ORIGINAL ARTICLE

FREQUENCY AND RISK FACTORS OF MULTI-DRUG RESISTANT TUBERCULOSIS IN KHYBER PAKHTUNKHWA, PAKISTAN: A RETROSPECTIVE STUDY

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ABSTRACT

Introduction: Multi-drug resistant TB (MDR-TB) is a major health problem worldwide especially in Pakistan. It infects around 7000 individuals annually. Many factors are related to the disease prevalence and disease transmission, however, limited data is available in Khyber Pakhtunkhwa (KP). We designed a study that provides an opportunity to mark the rich pockets and the predictors of the implications of MDR-TB in KP.

Material & Methods: A cross-sectional study was conducted for a period of 1-year (2016-2017) at the unit of Programmatic Management of Drug-resistant TB (PMDT) located in tertiary care hospital, Lady Reading Hospital (LRH).

Results: Out of 1015 cases, 137 (14%) were detected rifampicin-resistant (RR) by Xpert MTB/RIF. Mutation present in codon 531 of the *rpoB*gene was observed frequently. Females 529 (52%) with the dominant age range of (<44 years) were found more compared to males. Participants residing in rural areas have 5% lower chances of MDR-TB than urban ones. The rural (54%) participants using biomass were significantly associated with the disease. Diabetes prevalence was found in 22%, and the most obvious clinical manifestation was productive cough 95% of MDR-TB but the test was statistically insignificant.

Conclusion: The increase in patients of MDR-TB amongst prior exposure to anti-TB medications is an issue of incredible concern. MDR-TB issue is noticeable in rural inhabitants of KP. A major gap was found about the awareness of respondents cross-examined in regards to the study of disease transmission, risk factors, signs and side effects, and proper anticipation strategies. Xpert MTB/RIF is the best option in high settings due to the short turnout time.

Key Words: multidrug-resistant TB, *rpoB* gene, Xpert MTB/RIF assay

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INTRODUCTION

Tuberculosis (TB) that was resistant to antibiotics was reported first time during late 1940s, no longer after the application of antibiotics for the treatment of the disease. Provided that, the organism becomes resistant to first line of antibiotics such as isoniazid and rifampicin that are problematic and expensive to treat.[1,2] The dominant part of Multi-drug resistant TB (MDR-TB) examined so far is resistant to rifampicin that hinder the synthesis of mycobacterial RNA, binding with the DNA-dependent RNA polymerase β subunit. This enzyme is encoded by the *rpoB* gene, which is a site for the mutation that confers resistance to rifampicin by alteration in the rifampicin binding site of RNA polymerase. Mutation of the *rpo*B gene is responsible for 96.1% of resistance to rifampicin. This mutation takes place in an 81base pairs (bp) short region of *rpo*B gene called the Rifampicin Resistance Determinant Region (RRDR).[3]

Three different groups of mutations have been identified, group I (codons 507-533), group II (codons 563-572), and group III (codon 687). In resistant strains, 95% of the mutations are nonsense mutations and less frequently, small deletions or insertions. This occurs in the region of group I corresponding to the position of codons 507-533. Mutations in codons 526 and 531 contribute to a high level of resistance to rifampicin.[4,5] Codon 516, 526, and 531 are mostly involved in rifampicin-resistant TB, and mutation in codon 531 is one of the most common mutations.[6] Risk factors awareness associated with the disease transmission could reduce the infection rates. As generally speaking lower socioeconomic class were suffered from MDR-TB that frequently faces illiteracy,

unsafe cooking practices, overcrowding and malnutrition like problems.[7] It is discovered that smoking increases the incidence of the disease. The illness of various diseases including HIV, hepatitis and diabetes augment MDR-TB. As many a threefold increase in the repetitions was found in the case of diabetic patients.[8] However, the refugees and migrants from various countries having high disease incidence also responsible for disease transmission, and noticeably, these migrants' groups are responsible for disease dissemination in general populations.[9] In Pakistan, the burden of disease is high with the fourth highest prevalence of MDR-TB. Every year, over 300,000 cases of the disease are reported in Pakistan, causing 70,000 deaths. Pakistan, if such a worst-case scenario plays out, will rank fourth on the list by 2025 with 14.5 million infected cases.[10]

This study is one of the population-based epidemiological investigations to document the district-wise prevalence of the MDR-TB in KP so that to mark the rich pockets of MDR-TB in the province. This study might contribute to provide an opportunity make predictions of a high burden of MDR-TB in the districts of KP, Pakistan. Moreover, reference data on mutations in the *rpoB*gene in different regions of KP and the molecular nature of the MTB strains concerning the drug could be determined. The objectives of the present study were to assess the frequency of MDR- TB in various districts of KP and the risk factor associated with an MDR-TB, and to provide baseline data on *rpoB* mutations in diverse geographic regions of KP using Xpert MTB/RIF assay.

MATERIAL AND METHODS

Across-sectional study during 2016-2017 was conducted at the Department of Pulmonology, Lady Reading Hospital (LRH), Peshawar that offers a full scope of inpatient and outpatients services. The primary data were obtained using questionnaire method, verbal translation of English was done in Pashto and Urdu to remove any difficulty and ambiguity and for better understanding. A random sampling method was selected for this study. The XpertMTB/RIF assay was used for disease detection to run four tests at once. A known volume of reagent buffer (isopropanol-containing sample and sodium hydroxide) in a sample container was added and stirred manually for the time of 15 minutes. Followed by transferring to a single-use container avoiding bubble formation the uptake of solid materials. A container including all reagent necessary for bacterial lysis, nucleic acid isolation, amplification and detection of amplicon was used. The absence or presence of MTB, drug resistance, and indeterminate forms was confirmed with XpertMTB/RIF

The Statistical Package for the Social Sciences (SPSS) version 22 was used for data analysis. Microsoft excel was used for paper-based data and then transferred to the program software (SPSS) for analysis. Data analysis was carried out in different stages: univariate, bivariate, and logistic regression. Descriptive statistics for the understanding of study variable, raw data characteristics and platform for inferential statistics was generated. The chi-square analysis was done to find out any statistical significance between the risk factors and the MDR-TB prevalence. P-value of 0.05 was considered significant between dependent and independent variables. Variable were analysed using bivariate level entered for the multivariate analysis. The regression model was used to determine the association between contextual level variables and the complication of MDR-TB (using odds ratios). The level of significance was evaluated using a value of p= 0.05 and the values of R and R2 (Cox, Snell, and Nagelkerke) were used to evaluate the importance of the amount of variance explained by the model. The percentage accuracy (PAC) in the classification and the Wald criteria to judge the model were also checked.

RESULTS

Out of 1015 participants, 486 (48%) were male and 529(52%) females. The predominance age group was in range of <42 years (56%). More than half (66%) of the participants were married. The majority of the participants 553 (54%) were rural participants. A total of 137(14%) were rifampicin-resistant. The association of MDR-TB and various demographic factors is depicted in Table 1. Data was statistically significant between age groups. This disease in age group of <42 years having 36% of less chances (OR = 0.64, 95% CI [0.441-0.934], p = 0.020). Educated applicants were 69% more likely to contact MDR-TB than illiterate people and the result was significant (Table 1) (OR = 1.693, 95% CI [0.976-2.938], p = 0.059). There was no statistical significant result between the marital status and the disease (OR = 0.806, 95% CI [0.556-1.168], p = 0.254). Participants residing in rural areas have 5% lower chances of MDR-TB than urban ones. This result was statistically significant (OR = 0.650, 95% CI [0.448-0.943], p = 0.023). An individual having high burden country visit has 61% lower odds of disease and the result was significant (OR = 0.396, 95% CI [0.237-0.663], p= 0.01) (table 1).

MDR-TB association with Socio-Economic Factors

The results suggested that the association between dependent status and occupation with MDR-TB was non-significant (OR = 1.249, 95% CI [851-1,832], p = 0.256), (OR = 0.974, 95% CI [572-1659], p = 0.923). No association of the disease was present in case of house occupants and the overpopulation (OR = 0.782, 95% CI [0.532-1.151], p = 0.211), (OR = 1.023, 95% CI [0.707-1,480], p = 0.905). Participants having gas facilities were less prone to the disease, with 78% of higher chances (OR = 0.561, 95% CI [0.379-0.830], p = 0.004)(table 2).

Factors Related to Behaviour and Perception

Non-significance results were obtained between MDR-TB and active smoking (OR = 1.099, 95% CI [0.765-1.579], p = 0.610). In ex- smokers the risk of TB was 59% less and the result was significant (OR = 0.411, CI 95% [0.176-0.959], p = 0.034). The association between passive smokers and MDR-TB was not significant (OR = 1.398, CI 95% [0.936-2.087], p = 0.100) (Table 3). A contact case of MDR-TB has positive relation with the disease and the test was statistically significant. There are 5 folds high chances of being suffered with the source case of disease (OR = 5.189, 95% CI [2.832-9.508], p = 0.01). Knowledge about MDR-TB and its contagious nature had insignificant association with the increase of disease (OR = 0.883, 95% CI [0.559-1.395], p = 0.595), (OR = 0.757, 95% CI [0.484-1.185], p = 0.222) (table 3).

Association of MDR-TB with Underlying Diseases

No statistical association in case of Diabetic, Hepatitis and Arthritis was found in the included population (OR = 804, 95% CI [0.522-1.239], p = 0.807), (OR = 2.162,

95% CI [0.578-8.086], p = 0.241) and (OR =1.348, 95% CI [0.505-3.594], p = 0.549) (Table 4).

Prioritization of Clinical Manifestation of MDR-TB

Result was not significant in case of productive cough (OR = 1.098, 95% CI [0.487-2.476], p = 0.822). Patients having haemoptysis had significantly high risk for MDR-TB. Patients having haemoptysis had 61% more odds of disease (OR = 1.609, 95% CI [1.114-2.323], p = 0.011). MDR-TB was 58% higher in patients having weight loss symptoms, and significant results were obtained (OR = 1.582, 95% CI [0.977-2.563] p = 0.060) (table 5).

Relation of Acid-fast Bacilli (AFB) with disease

Positive AFB favours the disease with 77% of higher risk and the test was statistically significant (OR = 1.769, 95% CI [1.094-2.861], p = 0.019). Chi square test revealed, the association between MDR-TB and the bacillary load of $<1^+$ and $\geq 1^+$ was not statistically significant. (OR = 1.148, 95% CI [0.798-1.651], p = 0.456), (OR = 1.286, 95% CI [0.889-1.859], p = 0.181) (table 6).

Association of Clinical Indices with the Disease

The present study included patients who had already taken treatment for the disease. The group of these "follow-up" patients and the prevalence of the disease have a significant association. New patients were 42% less likely to have the disease (OR = 0.581, 95% CI [0.402-0.839], p = 0.003). Patients who have a "Category I" treatment have 89% high probability of the disease and the test was statistically significant (OR = 0.536, 95% CI [0.372-0.772], p = 0.01). The association between MDR-TB and “Cat II” treatment was statistically insignificant (OR = 1.277, 95% CI [0.770-2.119], p = 0.343). The patients having "completed treatment" were 33% higher chances of disease and the result was significant (OR = 0.759, 95% CI [0.512-1.125], p = 0.169). The Chi-square test revealed that there was no significant association between MDR-TB and the result "Cured" and "Failure" (OR = 0.807, 95% CI [0.439-1.481], p = 0.487), (OR = 0.775, 95% CI [0.445 - 1,488], p = 0.366). The result "Relapse" and “default” had no significant association with MDR-TB in our case (OR = 0.758, 95% CI [0.448-1.284], p = 0.326) and (OR = 1.522, CI of the 95% [0.655-3,537], p = 0.326) (table 7)

Final “Best Fit” Model of Logistic Regression on Factors Associated with MDR-TB

For the prediction of prevalence of MDR-TB logistic regression was conducted using diverse variables. Initial investigation of constant or mean-model can be enhanced by adding predictors distinctly. In our case all the eleven variables have significantly improved the model. Residence $\Delta\chi^2$ =5.197, p =0.023, Education $\Delta\chi^2$ =3.576, p =0.059, Age $\Delta\chi^2$ = 5.434p =0.020, Ex-smoker $\Delta\chi^2$ = 8.390, p =0.004, MDR-TB contact $\Delta\chi^2$ = 34.241, p =0.01, Haemoptysis $\Delta\chi^2$ =6.515, p =0.011, Bacillary load $\Delta\chi^2$ = 5.525, p =0.019, Follow up $\Delta\chi^2$ =8.536, p =0.003, Category I treatment$\Delta\chi^2$ =11.437, p = 0.01, Facility $\Delta\chi^2$ = 8.526, p =0.004, Visit to other high burden country $\Delta\chi^2$ =13.183, p =0.01, New cases $\Delta\chi^2$ =6.828, p =0.009.

After adding all the variables model’s goodness-of-fit was satisfied: -2log likelihood was 803.345, after adding predictors it was improved with the smallest of -2log likelihood = 732.780. Variance in the dependent variable by independent was ranged between 06% Cox & Snell R square and 12% Nagerkerke R Square (Cox & Snell R^2 =0.067, Nagelkerke R^2 =0.123). The percentage accuracy (PAC) in classification was overall 88%. The Wald criterion showed that significant contribution to prediction was made by all variable. The values of EXP (B) shows that positive relation was noticed in disease and ex-smokers although smokers were more probably [Exp (B) = 2.338] to develop MDR-TB rather than non-smokers.

Having visit to high burden disease country is strongest risk factor in our study that is followed by the smoking status [Exp (B) = 2.515], [Exp (B) = 2.338]. Biomass has a positive relationship with the disease prevalence [Exp (B) = 1.723]. Close contact and haemoptysis have negative relationship with the disease occurrence [Exp (B) = 0.208], [Exp (B) = 0.674]. A negative relationship was found in case of positive loaded bacilli and category I treatment [Exp (B) = 0.577], [Exp (B) = 0.587](table 8).

RRDR Mutations in the 81bp (codon 507–533) of *rpoB* Detected in *M. TB.*

The mutation in *rpoB*genewas mostly found in region of Probe E (91, 9%), followed by A, B, C and D with percent of (12, 1.2%), (26, 15.2%), (26, 15.2%), and (8, 0.8%), respectively. Two probes combination was observed in in 8 cases (2.9%): A&B in 2 cases, E & D in 4 cases, and B&D in 2 cases (table 9).

Baseline Data on *rpoB* gene in Diverse Division of KP

We have observed that Probe E was frequently observed in all the divisions of KP. The pattern of mutation was very similar in divisions except for Bannu and Peshawar. In the division of Peshawar, Probe A accounted for 6 patients and in Bannu Probe B, C and D were also associated with the disease (table 10).

DISCUSSION

In developing countries, the MDR-TB is a major health issue. On the WHO's 2011 Global TB Indicators list, Pakistan is ranked 5th in the world among the 27 countries with the highest prevalence of MDR-TB. There is an estimated 20% prevalence of MDR-TB in Pakistan, but it is not known what the actual prevalence is (WHO, 2017).[11] Based on our investigation, 14% of the TB patients attending Lady Reading Hospital, Peshawar were found to have MDR-TB (137/1015; 14%). Other studies reported similar findings of have almost same percentage of prevalence. Different cities of Pakistan show significant variance in their respective results. Akhtar *et al.* identified 69% of cases in Punjab. It is a complex disease that requires a strong health infrastructure with surveillance and monitoring activities for effective therapy and suitable mediation to limit its transmission and spread. Probably weak TB control programs at the country level do not properly diagnose and treat the disease.

A special laboratory test and technical staff are required to detect drug resistance. These facilities, however, are not present in some rural and flank areas of KP, so cases cannot be correctly diagnosed, cultured, or tested for sensitivity to drugs. Pakistan provides free treatment for MDR-TB. Among the public, it is generally perceived that government-provided free drugs are low quality and potent, making them ineffective. Another factor contributing to MDR-TB is self-medication. Because of the availability of medicines in small general stores across the country, patients have easy access to medication. Unfortunately, educated people self-

medicate more than others. Since competent authorities do not enforce relevant rules and regulations, antibiotics are readily available at medical counters. The use of antibiotics to treat TB leads to antibiotic-resistant strains of the disease due to insufficient guidance on the dosage, duration, and use of antibiotics.

Gender seems to have an impact on MDR-TB epidemiology. This study observed 71/137 (52%) of MDR-TB cases in female patients. These results are in line with those of Ahmad *et al*. and Ullah *et al.* who reported 52% and 68% of female cases, respectively. Similar findings have been reported in a study carrid out in Georgia where women were reported at high risk compared to their counterparts males.[12] Contrary to these studies Akhtar *et al*. reported in a study carried out in Punjab that male (53%) were more prone to the disease.

In KP, women are more likely to contract MDR-TB. Despite the fact that drug-susceptible tuberculosis is easily treatable, due to illiteracy, ignorance, and stigma attached to females, the illness is hidden, which contributes to the emergence of MDR-TB. Because of their close contact with sick patients, women, especially nurses, are more likely to contract MDR-TB than men. A significant association was found between age and MDR-TB prevalence. Both males and females are affected by MDR-TB during their economically productive growth stage. More than half of the cases (65%) occurred in persons under the age of 42 years. In a study carried out by Ahmad et al. 77% of patients with MDR-TB were under 42 years of age. Due to their high level of energy and activity, young people are more susceptible to MDR-TB than the elderly. This productive age group is very busy, and their inconsistent work time makes them unable to comply with prescribed anti-TB therapy, which results in poor treatment outcomes. Elder people may not have been used Rifampicin because it is familiarized in recent decades so younger age groups are at risk.

Significant association between education and MDR-TB was noticed. Thirteen percent of the study participants were educated (18%). A matriculation education reduces the risk of disease. According to Gobena, et al. 52 percent of illiterate individuals were suffering from TB. With education, we gain knowledge about the disease, how it is transmitted, and how it is treated. Due to lack of knowledge, patients are generally unable to understand the importance of prescription compliance and therefore quit treatment before completing the regimen that makes the condition adverse. Fear of stigmatization arises due to the poor knowledge about the cause, spread, and treatment of the disease.

The rural contributors had higher chances of MDR-TB, which is consistent with the research done by Ali *et al.* who recorded 53% of incidence in the rural area. However, conflicting results of 98% and 88% were found in urban areas of Pakistan.[13,14] As we know, majority of individual from rural area is not diagnosed properly due to lack of lab facilities and expertise to conduct diagnostic tests for TB. Moreover, in these areas, people are unable to recognize TB symptoms timely for seeking early treatment and their condition worsens.

Close contacts with MDR-TB enhance the risk of acquiring the disease. About 15% of the total investigated cases had family members that were already suffering from the disease. The contact cases or primary assumed MDR-TB was only 3%. The present findings are in line with those of Kandal *et al*. who reported 3.3 % of the contact cases. A meta-analysis of Shah *et al.* found 7.8% of contact cases of MDR-TB.

In our target area Probe E present in the gene region of codon 529–533 was the most frequent pattern of mutation in 81 base pairs. This probe accounts for 69% of the cases. A consistent result was found by Khan *et al.* in Sindh and Ullah *et al*. in KP Pakistan. An investigation in six districts of Punjab India found that probe E accounted for 56%.[16] The topmost mutation frequency in probe E could be because of the higher susceptibility of this genetic region to mutations. It may also be due to the selection pressure shaping (producing) probe E associated RIF's resistance is high in this region of KP province of Pakistan.

Initial treatment of patients with WHO recommended first-line antibiotics are at higher risk of to develop MDR-TB strains. We have found more than half of the patients were already treated for the disease (78/137: 57%). Forty two percent have previously got a category I remedy. Worldwide 4.1% new cases in 2016 and 19% earlier treated cases have MDR-TB (WHO, 2016). From China, one national survey reported the disease in previously and in new treated cases were 25.6% and 5.7% respectively.[17] Another study from Japan reported the disease in previously and in new treated cases were 9.8% and 0.7% respectively.[18] However, one study from Yemen done reported the disease in previously and in new treated cases were 9.4% and 3%, respectively.[19] This variation may be due to sample size, geographical location and the procedures used for sampling data. This can also be attributed to the difference in health care delivery systems between countries that lead to poor compliance, inadequate treatment supervision, and ineffective control programs which contribute to the spread of disease.

The present study found a significant association between smear-positive MDR cases in comparison to smear-negative. We have identified that positive bacilli 10 times increase the disease risk. This correlates with the study of Akhtar *et al.* that revealed that 69% of the positive cases have MDR-TB. Similar research conducted in Malaysia found that AFB increases the disease by more than8 times.[20]

CONCLUSION

Among patients who have previously taken anti-TB drugs, an increasing proportion have developed MDR-TB. Unless quick interventions in the treatment are put into effect, MDR strains are at risk of spreading rapidly, leading to the dominance of TB. Residents of rural KPK face a more severe problem of MDR-TB. A lack of knowledge about epidemiology, risk factors, signs and symptoms, and effective prevention was observed among respondents interviewed. Due to its quick turn-out time, Gene Xpert MTB/RIF offers the best performance in high settings.

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Table1: MDR-TB and Associated Demographic Factors

Factors	MDR-TB	Negative	Positive	p values	95% Confidence Interval Odds ratios	[Lower-Upper]
Gender	Female	458	71			
	Male	420	66			
	Total	878	137	0.941	1.014	[0.707-1.453]
Age	> 42	477	89			
	≤ 42	401	48			
	Total	878	137	0.02	0.642	[0.441-0.934]
Education	No	806	119			
	Yes	72	18			
	Total	878	137	0.059	1.693	[0.976-2.938]
Marital status	Single	582	84			
	Married	296	53			
	Total	878	137	0.254	1.241	[0.856-1.798]
Residence	Rural	466	87			
	Urban	412	50			
	Total	878	137	0.023	0.65	[0.448-0.943]
Visit to other country	No	65	23			
	Yes	813	114			
	Total	878	137	0.01	0.396	[0.237-0.663]

Note: Visit to high burden countries like Afghanistan, China, USA and UAE

Table 2: Associated Socio- economic Factors Related to MDR-TB

		MDR-TB			95% Confidence Interval	
Factors		Negative	Positive	p values	Odds ratios	Lower-Upper
Dependent status	No	253	46			
	Yes	625	91			
	Total	878	137	0.256	1.249	[0.851-1.832]
Occupation	Labour	760	119			
	Office work	118	18			
	Total	878	137	0.923	0.974	[0.572-1.659]
House occupants	<Than 10	324	43			
	≥Than 10	554	94			
	Total	878	137	0.211	0.782	[0.532-1.151]
Over crowding	No	543	84			
	Yes	335	53			
	Total	878	137	0.905	1.023	[0.707-1.480]
Biomass user	No	506	97			
	Yes	372	40			
	Total	878	137	0.004	0.561	[0.379-0.830]

Table 3. Factors Related to Behaviours and Perceptions and Their Association with MDR-TB

		MDR-TB				95% CI
Factors		Negative	Positive	p values	Odds ratios	[Lower-Upper]
	No	405	60			
Active smoker	Yes	473	77			
	Total	878	137	0.61	1.099	[.765-1.579]
	No	790	131			
Ex-smoker	Yes	88	6			
	Total	878	137	0.034	0.411	[.176-.959]
	No	678	97			
Passive smoker	Yes	200	40			
	Total	878	137	0.1	1.398	[.936-2.087]
	No	850	117			
MDR-TB contact	Yes	28	20			
	Total	878	137	0.01	5.189	[2.832-9.508]
	No	694	111			
MDR-TB?	Yes	184	26			
	Total	878	137	0.595	0.883	[.559-1.395]
	No	663	110			
Is this transmitting?	Yes	215	27			
	Total	878	137	0.222	0.757	[663-215]

Table 4: Association of MDR-TB with Underlying Diseases

		MDR-TB				95% CI
Comorbidity		Negative	Positive	p values	Odds ratios	Lower-Upper
	No	651	107			
Diabetes	Yes	227	30			
	Total	878	137	0.807	0.804	[0.522-1.239]
	No	869	134			
Hepatitis	Yes	9	3			
	Total	878	137	0.241	2.162	[0.578-8.086]
	No	854	132			
Arthritis	Yes	24	5			
	Total	878	137	0.549	1.348	[0.505-3.594]

Table 5: Prioritization of Clinical Manifestation of MDR-TB

		MDR-TB				95% CI
	Factors	Negative	Positive	p values	Odds ratios	Lower-Upper
Productive cough	No	49	7			
	Yes	829	130			
	Total	878	137	0.822	1.098	[0.487-2.476]
Haemoptysis	No	449	54			
	Yes	429	83			
	Total	878	137	0.011	1.609	[1.114-2.323]
Weight loss	No	204	22			
	Yes	674	115			
	Total	878	137	0.06	1.582	[0.977-2.563]

Table 6: Relation of Disease with Acid Fast Bacilli

		MDR-TB				95% CI
Factors		Negative	Positive	p values	Odds ratios	[Lower-Upper]
Bacillary load						
Positive	No	222	22			
	Yes	656	115			
	Total	676	1015	0.019	1.769	[1.094-2.861]
up to 1+	No	523	77			
	Yes	355	60			
	Total	676	1015	0.456	1.148	[0.798-1.651]
> 1+	No	577	82			
	Yes	301	55			
	Total	676	1015	0.181	1.286	[0.889-1.859]

Ø Up to 1^+ represent positive microscopy having scanty and $>1^+$represent 1^+2^+ and 3^+

TABLE 7. Association of Clinical Indices with the Disease

Registration group		MDR-TB		p values	Odds ratios	95% CI
		Negative	Positive			Lower-Upper
Follows up	No	268	59			
	Yes	610	78			
	Total	878	137	0.003	0.581	[0.402-0.839]
Category I	No	377	80			
	Yes	501	57			
	Total	878	137	0.01	0.536	[0.372-0.772]
Category II	No	769	116			
	Yes	109	21			
	Total	878	137	0.343	1.277	[0.770-2.119]
Treatment Outcome						
T. completed	No	539	100			
	Yes	339	37			
	Total	878	137	0.169	0.759	[0.512-1.125]
Cured	No	777	124			
	Yes	101	13			
	Total	878	137	0.487	0.807	[0.439-1.481]
Failure	No	750	121			
	Yes	128	16	0.366	0.775	[0.445-1.348]
	Total	878	137			
Relapse	No	732	119			
	Yes	146	18			
	Total	878	137	0.326	0.758	[0.448-1.284]
Default	No	848	130			
	Yes	30	7			
	Total	878	137	0.326	1.522	[0.655-3.537]

TABLE 8. Final "Best Fit" Model of Logistic Regression on Factors Associated with MDR-TB

Factors	Wald	Df	Sig.	Exp(B)	Lower–upper
Ex-smoker	5.893	1	0.015	2.338	[1.178-4.642]
MDR-TB contact	23.551	1	0	0.208	[0.110-0.392]
Hemoptysis	4.017	1	0.045	0.674	[0.458-0.991]
Positive Bacillary load	4.593	1	0.032	0.577	[0.349-0.954]
Category I treatment	7.416	1	0.006	0.587	[0.401-0.861]
Gas facility	6.567	1	0.01	1.723	[1.136-2.611]
Visit to high burden countries	10.892	1	0.01	2.515	[1.454-4.348]

Table 9: RRDR Mutations in the 81bp (codon 507–533) of *rpoB* Detected in *M. TB*

Probes	Codon	Frequency	Percent
ND	ND	878	86.5
A	511	12	1.2
B	513	9	0.9
C	522	9	0.9
D	526	8	0.8
E	531	91	9
A&B	511-513	2	0.2
B&D	513-526	2	0.2
E&D	531-426	4	0.4

Table 10: Baseline Data on *rpoB* Gene in Diverse Division of KP

Divisions	ND	A	B	C	D	E	A&B	B&D	E&D
Malakand	126	2	0	0	2	16	1	1	0
Hazara	38	1	0	0	0	10	0	1	1
Mardan	61	1	3	0	0	5	0	0	0
Peshawar	505	6	3	4	2	33	1	0	3
Kohat	81	1	0	0	0	16	0	0	0
Bannu	53	0	3	3	3	7	0	0	0
D.I. Khan	14	1	0	2	1	4	0	0	0