**Reviewer’s Comments**

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**The extent of Hepatotoxicity in response to anti-tuberculosis drugs, a cross-sectional study from Pakistan**

**ABSTRACT**

**Introduction:** Tuberculosis is an infectious disease with enhanced morbidity and mortality worldwide. The prevalence of Tuberculosis is comparatively greater in the under developed countries and its control is a serious issue. The most common adverse reaction of tuberculosis pharmacological theatment is drug induced hepatotoxicity. The incidence of hepatotoxicity effects the treatment adherence in a negative manner and reducing overall quality of life.

**Objective:** This current study was aimed to ~~access~~ the extent of hepatotoxicity as the result of tuberculosis pharmacological therapy.

**Methods:** The current study is a cross sectional study conducted upon tuberculosis patients undergoing tuberculosis treatment from public hospital of Islamabad, Pakistan. Hepatotoxicity is considered as an elevation in liver function tests with associated symptoms. A well structed data collection form was used to attain demographic data (age, gender) of the study subjects. Tuberculosis drug combinations used by the patients were also noted. Moreover, hepatotoxicity was evaluated by performing liver function tests (LFTs) of the tuberculosis patients undergoing tuberculosis pharmacological treatment.

**Results:** The study showed that out of 100 tuberculosis patients, 55 patients were hepatotoxic. Hepatotoxic population includes 26% males and 29% females including almost 10% children either male or female. The maximun hepatotoxicity was observed in the patients undergoing combination therapy. Around 3-5 % patients showed that the Serum-Glutamic Pyruvic-Transaminase (SGPT) values more than 2 times of their normal values. While other 50% showed hepatotoxicity 1-2 times of their normal values. Most of the patients found were in the age group ranging from 35-60 years. The main drugs used in tuberculosis treatment ~~are~~: Isoniazid, Rifampicin, Pyrazinamide, Ethambutal.

**Conclusion:** The current study concluded that as we move towards greater number of drugs in combination, the extent and chances of hepatotoxicity increases. Hepatotoxicity was indicated in tuberculosis patients undergoing anti-tuberculosis therapy. Tuberculosis pharmacological treatment was the major reason of hepatotoxicity. However, the combination of 3 anti-tuberculosis drugs (Isoniazid, Rifampicin and Pyrazinamide) causes maximun hepatotoxicity.

**KEYWORDS** Tuberculosis; Hepatotoxicity; SGPT; Isoniazid; Rifampicin; Pyrazinamide; Ethambutal.

**INTRODUCTION**

Tuberculosis is an infectious respiratory disease caused by the bacteria “Mycobacterium tuberculosis” [1]. Tuberculosis is characterized by the presence of casemate necrosis, destruction of parenchymal lungs, and the creation of cavities [2]. There exists a hypothesis suggesting that the deterioration of lung tissue caused by tuberculosis is influenced, to some extent, by the deposition of metalloproteinase that are released by mononuclear phagocytes [2].

Globally, the incidence of tuberculosis in 2020 was approximately 20 million cases, with a modest annual decline of only 1-2% [3]. Furthermore, it is often believed that a staggering number of approximately 2 billion individuals have encountered the tuberculosis bacillus, consequently placing them at potential jeopardy of developing an active manifestation of the ailment [1]. The issue is exacerbated by a significant rise in the prevalence of multidrug-resistant strains of M. tuberculosis [4].

Mycobacteria that evade immune responses can disseminate through the circulatory and lymphatic systems, reaching many organs, particularly those that are highly oxygenated such as the lungs, kidneys, and bones[5]. Pulmonary tuberculosis is the most prevalent kind of TB (tuberculosis) and skeletal tuberculosis accounts for approximately 33% of tuberculosis cases that manifest in places outside of the lungs [4].

The present treatment for tuberculosis (TB) involves a combination of four medications, namely rifampin (RIF), isoniazid (INH), pyrazinamide (PZA), and either ethambutol (EMB) or streptomycin (STR) [6]. The administration of these four medications spans a duration of 2 months, which is referred to as the intensive phase [7]. This is then followed by the administration of RIF and INH for a period of 4 to 7 months, known as the continuation phase [5]. Consequently, the entire duration of treatment ranges from 6-9 months [8]. Due to the challenges associated with eliminating Mycobacterium tuberculosis from tissues using existing medications and the prolonged duration of tuberculosis treatment, a significant number of patients exhibit non-adherence to their drug regimen or prematurely discontinue therapy [9]. This lack of compliance has contributed to the emergence of drug-resistant strains of M. tuberculosis [6]. Multidrug-resistant tuberculosis (MDR-TB) is characterized by the presence of Mycobacterium tuberculosis isolates that exhibit resistance to both rifampicin (RIF) and isoniazid (INH) [10]. To establish a cure, a treatment regimen consisting of a combination of second-line medications, which are comparatively less effective and more toxic, may need to be administered for a duration of up to 24 months [11].

Patients who exhibit resistance to these initial medications are administered second-line treatments [5]. The medications “ofloxacin and ciprofloxacin”, which belong to the class of fluoroquinolones, have demonstrated efficacy in these particular situations [12]. Resistance can potentially emerge in response to the administration of these medications [3]. Amino cyclic acid and ethionamide are both classified as second-line medicines [11]. Cycloserine and pyridoxine are medications that are generally well tolerated [5]. Injectable antibiotics such as amikacin, kanamycin, and capreomycin are employed, similar to streptomycin [12].

The adverse effects of anti-tuberculosis medications include hepatotoxicity, which is considered to be a significant concern [1]. Additional symptoms that may be present include nausea or vomiting, jaundice characterised by yellowish skin or eye discoloration, dark urine, unexplained fever or fatigue, tingling or numbness in the hands or feet, and joint discomfort [13].

Numerous risk factors have been proposed for the occurrence of hepatotoxicity in individuals undergoing short-term antituberculosis treatment [14]. Several factors have been identified as potential risk factors for the development of hepatotoxicity in patients with pulmonary tuberculosis who are undergoing anti-tuberculosis treatment [15]. These factors include age, sex, disease extent, nutritional status, past history of liver disease, infection with hepatitis viruses, acetylator status and high alcohol intake [5].

Hepatotoxicity is a widely recognised adverse effect associated with the use of drugs used for the treatment and prevention of tuberculosis [16]. The hepatotoxicity of isoniazid, which has been a long-standing cornerstone of tuberculosis medication therapy, has been established [1]. The primary medications, known as first-line pharmaceuticals, are widely regarded as the most efficacious and well-tolerated therapeutic choices for tuberculosis treatment [4]. These therapies encompass isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin [5].

The primary side effects commonly associated with anti-tuberculosis medication are hepatotoxicity, skin responses, gastrointestinal disturbances and neurological issues [9]. The occurrence of hepatotoxicity generated by anti-tuberculosis drugs is a significant contributor to both morbidity and mortality rates, while also compromising the efficacy of treatment [1]. Anti-tuberculosis treatment often leads to asymptomatic transaminase elevations, especially with hepatotoxic medications like isoniazid, rifampicin, and pyrazinamide which are metabolized in the liver [7]. Hepatic drug responses typically manifest within the initial two months of treatment, although they can potentially arise at any point over the course of treatment [3].

Hepatotoxicity can be detected through the use of liver function tests, which encompass alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK.P) and bilirubin measurements [17]. The increase in the levels of these enzymes indicates the presence of hepatotoxicity [1].

The objective of the current study was to assess the prevalence of hepatotoxicity in tuberculosis patients of various age groups. Additionaly, the present study was conducted to investigate the extend of heaptotoxity using different combinations of antituberculosis drugs.

**MATERIALS AND METHODS**

*Study approval, design & Settings and study subjects*

For the present study, ethical approval from ERB- Ethical review board of Shaheed Zulfiqar Ali Bhutto Medical University was attained with a protocol number:ERB/SZABMU/330.

A cross sectional observational study was conducted to access the extent of hepatotoxicity by different drug combinations of tuberculosis pharmacological therapy. The data was collected from tuberculosis patients undergoing tuberculosis therapy from PIMS hospital Islamabad, Pakistan. The study duration was of 4 months approximately, from; March-June, 2023.

The patient profiles were examined in order to determine hepatotoxicity in individuals receiving tuberculosis treatment. The liver function test (LFT) is essential criteria for the assessment of hepatotoxicity. The primary laboratory tests conducted to assess liver function included measurements Serum-Glutamic Pyruvic-Transaminase (SGPT) or alanine aminotransferase (ALT), alkaline phosphatase (ALP) and bilirubin levels.

Based upon convenient sample technique, 100 study subjects were included in the current study, who passed the inclusion criteria.

*Inclusion & exclusion criteria*

The tuberculosis patients who were undergoing anti-tuberculosis pharmacological therapy were included in the current study. However, the tuberculosis patients with co-morbidites were excluded from the present study. Moreover, the patients undergoing any other drug therapy in addition to anti-tuberculosis drug therapy were excluded from the current study. Pregnant females and patients with HIV/AIDS were excluded from the study. The study subjects who were willing to participate and presented an informed consent form were included in the present study.

*Data Collection form:*

A well structured data collection form was designed to collect data from study subjects. The data collection form gathered the demographic data of tuberculosis patients. For accessing the hepatotoxicity, the reports of liver function tests (LFTs) of patients were recorded. The study subjects data has been kept confidential and results were not disclosed.

*Statistical analysis*

The data of study subjects was analyzed through SPSS version 21, IBM corp., Armonk, NY, USA. Descriptive and inferential statistics were utilized to evaluate outcome variables. Categorical variables has been presented as percentages and frequencies.

The *p value< 0.05* was considered statistically significant.

**RESULTS**

A total of 100 tuberculosis patients (male and female) were included. The study subjects were of varing age and included children as well. Among 100 patients, 49% patients were male among which 26 were hepatotoxic. Whereas, 51% patients were female, among which 29 patients presented hepatotoxicity in response to anti-tuberculosis therapy. Table 1 demonstrates the demographic characteristics of the study subjects included in the present study.

**Table 1: Frequency of hepatotoxicity in patients receiving anti-tuberculosis therapy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Categories** | **Frequency (N)** | **Hepatotoxic** **N (%)** |
| Gender | Male | 49 | 26 (53) |
| Female | 51 | 29 (56) |

Table 2 indicates significant differences in cases of hepatotoxicity respective to different age groups. Most of the individuals that developed hepatotoxicity belonged to age group of 41-50 ~~31 to 40~~ years. Furthermore, it is ~~graphysically~~ represented in Figure 1.

The tests performed were SGPT, ALP and Bilirubin. The major indicator of hepatotoxicity was Serum-Glutamic Pyruvic-Transaminase (SGPT). Percentage of hepatotoxicity in both males and females indicates that females are more hepatotoxic as compared to male.

**Table 2: Age related hepatotoxicity in TB patients**

|  |  |  |
| --- | --- | --- |
| **Age (years)** | **Study Subjects N (%)** | **Hepatotoxic patients N (%)** |
| 1-10 | 4 | 1 (25) |
| 11-20 | 15 | 3 (20) |
| 21-30 | 20 | 12 (60) |
| 31-40 | 22 | 12 (54.5) |
| 41-50 | 15 | 13 (86.6) |
| 51-60 | 12 | 8 (66.6) |
| 61-70 | 9 | 5 (55.5) |
| 71-80 | 3 | 1 (33.3) |

**Figure 1: Age related hepatotoxicity in study subjects**

11-20

01-10

*Hepatotoxicity with respect to combination therapy*

The study centre administered a treatment regimen for tuberculosis (TB) that consisted of four medications: Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and Ethambutanol (EMB). The comparative hepatotoxicity of RIF and INH was evaluated using liver function tests, revealing that RIF exhibits a higher level of hepatotoxicity in comparison to INH. However, the co-administration of two medications, specifically INH and RIF, demonstrated a higher incidence of hepatotoxicity in comparison to the individual drugs.

Furthermore, it was discovered that the combination of isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA) exhibited a higher incidence of hepatotoxicity when compared to the combination of all four medications, namely INH, RIF, PZA, and ethambutol (EMB).

Table 3 presents the drug combination related hepatotoxicity where ‘a’ indicates INH, ‘b’ indicates RIF, ‘c’ indicates PZA, ‘d’ indicates EMB. Table 3 presents the extent of hepatotoxicity in response to different drug combination of anti-tuberculosis drugs and is graphically presented in Figure 2.

**Table.3: Drug related hepatotoxicity:**

|  |  |  |
| --- | --- | --- |
| **Drug combination** | **Total patients (N)** | **Patients hepatotoxic N (%)** |
| a | 10 | 3 (30) |
| b | 16 | 7 (43.7) |
| a+b | 31 | 17 (54.8) |
| a+b+c | 16 | 16 (100) |
| a+b+c+d | 27 | 18 (66.7) |

**Figure 2: Anti-tuberculosis drug combination related hepatotoxicity**

**Serum concentration**

Liver function tests (LFTs) were performed to assess hepatotoxicity. The SGPT serves as a primary biomarker for hepatotoxicity. The standard reference range for serum SGPT is 42 IU/L. The patients who exhibit an elevation in SGPT levels of around 45% demonstrate values that fall within the range of 84 IU/L. Approximately 5% of individuals exhibit elevated serum SGPT readings that are 2 to 3 times higher than the established normal range. Additionally, this study suggests that the occurrence of hepatotoxicity may vary depending on the length of treatment.

**DISCUSSION**

The incidence of hepatotoxicity, a significant adverse effect associated with tuberculosis therapy, exhibits variability across various countries, with rates extending from 1% to 10% [12]. The prevalence of the disorder varies based on criteria such as race, socio-economic status and geographical location [8]. The highest frequency of anti-tuberculosis related hepatotoxicity was observed in India, with a range of 8-10% [1]. In contrast, Western countries exhibited lower rates, with the United States having a prevalence of less than 1%, the United Kingdom at 4%, and Barcelona in Spain at 3.3% [5].

The risk factors associated with hepatotoxicity that have been reported in the literature include advanced age, paediatric age, female gender, compromised nutritional status, excessive alcohol use, pre-existing liver illness, presence of hepatitis B infection, co-infection with hepatitis B and C, extensive disease, low levels of albumin in the blood, and acetylator status [11]. Regular monitoring is necessary for patients in all disease categories, involving periodic clinical evaluations and laboratory examinations, throughout the course of treatment [15].

The current study presents that females present greater hepatotoxicity in response to anti-tuberculosis therapy as compared to male tuberculosis patients. And, it was observed that women had a higher risk of hepatotoxicity compared to men. The presence of advanced tuberculosis disease may potentially increase the risk of tuberculosis drug-induced liver injury, while it is challenging to completely eliminate the influence of other factors that may complicate the relationship [18].

Similar results were presented by a retrospective study conducted in Indonesia, presenting that drug induced hepatotoxicity tends to increase with greater number of drugs and is more common in female patients [13]. Similarly, a prospective cohort study conducted in Peshawar, Pakistan presented that anti-tuberculosis drug induced hepatotoxicity is comparatively greater in female patients as compared to male patients suffering from tubetculosis [6]. Contrarily, a prospective study conducted in Maharashtra, India presented no specific association of gender with hepatotoxicity in tuberculosis patients [1].

The present study presented that the incidence of hepatotoxicity is highest in the adults aged from 40-50 years of age. Advancing age is a significant risk factor for drug-induced liver injury associated with tuberculosis, the research population saw a higher incidence of hepatotoxicity in patients over the age of 40 compared to their younger patients in the present study. However, the higher occurrence of liver toxicity in older individuals may be attributed to a greater frequency of concurrent medical conditions and the usage of other medications within this age demographic [19]. Similarly, the study conducted upon tuberculosis patients from India, presented that hepatotoxicity is more common in adults aged greater than 40 years [1].

In contrast, a cross sectional study conducted in Toronto, Canada presented somewhat different results i.e., age is not a contributing factor for hepatotoxicity in case of chronic liver disease patients [19]. Moreover, a cross sectional study from Sindh, Pakistan presented no significant association of age with tuberculosis therapy induced hepatotoxicity [20].

There exist varying guidelines and clinical approaches on the follow-up of patients, the time of withdrawal of anti-tuberculosis treatment, and the treatment regimen subsequent to the development of hepatotoxicity [2].

According to the present study, the extent of hepatotoxicity increases when the combination used included Rifampicin. Similarly, a case report study conducted in Chennai, India presents that the incidence of severe hepatotoxicity among adults increase when rifampicin was included in a multidrug therapy regimen [21]. It has also been shown that pyrazinamide increases the likelihood or severity of hepatotoxicity [12]. Similarly, another case report conducted in Mangalagiri, India presented similar results that the extent of hepatotoxicity tends to increase with the simulantaneoud use of Levofloxacin with tuberculosis drugs [11].

It is recommended that patients undergo evaluation for hepatotoxicity through comprehensive assessment of medical history, thorough physical examination, and laboratory analysis [22]. Additionally, patients should be informed about the manifestations of hepatotoxicity, such as hepatitis symptoms including loss of appetite, nausea/vomiting, and abdominal pain [3]. Furthermore, patients should be educated about the precautions associated with the consumption of alcohol and hepatotoxic drugs, as well as the importance of routine follow-up during treatment has been recommended only in patients with initially abnormal liver function tests and risk factors [23].

As per the guidelines set forth by the World Health Organization (WHO), it was deemed satisfactory to monitor patients using clinical indicators alone [19]. Routine laboratory monitoring was not advised unless there was a documented history of liver disease, consistent alcohol usage, or the presence of advanced symptoms [20].

In the current study, laboratory controls were conducted exclusively on individuals with elevated levels of liver enzymes at the onset, while patients with normal laboratory results and no clinical symptoms were not subjected to routine laboratory monitoring. Although INH, RIF, and PZM are recognized as hepatotoxic medications, there is still no agreement among experts regarding the specific criteria for discontinuing treatment with these treatments [24]. According to the guidelines provided by the ATS, it is advised to discontinue the use of hepatotoxic medicines promptly if the levels of AST exceed five times the upper limit of normal, regardless of the existence of symptoms, or if they surpass three times the normal limit in the presence of symptoms [13]. When liver enzymes exhibit a fivefold increase from the standard levels, it is recommended that you discontinue the administration of all medications [24].

In the context of our clinical setting, the presence of hepatotoxicity was taken into account when there was an elevation of serum AST and/or ALT levels that exceeded three times the upper limit of normal [23]. Additionally, an increase in serum total bilirubin levels greater than 1.5 mg/dL, or any elevation in AST and/or ALT levels beyond the levels observed prior to treatment, accompanied by symptoms such as anorexia, nausea, vomiting, and jaundice, were also considered indicative of hepatotoxicity [11]. The specific medicine responsible for hepatotoxicity remains unidentified, and because to the potential for drug resistance, modifications to the treatment regimen are probable [24]. Consequently, in the event of hepatotoxicity development in our patients, the discontinuation of all ongoing tuberculosis medications was implemented [25]. Based on existing guidelines, in cases where drug-induced hepatitis is diagnosed, it is advised to discontinue the administration of anti-tuberculosis medications and refrain from their use until liver function tests return to normal [14]. The implementation of a novel treatment regimen should be considered after hepatotoxicity, as long as the ALT levels remain below twice the upper limit of normal [11]. In the examined cohort, the continuation of treatment occurred exclusively following the restoration of liver enzyme levels to a state of normal [7]. In our clinical setting, we initiated the administration of whole drug dosages following the restoration of enzyme values in 55 out of 100 cases that experienced recurring hepatotoxicity.

Similarly, in cases when patients experience long-term and severe hepatotoxicity and are able to tolerate the medications rifampin (RIF) and isoniazid (INH), it has been indicated that extending the treatment duration to 9 months is a safer approach compared to adding pyrazinamide (PZM) to the treatment regimen [25]. The (WHO) recommends a treatment regimen consisting of two months of isoniazid, ethambutol, and streptomycin, followed by ten months of isoniazid and ethambutol, in cases where rifampicin is implicated [23].

If the use of isoniazid is contraindicated, it is recommended to explore a treatment regimen consisting of rifampicin, pyrazinamide, and ethambutol for a duration of 6-9 months [19]. However, if pyrazinamide is discontinued before the completion of the intensive phase, the total duration of therapy with isoniazid and rifampicin may need to be prolonged to 9 months [25].

The present investigation mostly employs a combined therapy. The incidence of hepatotoxicity was higher in patients treated with RIF in comparison to those treated with INH. As the number of drugs in combination increased from two to more, the likelihood of hepatotoxicity also increased. Patients with up to two months of therapy were surveyed. There have been cases of hepatotoxicity after 15 days of therapy. Several age groups were studied, with hepatotoxicity cases concentrated in the 40-60-year range. These patients took no other drugs. One disease therapy was administered to patients.

**CONCLUSION**

Hepatotoxicity represents a prominent adverse effect associated with anti-tuberculosis medication. The findings of the current study demonstrates that female patients undergoing tuberculosis therapy imposes higher incidence of hepatotoxicity as compared to male population. The majority of the identified cases were between the age of 35 to 60 years. Furthermore, the majority of instances of hepatotoxicity were seen in the context of combination therapy. The extent of hepatotoxicity observed with drug combination (INH,RIF,PZA) is greater as compared to the drug combination (INH, RIF, PZA,EMB). A small percentage, approximately 3-5% of individuals, exhibit elevated SGPT levels that exceed twice the standard range. While the remaining 50% exhibits hepatotoxicity levels that are 1-2 times higher than the standard limits. Additionally, it is evident that when the utilization of drug combinations becomes more prevalent, the likelihood of experiencing hepatotoxicity is raised.

**LIMITATIONS**

Being a single centeres research study, the results can not be extrapolated nationwide. Moreover, sample size of present study wasnot large enough. The greater population size could have provided comparatively more accurate results.

**RECOMMENDATIONS**

Drawing concrete conclusions about the hazards associated with certain treatment regimens is challenging due to the utilization of diverse drug regimens in different study populations, the presence of differing definitions of hepatotoxicity, and the adoption of distinct monitoring and reporting practices in the management of hepatotoxicity. The identification of the specific drug responsible for hepatotoxicity is challenging due to the prevalent use of combination therapy in the treatment of patients. These treatment regimens typically involve the administration of two, three, or four drugs simultaneously. It is essential to implement rigorous monitoring of liver function tests throughout the administration of tuberculosis treatment to patients.

**SOURCE OF FUNDING**

No grant or funding was received from any organization for this project.

**CONFLICT OF INTERESTS**

The authors have no conflict of interest.

**ABBREVIATION**

**LFT;** Liver function test, **INH**; Isoniazid, **PZA**; Pyrazinamide, **RIF**; Rifampicin, **EMB**; Ethambutal, **SGPT**; Serum-Glutamic Pyruvic-Transaminase, **ALT**; Alanine aminotransferase, **AST**; Aspartate aminotransferase, **ALK.P**; alkaline phosphatase.

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