Received: 29 September 2022 | First decision: 29 October 2022 | Accepted: 11 December 2022

DOI: 10.1111/apt.17373

AP&T Alimentary Pharmacology & Therapeutics WILEY

Potential benefit and lack of serious risk from corticosteroids in drug-induced liver injury: An international, multicentre, propensity score-matched analysis

Hao Niu[1,2,3] | Jiayi Ma[4] | Inmaculada Medina-Caliz[1] | Mercedes Robles-Diaz[1,2] | Elvira Bonilla-Toyos[1,3] | Marwan Ghabril[4] | Mª Isabel Lucena[1,2,3] | Ismael Alvarez-Alvarez[1,2,3] | Raul J. Andrade[1,2]

[1]Servicios de Aparato Digestivo y Farmacología Clínica, Hospital Universitario Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina-IBIMA Plataforma BIONAND, Universidad de Málaga, Málaga, Spain

[2]Biomedical Research Network Center for Hepatic and Digestive Diseases (CIBERehd), Carlos III Health Institute, Madrid, Spain

[3]Platform for Clinical Research and Clinical Trials IBIMA, Plataforma ISCIII de Investigación Clínica, Madrid, Spain

[4]Division of Gastroenterology/Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence
Mª Isabel Lucena, Departamento de Farmacología, Facultad de Medicina, Universidad de Málaga, Boulevard Louis Pasteur 32, 29010, Málaga, Spain.
Email: lucena@uma.es

Funding information
Consejería de Salud, Junta de Andalucía, Grant/Award Number: PI-0310-2018 and POSTDOC_21_00780; European Cooperation in Science and Technology, Grant/Award Number: CA17112; Instituto de Salud Carlos III, Grant/Award Number: CD20/00083, PI18/00901, PI19/00883, PI21/01248 and PT20/000127; Agencia Española de Medicamentos y Productos Sanitarios

Summary

Background: The use of corticosteroids to treat patients with idiosyncratic drug-induced liver injury (DILI) relies on empirical clinical decisions.

Aim: To investigate the relationship between corticosteroids and risk of acute liver failure (ALF) in patients with DILI and to assess if corticosteroid therapy was associated with improved outcomes in DILI patients.

Methods: We analysed *bona fide* idiosyncratic DILI cases from the Spanish DILI Registry and Indiana University School of Medicine. Patients treated with corticosteroids were compared to those who did not receive any treatment. Nearest neighbour propensity score matching analyses were conducted.

Results: We enrolled 724 patients, 106 under corticosteroid therapy, in whom there was over-representation of more severe injury and autoimmune features, and 618 who did not receive any treatment. In an analysis of 80 pairs of propensity score-matched patients, corticosteroid administration was not associated with an increased risk of developing ALF (odds ratio = 0.65; 95% confidence interval [CI]: 0.18–2.40; $p = 0.518$). Furthermore, in an additional analysis, a Cox regression model that included 41 propensity score-matched pairs showed that patients receiving corticosteroids had a significantly higher normalisation rate of liver enzymes than untreated patients (hazard ratio [HR] = 1.84; 95% CI: 1.02–3.32; $p = 0.043$), particularly in patients with serious injury who did not resolve within 30 days (HR = 2.79; 95% CI: 1.20–6.50; $p = 0.018$).

Conclusion: Corticosteroid therapy did not worsen outcome in DILI patients. Indeed, corticosteroid administration was associated with a greater rate of normalisation of liver enzymes in patients with serious DILI.

Ismael Alvarez-Alvarez and Raul J Andrade share senior authorship.

The Handling Editor for this article was Professor Gideon Hirschfield, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Idiosyncratic drug-induced liver injury (DILI) is an unexpected and potentially severe adverse drug reaction to the use of conventional medications, herbal products or dietary supplements that jeopardises patient safety. The majority of DILI episodes recover spontaneously, but some may present with or progress to acute liver failure (ALF) that may require liver transplantation or lead to death.[1] Indeed, idiosyncratic DILI accounted for almost 11% of ALF in adults in the United States.[2]

The hallmark of management of DILI consists of a high level of suspicion and immediate discontinuation of the offending drug to prevent persistent damage, as well as supportive treatment if needed. Whereas majority of patients recover spontaneously, a small fraction continues to worsen despite discontinuation of the offending drug. Currently, there is no therapy with proven efficacy for these more serious cases of DILI.[3,4]

Corticosteroids are empirically prescribed, particularly to patients with immunoalergic features, although no properly designed clinical trials have established their safety and efficacy. The administration of corticosteroids to treat severe DILI remains controversial due to conflicting assessment of their risk–benefit balance. In a retrospective study including 15 patients, Wree et al[5] reported that patients treated with a combination of prednisone and ursodeoxycholic acid achieved a rapid reduction in bilirubin, liver enzymes and International Normalised Ratio (INR) levels. Likewise, in a retrospective study with 203 patients, a beneficial effect of corticosteroid therapy by decreasing mortality rate and shortening time to recovery in severe DILI patients was described.[6] Additionally, a positive response to treatment with budesonide, alone or in combination with ursodeoxycholic acid, was recently reported in two DILI cases without autoimmune features.[7] On the other hand, another retrospective study reported that corticosteroid administration was not associated with improvements in survival rate in 131 patients with DILI-related ALF. In fact, a deleterious effect was described in those patients with worse condition.[8] Moreover, in a cohort of 90 severe DILI patients, prednisone administration was not beneficial in reducing DILI severity, and high doses of corticosteroids (>40 mg/day) may have been detrimental.[9]

More recently, the role of corticosteroid therapy has been described in prospective DILI registries. Preliminary results from the Drug-Induced Liver Injury Network (DILIN) in the USA showed that patients who received systemic corticosteroids had higher mortality rates than those who were not treated with steroids.[10] In a recent analysis from the Spanish DILI Registry, patients who received corticosteroids had more serious liver injury, and they experienced a higher incidence of ALF, suggesting that patients with DILI who received corticosteroids may be exposed to a higher risk of ALF compared to those who did not receive corticosteroids.[11] However, the characteristics of DILI between these two groups were significantly different and were not matched.

In observational studies, treatment selection might be influenced by patient's characteristics. The propensity score was defined as the probability of treatment assignment conditional on observed baseline covariates. Thus, propensity scores matching consists of forming matched sets of treated and untreated patients who share similar propensity scores to remove the effect of confounding when estimating the effects of treatment on outcomes.[12,13]

Therefore, we examined the relationship between corticosteroid therapy and the risk of ALF in patients with DILI in a rigorous propensity score-matched analysis. A secondary objective of this analysis was to assess if corticosteroid therapy was associated with better outcomes in patients with DILI.

2 | MATERIALS AND METHODS

2.1 | Study population

This is an international collaborative observational study in which data were gathered from two prospective DILI registries. Information from 979 DILI cases enrolled from 1994 to November 2020 in the Spanish DILI Registry, a network of Spanish clinical centres, was collected. Details of the functioning of the Spanish DILI registry have been described elsewhere.[11] In addition, data from 195 DILI cases from the Indiana University School of Medicine, enrolled in the US DILIN between 2003 and 2018, were retrieved. The aims and design of the DILIN registry have been previously described.[14] Registry acquired data was supplemented by chart review to describe clinical phenotypes and outcomes, including corticosteroid therapy as described below. Study protocols were approved by the Institutional Review Board (IRB) of the Hospital Universitario Virgen de la Victoria and Indiana University. All subjects included in the study gave their informed consent.

2.2 | Case definition

In the Spanish DILI Registry, DILI was initially defined according to the criteria by the Council for International Organisations of Medical Sciences (CIOMS),[15] and later adapted to those criteria set in 2011[16]: alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2 times the ULN, or ALT ≥3 times the ULN and a simultaneous elevation of twofold the ULN of total bilirubin (TBL). DILI cases enrolled in the Indiana University cohort fulfilled the following criteria: elevations of ALT or aspartate aminotransferase (AST) >5 times the ULN, or ALP > 2 times ULN. Patients who developed jaundice (serum bilirubin ≥2.5 mg/dl) or coagulopathy (INR > 1.5), with any elevations in ALT, AST or ALP, were eligible.[14]

Case ascertainment in the Spanish DILI Registry was performed by three independent experts. Only cases who were scored at least "possible" when applying the Roussel Uclaf Causality Assessment Method (RUCAM) were included. Likewise, in Indiana University, the causal relationship between the suspected causative agent and liver injury was evaluated by three causality committee members. Those cases who were classified at least "possible" (25%–49% likelihood)

were included.[11,14] Of note, over 85% of cases were scored as "Probable" or "Definite".

The pattern of liver injury was classified using the R ratio, that is, (ALT/ULN) ÷ (ALP/ULN), into hepatocellular (R ≥ 5), cholestatic (R ≤ 2), or mixed injury (R > 2 and R < 5).[16] Severity of liver injury was graded according to the criteria defined by Aithal et al[16] into mild (TBL < 2 times ULN), moderate (TBL ≥ 2 times ULN), severe (TBL ≥ 2 times ULN, and either INR ≥ 1.5, ascites and/or encephalopathy or other organ failures due to DILI), or fatal or transplantation (death or transplantation due to DILI). The Hy's law (R ≥ 5 and TBL > 2 times ULN), the nR-based Hy's law (nR: ALT/ULN or AST/ULN, whichever highest ÷ ALP/ULN),[17] and the Model for End-stage Liver Disease (MELD) score[18] were calculated. Drug-induced autoimmune-like hepatitis (DI-AILH) was defined as a liver injury with laboratory and/or histological evidence of autoimmunity,[19] plus a comprehensive review of each case conducted by independent hepatologists. The Charlson Comorbidity Index (CCI) was calculated as a measure of the comorbidity burden.[20]

Corticosteroid treatment was defined as receiving corticosteroids, either alone or in combination with other treatments, for treating DILI. Decision to administer corticosteroids relied on the patient's attending physician. Timing, route of administration and dosing of corticosteroids were at the discretion of each responsible physician. Patients who received corticosteroids prior to the DILI episode for any reason or after DILI for non-liver-related indications were excluded. In addition, only patients who did not receive any treatment for DILI, as specified in their clinical history, were included and classified as the no treatment control group.

2.3 | Outcome

To study the association between corticosteroid use and risk of ALF, the primary outcome of the study was defined as liver-related death or liver transplantation within a maximum of 6 months since DILI onset.[17,21] For the secondary objective of this study, to assess if corticosteroid therapy was associated with better outcomes in patients with DILI, the outcome was defined as the normalisation of liver profile (ALT, AST, ALP and TBL below the ULN).

2.4 | Statistical analysis

Demographic and clinical data for subjects included in the study were examined using descriptive statistics. For quantitative data, mean and standard deviation (SD), or median and interquartile range (IQR) were calculated, while qualitative variables were presented using frequency distributions. Differences between groups were assessed with the Student's *t* test or Mann–Whitney *U* test, as appropriate, while qualitative variables were compared using the chi-square test or Fisher's exact test, as appropriate. Percentages were calculated based on available data. Patients with missing data were excluded from analyses.

For each analysis, independent propensity scores (PS) to determine the predicted probability of receiving corticosteroids to treat DILI were estimated using a multivariable logistic regression model, in which treatment status (corticosteroid therapy vs. no treatment) was regressed on observed baseline characteristics. Covariates were selected on the basis of sizeable differences in characteristics that could potentially affect the decision to use corticosteroids. In the primary propensity score-matched analysis to examine the relationship between corticosteroid therapy and risk of ALF, we matched on the following potential confounders: sex, jaundice, AST and TBL levels at DILI recognition, positive autoantibody titres and MELD score. In the ancillary propensity score-matched analysis to evaluate the effect of corticosteroid therapy on the normalisation of liver enzymes, after excluding those patients lost to follow-up, PS were re-estimated and patients were matched by jaundice, AST, ALP and TBL levels at DILI recognition, positive autoantibody titres and MELD score. A nearest neighbour one-to-one PS matching without replacement, using a calliper width equal to 0.2 of the standard deviation of the logit of the propensity score,[22] was conducted to reduce the influence of potential confounding factors. Balance between treatment groups was evaluated by standardised differences of all baseline covariates.

In the primary propensity score-matched analysis, within the matched sample, logistic regression models were fitted to evaluate the effect of corticosteroids on the risk of ALF. In the secondary propensity score-matched analysis to evaluate the effect of corticosteroid therapy on the normalisation of liver enzymes, Cox regression models were fitted with date of normalisation or date of ALF as exit time. Hazards proportionality assumption was assessed using the test based on the Schoenfeld residuals. Nelson–Aalen curves were used to depict the cumulative hazard function for normalisation of liver enzymes and the log-rank test to test for differences between groups. Unconditional analyses were used based on the rationale that the matching process has been considered sufficient, and the matched groups were considered as a whole in the analyses rather than as individual matched pairs.[23] Robust variance estimators were used in all regression models.

Statistical analyses were performed using STATA version 17 (Stata Corporation) and a two-sided *p*-value lower than 0.05 was deemed as statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of the study population

A total of 724 eligible subjects were included in the present study (547 from the Spanish DILI Registry and 177 from Indiana University) (Figure S1). Among them, 106 cases were under corticosteroid therapy, of whom four were concomitantly treated with ursodeoxycholic acid, and one also needed from the Molecular Adsorbent Recirculating System (MARS). The remaining 618 patients did not receive any treatment.

Baseline characteristics of the whole study population and each cohort separately are shown in Table S1. Half of the cohort were women, and mean age of patients was 53 years, being Indiana University patients younger than Spanish cases (50 ± 16 vs. 54 ± 18; $p = 0.017$). Hepatocellular damage was more common in the Spanish DILI Registry, 63% compared to 51% in the Indiana University cohort, while cholestatic injury was more frequent (27%) in Indiana cases compared to Spanish cases (19%) ($p = 0.012$). Most of the patients developed jaundice (70%), and 53% were hospitalised.

One-third of the patients in the whole cohort had positive autoantibody titres, and 6.4% of patients were diagnosed as DI-AILH cases. Indiana University patients had a significantly higher prevalence of positive autoantibody titres compared to Spanish patients (52% vs. 26%; $p < 0.001$) and were more likely to be diagnosed as DI-AILH cases (17% vs. 3.5%, respectively; $p < 0.001$). Conversely, treatment characteristics were similar across cohorts. Overall, 15% of patients were treated with corticosteroids (mainly prednisone). Data on the initial dose and duration of corticosteroids administration was available in 40% of patients. The median initial dose of corticosteroids was 40 mg per day, and the median duration of treatment was 59 days.

Most of the cases (60%) had a moderate damage, while 7.6% of patients developed a severe liver injury, and 2.9% of the whole cohort died or underwent a liver transplant. Liver-related death and liver transplantation rates were comparable between the two cohorts ($p = 1.000$ and $p = 0.097$, respectively).

3.2 | Baseline characteristics of treatment groups

A total of 106 patients were treated with corticosteroids and 618 did not receive any treatment (Table 1). Patients from both groups showed a similar age distribution ($p = 0.306$), whilst females were more likely to receive corticosteroid treatment (64%, compared to 48% who did not; $p = 0.002$). The pattern of liver injury was similar in both groups, being predominantly hepatocellular in the corticosteroid and the untreated group (64% and 59%, respectively; $p = 0.493$). Interestingly, the vast majority of patients who received corticosteroids had jaundice (85%) and were hospitalised (80%), compared to the 68% and 49% who were not treated, respectively ($p < 0.001$ for both).

According to World Health Organisation Anatomic Therapeutic Classification (ATC), the most frequent groups of drugs which caused DILI in either patients who were treated with corticosteroids or those who did not receive any treatment were anti-infectives (systemic administration) (42% and 41%, respectively), cardiovascular (13% and 12%, respectively), nervous system (8.5% and 9.7%, respectively), herbal and dietary supplements, including anabolic androgenic steroids (8.5% and 9.1%, respectively) and musculoskeletal system agents (9.4% and 8.7%, respectively) (Table S2). No differences were observed in ATC groups ($p = 0.948$), in relation to the duration of therapy or the time to DILI recognition (latency) ($p = 0.944$ and $p = 0.839$, respectively).

Compared to those who were not treated, patients receiving corticosteroid therapy presented with higher median AST and TBL levels ($p = 0.010$ and $p < 0.001$, respectively). Furthermore, as it might be expected, patients with positive autoantibody titres and those diagnosed as DI-AILH cases were more likely to be treated with corticosteroids. Characteristics of DI-AILH cases are presented in Table S3.

Also, patients who received corticosteroids developed more frequently severe liver injury (19%, compared to 5.7% in untreated patients), and fatal injury (6.6% vs. 2.3%, respectively; $p < 0.001$). Moreover, most of patients who fulfilled either the classic or the nR-based Hy's law, as well as those who had a higher MELD score, were more likely to be treated with corticosteroids. Overall, liver-related mortality rate was significantly higher ($p = 0.020$) in patients who received corticosteroids (5.7%) compared to untreated cases (1.6%). However, liver transplantation rates were similar across treatment groups (0.9% in patients treated vs. 0.7% in those with no treatment; $p = 0.548$). In addition, time until resolution of DILI was significantly longer in patients under corticosteroid therapy than in those with no treatment (median 147 and 103 days, respectively; $p = 0.039$).

3.3 | Corticosteroid therapy and risk of ALF

The incidence of ALF was higher among patients treated with corticosteroids compared to those untreated (6.6% vs. 2.3%, respectively). Before PS matching, a univariate analysis showed that corticosteroids administration was associated with an increased risk of developing ALF (odds ratio [OR] = 3.05; 95% confidence interval [CI]: 1.20–7.75; $p = 0.019$).

After matching by propensity scores based on abovementioned potential confounding factors, 80 pairs were matched. Except for hospitalisation (standardised bias = 0.380) and DI-AILH diagnosis (standardised bias = 0.641), treatment groups were well-balanced after PS matching (Table 2). Overall, these two groups were well-balanced, that is, had similar probabilities of being treated with corticosteroids (Figure 1).

The logistic regression model built to evaluate the effect of corticosteroid therapy on the incidence of ALF indicated that corticosteroid administration was not associated with a higher risk of developing ALF (OR = 0.65; 95% CI: 0.18–2.40; $p = 0.518$).

3.4 | Corticosteroid therapy and normalisation rate of liver enzymes

The efficacy of corticosteroid therapy in the normalisation of liver enzymes was evaluated through an additional PS matching analysis. A total of 41 pairs of DILI patients were matched in this ancillary analysis. Except for predominance of female sex (standardised bias = 0.348) and prevalence of DI-AILH (standardised bias = 0.823), higher in the corticosteroid group, there were no differences in clinical characteristics between the two groups (Table 3).

TABLE 1 Baseline demographics, clinical characteristics and outcome of unmatched patients with idiosyncratic drug-induced liver injury treated with corticosteroids and with no treatment

	Corticosteroids treatment ($n = 106$)	No treatment ($n = 618$)	Standardised bias	p value
Age (years), mean ± SD	55 ± 19	53 ± 18	0.106	0.306
Female, *n* (%)	68 (64)	297 (48)	0.328	0.002
Body mass index (kg/m^2), mean ± SD	26 ± 5.4	26 ± 4.7	−0.023	0.842
Diabetes, *n* (%)	11 (10)	76 (12)	−0.060	0.574
Hypertension, *n* (%)	27 (25)	159 (26)	−0.006	0.955
Charlson comorbidity index, median (IQR)	0 (0–1)	0 (0–1)	0.018	0.862
Type of liver injury, *n* (%)				
Hepatocellular	65 (64)	350 (59)	−0.127	0.493
Cholestatic	21 (21)	123 (21)		
Mixed	15 (15)	116 (20)		
Jaundice, *n* (%)	90 (85)	417 (68)	0.408	<0.001
Hospitalisation, *n* (%)	84 (80)	300 (49)	0.690	<0.001
Rash, *n* (%)	12 (12)	48 (8.3)	0.133	0.245
Eosinophilia, *n* (%)	28 (28)	116 (19)	0.207	0.045
Most frequent culprit drugs, *n* (%)	Amoxicillin-clavulanate 16 (15) Nitrofurantoin 9 (8.5) Anti-TBC drugs 5 (4.7)	Amoxicillin-clavulanate 135 (22) HDS 19 (3.1) Atorvastatin, flutamide, isoniazid 15 (2.4)		
Duration of therapy (days), median (IQR)	27 (8–78)	29 (8–72)	0.195	0.944
Time to DILI onset (days), median (IQR)	29 (8–75)	30 (11–67)	0.165	0.839
Liver parameters, median (IQR)				
Aspartate aminotransferase (AST), IU/L	439 (157–1055)	241 (112–758)	0.138	0.010
Alanine aminotransferase (ALT), IU/L	643 (224–1232)	438 (210–1019)	0.073	0.129
Alkaline phosphatase (ALP), IU/L	253 (167–406)	237 (146–377)	0.153	0.242
Total bilirubin, mg/dl	8.2 (2.9–13)	4.6 (1.3–9.6)	0.395	<0.001
Positive autoantibodies titres, *n* (%)	43 (44)	162 (31)	0.281	0.009
Drug-induced autoimmune-like hepatitis, *n* (%)	25 (24)	19 (3.3)	0.628	<0.001
Severity, *n* (%)				
Mild	16 (15)	197 (32)	0.547	<0.001
Moderate	63 (59)	372 (60)		
Severe	20 (19)	35 (5.7)		
Fatal/liver transplantation	7 (6.6)	14 (2.3)		
Hy's law, *n* (%)	53 (54)	200 (35)	0.385	<0.001
nR-based Hy's law, *n* (%)	55 (56)	204 (35)	0.426	<0.001
MELD score, mean ± SD	18 ± 6.7	15 ± 6.5	0.507	<0.001
Acute liver failure, *n* (%)	7 (6.6)	14 (2.3)	0.211	0.024
Liver-related death, *n* (%)	6 (5.7)	10 (1.6)	0.216	0.020
Liver transplantation, *n* (%)	1 (0.9)	4 (0.7)	0.033	0.548
Time to resolution (days), median (IQR)	147 (81–218)	103 (54–203)	0.144	0.039

Abbreviations: SD, standard deviation; IQR, interquartile range; ULN, upper limit of normal; DILI, drug-induced liver injury; HDS, herbal and dietary supplements; Anti-TBC drugs, rifampicin, isoniazid and pyrazinamide; MELD, Model for End-stage Liver Disease.

TABLE 2 Baseline demographics, clinical characteristics and outcome of 160 matched patients with idiosyncratic drug-induced liver injury by treatment groups

	Corticosteroids treatment ($n = 80$)	No treatment ($n = 80$)	Standardised bias	p value
Age (years), mean ± SD	55 ± 18	55 ± 18	0.011	0.945
Female, *n* (%)	53 (66)	53 (66)	0.000	1.000
Body mass index (kg/m^2), mean ± SD	27 ± 5.9	27 ± 5.4	−0.014	0.944
Diabetes, *n* (%)	8 (10)	10 (13)	−0.079	0.803
Hypertension, *n* (%)	22 (28)	22 (28)	0.000	1.000
Charlson comorbidity index, median (IQR)	0 (0–1)	0 (0–1)	−0.213	0.295
Type of liver injury, *n* (%)				
Hepatocellular	52 (68)	46 (58)	−0.181	0.485
Cholestatic	13 (17)	17 (22)		
Mixed	12 (16)	16 (20)		
Jaundice, *n* (%)	67 (84)	67 (84)	0.000	1.000
Hospitalisation, *n* (%)	64 (81)	51 (64)	0.380	0.015
Rash, *n* (%)	11 (15)	8 (10)	0.151	0.391
Eosinophilia, *n* (%)	23 (30)	16 (21)	0.220	0.180
Duration of therapy (days), median (IQR)	28 (9–94)	30 (9–76)	0.327	0.926
Time to DILI onset (days), median (IQR)	29 (11–86)	35 (16–71)	0.270	0.681
Liver parameters, median (IQR)				
Aspartate aminotransferase (AST), IU/L	592 (161–1030)	271 (130–1192)	−0.005	0.582
Alanine aminotransferase (ALT), IU/L	648 (241–1105)	461 (204–1318)	−0.026	0.613
Alkaline phosphatase (ALP), IU/L	243 (171–346)	240 (160–345)	0.099	0.890
Total bilirubin, mg/dl	8.9 (3.1–13)	9.7 (4.5–14)	−0.046	0.478
Positive autoantibodies titres, *n* (%)	38 (48)	35 (44)	0.078	0.634
Drug-induced autoimmune-like hepatitis, *n* (%)	23 (29)	6 (8.1)	0.641	0.001
Severity, *n* (%)				
Mild	11 (14)	8 (10)	0.035	0.143
Moderate	49 (61)	59 (74)		
Severe	16 (20)	7 (8.8)		
Fatal/liver transplantation	4 (5.0)	6 (7.5)		
Hy's law, *n* (%)	44 (57)	41 (52)	0.107	0.511
nR-based Hy's law, *n* (%)	45 (58)	41 (51)	0.147	0.365
MELD score, mean ± SD	18 ± 6.6	19 ± 7.1	−0.054	0.797
Acute liver failure, *n* (%)	4 (5.0)	6 (7.5)	−0.122	0.746
Liver-related death, *n* (%)	3 (3.8)	5 (6.3)	−0.134	0.719
Liver transplantation, *n* (%)	1 (1.3)	1 (1.3)	0.000	1.000
Time to resolution (days), median (IQR)	170 (81–247)	155 (69–273)	−0.347	0.732

Abbreviations: SD, standard deviation; IQR, interquartile range; ULN, upper limit of normal; DILI, drug-induced liver injury; MELD, Model for End-stage Liver Disease.

The Cox regression model, which fulfilled the proportional hazards assumption ($p = 0.704$), showed that patients with DILI undergoing corticosteroid treatment had a significantly increased normalisation rate compared to those patients who were not treated (hazard ratio [HR] = 1.84; 95% CI: 1.02–3.32; $p = 0.043$) (Figure 2, Table S4). Indeed, benefits of corticosteroid use were more evident in the subgroup of patients with a serious injury who fulfilled the nR-based Hy's law and did not resolve within 30 days (HR = 2.79; 95% CI 1.20–6.50; $p = 0.018$) (Figure 3, Table S5).

4 | DISCUSSION

In this international collaborative study that encompasses more than 700 well-vetted DILI cases enrolled in two prospective

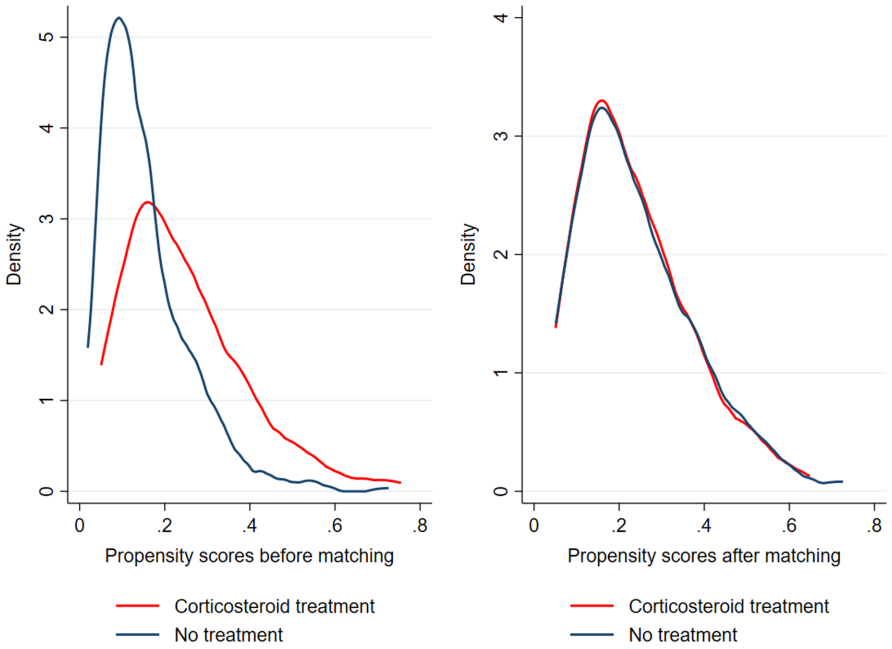

FIGURE 1 Propensity scores before and after matching

registries, and using methodologically rigorous propensity score analyses, we provide robust evidence that corticosteroid use was not only not harmful, but that DILI patients undergoing corticosteroid therapy exhibited a benefit in terms of higher normalisation rate of liver enzymes compared with untreated patients. Indeed, the benefit was more evident in severe cases who fulfilled the nR-based Hy's law and had no biochemical resolution within 30 days. Although MELD has been shown to have the highest predictive value for mortality after DILI,[21] given the limited number of patients with MELD scores over 25 points, an ancillary analysis to study the clinical benefit of corticosteroids in this subgroup could not be conducted. Nevertheless, the nR-based Hy's law has also been validated for predicting serious outcome in DILI patients.[17,21] Initiation of corticosteroids therapy, dosage and tapering were at discretion of the attending physician at local sites. Our analysis shows that patients who received corticosteroids had more severe DILI at presentation and/or features suggesting autoimmune hepatitis-like DILI. Unfortunately, the limited number of DI-AILH patients in the untreated group precluded our ability to perform PS-matched analyses to evaluate if corticosteroid treated patients with DILI and autoimmune phenotype would have a different outcome compared with untreated ones.

The rationale for using corticosteroids in the treatment of DILI relies on the role of the immune system in the pathophysiology of the condition.[24] The reactive metabolites, presumably produced in many cases of DILI, can bind to cellular proteins, forming drug-protein adducts, which would act as immunogenic haptens that are presented by the major histocompatibility complex, activating the adaptative immune response. In addition, reactive metabolites induction of oxidative stress is associated with the release of damage-associated molecular patterns, that trigger the innate immune response.[1] Corticosteroids have anti-inflammatory and immunosuppressive properties, and their effects are exerted by multiple pathways, that is, by upregulating the transcription of anti-inflammatory genes, downregulating the transcription of genes related to the production of enzymes involved in the initiation or maintenance of the host inflammatory response, and by blocking the activation of T cells.[25]

Intriguingly, in an unadjusted analysis, patients who were treated with corticosteroids showed threefold odds of developing ALF compared with non-treated patients. It can be hypothesized that these preliminary results were confounded by a reverse causality bias.[26] This means that exposure to corticosteroids was not the cause of worsening the clinical condition of DILI patients and the subsequent development of ALF. Instead, patients with pre-existing severe liver injury or rapidly deteriorating condition, who presumably would have evolved to ALF independently of the therapeutic option chosen, were more likely to be treated with corticosteroids.

Indeed, differences between treatment groups in prognostic factors that predict a fatal outcome were observed. For instance, ALF has been described to have a higher incidence in women.[27,28] Furthermore, increased bilirubin levels have been described in nationwide studies as an independent prognostic marker of mortality in DILI patients,[29] while the use of AST over ALT has gained relevance in the prediction of ALF in the past years.[17] Also, the MELD score has been reported as one of the best-performing predictors of mortality in DILI patients.[21] Thus, when reverse causality bias was controlled by matching DILI patients by these confounders, it was evident that corticosteroid therapy does not pose an additional risk in terms of aggravating the clinical condition towards ALF.

The benefit–risk ratio of corticosteroid administration remains controversial due to the scarcity of high-quality evidence. Despite the uncontrolled differences in clinical practice, the proportion of patients treated in both cohorts was similar, probably due to the

TABLE 3 Baseline demographics, clinical characteristics and outcome of 82 matched patients with idiosyncratic drug-induced liver injury by treatment groups

	Corticosteroids treatment ($n = 41$)	No treatment ($n = 41$)	Standardised bias	p value
Age (years), mean ± SD	55 ± 19	54 ± 16	0.091	0.674
Female, *n* (%)	29 (71)	22 (54)	0.348	0.171
Body mass index (kg/m^2), mean ± SD	27 ± 5.3	26 ± 4.8	0.169	0.485
Diabetes, *n* (%)	2 (4.9)	5 (12)	−0.230	0.432
Hypertension, *n* (%)	9 (22)	8 (20)	0.056	1.000
Charlson comorbidity index, median (IQR)	0 (0–1)	0 (0–1)	−0.216	0.265
Type of liver injury, *n* (%)				
Hepatocellular	28 (68)	25 (61)	−0.095	0.725
Cholestatic	5 (12)	8 (20)		
Mixed	8 (20)	8 (20)		
Jaundice, *n* (%)	34 (83)	35 (85)	−0.059	1.000
Hospitalisation, *n* (%)	31 (78)	30 (73)	0.095	0.798
Rash, *n* (%)	6 (16)	4 (10)	0.182	0.517
Eosinophilia, *n* (%)	14 (34)	10 (24)	0.229	0.467
Duration of therapy (days), median (IQR)	27 (9–94)	10 (7–76)	0.161	0.143
Time to DILI onset (days), median (IQR)	27 (19–86)	27 (8–47)	0.171	0.245
Liver parameters, median (IQR)				
Aspartate aminotransferase (AST), IU/L	695 (228–1174)	353 (157–1122)	0.037	0.538
Alanine aminotransferase (ALT), IU/L	680 (350–1111)	751 (220–1130)	−0.054	0.991
Alkaline phosphatase (ALP), IU/L	251 (151–344)	200 (134–426)	0.058	0.402
Total bilirubin, mg/dl	9.0 (3.3–13)	9.1 (4.7–12)	−0.074	0.969
Positive autoantibodies titres, *n* (%)	26 (63)	24 (59)	0.101	0.651
Drug-induced autoimmune-like hepatitis, *n* (%)	15 (38)	4 (11)	0.823	0.008
Severity, *n* (%)				
Mild	7 (17)	6 (15)	0.103	0.144
Moderate	24 (59)	30 (73)		
Severe	7 (17)	1 (2.4)		
Fatal/liver transplantation	3 (7.3)	4 (9.8)		
Hy's law, *n* (%)	23 (56)	19 (46)	0.199	0.377
nR-based Hy's law, *n* (%)	24 (59)	20 (49)	0.200	0.376
MELD score, mean ± SD	18 ± 6.2	18 ± 5.9	−0.081	0.588
Acute liver failure, *n* (%)	3 (7.3)	4 (9.8)	−0.119	1.000
Liver-related death, *n* (%)	2 (4.9)	3 (7.3)	−0.131	1.000
Liver transplantation, *n* (%)	1 (2.4)	1 (2.4)	0.000	1.000
Time to resolution (days), median (IQR)	170 (81–247)	119 (69–260)	0.012	0.403

Abbreviations: SD, standard deviation; IQR, interquartile range; ULN, upper limit of normal; DILI, drug-induced liver injury; MELD, Model for End-stage Liver Disease.

fact that the use of corticosteroids was founded or guided on the recommendations provided by the European and American clinical guidelines. Recommendations in these clinical practice guidelines in DILI discourage the routine use of corticosteroids or limit their use to a subset of patients who exhibit autoimmune features,[3,4] whereas clinical guidelines in oncology support the initiation of corticosteroid therapy in patients with DILI due to immune-checkpoint inhibitors who present marked elevations of transaminases.[30]

Remarkably, an additional PS-matched analysis highlighted that corticosteroid use was associated with an increased recovery rate in DILI patients. Hu et al[31] suggested, based on retrospective nature evidence, that corticosteroids should be used in patients with severe DILI, especially those with hyperbilirubinemia, who are prone to develop ALF. Recently, in a single-centre open-label trial, corticosteroid plus glycyrrhizin administration was observed to be more effective in achieving a sustained biochemical response in

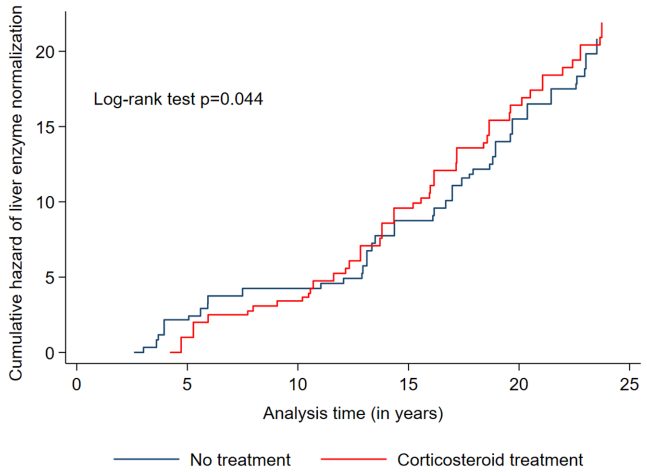

FIGURE 2 Nelson–Aalen curves of cumulative hazard function for normalisation of liver enzymes in patients treated with corticosteroids and patients with no treatment. Analysis time refers to origin of time-scale, and starts when the first DILI patient was enrolled.

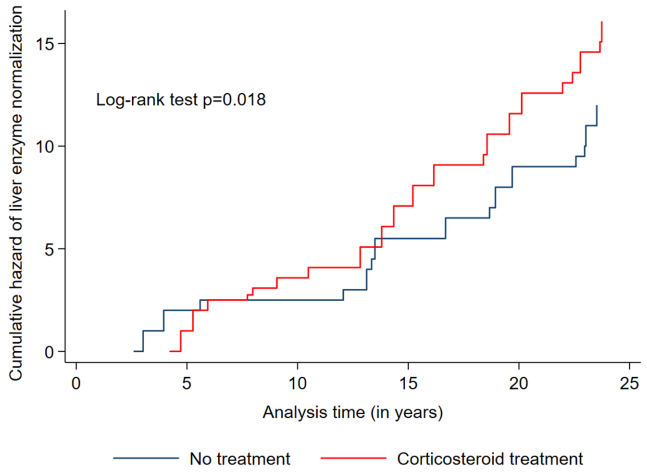

FIGURE 3 Nelson–Aalen curves of cumulative hazard function for normalisation of liver enzymes in patients who fulfilled the nR-based Hy's law and did not resolve within 30 days. Analysis time refers to origin of time-scale, and starts when the first DILI patient was enrolled.

mild-to-moderate chronic DILI patients than glycyrrhizin monotherapy.[32] Our findings, based on non-experimental data from a large cohort of patients with DILI, a relatively rare condition, provide evidence supporting the safety of using corticosteroids in the treatment of severe DILI.

Prospective registries are the most valuable source of data for idiosyncratic DILI research as they provide high-quality information from a large number of patients enrolled using a standardised protocol. Albeit DILI criteria slightly differed between registries, this may reflect the variability of DILI definitions in real world. Nonetheless, one of the strengths of the current study is the inclusion of *bona fide* DILI cases from the Spanish DILI Registry and the Indiana University cohort (using DILIN methodology) in an international collaborative effort. Furthermore, analyses were performed applying a rigorous statistical methodology based on PS. Altogether, both the internal and external validity of our findings are ensured. However, some limitations should be acknowledged. For instance, the lack of information about the dose of corticosteroids in some patients, along with the low number of ALF events, precluded conducting subgroup analyses.

In conclusion, this study provides robust evidence that corticosteroid therapy does not increase the risk of mortality in patients with DILI but exhibits a beneficial effect in terms of rate of normalisation of liver enzymes in patients with well-characterised DILI due to a variety of drugs. Although our analysis does not allow an incontrovertible recommendation for the use of corticosteroids in patients with severe DILI, the results of this study are encouraging enough to carry out prospective, well-designed randomised clinical trials to evaluate this therapeutic option in subjects with more serious hepatotoxicity.

AUTHOR CONTRIBUTIONS

Hao Niu: Formal analysis (lead); investigation (lead); methodology (lead); writing – original draft (lead); writing – review and editing (equal). **Jiayi Ma:** Data curation (lead); writing – review and editing (equal). **Inmaculada Medina-Cáliz:** Data curation (lead); writing – review and editing (equal). **Mercedes Robles-Diaz:** Writing – review and editing (equal). **Elvira Bonilla-Toyos:** Data curation (lead). **Marwan Ghabril:** Conceptualization (lead); formal analysis (equal); investigation (equal); writing – review and editing (equal). **Mª Isabel Lucena:** Conceptualization (lead); formal analysis (equal); investigation (lead); writing – original draft (lead); writing – review and editing (equal). **Ismael Alvarez-Alvarez:** Formal analysis (lead); investigation (lead); methodology (lead); writing – original draft (lead); writing – review and editing (equal). **Raúl J Andrade:** Conceptualization (lead); formal analysis (equal); investigation (lead); writing – original draft (lead); writing – review and editing (equal).

ACKNOWLEDGEMENTS

Declaration of personal interests: The authors gratefully acknowledge Prof. Dr. Naga Chalasani for his contributions to the design of the study and critical review of the manuscript.
Guarantor of the article: Mª Isabel Lucena.
Open access funding provided by Universidad de Málaga/CBUA.

FUNDING INFORMATION

This study was funded by Instituto de Salud Carlos III (ISCIII) cofounded by Fondo Europeo de Desarrollo Regional - FEDER (contract numbers: PI18/00901, PI19/00883, PI21/01248 and PT20/000127), Consejería de Salud de Junta de Andalucía (contract number: PI-0310-2018), and Agencia Española de Medicamentos y Productos Sanitarios. CIBERehd and Plataforma ISCIII Ensayos Clínicos are funded by ISCIII. HN holds a postdoctoral research contract funded by Junta de Andalucia (POSTDOC_21_00780). I.A.-A. holds a Sara Borrell contract funded by ISCIII (CD20/00083). This article/publication is based

upon work from COST Action CA17112, supported by COST (European Cooperation in Science and Technology). www.cost.eu. The funding sources have no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CONFLICT OF INTEREST

None.

PATIENT CONSENT STATEMENT

All subjects included in the study gave their informed consent.

ORCID

Hao Niu https://orcid.org/0000-0002-3030-3972
Jiayi Ma https://orcid.org/0000-0003-2920-7673
Inmaculada Medina-Caliz https://orcid.org/0000-0003-0471-6658
Mercedes Robles-Diaz https://orcid.org/0000-0002-2365-2787
Elvira Bonilla-Toyos https://orcid.org/0000-0001-7614-1510
Marwan Ghabril https://orcid.org/0000-0002-4784-3246
Mª Isabel Lucena https://orcid.org/0000-0001-9586-4896
Ismael Alvarez-Alvarez https://orcid.org/0000-0001-6271-0604
Raul J. Andrade https://orcid.org/0000-0002-1565-0757

REFERENCES

1. Andrade RJ, Chalasani N, Bjornsson ES, Suzuki A, Kullak-Ublick GA, Watkins PB, et al. Drug-induced liver injury. Nat Rev Dis Primers. 2019;5:58.
2. Reuben A, Tillman H, Fontana RJ, Davern T, McGuire B, Stravitz RT, et al. Outcomes in adults with acute liver failure between 1998 and 2013: an observational cohort study. Ann Intern Med. 2016;164:724–32.
3. European Association for the Study of the Liver. EASL clinical practice guidelines: drug-induced liver injury. J Hepatol. 2019;70:1222–61.
4. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR, Practice Parameters Committee of the American College of Gastroenterology. ACG clinical guideline: diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2021;116:878–98.
5. Wree A, Dechêne A, Herzer K, Hilgard P, Syn WK, Gerken G, et al. Steroid and ursodesoxycholic acid combination therapy in severe drug-induced liver injury. Digestion. 2011;84:54–9.
6. Hu PF, Wang PQ, Chen H, Hu XF, Xie QP, Shi J, et al. Beneficial effect of corticosteroids for patients with severe drug-induced liver injury. J Dig Dis. 2016;17:618–27.
7. Sundaram S, Vuppalanchi R, Saxena R, Chalasani N. Treatment of idiosyncratic drug-induced liver injury using steroids. ACG Case Rep J. 2020;7:e00319.
8. Karkhanis J, Verna EC, Chang MS, Stravitz RT, Schilsky M, Lee WM, et al. Steroid use in acute liver failure. Hepatology. 2014;59:612–21.
9. Wan YM, Wu JF, Li YH, Wu HM, Wu XN, Xu Y. Prednisone is not beneficial for the treatment of severe drug-induced liver injury: an observational study (STROBE compliant). Medicine (Baltimore). 2019;98:e15886.
10. Chalasani N, Fontana R, Davern T, Bonkovsky H, Rochon J, Serrano J, et al. Characteristics of patients with idiosyncratic drug induced liver injury (DILI) who receive systemic corticosteroids. Am J Gastroenterol. 2008;103:S144–5.
11. Stephens C, Robles-Diaz M, Medina-Caliz I, Garcia-Cortes M, Ortega-Alonso A, Sanabria-Cabrera J, et al. Comprehensive analysis and insights gained from long-term experience of the Spanish DILI registry. J Hepatol 2021;75:86–97.
12. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41–55.
13. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46:399–424.
14. Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. Drug-induced liver injury network (DILIN) prospective study: rationale, design and conduct. Drug Saf. 2009;32:55–68.
15. Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol. 1990;11:272–6.
16. Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89:806–15.
17. Robles-Diaz M, Lucena MI, Kaplowitz N, Stephens C, Medina-Cáliz I, González-Jimenez A, 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.e5.
18. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–70.
19. 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;6:160–8.
20. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47:1245–51.
21. Hayashi PH, Rockey DC, Fontana RJ, Tillmann HL, Kaplowitz N, Barnhart HX, et al. Death and liver transplantation within 2 years of onset of drug-induced liver injury. Hepatology. 2017;66:1275–85.
22. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10:150–61.
23. Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci. 2010;25:1–21.
24. Cueto-Sanchez A, Niu H, Del Campo-Herrera E, Robles-Díaz M, Sanabria-Cabrera J, Ortega-Alonso A, et al. Lymphocyte profile and immune checkpoint expression in drug-induced liver injury: an immunophenotyping study. Clin Pharmacol Ther. 2021;110:1604–12.
25. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9:30.
26. Hammerton G, Munafò MR. Causal inference with observational data: the need for triangulation of evidence. Psychol Med. 2021;51:563–78.
27. Lucena MI, Andrade RJ, Kaplowitz N, García-Cortes M, Fernández MC, Romero-Gomez M, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. Hepatology. 2009;49:2001–9.
28. Petronijevic M, Ilic K. Associations of gender and age with the reporting of drug-induced hepatic failure: data from the VigiBase™. J Clin Pharmacol. 2013;53:435–43.
29. Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. Hepatology. 2005;42:481–9.
30. Regev A, Avigan MI, Kiazand A, Vierling JM, Lewis JH, Omokaro SO, et al. Best practices for detection, assessment and management of suspected immune-mediated liver injury caused by immune checkpoint inhibitors during drug development. J Autoimmun. 2020;114:102514.
31. Hu PF, Xie WF. Corticosteroid therapy in drug-induced liver injury: pros and cons. J Dig Dis. 2019;20:122–6.

32. Wang JB, Huang A, Wang Y, Ji D, Liang QS, Zhao J, et al. Corticosteroid plus glycyrrhizin therapy for chronic drug- or herb-induced liver injury achieves biochemical and histological improvements: a randomised open-label trial. Aliment Pharmacol Ther. 2022;55:1297–310.

SUPPORTING INFORMATION

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

How to cite this article: Niu H, Ma J, Medina-Caliz I, Robles-Diaz M, Bonilla-Toyos E, Ghabril M, et al. Potential benefit and lack of serious risk from corticosteroids in drug-induced liver injury: An international, multicentre, propensity score-matched analysis. Aliment Pharmacol Ther. 2023;57:886–896. https://doi.org/10.1111/apt.17373