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Hepatotoxic Effects of Anti-Tuberculosis Medications: A Clinical Assessment

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ABSTRACT

Background: Tuberculosis (TB) is a contagious disease that is highly prevalent worldwide. Every year, Mycobacterium tuberculosis causes over 2 million fatalities and about 8 million new cases of active tuberculosis. Treatment for adult respiratory TB is a regimen of isoniazid, Rifampicin, and pyrazinamide for 2 months, followed by 4 months of isoniazid and Rifampicin. All these anti-TB medications have the potential to be hepatotoxic, but when used together, the toxicity is amplified synergistically. Drug-induced Liver Injury (DILI) is defined as a liver injury due to Xenobiotics, herbs, or medications that lead to either liver dysfunction or abnormal liver serology in the setting of no other identifiable cause. Serum biomarkers, including ALT AST, ALP, and T. Bilirubin, are routinely utilized in diagnoses and therapeutic outcome assessments of DILI in the clinic. The purpose of the study was to assess the hepatotoxicity effect of anti-tuberculosis medications. **Methods**: This study was observational. The data was collected from Sayyed Muhammad Hussain Government TB sanatorium, Samli Murree. This study was conducted from October 2023 to December 2023. A non-probability sampling technique was used for this research. Eighty-two random TB patients who were using antitubercular drugs for their treatment and had done their Liver Function Tests (LFTs) were selected. The data is presented in the form of tables and pie charts. **Results:** About 135 LFT reports of 82 TB patients were found with varying parameters. Throughout their course of therapy, 24% of patients developed ATT-induced hepatitis, 6% of patients merely had elevated bilirubin levels, 1% of patients had elevated ALP, 2% of patients had HCV+, and 1% patients had HbAg+. However, 65.80% of patients maintained normal liver function. This study found that the harmful effects of drugs also come along with treatment, which healthcare professionals shouldn't neglect. It showed the adverse effects of antitubercular drugs on the liver. Therefore, drug therapy must be stopped immediately after noticing any abnormal changes in the liver profile. **Conclusion:** In conclusion, anti-tuberculosis treatment has a notable impact on hepatocellular injury, with a significant proportion of patients experiencing elevated liver enzymes and bilirubin levels indicative of liver stress or damage. The treatment was associated with drug-induced hepatitis in some

patients, reflecting its potential to cause hepatocellular injury, particularly in those with predisposing factors. These findings highlight the importance of regular monitoring of liver function tests during therapy to detect and manage hepatocellular injury promptly, ensuring a balance between effective tuberculosis treatment and the prevention of serious liver complications.

Keywords: Tuberculosis, Mycobacterium Tuberculosis, Drug-induced Liver Injury (DILI), Serum biomarkers, ATT Induced Hepatitis

INTRODUCTION

An old disease, tuberculosis (TB), has a history related to human evolution and migration, as well as with the beginnings of microbiology. Mycobacterium tuberculosis (MTB), the primary causative agent of tuberculosis, is believed to have originated from an early progenitor in East Africa as long as 3 million years ago. Early in the nineteenth century, TB epidemics decimated most of Europe and North America, causing 800 to 1000 deaths per 100,000 people annually. Approximately 9 million new cases of TB are reported each year, and nearly 2 million people die from TB-related causes, making MTB the leading cause of bacterial pathogen-related mortality today [1]. Mycobacterium TB complex DNA has been found and characterized from the Predynastic era, and palaeopathological abnormalities, such as Pott's illness, have long been used to identify tuberculosis in Egyptian mummies [2]. TB is a contagious disease that is highly prevalent worldwide. Every year, MTB causes over 2 million fatalities and about 8 million new cases of active tuberculosis. A remarkable rise in the establishment of multidrug-resistant (MDR) strains has been documented in many parts of the world even though chemotherapy can be used to cure many instances. More than 50 million people are thought to be infected with MDR strains of MTB [3]. TB is more frequent in developing countries. The burden of TB is highest in Asia and Africa. In 2011, the largest number of cases were reported from India, China, South Africa, Indonesia and Pakistan [4].

As Pakistan is ranked as the sixth highest TB burden country according to WHO, therefore many TB control programs have been established in Pakistan for the public at the national level. TB can acquire its latent or active forms. Latent is the phase of disease in which the patient appears with no signs and symptoms, while the active phase gives the impression of being symptomatic. Almost one-fourth of the world's population is latently infected with MTB, with a risk of progression to active disease of about 3-15% during their lifetime [5]. Some manifestations of TB are a bad cough with blood or sputum, chest pain, sudden weight loss, chills, fatigue, fever, and sweating at night. When screening individuals with TB symptoms (such as a cough lasting more than two weeks, unexpected weight loss, and haemoptysis), healthcare professionals should take TB disease into account [6]. Tuberculosis (TB) is a leading cause of death, with patients facing high levels of prejudice and stigma [7]. The disease was designated a worldwide emergency in 1993 due to its severity [8]. People with low incomes are most at risk due to crowded living conditions and poor nutrition, which weaken their immune systems [9]. TB can be categorized into pulmonary and extrapulmonary forms. Pulmonary TB is the most common, with 79-87% involvement in subjects with active TB [10].

Extrapulmonary TB often involves lymph nodes, pleura, and osteoarticular regions. Hepatic TB is reported in 10-15% of patients with EPTB, but tubercular liver abscesses are rare [11]. The recommended standard treatment for adult respiratory TB is a regimen of isoniazid, Rifampicin, and pyrazinamide for 2 months, followed by 4 months of isoniazid and Rifampicin [12]. Ethambutol and streptomycin are recommended in retreatment cases in developing countries [13]. These medications can cause toxic reactions in organs, especially the liver, which can result in Drug-induced Hepatitis. Significant negative effects are Hyperuricemia, Peripheral Neuropathy, Hepatitis, Dermatitis, Gastrointestinal distress, and visual abnormalities. Drug-induced liver damage, which accounts for 4-10% of all adverse events, is still a significant clinical concern [14]. Isoniazid causes peripheral neuropathy and hepatotoxicity (elevated serum transaminases and serum bilirubin), Rifampicin causes immune allergic reactions and hepatotoxicity (elevated serum transaminases, alkaline phosphate, and serum bilirubin), pyrazinamide causes joint pains (increased serum uric acid) and hepatotoxicity (elevated serum transaminases and serum bilirubin) [15]. Drug-induced Liver Injury (DILI) is defined as a liver injury due to Xenobiotics, herbs, or medications that lead to either liver dysfunction or abnormal liver serology in the setting of no other identifiable cause. In fact, the liver is the major organ responsible for drug metabolism and detoxification in the body. Biochemical and organelle stress or the death of hepatocytes accompanied by inflammation induced by the accumulation of parental drugs or drug metabolites in the liver is the main pathogens of DILI.

Serum biomarkers, including Alanine Amino Transferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), and Total Bilirubin (TBIL), are routinely utilized in diagnoses and therapeutic outcome assessments of DILI in the clinic [16, 17]. Liver enzymes are significant indicators of any abnormal changes in liver function. The currently prescribed antitubercular (anti-TB) chemotherapy regimen containing isoniazid (INH), Rifampicin (RIF), and pyrazinamide (PZA) can have substantial side effects, including drug-induced liver toxicity. All these anti-TB medications have the potential to be hepatotoxic, but when used together, their toxic effects are amplified synergistically. Although the precise mechanisms of INH and RIF hepatotoxicity are not fully understood, toxic hydrazine derivatives and free radicals that cause oxidative stress, lipid peroxidation, and choline deficiency, as well as the subsequent decrease in phospholipid protein synthesis and resulting alteration in cell wall configuration, reduced glutathione levels, and activation of Cytochrome P450 2E1, are most likely to blame for hepatocyte injury and death [18, 19].

Clinically, it shows up as symptoms of jaundice, nausea, vomiting, and stomach discomfort, as well as elevated levels of bilirubin and hepatic transaminases. The most frequent adverse effect resulting in a therapeutic interruption is hepatotoxicity. If the medication is taken after the commencement of symptoms, there is a mortality rate of 6-12% [20-22]. Combining the medications increases the risk of hepatotoxicity. Patients undergoing intermittent, thrice-weekly treatment from Directly Observed Therapy (DOTS) clinics, however, are at comparatively lower risk [20]. Drug-induced toxicity, if left untreated, can potentially lead to the death of an organ. In terms of morbidity, the severity of anti-TB DILI cannot be ignored, given that anti-TB drug-induced ALF tends to result in the need for liver transplantation or death [20-22]. Anti-TB drugs can cause liver toxic effects due to dosage and combination of drugs [23]. Hepatotoxicity can range from 2.3% to 8.4%, with symptoms ranging from asymptomatic transaminase increase to severe liver failure [24]. Combination treatment increases the incidence of hepatotoxicity [25]. Hepatotoxicity is reported in 5%-28% of patients treated with anti-TB drugs. It can cause treatment interruption, poor compliance, increased mortality, and modification of treatment regimens [26]. Stopping offending medication is crucial, especially if there is increased transaminase and/or jaundice [27].

Additionally, we ought to support TB patients in using age-old, natural therapies that were in use before the discovery of pharmaceuticals. The era known as the sanatorium era saw the adoption of natural remedies to cure tuberculosis patients. As faith in medicine declined in finding a quick cure for tuberculosis, many 19th-century physicians stressed the importance of hygiene, change of climate, sunshine, mental tranquillity, exercise, fresh air, avoidance of excessive passions, and proper diet in the prevention and treatment of tuberculosis. In the middle of the 19th century, the primary therapy for tuberculosis was prolonged bed rest, nutritious food, fresh air, and change of climate. These therapies were typically practiced in the setting of special institutions called "sanatoria" [27, 28]. Therefore, the motive of this study is to focus on the unfavourable consequences of anti-TB drugs on the liver that lead to devastating effects on the liver profile. A neglected elevation in liver enzymes can result in permanent damage to the liver and ultimately appear in the form of acute liver failure. To avoid extreme conditions of damage, the liver profile of TB patients who are receiving treatment must need to be monitored throughout their treatment journey. After noticing any elevation in the liver enzymes, anti-TB drug treatment should be stopped immediately.

MATERIALS AND METHODS

This observational cross-sectional study was conducted using data from the Sayyed Muhammad Hussain Government TB Sanatorium, Samli Murree, between October 2023 and December 2023. A non-probability sampling technique was employed, with a sample size of 82 patients. The inclusion criteria focused on patients undergoing anti-TB drug therapy who had their liver function tests (LFTs) performed, while those without LFTs data were excluded. Statistical analysis was carried out using SPSS, and the findings were presented using pie charts, histograms, and tables for clear and comprehensive visualization.

DATA COLLECTION PROCEDURE

Data for this cross-sectional study were collected from 82 patients at the Sayyed Muhammad Hussain Government TB Sanatorium, Samli Murree (October–December 2023) using non-probability sampling. Only patients with liver function test (LFT) data were included. Analysis was done using SPSS, with results presented via charts and tables.

STATISTICAL ANALYSIS

In the analysis of this study, descriptive statistics were employed to determine the distribution of the LFT parameters of TBIL, ALT, AST, and ALP. Chi-square tests were used to compare two or more categorical variables whereas t-tests were used to

compare two groups of continuous variables. Furthermore, percentages and frequency distributions were used to report on the frequency of hepatotoxicity markers. To enhance the understanding of the results, tables, pie charts, and histograms were created.

RESULTS

The study of the total bilirubin (TBIL) level of 135 patients who received anti-tuberculosis treatment revealed that 80% of the patients had normal bilirubin levels and, thus, no severe liver impairment. However, 4% of patients reported borderline bilirubin levels, which indicates mild liver damage, and 16% of patients reported increased bilirubin levels, which may indicate moderate to severe liver damage and hepatotoxicity. These results suggest that bilirubin levels should be closely monitored during anti-tuberculosis treatment to identify liver abnormalities early, especially in patients with higher or borderline bilirubin levels, who may require more attention or dose modification.

Table 1: The Range of TBIL and Percentages of Patients Affected Out of 135

	TBIL RANGE	PERCENTAGE OF PATIENTS OUT OF 135
Normal Total Bilirubin	<1 mg/dl	80%
Borderline Bilirubin	1 mg/dl	4%
High Total Bilirubin	>1 mg/dl	16%

The analysis of changes in the alanine aminotransferase (ALT) in 135 patients during anti-tuberculosis treatment showed that 68.9% of the patients had normal ALT levels below 42 U/L, which suggests that most of the patients tolerated the medication well. However, 1.5% of patients had borderline ALT levels (42 U/L), and a substantial 29.6% had elevated ALT levels (>42 U/L), indicating that they experienced different levels of hepatotoxicity and possible liver stress or damage. From these results, the assessment of ALT levels is important in the early identification of liver disorders so that appropriate management measures, including dose modification or other supportive measures, can be implemented for the identified patients. The fact that nearly one-third of the patients had ALT levels above the normal range emphasizes the need to perform a pre-treatment liver function test to identify patients at risk of hepatotoxicity. This analysis also needs further work to identify which drugs or patient factors are responsible for these elevations to help strike the right balance in tuberculosis treatment without compromising liver health.

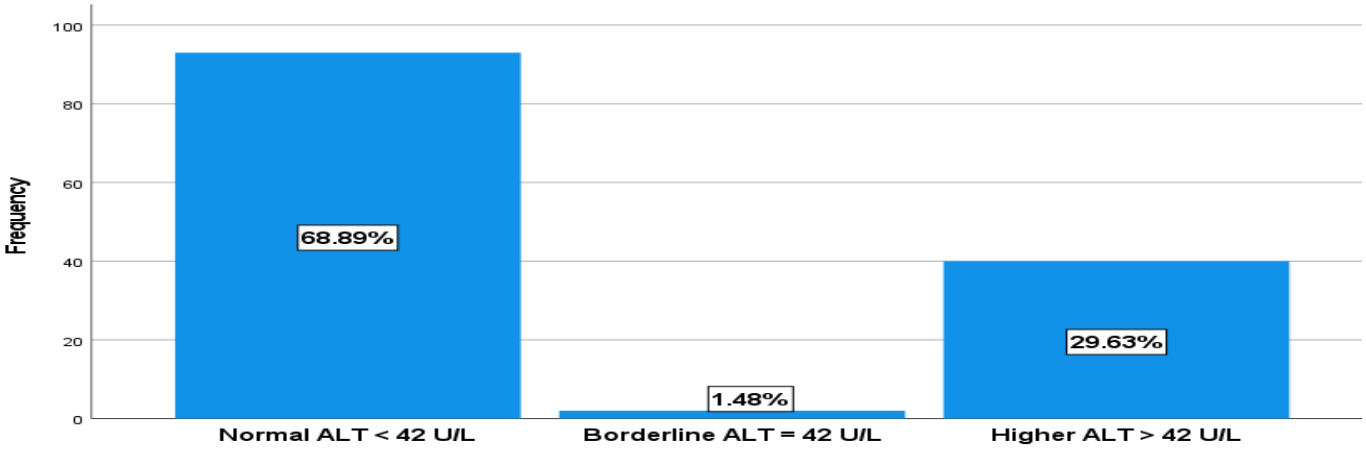

Figure 1: The range of ALT and percentage of patients affected out of 135.

The study of AST levels in 135 patients receiving anti-tuberculosis treatment shows that 58% of patients had normal AST levels, which means that they did not have severe liver disease; 39% of patients had high AST levels, which implies hepatotoxicity; 3% of patients had borderline AST level, which means that they are at risk for developing liver disease. These results suggest that

patients on anti-tuberculosis drugs should have their liver function closely checked because high AST levels point to liver toxicity. The study focuses on the need to achieve a balance between the efficacy of the treatment and the safety of the patient, especially the patients with raised AST who may need a dose adjustment or a change of regimen. It also emphasizes the importance of regular AST screening, knowledge of signs and symptoms of liver dysfunction, and future studies on the consequences and possible predictors of hepatotoxicity in tuberculosis therapy.

Table 2: The Ranges of AST and Percentages of Patients Affected Out of 135

STATUS OF AST	Level OF RANGES	PERCENTAGES OF PATIENTS AFFECTED OUT OF 135
Normal AST Level	<42 U/L	58%
Borderline AST Level	42 U/L	3%
Higher AST Level	>42 U/L	39%

Data obtained from 135 patients receiving anti-TB treatment shows that 92.6% of them had normal ALP levels ranging from 65 to 300 U/L, which suggests that the treatment was well tolerated with this liver and bone health enzyme. Nevertheless, 7.4% of patients had ALP levels between 300 and 400 U/L, which indicates liver or biliary tract abnormalities that need further assessment. Although the incidence of patients with elevated ALP levels is relatively low, these results underscore the need to monitor ALP levels during treatment and, especially in patients with comorbid conditions, to manage any hepatotoxicity promptly.

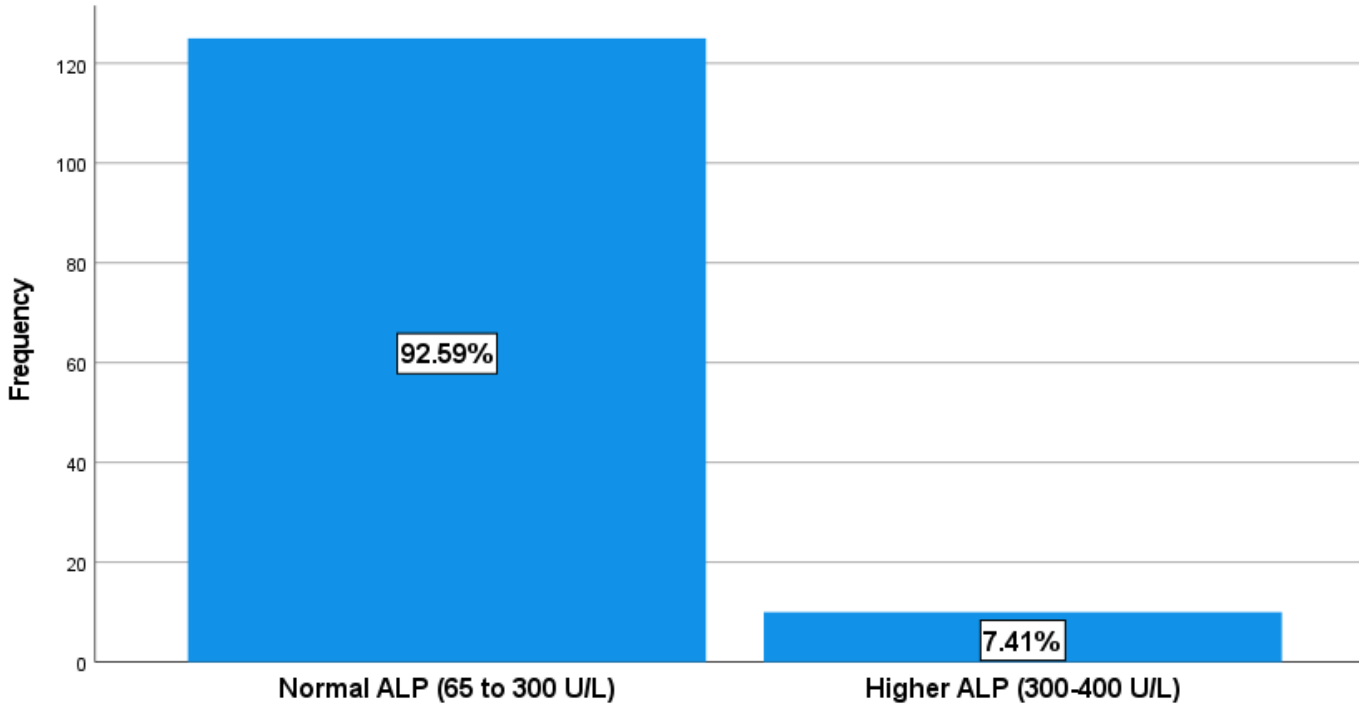

Figure 2: Range of ALP and Percentages of Patients Affected Out of 135 Reports

This study focuses on detecting TB patients who are using anti-TB medications and developing drug-induced liver damage. Across 135 LFT studies involving 82 TB patients, we found varying parameters. Throughout their course of therapy, 24% of patients developed ATT-induced hepatitis, 6% of patients merely had elevated bilirubin levels, 1% of patients had elevated ALP, 2% of patients had Hepatitis C positive (HCV+), and 1% of patients had Hepatitis B positive (HbAg+). However, 65.80% of patients maintained normal liver function.

Table 3: Results of 135 LFTs Reports of Tuberculosis Patients

Hepatocellular Injury	Percentage
Normal	65.80%
ATT induced hepatitis	24%
Raised Bilirubin	6%
Raised ALP	1%

DISCUSSION

Due to the liver's role in drug metabolism, anti-TB medications have a significant risk of causing drug-induced liver damage. LFTs are thus carried out to assess liver function. Our research is based on the prevalence of drug-induced liver damage caused by anti-TB medicines in 82 TB patients. Isoniazid, pyrazinamide, Rifampicin, and ethambutol are the four medications used in conjunction to treat tuberculosis. The LFT data of TB patients who are using Anti TB drugs was obtained from a TB sanatorium. Sayyed Muhammad Hussain Government TB sanatorium Samli Murree is a government sector TB hospital that provides all the treatment facilities for TB patients and serves humanity. According to a retrospective analysis conducted by Khadkaj et al. (2009), 35 percent of the 114 patients had aberrant liver function patterns, such as elevated blood bilirubin, serum ALT, and serum AST. A total of 114 TB patients receiving anti-TB medication had abnormal bilirubin levels in 13% of them, borderline levels in 22%, and normal bilirubin levels in 65.0% of patients. Comparably, 4% of patients had a little increase in ALT, 15% of patients had a substantial elevation, and 81% of patients had ALT levels that were within the normal range. Meanwhile, 9.0% of patients had a moderate rise in their AST level, 7% had a little elevation, and 96% of patients had an AST within the normal range [18].

Furthermore, in 135 LFT reports of 82 TB patients, our research revealed that 16% of patients had increased levels of TBIL, and 4% of patients were at the borderline. TBIL levels were normal in 80% of individuals. Among the patients, 26% had ALT levels that were unusually high, 1.50% had borderline values, and 72.50% had normal levels. 39% of patients had borderline or increased AST values, 3% had elevated levels, and 58% had normal AST levels. We have measured ALP levels; of the individuals we studied, 7% had elevated ALP levels, and 93% had levels within normal ranges in a prior study conducted by MI. According to Malik et al. (2014), 95 patients were observed. They found that 36.8% of patients with ATT-induced hepatitis had a severe degree of hepatotoxicity because of antitubercular medication [29].

Similarly, according to our study of 135 LFT data of 82 TB patients who were using anti-TB medications, our research includes this information obtained from Sayyed Muhammad Hussain Government TB Sanatorium Samli Murree. During their therapy, 65.80% of the patients remained normal, whereas 24% of them had ATT-induced hepatitis, 6% had elevated bilirubin alone, and 1% had increased ALP. 24% is a considerable percentage of ATT-induced hepatitis, and these patients must need treatment for liver damage along with Anti TB therapy. S. Wang et al. (2020) conducted research to pinpoint the clinical and laboratory characteristics as well as the factors that predict acute liver failure in individuals whose liver damage was caused by anti-tuberculosis medications. To determine the proportion of DILI in 155 TB patients, patients diagnosed with Anti-TB DILI between 2010 and 2016 at affiliated hospitals were retrospectively included in this study [21]. Studies by P Ichai et al. (2010) indicate that PZA and INH can have serious hepatotoxic effects. Fourteen individuals with severe drug-induced hepatitis resulting from INH and PZA therapy were diagnosed between 1986 and 2008 [24].

Similarly, we are researching drug-induced hepatitis caused by the anti-tuberculosis medication regimen, which includes ethambutol, pyrazinamide, isoniazid, and Rifampicin. The Sayyed Muhammad Hussain Government TB Sanatorium Samli Murree provided the data used in our study. This is a tuberculosis sanatorium that uses both natural remedies and pharmaceuticals to heal its patients fully. We acquired the liver profile information of eighty-two tuberculosis patients who were receiving anti-tuberculosis medication. The mechanism of hepatotoxicity by these four drugs is determined by different meth, such as by isoniazid. Normally, the liver is principally responsible for isoniazid clearance through acetylation by N-acetyl transferase 2 (NAT-2). In addition to numerous minor metabolites, the primary products of acetyl-isoniazid metabolism include monoacetyl hydrazine (MAH) and the non-toxic diacetyl hydrazine. Monoacetyl hydrazine's (MAH) reactive metabolites most likely cause tissue damage by generating free radicals. Acetyl hydrazine, another isoniazid metabolite, covalently bonds to liver macromolecules by the action of a microsomal enzyme. On rare occasions, Rifampicin may interfere with bilirubin uptake in a

dose-dependent manner, leading to jaundice or subclinical, unconjugated hyperbilirubinemia without causing harm to the hepatocyte.

Furthermore, Rifampicin's inhibition of the primary bile salt exporter pump is most likely the cause of conjugated hyperbilirubinemia. Inhibited secretion at the canalicular level or dose-dependent competition with bilirubin for clearance at the sinusoidal membrane can potentially cause asymptomatic increased bilirubin levels. Pyrazinamide has the potential to cause idiosyncratic and dose-dependent hepatotoxicity. Pyrazinamide changes the liver's levels of nicotinamide acetyl dehydrogenase, which may lead to the production of free radical species [30]. Given their somewhat similar chemical structures, isoniazid and pyrazinamide may have comparable causes of damage. Rifampicin and pyrazinamide cause more severe side effects in patients who have previously experienced hepatotoxic responses to isoniazid. One case of hepatic cholestatic jaundice linked to ethambutol has been reported; the circumstances surrounding the case are unknown [18]. All these drugs were used to treat the patients at the same sanatorium and thus led to increased liver enzymes.

LIMITATIONS AND RECOMMENDATIONS

The study was performed in Pakistan, and the data was taken from the Samli sanatorium in the year 2023. Also, the sample size was just 82 TB patients out of 135. Therefore, this study can be done in a broader region and with a large sample size. Also, some of the future directions should be considered: conduct research on TB treatment methods that are more effective and safer as compared to these Anti TB drugs which bring their adverse effects along, as well as provide knowledge to the TB patients that along with drug treatment they also try to make them recover with natural things like Sunlight, high protein food, complete bed rest, exercise and refreshing environment, including the use of Olive oil for TB treatment, its effectiveness and why it was used in the past for TB treatment and future studies should also Complete Anti TB therapy is very necessary to eradicate the infection from the body because TB cannot be cured in noncompliance patients.

CONCLUSION

In conclusion, anti-tuberculosis treatment has a notable impact on hepatocellular injury, with a significant proportion of patients experiencing elevated liver enzymes and bilirubin levels indicative of liver stress or damage. The treatment was associated with drug-induced hepatitis in some patients, reflecting its potential to cause hepatocellular injury, particularly in those with predisposing factors. These findings highlight the importance of regular monitoring of liver function tests during therapy to detect and manage hepatocellular injury promptly, ensuring a balance between effective tuberculosis treatment and the prevention of serious liver complications.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTION

The contribution of all authors was to highlight the serious issues arising from the use of antitubercular medication by observing the abnormal liver profile of TB patients. The goal of this research is to spread awareness among Health care providers about the adverse effects of TB therapy on the liver.

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FINDING SOURCE

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