FREQUENCY OF PRIMARY MULTIDRUG-RESISTANCE TO ANTI-TUBERCULOUS DRUGS IN PATIENTS PRESENTED TO TERTIARY CARE HOSPITAL

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ABSTRACT

OBJECTIVE: To determine the frequency of primary multidrug resistance to antituberculous drugs among patients diagnosed for the first time with pulmonary tuberculosis.

METHODOLOGY: This was a hospital based descriptive, cross sectional study performed in Pulmonology Department, PGMI, Govt. Lady Reading Hospital, Peshawar from December 28, 2013 to June 27, 2014. A total of 124 smear positive pulmonary tuberculosis patients with no history of previous anti tuberculosis treatment were selected and sputum samples were collected for culture and drug sensitivity against rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin. Susceptibility testing was performed using standard agar proportion method.

RESULTS: Out of 124 patients, 56 (45.2%) were males and 68 (54.8 %) female. Mean age of the patients was 35.59 years ±15.523 SD. 106 cultures (85.5%) were fully sensitive while 18 (14.5 %) samples showed primary resistance to one or more drugs. 9 (7.2%) isolates were resistant to a single drug, 3 (2.4%) were resistant to 2 drugs, 4 (4 %) to 3 drugs, 1 (0.8%) to 4 drugs while none to all 5 first line agents. Resistance to Streptomycin was seen in 7 (5.6%), Isoniazid in 12 (9.7%), Rifampicin in 6 (4.8%), Ethambutol in 2 (1.6%) and Pyrazinamide in 4 (4,0%) samples. Primary Multidrug resistance was 4.8 %.

CONCLUSION: The frequency of Primary MDR amongst never treated patients is 4.8%, which is a cause of concern and should be addressed through effective TB control programmes with DOTS strategy.

KEY WORDS: Multidrug resistant tuberculosis; Primary drug resistance; LRH; Pakistan

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INTRODUCTION

TB is a major public-health problem, particularly in developing countries. Where the prevalence of infection is 40%.[1] The global burden of 9.4 million annual cases of tuberculosis (TB) overwhelmingly falls on low-income countries, with 80% of cases occurring in just 22 high-burden countries.[2] The incidence of tuberculosis in Pakistan is 181/100,000 population.[3]

The emergence and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) is further hampering efforts to control and manage the disease. Since the emergence of MDR strains in the 1990s, the prevalence of MDR TB has constantly increased. In 2008, about 440000 MDR TB cases occurred in the world, leading to an estimated 150000 deaths.[4] Pakistan is one of 27 countries with a high drug-burden of MDR-TB.[5] The proportion of new TB cases reported as showing multidrug resistance in these years ranged from 0% to 28.9%.[6]

In high multidrug resistant (MDR) tuberculosis (TB) prevalence areas, drug susceptibility testing (DST) at diagnosis is recommended for patients with risk factors for MDR.[7] Although primary drug resistance is

less common than secondary drug resistance but primary drug resistance is increasing as Multi Drug Resistant Tuberculosis (MDR TB) patient may transmit the resistant organism to healthy person, resulting in primary drug resistant TB.

The rationale behind doing this study is that to identify resistant TB cases as early as possible so that proper treatment should be started. Because when not treated at earlier time these resistant TB cases will act as carrier and will transmit the resistant TB to healthy people. And also more reliable estimates of the magnitude of primary drug resistance TB will be available locally that would be helpful for planning and expanding the programmatic management of drug resistance TB to a primary care hospital by disseminating the result of this study to other health professionals and government and non government agencies working for the control of TB in Pakistan.

OBJECTIVE OF THE STUDY

The objective of study was to determine the frequency of primary multidrug resistance to antituberculous drugs among patients diagnosed for the first time with pulmonary tuberculosis.

OPERATIONAL DEFINITIONS

ATT: Means antituberculous treatment and include Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Streptomycin.

Primary Drug Resistance: Resistant strain of Mycobacterium tuberculosis bacilli (MTB) on culture and sensitivity report to anti tuberculosis drugs that is rifampicin, isoniazid, pyrazinamide and ethambutol in a patient with no history of previous anti TB treatment (ATT) or taken ATT for less than one month.

Multi Drug Resistant TB: Mycobacterium tuberculosis bacilli (MTB) resistant to at least Isoniazid and Rifampicin on culture and sensitivity report.

Smear positive pulmonary tuberculosis: The presence of at least one acid fast bacillus (AFB+) rod shaped bacteria, in at least one sputum simple done with ziehl neelsen staining on sputum microscopy.

MATERIALS AND METHODS

Setting: Pulmonology Department Postgraduate Medical Institute Lady Reading Hospital, Peshawar

Study design: Hospital based descriptive, (Cross Sectional).

Duration of study: Duration of study was Six months (from December 28, 2013 to June 27, 2014).

Sample size**:** Sample size was calculated to be 124 using 28.9 % proportion of primary drug resistance [6] among newly diagnosed tuberculosis patients, with 95% confidence interval and 8 % margin of error under WHO software for sample size determination.

Sampling technique: Consecutive sampling.

Inclusion criteria:

1) All smear positive pulmonary tuberculosis patients with no history of previous anti tuberclosis treatment (ATT).

2) Gender both male and female

Exclusion criteria

1) Sputum smear positive Patients with Atypical mycobacterium tuberculosis (MTB) on sputum culture and sensitivity report because Atypical MTB are usually resistant to standard ATT and there treatment is totally different.

2) Patient with diagnosis of HIV. Because these patients have high chances of drug resistance tuberculosis.

3) New sputum smear negative pulmonary tubercuosis patient as there are chances that culture will also be negative.

The above mentioned patients were excluded from the study, because they would act as a confounders and could interfere with our culture and sensitivity results.

DATA COLLECTION PROCEDURE

All Patients fulfilling the inclusion were enrolled in the study. Diagnostic criteria were according to the sputum smear result. Patients were admitted to Pulmonology Department lady reading hospital Peshawar from Out Patient Department and casualty. Informed written consent was taken from all the patients with ethical approval from the ethical committee of Postgraduate Medical Institute, Lady Reading Hospital Peshawar.

To fulfill the inclusion and exclusion criteria, patients were assessed clinically by taking detailed history, doing examination and initial base line investigations like chest x-ray, full blood count, urea and creatinine will be obtained. All patients were interviewed to obtain clinical data like age, sex, occupation, and clinical symptoms and drugs history regarding ATT. Two Sputum samples were taken from suspect patients and sent for AFB microscopy to the hospital laboratory. Only patient with positive result were included in the study. All sputum samples were collected in the early morning and in special sterilized

container and were send to AGHA KHAN UNIVERSITY laboratory for culture and sensitivity to detect resistance to Isoniazid, Rifampicin, Ethambutol, Pyrazinamide and Streptomycin. Exclusion criteria were strictly followed to minimize bias in our study. Data were recorded on a preformed proforma. To avoid error leading to any possible Bias, Sputum smear microscopic and culture sensitivity examination were done only from selected laboratory and by following the exclusion criteria strictly.

DATA ANALYSIS

Data were entered and analyzed in SPSS for window version 15.0. Qualitative variables like gender and primary drug resistance are presented as frequency and percentages. Quantitative variables like age of patients are presented as Mean± standard deviation. Drug resistance was stratified among age and gender to see effect modification. Results are presented as tables and charts.

RESULTS

In this study a total of 124 patients were included. There were 56 males and 68 females, with male to female ratio of 1:0.8 (Table 1). The age of patients ranged from 10-70 years with a mean age of 32.92 years and standard deviation of ±15.973 SD (Table No.2). Mean age of male patients was 35±15.52 SD and that of the female patients was 30±16.116 SD. Most of the patients presented in the age group of 15-24 years (38 %) followed 25- 34 years (26 %) (Figure 1).

Patients presented from almost all districts of Khyber pakhtunkhwa including federally admistered tribal areas (FATA). Most of the patiens belonged to district

Table 1. Gender wise distribution of patients (n=124)

Gender	Frequency	Percentage
Male	56	45.2
Female	68	54.8
Total	124	100.0

Figure 1. Different age groups of patients (n=124)

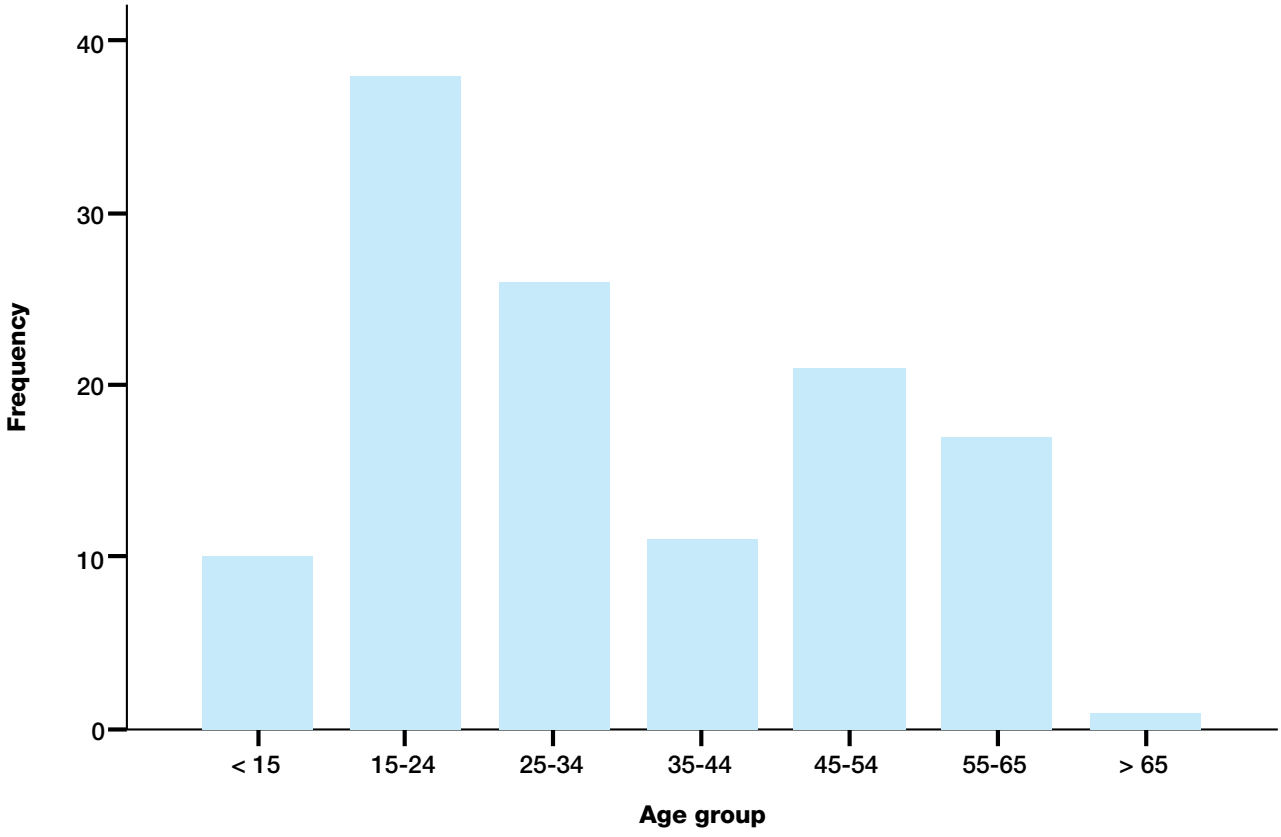

Table 2. Age-wise distribution of patients (n=124)

Gender of Patient	Minimum age	Maximum age	Mean age	Std. Deviation
Male	10	70	35.59	15.523
Female	13	60	30.72	16.116
Total	10	70	32.92	15.973

Table 3. District wise distribution of patients

District	Frequency	Percent
Peshawar	52	41.9
Charsadda	12	9.7
Kohat	9	7.3
Swat	8	6 .5
Bajaur Agency	7	5.6
Karak	7	5.6
Noshehra	6	4.8
Dir	3	2.4
Lakki Marwat	3	2.4
Mardan	3	2.4
Bannu	2	1.6
Hangu	2	1.6
Kurram Agency	2	1.6
Sawabi	2	1.6
South Wazirestan	2	1.6
Afghanistan	1	0.8
Dera Ismael Khan	1	0.8
Lower Dir	1	0.8
Mehmand Agency	1	0.8
Total	124	100.0

Peshawar followed by Charsadda, Kohat, Swat district and Bajaur Agency (Table 3).

Early morning Sputum specimens were collected in sterilized containers and sent for Acid Fast Bacilli culture and sensitivity testing. Out of 124 putum specimens 106 (85.5 %) were found to be fully drug sensitive while 18 (14.5 %) samples grew organisms that showed some resistance to atleast one drug antituberculous drug (Table 4).

Among the culture sensitive patients, 48 (45.3 %) were males and 58 (54.7 %) females. while among cultures showing any resistance, 8 (44.4 %) were males and 10 (55.6 %) females (Table 5).

Out of 18 cultures reports showing resistance, the isolates from 5 (4.0 %) patients were showing resistance to any three drugs tested, while 1 (0.8 %) patient showed resistance to all four oral anti tuberculous drugs. Resistance to Isoniazid in combination with

Table 4. Sputum Acid Fast Bacilli C/S result(n=124)

C/S Result	Frequency	Percent
Fully sensitive	106	85. 5
Any Resistance	18	14.5
Total Culture +ve	124	100.0

Table 5: Gender of patient and Drug Sensitivity testing Crosstabulation

Gender of patient	Drug Sensitivity testing		Total
	Fully sensitive	Any Resistance	
Male	48 (45.3 %)	8 (44.4%)	56 (45.2%)
Female	58 (54.7%)	10 (55.6%)	68 (54.8%)
Total	106 (100%)	18 (100%)	124 (100.0%)

other drugs (Any H resistance) was seen in 12 (9.7 %) patients. Resistance to Rifampicin in combination with other drugs (Any R resistance) was seen in 6 (4.8 %) patients. While resistance to Streptomycin in combination with other drugs (Any S resistance) was seen in 7 (5.6 %) patients (Table 6).

Resistance to only Isoniazid was seen in seen in 3 (2.4%) patients. Similarly resistance to only Streptomycin and only Ethambutol was reported in 4 (3.2 %) and 2 (1.6 %) patients respectivly. Resistance to any three drugs was noted in 5 (4 %) patients while resistance to all four oral drugs was seen in 12 (7.6%) patients (Table 6).

Primary Multi Drug Resistance was found in 6 (4.8 %) patients (Table 7). Among patients with MDR TB 4 (66.7 %) were male and 2 (33.3%) were male with male

Table 6: Resistance pattern of mycobacterium TB to different drugs (n=124)

Resistance patterns	Frequency	Percentage
Total Culture +ve	124	100.0
Fully sensitive	106	85.5
Resistance to only S	4	3.2
Resistance to only H	3	2.4
Resistance to only E	2	1.6
HR	3	2.4
HSP	2	1.6
HEP	1	0.8
HREP	1	0.8
HRP	1	0.8
HRS	1	0.8
Any H resistance	12	9.7
Any R resistance	6	4.8
Any S resistance	7	5.6
Any HR resistance	6	4.8

Key: H= Isoniazid, R=Rifampicin, E=Ethambutol, S=Streptomycin, P=Pyrazinamide

to female ratio of 2:1 (Table 7).

Primary multi drug resistance was stratified among gender and different age groups to see effect modification. In this study the effect of gender on primary multi drug resistance was statistically not signifficnat with p value of more than 0.05 (P-value=0.278) (Table 8).

When primary multidrug resistance was stratified among different age groups the effect of age was statistically significant on the developed of primary multi drug resistance with p value of less than 0.05 (P-value=0.031) (Table 9).

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Table 7: Primary Multidrug resistance (n=124)

Primary Multi drug resistance	Frequency	Percent
Present	6	4.8%
Abscent	118	95.2%
Total	12 4	100.0%

Table 8: Gender of patient and Multidrug resistance Crosstabulation

Gender of patient	Multidrug resistance		Total
	Present	Abscent	
Male	4(7.1%) (66 .7%)	52 (92.9 %) (44.1%)	56 (100.0%) (45.2%)
Female	2(2.9 %) (33.3%)	66 (97 .1 %) (55.9 %)	68 (100.0%) (54.8 %)
Total	6(4.8 %) (100%)	118 (95.2 %) (100%)	124(100.0%) (100%)

Chi-square test=1.17, P-value=0.278

Table 9: Age Group of patient and Multidrug resistance Crosstabulation (n=124)

Age group (years)	MDR TB		Total
	Present	Abscent	
< 15	0 (0.0 %)	10 (100 %)	10 (100 %)
15 - 24	1 (2.6 %)	37 (97.4 %)	38 (100 %)
25 - 34	1 (3.8 %)	25 (96.2 %)	26 (100 %)
35 - 44	3 (27.3 %)	8 (27.3 %)	11 (100 %)
45 - 54	1 (4.8 %)	20 (95.2 %)	21 (100 %)
55 - 65	0 (0.0 %)	17 (100 %)	17 (100 %)
> 65	0 (0.0 %)	1 (100 %)	1 (100 %)
Total	6 (4.8 %)	118 (95.2 %)	124 (100 %)

Chi - square test=13.90, P - value=0.031

DISCUSSION

Tuberculosis remains a major health problem both in developing and developed countries. Around one out of three people worldwide (i.e., approximately 1.9 billion) are infected with Mycobacterium tuberculosis. In Pakistan, its incidence is estimated to be 231 per 100,000 of population. Modern short-course chemotherapies based on the combination of isoniazid, rifampin, pyrazinamide and ethumbutol have proven to be highly effective tuberculosis treatment.

Inspite of effective chemotherapy Multi-drug resistant tuberculosis (MDR TB), defined as simultaneous resistance of Mycobacterium tuberculosis to both isoniazid and rifampicin, is an emerging worldwide public health problem especially in the developing world. Both biological as well as socioeconomic factors have been responsible for the emergence of drug-resistant TB, which is a purely man-made phenomenon; a result of sub-optimal chemotherapy .[8] Early detection and proper treatment of MDR strains of Mycobacterium tuberculosis are the most effective measures for the control of MDR TB.[9] Local knowledge of the drug susceptibility pattern of MDR clinical isolates is necessary to design an appropriate treatment regimen, thus preventing treatment failures and reducing the number of primary and secondary cases of MDR TB.[10]

In our study we observed quite high proportion of multi drug resistance TB (4.8%) in patients who had never taken antituberculous therapy. The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance reported considerable variation in the frequency of drug resistance among across the globe ranging from 2 % to 41% with median prevalence of Primary drug resistance of 9.9%. Overall, the median prevalence of primary MDR-TB was 1.4% ranging from 0 to 10%. In South East Asian Region (SEAR) countries the median prevalence of primary MDR-TB was reported to 2.5 % significantly higher than the global mean of 1.4%. [11] According to a study conducted in KPK by Javaid A, et al, in 2008 the primary resistance to found to be 2.5 %.[12]

MDR TB is an emerging peoblem across the globe affecting both developing and developed coutries. According to WHO "Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response report 2010" Tajikistan, in its first ever survey, found proportions of 16.5% MDR-TB among new TB cases and 61.6% MDR-TB among previously treated TB patients in Dushanbe city and Rudaki district.[13] China has reported the results of its first ever nation-wide drug resistance survey, with documented proportions of MDR-TB of 5.7% among new cases and 25.6% among those previously treated.[14]

The level of drug resistance to Isoniazid, Rifampicin, and MDR of 9.7 %, 4.8 %, and 4.8 %, respectively in previously untreated cases, as is evident from this study, is not as high as one would have expected, keeping in view that KPK has reached the WHO target of near 100% DOT coverage in recent years. These values are comparable with resistance studies in different 3rd world countries.[15-17] However the result of this study is different from other surveys conducted in Pakistan. According to a study conducted in KPK by Javaid A, et al, in 2008 the primary resistance to Isoniazed and Rifampicin was found to be 8.4%, 2.5% respectively.[18] However a study by Khan JA, et al, the primary resistance to Isoniazed and Rifampicin was reported to be 11% and 15% respectively.[19] An another study reported even higher resistance with H 25%, R 15%, E 12% and S19%.[20] This relatively high percentage of resistance to individual drugs in the studies from Pakistan was probably due to the faulty selection of patients and also efforts were not made to separate primary drug resistance from secondary drug resistance. These differences in drug resistance from different studies suggest a strong need to re-evaluate the primary drug resistance to Anti-tuberculosis drugs across the whole country.

This study also shows that in our population males were particularly at risk for MDR as compared to females. Our results are in contrast with a previous study from from Pakistan[21-22] and Georgia reporting female gender as a significant risk factor of MDR-TB.[23] While other studies have demonstrated a significant male preponderance among tuberculosis cases. [24] There are considerable gender differences with regard to stigma related to TB and its social consequences which may result in different health seeking behaviours between males and females. The association between males and MDR is likely to be multifactorial and cannot be explaned simply by different health seeking behaviours between the two groups; however this area requires further study.[25]

Moreover our study showed that most of the MDR TB patients suffered were young and were in their reproductive stage of life. This higher MDR cases in the age group below 34 years of age is also in agreement with reported findings from other studies and needs to be taken into considerationwhen planning for MDR programs at a national level. [26-27]

In view of these results from different studies it clear that there has been a gradual increase in primary drug resistance over the past few years. This emergence of

drug resistance in the community could be overcome by a strong TB control programme with implementation DOTS strategy. Also apart from a strong control programme, continuous surveillance of drug resistance is mandatory as it will provide information which will serve as a useful parameter in the evaluation of control programmes.

There was several limitation of this study first: this study included only those patients who visited the tertiary care hospital chest ward and out patient. There fore our reported frequency of MDR may not be true representation of the actual problem. Secondly the study only concentrated on the frequency of MDR TB and did not inquire about the causes of MDR TB. These limitations are potential area for further acive research.

CONCLUSION

Our study reports a primary MDR rate of 4.8%. The proportions of MDR are high among the males and affect relatively younger population. MDR TB defined as resistance to rifampicin and isoniazid; the two most effective and powerful anti-tuberculosis drugs available with us and increasing resistance against them is a matter of great concern as we would be left with only the less effective drugs for treatment of TB. Moreover proper surveillance data is lacking as there is currently no proper provision of diagnostic and treatment modalities for MDR-TB in National Tuberculosis Control Program across the Provence. To ensure optimal utilisation of limited resources i strongly advocate that these at risk groups should be a particular focus of DOTS program. The optimal approach would be primary prevention through vaccination, continued surveillance and appropriate therapeutic decisions with monitoring of the patients to help reduce this alarmingly high rate of primary MDR TB.

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