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ORIGINAL ARTICLE

Histopathological Predictors of Drug-Induced Liver Injury in Hospitalized Adults Receiving Long-Term Pharmacotherapy

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ABSTRACT

Background: Drug-induced liver injury (DILI) presents significant diagnostic and prognostic challenges among patients receiving long-term pharmacotherapy. Histopathological assessment may provide valuable insights into hepatic injury severity and subsequent biochemical recovery.

Objective: To evaluate the association between hepatic histopathological features and persistent biochemical abnormalities at six months among hospitalized adults with DILI.

Material and Methods: This multicenter retrospective observational study included 150 hospitalized adults evaluated for suspected DILI during prolonged pharmacotherapy at participating institutions in Sialkot, Lahore, and Quetta, Pakistan, from January 2022 to February 2023. Histopathological parameters included hepatocellular necrosis, interlobular bile duct paucity, portal and lobular inflammation, cholestasis, ductular reaction, and fibrosis. Associations with six-month biochemical outcomes were assessed using univariable statistical analyses.

Results: Of 150 patients, 72 (48.0%) were men and 78 (52.0%) were women. At six months, 111 patients (74.0%) achieved biochemical recovery, while 39 (26.0%) exhibited persistent abnormalities. Portal inflammation (67.3%) and lobular inflammation (66.0%) were the most frequently observed histopathological findings. Interlobular bile duct paucity was significantly associated with biochemical persistence (odds ratio [OR] 5.04; 95% confidence interval [CI] 1.92–13.19; p=0.001), as was confluent hepatocellular necrosis (OR 4.06; 95% CI 1.89–8.74; p<0.001).

Conclusion: Interlobular bile duct paucity and confluent hepatocellular necrosis demonstrated significant unadjusted associations with persistent biochemical abnormalities at six months. These histopathological features may contribute to identifying patients at increased risk of delayed biochemical recovery following DILI.

Keywords: Drug-induced liver injury; Histopathology; Bile duct paucity; Hepatocellular necrosis; Biochemical recovery; Long-term pharmacotherapy.

INTRODUCTION

Drug-induced liver injury (DILI) is a clinically significant cause of hepatic dysfunction and represents an important challenge in modern pharmacotherapy[1]. It includes a broad and diverse spectrum of liver abnormalities from raised liver enzymes which may be silent, through to acute liver failure, cholestasis and chronic liver abnormality. The use of long-term use of drugs to treat chronic diseases, especially for those with multiple co-morbidities and exposures to multiple drugs, has made the recognition and management of hepatotoxic reactions more complicated[2]. While biochemical improvement is seen in most patients after stopping the offending drug, a subset of patients has persistent liver dysfunction and/or ongoing liver injury, and reliable prognostic markers are important[3].

DILI pathogenesis is complex, and is related to the metabolism of drugs, mitochondrial dysfunction, oxidative stress, immune-mediated response, and individual susceptibility[4,5]. Hepatotoxic reactions can occur by direct dose-dependent and idiosyncratic mechanisms involving genetic, metabolic and immunological factors. Patients on pharmacotherapy for an extended period of time may present with other diagnostic problems due to polypharmacy, underlying metabolic disorders and pre-existing liver abnormalities. Therefore, careful evaluation of the pattern of biochemical injury, other causes of liver disease, and medication exposure is required during clinical assessment. Although conventional laboratory parameters, such as the alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, and international normalized ratio, remain important for the evaluation of liver injury, they are not always useful for the characterization of structural liver damage or prediction of recovery[6,7].

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Histopathological examination is an important complementary technique in understanding the morphological features and severity of DILI. Liver biopsy is not usually necessary in uncomplicated cases, but it can be useful for those who have severe, persistent or complex liver abnormalities that have not been diagnosed[8]. Histologic features include hepatocellular ballooning, lobular and portal inflammation, spotty or confluent necrosis, cholestasis, bile duct epithelial injury, ductular reaction, steatosis, granulomatous inflammation, and fibrosis to varying extents. These findings indicate varying mechanisms and localization of liver damage and may offer a prognostic clue in addition to the commonly used biochemical tests[9,10].

Pathological features of DILI consist of hepatocellular, inflammatory, cholestatic and bile duct abnormalities. Histological examination may be useful to aid the diagnostic evaluation when clinical and biochemical findings are inconclusive. Specifically, there may be bile duct injury in cholestatic DILI; and, the extent of the inflammation and fibrosis has been associated with biochemical nonresolution in published cohorts[11-13].

New clinicopathological studies validate the combination of liver biopsy with clinical evaluation. Ahmad et al. identified that review of a biopsy may increase a diagnostic certainty in a select patient with suspected DILI[14]. Wang et al. found associations with histological inflammatory activity, fibrosis stage, and biochemical nonresolution at 12 months in the large multicenter cohort. This combined data is in favour of structured histopathological interpretation, especially one that has well-defined clinical end points[15].

However, the significance of certain histopathology characteristics in the context of prolonged drug use among hospitalised adults remains to be explored[15]. Polypharmacy and comorbidities, together with the possibility of overlapping causes of liver injury, complicate this clinical scenario. Microscopic findings must be adjusted for baseline clinical characteristics and disease

severity in assessing whether these findings predict biochemical recovery[16].

The current study examined the histopathological characteristics of suspected drug-induced liver injury among hospitalized adults receiving long-term pharmacotherapy and their relationship with six-month biochemical status. Of interest were hepatocellular necrosis, fibrosis, cholestasis, bile duct abnormalities, ductular reaction and portal/lobular inflammation.

MATERIALS AND METHODS

Study Design and Setting: A multicenter retrospective observational study was conducted from January 2022 to February 2023 at Khawaja Muhammad Safdar Medical College, Sialkot, and the Department of Pharmacology, Allama Iqbal Medical College, Lahore, Pakistan. The clinical and pharmacological data were also collected from the Department of Pharmacology, Bolan Medical College, Quetta, Pakistan. This study assessed the hepatic histological features and their correlation to biochemical findings at 6 months in hospitalized adults with suspected drug induced liver injury (DILI) who are on long term pharmacotherapy.

Study Population and Eligibility Criteria: One hundred and fifty hospitalized adult patients over 18 years of age with suspected DILI who had received prolonged pharmacological therapy, were included in the study. Long-term pharmacotherapy: regular prescription drug use for at least 3 months prior to liver abnormalities. The criteria for inclusion were: documented history of medication exposure, clinical and biochemical features compatible with DILI, liver biochemical investigations, and histopathological findings from clinically indicated liver biopsies. If these conditions provided a good explanation for the liver abnormalities, patients with alternative established causes of liver injury, including active viral hepatitis, primary autoimmune liver disease, biliary obstruction or ischemic hepatitis, were excluded.

Clinical and Laboratory Assessment: Clinical evaluation involved demographic data, underlying medical conditions, and drug usage and duration of treatment, as well as other drugs being administered, clinical presentation and laboratory findings of liver damage. Laboratory parameters were Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), total bilirubin, serum albumin and international normalized ratio (INR).

The biochemical pattern of hepatic injury was determined by the R ratio, which is the ratio of the level of ALT to the upper limit of normal (ULN) divided by the ratio of the level of ALP to the ULN. Hepatocellular injury was defined as R ratio ≥5; cholestatic injury was defined as R ratio ≤2 and mixed injury as R ratio > 2 and < 5 . Drug causality was determined based on temporal association between liver injury and drug exposure, biochemical response to drug discontinuation, and ruling out other causes of liver injury.

Histopathological Evaluation: Histopathology of the liver was evaluated from the available liver biopsy record. The main morphological features were portal and lobular inflammation, hepatocellular ballooning, spotty necrosis, confluent necrosis, canalicular cholestasis, bile duct epithelial damage, interlobular bile duct loss, ductular reaction, eosinophilic infiltration, granulomatous inflammation, hepatic steatosis, and fibrosis.

The biochemical injury pattern was correlated with the pathological findings and the 6-month clinical outcome. Special focus was placed on abnormalities of the bile ducts, hepatocellular necrosis, inflammatory changes and fibrosis to assess their relationship to biochemical abnormalities.

Outcome Assessment: The main outcome was biochemical liver abnormalities at 6 months after the initial presentation with suspected DILI. Patients were classified into biochemical recovery and biochemical persistent abnormalities group based on biochemical status at 6-months. The two outcome groups were compared in terms of histopathological features and the baseline clinical data. Liver transplantation, the development of severe hepatic deterioration, and liver-related mortality were not examined as individual endpoints of the study.

Statistical Analysis: Categorical data were presented in frequencies and percentages and continuous data were presented as medians and interquartile ranges (IQRs). The outcome groups were compared with respect to their biochemical injury pattern and their medication exposure categories using Pearson's chi-square test. Comparisons of the histopathological characteristics were done using Fisher's exact test.

Association between selected histopathological features and biochemical abnormalities at follow-up were evaluated using 2 × 2 contingency tables and univariable odds ratios (OR) with 95% confidence intervals (CI). All statistical tests were two sided, and a p value of < 0.05 was deemed to be statistically significant.

Ethical Considerations: Before the study was started, ethical approval was received from the institutional ethics committee.

RESULTS

Demographic and Clinical Characteristics: The current study included 150 hospitalized adults with suspected DILI, comprising 72 men (48.0%) and 78 women (52.0%). The median age was 53 years (IQR, 44-60 years) and the median time of pharmacological exposure was 8.3 months (IQR, 5.8-11.1 months). Biochemical recovery was seen in 111 patients (74.0%) and biochemical abnormalities were present in 39 patients (26.0%) at six months.

Persisting biochemical abnormalities were more common among patients with a higher median age than those who attained biochemical recovery (59 years versus 51 years). The sex distribution in the persistent-abnormality group was 56.4% female, while in the recovery group, it was 50.5%, and this difference was not statistically significant (p=0.579). Pharmacotherapy was used for a median of 8.9 months in patients with persistent abnormalities vs 8.2 months in patients who recovered. Table 1 shows the baseline demographic and biochemical parameters.

Pharmacological Exposure and Biochemical Injury Patterns: Antitubercular drugs were the most frequently identified medication category, accounting for 33 patients (22.0%), followed by antiepileptic drugs in 29 (19.3%), immunomodulatory agents in 25 (16.7%), lipid-lowering medications in 21 (14.0%), other antimicrobial agents in 20 (13.3%), and other medications in 22 (14.7%). The distribution of medication categories did not differ significantly between patients with biochemical recovery and those with persistent abnormalities at six months (χ^2=7.89; df=5; p=0.163).

Hepatocellular injury was the predominant biochemical pattern, observed in 83 patients (55.3%), followed by cholestatic injury in 42 (28.0%) and mixed injury in 25 (16.7%). Among patients with persistent biochemical abnormalities, hepatocellular injury was present in 17 (43.6%), cholestatic injury in 15 (38.5%), and mixed injury in seven (17.9%). No statistically significant association was identified between biochemical injury patterns and six-month outcomes (χ^2=3.43; df=2; p=0.180) (Table 2).

Histopathological Characteristics: Portal inflammation was the most frequently observed histopathological finding, identified in 101 patients (67.3%), followed by lobular inflammation in 99 (66.0%). Histological cholestasis was present in 60 patients (40.0%), hepatocellular ballooning in 57 (38.0%), and confluent hepatocellular necrosis in 52 (34.7%). Eosinophilic infiltration was observed in 50 patients (33.3%), prominent ductular reaction in 47 (31.3%), hepatic fibrosis and steatosis in 32 each (21.3%), interlobular bile duct paucity in 21 (14.0%), and granulomatous inflammation in 10 (6.7%).

Confluent hepatocellular necrosis was significantly more frequent among patients with persistent biochemical abnormalities than among those who achieved recovery (59.0% versus 26.1%; p<0.001). Similarly, interlobular bile duct paucity was identified in 30.8% of patients with persistent abnormalities compared with 8.1% of those with biochemical recovery (p=0.001). Although hepatic fibrosis was more frequent in the persistent-abnormality group (28.2% versus 18.9%), this difference was not statistically significant (p=0.258). No statistically significant differences were

observed for the remaining histopathological characteristics (Table 3).

Association Between Histopathological Findings and Persistent Biochemical Abnormalities: Univariable analysis identified interlobular bile duct paucity and confluent hepatocellular necrosis as the histopathological features most strongly associated with persistent biochemical abnormalities at six months. Interlobular bile duct paucity was associated with approximately fivefold higher odds of biochemical persistence (OR 5.04; 95% CI 1.92–13.19; p=0.001), while confluent hepatocellular necrosis was associated with approximately fourfold higher odds (OR 4.06; 95% CI 1.89–8.74; p<0.001).

Hepatic fibrosis (OR 1.68; 95% CI 0.72–3.91; p=0.258), lobular inflammation (OR 1.43; 95% CI 0.65–3.18; p=0.435), prominent ductular reaction (OR 1.13; 95% CI 0.52–2.47; p=0.841), and histological cholestasis (OR 0.92; 95% CI 0.43–1.94; p=0.852) did not demonstrate statistically significant associations with biochemical persistence (Table 4).

Table 1: Baseline demographic and biochemical characteristics according to six-month biochemical outcome

Characteristic	Overall (N=150)	Recovery (n=111)	Persistent abnormalities (n=39)
Age, years	53 (44–60)	51 (44–58)	59 (51–66)
Male, n (%)	72 (48.0)	55 (49.5)	17 (43.6)
Female, n (%)	78 (52.0)	56 (50.5)	22 (56.4)
Pharmacotherapy duration, months	8.3 (5.8–11.1)	8.2 (5.5–11.1)	8.9 (6.6–10.8)
ALT, U/L	373 (256–523)	392 (275–554)	295 (180–428)
ALP, U/L	226 (153–363)	203 (150–332)	253 (180–379)
Total bilirubin, mg/dL	3.9 (2.5–6.6)	3.6 (2.5–6.7)	4.2 (2.7–6.6)

Continuous variables are presented as median (IQR); categorical variables are presented as n (%).

Table 2: Distribution of medication exposure categories and biochemical injury patterns according to six-month outcomes

Variable	Overall (N=150), n (%)	Recovery (n=111), n (%)	Persistent abnormalities (n=39), n (%)
Medication categories			
Antitubercular drugs	33 (22.0)	26 (23.4)	7 (17.9)
Antiepileptic drugs	29 (19.3)	23 (20.7)	6 (15.4)
Immunomodulatory agents	25 (16.7)	18 (16.2)	7 (17.9)
Lipid-lowering drugs	21 (14.0)	11 (9.9)	10 (25.6)
Other antimicrobial agents	20 (13.3)	14 (12.6)	6 (15.4)
Other medications	22 (14.7)	19 (17.1)	3 (7.7)
Biochemical injury patterns			
Hepatocellular	83 (55.3)	66 (59.5)	17 (43.6)
Cholestatic	42 (28.0)	27 (24.3)	15 (38.5)
Mixed	25 (16.7)	18 (16.2)	7 (17.9)

Table 3: Histopathological characteristics according to six-month biochemical outcomes

Histopathological feature	Overall (N=150), n (%)	Recovery (n=111), n (%)	Persistent abnormalities (n=39), n (%)	p-value
Portal inflammation	101 (67.3)	75 (67.6)	26 (66.7)	1.000
Lobular inflammation	99 (66.0)	71 (64.0)	28 (71.8)	0.435
Hepatocellular ballooning	57 (38.0)	41 (36.9)	16 (41.0)	0.703
Confluent necrosis	52 (34.7)	29 (26.1)	23 (59.0)	<0.001
Histological cholestasis	60 (40.0)	45 (40.5)	15 (38.5)	0.852
Prominent ductular reaction	47 (31.3)	34 (30.6)	13 (33.3)	0.841
Interlobular bile duct paucity	21 (14.0)	9 (8.1)	12 (30.8)	0.001
Eosinophilic infiltration	50 (33.3)	36 (32.4)	14 (35.9)	0.697
Granulomatous inflammation	10 (6.7)	8 (7.2)	2 (5.1)	1.000
Hepatic steatosis	32 (21.3)	25 (22.5)	7 (17.9)	0.653
Hepatic fibrosis	32 (21.3)	21 (18.9)	11 (28.2)	0.258

Table 4: Univariable associations between selected histopathological features and persistent biochemical abnormalities at six months

Histopathological feature	Unadjusted OR	95% CI	p-value
Interlobular bile duct paucity	5.04	1.92–13.19	0.001
Confluent hepatocellular necrosis	4.06	1.89–8.74	<0.001
Hepatic fibrosis	1.68	0.72–3.91	0.258
Lobular inflammation	1.43	0.65–3.18	0.435
Prominent ductular reaction	1.13	0.52–2.47	0.841
Histological cholestasis	0.92	0.43–1.94	0.852

DISCUSSION

The current multicenter retrospective study investigated the association between hepatic histopathological characteristics and six-month biochemical outcomes among 150 hospitalized adults with suspected drug-induced liver injury (DILI) receiving prolonged pharmacotherapy[1]. Of the 133 patients, 74.0% recovered biochemically, while 26.0% had persistent abnormalities at 6 months. The most highly associated findings with persistent biochemical abnormalities were interlobular bile duct paucity and confluent hepatocellular necrosis. These results suggest that certain structural abnormalities in the liver can be of clinical significance in the evaluation of delayed biochemical recovery from DILI[2].

Biochemical persistence was found to be significantly associated with interlobular bile duct paucity (OR 5.04; 95% CI 1.92–13.19; p=0.001)[3]. The significant difference between the prevalence of BD paucity between the persistent abnormalities and non-persistent abnormalities groups (30.8% vs. 8.1%) indicates that structural damage of biliary structures may be especially important in ongoing biochemical abnormalities[4]. Damage to the interlobular bile ducts may affect the excretion of bile, and is likely to be a contributing factor in the ongoing cholestatic abnormalities. The role of bile duct injury (BDI) in the histopathology evaluation of DILI has been highlighted in previous investigations [5,8]. The current findings also suggest that bile duct integrity should be taken into account in assessing liver biopsy results in patients with chronic liver dysfunction[5,6].

Persistent biochemical abnormalities (OR 4.06; 95% CI 1.89–8.74; p<0.001) were also significantly associated with confluent hepatocellular necrosis. High prevalence was observed in patients with persistent abnormalities as compared to patients with biochemical recovery (59.0% versus 26.1%)[7,8]. An extensive

hepatocellular necrosis is indicative of severe parenchymal injury and can be accompanied by a prolonged tissue repair and a delayed recovery of the hepatic function. There has been extensive clinicopathological studies that have reported significant variability in the histological features and severity of DILI[9]. Ahmad et al showed the utility of liver biopsy in select patients with suspected DILI, highlighting the need for combining the morphological and biochemical and clinical data[10].

By comparison, none of the other features of the liver biopsy (hepatic fibrosis, lobular inflammation, prominent ductular reaction, and histological cholestasis) were statistically significantly associated with persistent biochemical abnormalities. The incidence of fibrosis was higher in patients with persistent abnormalities, but this was not significant[11-13]. In a multicenter cohort of patients with chronic DILI, Wang et al. reported associations with biochemical nonresolution, histological inflammation and fibrosis [9]. These differences may be due to differences in study populations, the histological characteristics of the patients or differences in follow-up duration, since biochemical results were measured at 12 months in that study, whereas the current study measured biochemical results at 6 months[14].

The most frequent exposure category of medications was antitubercular, followed by antiepileptic and immunomodulatory drugs. Medication-category distributions, though, were not significantly related to the 6-month biochemical outcomes[15]. The biochemical presentation was more common hepatocellular, while there was no significant difference between the distribution of general biochemical injury-pattern and persistence. Taken together, these observations highlight the diversity of DILI and indicate that certain histopathological findings might be useful in supplementing general biochemical injury profiles and exposure to pharmacologic agents. These findings are comparable to clinical heterogeneity observed in previous studies of DILI populations[10-14].

The clinical relevance of these findings is that the histopathological evaluation may be useful in the follow-up planning of patients with suspected DILI. Biopsies obtained for clinically indicated indications that show interlobular bile duct paucity or confluent hepatocellular necrosis might lead to identification of patients who need more frequent biochemical follow-up and longer clinical follow-up. However, histological features must be taken in conjunction with clinical features, history of drug exposure and biochemical severity[16,17].

There are some study limitations: it is a retrospective observational study, with possible selection bias in those who underwent liver biopsy for clinical indications, and a relative small number of patients with persistently abnormal biochemistry[18,19]. Further, it was univariable and did not account for potentially influential clinical factors. Thus, the found relationships are unable to determine any independent prognostic effect or causality. However, the data presented here include relevant information about the association of certain hepatic histopathologic abnormalities and biochemical outcomes at 6 months in hospitalised adults with suspected DILI[20].

CONCLUSION

Persistent biochemical abnormalities at six months were most closely associated with interlobular bile duct paucity and confluent hepatocellular necrosis among hospitalized adults with suspected DILI receiving prolonged pharmacotherapy. The results indicated that certain histopathological traits could be helpful in clinical practice to learn more about delayed biochemical recovery.

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Authors' Contributions: BS and SDM contributed to the study conception, research design, and development of the methodology. BS, OA, and SI contributed to clinical data collection, assessment of medication exposure, and evaluation of pharmacological information. SBA and HNK contributed to histopathological assessment, interpretation of liver biopsy findings, and evaluation of pathological characteristics. SDM and BS contributed to data organization, statistical analysis, and interpretation of the findings. BS prepared the initial manuscript. OA, SBA, HNK, and SI contributed to critical revision of the manuscript for important scientific and intellectual content. All authors reviewed and approved the final manuscript and agree to be accountable for their respective contributions to the work.

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