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Elham N.A.S. Algabaly¹

Yaser H.A. Obady¹

Khalid Al-Mureish¹

Fahd A. Alsharjabi²

¹Dept. of Biology, Faculty of Applied Science
Taiz University, Taiz, Yemen

²Dept. of Microbiology, Faculty of Applied Science
Taiz University, Taiz, Yemen and Faculty of Medical
and Health Sciences, Al Saeed University
Taiz - Yemen

yaserobady52@yahoo.com

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Elham N.A.S. Algabaly¹

Yaser H.A. Obady¹

Khalid Al-Mureish¹

Fahd A. Alsharjabi²

¹Dept. of Biology, Faculty of Applied Science
Taiz University, Taiz, Yemen

²Dept. of Microbiology, Faculty of Applied Science
Taiz University, Taiz, Yemen and Faculty of Medical
and Health Sciences, Al Saeed University
Taiz - Yemen

Abstract

Tuberculosis (TB) is one of the most prevalent communicable infectious diseases worldwide and remains one of the leading causes of death globally. Despite increasing awareness of anti-tuberculosis (anti-TB) drug-induced hepatotoxicity (DIH) as a major obstacle to successful tuberculosis treatment, few studies in Yemen have assessed the ability of clinical characteristics and laboratory parameters to predict the risk of acute liver failure (ALF) among patients with anti-tuberculosis drug-induced liver injury (DILI). So, the aim of the present study was to characterize biochemical alterations in patients with tuberculosis before and during anti-tuberculosis treatment, to investigate their potential diagnostic and prognostic significance and to monitor treatment-related adverse effects. A total of 25 patients diagnosed with tuberculosis submitted to biochemical analysis (9 males and 16 females, aged ≥ 18 years). The pre-treatment phase serving as a control group. The same group of patients ($n = 25$) was followed longitudinally throughout the different phases of treatment. The statistical analysis revealed a statistically significant difference ($P \leq 0.05$) in liver enzymes (AST, ALT) across the study groups, but no significant difference ($P > 0.05$) in ALP, ALB. Based on control, t- test illustrated that AST and

ALT have significant increase in the second month of treatment, The values then decreased, returning to a level statistically non-significant from the control in sixth month. This is indicating an initial treatment impact. Furthermore, the Bias values indicates that multidrug (Four antibiotic types) caused a clinically relevant abnormality in liver function. And these results were compared with results of other authors.

Conclusion: It can be concluded that the anti-tuberculosis treatment impose hazardous on the patients liver leading to hepatotoxicity or drug induced liver injuries, So, necessary the development of anti-TB drugs with improved safety profiles further aims to enhance treatment adherence and reduce DILI incidence, ultimately improving patient.

Keywords: Tuberculosis, Multidrug, Liver injury, Yemen

Introduction

Tuberculosis (TB) is one of the most prevalent communicable infectious diseases worldwide and remains one of the leading causes of death globally. In 2013, an estimated 9.0 million people were infected with tuberculosis, and 1.5 million died from this disease [1, 2 and 3].

WHO [4] and [5], global tuberculosis report TB occurs in every part of the world. In Yemen, tuberculosis is a major public health concern and has severe negative economic and health consequences and situation of tuberculosis had been further exacerbated since the war started in 2015 [6, 7].

Tuberculosis (TB) is an infectious disease caused primarily by *Mycobacterium tuberculosis*, which most commonly affects the lungs (pulmonary tuberculosis) but can also involve other organs. *M. tuberculosis* is a pathogenic bacterium that was isolated by Robert Koch as the causative agent of tuberculosis in 1882. It is an acid-fast bacillus with a distinct lipid-rich, mycolic-acid-containing cell wall structure. Due to its lipid-rich cell wall, *M. tuberculosis* is characteristically acid-fast and cannot be reliably stained by conventional Gram staining method [8].

This bacterium is a sedentary, obligate aerobic, rod shaped bacterium, with long generation time and preference to localize in macrophage and typically affects the lungs (pulmonary TB) but can affect other sites as well as extra pulmonary [9, 10 and 11].

The infection is spread through air, droplets due to forceful activities like coughing, sneezing, etc. the person at high risk of exposure are HIV infected patients, coworker in industries especially working in mines, construction works, crushing and hospital staffs of DOT centers [12 and 13].

Despite increasing awareness of clinicians and people, anti-TB drug-induced hepatotoxicity (DIH) as a major obstacle to achieve successful treatment of tuberculosis. And it causes of hospitalization in life-threatening events [14].

Effective tuberculosis (TB) treatment requires a combination of bactericidal and/or bacteriostatic TB drugs. The combination of these regimens is the standard therapy recommended by World Health Organization (WHO). The standard therapy consists of 5 first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin).

Out of these four drugs are most commonly used. They are Isoniazid (INH), Rifampicin (Rifampin), Ethambutol (EMB) and Pyrazinamide (PZA). The cornerstone of TB management is a 6-month course of using anti-TB drugs where isoniazid, rifampicin, pyrazinamide, and ethambutol are taken for 2 months in the intensive phase followed by a fourth month use of isoniazid and rifampicin in the continuous phase of managing protocols of the disease [15].

Anti-tuberculosis drug-induced liver injury (ATB-DILI) is one of the most common adverse events associated with TB treatment and effects affecting TB treatment. The reported prevalence of ATB-DILI varies considerably, ranging from 2% to 28%, depending on diagnostic criteria and geographic region [16, 17 and 18].

Hepatotoxicity occurs both during treatment of tuberculosis and primary prophylaxis (preventive therapy). Thus, it is dependent on the drug host interactions, drug disease and dynamics of drugs [19].

Rifampicin and Ethambutal have potent activity against *M. tuberculosis* but along with that it induces hazardous side effects on patients liver like hepatitis, jaundice, liver failure in severe case. It is found that during antituberculosis therapy the level of liver enzymes such as Alkaline phosphatase [ALP], Serum Glutamic Pyruvate Transaminase [SGPT], Serum Oxaloacetic Transaminase [SGOT] or Aspartate Transaminase [AST] get elevated from its normal range hence cause toxicity or malfunction of human liver [20].

Among the first-line anti-TB drugs, isoniazid, rifampicin, and pyrazinamide are known to cause hepatotoxicity, but pyrazinamide attribute to a higher percentage for the drug induced liver toxicity compared to the other drugs [21 and 22]

Indicators of hepatocellular functions that usually are assayed in clinical toxicology studies are the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Changes in concentrations of the exudation enzymes ALT and AST show changes in cell membrane function, such as changes in permeability or the more obvious cell membrane disconnection [23 and 24].

Drug-induced hepatitis may be asymptomatic or symptomatic. It is defined in asymptomatic patients as a serum aspartate transaminase (AST) level of five times the upper limit of normal. It is defined in symptomatic

patients (most commonly presenting with abdominal pain, nausea, vomiting) as an AST of three times the upper limit of normal [25].

TB drugs have mild to severe side effects. Side effects that arise not only cause mortality and morbidity but also cause the cessation of treatment with the effect of not achieving cure, even arising drug resistance. Drug-induced liver injury (DILI) is a form of side effect that causes the cessation of TB treatment or regimen changes due to treatment failure, relapse, and drug resistance. DILI increases the problem, covering more than 7% of all side effects. DILI is also one of the concerns in the treatment of TB [26].

In Yemen, few studies have assessed the abilities of clinical characteristics and laboratory tests to predict the risk of acute liver failure (ALF) among patients with anti-TB DILI. Accordingly, the aim of the present study is to illustrate some biochemistry manifestations in tuberculosis patients before/after use anti-tuberculosis drugs in order to identify a relationship via which their diagnostic and prognostic significance could be detected and to monitor the eventual adverse events during anti-tuberculosis therapy.

Material and Methods

Study subjects

This study was conducted at the laboratories of the National Tuberculosis Control Program (NTP), Taiz City, Yemen, during the period from February 2023 to December 2025. Due to the limited availability of resources and the difficulty in obtaining the chemical solutions necessary for biochemical analysis, because of the war in Yemen, a total of 25 patients diagnosed with tuberculosis (People with tuberculosis were identified by National Tuberculosis Control Program) submitted to biochemical analysis (9 males and 16 females, aged ≥ 18 years). The pre-treatment phase serving as a control group.

The same group of patients ($n = 25$) was followed longitudinally throughout the different phases of treatment, assessments were performed before treatment. Eligible patients received a letter with information about the study and Informed consent was obtained from all participants.

Demographic and clinical data were collected, the questionnaires were filled out during face-to-face interviews with the individuals with tuberculosis after the questions were explained. These questions concerned

age, sex, weight, length, smoking, marital status, pregnancy status, education level, occupation, family income, place of residence, the presence of chronic illness or a diagnosis of diabetes mellitus and medications used. Patients with diabetes mellitus and liver disease were excluded from the study.

Based on National Tuberculosis center in Taiz City, Yemen [15], the patients during the intensive phase (two months) to take a four-drug regimen (rifampin, isoniazid, pyrazinamide, and ethambutol), and during the continuation phase (four months) with rifampin and isoniazid.

Blood samples were collected at three time points: prior to treatment initiation and at 2 and 6 months after the start of treatment according to [27].

Biochemical parameters

Blood samples were collected according to the method described by Monica [28]. Two milliliters of venous blood were drawn from each participant using a sterile, dry plastic syringe.

The blood samples were transferred into plain tubes without anticoagulant and then centrifuged to obtain serum, which was used for the determination of liver function enzymes, including alanine aminotransferase (ALT/GPT), aspartate aminotransferase (AST/GOT), alkaline phosphatase (ALP) and Albumin (ALB). These biochemical analyses were performed using an automated biochemistry analyzer at the laboratory of Al-Thawra General Hospital, Taiz Governorate, Yemen.

Statistical Analysis

The data are represented as the mean and SE, and were analyzed using one-way analysis of variance (One-way ANOVA), followed by paired t-test. The parameters were compared between the control group and across different treatment phases. A p-value of less than 0.05 was considered statistically significant. To evaluate the medical significant, accuracy and the strength of association between an exposure and an outcome, we used Bias analysis and Chi-square.

The statistical analysis was performed using the statistical package SPSS version 24 [29] and software PAST package release 3.25 [30].

Results

In Table (1), a one-way ANOVA revealed a statistically significant difference ($P \leq 0.05$) in liver enzymes (AST, ALT) across the study groups, but no significant difference ($P > 0.05$) in ALP, ALB.

Table 1.

Results of one-way ANOVA analysis of biochemical parameters in tuberculosis patients before and during multidrug therapy (n = 25).

Parameters	Variables	Pre-treatment	During treatment		F	P- value
			Four antibiotic types	Two antibiotic types		
			Second month	Sixth month		
AST (U/L)	Mean±SE	29.84±1.2	41.20±2.7	28.60±1.6	12.90	<0.0001
	Mini.-Maxi.	16.0-39.00	23.00-88.00	14.00-46.00		
ALT (U/L)	Mean±SE	26.88±1.4	37.76±3.3	27.20±1.6	7.40	<0.001
	Mini.-Maxi.	13.00-37.00	19.00-104.00	14.00-47.00		
ALP (U/L)	Mean±SE	159.96±8.4	168.72±11.3	148.68±6.7	1.24	0.30
	Mini.-Maxi.	80.02-241.00	97.00-308.00	85.0-231.00		
ALB (g/dl)	Mean±SE	3.94±0.1	4.10±0.1	4.06±0.1	1.00	0.37
	Mini.-Maxi.	3.20-4.60	2.50-5.00	3.00-4.80		

The significant difference ($P \leq 0.05$)

AST and ALT, showed a significant increase in the second month. The values decreased and became non-significant in the sixth month. However, the ALP and ALB showed no significant difference (Table 2).

Table 2.

Statistical significance of the comparison between obtained mean of biochemical parameters during treated with multidrug based on control (n=25)

Parameters	During treatment					
	Four antibiotic types			Two antibiotic types		
	Second month			Sixth month		
	Change (%)	t ₄₈	P- value	Change (%)	t ₄₈	P- value
AST (U/L)	38.06	-4.02	0.000	-4.15	0.58	0.565
ALT (U/L)	40.47	-3.43	0.002	1.19	-0.14	0.891
ALP (U/L)	5.47	-0.68	0.501	-7.05	0.97	0.343
ALB (g/dl)	4.16	-1.35	0.191	3.14	-1.18	0.248

- All values are reported as mean percent changes, degree of freedom and significant levels.

- The Statistical tests applied on all biochemical variables were paired t-tests.

- The significant p-values are in bold ($P \leq 0.05$).

The patient group was found to exhibit higher alkaline phosphatase (ALP) contents compared to the standard reference values.

The analytical bias showed that values of AST, ALT and ALB were clinically significant different than the normal international range in pre-

treatment, second month and sixth month. Nevertheless, the digression from the international range of data was clinically significant of ALT only in second month (Table 3).

Table 3.

Statistical and clinical significance of the comparison between obtained mean of biochemical parameters with international data (n=25)

Parameters		Parameters	International mean±SD	Current mean±SD	Change (%)	Current value of Bias %	Acceptable limit of Bias %
During treatment	Pre-treatment	AST (U/L)	25±21.2	29.84±5.9		19.36	6.50
		ALT (U/L)	25±21.2	26.88±6.8		7.52	11.48
		ALP (U/L)	75±63.6	159.96±42.0*		113.28	7.20
		ALB (g/dL)	5±1.4	3.94±0.4		21.20	1.43
	Second month	AST (U/L)	25±21.2	41.20±13.4*	38.06**	64.80	6.50
		ALT (U/L)	25±21.2	37.76±16.6*	40.47**	51.04	11.48
		ALP (U/L)	75±63.6	168.72±56.5*	5.47	124.96	7.20
		ALB (g/dL)	5±1.4	4.10±0.5	4.16	18.00	1.43
	Sixth month	AST (U/L)	25±21.2	28.60±8.1	-4.15	14.4	6.50
		ALT (U/L)	25±21.2	27.20±8.2	1.19	8.8	11.48
		ALP (U/L)	75±63.6	148.68±33.7*	-7.05	98.24	7.20
		ALB (g/dL)	5±1.4	4.06±0.4	3.14	18.8	1.43
** p-values are significant at ≤ 0.05.							
* Chi-square value is significant at 0.05							
- Chi-square value was calculated to compare between the mean values of obtained range and international range.							
- Chi-square value < 3.84 was considered as statistically non-significant at 95% confidence interval.							
- Chi-square value > 3.84 was considered as statistically significant at 95% confidence interval.							
- If the value of Bias % greater than the acceptable limit was considered as clinically significant difference between two mean values (Bold cells).							
- The acceptable limit of Bias % is according to Ricós <i>et al.</i> [31] and Linda <i>et al.</i> [32].							
- International range is according to ABIM Laboratory Test Reference Ranges [33].							

Gender effect

The results of study the effects of an multidrug anti-tuberculosis on liver function parameters in male and female patients over a period of six months show in Table 4.

Table 4 and Figures 1 and 2, showed the results of biochemical parameters in male and female patients based on pre-treatment. The AST and ALT values significant increase in second month then returned to the pre-treatment levels in sixth month (LSD analysis). Except AST in males, significant differences were found in AST and ALT values in female patients.

The results of ALP showed some change. In males, the results of ALP showed relative stability during treatment. On the other hand, statistically significant difference was found in values of ALP between pre-treatment and multidrug treatment in females, while ALB stayed relatively stable within the normal range.

Table 4.
Results from the one-way ANOVA and LSD analyses on biochemical parameters of tuberculosis patients and during multidrug treatment in males and females (n=25)

Antibiotics		Subjects	Parameters	Male				Female			
				AST (U/L)	ALT (U/L)	ALP (U/L)	ALB (g/dl)	AST (U/L)	ALT (U/L)	ALP (U/L)	ALB (g/dl)
		Pre-treatment	Mean±SE	30.4±2.0	27.9±2.7	136.7±15.2	3.9±0.1	29.5±1.5 _a	26.3±1.5 _a	173.1±8.7 _a	4.0±0.1
During treatment	Four antibiotic types	Second month	Mini.-Maxi.	17-39	16-37	80-215	3.3-4.6	16-39	16-37	110-241	3.2-4.6
			Mean±SE	39.1±3.4 _a	34.2±3.3 _a	150.9±19.9	4.1±0.1	42.4±3.8 _{a,b}	39.8±4.8 _{a,b}	178.8±13.5 _b	4.1±0.1
	Two antibiotic types	Sixth month	Mini.-Maxi.	26-55	25-59	100-299	3.7-4.8	23-88	19-104	97-308	2.5-5.0
			Mean±SE	28.8±3.3 _a	25.6±2.1 _a	161.2±12.6	4.0±0.1	28.5±1.8 _b	28.1±2.3 _b	141.6±7.5 _{a,b}	4.1±0.1
			Mini.-Maxi.	14-46	16-35	120-231	3.6-4.4	16-40	14-47	85-185	3.0-4.8
			F (P-value)	3.49 (0.05)	2.62 (0.09)	0.58 (0.57)	0.82 (0.45)	9.06 (<0.00001)	5.15 (0.01)	3.81 (0.03)	0.45 (0.64)

The Means with same letters in same columns indicate significant difference ($P \leq 0.05$)

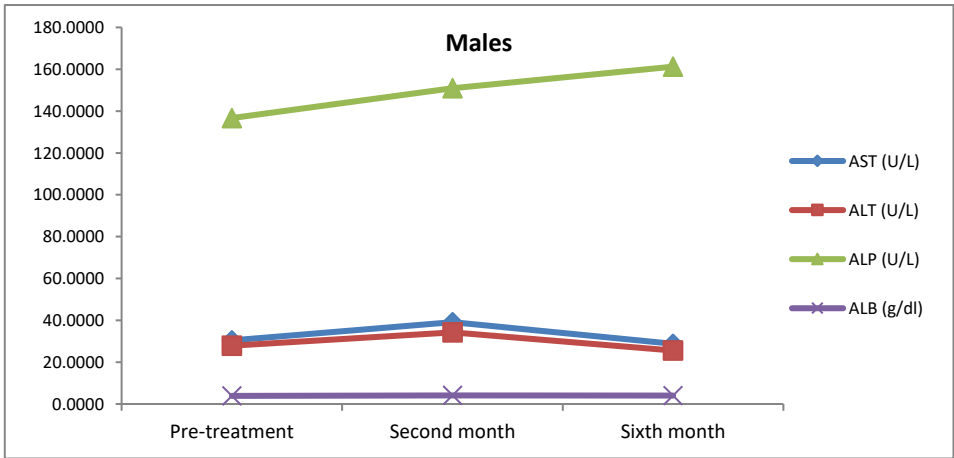


Fig.1 : The level of biochemical parameters in tuberculosis patients and during multidrug treatment in male patients

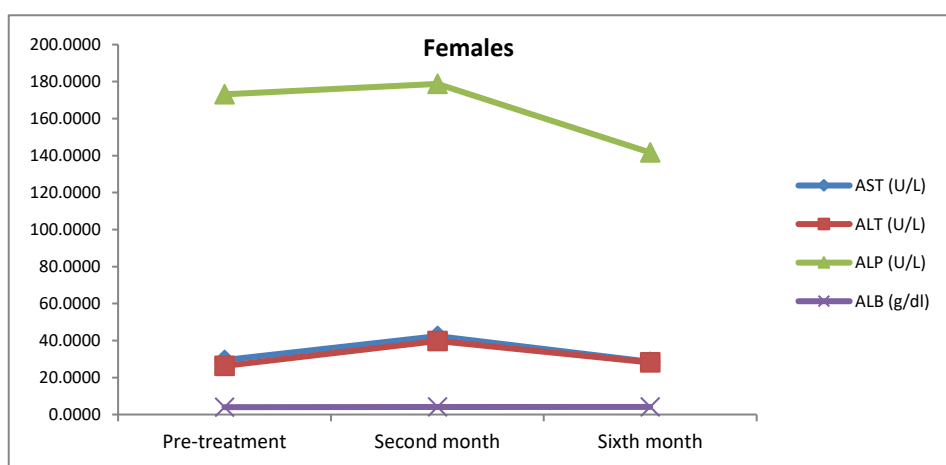


Fig. 2: The level of biochemical parameters in tuberculosis patients and during multidrug treatment in female patients.

Discussion

Tuberculosis is a national and world-wide spreading disease that many patients suffer from in addition to their battle with the disease itself, a new health challenging aspect is added which is the adverse effects of the anti-tuberculosis drugs and recognition of risk factors for it is essential to achieve successful therapy [34 and 35].

TB drugs have mild to severe side effects. Side effects that arise not only cause mortality and morbidity but also cause the cessation of treatment with the effect of not achieving cure, even arising drug resistance. Drug-induced liver injury (DILI) is a form of side effect that causes the cessation of TB treatment or regimen changes due to treatment failure, relapse, and drug resistance. DILI increases the problem, covering more than 7% of all side effects. DILI is also one of the concerns in the treatment of TB [26].

The World Health Organization (WHO) has reported that Yemen has a high burden of drug resistance and a worrying shortage of implemented diagnostic methods and drug treatment regimens [36].

Drug-induced liver injury (DILI), is often passed lightly; however, it can lead to the requirement of a liver transplant or may even cause death because of liver failure [37]. Suh [37], expressed hope that various biomarkers to accurately diagnose and predict the prognosis of drug-induced liver injury (DILI) will be developed and used conveniently, and various

new technologies of the fourth industrial revolution will be developed and applied to DILI.

Chinese Society of Hepatology make guideline, aims to provide professional guidance to clinicians on how to identify suspected DILI timely and standardize the diagnosis and management in clinical practice. The guideline specifically focused on DILI of common causing agents of DILI (herbal and dietary supplements, anti-tuberculosis drugs, and antineoplastic drugs) [38].

Gill *et al.* [19], suggested that Patients with TB disease are more prone to anti-TB drug induced hepatotoxicity. Moreover, during treatment of this disease, two or more drugs are given simultaneously which may further cause certain complications during the long duration of treatment due to drug-drug interactions.

Treatment regimens based on rifampicin plus ethambutol carry a low risk of hepatitis, First-line or second-line regimens containing pyrazinamide in accepted dosages, given daily or intermittently, carry a low and acceptable risk of hepatic toxicity [39].

Drug-induced liver injury (DILI) is approach for evaluating liver histology in DILI [40]. Ahmed [41], found that rifampicin and isoniazid showed clear histopathological changes in the rat's liver and lung tissues when given separately; however, changes were more intense when given in combination.

Hepatotoxicity is usually presented and diagnosed with jaundice or a high concentration of liver function marker proteins like aspartate aminotransferase (AST) alanine aminotransferase (ALT), alkaline phosphatase (ALP), or total bilirubin [42 and 43].

There is evidence to suggest that drug-induced hepatitis occurs with greater frequency and may be more severe when isoniazid (INH) and rifampin (RMP) are administered in combination than when INH is given alone [44].

Djabir *et al.* [45], found that liver toxicity from a four-drug fixed-dose combination (4FDC-AT) in rats was more evident and rapid than renal toxicity. Elevation of ALT appeared as early as 14 days in 50% of treated rats, with histopathological damage evident after 28 days.

Su *et al.* [46], found that treatment with the anti-tuberculosis drugs caused significant liver injuries, induced inflammatory responses and oxidative stress (OS), activated NLRP3 inflammations (NOD-like receptor protein 3), reduced the activity of drug-metabolizing enzymes, and altered the antioxidant defense system in rats and hepatic cells.

Lal *et al.* [47], studied the effect of rifampicin and isoniazid on liver function in 63 patients with pulmonary tuberculosis; 29% showed abnormalities of serum aspartate aminotransferase (AST) and a similar percentage abnormalities of serum bilirubin. These usually occurred during the first 12 weeks of therapy.

Dharmik *et al.* [43], observed elevated level of the liver enzymes like ALP and SGPT has been detected in most the tuberculosis patients with anti-tuberculosis treatment.

Mirlohi *et al.* [48], founded that liver enzyme activities (ALT, AST, and ALP) were decreased significantly ($p \leq 0.001$) after treatment. The anti-tuberculosis drugs impose a hazardous effect on the patient's liver, leading to hepatotoxicity, and are a major problem in tuberculosis patients.

Prasad *et al.* [49] observed that was an increase in liver enzyme level (ALT & AST) during intensive phase of anti-tubercular treatment while there was a decrease in liver enzyme level in continuation phase of treatment.

Jabbar *et al.*, [35], studied the effect of anti-tuberculous drugs (Combined therapy of pyrazinamide, rifampicin, ethambutol and Isoniazid) on liver enzymes. They founded that ALT, AST and ALP were markedly elevated in the first two months then a promising recovery to normal levels in the later four months.

Siregar *et al.*, [50] founded that the liver function test results are an increase in total bilirubin of 0.23 mg/dl after 3 months of respondents taking anti-tuberculosis drugs, as well as ALT and AST, each of which increased.

Perwitasari *et al.* [51], experienced increased levels of AST and ALT during 2 nd month of the treatment. The AST and ALT levels in the 6 th were 26 U/l and 25 U/l respectively.

Akkahadsee *et al.* [52] study 346 of TB patients were enrolled in Thailand. The study found an incidence of DILI at 14.45% (50 cases).

Hepatotoxicity Induced by Isoniazid (INH) is a significant clinical problem and the current mechanistic hypothesis involves metabolic idiosyncrasy, which is the bioactivation of acetylhydrazine that involve cytotoxicity, Acetylhydrazine is a metabolite of INH [17, 22 and 53].

The pyrazinamide is converted into pyrazinoic acid with the help of enzyme pyrazinamidase, which gets accumulate in bacteria cell and it get binds to ribosomal subunits thus inhibiting translation activity [54].

Sarma *et al.* [55] suggested perhaps by promoting the formation of toxic isoniazid metabolites by enhance metabolic hepatocellular idiosyncratic reaction in patients receiving isoniazid.

Liver enzyme microsomal amidase metabolised pyrazinamide to pyrazinoic acid (PA) and later oxidised by xanthine oxidase to 5-Hydroxy pyrazinoic acid (5-OH-PA). These metabolites of PZA are known to possess hepatotoxic potential [17, 56 and 57].

The pathway of rifampicin involves formation of desacetyl rifampicin from desacetylation and produces a 3- formyl rifampicin by a separate hydrolysis. In the early treatment, it induces hepatocellular dysfunction [58].

Isoniazid primarily causes hepatocellular damage via oxidative stress from toxic metabolites, while rifampicin induces cholestasis and endoplasmic reticulum stress, and pyrazinamide is linked to mitochondrial dysfunction [61].

In current work, the statistical analysis revealed a statistically significant difference ($P \leq 0.05$) in liver enzymes (AST and ALT) across the study groups, but no significant difference ($P > 0.05$) in ALP, ALB. Based on control, t- test illustrated that AST and ALT values were significantly higher during the second month of treatment compared to the control (pre-treatment) group, then decreasing and becoming non-significant in sixth months (two antibiotics). This is indicating a normalization of levels. This imbalance may be due to treating by rifampin, isoniazid, pyrazinamide and ethambutol in combination.

ALP and ALB, showed non-significant difference compared to the control. Table 5 and Figure 3, summarizes the results of the present work of biochemical analyses.

Accuracy is defined as the closeness of agreement between a test result and the accepted true value. So, the accuracy is an important feature of any diagnostic test. It is estimates play an important role in evidence based medicine. They guide clinical decisions and are used to clinical guidelines. Poor estimates of accuracy can contribute to patient injury. There has been an increasing awareness of deficiencies in study design that can create bias in estimates of test accuracy. Many pathologists are unaware of these sources of bias. Analytical bias or precision will move a patient result relative to a reference interval or clinical decision point [60, 61, 62 and 63].

The checking for clinical bias, remains the biochemical parameters exceed predefined limits in tuberculosis samples. Our study also indicated that the variation among the data sets for AST and ALT of samples was statistical significant and clinically significant in study groups. The Bias values indicates that multidrug (Four antibiotic types) caused a clinically relevant abnormality in liver function.

The disagreement and concord faces of biochemical parameters which may comparable with those recorded by different authors were summarized in Table 6.

Some people suffer liver injuries and others do not because every individual has different susceptibility to drugs. The risk factors for Drug-Induced Liver Injury (DILI) can be divided into genetic factors and environmental factors. Genetic factors include the changes in the levels of immune components. Environmental factors include old age, female gender, drug combination, previous drug adverse reactions, nutritional status, pregnancy, alcohol consumption, inflammation, and existing diseases. Changes in gut microbiota affect the drug metabolism and immune system, and it is interesting that it is one of the risk factors of DILI [64, 65, and 66).

Out of 20 patients, who include 14 males and 6 females, Dharmik *et al.* [43] found elevated level of ALT in two males. One male showed the levels of both the enzymes and reported to have drug induced hepatitis. In females no such effects was found on the liver as the level of the enzymes were found raised but the levels were within the normal range.

Blumberg *et al.* [67] found that the use of multidrug regimens for the treatment of tuberculosis based on the combination of isoniazid, rifampin, ethambutol, and/or pyrazinamide has proven to be a highly effective therapy.

Zhao *et al.* [68], found that female gender, combination therapy for anti-tubercular drugs (isoniazid, rifampicin and pyrazinamide) were the risk factors associated with the severity of anti-TB DILI.

In Yemen, Al-Shehari [7], notabled almost equal number of cases were diagnosed TB between males and females (a male to female ratio, 1.03: 1). The sharpest increase occurred in children under age 15.

Zade & Raut [69], noted that anti-TB drugs cause DILI in women four times more often than males and feminine CYP3A activity makes them more hepatotoxic.

Perwitasari *et al.* [70], recorded increased levels of aspartate aminotransferase (40%) and alanine aminotransferase (64%) of tuberculosis patients had good medication adherence. Female patients with poor adherence had high levels of these two enzymes.

Petros *et al.* [71], found that DILI was significantly associated with gender (odds ratio (OR) = 2.57, $P = 0.027$). The ALT and AST levels varied by sex status. Males had higher ALT (19.2 vs 15.3 U/l; $P = 0.009$) and AST (28.1 vs 24.0 U/l; $P = 0.009$) levels than females [72].

Based on pre-treatment, in present work found exalted levels of AST, ALT and ALP in second month of males and females. In females showed the significant levels of liver enzymes. On the other hand, no such effects was found on the ALT and ALP in males. Only one male reported high level of ALT enzyme but the levels of remains subjects were within the normal range. The results of females showed statistically significant different in ALP level compare for males. this indicating that the gender effect factor associated with multi-drug treatment of Tuberculosis.

Zade & Raut [69], reported that feminine CYP3A activity makes them more hepatotoxic. While, Airhomwanbor *et al.* [27] noted FSH, LH, Prolactin, Estrogen and Progesterone were significantly higher ($p < 0.05$) in female subjects compared with male subjects, while testosterone was non-significantly ($p > 0.05$) higher in male subjects compared with female subjects in pulmonary tuberculosis patients.

These results are in line with previous studies of Zhao *et al.* [68], Zade & Raut [69], Perwitasari *et al.* [70] and Petros *et al.* [71], while disagreement with Dharmik *et al.* [43] and Ebata-Mboussa *et al.* [72] in males status.

Conclusion

From the above, consistently showed significant decreases (negative change %) in the sixth month compared to second months. This quantitatively confirms the trend of recovery during the two-antibiotic phase (Two antibiotic types) and that four-antibiotic phase (Four antibiotic types) risk factor associated with multi-drug treatment of Tuberculosis. Thus, it can be concluded that the anti-tuberculosis treatment impose hazardous on the patients liver leading to hepatotoxicity or drug induced liver injuries, So, necessary the development of anti-TB drugs with improved safety profiles further aims to enhance treatment adherence and reduce DILI incidence, ultimately improving patient.

Recommendations

- 1- Routine liver function monitoring risk assessment are essential for early identification of ATB-DILI in hospitalized TB patients. Thus, should have liver function of patients are regularly monitored to reduce DILI.
- 2- Lei *et al.* [73], suggested persistent malnutrition within one month of treatment can adversely affect anti-tuberculosis treatment. Nutritional status during anti-tuberculosis treatment should be continuously monitored.
- 3- A study described of Makaminan *et al.* [74], unwanted side effects that grow during the treatment of pulmonary tuberculosis are itching and redness of the skin, joint pain, tingling and burning in the legs, red urine and sweat, nausea and vomiting. Thus, should health workers can provide health education to patients and their families about the conditions and effects related to the dose of the drug given, the patient's family must be able to ensure that patients with pulmonary tuberculosis who are in the treatment stage are obedient to taking medication and seek to recognize their condition, or signs and symptoms complained of due to the effects of the drug by the patient.

Table 5.

Comparison biochemical of tuberculosis patients and during treated with multidrug

Parameters	Pre- treatment	During treatment	
		Four antibiotic types	Two antibiotic types
		Second month	Sixth month
AST (U/L)	29.84	41.20	28.60
ALT (U/L)	26.88	37.76	27.20
ALP (U/L)	159.96	168.72	148.68
ALB (g/dl)	3.94	4.10	4.06

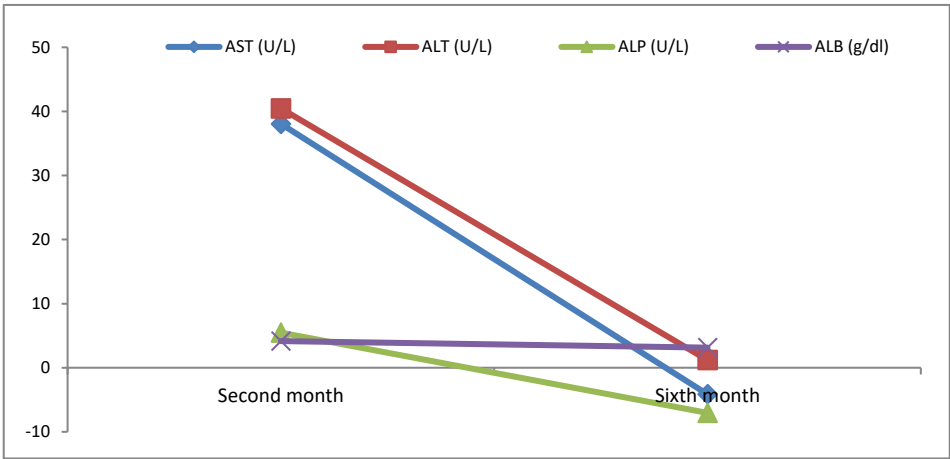


Fig. 3. Illustrated variation in biochemical parameters of tuberculosis patients and during treated with multidrug based

Table 6.
Biochemical parameters of different authors and current work from different localities and different methods

Biochemical parameters	Authors						Current study
	Khan & Warke [75]	Dharmik et al. [43]	Hadida et al. [76]	Mirlohi et al. [48]	Prasad et al.[49]	Das et al. [77]	
AST-GOT (U/L)		Incr.*	Incr.*	Decr.*	Incr.	Incr*	Incr.*
ALT-GPT (U/L)		Incr.*	Incr.*	Decr.*	Incr.	Incr*	Incr.*
ALP (U/L)		Incr.*	Incr.*	Decr.*		Incr*	Incr.
ALB (g/dL)	Incr.#						Incr.
Biochemical parameters	Authors						
	Wang et al. [25]	Jabbar et al. [35]	Molla et al. [78]	Makaminan et al.[76]	Akkahadsee et al. [52]	Perwitasari et al. [51]	
AST-GOT (U/L)	Incr.*	Incr.*	Incr*	Incr#	Incr.*	Incr.#	
ALT-GPT (U/L)	Incr.*	Incr.*	Incr*	Incr.#	Incr.*	Incr.#	
ALP (U/L)	Incr.*	Incr.*			Incr.*		
ALB (g/dL)	Incr.*	Incr.*					

*Values are significant at $p<0.05$ # The author did not statistical significant specify
Keys: Incr. –increased and Decr. –decreased

References

- [1] World Health Organization. (2014): Global Tuberculosis Report. Geneva. Available at (www.who.int)
- [2] Baddeley A., Dean A., Monica-Dias H., Falzon D., Floyd K., and Garcia I. (2013): Global Tuberculosis Report 2013. *World Health Organization. 2013; 306. Electronic physician Page 3009*
- [3] World Health Organization. (2022): Global Tuberculosis Report. Geneva: Licence: CC BY-NC-SA 3.0 IGO. Available at (<http://apps.who.int/iris>)
- [4] World Health Organization. (2018): Global Tuberculosis Report. Geneva. Available at (<http://apps.who.int/iris>.)
- [5] World Health Organization. (2020): Global Tuberculosis Report. Geneva. Available at (<https://www.iom.int>)
- [6] Anaam M.S., Alrasheedy A.A., Alsahali S., Alfadly S.O. and Aldhubhani A.H. (2019): Rate and risk factors of recurrent tuberculosis in Yemen: a 5-year prospective study. *Infectious Diseases. VOL. 0 (0): 1–9*
- [7] Al-Shehari W.A., Yin A., Wang X., Wang Y., Sun H., Yingmei F.u. and Zhang F. (2022): Prevalence and surveillance of tuberculosis in Yemen from 2006 to 2018. *Cambridge University Press, 1–10*
- [8] Hasnain S.E., Ehtesham N.Z. and Grover S. (2019): Mycobacterium tuberculosis: Molecular Infection Biology, Pathogenesis, Diagnostics and New Interventions. *Springer Nature Singapore Pte Ltd.*
- [9] Yukon Communicable Disease Control (CDC) (2016): Chapter 4: basic facts about Tuberculosis (TB). In *TB manual government of Yukon. Available at <https://yukon.ca>*
- [10] Shafee M., Abbas F., Ashraf M., Mengal M.A., Kakar N., Ahmad Z. and Ali F. (2014): Hematological profile and risk factors associated with pulmonary tuberculosis patients in Quetta, Pakistan. *Pak J Med Sci; 30(1): 36–40.*
- [11] Shah A.R., Desai K.N. and Maru A.M. (2022): Evaluation of hematological parameters in pulmonary tuberculosis patients. *J Family Med Prim Care. 11(8): 4424–4428*
- [12] Churchyard G., Kim P., Shah N.S., Rustomjee R., Gandhi N., Mathema B., Dowdy D., Kasmar A. and Cardenas V. (2017): What We Know About Tuberculosis Transmission: An Overview. *The Journal of Infectious Diseases. 216(S6): S629–35*

- [13] World Health Organization. (2021): WHO consolidated guidelines on tuberculosis: Module 2: Screening. Geneva: WHO.
- [14] Ambreen K., Sharma R., Singh K.P. and Kumar S. (2014): Anti-Tuberculosis Drug-Induced Hepatotoxicity: A Review. *International Journal of Advanced Biotechnology and Research (IJBR)*, Vol. (5) 3: 423-437
- [15] National Tuberculosis Control Program (NTP), Taiz City, Yemen, 2023.
- [16] Gülbay B.E., Gürkan O.U., Yildiz Ö.A., Önen Z.P., Erkeköl F.Ö., Baççcıoğlu A., Acıcan T. (2006): Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. *Respir Med.* 100, 1834–1842.
- [17] Tostmann A., Boeree M.J., Aarnoutse R.E., de Lange W.C.M, van der Ven A.J.A.M and Dekhuijzen R. (2008): Antituberculosis drug-induced hepatotoxicity: Concise up-to-date review. *J. of Gastroenterology and Hepatology* 192–202
- [18] Naidoo K., Hassan-Moosa R., Mlotshwa P., Yende-Zuma N., Govender D., Padayatchi N. and Abdool-Karim S.S.S. (2020): High Rates of Drug-induced Liver Injury in People Living With HIV Coinfected With Tuberculosis (TB) Irrespective of Antiretroviral Therapy Timing During Antituberculosis Treatment: Results From the Starting Antiretroviral Therapy at Three Points in TB Trial. *Clinical Infectious Diseases*, 70(12):2675–82
- [19] Gill M.K., Patyar R.R. and Patyar S. (2020): Antitubercular Drug Induced Hepatotoxicity: A Review. *European Journal of Molecular & Clinical Medicine* (7): 2840- 2847.
- [20] Koju D., Rao B.S., Shrestha B., Shakya R. and Makaju R. (2005): “Occurance of side- effects from antituberculosis drugs in urban Nepalese population under DOTS treatment”, *Kathmandu University Journal of Science, Engineering and technology. I* (1):1-8.
- [21] Yee D., Valiquette C., Pelletier M., Parisien I., Rocher I. and Menzies D. (2003): Incidence of Serious Side Effects from First-Line Antituberculosis Drugs among Patients Treated for Active Tuberculosis. *Am J Respir Crit Care Med* 167: 1472–1477
- [22] Marzuki O.A., Fauzi A.R.M., Ayoub S. and Imran M.K. (2008): Prevalence and risk factors of anti-tuberculosis drug-induced hepatitis in Malaysia. *Singapore Med J* 49(9): 688- 693

- [23] Lenaerts A.J., Johnson C.M., Marrieta K.S., Gruppo V. and Orme I.M. (2005): Significant increases in the levels of liver enzymes in mice treated with anti-tuberculosis drugs. *Int J Antimicrob Agents.*, 26(2): 152-8.
- [24] Sonika U. and Kar P. (2012): Tuberculosis and liver disease: management issues. *Tropical. Gastroenterology* 33(2); 102-106.
- [25] Wang S., Shangguan Y., Ding C., Li P., Ji Z., Shao J., Fang H., Yang M., Shi P., Wu J., Ren J., Yang S., Yuan J., Shi Y., Li J., Li L. and Xu K. (2018): Risk factors for acute liver failure among inpatients with anti-tuberculosis drug-induced liver injury. *J. of International Medical Research* 48(1) 1–10.
- [26] Soedarsono and Riadi A. R. W. (2020): Tuberculosis drug-induced liver injury. *J. Respirasi, VOL 06 (02);* 49-54.
- [27] Airhomwanbor K.O., Iyevhobu K.O., Omolumen L.E., Asibor E., Obowemu K.O., Usiobeigbe O.S., Akindele I.A., Bisiriyu A.H., Oikerhe E.G., Ajayi F.O., Lagundoye S.B., Uwaifo N.E., Osaiyuwu O.F., Osaiyuwu O.C., Jabbo A.A. and Edo E.O. (2024): Assessment of Sex Hormones (FSH, LH, Prolactin, Estrogen, Progesterone and Testosterone) of Pulmonary Tuberculosis Patients. *Journal of Clinical Medical Research:1-12*
- [28] Monica C. (2006): District Laboratory Practice in Tropica countries, Part1,2 (2ed). *Cambridge university press, The Edinburgh, Building, Cambridge, CB28RU, UK.*
- [29] SPSS, release version 24, Inc. (2016): Statistica for windows.
- [30] Hammer Ø., Harper, D.A.T. and Ryan, P.D. (2001): PAST: Paleontological Statistics software package for education and data analysis. *Palaeontologia Electronica* 4(1)pp:9.
- [31] Ricós C., Álvarez V., Cava F., García-Lario J.V. and Hernández A. *et al.* (1999): Current databases on biological variation: pros, cons and progress. *Scand. J. Clin. Lab. Invest.*, 59:491–500. Available from: [http:// www. Westgard.com / biodatabase - 2014](http://www.Westgard.com/biodatabase-2014).
- [32] Linda O. Henriksen, Faber N.R., Moller M.F., Nexø E. and Hansen A.B. (2014): Stability of 35 biochemical and immunological routine tests after 10 hours storage and transport of human whole blood at 21°C. *Scandinavian Journal of Clinical & Laboratory Investigation*, 74: 603–610
- [33] American Board of Internal Medicine (2025): ABIM Laboratory Test reference Ranges. Available at ABIM.org

- [34] Nader L.A., de Mattos A.A., Picon P.D., Bassanesi S.L., De Mattos A.Z. and Rodriguez M.P. (2010): Hepatotoxicity due to rifampicin, isoniazid and pyrazinamide in patients with tuberculosis: Is anti-HCV a risk factor? *Annals of Hepatology*; 9 (1): 70-74
- [35] Jabbar, A.A., Abed, S.A., Jasim, E.Y., and Shamkhi, T.K. (2020): The Effect of Anti – Tuberculosis Drugs on Liver Enzymes in Iraqi Patients. *Sys Rev Pharm.*11(2): 466 - 470.
- [36] Jaber A.A.S. and Ibrahim B. (2019): Evaluation of risk factors associated with drug-resistant tuberculosis in Yemen: data from centers with high drug resistance. *BMC Infectious Diseases*: 2-9.
- [37] Suh Ill J. (2020): Drug-induced liver injury. *Yeungnam Univ J Med* 37(1):2-12
- [38] Mao Y. Ma S. Liu C. Liu X., Su M., Li D., Li Y., Chen G., Chen J., Chen J., Zhao J., Guo X., Tang J., Zhuge Y., Xie Q., Xie W., Lai R., Cai D., Cai Q., Zhi Y. and Li X. (2024): Chinese guideline for the diagnosis and treatment of drug-induced liver injury: an update. *Hepatology Int.* 18:384–419.
- [39] Girling D.J. (1978): The Hepatic Toxicity of Antituberculosis Regimens Containing Isoniazid, Rifampicin and Pyrazinamide. *Tubercle* 59: 13-32
- [40] Kleiner D.E. (2014): Liver histology in the diagnosis and prognosis of drug-induced liver injury. *Clinical Liver Disease.* 4(1):12–16.
- [41] Ahmed D.F. (2011): The effect of rifampicin and isoniazid on liver and lung tissues in rats. *Iraqi Journal of Pharmacy* 11(2) pp: 34-45.
- [42] Saukkonen J., Cohn D., Jasmer R., Schenker S., Jereb J., Nolan C., Peloquin C., Gordin F., Nunes D., Strader D., Bernardo J., Venkataramanan R. and Timothy R. (2006): An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy. *Am J Respir Crit Care Med*,174: 935–952.
- [43] Dharmik P., Gomashe A., Dolas R. and Dhargave T. (2013): Effect of antituberculosis treatment on human liver. *Int. J.of Pharma Sciences and Research (IJPSR)*, 4: 1-5.
- [44] Steele M.A., Burk R.F. and DesPrez RM. (1991): Toxic Hepatitis with Isoniazid and Rifampin. *CHEST J.* 99(2):465-471
- [45] Djabir Y.Y., Arsyad A., Usmar U., Wahyudin E., Arwi H. and Rupang I.S. (2020): The Stages of Development of Liver and Renal Injuries

- in Rats Induced by Fixed Dose Combination of Antituberculosis Regimen. *FABAD. J. Pharm. Sci.*, 45, 1, 29-35.
- [46] Su Q., Kuang W., Hao W., Liang J., Wu L., Tang C., Wang Y., and Liu T. (2021): Antituberculosis Drugs (Rifampicin and Isoniazid) Induce Liver Injury by Regulating NLRP3 Inflammasomes. *Mediators of Inflammation*: pp: 1-13
- [47] Lal S., Singhal S.N., Burley D.M. and Crossley G. (1972): Effect of Rifampicin and Isoniazid on Liver Function. *British Medical journal*, 1: 148-150
- [48] Mirlohi M.S., Ekrami A., Shirali S., Ghobeishavi M. and Pourmotahari F. (2016): Hematological and liver toxicity of anti-tuberculosis drugs. *Electronic Physician*, Vol.8(9): 3005-3010.
- [49] Prasad U., Kumar J.M. and Madhu K. (2017): A Study of Changes in Liver Enzymes (ALT & AST) with Antitubercular Treatment in Newly Diagnosed Sputum Smear Positive Patients at Rims, Ranchi. *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) Vol. 16 (3 Ver. VIII): 09-11.*
- [50] Siregar S., Rezekiyah S., Karwiti W., Zuhdy N. and Putra E.S. (2024): Analysis of liver function and haemoglobin levels in pulmonary tuberculosis patients with anti-tuberculosis drug. *J. Kesehatan Manarang*, 10 (3), pp. 336 – 341
- [51] Perwitasari D.A., Setiawan D., Safaria T., Dania H., Faridah I.N. and Irham L.M. (2024): Liver Functions Profile of Tuberculosis Patients in Indonesia During Antituberculosis Treatment. *Int. J. of Applied Pharmaceutics*. Vol. 16(1):89-92
- [52] Akkahadsee P., Jantharaksa S., Sawangjit R. and Phumart P. (2024): Incidence, outcomes, and risk factors of antituberculosis drugs induced liver injury in Thailand: A retrospective cohort study. *Pharmacy Practice*; 22(2):1-7
- [53] Metushi I.G., Cai P., Zhu X., Nakagawa T. and Uetrecht J.P. (2011): A Fresh Look at the Mechanism of Isoniazid-Induced Hepatotoxicity. *Clinical Pharmacology & Therapeutics*, 89 (6):911-914.
- [54] Shi W., Zhang X., Jiang X., Ruan H., Clifton E., 3rd B., Wang H., Zhang W. and Zhang Y. (2011): Pyrazinamide inhibits trans-translation in Mycobacterium tuberculosis: a potential mechanism for shortening the duration of tuberculosis chemotherapy. *NIH Public Access Sci.*; 333(6049): 1630–1632.

- [55] Sarma G.R., Immanuel C., Kailasam S., Narayana A.S., Venkatesan P. (1986): Rifampin-induced release of hydrazine from isoniazid: a possible cause of hepatitis during treatment of tuberculosis with regimens containing isoniazid and rifampin. *Am. Rev. Respir. Dis.*, 133: 1072-1075.
- [56] Yew W.W. and Leung C.C. (2006): Antituberculosis drugs and hepatotoxicity. *Respirology*, 11:699–707
- [57] Ramappa V. and Aithal G. (2012): Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms and Management. *Journal of Clinical and Experimental Hepatology*: pp: 1–13
- [58] Ohno M., Yamaguchi I., Yamamoto I., Fukuda T., Yokota S., Maekura R., Ito M., Yamamoto Y., Ogura T., Maeda K., Komuta K., Igarashi T., Azuma J. (2000): Slow N-acetyltransferase 2 genotype affects the incidence of isoniazid and rifampicin-induced hepatotoxicity. *Intl. J. of Tuberc. Lung Dis.*, Vol.4(3): 256-261.
- [59] Skuhala T., Dragobratović A., Marinković L., Ramljak K., Rimac M., Pavelić A. and Lepej S.-Z. (2026): Antitubercular Drug-Induced Liver Injury in the Treatment of Tuberculous Lymphadenitis: A Comprehensive Review. *Livers* 6,(19):2-29 available at <https://doi.org/10.3390/livers6020019>.
- [60] Petersen P.H. (1999): Quality specifications based on the analysis of effects of performance on clinical decision-making, *Scand. J. Clin. Lab. Invest.* 59:517–521.
- [61] Petersen P.H. (2002): Importance of the choice of assumptions and models in the estimation of analytical quality specifications, *Accred Qual. Assur.* 7:488–493.
- [62] Schmidt R., and Factor R., (2013): Understanding Sources of Bias in Diagnostic Accuracy Studies. *Arch Pathol Lab Med*,137: 1-8
- [63] Tanner L.T.A. and Cheung K.L. (2020): Correlation between breast cancer and lifestyle within the Gulf Cooperation Council countries: A systematic review. *World J. of Clinical Oncology*; 11(4): 217-242
- [64] Chalasani N. and Björnsson E. (2010): Risk Factors for Idiosyncratic Drug-Induced Liver Injury. *Gastroenterology* Vol. 138, (7):2246–2259
- [65] Björnsson E.S. (2014): Epidemiology and risk factors for idiosyncratic drug-induced liver injury. *Semin Liver Dis*; 34:115–22.
- [66] Li H., He J., and Jia W. (2016): The influence of gut microbiota on drug metabolism and toxicity. *Expert Opin Drug Metab Toxicol*; 12(1): 31–40

- [67] Blumberg H.M., Burman W.J., Chaisson R.E., Daley C.L., Etkind S.C., Friedman L.N., Fujiwara P., Grzemska M., Hopewell P.C., Iseman M.D., Jasmer R.M., Koppaka V., Menzies R.I., O'Brien R.J., Reves R.R., Reichman L.B., Simone P.M., Starke J.R., Vernon A.A., (2003): American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. In, American Thoracic Society/Centers for Disease Control and Prevention/ Infectious Diseases Society of America: treatment of tuberculosis. *Am. J. Respir. Crit. Care. Med.*, 167: 603-662.
- [68] Zhao H., Wang Y., Zhang T., Wang Q. and Xie W. (2020): Drug-Induced Liver Injury from Anti-Tuberculosis Treatment: A Retrospective Cohort Study. *Med Sci Monit*, pp: 1-8
- [69] Zade D.D. and Raut P. (2023): Hepatotoxicity Induced by Anti-Tuberculosis Medications: Exploring Causes, Risk Factors, and Potential Mitigation Strategies. *J. of Drug Delivery and Biotherapeutics*. pp: 1-10
- [70] Perwitasari D.A., Safaria T., Setiawan D., Dania H., Fatimah S.A. and Faridah I.N. (2025): Liver functions and medication adherence in tuberculosis patients after 6 months of antituberculosis treatment in Indonesia. *J. of Inter. Med. Research*, 53(6) 1–10.
- [71] Petros Z., Tamirat A. and Assefa W. (2025): Antitubercular drug induced liver injury among tuberculosis patients in central Ethiopia. *Scientific Reports*, 15:1-8
- [72] Ebata-Mboussa E.F., Assiana D.O.E., Moyen N., Mouzinga F.H., Bonsi S.T., Elenga E.B., Okemba-Okombi F.H. and Ondzia F.R.O. (2026): Anti-tuberculosis drug-induced hepatotoxicity among patients undergoing tuberculosis treatment at the Antituberculosis Center of Brazzaville, Republic of Congo. *Int. Soc. for Infectious Diseases*, 19:1-6
- [73] Lei Z., Yang Y., Guo X., Zhao K., Zhang B. and Ma A. (2023): Effect of persistent malnutrition on pulmonary tuberculosis treatment: A cross-sectional study in Weifang, China. *Asia Pac J Clin Nutr*; 32(2):206-214.
- [74] Makaminan M.A., Tumbol M.V.L and Sumampouw J.E. (2022): Description of Liver Function on the Effect of Treatment on

Pulmonary Tuberculosis Patients at the Manado City Health Center. *International Conference of Medical Laboratory Technology (ICoMLT)* pp: 1-11.

- [75] Khan Z.H. Warke S.S. (2012): Effect of Antituberculosis Drugs on Levels of Serum Proteins in Pulmonary Tuberculosis Patients. *International Journal of Pharmaceutical Research & Allied Sciences*. 1(3):94-100
- [76] Hadida M, Abo-Smhadana A. and Draid M. (2013): Effects of Anti-Tuberculous Drugs on Liver Function Profile in Libyan Patients with Tuberculosis. *The Egyptian Journal of Hospital Medicine*, 52: 740–751
- [77] Das R.N., Mukherjee S. and Sharma I. (2018): Alkaline Phosphatase Determinants of Liver Patients. *J of The Pancreas*, 19(1):18-23.
- [78] Molla Y., Wubetu M. and Dessie B. (2021): Anti-Tuberculosis Drug Induced Hepatotoxicity and Associated Factors among Tuberculosis Patients at Selected Hospitals, Ethiopia. *Hepatic Medicine: Evidence and Research*, 13: 1–8