients selected in anti-TB therapy increased statistically from 941 (15.34 %) to 1348 (21.97 %) between the years under study. In comparison, the number of EP Tuberculosis has also increased statistically, from 750 (12.07%) to 1241 (20.13%) respectively (Table 1).

According to table 3.5, the highest number of males (N=1806) and females (N= 1764) were diagnosed in 2018, where in 2015, the lowest number of cases were recorded (N=1077), (N=985) for males, and females, respectively. The data also revealed that an average of 1616 men and 1496 females were infected with TB disease annually during the five-year study (Table 1).

Table 1

Overall Prevalence of Tuberculosis in The Population of District Swat

Distribution of All Cases according to the type of Tuberculosis (TB) registered from January 2014 to December 2019 in District Swat		
TB Patient Type	**Total**	**Percent**
Pulmonary Smear-positive	3266	20.9
Pulmonary Smear-negative	6136	39.4
Extra Pulmonary	6165	39.6
Total Cases	**15567**	**100**
Year-wise distribution of number of Tuberculosis cases from 2015-2019		
Year	**Frequency**	**Percent**
2015	2062	13.25
2016	3228	20.73
2017	3350	21.51
2018	3570	22.93
2019	3357	21.56
Total	**15567**	**100**
Demographic characteristics of tuberculosis cases		
Gender	**Frequency**	**Percent**
Male	8083	51.9
Female	7484	48.0
Age group (Y)	**Frequency**	**Percent**
0 – 4	2503	16.0
5 – 14	5065	32.5
15 – 24	2703	17.36
25 – 34	1793	11.5
35 – 44	1051	6.7
45- 54	865	4.4
55 – 64	782	5.0
>65	805	5.1
Total	**15567**	**100**

Patients started on anti-TB treatment by TB diagnostic class

TB Patient Type	2015 n (%)	2016 n(%)	2017 n(%)	2018 n (%)	2019 n (%)	Total
PBC	371 (11.36%)	635 (19.44%)	737 (22.57%)	755 (23.12%)	768 (23.52%)	3266
PCD	941 (15.34%)	1304 (21.25%)	1253 (20.42%)	1290 (21.02%)	1348 (21.97%)	6136
EP	750 (12.07%)	1289 (20.91%)	1360 (22.06%)	1525 (24.74%)	1241 (20.13%)	6165

PBC= Pulmonary Bacteriologically confirmed, **PCD=** Pulmonary Clinically diagnosed, **EP=** Extra Pulmonary

Gender-wise yearly Trend of Tuberculosis in District Swat

Gender	2015	2016	2017	2018	2019	Average
Male	1077(52.23	1702(52.73	1733(51.73	1806(50.59	1765(52.57	1616
Female	985	1526(47.27	1617(48.27	1764(49.41	1592(47.42	1496
Total	**2062**	**3228**	**3350**	**3570**	**3357**	**15567**

Treatment outcomes of PCD, PBC, and EP patients

Among 3266 PBC registered patients, 2,100 (64.2%) have been declared successfully cured while 967 (29.6%) had completed their treatment, 79 (2.4%) were dead, 99 (3.0%) were lost to follow-up, and the remaining 21 (0.6%) had failed treatment. Overall treatment success rate (TSR) for PBC cases was (3097) 93.9%. The cured rate increased from 195 (52.5%) in 2015 to 563 (74.5%) in 2018 but decrease to 496 (64.5%) in 2019. Patients who completed their treatment percent decrease from 40.1% in 2105 to 29.6% in 2019, patients who died during treatment was also steadily increased from 4 (1.0%) to 19 (2.4%) (Table 2).

Table 2

Treatment outcomes of PCD, PBC, and EP patients

Treatment outcome of registered TB patients in District Swat from 2015 to 2019							
Treatment outcome of Pulmonary Bacteriologically confirmed patients							
Year of Diagnose	**Total No. of cases**	**Cured n (%)**	**Treatment completed n (%)**	**Treatment failed n (%)**	**lost to follow-up n (%)**	**Died**	**Treatment success n (%)**
2015	371	195 (52.5)	149(40.1)	3(0.8)	20 (5.3)	4(1.0)	344 (92.7)
2016	635	334 (52.6)	259(40.7)	9(1.4)	16 (2.5)	17(2.6)	603 (94.9)
2017	737	512 (69.4)	190(25.7)	3(0.4)	16 (2.1)	16(2.1)	702 (95.2)
2018	755	563 (74.5)	143(18.9)	2 (0.2)	24 (3.1)	23(3.0)	706 (93.5)
2019	768	496 (64.5)	226(29.4)	4 (0.5)	23 (2.9)	19(2.4)	722 (94.0)
Total	**3266**	**2100 (64.2)**	**967(29.6)**	**21(0.6)**	**99 (3.0)**	**79 (2.5)**	**3097 (93.9)**
Treatment outcome of Pulmonary clinically diagnosed patients							
Year of Diagnosis	**Total No. of cases**	**Cured n (%)**	**Treatment completed n (%)**	**Treatment failed n (%)**	**Lost to follow- up n (%)**	**Died n (%)**	**Treatment success n (%)**
2015	941	------	924 (15.2)	0	17(1.8)	0	924 (98.1)
2016	1304	------	1283 (21.2)	0	11(0.8)	10(0.7)	1283 (98.3)
2017	1253	------	1239 (20.4)	0	4(0.3)	10(0.8)	1239 (98.8)
2018	1290	------	1278 (21.0)	0	7(0.5)	5(0.3)	1278 (99.0)
2019	1348	------	1335 (22.0)	0	9(0.7)	4(0.6)	1355 (99.1)
Total	**6136**	------	**6059(98.7)**	**0**	**48(0.7)**	**29(0.4)**	**6059 (98.7)**
Treatment outcome of Extra Pulmonary Bacteriologically Confirmed or clinically diagnosed							
Year of Diagnose	**Total No. of cases**	**Cured n (%)**	**Treatment completed n (%)**	**Treatment failed n (%)**	**Lost to follow-up n (%)**	**Died n %**	**Treatment success n (%)**
2015	750	------	724 (96.5)	0	26(3.46)	0	724 (96.5)
2016	1289	------	1258 (97.5)	0	23(1.7)	8(0.6)	1258 (97.5)
2017	1360	------	1337 (98.3)	0	18(1.3)	5(0.3)	1337 (98.3)
2018	1525	------	1499 (98.2)	0	18(1.1)	8(0.5)	1499 (98.2)
2019	1241	------	1215 (97.9)	0	21(1.6)	5(0.4)	1215 (97.9)
Total	**6165**	------	**6033 (97.8)**	**0**	**106 (1.7)**	**26 (0.4)**	**6033 (97.8)**

By observing the PCD cases, out of 6136 patients, 6059 (98.76%) have completed the treatment course (i.e., favorable treatment outcome). While 48 (0.78%) cases were lost to follow- up, 26 (0.42%) patients died before completing the course, while no treatment failure was recorded. The overall TSR for PCD cases was 98.76%.

Out of 6165 EPTB, 6033 (97.85%) patients have completed the treatment (i.e., favorable treatment outcome). Whereas 26 (0.42%) patients died, 106 (1.71 %) patients were lost to follow- up during treatment, and no patient was recorded with treatment failure. The overall TSR for EP cases was 6033 (97.85%). The overall five-year treatment success rate of the TB patients was 97.57% (15189/15567); see details in Table 2.

Prevalence of MDR-TB

Treatment History: A total of 69 enrolled MDR-TB patients were identified and regained from the PMDT Swat archive. These originated from across 7 Tehsils of District Swat. According to the patients' history among all MDR-TB isolates, 25 (36.2%) patients were identified as new, while the remaining 44 (63.7%) were previously treated. Among 44 previously treated patients, we also analyzed their previous TB outcomes, and we found that 24 (54.54%) are those whose treatment failed during treatment (Table 3).

Demographics of MDR-TB Isolates: The documents of 69 MDR-TB reviewed patients show that the proportion of MDR-TB in females was 55.0% (n=38), and in the males, the proportion was 44.9% (n=31) (Table 3). The median age was 26.0 years, having ages ranging from 2 to 67. The isolates were categorized into eight groups. It was observed that MDR-TB was more likely to infect the young and reproductive-age adults age group 15 - 24 years: 26 cases and age group 25 -34 years: 23cases (33.3%) (Table 3).

In our analysis, out of the total, 9 (13.0%) patients are those whom DR-TB close contacts were diagnosed with MDR-TB, while 36 (52.2%) patients were referred from private sector hospitals and 33 (47.8%) from the public sector. 66 (95.7%) of the MDR-TB cases were HIV negative while the 3 (4.3%) patients have unknown HIV status (Table 3).

As shown in Table 3, the prevalence of MDR-TB among pulmonary patients was 61 (87%), while in extra-pulmonary MDR-TB was in 7(10%), while two patients (3%) of the total had concurrent extra-pulmonary TB and pulmonary TB. A total of 28 (40.6%) MDR-TB cases were obtained from patients residing in Babuzai Tehsil; 10 (14.5%) were isolated from Tehsil Matta, 8 (11.6%) each from Tehsil Kabal and Bahrain, 6 (8.7%) from Tehsil Khawaza Khela, 5 (7.2%) from Charbagh, 4 (5.8%) from Tehsil Barikot. Over the period of five years, the highest number of MDR-TB patients were registered in 2015 and 2016, 16 cases in each year (23.2%), while the lowest number 11 (15.9%) of MDR-TB patients were reported during the Year 2017 and 2019 (Table 3).

Prevalence of XDR-TB

Among all 69 MDR patients in District Swat, only four XDR-TB samples were identified from two males and two females with a median age of 29. All of the patients were under the age of 40, i.e., between the ages of 15 and 44. Two of the XDR cases were identified in Tehsil Khawaza Khela, while one was from Tehsil Matta and one from Tehsil Babuzai, three of whom were previously treated cases having no previous history of anti-Tb treatment (Table 3).

Table 3

Prevalence of MDR-TB & XDR-TB

Proportion Of MDR-TB according to treatment history		
Treatment history	***n***	**Percent**
TB in New Cases	25	36.3
TB in Retreated Cases	44	63.7
Total	**69**	**100**
Previous TB outcome		
Cured	11	25.0
Failure	24	54.5
Unknown	9	20.4
Total	**44**	**100**
Gender wise prevalence of MDR-TB Patients		
Gender	***n***	**Percent**
Female	38	55.1
Male	31	44.9
MDR- TB patients according to age-groups		
Age Group	***n***	**Percent**
0 – 4	2	2.9

5 – 14	3	4.3
15 – 24	26	37.7
25 – 34	23	33.3
35 – 44	6	8.7
45 – 54	4	5.8
55 – 64	4	5.8
Total	**69**	**100**

Statistics of Patient Characteristics		
Treatment center	***n***	**Percent**
Public sector	33	47.8
Private sector	36	52.2
Previous contact with RR/MDR-TB patients		
No	60	87 %
Yes	9	13.0%
Patient HIV status		
Negative	66	95.7
Not Known	3	4.3
Total	69	100
Prevalence of MDR-TB according to Origin		
Pulmonary TB	61	87 %
Extra-pulmonary TB	7	10 %
Both	2	3 %

Tehsil wise distribution of MDR-TB	
Tehsil	***n***
Bari Kot	4
Babuzai	28
Kabal	8
Matta	10
Behrain	8
Khawaza khela	6
Charbagh	5

Year-wise trend of MDR-TB patients		
Year	***n***	**Percent**
2015	16	23.2
2016	16	23.2
2017	11	15.9
2018	15	21.7
2019	11	15.9
Total	**69**	**100.0**

Prevalence of XDR-TB

S. No	Age	Gender	Year	Site of DR-TB	Anti-Tb History	Tehsil
1	31	M	2015	Pulmonary	Treated	Khawaza Khela
2	30	F	2015	Pulmonary	Treated	Khawaza Khela
3	18	F	2017	Pulmonary	New	Babuzai
4	37	M	2018	Pulmonary	Treated	Matta

The pattern of anti-TB drug resistance among M. Tuberculosis isolated from MDR-Tb patients

Our study identified two groups of MDR-TB isolates according to the pattern (i) MDR isolates showing resistance to one or more first-line drugs (ii) MDR isolates showing resistance to first- line drugs and second-line drugs. DST of a total of 69 MDR-Tb isolates shows that sixty-two percent of the MDR-TB isolates were resistant to first-line drugs, while thirty-seven percent were resistant to first-line and second-line anti-TB drugs.

Drug-resistant pattern of MDR isolates resistance to one or more first-line drugs: DST profile of a total of 43 MDR-TB isolates shows that 36.2% of the MDR-TB isolates were resistant to isoniazid and rifampicin alone, 5.7% were resistant to rifampicin, isoniazid, and ethambutol only, 7.2% were resistant to rifampicin, isoniazid, and pyrazinamide only, 5.7% cases were resistant to Rifampicin, Isoniazid, and Streptomycin.

Isolates resistant to four drugs are: Rifampicin, Isoniazid, Ethambutol, Pyrazinamide 2.8% and 1.4% were resistant to Rifampicin, Isoniazid, Pyrazinamide, Streptomycin only 2.8 % being resistant to all four first-line TB drugs (Table 4).

Resistant pattern of MDR isolates resistance to one or more first-line drugs and at least resistant to aminoglycoside or fluoroquinolones second line drug (pre-XDR): Of the total, 22.8% (n=22) are the MDR isolates that were MDR and showed additional resistance to the first line and at least resistant to one drug in second-line drugs. Of these 22 isolates, 3 isolates were resistant to RHES + Ofx. 8 cases were resistant to RH + Ofx + Lfx, 2 cases to RHS + Ofx ,1 case to RHE + Ofx + Mfx, 3 cases to RHES + Ofx, 1 to RHP + Ofx + Lfx, 1 to RHZ + Ofx + Lfx and 1 case that were resistant to all first-line drugs and shows additional resistance to fluoroquinolone (RHEZS + Ofx + Lfx) as shown in Table 4. The most common resistance that was observed in second-line drugs was Ofx in 22 patients. All of the isolates were susceptible to Kanamycin (km).

Resistant pattern of MDR isolates resistance to one or more first-line drugs and resistant to both aminoglycoside and fluoroquinolones (second-line drug) (XDR): Only 4 (5.7%) MDR TB patients out of 69 isolates were resistant to both Fluoroquinolone and Aminoglycoside,1 patient was resistant to RH +Ak + Cm (second line anti TB injectable) and Lfx (Fluoroquinolone), 1 to RHS + Ak + Cp and Ofx, 1 to RHZ + Cp + Ofx and Lfx, 1 to RH + Cp + Ofx, all these cases met the definition of XDR-TB. Among all the XDR-TB cases,

Capreomycin was the most common drug that was Resistant to all four patients, and Ofx was found resistant to three patients (Table 4).

Table 4

The pattern of anti-TB drug resistance

Drug-resistant Pattern of MDR isolates resistance to one or more first-line drugs:	
(MDR)RH	25 (36.2%)
RHE	4 (5.7%)
RHZ	5 (7.2%)
RHS	4(5.7%)
RHEZ	2 (2.89%)
RHZS	1 (1.4%)
RHEZ	2 (2.89%)
Total	**43(62.31%)**
*Note: **R**=Rifampicin, **S**=Streptomycin, **H**=Isoniazid, **E**=Ethambutol **Z**=Pyrazinamide*	
MDR isolates showed resistance to first-line drugs and second-line drugs.	
RH + Cp	1(1.4%)
RH + Ak	1(1.4%)
Resistance to three drugs	
RH + Ak + Cp	1(1.4%)
RHE + OFX	3(4.4%)
RH + Ofx + Lfx	8(11.5%)
RHS + OFX	2(2.8%)
Resistance to five drugs	
RHE + Ofx + Mfx	1(1.4%)
RHES + Ofx	3 (4.4%)
RHZ + Ofx + Lfx	1(1.4%)
Resistance to seven drugs	
RHEZS + Ofx + Lfx	1(1.4%)
Total	22 (31.88%)
***Note:** **R**=Rifampicin **H**=Isoniazid **E**= Ethambutol **Z**=Pyrazinamide **S**=Streptomycin **Ofx**=Ofloxacin, **Lfx**=Levofloxacin, **Mfx**=Moxifloxacin, **Ak**= Amikacin, **Cp**=Capreomycin, **Km**=Kanamycin*	

Resistant patterns of XDR-TB isolates		
1st line Drugs	**2nd line Drugs**	
	Aminoglycoside	**Fluoroquinolone**
RH	Ak + Cp	Lfx
RHS	Ak + Cp	Ofx
RHZ	Cp	Lfx
RH	Cp	Ofx

***Note:** **R**=Rifampicin **H**=Isoniazid **E**= Ethambutol **Z**=Pyrazinamide **S**=Streptomycin **Ofx**=Ofloxacin, **Lfx**=Levofloxacin, **Mfx**=Moxifloxacin, **Ak**= Amikacin, **Cp**=Capreomycin, **Km**=Kanamycin*

DISCUSSION

Given that the first large-scale investigation in Swat revealed that the incidence of MDR-TB dropped from 16 to 11 individuals between 2015 and 2019, the rising prevalence of MDR is still a serious public health issue in Pakistan and worldwide.

In addition, there is a low-level HIV pandemic in Pakistan's general population. To monitor TB patients for HIV infection, the National TB Control program Pakistan has created 41 sentinel sites (NTP 2019). Nonetheless, Pakistan's implementation of TB/HIV joint initiatives has remained extremely low.

Every MDR-TB patient in District Swat who had an HIV test came up negative. Certain high-HIV/TB burden nations, such as Thailand, Malaysia, and Uganda, have shown that MDR-TB and TB/HIV co-infection are not related (Lukoye, Adatu et al. 2013, Chuchottaworn, Thanachartwet et al. 2015, Elmi, Hasan et al. 2016). In contrast, many other studies have indicated an association between HIV and MDR-TB, including a systematic analysis published in Europe and Ethiopia (Faustini, Hall et al. 2006, Mesfin, Hailemariam et al. 2014, Mulisa, Workneh et al. 2015, Workicho, Kassahun et al. 2017). The connection between co-infection with MDR-TB and HIV has to be further studied.

In this study, men (55.1%) had a somewhat larger prevalence of MDR than women (44.9%), and they were more susceptible to tuberculosis. The results of this study confirm other studies that found men to have far greater incidences of tuberculosis (TB) than women. This conclusion could be the consequence of a fundamental difference between sex and behavior and TB susceptibility (Yang, McManus et al. 2012). The outnumber of men in Tuberculosis is widely reported elsewhere (Ahmad, Akhtar et al. 2012, Chuchottaworn, Thanachartwet et al. 2015, Mulisa, Workneh et al. 2015, Elmi, Hasan et al. 2016, Gao, Ma et al. 2016). According to a different study, MDR-TB is strongly associated with young men, poverty, and people who have had prior treatment for tuberculosis (Khurram, Khaar et al. 2012).

With a median age of 26.0 years, most of the MDR-TB cases (71.01%) in our study were people in the productive age range of 15–34 years. There have also been reports of the productive age group for MDR-TB in Ethiopia and other parts of the world (Abate, Taye et al. 2012, Biadglegne, Sack et al. 2014, Mulu, Mekkonnen et al. 2015). In the current investigation, the prevalence of MDR-TB was shown to be lower among newly diagnosed cases (0.16%), whereas retreatment cases (20.85%)

showed a higher frequency. The Global Tuberculosis Report showed that 4.2 % of new TB patients and 16 % of previously treated cases in Pakistan had multidrug-resistant TB or rifampicin-resistant TB (MDR/RR-TB) (WHO 2019). The current proportion of MDR-TB cases among newly diagnosed patients was (0.16 %), which is lower or less similar to previous study findings like the Amhara Region (Yimer, Agonafir et al. 2012), eastern Ethiopia (Seyoum, Demissie et al. 2014), India (Vidyaraj, Chitra et al. 2017), Vietnam (Nguyen, Nguyen et al. 2016), Tanzania (Hoza, Mfinanga et al. 2015), and Dalian China (Lv, Lu et al. 2017) where they reported MDR prevalence of 1.0%, 1.1%, 2.9%, 4.2%, 4.3%, and 5.8% respectively.

Compared to Ethiopian studies that showed an MDR prevalence of 31.4% (Abdella, Abdissa et al. 2015) and 58% (Abate, Tedla et al. 2014), our research's percentage of MDR-TB among previously treated subjects (20.85%) was lower. Conversely, our finding was more or less similar to several other previous studies reported from northeastern China (Liu, Zhu et al. 2013), Vietnam (Nguyen, Nguyen et al. 2016), Somali Region (Brhane, Kebede et al. 2017), Dalian China (Lv, Lu et al. 2017), that demonstrated an MDR prevalence 27.6%, 23.1%, 22.6%, and 17.7%, respectively.

Due to their high risk of infection, TB contacts should be extensively and aggressively checked for TB infection and illness. 13.14% of cases in this research had interaction with patients who were MDR-TB patients. Contact with a known TB/MDR-TB patient has been linked to certain outcomes, according to a recent Oromia region study (Mulisa, Workneh et al. 2015). Several other studies have demonstrated the association between MDR-TB and contact with a known TB patient (Rahman, Hussain et al. 2005, Ahmad, Akhtar et al. 2012, Flora, Amin et al. 2013).

Patients' occupational profiles showed that the bulk of them was housewives (36%) and daily laborers (26%), with students (16%), coal workers (12%), children (7%), and prisoners (3%). Mukherjee et al. found out in their research that the majority of MDR-TB patients were household workers (27.90 %) and laborers (20.34%) (Basu, Kundu et al. 2021). The majority, 88%, of patients in our study had pulmonary MDR-TB, while 18% of patients had both PTB and EPTB. Others have reported similar findings (Dholakia and Shah 2013).

In the research population, 5.79 percent of the patients had XDR-TB. This figure is nearly identical to a number of recently released figures from India (Ramachandran, Nalini et al. 2009, Dholakia and Shah 2013, Porwal, Kaushik et al. 2013). A review of MDR-TB cases revealed that individuals with a history of prior TB therapy had a higher prevalence of XDR-TB (75%, 3–4%).

The prevalence of resistance to one or more first-line drugs was 62.31 % in our analysis. From Nigeria (Otu, Umoh et al. 2013), scientists have reported a comparable rate of resistance. A lower rate of resistance to one or more first-line anti-TB drugs has been reported from Jimma (18.4%) (Abebe, Abdissa et al. 2012) and at Arsi (18.2%) (Gebeyehu, Lemma et al. 2001).

Rifampin resistance was the most common drug resistance detected in this investigation (14.0%), which is likely related to the widespread use of rifampicin for various bacterial illnesses. Simultaneously, isoniazid ranked as the second most commonly detected resistance (10.1%). In the study, we also saw a twofold drug resistance trend among first-line medication resistant individuals to R + H (14.0%). However, there was also a significant amount of triple-drug resistance discovered. In this study; Quadruple drug resistance against all four first- line drugs was noted in 5.79% of cases. Five of the first-line anti-tuberculosis medications did not work on 35.2% of the MDR isolates analyzed by Irfan et al (Irfan, Hassan et al. 2006).

The result achieved in the present study is somewhat better than Poland's (30.4%) (Bakuła, Napiórkowska et al. 2016), lower than Shanghai (54.4%) (Chen, Yuan et al. 2016), India (44.8%) (Paramasivan, Rehman et al. 2010), and Russia (43.3%) (Smith, Ershova et al. 2015). This suggested that there is a serious resistance to SLDs in this area. By identifying individuals who are at risk of developing XDR TB, physicians mGay monitor these patients closely and prevent the spread of the disease, which is more difficult to treat and has a lower success rate.

CONCLUSIONS

Healthcare professionals who prescribe anti-TB drugs should be experts in diagnosing tuberculosis

(TB) and recommend new molecular diagnostic tests for TB, such as chest computed tomography and histopathological analysis of biopsy samples, especially to patients who have been diagnosed with smear-negative PTB and ETB, in order to facilitate an earlier and better diagnosis. In order to stop medication resistance from emerging, it is also crucial to diagnose TB as soon as possible and to provide DST and culture.

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