



A Clinical Study of Risk Factors for Extensive Drug Resistance (XDR) Tuberculosis in Tertiary Care Hospital

Authors

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Abstract

XDR-TB involves resistance to the two most powerful anti-TB drugs, isoniazid and rifampicin, also known as multidrug-resistance (MDR-TB), in addition to resistance to any of the fluoro quinolones (such as levofloxacin or moxifloxacin) and to at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin).

Aim: *To know the various risk factors for XDR tuberculosis and most common types of drug resistant patterns in XDR tuberculosis.*

Materials and Methods: *This study was a hospital based record based study Conducted at DR-TB CENTRE, Department of pulmonary medicine, Government hospital for chest and communicable diseases (GHCCD), Andhra medical college, Visakhapatnam. It's a 2 years study conducted from September 2017 to August 2019 .Total number of 18 XDR tuberculosis patients were enrolled in the study based on inclusion and exclusion criteria and all the patients were subjected to sputum for CBNAAT and line probe assay(first and second line).*

Results: *In the present study majority were males (83.3%), majority (38.8%) were younger age group between age 31 to 40 years, most of the drug resistance pattern noticed for kanamycin combined with ofloxacin, 66.6% were MDR-TB failures. Smoking (77.7%), alcohol (72.2%), lower BMI (77.7%) were major risk factors and HIV (33.3%), hypertension (38.8%), diabetes (55.5%) were major Comorbidities in the present study.*

Keywords: *XDR-TB, MDR-TB, CBNAAT, DR-TB CENTRE, LPA etc.*

Introduction

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. According to WHO global TB report 2018, there were an estimated 10.0 million new TB cases worldwide, of which children 1.0 million, males 5.8million, females 3.2 million. XDR-TB involves resistance to the two most powerful anti-TB drugs, isoniazid and

rifampicin, also known as multidrug-resistance (MDR-TB), in addition to resistance to any of the fluoroquinolones (such as levofloxacin or moxifloxacin) and to at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin). Information from countries with reliable data suggests that about 6.2% of MDR-TB cases worldwide have XDR-TB. In

2016, 8000 cases of XDR-TB were reported worldwide. Only a small proportion of the XDR-TB cases among them are detected given that many low and lower middle-income countries still lack sufficient diagnostic capacity to test for resistance to second-line drugs and thus detect XDR-TB. People may get XDR-TB in one of two ways. It may develop in a patient who is receiving treatment for active TB, when anti-TB drugs are misused or mismanaged, and is usually a sign of inadequate clinical care or drug management. The second way that people can develop XDR-TB is by becoming infected from a patient who is already ill with the condition. A person can be infected by XDR-TB bacteria but not develop the active disease, just as with drug-susceptible TB.^[1] The prevalence of multidrug-resistant tuberculosis (MDR-TB) and extensively-drug resistant TB tuberculosis (XDR-TB) are increasing throughout the world both among new TB cases as well as among previously treated ones.^[2] The global prevalence of XDR-TB has been difficult to assess. The prevalence of XDR-TB has been reported from India, which varies between low, i.e., 2.4% and as high as 21.1% in HIV infected persons suffering from MDR-TB.^[3,4] Treatment outcomes are significantly worse for patients with XDR-TB, compared with patients with drug-susceptible TB or MDR-TB.^[5,6] In the first recognized outbreak of XDR-TB, 53 patients in Kwa Zulu-Natal, South Africa, who were co-infected with XDR-TB and HIV, survived for an average of 16 days, with mortality of 98%.^[7]

Aims and Objectives

To know the various risk factors for XDR tuberculosis and to know the most common types of drug resistant patterns in XDR tuberculosis.

Materials and Methods

Study Design

This study was a Hospital based record study.

Study Setting: Conducted at DR-TB CENTRE, Department of pulmonary medicine, Government

hospital for chest and communicable diseases (GHCCD), Visakhapatnam.

Study Period: 2 years study from September 2017 to August 2019

Sample Size: Total number of 18 XDR tuberculosis patients were enrolled in the study based on inclusion and exclusion criteria and all the patients were subjected to sputum for CBNAAT and line probe assay (first and second line).

Inclusion Criteria

All XDR tuberculosis patients diagnosed by sputum for CBNAAT, line probe assay (LPA) and liquid culture whenever needed.

All the patients willing to participate in this study Adults of more than 18years of both males and females.

Exclusion Criteria

- 1) All the patients not willing to participate in this study.
- 2) Extra pulmonary XDR tuberculosis patients.
- 3) Drug sensitive tuberculosis were excluded in this study.
- 4) Multidrug resistant tuberculosis patients and pre XDR tuberculosis Patients were excluded in this study.

Procedure

All XDR-TB patients who were registered between September 2017 to August 2019 (total of 18 cases) at the above-mentioned DOTS plus were recruited in the study.

The diagnosis of XDR-TB was done at RNTCP accredited Intermediate Reference laboratory (IRL) in our hospital, using CBNAAT, line probe assay (LPA) and liquid culture whenever needed.

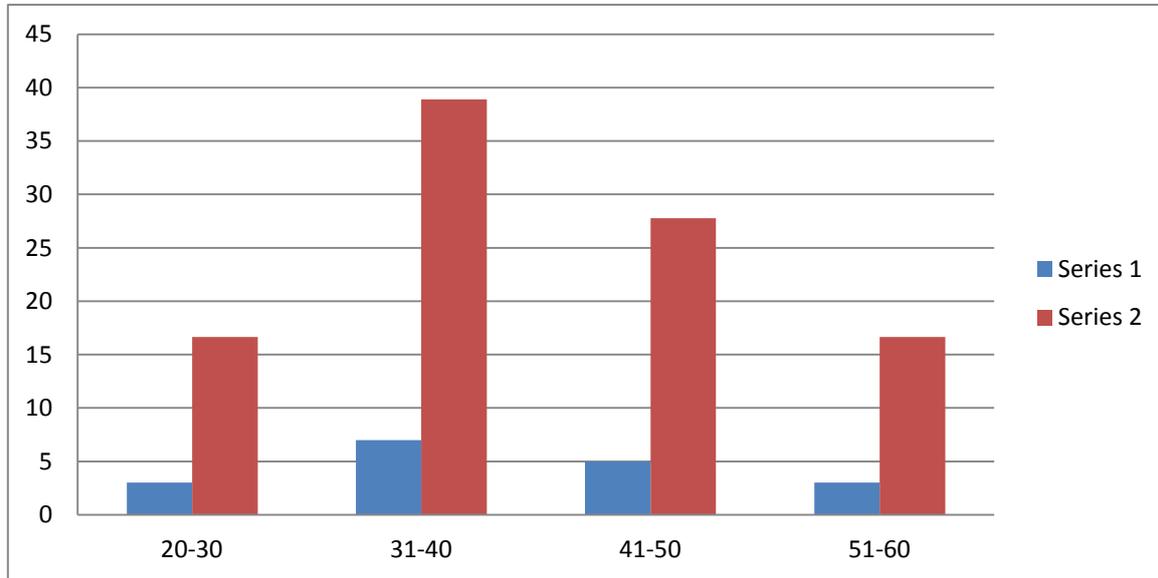
Information on demographic and clinical profile of patients including co-morbidities like HIV Status, diabetes, hypertension and risk factors like smoking and alcohol abuse, history of previous anti-tuberculosis treatment (ATT) was taken from patients at the DR-TB centre. Further details on the current course of XDR-tuberculosis treatment particularly time of initiation were retrieved.

Observations and Results

Table.1 Age wise distribution of patients

AGE(YEARS)	NUMBER	PERCENTAGE(%)
20-30	3	16.66
31-40	7	38.88
41-50	5	27.77
51-60	3	16.66
TOTAL	18	100

Chart-1

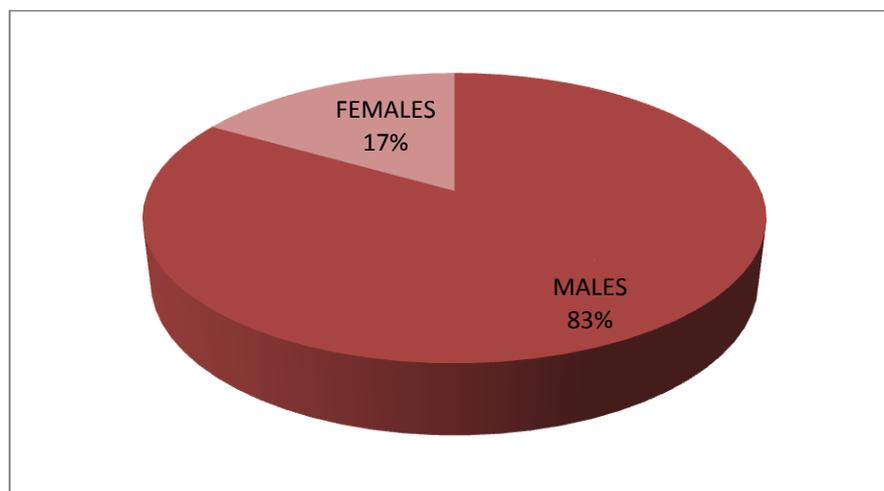


In the present study majority were 38.8% between the age group of 31 to 40 years. Followed by 27.7% between the age group of 41 to 50 years.

Table-2 Distribution of Study Population According to Gender

GENDER	NUMBER	PERCENTAGE (%)
MALES	15	83.33
FEMALES	03	16.66
TOTAL	18	100

Chart 2

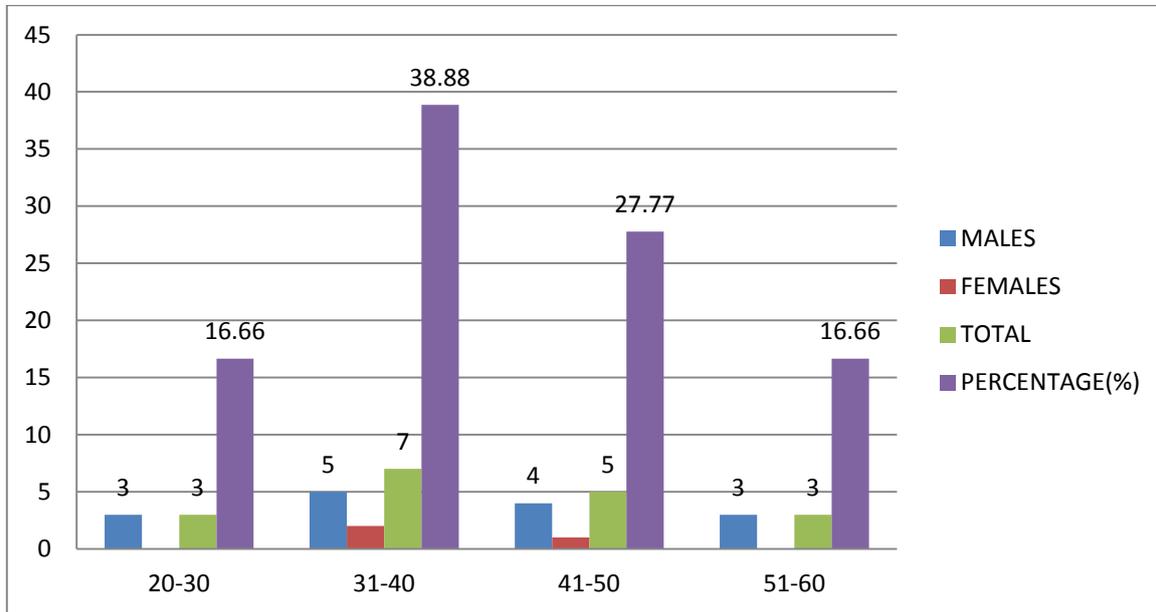


In the present study majority were males 83.3% and females were 16.6%.

Table-3 Distribution According to the Age and Gender

SEX/AGE	20-30	31-40	41-50	51-60	TOTAL	PERCENTAGE (%)
MALE	3	5	4	3	15	83.33
FEMALE		2	1		03	16.66
TOTAL	3	7	5	3	18	100

Chart-3



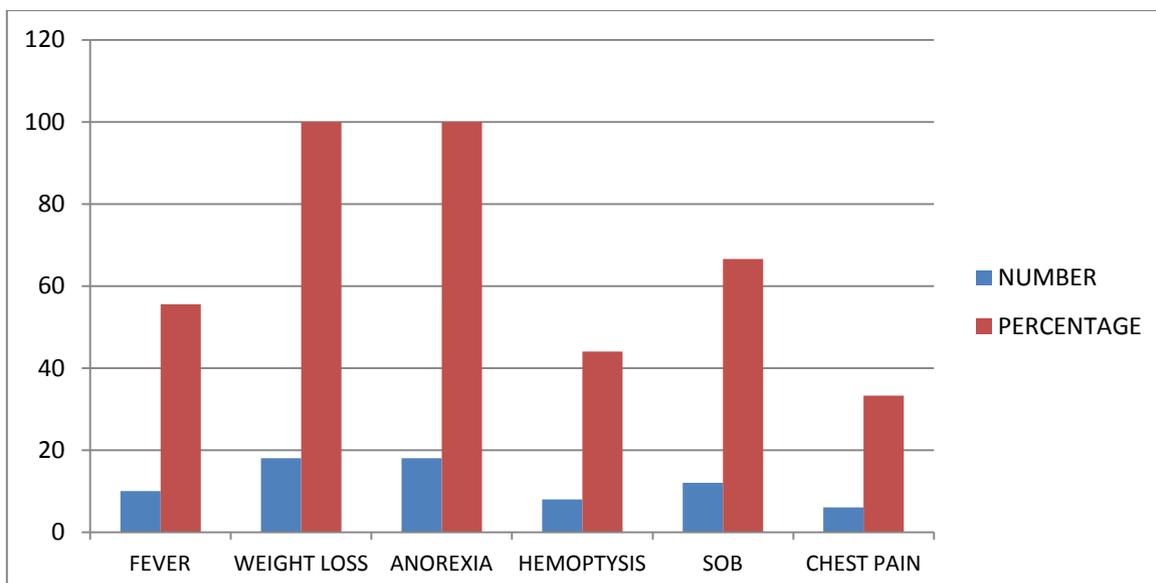
In the present study out of 83.3% of total males 27.77% were distributed between the age group of 31 to 40 years. Out of 16.66% of females 11.10%

were distributed between 31 to 40 years of age group.

Table.4 Distribution of study population according to TB Symptoms

Symptom	fever	Wt loss	anorexia	haemoptysis	SOB	Chest pain
Present	10	18	18	8	12	6
PERCENTAGE (%)	55.5	100	100	44	66.66	33.33

Chart: 4



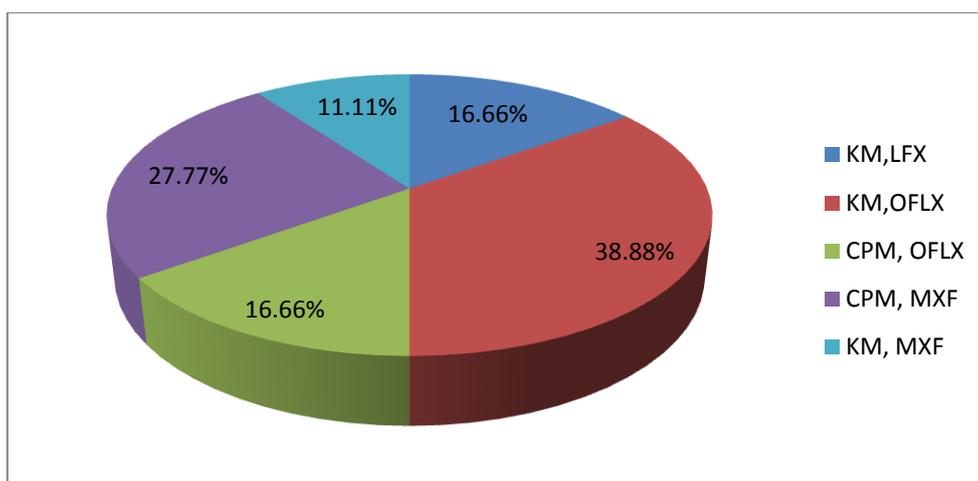
In the present study out of 18 patients ,100% of the patients had anorexia and weight loss, 66.66 % of the patients had shortness of breath.55.5% of

patients had fever, 44% of the patients had haemoptysis and 33.3% of the patients had chest pain.

Table.5 Drug Resistant Pattern

DRUG RESISTANT PATTERN	PERCENTAGE
KANAMYCIN+LEVOFLOXACIN	16.66%
KANAMYCIN+OFLOXACIN	38.8%
KANAMYCIN+MOXIFLOXACIN	16.66%
OFLOXACIN+CAPRIOMYCIN	16.66%
MOXIFLOXACIN+CAPRIOMYCIN	11.11%

Chart: 5

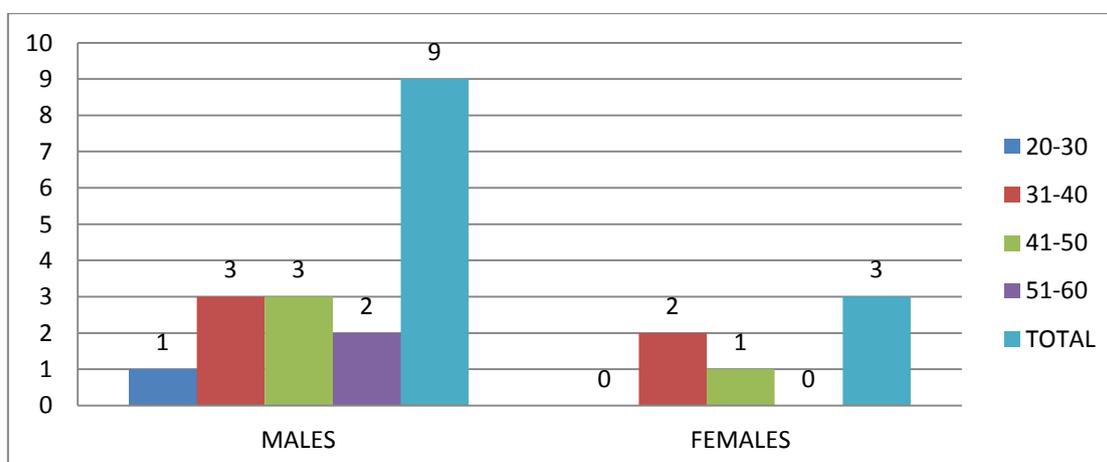


In the present study out of 18 patients, 38.8% patients had kanamycin combined with ofloxacin resistance pattern.

Table.6 Gender and Age Distribution among MDR Failures

SEX/AGE	20-30	31-40	41-50	51-60	TOTAL	PERCENTAGE(%)
MALE	1	3	3	2	9	75%
FEMALE	0	2	1	0	3	25%
TOTAL	1	5	4	2	12	100%

Chart: 6

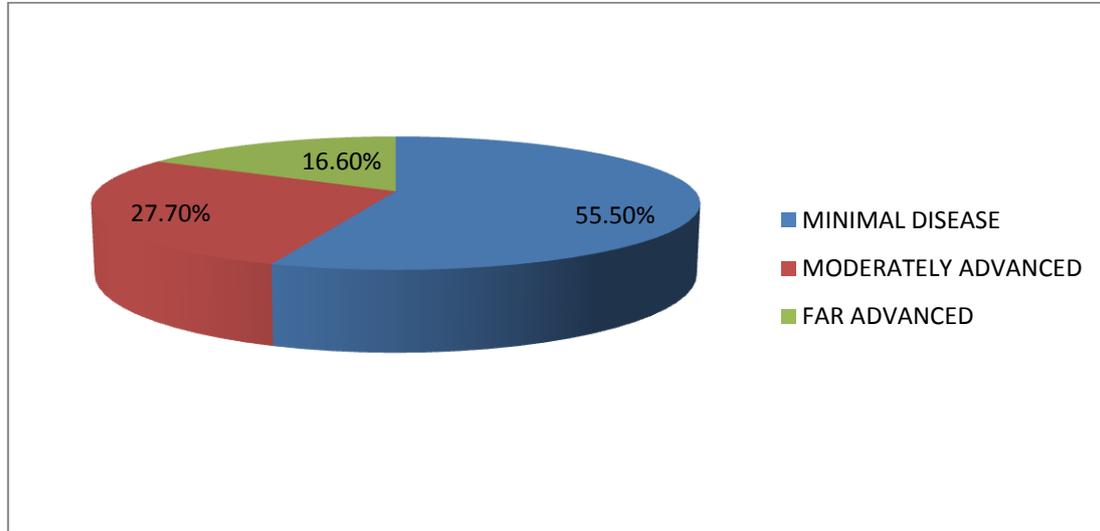


In the present study, MDR-tuberculosis failures were 66.66%.Out of 66.66%males were 50%and females were 16.66%.

Table.7 Radiological Features of CXR

CXR FEATURES	PERCENTAGE
MINIMAL DISEASE	55.5%
MODERATELY ADVANCED	27.7%
FAR ADVANCED	16.6%
TOTAL	100%

Chart: 7



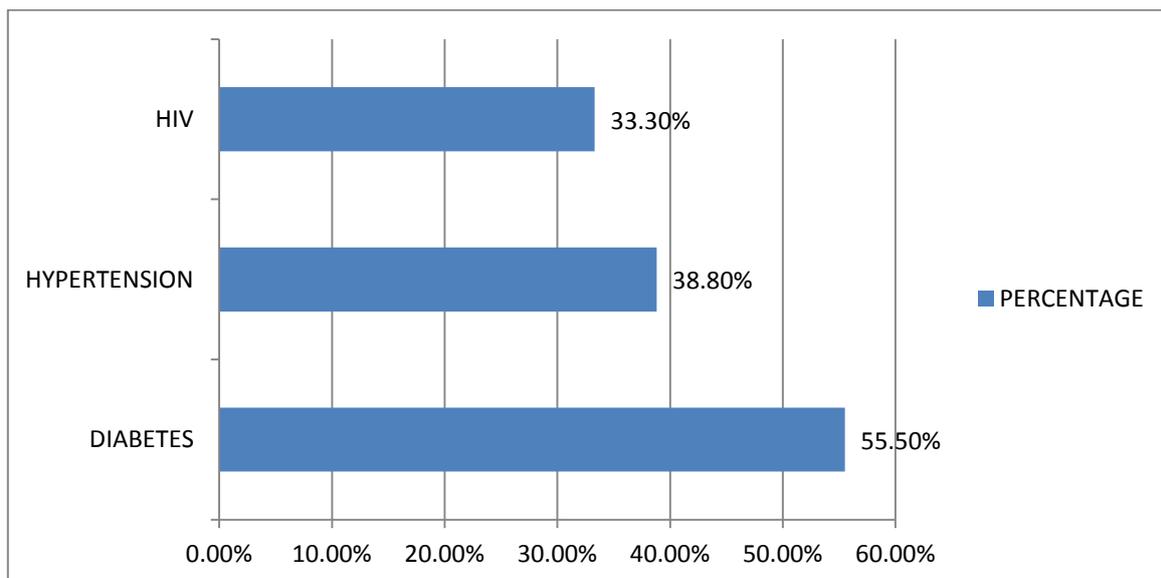
In the present study, out of 18 patients, radiological feature chest X-ray, 55.55% were

minimal disease, 27.7% were moderately advanced disease, and 16.6% were far advanced.

Table. 8 Comorbidities Distribution among Study Population

COMORBIDITIES	NUMBER	PERCENTAGE
DIABETES	10	55.5%
HYPERTENSION	7	38.8%
HIV	6	33.3%

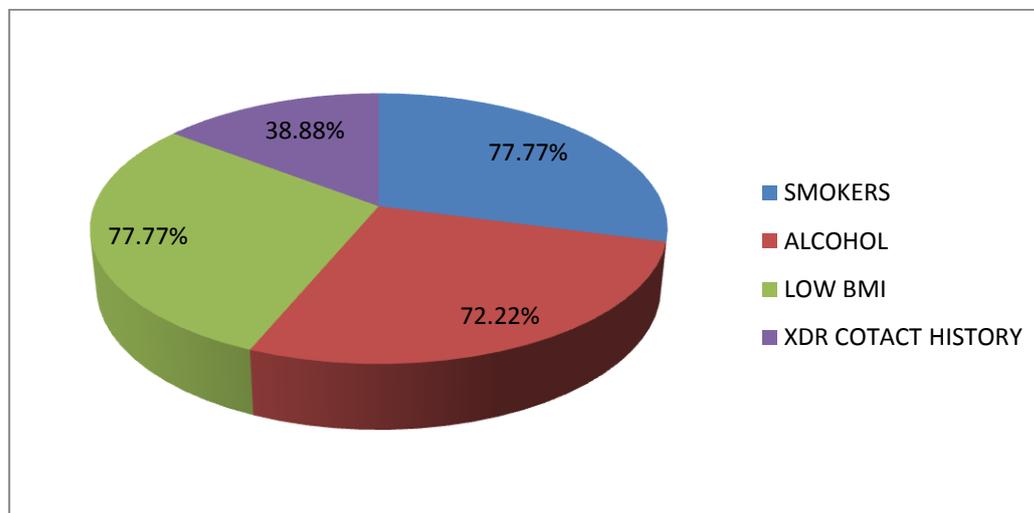
Chart: 8



In the present study, 55.5% had diabetes, 38.8% had hypertension and 33.3% had HIV .

Table.9 Risk Factors Distribution In Study Population

RISK FACTORS	NUMBER	PERCENTAGE
SMOKING	14	77.77%
ALCOHOL	13	72.2%
LOW BMI	14	77.77%
CONTACT HISTORY OF XDR	7	38.8%

Chart: 9

Out of the 18 patients, 77.7% were smokers, 77.7% were low BMI and 72.2% were alcoholics and 38.88% were history of XDR-contact history.

Discussion

Present study Conducted at DR-TB centre, department of pulmonary medicine, Government hospital for chest and communicable diseases (GHCCD), VISAKHAPATNAM, from September 2017 to August 2019. Total number of 18 XDR tuberculosis patients, who were registered under the Revised national TB control programme(RNTCP) were enrolled in the study. Drug resistance in *M. tuberculosis* is due to the mutations in the genome. Mismanagement of MDR-TB cases primarily results in this form of

TB due to the following reasons: faulty or improper treatment, non-adherence to treatment guidelines, inappropriate, incomplete or erratic use of SLDs and use of poor-quality SLDs. Our data suggests that association between HIV infection and extensive drug resistant tuberculosis .Larger studies in Latvia and Donetsk Oblast have suggested an association between HIV and MDR-TB ⁽⁸⁾,and in the united states, HIV was significantly more common among XDR cases as compared to drug susceptible cases.⁽⁹⁾

STUDY	SAMPLE SIZE	HIV TESTED	HIV positive	PERCENTAGE (%)
Present study	18	18	6	33.33%
Neel Gandhi et al ⁽⁷⁾	53	44	44	100%

In the present study out of 18 total XDR –TB patients 6 (33.33%) had HIV infection. Where as in Neel Gandhi et al study out of total 53 XDR –TB patients, all 44 (100%)patients with XDR tuberculosis who were tested for HIV were positive.

It was observed in a study at Lithuania and Estonia that younger age group, male gender, and known contact with an MDR-TB were associated with increased risk of primary infection with XDR-TB and MDR-TB strains while defaults and failures in the past triggered XDR-TB development ^[10]

Comparison of Risk Factors Like Male Gender, Younger age and Contact with MDR –TB

STUDY	Males (%)	Younger Age Group. (%)	Contact with MDR (%)
PRESNET STUDY	15/18(83.33%)	31-40(38.88%)	5/18(27.77%)
Ignatyeva Oet al ^[10]	20/28(71.42%)	30-39(32%)	5/28(17.8%)

In the present study risk factors like male gender, younger age group and contact history to MDR - TB Were like this males were **83.33%**, Most of the XDRTB patients were between 31 to 40 years, 27.77% had history of contact with MDR-TB .

These results were in similar with the study done by IGNATYEVA O,et al^[10] these risk factors were like this males were **71.4%**, ost (**32.1%**) of the XDR TB patients were between 30 to 39 years of Age group. **17.8%** had history of contact with MDR-TB.

A study conducted at Delhi predicted factors that were associated significantly with XDR-TB such as family history of TB, low socioeconomic status, comorbid illness and previous intake of SLIDs ^[11]. In the present study , majority of were distributed age between 31 to 40 years, majority of i.e,38.8% had drug resistance pattern for kanamycin and ofloxacin, 55.5% had diabetes, 88.8% had previous history of pulmonary tuberculosis , 33.3% had HIV infection and 11.11% were new cases of XDR and 70% had bilateral lesions in chest x ray. In **Chih-Cheng Lai et al,**^[12] study mean age 56.8±16.6, 100% had resistance to both ofloxacin and levofloxacin,60% had diabetes mellitus ,90% had previous history tuberculosis and 70% had radiological cavities.

In **Kwon et al,**^[13] study out of 27 cases 11% were new cases and 89% were previously treated tuberculosis.

In **Medea Gegia et al,**^[14] study out of 380 patients 88% were previously treated tuberculosis patients, 25% were alcoholics, 40% were smokers,9% were diabetics and 1% had HIV.

Summary

1. In the present study majority were 38.8% between the age group of 31 to 40 years. followed by 27.7% between the age group of 41 to 50 years.
2. In the present study males were 83.3% and females were 16.6%.
3. In the present study out of 83.3% of total males 27.77% were distributed between the age group of 31 to 40 years. out of 16.66% of females 11.10% were distributed between 31 to 40 years of age group.
4. In the present study out of 18 patients ,100% of the patients had anorexia and weight loss,66.66 % of the patients had shortness of breath.55.5% of patients had fever, 44% of the patients had haemoptysis and 33.3% of the patients had chest pain.
5. In the present study out of 18 patients ,38.8% patients had kanamycin combined with ofloxacin resistance pattern.
6. In the present study MDR-tuberculosis failures were 66.66%.Out of 66.66% males were 50% and females were 16.66%.
7. In the present study out of 18 patients, radiological feature chest X-ray, 55.55% were minimal disease, 27.7% were moderately advanced disease, and 16.6% were far advanced.
8. In the present study,55.5% had diabetes,38.8% had hypertension and 33.3% had HIV.
9. Out of the 18 patients , 77.7% were smokers,77.7% were low BMI and 72.2% were alcoholics

Conclusion

In present study we found out that majority were male gender and most them were younger age group. In the present study smoking, alcohol abuse, low BMI, HIV and diabetes, contact history of XDR- TB, low socioeconomic status, illiterates and bilateral extensive lesions on chest x -ray major risk factors were for development of extensive drug resistance(XDR) tuberculosis.

So these might be risk factors for development of extensive drug resistance (XDR) tuberculosis.

The development of drug resistance in TB in India is the result of a complex web of biomedical, socio-cultural and behavioural interactions,^[15] and the reporting of individual risk factors is an oversimplification. Health care worker ignorance, the wide misuse of TB drugs, lack of laboratory standardization and delay in laboratory results all contribute to the emergence of drug resistance.^[16]

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