Editorial

Mortality associated with drug-induced liver injury (DILI)

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Idiosyncratic drug-induced liver injury (DILI) is an important cause of liver failure and liver injury leading to transplantation, although in most cases self-remitting when administration of the offending drug is stopped (1-3). In rare cases DILI can lead to a persistent/chronic form of injury (4).

According to Hy's law drug-induced jaundice caused by a hepatocellular injury, leads to death from liver failure or need for a liver transplantation in approximately 10% of cases (2,3). When Hy's law cases with ALT > 3× upper limit of normal (ULN) and serum bilirubin >2 ULN occur in clinical trials it is usually predictive of severe hepatotoxicity post marketing.

There has though been a lack of studies where the role of DILI in death or LT is further characterized.

The article by Hayashi *et al.* published recently in *Hepatology* (5) is one of many important publications from the DILIN group in recent years. The DILIN network is a multicenter prospective DILI study which started recruiting patients in 2004. It consists of eight academic centers in the United States and a data-coordinating center sponsored by the National Institute of Health (5).

The DILIN group had previously published their findings on the prognosis of 660 DILI patients 6 months after onset of DILI, where 9.4% of patients died or underwent liver transplantation (6).

In this study Hayashi *et al.*, 107 of 1,098 patients with DILI died or needed liver transplantation 2 years after diagnosis of DILI. The all cause fatality rate was 9.6% and DILI-related fatality rate 7.6%. The percentage of Hy's law cases with hepatocellular damage and jaundice was 10%, which in is in line with results from previous studies (2,3). The nR modification of Hy's law proposed by Robles-Diaz *et al.* (7) yielded a higher percentage, 14%, so the nR version might offer some improvement beyond the original version when used in a clinical setting.

Patients who died or had liver transplant were significantly older and had higher BMI (5). Interestingly a lower proportion of patient who had poor outcome had a "definitive" or "highly likely" causality assessment, possibly because of the recovery phase being truncated by death like the authors state, but no data are provided regarding the causality score that can confirm this statement due to the causality assessment method used.

Like Hayashi *et al.* acknowledged in the paper categorization of primary versus contributory cause of death could be very difficult, as some of the patients were terminally ill when they developed DILI. In most cases these patients were included because DILI hastened the progression of their illness and contributed to their death. Although it was a difficult task to categorize these cases, it was important to include cases with a potential contributory cause of death as a large proportion of the disease burden can be observed in this group of patients. The authors defined a contributory role as one of the followings: (I) DILI left the patient in weakened or malnourished state

which contributed to death by another disease; (II) DILI prevented necessary care of another fatal illness; (III) DILI exacerbated or was part of another concurrent illness and (IV) the death was due to a complication from a test or a procedure done to evaluate DILI. The second category might be a highly underestimated one. Patients with potentially terminal diseases are often on potentially hepatotoxic drug (e.g., cancer patients) and a forced alteration in treatment due to DILI can have a profound effect on prognosis.

One of the strengths of the current study was the categorization of patients that proceeded to liver transplantation or had fatal liver injury primarily due to DILI. The four categories were acute liver failure (ALF), acute-on-chronic liver failure (ACLF), acute cholestatic liver failure and chronic liver failure. Most cases (50/68) were ALF, of whom 83% had a hepatocellular pattern. In five cases, patients had underlying cirrhosis and DILI as a primary cause of death. Nine patients had DILI-related chronic liver failure, needing liver transplantation >26 weeks after DILI onset, but no information was provided whether these patients had available baseline liver tests prior to the diagnosis of DILI, and whether other possible causes of chronic liver injury were excluded.

Herbal and dietary supplements (HDS) were important causes of liver injury requiring liver transplantation or liver related death. Overall 14/68 (21%) of deaths were due to HDS, 9/50 (18%) ALF, 2/5 (40%) ACLF and 3/9 (33%) chronic liver failure. Unfortunately names of the herbal/dietary supplements were not provided in the supplemental tables.

A number of variables were significantly associated with fatalities or liver transplantation. Understandably, markers of liver dysfunction were associated worse outcome on multivariate analysis: higher total bilirubin and serum ALT, lower albumin and thrombocytopenia. Elevated white blood cells (WBC) which was associated with poor outcome could reflect acute systemic illness or concurrent infection.

Chronic liver failure was associated with death or liver transplantation in univariate analysis but not in multivariate analysis, which is agreement with two previous studies by the DILIN group (6,8). It is conceivable, like the authors point out, that this is due to lack of power. Another likely explanation is that only patients with more advanced liver disease are in increased risk of death/LT after DILI, patients with preexisting liver disease were no stratified according to severity of the disease in this study. This will hopefully be addressed in further studies.

Steven-Johnson syndrome (SJS) and DRESS (drug reaction with eosinophilia and systemic symptoms) was associated with being higher risk of death or LT in a univariate but not multivariate analysis. This association is in line with high mortality in these drug reactions (9-11). In SJS mortality is higher in those with severe hepatic dysfunction (10) although it is unclear whether this is due to the effects of the idiosyncratic drug reaction on the liver or if those more severely affected by SJS develop liver dysfunction secondary to sepsis.

It is unclear why Asian race was associated with worse outcome. Alcohol intake was not mentioned in the paper (5), once found to be associated with less severity of liver injury although these findings were most likely to reporting bias and not reproduced in later papers (8).

In this study on a large cohort of DILI patents the DILIN confirmed the previous results regarding prognosis and risk factors of DILI. The authors are to be congratulated for the thorough analysis and detailed phenotypic information on their patients provided in the paper. Important classification of primary role and contributory role of DILI in the death of these patients was introduced and provides insight on the role of idiosyncratic liver injury on prognosis in these patients.

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Footnote

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

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