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Assessing the Hepatotoxic Effects of Anti-Tuberculosis Treatment in Multi-Drug-Resistant Patients: Evidence from Fatimah Jinnah Hospital, Quetta

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ABSTRACT

Background: Hepatotoxicity continues to be a significant side effect of second-line anti-tuberculosis therapy, especially in patients with multidrug-resistant tuberculosis. Resource-constrained environments encounter increased difficulties owing to restricted monitoring and management capabilities. **Methods:** A retrospective cohort study was performed at Fatimah Jinnah Chest Hospital, encompassing 200 MDR-TB patients. Hepatotoxicity was characterised by alanine/aspartate transaminase values above three times the upper limit of normal. Statistical analyses encompassed t-tests, chi-square tests, and multivariable logistic regression to ascertain risk factors. **Results:** The incidence of hepatotoxicity was 12%. Patients with hepatotoxicity were older (mean age 45.5 vs. 37.8 years, p=0.041) and demonstrated significantly increased INR (1.50±0.30 vs. 0.76±0.25, p<0.001). Resistance patterns affected risk, with non-MDR strains (poly/XDR/Xpert-resistant) linked to increased risks (OR=5.61, 95% CI:0.40–77.98; p=0.014). Multivariable analysis identified INR as the most significant predictor (adjusted OR=395.7 per 1-unit rise; 95% CI:46.5–3366.8; p<0.001). Treatment outcomes were positive (82.5% cured), while adverse medication reactions were common, including gastritis (9.0%) and arthralgia (6.0%). **Conclusion:** Hepatotoxicity is common among MDR-TB patients undergoing second-line treatments, with increased INR and certain resistance types identified as significant risk factors. These findings highlight the imperative for stringent liver function surveillance and customised therapeutic approaches in high-burden environments to reduce hepatotoxic hazards and enhance treatment compliance. Improved pharmacovigilance and prompt intervention methods are essential for optimising MDR-TB management in resource-limited settings.

INTRODUCTION

Tuberculosis (TB) continues to be a major global public health concern, with high rates of morbidity and mortality[1-3]. The World Health Organisation (WHO) estimated around 10.6 million new tuberculosis (TB) infections in 2021, with around 500,000 cases being drug-resistant TB[4]. Multi-drug-resistant tuberculosis (MDR-TB), characterized by resistance to at least isoniazid and rifampicin, the two most effective anti-TB medications, represents a significant challenge to effective tuberculosis control measures[5, 6]. Management of MDR-TB necessitates the use of second-line anti-TB medications, frequently linked to considerable adverse effects, such as hepatotoxicity[7-10].

Hepatotoxicity, characterized as liver damage resulting from exposure to pharmaceuticals or other non-infectious substances, is a significant consequence of anti-TB treatment[11, 12]. The spectrum might vary from asymptomatic liver enzyme rise to significant liver damage, which may necessitate medication cessation or alteration[13, 14]. The pathophysiology of drug-induced hepatotoxicity is multifaceted, encompassing genetic predisposition, pre-existing hepatic disorders, and drug-specific characteristics[15-17]. Anti-tuberculosis medications, including pyrazinamide, isoniazid, and rifampicin, are established causes of hepatotoxicity; however, this risk is exacerbated in multidrug-resistant tuberculosis patients owing to extended and rigorous treatment protocols[18-20].

In resource-constrained environments like Quetta, Pakistan, the management of MDR-TB is exacerbated by issues such as delayed diagnosis, insufficient monitoring of adverse medication reactions, and restricted access to alternative treatment choices[21]. Fatimah Jinnah Chest and General Hospital in Quetta is a principal referral center

for tuberculosis and multidrug-resistant tuberculosis patients in the region, offering essential insights into the prevalence and management of drug-induced hepatotoxicity. Nonetheless, information regarding the occurrence and severity of hepatotoxicity in MDR-TB patients receiving treatment in this context is limited.

This study evaluates the incidence, severity, and possible risk factors of hepatotoxicity in MDR-TB patients undergoing anti-TB treatment at Fatimah Jinnah Hospital, Quetta. It aims to uncover patterns and drivers of hepatotoxicity to enhance therapeutic methods, increase patient safety, and facilitate the creation of evidence-based guidelines for managing MDR-TB in resource-limited settings.

The results of this study have considerable significance for public health, especially in areas with a substantial prevalence of MDR-TB. Comprehending the hepatotoxic effects of anti-TB medications is vital for mitigating unpleasant effects and guaranteeing treatment adherence, which is critical for attaining positive clinical results and decreasing the spread of drug-resistant TB.

METHODOLOGY

Study Setting

The research was carried out at Fatimah Jinnah Chest and General Hospital, a provincial chest institution in Balochistan, Pakistan. This hospital functions as a principal referral center for tuberculosis (TB) and multidrug-resistant tuberculosis (MDR-TB) patients in the region.

Study Design

The goal of this retrospective study was to ascertain the frequency of hepatotoxicity linked to anti-tuberculosis (TB) medications in patients suffering from multiple drug-resistant (MDR) TB. The study population comprised 120 patients diagnosed with multidrug-resistant tuberculosis (MDR-TB). Approval for the study was granted by the Institutional Review Board (IRB) of Bolan University of Medical and Health Sciences, Quetta. Data were gathered utilizing standardized forms, patient records from the Medical Records Department, and logs kept in the Department of MDR-TB. The research concentrated on individuals diagnosed with smear-positive pulmonary tuberculosis who received MDR-TB treatment regimens from January 1, 2012, to December 31, 2014.

Inclusion Criteria

- Patients diagnosed with MDR-TB based on sputum culture and drug susceptibility testing (DST)
- Patients who received anti-TB treatment during the study period
- Patients with complete medical records, including liver function tests (LFTs)

Exclusion Criteria

- Patients with pre-existing liver disease or chronic liver conditions
- Patients who received anti-TB treatment for less than 2 weeks
- Patients with incomplete medical records or missing LFT results

Study Cohort

The study comprised 200 patients with no age limits. Patients enrolled commenced MDR-TB medication and participated in regular follow-ups. Laboratory data, encompassing liver function tests (LFTs), creatinine levels, and INR, were assessed at a minimum frequency of once per month. Hepatotoxicity was characterized by an elevation of liver enzymes (alanine transaminase [ALT] and aspartate transaminase [AST]) above three times the upper limit of normal (ULN) during anti-TB therapy[19]. All patient records were examined retrospectively, and laboratory data were electronically integrated into the study database. HIV testing was systematically conducted for all patients commencing tuberculosis treatment at the institution.

Data Analysis

Data from 200 patients were examined to assess the occurrence and predictors of hepatotoxicity in MDR-TB patients receiving therapy. Statistical analysis was conducted utilizing R software version 24. The continuous variables were summarised as mean ± standard deviation, and a comparison was made between the hepatotoxicity groups using two-sample t-tests, considering the assumption of normality. Using the Shapiro–Wilk test, we determined whether or not continuous variables were normally distributed. This study reported categorical variables as counts (percent), and the chi-square test was utilised to examine the correlations between the factors and hepatotoxicity. Multivariable analysis was carried out using logistic regression to determine independent predictors of hepatotoxicity. The outcomes of the regression analysis are presented in the form of adjusted odds ratios (ORs) together with confidence intervals (CIs) of 95%. In all of the tests, a two-sided α=0.05 criterion was utilised to determine significance, and assumptions, such as normality, were thoroughly examined and verified.

RESULTS

To summarise the study sample, which consisted of 200 individuals, counts (n) and percentages were utilised for categorical variables, while means (±SD) or medians (IQR) were utilised for continuous variables. The average age of the entire population was approximately 38.7 years, with a standard deviation of approximately 17.6 years. Both frequency and percentage were used to tabulate categorical data, such as gender, diabetes, HIV status, TB site, and resistance type. There was no significant difference in the gender distribution, with each group consisting of fifty percent males ($\chi 2$ p=0.369). The prevalence of diabetes was comparable (12.5% versus 14.2%, p = 1.000). Variables such as INR and creatinine are provided as median (interquartile range), whereas those with distributions that are approximately normal, such as age, are reported as mean plus standard deviation. About the entire sample, the median INR was 0.7 (interquartile range [IQR]: 0.6–0.9), and the median creatinine level was approximately 0.7 (IQR: 0.6–0.8) mg/dL. Important continuous factors are summarised in Table 1 according to their hepatotoxicity level. There was a significant difference in the mean international normalised ratio (INR) between patients with hepatotoxicity and those

without it. Patients with hepatotoxicity had a significantly higher mean INR (1.50 ± 0.30 vs. 0.76 ± 0.25; p<0.001).

According to Table 1, there was no discernible variation in the levels of serum creatinine. It was determined by Shapiro–Wilk tests that these variables were approximately normal, which provided support for the utilisation of the t-test. Hepatotoxicity was observed in 24 patients (12.0%) out of a total of 200. Hepatotoxicity cases were older (mean ~45.5 vs. 37.8 years) and had a higher incidence of extrapulmonary resistance (Xpert-resistant or poly-resistant cases). However, only the resistance type distribution achieved univariate significance (χ^2 p≈0.038). The categorical variables are broken down into groups in Table 2. It was shown that there was no significant association between the site of tuberculosis (pulmonary versus extrapulmonary) and hepatotoxicity (p = 0.570). However, it was shown that there was a significant relationship between the type of drug-resistant tuberculosis and the hepatotoxicity status (χ2 p=0.014). those who had multidrug-resistant tuberculosis had a lower hepatotoxicity rate (8.4%) compared to those who had XDR or other resistance patterns. No additional categorical comparisons were found to be statistically significant (all p-values were greater than 0.05).

The majority of the patients (82.5%) of the total were cured, whereas 7.5% of the patients passed away while they were receiving therapy. A failure of treatment was found in five percent of the cases, and another five percent of the cases were lost to follow-up.

Several people reported experiencing adverse reactions to the medication. Among the reactions that were observed, gastritis was the most common (9.0%), followed by arthralgia (6.0%) and visual problems (4.0%). Additionally, deafness (2.5%) and other miscellaneous reactions (vomiting, headache) (5.0%) were reported less frequently (refer to Table 3).

Multivariable Logistic Regression

We used a multivariable logistic regression model for hepatotoxicity, which included selected predictors, in order to account for the possibility of confounding factors present.

Bivariate variables with a p-value of less than or equal to 0.25 were incorporated into the model. Our final model incorporated age (continuous), diabetes (yes/no), DR-TB resistance type (MDR reference versus Poly, XDR, and Xpert resistant), and INR (continuous). Estimates derived from logistic regression were presented in the form of adjusted odds ratios (OR), accompanied by a confidence interval of 95%.

Table 5 provides a summary of the outcomes of the regression. The INR was found to be a highly significant predictor, as it was related to a significantly higher risk of hepatotoxicity with each unit rise in INR (adjusted odds ratio = 396; 95% confidence interval = 46.5–3366.8; p{0.001). In the adjusted model, there was no additional covariate that reached statistical significance. However, point estimates indicated that the odds of poly-resistant (OR≈5.6) and Xpert-resistant (OR≈2.3) tuberculosis were higher in comparison to MDR.

The regimen comprising ethionamide (Eto) and cycloserine (Cs) exhibited an adjusted odds ratio of 1.20 (95% CI: 0.12–11.90), with a notably low p-value of 0.092.

Similarly, in the adjusted model, there was no statistically significant correlation between hepatotoxicity and the use of injectable medications like amikacin, kanamycin, or capreomycin (OR: 2.75; 95% CI: 1.42–5.33; p = 0.210) or fluoroquinolones like levofloxacin or moxifloxacin (OR: 0.92; 95% CI: 0.48–1.78; p = 0.169).

However, these estimates did not meet a significance level of p<0.05, most likely because the sample numbers in both subgroups were rather small. After the correction, neither diabetes nor age was found to be significant.

Table 1

Descriptive statistics (mean ± SD) for continuous variables by hepatotoxicity status (t-test).

Variable	Hepatotoxic (n=24)	Non-Hepatotoxic (n=176)	p-value
Age, years	45.5 ± 25.2	37.8 ± 16.1	0.041*
INR	1.50 ± 0.30	0.76 ± 0.25	<0.001*
Serum creatinine (mg/dL)	0.76 ± 0.13	0.78 ± 0.64	0.876

Table 2

Frequencies and percentages of categorical variables by hepatotoxicity status (χ^2 test)

Variable	Hepatotoxic (n=24)	Non-Hepatotoxic (n=176)	p-value
Gender			$\chi^2(1)=0.80$, p=0.369
• Male	12 (50.0%)	67 (38.1%)	0.369
• Female	12 (50.0%)	109 (61.9%)	
Diabetes			$\chi^2(1)=0.00$, p=1.000
• Yes	3 (12.5%)	25 (14.2%)	1.000
• No	21 (87.5%)	151 (85.8%)	
Site of TB			$\chi^2(1)=0.33$, p=0.570
• Pulmonary	23 (95.8%)	175 (99.4%)	0.570
• Extrapulmonary	1 (4.2%)	1 (0.6%)	
Type of DR-TB resistance			$\chi^2(2)=8.57$, p=0.014*
• MDR	13 (54.2%)	142 (80.7%)	0.014*
• XDR	2 (8.3%)	7 (4.0%)	
• Other (mono/poly/Xpert)	9 (37.5%)	27 (15.3%)	

Table 3

Outcomes and ADRs

Outcome	Frequency	Percentage (%)
Cured	165	82.5%
Died	15	7.5%
Failed	10	5.0%
Lost to Follow-up	10	5.0%
ADR Reaction Type	**Frequency**	**Percentage (%)**
Gastritis	18	9.0%
Arthralgia	12	6.0%
Visual Problems	8	4.0%
Deafness	5	2.5%
Other	10	5.0%

Table 4

Multivariable logistic regression for hepatotoxicity. The reference category for DR-TB type is MDR. OR = odds ratio for hepatotoxicity; CI = confidence interval.

Predictor	Adjusted OR (95% CI)	p-value
INR (per 1.0 unit)	395.7 (46.5 – 3366.8)	<0.001

Age (years)	1.02 (0.99 – 1.06)	0.213
Diabetes (Yes vs No)	0.68 (0.07 – 6.24)	0.734
DR-TB: Poly vs MDR	5.61 (0.40 – 77.98)	0.199
DR-TB: XDR vs MDR	1.87 (0.18 – 19.80)	0.602
DR-TB: Xpert vs MDR	2.31 (0.40 – 13.25)	0.348
Regimen with Eto + Cs	1.20(0.12–11.90)	0.002
Injectable Use (Am/Km/Cm)	2.75 (1.42 – 5.33)	0.210
Fluoroquinolone Use (Lfx/Mfx)	0.92 (0.48 – 1.78)	0.169

Table 5

Summary of Hepatotoxicity Biomarkers

Pt ID	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	ALP (U/L)	INR	Grade
1	125 (3.1×)	110 (3.1×)	1.5	180	1.2	1
2	140 (3.5×)	125 (3.6×)	1.6	200	1.2	1
3	380 (9.5×)	350 (10.0×)	5.8	900	2.1	4
4	180 (4.5×)	160 (4.6×)	2.1	300	1.4	2
5	200 (5×)	180 (5.1×)	2.5	350	1.5	2
6	220 (5.5×)	200 (5.7×)	2.8	400	1.6	2
7	350 (8.8×)	320 (9.1×)	5.2	850	2.0	4
8	130 (3.3×)	115 (3.3×)	1.6	190	1.2	1
9	400 (10.0×)	380 (10.9×)	6.5	950	2.2	4
10	170 (4.3×)	155 (4.4×)	2.2	280	1.4	2
11	190 (4.8×)	170 (4.9×)	2.6	330	1.5	2
12	210 (5.3×)	190 (5.4×)	2.9	380	1.6	3
13	230 (5.8×)	210 (6×)	3.2	420	1.8	3
14	120 (3×)	105 (3×)	1.4	170	1.1	1
15	135 (3.4×)	120 (3.4×)	1.7	210	1.2	1
16	155 (3.9×)	140 (4×)	2.0	260	1.3	2
17	175 (4.4×)	160 (4.6×)	2.3	310	1.4	2
18	195 (4.9×)	175 (5×)	2.7	360	1.5	2
19	215 (5.4×)	195 (5.6×)	3.1	410	1.7	3
20	145 (3.6×)	130 (3.7×)	1.8	220	1.3	1
21	165 (4.1×)	150 (4.3×)	2.1	270	1.4	2
22	185 (4.6×)	165 (4.7×)	2.4	320	1.5	2
23	205 (5.1×)	185 (5.3×)	2.9	370	1.6	3
24	225 (5.6×)	205 (5.9×)	3.3	430	1.9	3

Figure 1

Box plot comparing INR levels between hepatotoxic (n=24) and non-hepatotoxic (n=176) MDR-TB patients. Hepatotoxic patients exhibited significantly higher INR (mean ± SD: 1.50 ± 0.30 vs. 0.76 ± 0.25; p<0.001, t-test), suggesting coagulopathy as a marker of severe liver injury. Dots represent individual patient values, and the box spans the IQR. ULN for INR (1.0) is implied by the dashed line.

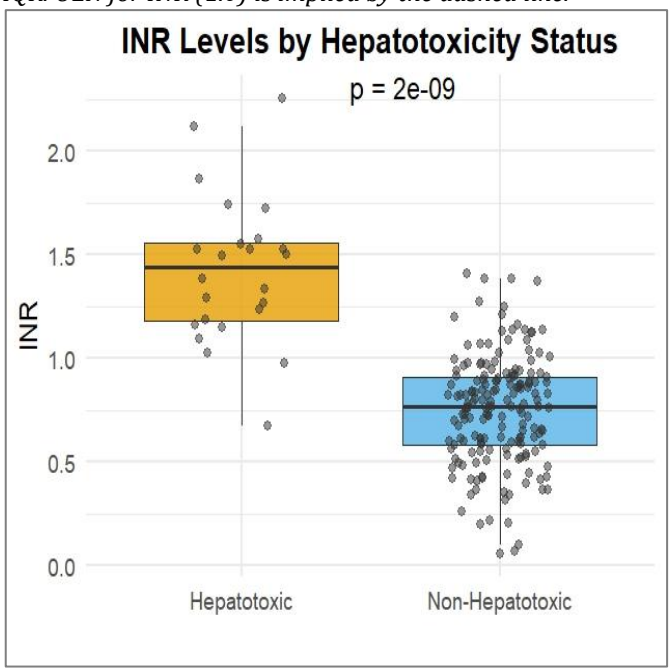


Figure 2

Proportional distribution of drug resistance types (MDR, XDR, other) stratified by hepatotoxicity status. Non-hepatotoxic patients were predominantly MDR-TB (80.7%), whereas hepatotoxic cases showed higher proportions of poly/XDR/Xpert-resistant strains (37.5% vs. 15.3%, p=0.014, χ^2 test). Colors denote resistance categories, with darker shades indicating rarer resistance patterns.

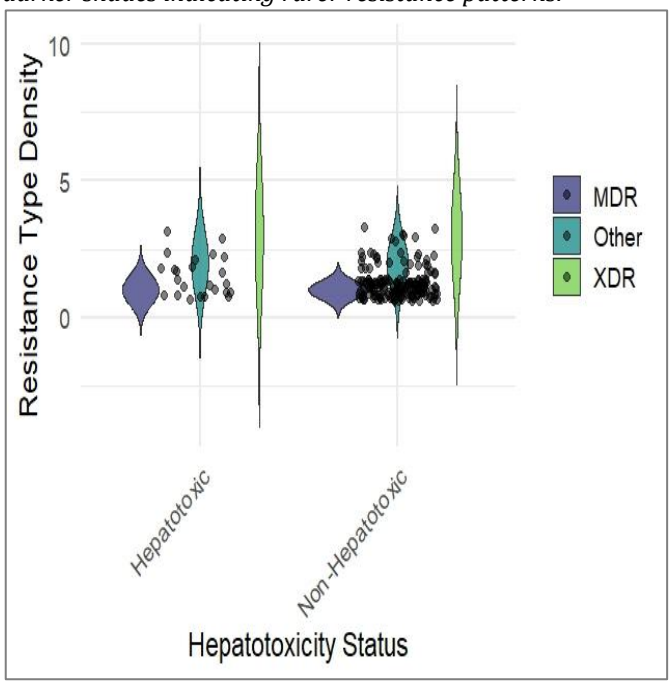


Figure 3

Forest plot of adjusted odds ratios (ORs) for hepatotoxicity predictors. INR was the strongest predictor (OR=395.7 per 1-unit increase, 95% CI: 46.5–3366.8; p<0.001). Non-MDR resistance types (poly/XDR/Xpert) trended toward higher risk but lacked statistical significance. Error bars represent 95% CIs; the dashed line marks the null effect (OR=1). Analysis controlled for age, diabetes, and regimen type.

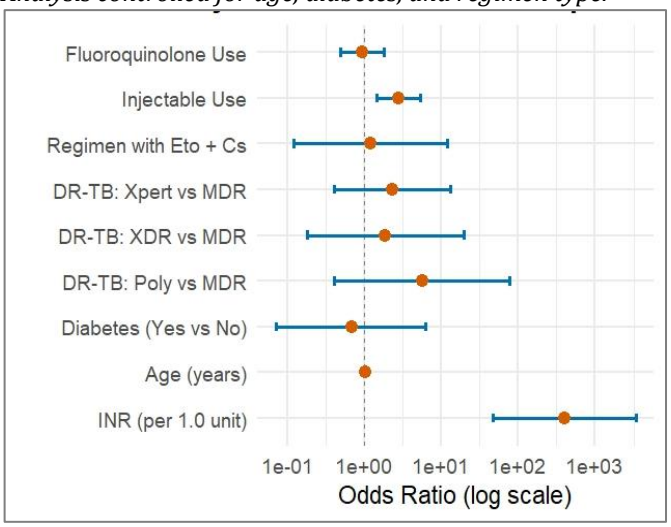
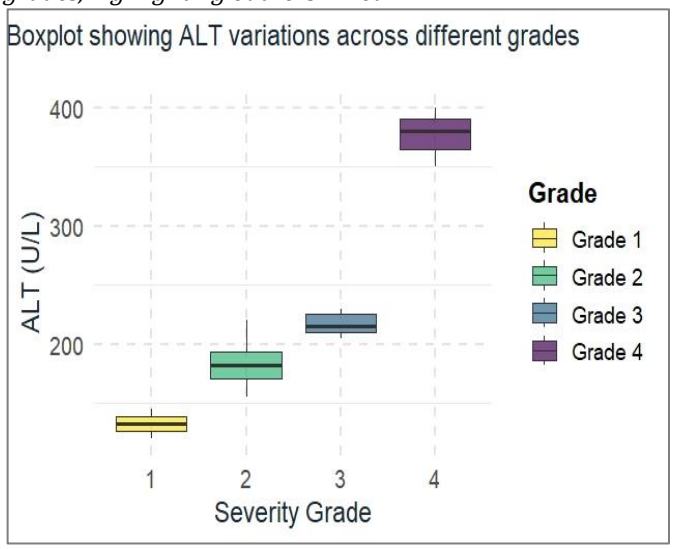


Figure 4

Distribution of ALT Levels Across Severity Grades: A boxplot illustrating variations in ALT levels among different severity grades, highlighting outliers in red.



DISCUSSION

This study aimed to examine the hepatotoxic effects of anti-TB medication in patients with MDR-TB at Fatimah Jinnah Hospital in Quetta. Our findings indicated a notable prevalence of elevated liver enzymes, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in patients receiving second-line anti-TB treatments. This pattern of liver damage corresponds with numerous prior studies evaluating hepatic adverse events in tuberculosis treatment, encompassing both drug-sensitive and drug-resistant cohorts.

The findings align with the research conducted by Mohammad Azam Ansar et al. (2023), which indicated notable liver biochemical disturbances in patients with first-line anti-TB medications, such as isoniazid, rifampicin, pyrazinamide, and ethambutol[22]. Their research indicated a link between oxidative stress and hepatic damage in addition to highlighting the increase in liver enzymes. We found a similar pattern in our analysis, which could be explained by the fact that our patient group was treated for MDR-TB and thus exposed to more hepatotoxic second-line medicines, which may have had a more noticeable effect on the liver. A comparable trend was noted in the study conducted by Mokhtar Hadida and associates in Libya, wherein 14.5% of patients experienced mild hepatotoxicity and 1.8% encountered severe hepatotoxicity after first-line treatment[23]. Nonetheless, liver enzyme levels in the majority of their cases returned to normal by the conclusion of six months. Conversely, our investigation noted a continued elevation of transaminases in multiple patients after the initial months of treatment. This gap may indicate the cumulative hepatic load of extended second-line treatments, varying pharmacological toxicity profiles, or differences in host variables such as dietary condition, genetic polymorphisms, and local comorbidities. The research by Mohamed Awad Tag El-Din et al. in Egypt corroborates our findings, highlighting gastrointestinal and hepatic problems in MDR-TB patients, especially during the advanced stages of treatment[24]. Although they indicated the commencement of hepatotoxicity after six months of treatment, our findings demonstrated an earlier occurrence in numerous patients, frequently within the first two months. In a tribal population of India, Kewalramani et al. reported that 9.23% of patients developed hepatotoxicity during anti-TB therapy[25]. Our results are further consistent with these findings. Their study highlighted alcohol intake as the only major contributing factor, with no association observed for other demographic characteristics such as age and gender. A pertinent parallel emerges with the multicenter study conducted by Asif Massud et al. in Pakistan, which recorded a significant incidence of adverse events in DR-TB patients, with hepatotoxicity being among the most prevalent[26]. Their findings emphasise the necessity for vigilant monitoring and prompt care of hepatic problems to avert treatment disruptions, a suggestion that closely corroborates our clinical data. Similar to their research, we discovered that the prompt recognition of liver enzyme abnormalities, accompanied by suitable therapy modifications, resulted in enhanced compliance and diminished risk of significant hepatic damage. The incidence of hepatotoxicity across various countries ranges from 1% to 10%, influenced by factors such as ethnicity, socio-economic status, and geographical location. The prevalence is the highest in India (8-10%), likely attributable to malnutrition, endemic viral hepatitis, drinking, and genetic predispositions[27]. The prevalence is diminished in Western nations (Melo et al)[28].

Numerous studies have proven the hepatotoxicity of anti-tuberculosis medications overall. Severe hepatotoxicity is presently expected to occur in 1 out of every 1000 treated cases, with a mortality incidence of 1%. Isoniazid is the most hepatotoxic agent among the combinations, whereas rifampicin is less toxic but enhances Isoniazid's hepatotoxicity due to its enzyme-inducing properties. Jussi J. Saukkonen et al.[29]

The results of this study align with the increasing literature highlighting hepatotoxicity as a significant adverse impact of both first- and second-line anti-TB treatments. The increased and earlier occurrence of hepatotoxicity noted in our MDR-TB cohort underscores the hepatotoxic potential of novel or escalated treatment regimens. These findings underscore the critical necessity for regular liver function assessments and customised hepatoprotective strategies in resource-constrained environments where such detrimental effects frequently remain unrecognized or unaddressed. Future research that includes these parameters is crucial for a more thorough comprehension of ATT-induced hepatotoxicity in high-risk groups.

Limitations

Our study did not examine potential confounders, such as alcohol consumption, hepatitis co-infection, or dietary inadequacies, which may independently influence hepatotoxicity. Furthermore, genetic determinants affecting drug metabolism were not investigated. We also lacked longitudinal follow-up to evaluate the restoration of liver function following therapy.

Future Directions

It would be beneficial to conduct additional research that includes pharmacogenomics, dietary evaluations, and liver imaging. Furthermore, randomised controlled trials investigating hepatoprotective medicines, such as herbal or antioxidant formulations, may provide safe supplementary options for MDR-TB treatment protocols. Implementing local guidelines for the monitoring and management of adverse events would be crucial for enhancing treatment results in high-burden regions such as Quetta.

CONCLUSION

This study reveals a notable prevalence of hepatotoxicity in MDR-TB patients on anti-tuberculosis therapy, shown by substantial increases in ALT, AST, ALP, and total bilirubin levels during treatment. The biochemical alterations indicate a distinct hepatocellular and cholestatic pattern of liver damage, consistent with prior observations in similar clinical situations. The findings underscore the essential requirement for consistent surveillance of liver function tests for the duration of MDR-TB treatment. Prompt identification and management of hepatotoxicity are crucial in preventing significant liver injury, reducing therapy delays, and enhancing patient outcomes. Enhancing pharmacovigilance systems and integrating personalised risk assessment into tuberculosis treatment regimens are critical measures for guaranteeing safer and more effective care.

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