Check for updates

Clinical Significance of Acute Kidney Injury in Idiosyncratic Drug-Induced Liver Injury: A Multicentric Propensity Scores Matched Study

José María Pinazo-Bandera[1,2,†], Hao Niu[2,3,†], Juan Pedro Toro-Ortiz[1,†], Inmaculada Medina-Caliz[3], Judith Sanabria-Cabrera[3], Aída Ortega-Alonso[1,2], Mercedes Robles-Díaz[2,3], Daniel Enrique Di Zeo-Sanchez[2,3], Nelia Hernández[4], Fernando Bessone[5], Vinicius Nunes[6], Raymundo Paraná[6,7], M. Isabel Lucena[2,3,*], Raul J. Andrade[1,2,*], Ismael Alvarez-Alvarez[2,3,‡] and Miren García-Cortés[1,2,‡]

Evidence about the role of acute kidney injury (AKI) in idiosyncratic drug-induced liver injury (DILI) is still scarce. We aimed to ascertain the incidence, clinical profile, culprit drugs, and prognosis associated with concomitant DILI and AKI. We include patients from two long-term prospective DILI registries, the Spanish DILI registry and the Latin American DILI (LATINDILI) Network. Demographics, clinical characteristics, and outcome of patients with DILI-AKI were compared to those patients with DILI and without AKI. Overall, 54 out of 978 patients had AKI at the time of DILI diagnosis (5.5%). The most frequent culprit drug implicated in DILI-AKI was amoxicillin–clavulanate (11%) followed by anabolic androgenic steroids, antituberculosis drugs, ebrotidine, and ticlopidine (5.5% each). DILI-AKI cases were older than patients without AKI (60 ± 18 vs. 52 ± 18; *P* = 0.001), and mostly men (63%; *P* = 0.022). Furthermore, DILI-AKI cases showed higher comorbidity burden, and cholestatic damage and lymphopenia were more prevalent. Notably, DILI-AKI cases had higher incidence of liver-related death and all-cause mortality than those patients with no renal dysfunction (*P* = 0.029 and *P* = 0.015, respectively). In both a multivariable logistic regression (odds ratio [OR] = 3.46; 95% confidence interval [CI] 1.39–8.59; *P* = 0.008), and a rigorous propensity score-matched analysis (OR = 5.20; 95% CI 1.06–25.52; *P* = 0.042), renal damage was found as a risk factor of poor outcome. In conclusion, AKI in DILI mostly occurs in older male patients with cholestatic injury, lymphopenia, and greater burden of comorbidities, but mortality is restricted to DILI-AKI patients with hepatocellular damage. Overall, AKI is a risk factor of poor outcome in idiosyncratic DILI.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Acute kidney injury (AKI) is a multifactorial condition associated with short- and long-term complications that can affect other organs, with a growing incidence in patients with liver disease over the past few decades. Nevertheless, AKI in the context of idiosyncratic drug-induced liver injury (DILI) has not been addressed.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The incidence, clinical characteristics, culprit drugs, and prognosis associated with AKI in idiosyncratic DILI are analyzed in two long-term prospective DILI registries, the Spanish DILI Registry and the LATINDILI Network.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ AKI in idiosyncratic DILI mostly occurs in older male patients with cholestatic injury, lymphopenia, and greater burden of comorbidities, but mortality is restricted to patients with DILI and AKI who had hepatocellular damage. Antibiotics (amoxicillin–clavulanate, antituberculosis drugs), anabolic androgenic steroids, ebrotidine, and ticlopidine were the most common causative agents responsible for cases of DILI-AKI. Renal damage was associated with a 3–5-fold higher risk of poor outcome in patients with DILI after conducting a multivariable logistic regression analysis and a rigorous propensity score-matched analysis.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our findings evidence that AKI is a risk factor for poor outcomes in idiosyncratic DILI, and support and contextualize the relationship between acute liver injury and renal dysfunction. DILI patients with renal impairment should undergo close monitoring and evaluation for hospitalization.

Received February 12, 2026; accepted August 6, 2026. doi:10.1002/cpt.70452

[1]Service of Gastroenterology and Hepatology, University Hospital Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina-IBIMA Plataforma Bionand, Universidad de Málaga, Málaga, Spain; [2]Centro de Investigación Biomédico en Red Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; [3]Service of Clinical Farmacology, University Hospital Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina-IBIMA Plataforma Bionand, Universidad de Málaga, Málaga, Spain; [4]Clínicas Hospital, Montevideo, Uruguay; [5]Centenario Hospital, Rosario National University, Rosario, Argentina; [6]Prof. Edgard Santos-UFBA University Hospital, Salvador de Bahia, Brazil; [7]School of Medicine, Universidad Nacional de Bahia, Salvador de Bahia, Brazil. *Correspondence: Raul J. Andrade (andrade@uma.es) and M. Isabel Lucena (lucena@uma.es)

[†]These authors have contributed equally to the manuscript and share authorship.
[‡]These authors share senior authorship.

Idiosyncratic drug-induced liver injury (DILI) is a complex and relatively rare condition, but it is an increasingly recognized global health concern. Unlike acetaminophen overdose (intrinsic drug-induced liver injury), idiosyncratic DILI is usually not dose-related, has a variable onset (days to weeks), jeopardizes patient safety, and compromises drug development. Its true incidence is uncertain due to its nonspecific presentation and lack of diagnostic biomarkers. DILI can mimic any other acute or chronic liver disease, with varying degrees of severity ranging from mild enzyme elevation to fulminant acute liver failure (ALF).[1]

Over the past few decades, the incidence of acute kidney injury (AKI), a complex disorder with short-term and long-term repercussions that can impact other organs,[2] has shown an upward trend in patients with liver disease, especially those with cirrhosis.[3,4]

Nevertheless, evidence regarding the role of AKI in DILI remains limited. In a nationwide cohort study, it was found that the incidence of AKI was almost three times higher in patients with intrinsic DILI than in those without acetaminophen intoxication, and acetaminophen toxicity was identified as a risk factor for AKI.[5] However, to date, the issue of AKI in the context of idiosyncratic DILI (DILI-AKI) has not been addressed.

The aim of this study was therefore to ascertain the incidence of DILI-AKI, characterize its clinical profile and the associated culprit drugs, and to assess the role of AKI in the prognosis of DILI episodes in a large cohort of patients.

MATERIALS AND METHODS

Study population

Information was retrieved from *bona fide* DILI cases prospectively enrolled in the Spanish DILI Registry and the Latin American DILI (LATINDILI) Network from their establishment until October 2024. Detailed information on these registries has been described elsewhere.[6,7] Cases of dose-related liver injury (intrinsic DILI) and cases where the analytical and/or diuresis-related parameters were unavailable for assessing renal injury at baseline, at the time of diagnosis, or during the course of DILI were excluded. For each DILI episode, a structured case report form was used to collect clinical and pharmacological data, blood tests, imaging techniques to rule out other causes of liver disease, and the outcome of the liver injury. The study protocol was approved by the local ethics committee, and all subjects gave written informed consent.

The biochemical criteria for DILI were first established based on the CIOMS guidelines,[8] and subsequently modified to align with those set by an international consensus,[9] namely serum alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN); alkaline phosphatase (ALP) ≥2 times the ULN; or ALT ≥3 times the ULN alongside total bilirubin (TBL) exceeding 2 times the ULN. A panel of three independent DILI experts evaluated the causal link between the suspected offending drug and the liver damage. Case likelihood was then categorized according to traditional RUCAM categories.[8] Only definite, probable, or possible DILI cases were included.

The pattern of liver damage was classified using the nR value of the first available blood test after DILI recognition.[10] Liver damage was categorized as mild, moderate, severe, or fatal.[9] Comorbidity burden was calculated using the Charlson's Comorbidity Index (CCI).[11] Hypersensitivity was defined as positive if any of the following were present at DILI recognition: fever, rash, serum eosinophilia, lymphopenia, or arthralgia. Eosinophilia was defined as serum eosinophils greater than 4–6% of the total leukocyte count, based on the blood count at the time of DILI recognition depending on the normal range of each hospital, and lymphopenia as serum lymphocytes <10%.

Renal damage

AKI was defined based on the criteria established in the Kidney Disease—Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI.[12] Cases of DILI that were considered DILI-AKI met at least one of the following criteria: (1) increase in serum creatinine ≥0.3 mg/dL within 48 h; (2) increase in serum creatinine ≥1.5 times the baseline value within the last 7 days; (3) urine output less than 0.5 mL/kg/h for 6 h. Cases fulfilling AKI criteria were clinically reviewed by a multidisciplinary team including hepatologists and a nephrologist with experience in acute kidney injury assessment.

The severity of renal damage was graded according to serum creatinine levels (mg/dL) at the time of DILI diagnosis, as follows: stage 1 if creatinine levels reach ≥1.5 to <2 times the baseline value (defined as creatinine in the last blood test available prior to hospital admission due to DILI) or creatinine increases ≥0.3 mg/dL; stage 2 if creatinine levels reach ≥2 to <3 times the baseline value; and stage 3 if creatinine levels reach ≥3 times the baseline value, or creatinine increases ≥4 mg/dL, or there is a need for renal replacement therapy.[12]

Patients with baseline eGFR <60 mL/min/1.73 m^2 and well-documented history of chronic kidney disease for at least the preceding 6 months before DILI onset were classified as having preexisting chronic kidney disease (CKD), in accordance with KDIGO recommendations.[13] If eGFR was not available, it was calculated using the CKD-EPI equation from baseline serum creatinine values obtained before and at DILI onset, as well as at creatinine peak value during follow-up.[14] Patients who were on dialysis before the diagnosis of the liver event were excluded from the analysis.

Outcome

Poor outcome was defined as mortality (where DILI was either the main or contributory cause of death) or liver transplantation.

Statistical analysis

Patient's clinical and demographic information was examined using descriptive statistics. Normal distribution in quantitative data was assessed with the Shapiro–Wilk test. Then, the mean and standard deviation (SD) or median and interquartile range (IQR) were calculated, and the Student's *t*-test, analysis of variance (ANOVA), Mann–Whitney U test, or Kruskal–Wallis test, as applicable, were used to examine group differences. Frequency distributions were used to represent categorical data, and Fisher's exact test or the chi-square test were used to compare differences. The analysis did not include patients whose data were missing.

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Association between renal damage and poor outcome was firstly evaluated through a multivariable logistic regression analysis, adjusting for potential confounders. In addition, propensity scores to determine the predicted probability of DILI patients of having AKI were estimated using a multivariable logistic regression model, in which renal damage (AKI vs. no AKI) was regressed on observed baseline characteristics. Covariates were selected based on sizeable differences in characteristics that could potentially be related to the presence of renal damage. Then, in a propensity score-matched analysis, we examined the relationship between AKI and poor outcome, defined as mortality (liver-related death and all-cause mortality in which DILI had a contributory role) or liver transplantation. We matched DILI patients on the following potential confounders: age, sex, comorbidity burden (measured with the CCI), liver injury pattern (hepatocellular, cholestatic, and mixed), TBL levels at DILI recognition, and polypharmacy (0–2 vs. ≥3 concomitant medications). A nearest neighbor one-to-one propensity scores matching without replacement, using a caliper width equal to 0.2 of the standard deviation of the *logit* of the propensity score,[15] was conducted to reduce the influence of potential confounding factors. Balance between treatment groups was evaluated by standardized differences of all baseline covariates.

All statistical analyses were conducted using R version 4.4.3 (R Core Team, 2025) and Stata version 18 (Stata Corporation). A two-sided *P*-value lower than 0.05 was deemed statistically significant.

RESULTS

A total of 978 patients with well-vetted idiosyncratic DILI and information to assess renal damage were included in the current study, including 725 from the Spanish DILI Registry and 253 from the LATINDILI Network. Among them, 54 cases (5.5%) had a well-documented AKI at the time of diagnosis of idiosyncratic DILI. No patients were on dialysis before the diagnosis of the liver event (**Figure S1**).

The pharmacological agent most frequently associated with concomitant liver and kidney damage was amoxicillin-clavulanate with six cases (11%), followed by anabolic androgenic steroids, antituberculosis drugs, ebrotidine (an anti-H2 drug already withdrawn from the Spanish market),[16] and ticlopidine with three cases each (5.6% of DILI-AKI cases each). The implicated agents responsible for DILI and AKI are summarized in **Table 1**. In addition, the relation between elevations in serum creatinine and total bilirubin varies between specific drugs (**Figure 1**). Thus, DILI-AKI due to simvastatin, allopurinol, pioglitazone, or methotrexate was characterized by notable increases in creatinine but normal bilirubin values, while anabolic androgenic steroids, fenofibrate, clomethiazole, cloxacillin, or itraconazole were associated with milder elevations of creatinine but significant increases of bilirubin. Main clinical characteristics of DILI-AKI cases according to ATC pharmacological groups are summarized in **Table S1**.

Comparison between DILI cases with and without concomitant acute kidney injury

Demographics, clinical characteristics, laboratory findings, and outcome of DILI-AKI and DILI patients without renal damage are shown in **Table 2**. DILI-AKI cases were older than patients without AKI (60 ± 18 vs. 52 ± 18; $P = 0.001$) and were predominantly men (63%; $P = 0.022$). Likewise, DILI-AKI cases showed a higher prevalence of diabetes mellitus and hypertension, as well as a higher comorbidity burden than those patients without concomitant AKI.

Despite hepatocellular liver damage being predominant in both groups (56% and 63% in DILI-AKI and DILI without AKI, respectively), 35% of DILI-AKI cases presented with cholestatic injury, whereas among DILI cases without AKI, 20% of patients had a cholestatic damage ($P = 0.018$). Furthermore, DILI-AKI cases presented more frequently with jaundice (83%, compared with 68% of patients with DILI but no renal involvement; $P = 0.017$), and had a higher hospitalization rate (73% vs. 54%, respectively; $P = 0.009$). Beside, DILI-AKI patients had a higher prevalence of lymphopenia than those cases with no renal damage (41% and 15%, respectively; $P < 0.001$). Regarding polypharmacy, DILI-AKI cases showed a J-shaped trend, observing 26% of patients who took five or more pharmacological agents (aside from the one responsible for DILI), while DILI patients with no renal damage showed a downward trend when the number of concomitant medications increased ($P = 0.002$).

Regarding liver parameters, DILI-AKI cases had a higher incidence of total hyperbilirubinemia (median 7.5 mg/dL) than DILI patients with no renal damage (median 4.9 mg/dL; $P = 0.006$), albeit there were no differences in other liver enzymes or coagulation parameters. The evolution of total bilirubin and creatinine is shown in **Table S2**. Conversely, DILI-AKI patients had significantly lower albumin and hemoglobin levels than those DILI cases who did not have renal damage.

Most of the patients in both groups presented with a moderate severity index (69% of DILI-AKI cases and 58% of DILI patients without renal damage), although the proportion of cases who developed fatal damage (liver-related death or liver transplantation) was notably higher in DILI-AKI cases compared to those DILI patients with no renal involvement (11% vs. 3.6%). Indeed, when we analyzed the outcome individually, we observed a significantly higher incidence of liver-related death among DILI-AKI cases compared to DILI patients without renal damage (7.4% vs. 1.9%; $P = 0.029$), but no differences in liver transplantation rates (3.7% and 1.6%, respectively; $P = 0.241$). The proportion of patients who met either the Hy's law or the nR-based Hy's law was similar in both groups. Likewise, death due to other causes (in which DILI had a contributory role) was higher among DILI-AKI cases than in patients with DILI but no renal damage (5.6% and 0.8%, respectively; $P = 0.015$). Details of DILI-AKI cases who evolved into poor outcome (all of whom had hepatocellular liver damage) are presented in **Table S3**.

Comparison between DILI cases with and without concomitant acute kidney injury by type of liver damage

A specific analysis of the type of liver injury revealed that only patients with hepatocellular damage and AKI were older than those cases with hepatocellular DILI but no renal damage. In addition, a higher frequency of males was observed in DILI-AKI exclusively in those patients with hepatocellular presentation. Furthermore, differences in comorbidity burden were only seen among hepatocellular DILI cases, in whom 20% of DILI-AKI patients had a high comorbidity burden compared with 3.3% of DILI patients without renal damage ($P = 0.001$).

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1 Main Anatomic Therapeutic Classification (ATC) pharmacologic groups and subgroups and culprit drugs in DILI cases with acute kidney injury

Pharmacologic group and subgroup	Frequency, *n* (%)
A (Alimentary tract and metabolism)	6 (11.1)
A02 Drugs for acid related disorders	3 (5.6)
Ebrotidine	3 (5.6)
A03 Drugs for functional gastrointestinal disorders	1 (1.9)
Methylatropine	1 (1.9)
A10 Drugs used in diabetes	1 (1.9)
Pioglitazone	1 (1.9)
A11 Vitamins	1 (1.9)
Retinol (vitamin A)	1 (1.9)
B (Blood and blood forming organs)	3 (5.6)
B01 Antithrombotic agents	3 (5.6)
Ticlopidine	3 (5.6)
C (Cardiovascular system)	11 (20.4)
C08 Calcium channel blockers	1 (1.9)
Verapamil	1 (1.9)
C09 Agents acting on the renin–angiotensin system	6 (11.1)
Enalapril	2 (3.7)
Aliskiren	1 (1.9)
Captopril	1 (1.9)
Losartan	1 (1.9)
Ramipril	1 (1.9)
C10 Lipid modifying agents	4 (7.1)
Simvastatin	2 (3.7)
Atorvastatin	1 (1.9)
Fenofibrate	1 (1.9)
J (Anti-infectives for systemic use)	16 (29.6)
J01 Antibacterials for systemic use	11 (20.4)
Amoxicillin	1 (1.9)
Amoxicillin–clavulanate	6 (11.1)
Ciprofloxacin	1 (1.9)
Cloxacillin	1 (1.9)
Levofloxacin	1 (1.9)
Oxacillin	1 (1.9)
J02 Antimycotics for systemic use	1 (1.9)
Itraconazole	1 (1.9)
J04 Antimycobacterials	3 (5.6)
Antituberculosis drugs	3 (5.6)
J05 Antivirals for systemic use	1 (1.9)
Nevirapine	1 (1.9)
L (Antineoplastic and immunomodulating agents)	2 (3.7)
L02 Endocrine therapy	1 (1.9)
Flutamide	1 (1.9)
L04 Immunosuppressants	1 (1.9)
Methotrexate	1 (1.9)
M (Musculo- skeletal system)	5 (9.3)
M01 Anti-inflammatory and antirheumatic products	3 (5.6)
Diclofenac	2 (3.7)
Rofecoxib	1 (1.9)
M04 Antigout preparations	2 (3.7)
Allopurinol	2 (3.7)
N (Nervous system)	6 (11.1)
N02 Analgesics	1 (1.9)
Dextropropoxyphene	1 (1.9)
N03 Antiepileptics	2 (3.7)
Carbamazepine	1 (1.9)
Phenytoin	1 (1.9)
N05 Psycholeptics	2 (3.7)
Clomethiazole	1 (1.9)
Olanzapine	1 (1.9)
N06 Psychoanaleptics	1 (1.9)
Imipramine	1 (1.9)
Herbal and dietary supplements	2 (3.7)
Anabolic androgenic steroids	3 (5.6)

ATC, Anatomic Therapeutic Classification.

Likewise, differences in clinical presentation were observed among hepatocellular DILI cases with and without AKI. Most DILI-AKI cases presented with jaundice (83%, compared with 62% of cases without renal involvement; $P = 0.020$), while nearly half of cases had lymphopenia (47% of DILI-AKI and 13% of cases without AKI; $P < 0.001$).

In addition, DILI-AKI cases who had hepatocellular damage had higher median bilirubin levels and INR, and lower albumin, hemoglobin, and platelet count than those cases without renal damage. These differences were also seen in the outcome of the DILI episode, as DILI-AKI cases had higher liver-related and all-cause mortality rates than those cases with no renal injury (13% vs. 2.6%; $P = 0.011$, and 6.7% vs. 0.7%; $P = 0.031$, respectively). Conversely, in DILI cases with cholestatic or mixed injury, clinical presentation and outcome of DILI were comparable across groups, except that cholestatic DILI-AKI patients had lower mean hemoglobin levels than those without renal damage (11.8 vs. 13; $P = 0.015$), and 80% of DILI-AKI cases with mixed injury had lymphopenia compared with 18% of patients with no renal damage ($P = 0.006$) (**Table 3**).

Analysis of cases with drug-induced liver injury and concomitant renal injury by type of renal damage

Patients with *de novo* AKI ($n = 45$) were compared with those with exacerbated chronic kidney disease (acute-on-chronic kidney injury) ($n = 9$) (**Table 4**). Patients with AKI showed a marginal

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

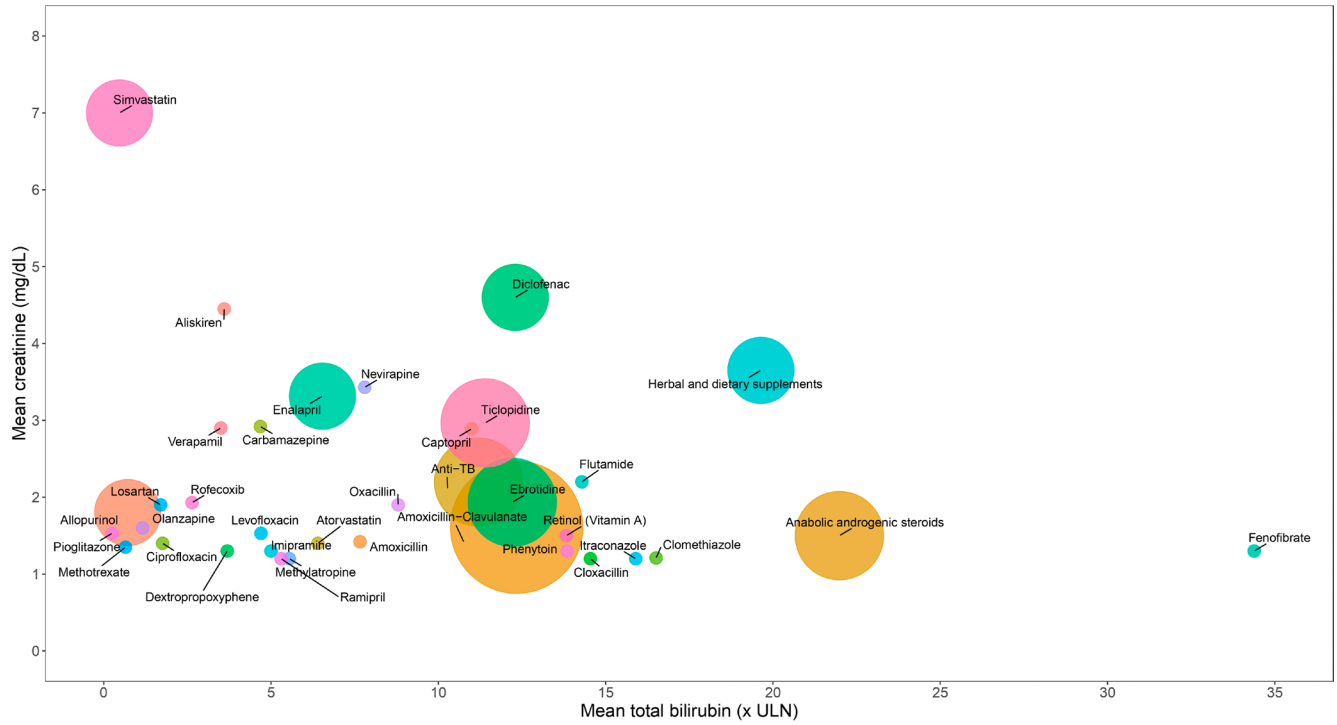


Figure 1 Relation between elevations in serum creatinine and total bilirubin in specific drugs in 54 DILI-AKI patients. The mean serum creatinine and total bilirubin levels were calculated for 54 patients with DILI-AKI. Anti-TB: antituberculosis medications, either alone or the combination of isoniazid, rifampicin, and/or pyrazinamide.

difference in age, being these cases younger than those who presented with acute-on-chronic kidney disease (mean age 58 and 71 years, respectively; $P = 0.052$). Likewise, jaundice was more prevalent in DILI cases with AKI than those with the worsened CKD (89% vs. 56%; $P = 0.033$).

Notably, nearly 70% of DILI cases with acute-on-chronic kidney disease were polymedicated patients (≥5 concomitant drugs), compared with 18% of cases with AKI ($P = 0.008$). In addition, both creatinine levels at DILI onset and peak creatinine levels were significantly lower in DILI patients with AKI compared to those with acute-on-chronic kidney disease. Median creatinine levels at DILI onset were 1.5 mg/dL (1.67-fold; IQR 1.44–2.38) and 2.9 mg/dL (1.58-fold; IQR 1.21–2.00), respectively ($P = 0.001$), while median peak creatinine levels were 1.5 mg/dL in DILI cases with AKI (1.82-fold; IQR 1.44–2.38) and 4.2 mg/dL (2-fold; IQR 1.62–2.05) in cases with worsened CKD ($P < 0.001$). Four out of 45 patients with *de novo* DILI-AKI and two out of nine cases with CKD had an increase in serum creatinine after DILI onset. Conversely, the type of kidney damage was not associated with hospitalization rate, nor mortality or liver transplantation.

Analysis of cases with drug-induced liver injury and concomitant renal injury by severity of renal damage

We also conducted an ancillary analysis stratifying the DILI-AKI cohort by stage of acute kidney injury: stage 1 ($n = 33$), stage 2 ($n = 13$), and stage 3 ($n = 8$). We found that most patients with more severe renal damage (stage 3) presented with eosinophilia (63%), compared to patients with stage 1 or 2 (33% and 0%, respectively; $P = 0.003$) (**Table S4**).

Association between acute kidney injury and poor outcome

We investigated the relationship between AKI and poor outcome in DILI cases using a propensity scores-matched analysis. The incidence of poor outcome was greater in DILI-AKI patients compared to DILI patients without renal damage (16.7% vs. 4.1%, respectively). In a multivariable logistic model adjusted for potential confounding variables, that is, age, sex, comorbidity burden (assessed by the CCI), type of liver injury (hepatocellular, cholestatic, and mixed), TBL levels, and polypharmacy (0–2 vs. ≥3 concurrent medications), AKI was associated with a significant risk of poor outcome in DILI patients (odds ratio [OR] = 3.46; 95% confidence interval [CI] 1.39–8.59; $P = 0.008$).

Furthermore, following the matching by propensity scores based on the abovementioned potential confounding variables, 54 pairs were successfully matched. Overall, after matching, these two groups had similar probabilities of developing AKI (**Figure 2**). The two groups were evenly matched, with the exception of lymphopenia prevalence (standardized bias = 0.557), which was significantly higher in DILI-AKI cases (**Table S5**). The association between renal damage and poor outcome remained consistent, revealing that DILI patients with AKI had over 5-fold higher risk of poor outcome than patients without AKI (OR = 5.20; 95% CI: 1.06–25.52; $P = 0.042$).

DISCUSSION

This study has highlighted the differential clinical profile of DILI-AKI cases compared with DILI patients without renal involvement. Our findings show that DILI-AKI cases are older, predominantly

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2 Demographic, clinical characteristics, laboratory parameters and outcomes in DILI cases with and without acute kidney injury from the Spanish and Latin American DILI registries

	DILI with acute kidney injury (*n* = 54)	DILI without acute kidney injury (*n* = 924)	*P* value
Age (years), mean ± SD	60 ± 18	52 ± 18	0.001
Female sex, *n* (%)	20 (37)	490 (53)	0.022
Body mass index (kg/m^2), mean ± SD	27 ± 5.8	26 ± 4.2	0.091
Diabetes, *n* (%)	11 (20)	101 (11)	0.034
Dyslipidemia, *n* (%)	9 (17)	107 (12)	0.261
Hypertension, *n* (%)	21 (39)	178 (19)	0.001
Underlying hepatic disease, *n* (%)	7 (13)	64 (6.9)	0.104
History of drug allergy, *n* (%)	5 (9.3)	69 (7.5)	0.595
Charlson comorbidity index, *n* (%)			0.002
≤2 points	46 (85)	888 (96.1)	
>2 points	8 (15)	36 (3.9)	
Type of liver injury, *n* (%)			0.018
Hepatocellular	30 (56)	581 (63)	
Cholestatic	19 (35)	181 (20)	
Mixed	5 (9.3)	162 (18)	
DILI episode characteristics			
Jaundice, *n* (%)	45 (83)	618 (68)	0.017
Hospitalization, *n* (%)	37 (73)	473 (54)	0.009
Hypersensitivity features[a], *n* (%)	31 (57)	397 (43)	0.038
Fever, *n* (%)	11 (20)	104 (11)	0.043
Rash, *n* (%)	7 (13)	83 (9.0)	0.329
Eosinophilia, *n* (%)	16 (30)	212 (23)	0.259
Lymphopenia, *n* (%)	22 (41)	138 (15)	<0.001
Arthralgia, *n* (%)	2 (3.7)	32 (3.5)	0.711
Positive autoantibody titers, *n* (%)	6 (11)	124 (13)	0.836
Total oral daily dose (mg), median (IQR)	300 (50–563)	400 (80–1,875)	0.113
Duration of therapy (days), median (IQR)	22 (8–46)	26 (8–66)	0.584
Time to onset (days), median (IQR)	17 (7–40)	24 (9–62)	0.099
Concomitant drugs, *n* (%)			0.002
None	10 (19)	257 (28)	
1–2	18 (33)	388 (42)	
3–4	12 (22)	187 (20)	
≥5	14 (26)	92 (10)	
Severity, *n* (%)			0.002
Mild	7 (13)	290 (32)	
Moderate	37 (69)	538 (58)	
Severe	4 (7.4)	59 (6.4)	
Fatal/transplantation	6 (11)	33 (3.6)	
Laboratory parameters at DILI onset, median (IQR)			
Total bilirubin (× ULN)	7.5 (3.2–14)	4.9 (1.2–10)	0.006
Aspartate aminotransferase (AST) (× ULN)	7.2 (2.5–23)	6.4 (3.0–20)	0.938
Alanine aminotransferase (ALT) (× ULN)	10 (3.7–21)	9.8 (4.9–24)	0.660
Alkaline phosphatase (ALP) (× ULN)	2.0 (0.8–3.2)	1.7 (1.0–2.6)	0.435
Gamma-glutamyl transferase (GGT) (× ULN)	7.5 (3.1–10)	5.5 (2.7–10)	0.286

(Continued)

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2 (Continued)

	DILI with acute kidney injury ($n=54$)	DILI without acute kidney injury ($n=924$)	*P* value
International Normalized Ratio (INR)	1.1 (1.0–1.7)	1.1 (1.0–1.3)	0.476
Creatinine (mg/dL)	1.6 (1.3–2.4)	0.8 (0.7–1.0)	<0.001
eGFR (mL/min/1.73 m^2)	39 (26–55)	92 (77–108)	<0.001
Maximum creatinine level (mg/dL), median (IQR)	1.6 (1.4–2.8)	0.9 (0.8–1.1)	<0.001
Basal eGFR (mL/min/1.73 m^2), median (IQR)[b]	80 (64–94)	97 (85–116)	<0.001
Minimum eGFR (mL/min/1.73 m^2), median (IQR)	38 (23–54)	83 (67–97)	<0.001
Albumin (g/dL), mean ± SD	3.5 ± 1.0	3.9 ± 0.9	0.033
Hemoglobin (g/dL), mean ± SD	12.5 ± 2.0	13.5 ± 1.7	<0.001
Platelets ($\times10^3/\mu L$), mean ± SD	220 ± 85	235 ± 85	0.274
Hy's law, *n* (%)	21 (40)	294 (35)	0.431
nR-based Hy's law, *n* (%)	22 (42)	307 (37)	0.404
Liver-related death, *n* (%)	4 (7.4)	18 (1.9)	0.029
Liver transplantation, *n* (%)	2 (3.7)	15 (1.6)	0.241
Death due to other causes[c], *n* (%)	3 (5.6)	7 (0.8)	0.015
Time to resolution (days), median (IQR)	71 (43–135)	94 (48–183)	0.341

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.
[a]If the subject presents at least one of the following: fever, rash, eosinophilia, lymphopenia, or arthralgia. [b]Estimated glomerular filtration rate prior to DILI.
[c]During the time of follow-up.

males, have a higher comorbidity burden, and are more frequently polymedicated patients. Notably, DILI-AKI cases exhibit a higher mortality rate (all of them presenting with hepatocellular damage), despite the percentage of patients meeting either Hy's law or the nR-based Hy's law being similar between DILI cases with and without associated renal damage. Finally, our analysis yields that renal damage is a risk factor for poor outcomes in DILI patients.

To date, the main prospective DILI registries have not thoroughly analyzed acute kidney damage in idiosyncratic DILI cases.[17–20] Only the Indian Network of Drug-Induced Liver Injury observed that patients who died from DILI had significantly higher serum creatinine levels than survivors. However, in this Indian cohort, patients who died also had significantly worse bilirubin levels and coagulopathy, suggesting that the poor prognosis could be attributed to liver failure itself.[20] In contrast, in our cohort, patients with DILI-AKI did not exhibit a significantly worse coagulation profile at diagnosis, indicating that poor outcomes were not solely attributable to the severity of liver injury.

There is evidence in the literature regarding the influence of age and sex on renal function.[21] Thus, a pharmacokinetic hypothesis for renally excreted drugs (such as amoxicillin–clavulanate) could be that older patients with vascular and glomerular impairment (due to diabetes and hypertension) have reduced renal clearance. This might result in greater antigen exposure in genetically predisposed patients, fostering a complex immunological niche that facilitates hepatocyte sensitization. Consequently, via the mitogen-activated protein kinase pathways, this could lead to mitochondrial and endoplasmic reticulum damage in hepatic cells.[22] Moreover, the immune system activation typical of DILI can lead to release of large quantities of pro-inflammatory cytokines, consequently providing a significant oxidative stress reaction. These reactive molecules not only affect the liver but also impact renal function. For instance, in animal models, some biomarkers such as TNF-α/HMGB1 have been postulated to be a major contributor to this type of reaction.[23]

However, there are other drugs whose renal damage is exclusively related to the level of jaundice, which pathogenic mechanism involves the direct toxicity of bile pigments, known as cholemic tubulopathy or cholemic nephrosis.[24,25] This occurs in cases of DILI due to anabolic steroids,[26] where renal damage resolves once the jaundice is corrected, sometimes even requiring extrinsic systems such as albumin dialysis with molecular adsorbent recirculating system (MARS).[27] Nevertheless, it is known that in these specific cases, renal damage does not confer a worse prognosis, as seen in a previous study where there were no fatalities in a cohort of 25 patients with anabolic steroid-induced liver damage.[26]

Furthermore, it is worth mentioning that lymphopenia was more prevalent in DILI-AKI patients compared to DILI patients without renal dysfunction. In this line, prior studies evidenced that higher neutrophil-to-lymphocyte ratio or monocyte-to-lymphocyte ratio were proportionally correlated with incidence of AKI,[28] suggesting that lymphopenia could reflect the activation of innate immune response to inflammation in kidney tissue.

Regarding genetic susceptibility, several HLA risk alleles have been associated with DILI caused by specific drugs or herbs.[29] However, no established HLA haplotypes have been specifically linked to the development of AKI in the context of DILI.

Notably, we consistently observed that renal damage was a risk factor for poor outcome. These findings support our hypothesis concerning the role of kidney damage in the prognosis of DILI and provide novel insights into this clinically uncertain and overlooked

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3 Demographic, clinical characteristics, laboratory parameters and outcome in DILI cases according to type of liver damage

	Hepatocellular liver injury (*n* = 611)			Cholestatic liver injury (*n* = 200)			Mixed liver injury (*n* = 167)		
	DILI with acute kidney injury (*n* = 30)	DILI without acute kidney injury (*n* = 581)	*P* value	DILI with acute kidney injury (*n* = 19)	DILI without acute kidney injury (*n* = 181)	*P* value	DILI with acute kidney injury (*n* = 5)	DILI without acute kidney injury (*n* = 162)	*P* value
Age (years), mean ± SD	59 ± 19	49 ± 17	0.006	65 ± 16	58 ± 17	0.127	55 ± 17	55 ± 19	0.939
Female sex, *n* (%)	11 (37)	327 (56)	0.034	9 (47)	84 (46)	0.936	0 (0)	79 (49)	0.061
Body mass index (kg/m^2), mean ± SD	26 ± 3.4	26 ± 4.3	0.555	28 ± 8.4	26 ± 3.9	0.102	28 ± 1.9	26 ± 4.2	0.624
Diabetes, *n* (%)	8 (27)	55 (9.5)	0.008	3 (16)	29 (16)	1.000	0 (0)	17 (10)	1.000
Dyslipidemia, *n* (%)	5 (17)	62 (11)	0.361	4 (21)	21 (12)	0.268	0 (0)	24 (15)	1.000
Hypertension, *n* (%)	9 (30)	98 (17)	0.065	10 (53)	52 (29)	0.032	2 (40)	28 (17)	0.220
Underlying hepatic disease, *n* (%)	6 (20)	38 (6.5)	0.016	1 (5.3)	14 (7.7)	1.000	0 (0)	12 (7.4)	1.000
History of drug allergy, *n* (%)	4 (13)	51 (8.8)	0.335	0 (0)	10 (5.5)	0.603	1 (20)	8 (4.9)	0.245
Charlson comorbidity index, *n* (%)			0.001			0.356			1.000
≤2 point	24 (80)	562 (96.7)		17 (89)	170 (93.9)		5 (100)	156 (96.3)	
>2 point	6 (20)	19 (3.3)		2 (11)	11 (6.1)		0 (0)	6 (3.7)	
DILI episode characteristics									
Jaundice, *n* (%)	25 (83)	356 (62)	0.020	15 (79)	134 (75)	1.000	5 (100)	128 (80)	0.584
Hospitalization, *n* (%)	18 (64)	276 (50)	0.153	14 (78)	106 (61)	0.205	5 (100)	91 (58)	0.082
Hypersensitivity features[a], *n* (%)	18 (60)	229 (39)	0.025	9 (47)	86 (48)	0.990	4 (80)	82 (51)	0.369
Fever, *n* (%)	6 (20)	50 (8.6)	0.047	3 (16)	24 (13)	0.726	2 (40)	30 (19)	0.244
Rash, *n* (%)	3 (10)	43 (7.4)	0.487	3 (16)	17 (9.4)	0.414	1 (20)	23 (14)	0.544
Eosinophilia, *n* (%)	7 (23)	113 (19)	0.602	6 (32)	51 (28)	0.791	3 (60)	48 (30)	0.167
Lymphopenia, *n* (%)	14 (47)	75 (13)	<0.001	4 (21)	34 (19)	0.763	4 (80)	29 (18)	0.006
Arthralgia, *n* (%)	1 (3.3)	18 (3.1)	1.000	1 (5.3)	9 (5.0)	1.000	0 (0)	5 (3.1)	1.000
Positive autoantibody titers, *n* (%)	4 (13)	97 (17)	0.803	1 (5.3)	13 (7.2)	1.000	1 (20)	14 (8.6)	0.379
Total oral daily dose (mg), median (IQR)	220 (35–400)	375 (80–1,500)	0.042	300 (63–1,800)	560 (50–1,875)	0.549	1,188 (475–1,875)	600 (80–1,875)	0.538
Duration of therapy (days), median (IQR)	21 (10–35)	32 (9–84)	0.298	31 (8–61)	18 (10–41)	0.492	8 (7–42)	15 (7–42)	0.704
Time to onset (days), median (IQR)	12 (7–26)	30 (10–75)	0.023	30 (12–52)	20 (8–37)	0.401	14 (7–35)	18 (7–36)	0.605
Concomitant drugs, *n* (%)			0.040			0.300			0.222
None	5 (17)	170 (29)		3 (16)	39 (22)		2 (40)	48 (30)	
1–2	10 (33)	251 (43)		7 (37)	76 (42)		1 (20)	61 (38)	
3–4	9 (30)	113 (19)		3 (16)	41 (23)		0 (0)	33 (20)	
≥5	6 (20)	47 (8.1)		6 (32)	25 (14)		2 (40)	20 (12)	
Severity, *n* (%)			0.005			0.281			1.000
Mild	5 (17)	218 (38)		1 (5.3)	41 (23)		1 (20)	31 (19)	

(Continued)

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3 (Continued)

	Hepatocellular liver injury (*n* = 611)			Cholestatic liver injury (*n* = 200)			Mixed liver injury (*n* = 167)		
	DILI with acute kidney injury (*n* = 30)	DILI without acute kidney injury (*n* = 581)	*P* value	DILI with acute kidney injury (*n* = 19)	DILI without acute kidney injury (*n* = 181)	*P* value	DILI with acute kidney injury (*n* = 5)	DILI without acute kidney injury (*n* = 162)	*P* value
Moderate	16 (53)	287 (50)		17 (89)	127 (71)		4 (80)	124 (77)	
Severe	3 (10)	44 (7.6)		1 (5.3)	10 (5.6)		0 (0)	5 (3.1)	
Fatal/transplantation	6 (20)	30 (5.2)		0 (0)	2 (1.1)		0 (0)	1 (0.6)	
Laboratory parameters at DILI onset, median (IQR)									
Total bilirubin (× ULN)	6.3 (2.3–14)	3.8 (1.0–9.8)	0.045	10 (4.1–15)	7.5 (2.8–13)	0.179	5.5 (5.0–7.4)	5.6 (2.8–9.2)	0.805
Aspartate aminotransferase (AST) (× ULN)	17 (7.1–40)	13 (5.4–31)	0.312	2.1 (1.6–3.6)	2.2 (1.4–3.9)	0.496	7.2 (5.2–9.4)	4.1 (2.9–6.9)	0.085
Alanine aminotransferase (ALT) (× ULN)	18 (10–30)	17 (8.9–37)	0.885	3.2 (2.4–5.6)	2.8 (1.8–4.8)	0.376	9.2 (8.0–11)	6.6 (4.8–9.8)	0.252
Alkaline phosphatase (ALP) (× ULN)	0.9 (0.7–1.9)	1.2 (0.8–1.8)	0.192	3.4 (2.6–6.6)	3.1 (2.2–5.5)	0.259	3.2 (2.9–3.6)	2.3 (1.7–3.0)	0.165
Gamma-glutamyl transferase (GGT) (× ULN)	3.9 (2.6–8.3)	4.8 (2.1–8.5)	0.735	9.6 (8.3–14)	7.8 (3.6–14)	0.087	8.9 (7.9–9.6)	8.0 (4.7–15)	0.896
International Normalized Ratio (INR)	1.4 (1.0–2.1)	1.1 (1.0–1.5)	0.137	1.0 (1.0–1.2)	1.0 (1.0–1.2)	0.819	1.0 (1.0–1.1)	1.0 (1.0–1.1)	0.674
Creatinine (mg/dL)	1.6 (1.3–2.8)	0.8 (0.7–1.0)	<0.001	1.6 (1.4–2.5)	0.9 (0.7–1.0)	<0.001	1.5 (1.4–1.5)	0.8 (0.7–1.0)	<0.001
eGFR (mL/min/1.73 m^2)	37 (24–52)	94 (79–110)	<0.001	33 (23–50)	87 (73–101)	<0.001	49 (49–58)	94 (75–105)	0.003
Maximum creatinine level (mg/dL), median (IQR)	1.9 (1.4–3.3)	0.9 (0.8–1.1)	<0.001	1.6 (1.4–2.4)	1.0 (0.8–1.1)	<0.001	1.5 (1.4–1.5)	0.9 (0.8–1.1)	0.001
Basal eGFR (mL/min/1.73 m^2), median (IQR)[b]	81 (67–101)	97 (85–118)	0.001	76 (60–87)	95 (65–110)	0.106	94 (71–100)	97 (90–111)	0.662
Minimum eGFR (mL/min/1.73 m^2), median (IQR)	36 (17–47)	85 (71–101)	<0.001	38 (25–50)	77 (64–90)	<0.001	49 (49–58)	81 (64–96)	0.018
Albumin (g/dL), mean ± SD	3.4 ± 0.8	3.9 ± 0.8	0.013	3.7 ± 1.2	3.8 ± 0.9	0.640	4.4 ± 0	4.0 ± 1.0	0.656
Hemoglobin (g/dL), mean ± SD	12.8 ± 2.0	13.7 ± 1.6	0.008	11.8 ± 1.8	13.0 ± 1.8	0.015	14.3 ± 2.3	13.6 ± 1.9	0.416
Platelets (×10^3/μL), mean ± SD	188 ± 78	225 ± 84	0.042	265 ± 84	249 ± 88	0.471	216 ± 45	254 ± 81	0.352
Hy's law, *n* (%)	21 (72)	294 (57)	0.092	0 (0)	0 (0)	–	0 (0)	0 (0)	–
nR-based Hy's law, *n* (%)	22 (76)	307 (59)	0.072	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Liver-related death, *n* (%)	4 (13)	15 (2.6)	0.011	0 (0)	2 (1.1)	1.000	0 (0)	1 (0.6)	1.000
Liver transplantation, *n* (%)	2 (6.7)	15 (2.6)	0.201	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Death due to other causes[c], *n* (%)	2 (6.7)	4 (0.7)	0.031	1 (5.3)	3 (1.7)	0.331	0 (0)	0 (0)	–
Time to resolution (days), median (IQR)	67 (48–105)	94 (44–191)	0.473	65 (37–94)	111 (61–211)	0.091	142 (105–265)	79 (52–139)	0.278

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

[a]If the subject presents at least one of the following: fever, rash, eosinophilia, lymphopenia, or arthralgia. [b]Estimated glomerular filtration rate prior to DILI. [c]During the time of follow-up.

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 4 Demographic, clinical characteristics, laboratory parameters and outcome in DILI cases according to type of renal damage (acute kidney injury vs. chronic kidney disease)

	Acute kidney injury (*n* = 45)	Acute-on-chronic kidney injury (*n* = 9)	*P* value
Age (years), mean ± SD	58 ± 18	71 ± 13	0.052
Female sex, *n* (%)	17 (38)	3 (33)	1.000
Body mass index (kg/m^2), mean ± SD	27 ± 5.7	29 ± 6.6	0.389
Diabetes, *n* (%)	9 (20)	2 (22)	1.000
Dyslipidemia, *n* (%)	7 (16)	2 (22)	0.635
Hypertension, *n* (%)	15 (33)	6 (67)	0.131
Underlying hepatic disease, *n* (%)	7 (16)	0 (0)	0.586
History of drug allergy, *n* (%)	4 (8.9)	1 (11)	1.000
Charlson comorbidity index, *n* (%)			0.608
≤2 points	39 (87)	7 (78)	
>2 points	6 (13)	2 (22)	
Type of liver injury, *n* (%)			0.397
Hepatocellular	26 (58)	4 (44)	
Cholestatic	14 (31)	5 (56)	
Mixed	5 (11)	0 (0)	
DILI episode characteristics			
Jaundice, *n* (%)	40 (89)	5 (56)	0.033
Hospitalization, *n* (%)	32 (76)	5 (56)	0.236
Hypersensitivity features[a], *n* (%)	26 (58)	5 (56)	1.000
Fever, *n* (%)	9 (20)	2 (22)	1.000
Rash, *n* (%)	7 (16)	0 (0)	0.586
Eosinophilia, *n* (%)	13 (29)	3 (33)	1.000
Lymphopenia, *n* (%)	18 (40)	4 (44)	1.000
Arthralgia, *n* (%)	2 (4.4)	0 (0)	1.000
Positive autoantibody titers, *n* (%)	4 (8.9)	2 (22)	0.259
Total oral daily dose (mg), median (IQR)	400 (50–825)	150 (50–300)	0.427
Duration of therapy (days), median (IQR)	22 (8–46)	35 (20–46)	0.413
Time to onset (days), median (IQR)	14 (7–38)	22 (19–41)	0.450
Concomitant drugs, *n* (%)			0.008
None	9 (20)	1 (11)	
1–2	18 (40)	0 (0)	
3–4	10 (22)	2 (22)	
≥5	8 (18)	6 (67)	
Severity, *n* (%)			0.508
Mild	5 (11)	2 (22)	
Moderate	30 (67)	7 (78)	
Severe	4 (8.9)	0 (0)	
Fatal/transplantation	6 (13)	0 (0)	
Laboratory parameters at DILI onset, median (IQR)			
Total bilirubin (× ULN)	7.8 (3.7–15)	3.6 (1.7–11)	0.097
Aspartate aminotransferase (AST) (× ULN)	9.1 (2.1–29)	3.2 (2.6–4.8)	0.280
Alanine aminotransferase (ALT) (× ULN)	10 (3.6–21)	6.0 (3.7–12)	0.485
Alkaline phosphatase (ALP) (× ULN)	1.9 (0.8–3.2)	2.5 (1.0–3.0)	0.354
Gamma-glutamyl transferase (GGT) (× ULN)	7.2 (3.1–10)	8.9 (6.4–9.5)	0.656

(Continued)

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 4 (Continued)

	Acute kidney injury ($n=45$)	Acute-on-chronic kidney injury ($n=9$)	*P* value
International Normalized Ratio (INR)	1.1 (1.0–1.8)	1.0 (1.0–1.2)	0.237
Creatinine (mg/dL)	1.5 (1.3–1.9)	2.9 (2.2–4.5)	0.001
eGFR (mL/min/1.73 m^2)	43 (31–57)	15 (11–27)	<0.001
Maximum creatinine level (mg/dL), median (IQR)	1.5 (1.3–2.0)	4.2 (3.2–4.5)	<0.001
Basal eGFR (mL/min/1.73 m^2), median (IQR)[b]	86 (73–96)	33 (18–40)	<0.001
Minimum eGFR (mL/min/1.73 m^2), median (IQR)	43 (31–57)	13 (9.3–17)	<0.001
Albumin (g/dL), mean ± SD	3.6 ± 1.1	3.2 ± 0.6	0.322
Hemoglobin (g/dL), mean ± SD	12.7 ± 2.0	11.8 ± 2.1	0.277
Platelets (×10^3/μL), mean ± SD	215 ± 88	246 ± 63	0.391
Hy's law, *n* (%)	20 (47)	1 (11)	0.067
nR-based Hy's law, *n* (%)	21 (49)	1 (11)	0.062
Liver-related death, *n* (%)	4 (8.9)	0 (0)	1.000
Liver transplantation, *n* (%)	2 (4.4)	0 (0)	1.000
Death due to other causes[c], *n* (%)	2 (4.4)	1 (11)	0.428
Time to resolution (days), median (IQR)	71 (44–152)	61 (44–77)	0.641

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.
[a]If the subject presents at least one of the following: fever, rash, eosinophilia, lymphopenia, or arthralgia. [b]Estimated glomerular filtration rate prior to DILI.
[c]During time of follow-up.

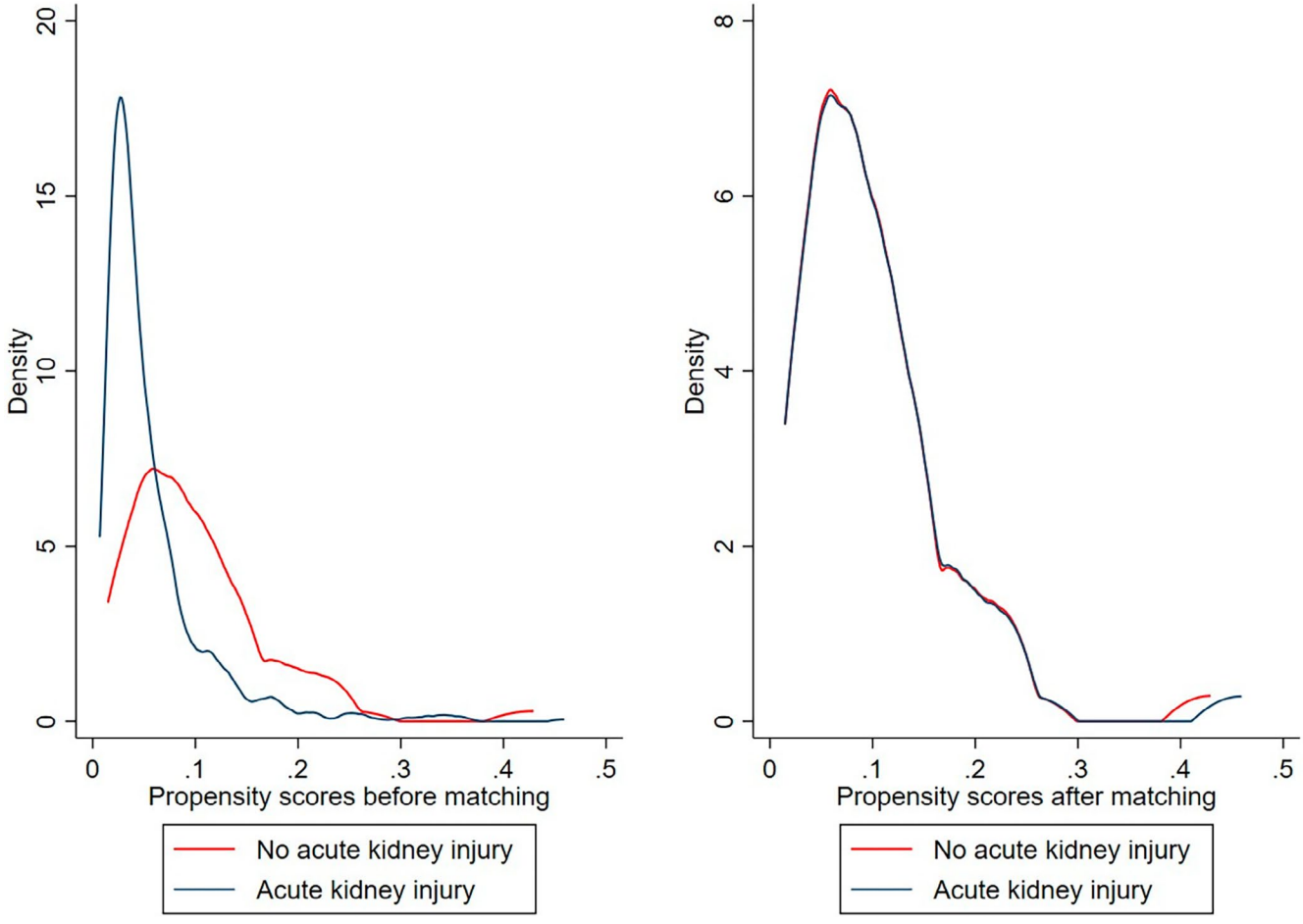


Figure 2 Propensity scores before and after matching.

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

area. Nevertheless, further studies are warranted to understand renal physiopathology and its implications in this specific clinical scenario, as well as the close and complex relationship of the liver–kidney axis.

In view of the prognostic significance of kidney impairment during DILI and the variability of serum creatinine levels according to sex, age, or patient's muscle mass, it is worth considering whether a novel urinary biomarker could play a role in diagnosis and prognosis, justifying its routine use in cases of idiosyncratic DILI. Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid-binding protein (L-FABP), kidney injury molecule-1 (KIM-1), monocyte chemotactic protein-1 (MCP-1), and cystatin C have been identified as indicators of early renal damage.[30] Some of these markers have proven effective in distinguishing between functional and parenchymal kidney damage (acute tubular necrosis) in certain hepatic conditions, for example, decompensated cirrhosis, and have even been shown to have prognostic implications in terms of mortality.[31] Interestingly, in most DILI-AKI patients in our cohort, serum creatinine levels peaked at presentation and improved progressively after drug withdrawal. Only a minority of patients showed further worsening of renal function after DILI onset. This pattern could suggest that, to a certain extent, the renal dysfunction observed in DILI-AKI patients may be related to transient functional hemodynamic alterations rather than sustained renal parenchymal injury. It is possible to speculate that early detection of renal injury using these novel blood or urinary biomarkers would enable us to identify patients at risk of liver and non-liver mortality in the setting of idiosyncratic DILI.

This study shows some strengths, such as the large number of idiosyncratic DILI cases included in the Spanish DILI Registry and the LATINDILI Network, identified using a rigorous and well-established methodology. Also, this is the first study that comprehensively examines liver and kidney injury associated with idiosyncratic hepatotoxicity. However, this study is restricted to the analysis of clinical data, which limits our understanding about the pathophysiology of DILI-AKI. Beside, the retrospective multicentric design precluded systematic nephrological phenotyping and classification of AKI subtypes, for example, prerenal AKI, hepatorenal syndrome, or acute tubular necrosis. Also, the lower incidence of poor outcomes may have imposed certain limitations on our risk estimates. Nonetheless, our findings are encouraging enough to plan further studies using biological samples intended to identify potential markers that unveil the mechanisms of damage in DILI-AKI cases.

In conclusion, more than 5% of patients with idiosyncratic DILI experienced acute kidney impairment. These patients were mostly older men with a greater burden of comorbidities and exhibited a greater mortality rate, although this was restricted to patients with hepatocellular damage. Antibiotics (amoxicillin–clavulanate, antituberculosis drugs), anabolic androgenic steroids, ebrotidine, and ticlopidine were the most common culprit drugs in DILI-AKI patients. Moreover, our findings evidenced that AKI is a risk factor of poor outcome in idiosyncratic DILI and support and contextualize the relationship between acute liver injury and renal dysfunction. Therefore, DILI patients with renal impairment should undergo close monitoring and evaluation for hospitalization.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

FUNDING

This study was funded by grants of Instituto de Salud Carlos III (ISCIII), cofounded by Fondo Europeo de Desarrollo Regional—FEDER, cofounded by European Union (grant number PI24/01205, PID2022-140169OB-C21, FORT23/00013, PI21/01248, PT23/00137, PPRO-CTS649-G-2023, PPRO-CTS1032-G-2023), and by the Agencia Española de Medicamentos y Productos Sanitarios. CIBERehd and Plataforma de Investigación Clinica are funded by ISCIII. JMPB holds a "Acción B-clinical research contract" from Junta de Andalucía (B-0006/2024) and a Juan Rodés contract funded by ISCIII (JR25/00027). JPTO holds a Rio Hortega contract funded by ISCIII (CM23/00126). JSC holds a Juan Rodés contract funded by ISCIII (JR21/00066) and a "Acción B-clinical research contract" from Junta de Andalucía (CI.2–0001–2025). IAA holds a Miguel Servet contract funded by ISCIII (CP25/00033). MGC holds a "Acción A-clinical research contract" from Junta de Andalucía (A1-0025-2025), and held an intensification grant for researchers during 2024 funded by the Spanish Association for the Liver Study (Asociación Española para el Estudio del Hígado, AEEH). Open Access funding provided thanks to the CRUE-CSIC agreement with Wiley. Funding for open access charge: Universidad de Málaga/CBUA.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.M.P.-B., M.I.L., R.J.A., and M.G.C. designed the research; J.M.P.-B., H.N., J.P.T.-O., N.H., F.B., V.N., R.P., and I.A.-A performed the research; J.M.P.-B., H.N., J.P.T.-O., and I.A.-A analyzed the data; J.M.P.-B., H.N., J.P.T.-O., and I.A.-A. wrote the manuscript; J.M.P.-B., H.N., J.P.T.-O., I.M.-C., J.S.-C., A.O.-A., M.R.-D., D.E.dZ.-S., N.H., F.B., V.N., R.P., M.I.L., R.J.A., I.A.-A., and M.G.-C. critically revised the manuscript.

© 2026 The Author(s). *Clinical Pharmacology & Therapeutics* published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

1. European Association for the Study of the Liver. EASL clinical practice guidelines: drug-induced liver injury. *J. Hepatol.* **70**, 1222–1261 (2019).
2. Ostermann, M., Lumlertgul, N., Jeong, R., See, E., Joannidis, M. & James, M. Acute kidney injury. *Lancet* **405**, 241–256 (2025).
3. Cullaro, G., Kanduri, S.R. & Velez, J.C.Q. Acute kidney injury in patients with liver disease. *Clin. J. Am. Soc. Nephrol.* **17**, 1674–1684 (2022).
4. Patidar, K.R. *et al*. Incidence and outcomes of acute kidney injury including hepatorenal syndrome in hospitalized patients with cirrhosis in the US. *J. Hepatol.* **79**, 1408–1417 (2023).
5. Chen, Y.G. *et al*. Risk of acute kidney injury and long-term outcome in patients with acetaminophen intoxication: a nationwide population-based retrospective cohort study. *Medicine* **94**, e2040 (2015).
6. Stephens, C. *et al*. Comprehensive analysis and insights gained from long-term experience of the Spanish DILI registry. *J. Hepatol.* **75**, 86–97 (2021).
7. Bessone, F. *et al*. Drug-induced liver injury in Latin America: 10-year experience of the Latin American DILI (LATINDILI) network. *Clin. Gastroenterol. Hepatol.* **23**, 89–102 (2025).
8. Danan, G. & Benichou, C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of international consensus meetings: application to drug-induced liver injuries. *J. Clin. Epidemiol.* **46**, 1323–1330 (1993).
9. Aithal, G.P. *et al*. Case definition and phenotype standardization in drug-induced liver injury. *Clin. Pharmacol. Ther.* **89**, 806–815 (2011).
10. Robles-Diaz, M., Lucena, M.I., 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* **147**, 109–118 (2014).
11. Charlson, M., Szatrowski, T.P., Peterson, J. & Gold, J. Validation of a combined comorbidity index. *J. Clin. Epidemiol.* **47**, 1245–1251 (1994).
12. Khwaja, A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin. Pract.* **120**, c179–c184 (2012).
13. Kidney Disease: Improving global outcomes CKDWG. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* **105**, S117–S314 (2024).
14. Inker, L.A. *et al*. New creatinine- and cystatin C-based equations to estimate GFR without race. *N. Engl. J. Med.* **385**, 1737–1749 (2021).
15. Austin, P.C. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm. Stat.* **10**, 150–161 (2011).
16. Andrade, R.J. *et al*. Acute liver injury associated with the use of ebrotidine, a new H2-receptor antagonist. *J. Hepatol.* **31**, 641–646 (1999).
17. Chalasani, N., Bonkovsky, H.L., Fontana, R. *et al*. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology* **148**, 1340–1352 (2015).
18. Suk, K.T. *et al*. A prospective nationwide study of drug-induced liver injury in Korea. *Am. J. Gastroenterol.* **107**, 1380–1387 (2012).
19. Aiso, M. *et al*. Analysis of 307 cases with drug-induced liver injury between 2010 and 2018 in Japan. *Hepatol. Res.* **49**, 105–110 (2019).
20. Devarbhavi, H. *et al*. The Indian network of drug-induced liver injury: etiology, clinical features, outcome and prognostic markers in 1288 patients. *J. Clin. Exp. Hepatol.* **11**, 288–298 (2021).
21. Yamamoto, T. & Isaka, Y. Pathological mechanisms of kidney disease in ageing. *Nat. Rev. Nephrol.* **20**, 603–615 (2024).
22. Iorga, A., Dara, L. & Kaplowitz, N. Drug-induced liver injury: cascade of events leading to cell death, apoptosis or necrosis. *Int. J. Mol. Sci.* **18**, 1018 (2017).
23. Wang, Y., Zhang, H., Chen, Q. *et al*. TNF-alpha/HMGB1 inflammation signalling pathway regulates pyroptosis during liver failure and acute kidney injury. *Cell Prolif.* **53**, e12829 (2020).
24. Bräsen, J.H. *et al*. Cholemic nephropathy causes acute kidney injury and is accompanied by loss of aquaporin 2 in collecting ducts. *Hepatology* **69**, 2107–2119 (2019).
25. Lucena, M.I., Andrade, R.J., Cabello, M.R., Hidalgo, R., Gonzalez-Correa, J.A. & Sanchez de la Cuesta, F. Aminoglycoside-associated nephrotoxicity in extrahepatic obstructive jaundice. *J. Hepatol.* **22**, 189–196 (1995).
26. Robles-Diaz, M. *et al*. Distinct phenotype of hepatotoxicity associated with illicit use of anabolic androgenic steroids. *Aliment. Pharmacol. Ther.* **41**, 116–125 (2015).
27. Diaz, F.C., Saez-Gonzalez, E., Benlloch, S. *et al*. Albumin dialysis with MARS for the treatment of anabolic steroid-induced cholestasis. *Ann. Hepatol.* **15**, 939–943 (2016).
28. Jiang, F. *et al*. Monocyte-to-lymphocyte ratio: a potential novel predictor for acute kidney injury in the intensive care unit. *Ren. Fail.* **44**, 1004–1011 (2022).
29. Daly, A.K. Genetic and genomic approaches to the study of drug-induced liver injury. *Liver Int.* **45**, e16191 (2025).
30. Tajima, S., Yamamoto, N. & Masuda, S. Clinical prospects of biomarkers for the early detection and/or prediction of organ injury associated with pharmacotherapy. *Biochem. Pharmacol.* **170**, 113664 (2019).
31. Allegretti, A.S. *et al*. Urinary NGAL as a diagnostic and prognostic marker for acute kidney injury in cirrhosis: a prospective study. *Clin. Transl. Gastroenterol.* **12**, e00359 (2021).

15326535, 0, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70452 by Capes, Wiley Online Library on [19/08/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License