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# Diagnostics and Outcome Predictorso Drug Induced Liver Injury: A Single Center Prospective Study

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## ABSTRACT

**Background:** Although drug-induced liver injury (DILI) is a rare clinical event, it carries significant morbidity and mortality. The diagnostic approach of DILI is still challenging because of lack of reliable markers that would allow distinguishing DILI from other causes of liver injury. **Objective:** To study the demographic, clinical and laboratory characteristics, and their relation to outcome of patients with DILI. **Patients and Methods:** Case control study conducted on 80 participants divided into two groups; **Group I** 40 patients with acute DILI and **Group II** 40 patients with acute viral induced liver injury. Subjects were systematically evaluated for clinical and laboratory characteristics, other etiologies, severity of DILI with application of Roussel Uclaf Causality Assessment Method (RUCAM) and liver biopsy whenever feasible and were all followed for 6 months thereafter. **Results:** Diclofenac was the most incriminated drug in DILI group (16 cases, 40%). Hepatocellular injury pattern was more common (28 cases, 70%). Infection with acute hepatitis B virus (HBV) and hepatitis A virus (HAV) were the commonest etiology of viral hepatitis (32 cases, 80%). All patients with acute viral hepatitis, improved with no recorded mortality nor chronicity. While 6 patients (15%) with DILI died. **Conclusion:** The diagnostic approach of DILI is still rudimentary and inaccurate and require high index of suspicion and thus, careful assessment is required to distinguish DILI from other causes of liver injury.

**Keywords**: Diclofenac, Drug-induced liver injury, Hepatocellular, Viral hepatitis.

## INTRODUCTION

Drug-induced liver injury (DILI) remains a challenging diagnosis and gains increased attention annually, as it poses a significant risk to the patient health. DILI broadly describes any injury to the liver that might occur as a result of medications (prescription or Over the Counter (OTC)), herbal and dietary supplements (HDS), or other xenobiotics that may develop from asymptomatic liver test abnormalities up to acute liver failure that cannot be attributed to other causes [(1, 2)].

Diagnosis is complex, with no unifying criteria and a relatively high index of suspicion is necessary. In addition, drugs that cause toxic effects on the liver exhibit diverse pathological responses that mimic all forms of acute and chronic hepatobiliary liver disease [(3)].

The differential diagnosis for acute hepatocellular injury includes acute viral hepatitis, autoimmune hepatitis (AIH), ischemic liver injury, acute Budd-Chiari syndrome, and Wilson disease. One should keep in mind that acute biliary obstruction may initially present with a hepatocellular pattern of injury but subsequently evolves into a cholestatic presentation [(4)]. A general approach to a suspected case of DILI includes taking a comprehensive medical and drug history, with clear timing around drug administration and exclusion of other potential factors that could contribute to the liver injury [(5)].

Recognizing the pattern of liver injury at the initial presentation is vital. It provides a useful foundation to establish a differential diagnosis and guides the diagnostic evaluation accordingly. The R-ratio is a quantitative expression of the injury pattern; it is defined as the ratio of serum ALT to alkaline phosphatase (ALP) values, both expressed as multiples of upper limit of normal (ULN), obtained at the onset of injury. An R-ratio of >5 indicates hepatocellular injury, <2 indicates cholestatic injury, and 2-5 indicates mixed injury [(6,7)].

Several clinical scales have been developed to establish a causal relationship between a certain medication and liver injury. The Roussel Uclaf Causality Assessment Method (RUCAM) continues to increase in use as a causality assessment tool. The success of RUCAM is attributable to its objective, standardized, and liver-injury-specific approach [(8)]. However, it has limitations in assessment method and arbitrary scoring, such as old age and alcohol use [(9)].

The aim of this study was to provide a more detailed description and characterization of patients with DILI and their outcome predictors and to improve our ability to diagnose DILI and perform a causality assessment in comparison with patients with acute viral hepatitis.

## PATIENTS AND METHODS

This prospective study was conducted on 80 patients, in Hepatology and Gastroenterology Department, National Liver Institute (NLI), Menoufia





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University in the period from January 2019 to June 2020.

**Patients were divided into two groups:**

**Group I:** Forty patients with acute DILI were enrolled and the diagnosis was confirmed relying on picture of acute liver injury based on levels of alanine aminotransferase more than 3-fold the upper limit of normal and/or alkaline phosphatase levels more than 2-fold the upper limit of normal. According to R ratio of ALT to ALP (as a multiple of their upper normal limits): patients were defined as hepatocellular if >5, 2-5 mixed, and <2 is considered cholestatic. Evident drug history added to the causality which was assessed by Roussel Uclaf Causality Assessment Method, and liver biopsy if feasible were also diagnostic prerequisites for DILI diagnosis after exclusion of all other causes of acute hepatitis, and **Group II**: Another group of 40 patients with acute viral hepatitis were enrolled with acute elevation liver function indices, in addition to serologic evidence of hepatotropic viral infection and exclusion of all other causes of acute hepatitis**.**

**Inclusion criteria:** Adults ≥ 18 years old with history of drug or herbal medicine use within the past 3 months.

**Exclusion criteria:** Patients with alcohol consumption, severe cardiopulmonary, renal disease, or any other associated comorbidity were excluded. Moreover, patients with chronic hepatitis, liver cirrhosis, and/or hepatocellular carcinoma weren't included in our study.

Baseline demographic data including age, gender, residence, and occupation in addition to a detailed history with emphasis on drug history (type, timing, and the dose) were recorded. Baseline laboratory indices such as ALT, AST, serum bilirubin, fasting blood sugar, complete blood counts, prothrombin time and international normalized ratio (INR) were measured. Also, serological tests for viral, autoimmune hepatitis and metabolic liver disease were performed.

Abdominal ultrasonography with Doppler was done for all recruited patients and liver biopsy, was done whenever eligible. The Roussel Uclaf Causality Assessment Method (RUCAM) was used to diagnose DILI. Only cases that had scored as highly probable or probable (more than or equal to 6 points) by RUCAM, were included.

Outcomes of interest: The study outcome was to evaluate the demographic, clinical and laboratory characteristics, and their relation to the primary outcome (either improvement and discharge or death) of patients with drug-induced liver injury in comparable to those with acute viral hepatitis, in an Egyptian cohort. Enrolled subjects were asked to return for repeated testing at 6 months thereafter for follow up.

**Ethical consent:**

**An approval of the study was obtained from Menoufia University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

***Statistical Analysis***

Results were collected, tabulated, and statistically analyzed by an IBM compatible personal computer with Statistical Package for the Social Sciences, version 20 (SPSS Inc. released 2011, IBM SPSS statistics for windows, version 20.0; IBM Corp., Armonk, New York, USA). Descriptive statistics, such as means with standard deviation (SD), median with interquartile ranges, frequency distributions, and percentage were used to describe the cohort. Student t-test was used to compare means and SD of 2 sets of quantitative normally distributed data. Paired sample T test was done to compare means and SD of the same set group of quantitative normally distributed data at different areas of time before and after treatment respectively. Chi- squared test ($X^2$) was done to study association between two qualitative variables. P value < 0.05 was considered significant.

**RESULTS**

Regarding socio-demographic characteristics of the enrolled patients, male represented 25% and female 75% with mean age ± SD 46.5 ± 10.4 in group I, while in group II, male represented 70% and female 30% with mean age ± SD 34.5 ± 10.4 with a statistically significant difference between the 2 groups (P = 0.002). 55% of patients in group I lived in rural area, while 65% of patients in group II lived in urban area (P = 0.182). In group I, 25%, 35% and 40% had primary, secondary and higher education respectively versus 0%, 60% and 40% in group II (P = 0.001).

Regarding the clinical criteria of the two studied groups, 60% had nausea and vomiting in group I vs. 95% in group II (P = 0.000). Fever was present in 100% of patients in group II and no patient complained of rash, while in group I, 5% of patients complained of fever and rash (P = 0.000). Abdominal pain was present in 30% and 55% in group I and II respectively (P = 0.003). Jaundice was the most prominent sign in both groups, 95% vs. 100% in group I and II respectively (P = 0.000). Pruritus was present in 30% in group I and in only 5% in group II (P = 0.003). Coagulopathy and encephalopathy were present in 15% of patients in group I vs. 0% in group II (P = 0.004). As regard the baseline laboratory measures **(Table 1).**

**Table (1): Laboratory data of the studied patient groups**

| Groups / Laboratory criteria | Group I (DILI) N=40 | Group II (Acute Viral hepatitis) N=40 | P value |
|---|---|---|---|
| **AST (U/L) (mean±SD)** | 570.5±51.1 | 577.5±39.4 | **0.001*** |
| **ALT (U/L) (mean±SD)** | 796.5±66.1 | 1022.5±56.1 | **0.001*** |
| **Total bilirubin (µmol/L) (mean±SD)** | 12.1±2.45 | 10.80±2.40 | **0.005*** |
| **Direct bilirubin (µmol/L) (mean±SD)** | 9.5±2.4 | 7.5±1.4 | **0.002*** |
| **PC (mean±SD)** | 60.5±6.1 | 78.5±3.1 | **0.001*** |
| **INR (mean±SD)** | 1.42±0.1 | 1.11±0.12 | **0.001*** |
| **ALP (U/L) (mean±SD)** | 198.7±16.4 | 160.5±8.1 | **0.001*** |
| **GGT (U/l) (mean±SD)** | 162.2±16.0 | 167.2±19.5 | **0.001*** |
| **Cholesterol (mg/dL) (mean±SD)** | 193.2±13. 4 | 181.3±7. 2 | 0.133 |
| **Triglyceride (mg/dL) (mean±SD)** | 164.5±5.4 | 194.5±11.4 | 0.711 |
| **FBS (mg/dl) (mean±SD)** | 84.5±9.1 | 87.5±5.1 | 0.413 |
| **Hb (g/dL) (mean±SD)** | 12.2±1.4 | 13.5±1.6 | **0.001*** |
| **WBCs (mcL) (mean±SD)** | 7.5±1.1 | 6.9±1.1 | 0.240 |
| **PLT (mcL) (mean±SD)** | 239.5±6.4 | 258.5±9.4 | 0.630 |

*: significant; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; DILI, Drug-induced liver injury; FBS, Fasting Blood Sugar; GGT, Gamma-glutamyl transferase; Hb, Hemoglobin; INR, International normalized ratio; PC, Prothrombin concentration; PLT, Platelet Count; SD, Standard Deviation; WBCs, White Blood Cell count.

Diclofenac was the most incriminated drug in DILI group (16 patients, 40%), followed by Amoxicillin clavulanic acid (N=8, 20%), Acetyl salicylic acid (N=4, 10%), Ibuprofen (N=4, 10%), Anti-rheumatoid treatment (Sulfasalazine) (N=2, 5%), Sulfamethoxazole; Trimethoprim (SMX/TMP) (N=2, 5%), Antiepileptic drug (carbamazepine) (N=2, 5%) and Anabolic steroid (N=2, 5%).

Regarding duration of drugs administration (mean ± SD, days), Diclofenac 10.5±1.5, Amoxicillin clavulanic acid 7.5±1.7, Acetyl salicylic acid 11.5±1.5, Ibuprofen was 7.21±1.12, Anti-rheumatoid treatment 75±0.00, Sulfamethoxazole; Trimethoprim 15±0.00, Antiepileptic drug (carbamazepine) 60±0.00 and Anabolic steroid 20±0.00.

As for the time interval till symptoms appearance (mean ± SD, days), Diclofenac 13.5±1.4, Amoxicillin clavulanic acid 9.5±1.9, Acetyl salicylic acid 11.5±1.5, Ibuprofen 8.5±0.51, Anti-rheumatoid treatment 75±0.00, Sulfamethoxazole; Trimethoprim 21±0.00, Antiepileptic drug (carbamazepine) 60±0.00, and Anabolic steroid 20±0.00.

Considering the dose of drug (mean ± SD, mg/day), Diclofenac 203.5±32.4, Amoxicillin clavulanic acid 2000±0.00, Acetyl salicylic acid 750.0±173.5, Ibuprofen 2400±0.00, Anti-rheumatoid treatment 2000±0.00, Sulfamethoxazole; Trimethoprim 960±0.00, Antiepileptic drug (carbamazepine) 800±0.00, and Anabolic steroid 100±0.00. Hepatocellular injury was present in 28 (70%) patients with DILI, 8 (20%) presented with cholestatic injury, while mixed type was found in 4 (10%) patients **(Table 2).**

**Table (2): Type of drugs and pattern of liver injury in DILI group**

| Variable / Drug type | Pattern of liver injury | | |
|---|---|---|---|
| | **Hepatocellular N=28 N (%)** | **Mixed N=4 N (%)** | **Cholestatic N=8 N (%)** |
| **Diclofenac (N=16)** | 14 (50%) | 2 (50%) | 0 (0%) |
| **Amoxicillin clavulanic (N=8)** | 2 (7.1%) | 2 (50%) | 4 (50%) |
| **Acetyl salicylic acid (N=4)** | 4 (14.2%) | 0 (0%) | 0 (0%) |
| **Ibuprofen (N=4)** | 4 (14.2%) | 0 (0%) | 0 (0%) |
| **Anti-rheumatoid treatment (N=2)** | 2 (7.1%) | 0 (0%) | 0 (0%) |
| **Sulfamethoxazole; Trimethoprim N=2** | 2 (7.1%) | 0 (0%) | 0 (0%) |
| **Antiepileptic drug (carbamazepine) N=2** | 0 (0%) | 0 (0%) | 2 (25%) |
| **Anabolic steroid (N=2)** | 0 (0%) | 0 (0%) | 2 (25%) |

As regard hepatotropic viruses in acute viral hepatitis patients, 40% of cases (16 patients) were caused by hepatitis B virus, 40% (16 patients) were caused by hepatitis A virus, 10% (4 patients) were caused by hepatitis C virus and 10% (4 patients) were caused by cytomegalovirus. All patients with acute viral hepatitis improved with no recorded mortality nor chronicity. Unfortunately, six (15%) patients in the DILI group died due to acute liver failure. While 34 patients (85%) improved with no chronicity nor need for liver transplantation. In the contrary, the survival rate in the viral hepatitis group was 100% (P = 0.033). Survived patients with DILI showed complete recovery without any residual liver affection and complete normalization of their laboratory indices **(Table 3).**

**Table (3): Laboratory indices in DILI patients at the beginning of the study and after 6 months follow up**

| Group / Laboratory criteria | DILI patients | | P value |
|---|---|---|---|
| | At the beginning | After 6 months | |
| **AST (U/L) (mean±SD)** | 385.5±35.4 | 23.5±5.1 | **0.001*** |
| **ALT (U/L) (mean±SD)** | 602.5±43.1 | 27.5±5.1 | **0.001*** |
| **Total bilirubin (µmol/L) (mean±SD)** | 12.52±2.45 | 0.6±0.1 | **0.001*** |
| **Direct bilirubin (µmol/L) (mean±SD)** | 9.8±1.4 | 0.07±0.01 | **0.001*** |
| **PC (mean±SD)** | 65.5±10.1 | 99.5±0.5 | **0.001*** |
| **INR (mean±SD)** | 1.21±0.12 | 1.12±0.02 | **0.001*** |
| **ALP (U/L) (mean±SD)** | 197.5±0.109 | 68.7±4.4 | **0.001*** |
| **GGT (U/L) (mean±SD)** | 158.2±12.5 | 30.2±5.01 | **0.001*** |

*: significant; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; DILI, Drug-induced liver injury; GGT, Gamma-glutamyl transferase; INR, International normalized ratio; PC, Prothrombin concentration; SD, Standard Deviation.

Regarding the relation of socio-demographic data, clinical criteria and RUCAM score to outcome in DILI patients, all mortality cases (6 patients, 15%) were female (P = 0.098), with mean age 31.5±3.4 vs. 48.5±12.4 in the survived patients (P = 0.002). Jaundice, coagulopathy, and encephalopathy were present in 6(100%) of patients who died, while the survived patients didn't experience any coagulopathy or encephalopathy (P = 0.000). Eight (23.3%) of the survived patients scored 7 according to RUCAM score, 12 (35.2%) scored 8 and 14 (41.5) scored 9, while 6 (100%) patients who died, had score 7 (P = 0.001). The rate of mortality was higher in patients with more elevated laboratory indices **(Table 4).**

**Table (4): Laboratory data and outcome in DILI patients**

| Groups / Laboratory criteria | Mortality | | P value |
|---|---|---|---|
| | No N=34 | Yes N=6 | |
| **AST (U/L) (mean±SD)** | 385.5±35.4 | 1622.5±43.1 | **0.001*** |
| **ALT (U/L) (mean±SD)** | 602.5±43.1 | 1889.5±85.1 | **0.001*** |
| **Total bilirubin (µmol/L) (mean±SD)** | 11.80±2.40 | 20±4.45 | **0.00*** |
| **Direct bilirubin (µmol/L) (mean±SD)** | 8.5±1.4 | 17.5±3.4 | **0.001*** |
| **PC (mean±SD)** | 65.5±10.1 | 30.5±9.1 | **0.001*** |
| **INR (mean±SD)** | 1.21±0.12 | 2.12±0.21 | **0.001*** |
| **ALP (U/L) (mean±SD)** | 197.5±19 | 208.7±8.4 | 0.211 |
| **GGT (U/L) (mean±SD)** | 158.2±22.5 | 187.2±8.01 | 0.401 |

*: significant; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, Gamma-glutamyl transferase; INR, International normalized ratio; PC, Prothrombin concentration; SD, Standard Deviation.

Multivariate analysis performed in this cohort group proved that middle age (31.5 ± 3.4 years) along with higher AST values (1622.5 ± 443.1), higher ALT values (1889.5 ± 385.1), higher level of total bilirubin (20 ± 6.45) and lower prothrombin concentrations (30.5 ± 9.1 %), are the predictors of poor outcome in the DILI group.

## DISCUSSION

Drug-induced liver injury (DILI) remains one of the most challenging diseases to treat by physicians and can be caused by many types of prescription and non-prescription medications [1, 2]. DILI is the single greatest cause for termination of development of drug candidates and withdrawal of approved drugs from the market [10].

In our study, age ranged from 32 to 62 years with a mean of 46.5 ± 10.4 years with female predominance 75% vs. 25% males. In accordance with our study, **Lucena *et al.*** [11] study, in which the overall mean age was 49 ± 18 years among the three age groups included. It showed that neither old age nor female sex, were predisposing factors to DILI. However, age was an important predictor of clinical expression of hepatotoxicity. Also, in a study done by **Chalasani *et al.*** [12] the mean age was similar to our study (49 ± 17 years) with only 16.6% of patients with DILI to be 65 years or older. This study showed a relatively equal sex distribution; 59% of patients with DILI were female. Also, a study done by **Reuben *et al.*** [13] on 1198 subjects meeting criteria for acute liver failure, showed that among 133 cases of DILI assessed, 71% were females. However, gender was not a predictor of survival in acute liver failure.

It would be speculative to explain the sex differences in the expression and severity of toxic liver injury. However, it had been found that genetically determined impairment of the glutathione detoxification process, which determines the level of exposure to the reactive metabolite, occurred predominantly in women with DILI [14]. In addition, there are multiple variations in expression of cytochrome p450 enzymes, which results in varying susceptibility to drugs [15].

Regarding the outcome in our study, 34 patients (85%) of our cohorts were survivors with complete recovery and return to normal liver functions after 6 months follow up. No chronicity or liver transplantation cases were recorded. While 6 patients (15%) died from fulminant liver failure. All were female with no statistical significance regarding gender with mean age of 31.5 ± 3.4 years. **Chalasani and his colleagues** [12] reported 6% (56 patients) mortality rate among 899 patients with confirmed DILI. Similarly, **Ostapowicz *et al.*** [16] showed that on a prospective cohort study done on 308 patients, the rate of mortality was 8% with 2% requiring urgent liver transplantation. In addition, **Lucena *et al.*** [11] revealed that females showed the worst immediate outcome with higher incidence of fulminant liver failure and liver transplantation.

In our work, diclofenac was the most common incriminated drug presented in 16 patients (40%), followed by amoxicillin clavulanate (8 patients, 20%). Acetyl salicylic acid and ibuprofen, each was responsible for 4 cases (10%). The six patients with mortality, 4 cases were administered diclofenac, one case by sulfamethoxazole; trimethoprim and one due to anti-rheumatoid treatment (sulfasalazine). In **Chalasani *et al.*** [12] antimicrobials were the most common class of causative drugs, accounting for 45%, followed by herbal agents and dietary supplements (HDS). While cardiovascular drugs accounted for 10%, central nervous system agents 9%, antineoplastic drugs 5% and analgesics 3%. Moreover, **Lucena *et al.*** [11] documented that, the antimicrobials and antiepileptics were the most common classes of implicated agents, followed by nonsteroidal anti-inflammatory drugs.

In our study, hepatocellular injury was the dominant pattern, presented in 28 patients (70%), cholestatic in 8 patients (20%) and mixed injury in 4 patients (10%). All six dead patients were of hepatocellular type of injury. In **Chalasani *et al.*** [12] study, the pattern of liver injury was hepatocellular in 54%, and cholestatic or mixed in 23% each. Patients with hepatocellular DILI tended to be younger. While in **Lucena *et al.*** [11] study, cholestatic presentation represented 61% of patients over 60 years versus 39% in younger patients, mixed injury was 50%, and the hepatocellular injury was found in 37% in this subgroup of age (over 60).

Multivariate analysis performed in our cohort study revealed that middle age (31.5 ± 3.4 years) along with higher AST values (1622.5 ± 443.1), higher ALT values (1889.5 ± 385.1), higher level of total bilirubin (20 ± 6.45), and lower prothrombin concentrations (30.5 ± 9.1 %), to be the predictors of poor DILI outcomes. **Lucena *et al.*** [11] showed that, neither older age nor female sex are predisposing factors to DILI, but that age, although not a modifiable risk factor, is an important predictor of clinical expression of hepatotoxicity. Older age (with an age cutoff 60 years) is a determinant for the development of cholestatic damage with a male predominance, whereas younger age is associated with cytolytic damage and a female overrepresentation. Mixed type of damage is independent of age. Moreover, **Alhaddad *et al.*** [17] reported that age and prothrombin concentration were the only predictors of unfavorable outcomes of DILI.

## CONCLUSION

The diagnostic approach of DILI is still rudimentary and inaccurate and require high index of suspicion and thus, careful assessment is required to distinguish DILI from other causes of liver injury.

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