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# Anti-tuberculosis, Drug-induced Hepatitis in Patients of Pulmonary Tuberculosis with Chronic HCV

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## ABSTRACT

**OBJECTIVE:** To determine the frequency of anti-tuberculosis drug-induced hepatitis in patients of pulmonary tuberculosis co-infected with chronic HCV.

**METHODOLOGY**: This cross-sectional descriptive study was conducted at Liaquat University Hospital after taking permission from the ethical review committee. 124 patients, irrespective of gender, aged 20 or greater were selected through nonprobability convenience sampling, from December 2020 to February 2021. Patients of pulmonary tuberculosis (TB), who were sputum positive and co-infected with chronic Hepatitis C Virus HCV with normal Liver Function Test (LFT) were picked. Chronic HCV was evidenced by positive Anti HCV on ELISA. Alcoholics, HBsAG-positive patients, and persons with altered LFT before the start of Anti-tuberculosis treatment (ATT) were exempted from the study. If LFT after one week of treatment displayed a rise in bilirubin greater than 1.5 mg and or increase in Aspartate aminotransferase(AST) and Alanine aminotransferase (ALT) greater than 120 IU/L then patients were further followed and LFT repeated thrice on the 15$^{th}$ day of holding the ATT. Drug-induced hepatitis was labeled when LFT normalize after 2 weeks of withholding treatment. All this data was itemized on proforma and analyzed through SPSS 17 software.

**RESULTS:** Out of a total of 124 patients, 70 were male and 54 were female. Age varied from 20 to 60 years (mean age was 42.4 years) .37.9% of patients were more than 50 years of age. In this study, only 16.93% of patients developed ATT-induced hepatitis.

**CONCLUSION**: Anti-tuberculosis-induced liver enzymes elevation is a common incident in inpatients of pulmonary tuberculosis co-infected with chronic HCV.


**KEYWORDS:** Hepatitis C Virus, Liver Function Test, Ammonia tolerance test, Drug-induced hepatitis, Pulmonary Tuberculosis

## INTRODUCTION

Mycobacterium tuberculosis was recognized as an infective agent with high mortality for many centuries. Even in this modern world tuberculosis contributes a lot, causing fatalities[1]. It is one of the deadliest diseases caused by a single infective organism[2]. TB possesses a great financial and health burden for nations globally, as it is still affecting 9.27 million new cases annually worldwide[3]. Tuberculosis became the cause of death of over 2,000,000 people annually, universally[2]. Based on these facts WHO have declared tuberculosis as a global emergency[3]. Among the countries that bear the burden of tuberculosis, third world countries share the foremost portion[3]. Pakistan ranked 7$^{th}$ globally among countries 4 with the highest number of tuberculosis and has an incidence of 275 per 100,000 populations[3]. Apart from the disease burden itself anti- ATT induced side effects are also troublesome and are more marked over the liver, a challenge for treatment[2].

Many first-line drugs may lead to hepatic dysfunction but the occurrence varied from 1% to 31% [4]. One researcher observed damage caused by ATT to the liver, found in up to 19.67% of patients [2]. Frequency is different in various geographical areas but more common in underdeveloped countries[4].

Although ATT-induced hepatotoxicity is a well-known problem the situation becomes harder in countries like Pakistan where liver diseases, themselves are very common. One of the major, clinically relevant side effects of the treatment of TB is liver damage manifested as raised liver enzymes which may lead to discontinuation of the patient's treatment[3]. There is a lack of detailed information about anti-tuberculosis therapy effects on the liver particularly in the background of chronic liver diseases.

Pakistan has such a huge sum of HCV cases that it stands among one of the top afflicted countries.[5] In one study researchers noted that 22% of patients were co-infected with tuberculosis n HCV[5].

About the prevalence of HCV in patients with TB and the impact that the infection has on these patients, few studies have been conducted worldwide, and there is still little validation concerning this topic[4]. Among first-line drugs for the treatment of tuberculosis Isoniazid and rifampicin may generate harm to the liver by causing changes in the cell wall structure, reduced glutathione level, and activation of CYP2E18[2].

This study was conducted to evaluate the effect of ATT on the liver in patients with pulmonary tuberculosis, who also suffered from chronic HCV. This would assess whether treating pulmonary Kock's with a standard regime pose a significant danger in patients who are co-infected with chronic HCV or not. That would help in identifying patients who need a change in treatment. This issue has paramount value because HCV and pulmonary tuberculosis, co-infection cases are abundant.

## METHODOLOGY

This cross-sectional descriptive study was conducted at Liaquat University Hospital after taking permission from the ethical review committee, 124 patients of either gender, aged 20 or greater were selected through nonprobability convenience sampling, from December 2020 to February 2021. Patients of pulmonary tuberculosis, who were sputum for AFB positive and co-infected with chronic HCV with normal LFT were picked. Chronic HCV was evidenced by positive Anti HCV on ELISA. Alcoholics, HBsAg-positive patients, and persons with altered LFT before the start of ATT were exempted from the study. After informed consent clinical data was noted, the examination was performed and a chest X-ray posteroanterior (PA) view was obtained along with another routine blood test. LFT was assessed at baseline and then after one week of initiating treatment. Patients who showed a rise in bilirubin greater than 1.5 mg and or increase in ALT and or AST greater than 120 IU/L were further followed and LFT was repeated thrice, on the 15$^{th}$ day of holding the ATT. Drug-induced hepatitis was labeled when in this selected group LFT normalize after 2 weeks of withholding treatment. All this data was registered on proforma and analyzed through SPSS 17 software.

## RESULTS

In this study total of 124 patients were registered. Out of them, 70 were male and 54 were female. The age range varied from 20 to 60 years, with a mean age of 42.4 years. The majority of patients (37.9%) were belonged to the older age group i.e. more than 50 years of age, as shown in **Figure I**. Out of 124 patients, 14 patients were lost to follow-up while only 21 patients (16.93%) developed ATT-induced hepatitis as shown in **Figure II.** Levels of bilirubin, ALT and AST at the start of treatment, end of 1$^{st}$ week, and end of the third week were shown in **Table I**.

**TABLE I: RESULTS OF LFT AT BASELINE, AFTER ONE WEEK, AND AFTER THREE WEEK (n=21)**

| LFT | Mean±SD | Range |
|---|---|---|
| **At baseline** | | |
| Serum bilirubin(mg/dl) | 0.86 ±0.13 | 0.1 to 1.5 |
| AST(IU/L) | 22.0±3.0 | ≤ 40 |
| ALT(IU/L) | 18.0 ±2.19 | ≤ 40 |
| **After one week** (n=21) | | |
| Serum bilirubin(mg/dl) | 2.36±1.6 | >1.5 |
| AST(IU/L) | 528± 312 | >120 |
| ALT(IU/L) | 428±298 | >120 |
| **After three week** (n=21) | | |
| Serum bilirubin(mg/dl) | 1.38 0±.26 | 0.1 to 1.5 |
| AST(IU/L) | 38.17 ±10.30 | ≤ 40 |
| ALT(IU/L) | 35.91 ±11.43 | ≤ 40 |

**FIGURE I: FREQUENCY OF AGE IN GROUPS**

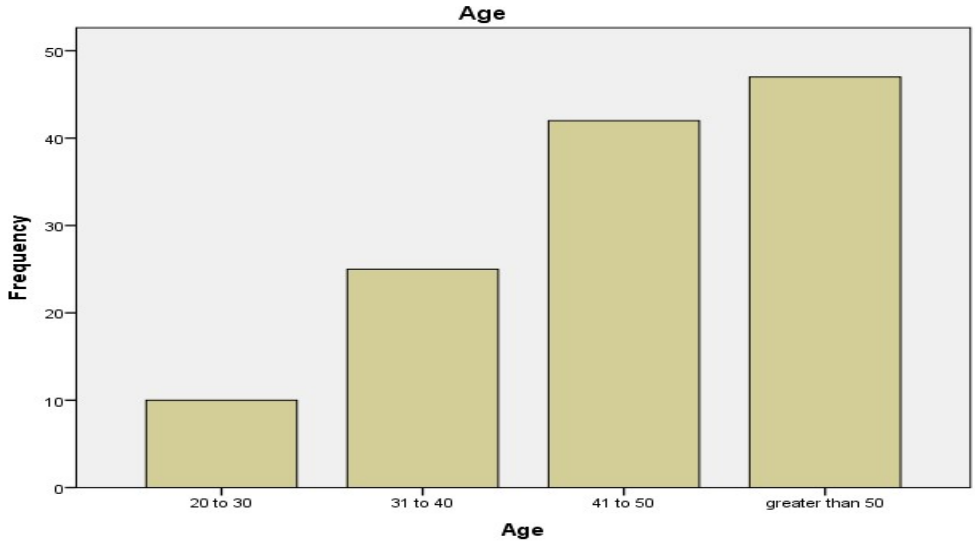
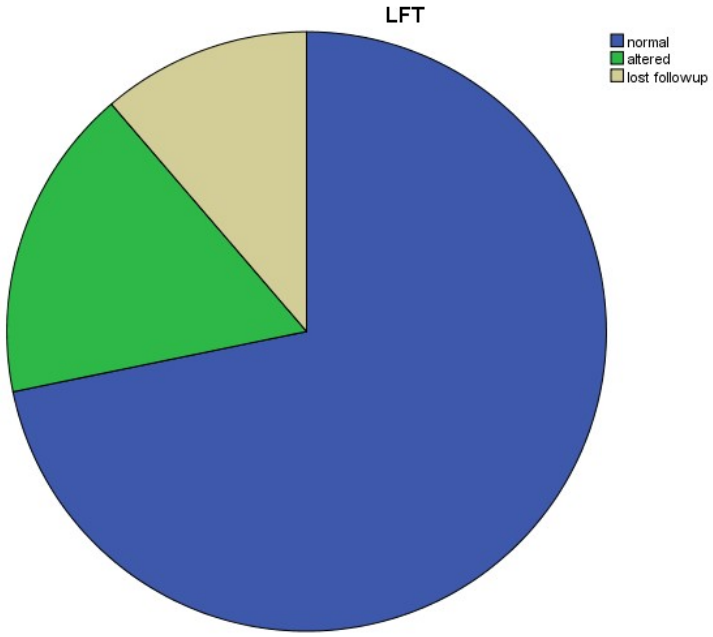



**FIGURE II: OUTCOME OF LFT**



## DISCUSSION

Tuberculosis is among one the disastrous infectious disease for mankind. According to reports two billion humans suffered from tuberculosis with the addition of approximately more than ten million new cases annually[6].

The world is also facing the problem of hepatitis viruses nowadays including HCV which was discovered in the year 1988[7]. Pakistan stands second in the world for the highest number of HCV cases[8]. According to a systematic review and meta-analyses by **Al -Kanaani Z** every 20th person of our homeland has HCV infections[9]. Situation is worst in Sindh as compared to other provinces of Pakistan[8]. Tuberculosis patients may also be co-infected with chronic HCV and this occurrence creates an additional challenge for treatment of tuberculosis, bearing in mind drug-induced hepatitis due to antituberculous treatment[10].

Medications for the treatment of tuberculosis may have deleterious effects on the liver, debate is still going on whether HCV co-infection in tuberculosis patients may worsen or precipitate drug-induced hepatotoxicity or not. In a study from Nepal, authors found 20.98% of the person affected by ATT in the form of liver damage and that found it comparable to other third world countries scenario[11], ATT induced drug toxicity is more common in our part of the world as compared to industrialized nations[12].

Our study was focused on first-line ATT-induced liver damage in patients of pulmonary tuberculosis who were co-infected with chronic HCV. We noted that out of 124 patients, only 21 patients developed alterations in liver enzymes. **Bartaula B** mentioned in his article about a study conducted in Florida on 128 persons which found that 30% of tuberculosis patients co-infected with hepatitis C suffered from elevation in liver enzymes, because of drugs used for the treatment of tuberculosis, while the ratio of hepatitis due to the treatment in non-HCV infected persons was 11%, so they suggested that HCV infection is a risk factor for causing liver enzymes alterations in patients of tuberculosis when they use anti-tuberculosis drugs[11].

In a retrospective study from India, the authors stated that hepatitis C is not ominously linked with drug-induced hepatitis[13]. This is contrary to many other[11,14] and our study as well.

In our study mean age of patients was 42.4 years, slightly higher than noted by **Diana Ivanova et al** in their study, which was 38 years[14], majority 37.9 of patients belongs from an age group greater than 50 years of age. Other studies also documented more liver damage in the older age group of 40-60 years[12]. In their study **Metanat M et al** found that old-aged persons were more likely to develop alteration in liver enzymes due to ATT, the majority of the participants in their study were older than 50 years of age[4,10].

Comparable to our study, the research work of TE Chang detected more serious liver damage with high elevation of liver enzymes, in persons who were anti-HCV positive especially in older than 65 years of age[15].

In our study males were 70 and females were 54, so slight male predominance was noted. In their meta-analysis of 8 years, Behzadifar M et al also noted TB and HCV were more common in men as compared to women[16].

In a study conducted in Egypt by Agha M, authors found HCV was strongly linked with DIH (drug-induced hepatitis) due to first-line ATT in patients of tuberculosis. They also discussed other studies which were in support of their results. They identified 40 % of their patient, from group 1 (tuberculosis and HCV co-infection) exhibited an alteration in liver enzymes while only 20.75% of patients from group 11 (tuberculosis without co-infection with HCV) showed elevation in liver enzyme[10]. This was a remarkable finding and highlight noteworthy

dissimilarity between both groups. Our study also disclosed a substantial number of cases who exhibited Drug-induced hepatitis (DIH )on first-line drugs for tuberculosis .i.e. about 17%.To assess liver damage due to ATT is of utmost value as if it goes unchecked, may result in mortality of 6% - 12% [4].

In our study, we selected patients with normal baseline LFT. 21 patients developed ATT-induced hepatitis as detected by elevation in bilirubin and AST and ALT. In our patient's bilirubin was not markedly raised. Mean with a standard deviation of levels of bilirubin AST and ALT were 2.36±1.6, 528± 312, 428±298 respectively.

The occurrence of DIH was substantially larger in the chronic HCV patients alone and patients of chronic HCV co-infection with chronic HBV [17].

How in the presence of HCV more hepatotoxicity occurred, is not fully understood. Some scientists postulated that amendment in the fat breakdown by HCV core protein was a major offender for liver injury because of drugs, in the HCV group. **Wedemeyer et al**. unveiled that HCV-induced fatty liver may lead to programmed cell death, contributing to hepatitis and sequel.[17]

We recommend that HCV-positive patients with tuberculosis on treatment should be followed meticulously.

## CONCLUSION

This study concluded that drug-induced hepatitis due to anti-tuberculosis treatment is not uncommon in patients of pulmonary tuberculosis who are co-infected with chronic HCV infection. Chronic HCV marks the liver more vulnerable to anti-tuberculosis treatment-induced hepatitis. Elevation in liver enzymes is more common in patients older than 50 years of age.

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**DATA SHARING STATEMENT**: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

## AUTHOR CONTRIBUTIONS

Memon N: Concept and design of the work, review, drafting of the manuscript.
Humaira M: Manuscript drafting, review, and final approval of the manuscript
Shaikh MA: Expert Opinion, Critical review, and final approval of the manuscript
Bano R: Acquisition, analysis, and interpretation of data and make it suitable for final revision
Anjum S: SPSS Analysis, interpretation of data, and review
Shah M: Data collection and sequencing the material, grammatical review
Kaka IH: Data collection and review of the manuscript

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