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FREQUENCY AND RISK FACTORS OF TUBERCULOSIS AT A TERTIARY CARE HOSPITAL IN KHYBER PAKHTUNKHWA, PAKISTAN: A RETROSPECTIVE STUDY

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ABSTRACT

Background: Tuberculosis (TB) has been one of the biggest health problems across the world in human history. Pakistan is at 5th amongst the 22 high TB burden countries in the world.

Objectives of the current study were to assess the frequency of TB in different districts of KP and to investigate different risk factors and the association between different risk factors and TB in KP, Pakistan

Material and Method: This study was conducted for a period of one year at Programmatic Management of Drug Resistant TB (PMDT) unit at tertiary care hospital, Lady Reading Hospital (LRH) Peshawar Pakistan. All the suspected cases were analyzed by LED-FM microscopy and Xpert MTB/RIF assay. The risk factors selected for investigation were demographic characteristics, socio economic, behavioral factors and clinical manifestations.

Results: Out of 1691 suspected TB cases; MTB was detected in 1015 (60%) cases. Out of MTB, 137(13.5%) were drug resistant. Females with productive age (<44 years) were found infected more than males. Among diabetes, arthritis and hepatitis which were analyzed as comorbidities with TB diabetes was found to be present in 9.3% of the cases of TB, followed by arthritis and hepatitis which was present simultaneously with TB in 3% and 9% of the cases. The most obvious clinical manifestation of TB was found to be productive cough which was present in 92% of the cases. Weight loss was recorded in 62.5% cases, while hemoptysis was reported by 58.1% TB patients.

Conclusion: The results of logistic regression showed that visit to high burden countries, age and active smoking were positively associated with the burden of this disease.

Keywords: Tuberculosis, risk factors, Xpert MTB/RIF assay, Khyber Pakhtunkhwa

INTRODUCTION

Tuberculosis (TB) considers as the largest public health mediation, which affects the world at different levels ranges from low frequency to an epidemic. According to the report by the Center for Disease Control and Prevention (CDC), one third of the world's population is infected with TB that claims almost 5,000 lives daily and 40,000 lives per week **(1)**. Increase in world population, inadequate treatment resources, and lower socioeconomic status of the population and some of the co-morbid conditions is the reasons for development of TB. Proper diagnosis and treatment are necessary to control the disease and decrease its transmission within communities. Limited access to health services and lack of awareness on part of the society about this scourge and its risk factors are also reasons for rise in TB. Familiarity with risk factors related to disease transmission can be used to decrease the infection rate. TB generally

target the lowest socioeconomic class that commonly faces problems such as malnutrition, unsafe cooking practices, illiteracy and overcrowding **(2)**. The morbidity of diseases such as diabetes, HIV and hepatitis worsens TB. A threefold higher recurrence of TB was found in diabetic patients **(3)**. Migrants and refugees from countries with high incidence are also responsible for the disease. To a certain extent, these groups can disseminate diseases in the general population **(4)**. Pakistan is the sixth largest state in the world with high population growth rate. This country also has high burden of communicable diseases and has to improve its health care delivery system specially to combat infectious diseases. TB remains a significant killer in Pakistan that has infected millions of people and ranks fifth among the 22 high-TB burden countries **(5)**.

This study aims at evaluation of the prevalence of TB in different divisions of Khyber Pakhtunkhwa. Moreover, this also will establish statistical association between the prevalence of infection and different risk factors. Beside the establishment of predictors of a high TB this study also provided the opportunity to increase the information on the prioritization of the risk factors in vulnerable populations. The statistical association established between various risk factors and TB in different areas also provides information that serves to reduce the potential for the spread of TB in the province. .

MATERIALS AND METHODS

Study Design and setting

We conducted a cross-sectional study during 2016-2017 at Department of Pulmonology, Lady Reading Hospital (LRH) Peshawar. It is located in the center of Peshawar city and comprises of districts Peshawar, Nowshehra and Charsadda. It also provides tertiary care facilities throughout the province

Participant and Data Collection

Through questionnaire method we obtained the primary data by simple random sampling. Questionnaire method was valid, unbiased and low cost. A structured questionnaire was developed in English language and translated verbally in Urdu and Pashto to the patients to remove ambiguity in the translation.

Disease detection Methods

Two distinct procedures were used for our examination and to analyze the disease. WHO has recommended different types of samples for pulmonary (sputum, bronchial lavage and pleural fluid) and extra pulmonary TB (lymph node biopsy, ascetic fluid, cerebrospinal fluid, pericardial fluid, urine and pus) for detection purposes.

Smear Preparation and Microscopy

For the quantification and observation of acid-fast bacilli (AFB) direct sputum smear microscopy of the samples were performed. Samples of patients suspected of TB were taken in 5 ml of sterile plastic bottles followed by processes like decontamination, specimen concentration, slide preparation and Fluorochrome staining with "auramine O". Direct smears were prepared in duplicate for staining with Auramin O. The smears were flooded with "Auramin O" for 10 minutes, distained with acid alcohol for 2 minutes and then counterstained with potassium permanganate for one minute. With "Auramine O" staining, mycobacteria appear as bright yellow fluorescent rods on a dark background. The smears stained with "Auramin O" were analyzed on the same day. Quantification and observation of acid-fast bacilli (AFB) was performed according to guidelines by WHO **(1)**. The presence or absence of AFB was reported using WHO guide.

Xpert MTB/RIF assay Analysis

Four cartridges Xpert MTB/RIF assay with capacity to run four tests at once was used to detect the disease. A volume of reagent buffer (sodium hydroxide and isopropanol-containing sample) was added to the sample container and manually stirred for a period of 15 minutes. It was transferred carefully to a single-use cartridge avoiding the pipetting of solid materials and the formation of bubbles. A special cartridge containing all the reagents necessary for the lysis of bacterial cells, the extraction of nucleic acids, the amplification and the detection of amplicons were used. The data obtained from Xpert MTB/RIF assay confirmed the presence or absence of MTB, as well as Drug resistance and indeterminate cases.

Data analysis

All the analyses were done using the software package Statistical Package for the Social Sciences (SPSS) version 22. All the analyses were done using the software package SPSS version 22. Descriptive statistics was generated to understand the distribution of scores of study variables and the underlying characteristics of the raw data, so that a platform for inferential statistics may be obtained **(6)**. The Chi-Square test was used to evaluate the statistical significant association between the factors and the prevalence of TB value of 0.05 and the confidence interval (CI) were used to evaluate the statistical significance of the association between independent and dependent variables. All the variables that

were analyzed at the bivariate level were entered into the multivariate analysis.

RESULTS

Study population

A total of 1691 respondents included, comprising 859 (51%) females and 832 (49%) males. Majority of the cases 910 (54%) were in most gainful age group of <42 years. The conjugal status indicated 1184 (70%) of married participants. The highest number of cases 866 (51%) belonged to Peshawar division.

Detection of *Mycobacterium tuberculosis*

Of the 1691 suspected patients, Xpert MTB/RIF detected MTB in 1015 (60%) (Fig.1), of which 384 (23%) of the cases were at a medium level which is followed by low level of cases 347(21%) **(Fig 2)**.

LED microscopic observation revealed 771(46%) of the cases as acid fast bacilli positive (Fig 3). Positive bacilli "Up to 1^{+}" represent 415 (25%) of the cases, while " > 1^{+}" were 356 (21%) **(Fig 4)**.

TB and Associated Demographic Factors

Table 1 indicates that there is no any significant distinction between male and female category and association was not statistically significant (OR = 0.876, 95% CI [0.721-1.065], p = 0.183. A statistically significant difference was found between the age groups; Age group <42 have 18% decrease in the chance of TB (OR = 0.822, 95% CI [0.676-0.999], p = 0.049). There was no significant association between TB and education (OR =7.80, 95% CI [0.564-1.077], p = 0.130). Marital status and the disease prevalence have statistically significant association. Married people are less likely to have TB with 42% of lower odds than single people (OR = 0.582, 95% CI [0.467-0.725], p = 0.01). Urban residents were less prone to disease with double decrease in risk and the test was statistically significant (OR =0.509, 95% CI [0.418-0.621], p = 0.01).Person having visit to high burden country has 92% higher risk of disease (OR = 0.528, 95% CI [0.390-0.715], p = 0.01) **(Table 1)**.

Socio-Economic Factors Associated with TB

Table 2 shows the relationship of TB with the socio- Economic status of patients. The study revealed statistically significant difference in bias of dependent and independent to TB. Dependents had double increased in chances of TB than the independent ones (OR = 1.464, 95% CI [1,168-1,836], p = 0.01). Association between TB and occupation was insignificant (OR = 0.861, 95% CI [0.653-1.135], p = 0.288). No association was found between house occupants and overpopulation case (OR = 1.097, 95% CI [0.897-1.341], p =

0.368), (OR = 1,054, 95% CI [862-1,893], p = 0.605). Significant association between TB and use of biomass as fuel was recorded. Biomass users were 30 times more likely to have the disease (OR = 1.307, 95% CI [1,073-1,592], p = 0.008) **(Table 2)**.

Factors Related to Behavior and Perceptions

The results are depicted in **(Table 3)**. In active smokers, the risk of TB was 46% higher and the result was statistically significant (OR = 1.465, 95% CI [1.205-1.781], p = 0.01). Association between Ex-smokers and TB was not statistically significant (OR = 0.943, 95% CI [0.678-1.313], p = 0.730). Passive smokers and TB have significant association with 51% of increased odds (OR = 1.511, 95% CI [1.205-1.781], p = 0.01).

Contact with TB cases were not considered as a risk factor in our case (OR = 1.055, 95% CI [868-1.290], p = 0.589). There was no any effect of knowledge of TB on prevalence of disease (OR = 1.033, 95% CI. 827-1.290], p = 0.777). A person with perception about the contagious nature of TB can reduce the risk by 11% (OR = 0.910, 95% CI [0.727-1.140], p = 0.413) **(Table 3)**.

Association of TB with Underlying Diseases

Diabetic patients had 51% lower risk of TB compared to non-diabetic patients **(Table 4)**. This result was statistically significant (OR = 0.491, 95% CI [0.381-0.632], p = 0.01). TB did not show any statistically significant association with Hepatitis and arthritis (OR = 2.010, 95% CI [0.346-0.551], p = 0.219), (OR = 0.916, 95% CI [0.519-1.623], p =0.767) **(Table 4)**.

Prioritization of Clinical Manifestation of TB

A significant association was found between TB and productive cough **(Table 5)**. Participants with productive cough were 2 times more susceptible to TB than others (OR = 2.299, 95% CI [1.609-3.283], p = 0.01). A statistically significant association was found between TB and hemoptysis. The probabilities of being TB were 56% lower in patients with hemoptysis (OR = 0.443, 95% CI [0.361-0.544], p = 0.01).TB was 5.315 times higher in individuals of lower weight compared to other patients, without having symptoms of weight loss. The test was statistically significant (OR = 5.315, 95% CI [4.293-6.580], p = 0.01) **(Table 5)**.

Relation of Disease with acid Fast Bacilli

The presence of bacilli favors the prevalence of the disease **(Table 6)**. The Chi-square test revealed that there was a significant association between TB and positive

bacillary load, patients with high bacillary load had 4 times higher risk of TB than a negative one (OR = 0.265, 95% CI [0.238-0.238], p = 0.01). A very strong association was found between TB and the bacillary load "up to 1^{+}" with a double probability of having the disease (OR = 0.470, 95% CI [0.444-0.498], p = 0.01). Participants who had "$\geq 1^{+}$" loaded bacilli have double increase in the risk to be TB. The test was statistically significant (OR = 0.494, 95% CI [0.468-0.521], p = 0.01) **(Table 6)**.

Final "Best Fit" Model of Logistic Regression on Factors Associated with TB

A logistic regression was conducted to predict the prevalence of TB using different variables. An initial test of constant-only model can be improved by adding predictors separately. In this case 10 variables were entered into multivariate analysis which was found significant at p value 0.05 in bivariate analysis. Visit to high burden countries $\Delta\chi^2 =$ 17.463, p= 0.01, Dependent status $\Delta\chi^2$ = 10.993, p= 0.01, Marital status $\Delta\chi^2$ = 23.436, p= 0.01, Age $\Delta\chi^2$ = 3.881 p= 0.049, active smoker $\Delta\chi^2$ = 14.688, p= 0.01, Passive smoker $\Delta\chi^2$ = 10.765, p= 0.01, Productive cough $\Delta\chi^2$ = 21.894,p= 0.01, Hemoptysis $\Delta\chi^2$ = 61.657, p= 0.01, Weight loss $\Delta\chi^2$ = 251.184, p= 0.01 and Diabetes $\Delta\chi^2$ = 31.074, p= 0.01.

The variance in the dependent variable varied independently between 24% of Cox and Snell R squared and 33% of Nagelkerke R Square (Cox and Snell R2 = 0.24, Nagelkerke R2 = 0.33). The percentage precision (PAC) in the classification was 60%, which was improved to 73%. Then, the success of the prediction in general was 73%.

After adding the variables only eight were significantly improved the model fit. Visit to high burden country, productive cough, weight loss, active smoking and age has positively associated with the burden of disease. TB was highly pronounced in weight loss individual that is followed by productive cough [Exp (B) = 7.853], [Exp (B) = 2.627]. Patients having symptoms of productive cough and weight loss are triple and 8 fold increased risk to be sick

Individual having a visit to high TB burden country has 85% more likelihood to be TB [Exp (B) = 1.852]. Young individuals were observed more to be TB [Exp (B) = 1.585]. Active smokers are more likely to suffer having double increased odds [Exp (B) = 1.531]. Diabetic patients were two timeless likely to be TB while Hemoptysis accounted for 4 folds high chances [Exp (B) = 0.423], Exp (B) = 0.237]. Married participants have double increase lower odd of disease than single once [Exp (B) = 0.543] **(Table 7)**.

Table 1: TB and Associated Demographic Factors

Factors	TUBERCULOSIS		p values	95% Confidence Interval	
	Negative	Positive		Odds ratios	[Lower-Upper]
Gender					
Female	330	529			
Male	346	486			
Total	676	1015	0.183	0.876	[0.721-1.065]
Age					
< 42	344	566			
≥42	332	449			
Total	676	1015	0.049	0.822	[0.676-0.999]
Education					
No	601	925			
Yes	75	90			
Total	676	1015	0.130	0.780	[0.564-1.077]
Marital status					
Single	158	349			
Married	518	666			
Total	676	1015	0.01	0.582	[0.467-0.725]
Residence					
Rural	256	553			
Urban	420	462			
Total	676	1015	0.01	0.509	[0.418-0.621]
Visit to high burden country					
No	573	927			
Yes	103	88			
Total	676	1015	0.01	0.528	[0.390-0.715]

Table 2: Socio-economic Factors Associated with TB

Factors	TUBERCULOSIS		p values	95% Confidence Interval	
	Negative	Positive		Odds ratios	[Lower-Upper]
Dependent status					
No	150	299			
Yes	526	716			
Total	676	1015	0.01	1.464	[1.168-1.836]
Occupation					
Labor	573	879			
Office work	103	136			
Total	676	1015	0.288	0.861	[0.653-1.135]
House occupants					
< Than 10	259	367			
≥Than 10	417	648			
Total	676	1015	0.368	1.097	[0.897-1.341]
Over crowding					
No	426	627			
Yes	250	388			
Total	676	1015	0.605	1.054	[0.862-1.289]
Gas facility					
No	406	543			
Yes	270	472			
Total	676	1015	0.008	1.307	[1.073-1.592]

Table 3: Factors Related to Behavior and Perceptions

Factors	TUBERCULOSIS		p values	95% Confidence Interval	
	Negative	Positive		Odds ratios	[Lower-Upper]
Active smoker					
No	374	465			
Yes	302	550			
Total	676	1015	0.01	1.465	[1.205-1.781]
Ex-smoker					
No	610	921			
Yes	66	94			
Total	676	1015	0.730	0.943	[0.678-1.313]
Passive smoker					
No	561	775			
Yes	115	240			
Total	676	1015	0.01	1.511	[1.180-1.935]
TB contact					
No	376	551			
Yes	300	464			
Total	676	1015	0.589	1.055	[0.868-1.283]
What is TB?					
No	503	749			
Yes	173	266			
Total	676	1015	0.777	1.033	[0.827-1.290]
Is this transmitting?					
No	503	773			
Yes	173	242			
Total	676	1015	0.413	0.910	[0.727-1.140]

Table 4: Association of TB with Underlying Diseases

Factors	TUBERCULOSIS		p values	95% Confidence Interval	
	Negative	Positive		Odds ratios	[Lower-Upper]
Comorbidity					
Diabetes					
No	515	880			
Yes	161	135			
Total	676	1015	0.01	0.491	[0.381-0.632]
Hepatitis					
No	672	1003			
Yes	4	12			
Total	676	1015	0.219	2.010	[0.646-6.258]
Arthritis					
No	655	986			
Yes	21	29			
Total	676	1015	0.767	0.917	[0.519-1.623]

Table 5: Prioritization of Clinical Manifestation of TB

Factors	TUBERCULOSIS		p values	95% Confidence Interval	
	Negative	Positive		Odds ratios	[Lower-Upper]
Productive cough					
No	80	56			
Yes	596	959			
Total	676	1015	0.01	2.299	[0.609-3.283]
Hemoptysis					
No	205	503			
Yes	471	512			
Total	676	1015	0.01	0.443	[0.361-0.544]
Weight loss					
No	408	226			
Yes	268	789			
Total	676	1015	0.01	5.315	[4.293-6.580]

Table 6: Relation of Disease with Acid Fast Bacilli

Factors	TUBERCULOSIS		p values	95% Confidence Interval	
	Negative	Positive		Odds ratios	[Lower-Upper]
Bacillary load Positive					
No	676	244			
Yes	0	771			
Total	676	1015	0.01	0.265	[0.238-0.238]
Up to1^+					
No	676	600			
Yes	0	415			
Total	676	1015	0.01	0.470	[0.444-0.498]
$>1^+$					
No	676	659			
Yes	0	356			
Total	676	1015	0.01	0.494	[0.468-0.521]

Note. Up to1^+ represent positive microscopy having scanty and $1^+$and Greater than 1^+ represent 2^+ and 3^+.

Table 7: Final "Best Fit" Model of Logistic Regression on Factors Associated with TB

Factors	Wald	Df	Sig.	Exp(B)	Lower–upper
Visit to high burden country	11.628	1	0.01	1.852	[1.299-2.638]
Diabetic	27.710	1	0.01	0.423	[0.307-0.583]
Productive cough	19.863	1	0.01	2.627	[1.718-4.017]
Hemoptysis	116.577	1	0.01	0.237	[0.183-0.308]
Weight loss	254.243	1	0.01	7.853	[6.096-10.117]
Active smoker	13.315	1	0.01	1.531	[1.218-1.925]
Marital status	14.897	1	0.01	0.543	[0.399-0.741]
Age	9.368	1	0.01	1.585	[1.180-2.130]

Note. df= degree of freedom, Sig= significant, Exp (B) = Exponentiated Beta coefficient

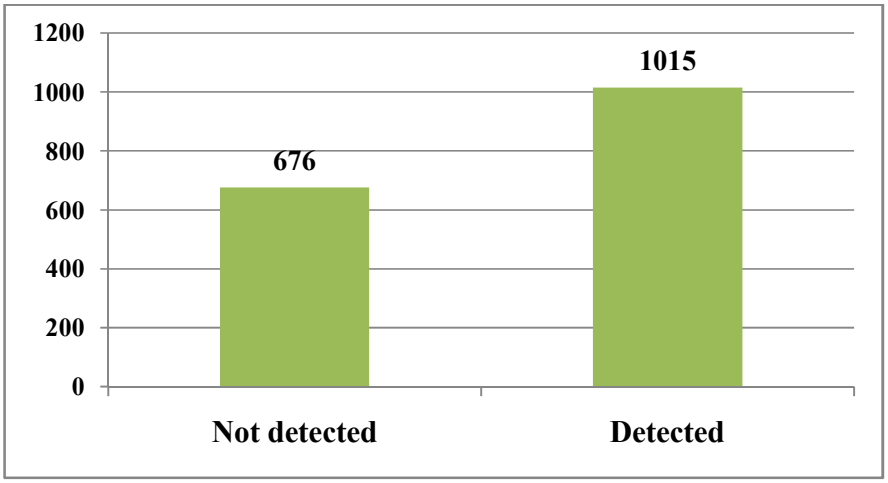

Figure 1: Frequency of MTB detected among suspected TB patients by Xpert MTB/RIF assay

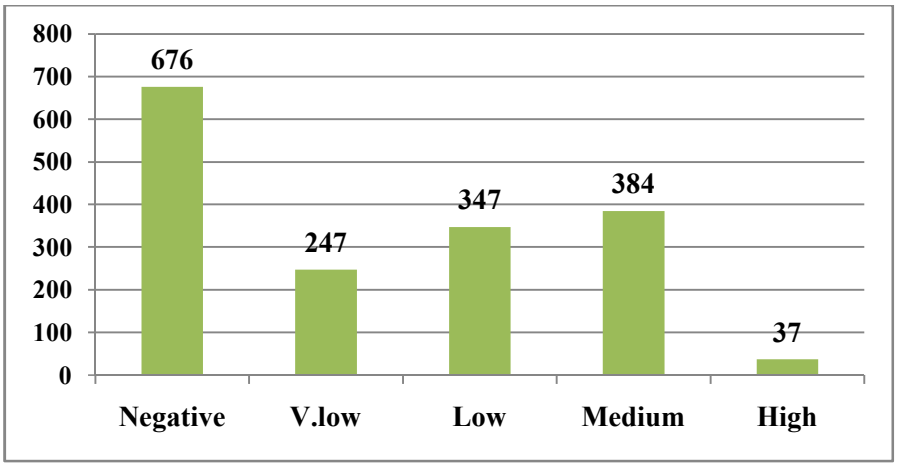

Figure 2: Level of severity of MTB detected cases by Xpert MTB/RIF

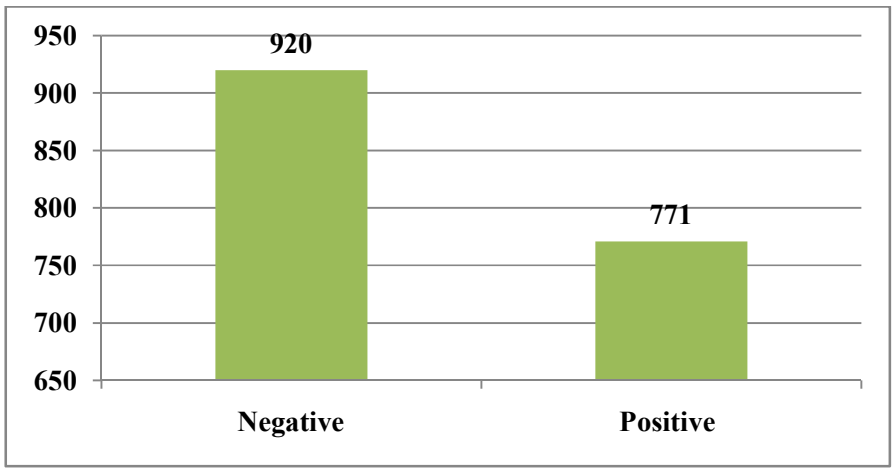

Figure 3: Frequency of MTB among suspected TB patients as determined by LED microscopy

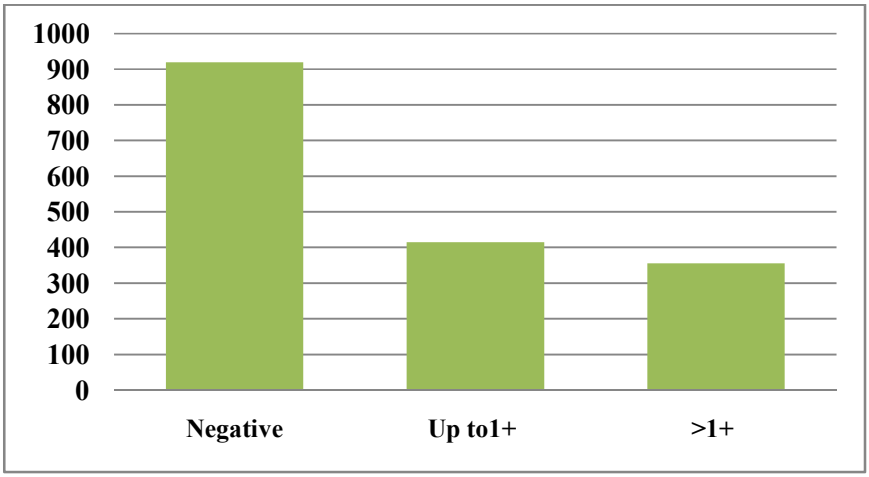

Figure 4: Grading of acid fast bacilli by LED microscopy (Up to1^+ includes cases of having positive microscopy of scanty and 1^+, and >1^+ represents 2^+ and 3^+

DISCUSSION

The Khyber Pakhtunkhwa province is harshly affected with TB with still high frequency of disease. In 2013, 32% of cases were documented in KP, which increased to 59% in 2016 **(7, 8)**. In this study TB cases accounted for more than half of the TB suspected patients attending Lady Reading Hospital Peshawar (1015/1691: 60%). Other studies in Sindh and Punjab found 61% and 77% of prevalence rate, respectively **(9, 10)**. The communicable disease surveillance and response by regional office for the eastern mediterian by WHO **(11)** reported high level of prevalence in the KP province is due to poverty, education and the lack of awareness about the seriousness of the disease. This may be the main predictors that are expected to worsen the progression as well as transmission of the disease **(11)**.

Poor medical facilities and unconcerned attitude of medical staff are some of the other drivers of TB in KP **(12)**. Another reason is the shortage of resources in the province to manage the increasing influx of locally displaced persons and international migrants from Afghanistan that reside in slums and informal settlements. This rise gives to rapid and unplanned urbanization that in turns drives TB. TB has noticeable impact on the female gender in our society. This study noted that TB prevalence is statistically significantly higher in female than male patients (529/1015: 52%). Study conducted in Iran showed similar results **(13)**. In India conflicting results were suggested, males were commonly affected with double increase in the risk **(14)**.

In KP some socio cultural risk factors related to gender makes females more prone to the disease. In some areas of KP majority

of the females are uneducated due to gender biased reasons. This make female economically dependent and ill-informed that can be the root causes of the disease. Even females have poor access to health care centers **(15)**. In some of the communities TB acts as a social stigma, which heavily falls on women because presence of TB infection in women leads to divorce or make it difficult to marry. Due to this fear most of the women neglect or even hide their illness instead of seeking health **(16)**.

Women in their reproductive age i.e. up to 42 years are found to be highly predisposed to TB. Major factors may be hormonal changes and reproductive burden associated with pregnancies, early marriages and less time interval between successive pregnancies. These factors impair the immunity thereby increasing predisposition to TB **(17)**.

Age is an important feature in epidemiology of TB. TB has infected most of the young and productive age group of our society. This study found highest occurrence of TB infection (566/1015: 56%) in the age group up to 42 years. In a previous study, Khatak *et al.* **(17)** found 62% of cases in most productive age group of 20-40 years. Another descriptive research in Malaysia is consistent with our findings which reported 67% of TB cases in mostly productive age group **(3)**. Ibn *et al*. (18) reported a high number of TB cases (49.5%) in the productive and economically important age 16–35 years in Nigeria. On contradictory, in United States TB rate is consistently higher in older people **(19)**. Pan American Health Organization, Washington, D.C. (2011) declared higher incident rate of disease among older people **(20)**.

Majority of study participants lack formal education. The risk of TB is 75% less in educated individuals (OR= .78, 95% CI .564-1.077). Lack of education is the root cause of many other factors that affect individual susceptibility to the disease. Education creates awareness about TB and its transmission. Educated individuals were more aware of TB and its transmission as compared to illiterate masses **(21)**. The rural areas of KP are mostly under the stress of TB. The present results observed that half of the rural participants had two times increase in the prevalence of TB (OR=0.5, 95% CI .418-.621). However a conflicting result was found in Bangladesh that recorded 69% of TB cases in urban areas **(21)**. The percentage of rural population in Pakistan is high (64%), and therefore the fraction of infected population from rural background is larger than that of urban background **(22)**. It is estimated that prevalence of disease depends

on the overall rural and urban population. For example any developing country where majority of the population is rural then the prevalence will also be high in rural **(23)**. Most of the urban facilities have functional laboratories compared to the rural facilities. The majority of patients from rural areas of KP are not properly diagnosed. Efficient diagnosis of all the patients is very difficult due to scarcity of labs and technical staff. Furthermore widespread illiteracy in rural KP majority of the people is unable to recognize symptoms of TB. Most of them are unaware of the serious nature of the infection and ways to prevent its dissemination. Since TB is associated with stigma, patients are reluctant to seek proper diagnosis or treatment even if they suspect it. Therefore, it is imperative to improve privacy of patients in rural health facilities to restore confidence of suspects and patients and attract them towards proper diagnosis and treatment.

An individual having visit to high disease burden country has increased risk of TB. In the present case majority of the participants had history of such visits. Immigrants were found to be 89% more under the risk of disease **(24, 25)**. Dawn News reported that due to economic reason and education the number of migrants from Pakistan is increasing day by day. Many of the individuals left their homeland country because of fear of violence and conflict. The more vulnerable and socially excluded Pakistani immigrants are more likely to live in the low income inner cities by making slums and informal settlements that provide proper conditions for TB. Their diagnosis and treatment is very challenging so more prone to disease.

Low socioeconomic status can drive TB. House hold income; house hold units and type of profession are some of the proxy measures for socioeconomic status that promotes TB. Majority of participants in the present study were (879/1015: 87%) with an income of Rs 20,000/ month. Majority (64%) of the cases had large family size with family unit greater than 10.Surprisingly overpopulation was not significantly associated with the disease in this case. On the contrary Rehman *et al.* **(21)** reported that congestion was related with poverty and increased susceptibility to disease. Despite the fact that the residents of KP traditionally have large families, overcrowding is an uncommon phenomenon. Families live in large open houses with sufficient sunlight is high and aeration. Smoking and indoor air pollution caused by using biomass as a fuel enhances predisposition to TB. Both active and passive smoking have been found

associated with TB, which is consistent with the research findings of Rehman *et al*. **(21)**. Pokhrel *et al*. **(18)** also found that second hand or passive smoking is the cause of TB. Indoor air pollution is another independent risk factor for the disease as observed in the present study with the risk of TB (543/1015:54%). Females were more susceptible in the indoor environment. Exposure to cigarette smoking in male was high. The finding agrees with the finding of Pokhrel *et al*. **(18)**.

Large particulate matter (PM), like carbon monoxide, nitrogen oxide, formaldehyde and large particulate matter emitted by the wood smoke deposit deep into the alveoli and compromise the phagocytic ability, surface adherence and bacterial clearance of the alveolar macrophages **(18)**. Exposure to smoke causes impaired mucosal secretions, allowing *M.TB,* to escape the first level of host defenses. This in addition to the reduced phagocytic activities of the alveolar macrophages put smokers at higher risk of TB infection **(26)**.

This study observed significant association between TB and diabetes and 13% of TB patient's comorbid with diabetes. This study reports that diabetes increased the disease by three folds. Our findings were similar to WHO report **(1)**. Pal *et al*. **(27)** found that diabetes increases the disease four times. In Pakistan both TB and diabetes are highly prevalent. A national diabetes survey (2016-2017) in all the four provinces of Pakistan found that twenty percent of Pakistani population is suffering from diabetes. Comorbidity of these two diseases complicates the treatment of each other. Diabetes weakens the immunity that increases individual susceptibility to TB. While in TB the level of blood sugar elevates temporarily beyond normal, which is termed as "impaired glucose tolerance. Impaired glucose tolerance can increase risk of developing diabetes mellitus. The treatment of TB complicates management of a patient's glucose levels on one hand and on other hand diabetic TB patients failed to complete their treatment successfully, which leads death **(27)**.

Early diagnosis of TB is necessary to disrupt the disease transmission chain. Smear positivity in present study was found to be 50% and Gene Xpert positivity for *M.TB* remained 60%, respectively. This result is in congruence with others **(21, 28)**. Smear positive is the main source of disease with triple increase in risk that is similar with the study conducted by Khattak *et al*. **(17)** in Pakistan. The positive load of bacilli determines the severity of disease. The

positive load can spread from person to person though the air by droplet nuclei. Smear negative cases have also the ability to transmit the disease but this ability is less than smear positive cases **(3)**. Our study concluded a high prevalence of drug susceptible TB in some districts of KP that challenges the disease control. The problem of TB is more pronounced in rural residents of KP. Gaps were found in awareness of respondents interviewed regarding epidemiology, risk factors, signs and symptoms and appropriate prevention methods. The disease has infected lower socio economic class in which the proxy measures are poverty, illiteracy and overcrowding. It is recommended that community be educated to effectively control this disease. Cleanliness and proper ventilation helps to reduce the infection so we can recommend the community to make living environment clean and properly ventilated. It should be kept in mind that one who maintains cleanliness keeps away the diseases. TB patients are advised not to spit everywhere and to cover their mouth while coughing. We recommend stakeholders including local authorities, NTP, and funding agencies to associate, strength and decentralize DOTs strategy in rural areas of KP to facilitate the establishment of health care facilities at least in tehsil level so that everyone get easily. Campaign about awareness of TB among the general population can be augmented by care workers, media, public leaders, councilors and local NGOs. We highly suggest them to take part and dispersed these facts to all of the community. Even we will recommend the religious leaders of our areas to support the community by mentioning the danger of TB and its spread in their sermons.

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