



BILE ACID CONJUGATION IMBALANCE FOR DIFFERENTIATING DRUG-INDUCED FROM NON- DRUG-INDUCED LIVER INJURY

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ABSTRACT

Drug-induced liver injury (DILI) remains difficult to distinguish from other forms of liver injury because conventional biochemical markers lack etiological specificity. This study evaluated whether bile acid conjugation patterns could provide additional discriminatory value. A secondary-data-based observational comparative analysis was conducted using 120 patients with DILI, 49 with non-drug-induced liver injury, and 25 healthy controls from a publicly available Mendeley source. Major bile acid measures included total, conjugated, glycoconjugated, tauroconjugated, and unconjugated bile acids together with derived ratios. Descriptive statistics, independent-samples t-tests, Pearson correlation, and simple binary logistic regression were applied. Absolute concentrations of total bile acids and major conjugated bile acid fractions were broadly similar between DILI and non-DILI groups. However, the glycine-to-aurine ratio was significantly higher in DILI, whereas the conjugated-to-unconjugated ratio was significantly lower. TSLCA, α MCA, HyoDCA, and SLCA were also significantly higher in DILI. Strong positive correlations were observed among conjugated, glycoconjugated, tauroconjugated, and total bile acids. Logistic regression further showed that the glyco/tauro ratio and conjugated/unconjugated ratio were significantly associated with DILI status. These findings suggest that relative bile acid conjugation patterns may provide more useful discriminatory information than absolute bile acid concentrations for differentiating DILI from non-DILI, although further validation in larger independent cohorts is required.

Keywords: Drug-induced liver injury; bile acids; conjugation imbalance; glyco/tauro ratio; biomarkers



1. Introduction

Drug-induced liver injury (DILI) is a significant clinical issue as it can cause mild and reversible biochemical perturbations to hepatic dysfunction, acute liver failure and, in some cases, chronic liver injury. The pathogenesis is complex, potentially involving the formation of reactive metabolites of the drug, mitochondria dysfunction, oxidative stress, immune activation and individual susceptibility, resulting in a very heterogeneous clinical picture (Saville et al., 2026). Emerging data further suggests that gut–liver interaction affects liver inflammation, bile acid metabolism, and sensitivity to hepatotoxic drug injury, thus gut–liver axis is also involved in the development of DILI (Tao et al., 2024). Early detection and prediction of severe DILI is still challenging, even with the improvements in clinical assessment, as consequences of liver damage are often the only changes detected by conventional laboratory markers (Hassan et al., 2025). Biological variability can also make interpretation difficult, with toxicokinetic responses and susceptibility to toxic exposures varying by factors such as sex and related metabolic factors (Gochfeld, 2017).

Common biochemical markers such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin are readily available and are used to detect hepatocellular or cholestatic damage, however they are not very specific and are not useful in distinguishing DILI from other liver diseases. Bile acids are also an appealing complementary family of markers, since they are made in the hepatocyte, are primarily conjugated with glycine or taurine, are excreted in bile and are recirculated through enterohepatic circulation. Recent studies have shown that plasma bile acid profiles correlate with the clinical course and outcome of DILI, providing a reflection of potentially key alterations in liver function (Monte et al., 2026). Biochemical studies also revealed that changes in bile acid metabolism are tightly coupled to drug-induced liver damage and could serve as a valuable biomarker for diagnosis and prognosis (Yu et al., 2025). In general, bile acids in circulation have been identified as potential markers of liver dysfunction, as their composition and levels do alter when there is a defect in their synthesis, transport, conjugation or excretion (Azer & Hasanato, 2021). The distribution of bile acid species in individual and conjugated form has also been found to be different between various liver diseases, which means that these acids can also be used for biochemical characterization of hepatic damage (Luo et al., 2018).

Bile acid profiling has been increasingly studied, but there are still some questions about the ability of bile acid levels to differentiate DILI from non-drug induced liver injury. Large changes in bile acid profiles by high resolution mass spectrometry have been seen after DILI, although the diagnostic significance of specific conjugation patterns has not been fully established (Mireault et al., 2024). While some metabolomic studies have identified specific bile acids as potential markers, the majority of studies have been centered on metabolomic signatures, and not conjugation indices, which are easily interpretable (Ma et al., 2019). Recent modifications in bile acids have also been linked to the progression and prognosis, but this data is not comprehensive enough to determine which bile acid changes are more suitable for etiological differentiation (Zhao et al., 2022). Moreover, metabolomic methods can differentiate DILI phenotypes, but there is not enough comparative evidence between glycine-conjugated, taurine-conjugated, total conjugated, and unconjugated bile acids and DILI and non-DILI patients (Quintás et al., 2021).

An assessment of bile acid conjugation could be a more clinically interpretable and simplified way of characterizing liver injury. Detailed plasma profiling has shown that individual bile acid species can be used as biomarkers for various types of hepatic disorders (Shi et al., 2018), and composite bile acid indices may be useful in order to have a better interpretation because they reflect more global disturbances in bile acid synthesis and transport (Alamoudi et al., 2021). Recent reviews on DILI biomarkers have identified the need for the development and use of biomarkers that complement the standard liver tests, and enhance the specificity of diagnosis (Atallah et al., 2021). Clinical guidelines also continue to acknowledge the fact that DILI is essentially a diagnosis of exclusion and there is a need for more biochemical markers to differentiate drug induced liver injury from other causes of liver injury (Chalasani et al., 2021). Hence, the present study assesses the bile acid conjugation imbalance in DILI and non-DILI patients focusing on glycine and taurine bile acid (GBA and TBA),



total conjugated bile acids (TCBA), and unconjugated bile acids (UBA) and their ratios.

Research Objectives

- 1.To compare the overall and individual bile acid profiles between patients with drug-induced liver injury (DILI) and non-drug-induced liver injury (NonDILI).
- 2.To evaluate differences in glycine-conjugated, taurine-conjugated, total conjugated, unconjugated bile acids, and their derived ratios between DILI and NonDILI patients.
- 3.To assess the relationships among major bile acid conjugation measures and determine whether selected bile acid indices are significantly associated with DILI status.

2. Methodology

2.1 Study Design

An observational comparative study was performed using secondary data to assess the bile acid profiles and conjugation patterns in drug induced liver injury (DILI) patients, and non-drug induced liver injury (NonDILI) patients. In the primary comparison, 120 DILI patients and 49 NonDILI patients were included and 25 healthy volunteers were kept as an additional reference group for descriptive comparison.

2.2 Data Source

The data were retrieved from the publicly available Mendeley Data repository, "Plasma bile acid profile as a biomarker for drug-induced liver injury (Grove et al., 2026)". The plasma bile acid concentrations, grouped plasma bile acid measures and derived plasma bile acid ratios were present in the source and could be compared directly between the bile acid composition and bile acid conjugation between the DILI, NonDILI and healthy reference groups.

2.3 Study Population

The participants were divided into DILI, NonDILI and healthy controls in the original article. Because the objective of the main analysis was to differentiate between drug-induced and non-drug-induced liver injury, the 169 DILI and NonDILI participants were used for this analysis. The overall bile acid profile was only included as an additional descriptive analysis in healthy subjects.

2.4 Study Variables

Individual bile acid species were analyzed and group measures of bile acids as listed in the source were included. Glycine-conjugated bile acids comprised GCA, GCDCA, GDCA, GLCA, and GUDCA and taurine- conjugated bile acids comprised TCA, TCDCA, TDCA and TLCA. Unconjugated bile acids were: CA, CDCA, DCA, LCA and UDCA. Total conjugated bile acids, glycoconjugated bile acids, tauroconjugated bile acids, unconjugated bile acids, total bile acids, glycine to tauro bile acid ratio, primary to secondary bile acid ratio, 12 α hydroxylated to non-12 α hydroxylated bile acid ratio and conjugated to unconjugated bile acid ratio were among the major derived measures.

2.5 Statistical Analysis

The summary of continuous variables was expressed as mean $\pm$ standard deviation and for the group distribution it was used frequency and percentage. Major and individual bile acid measures were compared between the DILI and NonDILI patients using independent-samples t-tests. Pearson correlation analysis was used to determine the relationships between the major bile acid conjugation parameters and the correlation coefficient and p values are reported. Simple binary logistic regression was performed to analyze selected bile acid indices as a single predictor of the DILI status coded as DILI = 1 and NonDILI = 0 and the results were presented as odds ratio (OR) with 95% confidence interval and p value. Only descriptive three-group comparisons were used with the healthy participants and a p value of < 0.05 was considered statistically significant.



2.6 Ethical Considerations

Secondary data from publicly available research repository was used in the study and no participants were recruited, no interventions were performed, and no new identifiable data was collected. Only variables available publicly in the original source were therefore analysed and the data were only used for research purposes as per the repository terms of use.

3. Results

3.1 Distribution of the Study Groups

A total of 194 patients (120 DILI and 49 NonDILI) and 25 healthy volunteers were included in the analysis. The study population consisted of 425 participants, 61.86% of which were DILI, 25.26% NonDILI and 12.89% healthy controls. The main comparative analysis was thus between 169 subjects categorized as DILI or NonDILI (Table 1).

Table 1. Distribution of participants according to study group

Study group	Frequency (n)	Percentage (%)
DILI	120	61.86
NonDILI	49	25.26
Healthy volunteers	25	12.89
Total	194	100.00

A visual impression of the relative representation of DILI, non-DILI and healthy participants included in the analysis is given in Figure 1.

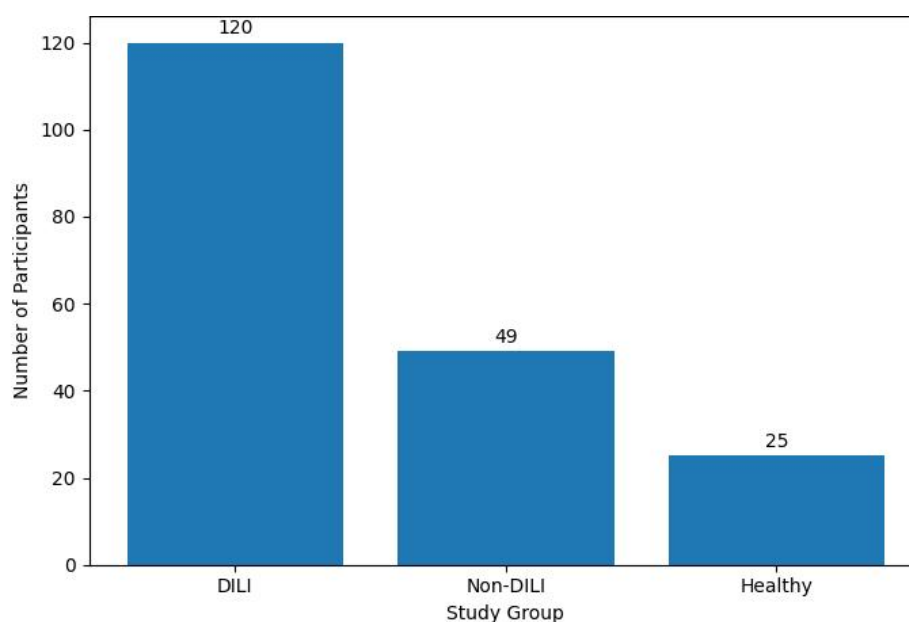


Figure 1. Distribution of Participants by Study Group

As can be seen in Figure 1, the majority of the study population was comprised of DILI patients, the



non-DILI group was a smaller comparison group and healthy participants were the reference group. This distribution is from the perspective of the study's main focus of differentiating DILI from other liver injuries.

3.2 Major Bile Acid Conjugation Profiles in DILI and NonDILI

Total, tauroconjugated, glycoconjugated, unconjugated and total bile acid absolute concentrations were overall similar in DILI and NonDILI patients. The glycine-to-aurine conjugation ratio, on the other hand, was significantly elevated in DILI, and the conjugated-to-unconjugated ratio was significantly reduced. There were no significant differences in both Primary-to-Secondary and 12 α -hydroxy to non-12 α -hydroxy ratios. These results suggest a relative difference in bile acid conjugation, but not the absolute bile acid load, that distinguished the two liver-injury groups (Table 2).

Table 2. Comparison of major bile acid measures between DILI and NonDILI

Variable	DILI, Mean $\pm$ SD	NonDILI, Mean $\pm$ SD	t-value	p-value
Conjugated bile acids	89.97 $\pm$ 122.70	93.43 $\pm$ 88.17	-0.20	0.838
Tauroconjugated bile acids	35.83 $\pm$ 53.78	32.83 $\pm$ 30.21	0.46	0.647
Glycoconjugated bile acids	54.14 $\pm$ 74.33	60.60 $\pm$ 61.58	-0.58	0.563
Unconjugated bile acids	0.61 $\pm$ 0.89	0.74 $\pm$ 2.25	-0.42	0.680
Total bile acids	90.59 $\pm$ 122.66	94.17 $\pm$ 87.97	-0.21	0.832
Glyco/Tauro ratio	2.50 $\pm$ 1.86	1.89 $\pm$ 0.95	2.82	0.005
Primary/Secondary ratio	83.34 $\pm$ 138.06	124.42 $\pm$ 160.48	-1.57	0.120
12 α OH/non-12 α OH ratio	1.76 $\pm$ 2.18	1.73 $\pm$ 0.93	0.12	0.902
Conjugated/Unconjugated ratio	350.70 $\pm$ 560.96	627.94 $\pm$ 785.35	-2.25	0.028

Major bile acid conjugates are presented in the overall distribution in Figure 2. Absolute concentrations were found to be similar for both liver-injury groups, with DILI exhibiting slightly higher tauroconjugate concentrations and non-DILI exhibiting somewhat higher glycoconjugate and total-conjugate concentrations.

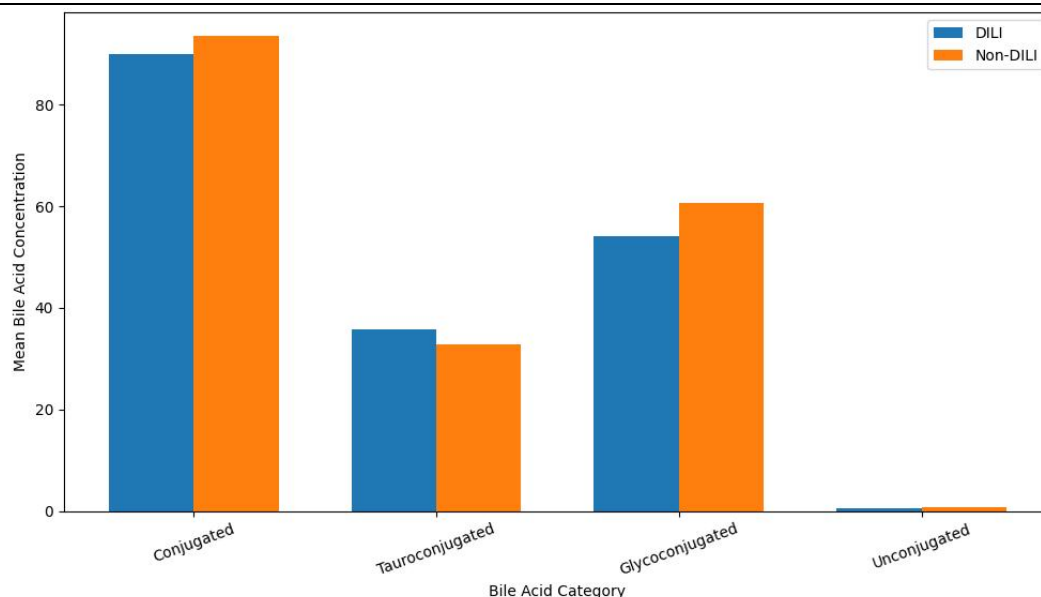


Figure 2. Major Bile Acid Conjugation Profiles in DILI and Non-DILI Patients

The visual pattern was confirmed where the highest differences between the groups did not occur when absolute concentrations of the conjugated bile acids were measured. This facilitated further investigation of relative conjugation indices which discriminated better between DILI and non-DILI: glycine-to-aurine ratio and conjugated-to-unconjugated ratio.

3.3 Individual Bile Acid Species Associated With DILI

Four of the individual bile acid species were statistically different among the liver-injury groups. TSLCA, α MCA, HyoDCA and SLCA were all higher in DILI compared to NonDILI. LCA indicated a margin difference (not significant). The majority of glycine- and taurine-conjugated species (TCA, TCDCA, GCA, GCDCA, GDCA and TDCA) did not differ significantly among groups, further suggesting that only specific molecular species contributed to the biochemical distinction observed (Table 3).

Table 3. Individual bile acids showing the strongest DILI–NonDILI differences

Bile acid	DILI, Mean $\pm$ SD	NonDILI, Mean $\pm$ SD	t-value	p-value
TSLCA	0.557 $\pm$ 0.709	0.309 $\pm$ 0.321	3.12	0.002
α MCA	0.0043 $\pm$ 0.0040	0.0026 $\pm$ 0.0022	3.39	<0.001
HyoDCA	0.0202 $\pm$ 0.0288	0.0110 $\pm$ 0.0177	2.53	0.013
SLCA	0.0117 $\pm$ 0.0183	0.0058 $\pm$ 0.0071	2.99	0.003
LCA	0.0087 $\pm$ 0.0124	0.0060 $\pm$ 0.0058	1.96	0.052

3.4 Correlation Among Major Bile Acid Measures

Pearson correlation analysis showed good correlation between the major conjugated bile acid measurements. Total conjugated bile acids were very strongly positively correlated with total bile acids, glycoconjugated bile acids and tauroconjugated bile acids. The concentration of



tauroconjugated bile acids also showed a high correlation with glycoconjugated bile acids, suggesting extensive similarity between the three major conjugated groups of bile acids. The relationships are shown in Figure 3.

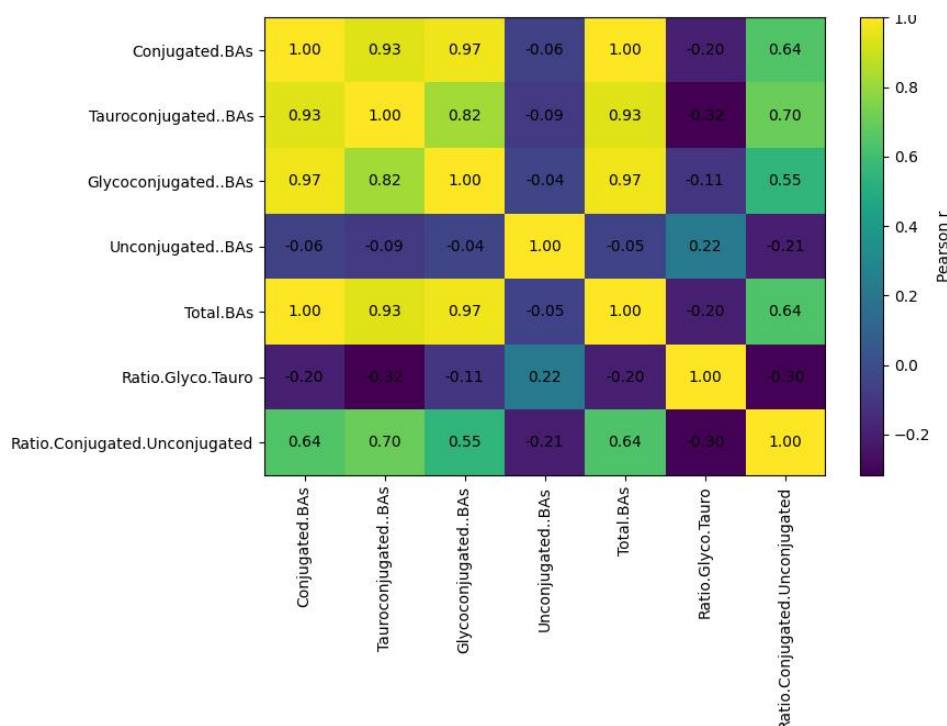


Figure 3. Correlation Among Major Bile Acid Measures

The heatmap also revealed moderately to strong positive association between the conjugated/unconjugated ratio and the levels of conjugated, tauroconjugated, glycoconjugated, and total bile acids. By contrast, the glyco/tauro ratio was inversely correlated with some of the indices of conjugated bile acids, especially with tauroconjugated bile acids. Unconjugated bile acids showed relatively low correlation with most of the major bile acid measures while the conjugated bile acid fractions showed a higher degree of interrelationship within the bile acid profile.

3.5 Bile Acid Conjugation Measures Associated With DILI

Two conjugation indices were found to be significantly associated with the DILI status using simple binary logistic regression. A one standard deviation increase in glyco/tauro ratio was accompanied by an increase in odds of DILI with an odd ratio of 1.60. In contrast, increased conjugated/unconjugated ratio was associated with decreased odds of DILI. Absolute levels of conjugated, tauroconjugated, glycoconjugated, unconjugated and total bile acids were not individually associated with DILI status, further supporting the importance of relative conjugation patterns and not absolute levels of total bile acids (Table 4).

Table 4. Simple binary logistic regression of bile acid measures associated with DILI

Predictor	Odds ratio	95% CI	P-value
Conjugated bile acids	0.97	0.70–1.35	0.857
Tauroconjugated bile acids	1.07	0.75–1.51	0.713
Glycoconjugated bile acids	0.91	0.66–1.27	0.590



Unconjugated bile acids	0.92	0.67–1.25	0.575
Total bile acids	0.97	0.70–1.35	0.852
Glyco/Tauro ratio	1.60	1.04–2.47	0.033
Conjugated/Unconjugated ratio	0.67	0.49–0.93	0.015

3.6 Bile Acid Profiles Relative to Healthy Participants

Descriptive analysis revealed a significant increase in total and conjugated bile acids in both liver injury groups compared to control. The mean values of total bile acids were 90.59 in DILI, 94.17 in NonDILI and 1.24 in healthy participants. The same differences were found between the concentrations of conjugated, glycoconjugated and tauroconjugated bile acids. The healthy group however showed a higher glyco/tauro ratio which suggests that there was also an altered handling of bile acids in both types of liver injury as compared to the reference group (Table 5).

Table 5. Descriptive comparison of major bile acid measures across all three groups

Variable	DILI, Mean $\pm$ SD	NonDILI, Mean $\pm$ SD	Healthy, Mean $\pm$ SD
Conjugated bile acids	89.97 $\pm$ 122.70	93.43 $\pm$ 88.17	0.69 $\pm$ 0.51
Tauroconjugated bile acids	35.83 $\pm$ 53.78	32.83 $\pm$ 30.21	0.15 $\pm$ 0.12
Glycoconjugated bile acids	54.14 $\pm$ 74.33	60.60 $\pm$ 61.58	0.54 $\pm$ 0.43
Unconjugated bile acids	0.61 $\pm$ 0.89	0.74 $\pm$ 2.25	0.55 $\pm$ 0.35
Total bile acids	90.59 $\pm$ 122.66	94.17 $\pm$ 87.97	1.24 $\pm$ 0.67
Glyco/Tauro ratio	2.50 $\pm$ 1.86	1.89 $\pm$ 0.95	5.19 $\pm$ 5.60
Primary/Secondary ratio	83.34 $\pm$ 138.06	124.42 $\pm$ 160.48	5.49 $\pm$ 19.52
Conjugated/Unconjugated ratio	350.70 $\pm$ 560.96	627.94 $\pm$ 785.35	1.63 $\pm$ 1.26

4. Discussion

The current study investigated whether there are differences in bile acid conjugation patterns that could assist in discriminating drug-induced liver injury (DILI) from non-drug-induced liver injury. The overall results were that there were no significant differences in the levels of absolute concentrations of total, conjugated, tauroconjugated, glycoconjugated, and unconjugated bile acids in the two liver-injury groups. The relative balance of bile acid conjugation, on the other hand, revealed more distinct differences. The conjugated/unconjugated ratio was significantly decreased while the glyco/tauro ratio was significantly increased in DILI. These findings indicate that the ratio of bile acids between the different conjugation pathways might be more useful than total bile acid concentrations alone to distinguish DILI from other liver injury processes.

This trend was also evident in the individual bile acid analysis. TSLCA, α MCA, HyoDCA, and



SLCA were significantly elevated in DILI and most major glycine- and taurine-conjugated species were not significantly different between groups. This means that the biochemical differences between DILI and non-DILI might be specific to the molecular species chosen and not necessarily consistent throughout the whole bile acid pool. Results of the correlation analysis also indicated that there were strong positive correlation between conjugated, tauroconjugated, glycoconjugated and total bile acids suggesting close metabolic relationship between the bile acids. In contrast, most of the major conjugated measures were only moderately correlated with unconjugated bile acids. The inverse relationships involving the glyco/tauro ratio in addition suggest that shifts in the relative balance of conjugation may be indicators of alteration in hepatic bile acid processing rather than merely of accumulation.

This is in line with previous studies that have highlighted the complexity of DILI and the need to not solely rely on traditional biochemical markers. DILI is a heterogeneous, sometimes exclusionary, diagnosis, as described by Andrade et al. (2019), in which there is a need for more mechanistic or metabolic markers. Likewise, Hosack et al. (2023) emphasized the challenge of determining a particular diagnosis from common clinical chemistry results due to the similarity of laboratory results for various types of liver damage. Cheng et al. (2022) also demonstrated that aminotransferases alone are not adequate to define drug-induced liver injury, further highlighting the importance of the use of complementary liver injury biomarkers. This current focus on bile acid conjugation is also biologically plausible as bile acid synthesis, transport and enterohepatic circulation is dysregulated in liver disease (Farooqui & Elhence, 2022). Moreover, the disruption of hepatobiliary transport of bile acids has been linked to drug-induced hepatotoxicity, explaining the changes in bile acid pattern after conjugation observed (Saran & Brouwer, 2023).

The logistic regression results support the potential clinical significance of these ratios. A higher glyco/tauro ratio was linked to a higher odd of DILI and a higher conjugated/unconjugated ratio was linked to a lower odd of DILI. Absolute bile acid concentrations, however, were not significant predictors. This indicates that relative indices may be a more straightforward and easily interpretable biochemical method of detecting bile acids abnormalities associated with DILI.

There are some restrictions to be taken into account. The analysis relied on secondary data, the non-DILI group was smaller than the DILI group and the underlying causes in the non-DILI group may have been heterogeneous. The study also used only one publicly available source, with no other clinical variables included for adjustment. The results of these studies should be confirmed in larger independent cohorts of patients, examined in separate groups of specific non-DILI diseases, evaluated longitudinally and analyzed if the combination of conjugation indices with existing clinical parameters can improve in discriminating diagnostics.

5. Conclusion

This study showed that bile acid conjugation patterns might be more helpful for discriminatory purposes between drug-induced liver injury (DILI) and non-DILI than absolute bile acid concentrations. Total bile acids, total conjugated bile acids, glycoconjugated bile acids, tauroconjugated bile acids, unconjugated bile acids were generally not different between the two groups but there were significant differences in the relative conjugation indices. The glycine/taurine ratio was significantly elevated in DILI, and the conjugated/unconjugated ratio was significantly decreased. Together, these results suggest that imbalance in bile acid conjugation may signify unique changes in bile acid handling that are unique to DILI. On the individual molecule level, the concentrations of TSLCA, α MCA, HyoDCA and SLCA were significantly elevated in DILI, indicating that this selective bile acid species may also be useful for differentiating liver injury categories. Correlation analysis revealed strong relationships between these major conjugated BA fractions, and logistic regression identified the glyco/tauro ratio and conjugated/unconjugated ratio as significant indicators correlated with DILI status. In total, results suggest that simple bile acid conjugation indices could be useful as biochemical markers to aid in differentiating DILI from non-DILI. Before these can be used for routine diagnostic use, however, larger prospective studies with



more extensive clinical characterization and independent validation are needed.

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