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Death and Liver Transplantation Within 2 Years of Onset of Drug-Induced Liver Injury

Paul H. Hayashi,[1] Don C. Rockey,[2] Robert J. Fontana,[3] Hans L. Tillmann,[4] Neil Kaplowitz,[5] Huiman X. Barnhart,[6] Jiezhan Gu,[6] Naga P. Chalasani,[7] K. Rajender Reddy,[8] Averell H. Sherker,[9] and Jay H. Hoofnagle,[9] for the Drug-Induced Liver Injury Network (DILIN) Investigators

Drug-induced liver injury (DILI) is an important cause of death and indication for liver transplantation (fatality). The role of DILI in these fatalities is poorly characterized, particularly when fatalities occur >26 weeks after DILI onset. We analyzed patients in the US Drug-Induced Liver Injury Network prospective study having a fatal outcome within 2 years of onset. Each case was reviewed by eight network investigators and categorized as DILI having a primary, a contributory, or no role in the fatality. We subcategorized primary role cases as acute, chronic, acute-on-chronic, or acute cholestatic liver failure. For contributory and no role cases, we assigned a primary cause of death. Among 1,089 patients, 107 (9.8%) fatalities occurred within 2 years. DILI had a primary role in 68 (64%), a contributory role in 15 (14%), and no role in 22 (21%); 2 had insufficient data. Among primary role cases, 74% had acute, 13% chronic, 7% acute on chronic, and 6% acute cholestatic failure. For the 15 contributory role cases, common causes of death included sepsis, malignancy, and severe cutaneous reactions with multiorgan failure. For the 22 no role cases, malignancies accounted for most fatalities. Higher bilirubin, coagulopathy, leukocytosis, and thrombocytopenia were independently associated with DILI fatalities. New R ratio Hy's law had a higher positive predictive value for overall fatality (14% versus 10%) and a stronger independent association with DILI fatalities within 26 weeks compared to the original version of Hy's law (hazard ratio, 6.2, 95% confidence interval 3.4-11.1, versus 2.2, 95% confidence interval 1.3-3.7). *Conclusions:* DILI leads directly or indirectly to fatality in 7.6% of cases; 40% of these had nonacute liver failure courses. New R ratio Hy's law better identifies risk for death compared to the original Hy's law. (HEPATOLOGY 2017;66:1275-1285).

Most patients suffering hepatotoxicity due to medications or herbal or dietary supplements (HDS) recover from the acute liver injury without long-term sequelae. However, a proportion does not survive the injury or requires liver transplantation (LT) (referred to hereafter as a death, mortality, fatality or fatal outcome). Most large registries of drug-induced liver injury (DILI) report a

Abbreviations: ACLF, acute on chronic liver failure; ALF, acute liver failure; ALT, alanine aminotransferase; Alk P, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; DRESS, drug reaction with eosinophilia and systemic symptoms; HDS, herbal and dietary supplements; HR, hazard ratio; INR, international normalized ratio; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; nR, new R ratio; ULN, upper limit of normal.

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mortality rate of approximately 10%.[1-3] However, the contribution of DILI in these fatalities is not always clear, particularly when they occur more than 26 weeks after DILI onset. There are emerging data on chronic or persistent DILI that continues beyond 6 or 12 months.[4-7] DILI may also contribute significantly to a fatality without being the primary cause of death. Such cases should be analyzed separately but counted as part of DILI's disease burden. Determining the contribution of liver injury to a fatality can be difficult if patient data are not collected prospectively and assessed systematically. Lastly, accurate classification of DILI-related fatalities allows more accurate analyses of predictors of death, such as Hy's law and its derivations.

For these reasons, we performed a systematic analysis of all patients who had a fatal outcome within 2 years of onset in the prospective study of the US Drug Induced-Liver Injury Network (DILIN). In addition, we categorized the DILI as playing a primary, a contributory, or no role in the fatality. Using these categories of fatal outcomes, we assessed clinical variables including Model for End-Stage Liver Disease (MELD), Hy's law, and its modified version using a new R ratio (nR) proposed by Robles-Diaz et al.[8]

Patients and Methods

DESIGN

The design of the DILIN prospective study has been described in detail.[9,10] Briefly, all patients suspected of having idiosyncratic drug-induced or HDS-induced liver injury were eligible if they could be enrolled within 6 months of onset of the injury and met specific criteria of laboratory abnormalities. These included serum alanine (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN) (or pretreatment baseline if abnormal) on two consecutive occasions, alkaline phosphatase (Alk P) levels >2 × ULN (or pretreatment baseline if abnormal) on two consecutive occasions, or total bilirubin at least 2.5 mg/dL or an international normalized ratio (INR) >1.5 accompanied by any elevation in AST, ALT, or Alk P. Acetaminophen overdose cases and cases with certain chronic liver diseases such as autoimmune hepatitis and primary biliary cirrhosis were excluded. Subjects were asked to return 6 months after onset and, if laboratory or clinical abnormalities related to the liver injury were still present, to return at 12 and 24 months. At enrollment, relevant medical information was extracted from the medical records and interim history, physical examination, and appropriate laboratory results were obtained.

CAUSALITY ASSESSMENT AND SEVERITY OF INJURY

The DILIN prospective study used a consensus expert opinion method of causality assessment.[9,10] The DILIN investigator who enrolled the patient and two investigators from two other centers were provided with a standardized clinical narrative and summary of relevant clinical, laboratory, histologic, and imaging results. The three investigators independently assigned a causality score representing percent likelihood of attribution, in which 1 = definite or >95% likelihood of DILI, 2 = highly likely or 75%-95% likelihood, 3 = probable or 50%-74%, 4 = possible or 25%-49%, and 5 = unlikely or <25%. Consensus on scoring was reached by e-mails and web-based conference calls which included all DILIN investigators. Each case was also assigned a

ARTICLE INFORMATION:

From the [1]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, NC; [2]Division of Gastroenterology, Medical University of South Carolina, Charleston, SC; [3]Division of Gastroenterology, University of Michigan, Ann Arbor, MI; [4]Division of Gastroenterology, East Carolina University, Greenville, NC; [5]Division of Gastroenterology, University of Southern California, Los Angeles, CA; [6]Duke Clinical Research Institute, Duke University, Durham, NC; [7]Division of Gastroenterology, Indiana University School of Medicine, Indianapolis, IN; [8]Division of Gastroenterology, University of Pennsylvania, Philadelphia, PA; [9]Liver Disease Research Branch, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Paul H. Hayashi, M.D., M.P.H.
Division of Gastroenterology and Hepatology,
University of North Carolina Liver Program
CB# 7584 Burnett-Womack Bldg., Room 8011
Chapel Hill, NC 27599-7584
E-mail: paul_hayashi@med.unc.edu
Tel: +1-919-966-2516

severity score of 1-5 (5 = fatal or needing LT) based on bilirubin, INR, hospitalization, need for LT, or fatality.[2]

STUDY COHORT

We identified all cases enrolled in the DILIN between September 2004 and April 2015 and scored as 1 (definite DILI), 2 (highly likely), or 3 (probable). We then selected and analyzed all patients who died or underwent LT during the 2-year period of follow-up. For the purposes of this analysis, we refer to all these cases as fatalities or deaths even though some survived beyond LT.

CATEGORIZATION BY ROLE OF DILI IN DEATH OR LT

Clinical death narratives and summaries of serial clinical, laboratory, histologic, and imaging results were prepared for each case of death or LT in the DILIN prospective cohort study. A Death Review Subcommittee consisting of eight DILIN hepatologists was established, and each case was assigned randomly to two members for independent review. Each reviewer subjectively categorized the cases for whether the DILI episode played a primary, a contributory, or no role in the death. We resolved discrepancies between reviewers by conference call discussion that included the entire Death Review Subcommittee. The subcommittee had the prerogative to ask that any case be sent back for full causality assessment described above if, on review of the fatal outcome, the original diagnosis of DILI was called into question.

PATTERN OF LIVER FAILURE FOR PRIMARY ROLE CASES

Cases where DILI clearly played a primary role in the death or transplant had to be subcategorized into one of four mutually exclusive clinical patterns of fatal liver failure:

1. Acute liver failure (ALF) deaths were defined as acute liver insult with INR $\geq$1.5, hepatic encephalopathy, no evidence of preexisting or underlying advanced liver disease or cirrhosis, and death occurring in less than 26 weeks.[11,12]
2. Acute-on-chronic liver failure (ACLF) deaths were defined as acute liver insult with INR $\geq$1.5, hepatic encephalopathy, clinical or histologic evidence of preexisting advanced liver disease or cirrhosis, and death occurring in less than 26 weeks.[13]
3. Acute cholestatic liver failure deaths had acute injury with an R value <2, no preexisting liver disease, no hepatic encephalopathy, and death occurring in less than 26 weeks (i.e., acute cholestatic failure not meeting ALF criteria).
4. Chronic liver failure deaths were defined as acute liver insult with consequent hepatic decompensation (e.g., ascites, jaundice, encephalopathy, coagulopathy) with or without evidence of preexisting liver disease and death occurring due to liver failure more than 26 weeks later.

CAUSE OF DEATH FOR CONTRIBUTORY AND NO ROLE CASES

Criteria used to categorize DILI as having a contributory role in the death included the following: (1) DILI left the patient in a weakened or malnourished state which contributed to death by another disease (e.g., cancer), (2) DILI prevented necessary care (e.g., surgery or chemotherapy) of another fatal illness, (3) DILI exacerbated or was part of another concurrent fatal illness (e.g., sepsis, multiorgan failure, drug reaction with eosinophilia and systemic symptoms [DRESS]), and (4) the death was due to a complication from a test or procedure done to evaluate the DILI (e.g., bowel perforation from an endoscopic retrograde cholangiopancreatography).

No role cases lacked any of the above criteria and often had recovered or nearly recovered from the DILI when they died of another illness. Both contributory and no role cases were then assigned 1 of 18 primary causes of death (Supporting Table S1). We resolved discrepancies between reviewers by conference call discussion that included the entire Death Review Subcommittee of eight members.

DESCRIPTIVE DATA, CLINICAL VARIABLES, AND ANALYSIS

Data analyzed included routine demographic, clinical, and laboratory test results as well as time from starting the implicated drug or HDS to onset of injury and time from injury onset to death or LT. The pattern of injury was categorized as hepatocellular, cholestatic, or mixed based upon the R ratio from laboratory tests taken at the time of onset: R ratio = (ALT/

ULN) ÷ (Alk P/ULN). R ratios >5 were considered hepatocellular, <2 were considered cholestatic, and 2-5 were considered mixed. We also classified cases by Hy's law and the nR Hy's law criteria at presentation:

1. Hy's law: bilirubin ≥2.5 mg/dL, ALT >3 times ULN and Alk P <2 times ULN
2. nR Hy's law: bilirubin ≥2.5 mg/dL, and [(ALT/ULN) ÷ (Alk P/ULN)] > 5. (AST is substituted for ALT if the AST yields a greater R ratio).[8]

Using these clinical variables, we described those who survived compared to those who died or underwent LT. We also compared primary, contributory, or no role cases. We determined performance characteristics for MELD, Hy's law, and nR Hy's law for identifying mortality risk due primarily or partially to DILI at 2 years and DILI-related ALF and ACLF on univariate and multivariate analyses.

STATISTICAL ANALYSIS

Standard descriptive methods (e.g., mean, standard deviation, median, quartiles, percentages) were used to describe the total cohort and subgroups. Comparisons between subgroups were performed using standard parametric and nonparametric tests where appropriate. We used Cox proportional hazard ratios to identify clinical variables independently associated with overall DILI-related deaths (primary or contributory role) at 2 years. We also determined the performance characteristics for MELD, Hy's law, and nR Hy's law (e.g., positive predictive value, hazard ratios, C statistic) in predicting deaths from DILI-related ALF and ACLF.

ROLE OF FUNDING SOURCE AND INSTITUTIONAL REVIEW BOARD

The DILIN is structured as a U01 cooperative agreement with funds provided by the National Institute of Diabetes and Digestive and Kidney Diseases. Separate institutional review board approvals were maintained at each DILIN center throughout the period of this study, and protocols were approved and all data monitored by a separate Data Safety and Monitoring Board appointed by the National Institute of Diabetes and Digestive and Kidney Diseases.

Results

SUBJECTS

As of April 10, 2015, a total of 1,509 patients were enrolled in the DILIN prospective study, of whom 1,332 underwent formal causality assessment and 1,089 were judged to have definite, highly likely, or probable DILI. Among these, 107 (9.8%) died or underwent LT (all-cause mortalities) within 2 years of onset (Fig. 1). The Death Review Subcommittee did not send any of the 107 fatalities back for causality reassessment.

Comparison of patients who survived with those who died or underwent LT is shown in Table 1. Patients with a fatal outcome were on average somewhat older than those who survived (mean = 53.1 versus 48.5 years) but were similar in other demographic aspects. Initial laboratory results showed higher levels of ALT, AST, bilirubin, and INR in those with fatal outcome; but the R ratio and distribution of patterns of injury were similar. Fatalities had higher proportions meeting Hy's law and nR Hy's law criteria, but only the latter reached statistical significance.

CATEGORIES BY ROLE OF DILI IN DEATH OR TRANSPLANT

DILI was considered to have a primary role in the death or need for transplantation in 68 (64%) patients (Fig. 1). DILI had a contributory role in 15 cases (14%) and no role in 22 cases (21%). The role could not be determined due to insufficient follow-up details for 2 patients. The clinical and laboratory features associated with the three categories are shown in Table 2. Patients in whom DILI was the primary cause of death were younger and more likely female; had higher levels of ALT, AST, bilirubin, INR, and R ratio; and were more likely to have hepatocellular injury than no role cases. Contributory role cases had features more like no role cases, except for female sex, which was similar to primary role cases. A higher proportion of primary role cases met Hy's law criteria (40.3%) compared to contributory or no role cases, but the difference was statistically significant only when compared to no role cases (Table 2). An even higher proportion of primary role cases met nR Hy's law (65.6%), and this was statistically higher than either contributory or no role cases. Listing and frequency of specific agents are shown in Supporting Tables S2-S5.

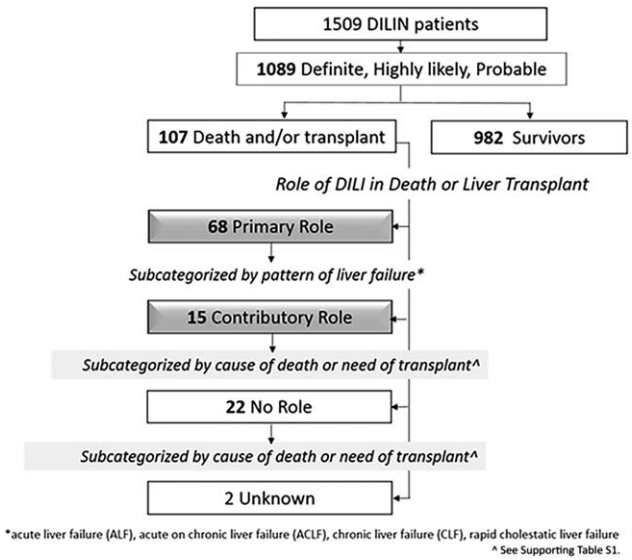

FIG. 1. Analysis of DILIN patients with definite, highly likely or probable DILI. Patients dying or needing transplant categorized by role of DILI. Patients where DILI had Primary Role subcategorized by pattern of liver failure. Contributory and No Role patients subcategorized by cause of death or transplant.

CLINICAL COURSE OF LIVER FAILURE IN DILI PRIMARY ROLE CASES

Clinical features of the patients in which DILI played a primary role in the fatal outcome are shown in Table 3, subcategorized by their clinical course of liver failure. Of these 68 primary role cases, 50 (74%) had ALF as shown by marked elevations in serum ALT and AST levels with relatively mild increases in Alk P and a median time to death or transplant of 24 days (range 2-123 days). Another 5 (7%) patients had ACLF with less marked increases in ALT and AST (and AST > ALT). Time to death or transplant ranged from 6 to 135 days. Nine patients (13%) had a DILI-related chronic liver failure accompanied by lower median values for ALT and AST and higher values for Alk P. For 7 of these 9, time from DILI onset to death or transplant ranged from 217 to 410 days. The other two had liver injury from methotrexate and amiodarone, both known to cause gradual fibrosis accumulation with only modest enzyme elevations. Therefore, a precise onset of DILI for these agents was indeterminable, but the exposure time for the amiodarone was 847 days and that for methotrexate, 2,129 days. Finally, 4 patients (6%) had a rapidly progressive cholestatic course, resulting in liver failure and death in 3 and transplantation in 1. Death or transplant occurred at 48-171 days of onset in these 4, who tended to be older (ages 75, 65, 61, and 48 years). ALF and ACLF cases had significantly higher proportions meeting Hy's law and nR Hy's law criteria (40%-79%) compared to relatively few patients meeting such criteria in the chronic or acute cholestatic group (0%-25%) (Table 3).

Gender, race, and ethnicity did not differ significantly among the cases with different patterns of liver failure, although those with typical ALF tended to be younger (mean age 48.7 years) than patients with other patterns. The percentage of LTs was low for ACLF (1

TABLE 1. Characteristics of Patients Dying or Requiring LT Within 2 Years of DILI Onset (n = 107) Compared to Those Alive at 2 Years Without LT

Characteristic	Died/LT Within 2 Years Post-DILI (n = 107)	Alive at 2 Years Post-DILI (n = 982)	*P*
Mean age, years (SD)	53.1 (16.4)	48.5 (17.0)	0.01
Gender, female (%)	57 (53.3%)	577 (58.8%)	0.30
Mean BMI, kg/m^2 (SD)	28.7 (6.82)	27.4 (6.81)	0.01
Race/ethnicity			
White	76 (72%)	781 (80%)	0.10
Black	17(16%)	110/ (11%)	
Asian	7(7%)	30 (3%)	
Other and unknown	7/(7%)	62 (6%)	
Latino	6 (6%)	110 (11%)	0.10
Alcohol use	48/104 (46%)	501 (52%)	0.30
Chronic liver disease	13/62 (21%)	144/866 (17%)	0.50
Liver biochemistries at DILI onset—mean (SD)			
ALT, U/L	1,162 (1326)	787 (1064)	0.02
AST, U/L	1,093 (1199)	634 (993)	<0.01
Alk P, U/L	281 (217)	280 (249)	0.36
Bilirubin, mg/dL	10.1 (8.0)	6.3 (6.3)	<0.01
INR	2.2 (1.8)	1.3 (0.7)	<0.01
R ratio*	14.9 (19.8)	12.7 (25.16)	0.43
Pattern of injury (102/925)			
Hepatocellular	61 (60%)	497 (54%)	0.11
Mixed	15 (15%)	220 (24%)	
Cholestatic	26 (26%)	208 (23%)	
Causality category			
Definite	16 (15%)	253 (25.8%)	<0.01
Highly likely	45 (42%)	523 (53.3%)	
Probable	46 (43%)	206 (21.0%)	
Hy's law†	34/101 (33.7%)	269/913 (29.5%)	0.42
nR Hy's law‡	50/103 (48.5%)	292/936 (31.2%)	<0.01

*R ratio = (ALT/ULN) ÷ (Alk P/ULN).
†Bilirubin ≥2.5 mg/dL, ALT > 3 × ULN and Alk P < 2 × ULN at presentation.
‡Bilirubin ≥2.5 mg/dL and R ratio >5 at presentation (AST substituted for ALT if AST yields greater R ratio).[8]
Abbreviations: BMI, body mass index; SD, standard deviation.

TABLE 2. Comparison of Patients Dying or Requiring LT Within 2 Years of DILI Onset (n = 105) by DILI Role in Death or Need for LT

Characteristic	DILI Role in Death or Need of LT (n = 105)*			*P*	
	Primary (n = 68)	Contributory (n = 15)	No role (n = 22)	Primary versus Contributory	Primary versus No Role
Mean age, years (SD)	50.7 (16.0)	58.9 (16.2)	57.9 (17.2)	0.06	0.08
Gender, female	42 (62%)	9 (60%)	6 (27%)	0.89	0.01
Mean BMI, kg/m^2 (SD)	29.2 (6.7)	31.3 (9.1)	25.6 (4.8)	0.31	0.02
Race/ethnicity					
White	46 (69%)	12 (80%)	17 (77%)	0.95	0.58
Black	11 (16%)	2 (13%)	3 (14%)		
Asian	6 (9%)	1 (7%)	0 (0%)		
Other	4 (6%)	0 (0%)	2 (9%)		
Latino	5 (7%)	1 (7%)	0 (0.0%)	1.00	0.33
Alcohol use	35/66 (53%)	4/14 (29%)	9/22 (41%)	0.10	0.33
Chronic liver disease	11 (16%)	3 (20%)	6 (27%)	0.13	0.25
Liver biochemistries at DILI onset					
ALT, U/L	1,470 (1483)	587 (694)	579 (740)	0.02	<0.01
AST, U/L	1,422 (1326)	503 (589)	446 (547)	0.01	<0.01
Alk P, U/L	252 (150)	343 (326)	331 (288)	0.34	0.66
Bilirubin, mg/dL	11 (7.5)	9.6 (8.8)	6.6 (7.5)	0.31	<0.01
INR	2.2 (1.0)	2.4 (2.1)	1.6 (0.9)	0.43	0.17
R ratio†	18.6 (22.4)	6.5 (6.6)	9.2 (15.5)	0.04	0.02
Pattern of injury					
Hepatocellular	50 (74%)	6 (40%)	8 (36%)	<0.01	0.01
Mixed	4 (6%)	6 (40%)	5 (23%)		
Cholestatic	14 (21%)	3 (20%)	9 (41%)		
Causality category					
Definite	9 (13%)	1 (7%)	5 (23%)	0.61	0.23
Highly likely	26 (41%)	5 (33%)	11 (50%)		
Probable	31(46%)	9 (60%)	6 (27%)		
Hy's law‡	25/62(40.3%)	5/15 (33.3%)	3/22 (13.6%)	0.62	0.02
nR Hy's law§	42/64(65.6%)	5/15 (33.3%)	2/22 (9.1%)	0.02	<0.01

*DILI role could not be determined in 2 patients.
†R ratio = (ALT/ULN) ÷ (Alk P/ULN).
‡Bilirubin ≥2.5 mg/dL, ALT >3 × ULN and Alk P <2 × ULN at presentation.
§Bilirubin ≥2.5 mg/dL and R ratio >5 at presentation (AST substituted for ALT if AST yields greater R ratio).
Abbreviations: BMI, body mass index; SD, standard deviation.

of 5, 20%) and for acute cholestatic liver failure (1 of 4, 25%) and higher for chronic liver failure (5 of 9, 56%) and ALF (34 of 50, 68%).

CAUSES OF DEATH IN CONTRIBUTORY ROLE CASES

Of the 15 patients whose DILI was considered to play a contributory role, the primary causes of death were judged to be sepsis in 3, malignancy in 3, another unrelated liver disease in 3 (nonalcoholic liver disease in 1 and autoimmune hepatitis in 2), and severe cutaneous reaction with systemic complications in 3 (Fig. 2). In many situations, the role of the liver injury was difficult to assess, the underlying comorbidities being severe and potentially fatal on their own. In these situations, the episode of DILI was believed to hasten the fatal outcome.

CAUSES OF DEATH IN NO ROLE CASES

Of the 22 patients where DILI played no role in the outcome, malignancies accounted for over half of cases (12, 55%). The remaining patients died from a variety of causes (Fig. 2).

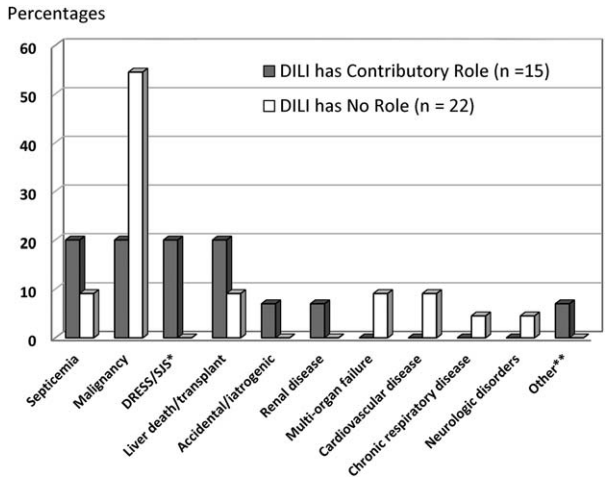

FIG. 2. Distribution of primary causes of fatal outcome in patients where DILI had a contributory role (gray bars) or no role (white bars). Percentages represent proportions within each subgroup: contributory role or no role.
*DRESS/SJS: Drug Reaction with Eosinophilia and Systemic Symptoms/Stevens-Johnson Syndrome
**Other: 80-year-old woman with acute liver injury which contributed to her death, but she had multiple medical problems and went home on hospice.

SPECIFIC AGENTS LEADING TO FATALITY

Specific agents and HDS products as a whole are shown in frequency tables by role of DILI in the fatalities (Supporting Tables S2-S5).

VARIABLES ASSOCIATED WITH DEATH OR LT

We compared patients with DILI-related death or LT (primary and contributory role patients, n = 83) to the rest of the cohort (survivors, no role cases, and unknown role cases = 1,006) (Fig. 1). Variables associated with fatality due primarily or partially to DILI on univariate and multivariate analyses are shown in Table 4. Higher bilirubin, higher INR, lower platelet count, and lower albumin were associated with mortality.

HY'S LAW, nR HY'S LAW, AND MELD

Hy's law had a lower positive predictive value for deaths primarily or partially due to DILI up to 2 years after onset compared to nR Hy's law (10% versus 14%). Specificities were about the same at 71% and 69%, respectively. When limited only to deaths primarily due to DILI, the positive predictive values fell to 8% for Hy's law and 12% for nR Hy's law. Specificities did not change. Because Hy's law and especially MELD were put forth to predict shorter-term mortality, we also analyzed their association with DILI fatalities occurring within 26 weeks due to ALF or ACLF. On this multivariate analysis, Hy's law was significantly associated with early mortality primarily due to DILI (hazard ratio [HR], 2.2, 95% confidence interval [CI] 1.3-3.7). However, the association with nR Hy's law was stronger (HR, 6.2, 95% CI 3.4-11.1), and that with MELD was stronger still. The HR per MELD point was 1.2 (95% CI 1.1-1.2), and at various MELD cutoffs the HRs were all over 10 (Supporting Table S6). The C statistic for a MELD cutoff of 19 was 0.83 compared to 0.73 for nR Hy's law and 0.60 for Hy's law. For the Hy's law Cox regression analyses, ALT, AST, and bilirubin were excluded as they are part of Hy's law and nR Hy's law. INR, creatinine, and bilirubin were excluded in the Cox modeling for MELD.

Discussion

It is well known that DILI can lead to death or LT (fatal outcome), but the precise role and course of DILI in these cases is poorly defined, particularly when fatalities occur more than 26 weeks after liver injury. In the DILIN prospective cohort, 107 of 1,089 patients with definite, highly likely, or probable DILI had a fatal outcome within 2 years of onset. Thus, the all-cause fatality rate was 9.8% (Fig. 1). Fatalities tended to be older and to have more hepatocellular injury and more underlying chronic liver disease than patients who survived (Table 1). Their DILI causality assessments also tended to be less certain, probably because the recovery, or washout, phase was truncated by the death. The majority of the fatalities were related to DILI, being the primary cause of death in 68 patients and a contributing cause in another 15. The remaining 22 patients had fatal outcomes unrelated to DILI (Fig. 1). Therefore, the DILI fatality rate (primary or contributory) was 7.6% (83/1089). This rate increased to 9.5% (68/712) if the denominator is limited to those presenting with jaundice (bilirubin $\geq$2.5 mg/dL).

Comparing DILI primary, contributory, and no role cases revealed important differences (Table 2). Primary and contributory role cases were predominantly women

TABLE 3. Characteristics and Course of Liver Failure in Those Patients Who Died or Needed LT Due Primarily to DILI Values Are Means (SD) for Continuous Variables

	Primary Role Cases (n = 68)				
Characteristic	ALF (n = 50)	ACLF (n = 5)	Chronic Liver Failure (n = 9)	Rapid Cholestatic Liver Failure (n = 4)	*P*
Mean age, years (SD)	48.7 (16.9)	60.1 (11.0)	51.5 (11.9)	62.3 (11.2)	0.19
Gender, female	31 (62%)	3 (60%)	6 (67%)	2 (50%)	0.96
Mean BMI, kg/m^2 (SD)	29.2 (7.3)	27.3 (7.1)	28.6 (4.2)	33.0 (2.6)	0.36
Race/ethnicity					
White	33 (67%)	2 (40%)	7 (78%)	4 (100%)	0.66
Black	8 (16%)	1 (20%)	2 (22%)	0 (0%)	
Asian	5 (10%)	1 (20%)	0 (0%)	0 (0%)	
Other or unknown	4 (6%)	1 (20%)	0 (0%)	0 (0%)	
Latino	4 (8%)	0 (0%)	0 (0%)	1 (25%)	0.49
Alcohol use*	28/48 (58%)	2/5 (40%)	4 (44%)	1 (25%)	0.54
Time (days) from onset to death/LT	35 (28)	59 (50)	236 (120)	132 (91)	<0.01
Liver biochemistries at onset					
ALT, U/L	1,864 (1534)	451 (449)	330 (478)	395 (248)	<0.01
AST, U/L	1,807 (1348)	699 (717)	279 (347)	375 (217)	<0.01
Alk P U/L	240 (108)	191 (133)	226 (106)	523 (367)	0.26
Bilirubin, mg/dL	12.5 (7.2)	11.3 (7.4)	7.0 (7.3)	2.9 (2.3)	0.01
INR	2.7 (2.0)	2.3 (0.7)	1.7 (1.1)	1.1 (0.0)	0.03
R ratio†	24.4 (23.7)	4.5 (3.4)	5.5 (11.6)	3.3 (2.9)	<0.01
Pattern of injury (n)	(45)	(5)	(9)	(4)	
Hepatocellular	38 (84%)	3 (60%)	2 (22%)	2 (50%)	<0.01
Mixed	3 (7%)	0 (0%)	1 (11%)	0 (0%)	
Cholestatic	4 (9%)	2 (40%)	6 (67%)	2 (50%)	
Causality category					
Definite	9 (18%)	0 (0%)	0 (0%)	0 (0%)	0.33
Highly likely	19 (38%)	1 (20%)	4 (44%)	3 (75%)	
Probable	22 (44%)	4 (80%)	5 (56%)	1 (25%)	
Hy's law‡	23/45 (51.1%)	2/5 (40.0%)	0/8 (0.0%)	0/4 (0.0%)	<0.01
nR Hy's law§	37/47 (78.7%)	3/5 (60.0%)	1/8 (12.5%)	1/4 (25.0%)	<0.01

*Any alcohol consumption in the 12 months prior to DILI.
†R ratio = (ALT/ULN) ÷ (Alk P/ULN).
‡Bilirubin ≥2.5 mg/dL, ALT > 3 × ULN and Alk P <2 × ULN at presentation.
§Bilirubin ≥2.5 mg/dL, and R ratio >5 at presentation (AST is substituted for ALT if AST yields greater R ratio).
Abbreviations: BMI, body mass index; SD, standard deviation.

compared to no role cases, who were predominantly men. Primary role cases were younger and usually followed a course typical of ALF (50 of 68, 74%). As expected, the majority (83%) of ALF cases presented with a hepatocellular pattern of enzyme elevations (high R ratios) (Table 3). This predominance of ALF is in line with DILI being a leading cause of ALF in the United States.[14,15] Our cases were similar to those reported by the US ALF Group. Most were young (<45) and women. Antimicrobials, isoniazid in particular, were the most common agents implicated; but HDS were also prominent (Supporting Tables S2-S4). The majority of patients with ALF were listed for LT (74%), and most of these were transplanted (68%). The remaining ALF patients were not listed due to medical or psychosocial contraindications.

DILI fatality by non-ALF injury patterns has not been well described, though a quarter of the DILIN deaths due directly to DILI followed such non-ALF courses. Five (7%) of the 68 primary role cases had underlying cirrhosis and were categorized as ACLF. For this study, we defined ACLF as a case with preexisting cirrhosis and DILI being the primary cause of death or LT within 26 weeks of onset. Our data set did not have the clinical information to determine more recently developed acute on chronic liver failure classifications and scores.[16,17] Of the five ACLF cases, three were listed for transplant but only one

TABLE 4. Variables Significantly Associated With Fatalities Due Primarily (Primary Role) or Partially (Contributory Role) to DILI on Univariate and Multivariate Analyses

	Cox Regression			
Variable	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Race				
Caucasian	Referent	-		
Black	1.5 (0.8-2.8)	0.16		
Asian	3.4 (1.6-7.5)	<0.01		
Other	1.1 (0.4-3.0)	0.89		
BMI (kg/m^2)	1.04 (1.0-1.1)	0.01		
Diabetes	2.3 (1.5-3.5)	<0.01		
Heart failure	3.3 (1.2-9.0)	0.02		
Chronic liver disease	1.9 (1.1-3.3)	0.03		
Neutropenia	3.6 (1.1-11.4)	<0.01		
Steven-Johnson syndrome/DRESS	5.0 (1.2-20.5)	0.02		
INR at onset ± 14 days	1.5 (1.4-1.6)	<0.01	1.6 (1.4-1.7)	<0.01
ALT (per 50 U/L)	1.01 (1.0-1.01)	<0.01		
Total bilirubin (mg/dL)	1.1 (1.0-1.1)	<0.01	1.1 (1.0-1.1)	<0.01
Hemoglobin (g/dL)	0.9 (0.8-1.0)	0.05		
White blood cells (10^9/L)	1.1 (1.0-1.1)	<0.01	1.06 (1.02-1.10)	<0.01
Platelets (10^{10}/L)	0.99 (0.99-0.99)	<0.01	0.99 (0.99-0.99)	<0.01
Albumin (g/dL)	0.4 (0.3-0.5)	<0.01	0.4 (0.3-0.6)	<0.01
Corticosteroids given	3.3 (2.2-5.1)	<0.01		

Abbreviation: BMI, body mass index.

received a liver. The other two became too ill and were removed from listing. The listed cases may not have met criteria for priority listing (status 1a) due to their underlying cirrhosis, which could explain the lower rate of LT.

Another 9 (13%) of the 68 primary role cases had a fatality due to chronic liver failure. These cases died or needed LT more than 26 weeks after DILI onset. Agents leading to chronic liver failure were varied, with three of nine being HDS products and another three antibiotics (Supporting Table S4). Amiodarone and methotrexate, both known to cause an insidious fibrosis, accounted for one each. Chronic liver injury after DILI has been described by our group and others.[6,7] While the definition, incidence, and significance of chronic DILI are unclear, this study clearly documents a small number of fatalities due to prolonged liver injury from DILI. These nine cases had lower initial transaminases and R ratios compared to those with ALF and ACLF, but no other distinguishing features could be gleaned from this small number of cases (Table 3). Larger numbers with robust prospective follow-up will be needed to fully understand these more insidious DILI deaths.

Four (6%) of the 68 primary role patients had a rapid (<26 weeks) and progressive cholestatic injury. DILI causing such severe cholestatic injury with ductopenia has been described.[18-20] These 4 all died or required transplant within 26 weeks of DILI onset. They tended to be older, 3 being over 60 years old. Two had a cholestatic pattern of injury from onset to demise, while 2 presented with a hepatocellular pattern of injury (R ratio just over 5) that quickly transitioned to cholestatic. The R ratios were <1 in all 4 at time of death or transplant. One patient underwent LT, and the explant histology showed absence of bile ducts. The remaining 3 had medical or psychosocial contraindications to transplantation. Liver biopsies in these 3 did not show ductopenia, but biopsies may have been obtained too early to capture vanishing bile duct histology. Autopsy liver tissues were not available for these cases.

DILI as a contributing cause of fatality has been poorly defined and rarely reported. Yet, such a contributory role in deaths may be an important part of the DILI disease burden. In this series, DILI contributed to death by worsening of an underlying liver disease (20%) or by contributing to a non-liver-related death such as DRESS/Steven-Johnson syndrome, sepsis, or malignancy (20% each) (Fig. 2). In the 3 patients with cancer, DILI significantly limited subsequent therapeutic options. In one case, evaluation of liver injury included an endoscopic retrograde cholangiopancreatography that was complicated by a fatal duodenal perforation.

While categorizing DILI as a primary versus contributory cause of death was occasionally difficult, assigning it as having no role was often straightforward. Many of these deaths occurred well after DILI had resolved. The majority of these cases were due to progression of a malignancy (Fig. 2). Certain comorbidities could forebode poor outcome even after apparent liver recovery. Identifying such factors by a comorbidity index (e.g., Charleson, Elixhauser) would be useful, but unfortunately the DILIN does not capture the detailed information on comorbidities needed to complete such indices.

After we had categorized all fatalities, we identified variables associated with DILI-related deaths (primary and contributory role cases). The current analysis differs from our prior studies examining DILI fatalities at just 26 weeks.[2,5] In this study, we included fatalities up to 2 years after DILI onset. Also, categorization of DILI's role in the fatality was done using a systematic approach and by a subcommittee of DILIN investigators, who used a new contributory role category and subcategorization of primary role cases by pattern of liver demise.

Variables independently associated with overall DILI-related fatality were all plausible. Higher INR, higher bilirubin, and lower albumin all reflect more severe liver dysfunction at onset. Higher white blood cell count could reflect more immune-mediated injury or concurrent infection (i.e., sepsis). The association of mortality with lower platelets is in line with a recent study identifying thrombocytopenia with poor outcome for ALF in general.[21] The lower platelet count may reflect multiorgan failure, sepsis, or disseminated intervascular coagulation. Interestingly, preexisting chronic liver disease was not associated with mortality on multivariate analysis, though it was on univariate. This finding is similar to our two prior studies that found an association between chronic liver disease and short-term mortality on univariate analysis only. Neither study detected an independent association.[2,5] With the inclusion of deaths up to 2 years later and DILI contributory role deaths, we thought this variable might now be independently associated. The persistent lack of association could be a result of too few patients to detect a smaller increased risk (underpowered), or the risk may apply only to more advanced liver disease. Our definition of prior chronic liver disease did not specify degree of fibrosis or liver dysfunction.

We show an incremental improvement in Hy's law by use of the modified nR form.[8] For deaths due primarily or partially to DILI, Hy's law had a 10% positive predictive value, precisely in line with Dr. Zimmerman's original suggestion.[22] However, the nR modification of Hy's law yielded a higher positive predictive value at 14%. The difference lay primarily in the ability to identify those who would die of DILI-related ALF: 79% of ALF fatalities met nR Hy's law versus only 52% meeting standard Hy's law (Table 3). The Alk P $<2 \times$ ULN criteria explained all the ALF deaths which met nR Hy's law but not standard Hy's law. In Dr. Zimmerman's text, the limit for Alk P was <1 to $3 \times$ ULN, but a cutoff of $2 \times$ ULN is typically used.[5,8,22] The ALF fatalities not meeting Hy's law had Alk P/ULN ratios ranging from 2.0 to 3.5, low enough to yield an R ratio >5 but too high for standard Hy's law. Thus, the use of nR Hy's law over the traditional Hy's law as a positive predictor of increased risk of death due to DILI may be warranted in clinical practice and drug development.

Compared to Hy's law or nR Hy's law, MELD was a better predictor of acute DILI deaths (<26 weeks) by ALF and ACLF (Supporting Table S6). The HR for a MELD >19 was 35.6 with a C statistic of 0.83, compared to an HR of 2.2 and a C statistic of 0.60 for Hy's law and an HR of 6.2 and a C statistic of 0.73 for nR Hy's law. MELD probably had the advantage of often being calculated later because INR was not always obtained with the first set of elevated liver enzymes. More importantly, Hy's law and MELD were put forth for different purposes. Dr. Zimmerman shared his astute observation as a warning to clinicians to be vigilant of a severe outcome when hepatocellular DILI meets certain ALT, Alk P, and bilirubin criteria. As such, it was merely a positive predictive value set low at 10% to cast a wide net for patients needing close follow-up. On the other hand, MELD was based on multivariate modeling to predict mortality risk surrounding therapeutic interventions, first transjugular intrahepatic portosystemic shunt and then transplant, where predictive precision is the goal, and not just a low threshold positive predictive value.

In this systematic examination of fatalities prospectively followed in the DILIN, 7.6% of patients died primarily or partially from the DILI within 2 years of onset. When DILI was the primary cause of death, typical ALF accounted for most fatalities, but one quarter had non-ALF courses including acute on chronic, chronic, and progressive cholestatic liver failure. When DILI contributed to death, most fatalities were due to sepsis, malignancy, DRESS/Steven-Johnson syndrome, or worsening preexisting chronic liver disease. However, preexisting liver disease was not

independently associated with fatality from DILI. The nR modification of Hy's law improved the positive predictive value for those at risk of death from acute hepatocellular injury by accepting moderately higher Alk P elevations into the criteria. The nR modification also has a stronger the association with deaths within 26 weeks directly related to DILI, but neither outperformed MELD in predictive value.

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