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PROSPECTIVE ASSESSMENT OF CHRONIC HEPATITIS B INFECTION AND CHRONIC HEPATITIS C INFECTION AS A RISK FACTOR IN ANTI-TUBERCULAR DRUGS INDUCED LIVER INJURY PATIENTS IN A TERTIARY HEALTH CARE HOSPITAL AT DEHRADUN, UTTARAKHAND (INDIA)

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ABSTRACT

Background: Anti-tubercular drug-induced liver injury (ATDILI) is a major safety concern for the treatment of tuberculosis (TB). The impact of chronic hepatitis B infection (CHBI) and chronic hepatitis C infection (CHCI) on the risk of ATDILI is still controversial. In this study, we aimed to assess systematically the influence of CHBI, CHCI on the susceptibility to ATDILI patients. Aims and objectives: To study of the Chronic Hepatitis B infection and Chronic Hepatitis C infection as a risk factor in anti-tubercular drug-induced liver injury: A Prospective observational study. Materials and method: Prospectively, we identified 24 cases of ATDILI among 172 patients diagnosed with confirmed pulmonary tuberculosis between July 2018 to December 2018. None of the patients with established risk factor as ATDILI as recognized by ATS guidelines was included in our study population. Regular clinical and liver function test monitoring was done at the commencement of ATT. Results: Among these, 02 (8.3%) patients had hepatitis B virus (HBV) and 02 (8.3%) patients had hepatitis C virus (HCV), out of 24 ATDILI patients. Among the ATDILI cases, 03 patients had grade-1 DILI, 06 patients had grade-2 DILI, and 14 patients had grade-3 DILI, and 01 patients had grade-4 of the DILI cases fulfilled the ATS/BTS criteria for TB DILI. There were no human immunodeficiency virus (HIV) co-infected patients. Among the total 24 patients are developed the ATT induce hepatotoxicity. Among the total 24 patients anti tubercular drug induce hepatotoxicity cases, female patients 14 (8.13%) account for the highest number of risks ATDILI. Conclusion: This study suggests that CHBI, CHCI may increase the risk of ATDILI in the standard combination therapy for active TB. In patients of pulmonary tuberculosis drug induced hepatitis is common. However viral marker should be considered to rule out hepatitis B and hepatitis C. Close follow-up and regular liver test monitoring, viral marker is mandatory to treat TB in chronic hepatitis B and C carriers. DILI is a common problem among patients on ATT in our population. Early detection not only reduces the risk of developing Hepatic Failure but also prevents mortality rate.

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INTRODUCTION

Tuberculosis has remained a major health problem in the world. Mycobacterium tuberculosis infects almost one-third of the world's population (around two billion persons), more so in developing countries. Even in developed countries, there is a resurgence of TB. The reasons are twofold. First, there is an increase in the immunocompromised population secondary to the pandemic of the human immunodeficiency virus (HIV) infection and increased rate of organ transplantation. Second, increased trans global migration and travel have led to an easy spread of the organism. Throughout the world, nine million new cases of TB are diagnosed; of which 1.7 million persons succumb to the disease annually. Life-time cumulative risk for active TB is more than 10%. The highest incidence and mortality rates of HIV are seen in Africa, whereas, the highest incidence and mortality rates of TB are seen in southeast Asia. Standard anti-tubercular drugs, including isoniazid (INH), rifampicin (RFP), ethambutol (EMB), and pyrazinamide (PZA) are highly effective in treating TB. However, drug induced liver injury (DILI) associated with anti-TB treatment is the most important adverse event, which results in a low treatment success rate[1]. The incidence of DILI during standard anti-TB treatment ranges from 2 % to 28 % [2,3,4]. Once DILI occurs, all anti-TB drugs should be withheld until a complete resolution of the hepatotoxicity is accomplished[5,6,7]. Advanced age, female gender, alcohol abuse, malnutrition, and underlying chronic liver disease have been reported to be significant risk factors for DILI during anti- TB treatment [8,9,10]. However, it remains unclear whether the incidence of DILI increases during anti-tubercular treatment in patients with chronic viral hepatitis (CVH). In a previous study, persistent liver dysfunction was shown to be more common in hepatitis B virus (HBV) infected patients[11]. In addition, several recent studies have suggested that HCV infections are also a significant risk factor for incident DILI during anti-tubercular therapy treatment. However, in still other studies, the incidence of transient liver dysfunction during anti-tubercular therapy was found to be higher in HBV or HCV infection[12,13,14].

The World Health Organization (WHO) estimates approximately 240 million people worldwide are chronically infected with hepatitis B virus (HBV). Areas of high prevalence are similar to the global TB epidemiological where the prevalence is estimated to be between 8 and 20%. The WHO estimate 3% of the World's population are infected with hepatitis C virus (HCV), with 170 million being chronic carriers. United Kingdom patients infected with TB are offered human immunodeficiency virus (HIV) screening due to an increased prevalence of co-infection, but viral hepatitis screening is not routinely offered and might be of value if the background prevalence of viral hepatitis is significant in patients with TB infection. Tuberculosis (TB) and hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are common in developing countries of south-east Asia, including India. Anti-tuberculosis therapy (ATT) can be hepatotoxic in around 10% of the patients, which may be a management issue that is difficult in the presence of already compromised liver functions due to HBV, HCV. Infectious diseases including TB, HBV, HCV and others are the most common causes of mortality (41%) in India. Adverse drug reactions are the sixth most common cause of death in hospitalized patients. Therefore, co-infection of TB and HBV, HCV is an important public health issue[15,16,17].

ANALYSIS OF ATT-HEPATOTOXICITY IN HBV AND HCV PATIENTS

Data on HBV and HCV as a risk factor for ATT induced hepatotoxicity

Studies looking into risk factors for ATT induced hepatotoxicity, which found HBV and HCV to be a risk factor, are summarizes this study on Chronic Hepatitis B infection and Chronic Hepatitis C infection is a risk factor for anti-tuberculosis drug-induced liver injury who developed hepatotoxicity during anti-tubercular drugs therapy. A major problem in defining ATT induced hepatotoxicity (defined on the basis of altered ALT or symptoms), which also result in altered ALT, AST and or symptoms. Most studies agree that hepatitis B and C co-infection causes more severe hepatitis due to anti-tuberculosis treatment. Difference in severe hepatotoxicity between the preventive therapy for PTBI and curative treatment for TB might reflect a difference in the intake of alcohol, immunogenetic differences in the development of ATT induced hepatotoxicity, and different backgrounds (HIV, hepatitis B and hepatitis C virus infections)[18,19].

MANAGEMENT OF ATT-INDUCED DILI

Possible regimens include[20]:

Two hepatotoxic drugs regimen (rather than the three in the standard regimen):

- 9 months of isoniazid and rifampicin, plus ethambutol
- 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin;
- 6–9 months of rifampicin, pyrazinamide and ethambutol.

One hepatotoxic drug regimen:

- 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.

No hepatotoxic drug regimen: In patients with advanced cirrhosis or portosystemic encephalopathy

- 18–24 months treatment with a combination of ethambutol, fluoroquinolone, cycloserine and capreomycin or aminoglycoside has been suggested as an option.

Patient Education

Patients should be educated about the importance of adherence to medications, follow up visits for monitoring and symptoms of hepatotoxicity with appropriate reminders wherever possible. In the event of symptoms that are attributable to hepatotoxicity, patients should be forewarned to stop all anti-TB medications and seek medical advice in the event of any symptoms of hepatotoxicity and seek immediate medical advice.

Monitoring

Regular clinical review of patients is helpful to monitor treatment adherence and directly observed short-course therapy (DOTS) enhances its effectiveness. Therapeutic drug monitoring has been shown to improve clinical response, but its use in predicting hepatotoxicity remains to be demonstrated. Within the first few weeks of initiation of anti-TB therapy, up to 20% of patients develop transient, asymptomatic elevations in ALT and as these spontaneously resolve these are thought to represent 'adaptation' rather than hepatotoxicity. The ATS guidelines do not recommend routine liver biochemistry testing in those without any obvious risk factors; but, liver biochemistry-based monitoring should be considered at 2 weekly intervals in the first 2–3 months of therapy in patients with risk factors for developing hepatotoxicity and in those who have abnormal baseline tests[21].

AIM AND OBJECTIVES

Aim: To assess Chronic Hepatitis B and Chronic Hepatitis C infection as a risk factor in anti-tuberculosis drug-induced liver injury: A Prospective observational study at tertiary care hospital Dehradun, Uttarakhand, INDIA.

Objectives: The main objectives of the proposed study include:

❖To assess the demographic status of patients.
❖To assess the anti-tubercular therapy, induced hepatitis.
❖To assess the Chronic Hepatitis B and Chronic Hepatitis C infection as a risk factor in anti-tubercular drug-induced liver injury.

METHODOLOGY

STUDY DESIGN:

Prospective observational study conducted in pulmonary medicine isolation department at Shri Mahant Indiresh Hospital, Dehradun, Uttarakhand, India after obtaining approval of the Institutional Ethics Committee (IEC).

STUDY DURATION:

Study duration was 6 months.

STUDY CRITERIA:

Inclusion Criteria:

- Patient admitted to pulmonary medicine isolation ward.
- Patients of either gender.
- Patients aged 18 years and above.
- Patients with abnormal baseline liver function tests.
- Subject who gave consent to participate in the study.

Exclusion criteria:

- Patients below 18 years of age.
- Patients with extrapulmonary tuberculosis.

SOURCE OF DATA

- Patients data from pulmonary isolation ward.
- Data should be collected during ward round participation.
- Patient counselling should be done during ward round participation.
- Patient's records and laboratory data records.

PROCEDURE

The Study was conducted on 172 smear positive pulmonary tuberculosis patients in Pulmonary Isolation Ward at Shri Mahant Indiresh Hospital, Dehradun from 1 July 2018 to 31 December 2018. In this study Hepatitis B surface antigen (HBsAg) and Hepatitis C viruses are positive in ATDILI patients, registered in the pulmonary isolation ward. All patients had marked in baseline liver function tests, serological markers for HBV, HCV infection. Data collected for demographic profile, patient medical medication history, family history, social history, present illness, current medication, laboratory investigation parameters was noted in the designed format of data collection. Serum bilirubin, SGOT and SGPT, Alkaline phosphatase and serum proteins were estimated regularly.

STATISTICAL ANALYSIS:

The data entry and analysis were done by using Statistical Graphical presentation.

RESULTS AND DISCUSSION

DEMOGRAPHIC STATUS:

The Study was conducted on 172 smear positive pulmonary tuberculosis patients in Pulmonary Isolation Ward at Shri Mahant Indiresh Hospital, Dehradun. All subjects under the inclusion and exclusion criteria were included as the study population analyzed and evaluate to get the accurate results.

Distribution of study sample according to sex

Demographic data 172 TB patients taking anti-TB drugs were involved in this study. Among them, 70 (40.6%) were males and 102 (59.3%) were female.

Table 1.1 Gender wise distribution of patients.

S No.	Gender (M/F)	No. Of Patients (%)
1.	Male	70 (40.6%)
2.	Female	102 (59.3%)
Total		**172 (100%)**

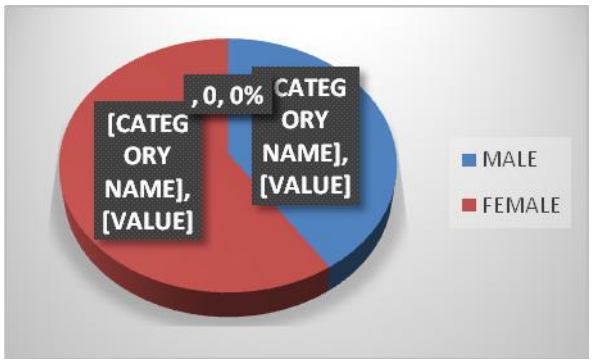

Figure 1.1Representing the gender wise distribution of the patients.

Patients distribution: Rural vs Urban Areas

According to this study out of 172 patients, 62 (36.04%) were rural and 110 (63.95%) were urbans areas.

Table 1.2 Patients distribution: Rural vs Urban Areas.

S No.	Patient Status	Frequency	Percentage (%)
1.	Rural	62	36.04%
2.	Urban	110	63.95%
Total		**172**	**100%**

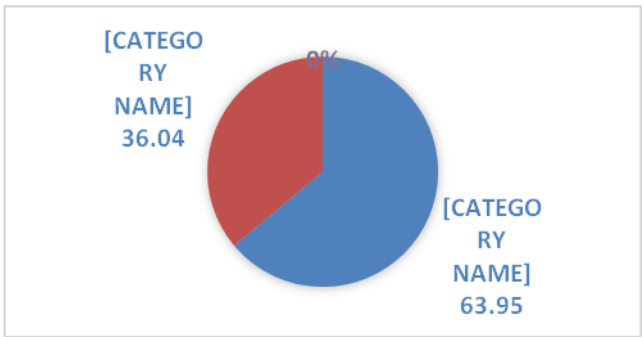

Figure 1.2 Distribution of patients on basis of Rural vs Urban Areas.

Age wise distribution of patients

Out of 172 patients, 14.53% patients were in age group of 18-36 years, 49.41% patients were in age group of 37-54 years, 26.16% patients were in age group of 55-72 years, 9.88% patients were in age group of 73 above years, shown in table 5.3 and figure 5.3.

Table 1.3 Age wise distribution of patients.

S No.	Age (Year)	No. Of Patients	Percentage (%)
1.	18-36	25	14.53%
2.	37-54	85	49.41%
3.	55-72	45	26.16%
4.	>73	17	9.88%
Total		**172**	**100%**

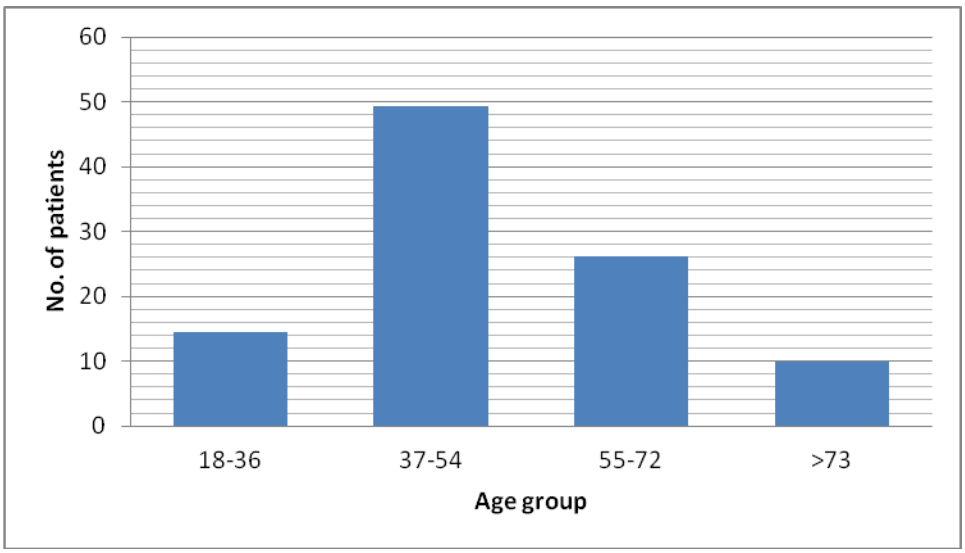

Figure 1.3 Representing the age wise distribution of patients.

Distribution of study sample according to Alcohol

According to this study out of 172 patients, 60 (85.71%) male patients were alcoholic and 05 (4.90%) female patients were non-alcoholic.

S. No.	Gender	No. Of Patients	No. Of Patients Taking Alcohol
1.	MALE	70	60(85.71%)
2.	FEMALE	102	05 (4.90%)
Total		**172**	**65 (37.79%)**

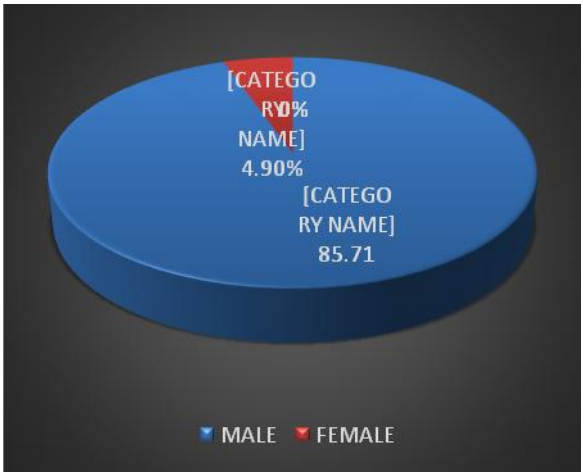

Figure 1.4 Distribution of study sample according to Alcohol.

Distribution of study sample according to Smoker

According to this study out of 172 patients, 60 (85.71%) male patients were smoker and 10 (9.80%) female patients were non-smoker.

S. No.	Gender	No. of Patients	No. of Patients Taking Smoker
1.	MALE	70	60 (85.71%)
2.	FEMALE	102	10 (9.80%)
Total		**172**	**70 (40.69%)**

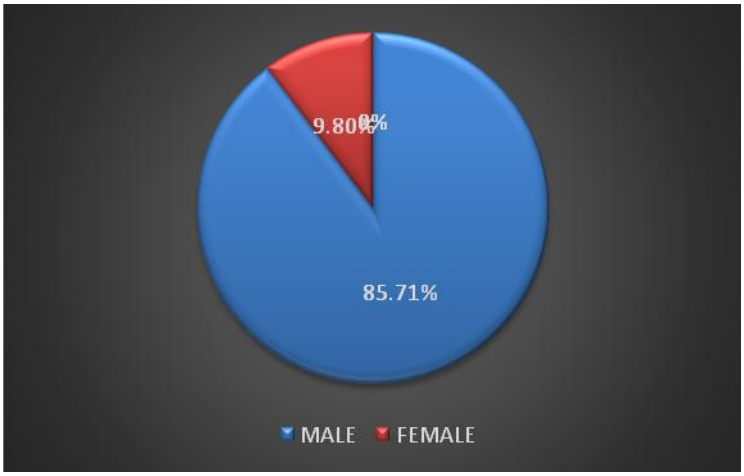

Figure 1.5 Distribution of study sample according to Alcohol.

ASSESSMENT THE ANTITUBERCULAR THERAPY INDUCED HEPATITIS

We identified 24 cases of DILI among 172 patients diagnosed with confirmed or presumed TB between July 2018 and December 2018. Among the DILI cases, 03 had grade-1 DILI, 06 had grade-2 DILI, and 14 had grade-3 DILI, and 01 had grade-4 of the DILI cases fulfilled the ATS/BTS criteria for TB DILI.

Table 2.1 Clinical Laboratory Data and Hepatotoxicity of Study Patients.
(According to WHO Guideline)

S .no	Variable	Grade (I, II, III, IV)	Patient with ATT Induced Hepatotoxicity (DIH), (n=24)	No. of Male Patients	No. of Female Patients	Percentage (%)
1.	ALT>2.5 times (51-125 I/U)	GRADE-I (MILD)	03	01	02	12.5%
2.	ALT>2.5-5 times (126-250 I/U)	GRADE-II (MILD)	06	03	03	25.0%
3.	ALT>5-10 times (250-500 I/U)	GRADE-III (MODERATE)	14	06	8	58.33%
4.	ALT>10 times (>500 I/U)	GRADE-IV (SEVERE)	01	00	01	4.16%
TOTAL			24 (13.95%)	10 (5.81%)	14 (8.13%)	100%

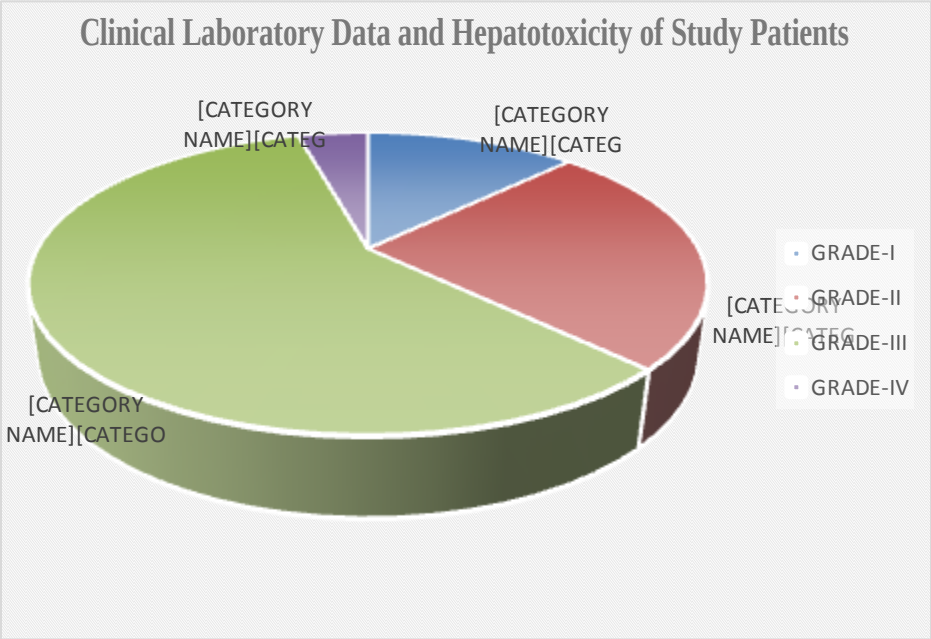

Figure 2.1 Clinical Laboratory Data and Hepatotoxicity of Study Patients.

STUDY TO DEFINED HBSAG / HCV AS A RISK FACTOR FOR ATDILI

Among this study, 02 (8.3%) patients had hepatitis B virus (HBV) and 02 (8.3%) patients had hepatitis C virus (HCV), out of 24 DILI patients. There were no human immunodeficiency virus (HIV) co-infected patients. Among the total 24 (13.95%) patients anti tubercular drug induces hepatotoxicity cases, female patients 14 (8.13%) account for the highest number of ATDILI risk in this study.

Months	Total no. of patients (N=172)	No. of patients developed hepatotoxicity (n=24)	Viral characteristic (viral marker)
July 2018	28	05	HCV (1)
August 2018	29	04	HBsAg (1)
September 2018	33	05	-
October 2018	27	06	HBsAg (1)
November 2018	26	01	-
December 2018	29	02	HCV (1)
Total	172	24 (13.95%)	HCV 02 (8.3%) HBsAg 02 (8.3%)

CONCLUSION

- HCV infection and HBV infection were associated with anti-tubercular drug induced liver injury.
- This study suggests that CHBI, CHCI may increase the risk of ATDILI in the standard combination therapy for active TB.
- In patients of pulmonary tubercular drugs induced hepatitis is common. However viral marker should be considered to rule out hepatitis B and hepatitis C.
- Close follow-up and regular liver function test monitoring, viral marker is mandatory to treat TB in chronic hepatitis B and C carriers.
- DILI is a common problem among patients on ATT in our population.
- Early detection not only reduces the risk of developing Hepatic Failure but also prevents mortality rate.

ABBREVIATIONS

TB : Tuberculosis;
TLI : Transient liver function impairment,
DIH , drug induced hepatitis;
HBV : Hepatitis B virus;
HCV : Hepatitis C virus;
LFT : Liver function test;
BMI : Body mass index;
HR : Hazards ratio;
CI : Confidence interval;
CVH : Chronic viral hepatitis.

COMPETING INTEREST

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

Dr. Rohit Bangwal, Dr. Jagdish Rawat and Dr. Dev Singh Jangpani participated in the study design and concept, performed the statistical analysis and participated in data interpretation, and participated in manuscript writing & data collection. Dr. Jagdish Rawat performed the statistical analysis and participated in data interpretation. All authors read and approved the final manuscript.

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