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TO STUDY THE CLINICO RADIOLOGICAL PROFILE OF ISONIAZID MONO RESISTANCE TUBERCULOSIS

Dilbag Singh*, Dr. Naveen Pandhi and Dr. N.C. Kajal

India.

***Corresponding Author: Dilbag Singh**

India.

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INTRODUCTION

Tuberculosis, a disease caused predominantly by Mycobacterium tuberculosis.[1] Tuberculosis (TB) is an old disease – studies of human skeletons showed that it has affected humans for thousands of years.[2] The cause remained unknown until 24 March 1882, when Dr. Robert Koch announced that he had discovered the bacillus Mycobacterium tuberculosis, an event that is now commemorated every year as World TB Day.[3] It causes ill-health in millions of people each year and in 2015, was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease.[4] In India more than 6000 people develop TB disease every-day and more than 600 people die of TB (i.e. 2 deaths every 5 min).[1]

As per India TB report 2019, Global incidence of TB is (including HIV) 1,00,00,000 and incidence of TB in India is 26,90,000 i.e. 199 cases per lakh population.[5] In 2018, TB caused an estimated 1.24 million deaths among HIV-negative people, and there were an additional 251,000 deaths from TB among HIV-positive people.[6]

It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory TB disease. Overall, a relatively small proportion (5–15%) of the estimated 1.7 billion people infected with M. tuberculosis will develop TB disease during their lifetime.[4] In healthy people, infection with Mycobacterium tuberculosis often causes no symptoms, since the person's immune system acts to "wall off" the bacteria. It is a disease of poverty affecting mostly young adults in their most productive years. The disease primarily affects lungs but can also affect intestine, meninges, bones and joints, lymph nodes, skin and other tissues of the body.

The vast majority of TB deaths are in the developing world. People with HIV are much more likely to develop TB. The risk for developing TB disease is also higher in persons with diabetes, other chronic debilitating diseases leading to immune-suppression, poor living conditions, tobacco smoking etc. The life time risk of developing disease is 10%-15% amongst infected and who are otherwise normal but it is increased to >30% if the person is diabetic. Amongst those co-infected with HIV, the risk is 10% per year.[1]

Before the chemotherapeutic era, the modalities of treatment were sanatorium treatment, collapse therapy and surgery. Real breakthrough on its treatment was discovery of streptomycin in 1944 by Sir Waksman. But after 1960's, with the advent of ambulatory chemotherapy, hospitalization was considered unnecessary which resulted in irregular treatment and development of drug resistance.

The Sustained Development Goals and the End TB Strategy share a common aim: to end the global TB epidemic. Targets set in the End TB Strategy include a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030, compared with 2015. The most immediate milestones, set for 2020, are a 35% reduction in TB deaths and a 20% reduction in the TB incidence rate, compared with levels in 2015. To reach these milestones, the TB incidence rate needs to be falling by 4–5% per year globally by 2020 and the proportion of people with TB who die from the disease (the case fatality ratio or CFR) needs to be reduced to 10% globally by 2020

END TB STRATERGY

PRINCIPLES

1. Government stewardship and accountability, with monitoring and evaluation.
2. Strong coalition with civil society organizations and communities.
3. Protection and promotion of human rights, ethics and equity.
4. Adaptation of the strategy and targets at country level, with global collaboration

The first pillar of the End TB Strategy is "Integrated, patient-centered care and prevention". It has four components:

1. Early diagnosis of TB including universal drug susceptibility testing (DST), and systematic screening of contacts and high-risk groups;
2. Treatment of all people with TB including drug-resistant TB, and patient support;
3. Collaborative TB/HIV activities, and management of comorbidities; and
4. Preventive treatment of persons at high risk, and vaccination against TB.

The second pillar of the End TB Strategy is "bold policies and supportive systems". It has four components:
1. Political commitment with adequate resources for TB care and prevention;
2. Engagement of communities, civil society organizations, and providers of public and private care;
3. UHC policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control.
4. Social protection, poverty alleviation and actions on other determinants of TB.

The third pillar of the End TB strategy is "intensified research and innovation". It has two components:
1. Discovery, development and rapid uptake of new tools, interventions and strategies.
2. Research to optimize implementation and impact, and promote innovations

Tuberculosis is principally a disease of poverty, with 95% of cases and 98% of deaths occurring in developing countries. Of these, more than half cases occur in five south-east Asian countries.[7]

Until the middle of the 20th century, there was no definitive treatment available for tuberculosis. With the availability of streptomycin, isoniazid and para-amino salicylic acid (PAS), in the mid-1940s, predictable curative treatment for tuberculosis became a reality.[8] The introduction of rifampicin, pyrazinamide and ethambutol in subsequent years ushered in the era of short course treatment. Further, fully supervised sanatorium based treatment of earlier days also gave way to the totally unsupervised domiciliary treatment. Soon, it was felt that tuberculosis could be easily contained and possibly eradicated.

Emergence of drug resistance has further worsened the situation and has become a significant health problem world over creating an obstacle to effective tuberculosis control as the treatment is much more toxic and much more expensive than the one of patients with sensitive organisms.[9]

Resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. During bacterial multiplication, resistance to anti-tuberculosis drugs develops spontaneously and with a defined frequency. Genetic mutations resulting in resistance of M. tuberculosis to RMP occur at a rate of 10^{10} per cell division and lead to an estimated prevalence of 1 in 10^8 bacilli in drug-free environments; the rate for INH is approximately 10^7 to 10^9, resulting in resistance in 1 out of 10^6 bacilli.[10] Bacillary populations larger than 10^7 are common in cavities.[11] Thus, genetic resistance occurs in the absence of antimicrobial exposure, but is diluted by the majority of drug-susceptible micro-organisms.

The presence of antimicrobials provides the selective pressure for resistant organisms to become predominant, especially in patients with a large load of bacilli, e.g. those with extensive cavitary disease.[12] Clinical characteristics of patients have also been recognized where appropriately administered drugs have not achieved necessary drug levels to deal with all populations of mycobacteria. Exposure to a single drug — due to irregular drug supply, inappropriate prescription or poor adherence to treatment — suppresses the growth of susceptible bacilli to that drug but permits the multiplication of drug-resistant organisms.[13] This phenomenon is called acquired resistance. Subsequent transmission of such bacilli to other persons may lead to disease which is drug-resistant from the outset, a phenomenon known as primary resistance. Every active drug against M. tuberculosis is bound to induce resistance, and the more active a drug is the more likely it is to induce clinical resistance.[11]

In anti-TB chemotherapy, the multidrug initial intensive phase is given to take care of the drug-resistant organisms and to achieve 'a quick kill' to reduce the bacillary load, which in turn reduces the number of "persisters' in the lesions. "Persisters" are drug-sensitive organisms, which become dormant and are later responsible for relapses. The continuation phase of chemotherapy, consisting of two drugs is therefore given to kill the "persisters," which show intermittent activity.[14]

Recurrence may be due to reactivation of disease with the same organism or re-infection with a new organism. Re-treatment TB patients are a challenge to TB control services as they are more likely to harbour and transmit drug-resistant mycobacterium tuberculosis and may also have poor treatment outcomes.[15]

After successfully establishing RNTCP services across the country in 2006, the PMDT services were introduced in 2007 and complete geographic coverage was achieved by 2013.[4] To begin with, DR-TB services were offered to the subset of TB patients with the highest risk to develop drug resistance i.e., treatment failures. This was followed by a horizontal and vertical scale-up. Definite criteria were set to assess the risk and eligibility for the drug susceptibility test (DST). The DST was thus offered to TB patients who remained smear positive during follow-up; to previously treated patients; those who were HIV positive and people who had contact with a known

DR-TB patient.[16] This would then lead to universal DST, i.e. DST to all diagnosed and notified TB patients.

For decades, people working in tuberculosis knew that mono resistance to isoniazid was common. INH has been in clinical use since 1950s, and drug resistance was expected because its use became widespread. But this knowledge did not necessarily lead to testing for INH resistance. Indeed, for decades, no DST for any drug was done unless patients failed first line therapy or had risk factors for drug-resistant TB. When the TB world woke up to the need for universal DST and included it as a key goal in END TB strategy, the focus became rapid testing for rifampicin resistance as a means of achieving universal DST. Novel technologies such as Xpert MTB/RIF were rolled out in 2010, but the technology did not include INH-resistance testing.[17]

It is to be noted that R resistance is quite rare without H resistance. Majority of DST results with R resistance will also be H resistant, i.e., MDR-TB. This has been substantiated in the National Drug Resistance Survey (2014-16).[18] Therefore, Revised National Tuberculosis Program (RNTCP) has taken the programmatic decision that patients, who have any rifampicin resistance should be managed as if they are multidrug resistant tuberculosis case[19] and this is in line with WHO global guidelines for PMDT. Therefore, it seems that patients with rifampicin resistance may have isoniazid resistance also that was not detected by line probe assay (LPA), thus rifampicin mono resistance may theoretically be same as isoniazid-rifampicin (HR) resistance.

In general, treatment is most successful when there is no resistance to any of the drugs designated for treatment of TB[20], and the drugs isoniazid (INH) and rifampicin (RIF) can be included in the treatment regimen. INH has long been an essential component of first-line treatment for active TB and an important drug in TB control because of its potent early bactericidal activity, low rate of adverse events and low cost.[21] Currently, there is no equivalent alternative available.[22] INH mono-resistance increases the likelihood of negative treatment outcome and progression to MDR TB. Population groups that are especially at risk of negative treatment outcome due to INH mono-resistance are children and HIV-positive patients.[23]

An analysis of individual patient data conducted in the framework of a World Health Organization (WHO) guideline development process showed that the addition of a fluoroquinolone to a regimen of 6 months of daily RIF, ethambutol (EMB) and pyrazinamide (PZA) was associated with improved treatment success in INH-resistant cases.[24] After an evaluation of all available evidence, WHO has issued new guidelines on treatment for patients with INH mono-resistance.[25]

The factors found to be associated with a higher risk of unsuccessful treatment outcome in INH mono-resistant TB –higher age, male sex, positive microscopy, positive HIV status–have been described before as associated with unsuccessful TB treatment outcome independent of drug resistance status.[26,27] Prior TB treatment has also been reported as a risk factor for unsuccessful outcome in patients with INH mono-resistant TB.[28]

A prodrug, INH is activated by the catalase-peroxidase KatG of Mycobacterium tuberculosis (M.tb). Following this, it binds InhA, an enoyl-acyl carrier protein reductase and so blocks fatty (mycolic) acid synthesis, a key component of the bacterial cell wall. In rapidly dividing bacteria INH is bactericidal, in slower dividing bacteria bacteriostatic. The drug is thought to provide a high initial kill at the start of active TB treatment, after which RMP largely takes over in terms of bactericidal activity and RMP and pyrazinamide (PZA) act as sterilising drugs.[29] From its earliest use as mono therapy for TB disease in the 1950s, rapid and frequent development of resistance to INH was reported. Such observations regarding INH and other drugs emphasised the need for combination regimens. INH, streptomycin (STM) and p-aminosalicylic acid (PAS) thus became the standard regimen for many years before the development of the current short course of two months of INH, RMP, PZA and ethambutol (EMB), followed by four months of INH and RMP.[30.31] The 1950s also saw the first studies of INH as a treatment for latent TB infections (LTBI),[32] for which it is now a standard mono- or combination therapy.[33,34]

INH-resistance, alone or in combination with other drugs, is now the second most common type of resistance worldwide with current estimates at 10.3% for new cases and 27.7% for previously treated cases (13.3% combined).[35]

The World Health Organization (WHO) has proposed a wide-scale implementation of rapid molecular methods to screen patients at risk of DR-TB. Rapid tests can provide results within days and thus enable rapid and appropriate treatment, decrease morbidity and mortality, and interrupt transmission.[36] Among these, line probe assay (LPA) has been developed for the rapid detection of M. tuberculosis complex and its resistance to rifampicin (RIF) and isoniazid (INH). The assay detects mutations in the rpoB gene for RIF resistance, the katG gene for high-level INH resistance, and the inhA gene for low-level INH resistance from smear-positive or culture-positive sputum sample.[37] However, 70–80% of INH resistance is associated with mutations in codon 315 of the katG gene.[38,39]

Molecular line probe assay (LPA) technology for rapid detection of multi-drug resistant tuberculosis (MDR-TB) was endorsed by WHO in 2008. It detects resistance to isoniazid (kat G and inh A gene) and rifampicin (rpoB gene) both. This assay requires only 1000- 10,000 cfu/ml for detection of mycobacteria. Results are obtained in 1 to 2 days. It has been validated for sputum positive

samples only as yet, with a clear advantage of providing drug susceptibility status in as early as few hours. On smear positive sputum specimens LPA holds a high sensitivity ≥ 97% and specificity ≥ 99% for the detection of RIF resistance alone or in combination with INH (sensitivity ≥ 90% specificity ≥ 99%) on isolates of MTB.

Earlier the treatment regimen consists of Second Line Injectable drugs + Fluoroquinolones + Rifampicin + two of the first line drugs (E & Z) to which the patient is sensitive to make a total of 5 effective drugs regimen given daily. The total duration of treatment will be 9 to 12 months. The Intensive Phase (IP) is for 3 months with scope for extension to a maximum of 6 months. The Continuation phase (CP) is for a fixed duration of 6 months. The patient is initiated on treatment at DR-TB Centre, and then sent back for ambulatory treatment to the DTO for continuation of treatment regimen and regular follow-up.

According to latest PMDT guidelines, the WHO recommends, substitution of isoniazid with levofloxacin for the treatment of laboratory confirmed Hr-TB and use of drug regimen consisting of REZ (ethambutol, rifampicin, pyrazinamide)-Lfx for a duration of six months without a split of intensive and continuation phases. It furthers advises against the addition of streptomycin or any other injectable agent in the regimen. Treatment may be extended up to nine months depending upon clinical, radiological and microbiological response.

The detection of isoniazid mono resistance have helped in reducing the inappropriate intake of DOTS. Secondly, earlier only CBNAAT was done that detects rifampicin resistance only. So, if CBNAAT detects Rifampicin sensitive MTB, the treatment given was DOTS as required which leads to failure of the regimens if isoniazid resistance is present. Therefore, it avoids failure of the regimens and the undue wastage of the drugs.

The development of drug resistance may involve departures by providers from the correct management of individual cases. Problems occur in selecting the appropriate chemotherapy regimen, sometimes due to lack of recognition of prior treatment, ignorance of the importance of standardized regimens, and errors such as addition of a single drug to a failing regimen. In addition, providers may not monitor patients appropriately while on therapy. Finally, patient's non-adherence to prescribed treatment also contributes to the development of drug resistance. Another patient factor that has been associated with Isoniazid mono resistance is HIV infection, although the results of studies in different countries have been inconsistent.

This research is believed to contribute to identifying the potential risk factors for Isoniazid mono resistance, so that the management of patients will also be strengthened through preventing these factors, alongside patient treatment which will have a positive impact on successful treatment outcome, and decrease the burden of the disease as a whole. IMR (Isoniazid mono resistance) is a key driver of emergent resistance in the high burden, low resource setting, due to which MDR TB arises. Isoniazid testing is not routinely performed and inadequate treatment for unrecognised IMR is therefore common. In the setting of under diagnosis IMR –TB may be properly considered pre MDR-TB, and it is unsurprising that evolutionary studies have identified IMR as a precursor to further drug resistance. Therefore, it is particularly important to identify the risk factors associated with Isoniazid mono resistance TB. Judicious use of drugs, supervised individualized treatment, focused clinical, radiological and bacteriological follow up are key factors in the successful management of these patients.

There is a paucity of studies on patients with Isoniazid mono resistant tuberculosis. In this study we present data regarding the clinico-radiological characteristics of Isoniazid mono resistant tuberculosis patients.

REVIEW OF LITERATURE

Tuberculosis is a disease of antiquity. In 1500 BC, the Rigveda described the illness as Rajyaksma, "King of diseases".[40] Until the mid1800s people thought that tuberculosis was hereditary. In 1865, a French Surgeon, Jean- Antoine Villemin proved that tuberculosis was contagious.[41]

Tuberculosis lesion found as early as 3700 BC in the vertebrae and the bones of Egyptians. Genetic studies suggest TB was present in the Americans from about the years 100 AD. Susruta in 600 BC described the disease and observed that it was difficult to cure. The name Tuberculosis was introduced for the first time by Gasperd Laurent Bayle in 1816.[42]

The term tubercle was coined by Franciscus Sylvius de la Boe (1614-1672) of Amsterdam. He noticed tubercles in the lungs of people with Phthisis. The English physician Richard Morton (1637-1698) confirmed that tubercles were always present in TB of the lungs. Benjamin Martin (1704 - 1722) suggested that TB may be an infectious disease in 1720.

The first genuine success in immunizing against tuberculosis was developed from attenuated bovine-strain tuberculosis by Albert Calmette and Camille Guerin in 1906. BCG (Bacille Calmette Guerin) vaccination started in India as a pilot project in 1948. In 1949, it was extended to schools in almost all states of India.

The development of drug resistance in Mycobacterium tuberculosis was first documented in the late 1940s, soon after antibiotic therapy was introduced for tuberculosis

treatment. It quickly became obvious that combination chemotherapy could prevent the emergence of drug resistance[43] and that patients infected with drug-resistant strains were less likely to be cured.[44] It was only in the early 1990s that drug-resistant tuberculosis began to receive global attention as a public health threat. This coincided with the detection of outbreaks of multidrug-resistant (MDR) tuberculosis that were associated with high mortality among patients co-infected with the human immunodeficiency virus (HIV).[45,46,47,48]

In 1994, the Global Tuberculosis Program of the World Health Organization (WHO), with the support of the International Union against Tuberculosis and Lung Disease (the Union), established the Global Project on Anti-Tuberculosis Drug Resistance Surveillance (hereafter referred to as "the project") to measure the magnitude of drug resistance and to monitor trends. This project remains the oldest and largest initiative on the surveillance of antimicrobial resistance in the world.

In a retrospective study conducted by garg et al to study clinical profile of isoniazid mono tuberculosis. Out of 103 DRTB patients enrolled, 50.5% (52/103) patients were diagnosed with isoniazid mono-resistance. 50/103 were MDR-TB and 1/103 were extensively-drug resistant TB (XDR-TB). Further analysis of these 52 isoniazid mono-resistant patients revealed:35 (67.3%) were males and 17 (32.7%) females. 27 (51.9%) patients were <30 years, 25 (48.1%) being ≥30 years of age. All patients were negative for HIV. 34/52 (65.4%) patients were declared cured, 15/52 were lost to follow up (LTFU) and 3/52 died (1 male, 2 females). Excluding these 3 patients who died, cure rates were significantly better in females (14/15 = 93.3%), with only 1/15 LTFU, than males (20/34 = 58.8% cure, 14/34 = 41.2% LTFU), (p = 0.019). Patients who were <30 years of age had significantly better cure rates (21/25 = 84%) with lesser LTFU's (4/25 = 16%), than those ≥30years of age (13/24 = 54.2% cure, 11/24 = 45.8% LTFU), (p = 0.032). Review of previous history of ATT revealed that 33 patients had primary isoniazid mono-resistance, 4 patients had previous history of being LTFU, 9 had recurrent TB and 3 were labeled as failure. Cure rates were significantly better in primary isoniazid mono-resistant patients (26/33 = 78.8%), than those with previous history of being LTFU(0/4), (p = 0.04). Type of mutation, weight band, total serum protein/albumin, history of smoking, presence of DM, presence of anemia, occurrence of ADR and duration of IP did not affect treatment outcomes.[49]

In another study conducted by Kamilia R et al; in British Columbia, Canada. One hundred sixty five cases of INH mono-resistant TB were included in analysis and over 30 different treatment regimens were prescribed. Median treatment duration was 10.5 months (IQR 9–12 months) and treatment was extended beyond 12 months for 26 patients (15.8%). Fifty six patients (22.6%) experienced an adverse event that resulted in a drug regimen modification. Overall, 140 patients (84.8%) had a successful treatment outcome while 12 (7.2%) had an unsuccessful treatment outcome of failure (n = 2; 1.2%), relapse (n = 4; 2.4%) or all cause mortality (n = 6; 3.6%).[50]

Another retrospective cross-sectional study done in peru to evaluate clinical profile and treatment outcome of isoniazid mono resistant tuberculosis. A total of 947 cases were evaluated (a further 403 without treatment end date were excluded), with treatment success in 77.2% (731 cases), loss to follow-up in 19.7% (186 cases), treatment failure in 1.2% (12 cases), and death in 1.9% (18 cases). Unfavorable outcomes were associated in multivariate analysis with male gender (OR 0.50, 95% CI 0.34–0.72, p<0.05), lack of rapid DST (OR 0.67, 95% CI 0.50–0.91, p = 0.01), additional use of an injectable second-line anti-tuberculous drug (OR 0.46, 95% CI 0.31–0.70, p<0.05), and treatment initiation in 2014 (OR 0.77, 95% CI 0.62–0.94, p = 0.01.[51]

Another study was conducted by Reanata et al; to assess the impact on Treatment Outcome and Survival of Isoniazid mono resistant Tuberculosis Patients in Southern Mexico 1995-2010. 1,243 patients with pulmonary TB were recruited; 902/1,243 (72.57%) had drug susceptibility testing; 716 (79.38%) harbored pan-susceptible and 88 (9.75%) IMR strains. Having any contact with a person with TB (adjusted odds ratio (aOR)) 1.85, 95% Confidence interval (CI) 1.15–2.96) and homelessness (adjusted odds ratio (aOR) 2.76, 95% CI 1.08–6.99) were associated with IMR. IMR patients had a higher probability of failure (adjusted hazard ratio (HR) 12.35, 95% CI 3.38–45.15) and death due to TB among HIV negative patients (aHR 3.30. 95% CI 1.00–10.84). All the models were adjusted for socio-demographic and clinical variables.[52]

A study was conducted to determine the prevalence and genetic profiles of isoniazid resistance in tuberculosis patients; a multicountry analysis of cross-sectional data. Aggregated drug resistance data reported to WHO from either routine continuous surveillance or nationally representative periodic surveys of TB patients for the period 2003–2017 were reviewed. Isoniazid data were available from 156 countries or territories for 211,753 patients. Among these, the global prevalence of Hr-TB was 7.4% (95% CI 6.5%–8.4%) among new TB patients and 11.4% (95% CI 9.4%–13.4%) among previously treated TB patients. Additional data on pyrazinamide and levofloxacin resistance were available from 6 countries (Azerbaijan, Bangladesh, Belarus, Pakistan, the Philippines, and South Africa). There were no cases of resistance to both pyrazinamide and levofloxacin among Hr-TB patients, except for the Philippines (1.8%, 95% CI 0.2–6.4) and Belarus (5.3%, 95% CI 0.1–26.0). Sequencing data for all genomic regions involved in isoniazid resistance were available for 4,563 patients. Among the 1,174 isolates that were resistant by either

phenotypic testing or sequencing, 78.6% (95% CI 76.1%–80.9%) had resistance-conferring mutations in the katG gene and 14.6% (95% CI 12.7%–16.8%) in both katG and the inhA promoter region. For 6.8% (95% CI 5.4%–8.4%) of patients, mutations occurred in the inhA promoter alone, for whom an increased dose of isoniazid may be considered. The main limitations of this study are that most analyses were performed at the national rather than individual patient level and that the quality of laboratory testing may vary between countries. In this study, the prevalence of Hr-TB among TB patients was higher than the prevalence of rifampicin resistance globally. Many patients with Hr-TB would be missed by current diagnostic algorithms driven by rifampicin testing, highlighting the need for new rapid molecular technologies to ensure access to appropriate treatment and care. The low prevalence of resistance to pyrazinamide and fluoroquinolones among patients with Hr-TB provides further justification for the recommended modified treatment regimen.[53]

Another study was conducted to assess the profile of Drug-resistant tuberculosis (MDR-TB) by Mishra et al; in tertiary care hospital setting, Ajmer, Rajasthan India. A total of 244 cases of Drug Resistant Pulmonary Tuberculosis registered under RNTCP (Revised National Tuberculosis Program) from 1st January 2012 to 30th September 2012 at PMDT. Out of 244 patients who were included in the study population (74.6%) patients were in the age group of 16 - 45 years. Majority of cases were males 195 (79.92%), with male: female sex ratio of 4:1. Mean age of males and females were 38.7 and 34.7 years respectively. 192 (78.7%) patients were from rural population and 52 (21.3%) patients belong to urban areas. 145 (59.42%) patients were having addiction habits like Smoking, Alcoholism, Tobacco chewing and Opium intake, while 99 (40.57%) patients had no history of addiction. And 57 (23.4%) patients were having history of smoking alone. Mostly smokers (45.08%) followed by alcoholic (25%). Alcoholism may contribute to the default behavior and negligence towards anti-tuberculosis medication of patients and therefore may have a negative impact on treatment outcome for tuberculosis. Most common co-morbid condition was COPD present in 104 (42.62%) cases which was mostly smoking related, followed by occupational lung disease (probably silicosis) in 26 (10.65%) cases, Diabetes mellitus in 11 (4.5%) cases, Hepatic disorder in 10 (4.1%) cases, Cor-pulmonale in 6 (2.5%) cases, HIV infection was present in 6 (2.5%) cases and 3 (1.2%) cases are HBsAg positive, in 5 (2.0%) cases neurological disorders were present. 60 (24.6%) patients had documented h/o contact with TB patients, of which 53 (88.3%) patients had h/o contact with PTB patients, whereas 7 (11.7%) patients had h/o contact with MDR-TB patients. 224 (91.8%) and 20 (8.2%) patients had bilateral and unilateral lung disease respectively. 209 (85.7%) patients had cavitatory lung disease, whereas rest had non-cavitatory lung disease. 95 (38.9%) patients had moderately advanced lung disease and 134 (54.9%) patients had far advanced lung disease.[54]

In another study to determine the clinical characteristics and treatment outcomes of patients with isoniazid-monoresistant tuberculosis by Adithya Cattamanch et al; During the study period, there were 137 cases of INH-monoresistant tuberculosis reported to the SFDPH Tuberculosis Control Section, for which 274 control subjects with drug-susceptible tuberculosis were selected as time-matched controls. Of the 137 patients with INH-monoresistant tuberculosis, 82 (60%) had high-level INH resistance. The percentage of patients who completed treatment at the SFDPH Tuberculosis Control Section clinic was similar for the group with drug-susceptible tuberculosis and the group with INH-monoresistant tuberculosis (87% vs. 83%; P=.17) (figure 1). However, 1-year posttreatment follow-up was completed by a greater percentage of the group with INH-monoresistant tuberculosis (98% vs. 86%; P=.03). In bivariate analysis, patients with INH-monoresistant tuberculosis were more likely to be foreign born (85% vs. 72%; P=.002) and to have received prior tuberculosis treatment (36% vs. 17%; P<.001), compared with patients with drug-susceptible tuberculosis (table 1). In contrast, other risk factors for tuberculosis were less common among the group with INH-monoresistant tuberculosis than among the group with drug-susceptible tuberculosis, including HIV infection (7% vs. 15%; P=.01), homelessness (8% vs. 19%; P=.004), and a history of substance abuse (13% vs. 20%; P=.07). The majority of patients in both groups were of Asian ethnicity, although there was a higher percentage of Asian persons (77% vs. 60%; P<.001) and a lower percentage of non-Hispanic black persons (4% vs. 13%; P=.006) in the group with INH-mono resistant tuberculosis, compared with the group with drug-susceptible tuberculosis. Filipino (37%) and Chinese (44%) persons accounted for 81% of Asian persons with INH-mono resistant tuberculosis. In a multivariate analysis, only a history of treatment for latent tuberculosis (OR, 3.1; 95% CI, 1.5 6.4; P=.003) or for active tuberculosis (OR, 2.7; 95% CI, 1.4 5.0; P=.002) were significantly associated with INH mono resistance.

The clinical presentation of tuberculosis did not differ significantly between the 2 groups. The percentages of patients with fever, night sweats, weight loss, and hemoptysis were similar (all P values $\geqslant$.2; data not shown). The same percentage of patients in each group presented with extrapulmonary tuberculosis (12%). Factors associated with the extent of disease, such as positive results of acid-fast bacilli smear test (47% vs. 41%; P=.29) and cavitation on initial chest radiograph (18% vs. 14%; P=.26), were not significantly different between the group with INH-monoresistant tuberculosis and the group with drug-susceptible tuberculosis. There were, however, some differences in characteristics associated with treatment. Patients with INH-monoresistant tuberculosis received a longer duration of treatment (median, 306 vs. 220 days; P<.001), were more

likely to experience an adverse drug reaction requiring an interruption in therapy (31% vs. 15%; P<.001), and were more likely to complete treatment at the SFDPH Tuberculosis Control Section clinic (82% vs. 65%; P<.001). Of note, patients who received treatment at the SFDPH Tuberculosis Control Section clinic overall were less likely to have extrapulmonary tuberculosis (10% vs. 19%; P=.01) and to die during tuberculosis treatment (5% vs. 16%; P<.001) and were more likely to receive directly observed therapy (59% vs. 37%; P<.001), compared with patients whose treatment was managed by non tuberculosis clinic providers.[55]

A study undertaken to determine the isoniazid Monoresistance and Rate of Culture Conversion among Patients in the State of Georgia with Confirmed Tuberculosis, 2009–2014 by Argita D. Salindri et al; Among 1,141 culture-confirmed patients with available drug susceptibility testing results, 998 (87.5%) were susceptible to TB first-line drugs, and 143 (12.5%) were patients with INH-monoresistant TB. In multivariable analysis, male sex (adjusted odds ratio [aOR], 1.62; 95% confidence interval [CI], 1.01–2.67) and homelessness (aOR, 5.55; 95% CI, 3.38–9.17) were associated with higher odds of INH-monoresistant TB. In the same multivariable model, older age (≥65 yr old) (aOR, 0.21; 95% CI, 0.07–0.55) and miliary disease (aOR, 0.19; 95% CI, 0.01–0.96) were associated with lower odds of INH-monoresistant TB. Among 1,116 patients with pulmonary TB, the median time to sputum culture conversion was 30 days (interquartile range, 13–58). The rate of culture conversion was similar among patients with and without INH monoresistance (adjusted cause-specific hazard ratio, 1.15; 95% CI, 0.95–1.40). INH-monoresistant TB was not significantly associated with poor TB treatment outcomes (aOR, 1.61; 95% CI, 0.67–3.70) or mortality during TB treatment (aOR, 1.72; 95% CI, 0.58–4.94).[56]

In comprehensive meta-analysis study by mohammad et al; to determine the Isoniazid-resistant tuberculosis in Iran. The meta-analysis showed that 12.8% (95% CI 9.4–15.8; I2 = 87.8; P < 0.001 test for heterogeneity) of new TB cases and 40.1% (95% CI 28.5–53.0; I2 = 88.2; P < 0.001 test for heterogeneity) of previously treated cases were resistant to INH. High prevalence of INH resistance among TB patients has been reported in many health-care settings, suggesting that better management of such cases, use of effective treatment regimens and establishing advanced diagnostic facilities are needed to avoid further emergence of INH-resistant TB.[57]

Another study was conducted to determine the Isoniazid-Monoresistant Tuberculosis in the United States, 1993 to 2003 by Andrea J. Hoopes et al; It shows that the the numbers of isoniazid-monoresistant TB cases increased from 303 (4.1%) in 1993 to 351 (4.2%) in 2005. In multivariate analysis of all TB cases reported from 1993 to 2003, the races/ethnicities of patients with isoniazid-monoresistant TB were significantly more likely to be US-born Asian/Pacific Islander (adjusted odds ratio [aOR], 1.9; 95% confidence interval [CI], 1.4-2.6), foreign-born Asian/Pacific Islander (1.8; 1.4-2.1), foreign-born black non-Hispanic (1.4; 1.1-1.7), or US-born Hispanic (1.3; 1.1-1.5). Isoniazid monoresistance was also associated with failure to complete therapy within 1 year (aOR, 1.7; 95% CI, 1.5-1.8), a history of TB (1.5; 1.3-1.7), and correctional facility residence (1.5; 1.2-1.7).[58]

In another study done to assess the Comparison of different treatments for isoniazid resistant tuberculosis: by Fregonese et al; Individual patient data was requested from authors of 57 cohort studies and 17randomized trials with 8089 patients with INH-R TB. We received 33 data sets with 6424 patients (27 cohorts and 6 RCT), of which 3923 patients in 23 studies (21 cohorts and 2 RCT) received regimens related to the study objectives. When compared to a daily regimen of 6 months of rifampin, pyrazinamide and ethambutol, with or without isoniazid (6(H)REZ), extending the duration to 8-9 months had similar outcomes, hence >6(H)REZ was used for subsequent comparisons. Addition of a fluoroquinolone to >6(H)REZ was associated with significantly greater treatment success (aOR: 2·8, 95% CI: 1·1, 7·3), and non-significantly lower mortality (aOR: 0·7, 95% CI: 0·4, 1·1) and acquired rifampin resistance (aOR: 0·1, 95% CI: 0·0, 1·2). When compared to >6(H)REZ, the standardized retreatment regimen (2 months streptomycin, 3 months pyrazinamide and 8 months isoniazid, rifampin plus ethambutol) was associated with significantly worse treatment success (aOR: 0·4 95% CI: 37 0·2, 0·7).[59]

Most of the studies found that cavity was the most common radiological lesion of Drug resistant tuberculosis patients on chest x-rays. According to a study by Mukherjee P et al. (2015), 43.02% drug resistant tuberculosis patients had moderately advanced disease, and 38.95% had far advanced disease, and 18.02% had minimal disease in chest radiographs. They also reported cavitatory lesions as the common radiographic presentation. The limited drug penetration into the cavity that harbours large mycobacterial load and a greater number of Acid fast bacilli (AFB) in moderately advanced or far advanced disease is believed to contribute to drug resistance.[60]

In a study to determine the Isoniazid-resistant tuberculosis in Birmingham, United Kingdom, 1999–2010 by M.L. Munang et.al; cases of H-resistant tuberculosis between January 1999 and December 2010 (n = 89) were compared with drug-susceptible cases (n = 2497). Treatment regimens and outcomes at 12 months from diagnosis were evaluated by case note review. No independent predictors for H-resistant TB were found. For 76/89 (85%) patients with full treatment details available, median treatment duration was 11 months (interquartile range 9–12 months). Only 27/72 (38%) patients with H-monoresistance were treated in line with

national guidelines. A further 14/72 (19%) were treated according to other recognized guidelines. Overall treatment success was 75/89 (84%). Treatment failure occurred in 6/89 (7%) patients, all developed multi-drug resistance. Poor adherence was documented in these patients and use of a non-standard regimen in one patient was not thought to have contributed to treatment failure.[61]

There was an outbreak of isoniazid resistant tuberculosis in north London in which by the end of 2001, 70 confirmed cases in London had been linked with a further 13 clinical cases in contacts and nine epidemiologically linked cases outside London. The epidemic curve suggests that the peak of the outbreak has not yet been reached. Cases in the outbreak largely belong to a social group of young adults of mixed ethnic backgrounds including several individuals from professional/business backgrounds. Compared with other cases of TB reported to the enhanced surveillance scheme in London during 1999–2001, the cases are more likely to be of white (26/70 (37%) *v* 1308/7666 (17%)) or black Caribbean ethnicity (17/70 (24%) *v* 312/7666 (4%)), born in the UK (41/70 (59%) *v* 1335/7666 (17%)), and male (52/70 (74%) *v*4195/7666 (55%)). Drug misuse and/or prison detention are factors common to many cases.[62]

In a retrospective cohort study to determine isoniazid resistance and death in patients with tuberculous meningitis between 1993 and 2005, showed that 1896 patients had a clinical diagnosis of tuberculous meningitis and positive cultures from any site. In 123 (6%) of these patients, isoniazid resistance was present on initial susceptibility testing. The unadjusted association between initial isoniazid resistance and subsequent death among these 1896 patients did not reach statistical significance (odds ratio 1.38, 95% confidence interval 0.94 to 2.02). However, among 1614 patients with positive cerebrospinal fluid cultures, a significant unadjusted association was found between initial isoniazid resistance and subsequent death (odds ratio 1.61, 1.08 to 2.40). This association increased after adjustment for age, race, sex, and HIV status (odds ratio 2.07, 1.30 to 3.29).[63]

A study conducted by Dholakia et al; to know chest X-rays and associated clinical parameters in pulmonary tuberculosis cases from the National Tuberculosis Program, Mumbai. Of the entire cohort, 68 treatment failures and 584 new cases for whom X-rays were available were analyzed. From April 2004 till September 2007, 2 groups of sputum positive PTB patients were screened: i) newly diagnosed patients at onset; and ii) treatment failures. The majority of the patients amongst both the treatment failures (66%) and new cases (62%) were males and majority were in the age group of 15-35 year. Briefly, the cohort of treatment failure and new cases revealed 17% and 35% of samples were sensitive, 41% and 24% were MDR, 26% and 20% were poly-resistant, and 16% and 21% were mono-resistant, respectively. They examined features of chest X-rays and their correlation with clinical parameters for possible application in suspected multidrug resistant TB (MDR-TB) and to predict outcome in new and treatment failure PTB cases. X-ray features (infiltrate, cavitation, miliary shadows, pleural effusion, mediastinal lymphadenopathy and extent of lesions) were analyzed. Failures demonstrated associations between extensive lesions and high glycosylated hemoglobin levels (P=0.028) and male gender (P=0.03). More patients with low hemoglobin levels also had extensive lesions on X-ray (73%) in comparison to those with normal hemoglobin (56%), but this was not significant (P=0.2). An association was also detected between cavitation and MDR (P=0.048). In new cases, bilateral cavities were associated with MDR (P=0.018) and male gender (P=0.01), low body mass index with infiltrates (P=0.008), and smoking with cavitation (P=0.0238).[64]

A record-based descriptive, cross-sectional study conducted by Sudhakar W. More et al; to determine the profile of drug resistant tuberculosis in western Maharashtra of drug-resistant TB cases that were referred to State TB Training and Demonstration Centre (STDC). The data were collected by means of use of TB patient treatment register of those tested at STDC during first two quarters of the year 2012 (from January to June 2012). Sputum samples of all the cases were subjected to concentrated microscopy, and all positive samples were tested by Gene-Xpert and Line Probe Assay for drug susceptibility testing (DST) for isoniazid and rifampicin. A total of 352 suspected patients were tested at STDC during January 2012 to June 2012 (6 months period). Of these, 96 (27.3%) patients diagnosed with drug-resistant TB and were included in the study. A total of 27 (28.13%) patients had a self-reported comorbidity which included 6 (29.62%) patients with diabetes mellitus and 2 (7.40%) patients with diabetes mellitus and hypertension, 3 (14.81%) patients who were HIV positive and 1 (3.70) had HIV with anemia, 1 (3.70%) patient was suffering from hypothyroidism and one patient had hypothyroidism with hypertension and one each had piles, meningitis, ischemic heart disease, and fibro-adenoma of breast.[65]

In a prospective observational cohort study by Leonela Villegas et.al in Lima, Peru to determine the prevalence, risk factors, and treatment outcomes of Isoniazid- and Rifampicin- Mono-Resistant Pulmonary Tuberculosis shows that out of 1292 patients enrolled, 1039 (80%) were culture-positive. From this subpopulation, isoniazid mono-resistance was present in 85 (8%) patients and rifampicin mono-resistance was present in 24 (2%) patients. In the multivariate logistic regression model, isoniazid mono-resistance was associated with illicit drug use (adjusted odds ratio (aOR) = 2.10; 95% confidence interval (CI): 1.1–4.1), and rifampicin mono-resistance was associated with HIV infection (aOR = 9.43; 95%CI: 1.9–47.8). Isoniazid mono-resistant

patients had a higher risk of poor treatment outcomes including treatment failure (2/85, 2%, p-value<0.01) and death (4/85, 5%, p<0.02). Rifampicin mono-resistant patients had a higher risk of death (2/24, 8%, p<0.01).[66]

In a Retrospective Analysis of Isoniazid-Monoresistant Tuberculosis: Among Iranian Pulmonary Tuberculosis Patients out of 4825 culture-positive isolates, 6.1% were resistant to INH, with an increasing trend over the study period. The INH-monoresistance from 4.4 in 2003 reached to 9.4% in 2011. Among the studied risk factors, age was significantly associated with INH-monoresistance ($p < 0.05$).[67]

In a systematic review and meta-analysis to study the treatment of isoniazid-resistant tuberculosis with first-line drugs by Medea Gegia et.al; identified 19 cohort studies and 33 trials with 3744 patients with isoniazid-resistant tuberculosis and 19012 patients with drug-sensitive disease. The pooled rates of failure or relapse, or both, and acquired drug resistance with all drug regimens were 15% (95% CI 12-18) and 3·6% (2-5), respectively, in patients with isoniazid-resistant tuberculosis and 4% (3-5) and 0·6% (0·3-0·9) in those with drug-sensitive tuberculosis. Of patients with initial isoniazid-resistant tuberculosis with acquired drug resistance, 96% (93-99) had acquired multidrug-resistant disease. Treatment of isoniazid-resistant tuberculosis with the WHO standard regimen for new patients resulted in treatment failure, relapse, and acquired multidrug resistance in 11% (6-17), 10% (5-15) and 8% (3-13), respectively; treatment with the standard WHO regimen for previously treated patients resulted in treatment failure in 6% (2-10), relapse in 5% (2-8), and acquisition of multidrug resistance in 3% (0-6). For patients with drug-sensitive disease treated with the standard retreatment regimen the rates were 1% (0-2), 5% (4-7), and 0·3% (0-0·6). Treatment of isoniazid-resistant tuberculosis with first-line drugs resulted in suboptimal outcomes, supporting the need for better regimens. Standardised empirical treatment of new cases could be contributing substantially to the multidrug-resistant epidemic, particularly in settings where the prevalence of isoniazid resistance is high.[68]

In another study to determine the bacterial risk factors for treatment failure and relapse among patients with isoniazid resistant tuberculosis by Phan Vuong Khac Thai et.al; Using only routine programmatic sputum smear microscopy for assessment, (months 2, 5 and 8) 30/239 (12.6%) showed an unfavourable outcome by WHO criteria. Thirty-nine patients were additionally detected with unfavourable outcomes during 2 year follow up, giving a total of 69/239 (28.9%) of isoniazid (INH) resistant cases with unfavourable outcome by 2 years of follow-up. Beijing lineage was the only factor significantly associated with unfavourable outcome among INH-resistant TB cases during 2 years of follow-up. (adjusted OR = 3.16 [1.54-6.47], P = 0.002). One third of isoniazid resistant TB cases suffered failure/relapse within 2 years under the old eight month regimen. Over half of these cases were not identified by standard WHO recommended treatment monitoring. Intensified research on early identification and optimal regimens for isoniazid resistant TB is needed. Infection with Beijing genotype of TB is a significant risk factor for bacterial persistence on treatment resulting in failure/relapse within 2 years. The underlying mechanism of increased tolerance for standard drug regimens in Beijing genotype strains remains unknown.[69]

From a clinical standpoint, if INH resistance is not detected, new patients are managed as if they had pan susceptible TB, which substantially increases the risk of treatment failure or relapse and a greater propensity to acquire further resistance. Yet most research and policy efforts so far have been focussed solely on Rifampicin resistance as proxy for MDR-TB. This means that hundreds of thousands of patients with Isoniazid resistance TB are staying in the shadows, not receiving appropriate care and all too often ending up developing MDR-TB.

AIMS AND OBJECTIVES

1) To study the clinical profile of Isoniazid mono Resistance Tuberculosis patients presenting in chest and TB Hospital.
2) To study the radiological profile of Isoniazid mono resistance tuberculosis patients.
3) To study the association of Isoniazid mono Resistance Tuberculosis patients with any other comorbidity.

MATERIALS AND METHODS

The present observational prospective study has been carried out in the department of Chest and Tuberculosis, Government Medical College, Amritsar. The study has included 50 diagnosed patients of Isoniazid mono Resistant tuberculosis from an RNTCP-Certified Laboratory after taking informed consent. The approval of institutional thesis and ethics committee has been taken before the start of study.

Inclusion criteria

1. Patients with documented evidence of Isoniazid mono resistance through Line Probe Assay (LPA).
2. Age more than 14 years.

Exclusion criteria

1. Multidrug resistance patients
2. Critically ill or moribund patients.
3. Patients having extra-pulmonary tuberculosis
4. Patients with extensively drug resistant tuberculosis XDR-TB

All diagnosed Patients of Isoniazid mono resistant Tuberculosis (referred to Drug resistant TB-centre (DR-TB) were admitted under PMDT-RNTCP in DOTS PLUS ward, department of TB & Chest, Government Medical College, Amritsar for pre-treatment evaluation.

The protocol was clearly explained to patient/care provider before enrolment and informed consent was taken from each patient as per PMDT guidelines.

1) Detailed clinical history (including screening for mental illness, seizure disorder, drug/alcohol abuse etc.)
2) Weight
3) Height
4) Complete blood count with platlets count
5) Blood sugar to screen for diabetes mellitus
6) Liver function test
7) Blood urea and serum creatinine to assess the Kidney function test
8) Urine examination- routine and microscopic
9) Pregnancy test (for all women in child bearing age group)
10) Chest x-ray
11) ECG (if moxifloxacin to be used)
12) Serum electrolyte (if capreomycin is to be used)
13) All cases were offered referral for HIV counselling and testing at nearest centre if the HIV status was not known or the HIV test was found negative with results more than 6 months old. If patient was HIV positive, he/she was referred to ART centre (if not on ART)

Demographic characteristics, socioeconomic status, complete detailed clinical history regarding total duration of illness, smoking history, drug/alcohol abuse, mental illness, diabetic history, previous anti tuberculosis therapy, family history of anti- tuberculosis therapy and any contact with tuberculosis patients was taken from the patients.

Base line data with specific reference to previous history of anti- tuberculosis treatment (ATT), pattern of drug resistance, extent of disease clinical as well as radiological, associated co-morbid conditions, socioeconomic status, addiction habits, body mass index (BMI), and baseline haematological investigations as per Revised National Tuberculosis Control Program (RNTCP) guidelines will be collected from the patients. All patients were subjected to chest radiograph.

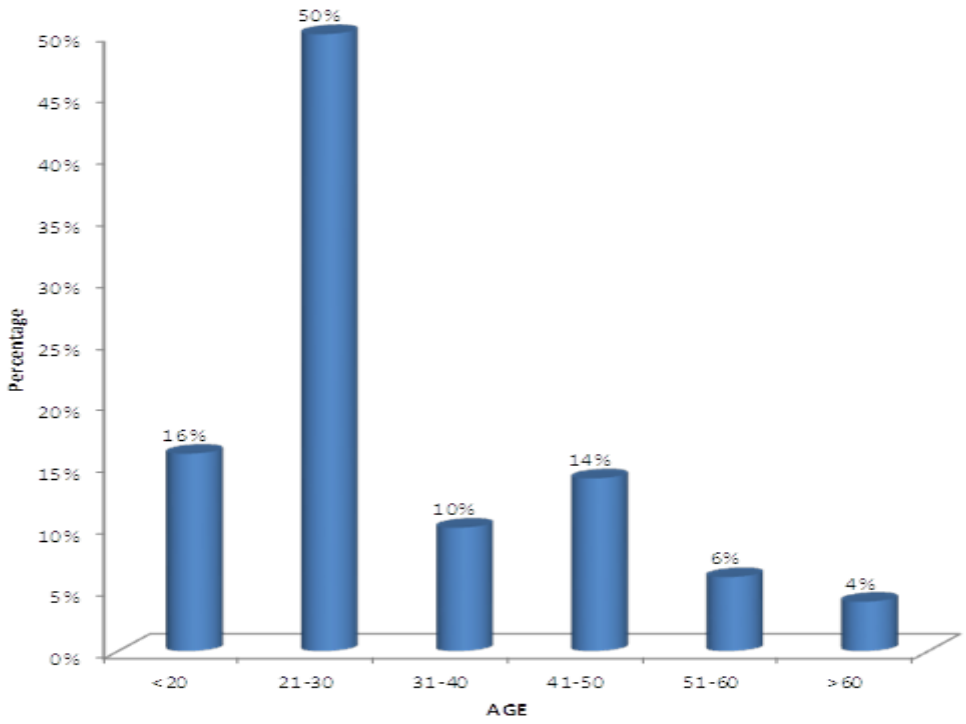
OBSERVATIONS

This study was conducted in the Department of Chest and Tuberculosis, Government Medical College, Amritsar, which included 50 patients who were microbiologically confirmed cases of Isoniazid Mono Resistant Tuberculosis. All the patients were confirmed cases of Isoniazid Mono Resistant Tuberculosis through Line Probe Assay. Study included isoniazid resistant cases. This study was conducted to determine the clinic-radiological profile of Isoniazid resistant cases. The observations and results of the studied patients were recorded and tabulated as follows:

Table I: Age-Wise Distribution of Cases.

AGE IN YEARS	NUMBER OF CASES	PERCENTAGE
<20	8	16%
21-30	25	50%
31-40	5	10%
41-50	7	14%
51-60	3	6%
>60	2	4%
TOTAL	50	100%

The above table shows that the maximum number of patients belonged to the age group of 21-30 years i.e. 50% followed by 16% in the age group of <20 years. Minimum patients were in age group >60 years i.e. 4%. Mean age was 31.6 years. The youngest patient was 16 year old and the oldest patient was 65 year in age.

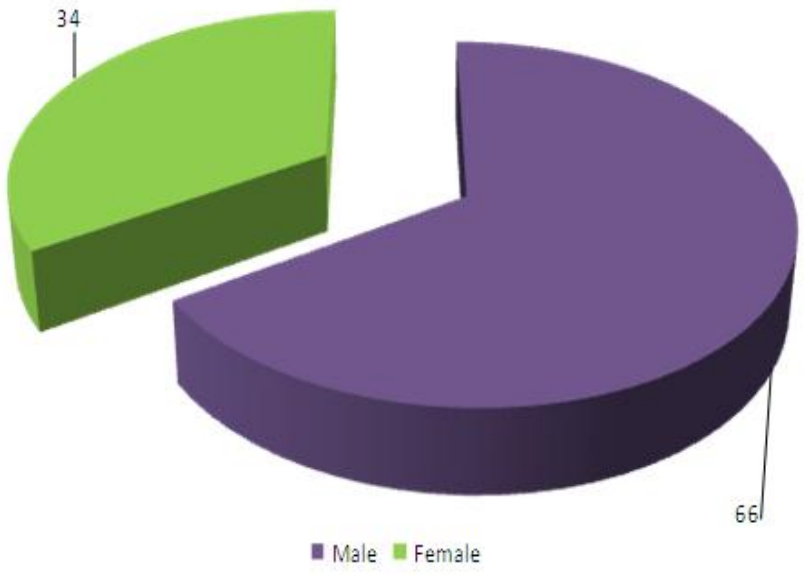


Graph I: Age-Wise Distribution of Cases.

Table II: Gender - Wise Distribution of Cases.

SEX	NUMBER OF CASES	PERCENTAGE
Male	33	66%
Female	17	34%
Total	50	100%

This table shows that maximum patients were males (66%), while females contributed (34%) of patients.

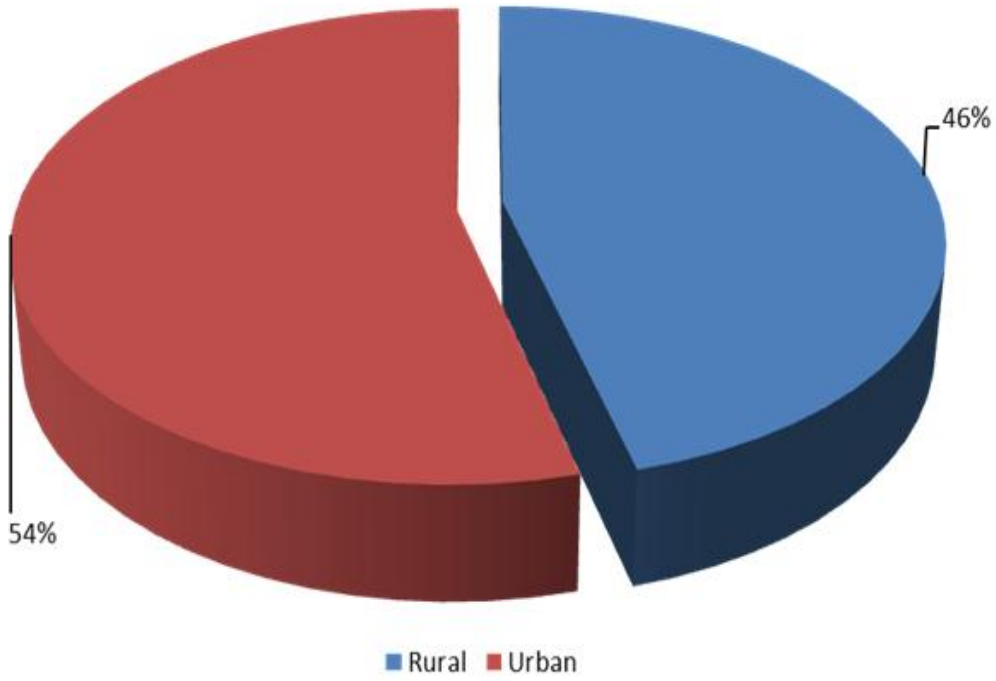


Graph II: Gender - Wise Distribution of Cases.

Table III: Residence – Wise Distribution of Cases.

RESIDENCE	NUMBER OF CASES	PERCENTAGE
Rural	23	46%
Urban	27	54%
Total	50	100%

Out of 50 patients, 23 (46%) patients were from rural population and 27 (54%) patients belonged to urban areas.



Graph III: Residence – Wise Distribution of Cases.

Table IV: Marital Status – Wise Distribution of Cases.

MARITAL STATUS	NUMBER OF PATIENTS	PERCENTAGE
Married	30	60%
Unmarried	20	40%
Total	50	100%

Among 50 cases, most of the patients 30 (60%) were married; 20 (40%) were unmarried.

Table IV: Marital Status – Wise Distribution of Cases.

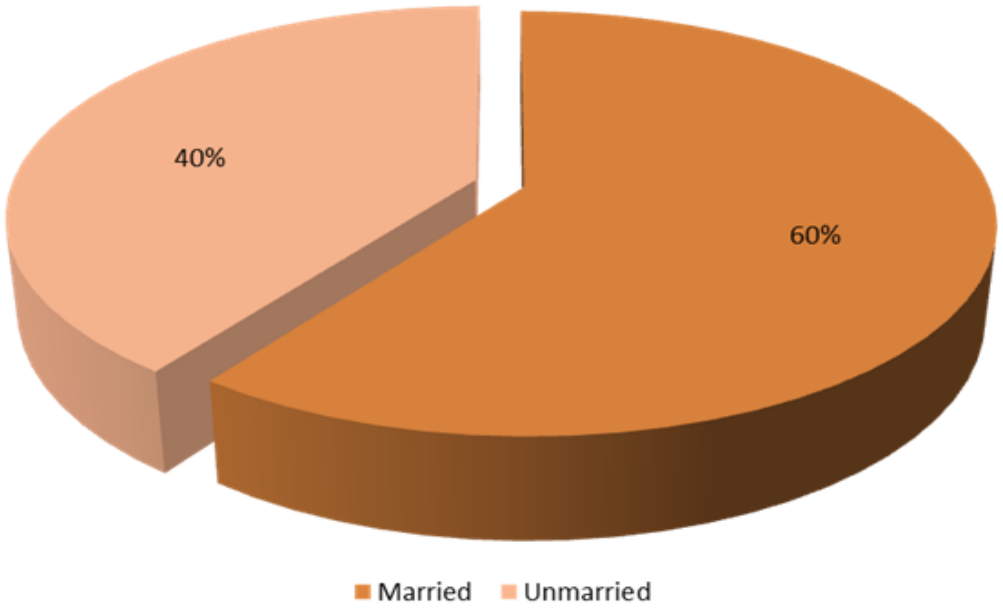
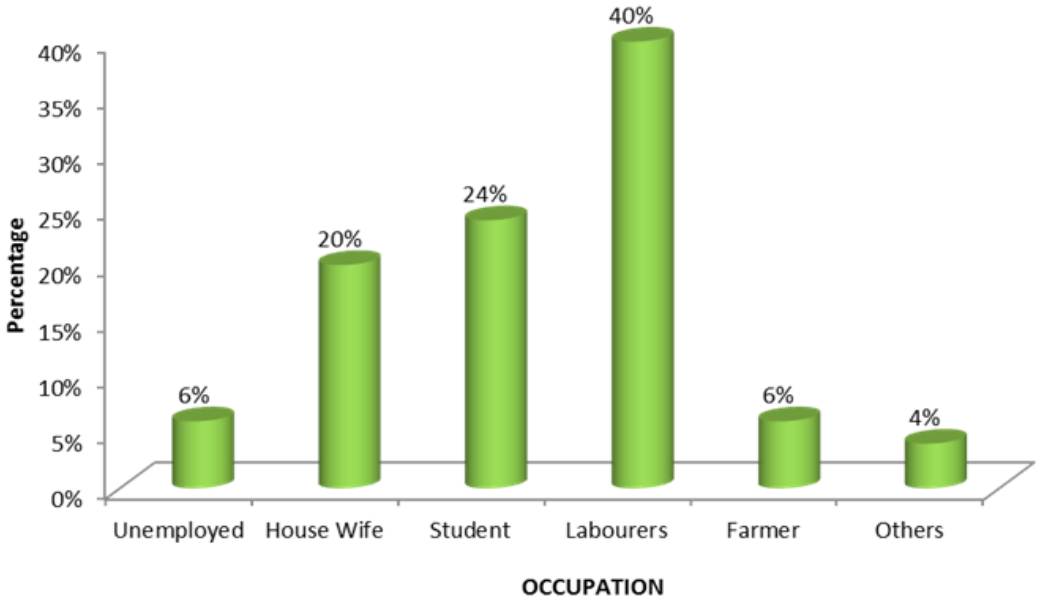


Table V: Occupation – Wise Distribution of Cases.

OCCUPATION	NUMBER OF CASES	PERCENTAGE
Unemployed	3	6%
House Wife	10	20%
Student	12	24%
Labourers	20	40%
Farmer	3	6%
Others	2	4%
Total	50	100%

Most of the patients were Labourers 20 (40%), followed by Studentss 12 (24%). Ten (20%) patients were Housewives; three (6%) patients were Farmers and three (6%) were unemployed in this study.



Graph V: Occupation – Wise Distribution of Cases.

Table VI: Resistance Pattern – Wise Distribution of Cases Type of Isoniazid Monoresistance.

RESISTANCE PATTERN	NUMBER OF CASES	PERCENTAGE
Kat G	42	84%
Inh A	8	16%
Total	50	100%

Out of 50 cases, 42(84%) patients were Kat G Isoniazid mono resistant and 8 (16%) were Inh A-isoniazid resistant cases in this study.

Table VI: Resistance Pattern – Wise Distribution of Cases Type of Isoniazid Monoresistance.

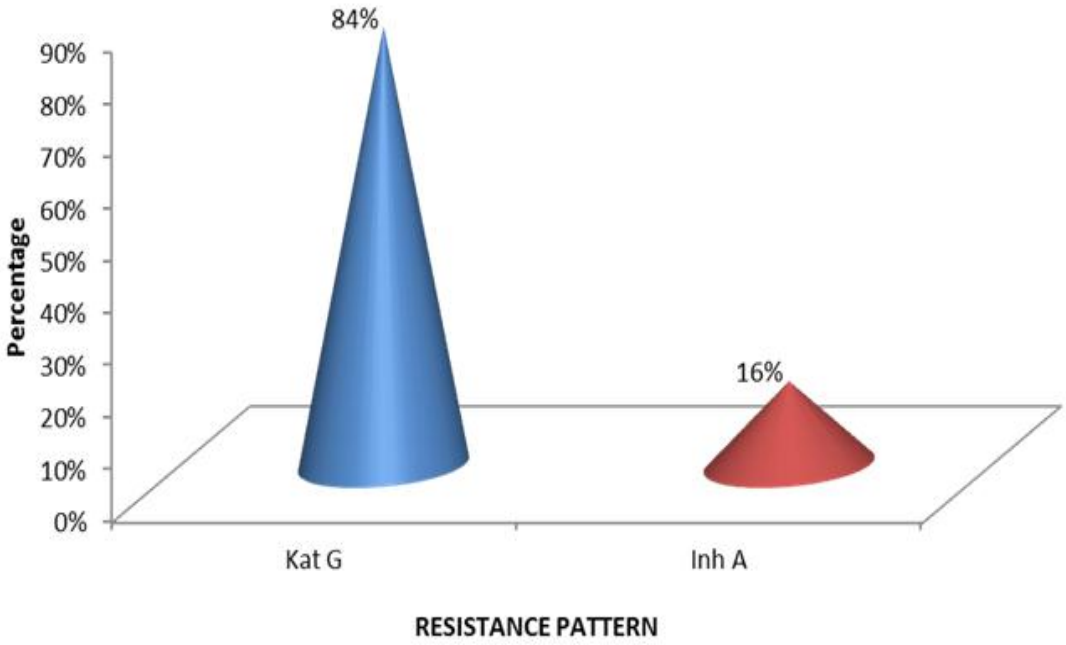


Table VII: Frequency of Presenting Symptoms.

SYMPTOMS	NUMBER OF CASES	PERCENTAGE
Cough with Expectoration	48	96%
Fever	33	66%
Breathlessness	22	44%
Hemoptysis	2	4%
Loss of Appetite	26	52%
Weight loss	27	54%

Most of the patients taken in the study were having more than one complaint for more than one month. As it can be seen from above table that most common symptom was cough with expectoration which was present in 48 (96%) of cases followed by fever which was present in 33 (66%) cases. Weight loss was present in 27 (54%) of cases, loss of appetite in 26 (52%) of patients, breathlessness was present in 22 (44%) of cases and hemoptysis was present in 2 (4%) of cases.

Table VII: Frequency of Presenting Symptoms.

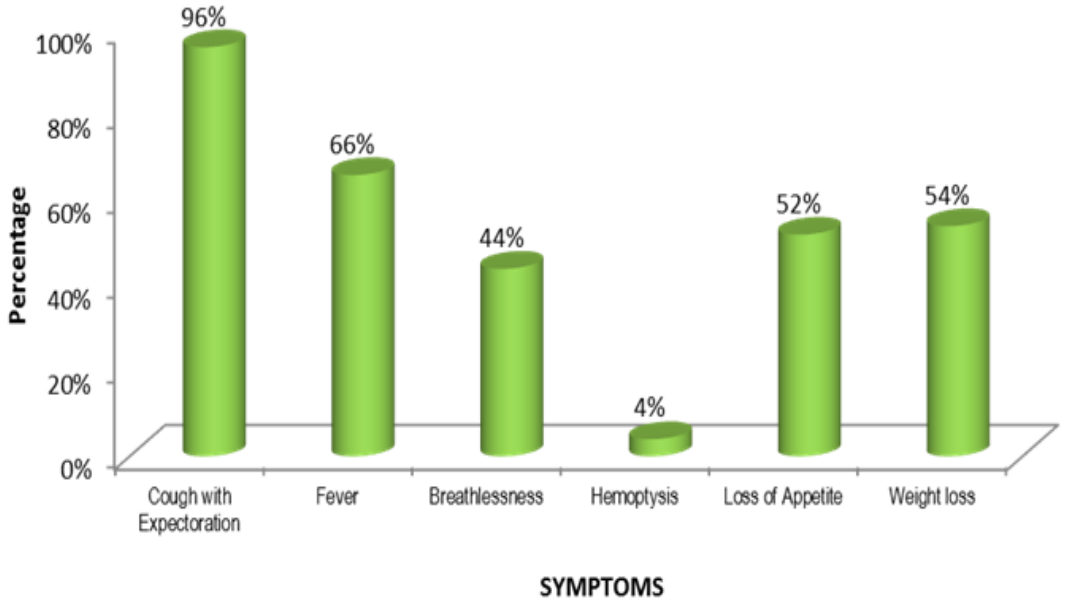


Table VIII: Distribution of Cases According To The History of Diabetes Mellitus.

DIABETES MELITUS	NUMBER OF PATIENTS	PERCENTAGE
Present	4	8%
Absent	46	92%
Total	50	100%

Table 8 shows that 4 (8%) patients were Diabetic and rest i.e. 46 (92%) were not.

Table VIII: Distribution of Cases According To The History of Diabetes Mellitus.

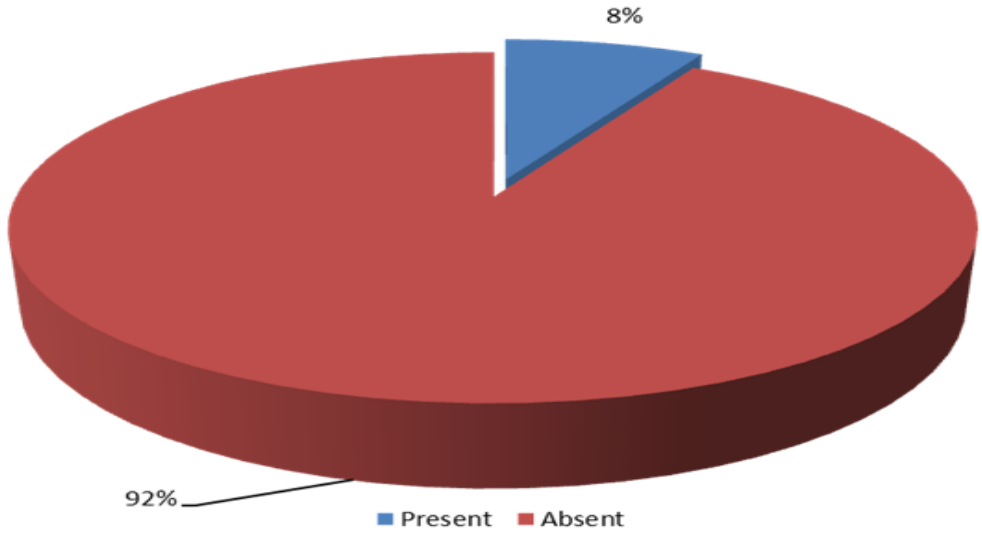


Table IX: Distribution of Cases According To Hiv Status.

HIV	NUMBER OF PATIENTS	PERCENTAGE
Positive	1	2%
Negative	49	98%
Total	50	100%

Table 9 shows that, out of 50 patients, 1 (2%) was diagnosed cases of HIV/AIDS. Rest all i.e. 49 (98%) were HIV negative.

Table IX: Distribution of Cases According To Hiv Status.

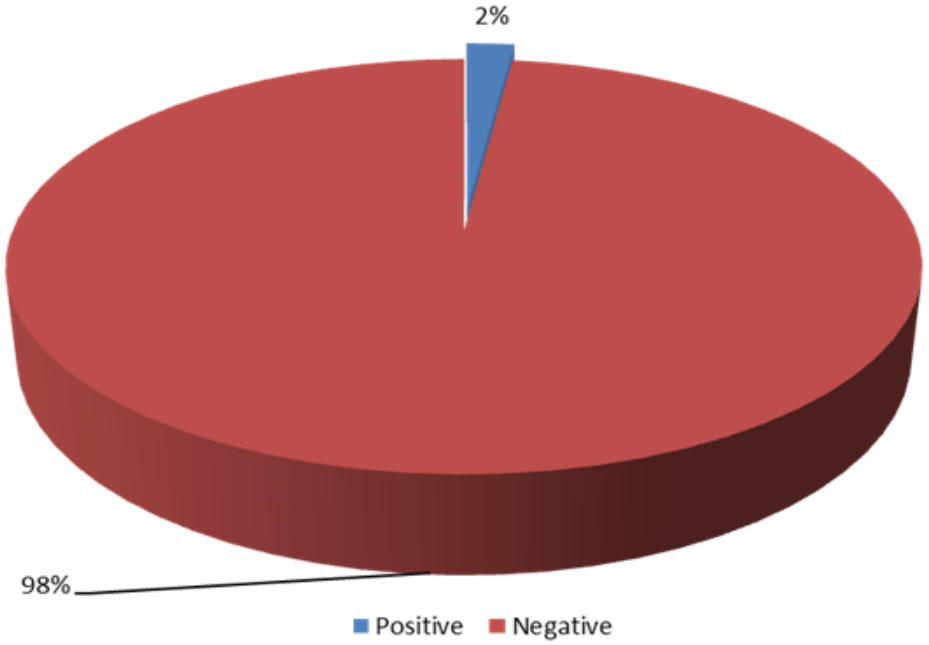


Table X: Other Comorbidities – Wise Distribution of Cases.

COMORBIDITIES	NUMBER OF PATIENTS	PERCENTAGE
COPD	3	6%
Depression	2	4%
Epilepsy	1	2%
Hypertension	2	4%
Hypothyriodism	1	2%
No comorbidities	41	82%
Total	50	100%

Among comorbidities other than diabetes and HIV, most common comorbid condition was COPD present in 3 (6%) which was smoking related, followed by Hypertension in 2 (4%) of cases. Depression in 2 (4%), Epilepsy in 1 (2%), hypothyroidism in 1 (2%).

Table X: Other Comorbidities – Wise Distribution of Cases.

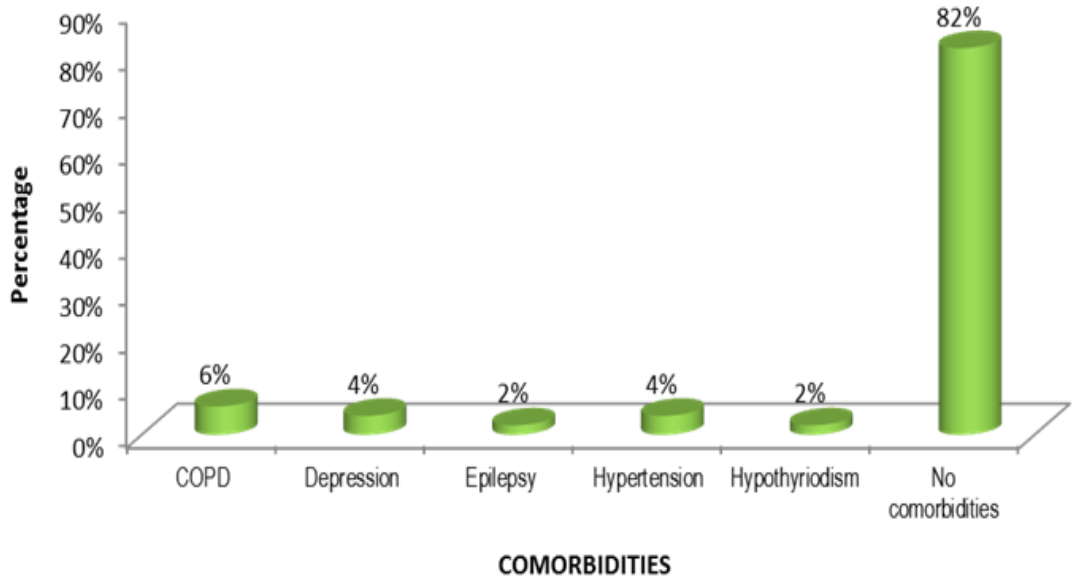


Table XI: Type of Addiction – Wise Distribution of Cases.

DRUG ADDICTION	NUMBER OF PATIENTS	PERCENTAGE
Smoking	10	20%
Alcohol	12	24%
Tobacco	2	4%
Others	2	4%
No Addiction	24	48%

As seen from above, the most common addiction was alcoholism, present in 12 (24%) of study subjects, followed by smoking which was present in 10 (20%) of the cases. 2 (4%) of the cases were having other types of drug addiction and 24 (48%) of study subjects were not having any drug addiction.

Table XI: Type of Addiction – Wise Distribution of Cases.

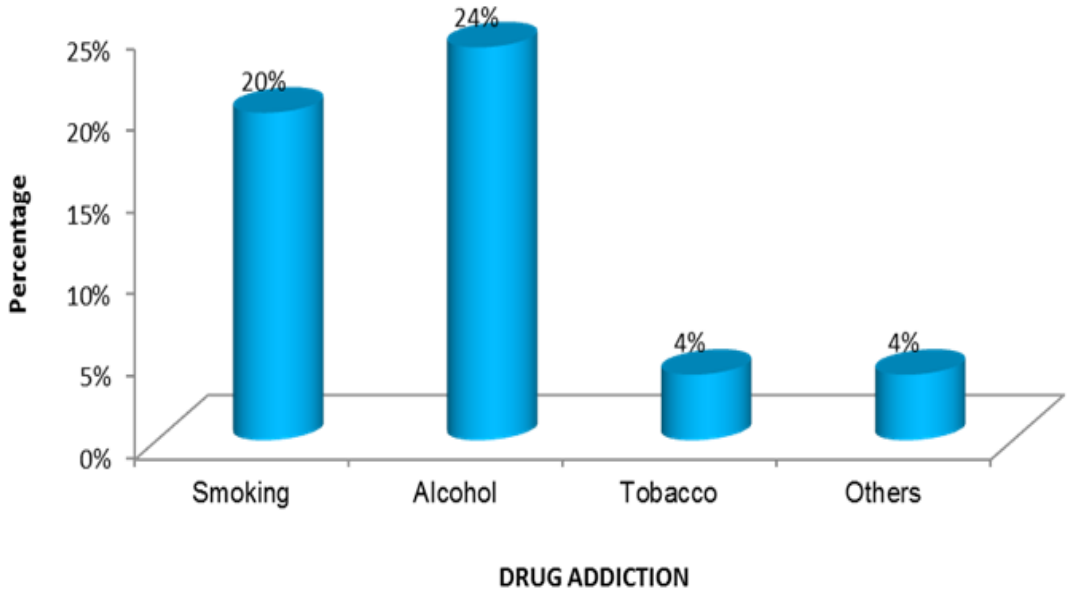


Table XII: Previous History of Att- Wise Distribution of Cases.

PREVIOUS H/O ATT	NUMBER OF PATIENTS	PERCENTAGE
Previous history of ATT	44	88%
New Cases	6	12%
Total	50	100%

Above table shows that out of 50 study subjects, 44(88%) patients were having previous history of ATT, 6 (12%) patients were not having any previous history of ATT. Previously treated cases included patients with recurrent TB (12%) and loss to follow up (10%).

Table XII: Previous History of Att- Wise Distribution of Cases.

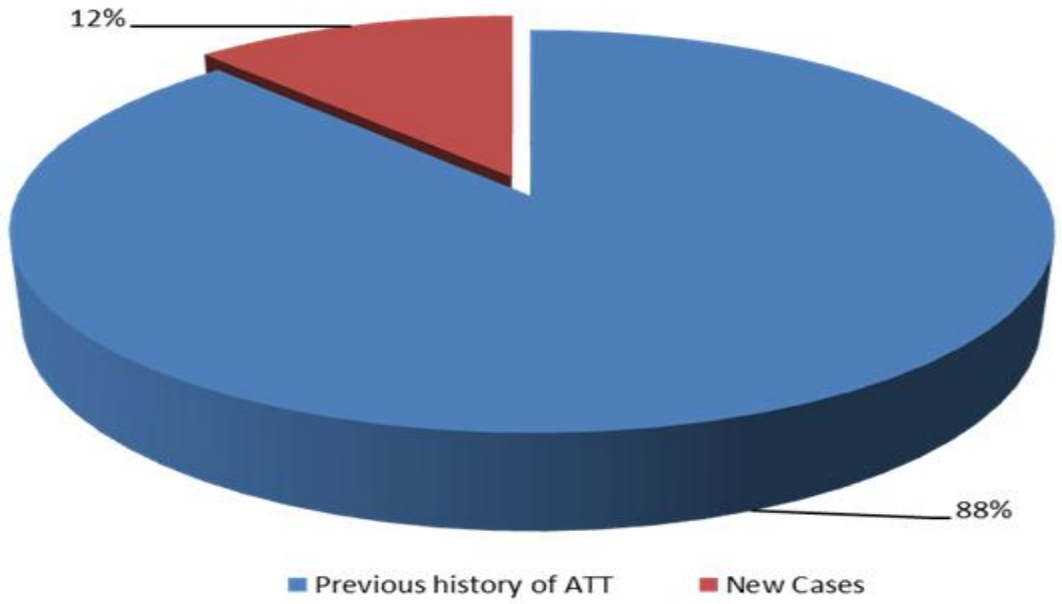


Table XIII: History of Contact- Wise Distribution of Cases.

HISTORY OF CONTACT	NUMBER OF PATIENTS	PERCENTAGE
Present	15	30%
- Pulmonary TB	12	24%
- MDR TB	3	6%
Absent	35	70%
Total	50	100%

Above table shows that out of 50 cases, history of contact was present in 15 (30%) patients. Among these 15 patients history of contact with pulmonary TB case was present in 12 (24%) of patients and contact history with MDR-TB case was present in 3(6%) of the study subjects. 35 (70%) of cases were not having any history of contact with TB case.

Table XIII: History of Contact- Wise Distribution of Cases.

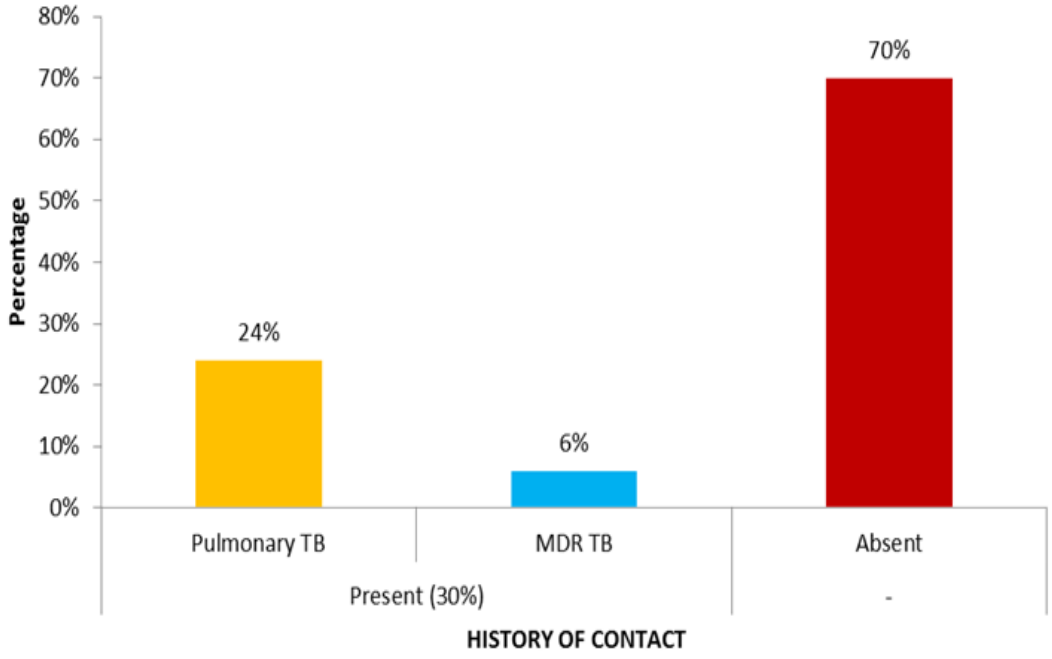


Table XIV: Clinical Signs- Wise Distribution of Cases.

SIGNS	NUMBER OF PATIENTS	PERCENTAGE
Pallor	44	88%
Clubbing	2	4%
Lymphadenopathy	3	6%

Most of the patients taken in the study were having more than one sign. Pallor, lymphadenopathy and clubbing were present in 44 (88%), 3 (6%),2 (4%) of the patients respectively.

Table XIV: Clinical Signs- Wise Distribution of Cases.

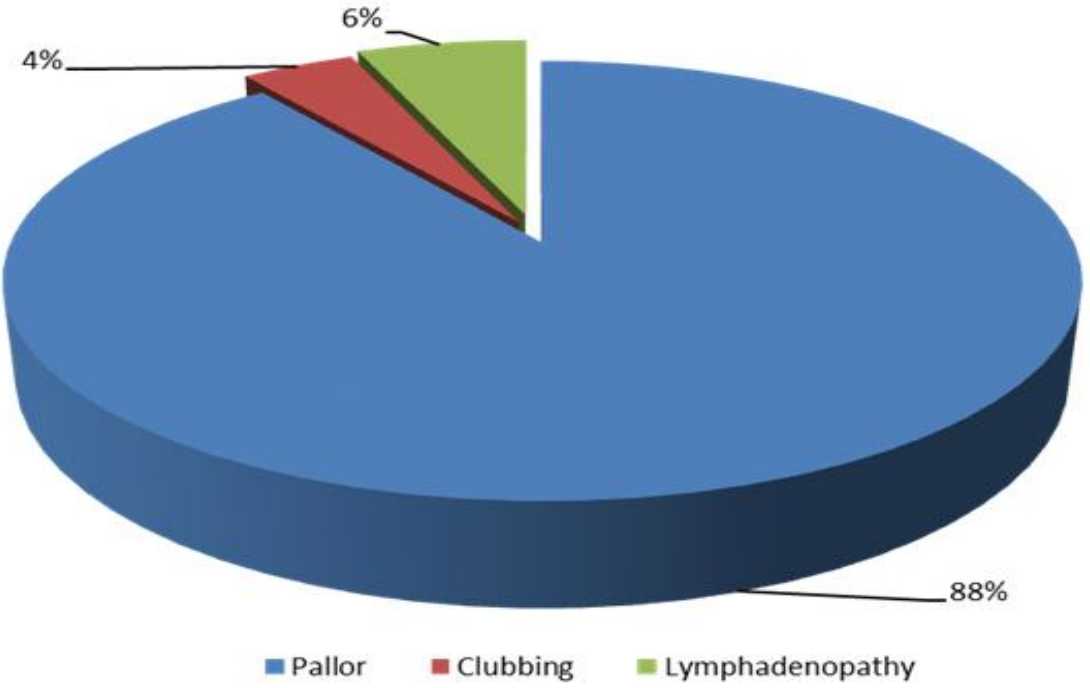


Table XV: Radiological Features –Wise Distribution of Cases.

RADIOLOGICAL FINDING	NUMBER OF PATIENTS	PERCENTAGE
Unilateral Disease	16	32%
Bilateral Disease	28	56%
Parenchymal Infiltration	26	52%
Cavitation	8	16%
Fibro Cavitary	11	22%
Fibrosis	13	26%
Pleural Effusion	1	2%
Pneumothorax	0	0%

In most of the patients taken in the study more than one finding was present in chest x-ray. Above table shows that unilateral disease was present in 16 (32%) patients, bilateral disease present in 28 (56%) patients. Parenchymal infiltration was present in 26 (52%) patients. Cavitation was present in 8 (16%), Fibrocavitary disease was present in 11 (22%) study subjects. On the other hand fibrosis was present in 13 (26%) study subjects. 1 (2%) patient was having pulmonary as well as extra-pulmonary involvement i.e. pleural effusion was present. Pneumothorax was not seen in any of the study subject.

Table XV: Radiological Features –Wise Distribution of Cases.

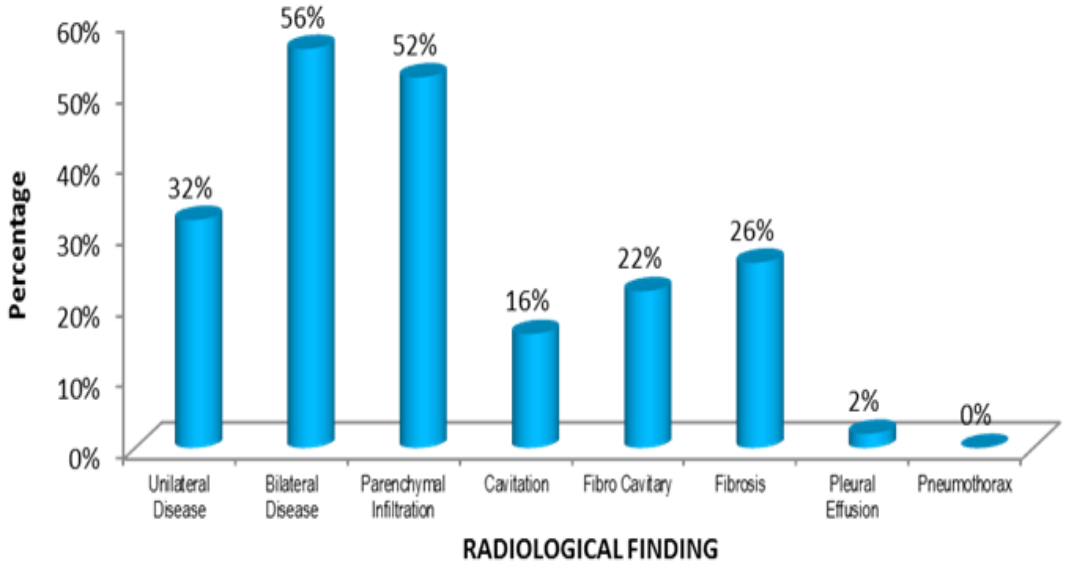


Table XVI: Extent of Lesion –Wise Distribution of Cases.

EXTENT OF LESIONS	NUMBER OF PATIENTS	PERCENTAGE
Minimal Disease	8	16%
Moderately Advance	25	50%
Far Advanced	17	34%

Above table shows that, among 50 study subjects, 8 (16%) patients were having minimal disease. 25 (50%) and 17 (34%) patients were having moderate and far advanced disease respectively.

Table XVI: Extent of Lesion –Wise Distribution of Cases.

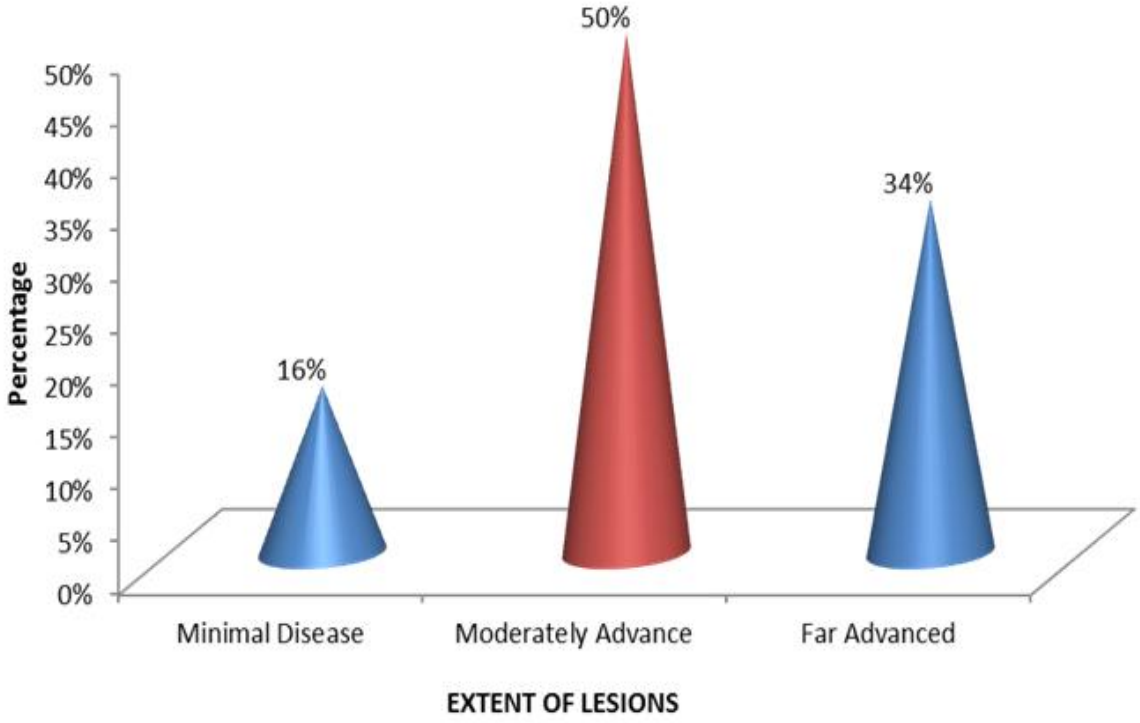
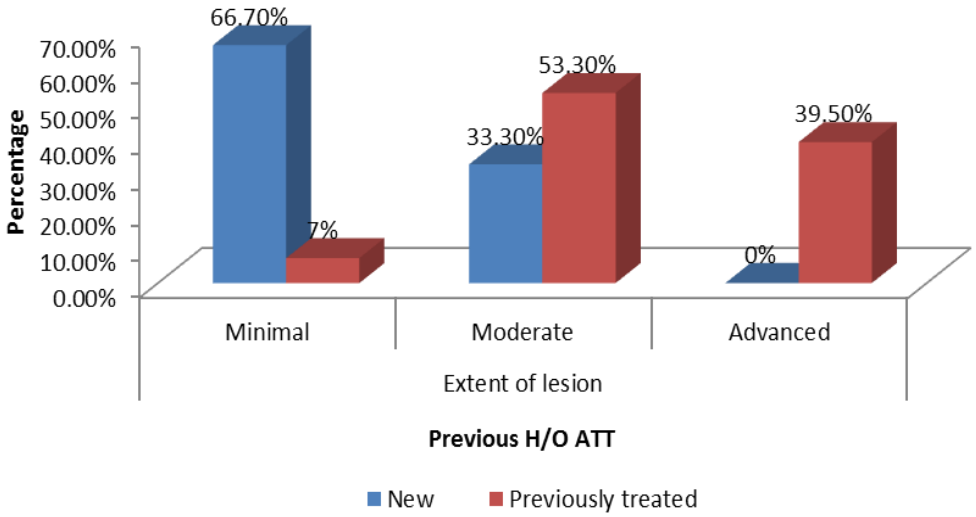


Table XVII: Association of Previous History of Att With Extent of Lesion.

Previous H/O ATT	Extent of lesion			Total
	Minimal	Moderate	Advanced	$\chi^2 = 15.923$ df = 2, 'p' <0.001**
New	4(66.7%)	2(33.3%)	-	
Previously treated	3(7%)	23(53.3%)	17(39.5%)	

**p<0.001; Highly significant

Table XVII: Association of Previous History of Att With Extent of Lesion.



From above table it is evident that previous history of ATT had significant association with extent of lesion on chest x-ray ($p < 0.001$).

DISCUSSION

Drug resistant TB has been known from the time Anti-TB drugs were first introduced for the treatment of TB. The problem of DR-TB cannot be addressed completely by standalone systems for detection and treatment of drug resistance. Strong system to detect, successfully treat and ensure long- term disease free status of TB patients, are required to prevent emergence of resistance. In clinical settings, an inadequate or poorly administered treatment regimen allows drug resistant mutants to become the dominant strain in a patient infected with TB. Therefore, clinico-radiological characteristics should always be recognized where appropriately administered drugs have not achieved necessary drug levels to deal with all the population of mycobacteria.

The present study was conducted in the Department of Tuberculosis and Chest Diseases to evaluate the clinical and radiological findings of Isoniazid mono Resistant Tuberculosis patients.

This prospective study included 50 diagnosed patients of Isoniazid Resistant Tuberculosis who were detected Isoniazid resistant through molecular methods i.e. LPA. We evaluated clinico-radiological profile of these patients.

In our study as shown in table 1, out of 50 patients taken out of study, the maximum number of patients belonged to the age group of 21-30 years i.e. 50% followed by 16% in the age group of <20 years. Minimum patients were in age group >60 years i.e. 4%. Mean age was 31.6 years. The youngest patient was 16 year old and the oldest patient was 65 year in age.

According to a study in U.S the highest proportions of isoniazid- mono resistant cases (43.0%) and drug-susceptible TB cases (36.9%) occurred in individuals between the ages of 25 and 44 years. Asian/Pacific Islander (Asian/PI) persons represented the highest proportion of isoniazid-mono resistant cases (33.0%). Demographic characteristics significantly associated with isoniazid mono resistance were age, race/ethnicity, and country of origin.[58]

According to RNTCP status report 2011, TB primarily affects people in their most productive years of life. Almost 70% of TB patients are aged between the ages of 15-54 years of age and more than 50% of the female cases occur before 34 years of age. This is almost in accordance with our data where majority of the patients are in 21-30 years of age.[70] Udwadia and Moharil, Sharma et al; also reported prevalence of younger age group with the mean age of their study groups being 29.7 years and 33.25 years respectively.[71] Malnutrition since childhood leading to weakened immune response, made the younger population more susceptible to DR-TB in developing countries. High level of drug resistance

among younger patients may be due to more exposure to drug-resistant cases.

A study done by Rasaki et al; to determine Isoniazid Resistant Tuberculosis in a Secondary Health Institution in Nigeria, reported that minimum age of the patients was 18years, while the maximum was 83. The mean age was 38.39± 13.75. There was male preponderance 84(60%), compared to 56(40%) female.[72]

In our study also maximum patients were males (66%), while females contributed (34%) of patients. This may be due to our male dominating society. In which males have more access to health facilities as compared to female. Moreover, males are more prone to DR-TB because of their social contacts, exposure to dust, smoking, and consumption of alcohol. Many international studies have presented risk factors for isoniazid resistant TB. These include previous history of TB treatment poor adherence to TB treatment regimens, younger age (15–40 years), alcohol use, smoking, male sex, diabetes, TB contact, and occupation. In addition to these factors, some studies have associated isoniazid mono-resistant TB (HR-TB) with history of imprisonment, and unemployment.[78]

In our study majority of patient belonged to urban area i.e. 54% and 46% patient belonged to rural areas. Study by Kliiman et al.; (2003-05), shows that 61.7% patients were from urban areas and 38.3% patients were from rural areas.[73] Among urban population narrow living spaces, poorly ventilated houses, overcrowding and unhealthy food habits could be cause of tuberculosis.

In our study most of the patients 30 (60%) were married; 20 (40%) were un-married. Similar results were reported by Mishra et al; out of 244 patients majority of the patients (92.2%) were married; only (7.8%) were unmarried.[54]

In our study most of the patients were labourers (40%), followed by students (24%), housewives (20%), farmers (6%), and unemployed (6%). Labourers belong to lower socioeconomic status and as we know tuberculosis affects especially those from lower socioeconomic background. Study done by Mishra et al; reported that among 244, most of the patients were Farmers (n=60, 24.6%), followed by manual labourers (n=42, 17.2%), 16 patients (6.6%) were drivers, 7 patients (2.9%) were professional, 38 (15.6%) were house wives, and 14 patients (5.7%) were students.[54] Study by Poulomi Mukherjee reported that, majority of patients were household workers (27.90%) and labourers (20.34%) followed by skilled workers (18.60%), students (10.46%), business men (9.30%), unemployed (6.97%) and service men (6.39%).[60] In the multivariable analysis of isoniazid mono-resistant individuals, the best prediction model consisted of illicit drug use, prior imprisonment, alcoholism, socioeconomic status, and type of transportation.[66]

Poverty could be a major predisposing factor, ranging in them from poor overall hygiene, poor living conditions, poor nutrition and immune status. Furthermore, treatment interruptions or defaults were found to be more common among poor families due to job seeking, travelling expenses, loss of work days due to travel for drug, are among other reasons. Propensity of simple tuberculosis developing into Isoniazid mono resistant tuberculosis could have a strong association with poverty. Illiteracy affects patient's knowledge about tuberculosis and its treatment.

In our study out of 50 cases, 42(84%) patients were Kat G Isoniazid mono resistant and 8 (16%) were Inh A-isoniazid resistant cases in this study. Our results show that isoniazid monoresistant pulmonary tuberculosis is on rise and that the prevalence of Kat G is greater than Inh A gene. Line probe assay (LPA) has been developed for the rapid detection of M. tuberculosis complex and its resistance to rifampicin (RIF) and isoniazid (INH). The assay detects mutations in the rpoB gene for RIF resistance, the katG gene for high-level INH resistance, and the inhA gene for low-level INH resistance from smear-positive or culture-positive sputum sample.[74] However, 70–80% of INH resistance is associated with mutations in codon 315 of the katG gene.[75]

Among 50 patients taken in the study, most common symptom was cough with expectoration present in 96% of cases followed by fever in 66%. Weight loss in 54% and loss of appetite in 52% of patients. Breathlessness was present in 44% and hemoptysis in 4% of cases. Majority of patients who were taken in the study had more than one symptom for more than one month. This is probably because patients may have come to medical college in late part of their illness.

Among 50 cases, 8% patients were diabetic, 92% were non- diabetic. Majority of diabetic patients had raised blood sugar level. This may be due to the fact that most of the diabetic patients were not taking any diabetic medicine or were on irregular medication. Diabetes is a one of the important risk factor for active tuberculosis. In our study diabetes mellitus was most common comorbidity. Among comorbidities other than diabetes, most common comorbid condition was COPD present in 6% which was smoking related, followed by Hypertension in 4% of cases. Depression in 4%, Hypothyroidism in 2%. Some of the patients in the study were having more than one comorbidity. Many international studies have presented risk factors for isoniazid resistant TB. These include previous history of TB treatment poor adherence to TB treatment regimens, younger age (15–40 years), alcohol use, smoking, male sex, diabetes, TB contact, and occupation. In addition to these factors, some studies have associated isoniazid mono-resistant TB (HR-TB) with history of imprisonment, and unemployment.[78]

Study done by More et al; reported that, out of 96 patients, 27 (28.13%) patients had a self-reported comorbidity which included 6 (29.62%) patients with diabetes mellitus and 2 (7.40%) patients with diabetes mellitus and hypertension, 3 (14.81%) patients who were HIV positive and 1 (3.70) had HIV with anemia, 1 (3.70%) patient was suffering from hypothyroidism and one patient had hypothyroidism with hypertension and one each had piles, meningitis, ischemic heart disease, and fibroadenoma of breast.[65]

Study done by Poulomi Mukherjee reported that Chronic obstructive pulmonary disease (COPD) was the commonest comorbidity (17.44%) among the study group followed by Diabetes Mellitus (15.69%) and hypertension (2.32%). Five patients (2.90%) were HIV positive though HIV status was not checked in 15(8.72%) cases.[60]

In our study, out of 50 patients, 2% were diagnosed cases of HIV/AIDS. Rest all i.e. 98% were HIV negative. There was a lack of association between isoniazid mono resistance and HIV status in most of the studies done on isoniazid mono resistance. Although rifampin resistance may result from inadequate TB treatment due to drug interactions between certain antiretroviral drugs and rifampin, the same mechanism of interaction does not occur with isoniazid.[58]

Datta et al; reported 1.9% HIV seropositivity among MDR -TB cases,[76] Tuberculosis is the commonest opportunistic disease in HIV positive persons in India. Intravenous drug abuse in HIV positive patients leads to non-adherence to treatment of TB, drug malabsorption especially of rifampicin and ethambutol, and repeated hospital admissions can lead to drug resistance and has been shown to cause treatment failure. The factors found to be associated with a higher risk of unsuccessful treatment outcome in INH mono-resistant TB –higher age, male sex, positive microscopy, positive HIV status– have been described before as associated with unsuccessful TB treatment outcome independent of drug resistance status.[26,27]

Most common drug addiction in our study was alcoholism, present in 24% of study subjects, followed by smoking in 20% of the cases. 4% of the cases were having other types of drug addiction and 48% of study subjects were not having any drug addiction. In the multivariable analysis of isoniazid mono-resistant individuals, the best prediction model consisted of illicit drug use, prior imprisonment, alcoholism, socioeconomic status, and type of transportation.[66]

Study conducted by More et al; reported that out of 96 patients, 9 (33.33%) patients who reported substance abuse, 5 (55.55%) reported alcohol consumption, 1 (11.11%) tobacco use, and 3 (33.34%) both tobacco and alcohol use. Study done by Mishra et al; reported that smoking was commonest drug addiction followed by alcohol. Out of 244 patients, 110 (45.08%) patients were smokers, 61 (25.0%) patients were alcoholic, 31 (12.7%) patients were tobacco chewer, 4 (1.64%) patients were opium abusers.[54]

Alcoholism or drug addiction may contribute to the default behavior and negligence towards anti-tuberculosis medication, leads to impaired immune responses and increases the risk of adverse drug effects and therefore may have a negative impact on treatment outcome for tuberculosis and can lead to drug resistance.

In our study, out of 50 study subjects, 44 (88%) patients were having previous history of ATT, 6 (12%) patients were not having any previous history of ATT. Previously treated cases included patients with recurrent TB (12%) and loss to follow up (10%). As evident from table 17 previous history of ATT had significant relation ($p < 0.001$) with extent of lesion on chest x-ray. Isoniazid monoresistance was significantly associated with a history of TB and with residence in a correctional facility according to a study done in U.S.[58] A study conducted among patients with isoniazid-resistant TB in Germany also identified younger age and a history of TB treatment as risk factors for isoniazid resistance.

Study done by Sudhakar W. more reported out of 86 cases, majority of the patients with drug-resistant TB had acquired drug resistance, i.e., 66 (68.75%).[65] Previous history of ATT is a strong risk factor for emergence of drug resistance, reason could be non-compliance or non-adherence to treatment, repeated hospitalizations which leads to exposure to drug resistant strains, use of anti-TB drugs as monotherapy, addition of one anti-TB drug to failing regimen, intolerance to drugs or adverse effects leading on to default behaviour may lead to emergence of drug resistance. Prior inadequate anti-TB treatment only suppresses the growth of susceptible bacilli and does not affect other resistant strains, leading to suitable conditions for the dominant multiplication of pre-existing drug resistant mutants, which is a rise and fall phenomenon. The proportion of new patients with drug-resistant TB in a population-based survey or surveillance is used as a measure of transmission of drug-resistant TB in a community. However, patients may not remember whether they have been previously treated with anti-TB drugs, or may not know that they were treated for TB.[14]

Globally, about 8% of TB cases presenting for care have Hr-TB, being higher in retreatment cases than in new TB cases (14% and 7% respectively according to most recent WHO estimates). Current epidemiological data indicates that more than three fourths of global burden of Hr-TB cases occurs among previously untreated (“new”) cases. INH-resistance, alone or in combination with other drugs, is now the second most common type of resistance worldwide with current estimates at 10.3% for new cases and 27.7% for previously treated cases (13.3% combined)[35] which is similar to our study.

In our study history of contact was present in 30% patients. Among 30% patients, 24% and 6% of cases had history of contact with pulmonary TB and DR-TB patients respectively. 70% of cases had no history of contact with TB patients. Study by Mulu et al; to determine risk factors for drug resistant tuberculosis patients in Amhara National Regional State, Ethiopia reported that out of 153 cases, 44 (28.8%) had history of contact with MDR- TB patients.[77] These findings were similar to our study. History of contact with DR-TB case raise the suspicion of primary resistance. Obtaining a detailed contact history is essential as a delay in starting appropriate DR treatment has potentially serious consequences.

In our study most of the patients taken were having more than one finding on chest x-ray. 16 (32%) and 28 (56%) patients were having unilateral and bilateral disease respectively. Parenchymal infiltration was present in 26 (52%) patients. Cavitation, fibrocavitary and fibrosis, pleural effusion was present in 8 (16%), 11(22%), 13 (26%), 1 (2%) respectively. Among 50 study subjects 8 (16%), 25(50%) and 17 (34%) patients were having minimal, moderate and far advanced disease. Mishra et al; reported similar findings, out of 244 patients, 224 (91.8%) patients had bilateral lung involvement, whereas 20 (8.2%) patients had unilateral lung involvement, along with it, 209 (85.7%) patients had cavitatory lung disease and 35 (14.3%) patients had non cavitatory lung disease. Of these patients, 130 (58.04%) had bilateral far advanced disease, 89 (39.7%) patients had bilateral moderately advanced disease and 5 (2.2%) patients had bilateral minimal lung disease. Of patients having unilateral lung involvement, 4 (20.0%) patients had unilateral far advanced disease, 6 (30.0%) patients had unilateral moderately advanced disease and 10 (50.0%) patients had unilateral minimal lung disease.[54]

This research is believed to contribute to identifying the potential risk factors for Isoniazid mono resistance, so that the management of patients will also be strengthened through preventing these factors, alongside patient treatment which will have a positive impact on successful treatment outcome, and decrease the burden of the disease as a whole. IMR (Isoniazid mono resistance) is a key driver of emergent resistance in the high burden, low resource setting, due to which MDR TB arises. Isoniazid testing is not routinely performed and inadequate treatment for unrecognised IMR is therefore common. In the setting of under diagnosis IMR –TB may be properly considered pre MDR-TB, and it is unsurprising that evolutionary studies have identified IMR as a precursor to further drug resistance. Therefore, it is particularly important to identify the risk factors associated with Isoniazid mono resistance TB. As expected, a history of TB was associated with IMR, presumably because patients were exposed to isoniazid during their previous TB episodes. This suggest need for more detailed examination of persons who have undergone prior treatment of TB. Because Isoniazid continues to have prominent role in treatment regimens for TB disease and for LTBI, it is essential to understand what factors may be contributing to Isoniazid mono resistance so that more informed treatment decision can be made when evaluating these patients.

This study provides an updated and detailed profile of Isoniazid mono resistance and examine demographic and patient characteristics associated with IMR.

SUMMARY AND CONCLUSION

The present study was carried out in the Department of Tuberculosis and Chest Disease, Government Medical College, Amritsar to evaluate the clinico-radiological profile of Isoniazid mono resistant tuberculosis patients. After taking informed consent, detailed history and clinical, radiological and examination was done. Various facts of the study are:-

- There were total of 50 confirmed cases of Isoniazid mono resistant tuberculosis.
- Maximum patients were in the most productive years of the life. The age of the patients was in the range of 15-65 years but majority of the patients (50%) were in the age group of 21-30 years
- There was an overall male preponderance in the study with 66% being males, 34% being females.
- Most of the patients (54%) were from urban areas.
- Most of the patients were married (60%).
- Out of 50 cases most of the patients were Labourers (40%), students (24%), and housewives (10%).
- Cough with expectoration (96%), fever (66%) and weight loss (54%) were the three most common presenting complaints of the patients which brought the patients to our hospital.
- Out of 100 patients, 4 were diabetic and 46 were non diabetic. Diabetes was commonest comorbidity.
- HIV positive patients in our study was 1 and rest were HIV negative.
- Among other comorbidities COPD (6%), hypertension (4%), followed by depression (4%) after diabetes COPD was commonest comorbidity.
- Out of 50 patients, 12 patients were alcoholic, 10 were smoker, 24 patients were not having any history of addiction.
- All the female patients didn't have history of any type of addiction.
- Majority of the patients (88%) were having previous history of ATT intake. Among these, 12% and 10% patients were of recurrent TB and loss to follow up. 12% of the patients were not having any prior history of ATT. Previous history of ATT had significant relation with extent of lesion ($p < 0.001$).
- 30% of patients were having history of contact with TB case. And among these, 24% and 6% of patients were having history of contact with pulmonary TB case and MDR-TB case respectively.
- Majority of the patients were having pallor (88%), followed by lymphadenopathy (3%) and clubbing (2%).
- Majority of the patients were having bilateral disease (56%). Parenchymal infiltrate, cavitation, fibrocavitary

disease, fibrosis, pleural effusion was present in 26 (52%), 8 (16%), 11 (22%), 13(26%) and 1 (2%) respectively. Majority of the patients were having cavitary disease and parenchymal infiltration.

• Out of 50 patients, 8 (16%), 25 (50%) and 17 (34%) were having Minimal, Moderate and far advanced disease respectively.

To maintain the usefulness of this important anti TB agent, it is necessary to understand the characteristics of patients with Isoniazid mono resistance TB. Nearly 90% of INH resistance in India is caused by KatG mutations, associated with high level resistance and poor treatment outcomes; the development of INH resistance precedes the development of MDR TB. Initial INH resistance increases incidence rates of treatment failure and relapse compared with pan sensitive strains (incidence rate ratio 10.9 and 1.8, respectively). Data from the most recent National workshop on DST guided treatment in India reveals poor treatment success rates for INH mono resistant TB, ranging from 31% to 53%. Studies will need to define clinical risk factors for INH mono resistance, perform universal DST to allow detection of INH resistance in all cases, and conduct prospective trials to determine optimal treatment regimens for patients with INH mono resistance. The year 2020 might bring some hope, as the Xpert MTB/XDR cartridge is expected to be released and will include resistance testing for INH, fluoroquinolones, and second line injectables.

Isoniazid mono resistant tuberculosis is a cause of great concern around the world. Not only does the emergence of Isoniazid mono resistant signal that control strategies are failing; it itself could become an obstacle to effective anti-tuberculosis treatment. So clinico-radiological characteristics should always be determined where appropriately administered drugs have not achieved necessary drug levels to deal with all the population of mycobacteria, to timely modify and strengthen the national programs, and evaluation of trends in drug resistance pattern. Therefore early detection of drug resistance among re-treatment cases is required. So studies will need to define clinical risk factors for INH mono resitance, perform universal DST to allow detection of INH resistance in all cases, and conduct prospective trials to determine optimal treatment regimens for patients with INH mono resistance.

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