Original Article

A retrospective case-controlled cohort study of inpatient drug induced liver injury: the RIDDLE study

Thomas Worland[1], Ken Lee Chin[2], Beverley Rodrigues[1], Amanda Nicoll[1,3]

[1]Department of Gastroenterology, Eastern Health, Box Hill, Victoria, Australia; [2]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; [3]Monash University, Eastern Health Clinical School, Box Hill, Victoria, Australia

Contributions: (I) Conception and design: T Worland, A Nicoll; (II) Administrative support: T Worland, B Rodrigues, A Nicoll; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: T Worland, B Rodrigues; (V) Data analysis and interpretation: KL Chin, T Worland, A Nicoll; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Thomas Worland. Department of Gastroenterology, Eastern Health, Level 3, 3West, 8 Arnold Street, BOX HILL VIC 3128, Australia. Email: tfworland@gmail.com.

Background: Identification of risk factors for drug-induced liver injury (DILI) has been hindered by the unpredictable incidence and idiosyncratic nature of DILI. The aim of this study was to identify characteristic host risk factors for DILI.

Methods: A retrospective cohort study was performed examining all patients admitted with a diagnosis of DILI over a 5.5-year period. Cases were compared to a control group non-exposed to DILI using propensity score-derived inverse probability weights. Patients with DILI due to alcohol or paracetamol were excluded from analysis.

Results: Seventy-two cases of DILI admitted to hospital were identified. Antimicrobials caused 56.9% of cases, with amoxicillin-clavulanate the single most common agent, responsible for 13.9% of cases. DILI cohort median age (50.2±36 years) was significantly younger than controls (65.0±38 years) (P<0.001). Pre-existing chronic liver disease (OR, 3.44; 95% CI, 1.38–8.59; P=0.008), length of stay (P<0.001) and in-hospital death (P=0.009) were more likely to be associated with DILI cases. There was no correlation with sex (OR male, 0.92; 95% CI, 0.50–1.67; P=0.78), presence of comorbid autoimmune disease (OR, 1.44; 95% CI, 0.68–3.05; P=0.35), past drug allergies (OR, 1.71; 95% CI, 0.92–3.16; P=0.09), or atopy (OR, 0.87; 95% CI, 0.42–1.82; P=0.72).

Conclusions: Younger age and presence of chronic liver disease were associated with an admission with DILI; however, it remains difficult to predict the population at risk of DILI on clinical grounds and putative risk factors such as female gender, and history of other drug allergies and autoimmunity, were not demonstrated in this study.

Keywords: Chemical and drug induced liver injury; drug related side effects and adverse reactions; toxic hepatitis

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Introduction

Drug-induced liver injury (DILI) is the most common cause of acute liver failure and indication for urgent liver transplantation in the United States and Europe (1,2). Although the most frequent cause of DILI is paracetamol, a direct and predictable hepatotoxin (3,4), non-paracetamol DILI is an important cause of morbidity and mortality that is unexpected and does not have a reversal agent.

The incidence of DILI is difficult to determine, due to inconsistent diagnostic criteria, lack of objective tests, reporting bias, and exclusion of low level/asymptomatic biochemical abnormalities. Several scoring systems have

been developed to assess the likelihood that hepatic injury is the result of an individual drug. The most widely used of these are the Roussel Uclaf Causality Assessment Method (RUCAM) score (5), as well as the non-DILI specific Naranjo Score for adverse drug reactions (6). Despite issues regarding subjective score attribution, and areas of ambiguity, the RUCAM score is commonly used clinically and in research publications investigating DILI (7,8).

Antimicrobials are the most common cause of DILI, accounting for almost 50% of cases (9). This is likely due to both their intrinsic hepatotoxic potential as well as ubiquity in medicine. Of the top ten causes of DILI listed by the United States DILI registry, nine are antibiotics (10), and amoxicillin-clavulanate is the most common cause of idiosyncratic DILI worldwide (9,11,12). However, there is a paucity of Australian data.

There are inconsistencies in the literature regarding DILI risk factors likely due to unpredictable and infrequent occurrence, and reliance on retrospective series. Many series have suggested that DILI occurs more frequently in females, who also experience a more severe reaction manifest as higher rates of DILI associated liver transplant and death (3,9,12-14). This has been attributed possibly to oestrogen or interleukin 6 (15). However, other studies suggest males are at a higher risk for DILI from amoxicillin-clavulanate (16) and thiopurines (17). Increased age is a putative independent risk factor for DILI; however, this may be due to confounders including increased polypharmacy, increased disease burden, and increased health monitoring (9,18). Background chronic liver disease is a risk factor for all-cause mortality if DILI develops (10); however, baseline chronic liver disease has not been shown to increase risk of DILI occurring (19,20). Alcohol intake is a risk for paracetamol toxicity and methotrexate hepatotoxicity (21), but does not seem to play an important role in other DILI (22). It has been estimated that fatty liver increases the risk of DILI by four-fold particularly to irinotecan, MTX, tamoxifen (23-25).

DILI remains an important reason for hospitalisation and is difficult to characterise as the emergence of new medications add to a growing list of potential toxins. The aims of this study were to describe the characteristics of DILI cases at a single tertiary institution and examine possible risk factors and confounders in an inpatient population compared to propensity matched inpatient controls.

Methods

A case-control study of adult patients admitted to Eastern Health over 5.5 years between November 2011 and June 2017 was performed. Eastern Health is a one of Melbourne's largest metropolitan health services with a catchment of over 750,000 people.

Electronic medical records were searched for patient episodes with DILI, using discharge coding diagnoses to identify cases of hepatic injury (*Table S1*), and case notes used to ascertain cases of DILI. Cases of paracetamol overdose and alcohol hepatotoxicity were excluded from analysis. Additional cases were identified by interrogation of data from a previous audit performed at our institution examining causes of alanine transaminase greater than 1,000 IU/L by an expert hepatologist (26). Data collected included patient demographics, history of liver disease, history of autoimmune conditions, atopy, chronic liver disease, alcohol intake, liver biochemistry, drug therapy, and outcome data. DILI specific scores including RUCAM score, Naranjo Score, and severity score were as defined by the US DILI network to grade severity of liver injury (27). The pattern of liver injury was described according to R factor (28) as hepatocellular, cholestatic, or mixed. Controls were randomly selected from all patients admitted to our institution during the study period, with inclusion criteria; over 18 years old, admitted as an inpatient, and did not have DILI during hospital stay. Randomisation of all patients was performed to yield 500 DILI-free patients. Of these 500, 178 were excluded for not meeting the inclusion criteria, leaving 322 subjects as controls. Charlson comorbidity scoring was calculated for controls and cases to ensure an equivalent comorbid burden between the groups existed. The same data fields were collected for controls as for the DILI cases.

The pattern of liver injury was described according to R factor (28) as hepatocellular, cholestatic, or mixed. Severity of DILI was in accordance with definitions published by the US DILI network (27). DILI was defined as previously described (9). Severe biochemical abnormality was defined as either bilirubin >200 µmol/L, Alanine transferase >1,000 IU/L, or Alkaline phosphatase >500 IU/L. Levels of alcohol intake were defined as abstinent, low risk, risky, or high risk according to definitions set out by the National Health and Medical Research Council (29). Causality was scored according to the Naranjo probability index and RUCAM scores (*Table S2*).

Baseline characteristics were assessed with descriptive statistics as appropriate. Univariate and multivariate logistic regressions were used to evaluate the association between potential risk factors and DILI. To minimise the

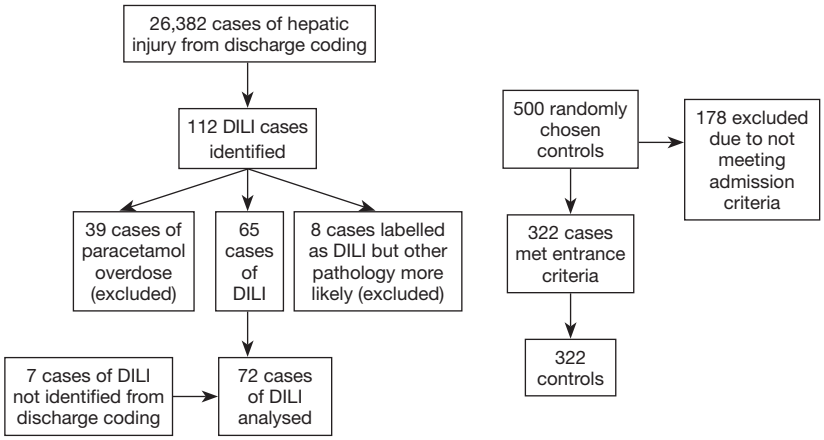

Figure 1 Flow chart for methods. DILI, drug-induced liver injury.

effect of confounding by differences in key characteristics between cases and controls, we constructed an inverse probability weighted multivariate logistic regression models as sensitivity analyses. Variables with P<0.05 in the multivariate model were considered to be independent associations. All analysis was performed using STATA 15 (StataCorp, College Station, TX).

This retrospective review was approved by the Office of Research and Ethics, Eastern Health, Melbourne QA43-2017.

Results

One hundred and nineteen cases of DILI were identified [112 from medical records (*Table S1*), seven from an audit of patients with raised alanine transaminases]. Forty-seven cases were excluded (39 due to paracetamol, 8 misdiagnosis), as shown in *Figure 1*. There were no instances of recurrent DILI in the same individual during this study period.

The final cohort of 72 DILI cases consisted of 42 (58.3%) females, with a median age at admission 50 (range, 18–89) years. Pre-existing liver disease was present in 13 (18.1%) DILI cases; diabetes (type 1 or 2) in 11 (15.3%); autoimmune disease in 13 (18.1%); and atopic conditions in 9 (12.5%) cases (*Table 1*). RUCAM scoring determined DILI to be unlikely in 3 (4.2%) cases; however, DILI was deemed the most likely diagnosis after review by an expert hepatologist, with low RUCAM score due to incomplete data. All other cases were possible: 17/72 (23.6%), probable: 34/72 (47.2%), or highly probable: 18/72 (25.0%) (*Table S2*).

Antimicrobials were the most common causative agents, identified in 41 cases (56.9%). The single agent most commonly associated with DILI was amoxicillin-clavulanate: 10 cases (13.9%), followed by flucloxacillin: 6 cases (8.3%) (*Table S3*).

The most common pattern of liver injury was hepatocellular, accounting for 39 cases (54.2%). Severe biochemical abnormality was seen in 48 cases (66.7%); and was associated with 30/39 (76.9%) hepatocellular DILI cases, 14/22 (63.6%) cholestatic cases, and 4/11 (36.4%) mixed cases (*Table 2*). Overall, antimicrobials were the most common causative agents (56.9%) in severe DILI cases [defined as grade 4 or 5 in the DILI network severity scale (27)], largely attributed by amoxicillin-clavulanate (13.9%) and flucloxacillin (8.3%) (*Table 3*, *Table S4*). There was no difference of rates of severe DILI between males: 20/30 (66.7%) and females: 28/42 (66.7%).

Three deaths occurred within the cohort but none were deemed to be as a direct consequence of DILI. One patient required liver transplantation following DILI secondary to methylenedioxymethamphetamine (MDMA) (*Table S5*).

When both groups were compared, younger age (50.2 *vs.* 65.0 years, P<0.001), presence of underlying liver disease (18.1% *vs.* 6.2%, P=0.004), average length of stay (7.5 *vs.* 4.0 days, P=0.0001) and in-hospital death (4.2% *vs.* 2.8%, P=0.009) were associated with DILI cases (*Table 1*). Pregnancy was more common in controls (1.4% *vs.* 9.9%, P=0.02) compared with DILI cases; however, the low number of pregnant cases included is likely to have influenced this result.

Alcohol drinking risk was higher in the control group compared to the DILI group, however, this was excluded from analysis due to high levels of missingness (approximately 50% in both cases and controls).

The prevalence of pre-existing liver disease (*Table S6*)

Table 1 Patient characteristics by group in the observed sample and after inverse-probability-weighting

Patient characteristics	As observed			After weighting to balance risk factors	
	DILI cases	Controls	P value	DILI cases	Controls
Number (n)	72	322		72	315
Age, median [IQR], years)	50.2 [36]	65.0 [38]	0.0004	45.7, [37]	65.0 [39]
Male, n (%)	30 (41.7)	129 (40.1)	0.80	26 (41.3)	130 (40.1)
Body mass index (mean ± SD, kg/m^2)	26.7±5.9	27.9±11.0	0.41	26.7	28.4
Pregnant, n (%)	1 (1.4)	32 (9.9)	0.02	1 (1.9)	32 (9.9)
Length of stay (median ± IQR, days)	7.5±10.0	4.0±5.0	0.0001	13.1	7.3
Died as inpatient, n (%)	3 (4.2)	9 (2.8)	0.009	3 (4.8)	8 (2.6)
Medical history, n (%)					
Diabetes mellitus (type 1 or 2)	11 (15.3)	72 (22.4)	0.214	10 (16.7)	78 (24.0)
Diagnosed liver disease	13 (18.1)	20 (6.2)	0.004	8 (12.9)	15 (4.7)
Hyperlipidaemia	19 (26.4)	95 (29.5)	0.59	17 (27.9)	99 (30.6)
Autoimmune disease	13 (18.1)	47 (14.6)	0.46	11 (16.9)	46 (14.2)
Charlson comorbidity score	2.9	4.1	0.01	3.3	4.3
Allergies, n (%)					
Drugs	27 (37.5)	110 (34.2)	0.78	24 (39.2)	111 (34.1)
Other	2 (2.8)	25 (7.8)	0.13	2 (3.7)	28 (8.8)
Atopy	9 (12.5)	44 (13.7)	0.79	8 (13.1)	46 (14.1)
Asthma/eczema/hay fever, n (%)					
Asthma	8 (11.1)	32 (9.9)	0.93	7 (11.4)	33 (10.3)
Hay fever	1 (1.4)	5 (1.6)		1 (1.7)	5 (1.7)
Asthma + hay fever	Nil	4 (1.2)		Nil	4 (1.2)
Asthma + eczema	Nil	1 (0.3)		Nil	1 (0.3)
Eczema + hay fever	Nil	1 (0.3)		Nil	1 (0.3)
Asthma + eczema + hay fever	Nil	2 (0.6)		Nil	2 (0.6)
No history	63 (87.5)	277 (86.0)		54 (86.9)	278 (85.5)

Table 2 DILI cases with severe hepatotoxicity as defined by the US DILI network (27)

Biochemical parameters	Hepatocellular (n=39)	Cholestatic (n=22)	Mixed (n=11)
Bilirubin >200 µmol/L (normal <19 µmol/L)	5	3	2
ALT >1,000 IU/L (normal <40 IU/L)	29	0	1
ALP >500 IU/L (normal <110 IU/L)	1	11	3
Bilirubin >200 µmol/L or ALT >1,000 IU/L or ALP >500 IU/L	30	14	4

ALT, alanine transferase; ALP, alkaline phosphatase.

Table 3 Drug to which the DILI was attributed by the treating doctor and study team with severity rating as defined by the US DILI network (27)

Drug	Value (N=72)	Severity rating (1/2/3/4/5)
Antimicrobial agents		
Total	41 (56.9%)	26/1/10/4/0
Amoxicillin-clavulanate	10 (13.9%)	4/0/3/3/0
Anti-mycobacterial	7 (9.7%)	4/1/1/1/0
Flucloxacillin	6 (8.3%)	4/0/2/0/0
Piperacillin-tazobactam	4 (5.6%)	3/0/1/0/0
Other antimicrobials	14 (19.4%)	11/0/3/0/0
Recreational drugs	6 (8.3%)	1/0/4/0/1
Alternative/herbal	4 (5.6%)	0/0/4/0/0
Antimetabolite	4 (5.6%)	0/0/4/0/0
Cardiac/antihypertensive	4 (5.6%)	4/0/0/0/0
Non-steroidal anti-inflammatory	4 (5.6%)	3/0/1/0/0
Psychiatric/anti-epileptic	3 (4.2%)	2/0/1/0/0
HMG-CoA reductase inhibitors	3 (4.2%)	1/0/2/0/0
Cancer therapies	2 (2.8%)	0/0/2/0/0
5-Aminosalicylic acid	1 (1.4%)	0/1/0/0/0

HMG-CoA reductase inhibitors, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors.

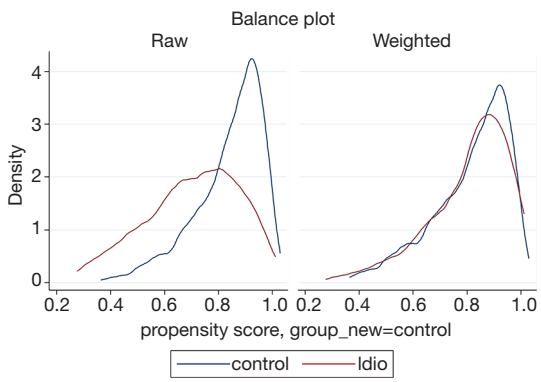

Figure 2 Balance plot.

were significantly higher in DILI cases versus controls for fatty liver (6.9% *vs.* 0.9%, P=0.001) and hepatitis C (6.9% *vs.* 1.2%, P=0.003), but not alcohol related liver disease (1.4% *vs.* 0.9%, P=0.726) and metastatic disease to the liver (1.4% *vs.* 1.6%, P=0.918). No significant difference in prevalence of autoimmune diseases were observed between cases and controls (18.1% *vs.* 14.6%, P=0.46); individually, significant differences were seen between groups for inflammatory bowel disease (4.2% cases *vs.* 0.6% controls, P=0.015), and rheumatoid arthritis (6.9% cases *vs.* 2.2% controls, P=0.033) but not for autoimmune thyroid disease (1.4% cases *vs.* 6.2% controls, P=0.100) (*Table S6*). Prevalence of allergy and of atopic conditions was not different between the two groups. A plot of covariate balance is shown in *Figure 2*.

Risk factors for DILI

On multivariate analysis, younger age (OR, 0.95; 95% CI, 0.93–0.98; P<0.001) and the presence of pre-existing liver disease (OR, 3.44; 95% CI, 1.38–8.59; P=0.008) were associated with DILI. Male gender (OR, 0.92; 95% CI, 0.50–1.67; P=0.78), presence of diabetes (OR, 0.51; 95% CI, 0.22–1.18; P=0.11), hyperlipidaemia (OR, 1.81; 95% CI, 0.84–3.88; P=0.13), concomitant autoimmune disease (OR, 1.44; 95% CI, 0.68–3.05; P=0.35), other drug allergies (OR, 1.71; 95% CI, 0.92–3.16; P=0.09), or presence of atopic conditions (OR, 0.87; 95% CI, 0.42–1.82; P=0.72) were not found to be associated with DILI. Charlson comorbidity scores were not significantly different between groups (OR, 1.06; 95% CI, 0.93–1.22; P=0.37), consistent with a similar comorbid disease burden (*Table 4*).

Discussion

This retrospective case control study has characterised patients with DILI admitted to an Australian Hospital and compared them to a similar inpatient control group. It did not identify any risk factors for the development of DILI. The only associations were age, which was likely confounded as the elderly are more frequently exposed to pharmacologic therapy, both as inpatients and in the community, than younger patients; and pre-existing liver disease, which is more likely to be identified and noted in patients presenting with abnormal liver biochemistry. The previously held conviction that female gender, older age, higher BMI, and history of allergies were more common in patients with DILI was not demonstrated in this cohort. It does not appear from our study that older patients were at greater risk of hospital admission from DILI. The presence of autoimmune disease was not more common despite current theories on the importance of the adaptive and innate immune system in the development of DILI (30,31).

Table 4 Multivariate logistic regression (account for weighting in inverse-probability-weighting model) (n=387)

Variable	Odds ratio	95% CI	P value
Age	0.95	0.93–0.98	<0.001
Male	0.92	0.50–1.67	0.78
Diabetes mellitus	0.51	0.22–1.18	0.11
Diagnosed liver disease	3.44	1.38–8.59	0.008
Hyperlipidaemia	1.81	0.84–3.88	0.13
Autoimmune disease	1.44	0.68–3.05	0.35
Charlson comorbidity score	1.06	0.93–1.22	0.37
Drug allergies	1.71	0.92–3.16	0.09
Asthma/eczema/hay fever	0.87	0.42–1.82	0.72

This is despite the fact that some DILI, such as with amoxicillin-clavulanate, have classic autoimmune/allergy features of eosinophilia, rash, and fever. Inflammatory bowel disease and rheumatoid arthritis were more commonly observed in the DILI cohort, however, this may reflect increased exposure to potential hepatotoxic drugs.

A large number of inpatient encounters were identified using search terms for liver toxicity (*Table S1*) resulting in only 72 likely cases on detailed case review. This is still likely an underestimation as many cases of DILI are not diagnosed or may not be recorded in patient case files correctly. Using our estimated catchment area population of 750,000 people this equates to a rate of 1.7 cases per 100,000 person years; less than other quoted estimates of DILI incidence in community settings, which range from 2.4–19 cases per 100,000 person years (11-13,32-34). This study did identify DILI as a significant cause of morbidity; average length of stay is longer in the DILI group compared to controls (7.5 *vs.* 4.0 days, P=0.0001), and patients in the DILI group were more likely to die (4.2% *vs.* 2.8%, P=0.009). This rate is not dissimilar to that of other series, in which 5–10% of patients admitted with idiosyncratic DILI undergo liver transplant or die within 6 months (9,35).

Compared to matched controls, DILI was statistically significantly more common in younger patients (P<0.001), however the difference was of minimal clinical significance (OR 0.95). This is despite the fact that older patients are more likely to be on a greater number of medications and undergo more frequent health monitoring. It is plausible that increasing age is associated with less effective drug metabolism and may result in greater drug toxicity, flucloxacillin has been shown to cause DILI more frequently in the elderly and in those on protracted courses (36). All patients, in both the DILI and control groups, were exposed to pharmacologic therapy and thus at risk for DILI. Although data was not collected it is plausible that DILI patients, who were older than the control group, were on more medications than the controls and hence at increased risk of DILI.

Chronic liver disease was more common in the DILI group compared to controls (OR =3.44, P=0.008), which is in contrast to other work which suggests no such relationship exists (19,20). Rather than a true association it is likely this represents confounding. Patients admitted with DILI were reviewed by a specialty gastroenterology service and extensively investigated for causes of abnormal liver biochemistry, increasing the chance of detecting background disease.

Alcohol use was higher in the control group compared to the DILI group. As with background liver disease, this is likely secondary to more accurate history taking in the DILI group due to their abnormal liver biochemistry. Control patients were more likely to have alcohol intake recorded only if deemed clinically relevant, usually if intake was to excess. Patients without recorded alcohol intake history had this covariate excluded from analysis. In contrast, DILI patients were more likely to have an alcohol history recorded (65% recorded *vs.* 44% recorded in control).

The single agent responsible for the greatest number of episodes of DILI in our cohort was the amoxicillin-clavulanate combined formulation, followed by flucloxacillin. This is consistent with previous series in which amoxicillin-clavulanate was the commonest cause of DILI, and in Australia this was followed by flucloxacillin (12,37,38). Some series have suggested DILI to amoxicillin-clavulanate to occur more frequently in males (16). Our study showed antibiotics to cause 46% of DILI cases, which is similar to published rates (9). In addition, according to R factor (28), 54.2% of patients had hepatocellular injury, 30.6% had cholestatic, and 15.3% mixed. These rates are similar to those quoted by a large prospective series, which found 57% of cases hepatocellular, 23% cholestatic, and 20% mixed (9).

Three deaths occurred in patients suffering DILI. DILI was not thought to be the primary cause of death in any of these cases. Death in these cases was due to neutropenic sepsis following an allogenic stem cell transplant, Escherichia coli sepsis, and exacerbation of chronic obstructive pulmonary disease, respectively. One patient required liver

transplantation following MDMA induced DILI.

A strength of this study was that it used a control group of propensity matched inpatient controls to try to characterise the DILI group. Charlson comorbidity scores were well matched between the DILI patients and controls confirming that their overall health and prognosis from underlying disease were similar. The limitations of this study are that it was retrospective and some data such as alcohol consumption and body mass index were incomplete. Also, for a study looking for characteristics and predictive factors for DILI, it is clear that very large patient samples are required as events are relatively rare.

Putative risk factors for DILI such as female gender, and history of other drug allergies and autoimmunity are not reflected in inpatient cohorts such as this. It is likely that clinical features of the host will not guide future research in DILI and other features such as genotypes and specific biomarkers may be more useful in advancing the science of this problem.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective review was approved by the Office of Research and Ethics, Eastern Health, Melbourne QA43-2017.

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Supplementary

Table S1 Discharge diagnosis codes included for review

Toxic liver disease
Toxic liver disease with cholestasis
Toxic liver disease with hepatic necrosis
Toxic liver disease with acute hepatitis
Toxic liver disease with chronic persistent hepatitis
Toxic liver disease with chronic lobular hepatitis
Toxic liver disease with chronic active hepatitis
Toxic liver disease with hepatitis, not elsewhere classified
Toxic liver disease with fibrosis and cirrhosis of liver
Toxic liver disease with other disorders of liver
Toxic liver disease, unspecified
Hepatic failure, not elsewhere classified
Acute and subacute hepatic failure
Chronic hepatic failure
Hepatic failure, unspecified
Fibrosis and cirrhosis of liver
Hepatic fibrosis
Hepatic sclerosis
Hepatic fibrosis with hepatic sclerosis
Secondary biliary cirrhosis
Biliary cirrhosis, unspecified
Other and unspecified cirrhosis of liver
Other inflammatory liver diseases
Phlebitis of portal vein
Nonspecific reactive hepatitis
Granulomatous hepatitis, not elsewhere classified
Autoimmune hepatitis
Other specified inflammatory liver diseases
Inflammatory liver disease, unspecified
Other diseases of liver
Fatty (change of) liver, not elsewhere classified
Chronic passive congestion of liver
Central haemorrhagic necrosis of liver
Infarction of liver
Peliosis hepatis
Hepatic veno-occlusive disease
Hepatorenal syndrome
Other specified diseases of liver
Liver disease, unspecified

Table S2 Probability scoring for drug-induced liver injury (DILI) cases

Probability scoring systems	Number (n=72)
Naranjo score	
Doubtful DILI (≤0)	0
Possible DILI (1–4)	37
Probable DILI (5–8)	35
Definite DILI (≥9)	0
RUCAM score	
RUCAM unlikely	3
RUCAM possible	17
RUCAM probable	34
RUCAM highly probable	18

Three cases deemed unlikely by RUCAM scoring were diagnosed as DILI following analysis of cases by the investigators.

Table S3 Full list of drugs responsible for drug-induced liver injury (DILI)

Drug	Number (n=72)
Amoxicillin-clavulanate	10
Flucloxacillin	6
Piperacillin-tazobactam	4
Erythromycin	3
Isoniazid	3
Illicit drugs unknown type	3
Pyrazinamide	3
Amiodarone	2
Asparaginase	2
Atorvastatin	2
Cefazolin	2
Cephalexin	2
Methylenedioxymethamphetamine	2
Methotrexate	2
Traditional Chinese herbals unknown type	2
Actaea racemosa	1
Ampicillin	1
Amoxicillin	1
Azathioprine	1
Benzyl penicillin	1
Camellia sinensis	1
Carbamazepine	1
Clozapine	1
Diclofenac	1
Duloxetine	1
Enoxaparin	1
Ibuprofen	1
Meloxicam	1
6-Mercaptopurine	1
Methamphetamine	1
Methyldopa	1
Minocycline	1
Naproxen	1
Nitrofurantoin	1
Rifampicin	1
Rosuvastatin	1
Roxithromycin	1
Sulphasalazine	1
Ticarcillin-clavulanate	1

Table S4 Severe drug-induced liver injury (DILI) according to type of injury (severe injury defined as Bilirubin >200 µmol/L or ALT >1,000 IU/L or ALP >500 IU/L)

Type of injury	Drug	n = 72
Cholestatic	Flucloxacillin	4
	Amoxicillin-clavulanate	2
	Asparaginase	2
	Piperacillin-tazobactam	2
	Ampicillin	1
	Atorvastatin	1
	Azathioprine	1
	Ticarcillin-clavulanate	1
Mixed	Amoxicillin-clavulanate	3
	Isoniazid	1
Hepatocellular	Amoxicillin-clavulanate	3
	Illicit drugs unknown type	3
	Erythromycin	2
	Methylenedioxymethamphetamine	2
	Pyrazinamide	2
	Actaea racemosa	1
	Amiodarone	1
	Benzyl Penicillin	1
	Camellia sinensis	1
	Carbamazepine	1
	Cephalexin	1
	Duloxetine	1
	Isoniazid	1
	Meloxicam	1
	Methamphetamine	1
	Methotrexate	1
	Methyldopa	1
	Minocycline	1
	Naproxen	1
	Rosuvastatin	1
	Roxithromycin	1
	Sulphasalazine	1
	Traditional Chinese Herbals unknown type	1

Table S5 Drugs according to drug-induced liver injury (DILI) severity grading

DILIN severity grading	Drug	Number
1	Amoxycillin-clavulanate	4
	Flucloxacillin	4
	Tazocin	3
	Amiodarone	2
	Erythromycin	2
	Pyrazinamide	2
	Amoxicillin	1
	Ampicillin	1
	Benzyl Penicillin	1
	Cefazolin	1
	Cephalexin	1
	Clozapine	1
	Diclofenac	1
	Duloxetine	1
	Enoxaparin	1
	Ibuprofen	1
	Illicit	1
	Isoniazid	1
	Methyldopa	1
	Meloxicam	1
	Minocycline	1
	Nitrofurantoin	1
	Rifampicin	1
	Rosuvastatin	1
	Roxithromycin	1
	Ticarcillin-clavulanate	1
	Total	37
2	Pyrazinamide	1
	Sulphasalazine	1
	Total	2
3	Amoxicillin-clavulanate	3
	Asparaginase	2
	Atorvastatin	2
	Flucloxacillin	2
	Illicit drugs unknown type	2
	Methotrexate	2
	Traditional Chinese Herbals unknown type	2
	Actaea racemosa	1
	Azathioprine	1
	Camellia sinensis	1
	Cefazolin	1
	Cephalexin	1
	Carbamazepine	1
	Erythromycin	1
	Isoniazid	1
	6-mercaptopurine	1
	Methamphetamine	1
	Methylenedioxymethamphetamine	1
	Naproxen	1
	Piperacillin-tazobactam	1
	Total	28
4	Amoxicillin-clavulanate	3
	Isoniazid	1
	Total	4
5	Methylenedioxymethamphetamine	1
	Total	1

Table S6 Background diseases

Background diseases	Cases	Controls
Liver disease	n=13	n=20
NAFLD/NASH	5	3
Hepatitis B	0	2
Hepatitis C	5	4
Alcoholic liver disease	1	3
Cryptogenic cirrhosis	0	1
Longstanding deranged liver biochemistry	0	1
Cardiac cirrhosis	1	0
Metastatic infiltration	1	5
Cholestasis of pregnancy	0	1
Autoimmune disease	n=13	n=47
Hypothyroidism/Hashimoto's	0	16
Rheumatoid arthritis	5	7
Grave's disease	1	4
IgA nephropathy	1	2
Multiple sclerosis	0	2
Ulcerative colitis/Crohn's disease	3	2
Granulomatous myositis	1	0
Type 1 diabetes	1	6
ANCA vasculitis	0	1
Antisynthetase syndrome	0	1
Coeliac disease	1	0
Pernicious anaemia	0	1
Myasthenia gravis	0	1
Autoimmune demyelinating polyneuropathy	0	1
Psoriasis	0	1
Granulomatosis with polyangiitis	0	1
Systemic lupus erythematosus	0	1