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STUDY OF PREDICTIVE FACTORS OF ANTI TUBERCULOSIS TREATMENT INDUCED HEPATOTOXICITY

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ABSTRACT
Tuberculosis is one of the commonest diseases prevalent in developing countries despite the availability of various chemotherapeutic agents for treatment. Combination chemotherapy is the basic mode of treatment, which may lead to various adverse effect of which hepatoxicity is one the commonest one. In this study we try to find the incidence of hepatoxicity and its predictors in all patients having tuberculosis and under anti tuberculosis treatment. Out of the 162 patients enrolled in our study, 34 patients (20.98%) developed drug induced hepatitis according to International Union against Tuberculosis and Lung Disease diagnostic criteria used for diagnosis of ATT induced hepatitis. Commonest clinical presentation of those developed drug induced hepatitis was Jaundice followed by anorexia, vomiting and nausea. In the study it is seen that low BMI, excess alcohol consumption and smoking is associated with ATT induced hepatitis. Identifying poor predictors and modifying the treatment regime prior the treatment of TB may decrease the chances of ATT induced hepatitis.

KEYWORDS: ATT, Hepatitis, Combination chemotherapy.

INTRODUCTION
Tuberculosis is one of the commonest public health problems leading enormous burden of suffering and deaths in Nepal. According to the National tuberculosis center the burden of TB in Nepal is as follows.

- 45% of total population are infected with TB
- 40,000 people get TB every year
- 20,000 new sputum positive cases every year
- 5000-7000 people die each year from TB.

Various chemotherapeutic agents like rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin used in the treatment of TB are highly effective but also hepatoxic, of which the regimen containing isoniazid, rifampicin and pyrazinamide[1-3] is the commonest one. Asymptomatic transaminase elevations are common during anti-tuberculosis treatment, but hepatotoxicity can be fatal when not recognized early and when therapy is not interrupted in time. Drug-induced liver injury (DILI) is diagnosis of exclusion. Other causes like acute viral hepatitis, chronic liver disease should be ruled out. Usually, the time of onset to acute injury is within months of initiating a drug. Confirmation of diagnosis is by rechallenge with the offending agent leading to more than twofold serum alanine aminotransferase (ALT) elevation, and discontinuation leading to a fall in ALT.[4] DILI accounts for 7% of reported drug adverse effects, 2% of jaundice in hospitals, and approximately 30% of fulminant liver failure.[5,6] DILI may result from direct toxicity of the primary compound, metabolite, or from an immunologically mediated response. The risk of TB DILI in different study ranges from 5 to 33%. Various factors are associated with risk of developing ATT induced hepatitis like increasing age, female sex, low BMI, hypo-albuminemia, consumption of alcohol. Presence of HIV, Hepatitis B and Hepatitis C are also risk for hepatotoxicity.

Because of large burden of TB and easily available ATT under DOTS for its treatment, but of the lack of sufficient studies to know the incidence of ATT induced hepatoxicity and predictors of poor outcome this study was conducted.

METHODS
This was prospective Observational hospital based study conducted in medicine ward, Department Of Internal Medicine BPKIHS, Dharan, Nepal. Study was conducted over a period of 1 year from 15th january 2012. All newly diagnosed patients with pulmonary or extra-pulmonary tuberculosis under anti-tuberculosis treatment as per DOTS were included in the study. Hundred sixty two

(162) patients of tuberculosis under anti-tuberculosis treatment were enrolled in the study for a period of one year from 15th january 2012. This sample size was taken based upon published literature to conduct such studies for convenience and practicality. Verbal and informed written consent was taken from all. ATT induced hepatitis was diagnosed according to International Union against Tuberculosis and Lung Disease as follows: Presence of at least one of the following:

- A rise of more than twice upper normal level ALT(35 IU/L) and/or AST(40 IU/L).
- Rise in total serum bilirubin more than 1.5 mg/dl.
- Any increase in AST and/or ALT above pretreatment levels together with symptoms like anorexia, nausea, vomiting, and jaundice.

Patient were followed up on 2 weeks,4 weeks,8 weeks or at any time with symptoms with liver function test report. During the follow up once the patient met one of the above criteria, patient was labeled as having drug induced hepatitis and were managed further on the basis of standard treatment protocol. Patients not giving consent, having active hepatitis, and chronic liver disease where modified drugs were used were not included in the study. A detailed socio-demographic data for every patient was collected and the information was recorded in structured proforma.

RESULTS

Socio demographic profile of 162 patients included in the study has been illustrated in **Table 1**.Mean age was 41.80 years and maximum patients were of age group less than 40 years having 52.5 percent. Male were predominant 66% and maximum patients had BMI between (18.5-24.9kg/m^2). Maximum numbers of patients were non-smoker and non-alcoholic as shown in table 1.

Table 1: Socio demographic characteristics of all tuberculosis patients attended to BPKIHS

Characteristics	Categories	Total Numbers	Percentage
Age in Years	<40	85	52.5
	40-60	49	30.2
	>60	28	17.3
Gender	Male	107	66.0
	Female	55	34.0
BMI(KG/M2)	<18.5	46	28.4
	18.5-24.9	109	67.3
	≥25	7	4.3
Alcohol in Grams	None	107	66.1
	≤40	33	20.3
	>40	22	13.6
Smoking IN Pack Year	None	105	64.8
	≤20	49	30.3
	>20	8	4.9

BMI-Body Mass Index

Table: 2 shows the past medical and treatment history of patients where HIV (8%) and tuberculosiss (7.4%) are the commonest one.

Table 2 Past medical and treatment history

Past medical history and co-morbidities	Categories	Number of patients	Percentage
Tuberculosis	Absent	150	92.6
	Present	12	7.4
Diabetes	Absent	154	95.1
	Present	8	4.9
Hypertension	Absent	156	96.3
	Present	6	3.7
Drugs	Absent	151	93.2
	Present	11	6.8
HBSAg	Present	1	0.6
	Absent	161	99.4
HCV	Present	2	1.2
	Absent	160	98.8
HIV	Present	13	8.0
	Absent	149	92.0

HIV-Human Immunodeficiency Virus, HCV-Hepatitis C, HBsAg- Hepatitis B surface antigen

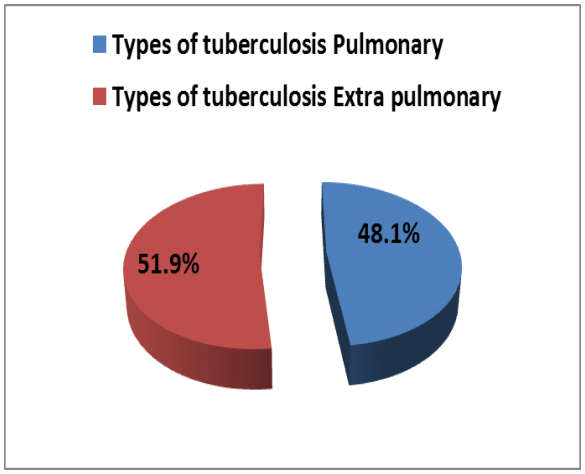

FIGURE: 1

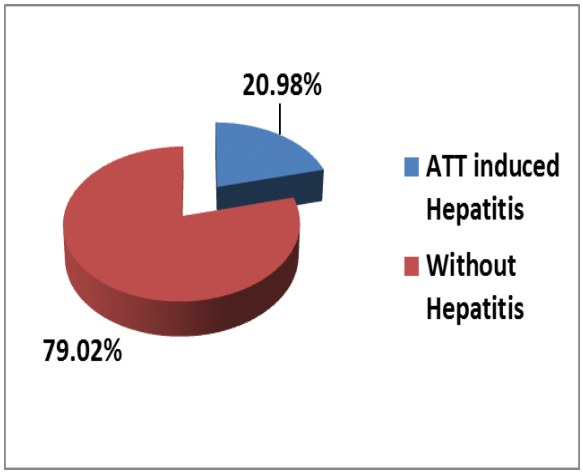

Figure-3

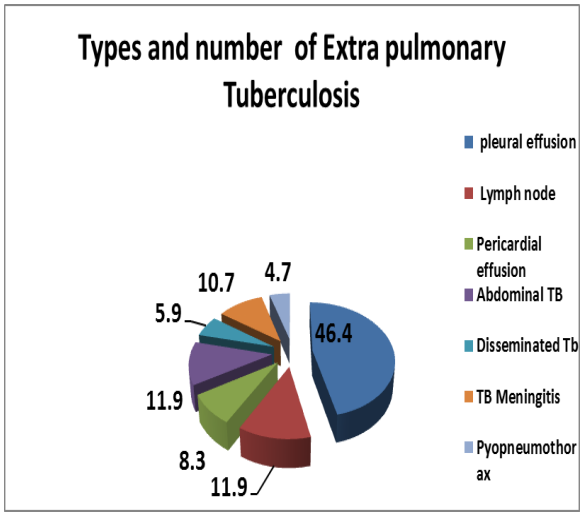

Figure: 2

Among the treated patients, predominant was extra-pulmonary (51.9%) with pleural effusion (46.4%) the commonest one followed by Abdominal TB (11.9%) and TB lymph node (11.9%) as shown in figure 1 and figure 2.

Figure 3 shows 20.98% of patients developed ATT induced hepatitis after the treatment of Tuberculosis. Among the patients who developed ATT induced hepatitis, Jaundice was the common clinical presentation.as shown in figure 4.

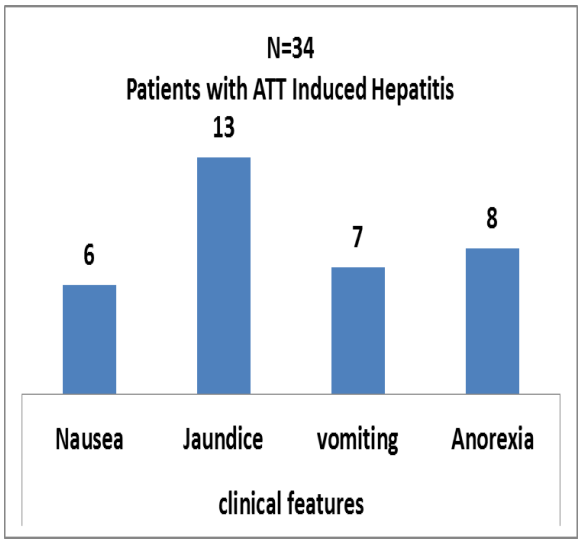

Figure-4

Table: 3 Baseline Investigations

Investigations	Number
Hemoglobin(mg/dl)	10.6±1.65
Total Protein(gm/dl)	6.61±0.94
Albumin(gm/dl)	3.42±0.69
AST(IU/L)	38.17±16.72
ALT(IU/L)	37.61±15.26
Total Bilirubin(mg/dl)	0.675±0.227

Note-All values in Table are Mean± SD

Table 4: Socio- demographic characteristics of all tuberculosis patients attended to BPKIHS with or without ATT induced Hepatitis

Characteristics	Categories	Hepatitis		p- value	Remarks
		Positive	Negative		
Mean age ± SD		44.44±19.05	41.09±16.88	0.319	NS
Gender	Male	23	84	0.825	NS
	Female	11	44		
BMI Status	<18.5	19	27	<0.001	Sig

	18-24.9	15	94		
	≥25	0	7		
Alcohol Intake	Absent	16	91	0.009	Sig
	Present	18	37		
Smoking	Absent	22	83	0.988	NS
	Present	12	45		

Note-BMI-Body Mass Index, SD-Standard Deviation, Sig-significant, NS-non-significant

Table 4 shows Body Mass index and excess alcohol consumption is significantly associated with ATT induced hepatitis whereas age, sex and smoking are not associated with ATT induced hepatitis.

In this study Mean± SD serum albumin in hepatitis group was 3.18±0.76gm/dl and in non-hepatitis group was 3.48± 0.66gm/dl which shows significant difference between two groups and was significant with P-0.025

DISCUSSION

The incidence of Anti-Tuberculosis treatment induced hepatoxicity varies worldwide and is higher in developing countries where factors like chronic liver disease, indiscriminate use of drugs, malnutrition and more advanced Tuberculosis are common.[1,7,8] The incidence of ATT induced hepatoxicity is 20.98% in our study which is similar to reports from Asia (8-19.8%)[9,10,11] and higher from west where the incidence is 4.3%.[12] One of the study from Nepal showed that the incidence of Anti-Tuberculosis treatment induce hepatoxicity was 8%.[13] The variation in incidence of hepatitis may be related to difference in patient's characteristics, different regimens used, different monitoring system and different Diagnostic criteria defining hepatoxicity.[14] In one of the study from Nepal by Shakey et al the incidence of ATT induced hepatitis was only 8% contrast to 20.98% in our study and the difference was probably due to the difference in diagnostic criteria as elevation of five times or more of ALT and/or AST had been included in the diagnostic criteria.

Age

Increasing age is potential risk factor for anti-Tuberculosis treatment induced hepatotoxicity[9,10,15,16-19] in different study.one of the study reported that rate of anti-TB-DIH ranges from 2-8% as the age increases with average of 5%.[19] Also Mahmood et al[20] reported that older age group was affected more than younger age group 25.8% and 14.4% respectively. In contrast, Shakey et al[21] reported that incidence of anti-TB-DIH is higher in younger patients and might be due to enrollment of patients of younger age group. In this study though the result was not statistically significant,similar to study of Shakey et al. Patients having anti-TB-DIH were of age group less than 40 years.

Sex

Different study showed that females are at increased risk of ATT induced hepatoxicity in comparison to males.[15,16,22,23] However the difference was not treatment limiting and not statistically significant.[22,23] Mahmood et al[20] reported higher incidence in females than males(26.3% vs 19.7%). The higher vulnerability of females could be due to variations in pharmacokinetics and slower acetylation pattern[24] and/or lower Body Mass Index of female.

Malnutrition

The state of nutrition is assessed by Body Mass Index and serum albumin level .BMI less than 18.5 and serum albumin less than 3.5 is considered as state of malnutrition in our study. It showed that malnutrition is strong predictor of ATT induced hepatoxicity which is similar to various other studies [21,25,20,19,26-28].The reason for malnutrition and hepatitis might be due to depletion of glutathione stores which makes patient more vulnerable to oxidative injuries and slower the pace at which the liver metabolize the drug.

Types of Tuberculosis

In a study by Singla et al. a disproportionately higher risk of developing drug induced hepatotoxicity in patients with extrapulmonary tuberculosis and most of them had abdominal tuberculosis probably these patients might have sub-clinical hepatic involvement which predisposed to anti-TB-DIH. Anand et al[29] also reported similar findings. In our study also Hepatitis was more in EPTB group though the result was not significant.

Hepatitis B carrier

Various previous study showed that anti-TB-DIH was associated with Hepatitis B carrier status[30,31,32] which was different from our study because of small number of cases.

Hepatitis C carrier

One study with 128 patients in Florida showed approximately 30% of hepatitis C infected individuals developed anti-TB-DIH compared to 11% among uninfected and hepatitis C was independent risk factor for hepatotoxicity.[33] But this study didn't show Increase risk of anti-TB-DIH in hepatitis C carrier probably the reason was due to presence of few Hepatitis C cases.

Human Immunodeficiency Virus

As in one of the study which showed HIV and viral hepatitis infection increase the risk of anti-TB-DIH 3-5 times.[34] But this study didn't show the increase risk of anti-TB-DIH in patient with HIV infection probably due to few cases of HIV infected patients.

ALCOHOL CONSUMPTION

Our study also showed strong association between alcohol consumption and ATT induced hepatitis like many other study.

SUMMARY AND CONCLUSION

Anti-tuberculosis treatment induced hepatoxicity is not uncommon manifestations with 20.98% of patients developed ATT induced hepatotoxicity in our study which was similar to the incidence in many developing countries. Among various factors, low BMI, significant alcohol and low albumin are associated with ATT induced hepatoxicity.

Close follow up, early recognition, and immediate withdrawal of the causative agents are essential to prevent progression.

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CONFLICT OF INTEREST

Conflicts of interest declared none.

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