Drug-induced liver injury at a tertiary care centre in Germany: Model for end-stage liver disease is the best predictor of outcome

Martin Reike-Kunze1 | Roman Zenouzi1,2 | Johannes Hartel1,2 | Till Krech3 | Sören Weidemann3 | Martina Sterneck1,4 | Christina Weiler-Normann1,5 | Ansgar W. Lohse1,2 | Christoph Schramm1,5 | Marcial Sebode1,2

1I. Department of Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
2European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Hamburg, Germany
3Department of Pathology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
4University Transplant Centre, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
5Martin Zeitz Centre for Rare Diseases, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

Correspondence
Marcial Sebode, I. Department of Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany.
Email: m.sebode@uke.de

Funding information
This study was supported in part by the YAEL Foundation and the Helmut and Hannelore Greve Foundation.

Abstract

Background & Aims: Agents most frequently inducing idiosyncratic drug-induced liver injury (DILI) differ between countries worldwide. Besides, there is no consistent data on the best model predicting mortality or the need for liver transplantation in DILI. We here analysed the DILI cohort of our centre with regard to causative drugs and clinical outcome.

Methods: A retrospective analysis of 157 consecutive severe DILI patients presenting to our tertiary care centre in Hamburg, Germany, from 2008 to 2018, was performed.

Results: The most frequent putatively causative drugs were phenprocoumon (n = 21), metamizole (n = 17) and flupirtine (n = 6). The mean values of ALT, bilirubin and Model for End-stage Liver Disease (MELD) score at the time of hospitalisation were 1201 U/L (SD: 1169 U/L), 6.8 mg/dL (SD: 7 mg/dL) and 17 (SD: 8). About 71% of all cases were treated with steroids or steroids combined with n-acetylcysteine. About 12.1% of all DILI cases had a poor outcome (liver transplantation and/or death). At the time of admission, MELD score performed better than Hy's law, the ratio (R) or the new ratio (nR) on their own or combined with bilirubin, regarding sensitivity or specificity for poor outcome. MELD score had a c-statistic of 0.847 (95% CI: 0.731-0.964). Furthermore, the cut-off of 18 MELD points had a sensitivity of 88% and a specificity of 72% for poor outcome.

Conclusion: Phenprocoumon and metamizole are frequent causative drugs for DILI in Germany. In comparison to other prognostic scores, MELD score ≥18 at the time of admission performed best in our cohort for the prediction of poor outcome in DILI.

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibodies; anti-LKM, anti-liver kidney microsomal antibodies; anti-SLA/LP, anti-soluble liver antigen/liver-pancreas antigen antibodies; anti-SMA, anti-smooth muscles antigen antibodies; AST, aspartate aminotransferase; c-statistic, concordance statistic; DILI, drug-induced liver injury; HAP, hospital-acquired pneumonia; HDS, herbal and dietary supplements; HE, hepatic encephalopathy; IQR, interquartile range; KCC, King’s College Criteria; LTx, liver transplantation; MELD, model for end-stage liver disease; nR, new ratio; R, ratio; ROC, receiver operating characteristics; RUCAM, Roussel Uclaf Causality Assessment Method; SD, standard deviation; TBL, total bilirubin; ULN, upper limit of normal.
1 | INTRODUCTION

Idiosyncratic drug-induced liver injury (DILI) is a heterogenic entity that can be induced by various drugs though the most frequent agents vary across the world. Amoxicillin-clavulanate is the most frequent agent responsible for idiosyncratic DILI in the western world.\textsuperscript{1,2} In contrast, tuberculostatic drugs and herbal and dietary supplements (HDS) are the leading causes of DILI in Southeast Asia.\textsuperscript{3,4} There are several reasons for the varying prevalences of agents causing DILI around the world, such as geographically different popularity or approval of single drugs or locally changing awareness for DILI-causing agents over time. As an example, the awareness for HDS as DILI-causing agents in the western world has increased only recently.\textsuperscript{5}

Severe DILI is rare, but one of the leading causes for acute liver failure (ALF).\textsuperscript{6} Population-based studies revealed that the rate of death or liver transplantation (LTx) due to idiosyncratic DILI ranges between 1% and 6%.\textsuperscript{2,5} In non-population-based studies, it reaches a rate between 7% and 15%.\textsuperscript{1,3,9-11} Therefore, markers for the prognosis of DILI progressing to ALF are urgently needed. The Model for End-stage Liver Disease (MELD) score seems to be suitable for the prognosis of poor outcome (defined as LTx and/or death) in DILI patients, with high sensitivity and good specificity.\textsuperscript{11-13} Other prognostic scores with a comparable sensitivity and specificity are Hy’s law, and the ratio (R) ≥5 and the new (n)R ≥ 5, each combined with total bilirubin (TBL) >2 × the upper limit of normal (ULN). R is defined as the ratio between alanine aminotransferase (ALT) and alkaline phosphatase (ALP), each related to their ULN, and nR uses the higher value of either ALT or aspartate aminotransferase (AST)\textsuperscript{11,14,15}

We herein characterised a cohort of idiosyncratic severe DILI cases at our tertiary care centre in Hamburg, Germany. Our study shows striking differences regarding the most frequent putatively causative drugs of DILI in comparison with previous cohorts from other regions of the world. Moreover, MELD score performed best for the prediction of poor outcome of DILI in our cohort.

Key points

- At a tertiary care centre in Hamburg, Germany, 157 consecutive severe DILI patients were retrospectively analysed with regard to causative drugs and clinical outcome.
- The most frequent putatively causative drugs were phenprocoumon and metamizole.
- About 12% of all DILI patients had a poor outcome and required liver transplantation and/or died.
- MELD score ≥ 18 at the time of admission performed best in this cohort for the prediction of poor outcome in DILI.

2 | METHODS

Consecutive idiosyncratic, non-acetaminophen-induced DILI cases presenting to the I. Department of Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany from January 2008 till July 2018 were analysed in this retrospective study. A case series of patients with metamizole-induced liver injury, being also included into this study, has been published elsewhere.\textsuperscript{16} Patients presented initially to our centre with symptoms of acute liver injury or were referred to our centre from another healthcare provider. For the latter cases, initial laboratory parameters of the referring centres or physicians were analysed. Diagnosis of DILI was based on the Roussel Uclaf Causality Assessment Method (RUCAM).\textsuperscript{17,18} When more than one drug was suspected to be responsible for liver injury, the RUCAM score was applied for each drug. Our inclusion criteria for DILI cases were the following: ALT ≥5 × ULN or ALP ≥2 × ULN or ALT ≥3 × ULN and total bilirubin ≥2 × ULN.\textsuperscript{19,20} A minimal follow-up time of 30 days was also needed for inclusion in the study, except for the cases progressing to liver transplantation or death. The calculation of the biochemical pattern of liver damage was based on the ratio (R) between ALT and ALP, each related to their respective ULN. The biochemical pattern was defined as hepatocellular when R > 5, as cholestatic when R < 2 and as mixed when R was equal to or between 2 and 5.\textsuperscript{21} For the calculation of R, the first available blood test at the time of initial presentation was used. For the new ratio (nR), we used the higher value of either ALT or AST.\textsuperscript{14} Five points in time were used for the analysis of blood values: the first presentation to any provider within the healthcare system, when the patient presented to a hospital for the first time and the peak values for ALT, ALP and total bilirubin. Hepatic encephalopathy (HE) was graded according to the West Haven Criteria.\textsuperscript{22} For the quantification of liver injury in DILI cases, the DILI Severity Index by Aithal et al\textsuperscript{19} was utilised.
MELD score was computed for each of the five points in time. Cases of phenprocoumon-induced DILI (n = 25) were excluded from MELD analyses because of therapeutic drug-induced INR elevations. If phenprocoumon cases were included into analyses including INR, this was highlighted in the text, figures and tables. In all other analyses, phenprocoumon cases were included. Fulfilment of Hy’s law was defined as ALT >3 × ULN and total bilirubin >2 × ULN at the time of the first presentation. Entities other than DILI causing acute liver damage were excluded by the following methods: Viral hepatitis A, B and C infections were excluded by serology, and viral hepatitis E infection was excluded by PCR in all patients. According to the clinical context, active Epstein–Barr virus-, Cytomegalovirus- or further herpes virus-infections were ruled out. Abdominal ultrasound was performed in all patients to exclude vascular liver disease. Acute Wilson’s disease was excluded by serum coeruleoplasmin levels >18 mg/dL and a ratio of ALP to total bilirubin <4 and a ratio of AST to ALT >2.2. Autoimmune hepatitis (AIH) was excluded by clinical follow-up as ensuring that liver enzymes did not rise again after weaning of steroid treatment. Autoantibodies such as antinuclear antibodies (ANA), anti-smooth muscles antigen antibodies (anti-SMA), anti-liver kidney microsomal antibodies (anti-LKM) and anti-mitochondrial antibodies (AMA) were detected by immunofluorescence on rat liver, kidney and stomach tissue and on HEp2 cells. Anti-soluble liver antigen/liver-pancreas antigen antibodies (anti-SLA/LP) were analysed by ELISA. Mini-laparoscopically guided liver biopsy was performed in 71.3% of patients (n = 112) of the total cohort at our centre. Additional 21 liver biopsies (13.4% of the total cohort) were performed in Menghini technique at the referring hospital. Regarding the start of steroid treatment, there were no clear cut-off values at our centre, and the decision was at the discretion of the treating physician.

Statistical Package for Social Sciences (SPSS; IBM Corp. Release 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) was used to analyse the data. For the statistical evaluation, categorial variables were presented by frequency and tested with the χ²-test. Accordingly, for the statistical evaluation of continuous variables, both the mean with standard deviation (SD) or the median with interquartile range (IQR) and the Kruskal–Wallis or Mann–Whitney U test were used. A logistic regression was performed for continuous and categorial variables. A receiver-operating characteristics (ROC) curve was used to identify the concordance statistic (c-statistic) of the MELD score. Statistically significant differences were defined when the P-value was less than .05. This study was approved by the local ethics committee (WF-064/12).

3 | RESULTS

3.1 | Demographic and clinical characteristics

For inclusion in the study, 177 idiosyncratic DILI cases between January 2008 and July 2018 were considered. Twenty subjects were excluded as two of them did not fulfill the biochemical definition of DILI. Eighteen cases were excluded due to a short follow-up time. Overall, the total cohort comprised 157 DILI cases, in which 88 different drugs or HDS were identified. In 128 cases (82%), a single drug was putatively causative for DILI, and in the other 29 cases (18%) two or more drugs had a ‘possible’ or better RUCAM score. Of the total cohort, 12 cases (8.6%) were classified as ‘possible’, 78 cases (56.1%) as ‘probable’ and 49 cases (35.3%) as ‘highly probable’ according to the RUCAM score. In 18 cases, it was not possible to calculate the RUCAM score because the point in time of the first drug intake within the last six months before liver injury could not be exactly determined retrospectively. One hundred and fifty-three cases (98%) of the cohort were hospitalised for the diagnostic evaluation of acute icteric hepatitis, and the median time of hospital stay was 11 days (IQR: 6–19 days, total range: 1–52 days). As shown in Table 1, 101 subjects of the total cohort (64%) were female, and the mean age was 53 years (SD: 17 years, total range: 19–79 years). One hundred and twenty-two subjects (71%) had a hepatocellular, 18 (11.5%) a mixed and 17 (10.8%) a cholestatic biochemical pattern. Significant differences between male and female DILI patients with regard to outcome could not be detected (Supplementary Table 1).

Male DILI patients tended to receive antimicrobials (n = 14, 25%) more often than female patients (n = 14, 14%; P = .081, data not shown). A significant difference in the latency of first drug intake until first presentation to the health care system was detected among the three groups of different biochemical patterns: DILI patients with a hepatocellular pattern showed the longest latency (median 70 days, IQR: 23–180 days) compared to patients with cholestatic biochemical pattern (median 35 days, IQR: 21–63 days) and to patients with mixed pattern (median 14 days, IQR: 10–56 days, P = .016, Supplementary Table 2). Excluding cases with a poor outcome (LTx and/or death), the median follow-up time of patients was 12.7 months (IQR: 3.5–36 months, Table 1). One hundred and eleven cases (71%) had a minimal follow-up time of three months. A history of frequent or excessive alcohol consumption was present in 11 patients (7%) at the time of acute liver injury. Another six subjects (4%) had a history of past alcohol abuse but were abstinent at the time of clinical manifestation of DILI. No significant differences were detected between patients with a good (survival without LTx) and poor outcome related to alcohol consumption. In 99 of 138 cases (71%), autoantibodies were detected. Ninety-five cases (68%) were positive for ANA, and in 15 patients (11%), anti-SMA were detected. Other autoantibodies such as AMA (detected in seven cases, 5%) or anti-LKM (detected in one case, 0.7%) were detected infrequently. Median titres of ANA and anti-SMA were 1:320 (IQR: 1:160–1:640, total range: 1:80–1:5120) and 1:160 (IQR: 1:160–1:160, total range: 1:80–1:320), respectively. Twenty-eight DILI patients (20% of the cases being tested for autoantibodies) had ANA titres of equal or greater than 1:640. Patients who were tested positive for autoantibodies had significantly higher peak AST and ALT values, and higher IgG levels within normal range, but did not differ significantly in other laboratory parameters and with regards to outcome (Table 2).

Sixteen patients (10%) were accidentally re-challenged by the DILI-causing drug. Metamizole was the most frequent drug involved in cases of re-challenge (Supplementary Table 3).
## TABLE 1 Clinical characteristics

| Characteristics                          | Entire cohort (n = 157) | Transplant-free survival (n = 138) | LTx and/or death (n = 19) | P value |
|------------------------------------------|-------------------------|-----------------------------------|---------------------------|---------|
| Age, mean ± SD                           | 53 ± 17                 | 52 ± 17                           | 59 ± 13                   | .177    |
| Females, %                               | 64                      | 65                                | 63                        | .909    |
| Body mass index, kg/m², mean ± SD        | 26 ± 5.5                | 26 ± 5.5                          | 28 ± 5.4                  | .247    |
| Follow up, months, median (IQR)          | 9.5 (2-33)              | 12.7 (3.5-36)                     | 0.7 (0.3-1)               | <.001   |
| RUCAM score                              |                         |                                   |                           |         |
| Possible/probable/highly probable        | 12/78/49                | 11/67/43                          | 1/11/6                   | —       |
| Biochemical pattern (R), %               |                         |                                   |                           |         |
| Hepatocellular                           | 78                      | 78                                | 79                        | .89     |
| Mixed                                    | 11                      | 13                                | 0                         | .094    |
| Cholestatic                              | 11                      | 9                                 | 21                       | .126    |
| Jaundice present at the time of hospitalisation (%) | 64 | 59 | 95 | .003 |
| Hy’s law fulfilled (%)                   | 53                      | 47                                | 95                        | <.001   |
| Presence of HE of any grade (%)          | 15                      | 4                                 | 95                        | <.001   |
| Admission on ICU (%)                    | 11                      | 4                                 | 58                        | <.001   |
| Fatty liver (%)                          | 14                      | 14                                | 17                        | .74     |
| Fibrosis of any grade (%)                | 18                      | 18                                | 17                        | .880    |
| Positive for ANA and/or anti-SMA (%)     | 71                      | 70                                | 80                        | .427    |
| Liver biopsy performed, n (%)            | 133 (85)                | 117 (85)                          | 16 (84)                   | —       |
| Presence of eosinophils, %              | 11                      | 10                                | 13                        | .784    |
| Presence of neutrophils, %              | 6                       | 6                                 | 6                         | .966    |
| Fibrosis of any grade (%)               | 20                      | 21                                | 6                         | .153    |
| Fibrosis of grade 4 (%)                 | 1.5                     | 1.7                               | 0                         | .598    |
| Confluent necrosis of any grade (%)     | 45                      | 41                                | 75                        | .01     |
| Confluent necrosis of 70%-100% (%)      | 5                       | 1                                 | 38                        | <.001   |
| Therapy (%)                              | —                       | —                                 | —                         | <.001   |
| No therapy                               | 29                      | 32                                | 5                         | —       |
| Prednisolone                             | 57                      | 57                                | 53                        | —       |
| Prednisolone and N-acetylcysteine       | 13                      | 9                                 | 42                        | —       |
| Budesonide                               | 1                       | 1                                 | 0                         | —       |
| Initial dose of prednisolone, mg/kg body weight, mean ± SD | 1.3 ± 1.8 | 1.3 ± 2 | 1.2 ± 0.6 | .401 |
| Latency between first drug intake and first presentation to the health care system, days, median (IQR) | 56 (2-168) | 56 (17-161) | 56 (30-245) | .365 |
| Latency of first presentation to ALT peak value, days, median (IQR) | 1 (0-10) | 2 (0-11) | 1 (0-4) | .394 |
| Latency of first presentation to ALP peak value, days, median (IQR) | 7 (1-18) | 7 (2-18) | 5 (1-23) | .854 |
| Latency of first presentation to TBL peak value, days, median (IQR) | 8 (3-20) | 8 (2-20) | 11 (5-21) | .296 |
| DILI severity Index (%) ^19             | —                       | —                                 | —                         | <.001   |
| Mild                                     | 17                      | 20                                | 0                         | —       |
| Moderate                                 | 43                      | 49                                | 0                         | —       |
| Severe                                   | 28                      | 31                                | 0                         | —       |
| Fatal                                    | 12                      | 0                                 | 100                       | —       |

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; ANA, Antinuclear antibodies; HE, Hepatic encephalopathy; ICU, Intensive care unit; LTx, Liver transplantation; RUCAM, Roussel Uclaf Causality Assessment Method; SMA, Smooth muscle antibodies; TBL, Total bilirubin. Significant results with P values <.0.05 are highlighted with bold font.
3.2 Prevalence of drug groups and individual drugs

The most frequent drug groups causing DILI with a single implicated drug (n = 128) were anti-infectious drugs with 32 cases (25%), followed by 29 cases (23%) induced by analgetics, 24 cases (19%) caused by anticoagulants and 9 cases (7%) by immunomodulatory and immunosuppressive drugs (Figure 1). HDS represented six cases (5%). The drugs most frequently causing DILI at our entire cohort were phenprocoumon (n = 21, 16%), metamizole (n = 17, 13%), flupirtine (n = 6, 5%), amoxicillin-clavulanate (n = 5, 4%), anti-tuberculous drugs (rifampicin, isoniazid and pyrazinamide, n = 4, 3%), diclofenac (n = 3, 2%) and amoxicillin (n = 3, 2%). Given that the seven most common causative drugs accounted for almost half of all DILI cases (47%) at our centre, the other half was caused by agents only responsible for liver injury in one or two cases (Supplementary Table 4). In 29 of the 157 DILI cases (19%), more than one implicated drug had a ‘possible’ or better probability for inducing DILI according to the RUCAM score. In this subgroup, 39 different drugs were involved, whereas metamizole and ibuprofen were the two most frequently putatively causative drugs (Supplementary Table 5). Here, the most common drug classes were analgetics (n = 29, 42%) and anti-infectious agents (n = 16, 23%).

The mean age of DILI patients due to phenprocoumon was significantly higher (66 years, SD: 8 years) in comparison to metamizole cases (41 years, SD: 14 years) and all other single drug cases (51 years, SD: 16 years, P < .001, Supplementary Table 6). Between these three groups, a significant difference was observed regarding the latency from first drug-intake until first clinical presentation due to liver injury: In phenprocoumon cases, the median latency was significantly longer (193 days, IQR 168-222 days) compared to metamizole cases (28 days, IQR 9-40 days) and all other single drug cases (32 days, IQR 14-119 days, P < .001). Of the 21 DILI cases due to phenprocoumon, 13 patients showed a prolonged latency with more than 6 months. Patients with DILI caused by phenprocoumon had a

### TABLE 2 Comparison between DILI patients being negative or positive for antinuclear antibodies

| Characteristics | ANA positive (n = 95) | ANA negative (n = 44) | P value |
|-----------------|-----------------------|-----------------------|---------|
| Age, mean ± SD  | 52 ± 17               | 53 ± 17               | .779    |
| Females (%)     | 68                    | 66                    | .768    |
| Pattern (%)     |                       |                       |         |
| Hepatocellular  | 82                    | 79                    | .719    |
| Mixed           | 12                    | 7                     | .386    |
| Cholestatic     | 6                     | 14                    | .153    |
| Follow-up, months, median (IQR) | 8 (2.4-31) | 11.5 (2.3-33) | .588 |
| Liver biopsy performed, n (%) | 86 (91) | 32 (73) | — |
| Death (%)       | 3                     | 2                     | .772    |
| LTx (%)         | 8                     | 7                     | .745    |

### Blood peak values, mean ± SD

| Characteristic | ANA positive | ANA negative | P value |
|----------------|--------------|--------------|---------|
| AST (U/L)      | 1446 ± 1503  | 808 ± 600    | .001    |
| ALT (U/L)      | 1771 ± 1637  | 1119 ± 812   | .005    |
| ALP (U/L)      | 276 ± 218    | 332 ± 411    | .441    |
| Total bilirubin (mg/dL) | 11.9 ± 10.6 | 9.9 ± 10.7 | .105 |
| INR            | 2.2 ± 1.6    | 2.0 ± 1.4    | .261    |
| IgG at the time of hospitalisation (g/dL) mean ± SD | 13.6 ± 3.9 | 11.4 ± 3.5 | .019 |

**TABLE 2** Comparison between DILI patients being negative or positive for antinuclear antibodies

| Most frequent drugs causing DILI, including all putatively causative drugs, n (%) | ANA positive | ANA negative | P value |
|---------------------------------------------------------------------------------|--------------|--------------|---------|
| Metamizole                                                                       | 19 (17)      | 8 (15)       | —       |
| Phenprocoumon                                                                    | 16 (14)      | 8 (15)       | —       |
| Ibuprofen                                                                        | 9 (8)        | 3 (6)        | —       |
| Flupirtine                                                                       | 6 (5)        | 3 (6)        | —       |
| Anti-tuberculous drugs                                                           | 3 (3)        | 0 (0)        | —       |
| Methylprednisolone                                                               | 3 (3)        | 0 (0)        | —       |

**Abbreviations:** ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; ANA, Antinuclear antibodies; AST, Aspartate aminotransferase; LTx, Liver transplantation; TBL, Total bilirubin. Significant results with P values <.0.05 are highlighted with bold font.
significantly higher prevalence of confluent necrosis of any grade on liver biopsy (70%) than metamizole cases (47%) and all other single drug cases (33%; \( P = .007 \)). However, there was no significant difference of the grade of necrosis between these groups.

### 3.3 | Outcome

Of the 157 DILI cases, 13 (8%) progressed to ALF and required LTx. Another six cases with ALF (4%) were not transplanted due to different reasons and died from liver failure or liver-related complications (Supplementary Table 7). Taken together, 12% of the idiosyncratic DILI cases at our centre had a poor outcome, defined as LTx and/or death (Table 1). The median duration from first presentation until death or LTx was 19 days (IQR: 10-32 days). Seven patients (54%) who received LTx died within the same hospital stay; 4 of them (57%) had septic complications, 1 patient developed intracerebral haemorrhage and another died of cardiogenic shock, most likely due to pulmonary embolism, and 1 patient died of haemorrhagic shock and toxic brain oedema (Supplementary Table 7). Excluding DILI cases due to phenprocoumon, 33 cases (25%) of the total cohort fulfilled the Kings College Criteria (KCC) and 16 of these cases had a poor outcome (11 received liver transplantation and 5 died).25

Among the 19 cases with poor outcome, 7 DILI cases (37%) were caused by a single drug, and in 12 cases, multiple drugs were identified to be responsible for liver injury (Supplementary Table 7), with the most frequent drugs being metamizole, ibuprofen and phenprocoumon. The majority of DILI cases (n = 112, 70%) was treated with prednisolone, including 21 cases (13%) with additional treatment with n-acetylcysteine. The mean initial dose of prednisolone was 1.28 mg/kg bodyweight (SD: 1.8 mg/kg bodyweight). Two cases (1.3%) were treated with budesonide. The median starting point of treatment was eight days after the first available blood tests (IQR: 3-20 days). In patients who underwent liver biopsy, steroids were started after the procedure. Infectious complications developed in seven patients (6.3%) under steroids and in two patients (4.4%) not treated with steroids (\( P = .66 \)). Five of the seven patients (71%) having an infection and being treated with steroids had a poor outcome (Supplementary Table 8). Two of them had urosepsis, another three suffered from hospital-acquired pneumonia (HAP). The two patients not being treated with steroids, but developing infections complications, did not have a severe course and survived. Nine patients under steroid treatment were admitted to the intensive care unit and received systemic antibiotic treatment without detection of bacteria in microbial cultures.

### 3.4 | Prediction of outcome

Confluent necrosis of any grade on liver histology was more prevalent in patients with poor outcome (n = 12, 75%) than in those with good outcome (n = 48, 41%, \( P = .01 \)). Six cases (38%) in the poor outcome group showed confluent necrosis involving 70% to 100% of liver tissue, whereas only 1 patient (0.9%) in the good outcome group showed this extent of necrosis (\( P < .001 \), Table 1).

Eighteen cases (95%) in the poor outcome group were jaundiced at the time of hospitalisation (total bilirubin, TBL ≥2 mg/dL, TBL mean: 14 mg/dL, SD: 9.5 mg/dL) compared to 74 patients (59%) who survived and who did not receive LTx (\( P = .003 \), TBL mean: 5.2 mg/dL, SD: 6 mg/dL, \( P < .001 \), Tables 1 and 3). Hy’s law was fulfilled in 77 patients (49% of the total cohort) including 18 DILI patients with poor outcome. Thus, Hy’s law indicated a sensitivity of 95%...
and a specificity of 54% for poor outcome. The sensitivity and specificity of R > 5 combined with TBL > 2 x ULN was 74% and 61%, and that of nR > 5 combined with TBL > 2 x ULN was 74% and 61%, each at the time of hospitalisation. Table 4 shows the association between clinical or laboratory parameters and poor outcome, based on logistic regression. The MELD score (OR: 1.25, 95% CI: 1.13–1.38, P < .001), ALT (OR: 1.00, 95% CI: 1.00–1.00, P = .003) and LDH (OR: 1.00, 95% CI: 1.00–1.00, P = .035), each at the time of hospitalisation, were significantly associated with poor outcome in univariate analysis. In a multivariate modelling approach, the MELD score was the only significant predictor for poor outcome. Regarding poor outcome, the c-statistics of the MELD score, TBL and INR, each at the

### TABLE 3 Comparison between selected laboratory parameters of DILI patients with poor and good outcome

| Characteristics | Entire cohort (n = 157) | Transplant-free survival (n = 138) | LTx and/or death (n = 19) | P value |
|-----------------|------------------------|-----------------------------------|--------------------------|---------|
| Blood values at the time of first presentation, mean ± SD |                       |                                   |                          |         |
| AST (U/L)       | 886 ± 1086             | 777 ± 1000                        | 1727 ± 1364              | .007    |
| ALT (U/L)       | 1103 ± 1165            | 986 ± 966                         | 1993 ± 1967              | .065    |
| ALP (U/L)       | 233 ± 276              | 210 ± 184                         | 386 ± 582                | .035    |
| TBL (mg/dL)     | 6.3 ± 7.1              | 5.2 ± 6                           | 14 ± 9.5                 | <.001   |
| INR             | 1.8 ± 1.3              | 1.6 ± 1.2                         | 2.6 ± 1.6                | .005    |
| LDH (U/L)       | 474 ± 417              | 424 ± 310                         | 742 ± 730                | .017    |
| Blood values at the time of hospitalisation, mean ± SD |                       |                                   |                          |         |
| AST (U/L)       | 968 ± 1092             | 855 ± 1013                        | 1786 ± 1308              | .003    |
| ALT (U/L)       | 1201 ± 1169            | 1072 ± 966                        | 2108 ± 1909              | .032    |
| ALP (U/L)       | 249 ± 259              | 232 ± 208                         | 358 ± 463                | .099    |
| TBL (mg/dL)     | 6.8 ± 7                | 5.6 ± 6                           | 13.7 ± 8.8               | <.001   |
| INR             | 1.8 ± 1.3              | 1.6 ± 1.2                         | 2.6 ± 1.6                | .002    |
| IgG (g/L)       | 12.8 ± 4.1             | 12.6 ± 3.9                        | 14 ± 6.2                 | .75     |
| IgA (g/L)       | 2.9 ± 1.8              | 2.7 ± 1.6                         | 5.1 ± 2.7                | .013    |
| LDH (U/L)       | 504 ± 416              | 455 ± 308                         | 762 ± 720                | .011    |
| Creatinine (mg/dL) | 0.9 ± 0.5            | 0.9 ± 0.4                         | 1.1 ± 0.6                | .112    |

| Blood peak values, mean ± SD |                  |                                   |                          |         |
|-------------------------------|------------------|-----------------------------------|                          |         |
| AST (U/L)                     | 1212 ± 1382      | 1066 ± 1286                       | 2267 ± 1617             | <.001   |
| ALT (U/L)                     | 1505 ± 1432      | 1376 ± 1305                       | 2441 ± 1941             | .029    |
| ALP (U/L)                     | 321 ± 318        | 301 ± 359                         | 465 ± 584               | .055    |
| TBL (mg/dL)                   | 11.5 ± 10.9      | 9.3 ± 9.3                         | 27.4 ± 7.7              | <.001   |
| INR                           | 2.1 ± 1.5        | 1.9 ± 1.3                         | 3.7 ± 1.7               | <.001   |

| MELD score, mean ± SD         |                  |                                   |                          |         |
|-------------------------------|------------------|-----------------------------------|                          |         |
| At the time of first presentation | 16 ± 7          | 14 ± 6                            | 25 ± 8                   | <.001   |
| At the time of hospitalisation | 16 ± 7          | 14 ± 6                            | 25 ± 8                   | <.001   |
| At the time of total bilirubin peak value | 18 ± 7 | 16 ± 6 | 30 ± 5 | <.001 |

| MELD score including patients taking phenprocoumon, mean ± SD |                  |                                   |                          |         |
|---------------------------------------------------------------|------------------|-----------------------------------|                          |         |
| At the time of first presentation                              | 17 ± 8           | 16 ± 7                            | 26 ± 8                   | <.001   |
| At the time of hospitalisation                                | 17 ± 8           | 16 ± 7                            | 26 ± 8                   | <.001   |
| At the time of total bilirubin peak value                      | 19 ± 8           | 17 ± 6                            | 32 ± 5                   | <.001   |

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; good outcome, (transplant-free survival); LDH, lactate dehydrogenase; LTx, liver transplantation; MELD, Model for End-stage Liver Disease score; Poor outcome, (LTx and/or death); TBL, total bilirubin.

Significant results with P values <.05 are highlighted with bold font.
time of hospitalisation, were 0.85 (95% CI: 0.73-0.96, P < .001), 0.78 (95% CI: 0.65-0.90, P < .001) and 0.74 (95% CI: 0.58-0.91, P = .002, Figure 2), respectively. At the time of TBL peak values, the c-statistic for the MELD score was 0.99 (95% CI: 0.97-1.00, P < .001, data not shown). For the MELD score at the time of hospitalisation, we detected the most convenient cut-off point at ≥18, with a sensitivity of 88% and a specificity of 72% for poor outcome, with a positive and negative predictive value of 0.3 and 0.98 (Table 5). Including DILI cases in which phenprocoumon was taken (n = 25), the c-statistic of the MELD score was 0.83 (95% CI: 0.72-0.93), and the most convenient cut-off point was still ≥18, with a sensitivity of 90% and a specificity of 67% for poor outcome at the time of hospitalisation (data not shown).

In total, 46 cases (35% of the entire cohort, DILI cases due to phenprocoumon excluded) had a MELD score ≥18 at the time of hospitalisation, including 14 cases (82%) of the poor outcome group and 32 cases (27%) of the good outcome group (Table 6). These two groups were further analysed in the following. The presence of HE of any grade was significantly more frequent in the poor outcome group (n = 14, 100%) than in the good outcome group (n = 0, 0%, P < .001). A combination of the MELD score ≥18 and the presence of HE had a sensitivity of 88% and a specificity of 100% for poor outcome. An extent of confluent necrosis between 70% and 100% on liver histology was significantly more frequent among patients with poor outcome (23%) than in patients with good outcome (0%, P = .006, Table 6). However, a combination of histological presence of confluent necrosis and MELD score ≥18 did not increase the predictive value of MELD score alone (data not shown). Frequency of steroid treatment, dosage of prednisolone or latency of steroid treatment initiation did not differ significantly between DILI patients with poor and good outcome. In a multivariate logistic regression for all cases, after adjustment for possible confounders by means of propensity scores, no significant association was detected between steroid treatment and outcome (P = .680, data not shown). Confounders included histological necrosis, sex, age, autoantibodies, MELD score and ALT levels at the time before treatment initiation.

### TABLE 4 Logistic regression for poor outcome

| Variables                          | Univariate | 95% confidence interval | P value | Multivariate | 95% confidence interval | P value |
|------------------------------------|------------|-------------------------|---------|--------------|-------------------------|---------|
|                                    | OR         | Lower                   | Upper   |              | OR                      | Lower   |
| Age                                | 1.025      | 0.992                   | 1.058   | .135         | 1.028                   | 0.976   |
|                                    |            |                        |         |              | 1.083                   |         |
| Sex                                | 1.060      | 0.392                   | 2.866   | .909         | 0.929                   | 0.170   |
|                                    |            |                        |         |              | 5.076                   |         |
| Confluent necrosis                 | 3.214      | 1.187                   | 8.701   | .022         | —                       | —       |
|                                    |            |                        |         |              | —                       | —       |
| HE                                 | 478.8      | 52.908                  | 4333    | <.001        | 0.999                   | 0.997   |
|                                    |            |                        |         |              | 1.002                   |         |
| AST                                | 1.001      | 1.000                   | 1.001   | .009         | 1.000                   | 0.999   |
|                                    |            |                        |         |              | 1.002                   |         |
| ALT                                | 1.001      | 1.000                   | 1.001   | .003         | 1.000                   | 0.999   |
|                                    |            |                        |         |              | 1.002                   |         |
| ALP                                | 1.001      | 1.000                   | 1.001   | .003         | 1.000                   | 0.997   |
|                                    |            |                        |         |              | 1.002                   |         |
| TBL                                | 1.144      | 1.070                   | 1.222   | <.001        | —                       | —       |
|                                    |            |                        |         |              | —                       | —       |
| INR                                | 1.550      | 1.147                   | 2.095   | .004         | —                       | —       |
|                                    |            |                        |         |              | —                       | —       |
| LDH                                | 1.001      | 1.000                   | 1.001   | .035         | 1.002                   | 0.998   |
|                                    |            |                        |         |              | 1.006                   |         |
| Hy's law fulfilledb                 | 21.356     | 2.768                   | 164.77  | .006         | 1.742                   | 0.145   |
|                                    |            |                        |         |              | 20.981                  |         |
| R > 5, TBL >2 × ULNc                | 4.424      | 1.501                   | 13.038  | .007         | 0.792                   | 0.143   |
|                                    |            |                        |         |              | 4.388                   |         |
| nR > 5, TBL >2 × ULNc              | 4.424      | 1.501                   | 13.038  | .007         | —                       | —       |
|                                    |            |                        |         |              | —                       | —       |
| MELD score at the time of first presentation | 1.244 | 1.126 | 1.374 | <.001 | — | — |
|                                    |            |                        |         |              | —                       | —       |
| MELD score at the time of hospitalisation | 1.246 | 1.127 | 1.376 | <.001 | 1.208 | 1.050 |
|                                    |            |                        |         |              | 1.390                   | .008    |
| MELD score at the time of hospitalisationd | 1.174 | 1.095 | 1.259 | <.001 | 1.114 | 1.027 |
|                                    |            |                        |         |              | 1.208                   | .009    |

Note: Laboratory values at the time of hospitalisation.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HE, hepatic encephalopathy; LDH, lactate dehydrogenase; MELD, Model for End-stage Liver Disease score; nR, new ratio; OR, odds ratio; R, ratio; TBL, total bilirubin; ULN, upper limit of normal.

a Excluding INR, creatinine and TBL for multivariable analysis with backwards elimination.
b Excluding ALT for multivariable analysis with backwards elimination, additionally.
c Excluding ALT and ALP for multivariable analysis with backwards elimination, additionally.
d Including 25 patients with DILI after the intake of phenprocoumon.

Significant results with P values <.05 are highlighted with bold font.
Idiosyncratic DILI can be induced by diverse drugs, whereas the most frequent drugs causing DILI vary between countries. Phenprocoumon was the most frequently implicated drug in DILI cases at our tertiary centre in Hamburg, Germany. Other reports from Germany support that phenprocoumon frequently causes DILI.

Flupirtine is a non-opioid analgesic drug and was used to treat neuronal hyperexcitability. It was withdrawn from the European market in 2018 due to hepatotoxicity, but it is still available in other countries. In contrast to our study, population-based studies from the USA, Spain, Iceland and France reported that amoxicillin-clavulanate is the most frequent drug causing DILI. The reason for this difference to our study probably

| Variables | AUC | Lower | Upper | P value |
|-----------|-----|-------|-------|---------|
| MELD score | .847 | .731 | .964 | <.001 |
| TBL | .776 | .654 | .898 | <.001 |
| INR | .744 | .577 | .911 | .002 |
| TBL | .771 | .633 | .908 | .001 |

Note: All parameters refer to the time of hospitalisation.
Abbreviations: HE, Hepatic encephalopathy; MELD score, Model for End-stage Liver Disease score; nR, New ratio; R, Ratio.

Including 25 patients with DILI after the intake of phenprocoumon.

4 | DISCUSSION

Flupirtine. We have recently published a case series of metamizole-induced liver injuries elsewhere. Flupirtine is a non-opioid analgesic drug and was used to treat neuronal hyperexcitability. It was withdrawn from the European market in 2018 due to hepatotoxicity, but it is still available in other countries. In contrast to our study, population-based studies from the USA, Spain, Iceland and France reported that amoxicillin-clavulanate is the most frequent drug causing DILI. The reason for this difference to our study probably
### TABLE 6  
Comparison between selected characteristics of cases with MELD score ≥18 and good outcome and MELD score ≥18 and poor outcome

| Characteristics                                      | Entire cohort MELD ≥18 (n = 46) | Transplant-free survival MELD ≥18 (n = 32) | LTX and/ or death MELD ≥18 (n = 14) | P value |
|------------------------------------------------------|---------------------------------|----------------------------------|----------------------------------|--------|
| Age, mean ± SD                                        | 49 ± 17                         | 45 ± 18                          | 58 ± 12                          | .018   |
| Biochemical Pattern (R) (%)                          |                                 |                                 |                                  |        |
| Hepatocellular                                       | 87                              | 91                              | 79                               | .264   |
| Mixed                                                | 2                               | 3                               | 0                                | .504   |
| Cholestatic                                          | 11                              | 6                               | 21                               | .128   |
| Hy’s law fulfilled (%)                               | 91                              | 87                              | 100                              | .182   |
| ICU stay (%)                                         | 22                              | 9                               | 59                               | .002   |
| Positive for ANA and/or anti-SMA (%)                 | 81                              | 79                              | 83                               | .767   |
| Presence of HE of any grade (%)                      | 30                              | 0                               | 100                              | <.001  |
| Liver biopsy performed, n (%)                        | 46 (100)                        | 32 (100)                        | 14 (100)                        |        |
| Confluent necrosis of 10%-29% (%)                    | 12                              | 10                              | 15                               | .613   |
| Confluent necrosis of 30%-49% (%)                    | 16                              | 13                              | 23                               | .427   |
| Confluent necrosis of 50%-69% (%)                    | 5                               | 7                               | 0                                | .340   |
| Confluent necrosis of 70%-100% (%)                   | 7                               | 0                               | 23                               | .006   |
| Therapy (%)                                          | –                               | –                               | –                                |        |
| No therapy                                           | 13                              | 16                              | 7                                | –      |
| Prednisolone                                         | 54                              | 59                              | 43                               | –      |
| Prednisolone and N-acetylcysteine                    | 31                              | 22                              | 50                               | –      |
| Budesonide                                           | 2                               | 3                               | 0                                | –      |
| Duration of first presentation to ALT peak value, d, median (IQR) | 0 (0-3)                        | 0 (0-2)                         | 2 (0-5)                         | .150   |
| Latency of first presentation to start of therapy, d, median (IQR) | 4 (2-12)                        | 3 (2-12)                        | 4 (2-12)                        | .750   |
| Duration of first presentation to TBL peak value, d, median (IQR) | 7 (3-15)                        | 6 (3-12)                        | 11 (5-17)                        | .147   |
| DILI severity Index (%)19                            | –                               | –                               | –                                | <.001  |
| Mild                                                 | 0                               | 0                               | 0                                | –      |
| Moderate                                              | 31                              | 44                              | 0                                | –      |
| Severe                                                | 39                              | 56                              | 0                                | –      |
| Fatal                                                 | 30                              | 0                               | 100                              | –      |

Blood values at the time of first presentation, mean ± SD

|                        | Entire cohort MELD ≥18 | Transplant-free survival MELD ≥18 | LTX and/ or death MELD ≥18 | P value |
|------------------------|------------------------|----------------------------------|---------------------------|--------|
| AST (U/L)              | 1649 ± 1590            | 1580 ± 1665                      | 1828 ± 1430               | .417   |
| ALT (U/L)              | 1810 ± 1602            | 1724 ± 1389                      | 2025 ± 2089               | .900   |
| ALP (U/L)              | 272 ± 389              | 197 ± 98                         | 468 ± 668                 | .091   |

Blood values at the time of hospitalisation, mean ± SD

|                        | Entire cohort MELD ≥18 | Transplant-free survival MELD ≥18 | LTX and/ or death MELD ≥18 | P value |
|------------------------|------------------------|----------------------------------|---------------------------|--------|
| AST (U/L)              | 1675 ± 1600            | 1612 ± 1682                      | 1829 ± 1430               | .427   |
| ALT (U/L)              | 1825 ± 1597            | 1745 ± 1380                      | 2023 ± 2090               | .881   |
| ALP (U/L)              | 264 ± 311              | 203 ± 95                         | 399 ± 528                 | .141   |

(Continues)
Prediction of clinical outcome for DILI is important since it represents one of the leading causes of ALF. In our study, the rate of poor outcome (LTx and/or death) was 12%. This corresponds well with previous data from non-population-based studies (7%-15%).

Several clinical, biochemical and histological predictors for poor outcome (LTx and/or death) were analysed with regard to outcome. For example, we observed that higher peak values of AST, ALT, ALP and bilirubin were associated with a higher risk of poor outcome. Additionally, a higher degree of liver injury, as assessed by histological scoring, was also associated with a higher risk of poor outcome.

In conclusion, our study provides valuable insights into the prediction of clinical outcome in DILI patients. We identified several clinical, biochemical and histological predictors that can help inform clinical decision-making and predict outcomes in these patients.

Note: In this table, patients with DILI after the intake of phenprocoumon were excluded.

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; ANA, Antinuclear antibodies; AST, Aspartate aminotransferase; good outcome, transplant-free survival; HE, Hepatic encephalopathy; ICU, Intensive care unit; LDH, Lactate dehydrogenase; LTx, Liver transplantation; MELD, Model for End-stage Liver Disease score; Poor outcome, (LTx and/or death); SMA, Smooth muscle antibodies; TBL, Total bilirubin.

Significant results with P values <0.05 are highlighted with bold font.

### TABLE 6 (Continued)

| Characteristics | Entire cohort MELD ≥18 <i>(n = 46)</i> | Transplant-free survival MELD ≥18 <i>(n = 32)</i> | LTx and/or death MELD ≥18 <i>(n = 14)</i> | P value |
|-----------------|--------------------------------------|----------------------------------|---------------------------------|---------|
| Blood peak values, mean ± SD | | | | |
| AST (U/L) | 1859 ± 1993 | 1745 ± 2239 | 2122 ± 1300 | .070 |
| ALT (U/L) | 2064 ± 2093 | 1981 ± 2129 | 2252 ± 2075 | .775 |
| ALP (U/L) | 346 ± 409 | 277 ± 202 | 506 ± 665 | .079 |

Note: In this table, patients with DILI after the intake of phenprocoumon were excluded.

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; ANA, Antinuclear antibodies; AST, Aspartate aminotransferase; good outcome, transplant-free survival; HE, Hepatic encephalopathy; ICU, Intensive care unit; LDH, Lactate dehydrogenase; LTx, Liver transplantation; MELD, Model for End-stage Liver Disease score; Poor outcome, (LTx and/or death); SMA, Smooth muscle antibodies; TBL, Total bilirubin.

Significant results with P values <0.05 are highlighted with bold font.
after a very long period of spontaneous remission, we cannot totally exclude that some AIH cases were falsely defined as DILI patients in our study.

Steroids as a treatment of DILI to improve outcome is controversial, and only very few studies have partly addressed this issue. Therefore, no substantiated recommendation for the use of steroids is given by current clinical practice guidelines for DILI. One of the reasons to withhold steroids from DILI patients is the potential risk of serious infections. However, a significant increase of serious infections under steroid therapy has not been detected in the setting of ALF in previous studies. As a member of the European Reference Network on Hepatological Diseases (ERN RARE-LIVER), our centre gets in contact with many suspected AIH cases. Acute presentation of AIH and DILI cannot be differentiated in most cases, even after obtaining liver histology. Therefore, we treat most cases of suspected AIH or DILI with prednisolone and differentiate between both entities by the clinical course: In AIH, liver enzymes will increase again after weaning of steroids, whereas, in DILI, they will not. Since most patients in our DILI cohort (70%) were treated with steroids (Table 1), we could not analyse thoroughly whether steroids had a positive effect on the outcome of DILI. The rate of infections was not significantly different between DILI cases treated with steroids (6.3%) and those who were not (4.4%, $P = .66$). However, it seems that patients under steroids who developed infectious complications were at higher risk of a poor outcome, although patient numbers in our study are very small (Supplementary Table 8). Future prospective studies are needed to address the risks and benefits of steroids for DILI patients.

The strength of our study is the size of the DILI cohort at a single tertiary care centre. Our study complements previous international studies on DILI, reflecting the special situation in Germany with a high rate of patients treated with phenprocoumon, metamizole and, until it was banished from the European market, flupirtine. Furthermore, the percentage of performed liver biopsies in DILI patients is relatively high at our centre. The histological analysis supported the prognostic value of confluent necrosis on liver histology. However, current guidelines are reluctant with the indication of liver biopsy for DILI patients. Future studies on DILI need to address to what extent histological characteristics such as necrosis can improve prognostic scores based on just laboratory parameters. Our study has several limitations, which are mainly due to the retrospective, single-centre, non-population-based study design.

In summary, our study underlines the need to identify the frequency of DILI-inducing drugs in each country separately. At our centre in Germany, phenprocoumon and metamizole were by far the most frequent causative drugs. Of note, these drugs could be replaced with lower risk drugs. As a prognostic score, MELD score ≥18 at the time of hospitalisation performed best in our study to predict outcome in DILI patients. It seems advisable to refer these patients to a transplant centre immediately and to proceed to liver transplantation if HE is noticed.

ACKNOWLEDGEMENTS
We thank Hans Pinnschmidt, Institute of Medical Biometry and Epidemiology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, for his support of the statistical analysis.

CONFLICT OF INTEREST
All authors do not have any conflict of interest.

ORCID
Martin Reike-Kunze https://orcid.org/0000-0003-0623-1742
Marcial Sebode https://orcid.org/0000-0002-5163-6979

REFERENCES
1. Andrade RJ, Lucena MI, Fernandez MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology. 2005;129:512-521.
2. Bjornsson ES, Bergmann OM, Bjornsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144:1419-1425, 1425 e1411-1413; quiz e1419-1420.
3. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology. 2015;148:1340-1352.e1347.
4. Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol. 2010;105:2396-2404.
5. Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. Am J Gastroenterol. 2012;107:1380-1387.
6. Andrade RJ, Medina-Caliz I, Gonzalez-Jimenez A, Garcia-Cortes M, Lucena MI. Hepatic damage by natural remedies. Semin Liver Dis. 2018;38:21-40.
7. Ostapowicz G, Fontana RJ, Schiadt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947-954.
8. Sgro C, Clinar F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology. 2002;36:451-455.
9. Bjornsson ES, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. Hepatology. 2005;42:481-489.
10. Fontana RJ, Hayashi PH, Gu J, et al. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. Gastroenterology. 2014;147:96-108.e104.
11. Jeong R, Lee YS, Sohn C, Jeon J, Ahn S, Lim KS. Model for end-stage liver disease score as a predictor of short-term outcome in patients with drug-induced liver injury. Scand J Gastroenterol. 2015;50:439-446.
12. Church RJ, Kulkak-Ublick GA, Aubrecht J, et al. Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: an international collaborative effort. Hepatology. 2018;69:760-773.
13. Ghabril M, Gu J, Yoder L, et al. Development and validation of model consisting of comorbidity burden to calculate risk of death within 6 months for patients with suspected drug-induced liver injury. Gastroenterology. 2019;157:1245-1252.
14. Robles-Diaz M, Lucena MI, Kaplowitz N, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology. 2014;147:109-118. e105.
15. Hayashi PH, Rockey DC, Fontana RJ, et al. Death and liver transplantation within 2 years of onset of drug-induced liver injury. *Hepatology*. 2017;66:1275-1285.

16. Sebode M, Reike-Kunze M, Weidemann S, et al. Metamizole: an underrated agent causing severe idiosyncratic drug-induced liver injury. *Br J Clin Pharmacol*. 2020;86:1406-1415.

17. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs—I. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol*. 1993;46:1331-1336.

18. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993;46:1323-1330.

19. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther*. 2011;89:806-815.

20. European Association for the Study of the Liver. Electronic address eee, clinical practice guideline panel C, panel m, representative EGB. EASL clinical practice guidelines: drug-induced liver injury. *J Hepatol*. 2019;70:1222-1261.

21. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol*. 1990;11:272-276.

22. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissborn K, Blei AT. Hepatic encephalopathy–definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology*. 2002;35:716-721.

23. Temple R. Hy’s law: predicting serious hepatotoxicity, *Pharmacopoeidmiol Drug Saf*. 2006;15:241-243.

24. Korman JD, Volenberg I, Balko J, et al. Screening for Wilson disease by oral anticoagulants: a population-based retrospective cohort study. *Br J Clin Pharmacol*. 1990;97:439-445.

25. O’Grady JG, Alexander JG, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*. 1989;97:439-445.

26. Hadem J, Tacke F, Bruns T, et al. Etiologies and outcomes of acute liver failure in Germany. *Clin Gastroenterol Hepatol*. 2012;10:664-669.e662.

27. Borlak J, van Bommel F, Berg T. N-acetylcysteine and prednisolone treatment improved serum biochemistries in suspected flupirtine cases of severe idiosyncratic liver injury. *Liver Int*. 2018;38:365-376.

28. European Medicines Agency. Withdrawal of pain medicine flupirtine endorsed. https://www.ema.europa.eu/en/news/withdrawal-pain-medicine-flupirtine-endorsed. Published 2018. Accessed July 26, 2019.

29. Bjornsson HK, Gudmundsson DO, Bjornsson ES. Liver injury caused by oral anticoagulants: a population-based retrospective cohort study. *Liver Int*. 2020;40:1895-1900.

30. Schimanski CC, Burg J, Mohler M, et al. Phenprocoumon-induced liver disease ranges from mild acute hepatitis to (sub-) acute liver failure. *J Hepatol*. 2004;41:67-74.

31. Douros A, Bronder E, Andersohn F, et al. Drug-induced liver injury: results from the hospital-based Berlin case-control surveillance study. *Br J Clin Pharmacol*. 2015;79:988-999.

32. Devabhavi H, Singh R, Patil M, Sheth K, Adarsh CK, Balaraju G. Outcome and determinants of mortality in 269 patients with combination anti-tuberculosis drug-induced liver injury. *J Gastroenterol Hepatol*. 2013;28:161-167.

33. Reuben A, Koch DG, Lee WM. Acute Liver Failure Study G. Drug-induced acute liver failure: results of a US multicenter, prospective study. *Hepatology*. 2010;52:2065-2076.

34. Bjornsson E, Kalaitzakis E, Olsson R. The impact of eosinophilia and hepatic necrosis on prognosis in patients with drug-induced liver injury. *Aliment Pharmacol Ther*. 2007;25:1411-1421.

35. Schmidt LE, Larsen FS. MELD score as a predictor of liver failure and death in patients with acetaminophen-induced liver injury. *Hepatology*. 2007;45:789-796.

36. Bjornsson E, Talwalkar J, Treeprasertsuk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology*. 2010;51:2040-2048.

37. Castiella A, Zapata E, Lucena MI, Andrade RJ. Drug-induced autoimmune liver disease: a diagnostic dilemma of an increasingly reported disease. *World J Hepatol*. 2014;6:160-168.

38. Alvarez F, Berg PA, Bianchi FB, et al. International autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol*. 1999;31:929-938.

39. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008;48:169-176.

40. Bernal W, Ma Y, Smith HM, Portmann B, Wendon J, Vergani D. The significance of autoantibodies and immunoglobulins in acute liver failure: a cohort study. *J Hepatol*. 2007;47:664-670.

41. de Boer YS, Kosinski AS, Urban TJ, et al. Features of autoimmune hepatitis in patients with drug-induced liver injury. *Clin Gastroenterol Hepatol*. 2017;15:103-112.e102.

42. Stephens C, Castiella A, Gomez-Moreno EM, et al. Autoantibody presentation in drug-induced liver injury and idiopathic autoimmune hepatitis: the influence of human leucocyte antigen alleles. *Pharmacogenet Genomics*. 2016;26:414-422.

43. Suzuki A, Brunt EM, Kleiner DE, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. *Hepatology*. 2011;54:931-939.

44. Gut E. European Association for the Study of the Liver. Randomised trial of steroid therapy in acute liver failure. Report from the European association for the study of the liver (EASL). 1979;20:620-623.

45. Rakela J, Mosley JW, Edwards VM, Govindarajan S, Alpert E. A double-blinded, randomized trial of hydrocortisone in acute hepatic failure. The acute hepatic failure study group. *Dig Dis Sci*. 1991;36:1223-1228.

46. Wree A, Dechene A, Herzer K, et al. Steroid and ursodesoxycholic acid combination therapy in severe drug-induced liver injury. *Digestion*. 2011;84:54-59.

47. Karkhanis J, Verna EC, Chang MS, et al. Steroid use in acute liver failure. *Hepatology*. 2014;59:612-621.

48. Chalasani NP, Hayashi PH, Bonkovsky HL, et al. ACG clinical guideline: The diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. 2014;109:950-966; quiz 967.

49. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis*. 1989;11:954-963.

50. Rolando N, Harvey F, Brahm J, et al. Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients. *Hepatology*. 1990;11:49-53.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.