European Review for Medical and Pharmacological Sciences 2023; 27: 560-569

Drug induced liver injury: causative agents and predictors for the outcome – a retrospective study at Tanta University Hospital, Egypt

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Abstract. – OBJECTIVE: Drug induced liver injury is a rare but an important cause of acute liver failure. It is associated with significant morbidity and mortality. This study aimed to analyze this disorder, causes, different patterns, and outcomes in Egyptian patients.

PATIENTS AND METHODS: This retrospective study collected data of 87 patients diagnosed with drug induced liver injury from 2019 through 2020 at Tanta University. Pattern of liver injury was classified as hepatocellular, cholestatic, and mixed. Data including Model for End-Stage Liver Disease (MELD), Glasgow coma scale, and Poison Severity Score were statistically analyzed. Predictors of mortality and fulminant hepatic failure were determined.

RESULTS: Participants were 46 females and 41 males with age ranging from 12-70 years. 39 patients had hepatocellular liver injury, 15 cholestatic, and 33 mixed. Fulminant hepatic failure was diagnosed in 40 patients. Acetaminophen was the most common causative agent. Overall mortality was 17%. Dead patients had significantly deteriorated liver functions (Model for End-Stage Liver Disease). On multivariate logistic regression analysis, Model for End Stage Liver Disease and SO_2 independently predicted mortality, and Model for End Stage Liver Disease and random blood glucose were predictors of fulminant hepatic failure development.

CONCLUSIONS: Drug induced liver injury is an important health problem in Egypt. Further studies are needed to know the natural history of this disorder. Acetaminophen is one of the most common leading causes. The MELD score is a useful predictor of the outcome of drug induced liver injury such as fulminant hepatic failure and mortality.

Key Words:
Fulminant hepatic failure, Model for end-stage liver disease.

Abbreviations

GSC = Glasgow coma scale; FHF = fulminant hepatic failure; MELD = Model for End Stage Liver Disease; PSS = poison severity score.

Introduction

Although drug induced liver injury (DILI) has low incidence, it is one of the main causes of acute liver failure in Europe, United States, and Australia[1]. The frequency of DILI ranges from 1.3 to 19.1 per 100,000[2]. Approximately, half of the DILI cases in the US and the United Kingdom are due to acetaminophen overdose[3]. Adding to that, DILI can be induced by various pharmaceutical agents. Anti-tuberculous drugs such as isoniazid and rifampicin; antibiotics such as amoxicillin-clavulanate, tetracycline, and macrolides; non-steroidal anti-inflammatory drugs such as diclofenac; antifungals; antiepileptics; and halothane are the most reported pharmaceutical agents that cause DILI[4]. Parallel to wide spread of COVID-19 since 2019 till now, many off-label drugs have been tried on large scale either prophylactic or therapeutic to manage this global emergency[5]. As a consequence of these trials of novel potentially hepatotoxic xenobiotics, DILI has been reported[6] in some COVID- 19-treated patients. Antiviral drugs, antibiotics, hydroxychloroquine, corticosteroids, and ivermectin have been the most reported causes of DILI in COVID-19-treated patients[7-9]. Some dietary and herbal products especially Chinese herbals, in addition to poisoning with some agents like organophosphates, heavy metals, and hydrocarbons are responsible for non-pharmaceutical induced acute liver injury[10,11]. Xenobiotics induced acute liver in-

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jury (ALI) can be predictable or unpredictable (idiosyncratic). Predictable injury tends to be dose-related, caused by the direct toxic effect of the drug or its metabolites for example, acetaminophen overdose. However, idiosyncrasy is the most common mechanism involved in DILI[12]. Preexisting subtle liver disease, co-medications, drug lipophilicity, overdoses, and genetic factors may predispose patients to the incidence of DILI[13]. The clinical manifestations of DILI widely range from asymptomatic shooting of liver enzymes to symptoms and signs of fulminant hepatic failure (FHF). Jaundice, abdominal pain, bleeding disorders, and encephalopathy are the common pathognomonic manifestations of DILI[14]. Drug induced liver injury can be hepatocellular, cholestatic, or mixed. Hepatocellular DILI is characterized by an alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN) and ALT/alkaline phosphatase (ALP) ratio ≥5 times the ULN. However, in cholestatic DILI, ALP ≥2 times the ULN and ALT/ALP ratio <2 times the ULN. In mixed DILI, ALT ≥3 times the ULN, ALP ≥2 times the ULN, and ALT/ALP ratio ranges between 2-5 times the ULN[12]. Although current clinical laboratory tests are helpful for the detection of liver injury or dysfunction in many cases, they are not sufficient for the diagnosis of etiology or determination of prognosis. So that, scoring system may be helpful in studying the prognosis of DILI and the possibility of organ transplantation[15]. In Egypt, there is shortage of data regarding DILI. There is limited information about prognosis and outcome of drug induced liver injury. Our study was conducted to investigate different causes of drug induced liver injury occurrence, and to analyze different patterns and outcomes of drug induced liver injury in Egyptian patients.

Patients and Methods

This retrospective observational study was conducted using two years of patient data from the start of 2019 to the end of 2020. Patients' data were obtained from the Tanta University poison control center (TUPCC) and the Tropical Medicine and Infectious Disease Department, Faculty of Medicine, Tanta University, during the same study period. Patients' clinical files were used to recruit data after obtaining approval from the Tanta University Hospital Director. Patients' data were kept confidential with the aid of coding numbers. This study was approved by the Research Ethics Committee (REC) of Tanta University (approval code: 35177/1/22). All admitted patients aged ≥12 years of both genders with suspected diagnosis of DILI including (pharmaceutical or non-pharmaceutical) were enrolled. DILI was defined by isolated elevation of ALT ≥5 × ULN or concomitant increase of ALT ≥3 × ULN and total serum bilirubin values or ALP values ≥2 × ULN[16]. Classification of DILI was made according to the Council for International Organizations of Medical Sciences (CIOMS) criteria, as hepatocellular, cholestatic or mixed based on its R-value[9]. Hepatocellular if R-values >5, cholestatic if R-values <2, and mixed if R-values ranges from 2-5. The R value is defined as the serum ALT/ULN divided by the serum ALP/ULN ratio[17,18]. The diagnosis of FHF was principally based on a history of drug or poison exposure (oral, injection, inhalation, or dermal) and the presence of highly suggestive symptoms and signs of FHF, including jaundice, hepatic encephalopathy, and systemic manifestations (tachycardia and hypotension). In addition to the laboratory criteria for acute liver failure, including elevated ALT, aspartate transaminase (AST), ALP, and total bilirubin level.

Patients with history of bone marrow or liver transplantation, history of primary or secondary liver tumors, and history of underlying chronic liver disease were excluded and cases lacking data in their medical records were also excluded.

Data were collected as following:

Historical Data

- Sociodemographic data (code, age, gender, and residence).
- History of any medical diseases other than those previously mentioned in the exclusion criteria.
- Toxicological data were recorded, including the name of the agent, route of exposure (oral, injection, inhalation or dermal), and manner of exposure (accidental, suicidal, or iatrogenic). In addition, the form of the agent (liquid, gas, tablet or powder), place of exposure (home, hospital or other place), and the time elapsed before hospital admission were reported.

Clinical Data

- Vital parameters (pulse, temperature, blood pressure, and respiratory rate).
- Level of consciousness as assessed by Glasgow coma scale (GCS).

Results of Laboratory Investigations (on Admission)

The results of arterial blood gas parameters (pH, $PaCO_2$, HCO_3, and SO_2), and electrolytes (sodium and potassium) were reported. In addition, liver enzymes (ALT and AST), international normalized ratio (INR), total bilirubin, urea, creatinine, and complete blood count (CBC) were recorded.

Calculation of the Following Scoring Systems was Done

PSS: The Poison Severity Score was used to measure the severity of poisoning and was expressed in three levels: (1) minor, (2) moderate, and (3) severe poisoning. On both sides of these grades there were extremes: (0) cases refer to asymptomatic cases related to not poisoning at all, and (4) fatal cases[19].

MELD

The Model for End-Stage Liver Disease score was calculated by this equation: 9.6 x In (creatinine mg/dL) + 3.8 x In (bilirubin mg/dL) + 11.2 x In (international normalized ratio) + 6.4[20].

Outcome Measures (Prognosis)

Hospital and predictors of mortality and fulminant hepatic failure were assessed.

Statistical Analysis

Data were statistically analyzed using MedCalc Statistical Software version 15.8 (Ostend, West-Vlaanderen, Belgium). The distribution of numerical data was determined using the Shapiro-Wilk test for normality. Mean and standard deviation were used to express continuous variables, whereas categorical variables were plotted as frequencies. Categorical variables were analyzed using the χ^2 test or Fisher's exact test if the cell's expected number is ≤ 5. The Mann-Whitney test was used to compare continuous variables. Kruskal-Wallis' test was used for comparisons of more than two groups of continuous variables. Multivariate analysis by logistic regression was performed to identify independent predictors of mortality and fulminant hepatic failure according to significant variables detected on univariate analysis. Receiver operating characteristic (ROC) curves were used define the optimal cut-off point, sensitivity, and specificity. The area under the curve (AUC) was graded as follows: 0.90-1=excellent; 0.80-0.90=good; 0.70-0.80=fair; and 0.60-0.70=poor. Pairwise comparisons of AUCs of the studied scores were performed. A *p*-value <0.05 was considered statistically significant.

Results

During the study period, a total of 87 patients, including 46 (53%) females, and 41 males (47%), with mean age (36.05±17.33), and range (12-70) fulfilled the criteria for inclusion in the study. Exposure to toxic substance was by oral route in 76 patients, 9 patients took drug intravenous, and 2 patient developed toxicity by inhalation. Forty patients made suicide attempts. However, accidental and iatrogenic causes were in 20 and 21 patients respectively (Table I).

39 patients (45%) were classified as hepatocellular, 15 (17%) as cholestatic, and 33 (38%) as mixed. Fulminant hepatic failure was diagnosed in 40 patients. Demographic and laboratory data of the patients with the 3 patterns of DILI are shown in Table I. No significant differences were detected between them regarding age and gender. The patients with hepatocellular liver injury had significantly higher proportion of fulminant hepatic failure, duration of hospitalization, and mortality. Also, these patients showed significant elevations of MELD score, liver enzymes, PSS, and GCS scores in comparison to patients with cholestatic and mixed liver injuries. Significant elevations of total serum bilirubin and alkaline phosphatase were detected in patients with cholestatic liver injury. Patients with mixed liver injury targeted medical care after a significantly longer delay time than others. Acetaminphen was the most common causative agent producing DILI [17 patients (19.5%)]. Hydrogen cyanamide (dormex) was the second cause [10 cases, (11.5%)]. Halothane was the third cause [9 cases (10.3%)]. Aluminum phosphide was the fourth cause [8 cases (9%)], followed by heroin and atorvastatin [4 cases (4.5%)], and herbal and amoxicillin clavulanic acid [3 cases (3.4%)], while the least encountered agent was strychnine, rodenticide, diclofenac, and clonazepam [one case (1.1%)]. Mortality and fulminant hepatic failure were higher for acetaminophen poisoning (Table II). Comparison between survivors and non survivors is presented in Table III. Overall mortality was 17%. There were 15 dead cases, 8 of them were females. The mean age of dead patients was 39.0±20.04 years. No signifi-

Table I. Demographic and laboratory data of the studied patients.

Data	Cholestatic (n = 15)	Mixed (n = 33)	Hepatocellular (n = 39)	Total	*p*-value
Age	34.4 ± 17.63	34.6 ± 17.97	37.9 ± 16.95	36.05 ± 17.33	0.363
Gender					
0.078					
Female	4	18	24	46	
Male	11	15	15	41	
Route of intake					0.002*
Oral	15	31	30	76	
Inhalation	0	2	0	2	
Intravenous	0	0	9	9	
Manner of intake					0.013*
Suicidal	10	12	18	40	
Accidental	1	11	8	20	
Addiction	3	3	0	6	
Iatrogenic	1	7	13	21	
Delay time (days)	4.97 ± 2.91	26.11 ± 40.59	18.9 ± 17.65	19.23 ± 28.39	0.012*
ALT (IU/L)	129.27 ± 19.1	227.52 ± 69.38	1,232.9 ± 1,093.33	661.25 ± 894.29	< 0.001*
AST (IU/L)	122.27 ± 29.74	205.73 ± 105.8	857.56 ± 596.82	483.54 ± 526.8	< 0.001*
Bilirubin (mg/dL)	6.93 ± 8.64	1.71 ± 0.58	3.06 ± 0.85	3.22 ± 3.98	<0.001*
INR	1.37 ± 0.37	1.26 ± 0.34	2.25 ± 1.74	1.72 ± 1.28	< 0.001*
MELD score	16.67 ± 8.28	12.82 ± 6.38	22.69 ± 8.31	17.91 ± 8.8	< 0.001*
Creatinine (mg/dL)	1.37 ± 0.41	1.34 ± 0.54	1.78 ± 0.69	1.54 ± 0.63	0.007*
PSS	1.89 ± 0.6	2.27 ± 0.7	2.51 ± 0.51	2.36 ± 0.61	0.03*
GCS	10.93 ± 4.95	12.73 ± 3.97	13.67 ± 2.65	12.84 ± 3.73	0.195
SO_2	80.53 ± 23.38	92.88 ± 6.14	93.79 ± 5.83	91.16 ± 11.92	0.223
HCO_3	21.32 ± 5.59	20.58 ± 6.56	17.58 ± 5.05	19.36 ± 5.92	0.019*
Random blood sugar	165.87 ± 89.8	157.64 ± 94.7	111.49 ± 57.03	138.72 ± 81.7	0.017*
Duration of hospitalization (days)	58.27 ± 41.44	60.39 ± 43.28	101.99 ± 41.04	78.67 ± 46.56	< 0.001*
Death	2	1	12	15	0.004*
Fulminant hepatic failure	4	7	29	40	< 0.001*

AST: Aspartate transaminase; ALT: Alanine transaminase; GCS: Glasgow coma scale; INR: International Normalized Ratio; MELD: Model for End Stage Liver Disease; PSS: Poison Severity Score. *Significant result.

cant difference was detected regarding age, gender, delay time, duration of hospitalization. Dead patients had significantly higher liver enzymes, MELD score, INR, total serum bilirubin, serum creatinine, PSS, and GCS.

On multivariate analysis by logistic regression, MELD score (odds ratio=1.525, p=0.01) and SO2 (odds ratio=0.927, p=0.0.25) were predictive risk factors for mortality. Also, MELD score (odds ratio=1.136, p=0.046) and random blood sugar (odds ratio=0.986, p=0.016) predicted FHF development (Table IV). The discriminatory power of the MELD score for the prediction of the likelihood of mortality and FHF was estimated. It was obvious that at a cut-off value of >24.5, the MELD score had sensitivity of 86.7% and specificity of 84.7% for mortality prediction (AUC=0.925). Moreover, the MELD score had 80% sensitivity and specificity of 87.2% at a cut-off value of >19 for FHF prediction (AUC=0.781) (Figure 1 and Figure 2), (Table V and Table VI). At a cut-off value of <91.5, SO_2 had sensitivity of 80% and specificity of 79.2% for mortality prediction (AUC=0.909). However, random blood sugar had 60% of sensitivity and specificity of 55.3% at a cut-off value of <111.5 for FHF prediction (AUC=0.609) (Figure 1 and Figure 2), (Table V and Table VI).

Discussion

Drug-induced liver injury is an under-estimated cause of liver injury. However, it constitutes a challenge in the fields of hepatology and clinical toxicology, with a significant increase in associated mortality across all regions of the world. It is important to study the features of DILI in developing countries, as most available studies13 regarding DILI have been conducted in well-de-

Table II. Causitive agents of drug induced liver injury.

Causative agent	Total	Hepatocellular	Mixed	Cholestasis	FHF	Dead
Dormex	10	5	4	1	6	2
Aluminium phosphide	8	0	5	3	3	3
Paraphenyldiamine	2	1	1	0	0	0
Amitriptyline	3	0	1	2	0	0
Carbamate	3	0	2	1	1	0
Heroin	4	0	2	2	0	0
Organophosphate	2	0	1	1	0	0
Tramadol	2	0	1	1	0	0
Chlorpromazine	2	0	1	1	1	0
Halothan	9	9	0	0	9	4
Clonazepam	1	0	0	1	0	0
Acetaminophen	17	17	0	0	15	5
Strychnine	1	1	0	0	1	1
Pheytoin	3	0	2	1	1	0
Ketoconazole	1	1	0	0	1	0
Fluconazole	1	1	0	0	1	0
Amoxicillin clavulanic acid	3	2	1	0	0	0
Isoniazid	1	1	0	0	0	0
Rifampicin	2	0	2	0	0	0
Carbamazipine	1	0	1	0	0	0
Testosterone	1	0	0	1	0	0
Herbal	3	0	3	0	1	0
Atorvastatin	4	0	4	0	0	0
Diclofenac	1	0	1	0	0	0
Ciprofloxacin	2	1	1	0	0	0

AST: Aspartate transaminase; ALT: Alanine transaminase; GCS: Glasgow coma scale; INR: International Normalized Ratio; MELD: Model for End Stage Liver Disease; PSS: Poison Severity Score. *Significant result.

veloped nations, such as the United States, Spain, and Iceland. The present study analyzed 87 patients suffering from drug induced liver injury who were admitted at the Tanta University poison control center (TUPCC) and at the Tropical Medicine and Infectious Disease Department in Egypt over a two-year period. The most common manner of drug exposure was suicide attempts [40 patients (46%)].

Similarly, Abdelhamid[21] at Ain Shams University, reported suicide attempts as the most common mode of acute poisoning. Poisoning, especially self-induced with overdose toxic agents, is common among young people, as reported in many studies[22]. It is well known that young people tend to be easily agitated, depressed, and more liable to stressful modern lifestyle, failure in love, and family problems. Therefore, they are more predisposed to suicide[23]. Our study included 46 (53%) females, and 41 males (47%) with a female-to-male ratio of 1.12:1. The mean age was (36.05±17.33) years, and the range was (12-70) years. This finding was in agreement with an Indian study made by Rathi et al[24] in which the male-to-female ratio was 1:1, and another study conducted by Andrade et al[25]. However, in previous studies[26,27], the median age was 58 years, and 56% of patients were females. In the current study, the most common causative agent was acetaminophen. This agrees with the findings of Colaci et al[28] who reported almost half of the cases of drug induced acute liver injuries in the United States due to acetaminophen overdose. Acetaminophen overdose produces exces-

Table III. Data variables for survivors and non-survivors.

Laboratory data	Survivors (n = 72)	Non-survivors (n = 15)	*p*-value
Age	35.43 ± 16.81	39.0 ± 20.04	0.529
Gender			1.000
Female	38	8	
Male	34	7	
Delay time (days)	20.42 ± 13.5	30.46 ± 14.22	0.826
ALT (IU/L)	629.35 ± 954	814.4 ± 516.5	0.022*
AST (IU/L)	416.11 ± 437.21	807.2 ± 774.41	0.019*
MELD score	15.54 ± 7.02	29.27 ± 7.62	< 0.001*
INR	1.46 ± 0.51	2.98 ± 2.58	< 0.001*
Bilirubin (mg/dl)	2.84 ± 3.31	5 ± 6.15	< 0.001*
Creatinine (mg/dl)	1.37 ± 0.49	2.38 ± 0.55	< 0.001*
Urea (mg/dl)	40.32 ± 26.11	39.2 ± 27.26	0.553
PSS	2.22 ± 0.6	2.79 ± 0.43	0.002*
GCS	13.01 ± 3.66	12 ± 4.09	0.007*
SO_2	92.68 ± 10.78	83.87 ± 14.67	0.001*
Random blood sugar	138.68 ± 70.46	136.87 ± 126.1	0.036*
Hospital stay	77.17 ± 46.07	85.9 ± 49.87	0.496
Fulminant hepatic failure	28	12	0.005*

AST: Aspartate transaminase; ALT: Alanine transaminase; GCS: Glasgow coma scale; INR: International Normalized Ratio; MELD: Model for End Stage Liver Disease; PSS: Poison Severity Score. *Significant result.

sive metabolites that deplete glutathione stores, resulting in mitochondrial oxidative stress and dysfunction, and eventually hepatocellular necrosis[29]. Asawari et al[30] reported that non-steroidal anti-inflammatory drugs and analgesics were the leading causes of pharmaceutical toxicity in their research. The second common causative agent in our study was hydrogen cyanamide (dormex), the third was halothane, the fourth was aluminum phosphide. Meanwhile, the least causes were remidisvir, isoniazid, ketoconazole, fluconazole, carbamazepine, phenytoin, diclofenac, testosterone, imipramine, amitriptyline, haloperidol, clozapex, and clonazepam. The current study was different from another Egyptian cohort study[31], which detected that diclofenac was the most common cause of DILI [(41.3%) of cases], amoxicillin clavulanate was the second cause, halothane was the third, followed by ibuprofen, khat, and tramadol. Meanwhile, the least causes were carbimazole, tenoxicam, methimazoles, and carbamazepine. Other studies[32] conducted in

Table IV. Multivariate analysis of risk factors for mortality and fulminant hepatic failure.

Multivariate analysis of risk factors for mortality			
Risk factor for mortality	**Odds ratio**	**95% confidence interval**	***p*-value**
MELD	1.525	1.108-2.1	0.01*
SO_2	0.927	0.868-0.991	0.025*
Bilirubin	0.925	0.673-1.272	0.633
PSS	3.296	0.302-35.989	0.328
HCO_3	0.244	0.659-1.097	0.244
Multivariate analysis of risk factors for fulminant hepatic failure			
MELD	1.136	1.002-1.286	0.046*
HCO_3	1.015	0.881-1.171	0.833
PSS	1.679	0.374-7.54	0.499
Bilirubin	1.565	0.6-4.083	0.36
Random blood sugar	0.986	0.974-997	0.016*

MELD: Model for End Stage Liver Disease; PSS: Poison Severity Score. *Significant result.

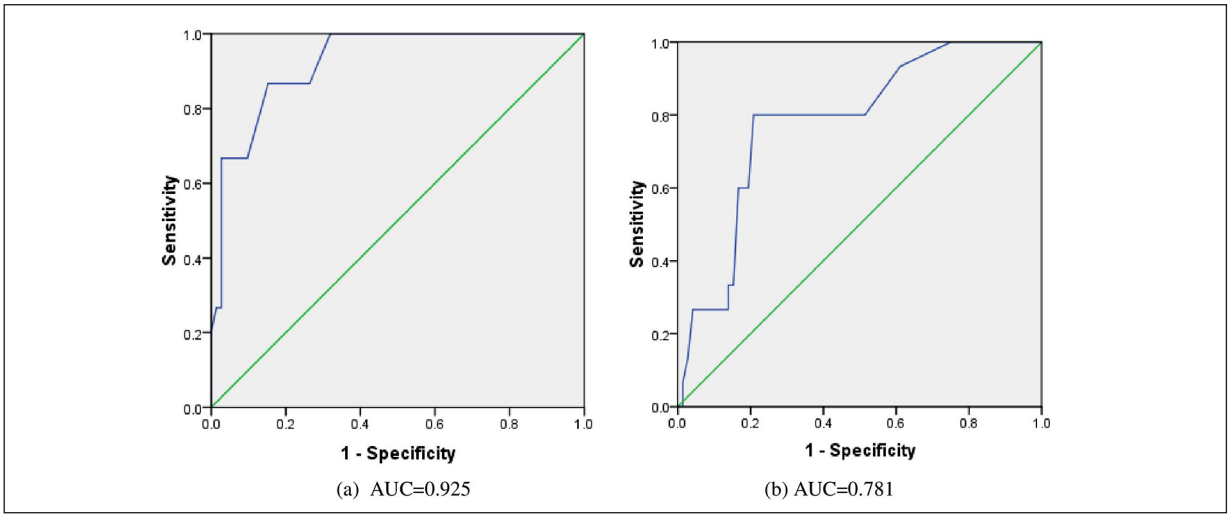

Figure 1. ROC curves plotting sensitivity *vs.* 1-specificity for different cut-off values in patients with or without mortality. **a**, Model for End Stage Liver Disease; **b**, SO_2.

different countries have shown that antimicrobial agents are the most common cause of DILI. They showed that amoxicillin-clavulanate was the most common causative agent among antimicrobials. Anti-tuberculous drugs have been reported[33] as a common cause of DILI in some Asian countries. This can be explained by the differences in the epidemiology of infectious diseases and the numbers observed in other studies from this region. Herbal and complementary alternative medicines

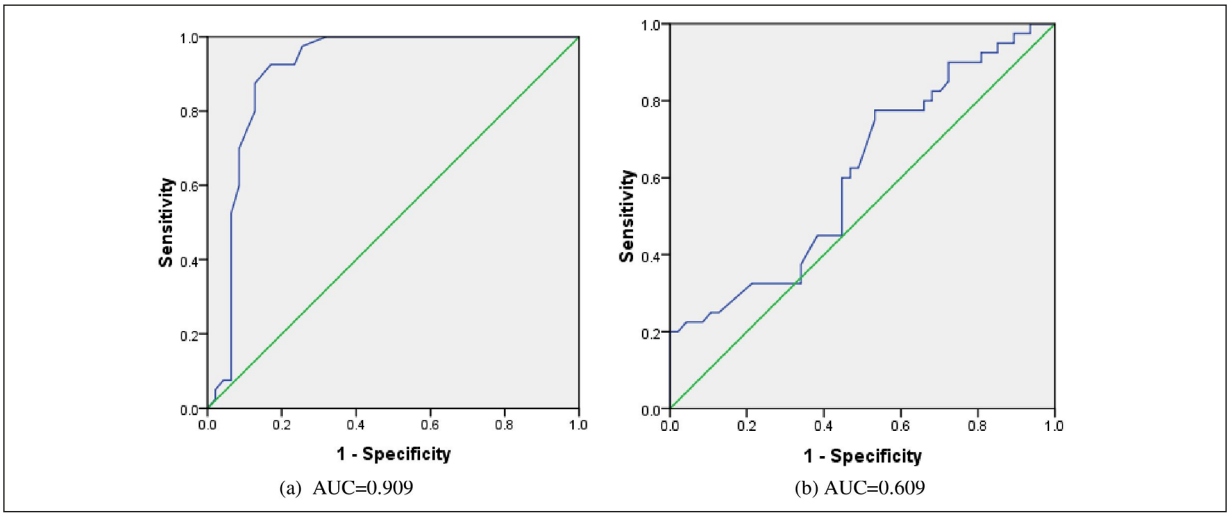

Figure 2. ROC curves plotting sensitivity *vs.* 1-specificity for different cut-off values in patients with or without fulminant hepatic failure. **a**, Model for End Stage Liver Disease; **b**, Random blood sugar.

Table V. Prognostic indicators for mortality in drug induced liver injury.

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MELD score	24.5	86.7	84.7	54	96.8
SO_2	91.5	80	79.2	44.4	95

MELD: model for end stage liver disease; NPV: negative predictive value; PPV: positive predictive value.

Table VI. Prognostic indicators for fulminant hepatic failure in drug induced liver injury.

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MELD score	19	80	87.2	84.2	83.7
Random blood sugar	111.5	60	55.3	53.3	61.9

MELD: model for end stage liver disease; NPV: negative predictive value; PPV: positive predictive value.

come after antimicrobials as drugs involved in liver injury[34]. In our study, the overall mortality [15 cases (17%)] was in agreement with an Indian study[24] in 2017, which reported overall mortality rate of 15.85%. Several studies[26,35] have reported an overall mortality rate between 10% and 17.3%. The highest mortality rate in our study was due to acetaminophen toxicity followed by halothane, aluminum phosphide, and Dormex respectively. Abdelhamid[21], in his study at Ain Shams Poison Control Centre, reported pesticides as organophosphates and rodenticides as aluminium phosphide as the third leading cause of death. In Thailand, one study[33] reported 26% mortality with DILI caused by antimicrobial agents.

In our study, hepatocellular liver injury was associated with higher proportion of fulminant hepatic failure, mortality, in addition to higher MELD score, liver enzymes, PSS, and GCS scores in comparison to patients with cholestatic and mixed liver injuries. Similar to these findings, a Chinese study[36] detected 9.9% mortality in patients with hepatocellular damage in comparison to 9.5% in patients with cholestatic/mixed damage with significant statistical difference. Also, Spanish[25] and Swedish[37] studies demonstrated that hepatocellular type of liver injury was associated with a higher mortality rate, depending on the presence of jaundice or drug involved. However, the association between poor outcome and cholestatic liver injury was observed in other studies[31,38]. This can be explained by the change of the pattern of liver injury which can occur on the progression of the condition. Hence, the importance of liver injury pattern in determining the outcome is still questionable[39]. In our study, we observed that mortality was significantly associated with hepatocellular pattern of liver injury, elevation of liver enzymes, MELD score, INR, total serum bilirubin, serum creatinine, PSS, and GCS, as well as low SO_2 and low random blood sugar. On multivariate analysis, MELD score (cut-off value of >24.5, sensitivity of 86.7%, and specificity of 84.7%) and SO_2 (cut-off value of <91.5, sensitivity of 80%, and specificity of 79.2%) were predictors of mortality. In addition, MELD score (cut-off value of >19, sensitivity of 80%, and specificity of 87.2%) and random blood sugar (cut-off value of <111.5, sensitivity of 60%, and specificity of 55.3%) predicted FHF development.

Few studies[31,33,36,37,40-42] have reported the predictors of FHF and mortality in DILI. These predictors included female patients, hepatocellular pattern of liver injury, high AST, high bilirubin, high MELD score, prolonged prothrombin time, low hemoglobin, and high leucocyte count.

In another study[43] that included 106 patients with acute liver failure, MELD score >30 was a predictor of mortality with sensitivity of 87% and specificity of 65%. In addition, the best cut-off points for MELD score to discriminate between survivors and non survivors was 35, with a sensitivity and specificity of 86% and 75% respectively. Similar to our study, a significantly higher MELD score was detected in patients who developed FHF than in those who did not. A cut-off of 18 was required to identify 95% of the FHF patients (positive predictive value 44%). MELD score of 33 had sensitivity of 60%, specificity of 69%, positive predictive value of 65%, and negative predictive value of 63%[44]. Our study has some limitations including the small sample size, retrospective nature of the study, absence of a liver transplantation facility, and absence of examination of liver histopathology in every patient to assess the possibility of liver regeneration.

Conclusions

Drug-induced liver injury results in significant overall mortality. Acetaminophen, halothane, atorvastatin, antimicrobials, and herbal preparations were the most common leading causes. The MELD score is a useful predictor of the outcome of drug induced liver injury such as fulminant hepatic failure and mortality. Additionally, national studies are needed to elucidate the natural history of this disorder in Egypt, which has a high percentage of patients with chronic liver disease.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethics Approval
This study was conducted according to the declaration of Helsinki principles. It was approved by the Ethical Committee of the Faculty of Medicine of Tanta University.

Availability of Data and Materials
The data that support the findings of this study are available from Tanta University. Restrictions apply to the data as the institute does not allow public sharing..

Funding
None.

Informed Consent
Not applicable.

Authors' Contribution
Nadia E. Helal and Shimaa A. Mashaal collected data. Samah M. Elbastawesy performed the data analysis and interpretation. Mahmoud Elkadeem wrote the manuscript. All authors read and approved the final manuscript. Authors contributed to making critical revisions related to important intellectual content of the manuscript; all authors approved the version of the article to be published.

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